

Importance of the Evaluation of Renal Function for the Prevention of Hypoglycemia in Elderly Diabetes Patients

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Objective: The Japan Diabetes Society and the Japan Gerontological Society Collaborative Committee recently released guidelines for the management of elderly diabetes patients. In these guidelines, patients are classified into categories I-III depending on age, cognitive function, activities of daily living (ADL), and presence or absence of multiple functional impairments. The target control value of HbA1c is set for each category. Low ($< 30 \text{ mL/min/1.73 m}^2$) estimated glomerular filtration rate (eGFR) is an independent high-risk factor for severe hypoglycemia, yet it is not included in the categorization factors. We surveyed elderly diabetes patients with normal cognitive function and ADL (Category I) who were admitted to the emergency department with severe hypoglycemia, retrospectively studied eGFR at the onset of hypoglycemic episode, and checked whether the HbA1c levels matched the guidelines.

Methods: Among 129 diabetes patients aged ≥ 65 years admitted to the Tokai University hospital for hypoglycemic emergencies, 73 had normal cognitive function and ADL. HbA1c level and eGFR at the onset of hypoglycemic attack were obtained from the medical records of these subjects.

Results: All subjects were prescribed anti-diabetes agents with high-risk of severe hypoglycemia, including insulin. Sixty-one patients showed $\text{eGFR} \geq 30 \text{ mL/min/1.73 m}^2$. Among them, 31 (50.8%) had HbA1c levels below the recommended range. Among 12 patients whose $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$, 6 (50%) had HbA1c levels below the recommended range.

Conclusion: Even with normal cognitive function and ADL, $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ alone is a strong risk factor for hypoglycemia in elderly diabetes patients. We propose that the target control HbA1c level in elderly patients with $\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$ should be 7.5-8.4 %, which is equivalent to that of category III patients.

Key words: hypoglycemia, elderly patients with diabetes, targets for blood glucose control, renal dysfunction

INTRODUCTION

Since Japan became a super-aged country with more than 25% of the total population aged 65 and more, the number of diabetes patients, especially elderly diabetes patients, has been steadily increasing. Elderly diabetes patients are at high risk of severe hypoglycemia [1], which leads to cognitive impairment [2] and cardiovascular events [2]. Therefore, it is clinically pertinent to set an appropriate blood glucose target level for elderly patients with diabetes.

In May 2016, the Japan Diabetes Society (JDS) and the Japan Gerontological Society (JGS) Collaborative Committee released guidelines for managing elderly patients with diabetes [3]. According to the guidelines, patients are categorized into three classes based on (i) age; (ii) cognitive function; (iii) basic activities of daily living (BADL) and instrumental activities of daily living (IADL); and (iv) presence or absence of multiple comorbidities or functional impairments. HbA1c target values are set for each category. The guidelines also set the lower limits of blood glucose levels reached with use or non-use of agents that carry the potential risk of severe hypoglycemia, such as insulin, sulfonylurea (SU),

and glinide (Fig. 1). However, due to lack of a detailed definition of “multiple comorbidities or functional impairments”, the utility of these guidelines is limited.

Low glomerular filtration rate is a frequent complication of diabetes and an important risk factor for severe hypoglycemia, especially in elderly patients [4]. However, renal function is not included in the criteria for categorization in these guidelines.

The aim of the present study is to retrospectively survey Category I elderly diabetes patients admitted to the emergency department with severe hypoglycemia and review HbA1c levels and estimated glomerular filtration rate (eGFR) at the onset of a hypoglycemic episode.

