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# Comparison of HbA1c levels and body mass index for prevention of diabetic kidney disease: A retrospective longitudinal study using outpatient clinical data in Japanese patients with type 2 diabetes mellitus

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ABSTRACT

*Aim:* This study examined the association among the onset of diabetic kidney disease (DKD), blood glucose levels ($HbA1_C$), and body mass index (BMI) in Japanese patients with type 2 diabetes mellitus.

*Methods:* Patients eligible for this study included those with type 2 diabetes who visited the outpatient clinic at Kawasaki Medical School Hospital between 2000 and 2018 and were followed up for more than two years. The Cox proportional hazards model was used in four categories of subjects: at the beginning of the follow-up period, "controlled" or "uncontrolled" glycemic control based on HbA1c and "overweight" or "non-overweight" based on BMI.

*Results:* After dividing the participants into four categories according to HbA1c (lower than 7.0% (C) or higher (U)), and BMI (25 $kg/m^2$ or higher (O) or lower (N)), hazard ratios for groups CO, UN, and UO were 1.40 (95% CI 1.03–1.90, P = 0.030), 1.40 (1.04–1.88, P = 0.027), and 1.54 (1.12–2.11, P = 0.008), respectively, compared with the CN reference group, after adjustment was made for age, sex, duration of diabetes, and medication for hypertension or dyslipidemia.

*Conclusion:* Maintenance of both an HbA1c level lower than 7.0% and a BMI lower than 25 $kg/m^2$ was important for the prevention of DKD in Japanese patients with type 2 diabetes mellitus. Both factors had a similar effect on DKD in this study.



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## 1. Introduction

The goal for patients with diabetes is to secure years of healthy life by controlling the disorder and thereby to maintain a quality of life equivalent to that of their healthy counterparts. To achieve this objective, it is important to prevent the onset and progression of various diabetic complications. Diabetic kidney disease (DKD) including diabetic nephropathy, for example, is the leading cause of end-stage renal disease (ESRD), which requires treatment with hemodialysis. The prevention of such complications therefore represents an important issue in clinical practice and public health [1]. In Japan, recommendations call for the setting of the HbA1c target level at <7.0% to ensure prevention of diabetic microvascular complications, a target that is also recognized as reasonable for most nonpregnant adults in the guidelines of American Diabetes Association and European Association for the Study of Diabetes [2]. At the same time, recommendations suggest that glycemic control goals be determined on an individual basis [3].

Obesity itself has also received increased attention for its close association with increased risk of developing kidney disease [4,5]. Obesity is a metabolic disorder whose prevalence has increased dramatically in many developed countries over the last 30 years. In fact, in 2015, data from the Global Burden of Disease Study suggested that 603.7 million adults across the globe were obese [6]. Intensive bodyweight management based on strict dietary therapy is a common treatment method for type 2 diabetes. This therapy often results in remission of the disease being one conceivable outcome [7], leading to the prevention of diabetic microangiopathy. In 2000, the Japan Society for the Study of Obesity (JASSO) defined obesity as body mass index (BMI) $\geq$25.0 kg/m$^2$; in Japan, this value has been established as the cut-off for increased risk of obesity-related complications such as hypertension, dyslipidemia, and hyperglycemia [8]. However, this definition is defined as "overweight" in World Health Organization (WHO) criteria [9].

Accordingly, to prevent DKD, it is almost certainly necessary to keep glycemic control of HbA1c lower than 7.0% and to maintain BMI below 25 kg/m$^2$ for Japanese patients with type 2 diabetes mellitus. While both indexes have broad utility, the clinical question of which index is more important naturally arises with respect to risk of DKD. This study retrospectively examined the association among target levels of HbA1c, BMI, and onset of DKD in Japanese subjects with type 2 diabetes, using outpatient clinic cohort data to clarify this underlying clinical question.

