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Is there evidence that estrogen therapy promotes weight maintenance via effects on leptin?

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Abstract

Objective—Leptin, a hormone secreted by adipocytes, plays a crucial role in regulating energy balance. Estrogen, like leptin, reduces food intake and adiposity while increasing energy expenditure in animals and humans of both sexes through its actions in the central nervous system. We reviewed the literature for studies of the effect of exogenously administered estrogen on serum leptin concentrations and adiposity in women.

Methods—Using PubMed/MEDLINE, we searched for studies of hormone therapy that enrolled healthy postmenopausal women. Studies were further evaluated to determine if leptin and adiposity were monitored both at baseline and throughout a treatment period of at least two months.

Results—Twenty articles met inclusion criteria. We found no consistent effect of exogenous estrogen on serum leptin concentrations, adiposity, or weight gain.

Conclusion—Despite suggestive data from animal studies, current literature does not provide compelling evidence that estrogen therapy attenuates weight gain, alters circulating leptin levels, or improves leptin action in postmenopausal women.

Keywords

leptin; estrogen; hormone replacement therapy; obesity

INTRODUCTION

In humans, signaling molecules and feedback systems regulate food consumption and satiety states to ensure that energy intake matches energy expenditure over time, a process called energy homeostasis.¹ The brain regulates energy homeostasis in response to signals from both adipose tissue and the gastrointestinal tract.² Leptin, a peptide hormone, plays a key role in this regulatory process. Leptin is synthesized and secreted by white adipocytes, the

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major form of stored energy in the body.³ Leptin circulates at levels proportional to body fat content,⁴ then enters the central nervous system (CNS) across the blood-brain barrier in proportion to circulating plasma levels.⁵ Administration of exogenous leptin reduces both spontaneous and fasting-induced hyperphagia, while chronic peripheral administration reduces food intake and fat mass.^{6–8} Disruption in leptin signaling, such as in animals or humans deficient in leptin^{3,9} or its receptors,^{10,11} causes an obese, hyperphagic phenotype.

Like leptin, treatment with estrogen also reduces food intake and adiposity while increasing energy expenditure in female animals and humans. Ovariectomy in female rats results in a sharp decrease in estrogen and an increase in body weight, but this weight gain is reversible by estrogen therapy (ET). Such results suggest that the cause of ovariectomy-induced obesity may be lack of estrogen.^{12,13} Further, the effects of estrogen on adiposity are apparently mediated by its actions on estrogen receptor alpha (ER α), since mice with ER α global deletion are obese.¹⁴ The brain is implicated in these effects, since site-specific destruction of ER α in the ventromedial hypothalamus also induces obesity.¹⁵ In addition, ER α is co-localized with leptin receptor expression in regions of the hypothalamus,¹⁶ and this co-localization suggests a potential scenario in which the two signaling pathways interact to regulate energy balance.

Both peripheral and central administration of estradiol to ovariectomized female rats restores central leptin sensitivity and returns body fat distribution to that of a female with intact ovaries.¹⁷ These findings provide the rationale for an analogous investigation examining the relationship between estrogen and leptin in humans. Human menopause is associated with a decrease in serum estrogen levels, as well as changes in energy expenditure and body composition.¹⁸ In particular, the increased deposition of intra-abdominal fat in postmenopausal women has been tentatively linked to estrogen depletion, perhaps causally in early menopause.^{19,20} Postmenopausal women who receive estradiol do not display the characteristic pattern of abdominal weight gain usually associated with menopause, suggesting that estrogen insufficiency may contribute to the increase in adiposity during menopause.

In response to these findings from animal and human studies, we sought to identify experimental evidence from randomized, placebo-controlled trials in humans regarding a direct effect of exogenous estrogen on serum leptin concentrations. We reviewed the literature to evaluate whether estrogen administration in the form of hormone therapy (HT) in postmenopausal women had any effect on serum leptin concentrations or measures of adiposity.

METHODS

From March to July 2011, we searched PubMed/MEDLINE by using the terms “leptin,” “estrogen,” “obesity,” “leptin levels,” “hormone replacement therapy,” and “estradiol.” We limited our search to studies of human females published in English after 1994, when leptin was discovered. We also searched the reference lists of articles found in this way. We included studies only if they enrolled healthy postmenopausal (surgical or natural) women who were receiving HT. In addition to varied therapeutic regimens of HT, we included tibolone, a synthetic steroid that selectively regulates estrogenic activity, and raloxifene, a non-steroidal benzothiophene that selectively modulates estrogen receptors.¹⁹ Studies were further evaluated to determine if leptin and adiposity were monitored at baseline and throughout a treatment period of at least two months. Although the focus of the review is on the effect of exogenous estrogen on leptin, because leptin is so closely linked to total adipose tissue mass²¹ data on leptin is impossible to interpret without taking changes in fat mass into account. Exclusion criteria included studies that did not report serum leptin

concentrations, studies without HT intervention, studies with multiple interventions, and studies that monitored serum leptin concentrations for less than one month. Out of an initial sample of 40 studies we identified 20 that met our inclusion criteria.

