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The Association of Increased Total Glycosylated Hemoglobin Levels with Delayed Age at Menarche in Young Women with Type 1 Diabetes

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Abstract

Context: Delayed menarche is associated with subsequent reproductive and skeletal complications. Previous research has found delayed growth and pubertal maturation with type 1 diabetes and with poor glycemic control. The effect of diabetes management on menarche is important to clarify because tighter control might prevent these complications.

Objective: To investigate age at menarche in young women with type 1 diabetes, and examine the effect of diabetes management (e.g. total glycosylated hemoglobin (GHb) level, number of blood glucose checks, insulin therapy intensity, insulin dose) on age at menarche in those diagnosed before menarche.

Design: The Wisconsin Diabetes Registry Project is a follow-up study of a type 1 diabetes population-based incident cohort initially enrolled 1987 – 1992.

Setting: Twenty-eight counties in south-central Wisconsin.

Patients or Other Participants: Recruited through referrals, self-report, and hospital/clinic ascertainment. Individuals with newly diagnosed type 1 diabetes, <30 years old, were invited to participate. Of 288 young women enrolled, 188 reported menarche by 2002; 105 were diagnosed before menarche.

Interventions: Not applicable.

Main Outcome Measure: Age at menarche.

Results: Mean age at menarche was 12.78 years, compared to 12.54 years in the United States ($p = 0.01$). Ages at menarche and diagnosis were not associated. For those diagnosed before menarche, age at menarche was delayed 1.3 months with each one percent increase in mean total GHb level in the three years prior to menarche.

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Conclusions: Age at menarche was moderately delayed in young women with type 1 diabetes. Delayed menarche could potentially be minimized with improved GHb levels.

Keywords

diabetes mellitus; insulin-dependent; longitudinal studies; menarche; risk factors

Abbreviations

BMD, bone mineral density; BMI, body-mass index; GHb, glycosylated hemoglobin; GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone; NHANES III, Third National Health and Nutrition Examination Survey; SD, standard deviation; SE, standard error

Delayed menarche is associated with irregular menstrual cycles (1;2) and decreased bone mineral density (BMD) (2;3), and therefore potentially with subsequent sub-fertility and osteoporosis. Later onset of menarche may occur with type 1 diabetes. Diabetes management (e.g. total glycosylated hemoglobin (GHb) level, number of blood glucose checks, insulin therapy intensity, insulin dose) is a modifiable factor that might prevent delayed menarche and later reproductive and skeletal complications.

Previous research found delayed growth and puberty with type 1 diabetes (4), and an association between poor glycemic control and retarded growth (5). Findings on the effect of type 1 diabetes specifically on age at menarche have been inconsistent. In 1954, Bergquist first described delayed menarche in patients with type 1 diabetes (6). Clinical studies and retrospective surveys that followed found delayed (7–11) and normal (5;12–16) ages at menarche. The first U.S. population-based study during the 1950s described delayed menarche (17). A more contemporary population-based study in Denmark reported a normal age at menarche (1). The different results could reflect variation in the select clinic populations and comparison data used, the ages at which menarche was recalled, and the effect of recent improvements in diabetes management.

Data on how type 1 diabetes and management influence age at menarche are limited. Age at diagnosis has had both negative (1;7) and null (11;12;14–17) associations with age at menarche. One study found delayed menarche associated with diabetic complications (14), which are related to GHb levels. Another clinical study found both low and high mean GHb levels before menarche associated with a delay (16).

In light of advances in diabetes management during recent decades, this study compares age at menarche in young women from the U.S. with that of a contemporary population-based cohort from Wisconsin with type 1 diabetes to determine whether age a menarche remains delayed. The longitudinal nature of this study provides the unique opportunity to examine the effect of diabetes management on age at menarche.

