

Estrogen deficiency during menopause:

1. Its role in the metabolic syndrome

CASE 1

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A 54-year-old woman (gravida 3, para 3) presented with moderate vasomotor symptoms—hot flushes during the day and nighttime sweats—that had affected her for the last 18 months. She complained that these symptoms disrupted her routine and impaired her ability to function in her middle-management position. She had tolerated her increasing discomfort in an effort to avoid hormone therapy (HT) but now seemed desperate.

When this patient first recognized menopausal symptoms and had difficulty sleeping, her family physician prescribed conjugated estrogens and intermittent progestogen, which provided virtually total relief. She was overweight, despite struggling to control her weight since the birth of her last child at age 37; during that pregnancy she had gestational diabetes that was controlled with a supervised diet. She was again referred to a nutritionist. She continued the HT for about 3 years, until the results of the Women's Health Initiative (WHI) caused her family physician to be concerned about the potential for increased cardiovascular disease (CVD) risk. After discontinuing HT, diet and exercise proved inadequate, so she was given low-dose labetalol to treat mild hypertension and low-dose atorvastatin to normalize plasma levels

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Series learning objectives: After completing this series of case studies, the reader should be able to:

- Recognize the connection between estrogen deficiency and metabolic syndrome
- Regard HT as an option in patients with both vasomotor symptoms and features of the metabolic syndrome
- Screen for bone loss in patients without vasomotor symptoms or osteoporosis and determine fracture risk, if appropriate
- Recognize when transdermal HT may be an alternative to nonhormonal agents used to prevent bone loss

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of low-density lipoprotein (LDL), high-density lipoprotein (HDL) cholesterol, and triglycerides.

On presentation, the patient was 5 ft 7 in tall and weighed 180 lb, with a waist circumference of 34 in. Her blood pressure was maintained at 140/86 mm Hg with labetalol. Her physical examination was otherwise unremarkable. The patient's lipid profile with continuing atorvastatin therapy showed a plasma triglyceride level of 148 mg/dL and an HDL cholesterol level of 52 mg/dL. Levels of fasting plasma glucose and LDL cholesterol were also within the normal range.

Family history was positive for CVD risk: the patient's maternal grandmother had died of stroke at age 64. The patient's mother was diagnosed with insulin-dependent diabetes mellitus at age 45, was later treated for mild congestive heart failure, and died suddenly at age 58. Her father, who had a history of undiagnosed myocardial infarction and controlled type 2 diabetes, died of extensive coronary atherosclerosis at age 60. An older sister has insulin-dependent diabetes and 2 brothers have type 2 diabetes controlled by diet and oral antihyperglycemic agents.

This patient describes her quandary: Can she be given relief of her vasomotor symptoms without placing herself at greater risk for cardiovascular events, venous thromboembolism, or other disease?

■ FEATURES OF THE METABOLIC SYNDROME

Estrogen deficiency that develops during menopause may be the common cause of many components of the metabolic syndrome,^{1,2} including central obesity and dyslipidemia with increased plasma levels of triglycerides and decreased levels of HDL cholesterol (**TABLE 1**).³ Furthermore, these components may interact, producing adverse effects.¹ For example, abdominal obesity is associated with insulin resistance, which impairs the beneficial effects that insulin normally has on lipid

metabolism as well as on insulin-stimulated vasodilation; impairment of the latter may demonstrate a link between elevated circulating insulin levels and hypertension.¹ Abnormalities of insulin action, not surprisingly, can lead to development of diabetes.⁴ In addition, CVD risk may be increased via associated effects on blood coagulation and fibrinolysis.⁴

The adverse changes in metabolic risk factors related to estrogen deficiency may be due directly to ovarian failure or may be consequences of abdominal fat deposition.² Central, visceral obesity correlates with increased mortality and risk for diabetes, hyperlipidemia, hypertension, and atherosclerosis to a greater extent than does peripheral fat deposition, including abdominal subcutaneous fat.⁵ Notably, postmenopausal women have increases in trunk fat mass and decreases in trunk lean muscle mass, while total fat mass is increased and fat deposition is centralized.⁶

■ HORMONE THERAPY

Postmenopausal women who are given HT may be protected from the changes in body fat distribution associated with the metabolic syndrome and its sequelae.^{1,6} Although some researchers found no role for HT in maintaining lean muscle mass or in preventing abdominal fat deposition,⁷ several controlled or comparative studies linked HT to the reversal of menopause-related visceral obesity and loss of muscle mass.⁸⁻¹⁰ These studies were relatively small; however, their findings should not be ignored.

