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ORIGINAL ARTICLE

Relation of metabolic syndrome with endometrial pathologies in patients with abnormal uterine bleeding

Suna Özdemir[1], Gonca Batmaz[2], Seda Ates[2], Cetin Celik[3], Feyzanur Incesu[3], and Celalettin Peru[4]

[1]Deparment of Obstetrics and Gynecology, School of Medicine, Medipol University, Istanbul, Turkey, [2]Department of Obstetrics and Gynecology, School of Medicine, Bezmialem Vakif University, Istanbul, Turkey, [3]Department of Obstetrics and Gynecology, School of Medicine, Selcuk University, Konya, Turkey, and [4]Department of Internal Medicine, School of Medicine, Bezmialem Vakif University, Istanbul, Turkey

Abstract

Purpose: We aimed to investigate the association of metabolic syndrome and metabolic risk factors with endometrial hyperplasia and carcinoma among women with abnormal uterine bleeding (AUB).

Methods: This study included 199 patients who had undergone endometrial curettage due to abnormal uterine bleeding. We divided the patients into two groups according to whether they had an abnormal ($n = 53$) or normal endometrium ($n = 146$). Waist circumference, blood pressure, fasting glucose and serum lipid levels were measured and statistically analyzed. The women in each group were matched with regard to mean age, gravidity, parity and menopausal status.

Results: We found increased prevalence of metabolic syndrome, diabetes, general and abdominal obesity, hypertension, elevated levels of glucose, total cholesterol and LDL-cholesterol and reduced levels of HDL-cholesterol among women with endometrial carcinoma and hyperplasia. These results were detected particularly in postmenopausal (>50 years) women compared to pre-menopausal cases (<50 years). All metabolic parameters were similar between hyperplasia and cancer groups.

Conclusion: Metabolic syndrome and its components have been shown to have profound impacts on initiation and progession of endometrial pathology, particularly during post-menopausal period.

Keywords

Endometrium, metabolic syndrome, pathology, uterine bleeding

History

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Introduction

Endometrial cancer, one of the commonest cancers in women worldwide is strongly linked to lifestyle factors. It is the seventh most common cause of death in women in Western Europe, accounting for 1–2% of all deaths from cancer [1]. The rising incidence of endometrial cancer has been associated with an increased life expectancy and an epidemic of obesity and physical inactivity. Abnormal uterine bleeding (AUB) is the primary presenting symptom of endometrial neoplasia, and prompts an endometrial biopsy to rule of carcinoma. Women with AUB are diagnosed with 75% benign findings, 15% with carcinoma and the last 15% with endometrial hyperplasia [2]. Two independent pathways have been identified in development of endometrial cancer, inactivation of the PTEN and p53 tumor-suppressor genes [3]. Cancers characterized by the PTEN pathway were described as type I and it is associated with excessive unopposed estrogen produced by adipose tissue [4]. The metabolic syndrome (MetS) is described as a cluster of diseases or conditions, including obesity, diabetes mellitus, low glucose tolerance, dyslipidaemia and hypertension [5]. Overweight/obesity, diabetes, metabolic syndrome, nulliparity, late menopause and unopposed estrogen stimulation are established risk factors for endometrial cancer [1]. Moreover, hypertension and high blood glucose levels are BMI-independent risk factors of this cancer [6,7]. There is less knowledge about these modifiable risk factors in relation to endometrial hyperplasia. MetS was investigated among the healthy controls and the cases with endometrial cancer. Moreover, there are limited data about effects of metabolic risk factors on the occurrence of endometrial cancer and hyperplasia in patients with AUB. In this study, we aimed to investigate the association of metabolic syndrome and metabolic risk factors with endometrial hyperplasia and carcinoma among women with AUB.

Materials and methods

Subjects

A total of 199 patients who had an endometrial biopsy due to AUB were enrolled prospectively in our study from June 2010 to May 2012. Current users of oral contraceptives or hormonal therapy were excluded, since they may have effects on lipid and glucose levels, and also blood pressure. This study was approved by the ethics committee of the Selcuklu School of Medicine. Each patient gave written informed consent to participate. The patient

Address for correspondence: Suna Özdemir, Associate Professor, Obstetrics and Gynecology Department, School of Medicine, Medipol University, Istanbul, Turkey. Tel: +90 212 4607000. E-mail: snmstf@yahoo.com

admitted to outpatient clinics of Selcuk University and Bezmialem Vakif University located in Konya and Istanbul were included.

