RAPID DECREASE OF FASTING C PEPTIDE LEVELS AFTER DIAGNOSIS OF TYPE 1 DIABETES MELLITUS

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Abstract

Introduction. Type 1 diabetes mellitus (T1DM) is characterized by absolute insulin deficiency. Fasting C peptide is a marker of endogenous insulin secretion. Small amounts of C peptide can be found in the sera of patients with T1DM at disease onset, but its concentration decreases thereafter. The purposes of this study were to evaluate, regarding endogenous insulin secretion, a group of T1DM patients from Romania, and to estimate the time trends of fasting C peptide.

Methods. T1DM patients (n=260), 15.1±4.7 years of age (range 3.7-27.7 years), 135 male (51.9%), were recruited from Clinical Medical Center "Cristian Şerban", Buziaş. Mean±SD diabetes duration was 2.1±2 years (range 0.1-15.7 years). Fasting C peptide was measured by immuno-enzymatic assay. The results were expressed as ng/ml. The normal range for fasting C peptide was defined by 5th and 95th percentiles from a control group (n=97), matched for age and sex: 0.57-4.44 ng/ml. The study group was divided, according to T1DM duration, into 5 subgroups: 0-6 months (n=47), 6-12 months (n=45), 1-2 years (n=70), 2-3 years (n=43) and >3 years (n=55).

Results. Mean±SD value for fasting C peptide was 0.34±0.56 ng/ml (range 0-3.09 ng/ml). The values, according to T1DM duration, were: 0.54±0.71 ng/ml (range 0-3,09 ng/ml) (0-6 months); 0.32±0,35 ng/ml (range 0.01-1.51 ng/ml) (6-12 months); 0.27±0.48 ng/ml (range 0-3.05 ng/ml) (1-2 years); 0.28±0.52 ng/ml (range 0-2.18 ng/ml) (2-3 years); 0.33±0.66 ng/ml (range 0-2.79 ng/ml) (>3 years). The difference between fasting C peptide in patients with disease duration 0-6 months and the rest was statistic significant (0.54±0.71 ng/ml versus 0.3±0.51 ng/ml, p=0.03).

Conclusions. Fasting C peptide decreases abruptly 6 months after T1DM onset and registers quite constant values thereafter. Consequently, a preventive method for T1DM, should it exist, has to be applied in the first 6 months after diagnosis.

Introduction

Type 1 diabetes mellitus (T1DM) is a disease that requires insulin therapy for survival. A lot of therapeutic progresses were registered since insulin was first administered as a drug in year 1922. Though, therapy of T1DM is far from being perfect. The general enthusiasm of the first years of insulin therapy was followed by the finding that therapy with this hormone converted a disease with rapid lethal evolution into a long-lasting sufferance, marked by the development of chronic complications, that shorten the life duration

and impair its quality, and by the occurrence of sometimes severe hypoglycemic events.

Taking this into account, the efforts of the researchers were focused towards the prediction of the disease by analyzing the sequence of pancreatic antibodies occurrence, in order to estimate, as accurate as possible, the exact time of the onset of hyperglycemia (2, 5, 9, 18). T1DM prediction does not represent a goal *per se*. The final aim is to select patients at high risk, that represent a target population for the administration of preventive drugs that stop or delay the onset of T1DM and avoid the inconvenience of insulin therapy and the risk of chronic complications. The research in the field of prevention represented, and continues to represent, a priority for the diabetologic community. The results obtained are disappointing because no efficient and harmless method that stops β-cell destruction has been developed, so far (1).

The prevention of T1DM can be *primary* (the reduction of the impact of environmental factors that trigger autoimmunity), *secondary* (methods aimed to stop or to slow autoimmune destruction, before hyperglycemia) or *tertiary* (the impeding of the autoimmune process after clinical onset, that results in the maintenance of the own insulin secretion and provides, in time, a better glycemic control) (12, 15).

T1DM prevention is a not accomplished dream, the main reasons being (3, 6, 7):

- lack of an efficient method in humans;
- side effects, sometimes extremely severe, of the various preventive methods experimented so far;
- need for a long duration (decades) of primary prevention, leading to a reduced compliance of the patient and, consequently, to lack of efficiency;
- difficulties in obtaining an accurate prediction.

