

Cardiovascular CORNER

Adiposity After Menopause and the Effects of Hormones

Rogerio A. Lobo, MD

It is well known that there is a worldwide epidemic of obesity, particularly in developed countries. This has important consequences in terms of the prevalence of metabolic syndrome (MBS) and the resultant concerns related to cardiovascular disease (CVD) and diabetes mellitus (DM). Even women who are not particularly overweight or obese are increasingly concerned about changes in body composition that tend to occur around the time of menopause. This review will not focus on current lifestyle issues, which are responsible for the increasing prevalence of obesity around the world, but rather will consider what is known about changes in body composition and the role of menopause, the possible relationship to changes in endogenous hormonal factors and, finally, the potential influence of exogenous hormones (such as estrogen and progestogens) on body fat.

Much has been written about changes in body habitus and health concerns. Normal reproductive-age women have been described as having a “pear” shape, with fat accumulation over the hips rather than in the abdominal area, as in men. The occurrence of the “apple” shape, with an increased central fat distribution in women, has been shown to be associated with an increase in CVD risk, while thigh/hip fat may be protective.¹⁻⁴ While it is generally acknowledged that this change in body composition occurs after menopause, it has not, until recently, been clear

when these changes begin to occur, and if they are due to age or hormonal factors.

Several lines of evidence point to the importance of premenopausal estrogen levels affecting body fat distribution and maintaining the “pear” shape.⁵ It is known that menopause is associated with a risk of accumulating visceral fat and a loss of subcutaneous fat. Specifically, estradiol has been shown to inhibit lipolysis (and thus allow fat distribution), but only in subcutaneous tissues, and not in the visceral/abdominal area.^{6,7} This effect of estrogen is mediated via adrenergic ($\alpha 2A$) receptors,⁷ and is consistent with findings from other studies (reviewed in more detail below) showing that estrogen treatment after menopause results in lower levels of abdominal fat accumulation.⁷⁻⁹

SWAN has provided us with a great deal of longitudinal data on the menopausal transition. It has been shown recently that there is an increase in waist size (abdominal fat) and total fat during the menopausal transition, which begins to increase before the final menstrual period (Figure).¹⁰ These changes have also been correlated with increases in follicle-stimulating hormone (FSH),¹⁰ which begin before the final menstrual period when menopause ensues.

Insulin resistance (IR) also increases at the time of menopause. While aging per se is known to increase IR, it is unclear if hormonal changes around menopause also contribute. Regardless of the proximate cause, a cycle of events begins soon after menopause, in which IR contributes to more abdominal fat, which, in turn, releases more adipocytokines and free fatty acid (FFA), which further enhances IR. Indeed, the greater the amount of abdominal fat, the less likely FFAs will be suppressed, and this mechanism is likely to be due to an inhibition of the re-esterification of FFA in the presence of abdominal obesity.¹¹

Adipocytokines are known to be abnormal after menopause, particularly in obese women. Leptin and resistin are elevated, and adiponectin is decreased. Ghrelin, a gastric hormone that relates to obesity, is also decreased.¹² Among the many risk factors that relate abdominal obesity to CVD and increased mortality, an elevated leptin/adiponectin ratio is an important marker.¹³ Our own studies¹² and those of others¹³⁻¹⁵ have

