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Review

Delayed menarche in children and adolescents with type 1 diabetes mellitus: a systematic review and meta-analysis

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Highlights

- Delayed menarche is associated with the onset of type-1 diabetes mellitus (T1DM).
- The age at menarche was later in patients who had menarche after T1DM diagnosis than in healthy subjects and those who had menarche before T1DM diagnosis.
- Awareness of delayed menarche in patients with T1DM should be addressed so that comprehensive management can be provided to achieve a higher quality of life and prevent further complications.

Abstract. Several studies have reported an association between age at menarche and the onset of type-1 diabetes mellitus (T1DM). This review compared the age at menarche in patients who had menarche after T1DM diagnosis with that of patients who were healthy and/or had menarche before T1DM diagnosis. Searches were conducted using four databases. The outcome was the age at menarche of patients who had menarche after T1DM diagnosis and patients who were healthy and/or had menarche before T1DM diagnosis. A qualitative analysis was performed using the JBI (Joanna Briggs Institute) Critical Appraisal. Quantitative analysis of the mean differences was performed using Revman 5.4 tool. A total of 1952 studies were obtained from the initial search. The final results were 13 articles that met the inclusion criteria for the qualitative assessment and eight for the quantitative assessment. Eight studies included 1030 patients who had menarche after being diagnosed with T1DM and 1282 patients who were healthy and/or had menarche before T1DM diagnosis. The meta-analysis showed a cumulative effect on a mean difference of 0.87 (95% CI: 0.75; 0.99, p-value < 0.00001), indicating a later age at menarche in patients who had menarche after T1DM diagnosis. The age at menarche was later in patients who had menarche after T1DM diagnosis compared to healthy subjects and those who had menarche beforehand.

Key words: delayed menarche, type 1 diabetes mellitus, children, adolescents

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Introduction

Type 1 diabetes mellitus (T1DM) is an autoimmune disease in which pancreatic beta cells are damaged for months to years. As these cells play a role in producing insulin, T1DM causes absolute insulin deficiency (1). The risk of T1DM is 0.4% in individuals without a family history, 1–4% in children with mothers with T1DM, and 3–8% in those with fathers with T1DM (2).

Insulin plays an important role in anabolic processes and affects glucose, lipid, protein, and mineral metabolism and growth. Insulin also plays a role in glucose storage in muscle cells, adipose tissue, and the liver, fatty acid synthesis, stimulation of amino acid uptake, inhibition of fat breakdown in adipose tissue, and stimulation of potassium uptake into cells. Insulin is secreted for metabolism after glucose ingestion. Glucose metabolism requires the secretion of glucokinase (GCK), which in turn, is related to insulin secretion. GCK gene dysfunction disrupts insulin secretion, which causes glucose intolerance and diabetes (3). Insulin also participates in metabolism and reproductive functions that are controlled by the hypothalamus. Insulin receptors act on GnRH neurons; therefore, a lack of insulin may disrupt normal GnRH function, delaying puberty (4). Diabetes mellitus is associated with increased levels of advanced glycation end products, which may disrupt GnRH pulse generator activation. Disruption of GnRH pulse generator activation is associated with delayed puberty (5).

The association between T1DM and delayed puberty needs to be understood as delayed puberty may cause decreased bone mineral density and irregular menstruation (6). A systematic review and meta-analysis were performed to compare the age at first menarche in patients who had menarche after T1DM diagnosis, with healthy subjects and those who had menarche before T1DM diagnosis, to optimize comprehensive care and management of T1DM as well as to prevent delayed puberty as a complication.

Method

Search strategy

Studies were selected according to PRISMA from four databases: PubMed, Scopus, Embase and ScienceDirect (7). The search terms were based on the PICO criteria: patient (children, adolescents, teenagers, pediatric), intervention (type 1 diabetes mellitus), comparison intervention, and outcome (delayed puberty or delayed menarche). The search terms used were (((((Children) OR (adolescent)) OR (teenager)) OR (pediatric)) AND (type 1 diabetes mellitus)) AND ((delayed puberty) OR (delayed menarche)).

Study selection and eligibility criteria

Studies were screened based on the inclusion and exclusion criteria. The inclusion criteria were children under 18 yr of age diagnosed with type 1 diabetes mellitus, menarche data were available, papers published in English, and full texts were available. The exclusion criteria were non-English studies, unavailable menarche data, and unavailable full texts. Duplicate studies were removed using the EndNote Software. The authors retrieved papers in English so that the authors could understand the evaluation of the reports. However, in this study, the authors still evaluated several reports from East Asia, including China (Mao 2011), Taiwan (HsU 2010), and Japan (Nakamura 2022).

