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Menopause, atherosclerosis, and coronary artery disease

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Abstract

Women have coronary heart disease (CHD) later than men. This review describes studies of CHD risk factors or outcomes based on studies of premenopausal women followed through the menopause transition, and prospective cohort studies of younger or older women with CHD risk markers or disease outcomes in the context of their menopause history. Major early reports from both types of studies are included in order to put more recent work in context. Most attention has been paid to the Healthy Women Study (HWS), Study of Women's Health across the Nation (SWAN), the Nurses' Health Study (NHS), and the Rancho Bernardo Study (RBS) because they continue to produce recent publications designed to distinguish the effect of age from the effect of menopause. Understanding these differences has important implications for women's cardiovascular health, but remains incomplete. Transition studies have relatively short (<10 years) follow up and exclude women with surgical menopause. Cohort studies suggest that women with oophorectomy are at greater risk for CHD than intact women, pointing to a greater risk from testosterone deficiency than from estradiol levels.

Introduction

How the type or timing of the menopause is related to atherosclerosis and coronary artery disease or, more generally, cardiovascular disease (CVD) remains unclear. This review considers two kinds of studies in women who are not patients, i.e., do not have CVD at baseline: 1) studies of repeated measures of change in CVD risk factors or CVD risk markers during the menopause transition; and 2) studies of CVD risk factors and outcomes in community-based cohorts that include information on the menopause. Until recently, transition studies were too small or too short for clinical outcomes, and most were cross-sectional. The cohort studies depend on age 50 as menopause, or self-reported year of last menstrual period or date of hysterectomy with or without oophorectomy; the latter rely on participants' ability to remember remote dates and details. Results from both types of studies are complementary.

This review includes recent original and review papers with an emphasis on longitudinal work. This review does not include studies of pre- or post-menopausal hormone therapy, which pose other problems, including selection bias for who was prescribed hormones and

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the pharmacologic (not physiologic) doses used for treatment. Given word limitations, this review does not summarize other characteristics and consequences of the menopause. An excellent review of the menopause by Nelson was published in the Lancet in 2008[1].

The Menopause transition

The first large study in the United States to describe the menopause transition with a focus on CVD was the Healthy Women Study; this study measured changes in CVD risk factors in 541 healthy women ages 40–52 years at baseline when they reported menstrual bleeding within the past three months[2]. Women were then asked to report their menstrual bleeding and menopause status on monthly postcards. After approximately 2 ½ years, women who had a natural (nonsurgical) menopause, and who did not choose to use postmenopausal hormone therapy, had significant reductions in HDL cholesterol and increases in LDL cholesterol compared to women who were still premenopausal, *changes expected to accelerate atherosclerosis*. In this study, natural menopause did not affect weight, blood pressure, plasma glucose, or insulin levels, and risk factor changes did not reflect the number of calories consumed in the diet or expended in physical activity[2]. It was later shown that premenopausal measures of lipids predicted subclinical CVD based on coronary and aortic calcium [3, 4].

The Healthy Women Study was the model for the Study of Women Across the Nation (SWAN); an entire monograph on the SWAN results was published in 2011[5]; it included a highly recommended summary of many menopause studies and cardiovascular risk by Chae and Derby[6]. SWAN is the largest U.S. study to follow perimenopausal community-dwelling women through the menopause. At entry there were 3201 still-menstruating women age 42–52 years. Women completed annual interviews on their menses, and the frequency and severity of hot flushes and night sweats in the past two weeks; at the same time height and weight were measured, and blood for lipids and lipoproteins, serum estradiol, and FSH were obtained. A 2012 review reported 8-year lipid changes in the context of menopause status and symptoms[7]. In this SWAN paper, women reporting hot flushes 6 or more days a week had significantly higher LDL and HDL cholesterol and triglyceride levels. These associations largely persisted after adjusting for estradiol or FSH. Associations were strongest for lean women.

In a major SWAN analysis based on 10 years of follow up, only total and LDL cholesterol and apolipoprotein B changed within one year of the last menstrual period independent of age, ethnicity, or baseline weight; other common CVD risk factor changes were associated with age, not menopause [8]. SWAN was the first to present detailed changes in lipids anchored specifically to the timing of the final menstrual period.

In a SWAN ancillary study comparing subclinical atherosclerosis in premenopausal/early perimenopausal (n = 316) with late perimenopausal/postmenopausal (n = 224) women not using hormone therapy, aortic calcification, coronary artery calcium (CAC), and intimal medial thickness (IMT) were measured; results suggest the protective effects of HDL-cholesterol may be diminished during the menopause transition[9]. Analyses in this small subset of the SWAN study also showed a shift during the later menopause transition to higher HDL particle number and smaller HDL particle size, thought to be atherogenic changes[9].

