The Impact of the type of Menopause and Menopausal Duration on the Development of Pre-Diabetes Mellitus and Diabetes Mellitus in Postmenopausal Women

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ABSTRACT

Aim: The onset of menopause is an important factor determining quality of life in females. The aim of this study was to evaluate the effect of natural or surgical menopause, the duration of the menopausal period, and serum gonadotropin levels on the development of pre-diabetes mellitus (pre-DM) and diabetes mellitus (DM) in postmenopausal women.

Material and Methods: This retrospective study included 140 postmenopausal women with pre-DM, 148 postmenopausal women with DM and 265 healthy postmenopausal women. The groups were compared in respect of menopause type, the duration of the menopausal period, and serum follicle stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) levels. Statistical evaluations were made.

Results: There was found to be no significant effect of natural or surgical menopause on the development of pre-DM or DM (p=0.393). Increased duration of menopause was mostly seen in women with DM and the difference was statistically significant compared to the controls (p=0.019). Serum decreased FSH and LH levels and increased E2 level were observed in the DM group and the difference was significant compared to the control group (respectively, p=0.001, p=0.001 and p=0.012).

Conclusion: The onset of natural or surgical menopause does not affect the development of pre-DM and DM. Women with DM have a longer menopausal period. Women with pre-DM and DM have lower serum FSH and LH levels and higher serum E2 levels. This can be explained in part by adiposity and insulin resistance.

Key Words: Diabetes mellitus, Natural menopause, Pre-diabetes mellitus, Surgical menopause

Menopoz Tipi ve Süresinin Postmenopozal Kadınlarda Pre-Diyabet ve Diyabet Gelişimine Etkisi

ÖZ

Amaç: Menopozal başlangıç kadınların hayat kalitesini belirleyen önemli faktörlerden biridir. Bu çalışmanın amacı postmenopozal kadınlarda doğal veya cerrahi menopozlu olmanın, menopozal sürenin ve serum gonadotropin düzeylerinin pre-diyabet (pre-DM) ve diyabet (DM) gelişimi üzerine etkisini incelemektir.

Gereç ve Yöntemler: Bu retrospektif olgu kontrol çalışmasına 140 pre-DM, 148 DM postmenopozal kadın ile 265 sağlıklı postmenopozal kadın dâhil edildi. Grupların menapoz tipi, süresi ve serum folikül stimüle edici hormon (FSH), luteinize edici hormon (LH) ve östradiol (E2) serum düzeyleri karşılaştırıldı. İstatistiksel değerlendirmede ANOVA ve Kruskal Wallis Testi kullanıldı.

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Bulgular: Doğal ya da cerrahi menopozlu olmanın pre-DM veya DM gelişimleri üzerine etkisi bulunmadı (p=0,393). Artmış menopoz süresi en fazla DM'li kadınlarda görüldü ve kontrollere göre farklılık istatistiksel olarak anlamlı bulundu (p=0,019). DM grubunda düşük serum FSH ve LH düzeyleri ile yüksek serum E2 düzeyleri gözlendi ve aradaki fark kontrol grubuna göre anlamlıydı (sırasıyla, p=0,001, p=0,001ve p=0,012).

Sonuç: Cerrahi veya doğal yolla menopoza başlangıç yapmak kadınlarda gelişebilecek pre-DM ve DM oluşumunu etkilememektedir. DM'li kadınların menapozal süresi daha uzundur. DM öncesi ve DM'li kadınlar daha düşük serum FSH ve LH ve daha yüksek serum E2 düzeylerine sahiptir. Bu durum kısmen adiposite ve insulin direnci ile açıklanabilir.

Anahtar Sözcükler: Cerrahi menopoz, Diyabet, Doğal menopoz, Pre-diyabet

INTRODUCTION

As a result of the loss of ovarian activity through natural or surgical means, menopause is the permanent termination of menstruation (1). This process, which is the end of the reproductive stage of life of a female, can give rise to many negative medical outcomes such as osteoporosis, cardiovascular disease, and diabetes mellitus (DM) (2). The menopausal transition is associated with significant changes in hormone profiles such as estradiol (E2), follicle stimulating hormone (FSH), luteinizing hormone (LH) and these changes in hormones may play a role in the pathogenesis of the diseases in question (3).

