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Characteristics of Glycemic Control and Long-Term Complications in Patients with Young-Onset Type 2 Diabetes

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Background: The prevalence of young-onset diabetes (YOD) has been increasing worldwide. As the incidence of YOD increases, it is necessary to determine the characteristics of YOD and the factors that influence its development and associated complications.

Methods: In this retrospective study, we recruited patients who were diagnosed with type 2 diabetes mellitus between June 2001 and December 2021 at a tertiary hospital. The study population was categorized according to age: YOD (age <40 years), middle-age-onset diabetes (MOD, 40≤ age <65 years), and late-onset diabetes (LOD, age ≥65 years). We examined trends in glycemic control by analyzing fasting glucose levels during the first year in each age group. A Cox proportional-hazards model was used to determine the relative risk of developing complications according to glycemic control trends.

Results: The fasting glucose level at the time of diagnosis was highest in the YOD group (YOD 149±65 mg/dL; MOD 143±54 mg/dL; and LOD 140±55 mg/dL; P=0.009). In the YOD group, glucose levels decreased at 3 months, but increased by 12 months. YOD patients and those with poor glycemic control in the first year were at a higher risk of developing complications, whereas the risk in patients with LOD was not statistically significant.

Conclusion: YOD patients had higher glucose levels at diagnosis, and their glycemic control was poorly maintained. As poor glycemic control can influence the development of complications, especially in young patients, intensive treatment is necessary for patients with YOD.

Keywords: Diabetes mellitus; Glycemic control; Young aged

INTRODUCTION

The prevalence of young-onset type 2 diabetes mellitus (T2DM) has been increasing worldwide [1-3]. Its pathological characteristics include rapid deterioration of β-cell function, development of insulin resistance, and rapid disease progression [2]. The onset of diabetes at a younger age is associated with prolonged exposure to hyperglycemia. Consequently, the risk of developing chronic complications is increased in this population [4,5]. Additionally, these factors result in decreased glycemic control, thereby influencing patient morbidity or mortality [1,2].

According to previous studies, young-onset diabetes (YOD) is associated with obesity and may occur concurrently with other metabolic diseases such as fatty liver disease or dyslipidemia

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[4,6,7]. According to results from studies based on the cohort from the Treatment Options for T2DM in Adolescents and Youth (TODAY) Study, the development of associated complications is more common in patients with comorbidities [1,7]. Additionally, patients with poor glycemic control experienced a rapid decline in β-cell function and an increased risk of complications [1,8]. These results imply that early aggressive treatment is needed in patients with YOD. However, previous studies were based on highly controlled clinical trials that explored limited treatment strategies, and it is unclear whether the glycemic control strategies utilized in older adults may also apply to younger patients. Further, the association between glycemic control and long-term complications in patients with YOD remains unclear. Understanding the characteristics of YOD will better prepare the healthcare system to respond accordingly [1,6,9]. Thus, it is necessary to determine whether the characteristics of patients with YOD are similar to those reported in previous studies in a real-world setting, rather than in a controlled clinical trial. In this study, we aimed to determine the characteristics of YOD and validate previous findings using real-world data. In addition, we aimed to determine how glycemic control during the first year of diagnosis influences the development of complications in the YOD group.

METHODS

Study population

In this retrospective study, we recruited patients who were diagnosed with T2DM for the first time between June 2001 and December 2021 at Seoul St. Mary's Hospital in Seoul, South Korea. Patient data were collected from electronic medical records (EMRs). T2DM diagnosis was defined as a patient diagnosed with diabetes mellitus, based on the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes E11–E14, with a metformin prescription at the same time. The first date of metformin prescription was defined as the date of T2DM diagnosis, and we considered this to be the index date. We defined T2DM based on the use of metformin for two reasons. First, metformin was the first-line therapy at the time of the study [10]. Second, metformin should be used carefully in patients with complications, such as renal failure [11]. Thus, metformin use would imply that the patients did not already have complications associated with T2DM.

We excluded patients who started therapy with an anti-diabetic agent other than metformin to simplify the analysis and because the use of a non-metformin agent could have implied that they had comorbidities such as malignancy, liver failure, or end-stage renal disease. Patients with type 1 diabetes or gestational diabetes mellitus were excluded from the study, as were patients with C-peptide levels lower than 0.6 ng/mL. As the study investigated glycemic control in the first year after treatment initiation, we excluded patients who did not have glucose or glycated hemoglobin (HbA1c) levels recorded in their EMRs at the start of treatment and 12 months later. We also excluded patients who had experienced complications at the start of treatment or within 12 months after the index date. Thus, we calculated the period starting from the index date until the date of complication development, and we excluded patients with a period of fewer than 12 months. The study population was divided into three groups according to age at the time of diagnosis: the YOD group (age <40 years), the middle-age-onset diabetes (MOD) group (40≤ age <65 years), and the late-onset diabetes (LOD) group (age ≥65 years).