In contrast to the lipid and lipoprotein changes, the ten-year follow up of the SWAN study showed that increases in blood pressure were related to chronological age and not related to the timing of the final menstrual period [8]. The risk of developing the metabolic syndrome (MetS) was unrelated to changes in estradiol or total testosterone, but increases in bio-available testosterone or SHBG were associated with increased risk of MetS[10]. In a nice

overview, Chae and Derby[6] concluded that the 10-year SWAN study results did not support a strong influence of the menopause transition on glucose or insulin levels or on the risk of developing diabetes.

It has not been clear whether changes in sex hormones during or after the menopause precede or follow changes in body weight during the menopause transition. A SWAN paper based on 9 years of follow up of premenopausal women (baseline and up to three other visits 3, 6 and 9 years later) [11] that included 1528 women (mean age 46, who had not had a hysterectomy) reported that the association between waist girth and estradiol appeared to be bidirectional, suggesting that adiposity may lead to changes in estradiol levels and that estradiol levels may lead to changes in adiposity. In contrast current waist circumference predicted future SHBG, testosterone, and FSH, but not the reverse.

This SWAN paper provides the strongest evidence to date suggesting that waist circumference precedes significantly increased total testosterone and SHBG and low FSH, but not vice versa. Estradiol was completely different: estradiol and waist circumference were negatively associated in the early menopausal stages, and positively associated in later transitions stages. For each standard deviation higher current waist circumference future estradiol levels were lower by 0.15 SD in pre- and early-stage menopause transition, and higher by 0.38 SD in late peri- and post-menopause transitions. The authors conclude that the predominant temporal sequence is that weight gain and increasing waist girth lead to changes in sex steroids, rather than the reverse. Although they conclude that weight gain is primarily due to aging rather than to menopause-related estrogen-deficiency, the effect sizes in women were larger for adiposity's effects on estradiol than the reverse, and were larger for waist circumference than for body weight, and were not explained by SHBG.

SWAN was not able to separate abdominal visceral from subcutaneous abdominal fat, or deal with the frequent changes in premenopausal estradiol levels (hour by hour and day by day), or the use of early estrogen immunoassays with less ability to detect low premenopausal estrogen levels than mass spectroscopy. Nevertheless, SWAN provides the strongest evidence to date suggesting that waist circumference predicts the magnitude of future estradiol levels to a much greater extent than the reverse.

Sleep disturbances

Perimenopausal women have more sleep disturbances than premenopausal women, but these disturbances are not always related to vasomotor symptoms. In SWAN, sleep disturbance was twice as common in women with vasomotor symptoms as in women without, and was associated with low estradiol levels [12]. These results differ from studies of symptomatic versus asymptomatic women as reviewed by Freedman [13], who found no difference in sleep disturbances in postmenopausal women with or without hot flashes and no evidence that hot flashes were related to estrogen deficiency or to objectively measured changes of body temperature. Freedman continues to make major contributions to the understanding of the etiology and treatment of hot flashes in relation to sleep, and to emphasize the separation between symptoms and objectively measured hot flashes.

Depression

Depression or depressed mood is a poorly understood but accepted risk factor for cardiovascular disease. The association of depressed mood with menopause was addressed using the 10^{th} annual SWAN visit when 90% of participants had reached a natural menopause [14]. All women experienced a *decrease in depressive and anxiety symptoms in the years after the menopause*. There were relatively few women who had hysterectomy with or without oophorectomy, and they did not have more negative mood symptoms after

surgery. (Different results were observed in African American women, but their numbers were small and differences may have been due to chance.) Because all SWAN women had to be in the menopause transition to participate, this could explain the inability to show an association of depressed mood with the menopause transition.

Cohort studies

One of the longest cohort studies of age at menopause and CVD is the Iowa Established Populations for the Epidemiological Study of the Elderly (Iowa EPESE), which included 1684 women from rural Iowa who were age ≥65 at baseline and were followed for up to 24 years[15]. Women whose reported menopause age was late (≥55 years) had an increased risk of all-cause and CVD mortality compared to women with an earlier menopause. The type of menopause (surgical 26% or natural 24%) was unrelated to these outcomes. Adjusting for confounding variables did not change the results. These results based on an exceptionally long follow-up *challenge the conventional wisdom that women's CVD risk is increased by the number of years of postmenopausal estrogen deficiency.* One plausible explanation (suggested by the authors) is that women who survive past age 65 have positive health characteristics not shared by those who died before age 65. Women less than age 65 were not included in the IOWA EPESE cohort.

