Effects of standard and low dose 17beta-estradiol plus norethisterone acetate on body composition and leptin in postmenopausal women at risk of body mass index and waist girth related cardiovascular and metabolic disease

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ABSTRACT

Objectives: To compare the effects of standard and low dose of 17beta-estradiol/norethisterone acetate (E2/NETA) on body composition and leptin in postmenopausal women at risk of body mass index (BMI) -and waist girth (WG) related cardiovascular and metabolic disease.

Methods: Ninety postmenopausal women aged 45-55 years with BMI ≥25 kg/m^2 participated in this 6-month prospective, randomized, single-blinded and controlled study, conducted between September 2004 and April 2006 at Adnan Menderes University Hospital. According to their WG, the subjects were divided into 2 risk groups: WG <88 cm (Group increased risk [IR], n=48) or WG ≥88 cm (Group high risk [HR], n=42). The subjects in each group were equally assigned to receive standard or low dose of E2/NETA (2 mg E2/1 mg NETA, or 1 mg E2/0.5 mg NETA). Accordingly, the 2 groups were divided into 4 subgroups. Serum leptin levels (SLLs), body weight/height, waist/hip girth, BMI and waist-to-hip ratio were evaluated before and after therapy.

Results: In the Group IR, WG decreased significantly only in low dose subgroup. In the Group HR, both standard and low dose subgroups had a significant reduction in WG. Those who had WG ≥88 cm showed more reduction than those who had WG <88 cm in response to both doses of E2/NETA, insignificantly. Basal SLLs had a significant correlation with body weight, BMI and WG.

Conclusions: Oral standard and low dose E2/NETA reduce WG and attenuate the BMI- and waist girth- related risk of cardiovascular and metabolic diseases in postmenopausal women.

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Controversy exists about whether menopause increases the risk of cardiovascular disease (CVD) independent of normal aging. Even after adjusting for confounding variables, age, body mass index (BMI), household income, and physical inactivity, postmenopausal status was still associated with a 60% increased risk of the metabolic syndrome.[1] The etiology of the effect of the menopause-transition on cardiovascular and metabolic diseases is unclear. However, it may possibly be linked to changes in body fat distribution. Indeed, several studies had shown the menopausal transition to be associated with an increase in body weight, BMI, fat mass, waist girth and waist-to-hip ratio, suggesting that an android fat distribution occurs during the postmenopausal period.[2] It was once theorized that estrogen (ERT) or hormone replacement therapy (HRT) could be used to improve the CVD risk profile in women by attenuating the menopausal shift in regional fat distribution. Observational studies have suggested that postmenopausal HRT may reduce the relative risk of heart disease by up to 50%.[3] However, recently in contrary to the expectations, the Women's Health Initiative (WHI) study demonstrated that postmenopausal hormone therapy (HT) in the form of continuous combined oral conjugated equine estrogens (CEE) and medroxyprogesterone acetate (MPA), resulted in increased rates of cardiac events, stroke and thromboembolic events in those given hormone therapy versus placebo.[4] Hence, it is fully understandable why other HRT agents have recently become

the focus of active investigations. One of the alternative therapies, 17beta-estradiol/norethisterone acetate (E2/NETA), has been marketed and is available in both standard and low dose forms. Obesity, defined as BMI ≥25.0 kg/m^2, and especially an increased waist girth of more than 88 cm for women,[5] has been shown to be an independent risk factor for CVD.[6] There is an increasing evidence that other measures of body anthropometry, such as waist girth and waist-to-hip ratio, which have been clearly associated with CVD risk, may be better predictors of obesity-related risk than BMI in European countries as well as in Turkey.[7] Leptin, the product of the obesity gene, is a hormone secreted mainly by adipocytes. Serum leptin levels (SLLs) were found to be highly correlated with BMI, fat mass and percentage body fat. However, no association was found between SLLs and visceral fat, waist girth or waist-to-hip ratio in women,[8] although some contradictions do exist. Several trials evaluated the effects of HT on body composition and/or SLLs in postmenopausal women. However, the results of the trials are in conflict.[9] Taking into consideration, all findings from WHI study indicating increased CVD risk with CEE/MPA combination, within the population at risk of anthropometric indices-related cardiovascular and metabolic disease, which type (CEE/MPA or E2/NETA) and dose (standard or low) of HRT would the clinician prefer to have opportunity to cure the symptoms as well as to prevent the metabolic consequences of estrogen deprivation? Accordingly, in this first prospective, randomized, controlled and single-blind trial, we aimed to compare the effects of standard and low dose E2/NETA on body composition and leptin in overweight and obese postmenopausal women at high risk of waist girth-related cardiovascular and metabolic disease.

