

Article

Impact of a History of Obesity on Diabetic Microvascular Complications in Patients with Type 2 Diabetes

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Abstract

Background/Objectives: The prevalence of obesity is increasing among Japanese patients with type 2 diabetes (T2D); however, the impact of obesity history and severity on microvascular complications remains poorly understood. This study aimed to investigate the association of lifetime maximum body mass index (BMI) and BMI at the first clinical visit with the development and progression of diabetic nephropathy and retinopathy. **Methods:** This retrospective cohort study included T2D patients who first visited the clinic of the Institute for Medical Sciences, Asahi Life Foundation between 2005 and 2022. Patients were categorized into five groups based on both lifetime maximum and first-visit BMI: underweight, normal weight, class I obesity, class II obesity, and severe obesity. The primary endpoints were renal events (sustained increase in proteinuria or $\geq 40\%$ decline in eGFR) and retinal events (worsening of diabetic retinopathy by ≥ 1 stage). **Results:** A history of severe obesity, based on the lifetime maximum BMI, was an independent risk factor for proteinuria progression. While a history of severe obesity was associated with all endpoints in unadjusted analyses, these associations with eGFR decline and retinopathy were not significant after adjusting for covariates. In contrast, the BMI at the first visit was significantly associated with retinal events but not with renal events. **Conclusions:** A history of maximum lifetime obesity is a critical predictor of the proteinuria progression. A history of obesity, a simple clinical metric, is a valuable tool for identifying high-risk patients and may contribute to more effective preventative strategies.

Keywords: lifetime maximum BMI; obesity; diabetic nephropathy; diabetic retinopathy



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1. Introduction

Diabetic kidney disease (DKD) is a primary microvascular complication affecting 30–40% of individuals with type 2 diabetes (T2D) and is the leading cause of end-stage renal disease (ESRD) worldwide [1]. While the classical pathway involves progression from albuminuria to a decline in the glomerular filtration rate (GFR), a non-albuminuria phenotype, characterized by GFR loss without preceding overt proteinuria, is increasingly recognized, particularly in the Japanese populations [2–4]. Diabetic retinopathy (DR) is the leading cause of blindness in the working-age population, with a global prevalence of 22.27% among individuals with diabetes [5,6]. As symptoms often manifest only in advanced stages, early risk assessment is crucial for preserving vision and quality of life [7].

Obesity with T2D has been continuously increasing in Japan [8,9] and worldwide [10]. Obesity is a key pathophysiological driver of diabetes and a modifiable risk factor for both DKD and DR [11–14]. The recent understanding of this relationship refers to it as cardiovascular–kidney–metabolic syndrome, which describes the complex, multisystem interactions among dysfunctional adiposity, metabolic risk factors, CKD, and cardiovascular disease. Under this progressive disease framework, excess adiposity triggers systemic low-grade chronic inflammation, oxidative stress, and severe insulin resistance [15], which can propagate vascular endothelial damage and accelerate both glomerular and retinal injury. Increasing BMI trajectory after the diagnosis of T2D is strongly associated with an increased risk of microvascular complications [16]. However, most studies evaluating this link rely on body mass index (BMI) measured at a single time point, such as at the diagnosis or study enrollment. There is a risk of overlooking the patient's condition, particularly when assessing patients at their initial diabetes presentation. This is because patients with type 2 diabetes (T2D) frequently experience significant weight loss prior to the clinical diagnosis due to hyperglycemic catabolism (glucosuria) and metabolic dysregulation [17–19]. Consequently, when used alone, a present BMI assessment may underestimate the historical exposure to adiposity and the hypothesized cumulative “metabolic memory” associated with past obesity. As an example of this proposed legacy effect, high adiposity over adulthood is associated with evidence of adverse cardiac structure and function. Some of these associations are independent of adiposity in later life [20].

This limitation underscores the need to investigate longitudinal weight trajectories, and a typical example of a representative value is the maximum weight in one's lifetime. A previous Japanese cohort study suggested that a lifetime maximum BMI of ≥ 25 kg/m² is a significant risk factor for microvascular complications [21]. However, that study dichotomized past obesity at a single cutoff of 25 kg/m², leaving the incremental impact of obesity severity unexamined. While a simple binary cutoff of 25 kg/m² is clinically convenient, it groups patients with mild obesity together with those with severe obesity. According to the Japan Society for the Study of Obesity (JASSO) guidelines [22], obesity is structured into distinct classes because advanced obesity severity (Classes II and III) is incrementally associated with an exponentially heightened burden of metabolic and renal disease [23]. Therefore, evaluating past obesity using a detailed stratified approach is necessary to determine the clinical rationale for severity-dependent risk. Therefore, this study aimed to determine the association between lifetime maximum BMI and BMI at the first clinical visit, stratified in detail by severity, with the long-term risk of developing diabetic nephropathy and retinopathy.

2. Materials and Methods

2.1. Study Design and Population

This retrospective cohort study utilized the electronic medical records of patients with diabetes who first presented to the Institute for Medical Science, Asahi Life Foundation, between January 2005 and December 2022. The study protocol was approved by the Ethics Committee of Meiji Pharmaceutical University, Tokyo, Japan (approval number: 202441) and complied with the principles of the Helsinki Declaration. We included patients diagnosed with T2D. Patients were excluded if they had other types of diabetes, had missing data for height or maximum lifetime weight, or if their baseline laboratory or ophthalmologic examinations were not performed within a specified timeframe (90 days for blood/urine tests and 365 days for fundus examination). Further exclusion criteria included fewer than three proteinuria measurements or two fundus examinations during follow-up, severe urinary protein (4+) or proliferative diabetic retinopathy (PDR) at baseline,

and a documented history of non-diabetic renal or ocular diseases that could confound the outcomes (Table A1).

2.2. BMI Classification

Lifetime maximum weight was defined as the highest value among the self-reported weight at age 20 years, self-reported lifetime maximum weight, and measured weight at the first clinical visit. Lifetime maximum BMI and first-visit BMI were calculated and categorized according to the Japan Society for the Study of Obesity criteria [22]:

Group I (Underweight): BMI < 18.5, Group II (Normal weight): BMI 18.5 to <25, Group III (Class I obesity): BMI 25 to <30, Group IV (Class II obesity): BMI 30 to <35, Group V (Severe obesity): BMI $\geq$ 35.

For the sub-analysis of pre-visit weight changes, within each first-visit BMI group, the historical BMI trajectory from the lifetime maximum to the first clinical visit was classified into two categories: “decrease,” defined as a reduction in one or more BMI categories, and “no change,” defined as remaining in the same BMI category.

2.3. Outcomes and Covariates

The three primary endpoints were as follows: a proteinuria event was defined as an increase of at least one grade in dipstick urinalysis (e.g., negative to trace, or 1+ to 2+), confirmed on two consecutive visits; an eGFR event was defined as a sustained decline of at least 40% in the estimated GFR (eGFR) from the baseline measurement; a retinopathy event was defined as progression of at least one stage in the modified Davis classification.

