Age of onset of puberty and menarche in type 1 diabetic girls

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Abstract
Introduction: Delayed pubertal maturation has been reported in girls with type 1 diabetes. Objectives: To report the age of onset of puberty and menarche in girls with type 1 diabetes diagnosed before puberty. To investigate the clinical factors affecting the occurrence of puberty and menarche in this population. Patients and methods: A retrospective study of 38 girls with type 1 diabetes, all of them on intensive insulin therapy since diagnosis and followed up at our hospital until menarche. The age of onset of puberty and the age of menarche were collected as dependent variables, and the time from onset of diabetes, glycosylated hemoglobin levels, daily insulin requirements, and body mass index standard deviation scores were collected as independent variables. Variables are expressed as mean ± standard deviation. Multivariate linear regression models tested the associations between dependent and independent variables. Statistical analysis was performed using SPSS software. Results: Thirty-eight girls were enrolled. Age of onset of puberty was 10.4 ± 1.1 years and age of menarche, 12.6 ± 1.0 years. The time from diabetes onset influenced age at onset of puberty (β = +0.12; p = 0.047). A negative association was found between body mass index standard deviation score and age at menarche (β = −0.39; p = 0.014). Conclusion: Diabetes duration and body mass index correlated to the age of onset of puberty and the age of menarche in girls with type 1 diabetes.

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KEYWORDS
Puberty;
Menarche;
Type 1 diabetes

Edad del inicio puberal y de la menarquia en niñas con diabetes tipo 1

Resumen
Introducción: En la diabetes tipo 1 se ha descrito un retraso en la maduración puberal. Objetivos: Describir la edad de inicio puberal y la edad de la menarquia en niñas con diabetes tipo 1 diagnosticadas antes de la pubertad. Analizar las variables relacionadas con las mismas.

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Introduction

Delayed pubertal maturation has been reported in patients with type 1 diabetes mellitus (T1DM) as compared to the non-diabetic population. Such delay is related to both the time from onset of T1DM and to metabolic control of the disease. However, these differences appear to be decreasing. While studies conducted 20 years ago reported a pubertal delay of approximately 12-16 months, publications in the past five years have reported a reduction of this delay to less than six months, most likely as a result of recent advances in insulin therapy.

Since the Diabetes Control and Complications Trial (DCCT) was published, intensive treatment has become the first choice therapy for young patients with T1DM. This study showed that improved metabolic control resulted in a decreased frequency and severity of chronic complications. While no agreement exists about the insulin regimen to be used in pediatric patients, there is a clear trend towards multiple injections of rapid-acting insulin plus glucagon-related insulin (human regular or human Lantus) in multiple doses (three or more daily injections) or as a continuous infusion and at least four daily measurements of capillary blood glucose and insulin dose modifications by the patients themselves or their parents.

Our study was designed to determine the age of onset of puberty and menarche in girls with T1DM diagnosed before puberty and treated with intensive insulin therapy from the start, and to analyze the related variables.

Patients and methods

A retrospective study was conducted at a pediatric endocrinology unit of a second level hospital attended by some 200 children and adolescents diagnosed with T1DM before 14 years of age.

Girls with T1DM diagnosed before puberty and followed up at the clinic every three months who had experienced menarche were included into the study. They all had been managed from diabetes onset with intensive insulin therapy in multiple doses (three or more daily injections) or as a continuous infusion and at least four daily measurements of capillary blood glucose and insulin dose modifications by the patients themselves or their parents.

Patients with other chronic disease (both autoimmune or of any other origin) or belonging to any ethnic minority were excluded from the study.

The dependent variables collected included age at onset of puberty (breast budding or Tanner stage II) and age at menarche, while independent variables included time from diabetes onset (from the first insulin dose, mean glycated hemoglobin levels in the previous three years (or the available values in patients with shorter disease duration), daily insulin requirements (in international units per kilogram [kg] and day), and body mass index (calculated by dividing weight in kg by height in meters squared), expressed as the standard deviation score (SDS) based on Spanish references. Obesity was defined as a body mass index greater than 2.5 times the mean for age and sex. Glycosylated hemoglobin was tested using high-performance liquid chromatography (normal range, 3.0%-5.0%). Variables are given as mean ± standard deviation. The association between the variables was tested using multiple linear regression. A value of alpha 0.05 was used as a threshold of statistical significance. SPSS version 11.0 software for Windows was used for all statistical calculations.

