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Reproductive Health and Metabolic Parameters in Women with Type 2 Diabetes

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ABSTRACT

Aim: This study evaluated the correlations between metabolic parameters and reproductive health data in women with type 2 diabetes mellitus (T2DM). **Material and methods:** In this observational retrospective study, data from the medical records of 324 adult women with T2DM attending their regular diabetes check-ups were collected and analyzed (i.e., anthropometric parameters at first outpatient visit and yearly thereafter, first recorded HbA1c and all HbA1c for the entire follow-up duration, as well as obstetrical/gynecological information). **Results:** Age at the diagnosis of T2DM correlated positively with age at menarche (r = 0.21, [95% CI: 0.09, 0.31], p = 0.0002) and age at menopause (r = 0.18 [95% CI: 0.07, 0.29], p <0.01). Age at menarche correlated negatively with mean weight (r = –0.21 [95% CI: –0.31, –0.10], p: 0.0002) and mean BMI (–0.22 [–0.32, –0.11], p <0.0001) over the follow-up time. Patients with shorter time difference between age at menarche and age at onset of T2DM (≤45 years) had higher mean weight (83.8 ± 14.5 kg vs. 78.4 ± 16.0 kg, p = 0.0001), BMI (33.2 ± 5.6 kg/m^2 vs. 31.8 ± 5.7 kg/m^2, p <0.05), and HbA1c over time (6.9 ± 0.8% vs. 6.6 ± 0.9%, p <0.0001). Women with T2DM with earlier menarche (<12 years old), with irregular menses during their reproductive life, and ≥3 pregnancies had higher overall BMI, but mean HbA1c were not significantly different. However, women diagnosed with T2DM before menopause had a higher mean HbA1c over time (7.1 ± 0.8% vs. 6.7 ± 0.9%, p <0.01). **Conclusion:** The BMI correlated with several indicators of reproductive health (earlier menarche, irregular menses, and higher number of pregnancies), while earlier onset of T2DM influenced metabolic control in women with T2DM.

Keywords: type 2 diabetic women, menarche, menopause, puberty

INTRODUCTION

Over the past decades, the worldwide prevalence of diabetes mellitus has increased, and it is estimated to affect 578 million adults by 2030 and 700 million by 2045.[1] Moreover, the increasing prevalence of type 2 diabetes mellitus (T2DM) has emerged in parallel with a secular decrease in the average age at menarche.[2,3] Thereby, the association between puberty onset and T2DM could relate not only to changes in lifestyle and environment, but also to the associated

biological processes.[2] On the other hand, sexual dysfunction occurs in a large proportion of diabetic women, which poses further burden on their reproductive lifespan.[4] Therefore, it is important to acknowledge the correlations between reproductive health and T2DM.

Some data show that women with a younger age at menarche have a greater risk to develop T2DM later in life, but not all studies agree.[5,6] Part of the explanation may be related to body adiposity, translated by a higher adult body mass index (BMI).[2] However, the association between early onset of puberty and adult BMI remains debated because girls with a younger age at menarche already have a higher BMI at that time.[7] Results from the EPIC-Norfolk cohort study indicate that the risk of diabetes is 10% lower with every year of delay in the age at menarche.[6] The study has also shown that age-adjusted adult BMI is lower by 0.43 kg/m^2 per year, while the waist circumference is lower by 0.74 cm per year for each year of delay in the onset of menarche.[8]

On the other hand, some studies have demonstrated that women with T2DM have an earlier onset of menopause, and metabolic disorders, such as T2DM, accelerate reproductive ageing with premature ovarian failure.[9,10] A study from 11 Latin American countries has shown that the presence of T2DM triples the risk of early menopause in women under the age of 45.[11]

There is, however, relatively scarce data regarding the correlations between long-term glycemic control and age at menarche/menopause, as well as other aspects of reproductive health in women with T2DM.

We therefore aimed to evaluate the correlations between metabolic data and age at menarche/menopause and other indicators of reproductive health in women with T2DM.