Data collection

Three reviewers independently screened the abstracts and titles to extract data and excluded studies with low applicability. The selected studies were reviewed, and the required data were extracted. The extracted data included author name, title, year of publication, number of samples in the study, population criteria, study location, and outcome data (age at menarche in the study group (post type-1 diabetes mellitus) and control group (pre type-1 diabetes mellitus and healthy subjects). The reviewers also extracted irregular menstruation data from several studies.

Quality assessment

A quality assessment of the included studies was performed using tools based on the study design. In this review, the included study designs were cohort, case-control, and cross-sectional. The Joanna Briggs Institute (JBI) Critical Appraisal tools were used for this systematic review. Cohort studies were assessed using the JBI Critical Appraisal Checklist for Cohort Studies, consisting of 11 items including group similarity, similarity exposure measurement, exposure validity, confounding factors identified, strategy to deal with, measurement outcome, follow-up, and statistical analysis (8). Case-control studies were measured using the JBI Critical Appraisal Checklist for case-control studies, consisting of 10 items including group comparability, case matches, criteria similarity, exposure measurement, confounding variable identification, confounding variable strategy, outcome assessment, follow-up, and statistical analysis (9). Cross-sectional studies were assessed using the JBI Critical Appraisal Checklist for cross-sectional studies, consisting of eight items including inclusion criteria, study detailedness, measurement validity and reliability, criteria objectivity, confounding variable identification, confounding variable strategy, outcome assessment, and statistical analysis (10).

Statistical analysis

The outcome measured in both the study and control groups was age at menarche. The outcome measured in the study group was age at menarche in patients

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who had menarche after T1DM diagnosis (post-T1DM), whereas in the control group, it was the age at menarche of healthy subjects and/or patients who had menarche before T1DM diagnosis (pre-T1DM). Data were analyzed using RevMan 5.4. Inverse variance was used as a statistical method with a fixed-effects model and mean difference as an effect measure to analyze the data. The 95% confidence intervals (CIs) and heterogeneity were measured and interpreted using forest plots.

Results

Study selection

The study selection is shown in the PRISMA flow diagram (**Fig. 1**). A total of 1952 articles were collected from four databases in the initial hit (101 articles from PubMed, 81 articles from Scopus, 184 from Embase, and 1585 from ScienceDirect), and one from manual searching. We removed 224 duplicate records using EndNote Software (version 20.4), while automation tools removed 1300 articles as ineligible. Three reviewers independently screened the titles and abstracts of the 428 articles. Finally, 13 studies were included in this systematic review, eight of which were used in the quantitative meta-analysis.

Included studies characteristics

The characteristics of the included studies are presented in **Table 1**. The studies consisted of seven cohort, four cross-sectional, and two case-control studies. All the studies were conducted in various locations in Asia (Japan, India, Saudi Arabia, Sudan, Taiwan, and China), Europe (Finland, Greece, Italy, and Germany), and the United States. Of the 2312 participants, there were 1030 participants in the study group (post-T1DM), and 1282 in the control group (healthy and pre-T1DM) (11-23).

Quality assessment

Out of the 13 studies assessed, 5 were marked yes for all items on the JBI Critical Appraisal Tools (**Fig.**

