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Endometrial Hiperplazi ile Komplike Obez ve Premenopozal Hastalarda Vücut Yağ Dokusu Dağılımının Etkisi

The Effect of Body Fat Tissue Distribution in Obese and Premenopausal Patients Complicated with Endometrial Hyperplasia

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ÖZ

Amaç: Obezite ile adet düzensizliği arasında yakın bir ilişki vardır.Bu çalışmanın amacı, endometriyal hiperplazili aşırı kilolu veya obez premenopozal hastalar ile benign patolojik lezyonları olan gönüllüler arasında biyoimpedans yöntemi kullanılarak lipoid doku dağılımının araştırılmasıdır.

Materyal ve Metot: Anormal uterin kanama tanılı obez veya aşırı kilolu gönüllüler incelendi. 88 hasta dahil etme kriterleini karşıladı. Multi-Frequency Body Composition Analyzer kullanarak vücut bölümlerinin yağ kütlesi, yağ yüzdesi ve empedans ölçümleri yapıldı. Tüm gönüllüler için kan lipid profili ölçümü ve endometriyal kalınlığın ultrasonografik ölçümü yapıldı.

Bulgular: Hiperplazi grubunda 33, kontrol grubunda 55 gönüllü mevcuttu. Endometriyal hiperplazi grubundaki 33 gönüllünün 28'inde (%84.8) en az bir artmış yağ asidi tespit edildi. Kontrol grubundaki 55 hastanın 41'inde (% 74.5) en az bir artmış yağ asidi mevcuttu. Total kolesterol düzeyleri hiperplazi grubunda kontrol grubuna göre daha yüksek bulundu (p=0.006). Biyoimpedans analizleri için hiperplazi ve kontrol grubu arasında anlamlı bir fark yoktu.

Sonuç: Hiperlipideminin endometriyal patolojilere katkıda bulunan önemli bir faktör olmaya devam ettiği yaptığımız bu çalışmada da görülmüştür. Endometrial hiperplazi grubunda serum kolesterol düzeyleri anlamlı olarak yüksek bulunması, endometriyal hiperplazi ile komplike olan obez bireylerde, lipoid doku dağılımından ziyade, artan kolesterol düzeyinin jinekolojik patoloji oluşumuna katkıda bulunabileceğini göstermektedir.

Anahtar Kelimeler: Endometrial hiperplazi, hiperlipidemi, kolesterol, obezite, yağ dağılımı

ABSTRACT

Objective: There is a close association between obesity and menstrual irregularity. This study aims to investigate lipoid tissue accumulation between overweight or obese premenopausal patients with endometrial hyperplasia and with benign pathologic lesions via using the bioimpedance method.

Materials and Methods: Obese or overweight volunteers with abnormal uterine bleeding were examined. Eighty-eight volunteers meet the inclusion criteria. We obtained fat mass, fat percentage and impedance of body parts by using Multi-Frequency Body Composition Analyzer. Blood lipid profile and ultrasonographic measurement of endometrial thickness were also performed.

Results: 33 volunteers were in the hyperplasia group and 55 were in the control group. 28 of the 33 volunteers (84.8%) had at least one increased fatty acid. 41 of the 55 patients (74.5%) had at least one increased fatty acid in the control group. Total cholesterol levels are higher in the hyperplasia group than in the control group (p=0.006). There was no significant difference between the groups for bioimpedance analyses.

Conclusion: Hyperlipidemia remains an important factor that contributes to endometrial pathologies. Serum cholesterols were significantly high in the endometrial hyperplasia group. Rather than lipoid tissue distribution, increased cholesterol may contribute to gynecologic pathology occurrence in obese individuals complicated with endometrial hyperplasia.