MATERIALS AND METHODS

The medical records of 129 patients with diabetes aged ≥ 65 years admitted to our hospital between 2008 and 2014 for hypoglycemia were examined (Fig. 2). Our study was retrospective in design. Detailed assessment of cognitive function and evaluation of activities of daily living (ADL) could not be found in the medical records of 8 patients; therefore, these patients were excluded. Eight patients with dementia

Patient background/ health status		Category I		Category II	Category III
		1. Intact cognitive function and 2. No impairment of ADL		1. Mild cognitive impairment to mild dementia or 2. Impairment(s) of instrumental ADL, no impairment of basic ADL	1. Moderate or severe dementia or 2. Impairment(s) of basic ADL or 3. Presence of multiple comorbidities or functional impairments
Use of drugs potentially associated with severe hypoglycemia (e.g., insulin or sulfonylureas, glinides)	No	< 7.0%		< 7.0%	< 8.0%
	Yes	65 ≤ age < 75 years < 7.5% (lower limit, 6.5%)	≥ 75 years < 8.0% (lower limit, 7.0%)	< 8.0% (lower limit, 7.0%)	< 8.5% (lower limit, 7.5%)

Fig. 1 Glycemic targets (HbA1c values) for elderly Japanese patients with diabetes

Patients with diabetes ≥ 65 years old who were admitted to our hospital with hypoglycemic emergencies (n = 129)

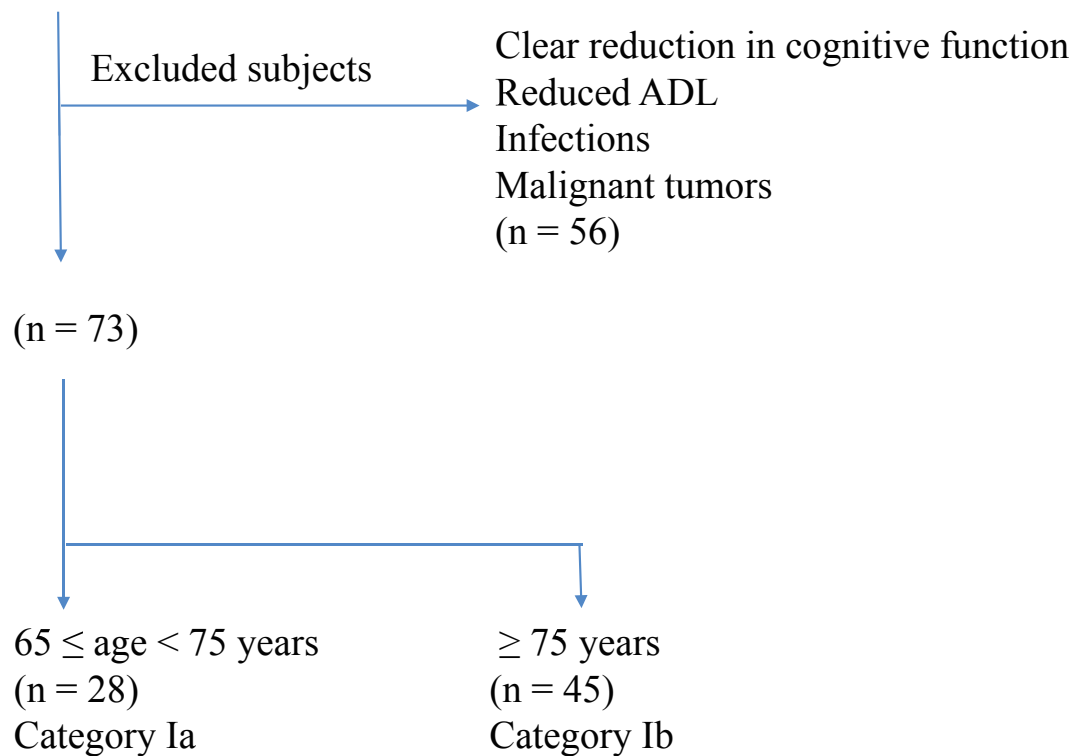


Fig. 2 Flow chart of the patient selection process applied in the present study

and four patients with reduced BADL were classified into Category II and III, respectively. Thirty-six patients with severe infection and/or malignant disease that could cause secondary hypoglycemia were regarded as Category III. The remaining 73 patients were regarded

as Category I. The following parameters were obtained from the medical records of these patients: age, sex, body weight, HbA1c level, eGFR, and types and doses of glucose-lowering agents that pose severe risk of hypoglycemia.

