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The Emergence of the Metabolic Syndrome with Menopause

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Women with the metabolic syndrome (central obesity, insulin resistance, and dyslipidemia) are known to be at especially high risk for cardiovascular disease (CVD). The prevalence of the metabolic syndrome increases with menopause and may partially explain the apparent acceleration in CVD after menopause. The transition from pre- to postmenopause is associated with the emergence of many features of the metabolic syndrome, including 1) increased central (intraabdominal) body fat; 2) a shift toward a more atherogenic lipid profile, with increased low density lipoprotein and triglycerides levels, reduced high density lipoprotein, and small, dense low density lipoprotein particles; 3) and increased glucose and insulin levels. The emergence of these risk factors may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency. It is unclear whether the transition to menopause increases CVD risk in all women or only those who develop features of the metabolic syndrome. This article will review the features of the metabolic syndrome that emerge with estrogen deficiency. A better understanding of these metabolic changes with menopause will aid in the recognition and treatment of women at risk for future CVD, leading to appropriate interventions. (*J Clin Endocrinol Metab* 88: 2404–2411, 2003)

THE RECENT RELEASE of data from the Women's Health Initiative has forced practitioners to reconsider their options for prevention of cardiovascular disease (CVD) in postmenopausal women (1). CVD risk increases after the menopause, which may be related to the substantial metabolic changes that occur as women transition from premenopause to postmenopause. In many women features of the metabolic syndrome (abdominal adiposity, insulin resistance, and dyslipidemia) emerge with estrogen deficiency. The aim of this article is to review the influence of menopause on the emergence of this constellation of cardiovascular risk factors known as the metabolic syndrome. A better understanding of these metabolic changes with menopause may help in the recognition of women at risk for future cardiovascular disease, leading to appropriate interventions.

Menopause

Menopause is best defined as the absence of menses for 12 consecutive months. Menstrual history is the most reliable indicator of the postmenopausal state, as specific hormonal measures, such as estradiol (E_2) and FSH levels both vary widely in the perimenopause during an individual menstrual cycle (2). The perimenopause has been defined as a period of menstrual irregularity and hormonal variability, beginning when menstrual cycle length changes from an established pattern into longer, shorter, or more variable cycles, with an average duration of 4 yr, ending 1 yr after the final menstrual period. This means that women can expect to have menstrual irregularities for approximately 4 yr before their final menses. Although it is commonly believed that E_2 levels fall gradually throughout the perimenopause, concentrations are preserved until relatively late in the perimenopausal period, as E_2 does not decline significantly until women experience at least 3 months of amenorrhea (2).

Cardiovascular disease (CVD) risk after menopause

CVD is the primary cause of death in women of westernized countries, with more than one in two women dying from CVD. However, atherosclerotic disease occurrence is distinct in men and women, as onset begins approximately 10 yr later in women than men, and myocardial infarction is uncommon until women reach their sixth decade (3). Premenopausal women appear to be protected from CVD compared with men of similar age. Although women below the age of 50 yr rarely develop CVD, by age 70 yr the incidence of CVD is equal in men and women, suggesting that estrogen deficiency causes a rapid acceleration in CVD risk.

Controversy exists about whether menopause increases the risk of CVD independent of normal aging. Some studies have demonstrated increased risk of CVD after menopause, and others have not (4). For example, Framingham investigators found a 4-fold increase in CVD in the 10 yr following natural menopause. Premature, surgically induced menopause has been shown to increase the risk for CVD (4). Yet the question of whether natural menopause is an independent risk factor for CVD has not been answered, as it is very difficult to design studies that can separate the effects of the normal aging process from menopause. Statistical adjustment for age or body weight in longitudinal studies may erase the influence of other closely related factors and underestimate the effect of estrogen deficiency on CVD risk. The metabolic and hormonal changes of menopause occur

Abbreviations: apo B, Apolipoprotein B; BMI, body mass index; CETP, cholesteryl ester transfer protein; CRP, C-reactive protein; CT, computed tomography; CVD, cardiovascular disease; E_2, estradiol; FFA, free fatty acid; HDL, high density lipoprotein; HL, hepatic lipase; HRT, hormone replacement therapy; LDL, low density lipoprotein; Lp(a), lipoprotein(a); PAI-1, plasminogen activator inhibitor-1; TG, triglycerides; tPA, tissue plasminogen activator; VLDL, very low density lipoprotein.

over several years and vary widely among women. Also, CVD risk factors may be predictors of early menopause. Finally, it may be that estrogen deficiency increases CVD risk in only a subset of women who develop features of the metabolic syndrome, and this subset has not been well studied.