Study design

For each patient included in this study, laboratory results for blood glucose levels, HbA1c, lipid profile (i.e., total cholesterol, triglyceride, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol [LDL-C] levels), and liver function tests (i.e., aspartate aminotransferase [AST], alanine aminotransferase [ALT], and γ-glutamyl transpeptidase [γ-GTP]) were recorded at the index date and 3, 6, and 12 months from the index date. If available, patients' height and weight were extracted from the EMR, and the body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Non-alcoholic fatty liver disease (NAFLD) was determined using the hepatic steatosis index (HSI), which was calculated as follows: 8×(ALT/AST ratio)+BMI (kg/m^2)+2 (if female)+2 (because everyone in our study cohort had diabetes). Patients with an HSI greater than 36 were defined as having NAFLD [12]. If available, homeostatic model assessment of insulin resistance (HOMA-IR) and homeostatic model assessment of β-cell function (HOMA-β) were calculated by the homeostatic model assessment [13]. Diabetic complications were searched for primarily based on the ICD-10 classification and treatment codes. We searched the name of the diagnosis for each complication as follows: retinopathy (E1122–E1422, E1140–E1142, E1240–1242, E1340–E1342, E1440–E1442), neuropathy (E1131–E1133, E1231–E1233, E1431–E1438), nephropathy (E1120–E1122, E1220–E1222, E1320–E1322, E1420–E1422, N083, N18), vascular insufficiency (E1150, E1250, E1350, E1450); cardiovascular disease (I20–25, I489), heart failure (E1165–E1465, I255, I50),

and stroke (I63–64). We also considered the results of fundoscopy for retinopathy and the microalbumin/creatinine ratio for nephropathy (microalbuminuria >30 mg/g). Patients who underwent coronary interventions were also considered to have cardiovascular disease; these patients were detected by searching for treatment codes specific to coronary intervention procedures. The complications were classified as microvascular and macrovascular. Microvascular complications included retinopathy, nephropathy, or neuropathy, and macrovascular complications included vascular insufficiency, cardiovascular disease, heart failure, or stroke. The date of diagnosis of complications was considered the date of development of complications. The period from the index date to the development of complications was considered the observation period.

Data protection and privacy

The data used in this study were approved by the Catholic University Data Review Committee and all data was anonymized. Anonymized data were stored in encrypted files and computers, rendering it impossible to re-identify patients. Due to the nature of retrospective cohort studies, there was no possibility of physical or mental harm to patients as a result of this study. Therefore, the requirement for informed consent was waived by the review board. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Institutional Review Board of the Catholic University of Korea (KC22RASI0094).

Glycemic variability, area under the curve for glucose, and statistical analysis

The standard deviation (SD) of the glucose level and HbA1c during the study period was calculated to determine the glycemic variability. The coefficient of variation (CoV) was calculated (SD/mean). The adjusted SD was calculated as $SD/\sqrt{\frac{n}{n-1}}$ to adjust for the influence of the different number of measurements, as previously suggested [14,15].

The area under the curve for glucose (AUCg) [16] was used to determine the degree of glucose control. It was defined as the definite integral of the glucose level with time. The trapezoidal method was used for the actual calculation, as follows:

$$AUCg=\frac{(\text{initial glucose level}+\text{glucose level at 3 months})}{2}[\text{mg/dL}]\times 3\ [\text{months}]+\frac{(\text{glucose level at 6 months}+\text{glucose level at 12 months})}{2}[\text{mg/dL}]\times 6\ [\text{months}]$$

The cutoff value for distinguishing between well-controlled and poorly controlled glucose levels was calculated using a receiver operating characteristic (ROC) curve. Using the ROC curve, the value for predicting the development of complications was determined when the sum of sensitivity and 1-specificity was maximized. With this cutoff value, we constructed a Cox proportional-hazards model for the development of complications. Using Z-transformed AUCg values, we calculated the hazard ratio (HR) associated with AUCg in each age group. We conducted survival analysis in each age group separately. Changes in values according to time were analyzed using the paired *t* test. SPSS version 24 (IBM Corp., Armonk, NY, USA) was used to construct the Cox proportional-hazards model and carry out the paired *t* test. The YOD, MOD, and LOD groups were compared using analysis of variance. We performed the analysis using R version 4.1.1 (R Project for Statistical Computing, Vienna, Austria). Graphs were generated using Prism version 8.02 (GraphPad Software Inc., La Jolla, CA, USA). Categorical variables were reported as numbers and frequencies (%). Continuous variables were reported as mean±SD. The HRs were reported with 95% confidence intervals (CIs). Statistical significance was set at $P<0.05$.

RESULTS

Baseline characteristics

A total of 3,479 study participants were enrolled in this study (Table 1). Of these, 8.5% (296/3,479 participants) were classified into the YOD group, 61.9% (2,154/3,479 participants) into the MOD group, and 29.6% (1,029/3,479 participants) into the LOD group. Among the patients who had available data to calculate the BMI, the ratio of patients with severe obesity (BMI >30 kg/m^2) was higher in the YOD group than in the MOD and LOD groups (16.2% in the YOD group vs. 9.0% in the MOD group vs. 4.9% in the LOD group, $P<0.001$). However, the mean values of BMI among these three groups did not show a statistically significant difference ($P=0.081$). In addition, the YOD group showed higher total cholesterol, triglyceride, and LDL-C levels than the other two groups (all $P<0.001$). The YOD group showed the highest ratio of NAFLD among the three groups (63.7% [72/113 participants] in the YOD group, 53.2% [477/896 participants] in the MOD group, and 38.6% [209/542 participants] in the LOD group; $P<0.001$). The AUCg was higher in the YOD group (1,728.2±605.7 [mg/dL]×mo) than in the other two groups (1,637.9±435.1 [mg/dL]×mo in the MOD group and 1,645.5±453.4 [mg/dL]×mo in the LOD group), albeit without statistical significance ($P=0.095$). Although there was a limited number of patients with available measurements ($n=31$), there were no significant differences in

