# Factors Influencing Frequency and Duration of Remission in Children and Adolescents Newly Diagnosed with Type 1 Diabetes

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: This study aimed to determine the frequency and duration of remission in children and adolescents newly diagnosed with type 1 diabetes and to investigate factors associated with these parameters.

Material/Method: Fifty patients newly diagnosed with T1DM were followed for 1 year. Daily insulin requirement of less than 0.5 U/kg/day dose when the HbA1c value is less than 8% was regarded as partial remission. Patients were grouped according to their remission duration. Clinical and laboratory characteristics of the remission groups and non-remission groups were compared to find factors influencing remission and to investigate their contribution to the duration of remission.

Results: Remission was observed in 24 (48%) out of 50 patients included in the study. Remission frequency was found to be associated with age, sex, and puberty. Longer duration of remission was more frequent in the younger age group, in pre-pubertal stage, and in male patients. Daily insulin dose and basal insulin requirement of those who went into remission was found to be significantly lower than in the other patients at discharge.

Conclusions: Decreased daily total and basal insulin requirement at discharge are valuable in predicting remission. The remission process in type 1 diabetes still has many characteristics that need to be clarified. Therefore, more extensive studies are needed.

MeSH Keywords: **C-Peptide • Diabetes Mellitus, Type 1 • Remission, Spontaneous**

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## Background

Type 1 diabetes (T1DM) is a clinical condition caused by autoimmune β cell destruction induced by environmental factors in individuals with a genetic predisposition. Indications and symptoms of diabetes become apparent after 90–95% residual β cell mass destruction [1]. Some patients present with severe metabolic decompensation and diabetic ketoacidosis, while others present with mild ketosis and hyperglycemia. This is closely related with the residual β cell mass [2]. For some patients, endogenous insulin secretion tends to continue for a while after the diagnosis. Insulin, fluid and electrolyte treatment corrects metabolic decompensation. With this treatment, many patients start to secrete endogenous insulin again. Thus, exogenous insulin requirement is decreased and even completely eliminated in some patients. This situation is called the remission or "honeymoon" period [3–5]. While there is agreement on the complete remission definition, no agreement exists on the definition of partial remission. Generally accepted approach includes the definitions based on daily insulin requirements and/or HbA1c levels. There are various factors affecting the function of residual β cells and, consequently, the frequency and duration of remission. These factors are diagnosis age, sex, pubertal stage, body mass index (BMI), symptoms before diagnosis and duration of these symptoms, ketoacidosis present at diagnosis, diabetes-related autoantibody-positive profile, and HLA tissue type [6–8]. Although factors affecting the remission are known, the results differ according to different studies. In this study we investigated the status of these remission-related factors. In addition to those factors, we evaluated the association between remission rate and c-peptides and stimulated c-peptide levels. Unlike other studies, we also evaluated the association between remission rate and the dosage of insulin given at discharge.

Additionally, evaluation of the functions of residual β cells provide important information about the disease prognosis. Endogenous insulin secretion provides better metabolic control, enabling delay of long-term diabetes complications [9,10].

The objective of this study was to investigate the frequency of remission in children and adolescents with newly diagnosed T1DM, and to determine factors associated with remission and their contribution to the duration of remission.

## Material and Methods

The study was conducted in the Pediatric Endocrinology Department of Ankara Children's Hematology and Oncology Research and Teaching Hospital from 1 February 2011 to 28 February 2013. Patients diagnosed with T1DM who had received their first treatment and care in our hospital and
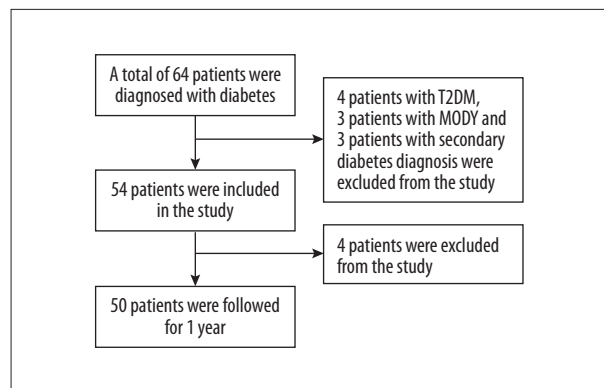


