



ORIGINAL ARTICLE

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

Emilio García-García^{a,*}, Rafael Galera^b, M. Ángeles Vázquez^b, Antonio Bonillo^b

^aUnidad de Endocrinología Pediátrica, Hospitales Universitarios Virgen del Rocío, Sevilla, Spain

^bUnidad de Gestión Clínica de Pediatría Hospital Torrecárdenas, Almería, Spain

Received 18 November 2010; accepted 23 February 2011

KEYWORDS

Puberty;
Menarche;
Type 1 diabetes

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 \pm 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 ($\beta = +0.12$; $p = 0.047$). A negative association was found between body mass index standard deviation score and age at menarche ($\beta = -0.39$; $p = 0.014$).

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.

© 2010 SEEN. Published by Elsevier España, S.L. All rights reserved.

PALABRAS CLAVE

Pubertad;
Menarquia;
Diabetes tipo 1

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.

*Corresponding author.

E-mail address: ggej@hotmail.com (E. García-García).

Pacientes y métodos: Estudio retrospectivo de las niñas diabéticas tipo 1 diagnosticadas antes de la pubertad y seguidas en nuestra consulta que han tenido la menarquia. Todas han sido tratadas desde el debut con insulino terapia intensiva. Se recogieron como variables dependientes las edades al inicio de la pubertad (brote mamario) y a la menarquia y como independientes el tiempo de evolución de la diabetes, el nivel de hemoglobina glucosilada, el requerimiento diario de insulina y el índice de masa corporal (en escala de desviación estándar para cada edad y sexo). Las variables se expresan como media \pm desviación típica. Se utilizó la regresión lineal múltiple con el programa SPSS.

Resultados: Se incluyeron 38 adolescentes. La edad de inicio puberal fue $10,4 \pm 1,1$ años y la edad de la menarquia $12,6 \pm 1,0$ años. El tiempo de evolución de la diabetes fue la única variable relacionada de forma estadísticamente significativa con retraso del inicio puberal ($\beta = +0,12$; $p = 0,047$). El mayor índice de masa corporal se asoció con adelanto de la edad de la menarquia ($\beta = -0,39$; $p = 0,014$).

Conclusión: La cronología de la pubertad en las niñas con diabetes tipo 1 se relaciona con el tiempo de evolución de la diabetes y con el índice de masa corporal.

© 2010 SEEN. Publicado por Elsevier España, S.L. Todos los derechos reservados.

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 disease¹⁻⁶. However, these differences appear to be decreasing. While studies conducted 20 years ago reported a pubertal delay of approximately 12-16 months^{1,5}, publications in the past five years have reported a reduction of this delay to less than six months^{2,4}, 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 complications⁷. While no agreement exists about the insulin regimen to be used in pediatric patients, there is a clear trend towards potentiating the use of intensive treatment^{8,9}.

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 enrolled 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 glycosylated 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 references¹⁰. Obesity was defined as a body mass index greater than 2 SD from 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 \pm 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 glycosylated 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.

Table 1 Variables at onset of puberty (mean \pm standard deviation [range])

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

Table 2 Variables at menarche (mean \pm standard deviation [range])

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

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 ($\beta = +0.12$; $p = 0.047$). The greater body mass index was significantly related to an earlier age at menarche ($\beta = -0.39$; $p = 0.014$) and non-significantly related (because of the small sample size) to age of onset of puberty ($\beta = -0.26$; $p = 0.085$).

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 population¹⁻⁵. 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 dose³.

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 secretion¹². A potential role of ovarian autoimmunity, occurring more commonly in T1DM, has not been elucidated yet¹³.

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 menarche¹⁴. 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 later¹⁵. 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 puberty¹⁷. In Germany, for example, the median age of menarche decreased from 15.5 years in 1869 to 12.5 years in 1978¹⁸.

Table 3 Variables related to age of onset of puberty

Independent variables	Age at onset of puberty (years)					
	Crude β	Standard error	p	Adjusted β	Standard error	p
Time from onset of diabetes (years)	+0.128	0.061	0.04	+0.121	0.059	0.047
Glycosylated hemoglobin levels (%)	+0.064	0.154	0.68			
Body mass index (standard deviation score)	-0.279	0.153	0.07	-0.260	0.147	0.085
Daily insulin dose (IU/kg/day)	+0.942	0.658	0.16			

Table 4 Variables related to age of menarche

Coefficient of determination R ² = 0.25		Age at menarche (years)				
Independent variables	Crude β	Standard error	p	Adjusted β	Standard error	p
Time from onset of diabetes (years)	+0.120	0.057	0.04	+0.085	0.055	0.132
Glycosylated hemoglobin levels (%)	+0.044	0.182	0.81			
Body mass index (standard deviation score)	-0.450	0.150	0.005	-0.390	0.152	0.014
Daily insulin dose (IU/kg/day)	-0.433	0.591	0.47			