Table 1. Baseline Characteristics of the Study Population

Characteristic	YOD	MOD	LOD	*P* value
Number	296 (8.5)	2,154 (61.9)	1,029 (29.6)	
Age, yr	31.5±6.6	54.4±6.5	71.3±5.4	0.081
Female sex	114 (38.5)	945 (43.9)	517 (50.2)	<0.001
BMI, kg/m^2	24.7±5.9	24.7±4.1	24.3±3.4	0.081
Obesity (25< BMI <30 kg/m^2)	27 (23.1)	283 (31.1)	200 (36.5)	<0.001
Severe obesity (BMI >30 kg/m^2)	19 (16.2)	82 (9.0)	27 (4.9)	<0.001
Glucose, mg/dL	149±65	143±54	140±55	0.009
HbA1c, mg/dL	7.8±2.1	7.4±1.6	7.2±1.4	<0.001
C-peptide, ng/mL	6.3±3.4	3.9±4.1	4.7±4.0	0.844
Insulin, μIU/mL	50.1±33.9	25.3±31.0	25.3±23.0	0.359
HOMA-IR	14.4±8.2	6.9±8.7	8.0±6.9	0.374
HOMA-β	372.8±190.5	167.1±326.1	184.8±190.1	0.519
BUN, mg/dL	13.2±4.8	15.6±5.9	17.1±6.2	<0.001
Creatinine, mg/dL	0.8±0.2	0.9±0.3	0.9±0.2	<0.001
AST, U/L	34±34	30±25	28±32	0.001
ALT, U/L	53.1±60.6	35.4±35.0	27.4±31.2	<0.001
γ-GTP, U/L	84.1±143.2	78.9±143.6	59.4±101.2	0.002
Total cholesterol, mg/dL	187.4±44.7	175.8±43.0	165.1±39.7	<0.001
Triglyceride, mg/dL	200.7±162.8	158.1±114.1	132.4±75.5	<0.001
HDL-C, mg/dL	44.6±13.7	45.6±13.4	45.5±14.1	0.585
LDL-C, mg/dL	108.9±34.8	100.3±35.1	93.3±32.1	<0.001
NAFLD	72/113 (63.7)	477/896 (53.2)	209/542 (38.6)	<0.001
AUCg[a]	1,728.2±605.7	1,637.9±435.1	1,645.5±453.4	0.095

Values are expressed as number (%), or mean±standard deviation. YOD (age <40 years), MOD (40≤ age <65 years), LOD (age ≥65 years).
YOD, young-onset diabetes; MOD, middle-age-onset diabetes; LOD, late-onset diabetes; BMI, body mass index; HbA1c, glycated hemoglobin; HOMA-IR, homeostatic model assessment of insulin resistance; HOMA-β, homeostatic model assessment of β-cell function; BUN, blood urea nitrogen; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NAFLD, non-alcoholic fatty liver disease; AUCg, area under the curve of the glucose level.
[a]AUCg: It was defined as the definite integral of the glucose level with time. The trapezoidal method was used for the actual calculations.

C-peptide, insulin, HOMA-IR, and HOMA-β levels among the three groups.

Glycemic control trends 1 year after treatment

Overall, the glucose and HbA1c levels were the highest in the YOD group at baseline; however, glycemic control significantly improved during the first 3 months of treatment in all three groups. The fasting glucose level at the time of diagnosis was the highest in the YOD group (149±65 mg/dL in the YOD group, 143±54 mg/dL in the MOD group, and 140±55 mg/dL in the LOD group, P=0.009). The HbA1c level at the time of diagnosis was also the highest in the YOD group (7.8%±2.1% in the YOD group, 7.4%±1.6% in the MOD group, and 7.2%±1.4% in the LOD group, P<0.001). As a reflection of improved glycemic control across all age groups after 3 months of treatment, lower glucose levels (138±52 mg/dL in the YOD group, 135±47 mg/dL in the MOD group, and 138±49 mg/dL in the LOD group, P=0.715) and HbA1c levels (7.0%±1.6% in the YOD group, 6.8%±1.2% in the MOD group, and 6.9%±1.1% in the LOD group, P=0.786) were found in all age groups, without statistical significance. Across all age groups, the glucose and HbA1c levels at 3 months showed statistically significant differences from the baseline values (P=0.002 for the YOD group, P<0.001 for the MOD group, and P=0.06 for the LOD group for glucose levels, and P<0.001 for all age groups for HbA1c levels). However, after 3 months, the glucose levels and HbA1c increased again, but only in the YOD group (Fig. 1). Consequently, all variability markers for fasting glucose levels