Methods. One hundred and twenty natural postmenopausal women participated in the study, which had been conducted between September 2004 and April 2006. They were recruited from a pool of women attending the Department of Obstetrics and Gynecology, Faculty of Medicine, Adnan Menderes University for the relief of menopausal symptoms. Menopausal status was confirmed by the absence of menstruation for at least 12 months and a serum concentration of FSH of >40 IU/l and estradiol of <20 pg/ml. Only women between the ages 45-55 with a BMI ≥25 kg/m^2 were included in this study. Exclusion criteria were: 1. undiagnosed vaginal bleeding, 2. endometrial hyperplasia, 3. any medication that could affect the metabolism (such as beta-blockers, glucocorticoids, diuretics, lipid-lowering drugs or other hormonal or hormone-mimetic medications) for the last year, 4. regular physical activity or exercise and medication or special diet for attempting weight loss for the last year, 5. history of cancer or any systemic disease such as hypertension, diabetes mellitus, liver or gallbladder disease, CVD, anemia or renal failure, and 6. use of alcohol and cigarettes. Before enrollment, a complete clinical, obstetric and gynecological history was taken. Dietary habits of the enrolled participants were also evaluated and all followed a similar diet. All women underwent physical and bimanual pelvic examinations, Pap smear, abdominal and transvaginal pelvic ultrasound, mammography, fasting blood glucose and SLLs, hepatic and renal function tests, complete blood count and biochemistry, lipid and coagulation profile. Subjects having any suspicious abnormal findings and contraindications to HRT during this initial evaluation were also excluded. According to their waist girth the subjects were divided into 2 risk groups: waist girth <88 cm (Group increased risk [IR], n=60) or waist girth ≥88 cm (Group high risk [HR], n=60). The subjects in each group were randomly and equally assigned to receive standard dose of E2/NETA (Kliogest® film tablet, 2 mg 17beta-estradiol plus 1 mg NETA, Novo Nordisk A/S Bagsvaerd, Denmark) or low dose of E2/NETA (Activelle® film tablet, 1 mg 17beta-estradiol plus 0.5 mg NETA, Novo Nordisk A/S Bagsvaerd, Denmark) by means of a computer-generated binary random number sequence. Accordingly, the 2 risk groups were divided into 4 HRT subgroups: 1st and 2nd subgroups, standard and low dose of IR, respectively; 3rd and 4th subgroups, standard and low dose of HR, respectively. All subjects received their medications daily at bedtime in a continuous manner for 6 months. Fasting blood glucose, hepatic and renal function tests, complete blood count and biochemistry, lipid and coagulation profile, SLLs, and anthropometric indices (body weight and height, waist and hip girth) were measured and BMI and waist-to-hip ratio were calculated at both the start of the trial and again after 6 months of treatment on each woman. All tests were performed after subjects had fasted overnight and voided. Body weight and height were measured to the nearest 0.1 kg and 0.5cm, respectively using a calibrated scale by an assistant while the subjects were wearing light indoor clothing and no footwear. Body mass index was calculated as the body weight in kilograms (kg) divided by the body height in meters squared (m^2) (BMI=kg/m^2). Waist girth was obtained as the minimum value between the iliac crest and the lateral costal margin, and the hip girth as the maximum value over the buttocks. Fasting blood samples were obtained from subjects between 08:00 and 10:00 am at baseline and at 6th month. Samples were allowed to clot and after centrifugation, serum was frozen at -80°C until measurement. Serum leptin levels were determined in duplicate using an Active Human Leptin ELISA kit by Biosource, USA. The intra-assay

coefficient of variation was 3.4-8.3%, and the inter assay coefficient of variation was 3.6-6.2% with a sensitivity of 0.5 ng/mL. A gynecologist and biochemist made all measurements, calculations and evaluations unaware as to which drug each participant had been prescribed in this single blind study. Values were expressed as mean±SD. All inter group comparisons were made with Mann-Whitney U test. The Wilcoxon test was used to compare the baseline and final data within the groups. The Spearman rank correlation test was used to evaluate the associations between SLLs, anthropometric indices and their changes. Statistical significance was set at level 0.05 for comparisons and level 0.01 for correlations. Statistical analysis was performed by Statistical Package for the Social Sciences version 10.0 for Windows. The study received the approval of the local ethical committee, and was carried out according to the requirements of the Declaration of Helsinki. We obtained informed written consent beforehand.