If we consider tertiary prevention, we have to take into account the fact that loss of insulin secretion is gradual and, at the time of diagnosis, there are only 10% to 20% of β cells left. The purpose of the prevention in this case is to maintain the viability of β cells as long as possible, knowing that T1DM patients that still have own insulin secretion have a better glycemic control, as well. The results of a preventive method can be assessed by the levels of C peptide (maintained at quite constant levels for a long time after diagnosis), on one side, and by the quality of therapy (good HbA_{1c} without marked glycemic excursions), on the other side. The benefits for the patient are represented by the low risk of hypoglycemia and chronic complications and by the use of more simple insulin regimens (6).

The aims of this work were to evaluate, regarding endogenous insulin secretion (evidenced by fasting C peptide), a group of young T1DM patients from Romania, and to reveal the time trends of C peptide.

Material and methods

In order to reach the proposed objectives, we analyzed 2 groups of subjects: the *study group*, represented by 260 children and young adults with T1DM, and the *control group*, composed by 97 healthy subjects, without family history of T1DM, matched for age and gender with the subjects from the study group.

The baseline characteristics of the patients from the two groups are shown in Table 1.

Table 1. Baseline characteristics of the patients from the study group and control group

Clinic parameter	Study group	Control group	p
*Number of subjects**	260	97	–
*Gender*** male female	 135 (51.9) 125 (48.1)	 50 (51.5) 47 (48.5)	1
Age (years) mean±SD median range	 15.1±4.7 15 3.7-27.7	 15±2 15 11.5-18.5	0.77
Disease duration (years) mean±SD median range	 2.1±2 1.7 0.1-15.7	–	–

Legend: *=values expressed as number; **=values expressed as number (%).

The subjects from the study group were recruited between years 2001 and 2002 from the patients admitted in the Clinical Medical Center "Cristian Şerban" for Evaluation and Treatment of Children and Adolescents, Buziaş. The subjects from the control group were pupils of a school from Buziaş. They had negative personal and family history for T1DM.

The clinical criteria for diagnosing T1DM were those accepted nowadays: age less than 40 years, normal weight or even underweight, marked symptoms (polyuria, polydipsia, weight loss), ketosis or ketoacidosis at onset and need for immediate insulin therapy (10). At inclusion in the study, the children (or their parents, upon case) were informed about the importance of the research and about the procedures they will be submitted to.

The blood tests were performed in the Clinical Laboratory of County Hospital Timişoara. For measuring the serum levels of fasting C peptide we used the quantitative „DRG C-Peptide ELISA", produced by „DRG Instruments GmbH" Germany. The test is based on the competition principle and the microplate separation. Normal range for fasting C peptide was considered between 5th and 95th percentiles of the values obtained from the control group (4).

Considering the time passed from T1DM diagnosis, the patients from the study group were divided into 5 subgroups: 0-6 months (n=47, 18.1%), 6-12 months (n=45, 17.3%), 1-2 years (n=70, 26.9%), 2-3 years (n=43, 16.5%) and >3 years (n=55, 21.2%).

For statistical analysis we used GraphPad Instat 3 program. The statistic methods were paired and unpaired t test, ANOVA, Fisher's test and linear regression. A value of $p < 0.05$ was considered significant.

Results

Mean value±SD of fasting C peptide in the 97 subjects from the control group was 2.01±1.37 ng/ml (range 0.2-9.92 ng/ml), and the median value was 1.79 ng/ml. The normal range for fasting C peptide, given by the percentiles 5 and 95, was 0.57-4.44 ng/ml.

Mean value±SD of fasting C peptide in the study group was 0.34±0.56 ng/ml (range 0-3.09 ng/ml). The median value was 0.15 ng/ml. These values were statistic significant lower than those of the control group (p <0.0001) (Fig. 1).