Baseline covariates included age, sex, duration of diabetes, HbA1c level, smoking and alcohol history, family history of diabetes, and use of antidiabetic and antihypertensive medications. The duration of diabetes was calculated using the date of diabetes based on the first documented diagnostic glucose value or physician’s note in the medical record. HbA1c values, if initially measured using the Japan Diabetes Society (JDS) scale, were converted to the National Glycohemoglobin Standardization Program (NGSP) equivalent values using the following established formula [24]:

$$\text{HbA1c (NGSP)} = 1.02 \times \text{HbA1c (JDS)} + 0.25$$

eGFR was calculated using the formula recommended for Japanese populations [25]:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Scr}^{-1.094} \times \text{Age}^{-0.287} (\times 0.739 \text{ if female})$$

2.4. Statistical Analysis

Baseline characteristics were compared across the BMI groups using ANOVA or the chi-squared test, as appropriate. Event-free survival was analyzed using the Kaplan–Meier method with the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using univariate and multivariate Cox proportional hazards models. The multivariable model (Model 2) was adjusted for age, sex, duration of diabetes, baseline HbA1c level, baseline proteinuria, baseline eGFR, baseline retinopathy stage, family history of diabetes, and use of antidiabetic and antihypertensive medications. All analyses were performed using JMP® Student Edition Ver. 19 (SAS Institute Inc., Cary, NC, USA). Two-sided *p*-values < 0.05 were considered to indicate statistical significance.

3. Results

3.1. Patient Characteristics

From an initial cohort of 4207 patients, 1041 (832 men; mean age 54.9 ± 10.5 years) were included in the final analysis (Figure 1). Based on the lifetime maximum BMI, the cohort was distributed as follows: Group I (underweight, $N = 1$), Group II (normal, 15.7%), Group III (class I obesity, 47.4%), Group IV (class II obesity, 25.9%), and Group V (severe obesity, 11.0%).

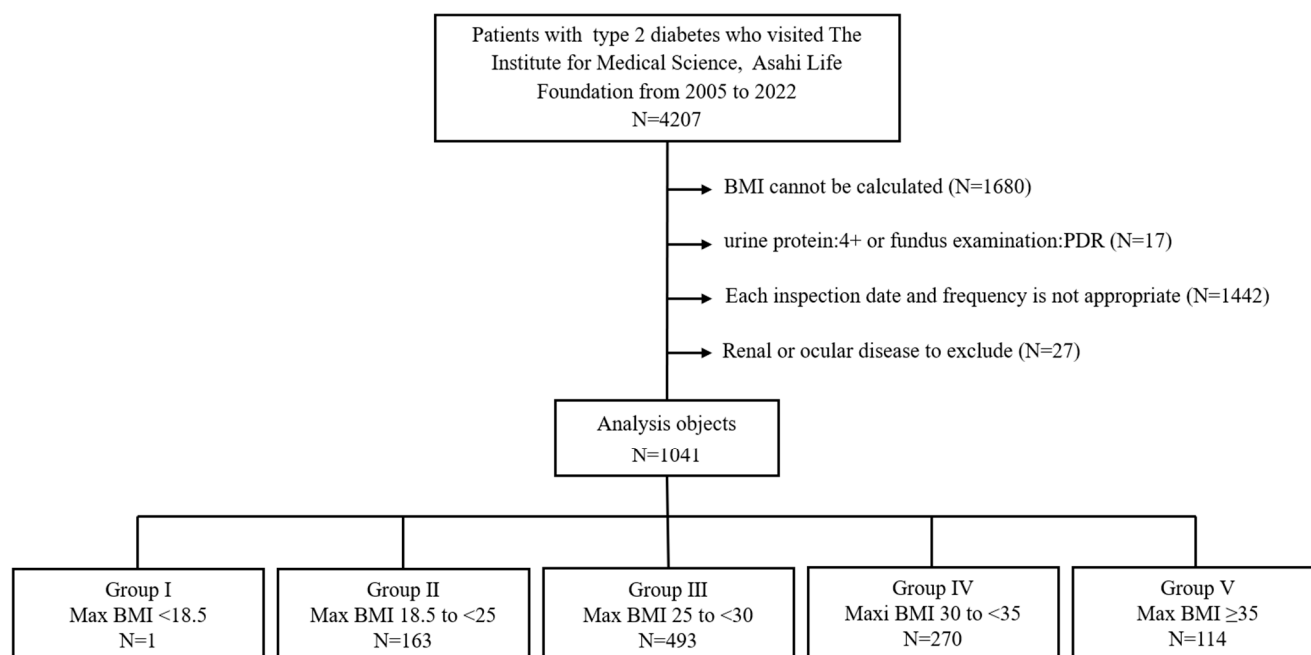


Figure 1. Flow diagram of the study participants.

The study analyzed 1041 participants divided into five groups based on their maximum BMI according to the Japanese criteria for obesity.

The baseline characteristics are presented in Table 1. Patients with a higher lifetime maximum BMI tended to be younger at their first visit, have higher HbA1c levels, greater weight gain since the age of 20 years, and a higher prevalence of a first-degree family history of diabetes. They were also more likely to be prescribed antidiabetic (e.g., biguanides and GLP-1 agonists) and antihypertensive (e.g., RAS inhibitors) medications.

3.2. Incidence of Microvascular Events

The overall incidence rates of proteinuria, eGFR decline, and retinopathy events were 55.2, 20.9, and 40.7 per 1000 person-years, respectively. The incidence of all three events increased in a dose-dependent manner with higher lifetime maximum BMI category.

3.3. Association of BMI with Clinical Endpoints

Owing to the limited sample size, Group I (lifetime maximum BMI $< 18.5 \text{ kg/m}^2$, $N = 1$) was excluded from both the Kaplan–Meier and proportional hazards regression analyses. In addition, individuals with a BMI at the first visit of $< 18.5 \text{ kg/m}^2$ ($N = 16$) were omitted from the Kaplan–Meier curve analysis. The Kaplan–Meier analysis demonstrated that a higher lifetime maximum BMI was associated with a significantly increased risk of all three endpoints (Figure 2A–C).

Table 1. Baseline characteristics.