MATERIAL AND METHODS

This was an observational retrospective study, in which data from the medical records of adult women with T2DM, attending the Diabetes Outpatient Unit of the Emergency Clinical County Hospital of Târgu Mureș, were collected. The study has been approved by the Ethics Committee of the Emergency Clinical County Hospital of Târgu Mureș. The patients attended the outpatient clinic for regular check-ups between February and August 2019. They have been diagnosed with diabetes mellitus according to the diagnostic criteria of the American Diabetes Association.[12] The following data were recorded: date of birth, age at diagnosis of diabetes, duration of diabetes, weight and height at first outpatient visit, weight (yearly thereafter, for the entire duration of follow-up), first recorded HbA1c and every HbA1c thereafter (for the entire duration of follow-up). The BMI was calculated at the first visit and once a year thereafter, for the entire duration of follow-up, based on the formula: BMI = weight/height^2 (kg/m^2). Mean weight, BMI, and HbA1c for the follow-up duration were calculated.

In addition, the following obstetrical/gynecological (Ob/Gyn) information was collected from the medical charts: age at menarche, number of pregnancies, number of births, age at menopause onset, regularity of menses, and age at which hysterectomy was performed (if applicable). For women who have reached menopause, the reproductive lifespan was calculated as the difference between age at menopause and age at menarche.

Statistical analysis was performed using descriptive and inferential statistics. Continuous variables with normal distribution were expressed as mean ± SD and those with non-gaussian distribution as median (min–max), while categorical variables were presented as frequency (%). Means and medians of different groups were compared using Student's t-test or the Mann-Whitney test, as well as ANOVA or the Kruskal-Wallis test, respectively. Fisher's exact test was employed to analyze categorical variables. The correlations between variables of interest were tested using the Pearson's or Spearman's tests, respectively, and data is presented as r (95% confidence interval [CI]). All tests were two-tailed, and statistical significance was set at $p < 0.05$.

RESULTS

Data from 324 female patients with T2DM were collected and analyzed, and are presented in Table 1.

The correlations between metabolic and Ob/Gyn data were analyzed. Age at diagnosis of diabetes correlated positively with age at menarche (r = 0.21 [95% CI: 0.09, 0.31], p = 0.0002, Figure 1) and age at menopause (r = 0.18 [95% CI: 0.07, 0.29], p <0.01), but not with the number of pregnancies (r = 0.09 [95% CI: –0.03, 0.20], p = 0.12), number of births (r = 0.05 [95% CI: –0.06, 0.16], p = 0.36), or having regular menses (r = –0.09 [95% CI: –0.20, 0.02], p = 0.11). On the other hand, age at diagnosis of diabetes correlated negatively with mean BMI over time (r = –0.24 [95% CI: –0.35, –0.14], p <0.0001) and mean HbA1c over time (r = –0.26 [95% CI: –0.36, –0.15], p <0.0001).

Age at menarche correlated negatively with mean weight over time (r = –0.21 [95% CI: –0.31, –0.10], p = 0.0002), first recorded weight (r = –0.21 [95% CI: –0.31, –0.10], p = 0.0002), mean BMI over time (r = –0.22 [95% CI: –0.32, –0.11], p <0.0001), and first recorded BMI

TABLE 1. Ob/Gyn and metabolic data of the study population. Data are presented as mean ± SD or median (min–max); *for women who have reached menopause

	Women with T2DM n = 324
Age (years)	65.3 ± 8.8
Age at menarche (years)	14.0 (9.0–20.0)
Number of pregnancies	2.0 (0–14.0)
Number of births	2.0 (0–8.0)
Regular menses (n/%)	284/87.6
Age at menopause (years)	49.0 (26.0–59.0)
Reproductive lifespan* (years)	35.0 (13.0–44.0)
Menopause due to hysterectomy (n/%)	38/11.7
Age at hysterectomy (years)	43.0 ± 7.1
Age at diagnosis of diabetes (years)	59.0 (24.0–82.0)
Duration of diabetes (years)	7.0 (0–31.0)
First recorded weight (kg)	79.7 (49.0–134.0)
Overall weight (kg)	78.7 (49.8–136.7)
First recorded BMI (kg/m2)	32.3 (20.1–52.7)
Overall BMI (kg/m2)	31.9 (20.2–51.4)
First recorded HbA1c (%)	6.6 (3.9–14.0)
Overall HbA1c (%)	6.7 (5.2–13.12)

(r = –0.22 [95% CI: –0.33, –0.11], p <0.0001, Figure 2). However, it did not correlate with HbA1c at first visit (r = –0.02 [95% CI: –0.13, 0.09], p = 0.69) or overall HbA1c (r = –0.04 [95% CI: –0.15, 0.07], p = 0.47).

