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# The Relationship Between Long-Term Glycemic Control and Partial Remission in Type 1 Diabetes: A Retrospective Study

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## ABSTRACT

**Aim:** Partial remission (PR) is a significant period in the early course of type 1 diabetes (T1D) with implications for diabetes management. We aimed to investigate whether long-term hemoglobin A1c (HbA1c) outcomes in T1D differed as a result of experiencing PR. We also analyzed the demographic and clinical factors that may influence long-term glycemic control.

**Material and Methods:** We retrospectively tracked the HbA1c values of 131 children and adolescents with T1D over a 5-year period. Patients were stratified into low (<7.5%) and high (≥7.5%) long-term HbA1c groups, and groups were compared using appropriate statistical procedures.

**Results:** Mean HbA1c±SD was 12.1±2.4% at diagnosis, 8.1±1.3% at 1 yr, 8.9±1.6% at 2 yr, 9.1±1.6% at 3 yr, 9.3±1.7% at 4 yr, and 9.5±1.4% at 5 yr from diagnosis. Of the patients, 87.8% had high long-term mean HbA1c levels. There were 75 remitters (%57.3). During follow-up, HbA1c levels were significantly lower in those with T1D who experienced PR than those who did not (8.9±1.3% vs. 9.6% ±1.6%, p=0.006). The group with low long-term HbA1c had higher fasting C-peptide levels at baseline than the higher HbA1c group [0.48 (0.12-1.4) ng/ml vs. 0.28 (0.05-1.5) ng/ml, p=0.048)]. They also had lower HbA1c levels at 3 months, 6 months, 9 months, and 12 months after diagnosis compared to the other group (p<0.001 or p=0.004).

**Conclusion:** Glycemic control was suboptimal throughout the follow-up period. After the first few months, HbA1c levels increased steadily through the first 2 years of T1D diagnosis but tended to stabilize in a "track" afterward. The trajectory of youth who experienced PR was lower than those who didn't. Understanding the HbA1c trajectory helps to identify opportunities for the intensification of T1D management to improve clinical outcomes.

***Keywords:*** *Type 1 diabetes, Partial remission, Glycemic control, Hemoglobin A1c*

# Tip 1 Diyabette Uzun Dönem Glisemik Kontrol ile Remisyon Dönemi Arasındaki İlişki: Retrospektif Bir Çalışma

## ÖZ

**Amaç:** Parsiyel remisyon (PR), tip 1 diyabet (T1D) tanısından kısa süre sonra izlenen ve diyabet yönetimine dair önemli etkileri olan bir süreçtir. T1D'de PR ile uzun dönem hemoglobin A1c (HbA1c) sonuçları arasındaki ilişkiyi araştırmayı amaçladık. Ayrıca uzun süreli glisemik kontrolü etkileyebilecek demografik ve klinik faktörleri de analiz ettik.

**Gereç ve Yöntemler:** T1D'li 131 çocuk ve adölesanın 5 yıllık takip süresindeki HbA1c düzeylerini retrospektif olarak değerlendirdik. Hastalar düşük (<%7,5) ve yüksek (≥%7,5) uzun dönem HbA1c gruplarına ayrılarak gruplar uygun istatistiksel yöntemlerle karşılaştırıldı.

**Bulgular:** Ortalama HbA1c±SD tanı anında %12,1±2,4; 1. yılda %8,1±1,3; 2. yılda %8,9±1,6; 3. yılda %9,1±1,6; 4. yılda %9,3±1,7 ve 5. yılda %9,5±1,4 idi. Hastaların %87,8'inde uzun dönem ortalama HbA1c düzeyleri yüksekti. 75 olguda (%57,3) parsiyel remisyon izlendi. Takip sırasında, PR izlenen T1D'lilerde HbA1c düzeyleri diğerlerine göre anlamlı olarak daha düşüktü (%8,9±1,3 ve %9,6 ±1,6; p=0.006). Düşük uzun dönem HbA1c grubu, yüksek HbA1c grubuna göre daha yüksek bazal açlık C-peptid seviyelerine sahipti [0,48

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(0,12-1,4) ng/ml ve 0,28 (0,05-1,5) ng/ml; p=0,048]. Ayrıca diğer gruba kıyasla tanıdan 3 ay, 6 ay, 9 ay ve 12 ay sonraki HbA1c seviyeleri de daha düşüktü (p<0,001 ya da p=0,004).