Increase in Waist and Fat Mass During Perimenopause

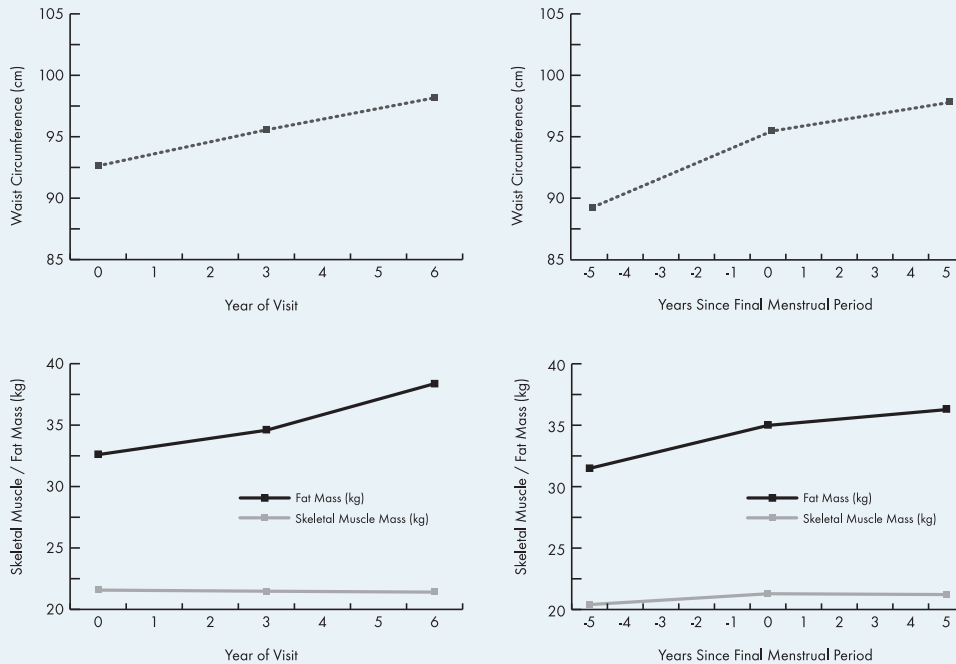


Figure. Data from SWAN showing increase in fat mass beginning before menopause and correlating with rising FSH levels. Adapted from Sowers M, et al. *J Clin Endocrinol Metab* 2007;92:895-901.

found that both leptin (positively) and adiponectin (negatively) also correlate with IR in postmenopausal women. Of some interest regarding the trend of increasing abdominal fat accumulation as women transition through menopause, adiponectin displays an interesting pattern. While leptin very well parallels fat gain around menopause, in early menopause the adiponectin blood level increases.^{16,17} Abdominal obesity is usually associated with a decrease in adiponectin. Accordingly, we have hypothesized that there is an ill-defined set point in menopause, possibly occasioned by a certain degree of IR, which begins to down-regulate adiponectin production and/or secretion.¹⁸

Effects of Estrogen on Fat Mass

As discussed previously, estrogen is known to be important in determining body composition

prior to menopause and in maintaining the “normal” female body habitus. There has been much controversy about the effects of estrogen administered after menopause. Many women believe that estrogen therapy (ET) taken after menopause results in fat gain. A Cochrane review concluded that there is no increase in weight in women receiving hormones when compared to placebo.¹⁹ Although the effects are relatively minor, another meta-analysis demonstrated that there is a decrease in abdominal weight gain and fat mass in women treated with estrogen as compared to placebo (Table).²⁰ The magnitude of this change, however, is small and is in the range of a 7% decrease in fat mass.

Recent data point to this effect of estrogen being mediated through the estrogen receptor ER α specifically,²¹ and possibly independent of the effects of the insulin/IR axis. Not included

Table. Meta-analysis of fat changes with HT

Percentage reduction in waist circumference	-0.8 (-1.2 to -0.4; 95% CI random)
Percentage reduction in abdominal fat	-6.8 (-11.8 to -1.9; 95% CI random)

Adapted from Salpeter SR, et al. *Diabetes Obes Metab* 2006;8:538-54.

in the meta-analysis is a fairly recent report from the WHI.²² In a sub-study at three sites, DEXA scans were obtained to look at body composition before treatment and at year 3 in 437 women receiving E₂+P (CEE 0.625 mg and MPA 2.5 mg) and 398 women on placebo. Results were similar in the intention-to-treat and sensitivity analyses, and showed that women randomized to E+P, compared to placebo, had greater lean mass ($P<0.001$), less trunk fat ($P<0.001$) and less percentage of fat mass ($P=0.05$).²²

Although there are several probable mechanisms for these findings, a direct effect of estrogen on adipocytes has clearly been established. Using affymetrics gene-chip technology, gene-message expression in abdominal subcutaneous tissue was examined before and after ET (estradiol valerate, 2 mg) in a recent study.²³ Although the data were mixed, the findings were consistent, with genes involved in fatty acid synthesis (lipogenesis) shown to be down-regulated by estrogen, as well as a gene (PPAR γ) responsible for adipogenesis shown to be decreased as well.²³ Although it is acknowledged that there is great variability in investigating fat tissue in clinical trials, the authors also found more consistent effects in their in vitro cell cultures.²³

Indirect Effects of Estrogen on Fat Metabolism

Other than direct effects of estrogen on adipocytes, the overall effects of estrogen treatment on body composition may be influenced by other factors as well. The major candidate for such an influence is the effect of estrogen on insulin sensitivity or IR. Further, hormone therapy (HT) may affect mood and lifestyle factors, which could have an impact on energy expenditure. These latter effects are more difficult to prove, while the effects on insulin sensitivity have been studied extensively, although the findings have not been uniform.

