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Hormones and Coronary Atherosclerosis in Women

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Heart disease is the major health issue facing women in the United States today. Yet, less than 50% of women are aware cardiovascular disease is a health problem. Atherosclerosis begins in childhood and lipid streaks have been identified in girls ages 15–19 in the abdominal aorta and the right coronary artery. Risk factors for cardiovascular disease in women include smoking, diabetes, hypertension, lipid disorders, and menopause. Observational studies have reported a 30–50% reduction in cardiovascular events when estrogen was administered to younger women for menopausal symptoms, yet randomized trials in older patients have failed to show benefit with hormonal replacement therapy. Recent studies have reported preservation of lipid and vascular vasodilatation with low-dose conjugated equine estrogens (CEE) in women and an absence of inflammatory and clotting changes that were observed in high-dose CEE. Recommendations for reducing cardiovascular risk in postmenopausal women include smoking cessation, regular exercise, and weight control. Should hormone therapy be continued beyond management of menopausal symptoms and treatment for osteoporosis, a statin drug should be added to eliminate future cardiovascular complications. Future research will examine low-dose hormonal therapy, earlier administration after menopause, newer agents, and routes of estrogen administration.

Key Words: Estrogen; coronary atherosclerosis; WHI.

Introduction

Heart disease is the major health issue facing women in the United States today *(1)*. In the past, women's health has focused on breast and uterine malignancies with minimal emphasis on cardiovascular disease. Despite efforts to publicize the incidence of heart disease in women, a recent survey revealed that less than 50% of women were aware that heart disease was a major health issue *(2)*. Compared to men, women experience a higher mortality with acute myocardial infarction, an increased recurrence rate of heart attacks the first year after the initial event, and more complications with angioplasty and bypass surgery *(3)*. Cardiovascular disease rapidly accelerates in women after menopause and loss of ovarian function. Although earlier observational studies reported a 30–50% reduction in coronary heart disease in women on hormonal therapy, recent clinical trials have failed to confirm the benefits of estrogen therapy in postmenopausal females.

This article will review the pathophysiology of atherosclerosis in women, risk factors for accelerated atherosclerosis, metabolic and vascular influences of female hormones, clinical trials of hormone therapy, recommended lifestyle changes and therapy for women with heart disease. Unresolved questions in areas for future research in hormonal therapy and heart disease will be discussed.

Pathophysiology

Epidemiologic studies and clinical trials recognize coronary artery disease as a myocardial infarction or sudden cardiac death. The underlying pathologic mechanism for the clinical manifestations of coronary artery disease is atherosclerosis. Atherosclerosis was defined by the pathologist Virchow years ago as an inflammatory and fibrotic response to cholesterol accumulation in the arterial wall *(4)*. As a result myocardial infarction and cardiac death are late manifestations of the atherosclerotic process. Atherosclerosis begins early in life and lipid streaks have been observed in the abdominal aorta in 100% of teenage girls ages 15–19 yr and 60% of these individuals exhibited lipid streaks in the right coronary artery *(5)*. Fetuses of hypocholesterolemic mothers have revealed lipid accumulation in the arterial tree *(6)*. Research on atherosclerosis has progressed from mechanisms of lipid accumulation in the arteries to inflammatory mechanisms responsible for accelerated development and rupture of atheromatous plaques (Fig. 1). Oxidaton of LDL cholesterol in the arterial wall is the initial event in atherosclerosis and estrogen inhibits the oxidation of LDL cholestrol while estrogen deficiency may accelerate artherosclerosis.

Clinical manifestations of coronary artery disease result from severe reductions or obstruction of coronary blood