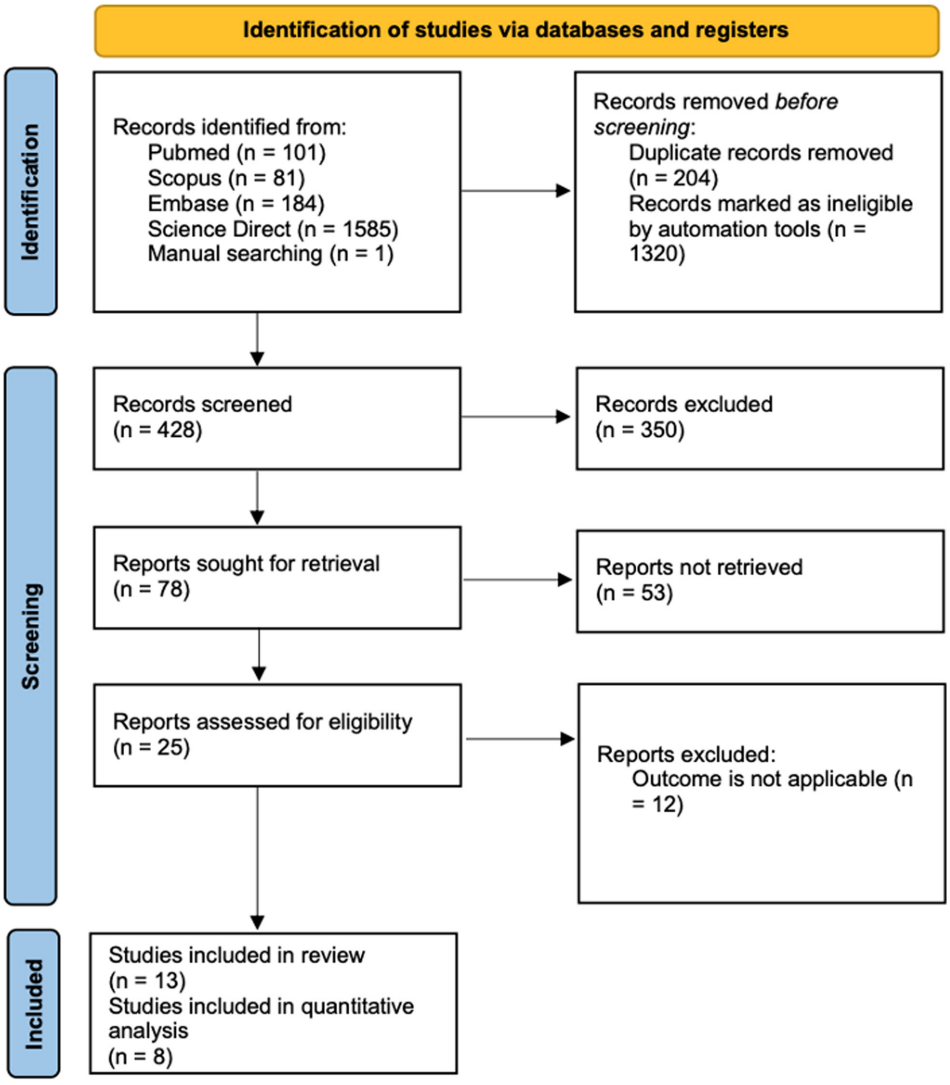

Fig. 1. PRISMA flow diagram.

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Table 1. Included studies characteristics

Study	Population	Study design	Location	Subject
Braham *et al*., 2017 (11)	Female with T1DM aged 13–29 yr old without other types of diabetes (T2DM, MODY) and other hormonal diseases (PCOS, hyperprolactinemia, Cushing syndrome)	Cross sectional	Saudi Arabia	102
Deltsidou *et al*., 2010 (12)	Female with T1DM aged 12–18 yr old	Case control	Greece	286
Elamin *et al*., 2006 (13)	Female with T1DM aged 7–13 yr old	Cohort	Sudan	35
Harjutsalo *et al*., 2015 (14)	Female with T1DM aged 18–85 yr old whose menarche data were available	Cross sectional	Finland	1304
HsU *et al*., 2010 (15)	Female with T1DM aged 10–17 yr old	Case control	Taiwan	81
Kristie *et al*., 2005 (16)	Female with T1DM aged below 30 yr old	Cohort	USA	188
Lombardo *et al*., 2009 (17)	Female with T1DM aged below 20 yr old	Cohort	Italy	93
Mao *et al*., 2011(18)	Female with T1DM aged below 6-10 yr old	Cohort	China	31
Nakamura *et al*., 2022 (19)	Female with T1DM	Cohort	Japan	155
Raha *et al*., 2013 (20)	Female with T1DM	Cohort	India	103
Rohrer *et al*., 2007 (21)	Female with T1DM aged below 20 yr old	Cross sectional	Germany	643
Schweiger *et al*., 2011 (22)	Female with T1DM aged 12–24 yr old who have had menarche at least once without any chronic diseases	Cross sectional	USA	228
Yan Yi *et al*., 2021 (23)	Female with T1DM aged 8–48 yr old who have finished filling out reproductive health questionnaire and never had hysterectomy/oophorectomy before menopause	Cohort	USA	105

T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; MODY, Maturity-onset diabetes of the young; PCOS, polycystic ovary syndrome.

