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Decline of C-peptide during the first year after diagnosis of Type 1 diabetes in children and adolescents

Johnny Ludvigsson [a,1,*], *Annelie Carlsson* [b,1], *Ahmed Deli* [c,1], *Gun Forsander* [d,1], *Sten-A. Ivarsson* [e,1], *Ingrid Kockum* [f,1], *Bengt Lindblad* [d,1], *Claude Marcus* [g,1], *Åke Lernmark* [c,1], *Ulf Samuelsson* [a,1]

[a] *Division of Pediatrics, Department of Clinical and Experimental Medicine, Linköping University, and Pediatric Clinic, Östergötland County Council, Linköping, Sweden*
[b] *Department of Pediatrics, Lund University Hospital, Lund, Sweden*
[c] *Department of Clinical Sciences, Lund University, Malmö, Sweden*
[d] *The Queen Silvia Children's Hospital, Göteborg, Sweden*
[e] *Department of Pediatrics, University Hospital MAS, Malmö, Sweden*
[f] *Department of Molecular Medicine, Karolinska Institute, Stockholm, Sweden*
[g] *Department of Pediatrics, Karolinska University Hospital, Huddinge, Sweden*

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ABSTRACT

Aims/hypothesis: We studied the decline of C-peptide during the first year after diagnosis of Type 1 diabetes (T1D), and its relation to various factors.
Methods: 3824/4017 newly diagnosed patients (95%) were classified as T1D in a national study. In a non-selected subgroup of 1669 T1D patients we determined non-fasting C-peptide both at diagnosis and after 1 year, and analyzed decline in relation to clinical symptoms and signs, initial C-peptide and occurrence of auto-antibodies.
Results: Younger children lost more C-peptide ($p < 0.001$) and the higher the C-peptide at diagnosis the larger the decline during the first year ($p < 0.0000$). Patients with higher BMI had higher C-peptide at diagnosis but lost more ($p < 0.01$), and those with lower HbA1c, without symptoms and signs at diagnosis, and with higher BMI, had higher C-peptide at diagnosis, but lost more during the first year ($p < 0.001$). Finally, patients diagnosed during autumn had higher C-peptide at diagnosis, but lost more during the coming year ($p < 0.001$). Occurrence of auto-antibodies did not correlate with C-peptide decline, except possibly for a more rapid loss in IAA-positive patients.
Conclusions/interpretation: Even in a restricted geographical area and narrow age range (<18 years), the natural course of Type 1 diabetes is heterogeneous. This should be considered in clinical trials.

1. Introduction

At diagnosis of Type 1 diabetes most children and adolescents have some residual insulin secretion [1,2]. This is true also for Type 1 diabetes in older ages [3]. Preservation of C-peptide is important and has become regarded a relevant endpoint [4,5] as already a quite small residual C-peptide seems to be related to both less acute diabetes complications [6,7] and late

* *Corresponding author at*: Division of Pediatrics, Department of Clinical and Experimental Medicine, Linköping University, and Pediatric Clinic, Östergötland County Council, Linköping, Sweden. Tel.: +46 101030000; fax: +46 13148265.
E-mail address: johnny.ludvigsson@liu.se (J. Ludvigsson).
[1] For the Better Diabetes Diagnosis (BDD) study group.
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diabetes complications [8,9]. C-peptide not only reflects residual insulin secretion but may even have positive effects per se [10].

During the last 30 years there have been a number of clinical intervention trials close to onset of Type 1 diabetes to save residual beta cell function [11–27]. Although progress has been made there is still no real success. Among many problems one basic question is who should be included in the trials.

Some immune interventions have shown some efficacy in adult Type 1 diabetes [23] but not in children [27]. In spite of this experience suggesting differences between children and adults, Type 1 diabetes has usually been regarded as a homogenous disease. Thus for instance in a recent Phase III trial on the efficacy of antiCD3 treatment [25], patients not only with a rather large age-range (8–35 years) were included but also patients with what is regarded as Type 1 diabetes from very different parts of the world e.g. from USA, Europe and India. That trial failed to reach primary endpoint for the whole patient group, but showed encouraging results for subgroups e.g. patients in USA and in certain ages mainly below the age of 20, suggesting that these groups differ from other groups in the trial. Another recent trial on GAD-alum treatment [24] included patients with an even larger age range (3–45 years). This trial also failed to reach the endpoint. A third recent European Phase III trial, on GAD-alum treatment [26], also failed to reach primary endpoint, but showed encouraging results in some pre-specified subgroups, suggesting heterogeneity, as all patients did not respond in the same way to the treatment.