The study was approved by the ethics and research committees of our hospital.

Results

Thirty-eight adolescent females were enrolled into the study. Age of start of puberty was $10.4 ± 1.1$ years, and age of menarche $12.6 ± 1.0$ years.

Table 1 shows the variables at onset of puberty. At that time, approximately two thirds of patients (26/38) had an acceptable metabolic control, i.e. mean glycated hemoglobin levels up to 7.5% in the previous three years. There were six obese girls (approximately 16% of the cohort), and insulin requirements exceeded one unit per kg body weight and day in 13 patients.

Table 2 shows variables at menarche. Metabolic control was poorer, as only one third (13/38) of the patients had had at that time an acceptable average metabolic control over the previous three years. The six girls were still obese, and insulin requirements had increased and were greater than one unit per kg and day in 24 patients.
Tables 3 and 4 show associations between the different variables and age of onset of puberty and age of menarche respectively. After adjusting for all other variables, time from diabetes onset was the only variable significantly related to age at onset of puberty ($b = +0.12; p = 0.047$). The greater body mass index was significantly related to an earlier age at menarche ($b = −0.39; p = 0.014$) and non-significantly related (because of the small sample size) to age of onset of puberty ($b = −0.26; p = 0.085$).

**Discussion**

The delayed timing of puberty in girls with T1DM has been shown in studies which compared them both to girls in whom diabetes was diagnosed after menarche$^{1,6}$ and to healthy girls from the same population$^{1-5}$. According to several studies, this delay is positively correlated to diabetes duration and the degree of metabolic control$^{3,4,11}$. Menarche is delayed by approximately 20-40 days per each 1% increase in mean glycosylated hemoglobin levels in the three previous years$^{3,4}$. In a large longitudinal study of 643 girls it was inversely related to body mass index and insulin dose$^3$.

Although there has been speculation about the presence of insulin receptors in the ovary, so supporting the concept of a role of insulin in gonadal maturation, it appears more likely that weight changes derived from insulin deficiency or excess and chronic hyperglycemia could affect gonadotropin secretion$^{12}$. A potential role of ovarian autoimmunity, occurring more commonly in T1DM, has not been elucidated yet$^{13}$.

Large studies in the general population have reported that the earlier the occurrence of puberty and menarche, the greater the body mass index. In the Third National Health and Nutrition Examination Survey, overweight girls had a greater prevalence of early onset of puberty and menarche$^{14}$. In a cross-sectional study of 1,840 healthy school girls, those with obesity and overweight reached menarche five months earlier than girls of normal weight, while girls of low weight had menarche 10 months later$^{15}$. It has been suggested that a given body weight threshold could trigger pubertal development regardless of age and height. Such a weight threshold has been estimated as being 47-51 kg for menarche$^{15,16}$.

Over the past century, improved nutritional support in developed countries has led to an earlier onset of puberty$^{17}$. In Germany, for example, the median age of menarche decreased from 15.5 years in 1869 to 12.5 years in 1978$^{18}$.

### Table 1 Variables at onset of puberty (mean ± standard deviation [range])

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Time from onset of diabetes (years)</th>
<th>Mean glycosylated hemoglobin in the previous 3 years (%)</th>
<th>Body mass index (kg/m$^2$)</th>
<th>Body mass index (standard deviation score)</th>
<th>Insulin dose (IU/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>10.45 ± 1.08 (8.1-13.2)</td>
<td>3.65 ± 2.78 (0.1-9.9)</td>
<td>7.41 ± 1.18 (5.5-11.5)</td>
<td>19.37 ± 2.71 (15.2-25.7)</td>
<td>0.62 ± 1.12 (-0.88. +2.92)</td>
<td>0.92 ± 0.26 (0.32-1.69)</td>
</tr>
</tbody>
</table>