As discussed above, the emergence of IR enhances fat accumulation, which, in turn, worsens IR through a variety of mechanisms. If estrogen alters IR, this would be an indirect mechanism whereby estrogen influences fat accumulation. While there have been many studies of the effects of ET and E+P on postmenopausal women, there has also been lack of consistency in these results related to the different populations of women studied, different types and doses of the estrogens and progestogens administered, differences in routes of administration and the length of the studies. The weight of evidence, however, points to a beneficial effect of HT on IR.²⁰ These results also are corroborated by the finding that the occurrence of new-onset DM is decreased in women receiving HT.^{24,25} These data would be consistent with the view that a beneficial effect of HT on IR may be an indirect mechanism whereby estrogen decreases fat accumulation in postmenopausal women.

Does Route of Administration or Type of Hormonal Treatment Matter?

Several studies have been carried out to characterize if there are differences in body composition when estrogen is administered orally versus transdermally. Although several studies point to an improved lean/fat mass ratio when transdermal estrogen is administered, not all studies are in agreement.

From a physiologic standpoint, oral estrogen, because of its first-passage effect, causes a decrease in lipid oxidation resulting in more fat accumulation. At the same time, growth hormone and its binding protein are increased, resulting in a decrease in insulin-like growth factor-1 (IGF-1) and a reduction in lean mass, while fat mass tends to increase. These changes were not found with transdermal estrogen.²⁶⁻²⁸ The increase in fat mass is highly associated with increases in

serum leptin. While this has been an observed change with oral estrogen, leptin does not appear to increase with transdermal estrogen.²⁹ As stated earlier, increases in leptin have been statistically associated with IR, which contributes to more abdominal fat accumulation. Using such indirect measures as the quantitative insulin sensitivity check (QUICKI) and homeostasis model assessment (HOMA), we have observed that oral estrogen may cause a worsening of IR parameters in obese postmenopausal women with MBS,³⁰ while the effects of transdermal estrogen were neutral. Concomitant with these findings, oral estrogen led to an increased leptin/adiponectin ratio, while with transdermal E₂ leptin was unchanged, and there was a significant increase in adiponectin in this obese population where baseline levels were low.³⁰

Although several studies have shown that transdermal estrogen does not decrease IGF-1, as compared with oral estrogen, at least one study found that higher levels of transdermal E₂ may suppress IGF-1 as much as does oral estrogen.³¹ Thus, one must once again use caution in interpreting these metabolic studies, in that they are influenced by many factors, as stated above.

Do Progestogens Have an Influence?

The effects of progestogen added to estrogen have not been adequately studied in terms of changes in lean and fat mass. In the case of IR, it is clear that higher doses of progestogen, particularly when used alone, can result in IR or can at least impede insulin sensitivity. However, as supported by data from HERS and the WHI,^{24,25} lower doses (such as MPA 2.5 g) in combination with CEE 0.625 mg have been shown to improve or decrease IR. In the body composition sub-study of the WHI,²² fat mass decreased with doses of 0.625/2.5mg as well. Recent data from the HOPE study of lower doses of CEE and MPA³² showed that the hormonal preparations tended to prevent weight gain over 2 years, compared to the placebo group; these findings are similar to older data.³³ The highest dose of estrogen alone (0.625 mg), however, tended to increase body fat, while CEE 0.625 mg plus MPA 2.5 decreased fat mass. The overall conclusion of this report was that lower-dose combination

treatment for 2 years does not affect body composition. One might envision that there may be some beneficial synergy with oral therapy when lower doses of progestogen are combined with estrogen. Clearly, much more work is needed in this area of investigation.

