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Clinical Characteristics of Korean Patients with Youth-Onset Type 2 Diabetes Mellitus in Remission

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Background: Improving β-cell function can lead to remission in some patients with type 2 diabetes mellitus (T2DM). However, research on pharmacotherapy-induced remission in youth-onset T2DM remains scarce. Our study aimed to identify the clinical characteristics of pediatric patients who experience remission.

Methods: We retrospectively reviewed 88 pediatric patients with T2DM followed for at least 1 year at Seoul National University Bundang Hospital between 2013 and 2023. Remission was defined as a glycosylated hemoglobin (HbA1c) level less than 6.5% for at least 3 months after ceasing glucose-lowering pharmacotherapy.

Results: Among 88 patients (60 males, 68.2%) diagnosed at an average age of 14.4±2.1 years, 19 patients (21.6%) achieved remission after a median duration of 1.4 years. The remission group had a larger proportion of males (89.5% vs. 62.3%, $P=0.024$) and a lower urinary albumin-to-creatinine ratio (ACR) at diagnosis ($P=0.011$). They also showed lower HbA1c levels at 1 year and more significant changes in HbA1c and body mass index (all $P<0.05$). Higher urinary ACR levels correlated with a longer duration to achieve remission (hazard ratio, 0.928; $P=0.013$). In three of the 19 remission patients (15.8%), recurrence occurred after a median of 1.5 years.

Conclusion: Among Korean youth with T2DM, 21.6% achieved remission after a median duration of 1.4 years. Those who experienced remission were predominantly male, had lower ACR at diagnosis, and had significant weight loss within the first year. Further investigation into the factors influencing remission and long-term outcomes is essential.

Key words: Diabetes mellitus, type 2, Remission, Pediatric obesity

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a highly prevalent metabolic disorder characterized by progressive hyperglycemia due to declining β-cell function, insulin resistance, increased hepatic glucose production coupled with elevated glucagon levels, and reduced production of glucagon-like peptide-1.[1,2] Traditionally, management of T2DM has assumed that it is irreversible, focusing on glycemic control through lifestyle modifications and glucose-lowering pharmacotherapy.[3] However, recent studies have indicated poor long-term outcomes in pediatric patients with T2DM.[4,5] The pursuit of effective management strategies for T2DM has sparked interest in the concept of remission, which is defined as achieving and sustaining normal blood glucose levels without ongoing glucose-lowering therapy.[6] Advances in diabetes management have enabled some patients to normalize blood glucose levels using traditional or new drug classes, alongside lifestyle interventions or bariatric surgery.[7] An expert consensus statement from 2009 introduced the concept of remission, categorizing it into partial, complete, and prolonged remission based on duration.[8] Initial studies reported low spontaneous remission rates without specific interventions—1.7% in the USA and 1.6% in the UK.[9,10] Conversely, in a study involving intensive lifestyle modifications, a remission rate of 37.5% was reported,[11] whereas remission rates of 53% were obtained for children and ad-

olescents who underwent bariatric surgery and of 86% for adults.[12]

In 2021, a consensus report by the American Diabetes Association (ADA) introduced a simplified diagnostic criterion for T2DM remission as a glycosylated hemoglobin (HbA1c) level less than 6.5% at least 3 months after cessation of glucose-lowering pharmacotherapy.[13]

Current research based on these recent definitions of T2DM remission remains scarce, particularly that concerning remission rates and predictors after pharmacotherapy in pediatric patients. This study explores clinical characteristics and factors associated with remission in pediatric patients who meet the criteria for T2DM remission.

METHODS

Participants

We initially screened 143 children and adolescents newly diagnosed with T2DM between January 2013 and April 2023 according to ADA criteria at Seoul National University Bundang Hospital (SNUBH).[14] Of these patients, 55 were excluded due to less than 1 year of follow-up (n = 18), unclear initial clinical information (n = 30), or co-morbidity (n = 7). Consequently, 88 patients were included in this study (Fig. 1).