2). Elamin *et al*. (2006), Kristie *et al*. (2005), Lombardo *et al*. (2009), and Hsu *et al*. (2010) did not identify confounding factors or describe strategies used to address these factors (13, 15–17). Harjutsalo *et al*. (2015) and Rohrer *et al*. (2007) did not state whether exposure was measured in the same manner for both cases and controls (14, 21). Harjutsalo *et al*. (2015), Rohrer *et al*. (2007), Schweiger *et al*. (2011), and Raha *et al*. (2013) did not describe strategies used to deal with confounding factors (14, 20–22). All 13 studies were included in this meta-analysis.

Age at menarche of patients who reached menarche before diagnosis of T1DM

The included studies revealed a later age at menarche in patients diagnosed with T1DM as compared to the normal or healthy groups. Patients who reached menarche after T1DM diagnosis had an age at menarche ranging from 12.5 yr old to 13.6 yr old, meanwhile healthy subjects and patients who reached menarche before T1DM diagnosis had an age at menarche ranging from 11.6 yr old to 12.9 yr old. All the studies showed significant differences between the two groups.

These results were supported by the meta-analysis we conducted (**Fig. 3**), which showed a cumulative effect on the mean difference of 0.87 (95% CI: 0.75; 0.99, p-value < 0.00001), indicating a later age at menarche in patients who had menarche after T1DM diagnosis, with the difference approximately 11 mon. All studies revealed a similar trend, with significant mean difference with higher age of menarche in the T1DM group as compared to the latter, with highest mean difference found in a study by Yan *et al.* with mean difference of 1.40 (0.80–2.00) yr (23) (**Table 2**).

Irregular menstruation

Three of the studies have shown irregular menstrual cycles. In a study by Braham *et al*. (2017), 35.42% of the subjects had irregular menstruation after T1DM diagnosis (11). In a study by Schweiger *et al*. (2011), subjects with irregular menstruation after T1DM diagnosis were fewer at 18.38% (22). In comparison, in the study by Deltsidou *et al*. (2010), there is a larger proportion of subjects with irregular menstruation after a T1DM diagnosis at 49.38% (12). Both Braham *et al*. (2017) and Deltsidou *et al*. (2010) reported a higher prevalence of irregular menstruation in patients with T1DM than in healthy subjects or patients with menarche before T1DM diagnosis (11, 12). Schweiger *et al*. (2011) reported a higher percentage of healthy participants. However, this might be explained by the incomparable sample sizes between the two groups (22) (**Table 3**).

Discussion

It was reported that the mean age of girls at menarche was 12.4 yr. This study included 848 schoolgirls in Lisbon, Portugal. (24) These findings are consistent with those reported in Europe and North America, ranging from 12.5–13.5 yr (25–28). Two studies conducted in Indonesia were consistent with these findings, ranging from 12.06 to 12.96 yr (29, 30). In this systematic review and meta-analysis, patients who