**Sonuç:** Glisemik kontrol takip süresi boyunca suboptimaldi. HbA1c seviyeleri, T1D teşhisi sonrası ilk 2 yıl boyunca (ilk birkaç aydan sonra) istikrarlı olarak arttı ancak daha sonra stabil seyretti. PR izlenen olguların izlemdeki HbA1c düzeyleri PR izlenmeyenlere göre daha düşüktü. T1D'de HbA1c seyrinin anlaşılması, klinik sonuçları iyileştirmek ve T1D yönetimini düzenlemek için imkânlar sunar.

***Anahtar Sözcükler:*** *Tip 1 diyabet, Parsiyel remisyon, Glisemik kontrol, Hemoglobin A1c*

## INTRODUCTION

Poor glycemic control, as reflected by hemoglobin A1c (HbA1c), is a strong predictor of chronic microvascular and macrovascular complications in individuals with type 1 diabetes (T1D) (1). Therefore, intensive glycemic control should be aimed at as early as possible in the course of T1D. Despite advances in diabetes care and management, many children and adolescents with T1D do not meet target HbA1c levels, and the frequency of hypoglycemia and diabetic ketoacidosis (DKA) remains intolerably high (2-4). The establishment of the cardiovascular disease risk in these children by understanding the trajectory of HbA1c can target interventions in the course of disease to reduce poor long-term glycemic control.

Partial remission (PR) is the early phase of T1D, where most individuals with new-onset T1D can achieve excellent glycemic control. With longer disease duration, glycemic control becomes more challenging. While greater residual beta-cell function is associated with more favorable short-term clinical outcomes (5,6), few previous studies have evaluated the impact of PR on the outcomes during the later phases of T1D. Poor glycemic control during the first few years of T1D in children is related to microalbuminuria and retinopathy on follow-up (7). HbA1c levels nearer to the diagnosis of T1D correlate with HbA1c levels in the subsequent years (8,9). This "glycemic tracking" in the natural history of childhood-onset T1D has not been fully understood (10).

Identifying factors early in the course of T1D that impact future glycemic control is an important research area. Although there are studies on factors associated with HbA1c in established T1D (11), limited studies have evaluated the impact of early glycemic control on long-term glycemic control in children and adolescents with T1D. A recent review identified only five longitudinal studies on this association (12). If a particular period during the initial phase of T1D could be determined, it will be possible to deliver intensified interventions and special care to children at risk of developing long-term complications.

In this article, we describe HbA1c outcomes in children with new-onset T1D over the first 5 years of diagnosis to understand the HbA1c trajectory in the course of the disease. In addition, we aimed to investigate whether the presence of PR influences long-term glycemic control in T1D, along with other factors.

## MATERIAL and METHODS

The study population consisted of 131 consecutive patients with T1D who were diagnosed from 2006 to 2019 at our clinic, had regular baseline visits throughout the first year (to determine the presence of PR), and were followed for at least two years from diagnosis.

### Ethics Committee Approval/Helsinki Declaration

The Institutional Review Board approved the study (Karadeniz Technical University Ethics Committee: 2022/159/2/24237859-460). All procedures were done in agreement with Helsinki declaration for studies on human subjects.

