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Research Article

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Patterns of disease progression in children with type 1 diabetes during the first six months

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ABSTRACT

This a prospective longitudinal study was carried out to assess the relation of disease progression of juvenile – onset type 1 diabetes, determined by preserved beta cell function 6 months after diagnosis, with systemic concentration of IL- 1ra. Thirty children with recent- onset of type 1 diabetes with a mean age of 6.5±2.2 years were enrolled. Meal – stimulated C- peptide and IL- 1ra were tested 1 and 6 months after diagnosis using ELISA technique. On the basis of the C- peptide course for the duration of 1- 6 months, three progression groups were defined: Patients with persistently low beta cell function (stable), rapid progressers, and remitters. IL-1ra did not differ between the groups at any time – point (p>0.05). Also, we found that body mass index (BMI) percentiles were significantly increased in diabetic patients during follow up compared to BMI percentiles at time of presentation (p= 0.014). The present study concluded that there are different progression patterns following diagnosis of type 1 diabetes in children pointing to different mechanisms of disease progression.

Key words: Interleukin (IL)-1ra, C-peptide, pediatric, residual beta cell function, type 1 diabetes.

INTRODUCTION

Type 1diabetes (T1D) is an organ – specific autoimmune disease that results from T cell- medicated destruction of insulin- producing pancreatic beta cells [1]. T1D commonly develop as a multifactorial disease in which environmental factors concur with a highly multigenic background [2]. Cell – mediated immunity and pro-inflammatory cytokines are implicated in the pathogenesis of type 1 diabetes [3]. One of these pro- inflammatory cytokines is interleukin (IL) -1β which seems to be associated with T1D inflammatory process [4]. Interleukin – 1 receptor antagonist (IL-1ra) is a naturally occurring cytokine and is the inhibitor of IL- 1β. There are mounting evidences to suggest that anti -inflammatory IL-1ra reduces the inflammatory effects of IL-1 and preserves beta cell function in both types of diabetes [5]. The progression of type 1 diabetes after diagnosis is poorly understood, particularly in the pediatric population. In the present study, we define disease progression on the basis of changes in beta cell function as assessed by stimulated C- peptide from 1 to 6 months after clinical onset of type 1 diabetes. Stimulated serum C- peptide is the gold standard measure of endogenous insulin secretion in patients with type 1 diabetes [6].

We hypothesize that patients can have different patterns of loss in beta cell function varying from rapid, stable or even actual increase in beta cell mass. Systemic cytokines such as IL-1ra could be potential biomarker of different patterns of disease progression [7].

Aim of the study: The current study was carried out to describe distinct patterns of disease progression after diagnosis in patients with newly diagnosed type 1 diabetes on the basis of changes in stimulated C- peptide. Furthermore, we investigated if the patterns of disease progression are confounded by parameters such as glycated haemoglobin (HbA1c), insulin dose, ketoacidosis at diagnosis, body mass index (BMI) percentiles or age and influenced by serum concentrations of potential biomarkers such as IL- 1ra.

The study was approved by the ethics committee of the National Research Centre and all subjects gave their informed consent prior to entering this study.

Research Design

I- Subjects

This prospective longitudinal study was conducted on 30 children who were newly diagnosed patients with type 1 diabetes. They were recruited from pediatric Diabetic Clinic, Children's Hospital, Ain Shams University, during the period from April 2011 to December 2012. All patients fulfilling the inclusion criteria were included in the study. Exclusion criteria were patients with type 2 diabetes and presence of other concomitant chronic conditions. Patients were diagnosed with type 1 diabetes according to the diagnostic criteria of the American Diabetes Association [8]. A written informed consent was obtained from parents after explanation of the aim of the study. All participants in the current study were subjected to full history taking, thorough physical examination and laboratory investigations. Of the included patients, 11 girls and 19 boys; mean age of 6.5±2.2 years, range 2.1 to 9.4 years at time of diagnosis. Of the patients included, 73.3% presented with diabetic ketoacidosis (HC03 < 15mmol/L and /or PH < 7.3) at time of diagnosis.

EXPERIMENTAL SECTION

C- Peptide

After 1 and 6 months of diabetes a meal was utilized to stimulate endogenous C- peptide release. The test was performed in the morning after at least 8 hours of fasting. The morning insulin dose was given after the test. Stimulated C- peptide was measured 90 minutes after ingestion of a meal equivalent to 1.75gm/kg maximum 75gm carbohydrate [9]. Serum C- peptide was anlaysed by ELISA technique using the DRG C- peptide kit.

