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Trend of Diabetes Care for Elderly Patients at a Single Center from 2009 to 2019

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Objective : We performed a narrative analysis of the data of diabetes of elderly patients how the Japanese Clinical Practice Guidelines have worked on glycemic control.

Methods : We analyzed two sets of data, one from patients who visited initially during April and June in 2009, 2014 and 2019, respectively, and the other from 168 patients followed for 10 years successively, with analysis on Hb (hemoglobin) A1c and the number of hypoglycemic agents (prescriptions)/patient.

Results : In the first set, the patient numbers were 351, 487 and 572 in each year with a mean age of 68.5, 70.5 and 71.7 years, respectively. The mean HbA1c, 7.3～7.4 %, was not significantly different from each year, but prescriptions/patient were greater in 2019 than in 2009, 1.7 ± 1.3 (mean ± SD) vs 1.2 ± 1.1. Upon division into Groups 1 to 3 by age, ＜65 years, 65 to 74 years, and ≥75 years old, respectively, HbA1c was greater in Group 1 than in Groups 2 and 3, and so were prescriptions/patient, especially DPP-4i and SGLT-2i. In the second set, the mean HbA1c was greater with time and so were prescriptions/patient, 1.2 ± 1.1 in 2009 vs 2.1 ± 1.4 in 2019. Upon division into three groups (T1, T2 and T3) by age tertile, with a mean age of 55.7, 66.0, and 75.4 years in 2009, respectively, HbA1c was higher and the fraction of the patients having ＜7.0 % HbA1c less in T1 than in T3. Prescriptions/patient were greater in T1 than in T3 all through the observation period.

Conclusion : Diabetes control has been at a reasonable level in the elderly patients (≥65 years) but not in the middle-aged. *Shinshu Med J 71 : 149—158, 2023*

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Key words : glycemic control, HbA1c, new class oral hypoglycemic agents, elderly patient

Abbreviations : RPG ; random sample plasma glucose, HbA1c ; hemoglobin A1c, SU ; sulphonylureas, α-GI ; alpha-glucosidase inhibitor, DPP-4i ; dipeptidyl peptidase-IV inhibitor, SGLT-2i ; sodium glucose cotransporter 2 inhibitor, CKD ; chronic kidney disease, CVD ; cardiovascular disease

I Introduction

The aim of the Clinical Practice Guidelines for the Treatment of Diabetes has been to widely implement evidence-based, rational, efficient and standardized clinical practice for diabetes all over Japan, and has undergone revisions every 3 years since 2004[1]. The notable changes in the recent Guidelines were made for the treatment of diabetes in elderly people. Currently[1], it is recommended the glycemic targets for older patients with diabetes be determined after careful consideration of the patient's age, duration of diabetes, risk of hypoglycemia, qualitative and quantitative help from surrounding people, and most importantly the patient's cognitive function. In addition, one should pay close attention to the basic/instrumental activities of daily living, and comorbidities/functional impairments[1].

In this study, we performed a narrative analysis of real world data of diabetes of elderly people during the last 10 years at a single center to see how the Guidelines have worked on the glycemic control of

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Table 1 Characteristics of the patients with diabetes registered in 2009, 2014 and 2019

Variable	2009	2014	2019
No. of patients	351	487	572
Female sex (%)	43	43	44
Ages (yr)	68.5 ± 10.2	70.5 ± 11.0	71.7 ± 11.8***
RPG (mg/dl)	167 ± 76.2	166 ± 62.9	170 ± 69.0^{ns}
HbA1c (%)	7.3 ± 1.1	7.3 ± 1.2	7.4 ± 1.1^{ns}
HbA1c＜7.0 %	46.7 ± 50.0	48.7 ± 50.0	40.6 ± 49.1^{ns}
Treatment (%)			
Drugs	71.7 ± 45.1	74.5 ± 43.6	78.2 ± 41.3^{ns}
No. of drugs	1.2 ± 1.1	1.4 ± 1.2	1.7 ± 1.3***
Insulin	16.0 ± 36.7	13.8 ± 34.5	12.9 ± 33.6^{ns}
SU	47.3 ± 50.0	45.2 ± 49.8	38.5 ± 48.7*
Metformin	13.4 ± 34.1	18.9 ± 39.2	26.2 ± 44.0***
α-GI	21.4 ± 41.0	14.8 ± 35.5	10.3 ± 30.4***
Pioglitazone	16.5 ± 37.2	8.8 ± 28.4	6.6 ± 24.9***
DPP-4i	0	40.5 ± 49.1	58.7 ± 49.3***
SGLT-2i	0	0.4 ± 6.4	17.3 ± 37.9***
Complications			
CKD	11.7 ± 32.2	17.5 ± 38.0	17.8 ± 38.3*
CVD	71.8 ± 45.1	76.6 ± 57.3	74.8 ± 43.4^{ns}