Keywords: Cholesterol, endometrial hyperplasia, fat distribution, hyperlipidemia, obesity

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INTRODUCTION

A body mass index equal to or greater than 25 kg/m2 is defined as overweight, and a body mass index equal to or greater than 30 kg/m2 is described as obesity.[1] Today it is accepted that 60 percent of women are overweight and 30 percent of those are obese. Obesity contributes to the deterioration of quality of life, reduced life expectancy and disability, especially in individuals who develop type 2 diabetes, cardiovascular diseases, osteoarthritis and cancer. However, there is a large variation in individual risk for developing obesity-related comorbid diseases that cannot be explained simply by the degree of adiposity. In addition to the degree of adiposity, the distribution of adipose tissue may also play a role here.[2]

Due to several mechanisms, there is a close association between obesity and menstrual irregularity.[3] Patients with abnormal uterine bleeding under 45 years old American College of Obstetrics and Gynecology (ACOG) Committee suggests endometrial biopsy in the presence of obesity, because obesity is a well-known risk factor for endometrial cancer. Moreover, ACOG Committee recommends endometrial sampling for all patients with abnormal uterine bleeding at the age of 45 or more.[4]

It is certain that adipose tissue is necessary for maintaining many of the physiological functions like pubertal development, and immune system functions however excess lipoid storage may lead to disturbances in the reproductive system.[5,6]

Excess lipoid storage can be measured via using dual-energy X-ray absorptiometry (DEXA) which is accepted as the best way to determine lipoid tissue accumulation, but it is not cheap and requires radiation exposure. On the other hand, bioimpedance is a portable, basic method without radiation exposure for exploring lipoid storage accumulation and this method is approved for the human the population. An experienced technician can easily use this device and not required specialized staff.[7]

This study aims to investigate lipoid tissue accumulation between overweight or obese premenopausal patients with endometrial hyperplasia and overweight or obese volunteers with benign pathologic lesions via using the bioimpedance method.

MATERIALS AND METHODS

Ethics Committee Approval: A prospective randomized and controlled trial was assessed at the Erciyes University Department of Obstetrics and Gynecology between March 2019 and March 2020. This study was approved by Erciyes University Ethics Committee (Date:15.01.2020, decision no:2020/27) according to Helsinki Declaration. All volunteers who participated in the study signed an informed consent form.

Patient Selection: Volunteers who have been admitted to Erciyes University Department of Obstetrics and Gynecology for abnormal uterine bleeding were examined. During an ultrasound examination, in the presence of equal or greater than 4 millimeters (mm) endometrial thickness without any structural abnormality such as uterine fibroids, uterine polyp, adenomyosis and ovarian cysts created our possible volunteers. A structured in-person interview form is used to reveal diabetes, hypertension, polycystic ovary syndrome, use of tobacco, alcohol, tamoxifen, steroid hormones and oral contraceptives or ongoing therapies, history of endometriosis, endometrial ablation operation, cardiovascular liver and kidney disease, family history of endometrial, breast and bowel cancers. Patients in the premenopausal state, fat mass percentage over 31% and BMI over 25 kg/m^2, evaluated endometrial thickness equal to or greater than 4 millimeters (mm) without any structural abnormality such as uterine fibroids, uterine polyp, adenomyosis, ovarian cysts and endometrial cell detection on cervical cytology were constituted inclusion criteria. Presence of diabetes, hypertension, polycystic ovary syndrome, surgically induced menopausal state (history of hysterectomy and bilateral oophorectomy), BMI under 25 kg/m^2, use of tobacco, alcohol, tamoxifen, steroid hormones, diuretic drugs and oral contraceptives during their lifetimes, history of endometriosis, endometrial ablation operation, liver and kidney disease, endometrial thickness under than 4 millimeters (mm), family history of endometrial, breast and bowel cancers were constituted exclusion criteria for the study. We excluded 296 volunteers and investigated 88 volunteers due to strict exclusion criteria. The flowchart of the study is given in Figure 1.