**Figure 1.** Flow chart of patients enrolled in the study.

who have been regularly followed were included in the study. We excluded patients who refused to participate, patients who did not show up for follow-up visits, patients with T2DM, patients with monogenic diabetes (MODY), patients with syndromic diabetes (e.g., Down-Turner, Prader-Willi, and Klinefelter syndromes), patients with secondary diabetes (diabetes developed secondary to an existing chronic disease or due to the medication use), and patients with neonatal diabetes. A total of 50 patients included in the study were followed for 1 year (Figure 1).

Age, sex, pubertal stage, BMI, time to diagnosis, and diabetes symptoms (e.g., polyuria, polydipsia, polyphagia, and weight loss) of patients at diagnosis were noted. Hyperglycemia (blood sugar >300 mg/dl), metabolic acidosis (pH <7.3 and/or HCO3 <15 mEq/L), and ketonemia/ketonuria (total body ketone bodies <4 mmol/L) results were interpreted as diabetic ketoacidosis [11]. Diabetic ketoacidosis levels were defined as: severe pH <7.10, moderate DKA pH 7.10–7.20, and mild DKA pH 7.20–7.30. Hyperglycemia and ketonemia without acidosis was defined as diabetic ketosis, and presence of high blood sugar (>200 mg/dl) was defined as hyperglycemia [12]. Intravenous treatment duration was determined according to clinical presentation (e.g., hyperglycemia, ketosis, ketoacidosis). Basal and stimulated c-peptide levels were evaluated in order to assess residual β-cell function at baseline (at the time of diagnosis), $3^{rd}$, $6^{th}$, and $12^{th}$ month. Glucagon was used to stimulate c-peptide secretion. Initial basal and stimulated c-peptide levels were evaluated after the acidosis had resolved and subcutaneous insulin therapy had been initiated. At the $3^{rd}$, $6^{th}$, and $12^{th}$ months of the outpatient clinic controls, stimulated c-peptide levels were evaluated after 8–10 hours of fasting and before the morning insulin treatment. According to the test procedure, c-peptide levels were measured at time zero and 6 min after 1 mg intravenous glucagon was given. Samples were preserved below 0°C and analyzed by radioimmunoassay (ECLIA) method with the C6000 instrument. The c-peptide levels were defined in terms of ng/ml.

Insulin requirements of patients are expressed in U/kg/day at diagnosis and at months 3, 6, 9, and 12. Metabolic control levels of patients were determined with HbA1c levels analyzed at diagnosis and at months 3, 6, 9, and 12.

Daily insulin requirement less than 0.5 U/kg/day dose when HbA1c value is less than 8% was regarded as partial remission (PR) [7] and requiring no insulin during follow-up was regarded as complete remission (CR) [13]. Patients were grouped according to their remission duration: shorter than 3 months, 3–6 months, 6–9 months, and 9–12 months. Clinical and laboratory characteristics of the remission groups and non-remission groups were compared to find factors influencing remission and to investigate their contribution to the duration of remission. The first assessment was made when they were first diagnosed to have diabetes, at time zero. At 3, 6, and 12 months after the discharge, HbA1c levels were measured and insulin requirements were assessed. Patients were grouped into a remission groups and a non-remission group). Retrospectively, patients were compared with clinical and laboratory characteristics at the time of initial diagnosis and at 3, 6, and 12 months.

### Statistical evaluation

Findings were evaluated using SPSS for Windows Version 11.5.0 (SPSS, Chicago, IL, USA). Data are presented as mean ± standard deviation (SS), and graphics for follow-up results are expressed as mean and standard error in 95% confidence interval.