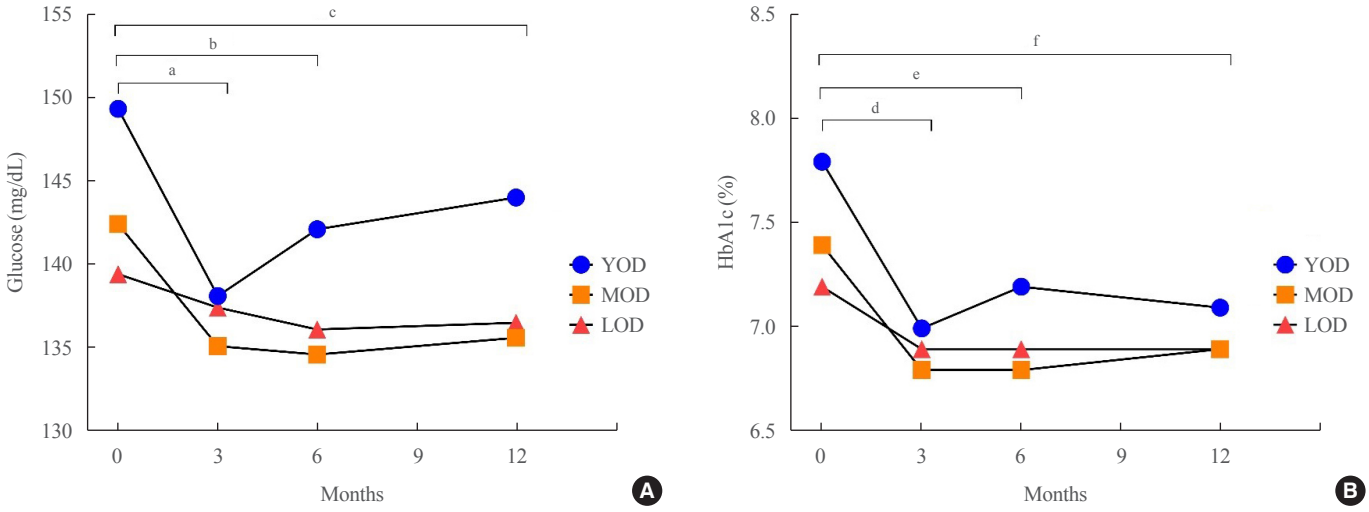

Fig. 1. Glycemic control during the first year of treatment. Each point represents mean values. (A) Glucose levels at the time of treatment initiation and 3, 6, and 12 months from treatment initiation. (B) Glycated hemoglobin (HbA1c) levels at the time of treatment initiation and 3, 6, and 12 months from treatment initiation. YOD, young-onset diabetes; MOD, middle-age-onset diabetes; LOD, late-onset diabetes. [a]$P<0.005$ (YOD), <0.001 (MOD); [b]$P<0.005$ (MOD), <0.001 (LOD); [c]$P<0.001$ (MOD), <0.005 (LOD); [d,e,f]$P<0.001$ in all age groups.

Table 2. Glycemic Variability in Each Age Group

Variable	Glucose				HbA1c			
	YOD	MOD	LOD	*P* value	YOD	MOD	LOD	*P* value
Standard deviation (SD)				0.013				<0.001
Mean±SD	27.3±27.8	23.1±24.5	24.6±26.4		0.7±0.7	0.6±0.6	0.5±0.5	
Median (IQR)	17.7 (9.1–36.6)	14.4 (7.8–29.3)	16.0 (8.2–30.5)		0.5 (0.3–1.0)	0.3 (0.2–0.7)	0.3 (0.2–0.6)	
Coefficient of variation (CoV)				0.010				<0.001
Mean±SD	0.17±0.13	0.15±0.13	0.16±0.13		0.09±0.08	0.08±0.07	0.07±0.06	
Median (IQR)	0.13 (0.08–0.24)	0.1 (0.06–0.20)	0.13 (0.07–0.22)		0.07 (0.04–0.13)	0.06 (0.03–0.10)	0.05 (0.03–0.08)	
Adjusted-SD				0.022				<0.001
Mean±SD	22.8±23.3	19.4±20.7	20.4±22.0		0.6±0.6	0.5±0.5	0.4±0.4	
Median (IQR)	14.6 (7.4–30.8)	12.0 (6.5–24.7)	13.0 (6.8–25.8)		0.4 (0.2–0.8)	0.3 (0.2–0.6)	0.3 (0.1–0.5)	

YOD (age <40 years), MOD (40≤ age <65 years), LOD (age ≥65 years).
HbA1c, glycated hemoglobin; YOD, young-onset diabetes; MOD, middle-age-onset diabetes; LOD, late-onset diabetes; SD, standard deviation; IQR, interquartile range; Adjusted SD, SD adjusted for the measurement time number ($SD/\sqrt{\frac{n}{n-1}}$), CoV, coefficient of variation.

and HbA1c were high in the YOD group (SD, $P=0.013$; CoV, $P=0.010$; adjusted SD, $P=0.022$). All variability markers for HbA1c were also high in the YOD group (SD, $P<0.001$; CoV, $P<0.001$; and adjusted SD, $P<0.001$). Detailed numbers are provided in Table 2. These results suggest that patients with YOD failed to maintain glycemic control.