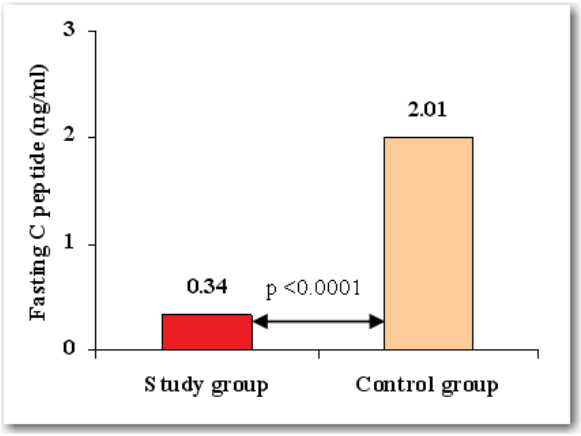

Fig. 1. Mean fasting C peptide in the study and control groups

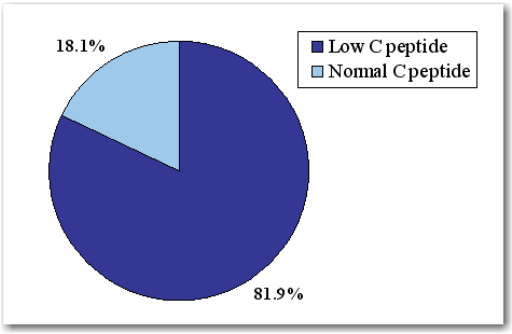

Fig. 2. Insulin secretion in patients with T1DM

From the study group, 213 patients (81.9%) had low fasting C peptide (<0.57 ng/ml) and 47 patients (18.1%) had normal fasting C peptide (0.57-4.44 ng/ml). Not a single subject had increased values of endogenous insulin secretion (Fig. 2).

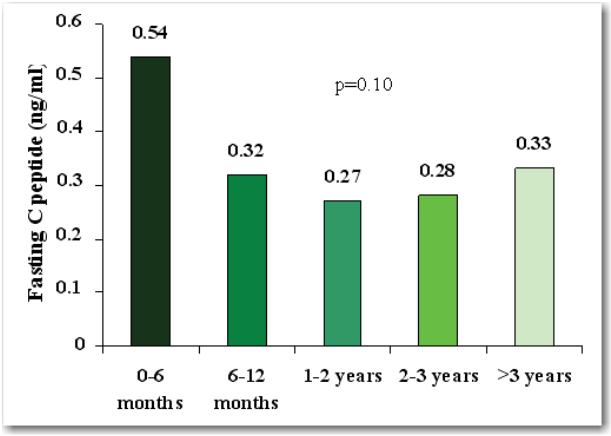

Fig. 3. Mean levels of fasting C peptide depending on T1DM duration

Mean value±SD for fasting C peptide, in the 5 subgroups, were 0.54±0.71 ng/ml (0-3.09 ng/ml), 0.32±0.35 ng/ml (0.01-1.51 ng/ml), 0.27±0.48 ng/ml (0-3.05 ng/ml), 0.28±0.52 ng/ml (0-2.18 ng/ml) and 0.33±0.65 ng/ml (0-2.79 ng/ml), respectively. ANOVA test showed not significant differences regarding fasting C peptide levels between the 5 groups, considered together (p=0.10) (Fig. 3). There was no linear correlation between endogenous insulin secretion and disease duration. The linear regression method revealed a correlation coefficient r=0.01, the slope of the regression line being not significant (p=0.77) (Fig. 4).

