Evaluation of Insulin Resistance in Obese, Postmenopausal Women Using Tibolone or Combined Oral Hormone Therapy

TİBOLON VEYA HORMON TEDAVİSİ KULLANAN OBEZ, POSTMENOPOZAL KADINLARDA İNSULİN DİRENCİNİN DEĞERLENDİRİLMESİ

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Abstract

Objective: To elucidate insulin sensitivity with clinical use of homeostasis model assessment in obese, postmenopausal women receiving tibolone or combined oral hormone therapy.

Material and Methods: In this cross-sectional study, 85 obese, postmenopausal women were enrolled. 25 women were receiving tibolone, 33 subjects were using oral estradiol (E2) (2 mg/day) + norethistheron acetate (NETA) (1 mg/day), and 27 subjects were not on treatment. Waist and hip circumferences, height, weight, blood pressure, serum estradiol, fasting insulin, glucose levels and lipid fractions were measured. Waist-hip ratio and body mass index were calculated. Homeostasis model assessment for insulin resistance and bioelectric impedance analyses for total body fat mass were used.

Results: The lowest waist, waist/hip ratio, systolic blood pressure measurements, and triglyceride level were observed in tibolone group. Women receiving tibolone had significantly lower fat mass and higher fat-free mass in comparison with women not on treatment. Homeostasis model assessment was significantly lower in both treatment groups compared to control group. Total body fat mass positively correlated both with fasting insulin and homeostasis model assessment, whereas it was correlated inversely with fat-free mass. There was a positive relationship between fat-free mass and estradiol.

Conclusions: Homeostasis model assessment, which can be used to evaluate insulin sensitivity quickly, revealed that tibolone and combined oral hormone therapy might have not any harmful effect on insulin sensitivity in obese, postmenopausal women who already have a tendency towards high insulin resistance.

Key Words: Insulin resistance, tibolone, hormone therapy

Özet

Amaç: Tibolon veya kombine oral hormon tedavisi alan obez, postmenopozal kadınlarda insulin duyarlılığının klinik homeostatic model kullanımıyla değerlendirilmesi.

Gereç ve Yöntemler: Bu olgu kesitsel çalışmaya 85 obez, postmenopozal kadın alındı. 25 kadın tibolon, 33 olgu oral östrojen + progesteron kullanıyorken 27 olgu herhangi bir tedavi almıyordu. Bel, kalça, boy, vücut ağırlığı, kan basıncı, serum östradiolu, açlık insulini, glukoz ve lipit seviyeleri ölçüldü. Bel/kalça oranı ve beden kitle indeksi hesaplandı. İnsulin direnci için homeostatik model değerlendirme ve toplam beden yağ kitlesi için de biyoelektrik direnç analizi kullanıldı.

Bulgular: Tibolon grubunda en düşük bel, bel/kalça oranı, sistolik kan basıncı ölcümü ve trigliserid düzeyleri gözlendi. Tedavi almayan kadınlarla karşılaştırıldıklarında tibolon alan kadınlar istatistiksel olarak anlamlı derecede düşük yağ kitlesine ve yüksek yağsız beden kitlesine sahiptiler. Her iki tedavi grubunda homeostatik model değerleri kontrol grubuna göre anlamlı derecede düşük bulundu. Toplam beden yağ kitlesi açlık insulini ve homeostatik model değerleri ile pozitif bir ilişki gösterirken; yağsız beden kitlesiyle ters orantılı bir bağlantıya sahipti. Östradiol ile yağsız beden kitlesi arasında pozitif bir ilişki olduğu gözlendi.

Sonuç: İnsulin duyarlılığını hızlı bir biçimde değerlendirmek için kullanılan homeostatik model tibolon ve kombine oral hormon tedavisinin, hali hazırda yüksek insulin direncine yatkın olan obez, postmenopozal hastalarda insulin duyarlılığı üzerine olumsuz bir etki taşımadıklarını göstermiştir.