In this study, severe renal dysfunction was defined as eGFR below 30 mL/min/1.73 m². This cutoff value is used for dose adjustment of oral hypoglycemic agents (e.g. biguanide and SU). As per the American Diabetes Association and the Japanese Society of Nephrology, these agents need to be withdrawn, or their doses reduced in accordance with deteriorating renal function [5-8]. Additionally, eGFR < 30 mL/min/1.73 m² is considered to reflect progression to renal failure in patients with diabetic nephropathy in Japan, [9].

The study protocol was registered in the University Hospital Medical Information Network Clinical Trials Registry (#UMIN000033413) and approved by the Tokai University's Institutional Review Board for Clinical Research (#17R-158).

To analyze differences in patient background parameters, the Pearson's χ^2 test was used for nominal and ordinal variables and the Wilcoxon rank-sum test was used for continuous variables. A p-value < 0.05 was considered to denote statistically significant differences. All statistical analyses were performed using the JMP software v12.0 (SAS Institute, Inc., Cary, NC).

RESULTS

Among the 73 study subjects, 28 were 65-74 years of age (designated as Category Ia) and 45 were \geq 75 years of age (designated as Category Ib). Table 1. shows the baseline data and statistical differences between study subjects of Category Ia and Category Ib. All of these subjects were prescribed drugs with high-risk of inducing hypoglycemia at the onset of the hypoglycemic attack.

HbA1c level of Category Ia patients was $6.84 \pm 1.10\%$ and that of the Category Ib was $6.65 \pm 0.76\%$. Eleven (42.9%) patients in Category Ia and 66.7% patients in Category Ib had HbA1c level less than the lower limit of the target range (6.5% in Category Ia; 7.0% in Category Ib). Insulin and SU drugs were more frequently used in patients of Category Ib than Category Ia. In addition, 5 subjects were treated with SU or metformin, which were contraindicated in patients with severe renal failure in Japan.

Three of 28 patients in Category Ia and 9 of 45 in Category Ib had eGFR < 30 mL/min/1.73 m² (Table 2). Notably, all these patients were treated with insulin or SU drugs.

We retrospectively applied the guidelines to HbA1c level at the onset of the hypoglycemic attack. Six patients (50%) showed HbA1c level below the lower limit of the target control range.

Furthermore, a high proportion of the elderly patients of Category Ib (73.3%) were treated with SU. In addition, among the patients with eGFR < 30 mL/min/1.73 m², 8 patients (66.7%) were treated with insulin and 4 patients (33.3%) with SU.

DISCUSSION

The frequency of hypoglycemia in patients with diabetes increases with age and is highest in those over 80 years of age [1]. Even mild hypoglycemia worsens depression, cognitive function, risk of fall, and quality of life. Furthermore, severe hypoglycemia may cause dementia, cardiovascular disease, and death, especially in elderly patients [2]. The American Diabetes

Association does not have evidence to justify the rigorous control of blood glucose in patients over 65 years of age who have diabetes. But instead, the American Geriatrics Society recommends that the target HbA1c level for elderly diabetes patients with predicted life expectancy of five years or less should be set at 8%, because the risk of hypoglycemia outweighs the advantages of preventing macrovascular and microvascular complications [10, 11]. Similarly, the guidelines of the Veterans Affairs (US Department of Defense) sets the target HbA1c level to less than 8.0% for patients with predicted life expectancy of 5-15 years and free of microvascular complications [12]. Recently, the JDS and the JGS Collaborative Committee released guidelines for management of elderly diabetes patients [3]. The target HbA1c level was set at lower levels than those of American guidelines without detailed justification. It is important to assess the validity of this target HbA1c level, especially for patients with renal dysfunction.

J-EDIT study showed that rigorous blood glucose control in elderly patients without causing hypoglycemia was difficult in practice. High HbA1c level (\geq 8.5%) and low HbA1c level (< 7.0%) were established as risk factors for cerebral stroke [13]. Thus, this study warned against rigorous glucose control and indicated that the best approach to managing elderly diabetes patients is to control multiple risk factors, including blood pressure, lipid profiles, physical activities, and nutritional factors for individual patients.