Subjects and Methods

Population

The Wisconsin Diabetes Registry Project is a population-based incident cohort of individuals with type 1 diabetes. Methods of recruitment and case ascertainment have been published previously (18). Briefly, recruitment occurred through referrals from physicians, nurses, and diabetes educators, and through self-report. Every three months, hospitals and clinics in the study area were called to ascertain missed cases. All individuals identified with newly diagnosed type 1 diabetes, <30 years old, and living in 28 contiguous counties in south-central Wisconsin, were invited to enroll between May 1987 and April 1992. A total of 733 individuals

were initially identified (an estimated overall ascertainment rate of 82%), of whom 597 agreed to enroll. Study approval was obtained from the Institutional Review Board at the University of Wisconsin and participants provided written informed consent at enrollment and at subsequent visits.

Among the 288 females enrolled, 188 reported menarche by September 2002. The 188 young women were similar to the women in the initial cohort except for a slightly older age at diagnosis (12.5 vs. 11.3 years, respectively, $p = 0.06$) and a smaller percentage of racial minorities (3.7% vs. 7.6%, $p = 0.06$). Of the 188 young women, 105 were diagnosed before menarche.

Age at menarche (dependent variable)

Individuals in the Registry participated in exams conducted by study personnel using standardized methods at four months (baseline), four, seven, and nine years after diagnosis. The date of menarche was collected during the exam with a self-administered reproductive health questionnaire. Age at menarche was calculated as the date of menarche reported at the first exam following the onset of menses minus the date of birth (in years rounded to the hundredths decimal). The concurrent age at menarche in the general U.S. population was obtained from the Third National Health and Nutrition Examination Survey (NHANES III), 1988 – 1994 (19;20).

Diabetes management (independent variables)

Number of blood glucose checks, insulin therapy intensity, and insulin dose— Questionnaires on diabetes care and management were mailed semiannually after enrollment. The number of blood glucose checks and insulin injections, and insulin dose were used for this analysis. Insulin injections were divided into two groups: intensive therapy (≥three injections per day or use of an insulin pump) or non-intensive therapy (< three injections per day). Insulin dose was analyzed as units of insulin per kilogram weight per day. Among the girls diagnosed prior to menarche, 100 (95%) returned at least one questionnaire within the three years prior to menarche.

Total GHb level—During each study exam, venipuncture was preformed for determination of total GHb level. Participants were also asked to submit a blood specimen from each routine visit to their clinic/physician, or every four months if no visit was scheduled. Prestamped mailing kits containing 5-ml EDTA-treated vacutainers were provided. Among those diagnosed prior to menarche, 102 girls (97%) had at least one GHb determination within the three years prior to menarche. The number of blood samples provided ranged from one to 11, with a mean of 5.5.

Whole blood samples were analyzed for total GHb level within seven days of collection by Isolab GlycAffin microcolumn affinity chromatography (Isolab, Akron, OH) (21). Assays were repeated when duplicate within-assay values differed by more than 2.5 % of their mean. Internal standards stored at −70°C were evaluated for stability over time and showed no trend. Within-assay variability was ±1.1% for case samples and ±0.9% for internal standards. Internal standards from nondiabetic children and young adults had a mean (standard deviation, SD) total GHb level of 5.5 (0.8)%.

Race, duration, and BMI (adjustment variables)

Demographic information including race was collected during telephone interviews with all original participants or parents/guardians two months after diagnosis. The date of diagnosis of type 1 diabetes, defined as the date of first insulin use, was determined from medical records.

For all 105 young women diagnosed prior to menarche, duration of diabetes at menarche was defined as the number of years from the date of diagnosis to the date of menarche.

The semiannual questionnaires collected self-reported data on height and weight. At study exams, height was measured by a standard height rod, and weight was measured with a Healthometer physician beam scale. Data on height and weight from both the questionnaires and exams were used for this analysis. Body-mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and converted to z-scores using data from NHANES III, 1988–1994 (22;23). Z-scores were calculated as the difference between participant BMI and the mean BMI of the respective age- and sex-matched group from NHANES III, divided by the respective BMI SD. BMI data within the three years prior to menarche were available on 93 (89%) young women diagnosed before menarche.