Of the 20 studies included in this review, six studies observed serum leptin levels over a six-month period and six studies observed serum leptin levels over a twelve-month period. Other studies consisted of one month, two months, three months, and four months of observation and intervention. One outlier exists in the twenty studies included; which observed responses to HT over 60 months.

For this review, we classified randomized, placebo-controlled studies as the highest level of evidence. We regarded non-placebo controlled studies as a lower level of evidence. We did not consider evidence from other types of studies.

RESULTS

Summary of studies classified by level of evidence

We reviewed a total of 20 studies (see Table 1). Only four^{19,22–24} were both randomized and placebo-controlled, so we consider them first.

Elbers et al.¹⁹ studied the effects of 2 mg of 17B-estradiol, compared to placebo, on 12 postmenopausal women. Women in the placebo group experienced more weight gain than women in the treatment group, but body fat content did not differ significantly between groups. Nevertheless, the treatment group experienced an increase in serum leptin concentrations from 17.6 µg/l to 24.1 µg/l after two months ($P = 0.008$). This increase differed significantly from the results for the placebo group, which showed no change in leptin from baseline to two-month follow-up. Similarly, Yüksel et al.²⁴ randomly assigned postmenopausal women to receive E₂/norethisterone acetate (NETA) or placebo. After six months of therapy, leptin levels increased in both groups, but with significantly more increase in the placebo group ($P = 0.033$) than in the treatment group, contradicting the findings of Elbers et al.¹⁹ BMI was not affected in either group. In contrast to both studies, Mattiasson et al.²² found no significant effect of estradiol valerate on serum leptin levels in postmenopausal women compared to a placebo group. Notably, leptin levels remained relatively stable in the treatment group, while showing a trend toward higher levels after 12 months in the placebo group. This study also found no effect of ET on BMI. Finally, Cagnacci et al.²³ evaluated transdermal estradiol administration vs. placebo in 40 women, finding no significant effect on serum leptin or BMI.

Ten additional studies were randomized^{24–31} or semi-randomized^{25,26} (i.e., some participants were randomly assigned to groups while others were allowed to choose their groups) but used no placebos. Castelo-Branco et al.²⁷ studied 333 healthy postmenopausal women for one year. Women were randomly allocated to one of three different doses of norethisterone, continuously combined with a fixed dose of 17B-estradiol for intranasal or oral administration. Both intranasal and oral therapy raised leptin levels after 24 weeks ($P < 0.001$). BMI in this study was reported only at baseline. Tommaselli et al.²⁸ studied 68 postmenopausal women, finding that serum leptin levels and total fat mass increased in 21 untreated women ($P < 0.05$), while women treated with tibolone ($n = 23$) or raloxifene ($n = 24$) experienced no change in serum leptin or total fat mass. In a related study by Di Carlo et al.,²⁹ serum leptin levels increased in 22 control women who did not receive transdermal 17B-estradiol and norethisterone ($P < 0.05$). Women who received treatment showed a trend toward reduced leptin levels while maintaining total fat mass and percentage fat mass, a finding that could indicate improved leptin sensitivity. In a prospective comparative study by Dedeo lu et al.,³⁰ 97 postmenopausal women were randomly assigned to no treatment,

HT, or tibolone. Untreated women had lower leptin levels ($P < 0.005$), whereas after six months of treatment the HT group had higher leptin levels ($P < 0.05$) and the tibolone group had lower leptin levels ($P < 0.001$). In the same study, women who received either HT or no treatment experienced no change in total fat mass, but the tibolone group saw a reduction in fat mass ($P < 0.05$), potentially accounting for the reduction in serum leptin levels.

A study by Kristensen et al.²⁵ had the longest follow-up period in our review, collecting data five years after participants were semi-randomized to receive either HT or no treatment. Leptin levels were higher in both treatment and control groups at the five-year follow-up, although increases were more pronounced in controls. Similarly, fat mass increased in both groups, but the increase was 2.4 times higher in controls than in the treatment group ($P < 0.05$). Adjusted analyses demonstrated no effect of HT on leptin, independent of differences in fat mass. In a less extensive study, Laivouri et al.³¹ randomized a small group of postmenopausal women to receive either oral or transdermal HT. After one year of treatment they found no effect on serum leptin levels. Konukoglu et al.³² grouped study participants into pre- and postmenopausal women and found that premenopausal women had higher serum leptin levels ($P < 0.001$) than postmenopausal women. They also found that leptin levels were elevated after six months of HT in 45 women ($P < 0.001$). However, studies led by Petzel,³³ Nar,³⁴ and Lambrinoudaki,²⁶ found no significant effect of HT on serum leptin levels.