Measurements

Electronic medical records were retrospectively reviewed. Height was measured to the nearest 0.1 cm using a stadiometer, and weight was measured to the nearest 0.1 kg on an electronic scale. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Height, weight, and BMI were converted into standard deviation scores (SDS) based on 2017 Korean National Growth Charts.[15] Blood pressure was measured three times after participants had rested for at least 5 minutes in a seated position. Blood samples were collected following a 12-hour fast. Plasma glucose, serum insulin, triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), aspartate transaminase (AST), alanine aminotransferase (ALT), and HbA1c levels were determined using an automated analyzer. Lipid concentrations were measured when blood glucose levels stabilized after the initial T2DM diagnosis. The homeostatic model assessment of insulin resistance was calculated using the formula: fasting insulin (mIU/L) × fasting glucose (mg/dL)/405.[16] Urinary albumin was analyzed by enzyme-linked immunosorbent assay (ELISA; Thermo Fisher Scientific), and urinary creatinine was measured using an enzymatic colorimetric assay.

Definition of remission in type 2 diabetes mellitus

Remission of T2DM was defined as HbA1c level less than 6.5% (48 mmol/mol) for a minimum of 3 months without the use of glucose-lowering pharmacotherapy.[13]

Statistical analysis

All statistical analyses were performed using Stata version 18.0 (StataCorp.). Continuous variables are presented as mean ± standard

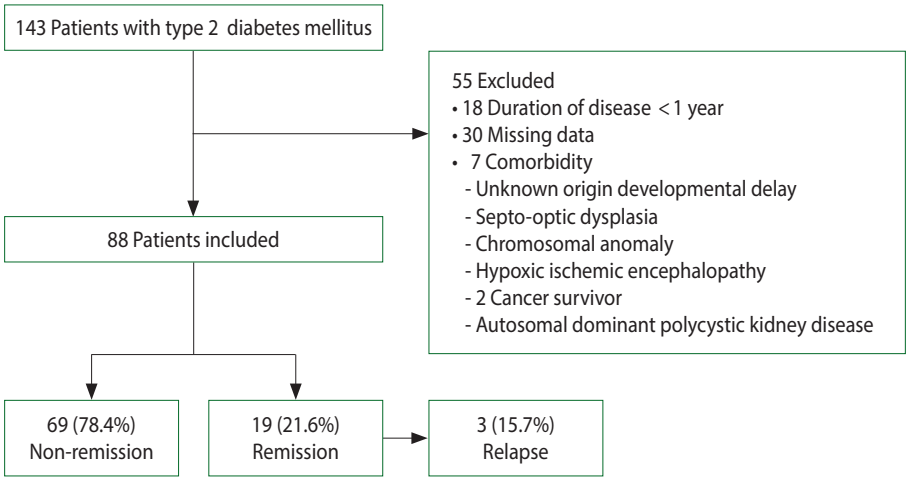

Figure 1. Flowchart of the study population.

deviation, while categorical variables are shown as count and percentage. Variables with skewed distributions were log-transformed for analysis and are reported as geometric mean ± standard error (SE). Comparisons between the remission and non-remission groups used Fisher's exact test for categorical variables, whereas Student's t-test, repeated measures analysis of variance (ANOVA), and a linear mixed model were used for continuous variables. Clinical characteristics in the remission group were analyzed at four time points: at the time of diagnosis, 3 months after diagnosis, 1 year after diagnosis, and at the time of remission. Cox regression analysis was used to evaluate prognostic factors for remission. A *P*-value less than 0.05 was considered statistically significant.

Ethics statement

This study was approved by the Institutional Review Board of SNUBH under protocol number B-2304-823-102. Informed consent was waived by the board.

RESULTS

Participant characteristics

Table 1 presents the baseline characteristics of the participants. Among the 88 patients (60 males and 28 females), the mean age at T2DM diagnosis was 14.4 ± 2.1 years, with a median follow-up duration of 3.2 years (range, 1.0 to 13.4). Nineteen (21.6%) patients achieved remission after a median of 1.4 years (range, 0.4 to 3.2) from diagnosis. The remission group had a larger proportion of males (89.5% vs. 62.3%, $P = 0.024$) and lower urinary albumin-to-creatinine ratio (ACR) (2.3 ± 1.2 mg/g vs. 9.9 ± 2.6 mg/g, $P = 0.011$) at diagnosis compared to the non-remission group. At 1 year post-diagnosis, HbA1c was significantly lower in the remission group than in the non-remission group (5.4% ± 0.5% vs. 6.8% ± 1.8%, $P = 0.002$). Considering the disparity in the number of male and female patients, baseline characteristics at diagnosis were compared (Supplementary Table 1). Although the overall metabolic profile did not differ significantly between the sexes, female patients exhibited significantly higher ACR levels at diagnosis. Changes in BMI and BMI SDS were also lower in the remission group at 3 months and 1 year after diagnosis compared to the non-remission group.