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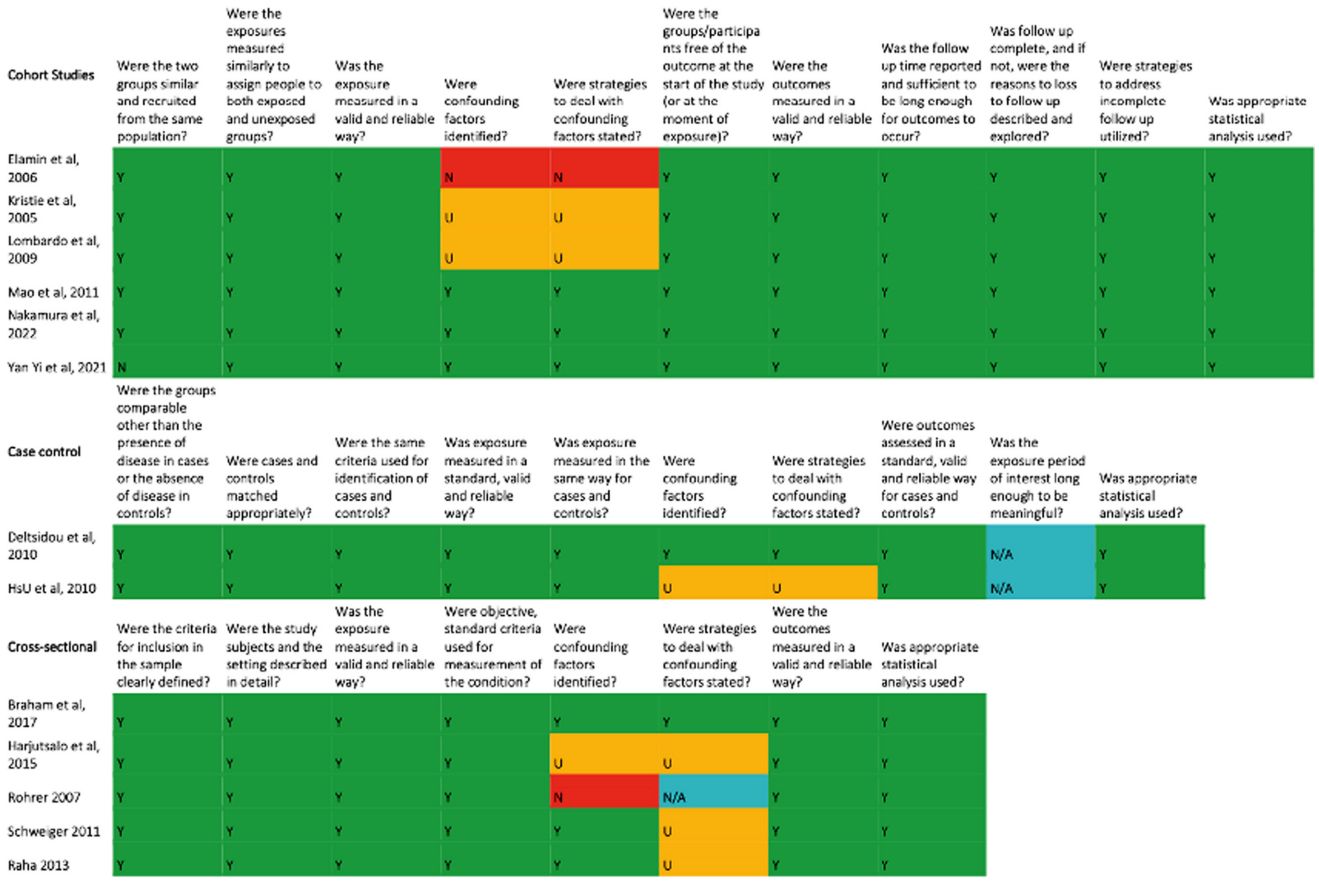

Fig. 2. JBI Critical Appraisal on cohort, case control, and cross-sectional studies. Y, yes; N, no; U, unclear; N/A, not applicable.

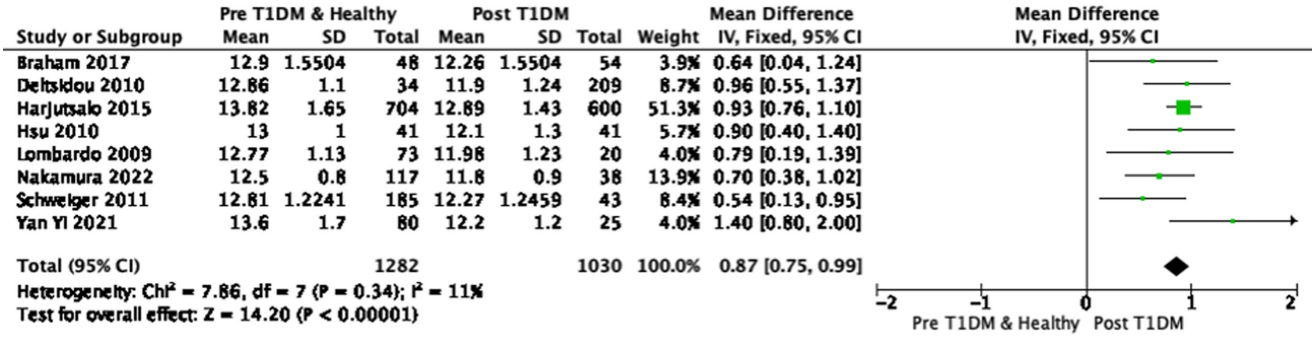

Fig. 3. Forrest plot of average of age at menarche in pre and post T1DM diagnosis. T1DM, type 1 diabetes mellitus.

were diagnosed with T1DM before menarche reached menarche at 12.5–13.6 yr old. When compared to results from previous studies done in healthy subjects, the age of menarche in T1DM patients who were diagnosed before menarche are not delayed; however, a delay was observed when compared to the more recent data on menarche in healthy subjects and T1DM patients diagnosed after menarche in studies included in this review (11.6–12.9 yr).