Data in 2009, 2014 and 2019 as a factor were analysed by one-way analysis of variance. Between groups comparison was made by Bonferroni test.
ns not significant, *p＜0.05, **p＜0.01, ***p＜0.001. The number of patients with type 1 diabetes was 3, 3, and 8 in the year 2009, 2014, and 2019, respectively.
Abbreviations : RPG ; random sample plasma glucose, HbA1c ; hemoglobin A1c, SU ; sulphonylureas, α-GI ; alpha-glucosidase inhibitor, DPP-4i ; dipeptidyl peptidase-Ⅳ inhibitor, SGLT-2i ; sodium glucose cotransporter 2 inhibitor, CKD ; chronic kidney disease, CVD ; cardiovascular disease

the patients. We also focused our attention on the impact of the newer class oral hypoglycemic agents (OHAs)[1)-6)] such as dipeptidyl peptidase-IV inhibitors (DPP-4i), sodium glucose cotransporter 2 inhibitors (SGLT-2i) and glucagon like peptide 1 receptor agonist (GLP-1a) on the glycemia attained in the patients with type 2 diabetes.

Ⅱ Methods

A Patients

Diagnosis of diabetes was made according to the Japanese Clinical Practice Guideline for Diabetes 2016[1)] and a total of 1396 patients with type 2 diabetes who visited our hospital for at least 3 months from April 1 to June 30 in each year of 2009, 2014 and 2019, were registered **(Table 1)**. The numbers of patients with diabetes were 351, 487 and 572 in 2009, 2014 and 2019, respectively **(Table 1)**. The small number of patients with type 1 diabetes were included **(Table 1)**. We analyzed them together to show the real world data of diabetes in our hospital. We extracted data such as gender, age (years), random sample plasma glucose (RPG) (mg/dl), HbA1c (%), and the information on prescribed drugs from the electronic charts. The information on the prescription included the classes and dosing of OHAs (glinides were combined with sulphonylureas (SU) because only a few patients were receiving glinides) and the preparations and dosing of insulin. We also recorded the presence of chronic kidney disease (CKD), which was diagnosed on the basis of the guideline, and hypertension and macrovascular events such as cere-

brovascular and cardiovascular (CVD) events on the basis of the patient's self-report.

B Study Design

Cross-sectional analysis

First, we compared the characteristics of the patients registered in 2009, 2014 and 2019 depending on the age.

The patients were classified into three groups according to the age at registration : the middle-aged (younger than 65 years), the elderly (65 to 74 years) and the advanced elderly (75 years and older) as needed.

Longitudinal analysis

Second, to determine the long-term trend of prescription of hypoglycemic agents and insulin preparations and the level of glycemic control, the data from 168 patients who had been continually seen by us for the 10 years from 2009 to 2019 were analyzed.

C Statistical analysis

The data are shown as mean ± SD. An analysis of variance (one-way or two-way mixed model) was used for the multiple comparisons and the Bonferroni test was used for comparisons between the two groups if necessary. P values of less than .05 were considered statistically significant.

Ⅲ Results

A Changes in HbA1c, RPG and drugs for the patients in 2009, 2014 and 2019

1 Characteristics of the patients registered in 2009, 2014 and 2019

The number of patients was 351, 487 and 572 in 2009, 2014 and 2019, respectively **(Table 1)**. The mean (± SD) age was progressively higher in the later years : 68.5 (± 10.2), 70.5 (± 11.0) and 71.7 (± 11.8) years, respectively. The fraction of the middle-aged patients was thus progressively less with time as 33 % (115 of 351) in 2009 and 22 % (125 of 572) in 2019 **(Table 2)**. On the other hand, the fraction of advanced elderly patients increased greater with time as 30 % (104 of 351) in 2009 and 45 % (259 of 572) in 2019.

The RPG and the mean HbA1c were not significantly different among the patients in 2009, 2014 and 2019 **(Table 1)**.

The proportion of the patients with a yearly mean HbA1c lower than 7.0 % was 46.7 (± 50.0), 48.7 (± 50.0) and 40.6 (± 49.1) % in 2009, 2014 and 2019, respectively, and the values were not significantly different from each other.

2 Use of OHAs

The number of OHAs prescribed per patient was 1.2 (± 1.1) in 2009 and 1.7 (± 1.3) in 2019, with the latter significantly greater than the former **(**$p < 0.001$, **Table 1)**. On the other hand, the proportion of the patients receiving exclusively non-pharmacological treatment decreased from 28 % in 2009 to 22 % in 2019 **(Table 1)**.

3 Pharmacological treatment including insulin **(Table 1)**

The fraction of patients with diabetes treated with insulin and/or OHAs insignificantly increased from 71.7 (± 45.1) % in 2009 to 78.2 (± 41.3) % in 2019. Detailed analysis revealed that the patients treated with SU, alpha glucosidase inhibitor (α-GI) and pioglitazone significantly decreased ($p < 0.05$). On the other hand, the fraction of patients receiving metformin, DPP-4i and SGLT-2i increased significantly ($p < 0.001$).

The patients with CKD, but not CVD, increased gradually ($p < 0.05$) during the 10 years.