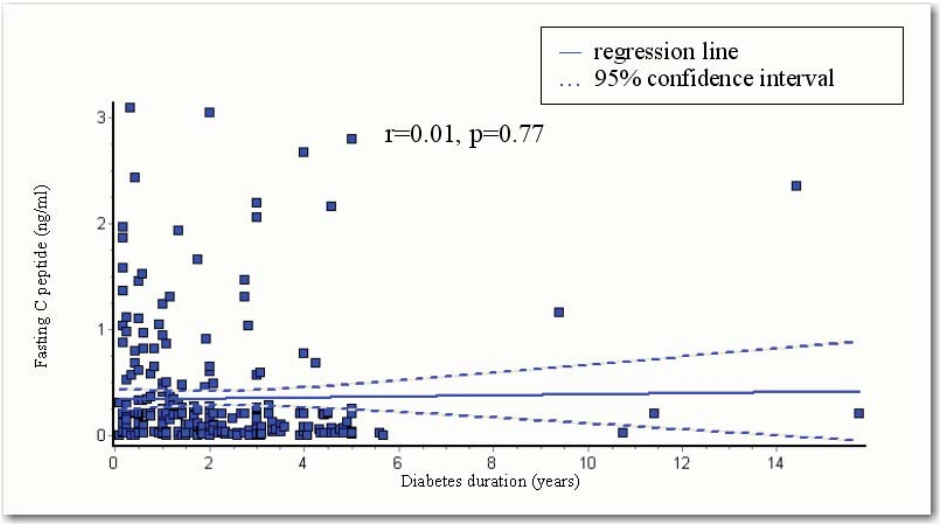

Fig. 4. Correlation between fasting C peptide and T1DM duration

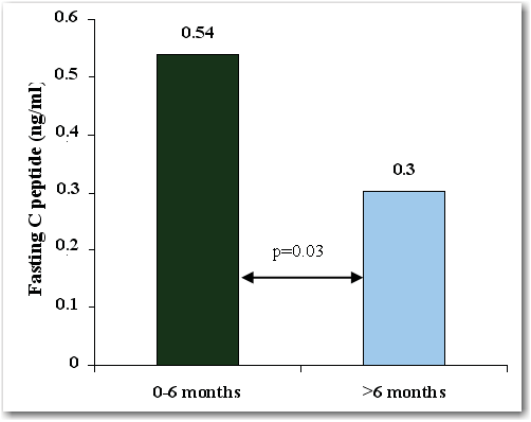

Fig. 5. Mean value of fasting C peptide in patients with disease duration of less or greater than 6 months

One can note (Fig. 3) that the subgroup of patients diagnosed most recently with T1DM (0-6 months) have a higher value of fasting C peptide, as compared to the other 4 subgroups, that have similar values. There is a statistical significant difference between fasting C peptide levels in patients having disease duration of less than 6 months and patients diagnosed more than 6 months ago (Fig. 5).

Furthermore, the percentage of patients with normal C peptide was significantly higher (p=0.011) in patients with disease duration of less than 6 months (31.9%) compared to those being diagnosed more than 6 months ago (15%) (Fig. 6).

Discussions

Normal value of fasting C peptide is different in various populations, being influenced by age, gender, and genetic background. That's why, in order to establish the "normal range" for a study group, it is recommended to determine this parameter in non-diabetic subjects and to consider percentiles 5 and 95 as limits for normality (8, 11, 13, 14, 16, 17, 19).

As expected, knowing that T1DM is characterized by insulin deficiency, mean value of fasting C peptide was significantly

lower in the subjects from the study group as compared to those from the control group. Due to the same reason, most of the patients from the study group (81.9%) had a fasting C peptide below lower limit of normal range.

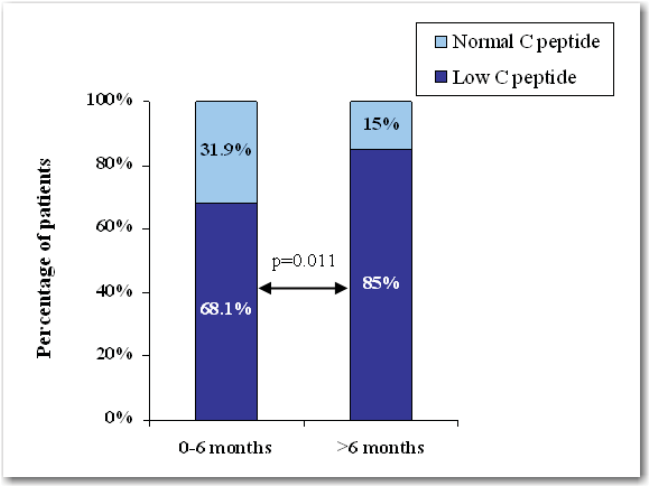

Fig. 6. Insulin secretion in patients having disease duration of less or greater than 6 months

It is known that, by the time of diagnosis of T1DM, the pancreas still has functional β cells. Sometimes these permit the reduction of insulin doses for a period of time (remission of diabetes mellitus). The process of β cell destruction continues even after the diagnosis of T1DM and, finally, the β cell mass becomes zero. Our study showed that fasting C peptide is not linearly correlated to the disease duration, but demonstrated that mean value of fasting C peptide and the proportion of patients having this parameter in normal range decrease abruptly 6 months after diagnosis. That's why, an efficient preventive method, should it exist, has to be applied in the first 6 months after diagnosis, when the patient still has enough viable β cells that help obtaining better long-term therapeutic results.

Conclusions

The conclusions that can be drawn from this paper are:

– T1DM patients have, in most of the cases, insulin deficiency;

– fasting C peptide decreases abruptly 6 months after the diagnosis of T1DM; consequently, a preventive method for T1DM, should it exist, has to be applied during this interval of time.

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