Previous studies have suggested that the age at menarche in patients who were diagnosed with T1DM before menarche was delayed compared to those who were healthy and diagnosed with T1DM after menarche (11–23). Few studies have assessed whether delayed puberty is associated with T1DM, and a systematic review and meta-analysis have never been conducted to assess objectivity.

It has been observed in newly diagnosed T1DM patients that leptin levels are lower than in T1DM patients who have received regular treatment with insulin and in healthy children. Leptin is inversely associated with the age at menarche (31). Leptin activates GnRH neurons, which act on insulin receptors. Insulin controls the hypothalamic functions in metabolism and reproduction. Inadequate administration of insulin to T1DM patients can delay puberty as it disrupts normal

Table 2. Average age at menarche in before and after T1DM diagnosis groups

Author, yr	Number of samples who had menarche		Average of age at menarche		p-value
	After T1DM diagnosis	Before T1DM diagnosis and/or healthy	After T1DM diagnosis (mean ± SD)	Before T1DM diagnosis and/or healthy (mean ± SD)	
Braham *et al*., 2017 (11)	48	54	12.90 ± 1.55	12.26 ± 1.55	0.0400
Deltsidou *et al*., 2010 (12)	34	209	12.86 ± 1.10	11.90 ± 1.24	0.0000
Harjutsalo *et al*., 2015 (14)	704	600	13.82 ± 1.65	12.89 ± 1.43	< 0.0001
HsU *et al*., 2010 (15)	41	40	13.00 ± 1.00	12.10 ± 1.30	0.0010
Lombardo *et al*.., 2009 (17)	73	20	12.77 ± 1.13	11.98 ± 1.23	0.0010
Nakamura *et al*., 2022 (19)	117	38	12.50 ± 0.80	11.80 ± 0.90	0.0024
Schweiger *et al*., 2011(22)	185	43	12.81 ± 1.22	12.27 ± 1.25	0.0020
Yan Yi *et al*., 2021 (23)	80	25	13.60 ± 1.70	12.20 ± 1.20	< 0.0001

T1DM, type 1 diabetes mellitus.

Table 3. Percentage of irregular menstruation in before and after T1DM diagnosis

Author	Irregular menarche after T1DM (n)	Percentage (%) of irregular menstruation in T1DM	Irregular menarche before T1DM and/or healthy	Percentage (%) of irregular menarche before T1DM and/or healthy
Braham *et al*., 2017 (11)	17/48	35.42	10/54	18.52
Deltsidou *et al*., 2010 (12)	40/81	49.38	72/204	35.29
Schweiger *et al*., 2011(22)	34/185	18.38	36/43	83.77

T1DM, type 1 diabetes mellitus.

GnRH neuronal function (32).

Many factors can contribute to delayed age at menarche in patients who were diagnosed with T1DM before menarche, such as poor glycemic control, late diagnosis and treatment of T1DM, duration of T1DM, BMI, and insulin dosage (33). Physiological insulin resistance (IR) occurs during puberty, and when combined with the effects of gonadal steroids, increased lean body mass, and poor therapeutic adherence, this leads to poor glycemic control (34, 35) Earlier studies on insulin use in patients with T1DM showed that there was a moderate to severe delay in the onset of puberty in most patients who had suboptimal glycemic control (36, 37). This emphasizes the importance of appropriate glycemic control and insulin treatment to maintain a normal pubertal status. To optimize diabetes management during adolescence, the ISPAD recommends communicating within the diabetes community or peer support groups and providing a supportive and inclusive environment for T1DM patients at schools, families, and healthcare facilities. Mental health disorders also need to be screened and addressed, as diabetes distress, depression, anxiety, drug and alcohol use, eating disorders, and body image may interfere with the success of diabetes treatment. Preconception counseling programs need to be implemented in adolescence, as unplanned pregnancies in hyperglycemic young women may have poor outcomes for the mother and baby (38).

Increased levels of advanced glycation end products can also contribute to delayed puberty by suppressing activation of the GnRH pulse generator (39). It was found that the lean body mass doubles during puberty. This condition increases the insulin requirement and worsens glycemic control. Additionally, insulin resistance increases during puberty, which is associated with behavioral and psychosocial issues that can contribute to worsening glycemic control. Glycemic control is considered the most modifiable factor in preventing delayed menarche (40). In contrast, another study found that T1DM patients can still have a delayed age of menarche despite adequate treatment with insulin and good glycemic control, as measured by HbA1c. This study noted that there could have been other factors that contributed to delayed age at menarche, and this finding did not have clinical significance even if it raised a pathophysiological concern (41).