Studies assessing the relationship of menopause with measures of atherosclerosis have yielded interesting results. Sutton-Tyrrell *et al.* (5) showed that 45% of postmenopausal women (n = 294) had clinically significant carotid intima-media thickness (≥0.75 mm) compared with 16% of age-matched premenopausal women. Carotid intima-media thickness has been shown to be a strong predictor of CVD risk (6). Aortic calcification, a measure of atherosclerosis, was higher in postmenopausal women, and the extent of calcification increased with the number of postmenopausal years (7). Similarly, coronary artery calcium deposits in women, measured by computed tomography (CT), was half that in men until the age of 60 yr, when the difference decreased (8).

The relative importance of factors that influence cardiovascular risk in postmenopausal women are unknown. Alterations in lipid metabolism with estrogen deficiency are thought to be a substantial component of CVD risk in postmenopausal women (9), but there are also direct effects of estrogen deficiency on body fat distribution (central obesity), insulin action, the arterial wall, and fibrinolysis that may influence cardiovascular risk. These factors contribute to an increased prevalence of the metabolic syndrome in postmenopausal women compared with premenopausal women (10), and this postmenopausal worsening of the metabolic profile may contribute to the future risk of CVD.

The metabolic syndrome

The metabolic syndrome has received more focus as the updated Adult Treatment Panel III guidelines emphasize treatment of the metabolic syndrome in addition to lowering of low density lipoprotein (LDL) levels (11). The metabolic syndrome may not be a single disease entity, but, rather, a constellation of closely related risk factors that together convey substantially increased cardiovascular risk after accounting for traditional CVD risk factors (12). The features of the metabolic syndrome include the accumulation of visceral (abdominal) adiposity, insulin resistance, hypertension, and dyslipidemia (hypertriglyceridemia, reduced high density lipoprotein (HDL), and small dense LDL particles; Table 1) (13). The metabolic syndrome is estimated to affect approximately 20–30% of the middle-aged population (10), and prevalence appears to be increasing in the U.S. population with increasing obesity and sedentary lifestyle (14). Postmenopausal status is associated with a 60% increased risk of the metabolic syndrome, even after adjusting for confounding variables, such as age, body mass index (BMI), household income, and physical inactivity (10). The risk of CVD attributed to the metabolic syndrome appears to be especially high in women, and it is estimated that half of all cardiovascular events in women are related to the metabolic syndrome (15).

TABLE 1. Features of the metabolic syndrome

1. Central obesity
2. Insulin resistance
3. Dyslipidemia
   a. Elevated TG
   b. Small dense LDL particles
   c. Reduced HDL
4. High blood pressure
5. Hypercoaguable state
6. Proinflammatory state

Although syndrome X was initially coined by Gerald Reaven in 1988 (16), the features of the metabolic syndrome were first described by Vague (17) and have subsequently been called the insulin resistance syndrome, the central obesity syndrome, and the deadly quartet. Diagnostic criteria for the metabolic syndrome, as defined by the National Cholesterol Education Program Adult Treatment Panel III, are shown in Table 2; these easily obtained measures are useful for classifying patients (11).

The etiology of the metabolic syndrome is unknown, but is thought to be a combination of factors. Selby *et al.* (18) studied 1028 male twins and found greater concordance of dyslipidemic hypertension in monozygotic than dizygotic twins. Within the discordant monozygotic twin pairs, the twin with dyslipidemic hypertension weighed significantly more as an adult, implying an interaction between genetic and environmental influences on the manifestation of the metabolic syndrome (19). Many believe that the underlying pathophysiology of the metabolic syndrome is related to increased visceral obesity and insulin resistance (13).