Statistical analyses

All statistical tests were two-sided and considered significant at $p < 0.05$. Analyses were performed using SAS statistical software (SAS Institute, Cary, NC).

Age at menarche—Means, SDs, percentiles, and percentages were used to describe the 188 young women and age at menarche. Differences in *mean* age at menarche were tested by T- and F-tests. Differences in the *median*, 10^{th} and 90^{th} percentile age at menarche were tested by determining whether the NHANES age at menarche fell outside the $1-\alpha/2$ confidence interval for the respective Registry percentile age at menarche. The Spearman correlation coefficient was calculated between ages at diagnosis and menarche.

Age at menarche and diabetes management—Mean total GHb level, number of blood glucose checks, insulin therapy intensity, insulin dose, BMI, and BMI z-score were computed for each of the 105 girls diagnosed before menarche by taking the average across the three years prior to menarche. For those diagnosed less than three years prior to menarche, the means were calculated using available data. Three years was chosen to capture the period of extensive growth and endocrine changes before menarche, including changes that affect GHb levels and insulin need (24), and to minimize the reverse effect of menstrual cycling on glucose metabolism (25).

Multivariable ordinary linear regression models tested the associations between the independent variables (total GHb level, number of blood glucose checks, insulin therapy intensity, insulin dose) and age at menarche in the subgroup of young women diagnosed before menarche. Models were adjusted for BMI z-score and race because of their associations with age at menarche (19;20) and diabetes management (26;27), and diabetes duration because of its association with GHb levels (28). Due to missing values, the multivariable analysis was based on 90 participants. Univariate results from the 90 were similar to those from the 105 young women diagnosed prior to menarche. Variables that were statistically significant and/or affected the diabetes management coefficients were retained for the final model. Two-way interactions were tested but none were significant. One participant with age at menarche over 18 years was excluded from the subgroup analysis because of her influence on conclusions.

Results

Age at menarche

The 188 young women were predominantly white with BMI at the baseline Registry exam approximately equal to that of U.S. girls in the same age range (mean BMI z-score not different from zero, $p = 0.36$) (Table 1). The average total GHb level within the first year of diabetes was 9.25%. The mean (SD) age at menarche was 12.78 (1.33) years and ranged from 9.59 to

18.10 years. The mean was significantly later than the overall mean age at menarche in the U.S. population, combined for whites and blacks, at 12.54 years ($p = 0.01$) (20). Eighteen percent of the young women with type 1 diabetes had an age at menarche ≥14 years, compared to approximately 4% of the young women in the U.S. ($p < 0.001$) (19;20).

Stratifying by race, white women with type 1 diabetes had a later age at menarche (12.82 years) than white women in the U.S. population (12.60 years) ($p = 0.03$) (20). The difference in age at menarche for black women with type 1 diabetes (11.71 years) and in the U.S. population (12.14 years) (20) was not significant ($p = 0.39$). In young women with type 1 diabetes, menarche occurred about a year earlier in blacks compared to whites ($p = 0.03$).

Age at menarche for select percentiles were compared between the Registry and NHANES III population (19). There was a significant delay in the median age at menarche among young women with diabetes (12.75 years) versus that in US women (12.43 years) ($p < 0.001$). The age by which 10% of girls reached menarche was similar for girls with type 1 diabetes (11.04 years) and in the U.S. (11.11 years). However, 90% of girls in the U.S. reached menarche by age 13.75, while 90% of girls with type 1 diabetes did not reach menarche until age 14.44 ($p < 0.001$).

The mean (SD) age at diagnosis of type 1 diabetes was 12.48 (6.29) (Table 1). The association between age at menarche and age at diagnosis was not significant ($r = -0.09$, $p = 0.23$).