In a controlled, crossover study of healthy postmenopausal women (age 55 [\pm 3] years), change in body weight during 12 weeks of HT was similar to that with placebo; however, lean body mass increased ($P<0.01$) while abdominal fat mass

TABLE 1

The metabolic syndrome in women*

Risk factor	Defining level
↑ Abdominal fat mass	Waist circumference [†] >35 in (>88 cm)
↑ Triglycerides	≥150 mg/dL
↓ High-density lipoprotein cholesterol	<50 mg/dL
↑ Blood pressure	≥130/≥85 mm Hg
↑ Fasting plasma glucose	≥110 mg/dL

*Presence of 3 or more risk factors is diagnostic.

[†]Waist circumference correlates better than body mass index; increase may be associated with insulin resistance.

Adapted from Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486-2497.³

decreased ($P=0.04$).⁸ Even overweight HT users have been found to have less visceral fat mass ($P=0.05$) than nonusers, although insulin sensitivity per kilogram of lean body mass remained similar in both groups.⁹ A 2-year prospective trial comparing 3 HT regimens found changes from baseline of increased lean mass and decreased central obesity in all treatment groups.¹⁰

Variation in efficacy

Routes of HT delivery can have distinctly different effects on body composition and components of the metabolic syndrome (**TABLE 2**).^{8,10-12} A 12-month study in postmenopausal women who had undergone hysterectomy compared the use of transdermal patches delivering 17 β -estradiol (50 mcg/d) and oral conjugated estrogens (0.625 mg/d); neither regimen included progestogen.¹¹ Findings revealed an increase in lean body mass and no change in total body fat in patch wearers, while oral HT users experienced a decrease in lean body mass and an increase in total body fat.

TABLE 2
Effect of oral and transdermal sex hormones on body composition

Study	Hormone regimen	Fat body mass	Lean body mass
Arabi et al ¹⁰ (N=109)	Tibolone* 2.5 mg/d	↓ [†]	↑ [‡]
	Tibolone* 1.25 mg/d	↓ [†]	↑ [‡]
	Estradiol 2 mg/d and norethisterone 1 mg/d	↑ [†]	↑ [‡]
dos Reis et al ¹¹ (N=23)	Oral conjugated estrogen 0.625 mg/d	↑ [‡]	↓ [‡]
	Transdermal estrogen patch 50 mcg/d	↔	↑ [‡]
O'Sullivan et al ¹² (N=18)	Oral conjugated estrogen 1.25 mg/d	↑ [§]	↓ [§]
	Transdermal estrogen patch 100 mcg	↔	↑
Sørensen et al ⁹ (N=16)	17β-estradiol 4 mg/d x 22, 1 mg/d x 6; norethisterone 1 mg/d x 10	↓	↑ [¶]

*A synthetic steroid with estrogenic, androgenic, and progestagenic properties; used in Europe for almost 2 decades to treat vasomotor symptoms and to prevent postmenopausal osteoporosis; not approved for use in the United States.
[†]Small but significant decrease in central obesity.
[‡]P<0.05 vs baseline.
[§]P<0.05 vs transdermal route.
^{||}Decrease in abdominal fat mass P<0.05 vs placebo.
[¶]P<0.05 vs placebo.

An open-label, randomized crossover study comparing the effects of oral conjugated estrogens (1.25 mg/d) and transdermal estrogen (100 mg) found oral estrogen to be associated with increased fat mass, probably due to suppressed lipid oxidation, as well as reduced lean body mass that was apparently due to a decrease in insulinlike growth factor-1 (IGF-1).¹²

Another study examined the effects of 4 differ-

ent progestogens that were coadministered with oral or transdermal estrogens.¹³ The researchers concluded that the androgenic properties of progestogens may give these agents a role in maintaining lean body mass via moderation of hepatic endocrine function (eg, potentially restoring IGF-1 levels).