Demographic, clinical, and laboratory characteristic data were collected retrospectively from medical records. T1D was diagnosed according to the International Society for Pediatric and Adolescent Diabetes guidelines (13). Diabetic ketoacidosis at diagnosis was determined as blood glucose >200 mg/dL, venous pH <7.3 or bicarbonate <15 mmol/L, and presence of ketonemia or ketonuria. PR was defined by the gold standard insulin dose-adjusted HbA1c (IDAA1c) of ≤9 as recommended and calculated using the formula: IDAA1c=A1c (%) + [4xinsulin dose (U/kg/day)] (14). Age, body mass index (BMI), pubertal status, glycemia, pH, fasting C-peptide level, and T1D-associated antibodies, including glutamic acid decarboxylase, islet cell, and anti-insulin, were examined at T1D onset. BMI standard deviation scores (SDSs) were calculated according to Turkish child growth reference data using an online calculator program (http://www.childmetrics.org) (15). Longitudinal HbA1c levels were measured at baseline and each subsequent visit every three months. Daily insulin dose (unit/kg/day) was recorded at 3, 6, 9, and 12 months and yearly afterward. If patients left follow-up, the data until the last clinic visit were included in the analysis. On average, %75 of all patients had follow-up measurements until 5 years after diagnosis. The average HbA1c was calculated during

each of the 5 years after diagnosis, and a further long-term average was calculated for the follow-up period (excluding the first year). A timeline of five years after diagnosis was selected following the ADA recommendation to screen for complications in children with T1D either at the start of puberty or 4-5 years after diagnosis (16). HbA1c was measured by spectrophotometric method, and C-peptide levels were estimated by electrochemiluminescence (ECLIA). The presence of diabetes autoantibodies was determined by chemiluminescence immunoassay (CLIA).

### Statistical Analyses

The main outcome of interest was tracking of early glycemic control based on HbA1c measurements with the study population's mean HbA1c level at baseline and follow-up. A further primary outcome was the difference in long-term HbA1c levels between the remitters and non-remitters. The American Diabetes Association recommended an HbA1c target of <7.5% for children with T1D until recently (17). Thus, patients were further stratified into the low HbA1c (mean long-term follow-up HbA1c <7.5%) group and the high HbA1c group (mean long-term follow-up HbA1c ≥7.5%). We further compared the characteristics between these two groups using a t-test or Mann-Whitney U test for continuous variables and chi square test for categorical variables. A test of normality was conducted with the Kolmogorov-Smirnov test. IBM SPSS Statistics for Windows, version 24 (IBM Corp., Armonk, N.Y., USA) was used for statistical analysis. The differences were considered statistically significant with a p-value <0.05. Power of the study based on normal approximation was 74.7% and normal approximation with continuity correction was 64.6% (18).

## RESULTS

At diagnosis, the mean±SD age of the patients was 8.4±3.9 yr, 56% were male, mean±SD HbA1c was 12.1±2.4%, 16% of participants were overweight or obese (BMI≥85th percentile), and 45% presented in DKA. There were 75 remitters (57.3%). Of the participants, 77% were positive for at least one diabetes autoantibody. While most participants (81%) were taking multiple daily insulin injections, the others were on a twice-a-day insulin regimen. The sample was followed for up to 16 years (mean±SD, 5.6±2.5) after diagnosis, with an average number of 14 HbA1c measurements after the first year of diabetes onset. In the yearly analysis, mean HbA1c declined at 1 yr postdiagnosis, with a slight and steady rise afterward. HbA1c mean±SD at 1, 2, 3, 4, and 5 years after diagnosis were as follows: 8.1±1.3% at 1 yr, 8.9±1.6% at 2 yr and 9.1±1.6% at 3 yr, 9.3±1.7% at 4 yr, 9.5±1.4% at 5 yr, respectively. Accordingly, median (minimum-maximum) insulin dose was gradually increased over the 5 years of diagnosis; 0.46 U/kg/day (0-1), 0.6 U/kg/day (0.1-1.4), 0.7 U/kg/day (0.2-1.6), 0.8 U/kg/day (0.2-1.4), 0.85 U/kg/day (0.2-1.5). In the monthly analysis, mean HbA1c was highest at diagnosis and lowest at 3 months post-diagnosis, with an upward trajectory starting afterward, continuing until 24 months, and remaining relatively stable for the remainder of the follow-up period (Figure 1).