	Total N = 1041	Group II N = 163 (15.7)	Group III N = 493 (47.4)	Group IV N = 270 (25.9)	Group V N = 114 (11.0)	p-Value
Male/female, N (%)	832 (79.9)/209 (20.1)	121 (74.2)/42 (25.8)	404 (81.9)/89 (18.1)	221 (81.9)/49 (18.1)	86 (75.4)/28 (24.6)	0.085
Age at first visit (years)	54.9 ± 10.5	58.1 ± 10.5	56.8 ± 9.9	52.2 ± 10.3	48.4 ± 9.2	<0.0001
Diabetes duration (years)	2.4 <0.1–7.5>	1.9 <0.1–8.9>	2.4 <0.2–7.5>	2.1 <0.1–6.5>	3.8 <0.3–8.1>	0.288
HbA1c (NGSP) (%)	8.9 ± 2.1	8.4 ± 1.9	8.7 ± 2.1	9.1 ± 2.2	9.6 ± 2.2	<0.0001
BMI at first visit (kg/m ²)	26.3 ± 4.3	21.5 ± 1.9	24.8 ± 2.2	28.4 ± 2.6	34.0 ± 4.0	<0.0001
Number of patients by BMI category at first visit (N, Underweight/Normal/Class I/Class II/Severe)	16/422/417/146/40	13/148/2/0/0	2/239/252/0/0	0/33/154/83/0	0/2/9/63/40	<0.0001
eGFR at first visit (mL/min/1.73 m ²)	85.1 ± 20.2	84.5 ± 17.4	82.9 ± 19.9	87.7 ± 20.8	89.7 ± 22.2	0.001
Maximum weight-weight at first (kg)	8.2 ± 7.0	4.7 ± 4.1	7.2 ± 5.4	10.4 ± 7.5	12.7 ± 10.4	<0.0001
Maximum weight-weight at age 20 (kg)	18 ± 10.7	9.3 ± 5.1	15.6 ± 6.6	22.8 ± 10.1	29.8 ± 15.6	<0.0001
N = 991						<0.0001
Urine protein, N (%)						<0.0001
–	799 (76.8)	141 (86.5)	402 (81.5)	188 (69.6)	67 (58.8)	
±	86 (8.3)	14 (8.6)	38 (7.7)	22 (8.1)	12 (10.5)	
1+	100 (9.6)	6 (3.7)	35 (7.1)	36 (13.3)	23 (20.2)	
2+	31 (3.0)	1 (0.6)	11 (2.2)	14 (5.2)	5 (4.4)	
3+	25 (2.4)	1 (0.6)	7 (1.4)	10 (3.7)	7 (6.1)	
Diabetic retinopathy, N (%)						0.003
NDR	858 (82.4)	141 (86.5)	412 (83.6)	227 (84.1)	78 (68.4)	
SDR	128 (12.3)	15 (9.2)	60 (12.2)	27 (10)	25 (21.9)	
PPDR	55 (5.3)	7 (4.3)	21 (4.3)	16 (5.9)	11 (9.6)	
Smoking history, N (%)						0.035
No smoking	390 (37.5)	61 (37.4)	164 (33.3)	110 (40.7)	54 (47.4)	
Past smoking	322 (30.9)	52 (31.9)	173 (35.1)	70 (25.9)	27 (23.7)	
Currently smoking	329 (31.6)	50 (30.7)	156 (31.6)	90 (33.3)	33 (28.9)	
Drinking history, N (%)						0.009
No drinking	186 (17.9)	37 (22.7)	76 (15.4)	44 (16.3)	28 (24.6)	
Past drinking	62 (6.0)	8 (4.9)	21 (4.3)	23 (8.5)	10 (8.8)	
Currently drinking	793 (76.2)	118 (72.4)	396 (80.3)	203 (75.2)	76 (66.7)	
Family history of type 2 diabetes, N (%)						
1st degree diabetics	291 (28.0)/750 (72.0)	32 (19.6)/131 (80.4)	137 (27.8)/356 (72.2)	81 (30)/189 (70)	41 (36)/73 (64)	0.020
2nd degree diabetics	125 (12.0)/916 (88.0)	26 (16)/137 (84)	57 (11.6)/436 (88.4)	30 (11.1)/240 (88.9)	12 (10.5)/102 (89.5)	0.402
3rd degree diabetics	50 (4.8)/991 (95.2)	12 (7.4)/151 (92.6)	18 (3.7)/475 (96.3)	11 (4.1)/259 (95.9)	9 (7.9)/105 (92.1)	0.091

Table 1. Cont.

	Total N = 1041	Group II N = 163 (15.7)	Group III N = 493 (47.4)	Group IV N = 270 (25.9)	Group V N = 114 (11.0)	p-Value
Baseline use of medications, N (%)						
SU, N (%)	151 (14.5)/890 (85.5)	24 (14.7)/139 (85.3)	75 (15.2)/418 (84.8)	35 (13)/235 (87)	17 (14.9)/97 (85.1)	0.864
BG, N (%)	432 (41.5)/609 (58.5)	52 (31.9)/111 (68.1)	178 (36.1)/315 (63.9)	128 (47.4)/142 (52.6)	74 (64.9)/40 (35.1)	<0.0001
DPP-4 inhibitor, N (%)	300 (28.8)/741 (71.2)	41 (25.2)/122 (74.8)	146 (29.6)/347 (70.4)	74 (27.4)/196 (72.6)	38 (33.3)/76 (66.7)	0.455
GLP-1, N (%)	35 (3.4)/1006 (96.6)	2 (1.2)/161 (98.8)	13 (2.6)/480 (97.4)	8 (3)/262 (97)	12 (10.5)/102 (89.5)	<0.0001
SGLT2 inhibitor, N (%)	58 (5.6)/983 (94.4)	2 (1.2)/161 (98.8)	18 (3.7)/475 (96.3)	22 (8.1)/248 (91.9)	16 (14)/98 (86)	<0.0001
Insulin, N (%)	229 (22.0)/812 (78.0)	41 (25.2)/122 (74.8)	102 (20.7)/391 (79.3)	60 (22.2)/210 (77.8)	25 (21.9)/89 (78.1)	0.695
Any of above antidiabetic drugs, N (%)	713 (68.5)/328 (31.5)	101 (62)/62 (38)	325 (65.9)/168 (34.1)	194 (71.9)/76 (28.1)	92 (80.7)/22 (19.3)	0.003
Calcium channel blocker, N (%)	177 (17.0)/864 (83.0)	15 (9.2)/148 (90.8)	80 (16.2)/413 (83.8)	46 (17)/224 (83)	35 (30.7)/79 (69.3)	<0.0001
RAS system blockers, N (%)	286 (27.5)/755 (72.5)	24 (14.7)/139 (85.3)	133 (27)/360 (73)	79 (29.3)/191 (70.7)	49 (43)/65 (57)	<0.0001
Diuretic, N (%)	30 (2.9)/1011 (97.1)	2 (1.2)/161 (98.8)	18 (3.7)/475 (96.3)	3 (1.1)/267 (98.9)	7 (6.1)/107 (93.9)	0.019
Beta-blocker, N (%)	31 (3.0)/1010 (97.0)	3 (1.8)/160 (98.2)	13 (2.6)/480 (97.4)	8 (3)/262 (97)	7 (6.1)/107 (93.9)	0.181
Alpha-blocker, N (%)	7 (0.7)/1034 (99.3)	0 (0)/163 (100)	1 (0.2)/492 (99.8)	4 (1.5)/266 (98.5)	2 (1.8)/112 (98.2)	0.061
Any of above antihypertensive drugs, N (%)	333 (32.0)/708 (68.0)	32 (19.6)/131 (80.4)	150 (30.4)/343 (69.6)	95 (35.2)/175 (64.8)	55 (48.2)/59 (51.8)	<0.0001

