

BODY FAT DISTRIBUTION, THE MENOPAUSE TRANSITION, AND HORMONE REPLACEMENT THERAPY

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SUMMARY - Endocrine changes resulting from the menopause transition dramatically modify women's hormonal milieu. The consequences of these changes not only lead to cessation of reproduction and accompanying symptoms in women, but also dramatically impact long-term health. Loss of estrogen has been associated with the development of cardiovascular disease. Central distribution and accumulation of adipose tissue, and the concomitant insulin resistant dyslipidemic state have emerged as important components of a cluster of metabolic abnormalities that are strongly related to coronary heart disease. Thus, estrogen deficiency may affect cardiovascular disease risk by mediating changes in body fat distribution. This article is an update of the literature in the area of menopause, hormone replacement therapy, and body fat distribution. Cross-sectional studies using anthropometric measurements of abdominal fat distribution most often failed to detect an effect of the menopause transition that was independent of advancing age and degree of obesity. The use of radiologic techniques such as DEXA and computed tomography, however, led to the conclusion that the menopause transition accelerates the selective deposition of intra-abdominal fat. Available longitudinal data also support an increase in central body fatness occurring with menopause. Most intervention trials on hormone replacement therapy and body fat distribution showed that the treatment prevented the increase in central adiposity that was noted in postmenopausal women receiving no treatment or placebo. These results are supported by retrospective studies that showed a lower WHR in hormone users vs non-users. Mechanisms potentially explaining the menopause-related acceleration in abdominal fat accumulation include changes in regional adipose tissue metabolism in the face of a positive energy imbalance. As some inconsistencies were found among studies, further investigations using longitudinal and intervention designs, as well as more precise methodologies to measure body fat distribution, are needed to clearly establish the effects of menopause and hormone replacement on abdominal body fat distribution and the concomitant increase in cardiovascular disease risk.


Key-words: menopause, hormone replacement therapy, estrogen, androgen, regional fat metabolism, abdominal adipose tissue, cardiovascular disease risk.

RÉSUMÉ - **Distribution des graisses corporelles, ménopause et traitement hormonal substitutif.**

Les changements endocriniens liés à la ménopause modifient considérablement l'environnement hormonal de la femme. Les conséquences de ces changements, outre l'arrêt des fonctions de reproduction et les symptômes fonctionnels de la ménopause, sont considérables sur la santé à long terme. La perte de la sécrétion œstrogénique est associée au développement de maladies cardio-vasculaires. La distribution centrale et l'accumulation de tissu adipeux et l'état concomitant de dyslipidémies et d'insulinorésistance apparaissent comme des composants importants d'un cortège d'anomalies métaboliques fortement corrélées à la coronaropathie. Ainsi, la carence œstrogénique peut influencer le risque cardio-vasculaire en induisant des changements dans la distribution des graisses corporelles. Cet article fait le point de la littérature dans le domaine de la ménopause, du traitement hormonal substitutif et la distribution des graisses corporelles. Des études transversales faisant appel à des mesures anthropométriques de la distribution des graisses abdominales n'ont pas le plus souvent mis en évidence d'effet de la ménopause, indépendamment de l'âge et du degré d'obésité.

Cependant, l'utilisation de techniques radiologiques comme la DEXA et le scanner a permis de conclure que la ménopause accélère le dépôt sélectif de graisse au niveau intra-abdominal. Les données longitudinales disponibles à ce jour sont également en faveur d'une augmentation de l'adiposité centrale lors la ménopause. La plupart des études d'intervention par traitement hormonal substitutif ont montré que le traitement permet de prévenir l'augmentation de l'adiposité centrale notée chez les femmes post-ménopausiques traitées par placebo ou sans traitement. Ces données sont également corroborées par des études rétrospectives qui montrent un rapport taille sur hanche plus faible chez les femmes sous traitement hormonal par rapport aux femmes non traitées. Les mécanismes potentiels pouvant expliquer l'accélération de l'adiposité abdominale pendant la ménopause comprennent des changements dans le métabolisme régional du tissu adipeux dans le cadre d'une balance énergétique positive. Dans la mesure où des données contradictoires ont été publiées, des études complémentaires longitudinales ainsi que des études d'intervention, recourant à des méthodologies plus précises pour mesurer la distribution adipeuse corporelle, sont nécessaires pour établir clairement les effets de la ménopause et du traitement hormonal substitutif sur la distribution des graisses abdominales et sur l'augmentation concomitante du risque cardio-vasculaire.