### Table 2 Variables at menarche (mean ± standard deviation [range])

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Age (years)</th>
<th>Time from onset of diabetes (years)</th>
<th>Mean glycosylated hemoglobin in the previous 3 years (%)</th>
<th>Body mass index (kg/m$^2$)</th>
<th>Body mass index (standard deviation score)</th>
<th>Insulin dose (IU/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>38</td>
<td>12.61 ± 1.01 (10.2-14.5)</td>
<td>5.81 ± 2.78 (1.53-11.30)</td>
<td>8.05 ± 0.93 (6.7-11.0)</td>
<td>21.31 ± 2.64 (16.4-25.6)</td>
<td>0.67 ± 1.00 (−0.93.+3.21)</td>
<td>1.18 ± 0.28 (0.71-2.00)</td>
</tr>
</tbody>
</table>

### Table 3 Variables related to age of onset of puberty

<table>
<thead>
<tr>
<th>Coefficient of determination $R^2 = 0.18$</th>
<th>Age at onset of puberty (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent variables</td>
<td>Crude $\beta$</td>
</tr>
<tr>
<td>Time from onset of diabetes (years)</td>
<td>+0.128</td>
</tr>
<tr>
<td>Glycosilated hemoglobin levels (%)</td>
<td>+0.064</td>
</tr>
<tr>
<td>Body mass index (standard deviation score)</td>
<td>−0.279</td>
</tr>
<tr>
<td>Daily insulin dose (IU/kg/day)</td>
<td>+0.942</td>
</tr>
</tbody>
</table>
In Spain, the timing of puberty was analyzed in the Aragón region in a longitudinal study. In healthy girls from Aragón, both age at onset of puberty, 10.7 ± 1.03 years (range: 8.64-12.76) and age of menarche, 12.6 ± 0.95 years (range: 10.7-14.5), were very similar to those in this study. The reason why no differences were found may be that current insulin schemes are becoming close to a quasi-physiological replacement therapy. It should also be noted that girls with diabetes in this study had a higher body mass index than the healthy Spanish population and would therefore have had an earlier onset of puberty because of such an increased body mass index. It would be interesting to compare diabetic girls to non-diabetic controls with the same body mass index.

We know that adolescents with T1DM have a trend to overweight related to higher insulinization. Body mass index is an accurate reflection of the amount of insulin administered, whereas the dose reported by patients may not be the dose actually taken at an age of difficult prescription compliance. Thus, girls with T1DM are at risk of pubertal delay because of their poor metabolic control and hypoinsulinization, and when they are hyperinsulinized they become a risk group in advanced puberty.

The main limitations of our study are its retrospective nature, which does not allow for establishing causal relationships, and its small sample size, which prevents statistical significance being given to some associations between variables. Multicenter, prospective studies with a sample size adequate for enabling our hypothesis to be demonstrated are needed. If an adequate patient sample were available, it would be interesting to compare the timing of puberty in girl subgroups with different insulin schemes and in different weight categories (normal weight, overweight, and obese).

Despite such limitations, it may be concluded from our study that the timing of puberty in girls with type 1 diabetes in our hospital was related to both the time from diabetes onset and body mass index.

**Conflict of interest**

The authors state that they have no conflict of interest.

### References


### Table 4  Variables related to age of menarche

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Crude β</th>
<th>Standard error</th>
<th>p</th>
<th>Adjusted β</th>
<th>Standard error</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from onset of diabetes (years)</td>
<td>+0.120</td>
<td>0.057</td>
<td>0.04</td>
<td>+0.085</td>
<td>0.055</td>
<td>0.132</td>
</tr>
<tr>
<td>Glycosilated hemoglobin levels (%)</td>
<td>+0.044</td>
<td>0.182</td>
<td>0.81</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body mass index (standard deviation score)</td>
<td>−0.450</td>
<td>0.150</td>
<td>0.005</td>
<td>−0.390</td>
<td>0.152</td>
<td>0.014</td>
</tr>
<tr>
<td>Daily insulin dose (IU/kg/day)</td>
<td>−0.433</td>
<td>0.591</td>
<td>0.47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>