We used the *t* test to compare means of 2 numeric variables from normally distributed data and the Mann-Whitney U test was used to compare numeric variables from non-normally distributed data. Comparison of nonnumeric variables was done using the chi-square test. One-way ANOVA test (post hoc Bonferroni) was used to compare more than 2 variables. P value of <0.05 was considered as significant.

### Ethical considerations

The study protocol was approved by the Ethics Committee of Ankara Children's Hematology and Oncology Research and Teaching with its decision date and number 2012/004. This study was conducted in accordance with the principles of the Declaration of Helsinki and the Good Clinical Practices Guidelines.

## Results

We enrolled 50 patients with T1DM (26 females and 24 males). There were 30 pre-pubertal patients in the study and the mean age at diagnosis was 8.75±4.15 years. Remission was observed in 24 (48%) out of 50 patients included in the study. PR was observed in 22 (44%) of the patients who went into remission, whereas CR was observed in 2 patients (4%). Fifteen of the male patients and 9 of the female patients went into remission, and the frequency of remission of male patients was higher (p=0.04). When mean age distribution of each group was reviewed, the mean age of the remission group was found to be younger (p=0.02). Similarly, the remission rate in the pre-pubertal group was higher in comparison to the pubertal group (p=0.01). No significant difference was found in pre-diagnosis symptom duration, weight loss, IV treatment duration, or BMI of the patients who went into remission compared with those who did not. Although it was observed that the non-remission group presented with more DKA and their DKA levels were moderate/severe, no statistically significant difference was found in the clinical characteristics between the groups at presentation (Table 1). No significant difference was found between the laboratory findings of the remission group and non-remission group. No significant difference was detected in the diabetes autoantibody profile of patients who went into remission and patients who did not. No significant difference was found in positive autoantibody levels and no difference was observed between tissue groups.

Daily total insulin requirements of patients who went into remission were significantly lower at discharge compared to those who did not (p<0.001). Patients with newly diagnosed type 1 diabetes are hospitalized for approximately 7 to 10 days. During this time, insulin dosage was regulated and patient education about diabetes was given. The duration of this period differs according to patient condition. Basal insulin requirement and the percentage of basal insulin to daily total insulin dose was also found to be significantly lower in the remission group (p<0.04 and p<0.001, respectively) (Table 2). Mean HbA1c levels of both groups were found to be similar during 1-year follow-up. No significant difference was found between the 2 groups in basal and stimulated c-peptide levels measured every 3 months during remission.

When patients who went into remission were grouped according to their remission periods (shorter than 3 months, 3–6 months, 6–9 months, and 9–12 months), we observed that those who had remissions of 6 months and longer were mostly males (p=0.027). When the duration of remission was evaluated according to pubertal stage, the duration of remission of the pre-pubertal group was longer (p=0.004). Nonetheless, no statistically significant differences were found in BMI, weight loss, symptom duration, clinical characteristics at presentation, DKA level, IV treatment durations, laboratory findings, diabetes autoantibody-positive, positive antibody count, tissue groups, or duration of remission.

**Table 1.** Demographics and clinical characteristics of the patients enrolled in the study at diagnosis.

| | | Remission (+) | Remission (–) | p* |
|---|---|---|---|---|
| Number of patients [n (%)] | | 24 (48%) | 26 (52%) | |
| Gender | Male | 15 (63%) | 9 (35%) | 0.04 |
| | Female | 9 (37%) | 17 (65%) | |
| Age (years) | | 7.43±3.50 | 9.97±4.40 | 0.02 |
| Pubertal stage | Pubertal | 5 (21%) | 15 (58%) | 0.01 |
| | Prepubertal | 19 (79%) | 11 (42%) | |
| BMI (kg/m²) | | 14.73±2.16 | 15.59±2.26 | 0.17 |
| Weight loss | Yes | 16 (67%) | 15 (58%) | 0.55 |
| | No | 8 (33%) | 11 (42%) | |
| Symptom durations (day) | | 41.20±12.75 | 28.50±4.70 | 0.33 |
| Clinical characteristics at presentation | DKA | 10 (42%) | 17 (65%) | 0.15 |
| | Ketosis | 7 (29%) | 5 (19%) | |
| | Hyperglycemia | 7 (29%) | 4 (16%) | |
| DKA level | Mild | 3 (13%) | 3 (12%) | 0.33 |
| | Moderate | 4 (16%) | 7 (27%) | |
| | Severe | 3 (13%) | 7 (27%) | |
| IV treatment duration (hour) | | 13.10±11.44 | 15.19±10.51 | 0.51 |