Mots-clés : ménopause, traitement hormonal substitutif, œstrogène, androgène, métabolisme régional des graisses, tissu adipeux abdominal, risque cardio-vasculaire.

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The menopause is the permanent cessation of menstrual cyclicity and reproductive function [1, 2]. Clinically, menopause is defined as the absence of menses for at least 6 months to a year, and the time at which menopause occurs is determined retrospectively as the final menstruation [3]. Although there is no precise criteria available to identify the perimenopause [4], this period, which occurs in the few years preceding menopause, is characterized by progressive alterations in endocrine and reproductive functions ultimately leading to termination of reproductive life [1, 3].

The primary endocrine event triggering the hormonal changes of the menopause transition has yet to be clearly identified, as it is unclear whether menopause results from exhaustion of ovarian follicles or from alterations in the neurochemical signals from the hypothalamus [5]. Nevertheless, endocrine changes resulting from this transition dramatically modify women's hormonal milieu. These changes include a progressive loss of ovarian function leading to a reduction of estrogen, progesterone, and inhibin secretion [1, 3, 6]. As the result of a reduced feedback from the ovaries, there is an increase in the secretion of both follicle stimulating hormone (FSH) and luteinizing hormone (LH) [1, 7]. On the other hand, androgen production from the ovary appears to be less affected by menopause [3] and the adrenal gland continues to secrete large amounts of precursor steroids such as dehydroepiandrosterone-sulfate (DHEA-S) and androstenedione, which can be converted into androgens and/or estrogens by peripheral tissues [3, 8]. The conversion of these precursor steroids to estrone by adipose tissue is considered as the major source of estrogen in postmenopausal women [9, 10]. These modifications alter the ratios of estrone to estradiol, and of androgens to estrogens, which are both increased in postmenopausal women [3, 10].

Consequences of the hormonal changes of the menopause not only lead to cessation of reproduction and accompanying symptoms in women, but also dramatically impact long-term health. Loss of estrogen has been associated with the development of chronic diseases such as osteoporosis and cardiovascular disease [11]. An increase in cardiovascular disease risk occurs in women in the fifth decade, corresponding with the onset of menopause [12].

In recent years, central distribution and accumulation of adipose tissue, and the concomitant insulin resistant dyslipidemic state have emerged as important components of a cluster of metabolic abnormalities that are strongly related to coronary heart disease [13-15]. Therefore, it has been suggested that estrogen deficiency may affect cardiovascular disease risk by mediating changes in body fat distribution. We have previously reviewed available literature on body fat distribution, the menopause-related estrogen defi-

ciency, and the use of hormone replacement therapy [16, 17]. This article is an update of the literature in this area.

■ IMPORTANCE OF BODY FAT DISTRIBUTION

Obesity is a heterogeneous condition with respect to its relationship to metabolic complications. In this regard, a growing body of evidence suggests that body fat distribution is a critical factor in the relationship between obesity and cardiovascular disease. Accumulation of fat in the abdominal region has been associated with an increased risk of developing cardiovascular disease and related mortality [18-25], whereas the gynoid type of obesity (with fat located in the femoral region), has been suggested to be metabolically benign and some investigators have even suggested that it could be a marker of a cardioprotective metabolic risk profile [26, 27].

Most studies have relied on the waist-to-hip ratio (WHR) to estimate the accumulation of adipose tissue in the abdominal region [28]. The waist circumference and sagittal diameter have also been used as anthropometric surrogates for abdominal obesity [29, 30]. With the development of imaging techniques such as computed tomography and magnetic resonance imaging, it is now possible to accurately quantify visceral fat. By performing a single cross-sectional scan at the abdominal level, usually between L4 and L5 vertebrae, these imaging techniques distinguish adipose tissue located in the abdominal cavity from the subcutaneous adipose tissue depot [31-33].

