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RESEARCH

THE EFFECT OF HORMONE THERAPY AND TIBOLONE ON GLUCOSE AND LIPID METABOLISM IN HEALTHY POSTMENOPAUSAL WOMEN

Filiz ÇAYAN[1]
Ramazan GEN[2]
Esen AKBAY[2]
Umut DİLEK[1]
Saffet DİLEK[1]

ABSTRACT

Introduction: To evaluate the effects of tibolone and conventional hormone therapy on insulin sensitivity and lipid metabolism in healthy postmenopausal women.

Materials and Method: The study included 85 normoinsulinemic healthy postmenopausal Turkish women. The participants were assigned to one of three groups: 26 women received 0.625 mg of CE-E+MPA daily, 32 received 2.5 mg of tibolone daily, and 27 had no treatment and served as a control group. Before and after 12 weeks of treatment, glucose metabolism, insulin resistance (HOMA-IR) and lipid metabolism parameters were compared.

Results: CEE/MPA treatment significantly decreased fasting glucose levels, fasting insulin levels, 2 h glucose levels, 2 h insulin levels, and HOMA-IR and LDL levels while increasing triglyceride and HDL levels ($p<0.01$). Tibolone treatment decreased fasting insulin, insulin resistance index (HOMA-IR), total cholesterol, triglyceride, LDL and HDL levels significantly, however it increased fasting glucose, 2-h glucose and 2-h insulin levels ($p<0.01$). The glucose and lipid parameters of the control group deteriorated at the end of the follow-up period.

Conclusion: CEE/MPA improves glucose and lipid metabolism in healthy postmenopausal women. Although less pronounced, tibolone also has favorable effects on these parameters.

Key Words: Postmenopausal insulin resistance; Glucose tolerance; Lipid metabolism; Combined hormone replacement; Tibolone.

ARAŞTIRMA

POSTMENAPOZAL SAĞLIKLI KADINLARDA KOMBİNE HORMON TEDAVİSİ VE TİBOLON'UN GLUKOZ VE LİPİD METABOLİZMASINA ETKİSİ

ÖZ

Giriş: Menapozla birlikte gelişen insülin direncinde artma ve lipid metabolizmasında kötüleşme, metabolik sendromun komponentleridir. Hormon tedavisi almayan kadınlarda, bu süreçin hızlandığı bilinmektedir. Bu çalışmada postmenapozal dönemde sık kullanılan oral östrojen ve progesteron kombine hormon preparatı ile tibolon tedavisinin glukoz intoleransı ve lipid metabolizması üzerine olan etkisinin araştırılması.

Gereç ve Yöntem: 85 normoglisemik sağlıklı postmenopozal hasta randomize olarak 3 gruba ayrıldı. Grup 1'e (n=26) konjuge equine östrojen (CEE) + medroksiprogesteron asetat (MPA), Grup 2'ye (n=32) ise tibolon tedavisi başlandı. Grup 3 (n=27) ise kontrol grubu olarak belirlendi ve hiçbir tedavi verilmedi. Hastaların tedavi öncesi ve 12. haftada karbonhidrat metabolizması, insülin direnci (homeostaz modeli-HOMA-IR) ve lipid parametreleri karşılaştırıldı.

Bulgular: CEE/MPA tedavisinin, açlık glukoz ve insülin, postgrandial 2. saat glukoz ve insülin, HOMA-IR, total kolesterol ve LDL değerlerini istatiksel anlamlı derecede azaltığı, ancak trigliserid ve HDL değerlerini artırdığı görüldü ($p<0,01$). Tibolon grubunda ise açlık glukoz, postgrandial 2. saat glukoz ve insülin düzeyleri artarken, açlık insülin, HOMA-IR, total kolesterol, trigliserid, LDL ve HDL değerleri istatiksel anlamlı derecede azaldı ($p<0,01$). Tedavi almayan grubun, takip süresinin sonunda glukoz ve lipid parametreleri kötüleşti ($p<0,01$).