Age at menarche and diabetes management

For the 105 girls diagnosed prior to menarche, total GHb levels were elevated during the three years prior to menarche despite the increased number of blood glucose checks (29) and insulin dose per day, and the large percentage of girls who used intensive insulin therapy (Table 2). BMI was approximately equal to that for U.S. girls in the same age range (mean BMI z-score not different from zero, $p = 0.31$). Duration of diabetes at menarche ranged from six months to 12 years, with a mean of 4.67 years (median 3.71 years).

Univariate analysis indicated that mean total GHb level (%) in the three years prior to menarche was the only diabetes management factor significantly associated with age at menarche (years) ($\beta = 0.10$, $p = 0.05$) (Table 2). Higher number of blood glucose checks and insulin dose were nonsignificantly associated with a younger age at menarche. Age at menarche was not associated with insulin therapy intensity. BMI z-score had a significant negative association, and diabetes duration had a significant positive association, with age at menarche.

Multivariable analysis showed that mean total GHb level (%) in the three years before menarche remained the only diabetes management factor associated with age at menarche (years) after adjustment for race and BMI z-score ($\beta_{GHb} = 0.11$, $p = 0.04$; $r^2_{Model} = 0.13$, $p = 0.009$). On average, age at menarche was delayed 1.3 months with each one percent increase in mean total GHb level in the three years prior to menarche, for whites and blacks, across all BMI z-scores.

Discussion

Our study demonstrates that age at menarche is delayed three months, on average, in young women with, or who later develop, type 1 diabetes compared to the concurrent overall mean age at menarche in the U.S. population. More than 50% of the young women with type 1 diabetes in our cohort had delayed menarche. Furthermore, a significant shift in the distribution towards later onset of menarche was indicated by the eight month delay in the age by which 90% of girls with type 1 diabetes reached menarche.

Delayed menarche is associated with irregular menstrual cycles (1;2) and decreased BMD (2;3). Anai et al. found significant odds ratios for irregular menstrual cycles of 5.9, 13.7, and 73 among those with menarche at 13-, 14-, and >14 years, respectively, versus those with menarche at ≤12 years. With each one year delay in age at menarche after age 12, there was approximately four points decline in BMD score (the ratio [as a percent] of mean BMD in those with delayed menarche to the mean BMD of young adult women). Based on these data in the literature, the 18% of young women with type 1 diabetes in our cohort who have an age at menarche ≥14 years may be at significantly increased odds of irregular menstrual cycles and reduced peak bone mass, with potential subsequent risk of sub-fertility and osteoporosis.

Our study is the first prospective population-based study to identify GHb levels in the years prior to puberty as an important modifiable factor affecting menarche in type 1 diabetes. Even after controlling for race and BMI z-score, increased total GHb level significantly delayed age at menarche. This association was indirectly suggested previously by an average seven month delay in age at menarche in young women with diabetic retinopathy/nephropathy (14). A recent clinical study found that low and high mean GHb levels in the years before menarche were associated with later age at menarche (16). The number of blood glucose checks, insulin therapy intensity, and insulin dose were not associated with age at menarche.

Our study found no association between age at menarche and age at type 1 diabetes diagnosis. Previous research analyzing age at diagnosis as a continuous variable similarly showed no association (12;14;17). Studies that divided age at diagnosis into categories <10–11 and ≥10–11 years found negative (1;14), positive (12), and no (17) association with age at menarche. Kjaer et al. showed a negative dose-response relationship between categorical age at diagnosis and mean age at menarche (1).

Studies that compared mean age at menarche between the two groups of women diagnosed *prior to* and *after* menarche often found statistically significant differences (7;8;14). Such categorization inherently biases age at menarche upward in those diagnosed prior to menarche and downward in those diagnosed after menarche. This bias becomes apparent when we look at our type 1 diabetes cohort data. The mean ages at menarche in those diagnosed *prior to* and *after* menarche were 13.06 and 12.35 years, respectively. Age at diagnosis was unrelated to age at menarche, yet this categorization makes it appear as though diagnosis before menarche delays menarche, and that menarche occurs even earlier than the general population in those diagnosed after puberty. One of the strengths of our study is the combination of women diagnosed before and after menarche to limit this bias.