We have further analyzed the correlations between age at menarche and T2DM. The study group was therefore divided into two subgroups based on the time difference between age at menarche and age of T2DM onset (≤45 years and >45 years, 45 years being the median value). Patients with a shorter time difference (≤45 years) had higher weight (83.8 ± 14.5 kg vs. 78.4 ± 16.0 kg, p = 0.0001), higher BMI (33.2 ± 5.6 kg/m^2 vs. 31.8 ± 5.7 kg/m^2, p <0.05), and higher mean HbA1c over time (6.9 ± 0.8% vs. 6.6 ± 0.9%, p <0.0001).

Finally, we have divided the study group into three subgroups based on age at the onset of menarche: early- (<12 years old; n = 23), normal- (12–16 years old; n = 263), and late-onset menarche (≥16 years old; n = 38). The earlier the menarche, the higher was the overall weight (84.8 ± 2 kg vs. 81.8 ± 15.3 kg vs. 75.3 ± 11.1 kg, p <0.05) and BMI (Figure 3), but the mean overall HbA1c was not significantly different between the groups (6.5 ± 0.5% vs. 6.8 ± 0.8% vs. 6.8 ± 1.4%, p = 0.23).

Women with T2DM who have self-reported to have had irregular menses during their reproductive lifespan had higher overall BMI (34.5 ± 6.0 kg/m^2 vs. 32.2 ± 5.6 kg/m^2, p <0.05) compared to women with regular menses, but there was no difference between their metabolic control (HbA1c: 6.7 ± 0.5% vs. 6.8 ± 0.9%, p = 0.87).

Women with T2DM with higher than median number of pregnancies (≥3) had higher overall BMI (33.1 ± 5.4 kg/m^2 vs. 32.1 ± 5.9 kg/m^2, p <0.05), but no different mean HbA1c (6.8 ± 0.7% vs. 6.8 ± 1.0%, p = 0.44) compared with women with <3 pregnancies. The same trend was seen for