Association between AUCg and the development of complications

A total of 61.1% (181/296 participants) of patients with YOD, 62.1% (1,338/2,154 participants) of MOD patients, and 52% (535/1,029 participants) of LOD patients developed complications after the first year of treatment. The optimal cutoff value for AUGg was determined via ROC curve analysis to predict the development of complications. Accordingly, the cutoff was set at 1,433 (mg/dL)×mo (approximately 119.4 mg/dL per month). In the Cox proportional-hazards model analysis, the overall median follow-up duration was 51 months (interquartile range [IQR], 48 to 54). For each age group, the median follow-up duration was 64 months (IQR, 50 to 77) in the YOD group, 51 months (IQR,

47 to 54) in the MOD group, and 46 months (IQR, 41 to 50) in the LOD group. As such, in patients with YOD and MOD, an AUCg ≥1,433 (mg/dL)×mo predicted a higher risk of developing complications than those with an AUCg <1,433 (mg/dL)×mo (YOD: HR, 1.846; 95% CI, 1.334 to 2.554; $P<0.001$ and MOD: HR, 1.538; 95% CI, 1.369 to 1.728; $P<0.001$). In contrast, the AUCg did not show a statistically significant relationship in the LOD group (HR, 1.176; 95% CI, 0.984 to 1.406; $P=0.074$). For microvascular complications, the AUCg values in all three groups were statistically significant (HR, 2.554; 95% CI, 1.387 to 4.733; $P= 0.003$ in the YOD group, HR, 1.656; 95% CI, 1.377 to 1.992; $P<0.001$ in the MOD group, and HR, 1.684; 95% CI, 1.240 to 2.287; $P=0.001$ in the LOD group). For macrovascular complications, the AUCg in the YOD group (HR, 1.900; 95% CI, 1.356 to 2.662; $P<0.001$) and in the MOD group (HR, 1.373; 95% CI, 1.215 to 1.551; $P<0.001$) showed significant differences. However, in the LOD group, the AUCg did not show a significant difference (HR, 1.066; 95% CI, 0.885 to 1.284; $P=0.501$) (Fig. 2).

