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Evaluation of the Effect of Visceral / Truncal Fat Rate and Insulin Resistance on Myoma Uteri Formation Among Premenopausal Women

Premenapozal Kadınlarda Myoma Uteri Gelişimi Üzerine Visseral/Trunkal Yağ Oranının ve İnsülin Direncinin Etkisinin Değerlendirilmesi

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Abstract
Objectives: Within the scope of this study, we aimed to analyze the effect of visceral and truncal fat rate and insulin resistance on myoma uteri progression in premenopausal women.
Materials and Methods: 100 patients, who have been applied to the gynecology department with myoma diagnosis and 50 control patients who had no myomas and had similar properties with the patient group were included in the study. Anthropometric measures, pre-prandial serum glucose, HbA1c, insulin, LDL-cholesterol, triglyceride, HDL-cholesterol and total cholesterol levels were studied. All statistical analyses were performed with SPSS 16.0 statistical soft-ware and a level of $p < 0.05$ is accepted statistically significant.
Results: Truncal fat rate of the patient group is found higher than the control group (p=0.014). Mean HbA1c was higher and statistically significant ($p< 0.001$) in the patient group. Mean HDL-C was found significantly lower in the patient group ($p= 0.001$).
Conclusion: In our study, higher levels of truncal fat rate in the patient group can be inferred to the production of estrogen in truncal fat tissue due to increased aromatase activity and thus myoma frequency was increased. We have also determined in this study that higher HbA1c levels in patient group caused an increase in the risk of myoma up to 3.5 times. Normal values of HOMA-IR suggest that insulin resistance is not a risk factor for the development of myoma. It is believed that there is a negative correlation between hyperlipidemia and myoma.
Key words: Myoma Uteri, visceral / truncal obesity, insulin resistance

Öz
Amaç: Biz bu kesitsel çalışmada premenapozal kadınlarda myoma uteri gelişimi üzerinde visseral-trunkal yağ oranı ve insülin direncinin etkisini araştırmayı amaçladık.
Materyal ve Metot: Bu çalışmada, Ankara Atatürk Eğitim ve Araştırma Hastanesi Kadın Hastalıkları ve Doğum Kliniği'ne Ocak-Mayıs 2012 tarihleri arasında başvuran, myoma uteri tanısı almış 100 hasta, kontrol grubu olarak hasta grubu ile benzer klinik özelliklere sahip myomu olmayan 50 kadın çalışmaya alındı. Hastaların antropometrik ölçümleri, açlık plazma glukozu, HbA1c, insulin, LDL-kolesterol, trigliserit, HDL-kolesterol ve total kolesterol seviyesi bakıldı. Tüm istatistiksel analizler için SPSS 16.0 programı kullanıldı ve anlamlılık düzeyi $p < 0,05$ olarak kabul edildi.
Bulgular: Hasta grubunun trunkal yağ oranı, kontrol grubundan istatistiksel olarak anlamlı derecede daha yüksek bulundu ($p= 0,014$). HbA1c ortalaması hasta grubunda istatistiksel olarak anlamlı derecede yüksek idi ($p < 0,001$). HDL-K ortalaması hasta grubunda istatistiksel olarak anlamlı düzeyde düşük bulundu ($p= 0,001$).
Sonuç: Çalışmamızda hasta grubunda trunkal yağ doku oranının yüksek bulunması trunkal yerleşimli yağ dokuda artmış aromataz aktivitesi nedeni ile östrojen üretiminin daha fazla olduğunu bu nedenle myoma sıklığının arttığını düşündürmüştür. Myoma uteri gelişimi üzerinde etkili metabolik parametrelerin değerlendirildiği ileri çalışmalara ihtiyaç vardır. Yine çalışmamızda hasta grubunda ki HbA_1c yüksekliğinin myom olma olasılığını 3,5 kat arttırdığını tespit ettik. HOMA-IR değerinin normal

saptanması üzerine insülin direncinin myom gelişimi için muhtemel bir risk faktörü olamayacağı sonucuna varılmıştır.
Anahtar kelimeler: Myoma uteri, visseral / trunkal obezite, insülin direnci

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Introduction

Myoma uteri, is the most commonly observed tumor type in women of reproductive age. [1] These tumors are the major indication for hysterectomy in premenopausal women. [2,3] Age, nulliparity, obesity, estrogen and progesterone effect are some of the factors accused, while the pathogenesis is not clearly understood. [4]

In premenopausal period, the insulin resistance caused by obesity effects the estrogen-progesterone balance by hyper-insulinemia and elevated insulin like growth factor-1 (IGF-1) levels. [5] The increase of aromatase enzyme activity in increased fat tissue and the decrease of sex hormone binding globulin (SHBG) levels causes the increase of free estrogen levels in circulation. [6,7] These mechanisms partially explain the hormonal correlation between obesity and myoma uteri.