After a complete history was taken and a physical examination was carried out, the patients were prepared for endometrial biopsy. Before the endometrial biopsy, transvaginal ultrasonography was performed to measure endometrial thickness. For endometrial aspiration, the endometrial cavity was curetted using the cannula with inner piston. Following a successful attempt, the specimen was placed in formalin and sent for histopathological examination. The endometrial sections were examined by two different pathologists who were blinded with respect to clinical status of the patients in two clinics.

Histopathological analysis

Patients were divided into two groups according to endometrial biopsy findings; women in group 1 ($n = 53$) were diagnosed with endometrial hyperplasia ($n = 26$) or carcinoma ($n = 27$), while women in group 2 ($n = 146$) had normal endometrium. Secretory and proliferative endometrium, atrophy, endometrial polyps and endometrial epithelial fragments with mucoid material were considered as normal endometrium. As mild hyperplasia with reversible proliferations may have different etiology and pathogenesis than carcinomas, we analyzed the data separately for endometrial cancer and hyperplasia.

Clinical and biochemical measurements

Waist circumference and blood pressure were recorded. Waist circumference was measured with a flexible steel tape between the lowest rib and the iliac crest with the subject standing at the end of gentle expiration. Blood pressure was measured twice 10 min apart with the participants in sitting position. The metabolic syndrome was diagnosed in accordance with National Cholesterol Education Program Adult Treatment Panel III (ATP III) criteria, when the participants presented with 3 or more of 5 risk determinants: abdominal obesity (waist circumference > 88 cm), increased serum levels of triglycerides (TG ≥ 150 mg/dL), decreased serum levels of high-density lipoprotein cholesterol (HDL < 50 mg/dL), elevated fasting serum glucose level (≥ 110 mg/dL) and increased blood pressure ($\geq 130/85$ mmHg) [8]. In addition, we used the ATP III cut-off values for total cholesterol (240 mg/dL for TC) and low-density lipoprotein cholesterol (160 mg/dL for LDL), above which levels are considered high. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters, and obesity was defined as a BMI of 30 or greater [9].

Serum analysis

After overnight fasting, venous blood samples were drawn into serum separator, clot activator tubes (Vacuette line, Greiner Bio-One, Germany) for all assessments. The samples were allowed to stand 15 min at room temperature for clot formation and sera were then separated by centrifugation. Glucose and lipid concentrations were determined using Synchron LX20 analyzers (Beckman Coulter, Fullerton, CA) with original Beckman reagents.

Statistical analysis

SPSS version 13.0 (SPSS Inc., Chicago, IL) was used for statistical analysis. The women in the groups were matched in regard to mean age, gravidity, parity and menopausal status. Values were expressed as mean ± SD for continuous variables and number and percentage for categorical variables. Odds ratio (OR) and its 95% confidence interval (CI) were calculated to estimate the relative effects and the associations between various factors and endometrial pathology.

Non-normally distributed variables were compared using Mann–Whitney's U test with the median values of each variable. Student's t-test was used, as the distributions of comparison values were normal. The Chi-square test was used for the comparison of percentage values. All p values were two tailed and $p < 0.05$ was considered statistically significant.

Results

The baseline characteristics and metabolic parameters among the two groups are described in Table 1. Mean age, gravidity, parity and abortus were similar between the two groups, and also menopausal status did not differ between the groups ($p = 0.06$). However, endometrial thickness was significantly higher the women in group 1 when compared with group 2 ($p < 0.001$).

The mean values of BMI and waist circumference were significantly higher among group 1 when compared with group 2 ($p < 0.001$ and $p < 0.001$). The MetS rate was also higher in group 1 ($p < 0.001$). Overall, the metabolic parameters including fasting glucose, total cholesterol, LDL and triglyceride levels were significantly higher in group1 when compared with group 2 (Table 1). However, HDL level was lower in group 1 compared to group 2 ($p = 0.009$). Similarly, the prevalences of hypertension and diabetes mellitus were significantly higher in group 1 compared to group 2 ($p = 0.006$ and $p = 0.006$).