Other considerations

Estrogen deficiency in postmenopausal women usually leads to disturbances in lipid metabolism and a less favorable plasma lipid profile, notably decreased levels of HDL cholesterol (<40 mg/dL in 87% of patients in one study).¹⁴ Total, LDL, and HDL cholesterol as well as triglycerides were measured at baseline and after 3 and 6 months of therapy with conjugated estrogens (0.625 mg/d), transdermal estradiol patches (50 mcg/d), or placebo.¹⁴ Both HT regimens resulted in significant decreases in total and LDL cholesterol while significantly increasing HDL cholesterol. Although the oral agent was more effective in raising plasma levels of HDL cholesterol, it also increased triglyceride levels. Conversely, transdermal HT use was associated with a significant decline in plasma triglycerides (FIGURE 1).^{14,15} The researchers con-

cluded that transdermal HT is preferable in women with high levels of plasma triglycerides.¹⁴

Other investigators found a significant decrease in triglyceride levels (P<0.01) when women taking oral HT switched to transdermal estradiol.¹⁶

The impact of elevated plasma triglyceride levels on CVD risk appears to be greater in women than in men.¹⁷ Thus, women taking oral HT may

paradoxically be at greater risk despite other improvements in plasma lipid profile. In postmenopausal women with hypertriglyceridemia, transdermal HT is recommended because it has limited effects on lipid metabolism and may correct plasma triglyceride levels.^{16,18}

ALTERNATIVES FOR SYMPTOMS

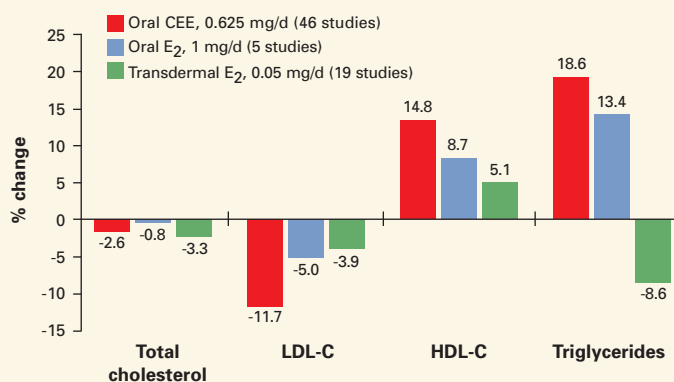
Selective serotonin reuptake inhibitors

Reports that selective serotonin reuptake inhibitors (SSRIs) may alleviate hot flashes in menopausal women were challenged by the results of a randomized, controlled trial of paroxetine.¹⁹ Of 165 menopausal women who experienced 2 or more hot flashes daily, 51 and 58 women received paroxetine controlled release (CR) 12.5 mg/d or 25.0 mg/d, respectively; the remaining 56 participants received placebo. After 6 weeks, the median reductions in frequency of symptoms with active treatment were significantly different from placebo: 62.2% ($P=0.007$) for the paroxetine 12.5-mg/d group, 64.6% ($P=0.03$) for the 25.0-mg/d group, and 37.8% for the placebo group. The investigators concluded that paroxetine CR showed some efficacy in reducing the frequency of menopausal hot flashes and thus may be an acceptable alternative to HT.

In prescribing any therapy, the clinician must weigh the risks and benefits, as well as obtain informed consent from the patient whenever possible. Despite the statistics quoted above, the mean frequency of daily hot flashes decreased by less than 50% in the 12.5-mg/d group (from 7.1 to 3.8) and by 50% in the 25.0-mg/d group (from 6.4 to 3.2).¹⁹ The physician and patient must determine whether the potential for drug interactions, adverse effects (including sexual dysfunction in up to 9% of women), and necessity for tapered dis-

FIGURE 1

Effects of oral and transdermal estrogen on lipid levels



CEE = conjugated equine estrogens; E₂ = estradiol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol. Meta-analysis of 248 prospective studies published between 1974 and 2000. Godsland IF. *Fertil Steril*. 2001;75:898-915.¹⁵

continuation of SSRIs²⁰ are acceptable in the context of need for alleviation of menopausal symptoms. It should be noted that paroxetine is not yet indicated for this use.

Gabapentin

An open-case series was conducted to determine the effectiveness of gabapentin in alleviating hot flashes in postmenopausal women.²¹ Data were available for 9 of the 11 women, who experienced a significant reduction ($P<0.001$) in symptoms with a dose of 300 mg/d (change in Green Climacteric Scale from mean of 25.72 to 19.25).