The body mass index (BMI) is a commonly accepted method for the diagnosis of obesity and is highly correlated with body fat rate. Nevertheless, the results of the studies about the correlation of myoma uteri and BMI are controversial. [1,8,9] Besides, as we know, there is not any study in literature which investigates the relationship of body fat distribution and insulin resistance with myoma uteri formation.

In this sectional study, we aimed to study the effect of body fat distribution (visceral-truncal fat rate) and insulin resistance on the myoma uteri formation in premenopausal women.

Materials and Methods

Study protocol

100 patients with myoma uteri diagnosis and 50 control patients who had no myoma uteri and who had the similar properties with the patient group were included in the study.

The patients with prediagnosed diabetes mellitus (DM), impaired fasting glucose, or impaired glucose tolerance, patients with any condition which effects glucose metabolism (Cushing, acromegaly, pheochromocytoma, hyperthyroidism, etc.) or patients using any drug effecting plasma glucose levels (antipsychotics, antivirals, beta agonists, diazoxide, phenytoin, steroids, interferon, thyroid hormones, etc.) and patients in post-menopausal period were excluded from the study. The study protocol was approved by the local ethical committee (Decicision: Date: 22.12.2011; Decision Number: 2011-137). All patients were informed about the procedure by the same clinician (B.K.) and gave written informed consent.

All patients were asked questions on their age, sex, menstruation regularity, obstetric history, drug usage, smoking and/or alcohol consumption, familial coronary artery disease history (CAD), diabetes, obesity, hypertension (HT), thyroidal disease history. All patients were undergone detailed physical examination.

The cases were evaluated by trans-vaginal or suprapubic ultrasound imaging. As Myoma Uteri is not our determined histopathological diagnosis, the patients were assessed through Esaote make MYLAB30 Gold model device with transvaginal and suprapubic probes and then, they were split into experiment or control groups regarding the existence of Myomas.

They were divided into two groups as patient and control groups according to presence of myoma uteri. The anthropometric measures of the cases (height, weight, BMI) were done. BMI's was calculated automatically and recorded using Tanita (Tanita TBF-410®) device.

Venous blood samples of all cases were collected from ante cubital vena after 10 hours of fasting. Fasting blood glucose, HbA1c, insulin, LDL-cholesterol, triglyceride, HDL-cholesterol and total cholesterol analysis were done with the blood samples. Standard OGTT with 75 gr glucose was done to patients whose fasting plasma glucose levels were higher than 100 mg/dl. Homeostasis model assessment- estimated insulin resistance (HOMA-IR) formula was used for calculating insulin resistance. [HOMA-IR= fasting insulin (mU/ml) x FPG (mg/dl) / 405]. In addition, blood samples were collected to analyze follicle stimulating hormone (FSH), luteinizing hormone (LH) and estradiol levels from patients who were in the 3rd day of their menstruation cycle. Biochemical and hormonal analyses were done in our hospital's biochemistry and hormone laboratories, using Roche Cobas 6000 and Roche Cobas 8000 modulators.

Visceral and truncal fat rates were measured with Tanita (Viscan TANITA Abdominal Fat Analyzer®) device. The patients were laid on bed with supine position. Alcohol was poured on umbilicus. Visceral and truncal fat measurement was made automatically with Tanita (Viscan TANİTA Abdominal Fat Analyzer®) device's soft-ware. The results of 10% and higher for visceral fat rate and 40% and higher for truncal fat rate were considered as pathological. [10]

Statistical analysis

All statistical analyses were performed with SPSS 16.0 (SPSS Inc., Il., USA) statistical soft-ware. Categorical variables were expressed as counts and percentages, and continuity-corrected chi-square test was used for comparisons. Kolmogorov-Smirnov test was used to analyze compliance of quantitative data with the normal distribution. The data with normal distribution were expressed as mean and standard deviation; the data with non-normal distribution were expressed as median, 25th quartile, and 75th quartile values. When the assumptions of parametric tests were verified independent samples t test, and when the assumptions were violated Mann-Whitney U test was used. Multivariate binary logistic regression analysis was used to determine the factors that affect development of myoma. The results were presented as Odds ratios and 95% confidence interval. In all analysis $p < 0.05$ was accepted as statistically significant.

Results

The comparative demographic and laboratory data of both patient and control groups are shown in Table 1.

25 cases with fasting glucose values between 100-126 mg/dL were undergone OGTT with 75 gr glucose. 20 of these cases were from patient group and 5 of them were from control group. According to OGTT results, 5 cases were of impaired fasting glucose, 6 cases were of impaired glucose tolerance and 2 cases were of type 2 DM diagnosis among the patient group. In the control group, 2 cases were of impaired fasting glucose and 3 cases were of impaired glucose tolerance diagnosis.