Results. Ninety patients (Group IR, n=48 and Group HR, n=42) with a mean age of 50.5±2.7 years completed the study. **Table 1** represents the baseline characteristics and the baseline; and the 6th month values of the subjects at BMI- and waist girth-related increased and high risk of cardiovascular and metabolic disease with standard and low dose of E2/NETA. The 2 risk groups and HRT subgroups were well matched at baseline for age and months since menopause. After 6 months of treatment, within the group comparisons, in increased risk group, waist girth decreased significantly only in low dose HRT subgroup (p=0.01), whereas in the high-risk group, both standard and low doses HRT subgroups had a significant reduction in waist girth (p=0.018, p=0.017). There were no significant changes in the other parameters. Comparing standard dose to low dose in each risk group, there were no differences in any parameters during the 6 months study period. **Table 2** represents the waist girth changes of the subjects at BMI- and waist girth-related increased and high risk of cardiovascular and metabolic disease with standard and low dose of E2/NETA within 6 months. At the end of the 6 months study, those who had waist circumference ≥88 cm showed more reduction compared to those who had waist circumference <88 cm in response to both doses of E2/NETA, however this finding was not statistically significant. **Table 3** represents the correlations between the baseline SLLs and all parameters and their 6-month changes as well as the correlations between the 6-month changes of SLLs and of all parameters. Whereas basal SLLs had a significant correlation with body weight, BMI and waist girth, SLLs changes only correlated with body weight and BMI. We noticed that there was a negative correlation between the changes in SLLs and basal SLLs.

Discussion. This study showed that those subjects with a waist girth <88 cm, having been administered with standard or low dose of E2/NETA over a 6-month

Table 2 - Waist girth changes of postmenopausal women.

Dose of E_2/NETA	Group increased risk (WG <88 cm, n=48)	Group high risk (WG ≥88 cm, n=42)	*P* value
Standard (n=44)	-1.4±2.5	-3.8±3.0	0.232
Low (n=46)	-1.8±1.7	-4.4±3.5	0.069

Values are expressed as mean±SD, WG - waist girth.
E2/NETA - 17beta-estradiol/norethisterone acetate

Table 1 - Baseline and 6th month values of postmenopausal women.

Variables	Group increased risk (WG <88 cm, n=48)				Group high risk (WG ≥88 cm, n=42)			
	Standard dose (n=23)		Low Dose (n=25)		Standard dose (n=21))		Low Dose (n=21)	
	Baseline	6th month	Baseline	6th month	Baseline	6th month	Baseline	6th month
Age (year)	49.4±2.9		51.4±2.2		49.9±3.5		51.1±2.1	
Months since menopause	18.0±12.4		24.9±16.8		23.7±11.7		27.4±16.5	
BW (kg)	66.8±4.9	68.7±4.3	66.9±5.8	67.2±6.5	78.1±9.8	77.1±7.5	77.1±8.8	77.6±8.4
BMI (kg/m2)	27.1±2.7	27.9±2.3	28.9±1.6	28.9±2.1	33.3±3.6	32.9±3.0	33.9±3.5	34.1±3.2
WG (cm)	79.6±3.6	78.2±2.3	81.9±3.4	80.1±3.1*	92.7±3.6	88.9±2.8*	93.3±4.2	88.8±4.8*
WHR	0.80±0.05	0.79±0.5	0.8±0.04	0.8±0.04	0.81±0.05	0.81±0.06	0.8±0.04	0.8±0.04
SLLs (ng/mL)	26.6±8.3	33.0±12.1	35.3±19.8	38.2±24.7	52.8±26.9	47.3±21.7	43.3±16.2	48.1±24.5

*p<0.05 intragroup comparisons; intergroup comparisons not significant; values are mean±SD,
WG - waist girth; BW - body weight; WHR - waist-to-hip ratio; SLLs - Serum leptin levels.

Table 3 - Correlations between serum leptin levels (SLLs) and parameters at baseline and correlations between SLLs and changes of SLLs and of parameters at the 6th month.