## 2. Materials and methods

### 2.1. *Study population and patient preparation*

Patients eligible for this study included those diagnosed with type 2 diabetes who visited the diabetes outpatient clinic at Kawasaki Medical School Hospital between 2000 and 2018 and could be followed for a continuous period of at least two years. Patients younger than 20 years of age at the beginning of follow-up were excluded in advance. BMI was calculated by dividing weight in kilograms by height in meters squared. To investigate the relationship among HbA1c, BMI, and onset of DKD, and subsequently neuropathy and retinopathy, a dataset was prepared of 2306 subjects without diabetic microangiopathy at the start of follow-up and during the initial three years to prevent bias due to reverse causation (Fig. 1). The hospital's ethics committee approved the study protocol, and information pertaining to the study was provided to the public via the Internet, instead of informed consent being obtained from each individual patient (No. 2847-1), based on the 2013 Helsinki Declaration. Data collection for variables such as type(s) of medication, duration of diabetes, and biochemical data were performed starting with the patient's first visit for the three-month period from August to October of each year. The aim of such data collection was to reduce the effects of seasonal variations in HbA1c level, as has been described previously [10,11].

We divided the subjects by HbA1c value at the beginning of the follow-up into two groups based on the Kumamoto Declaration [3], as follows: a "controlled" group (C), defined as having HbA1c < 7.0%, and an "uncontrolled" group (U), with HbA1c $\geq$ 7.0%. In addition, we divided the subjects by BMI level at the beginning of their follow-up into two groups based on JASSO criteria [8], as follows: a "non-overweight" group (N), with BMI < 25 kg/m$^2$, and an "overweight" group (O), with BMI $\geq$ 25 kg/m$^2$. All participants were divided into these four categories in accordance with the following various combinations of HbA1c and BMI: groups of controlled non-overweight (CN), controlled overweight (CO), uncontrolled non-overweight (UN), and uncontrolled overweight (UO).

The frequency of DKD onset was then compared among the aforementioned four groups. In all participants, DKD was classified from normal to dialysis stage in accordance with their classification of diabetic nephropathy in 2014 [12], based on eGFR of <30 mL/min/1.73 m$^2$ and/or microalbuminuria value of $\geq$30 mg/gCr. Furthermore, the frequency of diabetic microangiopathy onset apart from DKD was compared respectively. Diabetic retinopathy was diagnosed by ophthalmologists [13]. Diabetic neuropathy was assessed by the

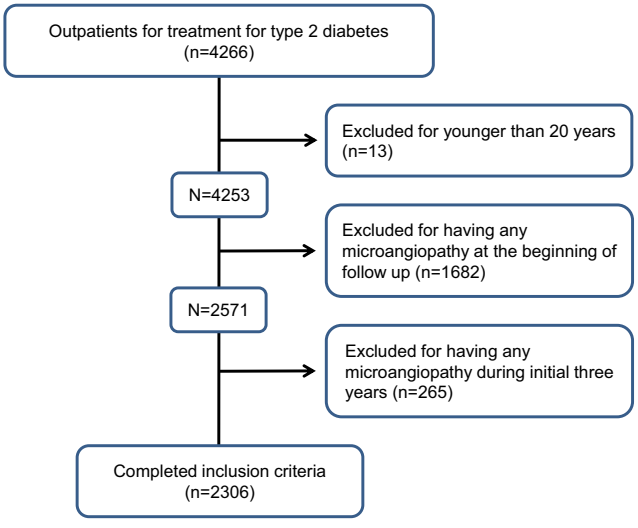


**Fig. 1 – Flow chart of the study participants.**

physician in charge based on the abbreviated criteria published by the Diabetic Neuropathy Study Group in Japan [14]. All complications were diagnosed by the physicians in charge based on the criteria described above.

The study used duration of diabetes and medication(s) for hypertension and/or dyslipidemia at the start of follow-up as possible confounding factors contributing to diabetic microangiopathy onset.