Another study—in 59 postmenopausal women experiencing more than 7 hot flashes daily—was designed to be randomized, double blind, and placebo controlled.²² After 12 weeks of gabapentin 900 mg/d, patients reported 45% fewer hot flashes and the composite score for frequency and severity decreased by 54%. Subsequent open-label dosing up to 2,700 mg/d further reduced frequency and composite score (54% and 67% from baseline, respectively).

In a separate case, a 32-year-old woman expe-

Do the WHI findings apply to this case?

Even though the Women's Health Initiative (WHI) was a large, multicenter, randomized, placebo-controlled study in postmenopausal women, its results may have little pertinence for a relatively young woman, menopausal for fewer than 5 years, who seeks treatment for vasomotor symptoms.

In his detailed review of the WHI literature, Speroff²⁵ points out a number of features that call into question generalization of WHI findings:

- Of the 16,608 women randomized to receive combined estrogen-progestin or placebo, only 574 (6.7%) of the 8,506 women in the estrogen-progestin arm were aged 50 to 54 years.
- Women in the estrogen-progestin arm were on average 63.3 years old and 18 years postmenopausal. Only about 16.5% of this treatment arm were menopausal for fewer than 5 years.
- To prevent a high drop-out rate in the placebo group, women with significant menopausal symptoms were not included. Those who had taken prior hormone therapy (HT) went through a 3-month wash-out phase; if they became symptomatic, they were discouraged from participating.
- During the course of the trial, discontinuation of study medication increased; at termination, about half of the participants had withdrawn. This precluded finding favorable changes in relative coronary heart disease (CHD) risk with treatment, despite reductions in plasma levels of total cholesterol, LDL cholesterol, glucose, insulin, as well as increases in HDL cholesterol.
- Subgroup analysis showed that a statistically significant increase in CHD existed only for women who had been menopausal for 20 years or longer. This group aside, the prevalence of CHD was identical in treatment and placebo arms. Data from the estrogen-only arm suggested that treatment in younger women confers a reduced risk of CHD.

Thus, one must not conclude that HT increases CHD risk in all postmenopausal women.

- The small difference in recorded cardiac events between treatment and placebo groups (57 and 38 cases, respectively) during the first trial year may reflect uncontrolled use of lipid-lowering medication in the placebo group. Statin drugs may reduce the risk of coronary events by 30%, similar to the benefit of HT, and concurrent estrogen use does not have an additive effect.
- Unless the WHI results are analyzed on the basis of years since menopause, the cardiovascular findings cannot be perceived as data related to primary prevention. Even with such an analysis, meaningful conclusions are hampered by the relatively few women in the early years of menopause.

The WHI investigators²⁶ point out that only one drug regimen (conjugated estrogens, 0.625 mg/d, plus medroxyprogesterone acetate, 2.5 mg/d) was tested in postmenopausal women with an intact uterus. Thus, their results do not necessarily apply to lower doses, other oral formulations, or to transdermal HT. They suggest that because transdermal HT acts more like endogenous hormones, transdermal formulations may be associated with a risk-benefit profile different from that of oral agents. The authors also acknowledge that the effects of estrogen were not distinguished from the effects of progestin.

On the basis of their findings—which Speroff²⁵ describes as flawed—the WHI investigators concluded that the above test regimen should not be initiated or continued for the primary prevention of CHD and that known or suspected risks must be weighed against the benefits seen in fracture prevention. Other researchers simply conclude that the WHI does not indicate increased cardiovascular risk in perimenopausal women taking HT.²⁷

rienced 20 to 30 severe hot flushes daily after surgical menopause.²³ For 17 years, she took a variety of HT formulations and an SSRI without relief. When gabapentin was tried, it elicited a marked response. These researchers found gabapentin effective in reducing the frequency and severity of hot flushes.²² They concluded that it may thus be useful for treating vasomotor symptoms in postmenopausal women who cannot take HT, especial-

ly in women with paresthesias or pain.²¹

Although gabapentin is not yet indicated for this use, the physician may want to consider it in recalcitrant cases. Notable treatment-emergent adverse events with gabapentin include dizziness (28.0% vs 7.5% with placebo), somnolence (21.4% vs 5.3% with placebo), and peripheral edema (8.3% vs 2.2% with placebo).²⁴ Side effects may lessen in severity a few weeks after treatment

has been initiated. Weight gain was also noted in up to 3.4% of recipients—at least twice the incidence that was seen with placebo.