Group I (N = 1) was omitted from the table. Categorical variables were expressed as numbers (%). Continuous variables are expressed as the mean $\pm$ standard deviation for normal distributions and as the median <interquartile range> for non-normal distributions. BMI at the first visit was classified into five groups, similar to the groups for the maximum BMI: group I (<18.5), group II (18.5 to <25), group III (25 to <30), group IV (30 to <35), group V ($\geq$ 35). Baseline tests were performed using an analysis of variance for continuous variables and the chi-squared test for categorical variables for groups II through V, excluding group I. Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; NDR, no diabetic retinopathy; SDR, simple diabetic retinopathy; PPDR, pre-proliferative diabetic retinopathy; SU, sulfonylurea; BG, biguanide; RAS, Renin-Angiotensin System. Group I, maximum BMI < 18.5; Group II, maximum BMI 18.5 to <25; Group III, maximum BMI 25 to <30; Group IV, maximum BMI 30 to <35; Group V, maximum BMI $\geq$ 35.

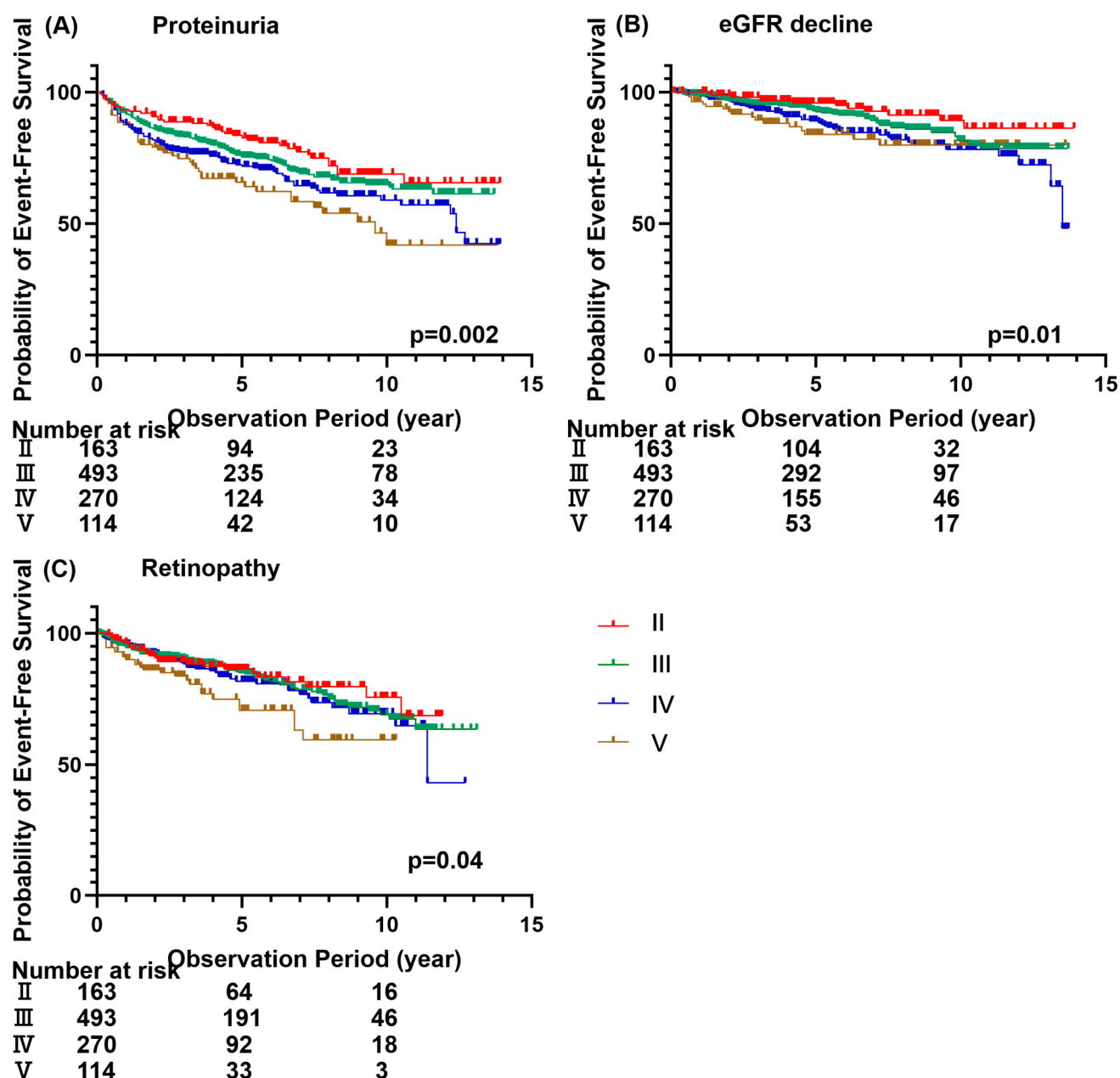


Figure 2. Kaplan–Meier plots illustrating event-free survival based on maximum historical BMI and BMI at first visit. The x-axis represents the time from the first visit to the occurrence of each event or the last examination, whichever occurred first. The y-axis represents the event-free survival rate. (A) Event-free survival rate for elevated urinary protein, (B) event-free survival rate for $\geq 40\%$ decline in eGFR, and (C) event-free survival rate for worsening retinopathy according to the modified Davis classification. Group II, maximum BMI 18.5 to <25 ; Group III, maximum BMI 25 to <30 ; Group IV, maximum BMI 30 to <35 ; Group V, maximum BMI ≥ 35 .

Notably, the severe obesity group (Group V) had a significantly worse prognosis for retinopathy progression than all other groups (log-rank $p = 0.04$). When analyzed by BMI at the first visit, a higher BMI was associated with an increased risk of proteinuria and retinopathy events but not with the eGFR lowering events (Figure 3A–C).