Using the various methods available to measure body fat distribution, abdominal or visceral obesity in both pre- and postmenopausal women has been associated with a dyslipidemic state which includes hypertriglyceridemia, hypoalphalipoproteinemia, a reduced HDL₂-Cholesterol to HDL₃-Cholesterol ratio, elevated apolipoprotein B concentration, a greater proportion of small, dense LDL particles and an increased LDL-cholesterol to HDL-Cholesterol ratio [34-39]. This condition is also associated with hyperinsulinemia resulting from an insulin resistant state [37, 40-42] and an increased 5-year risk of death [25]. Thus, irrespective of hormonal status, it appears that visceral obesity has been associated with an altered cardiovascular disease risk factors profile in women.

Recent reports from the Quebec Cardiovascular Study have suggested that the cluster of metabolic abnormalities associated with abdominal obesity mediates a substantial increase in the risk of cardiovascular disease of visceral obese patients [43-46]. These results demonstrated that elevated plasma apolipoprotein B levels [43, 44], elevated fasting insulin levels [44], and small, dense LDL particles [45], which are common features of visceral obesity, are significant risk factors for ischemic heart disease. A recent analy-

sis of the Quebec Study cohort showed that, according to previous studies, men with elevated LDL-cholesterol and triglyceride levels and reduced HDL-cholesterol concentrations had a 5.2 fold increase in IHD risk compared to men with normal lipids. However, the use of nontraditional risk factors such as elevated insulin and apolipoprotein B levels and dense LDL particles predicted a more than 20 fold increase in ischemic heart disease risk [46]. The strength of the relationship between nontraditional risk factors and ischemic heart disease risk was not affected by adjustment for traditional risk factors. Although this study was performed in men, the results emphasize the ability of features of the insulin resistant-dyslipidemic state of visceral obesity to identify individuals at risk for cardiovascular disease [46].

The nature of the relationship between cardiovascular disease risk factors and abdominal visceral obesity has not been clearly established. However, adipose cells from the abdominal cavity have been shown to be highly lipolytic, and poorly inhibited by insulin, compared to adipocytes from other fat depots [47, 48]. From these findings, it has been proposed that adipose tissue located inside the abdominal cavity releases high levels of fatty acids, which are drained by the portal circulation to the liver, which would in turn impair hepatic metabolism and lead to the metabolic complications of obesity [49]. Although this hypothesis awaits direct experimental confirmation, there is a growing body of supporting evidence. High free fatty acid levels have been associated with reduced hepatic clearance of insulin [50, 51]. This increased availability of lipids in the liver also leads to a reduced degradation of apolipoprotein B and to an increased production of triglyceride-rich lipoproteins (very-low density lipoproteins) by the liver [52]. Elevated levels of free fatty acids also contribute to stimulate hepatic glucose production, which may partially explain altered glucose tolerance of visceral obese patients [15]. Lipoprotein lipase (LPL) activity measured in post-heparin plasma has been reported to be lower in visceral obese women [53]. This reduced LPL activity also contributes to the increased apolipoprotein B containing lipoprotein concentration and to elevated triglyceride concentrations observed in this condition. High triglyceride levels favor an increased lipid transfer by cholesteryl-ester transfer protein (CETP). The activity of this enzyme leads to relative depletion of LDL and HDL particles in cholesterol ester and to their triglyceride enrichment. Since the enzyme hepatic triglyceride lipase has an increased activity in visceral obesity [15], triglyceride-rich LDL and HDL particles are submitted to hydrolysis by this enzyme, which generates small, dense LDL particles as well as cholesterol depleted HDL particles, especially in large HDL₂ particles subfraction. Therefore, it is possible that the increased free fatty acid flux to the liver resulting from the highly lipolytic intra-abdominal adipose cells ex-

plains part of the dyslipidemic and hyperinsulinemic state commonly observed in visceral obesity. It may contribute to increase triglyceride-rich lipoprotein production and to reduce their catabolism in the plasma, whereas it may exacerbate the hyperinsulinemia of insulin resistance. The etiology of the insulin resistance state of visceral obesity is still poorly understood and it is unclear at present whether it mainly results from an increased visceral fat accumulation, or whether visceral obesity is a marker of neuroendocrine abnormalities also leading to insulin resistance [54].