DISCUSSION

In menopausal women, the features and the severity of the metabolic syndrome are related to weight, body composition (proportions of lean mass, fat mass, visceral fat mass), and markers of inflammation.²⁸ During the early postmenopausal years, women may gain weight, with increases observed in both total body fat mass and lean body mass.

However, even without weight gain, some women may be predisposed to loss of muscle mass with body fat redistribution to the abdominal viscera, leading to central obesity and risk for development of the metabolic syndrome.²

Surprising importance of exercise

Reduction of lean body mass that occurs in menopause may also result from decreased physical activity, generally related to leisure-time activity.^{2,29} Exercise training can reverse this effect by significantly increasing lean mass and decreasing fat mass.^{30,31}

Even in overweight women, participation in physical activity helps to modify the adverse effects of greater fat mass;²⁹ a low-energy, high-protein diet may also offer a weight-loss advantage to obese women with features of the metabolic syndrome.³² Moreover, with weight loss by any means, centrally obese individuals will lose proportionately more visceral fat because visceral adipocytes exhibit a higher lipolytic rate than do other adipocytes.⁵

In central obesity, sustained moderate weight

loss—as little as 5% or 10% of initial body weight—can lessen insulin resistance and hypertension while improving the plasma lipid profile.³³ Thus, regular exercise and attention to diet can favorably alter body composition and contribute to decreasing CVD risk in postmenopausal women.

Role of inflammation

Inflammation is a major underlying condition in CVD and other chronic diseases. The proinflammatory state associated with the metabolic syndrome is characteristic of obesity³⁴ and is related to both insulin resistance and endothelial dysfunction.³⁵ Even minor impairment of glucose tolerance is associated with a chronic inflammatory response that contributes to the development of diabetes and arteriosclerosis.³⁶

A number of biomarkers of inflammation are increased in obesity, associated with insulin resistance, and predictors of type 2 diabetes and CVD.³⁴ C-reactive protein (CRP) is one of the most notable in this setting,^{34,36} correlating significantly with development of the metabolic syndrome in women

FIGURE 2

Effect of oral and transdermal estrogen on C-reactive protein levels

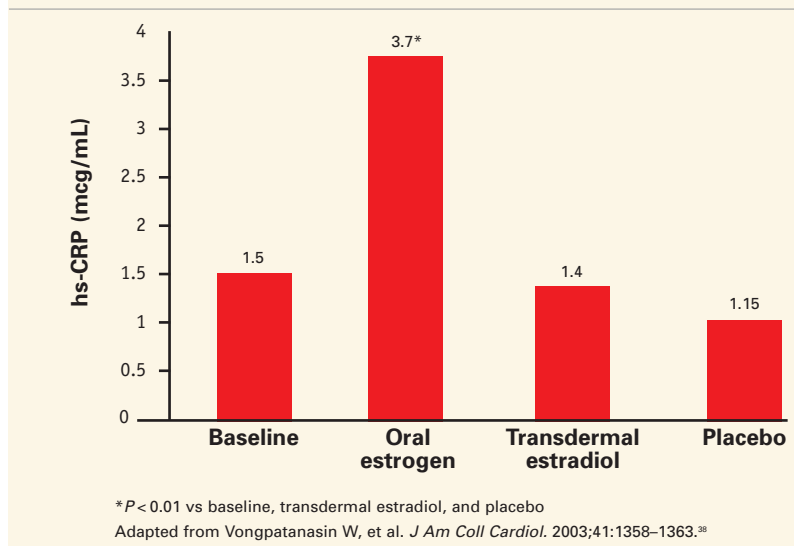
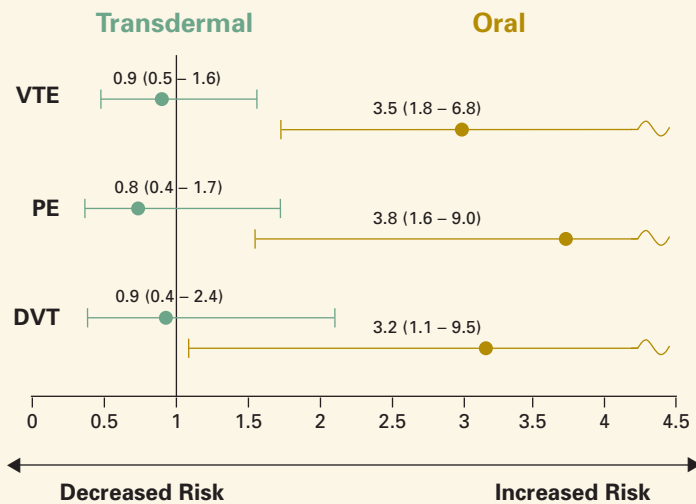