Finally, six studies^{35–40} were classified at our lowest level of evidence, as they neither randomized participants nor used a placebo. Lavoie et al.³⁵ studied the effect of HT on postmenopausal women in younger (45–55 years) and older (70–80 years) cohorts. They found that serum leptin levels increased more in younger women ($P < 0.01$) after transdermal estradiol therapy. Cento et al.³⁶ compared obese ($\text{BMI} > 25 \text{ kg/m}^2$) and non-obese ($\text{BMI} < 25 \text{ kg/m}^2$) postmenopausal women to obese and non-obese premenopausal women. They found no effect of HT on serum leptin levels in either group. Although they found higher baseline leptin levels in obese premenopausal women than in their postmenopausal counterparts ($P < 0.05$), it is uncertain if this difference was directly related to hypoestrogenism, to aging, or other potential factors. Tommaselli et al.³⁷ studied serum leptin levels six months after bilateral ovariectomy in women who received estradiol, raloxifene, or no HT, finding that leptin levels increased in women without HT ($P < 0.01$). They also monitored BMI, which increased non-significantly in women without HT. Leptin levels remained unchanged in women who received estradiol or raloxifene. Studies led by Gol,³⁸ and Panidis⁴⁰ found no effect of HT on serum leptin levels.

Figure 1 categorizes all studies in our review according to their findings on the effect of HT on endogenous serum leptin levels, with studies organized in subgroups according to study design. Among all studies and all subgroups, the majority showed no effect of HT.

Results of subgroup analyses by weight status

Among the studies that used randomization but no placebo, four^{25,26,30,32} also performed subgroup analyses to examine whether exogenous estrogen's effect on serum leptin levels varied according to weight status. Dedeo lu et al.³⁰ found that in all participants, leptin levels at baseline and at six-month follow-up were significantly higher in overweight women, regardless of HT or tibolone treatment. The same study also found that leptin levels in overweight women who were treated with tibolone did not decrease as much as leptin levels in lean women who received the same treatment (35% vs. 48.1%). Similarly, lean women who received HT experienced larger increases in leptin levels than did overweight women who received the same treatment (20% vs. 4.9%). Kristensen et al.²⁵ divided participants into non-obese ($\text{BMI} < 25 \text{ kg/m}^2$) and obese (defined as $\text{BMI} > 25 \text{ kg/m}^2$) groups. When subgroups of obese women using HT were analyzed separately, there was a

greater effect of treatment on fat mass accumulation in non-obese participants, but no obesity-related differences were seen in the effect of HT on leptin levels. Results of the latter analyses were not shown. Konukoglu et al.³² studied obese (BMI > 27 kg/m²) and non-obese (BMI < 27 kg/m²) pre- and postmenopausal women. After six months of HT, obese women experienced a larger increase in serum leptin levels than did non-obese women (29.05 vs. 14.78 ng/mL). However, on the whole, subgroup analyses suggested that provision of HT among overweight and obese women had little or no effect on leptin levels, independent of BMI. In sum, 2 of 4 studies showed less benefit of treatment on body weight or leptin levels in subgroups of overweight and obese women.

Summary of studies classified by findings

Studies that found higher serum leptin levels in women who did not receive ET^{24,25,28,29,37,39} also found that women who received ET avoided changes in body composition associated with menopause. Women without ET showed a parallel increase of serum leptin levels along with body fat content (total or percentage) or BMI. Most studies in this subgroup had relatively small sample sizes and short timeframes, enrolling fewer than 25 women in each study group and extending over a maximum of 6–12 months. The principal exception is the study by Kristensen et al.,²⁵ which included 267 women and lasted five years, making it the longest study in this review. However, that study was only partially randomized and did not use a placebo.

Five studies^{19,27,30,32,35} reported higher serum leptin levels in women who received hormonal intervention. These studies showed a consistent trend of higher leptin levels without any changes in adiposity or body weight. Castelo-Branco et al.²⁷ studied 333 postmenopausal women for one year in a randomized trial without placebo. This study was the largest and longest to find higher serum leptin levels in postmenopausal women who received estrogen treatment. Although it monitored the same dose of estrogen with different doses of norethisterone, findings demonstrated that intranasal and oral ET produce the same result.

Most studies in our review found no effect of estrogen administration on serum leptin levels. Studies that returned this finding generally used randomization but did not include a placebo and had limited sample sizes. Most studies with this finding were also of short duration, with three lasting for one year and the rest for six months or less. A partial exception is the study by Mattiasson et al.,²² who used a randomized, placebo-controlled design to examine postmenopausal women for one year. While serum leptin levels remained unchanged, percentage of fat mass decreased in the group who received estradiol. Their result represents a deviation from the changes in body composition typically associated with menopause.