Multinomial logistic regression analyze was done in order to define the most affecting factors on myoma formation. As the result of multivariate logistic regression analyzes, the factors which may be causing myoma uteri formation were shown at Table 2.

Table 1 . Demographical characteristics and the laboratory parameters of the groups

	CONTROL (n=50)	**CASE (n=100)**	**P Value**
AGE	42.88±6.45	44.12±5.25	0.215
HEIGHT(cm)	160.5 (157-165)	158.0 (155-163)	0.083
WEIGHT(kg)	75.35 (65.68 – 81.55)	73.45 (67.63 – 84.18)	0.697
BMI(kg/m2)	29.5 (25.6 – 32.12)	29,85 (25.97-32.60)	0.386
VFR (%)	10.40 (9.0 – 12.52)	11.55 (9.85 -13.50)	0.065
TFR (%)	40.85 (35.95- 47.00)	44.60 (40.85 – 47.65)	**0.014**
Pre-prandial serum glucose (mg/dL)	89.00 (82.00 – 93.50)	90 (85.00 – 98.00)	0.134
HBA1c (%)	4.98 (4.75 – 5.37)	5.61 (5.20 -6.10)	**<0.001**
INSULIN(U1u/Ml)	29.50 (25.60 – 32.12)	29.85 (25.95 – 32.60)	0.959
HOMA-IR	1.57 (1.24-2.16)	1.67 (0.97-2.78)	0.734
TG (mg/dL)	90.00 (63.75 – 122.25)	112.00 (79.00– 154.50)	0.062
HDL-K(mg/dL)	57.72±16.26	49.39±12.48	**0.001**
TK(mg/dL)	189.26± 41.20	186±38.62	0.700
LDL-K(mg/dL)	109.27±34.15	113.03±33.63	0.521
FSH(mIu/ml)	8.08 (4.94 – 11.68)	8.25 (5.67 – 11.58)	0.574
LH(mIu/ml)	5.54 (3.58 – 10.32)	5.44 (3.62 – 8.11)	0.814
E2(pg/ml)	63.54 (46.31 – 99.08)	62.90 (47.57 – 105.50)	0.595

BMI: Body Mass Index, VFR: Visceral Fat Rate, TFR: Truncal Fat Rate, HBA1c: Hemoglobin A1c, HOMA-IR: Homeostasis model assessment-Insülin resistance, TG: Triglyceride, HDL-K: High density

lipoprotein cholesterol, TK: Total cholesterol, LDL-K: low density lipoprotein cholesterol, FSH: Follicle stimulating hormone, LH: luteinizing hormone, E2: estrogen

Table 2. Assessment of risk factors that may be effective on myoma uteri growth in multivariate logistic regression analysis

	Multivariate odds ratio (95% CI)	**P value**
WEIGHT (kg)	0.947 (0.874-1.026)	0.182
BMI (kg/m2)	1.075 (0.878-1.316)	0.484
VFR (%)	0.975 (0.794-1.197)	0.806
TFR (%)	1.087 (0.993-1.190)	0.071
pre-prandial serum glucose (mg/dl)	1.001 (0.954-1.051)	0.958
HbA1c (%)	3.461 (1.518- 7.891)	**0.003**
LDL-K (mg/dl)	0.934 (0.766-1.137)	0.495
TG (mg/dl)	0.984 (0.945-1.024)	0.434
HDL-K (mg/dl)	0.906 (0.741-1.108)	0.336
T.Chol. (mg/dl)	1.074 (0.882-1.308)	0.479

BMI: Body Mass Index, VFR: Visceral Fat Rate, TFR: Truncal Fat Rate, HBA1c: Hemoglobin A1c, LDL-K: low density lipoprotein cholesterol, TG: Triglyceride, HDL-K: High density lipoprotein cholesterol, T.Chol: Total cholesterol

Discussion

In this study, we aimed to study the effect of visceral fat rate, truncal fat rate and insulin resistance on the myoma uteri progression in premenopausal women. In our study, truncal fat rate of the patient group was found significantly higher than the control group. What is more, a significant relationship is found between truncal fat rate and myoma uteri formation. There was no significant difference in mean visceral fat rate between both groups and no significant correlation was found between visceral fat rate and myoma formation. The high truncal fat tissue rate in the patient group supports the result that estrogen production is more in this tissue because of the high aromatase activity, and increases the risk for myoma uteri. [11] This result can also explain the visceral fat, in which the aromatase activity is low, has no effect on myoma progression.

There are some studies suggesting that myoma risk increases in obese women, similar to our study.[12,13] There are also studies opposing our results [14] and suggesting that obesity has no effect on the development of myoma. [15,16] In a study investigating the relationship between BMI and myoma uterine, the body fat percentage has been calculated by bioelectrical impedance method, it has been found that risk of development of myoma is higher in women with excess body fat, although they have not been accepted as obese according to BMI. [9] In a study investigating the relationship between myoma and obesity, it has been found that obesity increases the risk of myoma by 46% regardless of the hormone replacement therapy in patients receiving hormone replacement therapy. [17] These controversial results in the literature suggest the need for studies with larger series.