The Nurses' Health Study (NHS), the largest U.S. cohort study of younger women, included 116,700 premenopausal US women age 30 to 55 years who had no known heart disease at baseline[16]. More than 95% were followed by mail between 1976 and 1982 (before the major promotion of postmenopausal estrogen in the U.S.) In this cohort, women who had a natural (nonsurgical) menopause and who had never taken postmenopausal estrogen had no increased risk of coronary heart disease compared to premenopausal women (adjusted rate ratio 1.12; 95% CI 0.8–1.8). Women who had a natural menopause and took estrogen also showed no difference in risk. In contrast, women who reported a bilateral oophorectomy had a 2-fold increased risk if they did not use post-menopausal estrogen.

These results were confirmed in a 2006 international meta-analysis of 18 published studies of age at menopause in relation to cardiovascular disease[17] (6 studies of menopause status, 9 of menopause age, and 3 of both age and status were reviewed with consideration of multiple covariates). The pooled relative risk for postmenopausal vs. premenopausal women was not significant (0.96, 95% CI 0.77–1.21) after adjusting for age and smoking, but was significant (2.62, 95% CI 2.05–3.35) in women who had had a bilateral oophorectomy. The authors concluded there was no convincing relationship between postmenopausal status in intact women and cardiovascular disease. Their analyses dramatically illustrate the difficulty of pooling data with so many different methods and definitions.

Perhaps remembered age at menopause is inaccurate by age 65. Against this bias is the observation that remembered age at menopause matched the separately reported time when estrogen was prescribed; further, the hazard ratio and percent dead by end of follow up were similar for those who did or did not know their age at menopause, suggesting survival bias did not explain the results.

A 2006 study by Kok et al.[18], based on data from the Framingham cohort study established in1948, included 695 women who had reached a natural menopause after at least two rounds of clinical evaluations that were conducted every two years for an average of 4.9 evaluations. The authors reported that a higher premenopausal serum total cholesterol level was statistically significantly associated with earlier menopause age (as were relative weight and blood pressure). Also, a decrease in relative weight was associated with a significant earlier age at menopause (each 1% higher premenopausal Framingham risk score was associated with a decrease of 1.8 years in age at menopause (95% CI −2.72 to 0.92),

supporting the view that heart disease risk determines age at menopause and not vice versa. This is a novel explanation for inconsistent findings on rate of CVD in relation to age at menopause. Bittner's thoughtful editorial on this methodologically challenging study [19] noted that it is critical to separate the influence of chronologic aging from that of menopause.

Atrial fibrillation

Atrial fibrillation (AF) increases with age and is common enough to eliminate the female CVD survival advantage, but is not related to the menopause, according to a unique recent Framingham Heart Study publication[20]; the authors examined the association of incident AF with menopausal age, studying women without prevalent AF at baseline. In a multivariate model adjusted for AF risk factors, incident AF did not differ between women with early menopausal age (<45 yrs) vs. late menopausal age (> 53 yrs); the Framingham Heart Study does not identify menopausal age as significantly increasing AF risk.

Sex hormones

The implications of increased CVD risk with long postmenopausal life without estrogen are large given the rapid growth and improved survival of the aging population. In the French Three-City prospective cohort study, high plasma levels of endogenous estradiol emerged as a new predictor of ischemic arterial disease in older postmenopausal women[21].

There is increasing interest in the importance of testosterone instead of estrogen as an explanation for the harmful effect of oophorectomy on cardiovascular risk. Testosterone is made in the stroma of the ovaries, and is maintained after all follicles (the main premenopausal source of estradiol) are lost. A study of individual data from more than 6000 postmenopausal women [22] from 13 prospective studies showed that all hormones were lower in older intact women. Androgens were lower in women who had had a bilateral oophorectomy than in naturally menopausal women. Smokers of 15+ cigarettes per day (known to have an earlier menopause) had higher levels of all hormones than nonsmokers, with larger levels for testosterone. Drinkers of 20+ g of alcohol per day also had higher levels of all hormones. Cardiovascular outcomes were not reported.

A recent SWAN analysis [23] showed that low SHBG and high free androgen index were strongly and consistently associated with elevated CV risk factors (higher insulin, glucose, hemostatic and inflammatory factors, and adverse lipids) independent of BMI. Low levels of estradiol were associated with elevated CV risk factors to much lesser degree.