Diabetes mellitus is the most commonly seen chronic disease in the period following menopause (4). As menopause is related to a reduction in pancreatic insulin secretion and elimination, very little change occurs in insulin levels in circulation. However, insulin resistance predisposes postmenopausal women to the development of DM, and this increases with age (5). Premature menopause and menopause created surgically with ovariectomy are associated with an increased risk of DM (6).

According to the results of the Study of the Prevalence of DM, Hypertension, Obesity and Endocrinological Diseases in Turkey (TURDEP-II), 45.3% (3.4 million people) of patients diagnosed with DM in Turkey are aged 40-59 years (7). DM is a multi-factor disease with both changeable (obesity, physical activity, unhealthy diet) and unchangeable (age, gender, family history of DM, polycystic ovary syndrome) risk factors (8). In 2002, the Turkish Menopause Association reported that the mean age of menopause in the country in general was 46.7 years (9).

The menopausal transition is characterized by increased testosterone and low sex hormone binding globulin (SHBG), which are related to DM (10). In a multicenter study, an increase in FSH during menopausal transition was found to be significantly related to a reduced risk of DM (11). It was shown in that study that when serum FSH increased (>50 IU/L) during the menopausal transition, the metabolic profile improved, and the risk of DM decreased (12).

In postmenopausal women with high total and free serum testosterone and E2 levels, there seems to be a greater long-term risk of developing DM, independently of adiposity and insulin resistance (13).

The aim of this study was to investigate the effect of natural or surgical menopause, the duration of the menopausal period, and serum gonadotropin levels on the development of pre-DM and DM in postmenopausal women.

MATERIAL and METHODS

This retrospective cross-sectional study included postmenopausal women who underwent routine annual examination in the polyclinics of the Samsun Women and Children's Health Training and Research Hospital between 1 January 2016 and 1 June 2019. Approval for the study was granted by the Local Ethics Committee of Samsun Training and Research Hospital (decision no: GOKA / 2019/3/10).

The subjects included in the study were naturally or surgically postmenopausal women, aged 40-65 years, who were not using hormone replacement therapy (HRT). Exclusion criteria were chemotherapy applied for cancer, the use of exogenous steroid treatment or anti-lipid medication, or a history of pelvic radiotherapy.

From a total of 602 postmenopausal women identified, exclusion criteria were applied to 21 with HRT use, as the potential effects of estrogen and progesterone are masked in the relationship between menopause and lipid metabolism, and to 28 who were receiving chemotherapy. Thus, evaluation was made of 140 women diagnosed with pre-DM after menopause, 148 women diagnosed with DM after menopause and 265 healthy postmenopausal women. Comparisons were made of these three groups in respect of menopause type (natural/surgical), time since menopause, and gonadotropin (FSH, LH, E2) levels.

Menopause was accepted as a menorrhea for at least 12 consecutive months and FSH level >40 IU/L (14). Demographic characteristics were recorded of age, gravida, parity, the time since onset of menopause and body mass index (BMI). Height and weight were measured, and BMI was calculat-

ed as weight (kg) /height 2 (m²). Waist circumference was measured with a flexible band placed around the body in the horizontal plane at the level of the iliac crest while standing.

Venous blood samples were taken in the morning after a 12-hour fasting. Glucose, HbA1c, FSH, LH, and E2 values were examined using a 7600-110 Automatic Analyser (Hitachi Inc., Tokyo, Japan).

In accordance with the American Diabetes Association (ADA) criteria, the diagnosis of DM was made with fasting plasma glucose level of ≥126 mg/d L or ≥ 6.5% HbA1c value or the use of insulin, and the diagnosis of pre-DM with glucose level of 100-125 mg/d L or HbA1c of 5.7-6.4 (15).

Statistical Analysis

Data obtained in the study were analyzed statistically using NCSS software (Number Cruncher Statistical System, 2007, Kaysville, Utah, USA). Descriptive statistical methods were used when evaluating the data (mean, standard deviation and median (minimum-maximum) (when assumptions are not provided) for numerical data; number (n) and percentage (%) for categorical data). Conformity of quantitative data to normal distribution was assessed with the Kolmogorov-Smirnov test and graphic evaluations. In the comparison of 3 or more groups of data showing normal distribution, the One-Way Anova test was used, and the Tukey test was used in the comparisons of paired groups. In the comparisons of data not showing normal distribution, the Kruskal-Wallis test was applied to 3 groups or more, and the Dunn-Bonferroniwas used in the comparisons of paired groups. The Pearson Chi-square test was applied to the comparisons of qualitative data. A value of p<0.05 was accepted as statistically significant.