Sonuç: CEE/MPA, postmenapozal sağlıklı kadınlarda insülin direnci ve lipid metabolizması üzerinde faydalı etkiler göstermektedir. Ancak daha az oranda olmakla birlikte tibolonun dab u parametreler üzerine pozitif etkileri bulunmaktadır.

Anahtar Sözcükler: Postmenapozal insülin direnci; Glukoz intoleransı; Lipid metabolizması; Kombine hormon replasmanı; Tibolon.

İletişim *(Correspondance)*

Filiz ÇAYAN
Mersin Üniversitesi Tıp Fakültesi Hastanesi
Kadın Hastalıkları ve Doğum Anabilim Dalı MERSİN
Tlf: 0324 337 43 00
e-posta: filizcayan@yahoo.com

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[1] Mersin Üniversitesi Tıp Fakültesi Hastanesi
Kadın Hastalıkları ve Doğum Anabilim Dalı MERSİN
[2] Mersin Üniversitesi Tıp Fakültesi Hastanesi
Dahiliye-Endokrinoloji Anabilim Dalı MERSİN

Introduction

Menopause is associated with unfavorable changes in the carbohydrate and lipid metabolism such as deterioration in insulin sensitivity and dyslipidemia (1-4). It is well known that hyperinsulinemia, insulin resistance and alterations in lipid parameters are potential risk factors for cardiovascular diseases. These changes are in part due to the age related impairment of these metabolisms but may also be associated with postmenopausal hypoestrogenism (5,6).

Continous hormone replacement therapy (HRT) with a combination of an estrogen and a progestagen is the traditional first line therapy for alleviating hot flushes and other postmenopausal symptoms. Another HRT agent is tibolone which, after oral intake is rapidly converted into 3-- and 3,-hydroxyl tibolone, both having estrogenic properties, and the 4-ene epimer of tibolone, which is known to possess progestagenic as well as androgenic activity. Previous studies on mostly sequential treatment have shown slightly beneficial or no effects of HRT on insulin resistance and lipid metabolism (7-10). The same discrepancy holds for tibolone administration in postmenopausal women with normal glucose tolerance (11-13). The incongruity of the results may be attributable to the discrepancies in the method of assessing insulin sensitivity and differences in baseline characteristics among individuals, and/or also to differences in preparations.

The aim of the present study was to compare the effects of tibolone with those of a traditional HT combination of estrogen and progestin on insulin resistance and lipid parameters in postmenopausal women with normal glucose tolerance.

Materials and Method

A prospective randomized controlled study was conducted at the Gynecology and Obstetrics Clinics in the University of Mersin, School of Medicine, Turkey. It was conducted in accordance with the Declaration of Helsinki and was approved by the local ethics committee and informed consent was obtained from all subjects before enrollment in the study. Figure 1 is a flow chart of the patients through different stages of the study.

Group allocation was determined by one of the authors who was not involved in patient care. The study included 85 healthy postmenopausal women. Healthy postmenopausal women between 40 and 65 years of age with an intact uterus, having their last spontaneous menstrual cycle more than 12 months prior to the initiation of the study, with serum levels of follicle-stimulating hormone (FSH) within the postmenopausal range (FSH> 30IU/L) were eligible for the study.

All participants were evaluated with a detailed history and physical examination. Women with a history of severe medical illness (e.g., diabetes mellitus, hypertension (>160mmHg systolic or >100mmHg diastolic), endocrine disorders, myocardial infarction or ischemic heart disease, chronic renal or hepatic disease, cerebrovascular accident, stroke or transient ischemic attack, thrombosis or thromboembolic disorders related to estrogen use, known or suspected estrogen-dependent neoplasia, known hypersensitivity to estrogens, progestagens or tibolone, who was using any medications for at least 6 months before the study, including oral contraceptives; glucocorticoids; ovulation induction agents; antilipidemic, antidiabetic and antiobesity drugs; or estrogenic, antiandrogenic and antihypertensive medication were excluded from the study. The BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2). Weight, height and waist and hip circumferences were measured. Waist circumference was obtained as the smallest circumference at the level of the umbilicus. Hip circumference was obtained as the widest circumference at the level of the buttocks.