These results are in contrast with hormone associations in older postmenopausal women in the Rancho Bernardo Study [24]. There were 639 postmenopausal women (age 50 to 91 years, median age 74) followed for a median of 12.3 years, who had 134 incident CHD events (45 nonfatal, 79 fatal, 10 coronary revascularizations). Age-adjusted CHD risks for total testosterone were similar for the four highest quintiles of total testosterone, and significantly higher for women in the lowest testosterone quintile (≤80 pg/ml) (Figure 1). Additional adjustment for estradiol, ovarian status, lifestyle, adiposity, or CHD risk factors had minimal influence on these results. Bioavailable testosterone showed a U-shaped association, such that age-adjusted CHD risk for the lowest and highest bioavailable T quintiles relative to the third were 1.79 (95% CI 1.03–3.16) and 1.96 (95% CI, 1.13–3.41), respectively. These results may be direct or indirect. In experimental studies, androgens suppress proinflammatory cytokine activity, inhibit apoptosis, and enhance vascular smooth muscle proliferation, important factors inhibiting atheroma formation and maintaining plaque integrity, as reviewed by Malkin and colleagues[25].

Conclusion

Transition studies have relatively short (<10 years) follow up and exclude women with surgical menopause. Cohort studies suggest that women with oophorectomy are at greater risk for CHD than intact women, pointing to a greater risk from testosterone deficiency than from estradiol levels.

This brief review is about women only. This writer strongly believes that a better understanding can be obtained by studying sex and gender differences in CHD. A recent publication [26] used U.S. and U.K. national heart disease mortality data for three birth cohorts (1916–25, 1926–35, and 1936–45). In all birth cohorts linear heart disease mortality rates peaked in men around age 45, and age-related increases were much slower thereafter. In women there was no linear accelerated increase in heart disease mortality rates at age 50, the usual age at menopause. In both sexes proportional increases fit the data better than absolute increases. The authors concluded that deceleration of the increase in male heart disease mortality in midlife explains sex differences better than postmenopausal estrogen deficiency in women.

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pooling of studies is not feasible. They note the limitations of each study, the difficulties in separating the effects of hormone deficiency from those of age, and highlight the first 7 years of the SWAN follow up showing total and LDL cholesterol and triglycerides peaked during late perimenopause and early postmenopause, and remained high. HDL also peaked but these changes appeared to be transient. Their analysis may be the first to present changes in lipids anchored specifically to the last menstrual period. [PubMed: 21961715]

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Highlights

- Only total and LDL cholesterol and apolipoprotein B changed within one year of the last menstrual period.
- Increasing importance of testosterone instead of estrogen to explain harmful effect of oophorectomy on cardiovascular risk
- In adjusted analyses incident AF did not differ between early menopausal (<45 y) vs. late menopausal (>53 y) age.
- Methodologically challenging but critical to separate out the influences of chronologic aging and menopause.

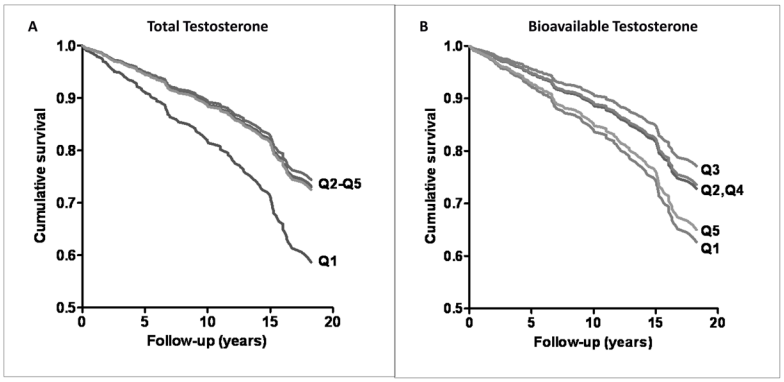

Figure 1.

A. Total testosterone and 20-year incident CHD in women (adjusted for age, BMI, WHR, smoking, exercise, alcohol). B. Bioavailable testosterone and 20-year incident CHD in women (adjusted for age, BMI, WHR, smoking, exercise, alcohol) (Laughlin GA, Goodell V, Barrett-Connor E. Extremes of endogenous testosterone are associated with increased risk of incident coronary events in older women. J Clin Endocrinol Metab 2010;95:740–7, *Copyright 2010, The Endocrine Society*).