### 2.2. Statistical analysis

The data are expressed as mean and standard deviation. Continuous variables at the start of follow-up were compared using an age- and gender-adjusted analysis of covariance (ANCOVA) for comparisons among the four groups divided by HbA1c and BMI. To confirm the effect of HbA1c and BMI levels on DKD onset, the Cox proportional hazards model was used, following adjustment for age, gender, duration of diabetes, and medication(s) for hypertension and/or dyslipidemia at the start of follow-up as confounders. The development of DKD was designated as a dependent variable (during observation period, 1, development; 0, no development). When using the Cox model to evaluate the hazards ratios of the CO, UN, and UO groups, the CN group was deemed the reference group. In addition, to confirm the effect of HbA1c and BMI levels on DKD onset, the same methods were utilized.

Other hazards ratios were evaluated for development of neuropathy, retinopathy, and microangiopathy, including the three complications in the same way to clarify the impact of glycemic control and overweight on other complications. *P* values of $< 0.05$ were considered to indicate statistical significance. Statistical analyses were performed using JMP software (version 13.2 for Windows, SAS Institute).

## 3. Results

### 3.1. Clinical characteristics of study participants and onset of DKD as HbA1c or BMI continuous data

Mean age at the start of the study and follow-up duration for all participants were 61.0 ± 12.2 years and 5.96 ± 6.89 years, respectively. The numbers for each group classified in accordance with HbA1c and BMI were as follows: 828 for group CN, 549 for CO, 520 for UN, and 409 for UO. Table 1 shows the clinical characteristics at baseline.

The hazard ratios for development of DKD for HbA1c (%) and BMI ($kg/m^2$) after adjustment for age, gender, duration of diabetes, and medication(s) used for hypertension or dyslipidemia at the start of the study were 1.20 (1.10–1.30, $P < 0.0001$) and 1.03 (1.01–1.07, $P = 0.020$). These data indicate the benefit of both strict glycemic control and intensive bodyweight management for the prevention of DKD in all participants in this study.

### 3.2. Onset of DKD in four categories by combined HbA1c and BMI

The Cox proportional hazards model for development of DKD was used in analysis of the four categories after adjustment was carried out for age, gender, duration of diabetes, and medication(s) used for hypertension or dyslipidemia at the start of the study. The hazard ratios of groups CO, UN, and

**Table 1 – Baseline clinical characteristics in each group based on HbA1c and BMI among patients with type 2 diabetes.**

| | Controlled non-overweight (CN) | Controlled overweight (CO) | Uncontrolled non-overweight (UN) | Uncontrolled overweight (UO) |
|---|---|---|---|---|
| M/F (n) | 504/324 | 339/210 | 310/210 | 234/175 |
| Development of microangiopathyduring follow-up period (Neuro/ Retino/Nephro) | 174 (84/34/102) | 105 (49/12/74) | 142 (95/58/80) | 102 (61/35/67) |
| Age (years) | 64.2 ± 10.4 | 57.4 ± 12.9* | 63.4 ± 10.8 | 56.4 ± 13.8* |
| Duration of type 2 diabetes (years) | 5.6 ± 6.7 | 4.8 ± 5.8 | 7.8 ± 8.2* | 5.8 ± 6.9 |
| BMI ($kg/m^2$) | 22.0 ± 2.1 | 28.6 ± 3.5* | 21.7 ± 2.3 | 28.7 ± 3.4* |
| Mean HbA1c (%) | 6.2 ± 0.4 | 6.2 ± 0.4 | 7.7 ± 1.1* | 7.9 ± 1.2* |
| SBP (mmHg) | 125 ± 16 | 127 ± 15 | 124 ± 15 | 129 ± 16* |
| DBP (mmHg) | 71 ± 11 | 75 ± 11* | 70 ± 10 | 75 ± 11* |
| TCH (mg/dl) | 193 ± 71 | 194 ± 64 | 195 ± 40 | 202 ± 38* |
| HDLC (mg/dl) | 56 ± 17 | 50 ± 13* | 55 ± 15 | 48 ± 12* |
| TG (mg/dl) | 129 ± 97 | 172 ± 110* | 152 ± 148* | 204 ± 241* |
| Treatment for diabetes (n) | | | | |
| Insulin/SU/Glinides/TZD | 57/88/80/67 | 28/48/55/74 | 125/121/65/51 | 78/67/35/58 |
| BG/α-GI/DPP-4I | 69/93/81 | 133/56/61 | 74/69/49 | 124/45/45 |
| SGLT2I/GLP-1RA | 4/1 | 2/4 | 3/0 | 4/6 |
| Treatment for dyslipidemia (n) | 259 | 233 | 150 | 161 |
| Treatment for hypertension (n) | 193 | 168 | 95 | 108 |