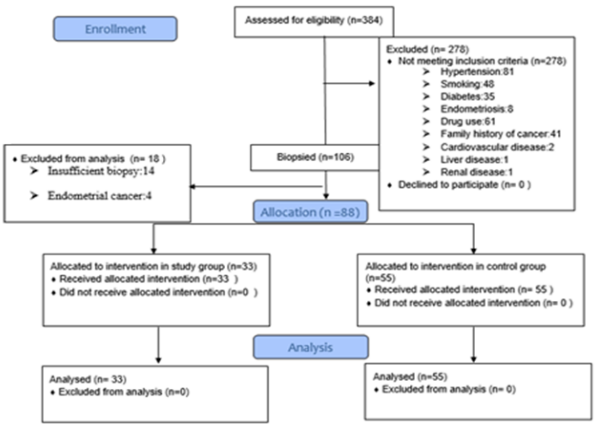

Figure 1. Flowchart of the study.

Study Protocol: After detailed examination, all patients received trans-vaginal ultrasounds in a sag-

ittal plane to measure the endometrial thickness and detect other uterine pathologies. A veteran technician obtained fat mass, fat percentage; whole body impedance, right leg impedance, left leg impedance, right arm impedance, left arm impedance, right arm fat mass, left arm fat mass, right arm fat percentage, left arm fat percentage, right leg fat percentage, left leg fat percentage, right leg fat mass, left leg fat mass, trunk fat mass and trunk fat percentage moreover adiposity was evaluated via using weight, height, BMI, waist, hip and waist-hip ratio too. After 12 hours of fasting, 5 cc venous blood from vena antecubitalis was obtained for detection of high density lipoprotein (HDL), low density lipoprotein (LDL), triglyceride, cholesterol levels and Tanita BC 532 (Tokyo- Japan) Multi-Frequency Body Composition Analyzer was used to weighing and fatty tissue distribution of the volunteers. During Tanita's assessment all volunteers had light clothes, took their shoes off and urinated. Volunteers with a fat mass percentage over 31% were accepted as overweight and 35% were accepted as obese. Moreover, a fixed wall scale was used to determine the height of the volunteers. Body mass index (BMI) was calculated by using formula (weight/height^2) to discriminate individuals as overweight (≥25), or obese (≥30). After a detailed examination of interview forms, patients were asked to be a volunteer according to exclusion and inclusion criteria. Our control and hyperplasia groups were constituted of overweight and obese volunteers via using the Tanita bioimpedance analyzer thus all volunteers received pipelle biopsy according to ACOG committee recommendation. Results of biopsy; classified according to WHO recommendation in 2015 as basic non-atypical, complex non-atypical, basic atypical and complex atypical hyperplasia.[8] Patients with all types of hyperplasia (as illustrated above) were included in the study group but patients with reported endometrial cancer cases were excluded from the study. Patients with proliferative endometrium, atrophic endometrium, endometrial polyp and secretory endometrium were included in the control group but patients with insufficient biopsy results were excluded from the study. Then comparisons were made for two groups; the study group consisted of precancerous lesions (endometrial hyperplasia n=33) and the control group consisted of non-precancerous in other words normal group (proliferative endometrium, atrophic endometrium, endometrial polyp and secretory endometrium n=55).

Statistical Analyses: To test the normality assumption of the data, Shapiro Wilk was used. Variance homogeneity assumption was tested with the Levene test. Values are expressed as mean ± standard deviation or median (25th percentile – 75 percentile). Parametric comparisons were made with t-test and z test, and non-parametric comparisons were made with Mann–Whitney U test. PASW Statistics 18 program was used for all comparisons. $p<0.05$ probability value was considered as statistically significant.

RESULTS

Baseline characteristics and anthropometric measurements of both groups are illustrated in Table 1.

According to Table 1; there was no difference between hyperplasia and control group for age, height and BMI. All patients in the two groups were obese or overweight. All patients were at the premenopausal stage. Both endometrial thickness and cholesterol levels were significantly different between hyperplasia and control group. 28 of the 33 volunteers (84.8%) had at least one increased fatty acid in en-

Table 1. Demographic features, Blood lipid levels and anthropometric measurements of hyperplasia and control groups.