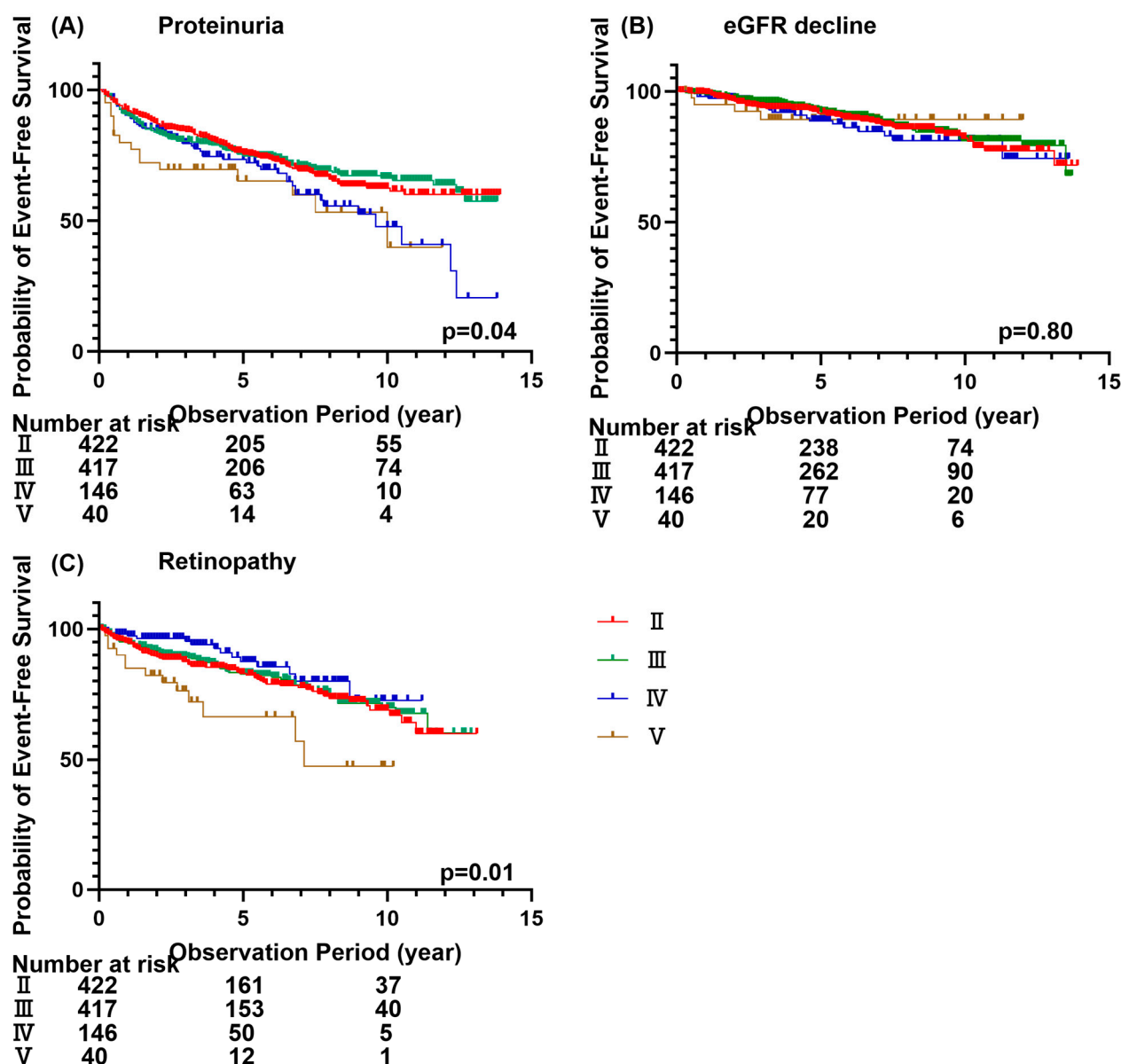


Figure 3. Kaplan–Meier plots illustrating event-free survival based on BMI at first visit. The x-axis represents the time from the first visit to the occurrence of each event or the last examination, whichever occurred first. The y-axis represents the event-free survival rate. Panels display event-free survival for (A) Event-free survival rate for elevated urinary protein, (B) $\geq 40\%$ decline in eGFR from the first examination, and (C) worsening of one or more levels according to the modified Davis classification. The severely obese group based on BMI at the first visit had a higher risk of retinal events than the normal weight group (log-rank $p = 0.01$). No significant risk differences were observed for eGFR lowering events across the BMI classifications at the first visit. Group II, BMI 18.5 to <25 ; Group III, BMI 25 to <30 ; Group IV, BMI 30 to <35 ; Group V, BMI ≥ 35 .

3.4. Cox Proportional Hazards Analysis

In the unadjusted Cox analysis (Model 1), the lifetime maximum BMI in the class II and severe obesity groups was associated with a significantly higher risk of both proteinuria and eGFR events than that in the normal weight group. Only the severe obesity group had a significantly elevated risk of retinopathy (Table 2).

Table 2. Results of univariate and multivariate Cox regression analysis.

Event	Model	BMI Group	HR	[95% CI]
Proteinuria	Uni	III vs. II	1.29	[0.90–1.85]
		IV vs. II	1.64	[1.12–2.40]
		V vs. II	2.10	[1.36–3.26]
	Multi	III vs. II	1.30	[0.90–1.87]
		IV vs. II	1.77	[1.19–2.62]
		V vs. II	1.98	[1.24–3.17]
eGFR decline	Uni	III vs. II	1.63	[0.87–3.04]
		IV vs. II	2.42	[1.28–4.60]
		V vs. II	2.59	[1.23–5.42]
	Multi	III vs. II	1.60	[0.85–3.00]
		IV vs. II	1.73	[0.89–3.37]
		V vs. II	1.30	[0.59–2.85]
Retinopathy	Uni	III vs. II	1.16	[0.74–1.80]
		IV vs. II	1.25	[0.77–2.03]
		V vs. II	2.03	[1.18–3.48]
	Multi	III vs. II	1.16	[0.74–1.82]
		IV vs. II	1.09	[0.65–1.81]
		V vs. II	1.60	[0.89–2.88]

The results of the univariate and multiple regression analyses using the Cox proportional hazards model are expressed as HRs and 95% CIs. The Uni model was adjusted for maximum BMI only, while the Multi model was adjusted for age, sex, duration of diabetes, HbA1c (NGSP), urine protein at first visit, eGFR at first visit, retinopathy classification at first visit, 1st degree family history of diabetes, and use of diabetes and hypertension medications. BMI, body mass index; HR, hazard ratio; CI, confidence interval. Group II, BMI 18.5 to <25; Group III, BMI 25 to <30; Group IV, BMI 30 to <35; Group V, BMI $\geq$ 35.

After multivariable adjustment (Model 2), the association between lifetime maximum BMI and proteinuria events remained strong and significant for Group IV (HR 1.77, 95% CI 1.19–2.62) and Group V (HR 1.98, 95% CI 1.24–3.17). However, the associations between lifetime maximum BMI and eGFR and retinopathy events were no longer statistically significant after adjusting for clinical covariates.

3.5. Stratified Analyses

The stratified analysis of eGFR lowering events showed that among patients *not* taking antihypertensive medications, a history of severe obesity (Groups IV and V) was associated with a higher event risk. In contrast, among patients *taking* antihypertensives, the risk was similarly elevated across all groups, masking the effect of obesity (Figure 4). For retinopathy, the increased risk associated with past severe obesity (Group V) was evident only in patients receiving antidiabetic medication (Figure 5).

