

## Remission in Type 1 Diabetes - What's New?

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### Abstract

Type 1 diabetes is an autoimmune disease, in which there is a destruction of pancreatic islets  $\beta$  cells. In the natural course of the disease we deal with a gradual progress during the few years of reduction of cell mass. The symptoms of diabetes appear when the mass of insulin-secreting  $\beta$  cells will be reduced by about 80-90%. In this state, the amount of insulin is insufficient to ensure normoglycemia. Many patients shortly after diagnosis of diabetes type 1 and initiation of insulin therapy come to partial cell  $\beta$  renewal and consequently to reduce the need for exogenous insulin. This phenomenon is called the remission of the disease. This period is also called honeymoon. The glucose concentration decreases so the insulin dose should be also reduced, however complete cessation of insulin is not recommended. Accuracy to determine and compare the prevalence of type 1 diabetes remission is difficult because of ambiguous criteria for its diagnosis: most remission criteria take into account the following parameters: glycated hemoglobin (HbA1c), daily need for exogenous insulin, and the concentration C-peptide in the blood. In all definitions of remission, although different criteria are used, residual insulin secretion is underlined, as well as demonstrated measurement of C-peptide and low demand on exogenous insulin.

**Keywords:** Type 1 diabetes; Clinical remission; Insulin secretion; Insulin therapy; C-Peptide level

### Abbreviations:

IDDM: Insulin-dependent Diabetes Mellitus; DM: Diabetes Mellitus; T1D: Type 1 Diabetes; A1C: Glycosylated Hemoglobin; DKA: Diabetic Ketoacidosis

### Introduction

Type 1 diabetes is an autoimmune disease, in which there is destruction of pancreatic islet  $\beta$  cells. In the natural course of the disease we deal with a gradual progress during the few years of reduction in cell  $\beta$  mass. The symptoms of diabetes appear when the mass of insulin-secreting  $\beta$  cells will be reduced by about 80-90%. In this state, the amount of insulin is insufficient to ensure normoglycemia. Many patients shortly after diagnosis of diabetes type 1 and initiation of insulin therapy come to partial cell renewal  $\beta$  and consequently to reduce the need for exogenous insulin. This phenomenon is called the remission of the disease. The remission period often follows the clinical onset of insulin-dependent (type 1) diabetes, and is characterized by residual  $\beta$  cell function, reduced insulin requirements, and good metabolic control. Studies on the occurrence of remission in diabetes have a long history. In 1946, Glassberg presented a description of diabetes remission [1]. In subsequent years there have been many reports on the occurrence and behavior of remission in juvenile diabetes mellitus and of insulin secretion during this period [2-7]. This assessment of insulin secretion also allowed for the exclusion of patients with diabetes mellitus with other type than juvenile diabetes. The first description of juvenile diabetes patients remission in Polish literature was presented in 1971 [8]. Many studies have shown that early diagnosis and rigorous intensive insulin therapy as well as very careful metabolic disease

control from the time of diagnosis determine beginning and duration of post initial remission. These studies have a long history [9-12].

### Factors Promoting T1D Remission

A number of factors promote to the occurrence of remission. Böber et al. conducted a retrospective study performed on patients diagnosed with IDDM [13]. In conclusion, history of infection prior to presentation and DKA at diagnosis was associated with young age and were the most important factors negatively influencing the remission rate in newly diagnosed IDDM patients. Knip et al. demonstrated that the boys had a remission more often and of longer duration than the girls. The children with remission had lower blood glucose, milder hyperketonemia and ketonuria, higher pH and PCO<sub>2</sub> at onset than those without remission [14]. Swedish multicenter study showed remissions in 43% of the patients with a median duration of 8 months (range 1-73) [15]. In islet antibody-positive diabetes, normal body weight was the strongest factor for entering remission, whilst a low number of islet antibodies were of importance for the remission duration. Vetter et al. in the present study have used the HbA1c concentration at the time of diagnosis as an indicator of the duration of the remission phase in 23 juvenile diabetic children [16]. The results suggest that the initial HbA1c concentration may serve as a useful indicator to predict the duration of the remission phase in juvenile-onset diabetic patients. Researches conducted in recent years indicate that the low prevalence of remission is observed in the youngest children, aged <5 year and in adolescents aged >12 year [17]. It is possible that the low frequency of honeymoon phase in young children reflect more aggressive  $\beta$ -cell destruction in young children. In adolescents insulin resistance contributes to less likelihood of having partial remission. Other authors have similar observations [18]. They asserted that young age and severe disease in initial period are associated with decreased residual beta-cells function what is reflected by a lower incidence of partial remission. Many authors indicates  $\beta$  cell