Data are shown as mean ± SD. *: $P < 0.05$ compared to category of CN after adjustment for age and sex. Neuro: neuropathy; Retino: retinopathy; Nephro: nephropathy; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TCH: total cholesterol; HDLC: high density lipoprotein cholesterol; TG: triglycerides; SU: sulfonylureas; TZD: thiazolidinedione; BG: biguanide; α-GI: alpha-glucosidase inhibitors; DPP-4I: dipeptidyl peptidase-4 inhibitors; SGLT2I: sodium-glucose co-transporter 2 inhibitors; GLP-1RA: glucagon-like peptide 1 receptor agonist.

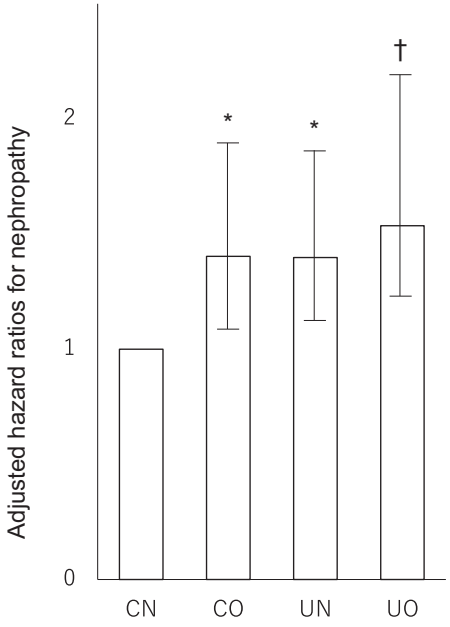


**Fig. 2 – Adjusted hazard ratios for DKD. The subjects were divided into four groups by HbA1c and BMI. Group CN: HbA1c < 7.0% and BMI < 25 kg/m$^2$; group CO: HbA1c < 7.0% and BMI ≥ 25 kg/m$^2$; group UN: HbA1c ≥ 7.0% and BMI < 25 kg/m$^2$; and group UO: HbA1c ≥ 7.0% and BMI ≥ 25 kg/m$^2$. *P < 0.05 compared with group CN. †P < 0.01 compared with group CN.**

UO, compared with group CN as a standard, were 1.40 (95% CI 1.03–1.90, $P = 0.03$), 1.40 (1.04–1.89, $P = 0.028$), and 1.54 (1.12–2.11, $P = 0.008$), respectively ($P = 0.005$ for trend) (Fig. 2). For the prevention of DKD, therefore, there may be similar importance in maintaining HbA1c < 7.0% and BMI < 25 kg/m$^2$, in consideration of the hazard ratios of groups CO and UN (see Fig. 3.).

### 3.3. *Onset of neuropathy, retinopathy, and total microangiopathy in the four categories by combined HbA1c and BMI*

Adjusted hazard ratios for development of neuropathy, retinopathy, and total microangiopathy for HbA1c (%) and BMI (kg/m$^2$) were 1.28 (1.18–1.38, P < 0.0001) and 1.01 (0.98–1.04, P = 0.69), 1.43 (1.30–1.58, P < 0.0001) and 0.98 (0.93–1.03, P = 0.30), and 1.19 (1.11–1.27, P < 0.0001) and 1.02 (0.99–1.04, P = 0.18), respectively. These data suggest the benefit of strict glycemic control for the prevention of diabetic neuropathy, retinopathy, and total microangiopathy in all study participants. However, intensive bodyweight management appears to not be beneficial for the prevention of the two microangiopathies of neuropathy and retinopathy.