Due to wide age range of the cases, the groups were stratified according to the ages as ≤ 50 or >50 years. Data concerning the subgroups of women with ages ≤ 50 ($n = 93$) are shown in Table 2. The mean age was similar between two groups. The mean values of endometrial thickness, BMI and waist circumferences were detected higher in group 1compared to group 2 ($p = 0.02$, 0.03 and 0.01). Only the prevalence of MetS was higher in group 1 ($p = 0.001$), but hypertension and diabetes mellitus were similar between groups. Other than fasting glucose level,

Table 1. Baseline characteristics and metabolic parameters of the total study population ($n = 199$).

	Mean ± SD		
Variables	Group 1 ($n = 53$)[a]	Group 2 ($n = 146$)[a]	p
Characteristics			
Age (years)	51 ± 5.0	52 ± 5.9	0.16
Gravidity (n)	4.6 ± 2.5	4.4 ± 1.7	0.76
Parity (n)	3.4 ± 1.8	3.5 ± 1.4	0.34
Abortus (n)	1.0 ± 1.4	0.9 ± 1.0	0.68
Endometrium (mm)	9.9 ± 4.3	13.2 ± 3.6	<0.001[b]
Menopause (%)	46.5	57.4	0.06
BMI (kg/m^2)	30.9 ± 5.9	35.2 ± 6.9	<0.001[b]
Waist circumference (cm)	100.8 ± 13.7	112.6 ± 16.2	<0.001[b]
Metabolic parameters			
Met S (%)	27.1	67.3	<0.001[b]
Fasting glucose (mg/dL)	97.8 ± 31.9	125.8 ± 46.3	<0.001[b]
Total cholesterol (mg/dL)	194.1 ± 36.1	213.7 ± 39.2	0.001[b]
Triglyceride (mg/dL)	135.8 ± 62.5	155.8 ± 95.6	0.041[b]
HDL (mg/dL)	50.2 ± 11.6	45.3 ± 11.2	0.009[b]
LDL (mg/dL)	121.1 ± 23.1	149.1 ± 51.2	0.005[b]
Hypertension (%)	22.2	41.8	0.006[b]
Diabetes mellitus (%)	16.7	34.5	0.006[b]

A cross-sectional study of women with abnormal uterine bleeding.
Abbreviations: BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein.
[a]Group 1: women with endometrial pathology; Group 2: women with normal endometrium.
[b]$p < 0.05$ (statistically significant).

all metabolic parameters were similar among the subgroups (Table 2).

Data concerning the subgroups of women with ages >50 years ($n = 106$) are displayed in Table 3. The mean age of two groups was similar. The mean values of endometrial thickness, BMI and waist circumference were significantly higher in group1 than group 2. Similarly, all metabolic parameters were found significantly higher in group 1 compared to group 2 (Table 3). Only hypertension prevalence was similar among the groups.

Women with abnormal endometrium ($n = 53$) was separately analyzed as cancer ($n = 27$) and hyperplasia ($n = 26$), and data are shown in Table 4. All variables were detected similar between the groups. However, the mean age was significantly higher in cancer group compared with hyperplasia group ($p = 0.03$).

Table 5 shows the distribution of cases with endometrial pathology and controls and the corresponding ORs according to the components of MetS. Binary logistic regression analysis was used to estimate the multivariate ORs. ORs of endometrial pathology were 2.63 for diabetes, 2.51 for hypertension and 5.53 for the presence MS. With reference to measure of central obesity, the OR was 2.84 for the women with waist circumference >88 cm. The OR was 2.94 for the women with BMI >28 kg/m^2 to measure the general adiposity. Most of lipid parameters including total cholesterol, LDL and HDL cholesterol were significantly related to endometrial pathologies. Only triglyceride was not significantly related with the presence of endometrial pathology. The ORs of endometrial pathology according to fasting glucose level $>$ 88 mg was 0.11, and there was significant correlation specified by Chi-Square test ($p < 0.001$).