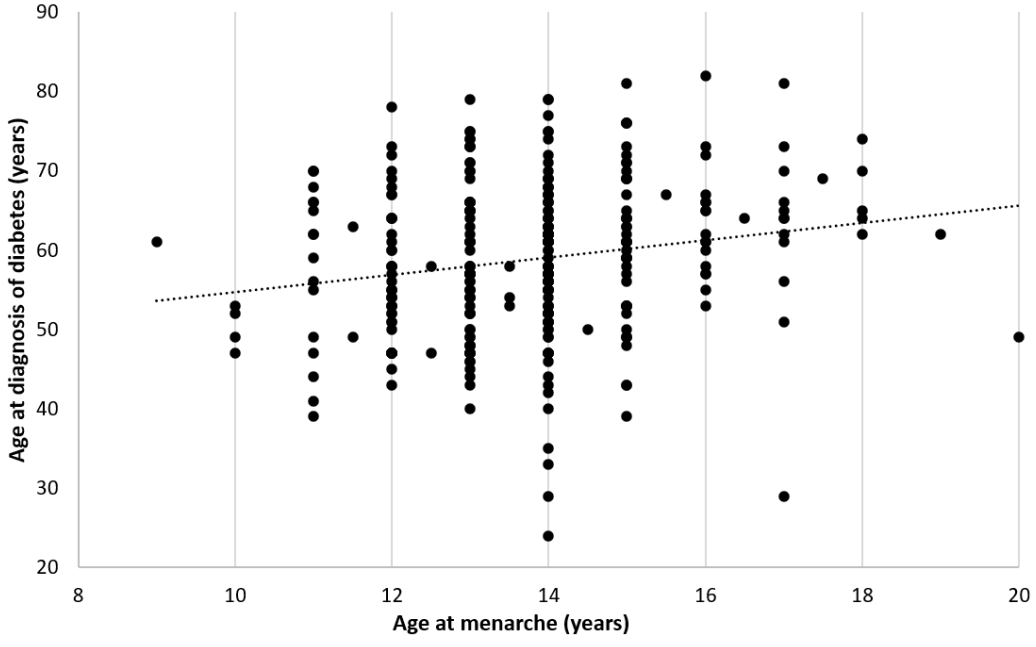

FIGURE 1. Correlations between age at menarche and age at diagnosis of T2DM (data are r [95% CI])

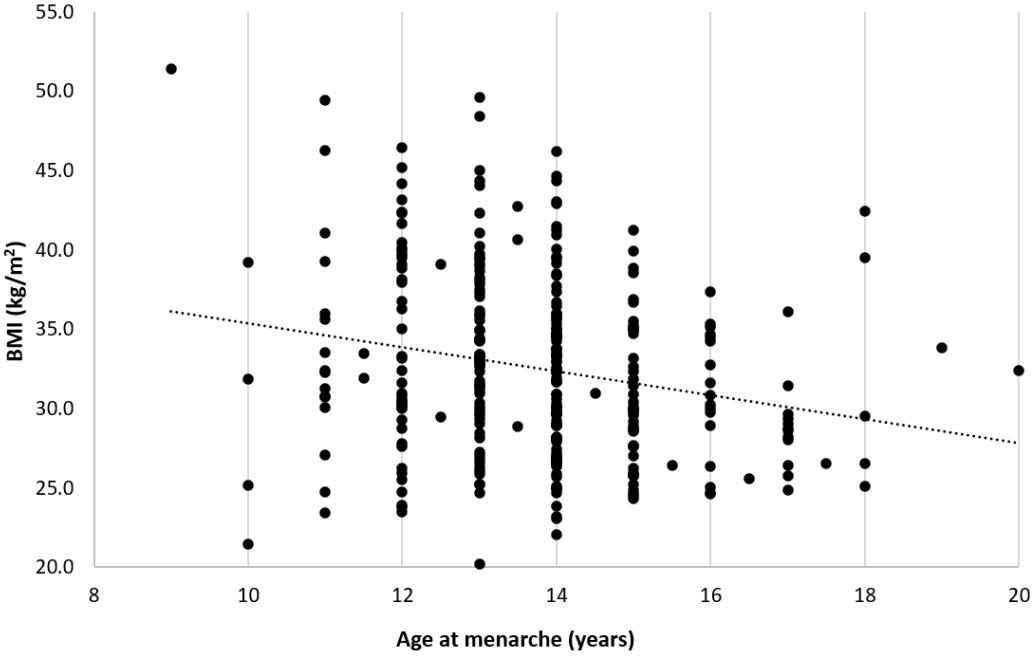

FIGURE 2. Correlations between age at menarche and mean overall BMI (data are r [95% CI])

the number of births (≥3 versus < 3 births), but it did not reach statistical significance (mean BMI: 33.2 ± 5.4 kg/m² vs. 32.3 ± 5.8 kg/m², p = 0.08; mean HbA1c: 6.8 ± 0.7% vs. 6.7 ± 0.9%, p = 0.09).

Age at menopause did not correlate with the first recorded BMI (r = 0.01 [95% CI: –0.10, 0.12], p = 0.85), mean overall BMI (r = 0.01 [95% CI: –0.11, 0.12], p: 0.90), first recorded weight (r = 0.01 [95% CI: –0.10, 0.13], p = 0.82), or overall weight (r = 0.002 [95% CI: –0.11, 0.12], p = 0.97). The same was true for mean overall HbA1c (r = 0.06 [95% CI: –0.06, 0.17], p = 0.30), or HbA1c at first visit (r = 0.08 [95% CI: –0.04, 0.19], p = 0.18).