**Table 2.** Insulin requirements of patients at discharge.

| | Remission (+) | Remission (–) | p* |
|---|---|---|---|
| Total insulin requirement (unit/kg/day) | 0.63±0.40 | 1.03±0.28 | <0.001 |
| Basal insulin requirement (unit/kg/day) | 0.16±0.12 | 0.29±0.09 | <0.001 |
| The percentage of basal insulin dose to total insulin dose ratio (%) | 24.80±9.38 | 28.85±7.15 | <0.04 |

## Discussion

We found that 48% of the 50 patients with T1DM in our study went into remission. There are many studies in the literature that have identified factors influencing the frequency and duration of remission in T1DM [2–5,9,14,15]. While the frequency of remission in children with type 1 diabetes is reported to be 11–80%, it is reported to be 30–61% in adults with type 1 diabetes. The reason for this is the use of different diagnostic criteria for PR [2–4,7,13,15].

CR at 1 month and 2 months was observed in 2 patients (4%); 1 was 13 years 10 months old and the other was 3 years 8 months old. No significant determining factor was found in the patient who went into complete remission, except that both were male. It is reported in the literature that complete remission is rare in children (0–3.2%). Abdul Rasoul et al. reported

complete remission in 3 patients (a 6-year-old male, a 10-year-old male, and a 1-year-old female), and the mean duration of complete remission was 112.4±29.7 days. No determining factor was found in these patients who went into complete remission [16]. Similarly, Schölin et al. observed complete remission in 5 patients (6%) in their study of 62 adults with T1DM, and they noted that all of these patients had short symptom durations [4].

Studies have shown that T1DM age of onset affects the frequency and duration of remission. However, studies on the relationship between partial remission and age indicate varied results due to using different methods. Some studies reported that the frequency of PR in children younger than 5 years was lower [7,16–18]. A study conducted in Finland with 745 young children and adolescents observed that the rate of partial remission in children younger than 2 years was far lower than

in the other older age groups [2]. A similar study reported no remission for those younger than 2 years, while the rate of remission for patients 2–10 years old was 40% [3]. Fast progression of the disease and low c-peptide levels at diagnosis were considered to be the reason for lower remission rates in younger patients [2]. In our study, the partial remission group was younger than the non-remission group. Similarly, Böber et al. found no difference in PR frequency in children older and younger than 10 years, but when they divided children <10 years into 2 group (2–5 years and 6–10 years), they observed more remission in the younger group [19]. However, there are also studies reporting that age at diagnosis does not influence the rate of PR [20,21]. Additionally, in our study, although there was no statistically significant difference, the duration of remission of those younger than 7 years was longer. On the other hand, Dost et al. reported that partial remission duration was shorter in children younger than 10 years of age [17]. Abdul Rasoul et al. indicated that longer remission periods were observed in children older than 5 years old when compared to children ages 3–5 years. The conflicting results in the literature may be due to different ethnic origins and HLA tissue groups believed to influence the frequency of remission.

Another important factor influencing the frequency and duration of remission is the pubertal stage. Partial remission was more frequently observed in the pre-pubertal group in our study. This is associated with the increased insulin requirement due to decreased insulin sensitivity in puberty. Contrary to results of the present study, Bonfanti et al. found a significantly higher rate of remission (post-pubertal 20%, pubertal 5%, pre-pubertal 1%) in post-pubertal children among 157 patients with type 1 DM (77 pre-pubertal, 39 pubertal, and 41 post-pubertal) [22]. However, in a Finnish study, pubertal children were reported to have lower remission rates in comparison to pre-pubertal children [2].