Table 2. Baseline characteristics and metabolic parameters of women ages 50 years or below ($n = 93$).

Variables	Mean ± SD Group 1 ($n = 19$)[a]	Mean ± SD Group 2 ($n = 74$)[a]	p
Characteristics			
Age (years)	46.2 ± 2.1	42.5 ± 3.8	0.16
Endometrium (mm)	12.6 ± 2.9	10.2 ± 4.3	0.02[b]
BMI (kg/m^2)	33.1 ± 4.6	29.9 ± 5.4	0.03[b]
Waist circumference (cm)	108.9 ± 14.6	98.6 ± 12.3	0.01[b]
Metabolic parameters			
Met S (%)	68.3	24.7	0.001[b]
Fasting glucose (mg/dL)	118.5 ± 34.5	96.7 ± 29.4	0.001[b]
Total cholesterol (mg/dL)	215.2 ± 43.4	191.2 ± 31.2	0.062
Triglyceride (mg/dL)	178.2 ± 92.5	133.8 ± 64.2	0.052
HDL (mg/dL)	45.2 ± 10.3	52.7 ± 11.2	0.056
LDL (mg/dL)	151.1 ± 62.3	122.5 ± 22.6	0.1
Hypertension (%)	31.6	12.3	0.07
Diabetes mellitus (%)	26.5	12.3	0.15

A cross-sectional study of women with abnormal uterine bleeding.
Abbreviations: BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein.
[a]Group 1: women with endometrial pathology; Group 2: women with normal endometrium.
[b]$p < 0.05$ (statistically significant).

Table 3. Baseline characteristics and metabolic parameters of women ages 50 years or above ($n = 106$).

Variables	Mean ± SD Group 1 ($n = 34$)[a]	Mean ± SD Group 2 ($n = 72$)[a]	p
Characteristics			
Age (years)	58.4 ± 4.3	55.1 ± 4.2	0.16
Endometrium (mm)	13.4 ± 4.1	9.1 ± 4.0	0.001[b]
BMI (kg/m^2)	36.6 ± 7.6	31.9 ± 6.2	0.001[b]
Waist circumference (cm)	114.9 ± 17	103 ± 14.6	0.001[b]
Metabolic parameters			
Met S (%)	69.4	34.3	0.001[b]
Fasting glucose (mg/dL)	97.8 ± 31.9	125.8 ± 46.3	<0.001[b]
Total cholesterol (mg/dL)	194.1 ± 36.1	213.7 ± 39.2	0.001[b]
Triglyceride (mg/dL)	135.8 ± 62.5	155.8 ± 95.6	0.041[b]
HDL (mg/dL)	50.2 ± 11.6	45.3 ± 11.2	0.009[b]
LDL (mg/dL)	121.1 ± 23.1	149.1 ± 51.2	0.005[b]
Hypertension (%)	48.6	31.9	0.14
Diabetes mellitus (%)	16.7	34.5	0.006[b]

A cross-sectional study of women with abnormal uterine bleeding.
Abbreviations: BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein.
[a]Group 1: women with endometrial pathology; Group 2: women with normal endometrium.
[b]$p < 0.05$ (statistically significant).

Discussion

Abnormal uterine bleeding (AUB) is the commonest presenting symptom in gynecology outpatient department, and it comprises from benign finding to endometrial carcinoma. The causes of AUB include a wide spectrum of the disease of the reproductive system and non-gynecologic causes as well [2]. Further evaluation of abnormal uterine bleeding depends on the patient's age and the presence of risk factors for endometrial cancer, which include anovulatory cycles, obesity, nulliparity, age greater than 35 years. In this study, the metabolic syndrome and its components were investigated as a risk factor for endometrial pathology. We found increased prevalence of metabolic syndrome, diabetes, general and abdominal obesity, hypertension, elevated levels of glucose, total cholesterol and LDL and reduced levels of HDL among women with endometrial carcinoma and hyperplasia.