3.6. Analysis of the BMI Trajectory Before the First Visit

As demonstrated in Figure 6A–I, a sub-analysis stratified by historical BMI trajectory prior to the first clinical visit revealed a counterintuitive yet pathophysiologically profound trend. Across most baseline BMI categories, patients who experienced a pre-visit weight “decrease” (blue lines) exhibited significantly a higher incidence of microvascular complications compared to those whose weight remained “no change” (red lines).

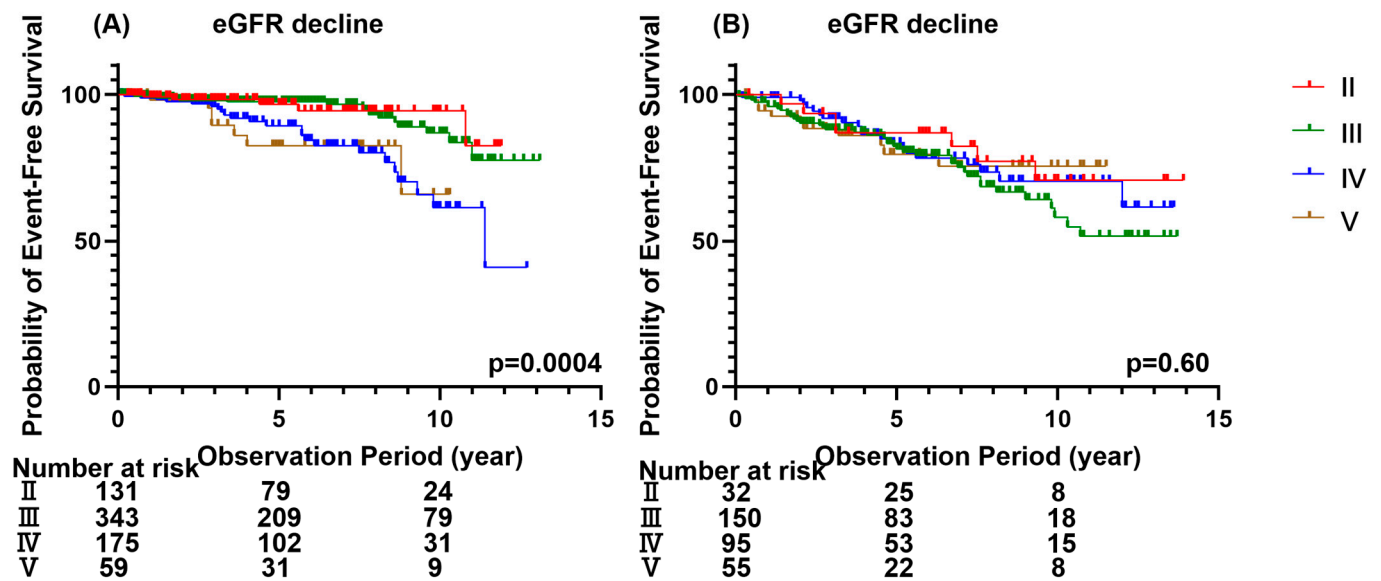


Figure 4. Kaplan–Meier plot of the survival rate of the observation period of eGFR decline stratified by hypertension medication use. (A) Without hypertension medications. (B) With hypertension medications. Group II, BMI 18.5 to <25; Group III, BMI 25 to <30; Group IV, BMI 30 to <35; Group V, BMI ≥ 35 .

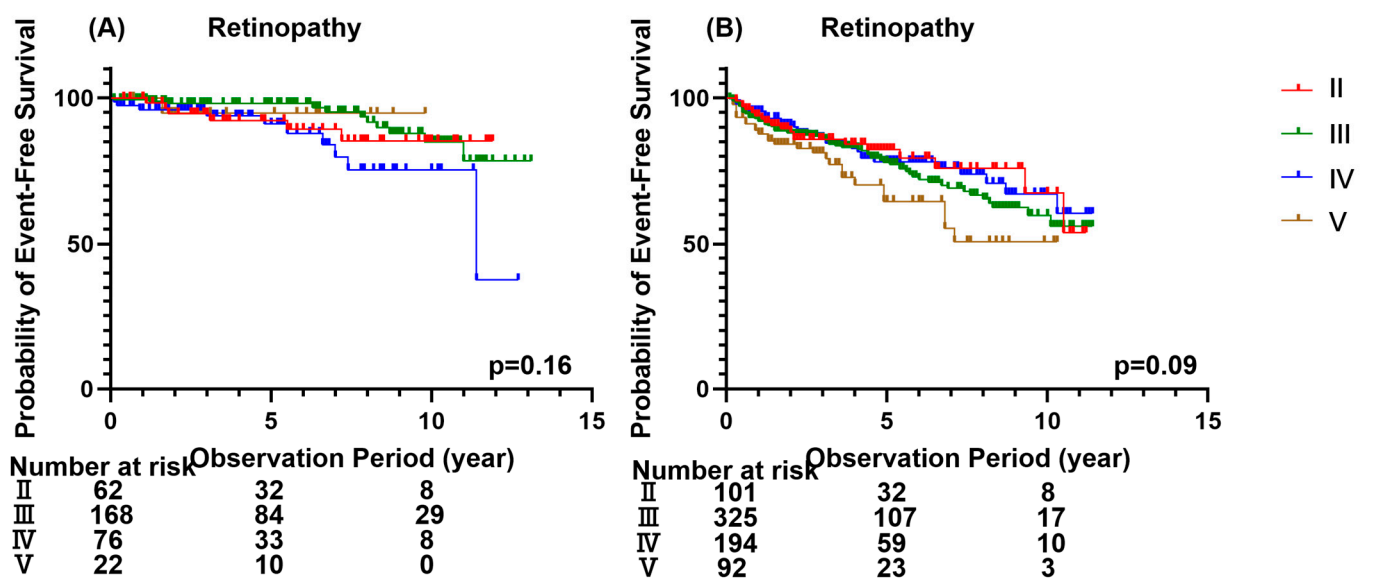


Figure 5. Kaplan–Meier plot of the survival rate of the observation period of worsening retinopathy stratified by diabetes medication use. (A) Without diabetes medications. (B) With diabetes medications. Group II, BMI 18.5 to <25; Group III, BMI 25 to <30; Group IV, BMI 30 to <35; Group V, BMI ≥ 35 .