Summary of studies classified by duration of HT

Of the six studies that lasted at least twelve months, four^{27–29,39} studies showed an increase in serum leptin in groups who received placebo or no HT. Two^{31,40} studies showed no difference in leptin levels.

DISCUSSION

This review encompasses studies that evaluated the effect of ET on endogenous serum leptin levels, weight gain, and adiposity in postmenopausal women. These studies returned mixed results, with findings running the gamut from higher levels to lower levels to no change at all. Such variability may be the result of differences in study samples and designs (e.g., time since menopause, ET dose and type, length of study). In addition, the quality of evidence in these studies is relatively low. Most included some sort of randomization of study

participants but no placebo. Only four^{19,22–24} out of 20 studies were randomized, controlled trials with a placebo. This more rigorous subset showed no consistent effect of ET on leptin levels. Overall, the majority of trials reviewed showed no effect of ET on leptin levels.

Our current understanding of leptin's function and its relationship with estrogen and adiposity suggests that withdrawal of estrogen by ovariectomy or menopause should lead to higher leptin levels and more accumulation of body fat. Consistent with this, recent studies have shown that mice lacking ER α have higher fat mass, and that mice and humans lacking aromatase develop obesity and hyperlipidemia.⁴¹ A related study by Kakolewski et al.⁴² found that ovariectomy in female rats lowered serum estrogen to a negligible level and resulted in a 22% increase in body weight after 10 weeks. In rats, such weight gain can be reversed by estrogen administration, suggesting a causal role for estrogen depletion in this form of obesity.⁴¹ Theoretically, the replacement of endogenous estrogen concentrations with exogenous estrogen supplements should therefore reverse these changes.

Six studies^{24,25,28,29,37,39} of postmenopausal women did in fact demonstrate increases in serum leptin levels in women without hormonal intervention, but not in women with HT. For untreated women, this subgroup of studies reported a significant increase of BMI or body fat content (total or percentage) along with increases in serum leptin levels, consistent with current understanding how leptin levels rise with adiposity. HT prevented these changes in women who received it. Of note, the subgroup of six articles included only one randomized, placebo controlled study,²⁴ along with one randomized, non-placebo controlled study²⁵ extending over five years. Although these selected findings support the hypothesis that HT prevents menopause-associated changes in weight and body composition, these observations are not uniform across studies and there is no consistent effect of HT to suppress weight gain or improve leptin sensitivity.

In contrast, several studies reported an increase in leptin levels in treated women^{19,27,30,32,35}, independent of change in fat mass or BMI. One potential explanation for these observations is the development of leptin resistance, which is thought to be attributed to impaired cellular leptin receptor signaling in key hypothalamic brain areas associated with feeding and metabolism;⁴³ the impaired ability of leptin to cross the blood-brain barrier; or both.⁴⁴ Studies that found elevated serum leptin, but no change in fat mass or BMI, typically had small sample sizes. However, one such study included the largest number of participants in our review.²⁷ Thus, a proportion of the results indicate that hormonal intervention increases serum leptin levels without affecting adiposity. These findings might be indicative of changes in leptin's central action, such that rising leptin levels are required to maintain stable body weight.

Limitations of this review include that the studies recorded body weight and leptin levels, but few measured adiposity or changes in either subcutaneous or visceral fat deposits, and results could have differed if these endpoints had been assessed. Moreover, the duration of most studies was less than 12 months, arguably an inadequate timeframe to observe significant changes in energy balance. Of note, none of the 6 studies of at least 1-year duration demonstrated increases in leptin levels in HT-treated groups, although leptin levels rose in untreated women in 4 of the studies. Finally, some studies described findings on selective estrogen receptor agents^{26,28,33,37,38,40} whose effects on serum leptin levels and body weight are poorly understood.

HT has been shown to protect against colorectal cancer⁴⁵ and bone loss.⁴⁶ Unfortunately, prolonged use of combined HT during menopause is associated with a higher risk of breast cancer⁴⁷ and thromboembolic events.⁴⁸ As a result, current recommendations for estrogen or

estrogen plus progesterone to alleviate or prevent postmenopausal symptoms are for short duration only.

CONCLUSION

Despite evidence from rodent studies, we found no clear evidence for any effect of hormonal intervention on serum leptin levels in human clinical studies. Clinicians should be aware that patients may receive misleading information from popular media or Web sites that still cite isolated findings or appeal to animal studies to promote estrogen's beneficial effects. Overall, given the inconsistent effects of exogenous estrogen to alter leptin or attenuate postmenopausal weight gain, any potential benefits need to be considered in relation to the cardiovascular and neoplastic risk associated with prolonged HT.