Clustering of the MetS is additionally associated with risk of endometrial cancer development especially among overweight women. In a cross-sectional study including pre-menopausal women, it was shown that low serum HDL was associated with increased free estradiol levels but unchanged progesterone levels [10]. This result reflects increased exposure to unopposed estrogens that is a major etiologic determinant of endometrial cancer. Similarly, low HDL was proposed as a potential relevant marker for endometrial cancer risk [10]. In a recent study, HDL

Table 4. The comparison of metabolic parameters between cancer and hyperplasia groups in 53 women with endometrial pathology.

Variables	Mean ± SD Cancer ($n = 27$)[a]	Mean ± SD Hyperplasia ($n = 26$)[a]	p
Characteristics			
Age (years)	55.6 ± 6.7	49.8 ± 9.6	0.03[b]
BMI (kg/m^2)	36.6 ± 7.9	33.2 ± 5.4	0.31
Waist circumference (cm)	115.5 ± 16.7	109.6 ± 15.2	0.27
Metabolic parameters			
Met S (%)	64.3	69.2	0.92
Fasting glucose (mg/dL)	121.6 ± 38.3	130.5 ± 54.6	0.89
Total cholesterol (mg/dL)	214.1 ± 36.1	213.7 ± 39.2	0.79
Triglyceride (mg/dL)	147.8 ± 90.5	163.7 ± 103	0.34
HDL (mg/dL)	45.5 ± 12.7	44.9 ± 9.6	0.87
LDL (mg/dL)	137.8 ± 40.5	147.8 ± 61.2	0.89
Hypertension (%)	46.2	39.3	0.81
Diabetes mellitus (%)	38.5	32.1	0.84

Abbreviations: BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein.
[a]27 women in cancer group; 26 women in hyperplasia group.
[b]$p < 0.05$ (statistically significant).

Table 5. Odds ratio with 95% confidence interval (CI) for endometrial pathologies according to metabolic risk factors in women with abnormal uterine bleeding.

Parameters	Group 1 ($n=53$)[a]	Group 2 ($n=146$)[a]	OR (CI)	p
BMI >30 kg/m^2				
Yes	43 (78.2%)	65 (45.1%)	2.94 (1.4–6.0)	0.003[b]
No	12 (21.8%)	79 (54.9%)		
Waist circumference >88 cm				
Yes	41 (74.5%)	46 (31.9%)	1.05 (1.0–1.1)	0.016[b]
No	14 (25.5%)	98 (68.1%)		
Metabolic syndrome (%)				
Yes	37 (67.3%)	39 (27.1%)	5.53 (2.8–0.8)	<0.001[b]
No	17 (32.7%)	105 (72.9%)		
Hypertension (%)				
Yes	23 (41.8%)	32 (22.2%)	2.51 (0.2–0.8)	0.006[b]
No	32 (58.2%)	112 (77.8%)		
Diabetes mellitus (%)				
Yes	29 (34.5%)	24 (16.7%)	2.63 (1.3–5.1)	0.006[b]
No	36 (65.5%)	120 (83.3%)		
Fasting glucose >88 mg/dL				
Yes	51 (92.7%)	60 (41.7%)	0.11 (0.03–0.3)	<0.001[b]
No	4 (7.3%)	84 (58.3%)		
HDL <50 mg/dL				
Yes	41 (74.5%)	73 (50.7%)	2.84 (1.4–5.6)	<0.001[b]
No	14 (25.5%)	71 (49.3%)		
LDL >130 mg/dL				
Yes	28 (50.9%)	45 (31.3%)	2.28 (1.2–4.3)	0.01[b]
No	27 (49.1%)	99 (68.7%)		
Triglyceride >160 mg/dL				
Yes	19 (34.5%)	43 (29.9%)	1.24 (0.6–2.4)	0.523
No	36 (65.5%)	101 (70.1%)		
Total cholesterol >240 mg/dL				
Yes	15 (27.3%)	18 (12.5%)	2.62 (1.2–5.6)	0.012[b]
No	40 (72.7%)	126 (87.5%)		

Abbreviations: BMI: body mass index; HDL: high density lipoprotein; LDL: low density lipoprotein; CI: 95% confidence interval; OR: odds ratio.
[a]Group 1: women with endometrial pathology; Group 2: women with normal endometrium.
[b]$p<0.05$ (statistically significant).

levels were negatively correlated with estrogens and positively correlated with SHBG and adiponectin [7]. A large sample-sized study showed positive correlations of serum TG, TC, LDL and dyslipidaemia and a negative correlation of serum HDL with endometrial cancer [4]. Consistent with these findings, we observed an inverse association between HDL levels and risk of endometrial pathologies in this study. We detected that 75% of the women abnormal endometrium had HDL levels under 50 IU. However, low HDL level was found in 50.7% of control women.