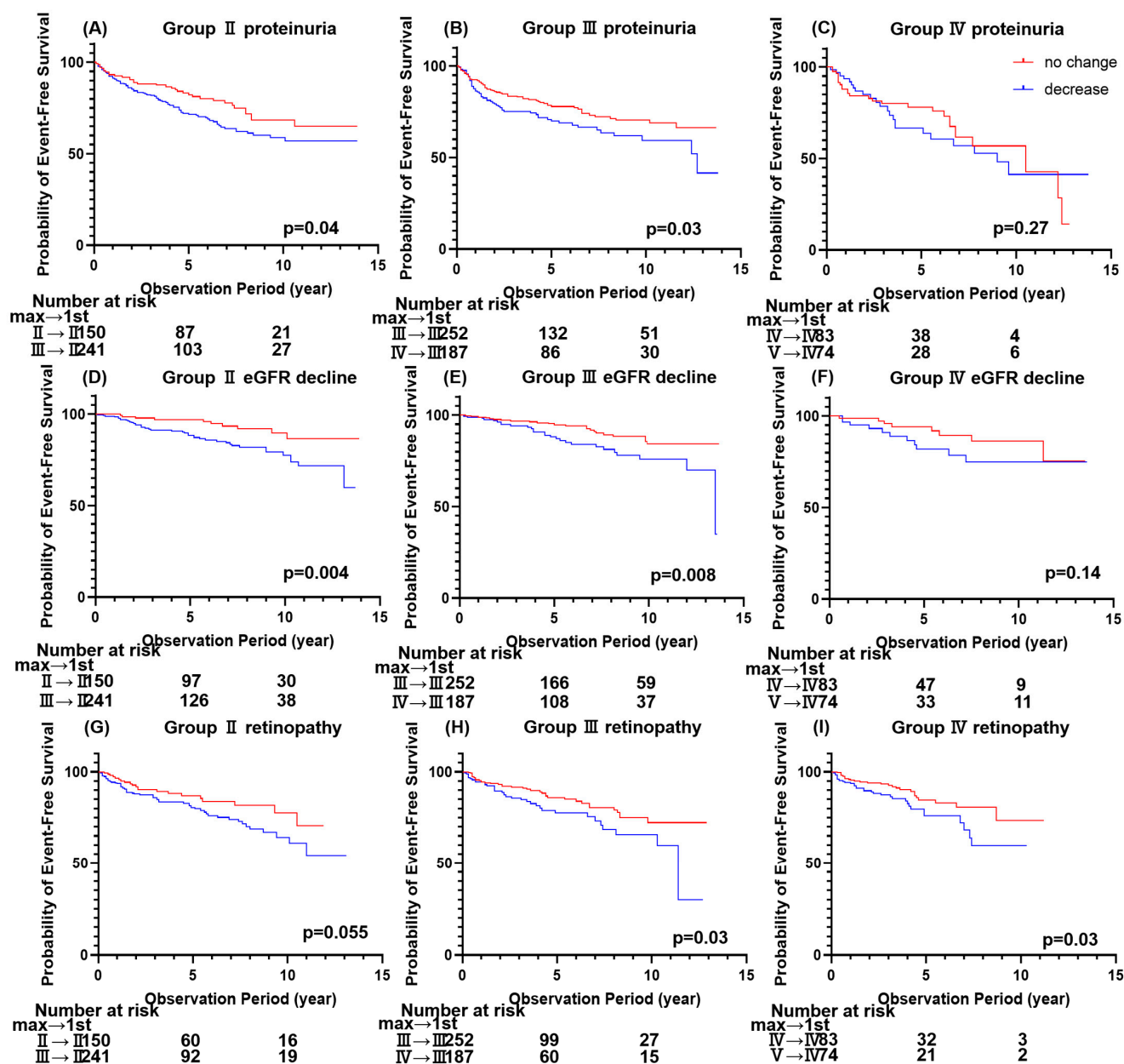


Figure 6. Kaplan–Meier plots illustrating microvascular event-free survival stratified by historical BMI trajectory (no change vs. decrease) across different BMI categories. The x-axis represents the observation period from the first clinical visit (years), and the y-axis shows the probability of event-free survival. The red lines indicate patients with a stable or increased weight trajectory (“no change”), whereas the blue lines represent patients who experienced a pre-visit weight reduction (“decrease”). Panels display the event-free survival rates for proteinuria progression (A–C), a $\geq 40\%$ decline in eGFR (D–F), and worsening of diabetic retinopathy (G–I), sub-analyzed within Group II (normal weight), Group III (class I obesity), and Group IV (class II obesity) based on BMI at the first clinical visit. Here, “decrease” indicates a reduction in one or more BMI categories from the lifetime maximum BMI to the first clinical visit, while “no change” indicates no category change. *p*-values were determined using the log-rank test.

4. Discussion

This retrospective cohort study demonstrated that a history of severe obesity, represented by the lifetime maximum BMI, is a robust predictor of proteinuria progression in Japanese patients with T2D. The association of maximum BMI was an independent predictor of proteinuria progression. Although past obesity was also correlated with eGFR decline

and retinopathy, these associations were attenuated after multivariate adjustment. Crucially, our utilization of the five-tiered JASSO classification [22] revealed severity-dependent pathological dynamics, thereby demonstrating a clinical advancement over the previous benchmark Japanese cohort study [21].

Importantly, BMI at the first clinical visit was primarily associated with retinopathy, suggesting differential contributions of past and current obesity to renal versus retinal damage. This negative legacy effect suggests that the peak metabolic and physical stress of historical obesity leaves a durable pathological imprint on the microvasculature, which persists even after substantial weight loss. This is further supported by evidence that adiponectin levels remain chronically suppressed in individuals with a history of obesity, even after they return to a normal weight [26], indicating a persistent alteration in adipose tissue function and systemic metabolism. Our sub-analysis stratified by historical BMI trajectory further corroborates this phenomenon. It is important to note that weight loss prior to the first visit may reflect distinct phenomena: voluntary lifestyle improvements or weight loss secondary to uncontrolled diabetes (hyperglycemic catabolism). The ‘decrease’ group in our study exhibited a higher incidence of complications, this trajectory most likely represents historical exposure to severe, untreated hyperglycemia and metabolic dysregulation prior to clinical presentation, rather than protective weight loss.

The independent association between past obesity and proteinuria suggests that obesity induces irreversible structural kidney damage. The pathophysiological mechanism underpinning the strong association between past severe obesity and progressive proteinuria is possibly rooted in obesity-related glomerulopathy (ORG) [27]. Characterized by glomerular hypertrophy and focal segmental glomerulosclerosis (FSGS), ORG often causes treatment-refractory proteinuria [28,29]. Once podocyte loss exceeds a critical threshold, irreversible glomerular scarring and treatment-refractory proteinuria ensue, explaining why historical peak adiposity exerts a lasting deleterious effect on renal function. If pre-diabetic obesity incites ORG, vigilant renal monitoring and early intervention in obese individuals become imperative.