4 Age-related characteristics of the patients **(Table 2)**

The patients were classified into three groups on the basis of age : < 65 years (adults group : G1), 65-74 years (elderly group : G2) and ≥ 75 years (advanced elderly group : G3).

The number of elderly (G2) and advanced elderly patients (G3) with diabetes increased with time but the number of adults (G1) was not significantly different during the 10 years.

RPG exhibited no significant change during the 10 years. HbA1c in each group did not show significant change either except for the value in G1 being greater in 2019 than those in G2 and G3 ($p < 0.001$).

5 Fulfillment of the recommended HbA1c value

The HbA1c target was recommended to be < 7.0 % for the patients with diabetes at large and < 8.0 % for the patients ≥ 75 years being treated by SU and/or insulin or having dementia (1). As shown in Table

Table 2 Characteristics of the 3 groups, G1, G2 and G3, of the patients with diabetes in 2009, 2014 and 2019

Glycemia	2009	2014	2019
G1 ＜65 yrs.	57.1 ± 6.7 (n = 115)	56.2 ± 7.4 (n = 125)	54.4 ± 8.0 (n = 125)
G2 65～74 yrs.	69.5 ± 2.9 (n = 132)	69.4 ± 2.8 (n = 175)	69.7 ± 2.6 (n = 188)
G3 75≤ yrs.	79.9 + 3.9 (n = 104)	81.1 + 4.6 (n = 187)	81.6 + 5.3 (n = 259)
G1 RPG (mg/dl)	159.4 ± 89.2$^{\#}$	154.6 ± 65.0$^{\#}$	164.6 ± 79.5$^{ns\#\#\#}$
G2 RPG (mg/dl)	163.4 ± 60.8	166.9 ± 62.3	155.5 ± 60.2^{ns}
G3 RPG (mg/dl)	186.6 ± 75.8	173.8 ± 61.2	183.3 ± 67.3^{ns}
G1 HbA1c (%)	7.4 ± 1.2^{NS}	7.4 ± 1.2^{NS}	7.6 ± 1.4$^{ns\#\#\#}$
G2 HbA1c (%)	7.2 ± 1.0	7.3 ± 1.2	7.2 ± 0.8^{ns}
G3 HbA1c (%)	7.2 ± 1.1	7.2 ± 1.2	7.4 ± 1.0^{ns}
G1 HbA1c＜7.0 %	45.2 ± 50.0^{NS}	42.4 ± 49.6^{NS}	34.4 ± 47.7$^{ns\ NS}$
G2 HbA1c＜7.0 %	47.7 ± 50.1	50.9 ± 50.1	43.1 ± 49.7^{ns}
G3 HbA1c＜7.0 %	47.1 ± 50.2	46.5 ± 50.0	41.7 ± 49.4^{ns}
G1 HbA1c＜8.0 %	77.4 ± 42.0^{NS}	72.8 ± 44.7^{NS}	73.6 ± 44.3$^{ns\#}$
G2 HbA1c＜8.0 %	79.5 ± 40.5	80.6 ± 39.7	85.6 ± 35.2^{ns}
G3 HbA1c＜8.0 %	81.7 ± 38.8	80.7 ± 39.7	76.1 ± 42.8^{ns}
Treatment (%)			
G1 No. of drugs	1.4 ± 1.2$^{\#}$	1.5 ± 1.2^{NS}	2.2 ± 1.4$^{***\#\#\#}$
G2 No. of drugs	1.1 ± 1.0	1.5 ± 1.2	1.7 ± 1.3***
G3 No. of drugs	1.0 ± 0.9	1.3 ± 1.1	1.5 ± 1.3**
G1 Insulin	22.6 ± 17.7$^{\#}$	18.4 ± 15.1^{NS}	19.2 ± 39.5$^{ns\#\#}$
G2 Insulin	14.4 ± 12.4	12.6 ± 11.1	7.4 ± 26.3^{ns}
G3 Insulin	10.5 ± 9.6	11.8 ± 10.4	13.9 ± 34.7^{ns}
G1 SU	47.8 ± 25.2^{NS}	40.0 ± 24.2^{NS}	43.2 ± 49.7$^{ns\ NS}$
G2 SU	44.7 ± 24.9	46.3 ± 25.0	39.4 ± 45.0^{ns}
G3 SU	50.0 ± 25.2	47.6 ± 25.1	35.5 ± 48.0**
G1 Metformin	14.8 ± 12.7^{NS}	22.4 ± 17.5^{NS}	39.2 ± 49.0$^{***\#\#\#}$
G2 Metformin	14.4 ± 12.4	21.1 ± 16.8	29.8 ± 45.9**
G3 Metformin	10.6 ± 9.6	14.4 ± 12.4	17.4 ± 38.0^{ns}
G1 α-GI	21.7 ± 17.2^{NS}	13.6 ± 11.8^{NS}	8.8 ± 28.4^{*NS}
G2 α-GI	18.9 ± 15.5	15.4 ± 13.1	10.1 ± 30.2^{ns}
G3 α-GI	24.0 ± 18.4	15.0 ± 12.8	11.2 ± 31.6**
G1 Pioglitazone	31.3 ± 21.7$^{\#\#\#}$	10.4 ± 9.4^{NS}	6.4 ± 24.6^{***NS}
G2 Pioglitazone	14.4 ± 12.4	10.9 ± 9.7	7.4 ± 26.3^{ns}
G3 Pioglitazone	2.9 ± 2.8	5.9 ± 5.6	6.2 ± 24.1^{ns}
G1 DPP-4i	0	44.0 ± 24.8^{NS}	60.8 ± 49.0^{***NS}
G2 DPP-4i	0	42.3 ± 24.5	61.2 ± 48.9***
G3 DPP-4i	0	36.4 ± 23.3	56.0 ± 49.7***
G1 SGLT-2i	0	0.8 ± 0.8^{NS}	40.0 ± 49.2$^{***\#\#\#}$
G2 SGLT-2i	0	0.6 ± 0.6	14.9 ± 35.2***
G3 SGLT-2i	0	0	8.1 ± 27.3***
Complications			
G1 CKD	10.4 ± 30.7^{NS}	13.6 ± 34.4^{NS}	13.6 ± 34.4$^{ns\#\#\#}$
G2 CKD	8.3 ± 27.7	16.0 ± 36.8	10.1 ± 30.2^{ns}
G3 CKD	17.3 ± 38.0	21.4 ± 41.1	25.5 ± 43.7^{ns}
G1 CVD	52.2 ± 50.2$^{\#\#\#}$	60.8 ± 49.0$^{\#\#\#}$	56.0 ± 49.8$^{ns\#\#\#}$
G2 CVD	76.5 ± 42.6	73.1 ± 44.4	70.7 ± 25.1^{ns}
G3 CVD	87.5 ± 33.2	85.6 ± 35.2	86.9 ± 33.8^{ns}