Among the 19 patients who achieved remission, three attained remission within the first year of treatment (at 4, 9, and 11 months). Three patients who achieved remission at 4, 15, and 16 months after diagnosis subsequently experienced relapse at 3, 38, and 18 months, respectively (Fig. 1). Blood glucose levels were maintained within the target range in two patients receiving triple oral hypoglycemic agents, whereas one patient achieved glycemic control through a combination of insulin and oral hypoglycemic agents. The median relapse-free duration for patients who achieved remission and was 1.0 year (range, 0.0 to 5.5). One patient who achieved remission continued to have proteinuria, necessitating the use of an angiotensin receptor blocker for 1 year post-remission.

Changes in clinical characteristics over time in the remission group

The clinical characteristics of the 19 patients who achieved remission were compared at diagnosis, 3 months after diagnosis, 1 year after diagnosis, and at the point of remission. Although not statistically significant, gradual decreases in weight SDS and BMI SDS were observed. HbA1c also demonstrated a gradual reduction over time. At the point of remission, HDL-C increased significantly compared to that at the time of diagnosis (39.4 ± 5.0 mg/dL vs. 46.3 ± 6.1 mg/dL, $P < 0.001$). Additionally, ALT levels decreased significantly at the point of remission compared to the time of diagnosis (52.0 ± 12.4 IU/L vs. 21.5 ± 2.8 IU/L, $P = 0.031$) (Table 2).

Body weight, BMI, and metabolic profiles of the remission and non-remission groups were analyzed using a linear mixed model at diagnosis, 3 months, and 1 year. The remission group had higher mean values for weight SDS, BMI, BMI SDS, and HbA1c compared to the other group, but these differences were not significant (all $P > 0.05$). However, over time, weight SDS ($\beta = -0.4$, SE = 0.1, $P = 0.001$), BMI ($\beta = -2.1$, SE = 0.6, $P = 0.001$), and BMI SDS ($\beta = -0.4$, SE = 0.1, $P = 0.002$) showed a significant decrease within the remission group. HbA1c also decreased significantly over time, with a more pronounced reduction observed in the remission group ($\beta = -1.6$, SE = 0.6, $P = 0.009$). Regarding lipid profiles, total cholesterol and LDL-C levels significantly decreased over time, whereas HDL-C levels increased (all $P < 0.05$). There was no significant difference in lipid changes between the groups over time (all $P > 0.05$). Additionally, there were no significant changes in C-peptide, insulin, AST, and ALT levels over time or between groups.