Interestingly, the association between lifetime maximum obesity and eGFR decline varied depending on the use of antihypertensive medication. In patients not receiving antihypertensive therapy, the deleterious effect of past severe obesity on GFR was clearly pronounced. In contrast, among patients taking antihypertensives, the event risk tended uniformly elevated across all BMI categories, including normal weight and Class I obesity. This suggests the presence of confounding by indication; patients with advanced underlying hypertensive stress or baseline renal vulnerability, regardless of their weight history, were appropriately channeled into receiving antihypertensive therapy, thereby elevating the risk of the entire treated sub-cohort. Interestingly, the severe obesity groups did not exhibit further renal deterioration. This lack of incremental risk in the severe obesity under treatment could point to a ceiling effect. Alternatively, the potential for a genuine renoprotective therapeutic effect remains; since renin-angiotensin system (RAS) blockers were highly prescribed in this cohort, these agents may have actively counteracted the intrarenal RAS pathway that drives obesity-induced glomerular hyperfiltration and subsequent renal injury [29,30].

The pathophysiology linking obesity to retinopathy appears to be distinct from its association with DKD. Both lifetime maximum and current BMI correlated with retinopathy, suggesting either a significant contribution of ongoing metabolic stress from obesity or the potential for risk mitigation through the resolution of obesity. The severely obese group was the most at risk for retinopathy, a finding potentially revealed for the first time in this analysis, given their previously lower prevalence in Japanese type 2 diabetes populations [8]. Obesity was identified as a risk factor for retinopathy only when severe

obesity was included in the analysis. An earlier analysis [21], which dichotomized at a BMI of 25 kg/m², likely overlooked this risk, partly because obesity has historically been less prevalent in Japan [8]; thus severe obesity may have been insufficiently risk evaluated in Japanese patients with type 2 diabetes. Severe obesity is strongly associated with conditions that cause intermittent hypoxia, such as obstructive sleep apnea, a known accelerator of retinal neovascularization. However, the direct causal relationship between OSA parameters and DR remains highly debated in the recent clinical literature [31–35]. Our finding that the retinopathy risk was most evident in patients already on antidiabetic medication suggests a “two-hit” mechanism: a history of sustained hyperglycemia initiates microvascular damage [36], which is then exacerbated by obesity-related factors such as hypoxia. Since diabetic retinopathy does not develop in the absence of diabetes, obesity-related factors likely play a promoting rather than an initiating role.

From a practical perspective, inquiring about a patient’s historical peak weight during routine clinical evaluations represents a simple, noninvasive, and cost-effective screening tool for risk stratification. Identifying patients with a history of severe obesity can serve as a vital trigger for closer clinical monitoring. While our study did not directly evaluate specific pharmacological interventions, modern guidelines, including the KDIGO and ADA Standards of Care, recommend considering next-generation cardiometabolic therapies such as SGLT2 inhibitors and GLP-1 receptor agonists for patients with T2D at high risk of renal and vascular complications [37,38].

Limitations

This study has several limitations. First, the lifetime maximum weight was self-reported, introducing potential recall bias. Second, out of 4207 initial patients, a significant portion was excluded due to missing historical weight data or insufficient follow-up intervals, which introduces a potential selection bias. For example, the final analyzed cohort may represent individuals with high health literacy or clinical adherence to remember the lifetime maximum body weight, which could limit the generalizability of our findings to the broader diabetic population. Third, the data were obtained from a single specialized center in Japan, which may limit the generalizability to other ethnicities or healthcare systems. Fourth, the proteinuria endpoint was semi-quantitative (dipstick test). Finally, although the exclusion of non-diabetic nephropathy was based on the clinical diagnosis, differentiating the coexistence of other nephropathies was challenging because renal biopsy was rarely performed. Furthermore, since no patients had been formally diagnosed with obesity-related nephropathy, such patients could not be excluded.

5. Conclusions

A history of severe obesity is a significant independent risk factor for the long-term development of proteinuria in patients with T2D, representing a durable legacy effect that persists even after weight loss. In clinical practice, physicians should look beyond a patient’s current BMI and inquire about their maximum lifetime weight. This simple, noninvasive metric can serve as a powerful tool for risk stratification, enabling earlier and more targeted interventions to prevent diabetic microvascular complications.

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Informed Consent Statement: Patient consent was waived due to the retrospective study design, and an opt-out consent procedure was adopted.

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request and subject to prior approval from the data-contributing institution.

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Abbreviations

The following abbreviations are used in this manuscript:

ADA	American Diabetes Association
ANOVA	Analysis of Variance
ANCA	Anti-Neutrophil Cytoplasmic Antibody
BG	Biguanide
BMI	Body Mass Index
CI	Confidence Interval
CKD	Chronic Kidney Disease
DKD	Diabetic Kidney Disease
DPP-4	Dipeptidyl Peptidase-4
DR	Diabetic Retinopathy
eGFR	Estimated Glomerular Filtration Rate
ESRD	End-Stage Renal Disease
FSGS	Focal Segmental Glomerulosclerosis
GFR	Glomerular Filtration Rate
GLP-1	Glucagon-Like Peptide-1
HbA1c	Hemoglobin A1c
HR	Hazard Ratio
JDS	Japan Diabetes Society
KDIGO	Kidney Disease: Improving Global Outcomes
Multi	Multivariate (Model)
NDR	No Diabetic Retinopathy
NGSP	National Glycohemoglobin Standardization Program
ORG	Obesity-Related Glomerulopathy
OSA	Obstructive Sleep Apnea
PDR	Proliferative Diabetic Retinopathy
PPDR	Pre-Proliferative Diabetic Retinopathy
RAS	Renin-Angiotensin System
Scr	Serum Creatinine

SDR	Simple Diabetic Retinopathy
SGLT2	Sodium-Glucose Cotransporter 2
SU	Sulfonylurea
T2D	Type 2 Diabetes
Uni	Univariate (Model)

Appendix A

Table A1. Renal and ocular diseases before the observation period for patient exclusion.

Renal Diseases	Ocular Diseases
Chronic Glomerulonephritis	Epiretinal Membrane
Acute Glomerulonephritis	Macular Hole
IgA Nephropathy	Preretinal Membrane
Rapidly Progressive Glomerulonephritis	Vitreous Hemorrhage
Nephrotic Syndrome	Retinal Break/Retinal Tear
Chronic Pyelonephritis	Retinal Detachment
Acute Pyelonephritis	Vitreous Hemorrhage
Crescentic Glomerulonephritis	Retinal Vein Occlusion
ANCA-Associated Vasculitis	Retinal Artery Occlusion
Acute Renal Failure	Branch Retinal Artery Occlusion
Kidney Tumor	Branch Retinal Vein Occlusion
Renal Cancer	Pit Maculopathy
Hydronephrosis	Behçet's Disease
Kidney Tuberculosis	Post-vitrectomy
Renal Cyst	Post-iridectomy
Renal Infarction	Photocoagulation
Polycystic Kidney Disease	
Renal Transplantation	
Post-renal Surgery	

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