In addition to HbA1c, the same study also found that BMI was not associated with delayed age at menarche in T1DM patients. We hypothesized that the range of BMI and HbA1c values in the study population was so wide that no association could be identified (41). However, another study found that BMI is negatively associated with older age at menarche. This finding is consistent with that of a previous study conducted in healthy subjects (29). It is also consistent with other studies that have found that the age at menarche in T1DM patients with a higher BMI was earlier than in those with a lower BMI (42–44). This was supported by the fact that

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a body fat gain of 1 kg was associated with an earlier age at menarche of 13 days (36). It was hypothesized that a higher BMI induces early menarche because leptin secreted from a higher percentage of body fat affects the hypothalamus to stimulate GnRH and increase the secretion of LH and FSH from the pituitary gland. These events lead to the stimulation of the enzymes required to synthesize androgens in the adrenal glands, which increases the secretion of sex hormones (45).

The duration of T1DM diagnosis was significantly correlated with age at menarche. Minimum body fat mass is required for menarche. When a child is diagnosed with T1DM and has not received insulin treatment, body weight may be lost, which may affect gonadal maturation and hence, the age of menarche (41).

More attention should be paid to these aspects in order to treat T1DM patients comprehensively and prevent T1DM complications.

Several studies were included in the meta-analysis. However, there may have been different socioeconomic backgrounds in each included study, and the number of samples might affect the applicability of the results. In addition, each study had different definitions of delayed menarche and methods; some studies did follow-up, whereas others distributed a one-time questionnaire to be filled by subjects.

This systematic review and meta-analysis summarize the results of previous studies on the association between delayed puberty and T1DM and emphasizes the importance of early diagnosis of T1DM. Early diagnosis of T1DM allows early management of T1DM that can optimize the growth and development of children and adolescents and prevent problems, including delayed menarche (46).

Apart from T1DM, the age at menarche can be affected by other diseases, such as autoimmune thyroid disease. In a study of Kotopouli *et al*. in 2019, it was reported that thyroid autoimmunity is more frequently diagnosed in women with subclinical hypothyroidism. The study showed that early age at menarche was independently associated with subclinical hypothyroid, with age at menarche (mean ± SD) of cases and control at 12.6 ± 1.2 yr old and 13.3 ± 0.8 yr old ($p < 0.001$), respectively. Age at menarche has been linked to several factors such as genetic, racial, environmental, and metabolic syndromes. Puberty is influenced by the hypothalamus-pituitary-gonadal (HPG) axis, adrenal androgens, growth hormones, estrogen, and insulin growth factors-1. Early menarche may be associated with early estrogen exposure, which may trigger thyroid autoimmunity (47). In contrast to the 2013 case report by Larson, a 13-yr-old girl with primary hypothyroidism showed poor linear growth and delayed puberty (48). In the 2017 review by Tstsui, the interaction between the hypothalamus-pituitary-gonadal (HPG) and hypothalamus-pituitary-thyroid (HPT) axes played a role in delayed puberty. The role of thyroid hormone in pubertal development was shown by the increased conversion of T4 to T3 at pubertal onset. Elevated TRH levels in hypothyroidism alter GnRH secretion, which can delay the LH response. Gonadotropin-inhibitory hormone (GnIH) expression is increased in hypothyroidism and may delay pubertal onset by inhibiting the activity of GnRH, reducing LH and FSH levels (49).

Delayed age at menarche can have possible consequences such as decreased bone mineral density and irregular menstruation. In addition, more knowledge regarding menarche can help healthcare workers provide information and reassurance to patients and their parents about what is expected to occur with T1DM. More research is required in this area so that additional factors related to delayed age at menarche can be explored for its prevention.

Conclusion

The age at menarche was later in patients who had menarche after T1DM diagnosis compared to healthy subjects and those who had menarche beforehand. This can be influenced by the interactions between reproductive hormone imbalance, T1DM duration, and metabolic control. These findings highlight the importance of recognizing the potential delay in menarche among patients diagnosed with T1DM before menarche. Early identification can inform comprehensive management strategies, ultimately aiming to improve quality of life and prevent further complications.

Conflict of interests: The authors have nothing to disclose.

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