	Hyperplasia Group (n=33)	Control Group (n=55)	p Value
Age (years)	42 (40-45)	43 (41-46)	0.411
Height (cm)	158.42±4.96	158.33±4.45	0.922
Mass (kg)	76.50 (71.60-86.50)	77.80 (66.80-87.30)	0.521
BMI (kg/m^2)	31.20 (29.15-34.15)	30.30 (26.20-34.50)	0.326
Endometrial Thickness (millimeter)	14 (11-17)	10 (8-12)	0.001
High Density Lipoprotein (HDL) (mg/dl)	53 (42.50-63)	50 (44-59.50)	0.786
Low Density Lipoprotein (LDL) (mg/dl)	109.42±29.04	97.57±28.60	0.065
Triglyceride (mg/dl)	159 (111.50-223)	148 (104-191)	0.428
Cholesterol (mg/dl)	201 (184.50-221.50)	183 (164-204)	0.006
Arm (centimeter)	34 (31.50-36.50)	32 (30-35)	0.022
Leg (centimeter)	57 (53.50-63.50)	56 (53-61)	0.337
Waist (centimeter)	95 (91-102.50)	94 (84-102)	0.190
Hip (centimeter)	113 (111-120)	112 (106-120)	0.596
Waist/hip ratio	0.92±0.11	0.90±0.07	0.404

Table 2. Tanita BC 532 bioimpedance analyzer evaluation of hyperplasia and control groups.

	Hyperplasia Group (n=33)	Control Group (n=55)	p Value
Fat percentage (%)	36.90 (33.55-40.05)	36.10 (33.40-40.50)	0.569
Fat Mass (kg)	30.10 (25.20-32.90)	29.40 (22.30-33.90)	0.428
Whole Body Impedance (Ω)	558.39±47.09	571.36±71.21	0.307
Right Leg Impedance (Ω)	227.30±22.50	236.71±30.14	0.125
Left Leg Impedance (Ω)	227.73±21.70	235.42±30.38	0.207
Right Arm Impedance (Ω)	307.03±24.51	310.65±39.44	0.596
Left Arm Impedance (Ω)	312.45±27.24	313.71±41.47	0.865
Right Leg Fat Percentage (%)	42.95±4.42	42.42±4.17	0.578
Right Leg Fat Mass (kg)	6.10 (5.40-7.10)	6.20 (4.80-7)	0.521
Left Leg Fat Percentage (%)	42.98±4.20	42.25±4.24	0.437
Left Leg Fat Mass (kg)	6.10 (5.35-6.95)	6.10 (4.70-7)	0.461
Right Arm Fat Percentage (%)	41.40 (37.15-45.45)	39 (34-45.10)	0.219
Right Arm Fat Mass (kg)	1.70 (1.40-2.15)	1.60 (1.10-2.10)	0.318
Left Arm Fat Percentage (%)	42.20 (38.65-46.30)	40.50 (35-46.20)	0.193
Left Arm Fat Mass (kg)	1.80 (1.55-2.35)	1.70 (1.20-2.30)	0.355
Trunk Fat Percentage (%)	33.10 (29.20-35.85)	32.10 (28.20-65.80)	0.356
Trunk Fat Mass (kg)	13.40 (11.15-15.70)	13.40 (10.20-15.50)	0.384

dometrial hyperplasia group. 41 of the 55 patients (74.5%) had at least one increased fatty acid in control group.

Tanita BC 532 bioimpedance analyzer evaluation is illustrated in Table 2.

According to Table 2; There was no significant difference between hyperplasia and control group for bioimpedance analyses. Both fat percentages, fat masses, and impedances of body parts are found to be similar between the groups.