The results of the baseline glucose test compared with the test

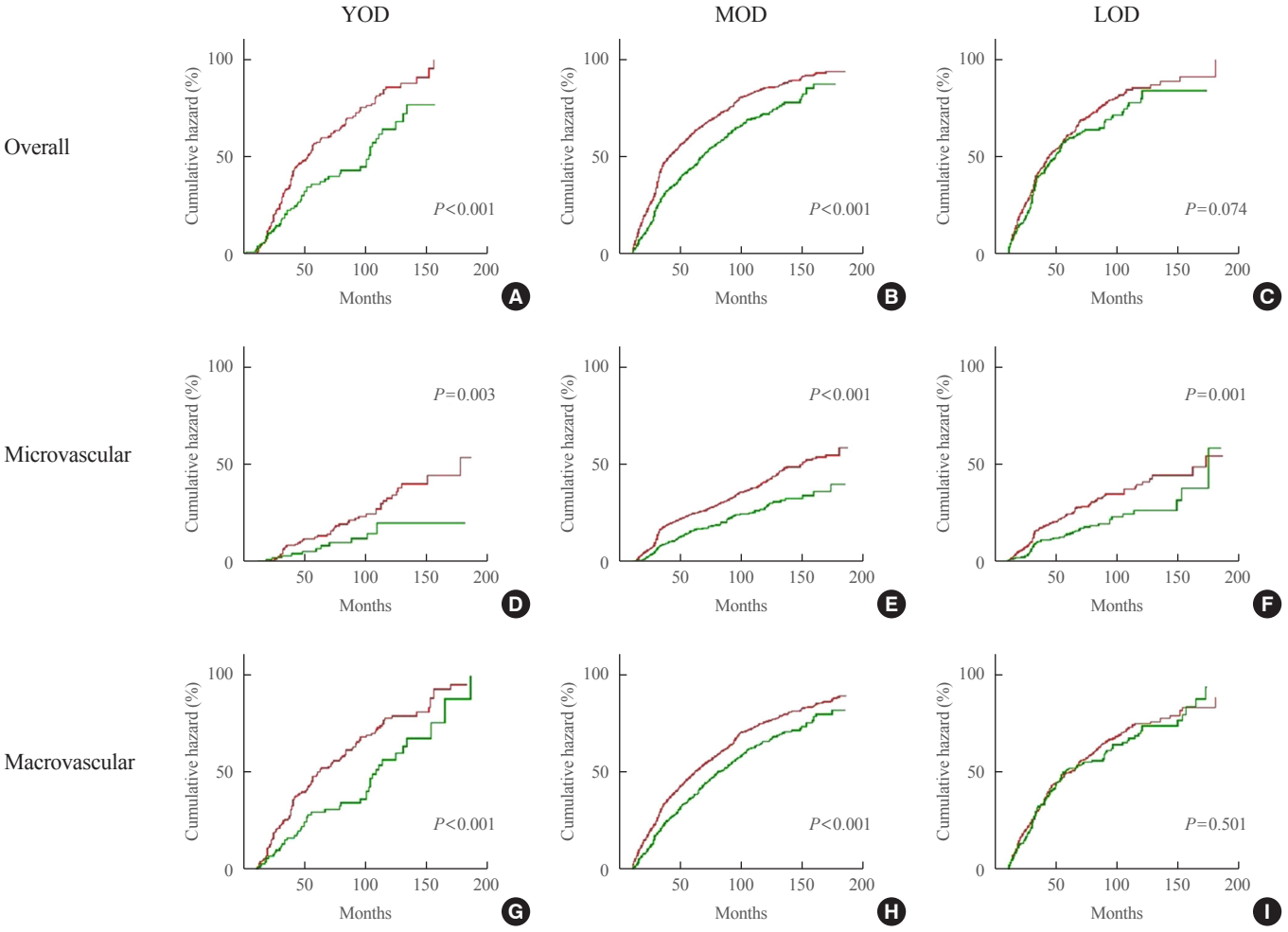

Fig. 2. The cumulative hazard curve for complications in each age group, according to glycemic control. The red line represents patients with area under the curve of the glucose level (AUCg) ≥1,433 (mg/dL)×mo and the green line represents the participants with AUCg <1,433 (mg/dL)×mo. (A) The cumulative hazard curve for overall complications in patients with young-onset diabetes (YOD). (B) The cumulative hazard curve for overall complications in patients with middle-age-onset diabetes (MOD). (C) The cumulative hazard curve for overall complications in patients with late-onset diabetes (LOD). (D) The cumulative hazard curve for microvascular complications in patients with YOD. (E) The cumulative hazard curve for microvascular complications in patients with MOD. (F) The cumulative hazard curve for microvascular complications in patients with LOD. (G) The cumulative hazard curve for macrovascular complications in patients with YOD. (H) The cumulative hazard curve for macrovascular complications in patients with MOD. (I) The cumulative hazard curve for macrovascular complications in patients with LOD.

results from 1 year after treatment initiation showed a pattern similar to that of AUCg. The HR for overall complications according to the baseline glucose level showed statistical significance in patients with YOD (HR, 1.002; 95% CI, 1.000 to 1.004; P=0.044) and MOD (HR, 1.001; 95% CI, 1.000 to 1.002; P=0.024), but not in those with LOD (HR, 1.0; 95% CI, 0.998 to 1.002; P=0.855). A specific analysis of microvascular complications showed statistical significance across all age groups (HR, 1.004; 95% CI, 1.001 to 1.007; P=0.003 in patients with YOD; HR, 1.002; 95% CI, 1.001 to 1.003; P=0.004 in patients with MOD; HR, 1.003; 95% CI, 1.001 to 1.005; P=0.014 in patients with LOD). An analysis of macrovascular complications showed statistical significance in patients with YOD (HR, 1.002; 95% CI, 1.000 to 1.004; P=0.029) and MOD (HR, 1.001; 95% CI, 1.000 to 1.002; P=0.012), but not in patients with LOD (HR, 1.000; 95% CI, 0.998 to 1.001; P=0.752). The HR according to the glucose level at 12 months after treatment initiation also showed a similar pattern to that of the baseline glucose (HR, 1.004; 95% CI, 1.002 to 1.005; P<0.001 in patients with YOD; HR, 1.003; 95% CI, 1.002 to 1.004; P<0.001 in patients with MOD; and HR, 1.001; 95% CI, 0.999 to 1.002; P=0.402 in patients with LOD). Similarly, the HR according to HbA1c levels at the start of treatment and at 12 months after treatment initiation was statistically significant in all age groups. The HR for macrovascular complications showed statistical significance in patients with YOD (HR, 1.135; 95% CI, 1.021 to 1.262; P=0.019) and MOD (HR, 1.047; 95% CI, 0.993 to 1.105; P=0.092), but not in those with LOD (HR, 1.035; 95% CI, 0.947 to 1.130; P=0.450). However, the HR was lower for glucose and HbA1c than it was for AUCg (Table 3). An analysis of Z-transformed AUCg data (Fig. 3) showed that the HR for the development of complications was statistically significant only in patients with YOD (for overall complications, HR, 1.236; 95% CI, 1.098 to 1.392; P<0.001; for microvascular complications, HR, 1.389; 95% CI, 1.163 to 1.658; P<0.001; for macrovascular complications, HR, 1.252; 95% CI, 1.110 to 1.413; P<0.001).

However, patients with MOD did not show a statistically significant risk of developing complications (for overall complications, HR, 0.985; 95% CI, 0.921 to 1.053; P=0.656; for microvascular complications, HR, 1.054; 95% CI, 0.961 to 1.155; P=0.264; for macrovascular complications, HR, 0.994; 95% CI, 0.927 to 1.066; P=0.870). Similarly, patients with LOD showed no significant risk for developing complications (for overall complications, HR, 1.018; 95% CI, 0.932 to 1.113; P=0.692; for microvascular complications, HR, 1.113; 95% CI,

Table 3. Hazard Ratio for Complications according to Glucose Level and HbA1c at the Time of Treatment Initiation and 1 Year after Treatment Initiation