In Spain, the timing of puberty was analyzed in the Aragón region in a longitudinal study¹⁰. 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 maybe 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^{11,19}. Body mass index is an accurate reflection of the amount of insulin administered, whereas the dose prescribed to or 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

- Burkart W, Fischer-Gunterhörner E, Standl E, Schneider HP. Menarche, menstrual cycle and fertility in diabetic patients. *Geburtshilfe Frauenhilkd.* 1989;49:149-54.
- Picardi A, Cipponeri E, Bizzarri C, Fallucca S, Guglielmi C, Pozzilli F. Menarche in type 1 diabetes is still delayed despite good metabolic control. *Fertil Steril.* 2008;90:1875-7.
- Rohrer T, Stierkorb E, Grabert M, Holterhus PM, Kapellen T, Knerr I, et al. Delayed menarche in young German women with type 1 diabetes mellitus: recent results from the DPV diabetes documentation and quality management system. *Eur J Pediatr.* 2008;167:793-9.
- Danielson KK, Palta M, Allen C, D'Alessio DJ. The association of increased total glycosylated hemoglobin levels with delayed age at menarche in young women with type 1 diabetes. *J Clin Endocrinol Metab.* 2005;90:6466-71.
- Kjaer K, Hagen C, Sando SH, Eshoj O. Epidemiology of menarche and menstrual disturbances in an unselected group of women with insulin-dependent diabetes mellitus compared to controls. *J Clin Endocrinol Metab.* 1992;75:524-9.
- Codner E, Cassorla F. Puberty and ovarian function in girls with type 1 diabetes mellitus. *Horm Res.* 2009;71:12-21.
- DDCT Research Group. Diabetes Control and Complication Trial: the effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin dependent diabetes mellitus. *N Engl J Med.* 1993;329:977-86.
- Bangstad HJ, Danne T, Deeb LC, Jarosz-Chobot P, Urakami T, Hanas R. 2000 International Society for Pediatric and Adolescent Diabetes (ISPAD) clinical practice consensus guidelines drafts: insulin treatment. *Pediatr Diabetes.* 2009;10 (Suppl12): S82-99.
- Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, et al. American Diabetes Association. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. *Diabetes Care.* 2005;28:186-212.
- Ferrández Longás A. Estudio longitudinal de niños españoles normales desde el nacimiento hasta la edad adulta. Datos antropométricos, puberales, radiológicos e intelectuales. Zaragoza: Fundación Andrea Prader; 2005.
- Elamin A, Hussein O, Tuvemo T. Growth, puberty, and final height in children with type 1 diabetes. *J Diabetes Complications.* 2008;20:252-6.
- Dunger D, Ahmed L, Ong K. Growth and body composition in type 1 diabetes mellitus. *Hormon Res.* 2002;58:66-71.

13. Luborsky J. Ovarian autoimmune disease and ovarian autoantibodies. *J Womens Health Gend Based Med*. 2002;11:585-99.
14. Rosenfield RL, Lipton RB, Drum ML. Thelarche, pubarche, and menarche attainment in children with normal and elevated body mass index. *Pediatrics*. 2009;123:84-8.
15. Bau AM, Ernert A, Schenk L, Wiegand S, Martus P, Grüters A, et al. Is there a further acceleration in the age at onset of menarche? A cross-sectional study in 1840 school children focusing on age and bodyweight at the onset of menarche. *Eur J Endocrinol*. 2009;160:107-13.
16. Frisch R, Revelle R. Height and weight at menarche and hypothesis of menarche. *Arch Dis Child*. 1971;46:695-701.
17. Parent AS, Teilmann G, Juul A, Skakkebaek NE, Toppari J, Bourguignon JP. The timing of normal puberty and the age limits of sexual precocity: variations around the world, secular trends and changes after migration. *Endocrine Reviews*. 2003;24: 668-93.
18. Reibig M. Körperliche Entwicklung und Akzeleration Jugendlicher. Ergebnisse einer Längsschnittuntersuchung an Schülern vom 12-16. Lebensjahr. Berlin: Verlag Volk und Gesundheit; 1985. p. 86-8.
19. Roldán Martín MB, Escobar-Morreale H, Alonso BM, Barrio CR. Crecimiento puberal, talla final y ganancia ponderal en niñas con diabetes mellitus tipo 1 diagnosticadas en estadio prepuberal. *An Esp Pediatr*. 1999;51:493-8.