Thus, one part of the explanation why immune interventions fail in several clinical trials can be that patients with Type 1 diabetes, irrespective of age, sex, ethnic origin, geographical area are lumped together into one group regarded to be homogenous. We need more knowledge on natural course of residual beta cell function. We have previously shown the natural course of C-peptide decline of C-peptide in 316 children with Type 1 diabetes [1] but could not find any factors related to the course. In a recent publication [28] Greenbaum et al. studied fall in C-peptide during the first 2 years from diagnosis of Type 1 diabetes. This study based on careful collection of data from mixed meal tolerance tests gave important information showing that patients with initially reasonably good residual beta cell function loose that function rather slowly. There was some relation between decline and factors such as age and BMI. However that study only included patients in trials, that is especially active and motivated patients, and we know that active treatment may influence beta cell function. Furthermore they were 7–45 years old, and first sample was collected not until 2 months after diagnosis (mean 79/median 55 days). In another study of a large number of patients <age 20 [29] fasting C-peptide was followed for approximately 30 months, but not from diagnosis but from 8 months duration. They noticed a gradual decline in C-peptide independent of age, sex, race, BMI, etc. Here we report non-fasting C-peptide decline data based on a large unselected patient population, to some extent compensating for a less strict methodological approach. Thus, in Sweden all newly diagnosed diabetic children are included in a national study to better classify their diabetes [30]. Certain symptoms and signs are registered and auto-antibodies and non-fasting initial C-peptide at diagnosis is determined. Many of these patients have been followed-up with another determination of non-fasting C-peptide 1 year later, and we therefore decided to study the loss of C-peptide during the first year, and how the natural course was related to different factors.

2. Patients

In Sweden all children, without exceptions, with new onset diabetes below the age of 18 years, are referred to a pediatric clinic. A prospective national study, the Better Diabetes Diagnosis (BDD), was started in Sweden 2005 to classify the type of diabetes in all newly diagnosed children and adolescents. Thus this ongoing study is based on patients from all 43 Swedish pediatric clinics.

Diagnosis of diabetes is based on the American Diabetes Association (ADA) criteria for diagnosis and classification of diabetes (i.e. casual plasma glucose >11.1 mmol/L, or a fasting plasma glucose >7.0 mmol/L and symptoms of polyuria, polydipsia and weight loss) [31]. In total 4017 patients were included in the present study. Questions on family history regarding diabetes and autoimmune disorders among first degree relatives, symptoms and signs as well as height and weight were registered in SWEDIABKIDS, a national incidence and quality control registry [32]. The diagnosis and classification of diabetes was initially based on clinical symptoms and signs, later on strengthened by information on diabetes-related auto-antibodies, HLA-types, C-peptide, and in some cases MODY genetics [33] 3824/4017 patients (95%) were classified as Type 1 diabetes and out of them we hade determined non-fasting C-peptide both at diagnosis, before first insulin injection, and a random non-fasting C-peptide after ca 1 year in a non-selected subgroup of 1669 patients. The clinical characteristics of these patients were almost identical with the total Type 1 diabetes population as shown in Table 1.

The Karolinska Institute Research Ethics Board approved the study and informed consent from the patients and parents/caregivers were obtained.

Table 1 – Clinical characteristics of the studied sub-group of patients in comparisons with all patients included in the BDD-study.

Variable	All 3824 T1D patients	Sub-group of 1667 T1D patients
	Mean ± SD	Mean ± SD
C-peptide (nmol/L) at diagnosis	0.14 ± 0.37	0.15 ± 0.51
Age at diagnosis	9.83 ± 4.4	9.96 ± 4.2
BMI-SDS at diagnosis	−0.43 ± 1.48	−0.44 ± 1.48
	%	%
T1D in the family	12.8	13.7
Males	55.7	56.8
Polyuria at diagnosis	95	95
Polydipsia at diagnosis	95	95
Weight loss at diagnosis	75	76
IAA-positive	33	34
IA-2A-positive	72	60
GADA-positive	55	56