Table 1. Baseline characteristics of study participants

Characteristic	Total (n=88)	T2DM remission (n=19)	Non-T2DM remission (n=69)	*P*
At the time of diagnosis				
Age (yr)	14.4±2.1	14.5±1.4	14.3±2.3	0.765
Male sex	60 (68.2)	17 (89.5)	43 (62.3)	0.024
Weight SDS	1.7±1.0	2.0±1.0	1.6±1.0	0.130
BMI (kg/m^2)	27.0±5.6	29.0±5.0	26.5±5.6	0.078
BMI SDS	1.5±1.0	1.8±0.9	1.5±1.0	0.148
Systolic blood pressure (mmHg)	116.8±11.0	116.5±9.1	116.9±11.6	0.878
Diastolic blood pressure (mmHg)	65.9±9.4	63.8±9.2	66.4±9.5	0.300
Initial plasma glucose (mg/dL)	269.4±128.3	228.0±28.0	244.7±14.0	0.590
HbA1c (%)	11.0±2.4	11.2±2.4	11.0±2.3	0.720
C-peptide (ng/mL)*	3.6±0.3	3.5±0.6	3.6±0.3	0.852
Insulin (μIU/mL)*	15.7±1.6	12.1±3.1	17.0±1.9	0.172
Total cholesterol (mg/dL)*	175.5±5.7	158.1±8.6	180.8±6.9	0.087
LDL-C (mg/dL)	111.1±36.2	99.3±28.8	114.6±37.6	0.106
HDL-C (mg/dL)	41.1±14.8	39.4±5.0	41.6±16.7	0.564
Triglycerides (mg/dL)*	131.1±10.1	113.7±10.9	136.7±13.1	0.318
Uric acid (mg/dL)*	6.2±0.2	7.1±0.4	6.0±0.3	0.053
AST (IU/L)*	31.1±3.0	35.6±6.5	33.7±3.4	0.796
ALT (IU/L)*	48.3±5.2	52.0±12.4	47.3±5.7	0.718
Urinary albumin/creatinine ratio (mg/g)*	7.0±1.7	2.3±1.2	9.9±2.6	0.011
1st-degree relative family history	43 (50.0)	8 (42.1)	35 (52.2)	0.436
2nd-degree relative family history	60 (69.8)	15 (79.0)	45 (67.2)	0.324
DKA	7 (8.0)	1 (5.3)	6 (8.7)	0.624
Initial treatment (lifestyle modification only/ OHA only/insulin+OHA)	1/18/69 (1.1/20.5/78.4)	0/4/15 (0/21.1/79.0)	1/14/54 (1.5/20.3/8.3)	0.869
At 3 months of treatment				
HbA1c (%)	6.3±0.9	5.9±0.2	6.4±0.1	0.066
ΔHbA1c (%)	−4.7±2.5	−5.3±2.3	−4.6±2.5	0.304
ΔBMI (kg/m^2)	−0.06±2.0	−1.05±2.72	0.22±1.61	0.012
ΔBMI SDS	0.018±0.373	−0.19±0.43	0.08±0.34	0.053
At 1 year of treatment				
HbA1c (%)	6.5±1.7	5.4±0.5	6.8±1.8	0.002
Insulin (μIU/mL)*	15.7±1.6	12.1±3.1	17.0±1.9	0.172
C-peptide (ng/mL)*	3.5±0.2	3.8±0.3	3.4±2.7	0.461
HOMA-IR*	4.6±0.4	3.9±0.5	4.9±0.6	0.300
ΔHbA1c (%)	−4.5±2.8	−5.7±2.6	−4.2±2.8	0.033
ΔBMI (kg/m^2)	0.41±3.18	−1.20±3.29	0.86±3.02	0.012
ΔBMI SDS	0.02±0.60	−0.27±0.60	0.10±0.57	0.016

Values are presented as mean±standard deviation or number (%) except for log-transformed variables. Log-transformed for the analysis and expressed as geometric mean±standard error.
*Log-transformed values were used for the analysis.
T2DM, type 2 diabetes mellitus; SDS, standard deviation score; BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase; DKA, diabetic ketoacidosis; OHA, orally administered antihyperglycemic agent; HOMA-IR, homeostatic model assessment of insulin resistance.

Prognostic factors associated with T2DM remission

Univariate Cox regression analysis identified that an increase in BMI SDS 3 months post-diagnosis (hazard ratio [HR], 0.193; 95% confidence interval [CI], 0.069 to 0.538) and urinary ACR at diag-

Table 2. Clinical characteristics of study participants who achieved type 2 diabetes mellitus remission

Characteristic	At diagnosis	3 months after diagnosis	1 year after diagnosis	At remission	*P*
Weight (kg)	83.5±17.0	80.7±15.0	82.0±15.7	80.2±14.5	0.910
Weight SDS	2.0±1.0	1.8±1.0	1.7±1.0	1.4±0.8	0.303
Height (cm)	169.4±5.6	169.7±5.5	171.5±5.4	172.1±5.4	0.333
Height SDS	0.9±0.9	0.8±0.9	0.7±0.9	0.7±0.9	0.788
BMI (kg/m^2)	29.0±5.0	28.0±4.7	27.8±4.8	26.9±3.8	0.582
BMI SDS	1.8±0.9	1.6±0.9	1.6±1.0	1.5±0.9	0.736
HbA1c (%)	11.2±2.4	5.9±0.7	5.4±0.5	5.3±0.5	<0.001
C-peptide (ng/mL)*	1.2±0.7	1.2±0.4	1.3±0.3	1.0±0.4	0.387
Insulin (μIU/mL)*	12.1±3.1	15.7±2.0	16.3±1.9	14.1±1.5	0.603
Total cholesterol (mg/dL)*	158.1±8.6	157.2±6.3	165.5±6.6	157.8±5.9	0.818
LDL-C (mg/dL)	95.1±6.8	98.4±5.7	116.8±6.5	94.5±5.6	0.051
HDL-C (mg/dL)	39.4±5.0	42.8±6.4	47.7±8.0†	46.3±6.1†	<0.001
Non-HDL-C (mg/dL)*	117.3±8.6	118.4±7.2	98.6±4.5	113.1±6.1	0.111
Triglycerides (mg/dL)*	113.7±10.9	104.0±11.5	100.9±8.8	88.1±7.1	0.270
AST (IU/L)*	35.6±6.5	31.4±6.0	27.8±4.7	22.7±1.9	0.236
ALT (IU/L)*	52.0±12.4	39.3±9.5	30.7±7.2	21.5±2.8†	0.031
Urinary albumin/creatinine ratio (mg/g)*	2.3±1.2	-	5.2±1.7	4.5±1.0	0.271