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Figure 1.

Subgroupings of studies characterized by the effect of HT on serum leptin levels. Studies were categorized by level of evidence, with randomized placebo controlled studies being the highest level, followed by randomized, non-placebo controlled and finally non-randomized, non-placebo controlled as the lowest level of evidence. Randomized, placebo controlled studies were least prominent in our review. Randomized without placebo and non-randomized without placebo were fairly comparable in prevalence. Studies were also categorized by the increase in serum leptin levels depending on presence of HT. Overall, our findings show that HT has no effect on serum leptin levels.

Table 1

Articles reviewed, listed from highest to lowest level of evidence

Author (Year)	Design (Duration)	Study participants	Estrogen Therapy	Progestin Therapy	Leptin ^a	BMI ^b	Results	Conclusion
Mattiasson (2002)	Randomized, placebo-controlled (12 mo)	Phase 1 n=27 E2 Phase 2 n=24 placebo Phase 2 n=23 E2+MPA n=23 placebo	2 mg E2 valerate	MPA every 3 months for 10 days in phase 2 participants	Median at 0, 3 & 12 mo: E2 group: 17.9, 20.6, 26.3, 26.7, 26.4 Placebo group: 22.3, 26.0, 27.7, 28.2	Median at 0, 3 & 12 mo: E2 group: 26.3, 26.7, 26.4 Placebo group: 27.8, 28.4, 28.2	No effect of E2 on leptin; % fat mass decreased in E2 group (P=0.024)	E2 treatment did not alter serum leptin levels but lowered % fat mass. Serum leptin levels were higher in control group at baseline and increased non-significantly by 12 months. Leptin levels did not change significantly in either treatment group.
Cagnacci (2002)	Double-blind, placebo-controlled, with crossover (4 mo)	n=20 E2 n=20 placebo	50 µg/day 17B-E2; transdermal	MPA 10 mg/day for 12 days after 4 months	Mean (SE): ET after 2 mo: 18.6 (2) µg/l Placebo after 2 mo: 19.1 (2.4) µg/l	ET after 2 mo: 25.1 (0.5) Placebo after 2 mo: 25.0 (0.5)	No effect of ET on serum leptin concentration	No effect of ET on fasting leptin.
Elbers (1999)	Randomized, double-blind, placebo-controlled (2 mo)	n=12 E2 n=13 placebo	2 mg 17B-E2	None	Median µg/l at 0 & 2 mo: E2: 17.6, 24.1 Placebo: 12.8, 12.7	At baseline: E2: 27.6 (4.8) Placebo: 25.2 (3.2)	Median leptin level increased in E2 group (P=0.008). Adiposity did not change in either group.	ET raised serum leptin levels in POM women compared to placebo.
Yuksel (2006)	Randomized, prospective, double-blind, placebo-controlled (6 mo)	n=22 E2 + NETA n=21 placebo	2 mg E2	1 mg NETA	Mean (SE) at baseline: Placebo: 31.3 (3.7) E2 + NETA: 40.7 (5.3)	Mean (SE) at baseline: Placebo: 28.9 (1.1) E2 + NETA: 30.5 (1.0)	Serum leptin increased in placebo group (P=0.033)	Placebo group experienced more change in serum leptin levels than HT group. HT prevented changes in leptin levels.
Tommaselli (2006)	Randomized, prospective, no placebo group (12 mo)	n=21 no HT n=23 tibolone n=24 raloxifene	Tibolone 2.5 mg/day Raloxifene 60 mg/day	None	0, 1, 3, 6, 12 mo median (range): No HT: 18.3 (5.4–34.3) 18.9 (7.2–42.2) 16.8 (9.2–52.8) 20.1 (6.3–37.8) 22.5 (10.3–42.1)	0 & 12 mo: No HT: 26.5 ±4.3 26.6 ±2.1 Tibolone: 26.0 ±3.8 25.8 ±3.8 Raloxifene: 25.6 ±5.1 25.5 ±4.3	Serum leptin levels increased in no HT group at 12 months (P<0.05). No change in serum leptin in tibolone and raloxifene groups. Total fat mass higher in no HT group than tibolone and raloxifene groups at 12 months (P<0.05). No	Hypogonadism leads to an increase in total fat mass and serum leptin concentration. Tibolone and raloxifene treatment prevent an increase in total fat mass and maintain serum leptin levels.

