Early age at menarche: A risk factor for overweight or obesity in patients with type 1 diabetes living in urban areas?

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ABSTRACT

Aims: Determine the relationship between age at menarche, glycemic control and cardiovascular risk factors in patients with type 1 diabetes living in urban areas.

Methods: This was a multicenter cross-sectional study conducted in 20 cities in four Brazilian geographic regions. Data were obtained from 1527 female patients, 59.3% Caucasians, aged 25.1 ± 10.6 years. Diabetes duration was 11.4 ± 8.1 years. Age at menarche was stratified in four groups: 8–11 (group 1, early menarche), 12 (group 2), 13 (group 3) and 14–18 years (group 4, late menarche).

Results: The mean age at menarche was 12.7 ± 1.7 years without difference among geographical regions, economic status, level of care and ethnicity. BMI had an inverse correlation with age at menarche ($r = -0.14$, $p < 0.001$). No significant difference was observed among the four groups for blood pressure, lipid profile and diabetes-related chronic complications. Logistic regression analysis showed that early age at menarche, 8–11 years (odds ratio (ORs) 1.77 [1.30–2.41], $p < 0.001$) and duration of diabetes [ORs 1.01 (1.00–1.03), $p = 0.02$], were related to greater risk of patients' overweight or obesity; adherence to diet [ORs 0.78 (0.60–0.93), $p = 0.01$], physical activity [ORs 0.75 (0.94–0.94), $p = 0.01$], and lower insulin dose (U/kg) [ORs 0.54 (0.59–0.90), $p = 0.001$] were related to lower risk for overweight or obesity.

Conclusions: Early menarche occurred in 23.4% of women with type 1 diabetes living in Brazilian urban areas and was strongly associated with overweight/obesity in pubertal/adult life. Further studies are warranted to establish the relationship between early menarche, glycemic control and cardiovascular risk factors.

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1. Introduction

Puberty is an early life event that may have several relations to later life diseases risks. Age at menarche; the age when girls present their first menstruation; is an important indicator of growth and sexual maturation. It is usually well recalled by adult women and is usually a reliable measure of pubertal initiation [1].

Age of menarche onset has been decreasing in girls all over the world in the past century [2–4] and also in Brazil in recent decades [5]. This change can result from several factors such as environment, psychological stress, chronic diseases, genetics, ethnicity, overweight/obesity, childhood diet, obesity, lifestyle and socioeconomic status [6].

Earlier age of menarche onset has been associated with several adverse outcomes, which include type 2 diabetes [7,8] obesity [9,10], cardiovascular diseases [11], metabolic syndrome [12] and all causes mortality, showing that the timing of pubertal development may have lifelong effects on a woman's health [13]. The majority of studies found an association of adverse metabolic outcomes with early pubertal maturation [7–13], and a strong relation with increased adiposity [9,10].

So far, many kinds of deviations from normal sexual development have been described in women with type 1 diabetes, like early and delayed menarche timing [14], menstrual cycle irregularities and early menopause [15]. In general, a higher age at menarche is observed in women with type 1 diabetes, in comparison to controls of the same population [16], but this difference is not so significant. The influence of glycemic control upon age at menarche is still controversial [14,16]. Some studies have shown the influence of HbA1c levels upon age at menarche [16,17], but this is not confirmed by other authors [14]. In fact, the Wisconsin study showed that high HbA1c levels detected 3 years before menarche delayed its onset [16]; also the Barbara Davis Center's study has examined HbA1c levels three months prior to menarche and also found that higher levels of HbA1c were associated with a delay in the age at menarche. In the USA and Europe, different studies have also shown that women who had type 1 diabetes diagnosed before menarche had a lag time of delayed age at menarche varying from 1.3 to 6 months [14,16,17]. The Brazilian Type 1 Diabetes Study Group (BrazDiab1SG) is a survey that analyzed the demographic, clinical, and economic data of patients with type 1 diabetes who received medical care at public clinics in Brazil. In the present study we aimed to investigate the relationship between age at menarche and glycemic control and cardiovascular risk factors.

2. Patients and methods

This multicenter, cross-sectional, observational study was conducted between December 2008 and December 2010 in 28 public secondary (ambulatory outpatient clinics) and tertiary care-level clinics (ambulatory outpatient clinics in university hospitals) located in 20 cities in four Brazilian geographic regions (north/northeast, mid-west, southeast, and south). The details of the data collection methods have been published previously [18,19]. All patients received healthcare from the National Brazilian Health Care System (NBHCS) and lived in urban areas. All eligible participating centers had a diabetes clinic with at least one endocrinologist, which provided data from a minimum of 50 consecutive outpatients with diagnosis of type 1 diabetes who regularly attended the clinic. A total of 3591 (2010, 56% female) patients were included in the study. All patients were diagnosed between 1960 and 2010. Patients who did not fulfill these criteria were excluded from the study. For the present report, among the 2010 enrolled women, only those reporting age at menarche between 8 and 18 years (completed whole years) were included (n = 1527, 76%). Patients that had menarche before 8 years and after 18 years were excluded because they might present a background pathology. Women who did not have menarche (n = 467, 23.2%), women who reported menarche after 18 years (n = 5, 0.2%), women with missing information for age at menarche (n = 11, 0.5%) were excluded.

The local ethics committees of each center approved the study (Appendix 1). Written informed consent was obtained from all patients or their parents, as appropriate.

Demographic, educational, economic and the following variables were assessed in an interview by a questionnaire during a clinical visit: age, age at diagnosis, age at the first menstruation, duration of diabetes, height (m), weight (kg), blood pressure, self-reported adherence to the diet (defined as following at least 80% of the time of the reported diet), self-reported physical activity (at least once a week), self-reported birth weight, comorbidities, smoking status, use of metformin, of any antihypertensive agent and of any type of statins.

The levels of glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides measured at the last clinical visit were obtained from medical records. Patients with a diabetes duration greater than or equal to five years were screened for chronic diabetes-related complications: retinopathy (by fundoscopy; classified as absent, non-proliferative, or proliferative), clinical nephropathy (according to ADA recommendations [20]), macrovascular diseases (clinical coronary artery disease, stroke, and peripheral vascular disease), and foot pathologies. The following ADA goals for adequate metabolic and clinical control [20] were adopted by the (BrazDiab1SG): Good glycemic control (HbA1c at goal) was defined as HbA1c levels of <58 mmol/mol (7.5%) for patients with type 1 diabetes between 13 and 19 years old; <64 mmol/mol (8%) for patients between 6 and 12 years old; between 58 mmol/mol (7.5%) and 69 mmol/mol (8.5%) for patients < 6 years old; and <53 mmol/mol (7%) for adult patients (20). Poor glycemic control was defined as HbA1c levels higher than 75 mmol/mol (9%).

In adults, hypertension was defined as a sBP $\geq$ 140 mmHg and/or dBP $\geq$ 90 mmHg obtained during the last visit [18,19] or self-reported and in children and adolescents as an sBP or dBP $\geq$ 95th percentile for age, sex and height [21].

The body mass index (BMI) was determined by dividing an individual's weight (kg) by the square of the height (m^2). Overweight was defined as a BMI $\geq$ 25 kg/m^2, and obesity was defined as a BMI $\geq$ 30 kg/m^2 [20]. In children and adolescents, overweight was defined as a BMI of $\geq$85th percentile for age and gender, and obesity was defined as a BMI of $\geq$95th