The mean three month delay in age at menarche identified in our study falls between the results of two previous population-based studies on age at menarche in type 1 diabetes. The first from the Children=s Hospital of Pittsburgh Type 1 Diabetes Registry for 1950 – 1965 showed that the mean age at menarche in women with type 1 diabetes was delayed one year compared to two control groups consisting of the probands' sisters and women from the general population (17). The one year delay in menarche may reflect a time period effect. The Pittsburgh women entered puberty during the mid-twentieth century at a time when tight diabetes control was more difficult to achieve. Consistent with our results demonstrating an association between increased total GHb levels and delayed menarche, the probable increased glycemic exposure in the Pittsburgh group may have resulted in the longer delay in the onset of menarche compared to the Wisconsin cohort.

The second population-based study by Kjaer et al. reported no difference in the mean age at menarche between all women with type 1 diabetes between 18 – 49 years old in the Funen county of Denmark in 1987 and a random sample of all nondiabetic women from the underlying general population (1). However, similar to our study, the range of age at menarche reported

in those with diabetes (9–30 years) was wider than among the nondiabetic women (10–17 years). The absence of a delay in menarche may be the result of increased error in the recall of age at menarche by the older women in the population (30). Age at recall for the Danish study extended to 49 years whereas the oldest age at recall in our study was approximately 30 years. This bias by older women may also have underestimated the delay found in the Pittsburgh study. Our study provides the more valid current estimate of age at menarche in young women from the U.S. with type 1 diabetes.

Several plausible biological explanations exist for delayed menarche in young women with type 1 diabetes. First, insulin receptors have been found on ovarian cells (31) and research supports the role of insulin in ovarian function (32). Ovarian physiology and steroidogenesis is impaired in female animals with diabetes (33). However, research on women with type 1 diabetes has found decreased (34), increased (35), and normal (36) levels of estradiol compared to nondiabetic women. Thus, the lack of tightly regulated insulin levels in type 1 diabetes, and subsequent increased levels of GHb, may affect ovarian maturation and function.

Second, the hypothalamic-pituitary-ovarian axis has been shown to be disrupted in type 1 diabetes. For example, research findings have shown low serum levels of luteinizing hormone (LH), a diminished response by LH to gonadotropin-releasing hormone (GnRH), and an attenuated release of GnRH from the hypothalamus in type 1 diabetes. These factors may also be linked to GHb levels (33). Therefore, a disruption in this axis by type 1 diabetes may delay ovarian maturation and sex hormone production, leading to delayed menarche.

Third, increased levels of ovarian autoantibodies have been found in adolescent girls with type 1 diabetes compared to nondiabetic controls (37). Ovarian autoantibodies are associated with impaired ovarian function (38) and may therefore be an additional factor influencing delayed menarche in type 1 diabetes.

Fourth, it has been proposed that the weight loss at diabetes diagnosis may be associated with a later age at menarche (17) through the reduction of body fat needed for menstruation to occur (39). However, recent research shows an increase in weight and body fat in children with type 1 diabetes after diagnosis, particularly in girls, related to the heightened intensity of insulin therapy (40). Our study found that BMI was approximately equal to that of U.S. girls in the same age range. Historically, the decrease in body fat associated with poor diabetes control may have delayed menarche, but with improved methods of diabetes management and increased BMI, the small but significant delay in age at menarche demonstrated here is unlikely to be explained by decreased body fat.

There are limitations to our study. First, participants were predominantly white, thus we were not able to provide a reliable estimate of age at menarche in black girls with type 1 diabetes. Any interpretations of the data on menarche in black girls should therefore be limited. Second, the young women diagnosed with type 1 diabetes after menarche had to rely on recall to report their date of first menses. Research on the recall of age at menarche has found that there is more absolute error in reporting when the woman’s age at menarche is older. However, the error in recall is relatively small and overall there is a tendency to report younger age at menarche (30).