■ MENOPAUSE TRANSITION AND BODY FAT DISTRIBUTION

Studies that examined the effect of the natural menopause on body fat distribution will be reviewed in this section. Both longitudinal and cross-sectional approaches have been used to study the effects of the menopause transition on body fat and body fat distribution. The most rigorous approach to examine the effects of the menopause transition is the longitudinal design, which involves a follow-up of women as they traverse the menopause. However, because these studies are very difficult to perform, most studies examining the effects of the menopause on body fat distribution have been cross-sectional. In this latter type of design, groups of women with different menopausal status are compared, and the possible confounding effects of age and degree of obesity are accounted for using statistical approaches. Results of cross-sectional studies on the topic have been somewhat equivocal, as some inconsistencies were reported. In a recent analysis of these publications [16], we concluded that discrepancies could be attributed to the various methods used for the measurement of body fat distribution, such as circumference measures, dual x-ray absorptiometry, or computed tomography.

In studies where the WHR was used as a surrogate of abdominal obesity, no effect of the menopause on body fat distribution was found when statistical adjustment for potential confounding variables such as the degree of obesity and age was performed [55-62]. Similarly, studies using waist circumference also failed to detect a significant age- and BMI-adjusted effect of the menopause [60-64].

Dual x-ray absorptiometry can also be used to measure the proportion of fat located in the trunk region. Although this technique does not differentiate subcutaneous from intra-abdominal adipose tissue compartments, a significant effect of the menopause transition on body fat distribution that was independent of age [65, 66] and total fatness [67, 68] was reported in studies in which this methodology was used. Similarly, a recent study by Gambacciani and colleagues [69] examined dual X-ray absorptiometry-measured trunk fat in a sample of 380 premenopausal,

263 perimenopausal, and 432 postmenopausal women. Both perimenopausal women (menstrual bleeding at 35 to 90 days intervals) and postmenopausal groups had higher total and central body fat compared to premenopausal women. This effect of the menopause was also observed in subgroups of 63 women matched for age and BMI. These results suggest that an increase in abdominal fat accumulation can be observed even during the perimenopausal period [69].

Studies using the current gold standard measure for body fat distribution (computed tomography), to examine subcutaneous and intra-abdominal adipose tissue areas also found an effect of the menopause transition on body fat distribution that was significant, after controlling for BMI [62] or age [70]. In a study by Kotani *et al.* [70], a steeper regression line for the association between visceral adipose tissue area and age was found in postmenopausal women, suggesting that the accumulation of visceral adipose tissue with age was accelerated after menopause [70].

Recent results from our laboratory also support an increase in intra-abdominal adipose tissue accumulation with the menopause. In that study, Toth and colleagues [71] compared computed tomography measured intra-abdominal adipose tissue areas in middle-aged pre- and early postmenopausal non-obese women. The study of women that were close to the menopause transition as well as matching analyses allowed for a rigorous comparison of the effects of menopause, independent of the confounding effects of age and fatness. It was found that postmenopausal women had significantly more intra-abdominal adipose tissue compared to premenopausal women, independent of age and total fat mass [71].

It should be pointed out that a few studies using radiologic techniques reported no significant effect of the menopause on abdominal fat accumulation. Magnetic resonance imaging has been used in a study by Schreiner *et al.* [72], and it was concluded that menopause did not accelerate intra-abdominal fat accumulation. Women had higher intra-abdominal fat with increasing body weight in the same proportion before, and after the menopause. Negative results were also obtained in another study, from Wang and colleagues [73], in which the association between age and the proportion of trunk fat was stronger than the relationship between time since menopause and the proportion of trunk fat. This result suggests that there is no independent effect of the menopause transition on body fat distribution. In these two studies, however, a very small number of postmenopausal women [72], or no postmenopausal women [73] were studied.

Only a few studies have examined the effects of the menopause transition on body fat distribution in a longitudinal design [74, 75]. This is attributable to the fact that these studies are more difficult to perform because of costs and subject retention over several years of follow-up. Two 6 year-longitudinal studies

where women who changed their menopause status were compared to those who remained premenopausal over follow-up are available. In the study by Poehlman and colleagues [75], 18 women became postmenopausal over the follow-up, while 17 remained premenopausal. Significant increases in WHR were noted only in women who changed their menopause status. Similarly, in the study by Björkelund *et al.* [74], the 208 women who changed their menopause status over follow-up had a greater increase in WHR compared to the 60 women who remained premenopausal. On average, the change in WHR was two-fold higher in women who became postmenopausal compared to women who remained premenopausal [74, 75].