Values are presented as mean±standard deviation except for log-transformed variables. Log-transformed for analysis and expressed as geometric mean±standard error. Urine microalbumin/creatinine ratio was excluded from statistical analysis because these variables were not measured at 3 months after diagnosis in most patients.
*Log-transformed values were used for the analysis; †$P<0.05$ compared to the time of diagnosis.
SDS, standard deviation score; BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine aminotransferase.

Table 3. Factors associated with type 2 diabetes mellitus remission

Prognostic factor	Univariate		Multivariate*	
	Hazard ratio (95% CI)	*P*	Hazard ratio (95% CI)	*P*
Age (yr)	1.021 (0.822–1.268)	0.854	-	-
Male sex	4.279 (0.988–18.524)	0.052	2.261 (0.495–10.328)	0.293
Initial BMI SDS	1.398 (0.880–2.222)	0.156	-	-
Increased BMI (kg/m^2) at 3 months	0.193 (0.069–0.538)	0.002	0.449 (0.143–1.412)	0.171
Initial insulin (μIU/mL)	1.005 (0.997–1.013)	0.246	-	-
Initial C-peptide (ng/mL)	1.025 (0.891–1.179)	0.728	-	-
Initial HbA1c (%)	1.021 (0.840–1.241)	0.834	-	-
HbA1c (%) at 3 months	0.506 (0.254–1.005)	0.052	0.457 (0.159–1.309)	0.145
Δ HbA1c (%) after 3 months of treatment	1.094 (0.906–1.320)	0.349	-	-
Total cholesterol (mg/dL)	0.990 (0.980–1.001)	0.056	0.995 (0.982–1.009)	0.500
LDL-C (mg/dL)	0.990 (0.976–1.003)	0.143	-	-
HDL-C (mg/dL)	0.985 (0.948–1.023)	0.438	-	-
Triglycerides (mg/dL)	0.997 (0.991–1.004)	0.388	-	-
Urinary albumin/creatinine ratio (mg/g)	0.931 (0.876–0.989)	0.020	0.928 (0.874–0.984)	0.013

*Multivariate analysis adjusted for age and BMI SDS.
CI, confidence interval; BMI, body mass index; SDS, standard deviation score; HbA1c, glycosylated hemoglobin; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

nosis (HR, 0.931; 95% CI, 0.876 to 0.989) were negatively associated with T2DM remission. Urinary ACR remained significant, with an HR of 0.928 (95% CI, 0.874 to 0.984) after adjusting for age and BMI SDS (Table 3).

DISCUSSION

Our study found that 21.6% of patients with youth-onset T2DM who underwent medical treatment achieved remission. The remission group had a larger proportion of males, lower urinary ACR at diagnosis, and exhibited more significant weight and BMI loss at 3 months and 1 year post-diagnosis compared to the non-remission group. Individuals who experienced remission showed favorable changes in HDL-C and ALT levels at the time of remission. We also identified urinary ACR at diagnosis as a prognostic factor associated with remission.

Observational studies have shown that the diabetes remission rate is low in the absence of intensive interventions.[9,10] A study in the United States involving 122,781 adults reported a 1.6% cumulative incidence of remission over a 7-year period. However, the remission rate was higher at 4.6% among individuals with early-onset T2DM (within 2 years of diagnosis).[9] According to the UK National Diabetes Audit, which covered 2,297,700 individuals diagnosed with T2DM, the general remission rate was only 1.7%. Among those diagnosed within 1 year, the rate increased to 3.3% and then to 8.3% among individuals who achieved a reduction in BMI.[10] Additionally, a high rate of diabetes remission was observed following intensive lifestyle modification.[11,17] The UK Diabetes Remission Clinical Trial (DiRECT) assessed the effectiveness of a low-energy diet in achieving T2DM remission compared to conventional care and found a significantly higher remission rate in the intervention group (46%) versus the control group (4%).[11] In our study of patients with youth-onset T2DM, the remission rate was higher than those observed in previous observational studies of the adult population. This is probably due to the relatively short duration since diagnosis and differences in criteria defining T2DM remission.