DISCUSSION AND CONCLUSION

The relationship between fat distribution and hyperplasia has been a debate among authors. Some of the studies showed a positive correlation between upper body obesity and cancer, other studies claimed there is a link between central obesity and cancer. Opposite of these studies, some of the authors suggested that fat distribution is unrelated to cancer.[9]

These dissimilar results may depend on insufficient homogenization of independent risk factors. One of the risk factors for hyperplasia development is diabetes mellitus and blamed for both occurrences of cancer and responsiveness to the progesterone therapy.[10]

No patient complicated with diabetes was included in either the study group or the control group. Due to many strict criteria of the study, nearly three fourth of the volunteers were eliminated from the study. In literature, many of the authors used weight, height, BMI, waist, hip and waist-hip ratio in their materials and methods section to clarify relationship between hyperplasia and lipoid tissue distribution. However, measurement errors and differences in standardization of measurements may be related to with conflicting results in the literature. Discrimination of the overweight and obese volunteers was done according to fat mass percentage via using bioimpedance analyzer moreover BMI was calculated. Tanita's evaluation showed similar results between groups and there was no significant difference between groups for lipoid tissue distribution.

Prior to body electrical resistance detection depending on lipoid tissue, water and electrolyte content of the tissue, Tanita bioimpedance uses very low an alternating electrical current (500 μA-800μA) flow with a 50 kHz frequency.[11]

We are of the opinion that the Tanita bioimpedance analyzer eliminates measurement errors or other confounders.

In premenopausal women, both ovarian follicle and excess adipose tissue are the major sources of aromatase where estrogens are produced from androgens via using the classical cholesterol metabolic pathway. CYP19A1 gene has primary responsibility for aromatase activation. FSH is the primer regulatory hormone on aromatase function.[12]

Perimenopause in other words menopausal transition refers to a volatile time frame condition in which reproductive changes occur. The average age for this term is generally accepted as 47 and one of well-known features is elevated FSH levels. Moreover, these levels maintain for several years and have a positive effect on aromatase activity.[13]

In a recent study, investigators tried to find a cut-off value for endometrial thickness in premenopausal patients with endometrial hyperplasia complicated with diabetes mellitus and obesity. They reported that endometrial precancerous and cancerous lesions increase by 25% when cut-off value for endometrial thickness is 11 mm.[14]

Endometrial thickness was significantly thicker in the hyperplasia group than in the control group. The median value for endometrial thickness was 10 mm for the control group and 14 mm for the hyperplasia group respectively. Although mentioned values are

close between the study of Gianella et al and ours, they evaluated endometrial hyperplasia patients complicated with diabetes mellitus but we excluded these patients.

Although all efforts to eliminate risk factors for endometrial cancers except for obesity, it seems that hyperlipidemia remains an important factor that contributes to endometrial pathologies. Serum cholesterol levels were significantly high in the endometrial hyperplasia group. In literature, Kaya S et al investigated these patients and reported that both serum cholesterol and LDL levels were high in the hyperplasia group and the possibility of endometrial precancerous lesions was increased 1.8 fold due to hypercholesterolemia.[15]

In conclusion**,** according to our findings, rather than lipoid tissue distribution, increased cholesterol may contribute to gynecologic pathology occurrence in obese individuals complicated with endometrial hyperplasia. When we consider the high prevalence of increased blood lipids in the hyperplasia and control group, cholesterol, LDL, triglyceride and HDL levels may be routinely evaluated by health care providers.

Ethics Committee Approval: Our study was approved by the Erciyes University Ethics Committee (Date: 15.01.2020, decision no: 2020/27). The study was carried out following the international declaration of Helsinki. All volunteers who participated in the study was signed an informed constent form.

Conflict of Interest: No conflict of interest was declared by the authors.

Author Contributions: Concept – FO; Supervision – FO, GA; Materials – BA, SM; Data Collection and/or Processing – FO, BA; Analysis and/or Interpretation – FO, GA, IIM; Writing –FO, IIM.

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