Women were randomized to receive either of the following treatment regimens: oral 0.625 mg conjugated equine estrogens plus 5mg medroxyprogesterone acetate (CE-E/MPA), daily as group 1 (n=26) or tibolone 2.5 mg daily (n=32) as group 2 and no treatment (n=27) for 12 weeks as group 3. Before and after the treatment, blood samples were obtained after 12 hours of overnight fasting, for serum glucose, total cholesterol (TC), triglyceride (TG), HDL-cholesterol (HDL-C) and insulin measurements. Glucose metabolism was investigated by an oral glucose tolerance test (OGTT). The OGTT test was performed after a standard carbohydrate diet (300 g/day) for 3 days, followed by fasting overnight for 12 h. OGTT blood samples were obtained at baseline and 120 minutes after ingestion of 75 g of glucose in 150 ml water. A normal glycemic response to OGTT was defined according to the criteria of the American Diabetes Association (15). The insulin sensitivity was determined by Homeostasis Model Assessment Model (HOMA) index with formula: HOMA IR = fasting insulin (mU/ml) x fasting glucose (mg/dl)/405 (14).

Biochemical and Hormonal Analysis

Assays for glucose, total cholesterol, HDL triglyceride were performed using a Cobas Integra 800 automated analyzer. The serum low-density lipoprotein (LDL)-cholesterol was calculated according to the Friedewald's formula. Insulin tests were performed using Modular E170 automated analyzer.