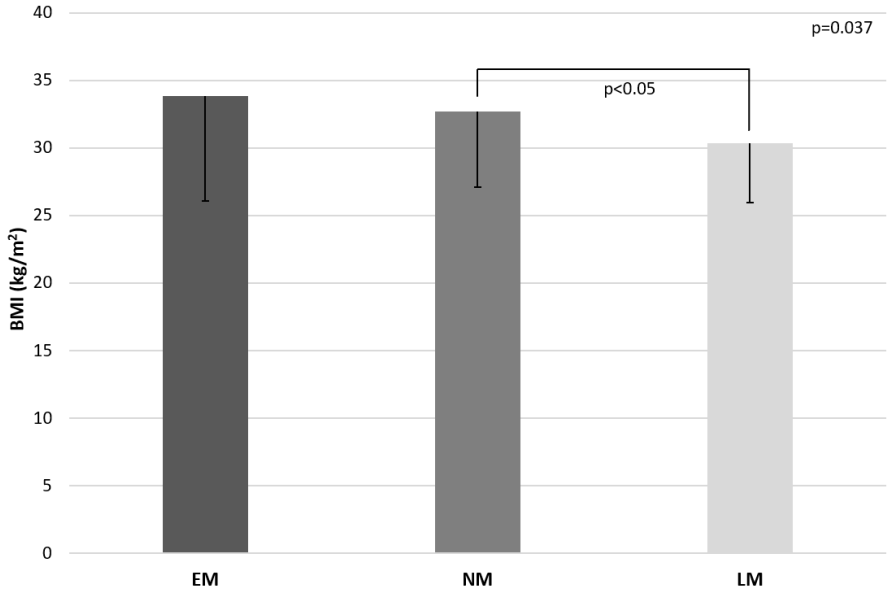

FIGURE 3. Overall mean BMI in the three subgroups divided based on age at the onset of menarche (EM – early menarche, <12 years old; NM – normal menarche, 12–16 years old; LM – late menarche, >16 years old)

There was no difference in BMI between the group that developed T2DM before/at the same time with menopause and the group that was diagnosed with T2DM after the menopause (32.9 ± 6.7 kg/m2 vs. 32.5 ± 5.6 kg/m^2, p = 0.80), and the same was true for weight (84.1 ± 16.8 kg vs. 80.9 ± 15.2 kg, p = 0.26). However, women who were diagnosed with T2DM before the onset of menopause had a higher mean HbA1c over time (7.1 ± 0.8% vs. 6.7 ± 0.9%, p <0.01).

DISCUSSIONS

The first finding of this study was the positive association between age at menarche and age at the onset of T2DM, which was in agreement with reported data showing that pubertal timing in younger ages is associated with a higher risk of T2DM.[2] In our study, women with early menarche (<12 years old) had higher overall weight and BMI, which may explain the onset of T2DM later in life. According to the (EPIC)-InterAct case-cohort study, women with an early menarche (8–11 years old) had a 70% higher risk of T2DM compared to those with age at menarche between 12–16 years.[2] Apart from body adiposity, there are other suggested explanations for the link between puberty timing and diabetes. One of them is that low serum sex hormone-binding globulin (SHBG) levels associated with high plasma sex hormones (estradiol and testosterone) induced by earlier menarche could influence the glycemic status and correlate with higher risks of diabetes.[13,14]

T2DM patients with a shorter duration between age at menarche and age at the onset of diabetes had higher mean HbA1c, but age at the onset of puberty was not correlated with later glycemic control. Contrary to our findings, a large study from China has indicated that early age at menarche was associated with worse metabolic control (HbA1c >7%).[15] However, the thresholds for menarche age used to separate the subgroups in that study were different (<15 years old, 15–18 years old, and >18 years old, respectively).[15] Moreover, the mean HbA1c in these subgroups were similar (p = 0.37), which is in concordance with our study.

