INTRODUCTION

Type 1 diabetes (T1D) is a chronic disease that impairs pubertal development and growth in children and adolescents of both sexes. The impact of T1D on puberty development and growth is greater if it appears early (1). Diabetes duration and glycemic control correlate most closely with delayed puberty (2). Although there are several studies evaluating diabetic children growth, only a few have focused on pubertal development. (1). A pubertal delay of about 12 to 16 months was mentioned in studies published in the previous 20 years. However, this delay is reduced to less than 6 months in recently published studies, most likely due to recent advances in treatment, contributing to better control of the disease (2).

The objective of this study is to evaluate the pubertal status in youth with type 1 diabetic patients and to determine factors that may influence pubertal development.

PATIENTS AND METHODS

We conducted an analytical retrospective study during the period between January 2010 and November 2017, in young people with T1D, in the Ibn Rochd University Hospital of Casablanca - Morocco.
Casablanca Endocrinology- Diabetology and Metabolic Diseases Department

Inclusion criteria were

1. Patients with T1D, aged between 14 to 20 years old, hospitalized during the study period following acute decompensation or chronic uncontrolled HbA1c.
2. Patients with type 1 diabetes who were admitted for therapeutic education or followed on the transition consultation.

Exclusion criteria were

Presence of another chronic co-existing disease that may affect pubertal development or growth (malabsorption, dysthyroidism).

Determination of studied variables

Socio-demographic characteristics: Age, gender, educational level, rural or urban origin and the socio-economic level.

Characteristics of diabetes

Parameters evaluated were age of diagnosis, age of the onset of T1D, the treatment regimen used with determination of the mean daily dose of insulin expressed in international units (IU) of insulin per kilogram of weight per day (IU/kg/day). Hypoglycaemia frequency has been expressed as the number of hypoglycaemia per week.

The level of glycemic control was evaluated by the assay of glycosylated hemoglobin (HbA1c) by standardized HPLC method.

The search for degenerative complications was made by clinical examination, exploration of renal function and microalbuminuria for 24 hours if possible and fundus eye examination.

Clinical features

Anthropometric parameters, including weight (in kilograms) and height (in centimeters), were compared to age targets, according to the WHO curves.

Stunting is defined as a weight and / or size less than – 2 standard deviation (SD) relative to the reference curves.

Tanner scoring was used to assess puberty and compared to chronologic age. The age of menarche in girls and the menstruation regularity were also studied.

The menarche onset was considered precocious before the age of 8 and delayed after 16 years.

The delayed puberty was defined in the boy by the absence of increase in testicular volume (<4 ml or length <25 mm) beyond 14 years, and in the girl by the absence of development of the breasts at 13 years or the absence of menarche at 15 years.

Data collection and analysis

Data was collected from the medical records using Excel. Statistical analysis was performed with SPSS®.

For the descriptive part, the means, standard deviations and percentages were calculated to summarize the qualitative variables distributions.

Analytical study was done by the Pearson Chi 2 test with a significant p if it was <0.05.

RESULTS

Our study focused on 200 patients, with female predominance: 114 girls (57%) and 86 boys (43%). Average age of patients was 17 ± 2 years. Average diabetes duration was 7.9 years (2-13 years). Low socioeconomic status was found in 124 patients (62%). Rural origin was noted in 58 patients (29%). Four girls were married, and one of them had an ongoing pregnancy.

The average body mass index (BMI) was 20 kg / m² (13-28) with an average of 18 kg / m² for boys and 21 kg / m² for girls.

Regimen of insulin therapy

The majority of patients received premixed regimen: 114 patients (57%), an intensive basal-bolus insulin regimen was adopted in 86 patients (43%), three of whom were under insulin pump. The average daily dose of insulin was 1.4 IU / kg / day.

Glycemic control: The average HbA1c in our patients was 11% (4-16). Table I illustrates the demographic characteristics of our patients as well as the characteristics of diabetes.

Table I Clinical and Demographic Characteristics of our patients

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Boys</th>
<th>Girls</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>86 (43%)</td>
<td>114 (57%)</td>
</tr>
<tr>
<td>Mean age(y)</td>
<td>16.5 (12-20)</td>
<td>18 (14-20)</td>
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<tr>
<td>Age of onset of T1D(y)</td>
<td>10.5 ± 1.6</td>
<td>9.2 ± 2</td>
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<tr>
<td>Mean duration of T1D(y)</td>
<td>8(2-13)</td>
<td>7 (5-10)</td>
</tr>
<tr>
<td>Menarche(y)</td>
<td>------</td>
<td>12 (9-16)</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>11.3 (4-14.7)</td>
<td>10.8 (7-16)</td>
</tr>
<tr>
<td>Insulin dose UI/kg/d</td>
<td>0.98 (0.5-2.6)</td>
<td>1.05 (0.4-2.4)</td>
</tr>
<tr>
<td>Mean BMI (Kg/m²)</td>
<td>18 (13-25)</td>
<td>21 (17-28)</td>
</tr>
</tbody>
</table>

Regarding degenerative complications, 32% of our patients were at the stage of microangiopathies. Diabetic nephropathy was the most common complication.(figure 1)

Evaluation of pubertal development and growth

A pubertal delay was observed in 11 (13%) boys and in 4 (3.5%) girls.