FIGURE 3

VTE risk with transdermal and oral estrogen



VTE=venous thromboembolism; PE=pulmonary embolism; DVT=deep-vein thrombosis. Scarabin PY, et al. *Lancet*. 2003;362:428-432.⁴⁸

and predictive of an adverse prognosis.^{37,38}

Recently, obesity has been linked to insulin resistance and inflammation via adipocytokines, including tumor necrosis factor (TNF)- α .^{34,39} Therefore, it may not be too surprising to find that compared to sedentary subjects, individuals with the metabolic syndrome who exercise and maintain cardiorespiratory fitness have significantly lower levels of CRP, TNF- α , fibrinogen, and other markers of inflammation,⁴⁰⁻⁴² again highlighting control or reversal of central obesity as an essential strategy for modulating the metabolic syndrome and reducing risk for chronic disorders such as diabetes and CVD.

Controlling metabolic risk factors while treating vasomotor symptoms

Virtually all the central features of the metabolic syndrome may be induced—either directly or indirectly—by estrogen deficiency.¹ Therefore, HT is a logical option for amelioration of both vasomotor symptoms and susceptible components of the

metabolic syndrome. The North American Menopause Society⁴³ recommends that an individual risk profile should be compiled for each patient considering HT and that HT “be limited to the shortest duration consistent with treatment goals, benefits, and risks.” The lowest effective doses of estrogen and progestogens should be considered; in fact, less than monthly administration of progestogen may be sufficient.⁴⁴

In a menopausal patient who presents with features of the metabolic syndrome, special care must also be taken to avoid therapies that may worsen her condition: if the metabolic syndrome worsens or if other hormonal problems

manifest, such as thyroid imbalance, it would be prudent to refer the patient to an endocrinologist.

Choices of HT to alleviate vasomotor symptoms should take into account their ranges of activity. Conclusions reached about one formulation cannot be extrapolated to another,⁴³ and many alternatives to a regimen of conjugated equine estrogens and medroxyprogesterone acetate may exhibit better safety without loss of efficacy.⁴⁵

In addition to having distinctly different effects on body composition and plasma lipid profiles (see “Hormone Therapy” on page S3), oral and transdermal formulations have divergent effects on biomarkers for inflammation. For example, in one study, oral estrogen use was found to be associated with significant elevations in CRP—as much as 4-fold—whereas transdermal estradiol had no effect (FIGURE 2).³⁸ Transdermal estradiol also had no effect on IGF-1 levels while oral estrogen reduced IGF-1 levels significantly ($P<0.01$) in the same women. Other studies found no elevation in CRP levels during 12 months of transdermal HT⁴⁶ and a

lower rate of treatment-related impaired glucose tolerance than in oral-HT users,⁴⁷ a feature important to women concerned about risk for diabetes.

Because oral HT affects coagulation factors, it is associated with increased risk for venous thromboembolism; transdermal HT is not (FIGURE 3).^{48,49} Furthermore, the first-pass hepatic metabolism of oral HT formulations has been associated with increased levels of other acute-phase proteins that interfere with HDL function and increase CVD risk after menopause.⁵⁰ Finally, as part of the metabolic syndrome, low plasma HDL cholesterol levels also may play a contributing role in the increased risk for breast cancer after menopause.⁵¹

In conclusion, menopausal women seeking relief from vasomotor symptoms may derive additional benefit from HT when the clinical presentation includes features of the metabolic syndrome. The HT regimen should be selected carefully in such cases, because all regimens do not confer the same metabolic benefit.

■ CASE RESOLUTION

The patient was encouraged to know that any weight loss would likely improve her metabolic condition; she maintained a more healthy diet and pursued a regular exercise program. With low-dose transdermal HT, she experienced significantly fewer and less severe vasomotor symptoms, which allowed her to sleep well and function optimally in her profession.

She decided to stop taking atorvastatin to see whether the transdermal HT would maintain her normalized level of plasma triglycerides. At her next follow-up visit, her triglyceride levels were still normal. Encouraged by this progress, she proposed withdrawal from labetalol as well.