Effects of menopause on body composition

Two patterns of body fat distribution have been observed, the accumulation of fat centrally, as intraabdominal fat (android or apple shape) and the accumulation of fat in the gluteo-femoral region (gynoid or pear shape; Fig. 1). The accumulation of fat in a central distribution (intraabdominal) has emerged as a cardiovascular risk factor independent of overall obesity (20). Android fat deposition is associated with a higher risk of diabetes, hypertriglyceridemia, small dense LDL particles, hypertension, and CVD (13). Estrogen promotes the accumulation of gluteo-femoral fat (21), and the loss of estrogen with menopause is associated with an increase in central fat (22). The sexual dimorphism in adipose tissue distribution may partially explain the greater CVD risk in men compared with premenopausal women.

Although it is commonly believed that menopause is as-

TABLE 2. Diagnostic criteria for the metabolic syndrome (requiring three or more risk factors)

Risk factor	Defining level
Waist circumference	
Men	>102 cm (>40 inches)
Women	>88 cm (>35 inches)
Triglyceride	≥1.7 mmol/liter (≥150 mg/dl)
HDL	
Men	<1.0 mmol/liter (<40 mg/dl)
Women	<1.3 mmol/liter (<50 mg/dl)
Blood pressure	≥130/≥85 mm Hg
Fasting glucose	≥6.1 mmol/liter (≥110 mg/dl)

Data are from the Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III), *JAMA* 285:2486–2497, 2001.

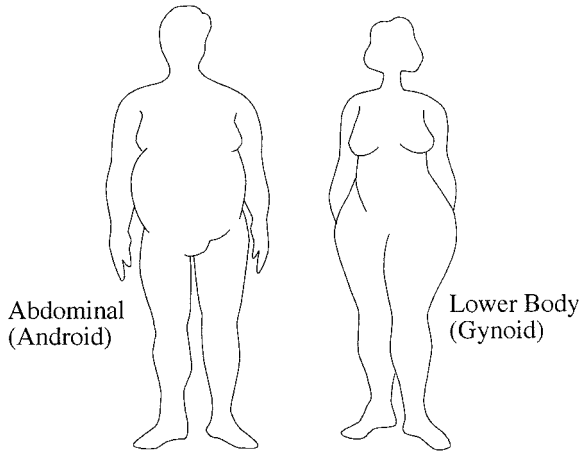

FIG. 1. Patterns of body fat distribution.

sociated with weight gain, most studies do not reveal increases in BMI independent of normal aging (23, 24). Although it is estimated that middle-aged women gain approximately 0.55 kg (~1 lb)/yr, there does not appear to be an independent effect of menopause on body weight (25, 26). However, even in the absence of weight gain, body fat distribution changes across the menopause. Cross-sectional (27) and longitudinal studies (22, 28) have shown that the menopausal transition is associated with a preferential increase in abdominal adiposity, independent of the effect of age and total body adiposity. Poehlman *et al.* (22) prospectively compared women who became postmenopausal to age-matched controls who remained premenopausal and found that the transition to menopause was associated with an increase in the waist to hip ratio and total body fat. Abdominal fat, measured by CT scan, has also been shown to increase with menopause in both cross-sectional (29) and prospective studies (30). Visceral fat accumulation is thought by many to be the major determinant of the metabolic syndrome.

Women with high amounts of visceral fat have an excess of cardiovascular mortality and associated metabolic abnormalities (31). When Pascot *et al.* (32) matched women for abdominal fat (by CT scan) and menopausal status, the differences initially found in very low density lipoprotein (VLDL), LDL, HDL, large buoyant HDL_2 particles, LDL particle size, fasting glucose, C peptide, and blood pressure were eliminated, implying that the differences in visceral fat and menopausal status accounted for the metabolic differences. Regional differences in adipose tissue lipoprotein lipase activity in postmenopause may account for the menopausal changes in fat accumulation, but results to date are conflicting (33, 34). Adiponectin, a novel adipocyte-derived peptide, may play a role in the metabolic syndrome, as concentrations are inversely related to obesity and insulin resistance. However, the only study evaluating adiponectin in menopause revealed no difference in pre- and postmenopausal women (35).

Menopause is also associated with reduced lean body mass (muscle) and this appears to be related to decreased physical activity (36). Lynch *et al.* (37) recently reported lower maximal oxygen consumption (VO_2 max) in sedentary postmenopausal (VO_2 max) women compared with sedentary age-matched premenopausal women and found an inverse relationship between visceral adiposity and maximal oxygen consumption. The reductions in exercise capacity and activity may contribute to the reduced lean body mass and increased central adiposity with menopause.