It has been also observed that the sex of patients with type 1 diabetes can affect the frequency and duration of remission. In our study, more male patients were found to go into remission. Similarly, the remission period in male patients was longer than in female patients. Studies have found that adult male and pubertal male patients are more likely to go into remission [4,15]. The fact that less remission was observed in female patients than in male patients in our study can be explained by the increased β cell destruction in females and the increased insulin resistance in females in puberty.

When the relationship between the clinical characteristics of the patients at presentation and the remission was assessed, we found that the patients in the non-remission group presented with more DKA and their DKA levels were moderate/severe. The lack of a statistically significant difference between the remission group and non-remission group was probably due to the small number of patients in our sample. In a large-cohort study, c-peptide levels were low and the remission rate was lower in patients presenting with DKA [2].

In our study, basal and stimulated c-peptide levels were measured to evaluate β cell function. No relationship was found between basal and stimulated c-peptide levels at presentation and the frequency of remission. The most important limitation of our study is the small sample size, and the difference between the 2 groups in both basal and stimulated c-peptide levels would likely be more significant with larger sample sizes.

In the literature, there are studies reporting different results. While no relationship is reported between basal and stimulated c-peptide levels and the rate of remission in some studies [9,21], other studies report that patients who went into remission had significantly higher basal and stimulated c-peptide levels [13,23,24].

Insulin requirement (u/kg/day) at discharge approximately 7–10 days after the diagnosis is an important parameter in predicting remission. We found that patients with a lower insulin requirement had a higher rate remission in this period. Additionally, as a noteworthy finding, we observed that patients who went into remission had lower basal insulin requirement. This leads us to think that patients who go into remission can meet their basal insulin requirement to a greater extent due to endogenous insulin secretion in the early phase. However, they need extra insulin to meet the higher insulin requirement during meals. It seems that a lower basal insulin requirement at discharge is associated with a higher likelihood of going into remission. Muhammad et al. indicated that, among 95 children with T1DM, those who went into remission had lower insulin requirements at discharge from hospital [3]. A study conducted with 268 patients with T1DM, including adults, observed that patients who did not go into remission needed higher doses of insulin at discharge [13]. Lombardo et al. reported that patients who had higher insulin requirements at onset tended to be young people with diabetes with a lower rate of remission [18].

Strengths of our study are its prospective design and patients were followed up for a year. Residual β cell functions of the patients were evaluated at 3-months intervals for 1 year. Stimulated c-peptide levels were evaluated to assess residual β cells. The main problem in diabetic patients is chronic complications. Better the residual β cell function is associated with better metabolic control. For this reason, it is important to know the residual β cell function in diabetic patients.

The most important limitation of our study is the small number of patients sampled. We believe that differences in certain parameters for patients with diabetes who go into remission

and those who do not would be more clearly assessed in a study with a larger sample size.

## Conclusions

This study found that remission in T1DM and longer duration of remission were more frequent in the younger age group, in pre-pubertal stage, and in male patients. Higher remission ratees were found in patients who were discharge with lower daily total insulin dose and basal insulin requirement. However, no relationship was found between the development of remission and clinical and laboratory data at diagnosis. If we can foresee the status of remission of patients, we can predict their insulin requirements, risks of long-term complications, and the possibility of developing diabetic ketoacidosis. Residual β cell function gives information about status of remission. If the residual β cell function is good, the possibility of remission increases and this provides better metabolic control

The remission process in type 1 diabetes still has many characteristics that need to be clarified. Therefore, more extensive studies are needed. Residual β cells are very important for metabolic control. New treatment studies aiming to protect residual β cells in patients with type 1 diabetes should be developed. Thus, long-term complications of diabetes would be significantly reduced and the quality of life of the patients would be improved.

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