2, the fraction of the patients with mean HbA1c ＜7.0 % and ＜8.0 % in G1 (＜65 years) was not significantly different except in 2019, when the fraction having ＜ 8.0 % in G2 was greater than in G1 and G3.

6 The trend of prescription of hypoglycemic agents

The number of the OHAs prescribed/patient with diabetes was significantly larger in G1, G2 and G3 groups with time over the 10 years ($p<0.01$). The number of prescribed OHAs in G1 was significantly greater ($p<0.05$) than in G2 and G3 groups in 2009 and 2019.

The fraction of insulin-treated patients was not significantly different between each other over the 10 years. However, in each year, the fraction of insulin usage in G1 was greater than in G2 and G3 ($p<0.05$, except for 2014). SU treatment tended to decrease in the elderly groups during the 10 years. On the other hand, the fraction of metformin prescription has increased significantly ($p<0.001$) during the 10 years. In 2019, the younger the patients (G1), the more were treated by metformin ($p<0.001$). The fraction of the α-GI treatment also significantly decreased during the same period in G1 and G3 ($p<0.05$). The fraction of the patients treated by pioglitazone did not change significantly in G2 and G3 but that in G1 was significantly decreased ($p<0.001$). Consequently, the fraction of the pioglitazone treatment in G1, at 2009, was greater than those in G2 and G3 ($p<0.001$) but such an age-related difference was not apparent in 2014 and 2019. Treatment by the newly developed drugs, DPP-4i and SGLT-2i, increased significantly ($p<0.001$) yearly after marketing. DPP-4i treatment was not significantly different among the 3 groups but the younger they were, the more SGLT-2i was prescribed after 2014 ($p<0.001$).

CVD and CKD of patients with diabetes increased during the 10 years ($p<0.001$), especially ($p<0.001$) in the older groups (G2 and G3).

B Changes in HbA1c, RPG and drugs for patients seen continuously from 2009 to 2019 : a longitudinal analysis

The mean age (±SD) of the 168 patients with diabetes treated successively for 10 years was from 65.7 (±9.1) to 75.4 (±9.1) years **(Table 3)**.

The mean HbA1c of the 168 patients increased significantly ($p<0.05$) from 7.3 (±1.1) to 7.6 (±1.1) % during the 10 years.

The fraction of patients with HbA1c ＜7.0 % decreased from 47.0 (±50.1) to 26.8 (±44.4) % ($p<0.001$) but that with HbA1c ＜8.0 % did not decrease during the 10 years.

The mean fraction of the patients receiving pharmacological agents has significantly increased from 69.0 % (±46.4) to 86.9 % (±33.8) ($p<0.001$) **(Table 3)**. This was naturally associated with a decrease in the patients exclusively treated with diet and exercise. The fraction of the patients treated with insulin injection did not significantly change during the 10 years. This was also the case for those receiving SU, α-GI and pioglitazone. On the other hand, the fraction of the patients treated with metformin, DPP-4i or SGLT-2i significantly increased ($P<0.001$) **(Table 3)**.

Upon dividing the 168 patients into three groups by age tertiles, the mean age of the three groups, T1, T2 and T3, were 55.7 (±6.2), 66.0 (±2.4) and 75.4 (±3.2) years, respectively in 2009 **(Table 4)**.