Mean HbA1c at long-term follow-up was <7.5% for only 12.2% of participants. The characteristics of the study population by mean long-term follow-up HbA1c level are shown in Table 1. The group with low long-term HbA1c had higher fasting C-peptide levels at baseline than the higher HbA1c group [0.48 (0.12-1.4) ng/ml vs. 0.28 (0.05-1.5), p=0.048)]. They also had lower HbA1c levels at 3 months, 6 months, 9 months, and 12 months after diagnosis compared to the other group (p<0.001 or p=0.004). Insulin requirement during the first year was not associated with long-term HbA1c levels (p>0.05 for all). Patients with low long-term HbA1c were more likely to be pubertal than the higher HbA1c group (62.5% vs. 34.8%, p=0.032) and presented more frequently with DKA at diagnosis (68.8% vs. 41.7%, p=0.042).

During long-term follow-up, HbA1c levels (long-term average) were significantly lower in those with T1D who experienced PR vs. those who did not (8.9±1.3% vs. 9.6%±1.6%, p=0.006). Remitters were more likely to achieve an overall low mean long-term follow-up HbA1c level than non-remitters (18.7% vs. 3.6%, p=0.009). The trajectory of HbA1c differed by remission status over the study period (Figure 2). Mean HbA1c was similar at diagnosis between remitters and non-remitters, and both groups experienced an increase in HbA1c from 3- 6 months after diagnosis. However, HbA1c became significantly lower in the remitters from 3 to 27 months and remained non-significantly lower after that, with the mean difference in HbA1c levels between