The majority of patients in the present study belonged to Category Ib, i.e., aged 75 years and above, and were all prescribed anti-diabetes drugs with high risk for hypoglycemia such as glinides, SU, and insulin. In addition, the mean HbA1c level of this group was 6.7%, and HbA1c in 61% patients was below the lower limit of the target range recommended by the guidelines (7.0%). These findings indicate that old age (\geq 75) alone is a potent risk factor for hypoglycemia regardless of other physical or mental complications and that high-risk drugs should be used with caution in these patients.

Many anti-diabetic drugs are excreted into urine and renal dysfunction is a risk factor for drug-related hypoglycemia [13]. This risk is often overlooked by general physicians and medical care staff, as seen in this study, where patients were inappropriately treated with SU. In this regard, education of these non-specialists, as well as patients, is important. Importantly, when the current JDS/JGS guidelines are applied to the 12 patients of the present study with eGFR < 30 mL/min/1.73 m², HbA1c level of 6 patients was within the recommended range. This suggests that the lower limit of the target HbA1c level was too strict for patients with eGFR < 30 mL/min/1.73 m². We propose that the lower limit of the target HbA1c level should be 7.5% for all elderly (\geq 65) diabetes patients with eGFR < 30 mL/min/1.73 m². In other words, eGFR < 30 mL/min/1.73 m² should be included as an independent condition for Category III. Further clinical studies are necessary to validate this proposal.

CONCLUSIONS

This study suggested that the current JDS/JGS guidelines are too strict for diabetes patients aged 65 or above and with eGFR below 30 mL/min/1.73 m².

Table 1 Patient backgrounds in the two Categories Ia/Ib

	Category Ia (n = 28)	Category Ib (n = 45)	p value
Age (yr)	68.8 ± 2.8	82.4 ± 5.3	N/A
Sex (F/M)	6/22	27/18	0.0013
HbA1c (%)	6.8 ± 1.1	6.7 ± 0.8	0.5814
eGFR (mL/min/1.73 m ²)	64.4 ± 29.3	51.5 ± 26.7	0.0565
Proportion below HbA1c lower target (%)	Category I HbA1c < 6.5% 42.9% (12 of 28)	Category I HbA1c < 7.0% 66.7% (30 of 45)	0.1244
Therapeutic agents at admission	n = 17 (60.7%)	n = 13 (28.9%)	0.0072
Insulin formulations			
BBT/BOT: Combined formulation	14:3	11:2	0.8691
Insulin: units/kg	0.61 (n = 16)	0.43 (n = 12)	0.860
SU agents	13(46.4%)	33 (73.3%)	0.0209
Glinide agents	1 (3.6%)	5 (11.1%)	0.2541

Data are expressed as mean ± SD or n (%).
N/A; not applicable

Table 2 Elderly patients with eGFR < 30 mL/min/1.73 m² (n = 12)

Age at admission (years)	Sex	HbA1c(NGSP)	eGFR	Drug
66	F	5.8	20.2	Glimepiride Voglibose
68	M	6.7	18.6	Biosynthetic human biphasic isophane insulin: 38-0-38 Pioglitazone hydrochloride: 30 mg/day Metformin hydrochloride: 500 mg/day
70	M	6.3	5.8	Insulin aspart: 6-2-8-0 Human insulin: 0-0-0-6
76	M	7.0	7.2	Biosynthetic human biphasic isophane insulin: 16-0-0-0
76	F	5.5	7.6	Insulin glargine: 8-0-0-0
78	F	6.4	19.0	Insulin aspart: 6-8-8-0 Insulin glargine: 19-0-0-0
78	F	6.4	22.4	Insulin aspart: 4-4-4-0 Insulin glargine: 0-0-0-4
79	F	7.8	29.7	Insulin aspart: 12-10-2-0 Insulin glargine: 0-0-0-6
80	F	7.0	10.5	Glimepiride: 6 mg/day
80	F	7.0	11.7	Mitiglinide calcium hydrate: 30 mg/day Insulin glargine: 10-0-0-0
81	M	7.0	27.2	Glimepiride: 1 mg/day Sitagliptin phosphate monohydrate: 50 mg/day
95	F	6.0	19.5	Glimepiride: 2 mg/day