Anahtar Kelimeler: İnsulin direnci, tibolon, hormon tedavisi

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Menopause status is associated with an increase in total and central body fat, and as known, there is a strong relationship between fat accumulation and insulin resistance, which is an independent risk factor for

cardiovascular disease.[1-3] In terms of insulin sensitivity, the differences between women receiving hormone therapy (HT) and those not on HT could also emerge from visceral fat deposition. Hormone therapy has been reported to improve insulin sensitivity and fat distribution by avoidance of the increment in central obesity in postmenopausal women, even though the outcomes of some studies have conflicted with these results.[1,4-12] The type or administration route of replacement therapy may contribute to discrepancies in the effects of HT on insulin sensitivity.[13,14] All of the aforementioned data can address the questions as to whether tibolon and combined oral HT would improve insulin sensitivity owing to a reduction in total body fat mass. We need to explore the effect of tibolon on insulin sensitivity, and compare this effect with that of classical combined oral HT.

In this cross-sectional study, we aimed to compare insulin sensitivity with clinical use of homeostasis model assessment in obese, postmenopausal women receiving tibolon that is frequently used in Turkey or combined oral HT.

Material and Methods

Eighty-five obese, postmenopausal women were enrolled into this cross-sectional study. Twenty-five of subjects were using tibolon (2.5 mg/day) (Group A), 33 of women were taking oral estradiol (E2) (2 mg/day) + norethistheron acetate (NETA) (1mg/day) (Group B), and 27 subjects were not on HT (Group C). All women in-group A and B had been receiving HT for at least 12 months before entering the study. In non-user women who had not received HT previously, menopause was established by the lack of menstruation for at least 12 months and by high serum levels of follicle-stimulating hormone (FSH) (> 30 mIU/mL) and low serum levels of E2 (< 20 pg/mL). All subjects were evaluated by medical history, physical, and gynecological examination. Exclusion criteria included alcohol abuse, regular smoking, cardiac dysfunction, diabetes mellitus, and other endocrinologic diseases, chronic liver and renal disease, cancers, and medical disorders. None of the women was taking any drugs, which can interfere with insulin resistance. This study was approved by local medical ethics committee and all participants gave informed consent before the onset of study.

Waist and hip circumferences, height and weight were measured, and body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was divided by the circumference of the hip to find waist-hip ratio (WHR). Blood pressure was measured three times by a mercury sphygmomanometer in supine position before the examination and mean values were calculated. All blood samples were taken after 10-hour fasting and serum glucose, total cholesterol, triglyceride (TG), high density lipoprotein (HDL) levels were measured by Hitachi 911 automated analyzer by using commercial kits supplied from Roche Diagnostics. Low-density lipoprotein (LDL) levels were calculated by using Friedewald's formula. Fasting insulin level was measured by using ELISA kits (DSL Inc, Webster, Tx, USA). Serum FSH and E2 levels were determined by using commercially available diagnostic kits (Bayer Corporation, Tarrytown, NY, USA) in Advia Centaur Immunoassay System.

Homeostasis model assessment (HOMA) presented by Matthews et al.[15] was used to estimate insulin resistance. Homeostasis model assessment (HOMA-R for insulin resistance and HOMA-F for β-cell function) is a structural computer form of the glucose-insulin feedback system and performs well in comparison with various tests of insulin sensitivity.[16] Consequently total body fat mass and fat-free mass was measured using a non-invasive hand-held machine (Bodystat®1500, UK) by bioelectric impedance analyzing (BIA). Impedance to electrical flow in tissues is lower with increasing water content of the tissue.

Statistical analysis was made with Mann-Whitney-U, Kruskal-Wallis Tests, and Pearson correlation analysis. The data are expressed as means ± SE (Standard Error). Statistical significance was set at $p< 0.05$ and the categorical vari-

ables were expressed as percentages. Data was analyzed with the SPSS (Statistical Package for the Social Science, version 10.0) for Windows 98 (Microsoft Corp.).