destruction and reduction of insulin secretion play important role in the manifestation of diabetes and tissue sensitivity to the insulin action [19-21]. In some diabetic patients in the first year there is clinical remission, characterized by a significantly reduced need for exogenous insulin at normal levels of persistent glucose. It is believed that its presence is related mainly to the improvement of insulin secretion; few studies indicate that remission may also be the result of improving sensitivity for insulin. Lower C-peptide and endogenous insulin levels in younger children may indicate lower regeneration ability and smaller  $\beta$  cell numbers in this age group at the onset of DM 1. Patients with remission had higher C-peptide levels observed in the first 6 months of T1D than children without clinical remission [22]. C-peptide level may be a good predictor of the clinical partial remission during the first year of T1D [23]. Pecheur et al. presented the results of retrospective studies in 242 children with type 1 diabetes diagnosed on the occurrence of partial remission. They show that, at diagnosis of T1D, parameters associated with  $\beta$ -cell mass reserve (A1C, C-peptide, and DKA) correlate with the occurrence of Partial Remission (PR) [24]. The Martin et al. in their study show a higher spontaneous clinical remission rate than expected during the 1st year after diagnosis. Preserved  $\beta$ -cell function at entry level predicts a greater chance for entering a remission. More rapid loss of beta-cell function was seen in patients without HLA-DR3 and -DR4 [25]. Surprisingly, the beginning and the end of the remission were associated with neither major changes in C-peptide levels nor islet cell antibody and insulin-antibody level. A more rapid loss of stimulated C-peptide occurred in patients who lacked HLA-DR3 and -DR4. The clinical significance of studies on mechanisms leading to the occurrence of partial remission are the potential possibility for pharmacological intervention during this period to either slow down or arrest the ongoing destruction of the remaining  $\beta$ -cells [18]. Many attempts have been undertaken to stimulate the occurrence of remission, and extending the duration of remission. It was pointed out that the intensification of insulin therapy is preferred since the onset of the first symptoms of the disease [26-29]. Mirouze et al. found that early effective treatment by means of the artificial pancreas may lead to frequent and sustained remissions of juvenile diabetes [30,31]. Similar observations have made also by other authors [32]. Attempts were also made with use of immunosuppressive drugs [33,34].

Recently series of reports devoted the study of the incidence of remission in type 1 diabetes was published. Among other studies was the one conducted by Kaas et al. in a group of juvenile patients in the first year after diagnosis of diabetes based on the monitoring of levels of C-peptide, proinsulin, GLP-1, glucagon, and insulin antibodies (IA) [35]. The authors concluded that during partial remission patients had significantly higher levels of proinsulin and a lower level of GLP-1 and glucagon. Proinsulin was positively associated with C-peptide.

Mortensen et al. presented the attempt of the new definition of partial remission in type 1 diabetes [36]. The study was a multicenter longitudinal investigation in 18 pediatric departments representing 15 countries in Europe and Japan. Their definition of partial remission was proposed, including both glycemic control and insulin dose. It reflects residual  $\beta$ -cell function and has better stability compared with the conventional definitions. The authors consider stimulated C-peptide to be a very useful parameter of a residual  $\beta$ -cell function measurement. The usefulness of this parameter was also pointed out by other authors [37].

## Possible Mechanisms of T1D Remission

Studies on the mechanisms of partial remission of type 1 diabetes are particularly relevant in light of the opening of new possibilities of treatment. The evaluation of residual beta cells function and severity of autoimmune processes in newly diagnosed of type 1 diabetes patients become important because it can provide opportunities for therapeutic interventions [38,39]. In recent years, research on the use of infusion of autologous Tregs to prolong remission in recently diagnosed type 1 diabetes in children has been conducted in Poland [40-42].

Type 1 diabetes is a condition in which pancreatic islets are destroyed by self-reactive T cells. The process is facilitated by deficits in the number and suppressive activity of regulatory T cells (*Tregs*). The infusion of autologous Tregs prolongs remission in recently diagnosed type 1 diabetes in children. The authors concluded that most of the patients responded to the therapy with increase in C-peptide levels and Tregs administration resulted also in lower requirement for exogenous insulin. Other methods of prolonging remission are also proposed: one of them is the use of sitagliptin. The use of sitagliptin in T1DM patients could help to decrease daily requirement of insulin by delaying  $\beta$ -cell loss and improving endogenous insulin production [43]. Efforts are also made to use of other drugs; anti-CD3 monoclonal antibodies significantly improved the insulin secretion and affected the frequent occurrence of and a prolongation of remission. Among other medications was also alefacept - protein complex of molecules CD58 / LFA-3 and human IgG) or Dia- Pep277 whose function is to stop or slow down the process of destruction of the  $\beta$ -cell and improve insulin secretion. DiaPep277 is a molecule consisting of 24 amino acids obtained a fragment of a heat shock protein (HSP60) having immunomodulatory activities affecting on T-lymphocytes on the basis of previous results study showed a higher C-peptide patients receiving DiaPep277 [44]. The final results of clinical studies are still awaited.

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