Effects of menopause on lipid metabolism

Although the association between abdominal adiposity and the constellation of lipid abnormalities is well known, the underlying pathophysiology is not clear. High amounts of abdominal fat are associated with increased insulin resistance, free fatty acid (FFA) levels, and decreased adiponectin (Fig. 2). These factors contribute to increased secretion of apolipoprotein B (apo B)-containing particles, leading to hypertriglyceridemia and increased hepatic lipase (HL) activity resulting in a predominance of small dense LDL particles and a reduction in large antiatherogenic HDL_2 particles. A similar pattern of lipid abnormalities emerges with menopause (Table 3).

Changes in LDL with menopause

Postmenopausal women have higher total cholesterol, LDL cholesterol, triglycerides (TG), and lipoprotein(a) [Lp(a)] levels and lower HDL cholesterol levels than premenopausal women (38–40). Although elevated LDL is not a component of the metabolic syndrome, LDL levels increase by 10–20% (23, 41) with menopause, and the greatest change

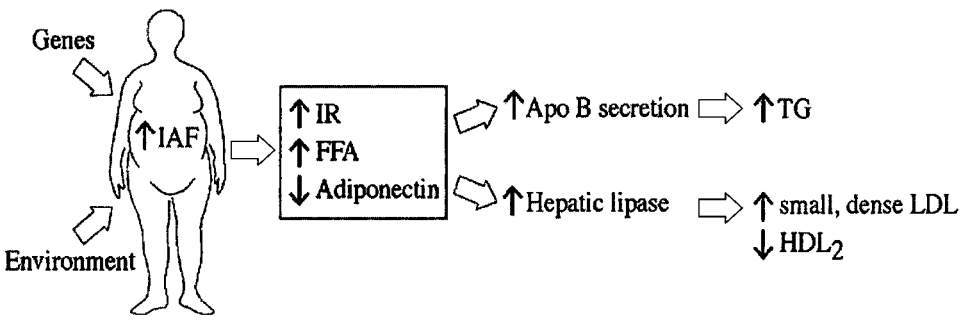

FIG. 2. The interaction of genetic and environmental factors influences the manifestation of the metabolic syndrome. High amounts of intraabdominal fat (IAF) are associated with increased insulin resistance (IR) and FFA levels, and decreased adiponectin. These factors contribute to increased secretion of apo B-containing particles, leading to hypertriglyceridemia and increased HL activity, which lead to a predominance of small dense LDL particles and a reduction in the large antiatherogenic HDL_2 particles.

TABLE 3. Lipoprotein changes with menopause (longitudinal studies)

Cohort size	Total cholesterol	LDL	HDL	Triglycerides
150	–	–	↓	–
18	–	↑	↓	↑
10	↑	↑	↓	↑
69	↑	↑	↓	↑
343	↑	ND	ND	↑

–, No significant change; ND, not done; ↑, significant increase; ↓, significant decrease. Data are from Lindquist (50), Matthews *et al.* (41), Jensen *et al.* (38), Poehlman *et al.* (23), and Do *et al.* (51).

TABLE 4. Percentage of women who maintain or change LDL size with menopause

	Premenopause		Postmenopause
51%	lbLDL	➪	lbLDL
36%	lbLDL	➪	sdLDL
13%	sdLDL	➪	sdLDL

Data are from Austin *et al.* (43). lbLDL, Large, buoyant LDL; sdLDL, small, dense LDL.

in LDL concentration appears to occur early in the transition from premenopause to postmenopause (42). Apo B, the primary apolipoprotein of LDL particles, and other apo B-containing particles are also higher in postmenopausal compared with premenopausal women (40).

LDL particle composition also changes with menopause. The prevalence of small, dense LDL is low in premenopausal women (10–13%), but increases to 30–49% in postmenopausal women (39, 43, 44) (Table 4). LDL are comprised of a spectrum of particles that vary in size, density, chemical composition, and atherogenic potential. A preponderance of small, dense LDL is associated with an increased risk of myocardial infarction (45) as well as the severity of CVD (46). The risk of CVD is 3-fold higher in women with small, dense LDL than in those with large, buoyant LDL (45). Mackey *et al.* (47) recently showed by electron beam CT that postmenopausal women with high coronary calcium scores had smaller LDL particle size, higher LDL levels, and fewer large HDL_2 particles than postmenopausal women with low coronary calcium scores.