The Cox proportional hazards model for development of neuropathy was used in analysis of the four categories after adjustment was carried out for age, gender, duration of diabetes, and medication(s) used for hypertension or dyslipidemia at the start of the study. The hazard ratios of groups CO, UN, and UO, compared with group CN as a standard, were 1.18 (0.82–1.68, $P = 0.37$), 1.83 (1.36–2.47, $P < 0.0001$), and 1.62 (1.16–2.28, $P = 0.005$), respectively (Fig. 2a). The Cox proportional hazards model for development of retinopathy was used in analysis of the four categories after adjustment was carried out for age, gender, duration of diabetes, and medication(s) used for hypertension or dyslipidemia at the start of the study. The hazard ratios of groups CO, UN, and UO, com-

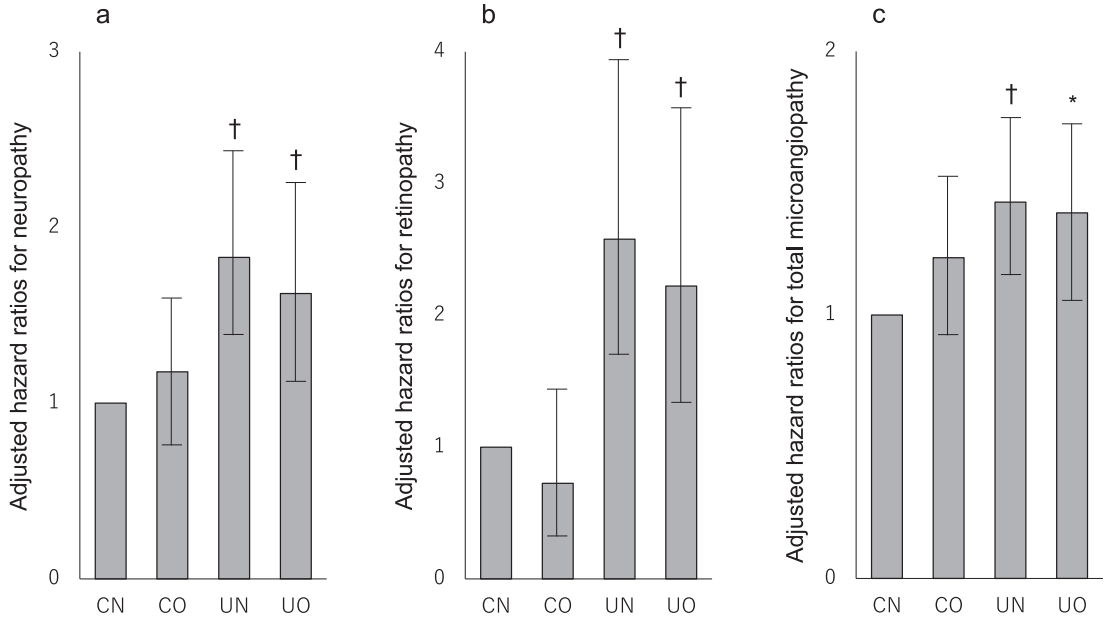


**Fig. 3 – Adjusted hazard ratios for neuropathy (a), retinopathy (b), and total microangiopathy (c). The subjects were divided into four groups by HbA1c and BMI. Group CN: HbA1c < 7.0% and BMI < 25 kg/m$^2$; group CO: HbA1c < 7.0% and BMI ≥ 25 kg/m$^2$; group UN: HbA1c ≥ 7.0% and BMI < 25 kg/m$^2$; and group UO: HbA1c ≥ 7.0% and BMI ≥ 25 kg/m$^2$. *P < 0.05 compared with group CN. †P < 0.01 compared with group CN.**