The mean HbA1c and RPG of the patients increased slightly during the 10 years ($p<0.05$) **(Fig. 1a, b)**.

Table 2 The three groups, G1, G2 and G3, were less than 65 years (middle-aged group), 65 years and more than 65 and less than 75 years (elderly group) and 75 years and more (advanced elderly group), respectively.
Data among the 3 groups, G1, G2 and G3 as a factor were analysed by one-way analysis of variance and data in 2009, 2014 and 2019 as a factor were analysed by one-way analysis of variance. Between groups comparison was made by the Bonferroni test.
ns not significant, $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$ in each group, G1, G2 and G3 among three years.
NS not significant, # $p<0.05$, # # $p<0.01$, # # # $p<0.001$ among the 3 groups, G1, G2 and G3, in 2009, 2014 and 2019.
Abbreviations are the same as Table 1.

Table 3 Characteristics of the patients with diabetes treated successively for 10 years from 2009 to 2019

	2009	2014	2019
No. of patients	168		
Female sex (%)	47.6		
Ages (yr)	65.7 ± 9.1	70.5 ± 9.1	75.4 ± 9.1***
Glycemia			
RPG (mg/dl)	161 ± 67.2	171 ± 60.8	180 ± 69.4*
HbA1c (%)	7.3 ± 1.1	7.4 ± 1.2	7.6 ± 1.1*
HbA1c＜7.0 %	47.0 ± 50.1	38.7 ± 48.8	26.8 ± 44.4***
HbA1c＜8.0 %	80.4 ± 39.8	77.4 ± 42.0	73.2 ± 44.4ns
Treatment (%)			
Drugs	69.0 ± 46.4	80.4 ± 39.8	86.9 ± 33.8***
No. of drugs	1.2 + 1.1	1.7 + 1.3	2.1 + 1.4***
Insulin	14.3 ± 35.1	14.9 ± 35.7	19.0 ± 39.4ns
SU	48.2 ± 50.1	50.6 ± 50.1	49.4 ± 50.1ns
Metformin	13.7 ± 34.5	26.8 ± 44.4	35.1 ± 47.9***
α-GI	20.8 ± 40.7	22.0 ± 41.6	16.7 ± 37.4ns
Pioglitazone	19.0 ± 39.4	11.9 ± 32.5	12.5 ± 33.2ns
DPP-4i	0	42.3 ± 49.5	64.9 ± 47.9***
SGLT-2i	0	1.2 ± 10.9	16.1 ± 36.8***
Complications			
CKD	4.8 ± 21.4	14.9 ± 35.6	24.4 ± 43.1***
CVD	64.9 ± 47.9	77.4 ± 42.0	82.7 ± 37.9***

Data in 2009, 2014 and 2019 as a factor were analysed by one-way analysis of variance. Between groups comparison was made by the Bonferroni test.
ns not significant, *p＜0.05, **p＜0.01, ***p＜0.001.
Abbreviations are the same as Table 1.

HbA1c was not significantly different between T1, T2 and T3. However, an increase in RPG was significant among the 3 groups (p＜0.01, **Fig. 1a)**. The percent of the patients with HbA1c ＜7.0 % decreased during the 10 years (p＜0.001) and the decrease was less in T1 than in T2 and T3 (p＜0.05, **Fig. 1c)**. Percent changes in the fraction of HbA1c ＜8.0 % were not significantly different among the three groups during the 10 years **(Fig. 1d)**.

In general, insulin and/or oral hypoglycemic agents were prescribed more frequently in the patients successively seen for 10 years than in others. The fraction increased up to 92.9 ± 26.0 % in T1 (p＜0.001) **(Table 4)**. Younger patients (T1) were treated with a greater number of pharmacological agents than in T2 and T3 (interaction between years and tertiles was p＜0.05, **Fig. 1e)**.

The profile of pharmacological treatment was significantly different among the 3 groups **(Table 4)**. The fraction of the patients treated with metformin significantly increased (p＜0.001) and the younger the patients, the more metformin (interaction between years and tertiles was significant (p＜0.01). In addition, the fraction of the treatment with pioglitazone was greater (p＜0.001) in T1 and T2 than in T3 ; however, it tended to decrease in T1 and T2 during the 10 years. Use of the newer oral hypoglycemic drugs, DPP-4i and SGLT-2i, was significantly (p＜0.001) increased year by year after their appearance on the market. The frequency of use of the DPP-4i treatment was not significantly different among the three tertiles. The younger the patients, the greater was the frequency of use of SGLT-2i (interaction between years and tertiles was p＜0.001). On the other

hand, in each fraction of the drug treatment with insulin, SU, alpha-GI, there were no significant changes among years and the three tertiles.

The prevalence of CKD and CVD of the 168 patients with diabetes increased year by year. The older the patients, the greater the prevalence was (the interaction for CKD but not CVD was $p<0.05$) **(Table 4)**.