The average age of menarche was 12 years (range 9 to 16 years). Irregular cycles were found in 21% of girls with secondary amenorrhea reported in a girl. Menarche was
delayed in 14 patients with normally developed secondary sexual characteristics.

A clear predominance of disorders of growth has been observed in female patients. Short stature was observed in 16 girls and 9 boys, with an average of -3 SD.

One of our patients had a severe growth delay with a weight at -4 SD and a height at -3 SD.

Underweight was found in 20% of patients, normal weight in 75% and overweight in 5% of cases.

Figures 2 and 3 illustrate pubertal development and growth abnormalities in our patients.

### Table II factors influencing pubertal development analysis in our patients

<table>
<thead>
<tr>
<th>Factors</th>
<th>No(%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TD1 duration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- &lt; 5 years</td>
<td>45 (32)</td>
<td>0.8</td>
</tr>
<tr>
<td>- &gt; 5 years</td>
<td>94 (68)</td>
<td>0.02</td>
</tr>
<tr>
<td>HbA1c:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- ≤ 7.5%</td>
<td>10 (7)</td>
<td>0.2</td>
</tr>
<tr>
<td>- &gt; 7.5%</td>
<td>129 (92)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypoglycemia (2-3/week)</td>
<td>51 (36)</td>
<td>0.02</td>
</tr>
<tr>
<td>Microvascular complications</td>
<td>36 (26)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

### DISCUSSION

Puberty is the period of sexual development marking the transition from childhood to adulthood. Generally, it occurs around the age of 11 years for girls and 12 years for boys (1). It involves physical, psychological and social changes that affect diabetes management.

Studies have shown that glycemic control often worsens during adolescence and HbA1c levels may be higher than at any other time (3) This deterioration could be related on the one hand to the body mass increase, which doubles mainly over a period of 2 to 5 years, which increases the insulin requirements. On the other hand, there is an increase in insulin resistance during puberty as a result of growth hormone. In addition, certain behavioral changes and psychosocial difficulties occurring during adolescence also affect glycemic control. (3)

Insulin is known to affect central nervous system functions, including hypothalamic-pituitary-gonadal axis. Thus, insulin deficiency in type 1 diabetics may delay the function of this axis by subsequent delayed release of gonadotropin-releasing hormone (GnRH), leading to pubertal delay (4). Indeed, somatomedin C or IGF-1 (insulin-like growth factor-1) level, which stimulates and promotes growth and puberty by being a direct regulator of GnRH, has been shown to be low in T1D, because of hypoinsulinemia (5). On the other hand, this can be explained also by the increase of the final products of advanced glycation, related to chronic hyperglycemia, thus suppressing the pulse generator GnRH activation and causing a pubertal delay [6].

Baccetti et al. (7), reported lower GnRH pulses in T1D, with subsequent lower FSH, LH, and testosterone levels. Ballester et al. (8) found that T1D could lead to an insulin-dependent decrease in FSH and LH, with a reduction in Leydig cell functions and consequently a decrease in testosterone production.

Girls with type 1 diabetes are more are more likely to be obese or overweight (11). However, the menarche age decreases as the percentile of BMI increases, and vice versa. Ovarian function appears to be modified in adolescent type 1 diabetic patients, pertaining to the disruption of ovarian androgen
production, which could explain the observed menstrual disorders(3).

Regarding factors influencing pubertal development, a German study in a population of T1D children had reported a significant delay in the onset of puberty and the age of menarche. Without causing a delay in adulthood, because all patients have reached sexual maturity (Tanner stage 5) at a normal age. This study also showed that pubertal delay increases with HbA1c and BMI. (9) Another study in Sudan in boys with type 1 diabetes, concluded that chronic hyperglycemia was a factor likely to cause pubertal delay in these boys (10). Pozo et al (12) reported that the degree of affection of growth parameters in boys with T1D is proportional to age of onset, duration of illness and severity.

IN CONCLUSION

Adolescence is a critical phase of development that represents a major challenge for young diabetics, their families as well as for health professionals. Our study shows frequent stuning on uncontrolled patients and old diabetes. Therefore, perfect glycemic control is especially important during puberty for normal pubertal development and growth and to reduce the risk of long-term degenerative complications.

References


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