Author (Year)	Design (Duration)	Study participants	Estrogen Therapy	Progestin Therapy	Leptin ^a	BMI ^b	Results	Conclusion
					Tibolone: 17.0 (5.6–28.7) 16.6 (5.0–34.6) 16.2 (7.6–36.1) 16.8 (6.1–38.2) 16.3 (4.2–39.8) Raloxifene: 17.5 (6.7–29.8) 17.4 (3.8–32.6) 16.3 (5.6–40.3) 15.9 (4.5–32.8) 15.1 (6.7–26.5)			
Di Carlo (2004)	Randomized, longitudinal, no placebo group (12 mo)	n=22 no HT n=22 17B-E2 and norgestrol	17B-E2 50 µg/day; transdermal	Norgestrol 5 mg/day; 12 days/month sequential regimen	Median (range) at 0 & 12 mo: No HT: 14.5 (6.2–33.6) 17.5 (8.6–33.7) HT: 12.1 (5.9–26.5) 10.5 (4.9–32.4)	0 & 12 mo: No HT: 26.7 (4.7) 26.8 (4.5) HT: 25.7 (3.5) 25.8 (2.4)	Total fat mass (P<0.05) and total % fat mass were higher in no Tx group (P<0.05) at 1 year. No significant changes in HT group in total fat mass or % fat mass. No changes in BMI in either group. Leptin levels increased in untreated group (P<0.05) at 12 months. Leptin showed a trend toward reduction at 12 months in HT group (P=0.07)	Untreated POM women show an increase in total fat mass, total % body fat, and serum leptin concentrations. HT prevents these changes and maintains serum leptin concentrations.
Castelo-Branco (2007)	Randomized, multicenter, double-blind double-dummy, no placebo group (12 mo)	n=94 intranasal HT n=80 intranasal HT n=79 intranasal HT n=80 oral HT	1. 350 µg E2 + 50 µg NET 2. 350 µg E2 + 175 µg NET 3. 350 µg E2 + 550 µg NET 4. 2 mg E2 + 1 mg NETA (oral)	NET (intranasal) and NETA (oral)	pg/mL at 0, 3, 6, 12 mo: 1. Intranasal: 6.8 (4.3), 8.2 (5.5), 10.1 (7.9), 9.6 (6.4) 2. Intranasal: 7.4 (4.4), 9.0 (5.6), 9.3	Baseline: 1. Intranasal: 26.1 (3.1) 2. Intranasal: 26.5 (3.4) 3. Intranasal: 26.3 (3) 4. Oral: 26.5 (3.7)	All groups increased in serum leptin from baseline to 6 months (P<0.01). No difference in serum leptin between 6 months and 12 months.	Intranasal and oral administration of HT were associated with increase in serum leptin levels, regardless of dose.

Author (Year)	Design (Duration)	Study participants	Estrogen Therapy	Progestin Therapy	Leptin ^a	BMP ^b	Results	Conclusion
Dedeoglu (2009)	Randomized, prospective, comparative, no placebo group (6 mo)	n=34 no HT n=31 HT n=32 tibolone	CEE 0.625 mg + MPA 2.5 mg Tibolone 2.5 mg	MPA 2.5 mg	(5.4), 10.3 (6.0) 3. Intranasal: 6.9 (5.0), 9.1 (6.4), 10.5 (8.9), 8.9 (5.9) 4. Oral: 7.8 (5.2), 8.3 (5.0), 9.0 (6.0), 9.4 (6.0)	0 & 6 mo: No HT: 25.6, 26.6 HT: 26.2, 26.5 Tibolone: 25.9, 26.3	Untreated group had lower leptin levels at 6 months (P<0.005). HRT group had higher leptin (P<0.05). Tibolone group had lower leptin (P<0.001) No effect of interventions on BMI. No change in total fat mass in untreated & HT groups. Tibolone group had a reduction in total fat mass (P<0.005).	HT caused an increase in leptin while maintaining total fat mass. While no treatment group experienced a decrease in leptin, total fat mass remained stable, but weight increased. Tibolone lowered serum leptin & total fat mass.
Kristensen (1999)	Semi-randomized, observational, no placebo group (5 years)	n=89 HT n=178 no HT	Sequential oral estrogen and progesterone (n=69) and oral continuous E2 (n=20)	progesterone (additional information not provided)	% increase at 5 yr: HT: 21.2 (4.6) No HT: 41.8 (5.1)	0 & 5 yr: HT: 24.3 (0.4), 25.1 (0.5) No HT: 24.4 (0.3), 25.5 (0.3)	Leptin increased in both groups but more so in no HT group (P<0.01). Fat mass was higher in no HT group (P<0.01)	HT group had smaller increase in leptin and fat mass than untreated group.
Laivuori (2001)	Randomized, observational, no placebo group (12 mo)	n=19 oral HT n=19 transdermal HT	Oral: 2 mg E2 days 1–12, 2 mg E2 + 1 mg NETA days 13–22, 1 mg E2, days 23–28 n=19 Transdermal: 50 µg/d E2 days 1–13, 50 µg E2 + 250 µg/d NETA days 14–28, n=19	NETA	Mean (geometric) 0, 2, 6, 12 mo: Oral: 13.9, 14.2, 15.3, 14.8 Transdermal: 12.0, 13.0, 14.6, 13.5	Mean (geometric) 0, 2, 6, 12 mo: Oral: 26.2, 26.2, 26.2, 26.1 Transdermal: 24.7, 24.7, 24.5, 24.8	No effect on serum leptin levels in either group.	No effect of oral or transdermal regimen on plasma leptin concentrations or change in BMI.
Lavoie (1999)	Non-randomized, observational, no placebo group (2 mo)	Younger group: n=11 (45–55 yrs) Older group: n=10 (70–80 yrs)	Transdermal E2 50 µg/day	Progesterone 100 mg vaginally bid; during second month of Tx with transdermal E2	Mean (SE) at 0, 1, 2 mo: Younger group:	Mean (SE) at 0, 1, 2 mo: Younger group:	Leptin increased more in younger group (P<0.01) than in older (P=0.06).	HT was associated with higher leptin levels in both groups, but more prominent in younger group.