Summary and Conclusions

Important body fat accumulation occurs at menopause, probably preceding the final menstrual period. Adipocytokine changes (first, an increase in leptin and then, a decrease in adiponectin), enhancing CV risk and IR. These changes may be viewed as setting up a vicious cycle of increased abdominal fat gain, and liberation of adipocytokines and FFA with resultant IR, which further enhances fat gain. At the same time, lean body mass decreases with aging. Estrogen has direct effects on adipose tissue through ER α , resulting in important effects on body composition; therefore, ET after menopause tends to decrease abdominal fat mass. Indirect effects of estrogen on body composition are also operative and relate to an amelioration of IR as well as other changes. While in certain women transdermal estrogen results in better body composition changes when compared to oral therapy, these results are mixed and confusing. Moreover, data on added progestogen have not been well studied, although lower doses of E+P do not appear to have a detrimental effect on weight gain or body fat accumulation, and may actually contribute to reduced abdominal fat. ■

Rogério A. Lobo, MD, is Professor of Obstetrics and Gynecology at Columbia University College of Physicians and Surgeons, New York, NY.

The author reports no potential conflicts related to the content of this article.

References

1. Seidell JC, Perusse L, Despres JP, et al. Waist and hip circumferences have independent and opposite effects on cardiovascular disease risk factors: the Quebec Family Study. *Am J Clin Nutr* 2001;74:315-21.
2. Tanko LB, Bagger YZ, Alexandersen P, et al. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation* 2003;107:1626-31.
3. Tanko LB, Bagger YZ, Alexandersen P, et al. Central and peripheral fat mass have contrasting effect on the progression of aortic calcification in postmenopausal women. *Eur Heart J* 2003;24:1531-37.
4. Rexrode KM, Carey VJ, Hennekens CH, et al. Abdominal adiposity and coronary artery disease in women. *JAMA* 1999;281:2284-85.