In summary, the discrepancies among previous cross-sectional studies appear to be related to the methodology used for the measurement of body fat distribution and the confounding effect of age [16]. Studies using anthropometric measurements (WHR, waist circumference) most often failed to detect an effect of the menopause transition that was independent of age and/or BMI. On the other hand, the use of radiologic techniques, such as DEXA and computed tomography, led to the conclusion that the menopause transition accelerates the selective deposition of intra-abdominal fat. More importantly, available longitudinal data also support an increase in central body fatness occurring with menopause. As some inconsistencies were found among studies, further investigations using longitudinal designs and more precise methodologies to measure body fat distribution are needed to clearly establish the effects of the natural menopause transition.

■ HORMONE REPLACEMENT THERAPY AND BODY FAT DISTRIBUTION

Several cross-sectional and longitudinal studies used a retrospective approach to examine the effects of hormone replacement therapy on body fat distribution. In these studies, hormone users were compared to nonusers. Although this type of design can provide useful information on the effects of hormone replacement therapy, the possibility cannot be ruled out that observed differences may be attributable to a study bias where more health conscious and more healthy women may have chosen hormone replacement thereby exaggerating the effects of hormone replacement.

In two studies by den Tonkelaar and colleagues [55, 57], use of estrogen (estriol and estradiol valerate, oral or vaginal) was associated with a lower WHR, although the difference was lost after adjustment for age in one of these studies [57]. Results from two other reports [61, 76] with very large sample sizes (44,487 and 40,980 women respectively), showed that women who were receiving hormone replacement

therapy had a lower self-reported WHR compared to past or never users [61, 76]. In one of these studies [61], no association was found with either the type of therapy (unopposed estrogen and combined estrogen and progesterone) or the duration of therapy [61]. A study by Perry and colleagues [77] recently showed lower WHR and waist circumference values in women receiving conjugated estrogens daily and cyclic medroxyprogesterone acetate. In contrast, Heiss and colleagues [78] reported no significant difference in WHR or dual x-ray absorptiometry-measured trunk fat between hormone users and nonusers. These results were observed despite a significantly more androgenic hormonal profile (higher testosterone to SHBG ratio) in postmenopausal women not using estrogen. As suggested by the investigators, this finding may be explained by the small sample size (52 women). A small number of estrogen users were also examined in the longitudinal study by Björkelund *et al.* [74]. In this study, early postmenopausal women taking estrogen replacement had lower WHR values compared to non-users, but no difference was found in older postmenopausal women, suggesting that estrogen use may delay the abdominal fat accretion associated with menopause. In another prospective/cross-sectional study from Kritz-Silverstein and Barrett-Connor [79], continuous hormone replacement therapy users and intermittent hormone therapy users were compared to women who never used hormone replacement. It was found that hormone use, either continuous or intermittent had no effect on WHR. No relationship was found between WHR at follow-up, estrogen use, or years of estrogen use [79].

The effects of different hormone therapy regimens on body fat distribution have also been examined in a few intervention studies [80-84]. In these five studies, body fat distribution was measured either by anthropometry, dual x-ray absorptiometry, or dual photon absorptiometry [80-83], with treatment regimen ranging from 1 to 3 years of duration. On average, a 6.5% increase in central adiposity was noted in placebo or control groups. In four studies, the various combinations of estrogens used in treatment groups prevented the increase in abdominal adiposity that was noted in the control or placebo groups, whereas small or no changes were noted in treatment groups [80-83]. In contrast, the study by Aloia *et al.* [84] found no effect of combined estrogen and medroxyprogesterone replacement therapy on trunk/extremity fat ratio measured by DEXA.

In a recent study, Kohrt and colleagues [85] examined changes in body composition and body fat distribution in response to hormone replacement therapy alone (conjugated estrogens and medroxyprogesterone) or in combination with exercise. The study included an 12-month treatment period and a 6-month post-treatment follow-up examination. Although women receiving exercise alone or hormone and ex-

ercise treatment had a similar reduction in waist circumference after 12 months, women on hormone and exercise had a lower 6-month post-treatment waist circumference compared to women on exercise treatment alone. This suggests that hormone replacement may also be used as an efficient adjunct to exercise in preventing menopause-induced changes in body fat distribution [85].