Results

Table 1 demonstrates the physical and metabolic characteristics of the women. The comparison among the groups showed no differences in age, treatment periods, BMI, body weight and height measurements. There were statistically significant lower waist measurement and waist/hip ratio in women using tibolon compared with combined oral HT users and with subjects in control group. Total cholesterol, HDL, LDL, fasting insulin levels, and diastolic blood pressure (DBP) did not differ significantly by hormone therapy type. The control group had significantly higher systolic blood pressure (SBP) than each treatment group. As tibolon users had the lowest triglyceride levels, the highest triglyceride levels were found in women on combined oral HT. Estradiol level was significantly higher in each treatment group than in control group, and in addition, women receiving combined oral HT had higher E2 levels than tibolon users. Women receiving tibolon had significantly lower fat mass and higher fat-free mass in comparison with women not on HT (for each parameter; $p< 0.05$). HOMA-R was significantly lower in both treatment groups compared to control group (for each treatment group; $p< 0.05$), but there was not any significant difference between each treatment group.

In correlation analysis, fat mass was positively associated with fasting insulin ($r= 0.40$, $p< 0.01$) and HOMA-R ($r= 0.34$, $p< 0.01$), on the other hand, fat-free mass was inversely correlated with fasting insulin ($r= -0.35$, $p< 0.01$) and with HOMA-R ($r= -0.33$, $p< 0.01$). There was a positive relationship between fat-free mass and serum estradiol level ($r = 0.31$, $p< 0.01$). However, total cholesterol ($r= -0.23$, $p< 0.05$) and LDL level ($r= -0.30$, $p< 0.05$) were negatively correlated with estradiol.

Conclusion

Hormone therapy have been reported to worsen carbohydrate metabolism.[10,12,13,17] On the contrary, some recent reports concluded that HT could have improved glucose homeostasis[4,6,7,18-20] and some other studies also showed that HT had not any harmful effect on glucose utilization.[4,6,7,18-22] Similar to these reports, in our study the significantly lower HOMA-R was found in treatment groups compared with control group, even though fasting insulin level was almost similar in each group. This outcome suggested that the use of tibolon or combined oral HT could contribute to insulin sensitivity.

Table 1. Physical and metabolic characteristics of obese postmenopausal women by HT status.

Variable	Group A (tibolone) (n = 25)	Group B (oral HRT) (n = 33)	Group C (control) (n = 27)
Age, years	51.2 ± 1.0	52.9 ± 0.2	53.3 ± 0.3
Waist, cm	92.2 ± 2.0*	100.2 ± 3.0Ψ	102.6 ± 2.0
Waist/hip ratio (WHR)	0.81 ± 0.01*	0.86 ± 0.01*,Ψ	0.91 ± 0.02
Height, cm	158.8 ± 3.9	156.7 ± 1.0	153.4 ± 1.2
Weight, kg	84.1 ± 2.0	85.8 ± 2.5	84.8 ± 2.7
BMI, kg/m^2	34.1 ± 1.1	35.2 ± 1.0	36.9 ± 0.9
SBP, mmHg	123.7 ± 4.2*	127.3 ± 3.5*	139.3 ± 3.2
DBP, mmHg	82.7 ± 2.7	82.7 ± 1.9	87.8 ± 1.8
Estradiol, pg/mL	28.9 ± 2.0*	112.6 ± 12.2*,Ψ	13.9 ± 0.6
Fasting Insulin, µIU/mL	10.3 ± 1.1	11.3 ± 0.7	14.4 ± 1.9
HOMA-R	2.5 ± 0.3*	2.8 ± 0.2*	5.0 ± 1.4
Fat mass, %	44.2 ± 0.7*	45.4 ± 0.8	47.4 ± 0.8
Fat-free mass, %	57.3 ± 0.8*	55.0 ± 1.0	52.6 ± 0.8
Total cholesterol, mg/dL	205.9 ± 6.7	201.7 ± 4.0	209.6 ± 5.0
Triglyceride, mg/dL	113.2 ± 15.1*	154.0 ± 13.2Ψ	143.2 ± 10.8
HDL, mg/dL	50.1 ± 2.3	55.6 ± 2.2	55.4 ± 2.6
LDL, mg/dL	132.5 ± 6.9	114.5 ± 5.0	122.3 ± 4.5

* $p< 0.05$: Each treatment group versus control group, Ψ $p< 0.05$: Group A versus Group B, ± SE (Standard Error).