Changes in TG with menopause

Many longitudinal studies have shown that TG levels increase with the transition through the menopause (38), and the increase in TG also appears early in the postmenopausal period (42). Poehlman *et al.* (23) found that the prospective transition to postmenopause was associated with a 16% increase in TG. Although men generally have higher TG levels than women, TG increases in middle-age (between 40–69 yr) in women, but not in men (48), and TG appears to be a better predictor of CVD risk in women than in men (49). Lindquist (50) reported a prospective increase in TG levels in women who became postmenopausal during a 6-yr period, whereas there was no change in TG in the similarly aged women who remained either premenopausal or postmenopausal. Increasing TG with menopause may be related to the fact that TG levels are highly correlated with increasing abdominal fat content and insulin resistance.

Changes in HDL with menopause

Most studies show that total HDL levels fall slightly with menopause (23, 38, 41, 51), whereas others reveal no changes (52). Menopausal changes in HDL metabolism are more complex than the measurement of total HDL reveals, because the more antiatherogenic HDL_2 levels decrease (by 25%), whereas HDL_3 levels increase (26, 30, 40, 53). HDL_2 particles are the large, buoyant, and more cardioprotective subspecies of total HDL. The strong inverse relationship between HDL cholesterol and abdominal adiposity appears to be largely dependent on variations in HDL_2 levels (54).

Changes in Lp(a) with menopause

Lp(a), an LDL-like particle with structural homology to plasminogen, is not frequently measured in clinical practice, but has been shown to predict cardiovascular events in women independent of LDL levels (55). Lp(a) levels are primarily genetically determined, but several studies have now shown significant increases in Lp(a) levels (by 25–50%) with menopause (30, 56, 57). This rise in Lp(a) levels with menopause may reflect the fact that Lp(a) levels are sensitive to sex steroid hormones and return to premenopausal levels with estrogen replacement (57).

Changes in proteins of lipid metabolism with menopause

Proteins of lipid metabolism underlying the menopausal change in lipids have been evaluated in few studies. The increased prevalence of small, dense LDL with menopause may be explained by higher HL activity in postmenopausal women (30, 58). Endogenous estrogen levels are inversely associated with HL activity (59). HL hydrolyzes the TG and phospholipid in LDL and HDL and is one factor that determines the size and density of LDL and HDL particles (60). The higher the HL activity, the more TG and phospholipid hydrolyzed, resulting in smaller, denser more atherogenic lipoprotein particles. Lipoprotein lipase hydrolyzes TG in triglyceride-rich lipoproteins, generating FFA that can serve as an energy source or can be stored in adipocytes. We have recently shown a small, but significant, rise in lipoprotein lipase activity with the transition through menopause (unpublished observation). Cholesteryl ester transfer protein (CETP) catalyzes the exchange of cholesterol ester in HDL and LDL particles for TG in VLDL, and high CETP concentrations are associated with reduced HDL levels. Menopausal status does not appear to affect CETP activity (61). The mechanisms underlying the menopausal changes in lipid metabolism are not clear and require further study.

The perimenopausal changes in lipid metabolism reveal an overall shift toward a more atherogenic lipid profile with increased LDL and TG levels, reduced HDL_2 concentration, and smaller, denser LDL particles, similar to the metabolic syndrome. This classic dyslipidemia is closely associated with increasing amounts of visceral fat, which may explain why these features emerge with the menopause. It is likely that these adverse changes in lipid metabolism during the menopausal transition will contribute to future CVD risk.

Insulin resistance changes with menopause

Two of the most important pathophysiological components of the metabolic syndrome are increased visceral fat accumulation and insulin resistance. Abdominal obesity is closely associated with increased insulin resistance, compensatory hyperinsulinemia, and increased risk of type 2 diabetes, independent of an individual's total body fat content (62). The pathophysiology underlying the insulin-resistant state is complex. Insulin resistance, with inadequate compensatory hyperinsulinemia, diminishes the normal suppression of FFA arising from adipose tissue by insulin. The increased levels of FFA may impair peripheral glucose uptake, increase hepatic gluconeogenesis, and reduce hepatic clearance of insulin (13).