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CME POSTTEST

To obtain 1 AMA category 1 credit for this course of study, circle the correct responses below and complete the CME credit application and program evaluation on page 12. Mail or fax pages 11 and 12 to: *Estrogen deficiency during menopause: Case 1*, University of Wisconsin Medical School Office of Continuing Medical Education, 2701 International Lane, Suite 208, Madison, WI 53074. Fax: 608.240.2151. No fee is required for this CME program. This test is valid through May 2006; no credit will be given after this date. You must correctly answer 7 of the 10 (70%) questions to receive credit.

1. In women, risk factors for the metabolic syndrome include
 - a. Waist circumference greater than 35 inches
 - b. Plasma high-density lipoprotein (HDL) cholesterol levels below 50 mg/dL
 - c. Plasma triglyceride levels of at least 150 mg/dL
 - d. All of the above
2. Central (visceral) obesity
 - a. Correlates poorly with increased mortality
 - b. Correlates well with risk for diabetes and atherosclerosis
 - c. Carries the same risk as abdominal subcutaneous fat
 - d. Answers b and c
3. Postmenopausal hormone therapy (HT) is likely
 - a. Associated with no change in body fat distribution
 - b. To cause an increase in total fat mass and a decrease in total lean mass
 - c. To cause an increase in total lean mass and a decrease in central obesity
 - d. None of the above
4. Compared to oral conjugated estrogens, transdermal estrogen
 - a. Causes significantly greater increases in lean body mass
 - b. Is associated with a significant decrease in plasma triglyceride levels
 - c. Has no effect on plasma lipid profile
 - d. Answers a and b
5. When HT is chosen to alleviate vasomotor symptoms and modulate features of the metabolic syndrome, the lowest effective doses should be considered and limited to the shortest duration consistent with treatment goals.
 - a. True
 - b. False
6. In the metabolic syndrome, the proinflammatory state is
 - a. Unrelated to obesity or insulin resistance
 - b. Associated with biomarkers predictive of poor prognosis
 - c. Unlikely to be ameliorated by exercise
 - d. Inconsequential in menopausal women
7. Compared to transdermal HT, oral HT use is associated with
 - a. Significant elevations in C-reactive protein
 - b. Higher rate of treatment-related impaired glucose tolerance
 - c. Effects on coagulation factors, increasing risk for venous thromboembolism
 - d. All of the above
8. Overweight menopausal women
 - a. Maintain a greater visceral fat mass regardless of HT use
 - b. Cannot affect central obesity by weight loss alone
 - c. Can modify the adverse effects of greater fat mass via physical activity
 - d. None of the above
9. In central obesity, sustained moderate weight loss
 - a. Can lessen insulin resistance and hypertension
 - b. Will not improve the individual's plasma lipid profile
 - c. Must be greater than 10% of the patient's initial body weight to have an effect
 - d. None of the above
10. Alternative therapies to alleviate vasomotor symptoms, including paroxetine and gabapentin
 - a. Deliver virtually complete relief
 - b. Rarely cause adverse effects
 - c. May be associated with weight loss compared to placebo
 - d. None of the above

APPLICATION FOR CME CREDIT

To obtain 1 AMA category 1 credit for this course of study, complete the CME posttest on page 11, as well as the CME credit application and program evaluation on this page. Mail or fax both pages to the address below. No fee is required. This CME program is valid through May 2006; no credit will be given after this date.

Name _____

Specialty _____ Institution _____

Address _____

City _____ State _____ Zip _____

Telephone _____

Please check one: MD DO Other

I claim ____ credit(s) of category 1 AMA PRA credit (up to 1 credit).

Signature _____

PROGRAM EVALUATION

The University of Wisconsin Medical School values your opinion. Please check the box that best reflects your views on the following statements about this educational activity.

	Yes	No
1. Learning objectives were met.	<input type="checkbox"/>	<input type="checkbox"/>
2. Content was relevant to my practice.	<input type="checkbox"/>	<input type="checkbox"/>
3. Presentation was clear and organized.	<input type="checkbox"/>	<input type="checkbox"/>
4. Author demonstrated expertise in topic.	<input type="checkbox"/>	<input type="checkbox"/>
5. Content was fair, balanced, and free of commercial bias.	<input type="checkbox"/>	<input type="checkbox"/>

If no, please explain. _____

Estrogen deficiency during menopause: Case 1

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