In a prospective study including 130 cases, a weak age-adjusted inverse association between serum total cholesterol and endometrial cancer risk, and no association with triglycerides were observed [11]. A previous studies has shown that dietary lipid, especially saturated animal fat and cholesterol had increased endometrial cancer risks [12]. Few studies were performed on dyslipidemia and its cancer risks, and these results were controversial [13,14]. Lindemann et al. [13] reported a positive correlation of serum TG with endometrial cancer risk and no association of TC, LDL or HDL. Cust et al. [7] suggested that TG was positively and HDL level was negatively associated with endometrial cancer risk, while TC and LDL were not. According to multivariate ORs, all lipid parameters, except TG, were significantly related with the presence of endometrial pathology in this study.

High concentrations of insulin activate the insulin receptor, which stimulates cell growth and cell division [1]. Goldman et al. [15] found that high glucose levels could increase cancer risk by acting as an energy source for the proliferation of tumor cells generating free radicals, or causing oxidative damage to DNA and DNA repair enzymes. He also proposed glucose transporter (GLUT) 1, 4 and 8 expression was upregulated in endometrial cancer cells. Several previous studies have also observed increased risks associated with high glucose levels [11,16,17]. In consistent with this finding, it has been reported that type 2 diabetes characterized by elevated glucose and insulin levels, is associated with increased endometrial cancer risk [18,19]. Similarly, we determined that 92.7% of the women with endometrial pathology had higher fasting glucose level (>88 mg/dL) when compared with 41.7% of healthy controls.

Obesity is a significant contributory factor to the development of gynecological cancer [1]. A prospective American study showed that women with a BMI $\geq$ 35 had an increased risk of death from ovarian or cervical cancer, whereas women with a BMI $\geq$40 had a 6.25 relative risk of dying from endometrial cancer [20]. A strong association between obesity and endometrial cancer was demonstrated in a Dutch case-cohort study [21]. The key feature of MetS on endometrial carcinogenesis appears to be obesity, although the presence of other MetS components leads to an additional increase in risk [22]. In post-menopausal women, the conversion of androgens to estrogens occurs in adipose tissue, thus the level of adiposity directly influences the amount of circulating estrogens [10]. As estrogen levels decrease after menopause, women also accumulate fat around the abdomen. Consequently, waist circumference measurement may be an important predictor of endometrial cancer after menopause. This study showed that the prevalence of the overall MetS was higher in women diagnosed with endometrial cancer and hyperplasia than in those diagnosed with normal endometrium. However,

single traits of the MetS were more strongly related to endometrial cancer and hyperplasia among the older women. It has also been reported that obesity is a major determinant of insülin resistance [22]. Insulin resistance has potential modifying effects on endometrial cancer development [23]. Hyperinsulinemia has been noted as important risk factors associated with endometrial carcinoma independently of obesity [7,24]. Insulin may act directly on endometrial tissue as a mitogenic and anti-apoptotic growth factor. It was shown that higher prevalence of hypertension in patients with endometrial carcinoma could again be related to hyperinsulinemia and insulin resistance [5]. In a recent study, hypertension, diabetes, glucose levels and the consumption of high-glycemic load foods have been found to be positively associated with endometrial cancer risk only among overweight or obese women [25]. In consistency with that finding, the prevalence of hypertension and diabetes were detected higher among the women with cancer and hyperplasia.

In conclusion, metabolic syndrome and its components have been shown to have profound impacts on initiation and progression of endometrial pathology. Continued efforts to make lifestyle interventions, such as weight loss and increased physical activity, measures to control insulin resistance and hypertension could reduce the prevalence of endometrial pathology in the general population. This could potentially provide an improved basis for risk stratification, follow-up and targeted cancer preventive efforts among women with AUB particularly at post-menopausal period.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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