pared with group CN as a standard, were 0.73 (0.37–1.41, $P = 0.34$), 2.58 (1.67–3.99, $P < 0.0001$), and 2.22 (1.36–3.62, $P = 0.001$), respectively (Fig. 2b). The Cox proportional hazards model for development of total microangiopathy was used in analysis of the four categories after adjustment was carried out for age, gender, duration of diabetes, and medication(s) used for hypertension or dyslipidemia at the start of the study. The hazard ratios of groups CO, UN, and UO, compared with group CN as a standard, were 1.22 (0.95–1.56, $P = 0.12$), 1.43 (1.14–1.79, $P = 0.002$), and 1.39 (1.08–1.78, $P = 0.011$), respectively (Fig. 2c). Therefore, for the prevention of diabetic microangiopathy, excluding nephropathy, there may be more importance in maintaining HbA1c < 7.0% than intensively managing BMI < 25 kg/m$^2$.

## 4. Discussion

This retrospective study clarified the significance of keeping HbA1c lower than 7.0% and BMI lower than 25 kg/m$^2$ for preventing DKD in patients with type 2 diabetes mellitus. Each of the factors appeared to contribute in an equivalent manner to the prevention of DKD. At the same time, however, the study verified the greater importance of maintaining HbA1c lower than 7.0% compared with managing BMI at a level lower than 25 kg/m$^2$ for the prevention of microangiopathy including neuropathy and retinopathy. These results suggest the importance of the combination of bodyweight control and glycemic control especially in the prevention of DKD in Japanese patients with type 2 diabetes mellitus.

Glycemic control is a fundamental tool in effective diabetes management. To prevent diabetic microangiopathy, it is recommended that a patient have HbA1c of lower than 7.0% as a reasonable goal for nonpregnant adults [2,3]. Certainly, in this study, level of HbA1c was shown to be an important determinant factor in the development of all microangiopathies. Contrary to HbA1c, BMI was only a determinant factor for nephropathy in this study. The discrepancy may suggest that neuropathy and retinopathy were determined primarily by glycemic control, and nephropathy was somewhat systematically affected by factors including overweight in addition to glycemic control. Overweight and obesity are evidently associated with glomerular hyperfiltration, either per nephron or per total kidney [15]. In a community-based study in Japan, overweight was a significant predictor of developing proteinuria [16]. Moreover, in a Japanese cohort, increased BMI was associated with an increased risk for the development of end-stage renal disease, especially in men, even after adjustment for blood pressure and proteinuria [17]. In addition, Todd et al. provided genetic evidence for a causal link between obesity and diabetic kidney disease in patients with type 1 diabetes using the Mendelian randomization method [18]. Our study suggests that overweight was a significant risk factor, along with poor glycemic control, for development of DKD in Japanese patients with type 2 diabetes mellitus.

In this study, although the UO group had the highest hazard ratio among the four groups, it was not an additive increase to the hazard ratios of groups CO and UN. The UN group participants had a significantly longer duration of type 2 diabetes than the CN group participants, as described in Fig. 1. Accordingly, the UN group participants may have had a higher incidence of DKD compared with the other three groups, leading to unexpectedly high hazard ratios in that group, despite the fact that duration of diabetes was statistically adjusted. In addition, obese participants in groups CO and UO were significantly younger in age than the CN group participants, and had symptoms associated with metabolic syndrome when compared to non-obese subjects. Patient age may have affected the choice of medication for type 2 diabetes, dyslipidemia, and hypertension. Indeed, medication for these participants differed slightly, such as the use of biguanides, glucagon-like peptide 1 receptor agonist (GLP-1RA), insulin, and treatment for dyslipidemia and hypertension, among the four groups. These differences in medication may have affected onset of DKD. Further study is warranted for assessment of glycemic control and overweight in terms of development of DKD.