In summary, most intervention trials on hormone replacement therapy and body fat distribution showed that the treatment prevented the increase in central adiposity that was noted in postmenopausal women not receiving treatment [80-83, 85]. In all studies but one, significant effects were observed with the use of various estrogens and progesterone regimens. Results of intervention studies are supported by retrospective studies that showed a lower WHR in hormone users vs non-users [55, 57, 61, 76]. Taken together, these results suggest that hormone replacement prevents or delays the increase in abdominal adipose tissue accumulation observed at menopause. However, more studies are needed to establish whether the various compartments of abdominal adipose tissue are affected differently by hormone replacement therapy.

■ PHYSIOLOGICAL MECHANISMS

Overall, the studies reviewed above on menopause transition and hormone replacement therapy suggest a significant effect of menopause-induced hormonal changes on body fat distribution. More specifically, estrogen deficiency appears to accelerate abdominal fat accumulation. From a hormonal standpoint, the menopause transition induces dramatic reductions in estrogen levels, whereas the adrenal glands continue to secrete androgen precursors [3, 7, 10]. In this regard, several cross-sectional studies have shown evidence that the intracrine conversion of these inactive steroid precursors to estrogens is likely to occur in adipose tissue [86-88]. Similarly, a study by O'Brien *et al.* [89] recently demonstrated that the estrone content of adipose tissue was correlated with the menstrual cycle in premenopausal women, but with body mass index in postmenopausal women. Thus it is likely that postmenopausal hormone metabolism is significantly modulated by the size of the adipose tissue organ [9, 86-89].

On the other hand, abdominal adiposity has been associated with a more androgenic profile, namely increased free testosterone levels and lower sex-hormone binding globulin in pre- and postmenopausal women [90, 91]. The dramatic modifications in the dynamics of estrogens, free androgens, and SHBG, or the relative androgenicity, have been suggested to be responsible for changes in body fat distribution during this period [35]. Reports by Rebuffé-Scrive and colleagues [92, 93] showed that menopausal women have lower lipoprotein lipase (LPL) activity in femoral adi-

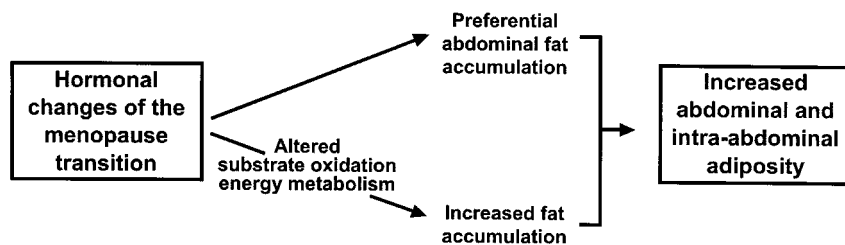


FIG. 1. Potential mechanisms explaining menopause-related increases in abdominal and intra-abdominal adiposity.

pose tissue compared to premenopausal women, whereas abdominal LPL activity is not different. These results are concordant with a shift of adipose tissue accumulation from the gluteal-femoral to the abdominal area [92, 94]. Accordingly, hormonal treatment either with unopposed estrogen or combined estrogen and progestin stimulated LPL activity in the femoral region [93], which suggests that estrogen, or estrogen deficiency, directly influences regional adipose tissue metabolism. More recently, a study by Price and colleagues [95] showed that transdermal estradiol treatment significantly decreased adipose tissue LPL activity, and that this phenomenon was attributable to post-transcriptional modification of protein levels. Evidence is also available to suggest that androgens regulate adipose tissue metabolism in studies of men and rats, in which testosterone treatment inhibited adipose tissue LPL activity and stimulated lipolysis [96-98]. Taken together, these observations suggest that hormonal changes of the menopause may lead to body fat distribution changes by affecting regional adipose tissue metabolism (Fig. 1).

Changes in the various components of energy expenditure have also been suggested to play an important role in the increased overall and central adiposity of women undergoing the menopause transition. As demonstrated in the study by Poehlman and colleagues [75], women who became postmenopausal had significantly greater reductions in resting metabolic rate (≈ 100 kcal/d) than women who remained premenopausal. Reported physical activity levels were also lower in women who became menopausal (≈ 127 kcal/d) than women who remained premenopausal [75]. Such decreases in resting metabolic rate and physical activity have been suggested to result partly from reduced fat-free mass [75]. It is important to emphasize that a reduced energy expenditure with no change or increases in energy intake will place women in positive energy balance, which will increase total fatness and possibly central adiposity (Fig. 1).