Ⅳ Discussion

Good control of blood glucose and HbA1c of patients with diabetes lowers the risk of diabetes-related events and mortality[7)-11)]. However, too rapid and/or too much lowering of glycemia especially in the elderly are most likely associated with paradoxically increased morbidity and mortality[12)13)]. Guidelines provided by the authorities thus indicate it is advisable to keep finely adjusted glycemic targets in the elderly, which is not always practically feasible in the real world. Thus, we looked back and analyzed in detail our real world-data obtained during a 10-year period to evaluate the practical outcomes.

The primary data was that the patients older than 65 years were treated relatively well for the 10 years from 2009 to 2019, in consideration of the guidelines in Japan and the ADA[1)2)]. However, the glycemic outcomes in the adult patients younger than 65 years were far from optimal. In other words, we need additional efforts for the patients with diabetes to achieve better glycemic control in this segment of patients.

The UK Prospective Diabetes Study (UKPDS) Group strongly reinforced metformin to treat patients with type 2 diabetes in 1998[8)]. DPP-4i, SGLT-2i and GLP-1a were introduced into the market thereafter, in 2010s[3)5)6)]. The guidelines recommend judicious use of the newer agents in patients with diabetes[1)]. We have employed such newly developed agents positively and tended to replace SU with them **(Table 1)**.

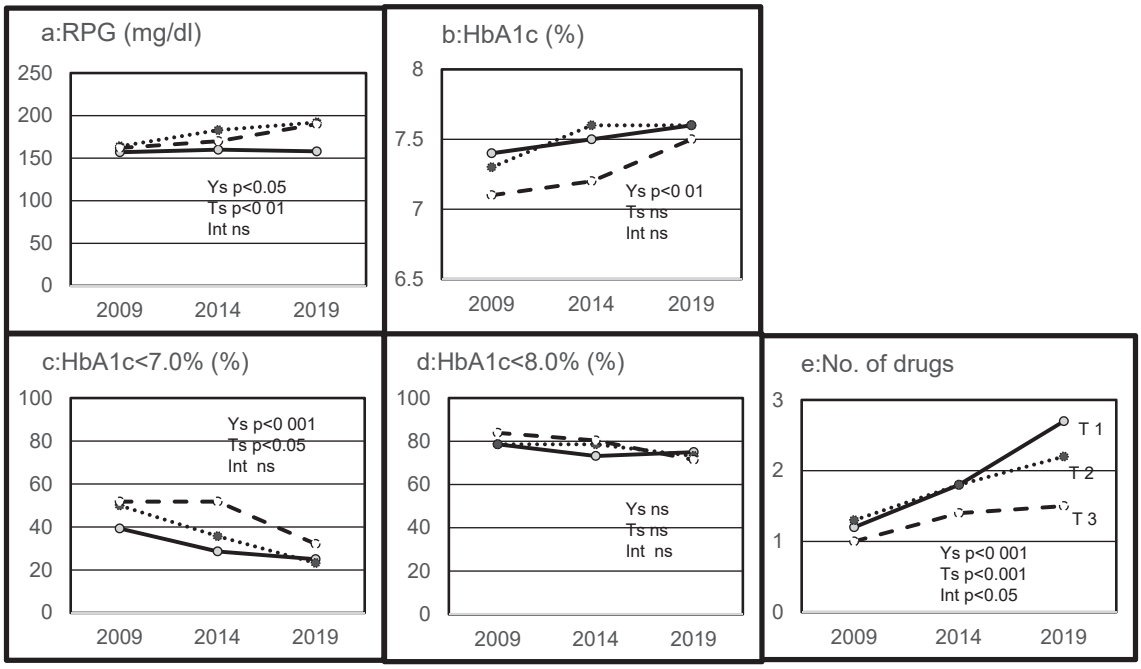

Fig. 1 Changes in characteristics of the 3 tertiles, T1, T2 and T3 from the 168 patients with diabetes treated successively for 10 years.

We divided the 168 patients into thirds, 56 patients each (T1 : solid line, T2 : dotted line and T3 : broken line). Panels a : RPG (mg/dl), b : HbA1c (%), c : HbA1c<7.0 %, d : HbA1c<8.0 % and e : No. of drugs present mean changes in RPG, mean changes in HbA1c (%), mean fraction of the changes in completed less than 7 %, mean fraction of the changes in completed less than 8 % and mean number of drugs prescribed in 3 tertiles patients with diabetes in 2009, 2014 and 2019, respectively. Standard deviations (Table 4) are not shown. Ys, 3 years, Ts, 3 tertiles, Int, interaction between Ys and Ts.