Another finding of this study is that there was a weak positive correlation between age at the diagnosis of T2DM and age at menopause. A South Indian study found a significant difference between age at menopause in women with and without diabetes (p <0.01), and that in women with diabetes, the average age at menopause was 4 years younger than in the general population.[10] The process of premature ovarian failure and progressive reproductive ageing could be partially explained by the presence of diabetes.[10] However, the literature is not completely concordant, as an earlier study did not indicate a significant difference between age at menopause in women with or without T2DM.[16] There is limited data regarding metabolic control and age at menopause in women with T2DM. A study by Shen *et al*. indicated that Chinese women with T2DM with early and late menopause had worse glycemic control.[15] We found no direct correlation between age at the onset of menopause and overall glycemic control, but women who were diagnosed with diabetes before menopause had higher overall HbA1c, although there were no differences between BMIs. This may imply that poorer glycemic control was not mediated by body adiposity, and other factors may have a role.

Additionally, the frequency of irregular menses and oligomenorrhea is much higher in both type 1 and type 2 diabetic patients compared to healthy subjects.[17] The prevalence of irregular menstrual cycles varies from 5% to 35.6% in different studies depending on age, occupation, and residence.[18] In our study, this prevalence was 12.4%. One small study in Korean women reported that the frequency of oligomenorrhea was about two-fold higher in women with T2DM vs. controls (16.1% vs. 8.5%).[19] Similar results were shown in a North Indian study reporting that the prevalence of oligomenorrhea was higher in obese vs. non-obese women with T2DM vs. healthy controls (16.4% vs. 8.8% vs. 0%; p = 0.014).[20] It seems that there is a bidirectional relationship between T2DM and menstrual cycle irregularities, as several studies have shown that women with irregular menstrual cycles have a significantly higher risk for developing T2DM.[21] In a more recent report from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study, menstrual dysfunction was more frequent in girls with recently diagnosed T2DM (21%) and was associated with alterations in sex steroids and SHBG levels, but not in β-cell function or insulin sensitivity.[22] This apparently did not improve significantly after two years of antihyperglycemic therapy, but it was slightly lower at 12 and 24 months (15% and 11%, respectively).[22] Similarly, our data indicate that women with self-reported irregular menses during their reproductive life had higher BMI, but not a significantly different metabolic control. A cross-sectional study in 220 young women indicated a significant association between overall and central obesity with menstrual cycle irregularity, while an earlier report of the Nurses' Health Study II showed that women with long/highly irregular menses present a higher risk of T2DM not entirely explained by obesity.[23,24] Thus, the complex association between obesity, T2DM, and menstrual cycle irregularities needs further research.

In our study, a shorter duration between menarche and onset of T2DM (≤45 years) was associated with worse outcomes in terms of glycemic control over time compared with women with longer duration, and also with higher body adiposity, but this could be rather related with earlier onset of T2DM.

CONCLUSIONS

This study has shown that age at the diagnosis of T2DM correlated positively with age at menarche and age at menopause. The BMI correlated with several indicators of reproductive health (earlier menarche, irregular menses, and higher number of pregnancies), while earlier onset of T2DM influenced metabolic control in women with T2DM.

CONFLICT OF INTEREST

Nothing to declare.