Author (Year)	Design (Duration)	Study participants	Estrogen Therapy	Progestin Therapy	Leptin ^a	BMP ^b	Results	Conclusion
Cento (1999)	Non-randomized, observational, no placebo group (12 wk)	PRM n=5 obese n=6 lean POM: n=9 obese n=8 lean	Transdermal 50 µg 17B-E2 daily (POM women only)		PRM ^c obese: 35 (49) PRM lean: 15 (20) Before and after HT: POM obese: no Tx: 25 (32) Tx: 30 (36) POM lean: no Tx: 15 (21) Tx: 19 (25)	PRM obese: 31.54 (5.25) PRM lean: 22.87 (1.17) POM obese: 31.34 (6.67) 30.93 (5.97) POM lean: 23.12 (1.68) 23.25 (1.25)	No effect of HT in obese or lean women. Leptin is higher in obese PRM women compared to obese POM (P<0.05).	POM women had lower leptin levels than PRM women. Leptin levels showed a non-significant trend toward increasing in women with transdermal E2 therapy. BMI was unchanged in treatment groups.
Konukoglu (2000)	Randomized, observational, no placebo group (6 mo)	n=25 estrogen n=20 estrogen +MPA n=30 PRM control	conjugated estrogens (study did not give any additional specifics about estrogen therapy)	MPA 5 mg/day	0 and 6 mo: HT: 3.67 (2.44), 23.05 (10.72) 0 mo: PRM: 18.6 (5.9)	0 and 6 mo: HT: 26.7 (4.8) 26.6 (3.4) 0 mo: PRM: 26.5 (3.2)	PRM women had higher leptin levels than POM (P<0.001). Leptin levels were higher after HT (P<0.001).	Plasma leptin was significantly higher in PRM women than in POM women at baseline. Leptin increased significantly in HT group from baseline.
Tommaselli (2003)	Non-randomized, longitudinal, no placebo group (6 mo)	n=18 E2 n=19 raloxifene n=19 control	50 µg/d transdermal 17B-E2 60 mg/d raloxifene	None	Median (0, 1, 5, 15, 180 days): Control: 10.7, 18.2, 12.4, 13.9, 19.7 E2: 7.9, 12.5, 8.1, 8.9, 11.0 Raloxifene: 13.1, 20.5, 22.4 (3.9), 12.0, 12.9, 13.3	Control: 24.1 (6.7), 22.9 (5.5), 23.2 (3.5), 26.2 (7.2) E2: 23.4 (4.4), 22.8 (6.1), 23.1 (4.8), 24.5 (6.1) Raloxifene: 25.7 (5.5), 22.4 (3.9), 23.3 (4.1), 25.0 (4.5)	Leptin levels increased in control group 6 months after surgery ^d (P<0.01). BMI did not change.	HT after ovariectomy maintained leptin levels and BMI in both treatment groups. The control group experienced an increase in leptin levels at 6 months.
Gol (2005)	Prospective, no placebo group (6 mo)	n=20 POM (43-60 yrs)	Tibolone 2.5 mg/day	None	0, 3, 6 mo: 23.9 (11.0) 22.7 (11.3) 22.58 (11.1)	0, 3, 6 mo: 29.7 (4.1) 29.8 (4.3) 29.7 (4.4)	No effect	Tibolone had no effect on leptin levels or BMI.