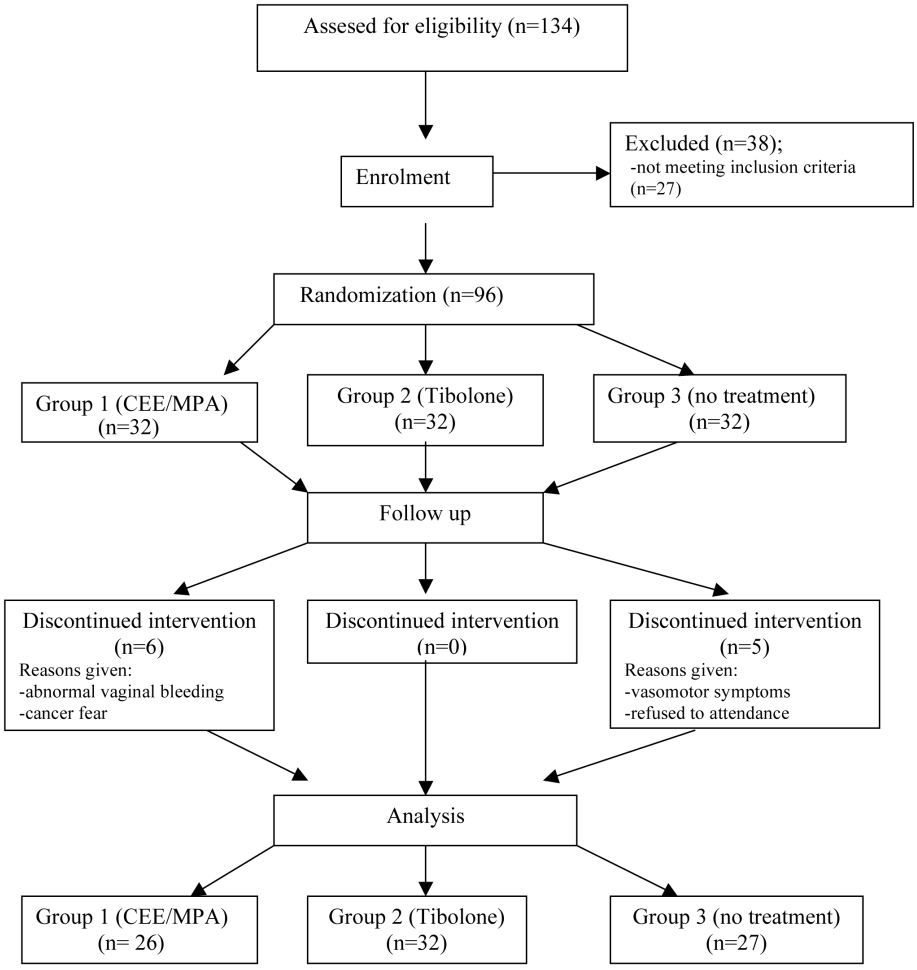

Figure 1— Flow chart of the patients through the different stages of the study.

Statistical Analysis

SPSS package program (version 11.0, Chicago, IL) was used for statistical analysis. Data were presented as mean±sd. Differences among groups in baseline measurements were evaluated using one-way ANOVA. A P-value of <0.05 was taken to indicate statistical significance.

Results

Baseline characteristics of the groups participating in the study are presented in Table 1. There were no significant differences among the groups with regard to age, BMI, waist/hip ratio, parity and time since menopause onset (p >0.05) (Table 1).

Table 2 shows the carbohydrate and lipid parameters of the studied patients before and after 12 weeks. At baseline, there were no significant differences among the groups with regard to serum concentrations of fasting glucose, fasting insulin, 2 h glucose, 2 h insulin, total cholesterol, HDL-C, LDL-C, triglyceride and HOMA-IR (p >0,05).

After treatment with CEE/MPA in group 1, the serum fasting glucose, fasting insulin, 2 h glucose, 2 h insulin, total cholesterol, and LDL-C concentrations, and HOMA-IR decreased significantly from baseline levels (p <0.01). However, statistically significant increases were observed in serum HDL-C and triglyceride concentrations (p <0.01).

Table 1— Baseline Demographic Characteristics of the Patients

	Group 1 (n=26)	Group 2 (n=32)	Group 3 (n=27)
Age (years)	50.5±3.4 (42-60)	51.5±4.1 (44-63)	52.3±4.79 (43-65)
BMI (kg/m²)	26.1±2.3 (20.9-30.8)	28.2±4.1 (21.3-35.7)	28.7±3.5 (23.4-35.6)
Waist/Hip Ratio	0.78±0.05 (0.69-0.86)	0.80±0.06(0.70-0.93)	0.81±0.06(0.69-0.94)
Parity	4.4±2.4 (1-11)	4.0±2.0 (0-9)	4.7±2.3 (2-11)
Years Since Menopause	4.2±5.2 (1-25)	4.3±3.6 (1-13)	4.3±4.9 (1-25)

Table 2— Metabolic and Lipids Parameters of the Groups at Baseline and After12 Weeks

	Group 1 (n=26)	Group 1 (n=32)	Group 1 (n=27)
Fasting glucose (mg/dl)			
Baseline	93.07±16.50	89.36±11.94	90.02±17.31
12 weeks	84.50±13.43[a]	91.63±14.14[b]	102.78±26.88[c]
Fasting insulin (mIU/ml)			
Baseline	10.47±5.51	12.08±4.97	15.24±14.84
12 weeks	7.82±2.94[a]	10.89±4.48[b]	17.41±14.17[c]
2 hr glucose (mg/dl)			
Baseline	112.05±42.12	109.80±30.79	106.28±44.94
12 weeks	102.62±33.28[a]	117.72±35.99[b]	122.97±54.92[c]
2 hr insulin (mIU/ml)			
Baseline	47.58±44.73	55.98±33.86	47.31±30.44
12 weeks	38.96±38.92[a]	59.15±30.54[b]	53.13±35.38[c]
HOMA-IR			
Baseline	2.53±1.45	2.67±1.09	3.44±3.58
12 weeks	1.67±0.06[a]	2.46±1.03[b]	4,38±3.53[c]
Total cholesterol (mg/dl)			
Baseline	192.26±34.39	203.31±31.07	212.03±33.43
12 weeks	189.84±31.41[a]	198.96±27.77[b]	221.96±31.65[c]
HDL-C (mg/dl)			
Baseline	50.76±13.29	58.37±18.27	54.25±11.59
12 weeks	51.53±11.98[a]	52.53±14.92[b]	44.51±15.62[c]
LDL-C (mg/dl)			
Baseline	112.80±30.71	120.28±25.02	127.18±33.88
12 weeks	106.38±23.31[a]	112.15±24.79[b]	148.25±39.80[c]
Triglyceride (mg/dl)			
Baseline	136.61±55.28	136.50±59.91	153.51±81.48
12 weeks	142.53±48.30[a]	129.62±62.96[b]	173.71±81.32[c]