RESULTS

A total of 553 postmenopausal women were evaluated in this study. No significant difference was determined in respect of age, gravida, parity and number of abortus when the pre-DM and DM groups were compared with the control group. BMI and waist circumference values were found to be increased in the pre-diabetic and diabetic groups (Table 1).

There was found to be no significant effect of natural or surgical menopause on the development of pre-DM or DM (p=0.393). Increased mean duration of menopause was mostly seen in women with DM and the difference was sta-

Table 1: Descriptive and clinical characteristics of the postmenopausal women according to glycemic status.

	Control (n=265)	Pre-DM (n=140)	DM (n=148)	p value
Age (year)	55.52 ± 8.86	56.36 ± 9.28	57.66 ± 8.74	0.068[A]
Gravida	3 (0-15)	4 (0-15)	4 (0-16)	0.088[B]
Parity	3 (0-7)	3 (0-8)	3 (0-10)	0.122[B]
Abortus	1 (0-5)	1 (0-4)	1 (0-6)	0.199[B]
BMI (kg/m²)	29.35 ± 5.00[a]	31.02 ± 6.04[ab]	33.94 ± 6.29[bc]	0.001[A]
Waist circumference (cm)	85.20 ± 11.80[ab]	85.39 ± 9.35[ab]	90.42 ± 12.29[c]	0.001[A]

Type of menopause
    Natural
    Surgical
	
	188 (70.9%)
	77 (29.1%)
		
		107 (76.4%)
		33 (23.6%)
			
			112 (75.7%)
			36 (24.3%)
				
				0.393[C]

Duration of menopause (year)	6.86 ± 6.22[a]	7.77 ± 6.73[ab]	8.71 ± 7.28[bc]	0.019[A]

BMI: Body mass index. **A:** Oneway ANOVA Test, mean ± standard deviation; **B:** Kruskal Wallis Test, median (minimum-maximum); **C:** Pearson Chi-square Test, n (%). **a-b-c:** There is no difference between groups labeled under the same letter.

Table 2: Laboratory test results of the postmenopausal women according to glycemic status.

	Control (n=265)	Pre-DM (n=140)	DM (n=148)	p value
Glucose (mg/dL)	85.66 ± 16.57	112.22 ± 14.58	130.52 ± 19.88	0.035[A]
HbA1c (%)	5.2 (5.0-5.6)[a]	6.1 (5.5-6.4)[bc]	6.7 (5.0-11.9)[bc]	0.048[B]
FSH (IU/L)	71.83 ± 28.22[a]	62.97 ± 25.76[bc]	55.80 ±22.16[bc]	0.001[A]
LH (IU/L)	46.57 ± 24.25[a]	40.95 ± 36.62[bc]	37.64 ± 22.69[bc]	0.001[A]
E2 (ng/L)	31.38 ± 33.29[a]	33.74 ± 26.17[abc]	37.10 ± 29.36[bc]	0.012[A]

FSH: follicle stimulating hormone, **LH:** luteinizing hormone, **E2:** estradiol. **A:** Oneway ANOVA Test, mean ± standard deviation; **B:** Kruskal Wallis Test, median (minimum-maximum). **a-b-c:** There is no difference between groups labeled under the same letter.

tistically significant compared to the controls (p=0.019). At least serum FSH and LH levels were observed in the DM group and the difference was significant compared to the control group (p=0.001 and p=0.001, respectively) Table 2. In addition to this, the highest serum E2 level was observed in the DM group and the difference was significant compared to the control group (p=0.012).

DISCUSSION

The results of this retrospective cross-sectional study demonstrated that while the onset of natural or surgical menopause was not observed to have an effect on the development of pre-DM or DM. However, increased duration of menopause was detected women with DM and then women with pre-DM. In addition, at least serum FSH and LH levels and highest E2 levels were detected in women with DM.

Menopause is associated with changes in body composition such as increased abdominal fat and reduced body muscle mass (16). The emergence of hyperglycemia in this period may be a direct result of ovarian failure or indirectly a result of central fat redistribution related to E2 deficiency (17). A previous study reported that no significant difference was seen between premenopausal and postmenopausal women in respect of the presence of type 2 DM, impaired glucose tolerance, impaired fasting glucose and other cardiometabolic signs (18).