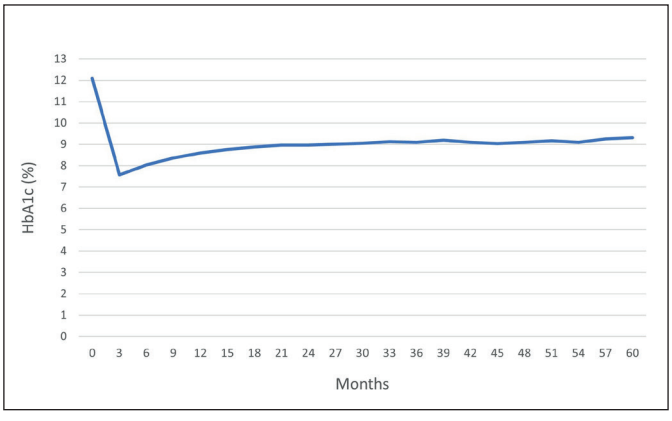


**Figure 1.** HbA1c trajectory of the study population.

**Table 1:** The characteristics of the study population stratified by mean long-term follow-up HbA1c level.

| | Low HbA1c | High HbA1c | p |
|---|---|---|---|
| **Gender** | | | 0.623 |
| Female | 8 (13.8) | 50 (86.2) | |
| Male | 8 (11) | 65 (89) | |
| **Puberty** | | | **0.032** |
| Prepubertal | 6 (7.4) | 75 (92.6) | |
| Pubertal | 10 (20) | 40 (80) | |
| **Diabetic ketoacidosis** | | | **0.042** |
| No | 5 (6.9) | 67 (93.1) | |
| Yes | 11 (18.6) | 48 (81.4) | |
| **Age** (yr) | 10.1±5.2 | 8.1±3.7 | 0.157 |
| **Body mass index SDS** | -0.4±1.5 | -0.4±1.4 | 0.951 |
| **pH** | 7.26 (7.04-7.41) | 7.33 (6.87-7.5) | 0.185 |
| **C-peptide** (ng/ml) | 0.48 (0.12-1.4) | 0.28 (0.05-1.5) | **0.048** |
| **Presence of autoantibodies** | | | 0.761 |
| No | 4 (13.3) | 26 (86.7) | |
| Yes | 12 (11.9) | 89 (88.1) | |
| **Overweight/obese** | | | 0.467 |
| No | 15 (13.6) | 95 (86.4) | |
| Yes | 1 (4.8) | 20 (95.2) | |
| **Remission** | | | **0.009** |
| No | 2 (3.6) | 54 (96.4) | |
| Yes | 14 (18.7) | 61 (81.3) | |
| **Insulin treatment** | | | 0.510 |
| Multiple daily doses | 12 (11.3) | 94 (88.7) | |
| Twice a day | 4 (16) | 21 (84) | |
| **Total daily insulin dose** (U/kg/day) | | | |
| At discharge | 0.58±0.33 | 0.53±0.23 | 0.472 |
| After 3 months | 0.42±0.21 | 0.44±0.18 | 0.719 |
| After 6 months | 0.48±0.21 | 0.47±0.2 | 0.873 |
| After 9 months | 0.47±0.23 | 0.52±0.2 | 0.323 |
| After 12 months | 0.49±0.23 | 0.57±0.21 | 0.168 |
| Year 1 | 0.48 (0-0.8) | 0.45 (0.05-1) | 0.675 |
| Year 2 | 0.5 (0.1-0.9) | 0.6 (0.1-1.4) | 0.359 |
| Year 3 | 0.5 (0.2-0.85) | 0.7 (0.2-1.6) | **0.021** |
| Year 4 | 0.7 (0.15-1.1) | 0.8 (0.2-1.4) | 0.335 |
| Year 5 | 0.75 (0.2-1.15) | 0.85 (0.38-1.45) | 0.150 |
| **HbA1c** | | | |
| At diagnosis (%) | 11.8±2.1 | 12.2±2.5 | 0.607 |
| After 3 months (%) | 6.7±0.9 | 7.7±1.3 | **0.004** |
| After 6 months (%) | 6.6±0.9 | 8.2±1.6 | **<0.001** |
| After 9 months (%) | 6.6±0.7 | 8.6±1.8 | **<0.001** |
| After 12 months (%) | 6.8±0.7 | 8.9±1.6 | **<0.001** |

Data presented as number (%) or mean±standard deviation or median (minimum-maximum).

the two groups decreasing over time. Outcomes of remitters and non-remitters are presented in Table 2. Median insulin doses of patients who didn't experience PR were also higher than those who experienced PR, until year 5.

## DISCUSSION

This study presents real-world data on HbA1c trajectory in children with T1D followed from the onset of T1D and reports characteristics associated with glycemic control over 5 years following diagnosis. Following the first few

**Table 2:** Outcomes of the study population stratified by remission status.

| | Remission | No remission | p value |
|---|---|---|---|
| **Total daily insulin dose** (U/kg/day) | | | |
| Year 1 | 0.4 (0-0.9) | 0.5 (0.15-1) | **0.006** |
| Year 2 | 0.5 (0.1-1.2) | 0.65 (0.3-1.4) | **<0.001** |
| Year 3 | 0.6 (0.2-1.1) | 0.8 (0.35-1.6) | **<0.001** |
| Year 4 | 0.75 (0.15-1.4) | 0.8 (0.35-1.3) | **0.009** |
| Year 5 | 0.83 (0.2-1.45) | 0.85 (0.38-1.2) | 0.525 |
| **HbA1c** (%) | | | |
| Year 1 | 7.5±1 | 9.1±1.2 | **<0.001** |
| Year 2 | 8.6±1.6 | 9.5±1.8 | **0.004** |
| Year 3 | 8.9±1.5 | 9.5±1.4 | **0.033** |
| Year 4 | 9.1±1.8 | 9.7±1.6 | 0.130 |
| Year 5 | 8.9±1.6 | 9.6±1.4 | 0.073 |

Data presented as mean±standard deviation or median (minimum-maximum).