Parameters	Serum leptin levels			
	Baseline		Changes from baseline	
	P value	r	*P* value	r
Baseline				
Age	0.868	0.030		
Months since menopause	0.699	0.070		
Body weight	0.000	0.578		
Body mass index	0.000	0.649		
Waist girth	0.002	0.520		
Waist-to-hip-ratio	0.871	0.029		
Changes from baseline				
Body weight	0.087	-0.303	0.000	0.834
Body mass index	0.089	-0.301	0.000	0.865
Waist girth	0.476	-0.129	0.509	0.119
Waist-to-hip-ratio	0.805	0.45	0.376	0.159
SLLs	0.001	-0.533		

study period, had their waist girth reduced by 1.4 ± 2.5 and 1.8 ± 1.7cm, respectively. Those women with a waist girth ≥88 cm had a significant reduction 3.8 ± 3.0 and 4.4 ± 3.5 cm in waist girth, respectively. Even though the reduction in waist girth was significant only with low dose E2/NETA, it is worth to mention that the changes were very similar in size regardless whether the subject was treated with low or standard dose. As a result, it may be postulated that there is no significant difference between standard and low dose E2/NETA therapies in terms of waist girth decrease in postmenopausal women regardless whether they had more or less than a waist girth of 88cm, whose levels ≥88 cm was considered as an independent risk factor for CVD. There were no significant changes in any of the other parameters including SLLs in between study groups before and after the therapy. The correlations between SLLs and body weight, BMI and waist girth observed at the beginning of the study were only present between changes in SLLs and both changes of body weight and BMI at the end of the study. Furthermore, correlation between leptin changes and waist girth changes at the end of the treatment did not occur as expected. According to the National Institutes of Health, if BMI ≥25 and waist girth <88 cm, the risk for diabetes, high blood pressure, or heart disease "increasing" whereas if BMI is ≥25 and waist girth is ≥88 cm, the risk is "high".[10] It is established that the percentage of risk reduction per 1 unit of BMI ranges from 2-11%.[11] Body mass index does not account for the wide variation in body fat distribution that exists at any level of relative body size.[12] There are many analyses that demonstrate the waist circumference provides a reasonable indicator of the quantity of abdominal fat, which correlates with the amount of intra-abdominal or visceral fat.[13] Furthermore, it has also been shown that waist circumference has an independent association with cardiovascular disease, suggesting that combined measures of BMI and waist circumference, may provide a higher overall test performance for cardiovascular disease risk factors in the clinical settings.[14] The same HRT agent, CEE/MPA, had been applied in both the WHI study and the Postmenopausal Estrogen/Progestin Interventions (PEPI) trial.[15] The WHI study indicated a rise in cardiac problems whereas in the PEPI trial, absence of a significant change in waist circumference when compared to placebo brings to mind that there may be some other factors other than waist circumference in the development of cardiac problems derived from HRT. Samaras et al[9] study population were more at risk than ours and they concluded that postmenopausal CEE/MPA in the overweight and obese women with type 2 diabetes mellitus was associated with a reduction in central adiposity and improvement in lipid metabolism and glycemic control without deterioration in weight status or cardiovascular parameters measured. Besides the possible beneficial effects on body composition, the cardioprotective effect of HRT is also attributed to the beneficial estrogen effects on blood lipids, to its antioxidant and direct effects on peripheral vasculature, by which it increases coronary blood flow and decreases peripheral resistance. The conflicting findings in the studies evaluating the effects of E2/