The risk of DM is known to increase with advancing age. An increase in the duration of the postmenopausal period also increases the risk of DM development (19). In the current study, the mean duration of the postmenopausal period was found to be significantly longer in the pre-DM and DM groups than in the control group.

Natural menopause is characterized by increasing relative androgenicity, which has been reported to be related to glucose metabolism (20). In the postmenopausal period, while E2 terminates ovarian production, testosterone levels increase, and SHBG levels decrease. Testosterone and SHBG levels have been associated with insulin resistance and DM (21). Unlike natural menopause when falls in E2 occur within a few years, in surgical menopause created by bilateral oophorectomy, E2 ovarian production is cut rapidly and the reproductive life is suddenly terminated. Two previous studies have shown that there is a greater risk of DM in women with surgical menopause (22, 23).

Having undergone oophorectomy leads to impairment in both glucose and insulin metabolism and lipid and lipoprotein metabolism caused by a reduction in ovarian steroid production and secretion (24). However, taking exogenous hormone treatment because of surgical menopause may be

a treatment option with a protective effect against the risk of DM, which is already increased in females (25). In the current study, no difference was determined between women with natural or surgical menopause in respect of postmenopausal development of pre-DM and DM. This result could be attributed to the fact that almost three-quarters of the women in all 3 groups had undergone natural menopause.

After menopause, E2 production shifts from the ovaries to fat tissue. The formation of relatively more fat tissue may play a large role in increasing the risk of DM with an insufficient decrease in endogenous E2 levels and even by forming insulin resistance related to obesity (26). Premenopausal FSH levels have been reported not to show any difference between obese and non-obese females, but a significantly lower increase in FSH and therefore lower FSH levels have been reported in postmenopausal obese women (27).

In a study of postmenopausal women not using HRT, it seems to be a significant inverse correlation of serum FSH value with fasting glucose and HbA1c (28). In the current study, the lowest serum FSH and LH levels were seen in women with DM. In other words, the FSH and LH values of the newly diagnosed pre-DM and DM women were lower than those of the control group. In addition, the serum E2 values of these women were determined to be higher. The BMI and waist circumference measurements of the postmenopausal women in the pre-DM and DM groups were also found to be higher than those of the control group.

The results of this study showed that when postmenopausal women gain weight and increase abdominal fat, the endogenous E2 levels do not fall sufficiently and the serum FSH and LH values do not increase sufficiently, thereby leading to an increased possibility of the development of pre-DM and DM. However, it is difficult to directly compare the current study findings of low FSH, low LH, and high E2 values in postmenopausal women with pre-DM and DM with studies of DM in the postmenopausal period, and to make generalizations because the premenopausal levels of FSH, LH and E2 of the current study participants were not examined. There is a need for further longitudinal studies on this subject.

Limitations of this study can be said to be the retrospective design and the limited number of postmenopausal women. No OGTT was applied for the diagnosis of dysglycemia and this could have caused an underestimation of the relationships between menopause and DM prevalence. There is a need for further prospective studies including OGTT data to confirm the results of this study.

In conclusion, the onset of menopause naturally or surgically was not determined to have had an effect on the develop-

ment of pre-DM or DM, but with an increase in the menopausal period there was seen to be an increase in pre-DM and DM. As the majority of women with DM are in the older population, and the majority of DM cases are diagnosed in the postmenopausal period, the common effect on other comorbities of this status makes it a critical public health priority. When it is considered that obesity plays an important role in FSH, LH and E2 levels in the risk of developing DM, providing weight control at an earlier age is important for the prevention of DM which could develop later.

Ethical Approval

Approval for the study was granted by the Local Ethics Committee of Samsun Training and Research Hospital (decision no: GOKA / 2019/3/10).

Conflict of Interests

The authors have no conflict of interests to declare.

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Author Contrubitions

Study concept / Design: **Canan Soyer, Samettin Çelik**, Data collecting: **Canan Soyer, Samettin Çelik, Hasan Ulubaşoğlu,** Data analysis and interpretation: **Banuhan Şahin,** Post draft: **Banuhan Şahin, Görker Sel,** Critical review of the content: **Banuhan Şahin,** Final approval and responsibility: **Banuhan Şahin,** Supervision: **Banuhan Şahin, Görker Sel.**

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