HOMA-IR, homeostasis model assessment insulin resistance index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; [a]significantly different from baseline level after treatment CEE+MPA, p <0.01; [b]significantly different from at baseline after treatment tibolone, p <0.01; [c]significantly different from baseline after no treatment, p <0.01.

Participants treated with tibolone showed a significant increase in fasting glucose, 2 h glucose and 2 h insulin concentrations from baseline (p<0,01). However, fasting insulin, total cholesterol, LDL-C, HDL-C and triglyceride concentrations, and HOMA-IR decreased significantly from baseline levels (p<0.01).

In the control group with no therapy, insulin sensitivity and lipid parameters deteriorated significantly after 12 weeks,

as expected. The serum concentrations of fasting insulin, fasting glucose, 2 h glucose, 2 h insulin, total cholesterol, LDL-C, and triglyceride, and HOMA-IR increased significantly from baseline levels ($p<0.01$). However, A statistically significant decrease was observed in HDL-C level ($p<0.01$).

Discussion

Menopause constitutes an important health problem for aging women, despite being a physiologic phenomenon (15). Hypoestrogenism seems to reduce both insulin secretion and elimination as well as increasing insulin resistance, thereafter bringing about an increase in the circulating insulin concentration and an increased incidence of both diabetes and metabolic syndrome (16-18). Menopause is also followed by a progressive deterioration in lipid metabolism in which catabolism of triglycerides decreases, yielding a decrease in HDL-C and increase in LDL-C (19). All these changes are features of the metabolic syndrome that implicate the necessity of undertaking effective actions aimed at preventing these unfavorable events.

Insulin resistance and thus glucose metabolism are complex metabolic events which are influenced by physical activity, abdominal adiposity and many other medical conditions. In a recent study, Villa et al. demonstrated that both menopause and insulin resistance have significant effects on the metabolic syndrome, independently of age and obesity. They also reported that after adjustment for age, body mass index, lifestyle, and diet, both menopause and insulin resistance were independently and significantly correlated with metabolic syndrome (20). Consistent with the literature, we detected a worsening of both carbohydrate and lipid parameters of untreated patients (control group) after 12 weeks. In these patients, fasting insulin, fasting glucose, 2-h glucose, 2-h insulin, total cholesterol, LDL-C, and triglyceride concentrations and HOMA-IR values increased significantly. These changes in the control group may be in part due to postmenopausal hypoestrogenism and also abdominal fat distribution, as discussed above.