IL- 1 ra

Blood for IL-1ra measurement was drawn 90 minutes after the ingestion of the meal. IL-1ra was measured by ELISA technique using quantikine human IL-1ra Immunoassay kit (R and D systems). Serum samples were labeled and frozen at -20°C until time of analysis.

Definition of type 1 diabetes progression patterns

The progression of type 1 diabetes was determined on the basis of the change in stimulated C- peptide from 1 to 6 months after diagnosis, which could be an increase, a decrease or stable C- peptide level. When calculating the change in C- peptide, we acknowledged that minor changes due to measurement errors might occur and should be interpreted with caution. Therefore, the change should be of at least 20% between the largest and the smallest value of a relative scale and according to this, three courses of C- peptide change were defined: [1] patients eliciting stable but low C- peptide production (stable); [2] patients losing more than 20% C- peptide during the first 6 months after diagnosis (rapid progressers); [3] patients with an increase of more than 20% in C- peptide production after diagnosis (remitters); [7].

Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using SPSS program (Statistical Package for Social Sciences) software version18. Descriptive statistics were done for numerical parametric data as mean±SD (standard deviation) and minimum& maximum of the range, while they were done for categorical data as number and percentage.

Inferential analyses were done for quantitative variables using:

F analysis of variance(ANOVA): test for more than two independent groups with parametric data.
Inferential analyses were done for qualitative data using:

a. Chi square test(χ^2): for independent variables.
b. Fisher's Exact test(^): for independent variables with small expected numbers.
c. McNemar test: for paired categorical data.

The level of significance was taken at P value < 0.05 is significant, otherwise is non significant. The p-value is a statistical measure for the probability that the results observed in a study could have occurred by chance [10].

RESULTS AND DISCUSSION

On the basis of the change in C- peptide level from 1 to 6 months after diagnosis, three progression groups were made: (i) stable, (ii) rapid progresses; (iii) remitters. From the total number of patients included 56.7% (n= 17) were stable, 20% (n=6) were rapid progresses and 23.3% (n=7) were remitters.

We present a strategy to define patterns of disease progression in type 1 diabetes on the basis of changes in stimulated C- peptide from 1 to 6 months after diagnosis. The progression pattern groups we define are not confounded by age, gender, daily insulin dose at time of diagnosis and at follow up, ketoacidosis, HbA1c, BMI percentiles ($p > 0.05$). Kaas et al similarly reported no significant difference between the progression groups regarding sex, daily insulin dose, ketoacidosis, HbA1c, and BMI at diagnosis [7]. However, Kaas et al [7] reported that the groups differed significantly in age, patients from the stable and the rapid progressed groups were the youngest, followed by patients from the remitter groups. This is in agreement with the majority of studies, which have shown that younger age is associated with greater loss of beta cell function both before and after diagnosis [11*and 12*]. Meanwhile, our data as regards age influence is correspondent with that reported by [13]who did not find any association between age and the degree of loss of beta cell function. Also, Kaas et al had reported that at 6 months after diabetes diagnosis there were a significant difference as regards glycated hemoglobin (HbA1c) and daily insulin dose where rapid progress had the highest HbA1c and the highest daily insulin dose compared to the other groups while at 12 months after diagnosis, there was no difference regarding HbA1c in the group of rapid progress compared to other patients but the daily insulin dose of the rapid progress patients was still the highest[7]. In the present study, we tested if the cytokine IL-1ra could be potential biomarker for the three patterns of progression. We selected this cytokine because of its putative involvement in the immunopathogenesis or modulation thereof in type 1 diabetes [14]. Interleukin -1 receptor antagonist (IL-1ra) is the natural antagonist to IL-1β [15]. IL-1ra is able to counteract inflammatory effects of IL-1β implicated in insulin resistance and diabetes [16]. In the present work, there was no significant difference between the progression groups as regards IL- 1ra ($p > 0.05$).