REFERENCES

1. International Diabetes Federation. Worldwide Toll of Diabetes. IDF Diabetes Atlas 9th edition. https://diabetesatlas.org/en/sections/worldwide-toll-of-diabetes.html (07 January 2020)
2. Elks CE, Ong KK, Scott RA, et al. Age at menarche and type 2 diabetes risk: the EPIC-InterAct study. *Diabetes Care*. 2013;36:3526-3534.
3. Ong KK, Ahmed ML, Dunger DB. Lessons from Large Population Studies on Timing and Tempo of Puberty (Secular Trends and Relation to Body Size): The European Trend. *Mol Cell Endocrinol*. 2006;254-255:8-12.
4. Elyasi F, Kashi Z, Tasfieh B, Bahar A, Khademloo M. Sexual Dysfunction in Women with Type 2 Diabetes Mellitus. *Iran J Med Sci*. 2015;40:206-213.
5. Janghorbani M, Mansourian M, Hosseini E. Systematic review and meta-analysis of age at menarche and risk of type 2 diabetes. *Acta Diabetol*. 2014;51:519-528.
6. Saquib N, Kritz-Silverstein D, Barrett-Connor E. Age at menarche, abnormal glucose tolerance and type 2 diabetes mellitus: The Rancho Bernardo Study. *Climacteric*. 2005;8:76-82.
7. Kaplowitz PB, Slora EJ, Wasserman RC, Pedlow SE, Herman-Giddens ME. Earlier Onset of Puberty in Girls: Relation to Increased Body Mass Index and Race. *Pediatrics*. 2001;108:347-353.
8. Ekelund U, Ong KK, Linné Y, et al. Association of Weight Gain in Infancy and Early Childhood with Metabolic Risk in Young Adults. *J Clin Endocrinol Metab*. 2007;92:98-103.
9. Yazdkhasti M, Tourzani ZM, Roozbeh N, Hasanpour V, Esmaelzadeh S, Abdi F. The Association between Diabetes and Age at the Onset of Menopause: A Systematic Review Protocol. *Systematic Reviews*. 2019;8:80.
10. Sekhar TVDS, Medarametla S, Rahman A, Adapa SS. Early Menopause in Type 2 Diabetes – A Study from a South Indian Tertiary Care Centre. *J Clin and Diagn Res*. 2015;9:OC08-OC10.
11. Monterrosa-Castro A, Blümel JE, Portela-Buelvas K, et al. Type II diabetes mellitus and menopause: a multinational study. *Climacteric*. 2013;16:663-672.
12. American Diabetes Association. Standards of Medical Care in Diabetes – 2019. *Diabetes Care*. 2019;42:S13-S28.
13. Yang L, Li L, Peters SAE, et al. Age at Menarche and Incidence of Diabetes: A Prospective Study of 300,000 Women in China. *Am J Epidemiol*. 2018;187:190-198.
14. Ding EL, Song Y, Malik VS, Liu S. Sex Differences of Endogenous Sex Hormones and Risk of Type 2 Diabetes: A Systematic Review and Meta-Analysis. *JAMA*. 2006;295:1288-1299.
15. Shen C, Wen J, Pan X, et al. Age at menarche and age at natural menopause as predictors of glycemic control in type 2 diabetic patients. *J Diabetes Complications*. 2018;32:623-629.
16. López-López R, Huerta R, Malacara JM. Age at Menopause in Women with Type 2 Diabetes Mellitus. *Menopause*. 1999;6:174-178.
17. Livshits A, Seidman DS. Fertility Issues in Women with Diabetes. *Womens Health*. 2009;5:701-770.
18. Kwak Y, Kim Y, Baek KA. Prevalence of Irregular Menstruation according to Socioeconomic Status: A Population-Based Nationwide Cross-Sectional Study. *PLoS ONE*. 2019;14:e0214071.
19. Shim U, Oh JY, Lee HJ, Hong YS, Sung YA. Long menstrual cycle is associated with type 2 diabetes mellitus in korean women. *Diabetes Metab J*. 2011;35:384-389.
20. Zargar AH, Gupta VK, Wani AI, et al. Prevalence of ultrasonography proved polycystic ovaries in North Indian women with type 2 diabetes mellitus. *Reprod Biol Endocrinol*. 2005;3:35.
21. Rostami Dovom M, Ramezani Tehrani F, Djalalinia S, et al. Menstrual Cycle Irregularity and Metabolic Disorders: A Population-Based Prospective Study. *PloS One*. 2016;11:e0168402.
22. Kelsey MM, Braffett BH, Geffner ME, et al. Menstrual Dysfunction in Girls From the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) Study. *J Clin Endocrinol Metab*. 2018;103:2309-2318.
23. Mustaqeem M, Sadullah S, Waqar W, Farooq MZ, Khan A, Fraz TR. Obesity with irregular menstrual cycle in young girls. *Mymensingh Med J*. 2015;24:161-167.
24. Solomon CG, Hu FB, Dunaif A, et al. Long or highly irregular menstrual cycles as a marker for risk of type 2 diabetes mellitus. *JAMA*. 2001;286:2421-2426.