The route of HT administration may affect the insulin sensitivity. It was reported that transdermal HT improved insulin sensitivity or had comparatively few effects on insulin metabolism.[4,6,11,22] Although it was suggested that there was a destructive effect of oral HT on glucose tolerance,[13,14] it was not confirmed in some previous studies.[20,23,24] The liver may play a pivotal role in improvement of insulin resistance in oral HT use. Oral route exposes the liver to higher estrogen concentrations, and consequently this exposure may improve insulin sensitivity, because HT can increase insulin sensitivity of the liver, pancreatic insulin secretion in which postmenopausal status is associated with a decline and hepatic insulin uptake, and these effects cause a suppression in hepatic glucose production and increase hepatic insulin clearance.[4,5,18,25,26] Furthermore, the reduction in hepatic glucose production after replacement therapy may also be mediated by the reduced central obesity in women on HT.[27] In our study, the negative correlation between fat-free mass and HOMA-R, and positive relationship between fat-free mass and serum estradiol level appear to contribute this hypothesis. The fact that estrogen suppresses hepatic gluconeogenesis and regulates insulin-induced glucose transport into skeletal muscle in animal models may be another explanatory point.[28,29]

The effect of progestogens on glucose metabolism is unclear owing to the rarely use alone. It has been postulated that progestogens may weaken the useful effects of estrogen on glucose metabolism, even though some studies have reported that progestogens do not antagonize the favorable effects of estrogen.[5,7,11,24] Nevertheless, any conclusion gleaned from our outcomes cannot be extrapolated to the effect of the progestogen only on glucose utilization.

Postmenopausal women gain body fat due to the lower lipolysis and higher adipose tissue lipoprotein lipase (AT-LPL) in menopause status, which is inversely correlated with body lean mass, and is associated with reduced energy expenditure.[30-33] It was postulated that HT could have prevented central obesity in postmenopausal period, although a previous study did not show any significant positive effect of combined HT on fat accumulation.[20,34-36] Perhaps the strong gestagenic effect of combined HT could also attenuate the beneficial effect of estrogen on android distribution of body fat. The current study showed that tibolon, which has weak androgenic, gestagenic and estrogenic effects, had favorable effects on central obesity and fat-free mass.[37] The weak gestagenic effect of tibolon might have been responsible for these outcomes. In addition, the weak androgenic effect of tibolon might also have contributed these favorable effects mentioned above.[35]

In current study the lower systolic blood pressures were seen in women receiving tibolon or combined oral HT, and our data were consistent with some previous studies, which postulated that HT did not have unfavorable effect on blood pressure in postmenopausal women because of endothelium mediated vasodilatation.[38-41]

There were not any worsening effects of both replacement therapies on lipid profile, except the higher triglyceride concentration observed in combined oral HT, which was consistent with previous reports, and the higher estradiol levels were negatively associated with total cholesterol and LDL levels.[42]

Our study has a limitation; it was a cross-sectional study, for that reason patients were not evaluated before and during tibolon and oral HT administration within each group. Therefore the comparison could have not been done in greater detail regarding the effects of treatments.

In conclusion HOMA-R, which can be used to evaluate insulin sensitivity quickly, indicated that tibolon or combined oral HT use may improve insulin sensitivity in obese, postmenopausal women, who have a tendency towards high insulin resistance, even though there is a limitation mentioned above. Additional researches are needed to determine the effects of tibolon and other classical oral HT regimens on insulin sensitivity in high-risk patients for insulin resistance, especially in molecular basis.

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