The present study has several limitations. First, it was a retrospective observational study with a limited participant population and a limited observation period. Second, diabetes medication was not taken into consideration. Diabetes medication was instead chosen by the physician in charge based on a patient-centered approach considering the best available evidence in terms of benefit, harm, patient values, preferences, and context in time, not only target HbA1c level. It was therefore difficult to evaluate the influence of medication. Indeed, in our study, based on Fisher's exact test, the use of insulin, SU, biguanides, and GLP-1RA tended to be greater in categories UN and UO; the use of biguanides or dipeptidyl peptidase-4 inhibitors (DPP-4Is) were found to be related to high risks for development of DKD; and no patients taking sodium-glucose co-transporter 2 inhibitors (SGLT2Is) developed DKD during the course of the observation period. However, none of the medications affected our results directly (data not shown). Third, the habits and comorbidity factors such as smoking, diet, cognitive function, frailty, and daily activities also were not evaluated. Fourth, the results of this study may not be applicable to different ethnicities. The definitions of overweight and obesity differ in JASSO [8] and WHO [9], because the proportion of Asian people with a higher risk of type 2 diabetes and cardiovascular disease was substantially large, even though their BMIs were lower than the existing WHO cut-off point for the overweight classification of 25 kg/m$^2$ or higher. Lastly, in this study, we used the initial data regarding HbA1c and BMI. On the other hand, using the average HbA1c and BMI during observation period, the hazard ratios of groups CO, UN, and UO, compared with group CN as a standard, were 1.43 (95% CI 1.06–1.94, $P = 0.02$), 1.49 (1.09–2.04, $P = 0.01$), and 1.91 (1.39–2.62, $P < 0.0001$), respectively ($P < 0.0001$ for trend). Needless to say, these results indicated the importance of maintaining appropriate glycemic and bodyweight controls as well as the initial data.

## 5. Conclusions

In conclusion, to prevent diabetic microangiopathy, any glycemic control target should be set at a level lower than 7.0% for

HbA1c. Moreover, the bodyweight target of lower than 25 kg/$m^2$ of BMI should be considered in combination to prevent DKD among Japanese patients with type 2 diabetes mellitus. Lastly, each of poor glycemic control and overweight may put Japanese patients with type 2 diabetes mellitus at equivalent risk for development of DKD.

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## Authors' contributions

The study was designed by SN and HK; SN, HH, MS, FT, KK, AO, SO, YK, JS, YF, MN, YK, AT, HI, HI, and KT analyzed and interpreted the data; SN, TM, HK and KK were responsible for drafting the manuscript; The manuscript was reviewed by HK. All authors have collected data, read and approved the final manuscript for publication.

## Declaration of Competing Interest

Hideaki Kaneto has received honoraria for lectures and received scholarship grants from Sanofi, Novo Nordisk, Eli Lilly, Boehringer Ingelheim, Taisho Toyama Pharma, MSD, Takeda, Ono Pharma, Daiichi Sankyo, Sumitomo Dainippon Pharma, Mitsubishi Tanabe Pharma, Kissei Pharma, Astellas, Novartis, Kowa, Chugai, Japan Foundation for Applied Enzymology, and A2 Healthcare. Kohei Kaku has been an advisor to, received honoraria for lectures from, and received scholarship grants from Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Takeda, Taisho Pharmaceutical Co., MSD, Taisho Toyama Pharma., Astellas, Kissei Pharma., Mitsubishi Tanabe Pharma. Co., Ono Pharma. Co., Sumitomo Dainippon Pharma, Novartis, Mitsubishi Tanabe Pharma, AstraZeneca, Nippon Boehringer Ingelheim Co., Fujifilm Pharma Co., and Sanofi. Masashi Shimoda and Shuhei Nakanishi have received honoraria for lectures from AstraZeneca and Sanofi, respectively.

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