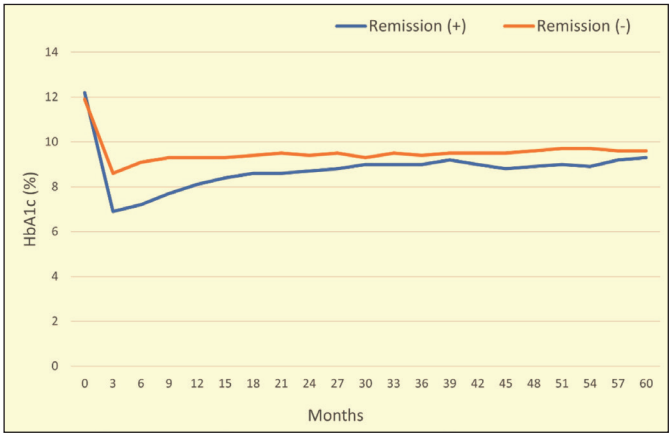


**Figure 2.** HbA1c trajectories of remitters and non-remitters.

months of T1D, which includes PR period, a deterioration in glycemic control starts by 6 months, and target HbA1c levels are surpassed. This trajectory is consistent with prior reports from other countries (19,20). We also found that PR in the first year of T1D is associated with better glycemic control over time. Both groups' initial low and high HbA1c levels "track" in their respective tracks during long-term follow-up.

The American Diabetes Association (ADA) and the International Society for Pediatric and Adolescent Diabetes (ISPAD) recommend a target HbA1c of <7.5% and <7% for children and adolescents with T1D, respectively (21,22). Previous studies have shown that children with T1D exceed this target in the first few years, and clinically meaningful and lasting HbA1c improvement rarely occurs after 5 years of T1D (10,19,20,23). In a recent meta-analysis on long-term glycemic control, all studies reported sub-optimal estimated mean glycemic control during the 10-year follow-up period (12). Furthermore, glycemic control worsens as youth progress through adolescence and adulthood (3,24). Our observations extend on these results, demonstrating the trajectory of glycemic control over time by PR status.

Limited studies report that the overall glycemic control settles in a "track" after 6 months of diagnosis (12,25). Additionally, early glycemic control tracks in its respective tract during long-term follow-up in the initial low and high HbA1c groups (26). A large Swedish cohort study reported that children with higher early mean HbA1c levels of ≥8.7% 3 to 15 months after diagnosis of T1D were more likely to develop albuminuria and retinopathy in early adulthood (27). In contrast, some authors suggest that as the clinical outcome of T1D during the first year is characterized by residual beta-cell function and PR, it may not correlate with the trajectory of long-term glycemic control (28,29). Our data provide strong evidence that PR in T1D is not just an acute benefit in the early stages of clinical disease but also a predictive factor for long-term glycemic control.

A significant proportion of children and adolescents diagnosed with T1D experience PR (30). PR is identified by partial residual beta-cell recovery with improved endogenous insulin secretion and insulin sensitivity (31). A similar longitudinal HbA1c pattern throughout the first 5 years of diagnosis was observed in both remitters and non-remitters. As expected, both groups reached their lowest HbA1c 3 months after diagnosis, followed by deterioration of glycemic control occurring across all patients irrespective of remission status. However, the mean HbA1c of children who experienced PR remained lower than those who didn't experience PR throughout the 5 years of diabetes diagnosis. Some authors have suggested presenting non-remission as an independent clinical entity with significantly poorer long-term outcomes than PR (31). Similar to our results, Yazidi et al. have shown that the occurrence of remission defined by an HbA1c <6.5% with a daily insulin dose <0.5 IU/kg/day in adolescents and young adults with newly diagnosed T1D is associated with better glycemic control and lower insulin requirements during the first 5 years of follow-up (32). Niedzwiecki et al. reported that the absence of remission was associated with the occurrence of chronic complications of diabetes at a seven year follow-up in young adults (33). Our results will contribute to the basis for recommendations for early detection and monitoring of PR in children and adolescents with T1D to prevent long-term microvascular and macrovascular complications.