Third, data were lacking on the presence of comorbid conditions that might affect menstruation (e.g. thyroid disease and polycystic ovary syndrome) to adjust for potential residual confounding in the analysis. Lastly, the 188 young women reporting menarche differed from the women in the initial cohort by age at diagnosis. The slightly older age at diagnosis of the study group should not have affected our estimates because age at diagnosis was not related to age at menarche.

In conclusion, our study showed that age at menarche remains moderately delayed in young women with type 1 diabetes compared to the U.S. population. This study was also the first population-based study to identify GHb control as an important modifiable factor affecting menarche in type 1 diabetes.

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23. **National Center for Health Statistics** 2003 Table 9. Body mass index (kilograms divided by height in meters squared) for females 20 years and over-number of examined persons, mean, standard error of the mean, and selected percentiles, by race-ethnicity and age: United States, 1988–1994. Available from http://www.cdc.gov/nchs/about/major/nhanes/Anthropometric%20Measures.htm Accessed January 2004
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TABLE 1

Characteristics of the young women with type 1 diabetes reporting menarche from the Wisconsin Diabetes Registry cohort, 1987 – 2002 (n=188)

Characteristic	Description
Age at diagnosis (years)	
Mean (SD)	12.48 (6.29)
Minimum	1.14
Maximum	29.84
Racial composition, n (%)	
White	181 (96)
Black	7 (4)
BMI at baseline exam	
Mean (SD)	20.24 (4.29)
BMI z-score at baseline exam[a]	
Mean (SD)	0.03 (0.45)
Total GHb level (%) during first year of diabetes[b]	
Mean (SD)	9.25 (2.49)
Age at menarche (years)	
Mean (SD), Overall	12.78 (1.33)[c]
Mean (SD), White	12.82 (1.32)[d]
Mean (SD), Black	11.71 (1.22),[ef]
Minimum	9.59
Maximum	18.10

SD, standard deviation; BMI, body-mass index; GHb, glycosylated hemoglobin

[a] BMI was transformed to z-scores using age- and sex-specific means and standard deviations from the U.S. population-based NHANES III (1988–1994)

[b] Mean of within-individual mean total GHb levels

[c] p = 0.01, compared to mean age at menarche, 12.54 years, in the combined white and black U.S. population from NHANES III

[d] p = 0.03, compared to mean age at menarche, 12.60 years, in the white U.S. population from NHANES III

[e] p = 0.39, compared to mean age at menarche, 12.14 years, in the black U.S. population from NHANES III

[f] p = 0.03, compared to mean age at menarche in white young women with type 1 diabetes

TABLE 2

Characteristics of, and univariate associations with age at menarche (years) in, those diagnosed with type 1 diabetes prior to menarche from the Wisconsin Diabetes Registry cohort, 1987 – 2002 (n=105)

	Mean[a] (SD) / %	βvalue	SE (β)	p-value
Total GHb level (%)	10.99 (2.45)	0.10	0.05	0.05
No. of blood glucose checks	3.44 (1.00)	−0.19	0.12	0.13
Insulin therapy intensity[b]	Nonintensive = 62% Intensive = 38%	0.07	0.26	0.79
Insulin dose (units/kg)	1.00 (0.27)	−0.49	0.47	0.29
BMI	19.53 (2.39)	0.05	0.05	0.36
BMI z-score(0.1 z-score)[c]	−0.03 (0.30)	−0.12	0.40	0.004
Race[b]	White = 96% Black = 4%	−0.95	0.62	0.13
Duration at menarche (years)	4.67 (2.75)	0.09	0.04	0.04

SD, standard deviation; SE, standard error; GHb, glycosylated hemoglobin; BMI, body-mass index

[a] Mean of within-individual means during three years prior to menarche

[b] Intensive and blacks coded as 1, nonintensive and whites coded as 0

[c] BMI was transformed to z-scores using age- and sex-specific means and standard deviations from the U.S. population-based NHANES III (1988–1994)