NETA on anthropometric indices may partly be explained by differences in study design and study population, and by differences in the type, duration and dosage of hormone intervention.[16-19] A Cochrane meta-analysis of 22 randomized controlled trials,[20] showed that there is evidence of no effect of combined estrogen and progestogen on the BMI increase normally experienced at the time of menopause. However, insufficient evidence currently exists to enable examination of the effect of HRT on waist-hip ratio, fat mass or skinfold thickness in this meta-analysis. Consequently, the reviewers were unable to determine whether or not hormone replacement therapy has a preventive effect on the redistribution of body fat from the hips and thighs to the abdomen associated with the menopause. Arabi et al[16] showed a non-significant decrease in body fat but a significant increase in BMI with standard dose of oral continuous E2/NETA treatment over 2 years. Thus, this decline was associated with changes in fat distribution with a slight but significant decrease in the percentage of android fat and the android index from baseline. In our present study, while the reduction in waist girth (the index of android fat gain) of our high-risk group (waist girth ≥88) was similar with their study, changes in BMI were contradictory. However, in our increased risk group (waist girth <88), waist girth tended to decrease but not significantly. It is noticeable that baseline BMIs of their participants were relatively low (23 kg/m^2). The cause for this contradiction mentioned above, could possibly be due to this reason. Furthermore, this difference might also be attributable to the time length of our study. Walker et al,[19] in their single-blinded and placebo-controlled 6 months study, concluded that HRT as standard dose of oral sequential E2/NETA, does not promote an increase in weight and BMI, nor the more android distribution of body fat. The results of BMI and body weight of subjects treated with standard dose were consistent with those of our subjects. The BMIs baseline as well as central abdominal fat distribution changes of their subjects, were similar to those of our increased risk group (waist girth <88). In terms of abdominal fat, subjects taking low dose E2/NETA observed a more beneficial effect than those taking standard dose as well as subjects at high risk than those at increased risk. The main differences with their trial were applied regimen and the technique used to measure the android fat tissue. Total body fat is known to influence leptin levels, but it is still unclear whether body fat distribution or menopausal status may influence leptin concentrations. For example, Tufano et al[21] concluded that the rise of leptin levels may be related to the greater abdominal fat deposition rather than menopausal status. On the other hand, Martinez et al,[22] concluded that SLLs does not seem to be influenced by fat mass distribution (android or gynoid type). While in the same study, the authors found that significant correlations exist between leptin and weight, BMI, and waist and hip circumferences, they did not however, find any between leptin and waist-to-hip ratio in agreement with Lofgreen et al[23] and our present study. Interestingly, women with BMI ≥30 kg/m^2 or waist circumference ≥88 cm had significantly higher leptin concentrations than their light or lean counterparts.[23] The trial using leptin in addition to anthropometric indices as an indicator by Laivuori et al,[18] showed that standard dose sequential E2/NETA as a whole, or as considered either as an oral or transdermal route separately, failed to affect BMI or SLLs after 6 or 12 months of treatment. However, their subjects had obviously lower mean BMI than ours. They also found that baseline SLLs were significantly associated with BMI which was very similar to our finding. Kristensen et al[17] had a control group and subdivided the subjects as obese (BMI >25 kg/m^2) and non-obese (BMI <25 kg/m^2) in their trial. Without measuring any anthropometric indices in their study, they found that all estimates of body composition increased in the standard dose hormone therapy group, but to a lesser extent than observed in the control group. They also found that 5 years of HRT significantly reduced fat mass accumulation, especially in the trunk region. However, this effect of HRT was more pronounced in non-obese when compared with obese subjects. In their study, SLLs correlated well with most estimates of adipose tissue, but not with waist-to-hip ratio, a similar finding to our own. Furthermore, we were not able to find any correlation with changes of waist girth and of SLLs in our study. Therefore, we agree with their conclusions that HRT induced reduction in fat mass does not seem to be mediated by leptin. The basal BMIs of our increased risk group (waist girth <88) were similar to the basal BMIs of their obese group whereas high-risk group (waist girth ≥88) in our study had higher basal BMIs compared to the obese group. Because our aim was to study with high-risk group, subjects with BMI less than 25 were excluded from the study. Kristensen et al,[17] at the end of 5 years, observed changes in BMI, trunk fat and SLLs of obese control group but not in HRT group. They speculated that the usage of HRT was preventative against trunk fat increase in obese women. However, in our study we observed that both standard and low doses of HRT had not only prevented the increase in waist circumference but also had decreased the waist girth in obese high risk women with waist girth ≥88 cm. Women with waist girth <88 cm (increased risk group) on low dose HRT had a much greater reduced

waist girth than those on standard dose which although reduced waist girth also, did to a lesser extent. The controversy may relate to differences in the type and dosage of HRT, the length of the observation periods, the number of study subjects or the method used for estimating adipose tissue. Furthermore, the controversy may relate to some limitations within their study design. Firstly, the allocation of subjects was not totally randomized and partially carried out according to the wish of the patients. Secondly, in the treatment group, not only they included the oral HRT, also they included the oral ERT subjects. Progestogens with their androgenic properties are thought to influence body fat distribution, which may or may not negate some of the beneficial effects of estrogen therapy.[19] In agreement to our findings, Perrone et al[24] found that the waist girth of 3-year sequential transdermal estradiol/MPA users was significantly lower than that of non-users in postmenopausal women not categorized as low- or high- CVD risk. The limitation of our study was the fact that we did not have a control group. However, it is a well-known fact that BMI, waist girth and waist-to-hip ratio significantly increase at postmenopausal period.[2,25] It was interesting that in our study, oral administration had similar results with transdermal estrogen 50 µg/day continuously combined with intravaginal progesterone (100 mg twice daily) for 7 days.[24] In fact, due to the presence or lacking of first pass effect of estrogen, it was expected to show that the way of administering HRT should have different effects because the route of estrogen administration has distinct and divergent effects on lipid oxidation and body composition in postmenopausal women.[26] However, in contrast to this, Laivuori et al[18] found that neither oral nor transdermal E2/NETA caused any significant changes in BMI after 6 or 12 months of treatment.

We conclude that HRT with oral continuous standard or low dose E2/NETA is expected to reduce waist circumference significantly and also attenuate the BMI- and waist girth-related risk of cardiovascular and metabolic diseases in postmenopausal women.

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