This limit was selected on the basis of blood glucose control indices in elderly patients with diabetes. More appropriate blood glucose control should be considered to prevent hypoglycemia in these patients. We propose that all elderly patients with eGFR below 30 mL/min/1.73 m² should be classified into Category III, and that the target HbA1c level should be 7.5-8.5%. In addition, education of general practitioners is necessary.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to this article.

ETHICS APPROVAL

The research project was approved by the Institutional Review Board for Clinical Research, Tokai University Hospital (17R-158).

REFERENCES

- 1) Huang ES, Laiteerapong N, Liu JY, John PM, Moffet HH, Karter AJ. Rates of complications and mortality in older patients with diabetes mellitus: the diabetes and aging study. *JAMA Intern Med.* 2014; 174: 251-8.
- 2) Bremer JP, Jauch-Chara K, Hallschmid M, Schmid S, Schultes B. Hypoglycemia unawareness in older compared with middle-aged patients with type 2 diabetes. *Diabetes Care.* 2009; 32: 1513-7.
- 3) Haneda M, Ito H. Japan Diabetes Society (JDS)/Japan Geriatrics Society (JGS) Joint Committee on Improving Care for Elderly Patients with Diabetes. Glycemic targets for elderly patients with diabetes. *Diabetol Int.* 2016; 7: 331-3.
- 4) Kagansky N, Levy S, Rimon E, Cojocaru L, Fridman A, Ozer Z, *et al.* Hypoglycemia as a Predictor of Mortality in Hospitalized Elderly Patients. *Arch Intern Med.* 2003; 163: 1825-1829.
- 5) Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, *et al.* Diabetes in older adults. *Diabetes Care.* 2012; 35: 2650-64.
- 6) American Geriatrics Society Expert Panel on Care of Older Adults with Diabetes Mellitus, Moreno G, Mangione CM, Kimbro L, Vaisberg E. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. *J Am Geriatr Soc.* 2013; 61: 2020-6.
- 7) Dunning T, Sinclair A. The IDF global guideline for managing older people with type 2 diabetes: Implications for nurses. *J Diabetes Nurs.* 2014; 18: 145-50.
- 8) Japan nephrology society. Clinical Practice Guidebook for Diagnosis and Treatment of Chronic Kidney Disease. *Nihon Jinzo Gakkai Shi.* 2012; 54: 1034-191.
- 9) Haneda M, Utsunomiya K, Koya D, Babazono T, Moriya T, Makino H, *et al.* A new Classification of Diabetic Nephropathy 2014: A report from Joint Committee on Diabetic Nephropathy. *J Diabetes Investig.* 2015; 6: 242-6.
- 10) American Diabetes Association. Standards of medical care in diabetes-2006. *Diabetes Care.* 2006; 29 (Suppl 1): S4-42.
- 11) Brown AF, Mangione CM, Saliba D, Sarkisian CA. California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc.* 2003; 51 (5 Suppl Guidelines): S265-80.
- 12) Pogach LM, Brietzke SA, Cowan CL, Conlin P, Walder DJ, Sawin CT. Development of Evidence-Based Clinical Practice Guidelines for Diabetes: The Department of Veterans Affairs/ Department of Defense Guidelines Initiative. *Diabetes Care.* 2004; 27 (Suppl 2): B82-9.
- 13) Araki A, Iimuro S, Sakurai T, Umegaki H, Iijima K, Nakano H, *et al.* Non-high-density lipoprotein cholesterol: An important predictor of stroke and diabetes-related mortality in Japanese elderly diabetic patients. *Geriatr Gerontol Int.* 2012; 12 (Suppl 1): 18-28.