Author (Year)	Design (Duration)	Study participants	Estrogen Therapy	Progestin Therapy	Leptin ^a	BMP ^b	Results	Conclusion
Petzel (2008)	Randomized, observational, no placebo group (3 mo)	n=22: no HT n=25 E2 n=10 tibolone	1 mg E2 2.5 mg tibolone	None	5 days post-op ^c & 3 months: No HT: 19.8 (16.9) 20.2 (13.4) E2: 17.4 (12.1) 24.5 (13.8) Tibolone: 19.4 (13.7) 18.9 (13.5)	Not reported	No significant effect	Leptin levels did not change significantly in either group. E2 group showed a trend toward higher leptin levels at 3 months.
Nar (2009)	Randomized, observational, no placebo group (8 wk)	n=12 no HT n=12 E2	2 mg 17B-E2 (oral)		0, 4, 8 wk: No HT: 30.6 (31.6) 26.1 (2.5) 33.5 (24.2) 38.1 (23.5) E2: 25.9 23.1 (17.2) 24.1 (18.3) 19.4 (9.1)	0, 4, 8 wk: No HT: 26.1 (2.5) 25.9 (2.4) 26.0 (2.5) E2: 25.9 (3.0) 26.1 (4.1) 26.2 (3.3)	No significant effect	Untreated group showed a trend toward higher leptin levels; E2 group showed a trend toward lower leptin levels. Neither trend was statistically significant.
Lambrinoudaki (2004)	Semi-randomized, prospective, no placebo group (6 mo)	n=20 CEE n=40 CEE+MPA n=40 tibolone	CEE 0.625 mg or tibolone 2.5 mg	MPA 5 mg	0 & 6 mo: CEE: 25.8 (11.9) 27.1 (12.7) CEE+MPA: 20.93 (10.9) 21.03 (9.1) Tibolone: 19.4 (8.9) 18.3 (9.8)	0 & 6 mo: CEE: 25.9 (4.3) 25.4 (4.8) CEE+MPA: 23.5 (3.0) 24.1 (3.9) Tibolone: 24.5 (2.6) 25.1 (2.8)	No effect of various treatments on leptin	No significant changes
Di Carlo (2000)	Cross-sectional, prospective, no placebo group (duration not stated)	n=14 no HT n=12 E2+MPA n=20 PRM as control	transdermal 17B-E2 50 µg/d	Medroxyprogesterone acetate 10 mg/d for 12 days/cycle for at least 1 year	No HT: 15.8 (6.6) HT: 8.1 (4.17) Control: 10.1 (5.48)	No HT: 24.5 (3.0) HT: 23.8 (3.36) Control: 23.1 (2.87)	Serum leptin levels were higher in no HT group than in control group (P=0.02) and HT group (P=0.004)	No HT was associated with increased serum leptin levels compared to POM & PRM women with HT.
Panidis (2001)	Non-randomized, observational, no placebo group (12 mo)	n=5 in each group Group 1: normal BMI, tibolone Group 2: BMI 28-30 kg/m ² + tibolone Group 3: BMI 28-32 kg/m ² , no tibolone	Tibolone 2.5 mg/day, had used for 1 year	None	1, 2, 6, 9, 12 mo: Group 1: 11.1 (4.0), 14.2 (3.9), 15.6 (7.7), 14.1 (4.7), 12.9 (6.7), 10.3 (2.7) Group 2: 18.8 (0.7), 20.2 (1.1), 20.1 (0.7),	Group 1: 24.1 (0.8) Group 2: 29.5 (0.30) Group 3: 30.1 (0.8)	No effect of tibolone on serum leptin. Leptin levels were higher before tibolone administration in groups II and III than in group I (p<0.01 for both)	Tibolone administration was not associated with change in serum leptin levels in either group.

Author (Year)	Design (Duration)	Study participants	Estrogen Therapy	Progestin Therapy	Leptin ^a	BMI ^b	Results	Conclusion
					21.1 (0.9), 19.3 (1.2), 18.1 (1.0) Group 3: 23.9 (3.5), 23.8 (4.0), 24.3 (3.8), 24.8 (3.3), 23.6 (2.7), 22.5 (2.9)			

^aUnits are ng/mL unless otherwise noted, statistical representation of data and time of data collection

^bUnits are kg/m² unless otherwise noted

^cLeptin levels interpreted from Figure 1 in the study

^dTotal abdominal hysterectomy and bilateral ovariectomy

^eVaginal or abdominal hysterectomy with bilateral adnexectomy

^fPost total abdominal hysterectomy and bilateral ovariectomy

Abbreviations:

- BMI = body mass index
- CEE = conjugated equine estrogens
- DRSP = drospirenone
- E2 = Estradiol
- EE = ethinyl E2
- ET = estrogen therapy
- HT = hormone therapy
- MPA = medroxyprogesterone
- NET = norethisterone
- NETA = norethisterone acetate
- POM = postmenopausal
- PRM = premenopausal
- Tx = treatment