Variable		YOD			MOD			LOD		
		HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value
Fasting glucose										
Baseline	Total	1.002	1.000–1.004	0.044	1.001	1.000–1.002	0.024	1.000	0.998–1.002	0.855
	Microvascular	1.004	1.001–1.007	0.003	1.002	1.001–1.003	0.004	1.003	1.001–1.005	0.014
	Macrovascular	1.002	1.000–1.004	0.029	1.001	1.000–1.002	0.012	1.000	0.998–1.001	0.752
12 months	Total	1.004	1.002–1.005	<0.001	1.003	1.002–1.004	<0.001	1.001	0.999–1.002	0.402
	Microvascular	1.006	1.003–1.009	<0.001	1.003	1.002–1.005	<0.001	1.001	0.998–1.004	0.691
	Macrovascular	1.004	1.002–1.006	<0.001	1.003	1.002–1.004	<0.001	1.002	1.000–1.004	0.021
HbA1c										
Baseline	Total	1.099	1.024–1.179	0.009	1.055	1.020–1.091	0.002	1.065	1.001–1.132	0.046
	Microvascular	1.194	1.067–1.336	0.002	1.108	1.057–1.161	<0.001	1.212	1.118–1.313	<0.001
	Macrovascular	1.115	1.038–1.199	0.003	1.052	1.014–1.091	0.007	1.001	0.938–1.068	0.975
12 months	Total	1.134	1.024–1.256	0.015	1.123	1.070–1.179	<0.001	1.107	1.021–1.200	0.014
	Microvascular	1.347	1.176–1.544	<0.01	1.274	1.194–1.358	<0.001	1.262	1.134–1.405	<0.001
	Macrovascular	1.135	1.021–1.262	0.019	1.047	0.993–1.105	0.092	1.035	0.947–1.130	0.450

YOD (age <40 years), MOD (40≤ age <65 years), LOD (age ≥65 years). HRs for 1-mg/dL increases in glucose levels or 1% increases in HbA1c.
HbA1c, glycated hemoglobin; YOD, young-onset diabetes; MOD, middle-age-onset diabetes; LOD, late-onset diabetes; HR, hazard ratio; CI, confidence interval.

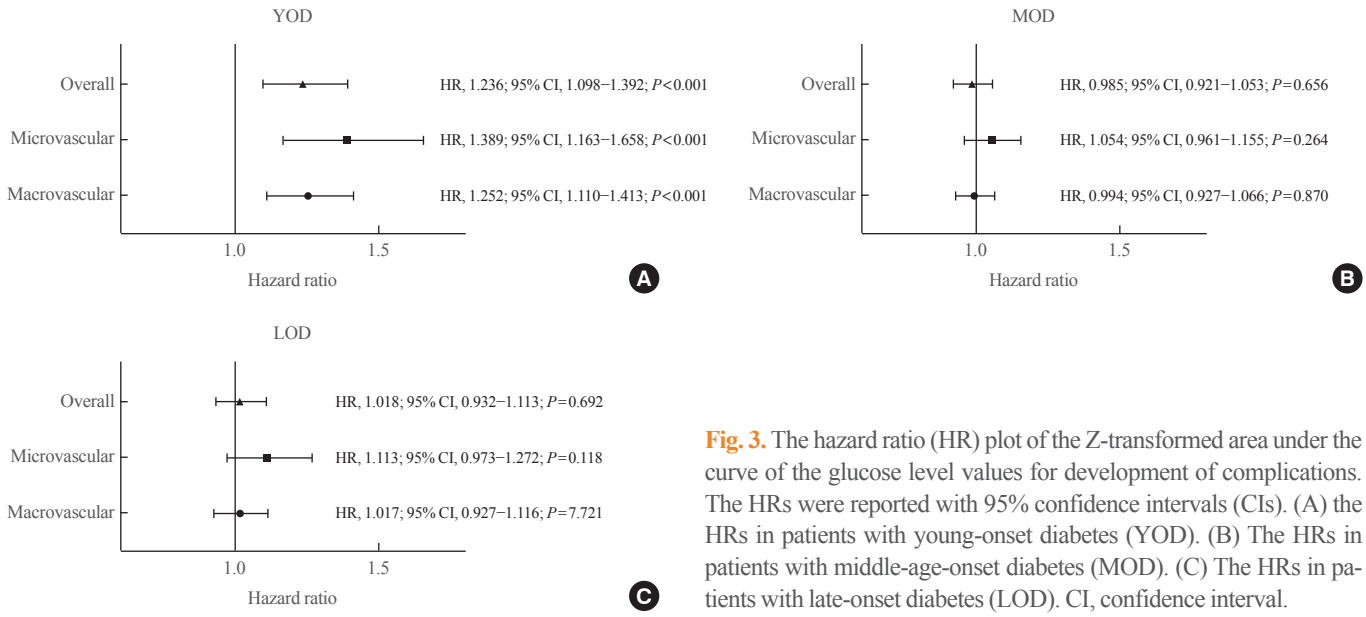

Fig. 3. The hazard ratio (HR) plot of the Z-transformed area under the curve of the glucose level values for development of complications. The HRs were reported with 95% confidence intervals (CIs). (A) the HRs in patients with young-onset diabetes (YOD). (B) The HRs in patients with middle-age-onset diabetes (MOD). (C) The HRs in patients with late-onset diabetes (LOD). CI, confidence interval.

0.973 to 1.272; $P=0.118$; for macrovascular complications, HR, 1.017; 95% CI, 0.927 to 1.116; $P=7.721$).