Table 4 Characteristics of the 3 subgroups, tertiles T1, T2 and T3, of the patients with diabetes treated successively for 10 years from 2009 to 2019

Variable	2009	2014	2019
T1 Ages (n＝56)	55.7＋6.2	60.5＋6.2	65.4＋6.3
T2 Ages (n＝56)	66.0＋2.4	70.9＋2.4	75.7＋2.3
T3 Ages (n＝56)	75.4＋3.2	80.2＋3.2	85.0＋3.2
T1 RPG (mg/dl)	157＋72.6	160＋53.0	158＋64.9*♯♯
T2 RPG (mg/dl)	164＋58.4	183＋70.5	192＋80.0
T3 RPG (mg/dl)	162＋70.8	170＋56.5	190＋57.4
T1 HbA1c (%)	7.4＋1.1	7.5＋1.0	7.6＋1.3*NS
T2 HbA1c (%)	7.3＋1.1	7.6＋1.5	7.6＋0.9
T3 HbA1c (%)	7.1＋1.0	7.2＋1.1	7.5＋1.0
T1 HbA1c＜7.0 %	39.3＋49.3	28.6＋45.6	25.0＋43.7***♯
T2 HbA1c＜7.0 %	50.0＋50.5	35.7＋48.3	23.2＋42.6
T3 HbA1c＜7.0 %	51.8＋50.4	51.8＋50.4	32.1＋47.1
T1 HbA1c＜8.0 %	78.6＋41.4	73.2＋44.7	75.0＋43.7nsNS
T2 HbA1c＜8.0 %	78.6＋41.4	78.6＋41.4	73.2＋44.7
T3 HbA1c＜8.0 %	83.9＋37.1	80.4＋40.1	71.4＋45.6
Treatment (%)			
T1 Drugs	69.6＋46.4	85.7＋35.3	92.9＋26.0***♯
T2 Drugs	71.4＋45.6	80.4＋40.1	91.1＋28.8
T3 Drugs	66.1＋47.8	75.0＋43.7	76.8＋42.6
T1 No. of drugs	1.2＋1.1	1.8＋1.3	2.7＋1.4***♯♯♯＋
T2 No. of drugs	1.3＋1.2	1.8＋1.4	2.2＋1.4
T3 No. of drugs	1.0＋0.9	1.4＋1.2	1.5＋1.2
T1 Insulin	21.4＋41.4	19.6＋40.1	17.9＋38.6nsNS
T2 Insulin	12.5＋33.4	14.3＋35.3	25.0＋43.7
T3 Insulin	8.9＋28.8	10.7＋31.2	14.3＋35.3
T1 SU	41.1＋49.6	50.0＋50.5	62.5＋48.9nsNS
T2 SU	53.6＋50.3	53.6＋50.3	46.4＋50.3
T3 SU	50.0＋50.5	48.2＋50.4	39.3＋49.3
T1 Metformin	12.5＋33.4	28.6＋45.6	57.1＋49.9***♯♯♯＋＋
T2 Metformin	17.9＋38.6	33.9＋47.8	32.1＋47.1
T3 Metformin	10.7＋31.7	17.9＋38.6	16.1＋37.1
T1 α-GI	16.1＋37.1	19.6＋40.1	10.7＋31.2nsNS
T2 α-GI	23.2＋42.6	23.2＋42.6	23.2＋42.6
T3 α-GI	23.2＋42.6	23.2＋42.6	16.1＋37.1
T1 Pioglitazone	26.8＋44.7	17.9＋38.6	17.9＋38.6ns♯♯♯
T2 Pioglitazone	26.8＋44.7	12.5＋33.4	10.7＋31.2
T1 Pioglitazone	3.6＋18.7	5.4＋22.7	8.9＋28.8
T1 DPP-4i	0	46.4＋50.3	67.9＋47.1***NS
T2 DPP-4i	0	42.9＋49.9	69.6＋46.4
T3 DPP-4i	0	37.5＋48.9	57.1＋49.9
T1 SGLT-2i	0	1.8＋13.4	35.7＋48.3***♯♯♯＋＋＋
T2 SGLT-2i	0	1.8＋13.4	12.5＋33.4
T3 SGLT-2i	0	0	0
Complications			
T1 CKD	7.1＋26.0	10.7＋31.2	10.7＋31.2***♯♯♯＋
T2 CKD	1.8＋13.4	8.9＋28.8	25.0＋43.7
T3 CKD	5.4＋22.7	25.0＋43.7	37.5＋48.9
T1 CVD	46.4＋50.3	64.3＋48.3	67.9＋47.1***♯♯♯
T2 CVD	62.5＋48.9	75.0＋43.7	85.7＋35.3
T3 CVD	85.7＋35.3	92.9＋26.0	94.6＋22.7

At the same time, we were enthusiastic regarding a team effort to sustain the patient's positive stance toward diabetes management. Namely, we recommend the patients with diabetes to learn how to cope with diabetes through nursing, nutritional and pharmacological counseling by qualified medical staff. However, the patients less than 65 years were in general rather reluctant to join these activities mostly due to their busy working and life styles. This, on the other hand, may have pushed us to prescribe a larger number of drugs to improve their glycemic control.

Duration of diabetes is an important risk factor for mortality and morbidity in patients with diabetes[14]. Our longitudinal data in the patients successively treated for 10 years clearly indicated the treatment outcome was far from ideal. The HbA1c target was recommended to be <7.0 % for patients with diabetes at large and <8.0 % for patients >75 years who are treated by SU and/or insulin or having dementia[1]. The Guidelines might relate in part to the tendency of the worse fraction of the patients with mean HbA1c <7.0 % in 2019 **(Table 2)** because the fraction of the patients with mean HbA1c <7.0 % in G3 in 2019 tended to be less than that in 2009. Now, we need to strengthen our strategies to obtain better glycemic control. The so-called empowerment approach[15] and syndemic approach[16] would be appropriate here, although the adherence of the adult patients would be worse than that of the elderly patients, which is not shown exactly from the present study.