In our study, no significant difference was found between both groups regarding to mean BMI. In literature, waist circumference is considered more valuable than waist-hip ratio and BMI in diagnosing abdominal obesity. [18]

Similarly, Sato et al found no significant differences between groups in terms of body weight, height and BMI values.[9] Sadlonova et al. also suggested that higher BMI is not a cause for myoma uteri. [1] The authors suggest that of BMI is not a main factor in obesity whereas increases of distribution of body fat, waist circumference and waist-hip ratio may be associated with certain diseases including myoma uteri. [9]

Unlike these studies, in the study of Takeda et al, [19] BMI was found significantly higher in the patient group and obesity was reported as a risk factor for myoma uteri formation. In this study, the waist circumference was ignored because although waist circumference is diagnostic on abdominal obesity, it is reported that, visceral fat rate could not be measured by waist circumference on patients with myoma uteri due to enlarged uterus volume. Considering contradictory results in literature, it can be told that further studies are essential about that subject.

In our study, there was no significant difference between both groups regarding insulin resistance which is measured by HOMA-IR formula. Concerning this subject, in the study of Sadlonova et al, [1] the short insulin resistance test was done for insulin resistance and the results were reported as insignificant. Supporting our study, the authors were convinced about the insulin resistance could not be considered as a risk factor for myoma formation. Although there is no consensus about the sensitivity and specificity of insulin resistance measurement techniques, euglisemic clamp technique is widely accepted as a gold standard for determining insulin resistance. [20] Whilst it is not practically applicable, we think that this technique would be useful in future studies which will investigate the relationship between insulin resistance and myoma formation.

In our study, HbA1c values were found higher in the patient group, although fasting plasma glucose levels were similar in both groups. There are few studies in literature investigating the relationship between myoma formation and glucose metabolism. In these studies, no significant correlation was found between fasting blood glucose level and myoma formation. [1,19] In one of these studies, the idea of "hyperglycemia may increase likelihood of myoma uteri formation" was inferred, because of fasting plasma glucose levels were found higher in the patient group. [1] No studies were found in literature which investigates the effect of HbA1c on myoma uteri formation.

In our study we found no significant relationship between fasting plasma glucose and the development of myoma. However, we found a direct correlation between higher HbA1c levels and myoma formation. In this case, we thought whether higher HbA1c levels resulted from higher postprandial blood glucose levels, but we could not comment on because we had not measured postprandial blood glucose.

In our study, considering lipid parameters, no statistical difference was found between both groups in terms of LDL-C, triglyceride, total cholesterol levels. However, HDL-C levels were found significantly lower in the patient group. In the study of Takeda et al., it was found that, triglyceride levels were higher when myoma and univariate risk factors were compared, but this elevation was considered as a contributory factor instead of being a risk factor and other lipid parameters were not analyzed. [19] In our

study we found triglyceride levels to be higher in the patients group, but the difference was not statistically significant; we concluded that higher triglyceride levels may contribute to development of myoma**.** Sadlonova et al reported that HDL-C levels were significantly higher in the group with myoma uteri. However, it was obvious that there was a prominent age difference between the patient and the control groups in that study. [1] In literature, it is reported that, high concentrations of fatty acids corrupts lipoprotein lipase activity in vivo in obese patients, thus a decrease occurs on free cholesterol and apo-lipoprotein transfer from VLDL and LDL-C traces to HDL-C and finally a decrease occurs on HDL-C levels. [21] In our study, HDL-C levels were found lower in the patients with myoma uteri. In the group of the patients with myoma uteri, HDL-C levels are also expected to be increased due to high estrogen levels. Besides, supporting our results, there are also some studies in the literature in which a negative correlation was reported between estrogen levels and HDL-C levels. [22]

It has been revealed that there is a negative correlation between presence of hyperlipidemia and myoma uteri because of myomas are estrogen dependent tumors. On the other side, no correlation was found between myoma uteri and hyperlipidemia in the study of Parazzini et al. [12] Similarly, Brunero et al. reported that, HDL-C levels decreased in patients with BMI over 25 kg/m^2.[23] In QUEBEC study, it is found that, abdominal obesity causes an increase on triglyceride levels and a decrease on HDL-C levels. However, researchers could not find a correlation between subcutaneous fat tissue and triglyceride or HDL-C levels.[24] Considering contradictory results in the literature, it can be told that further studies are essential about that subject.

Our study is important as it is the first research in which visceral and truncal fat rates are separately investigated in patients with myoma uteri. The metabolic parameters effective on myoma uteri formation should be supported by future research, because of the inconsistency in the literature.

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