The literature to date is not clear as to whether menopause is associated with increased insulin resistance. What little data there are remain contradictory. Several groups have shown increased fasting insulin (22, 48) and increased fasting glucose levels (37, 63) in postmenopausal compared with premenopausal women, which would imply worsened insulin resistance with the menopause. However, insulin sensitivity is known to worsen with advancing age and increasing central obesity, making it difficult to tease out the effect of menopause from these processes. Studies using accurate measures of insulin resistance, such as the euglycemic-hyperinsulinemic clamp or the frequently sampled iv glucose tolerance test, are scarce (64–67).

Lindheim *et al.* (64) showed reduced insulin sensitivity (*i.e.* higher insulin resistance) in postmenopausal women compared with BMI-matched premenopausal women. However, others have shown no differences in insulin sensitivity in postmenopausal compared with premenopausal women (65, 66). DeNino *et al.* (67) compared measures of insulin resistance and visceral adipose tissue in age-grouped women ranging from 20–78 yr. They found that reduced insulin sensitivity did not appear until women were older than 60 yr and had accumulated levels of visceral fat that approximated the levels seen in men, suggesting a possible threshold effect of abdominal fat on insulin resistance (67).

Guthrie *et al.* (68) reported prospective data on 265 healthy perimenopausal women with normal fasting glucose. The group of women (16%) who developed impaired fasting glucose (≥6.1 mmol/liter) over the 5-yr period had higher baseline BMI, fasting glucose and insulin, waist circumference, and TG; lower HDL levels; as well as greater increases in BMI and insulin over the study period compared with women who maintained normal fasting glucose. There was no difference in menopausal status between the two groups; this implies that weight gain had a stronger influence on the development of impaired fasting glucose than menopause itself (68).

Effects of menopause on fibrinolytic and inflammatory markers

Markers of impaired fibrinolysis, plasminogen activator inhibitor-1 (PAI-1) and tissue plasminogen activator (tPA), and subclinical inflammation, C-reactive protein (CRP) and IL-6), are also associated with the metabolic syndrome and appear to play a role in the pathogenesis of CVD (69). Fibrinolytic activity is a balance between plasminogen activators (tPA) and inhibitors (PAI-1). Elevated PAI-1 activity causes prolonged clot lysis times and potentiates thrombosis. High PAI-1 activity is associated with high plasma levels of tPA antigen (which represents t-PA/PAI-1 complexes), which has been found to be independently associated with CVD in both men and women (70). PAI-1 is produced by liver and adipose tissue, particularly visceral adipose tissue (71), and is thought to be a marker of insulin resistance.

Postmenopausal women have higher levels of PAI-1 and tPA antigen than premenopausal women (72). Age-matched men have higher levels of tPA antigen than premenopausal women (73). These data imply that estrogen deficiency and increased visceral adiposity are associated with a decrease in fibrinolytic potential. Given that PAI-1 is positively associated with abdominal fat content and plasma TG, higher PAI-1 levels with menopause may be a marker of women at higher risk of CVD.

CRP is a marker of the presence and intensity of subclinical inflammation that independently predicts CVD risk in men and women (74). Like PAI-1, CRP is positively associated with total body fat mass and abdominal fat, and weight loss in postmenopausal women has been shown to reduce CRP levels by 32% (75). Sites *et al.* (76) recently found no differences in CRP between premenopausal (mean age, 47 yr) and early postmenopausal (mean age, 51 yr) women; however these healthy women may have had relatively few differences in atherosclerotic plaque burden.

IL-6 is a proinflammatory cytokine produced by macrophages and monocytes that induces the production of CRP, and elevated IL-6 levels are associated with increased risk of cardiovascular death (77). Recent data from the Women's Health Initiative revealed that higher baseline CRP and IL-6 levels predicted cardiovascular outcomes in apparently healthy older women (78). Several studies have shown higher IL-6 levels in postmenopausal compared with premenopausal women (79).

Treatment of the metabolic syndrome in women

Postmenopausal women who develop features of the metabolic syndrome should be aggressively treated to reduce CVD risk. Management guidelines suggest a combination of lifestyle modification and drug therapy. Until recently, hormone replacement therapy (HRT) was an option for treatment of the postmenopausal metabolic syndrome, because it improved many of the metabolic abnormalities (63). However, with the recent release of data from the estrogen-progestin arm of the Women's Health Initiative demonstrating increased CVD risk in HRT users, HRT is no longer recommended for preventative therapy of CVD (1).