DPP-4i and SGLT-2i were introduced to the market in 2009 and 2014, respectively, in Japan. Thus, we often prescribed them in addition to metformin according to the guidelines by the JDS and the ADA[1)17]. Our data suggest that these drugs improved the glycemic control of the adult and older patients with diabetes to some extent.

Complications, especially CVD, of the patients with diabetes are major factors determining long-term prognoses. Although the direct treatment outcome in this aspect was not obtainable in our study, relatively poor glycemic control especially in the younger patients was an alarming sign. We need to pay close attention to a possible relationship between undesirable HbA1c values of the patients less than 65 years and vascular events.

The present study is retrospective. It contains many limitations, not determining the order of OHAs, not averaging the number of patients seen by each doctor, not normalizing the backgrounds of patients, and so on. Most importantly, the treatment targets were not pre-determined between four doctors mainly responsible for the management of the patients with diabetes. The data collection, especially regarding vascular complications, was far from complete. However, within these limitations, we believe this paper describes the important faces of treatment outcome regarding HbA1c and glycemia of patients with diabetes at large.

V Conflict of Interests

None.

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Compliance with Ethical Standards

The project was studied with humans but it is retrospective, and was approved by the ethics committee of Shiojiri Kyoritsu Hospital.

Table 4 Data were analysed by two-way analysis of variance. Two factors were years, 2009, 2014 and 2019, and tertiles, T1, T2 and T3. Between groups comparison was made by the Bonferroni test.
ns not significant, *p<0.05, **p<0.01, ***p<0.001 among years, 2009, 2014 and 2019.
NS not significant, # p<0.05, # # p<0.01, # # # p<0.001 among tertiles, T1, T2 and T3.
+p<0.05, + +p<0.01, + + +p<0.001 interaction between years and tertiles.
Abbreviations are the same as Table 1.

References

1) Haneda M, Noda M, Origasa H, et al : Japanese clinical practice guideline for diabetes 2016. J Diabetes Investig 9 : 657–697, 2018 [Erratum, J Diabetes Investig 10 : 190, 2019]
2) Davies MJ, D'Alessio DA, Fadkin J, et al : Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 41 : 2669–2701, 2018
3) Hermansen K, Kipnes M, Luo E, et al : Efficacy and safety of the dipeptidyl peptidase–4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab 9 : 733–745, 2007
4) Kadowaki T, Tajima N, Odawara M, et al : Addition of sitagliptin to ongoing metformin monotherapy improves glycemic control in Japanese patients with type 2 diabetes over 52 weeks. J Diabetes Invest 18 : 174–181, 2013
5) Monami M, Nardini C, Mannucci E : Efficacy and safety of sodium glucose co–transport–2 inhibitors in type 2 diabetes : a meta–analysis of randomized clinical trials. Diabetes Obes Metab 16 : 457–466, 2014
6) Zinman B, Wanner C, Lachin JM, et al : EMPA–REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 373 : 2117–2128, 2015
7) UK prospective diabetes study (UKPDS) Group. Intensive blood–glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 352 : 837–853, 1998 [Erratum, Lancet 354 : 602, 1999]
8) UK Prospective Diabetes Study (UKPDS) Group : Effect of intensive blood–glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352 : 854–865, 1998 [Erratum, Lancet 352 : 1558, 1998]
9) Duckworth W, Abraira C, Moritz T, et al for the VADT investigators : Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 360 : 129–139, 2000
10) The ADVANCE Collaborative Group : Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 358 : 2560–2572, 2008
11) The ACCORD Study Group : Effects of intensive blood glucose lowering in type 2 diabetes. N Engl J Med 358 : 2545–2559, 2008
12) Kuusisto J, Mykkanen L, Pyorala K, Laakso M : NIDDM and its metabolic control predict coronary heart disease in elderly subjects. Diabetes 43 : 960–967, 1994
13) Cukierman T, Gerstein HC, Willamson JD : Cognitive decline and dementia in diabetes––systematic overview of prospective observational studies. Diabetologia 48 : 2460–2469, 2005
14) Rawshani A, Rawshani A, Franzen S, et al : Risk factors, mortality, and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 379 : 633–644, 2018
15) Coppola A, Sasso L, Banasco A, Giustina A, Cazzaruso C : The role of patient education in the prevention and management of type 2 diabetes : an overview. Endocrine 53 : 18–27, 2016
16) Mendenhall E, Kohrt BA, Norris SA, Ndetei D, Prabhakaran D : Non–communicable syndemics : poverty, depression, and diabetes among low–income populations. Lancet 389 : 951–963, 2017
17) American Diabetes Association : Standards of medical care in Diabetes–2020. Diabetes Care 43 : S4–S212, 2020

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