DISCUSSION

In our study, patients with YOD had higher fasting glucose and HbA1c levels at the time of diagnosis. Additionally, the proportion of patients with simultaneous NAFLD and severe obesity was the highest in the YOD group. In addition to the higher glucose level at diagnosis, the glycemic control of patients with YOD was poor compared with that of other age groups. Glycemic variability was also higher in patients with YOD. Glycemic control in the first year could affect the future development of long-term complications, particularly in patients with YOD.

In this study, the fasting glucose level at diagnosis was the highest in the YOD group. Results from previous studies, which recruited patients of varying ethnicities, have shown similar patterns [4,6,17-19]. In the YOD group, glycemic control improved in the first 3 months but then worsened 12 months after treatment initiation. The MOD and LOD groups maintained glycemic control for 12 months after treatment initiation. Therefore glucose variability was also high in the YOD group. We hypothesize two reasons for these observed characteristics in patients with YOD. First, the pathogenic mechanisms of YOD may differ from those of later-onset diabetes. Previous research has observed a rapid β-cell decline in YOD patients [8,20]. Considering that a family history of diabetes is also a risk factor for YOD [21,22], both pathogenesis and genetic factors may play an important role in the YOD group [18]. Second, suboptimal adherence to medical therapy or failure to make lifestyle modifications could be another potential reason. Younger patients, particularly those without complications, may not take their disease seriously. A Korean population study showed that despite the fact that younger patients experienced poorer diabetes-related quality of life [23], clinic attendance rates were lower in the YOD group than in other age groups [6]. In an Australian study, younger patients tended not to follow self-care practice recommendations [24], and in the TODAY study, the effects of lifestyle modifications were not maintained for a prolonged period of time in young patients [25]. Lastly, research also suggests that younger patients had lower rates of reaching glycemic control targets [26]. Taken together, the results from our study are consistent with other studies in the literature.

In our study, the YOD group had the highest proportions of severe obesity and NAFLD. Previous studies have pointed out that YOD may be more strongly associated with obesity or NAFLD [2,4,6,27], which could lead to the development of complications. A recent study using the TODAY study cohort showed that comorbidities such as hypertension, dyslipidemia, and hyperglycemia could affect the development of complications in T2DM [1]. However, as this study was conducted in a clinical trial setting, the treatment strategy was limited. In our study, participants with poorly controlled glucose levels in the first year showed a 1.85 times higher risk of developing complications, regardless of the treatment strategy. In other words, our analysis showed that patients with well-controlled glucose lev-

els had a lower risk for complications.

We found that the degree of glycemic control over the first year of treatment more accurately reflected the risk of complications than the glucose or HbA1c levels at a specific time point. In particular, the risk increased according to the blood glucose and HbA1c values at 12 months and was relatively larger than at baseline. Additionally, the Z-transformed analysis reflected a risk of complications only in patients with YOD. It seems that the association between glycemic control and the development of complications in older patients is weaker than that in younger patients. This may be because older patients have more comorbidities, which are linked to poorer functionality and a higher risk of developing complications [28-30]. In contrast, in young patients, diabetes alone has a greater impact on the occurrence of complications. This finding implies that early aggressive management is important for young patients with diabetes. Glycemic control in the first year has an important influence on the development of complications.

Due to the retrospective nature of this cohort study, it has some limitations [31,32]. First, we selected patients who were initially treated with metformin as their first anti-diabetic agent and who visited a tertiary hospital; thus, the study results could have underestimated the true relationship due to selection bias. The authors assume that this selection bias could affect the results of obesity distribution, as moderately obese young people may have visited tertiary hospitals more frequently. Second, our EMR analysis could only assess correlation and not causation. In addition, the 1-year follow-up glucose levels might be a relatively short time period when used to assess complications. As this was not a prospective study, there was a lack of data for C-peptide, insulin, HOMA-IR, and HOMA-β. Furthermore, although we checked the results of fundoscopy and microalbuminuria testing, the data were not sufficient to evaluate complications. At our hospital, glucose levels were checked when patients were fasting. However, due to the retrospective study design, it was difficult to ensure that the glucose measurements had been performed properly in all patients, which could be a significant limitation that impacted the results. Lastly, it was difficult to assess patients' compliance. Therefore, a well-designed prospective study with a large population and a long-term observation period should be conducted in the future.

Overall, in this study, we found an association between glycemic control in the first year of treatment and the development of complications in young patients with diabetes, using real-world data. This implies that physicians should aim for stricter control of glucose levels, especially in younger patients. In addition, a similar regimen for glycemic control could be used for young patients as well as other age groups. We also found that patients with YOD were more obese and had a higher prevalence of NAFLD. This should be taken into consideration when drafting policies concerning younger patients with diabetes; policies should focus on the improvement of lifestyle modifications as well as disease control. In the future, a prospective study should be used to validate our findings.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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AUTHOR CONTRIBUTIONS

Conception or design: H.B., J.Y.P., H.S.K. Acquisition, analysis, or interpretation of data: H.B., J.Y.P., H.S.K. Drafting the work or revising: H.B., J.Y.P., H.S.K. Final approval of the manuscript: H.B., J.Y.P., J.Y., J.L., Y.Y., J.H., S.H.L., J.H.C., D.J.L., H.S.K.

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