Previous studies showed that oral estrogen therapy (ET) improves insulin resistance and also has beneficial effects on the lipid profile in postmenopausal women (21). However, progestagens are known to counteract possible beneficial effects of estrogens on carbohydrate metabolism. According to their chemical structure, especially their androgenic potency, progestins show different metabolic effects (22). Since the continuous combined HRT and tibolone are now the most

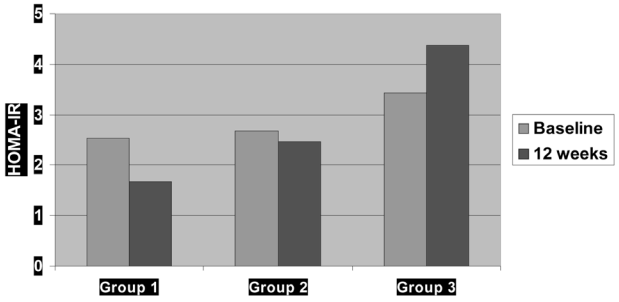

Figure 2— HOMA-IR values of the patients, at baseline and after 12 weeks.

frequently prescribed regimens, we aimed to investigate the effects of these drugs on carbohydrate and lipid metabolism. Our findings are in agreement with those of two recent studies, which showed that CEE/MPA treatment improved insulin sensitivity and lipid metabolism (11,19,23). Consistent with the previous reports, we detected that CEE/MPA decreased fasting insulin, fasting glucose, HOMA-IR, total cholesterol, and LDL-C levels. Also both triglyceride and HDL-C levels were increased with CEE/MPA therapy.

Tibolone has specific effects on different tissues due to tissue-selective metabolism, enzyme regulation and/or receptor binding and activation. Therefore, it is referred to as a selective tissue estrogenic activity regulator. Data on the effects of tibolone on glucose metabolism and insulin sensitivity are conflicting. Tibolone in the standard dose of 2.5 mg daily given to postmenopausal women has been reported to slightly increase (24), decrease (25) or have no effects (26,12,13) on fasting insulin.

All OGTT-derived indexes rely upon the measurement of plasma glucose and insulin concentrations, either from fasting values (homeostasis model assessment [HOMA]) or postload values, to provide an assessment of the whole-body insulin resistance without reference to the contribution of individual organs, e.g., liver and muscle. Many tissues, including the liver, skeletal muscle, and adipocytes, manifest resistance to insulin. Although in many individuals insulin resistance develops simultaneously in multiple organs, the severity of insulin resistance may differ among the various tissues. Indexes derived from measurements of fasting plasma glucose and insulin concentrations (HOMA and QUICKI) primarily reflect hepatic insulin resistance (27).

A suppressive effect of tibolone on circulating SHBG level has been reported previously and is believed to reflect a

suppressive effect of its androgenic 4-ene epimer on hepatic SHBG synthesis. However, the relationship between hyperinsulinemia and hyperandrogenemia may not be causative. Since low SHBG is defined as a risk factor for insulin resistance (28), the effect of tibolone on insulin sensitivity is expected to be less than that of CEE/MPA.

Fasting hyperinsulinemia has a primary pathogenic role in the development of diabetes, independent of insulin resistance. Chronic hyperinsulinemia may result in downregulation of insulin receptors in pancreatic ß cells, leading to impaired glucose sensing which results in impaired early-phase insulin secretion (29). In the present study, the HT group and the tibolone group showed a significant decrease in fasting insulin levels after treatment. Fasting glucose level reflects glucose secretion by the liver, while the 2-h glucose reflects muscle insulin action (30). Our data revealed that fasting glucose and 2-h glucose levels decreased in the HT group, but increased in tibolone and control groups. This adverse effect may be related to the progestagenic and androgenic potency of the tibolone. Moreover, a decrease in peripheral insulin sensitivity might be explained by a reduction in glucose uptake by skeletal muscle and reduction in glycogen synthase (31). On the basis of these reports, tibolone treatment may have positive effects on hepatic insulin resistance but no effect on muscle insulin resistance.

In conclusion, CEE/MPA had a positive effect on glucose and lipid metabolism in healthy postmenopausal women. However tibolone was associated with less improvement in these risk factors when compared to CEE/MPA. A potential limitation of the present study is the short-follow–up period. Therefore, further studies with a larger population are needed to confirm our findings.

Not: Çalışmamız ilaç firmaları tarafından desteklenmemiştir.

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