Kaas et al similarly did not reveal any difference between the progression groups regarding IL-1ra which indicates that at 1 month of diabetes diagnosis, IL-1ra could not predict the progression pattern group after 6 months [7]. However, a trend of higher IL-1ra concentration in the rapid progresser group compared to other groups was noted in our study which is unexpected. Possible explanations for this is that the rapid progresser group could have more aggressive immune response than other groups and higher levels of proinflammatory cytokines for example IL1-beta (which is known to be important for the beta cell lysis in type 1 diabetes) [17]which predispose to reduced IL-1ra: IL-1 balance which sensitizes β-cells to inflammatory destruction [18]. While an increased IL-1ra: IL-1 ratio is known to be correlated with the "honeymoon" remission in new-onset type 1 diabetes [14].Residual beta-cell function is mainly determined by the intensity of immunological destruction [19]. Another explanation is that IL-1ra displays anti-inflammatory and insulin-sensitizing effects [20] so the increased IL-1ra concentration in patients with a rapid progression of type 1 diabetes may be to boost remaining insulin action. In the present study, BMI percentiles were significantly increased in diabetic patients 6 months after diagnosis compared to BMI percentiles at time of diagnosis (P=0.014). This result is in accordance with that observed by [21] who reported that despite the initial weight loss at diagnosis of type 1 diabetes, by 10-20 weeks post-diagnosis, almost one third were overweight and obese. The weight gain is independent of weight at diagnosis and duration of diabetes, but is positively correlated with the daily dose of insulin and HbA1c concentration [22]**.** The weight gain caused by insulin treatment in type1 diabetes could interact with decreased beta-cell function, and it is a known factor increasing insulin resistance in type1 diabetes [23]. So, in light of obesity epidemic, closer attention to overall caloric intake in children with new onset diabetes is prudent [21]**.** Our results support the importance of studying different patterns of progression of type 1 diabetes in detail after diagnosis, rather than simply determining clinical remission on the basis of insulin needs.

Table (1): Comparison between different patterns of diabetes progression (according to the change of stimulated C-peptide level) in diabetic patients as regards to age, gender, daily insulin dose, DKA, glycated haemoglobin (GlyHb), BMI, and IL-1ra at 6 months after diagnosis

Parameter	Rapidly progressers (N=6)	Stable (N=17)	Remitters (N=7)	F/χ^2	p
Age (years)	5.5±2.7	7.1±1.6	5.8±2.8	1.857	0.176
Gender					
• Female	2 (33.3%)	6 (35.3%)	3 (42.9%)	0.158	0.924
• Male	4 (66.7%)	11 (64.7%)	4 (57.1%)		
Insulin dose at diagnosis	1.3±0.4	1.4±0.5	1.2±0.2	0.348	0.709
Insulin dose at 6 months	0.9±0.4	1.2±0.5	1.1±0.5	1.009	0.378
DKA					
• Present	4 (66.7%)	14 (82.4%)	4 (57.1%)	2.012^	0.453
• Absent	2 (33.3%)	3 (17.6%)	3 (42.9%)		
BMI percentile					
• <25	6 (100%)	9 (52.9%)	3 (42.9%)	5.21	0.074
• ≥25	0 (00%	8 (47.1%)	4 (57.1%)		
GlyHb	7.9±0.9	8.6±2.1	8.7±1.6	0.419	0.662
IL-1ra (pg/mL)	240.1±55.9	198.8±57.1	179.6±41.3	2.140	0.137

F: ANOVA test, χ^2: Chi square test, ^Fisher's Exact t

There were no significant differences between the progression groups regarding age, gender, daily insulin dose and ketoacidosis at diagnosis ($p > 0.05$). At 6 months there were no significant difference between the progression groups regarding daily insulin dose and HbA 1C ($p>0.05$).

IL- 1ra: There was no significant difference between the progression patterns regarding IL-1ra. Levels of IL-1ra at 1 month did not reveal any predictive value of IL-1ra.

Table (2): Comparison between diabetic patients at admission and 6 months after diagnosis as regards BMI percentiles

FU Admission	<25	25-	50-	75-100	Total
<25	5 (27.8%)	5 (27.8%)	6 (33.3%)	2 (11.1%)	**18 (100%)**
25-	0 (0.0%)	0 (0.0%)	3 (75.0%)	1 (25.0%)	**4 (100%)**
50-	0 (0.0%)	2 (66.7%)	1 (33.3)	0 (0.0%)	**3 (100%)**
75-100	0 (0.0%)	0 (0.0%)	0 (0.0%)	5 (1000%)	**5 (100%)**
Total	**5**	**7**	**10**	**8**	**30**
Test value#	14.2		**P**	**0.014***	
Elevation of BMI	26 (86.7%)				

*# McNemar test, *Significant*

BMI percentiles were significantly increased in diabetic patients during follow up compared to BMI percentiles at time of presentation ($p=0.014$).

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