In several studies, weight reduction has consistently been associated with T2DM remission.[11,18] Remission rates increased with greater weight loss: 0% for those who gained weight, 7% for a 0–5 kg loss, 34% for a 5–10 kg loss, 57% for a 10–15 kg loss, and 86% for those who lost 15 kg or more.[11] In our research, we observed a significant reduction in BMI at 3 months and 1 year post-diagnosis in patients who achieved remission compared to those who did not. Weight loss, particularly visceral fat reduction, has been reported to play a crucial role in remission.[19] Taylor's twin cycle hypothesis, introduced in 2008, proposes that T2DM arises from a cycle of fat accumulation in the liver and pancreas.[20] Chronic excessive caloric intake leads to liver fat accumulation, resulting in elevated lipid levels in the bloodstream. This diminishes insulin production and sensitivity, triggering a cascade of events. Decreased insulin sensitivity enhances lipolysis, releasing more abundant free fatty acids and exacerbating pancreatic fat accumulation. Ultimately, this impairs β-cell function, perpetuating the T2DM cycle. Reducing excess fat in the liver and pancreas can often normalize hepatic glucose production and potentially redifferentiate β-cells.[21] In this retrospective study, changes in fat disposition were not evaluated. Therefore, further study is warranted to elucidate the mechanisms of remission.

In our study, lower urinary ACR levels at diagnosis were associated with a higher likelihood of remission. While overt proteinuria or kidney failure is rare in children and adolescents with type 1 diabetes mellitus (T1DM), those with T2DM may exhibit significantly elevated albuminuria at or shortly after diagnosis.[22] This suggests that prolonged exposure to hyperglycemia before diagnosis may lead to early onset of microvascular complications in T2DM, in contrast to T1DM. In this context, our patients with higher ACR levels at diagnosis may have been exposed to hyperglycemia for a longer duration before being diagnosed. Given that previous research identifies the duration of diabetes as a key predictor of remission, the correlation between ACR levels at diagnosis and remission could be attributed to impaired β-cell function recovery associated with disease duration.[23-25]

In our study, two patients relapsed after 1 year. All relapsed patients continued glucose-lowering therapy until the final follow-up, with their HbA1c remaining within the target range. Together, these results suggest that remission does not indicate permanent resolution. Furthermore, according to the 'legacy effect' or 'metabolic memory,' hyperglycemia appears to exert lasting effects on the body even after glucose levels normalize.[26] This can lead to microvascular complications. Therefore, continuous monitoring for relapse and complications is necessary even after remission is achieved.

This study has several limitations. First, due to the retrospective nature of our research and the relatively short follow-up period, we could not evaluate the long-term effects of remission in pediatric T2DM patients. Since T2DM remission does not imply complete resolution, long-term monitoring for potential relapse and diabetic

complications is essential.[13] Second, selection bias may have occurred as our study was conducted at a single tertiary center. Third, the relatively small number of patients who achieved remission could impact the statistical significance of our analysis. Finally, we were unable to analyze changes in β-cell function in the remission group due to the lack of dynamic studies, such as glucose tolerance tests to assess insulin secretion. Nevertheless, to the best of our knowledge, this is the first study to investigate remission in a pediatric population diagnosed with T2DM.

In conclusion, 21.6% of our patients with youth-onset T2DM experienced remission after initial medical and lifestyle interventions. Patients who achieved remission were predominantly male, exhibited lower ACR at diagnosis, and achieved greater weight reduction than those who did not achieve remission. Further prospective studies involving larger cohorts are warranted to validate these findings and advance the development of personalized interventions for pediatric patients with T2DM.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found online at https://doi.org/10.7570/jomes24042.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: SS and JK; acquisition of data: SS and SYK; analysis and interpretation of data: SS and SYK; drafting of the manuscript: SS, HYK, and JK; critical revision of the manuscript: SS, HYK, and JK; statistical analysis: SS and SYK; administrative, technical, or material support: SS and SYK; and study supervision: SYK and JK.

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