Changes in fat oxidation may also partly explain the menopause-induced changes in body fat and body fat distribution. In addition to a low resting metabolic rate [99], reduced fat oxidation predicts fat gain in older individuals [100, 101]. Maintenance of body composition requires that individuals attain both energy balance (energy intake = energy expenditure) and

macronutrient balance. Macronutrient balance is achieved when an equilibrium between intake and oxidation of protein, carbohydrate and lipid is attained. Protein and carbohydrate balances are tightly regulated by mechanisms which couple intake to oxidation [101]. In contrast, changes in fat intake do not result in compensatory adjustments in oxidation. Thus, an increase in fat intake or a decrease in fat oxidation may promote an increase in total and intra-abdominal fat [100-102] in postmenopausal women. Accordingly, evidence suggests that preferential carbohydrate oxidation predicts weight gain in various populations [103]. Loss of estrogen may be associated with reduced fat oxidation and a greater reliance on carbohydrate stores (Fig. 1). Although a recent study by O'Sullivan suggested that oral estrogen treatment reduces fat oxidation [104], preliminary evidence from our laboratory showed that the respiratory quotient (RQ) increased in women who became postmenopausal after a 6-yr follow-up, whereas it did not change in women who remained premenopausal (Fig. 2, Poehlman *et al.* unpublished results). This finding suggests that the menopause may shift fuel utilization towards a greater reliance on carbohydrate oxidation and nonoxidative disposal of fatty acids. Although the mechanism(s) underlying shifts in sub-

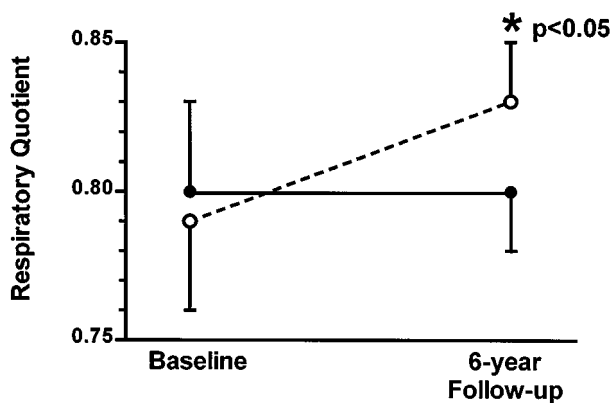


FIG. 2. Changes in respiratory quotient observed in the 6-year follow-up of 38 women. Dotted lines, women who became postmenopausal; solid lines, women who remained premenopausal. Poehlman *et al.* unpublished results.

strate oxidation with menopause are unknown, the menopause-related loss of fat-free mass may contribute to this phenomenon. We have shown a decrease in fat oxidation with advancing age, that was partially explained by the decrease in fat-free mass [102].

Previous findings suggest that the menopause transition may be a period where energy and expenditure and substrate utilization are dysregulated. Potential mechanisms for the effects of menopause on energy metabolism include possible effects of circulating estrogens and/or androgens on fat free mass and changes in food intake induced by estrogen deficiency. Whether there is a direct effect of estrogen on energy expenditure and on the respiratory quotient remains unclear at present.

CONCLUSIONS

Careful examination of available studies on body fat distribution and menopause suggests that menopause is associated with an acceleration in the accumulation of abdominal adipose tissue, and most likely, intra-abdominal fat. Cross-sectional studies in which adequate methodology was used to measure body fat distribution such as computed tomography for visceral adipose tissue or dual x-ray absorptiometry for total abdominal fat have reported higher accumulations of abdominal and intra-abdominal fat in postmenopausal women. These results are further supported by longitudinal studies and hormone replacement studies, in which the menopause-induced redistribution of fat was prevented by hormone replacement. However, additional longitudinal studies using adequate methodology to assess body fat distribution are clearly required. Given the central role of body fat distribution in the association between obesity and risk factors for cardiovascular disease, it is possible that some of the adverse effects of menopause are mediated through increased abdominal (and intra-abdominal) fat accumulation in postmenopausal women. Thus, as suggested previously [85, 105], intervention strategies aimed at reducing intra-abdominal fat accumulation such as increased physical activity and adherence to a diet promoting a negative energy balance are likely to provide beneficial health outcomes in the postmenopausal years. This hypothesis will also require experimental testing in a randomized trial.

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