Lifestyle modification

Weight loss and physical exercise are both mainstays of therapy, as they address the underlying etiology of the metabolic syndrome (visceral obesity and insulin resistance). Even modest weight loss has been shown to improve visceral adiposity and insulin resistance. There is a preferential loss of abdominal fat with aerobic exercise, as visceral adipocytes appear to respond more quickly to exercise-induced weight

loss than subcutaneous adipocytes (80). Regular endurance exercise may improve insulin sensitivity independent of total weight loss. Therefore, the aim of lifestyle modification therapy is to promote regular prolonged low intensity exercise (*i.e.* walking) to maintain weight and reduce visceral adipose tissue, rather than to set unobtainable weight loss goals.

Lipid lowering

Lifestyle changes may be inadequate to treat the dyslipidemia of the metabolic syndrome (increased TG, reduced HDL, and small dense LDL particles). Although LDL cholesterol has remained the primary target of lipid-lowering therapy, triglyceride lowering is an important secondary target to reduce CVD risk (11). Nicotinic acid and fibric acid derivatives both act to reduce TG and increase HDL cholesterol. They are frequently used with statin medications, but caution should be used in combining these drugs. Although niacin is an inexpensive monotherapeutic agent that corrects the combined dyslipidemia of the metabolic syndrome, it has the disadvantage of increasing glucose levels in some patients.

Recent evidence has suggested an underutilization of lipid-lowering therapy in women. Baseline data from the Heart and Estrogen/Progestin Replacement Study revealed that more than 60% of women with proven CVD did not meet the National Cholesterol Education Program goals for LDL lowering (81). It is also important to note that lipid abnormalities associated with the metabolic syndrome can be subtle. The metabolic syndrome is associated with small dense LDL particles, moderately elevated TG ($\geq$1.7 mmol/liter/$\geq$150 mg/dl), and reduced HDL ($<$1.3 mmol/liter/$<$50 mg/dl), but not elevated LDL cholesterol levels (Table 2) (11). There has been increasing interest in LDL and HDL particle size and composition as additional risk factors for atherosclerosis. Given that LDL levels may underestimate CVD risk in the presence of small dense LDL particles, practitioners must treat the dyslipidemia of the metabolic syndrome in addition to treating elevated LDL cholesterol levels. Measurement of LDL particle size may aid in identifying women at risk for CVD and targeting these women for aggressive lipid lowering.

Conclusion

CVD is the leading cause of death of women in developed countries, but very little is known about atherosclerotic disease progression in women. There has been recent emphasis on the metabolic syndrome as an atherosclerotic risk factor and its impact on CVD risk in women (11). Many of the features of the metabolic syndrome (central obesity and dyslipidemia with elevated TG, reduced HDL, and small dense LDL particles) emerge with estrogen deficiency in postmenopausal women, which may explain the acceleration of CVD in women after menopause. Accumulation of excess abdominal fat with transition through the menopause plays a central role in connecting the metabolic syndrome with the metabolic alterations of menopause and may account, in part, for the temporal separation in CVD risk between men and women (82).

It is unclear whether menopause is a cardiovascular risk factor for all women or only those who carry a predilection toward central adiposity. Endogenous estrogen appears to be cardioprotective, and postmenopausal estrogen deficiency unveils a constellation of closely associated adverse changes in metabolic risk factors. The emergence of these risk factors may be a direct result of ovarian failure or, alternatively, an indirect result of the metabolic consequences of central fat redistribution with estrogen deficiency. It is not clear whether the transition to menopause increases cardiovascular risk in all women or only those that develop the features of the metabolic syndrome. Women who develop insulin resistance with small, dense LDL and elevated PAI-1 after menopause may be carriers of a genetic predisposition that is masked by the effects of estrogen and unmasked after menopause. This subset of women may require targeted management to prevent future cardiovascular risk. Current evidence implies that multiple risk factors for CVD emerge in the postmenopausal period, but features of the metabolic syndrome may be present even before menopause. More research is clearly needed to further characterize the mechanisms by which women develop these metabolic changes with menopause.

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