5. Toth MJ, Tchernof A, Sites CK, et al. Menopause-related changes in body fat distribution. *Ann NY Acad Sci* 2000;904:502-06.
6. Lindberg UB, Crona N, Silfverstolpe G, et al. Regional adipose tissue metabolism in postmenopausal women after treatment with exogenous sex steroids. *Horm Metab Res* 1990;22:345-51.
7. Pedersen SB, Kristensen K, Hermann PA, et al. Estrogen controls lipolysis by up-regulating alpha2A-adrenergic receptors directly in human adipose tissue through the estrogen receptor alpha. Implications for the female fat distribution. *J Clin Endocrinol Metab* 2004;89:1869-78.
8. Kristensen K, Pedersen SB, Vestergaard P, et al. Hormone replacement therapy affects body composition and leptin differently in obese and non-obese postmenopausal women. *J Endocrinol* 1999;163:55-62.
9. Haarbo J, Marslew U, Gotfredsen A, et al. Postmenopausal hormone replacement therapy prevents central distribution of body fat after menopause. *Metabolism* 1991;40:1323-26.
10. Sowers M, Zheng H, Tomey K, et al. Changes in body composition in women over 6 years at midlife: ovarian and chronological aging. *J Clin Endocrinol Metab* 2007;92:895-901.
11. Yeckel CW, Dziura J, DiPietro L. Abdominal obesity in older women: potential role for disrupted fatty acid reesterification in insulin resistance. *J Clin Endocrinol Metab* 2008;93:1285-91.
12. Chu MC, Cosper P, Orzio F, et al. Insulin resistance in postmenopausal women with metabolic syndrome and the measurements of adiponectin, leptin, resistin, and ghrelin. *Am J Obstet Gynecol* 2006;194:100-04.
13. Kotani K, Sakane N. Leptin-to-adiponectin ratio as a new marker associated with metabolic disease. *Nippon Rinsho* 2006;64(Suppl 9): 540-43.
14. Kumagai S, Kishimoto H, Masatakasuwa ZB. The leptin to adiponectin ratio is a good biomarker for the prevalence of metabolic syndrome, dependent on visceral fat accumulation and endurance fitness in obese patients with diabetes mellitus. *Metab Syndr Relat Disord* 2005;3:85-94.
15. Oda N, Imamura S, Fujita T, et al. The ratio of leptin to adiponectin can be used as an index of insulin resistance. *Metabolism* 2008;57:268-73.
16. Tamakoshi K, Yatsuya H, Wada K, et al. The transition to menopause reinforces adiponectin production and its contribution to improvement of insulin-resistant state. *Clin Endocrinol* 2007;66:65-71.
17. Sowers MR, Wildman RP, Mancuso P, et al. Change in adipocytokines and ghrelin with menopause. *Maturitas* 2008;59:149-57.
18. Douglas, NC, Carmina E, Lobo RA. *Effects of fat distribution and quantity on adipocytokines levels and bone mineral density (BMD) in normal weight early postmenopausal women (abstract)*. Fifty-fifth Annual Meeting of the Society for Gynecologic Investigation, San Diego, CA, March 2008.
19. Norman RJ, Flight IHK, Rees MCP. Oestrogen and progestogen hormone replacement therapy for peri-menopausal and post-menopausal women: weight and body fat distribution.(Cochrane Review). *Cochrane Libr* 2002;1:1-61.
20. Salpeter SR, Walsh JM, Ormiston TM, et al. Meta-analysis: effect of hormone-replacement therapy on components of the metabolic syndrome in postmenopausal women. *Diabetes Obes Metab* 2006;8:538-54.
21. Dieudonne MN, Leneuve MC, Giudicelli Y, et al. Evidence for functional estrogen receptors alpha and beta in human adipose cells: regional specificities and regulation by estrogens. *Am J Physiol Cell Physiol* 2004;286:C655-61.
22. Chen Z, Bassford T, Green SB et al. Postmenopausal hormone therapy and body composition-a substudy of the estrogen plus progestin trial of the Women's Health Initiative. *Am J Clin Nutr* 2005;82:651-56.
23. Lundholm L, Zang H, Hirschberg AL, et al. Key lipogenic gene expression can be decreased by estrogen in human adipose tissue. *Fertil Steril* 2008;90:44-8.
24. Kanaya AM, Herrington D, Vittinghoff E, et al. Glycemic effects of postmenopausal hormone therapy: the Heart and Estrogen/progestin Replacement Study. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 2003;138:1-9.
25. Margolis KL, Bonds DE, Rodabough R, et al. Effect of oestrogen plus progestin on the incidence of diabetes in postmenopausal women: results from the Women's Health Initiative Hormone Trial. *Diabetologia* 2004; 47:1175-87.
26. O'Sullivan AJ, Crampton LJ, Freund J, et al. The route of estrogen replacement therapy confers divergent effects on substrate oxidation and body composition in postmenopausal women. *J Clin Invest* 1998;102: 1035-40.
27. Ho KK, O'Sullivan AJ, Wolthers T, et al. Metabolic effects of oestrogens: impact of the route of administration. *Ann Endocrinol (Paris)* 2003;64:170-7.
28. dos Reis CM, de Melo NR, Meirelles ES, et al. Body composition, visceral fat distribution and fat oxidation in postmenopausal women using oral or transdermal oestrogen. *Maturitas* 2003;46:59-68.
29. Di Carlo C, Tommaselli GA, Sammartino A, et al. Serum leptin levels and body composition in postmenopausal women: effects of hormone therapy. *Menopause* 2004;11:466-73.
30. Chu M, Cosper P, Nakhuda GS, et al. A comparison of oral and transdermal short-term estrogen therapy in postmenopausal women with metabolic syndrome. *Fertil Steril* 2006;86:1669-75.
31. Lissett CA, Shalet SM. The impact of dose and route of estrogen administration on the somatotrophic axis in normal women. *J Clin Endocrinol Metab* 2003;88:4668-72.
32. Thorneycroft H, Lindsay R, Pickar JH. Body composition during treatment with conjugated estrogens with and without medroxyprogesterone acetate: analysis of the women's health, osteoporosis, progestin, estrogen (HOPE) trial. *Am J Obstet Gynecol* 2007;137:e1-7.
33. Espeland MA, Stefanick ML, Tritz-Silverstein D, et al. Effect of postmenopausal hormone therapy on body weight and waist and hip girths. *J Clin Endocrinol Metab* 1997;82:1549-56.