The relationship between greater beta-cell function and improved glycemic control provides the basis for research that aims to preserve beta-cell function to prevent long-term complications of diabetes (34). C-peptide, a

surrogate marker of residual beta-cell function, improves microvascular blood flow and endothelial function through endothelial nitric oxide (35). Mortensen et al. (14) demonstrated that an IDAA1c value ≤9.0, the criterion used to define PR in the present study, corresponds to a predicted stimulated C-peptide >300 pmol/L. Residual beta-cell function in patients with T1D has been linked to a reduced risk of severe hypoglycemia (36), development of diabetic retinopathy (37), and improvement in long-term glycemic control (5). Therefore, the long-term prognostic advantage of remitters over non-remitters should be considered during the early phase of diabetes management to search for specified strategies to prevent early dysglycemia in non-remitters.

It is essential to study the demographic and clinical factors that lead to the deterioration of glycemic control over time to develop strategies to improve diabetes care in individuals with T1D. In line with our findings, it was shown that lower fasting C-peptide levels at baseline predicted higher HbA1c levels over time (29). Despite the known association between age and better short-term clinical outcomes (38), in this study, age was not related to long-term glycemic control, which is contrary to studies in established T1D, which found that adolescence is related to higher HbA1c (39) but is similar to others (28,34). However, we demonstrated that puberty at diagnosis was associated with lower long-term HbA1c. This finding could be explained by the possible association of puberty with C-peptide levels (40). The frequency of DKA at diagnosis was moderately similar to that reported in previous studies (41,42) . In contrast to our results, Duca et al. reported that DKA at diagnosis of T1D in children predicts poor long-term glycemic control, independently of established risk factors (43). This discrepancy may be related to the limited number of patients with low HbA1c in our study. However, it could be speculated that an experience of a severe presentation of T1D at diagnosis may have led to more careful and vigilant management of the disease by patients and their families. Additionally, several studies could not find a difference in long-term prognosis between the DKA and non-DKA groups (44,45).

We were unable to analyze psychological and socioeconomic factors that may impact treatment adherence, and 75% of the participants have completed the entire five year-follow-up duration. This study, however, has significant strengths. First, tracking of early glycemic control has been evaluated comprehensively within the context of the occurrence of PR. In our study, HbA1c levels were measured during standardized clinical visits for up to 16 years after diagnosis, allowing for a precise analysis of the relationship between PR and long-term glycemic control.

In conclusion, most children with T1D exceed the HbA1c target of <7.5% by 6 months after diagnosis, which may be an ideal time to inform families about the disease course, glucose trends, and insulin doses in the upcoming months. The overall glycemic control stabilizes in a "track" during the first few years of T1D, and this period may provide an opportunity to intensify management. Furthermore, HbA1c levels at baseline related to PR status also seem to have metabolic memory, which shows glycemic "tracking" during the 5-year follow-up. It is crucial to understand the unique disadvantages of non-remitters to ensure the institution of intensive glycemic control very early in the course of the disease, as this may translate into improved glycemic control over time.

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None.

**Author Contributions**

All authors contributed to the study conception and design. Material preparation and data collection were performed and analyzed by **Emine Ayça Cimbek, Semiha Bekfilavioğlu,** and **Gülay Karagüzel.** The first draft of the manuscript was written by **Emine Ayça Cimbek,** and all authors commented on previous versions of the manuscript. All authors have read and approved the final manuscript. All agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

**Conflicts of Interest**

The authors have no conflicts of interest to declare that are relevant to the content of this article.

**Financial Disclosure**

No funding was received for conducting this study.

**Ethical Approval**

The Institutional Review Board approved the study (Karadeniz Technical University Ethics Committee: 2022/159/2/24237859-460). All procedures were done in agreement with Helsinki Declaration for studies on human subjects.

**Peer Review Process**

Extremely peer-reviewed and accepted.

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