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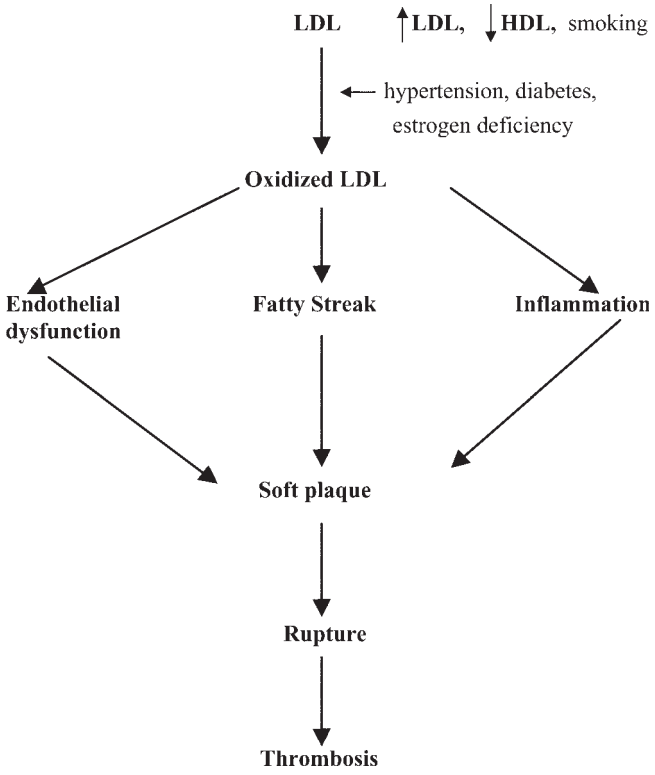

Fig. 1.

flow. Myocardial ischemia is caused by 70% stenosis in one or more coronary arteries and myocardial infarction is associated with complete occlusion of a coronary vessel *(7)*. Traditionally, angiographic lesions less than 50% have been considered hemodynamically insignificant and inadequate to cause myocardial ischemia. Patients were often reassured about the absence of heart disease when coronary angiograms revealed plaques with less than 50% narrowing. Over the past 15 yr angiographic studies performed 1 yr prior to a myocardial infarction demonstrated that the majority of coronary occlusions resulted from lesions with less than 50% stenosis that subsequently ruptured with clot formation *(8)*. Thus, previous theories that acute myocardial infarction was caused by a severely stenotic lesion with clot formation required an additional explanation. A cholesterol model had been proposed to explain events progressing from an early lipid deposit to plaque rupture and an acute event *(7)*. Endothelial dysfunction, inflammation, and plaque instability can accelerate changes in a lipid streak to provoke a clinical event of myocardial infarction or sudden death. Thus, a new paradigm for coronary atherosclerosis must be added to the previous stenotic and occlusive mechanisms to recognize factors that accelerate plaque instability and induce acute coronary events.

Risk Factors

Risk factors are clinical characteristics that render an individual at risk for a cardiac event. Conditions in women which may accelerate the atherosclerotic process include smoking, diabetes, hypertension, lipid abnormalities, and menopause *(9)*. Additional factors include inflammatory and thrombogenic substances in the blood such as a C-reactive protein, fibrinogen, and plasminogen activator inhibitor. The Women's Health Initiative Observational Study of 92,152 women followed for the natural history of coronary disease reported elevated cholesterol as a major characteristic of those developing angina and the use of cigarets and diabetes as prevalent findings in women sustaining an acute myocardial infarction *(10)*.

Table 1
Clinical Features of the Metabolic Syndrome

Risk factor	Defining level
Abdominal Obesity (waist circumference) Women	>88cm (35 in.)
Triglycerides	≥150 mg/dL
High—density lipoprotein cholesterol Women	<50 mg/dL
Blood pressure	≥130/≥85 mmHg
Fasting glucose	≥110 mg/dL

A metabolic syndrome has been proposed by the National Cholesterol Expert Education Program as a coronary risk equivalent *(11)* (Table 1). Components of the metabolic syndrome include obesity, hypertension, lipid abnormalities, and insulin resistance. Obesity in a female is defined as a waist circumference exceeding 35 in., hypertension as blood pressure above 130/85 mmHg, triglycerides above 150 mg, HDL cholesterol less than 50 mg, and insulin resistance as fasting blood sugar above 110 mg. Three of these five characteristics are required to establish the presence of the metabolic syndrome. The incidence of the overall metabolic syndrome in society varies from 20% in younger age groups to 40% in older individuals. Overt diabetes also increases with the development of the metabolic syndrome.

Obesity is increasingly recognized as a contributing factor not only to the metabolic syndrome but also to the risk for accelerating atherosclerosis. Abdominal or visceral obesity has been associated with elevated levels of C-reactive protein, an inflammatory marker that may be involved in the atherosclerotic process. Weight reduction in overweight women can reduce the C-reactive protein within 6 mo *(12)*. The Women and Ischemic Syndrome Evaluation (WISE) study compared angiographic coronary atherosclerosis to obesity in women with and without the metabolic syndrome *(13)*. Anatomic coronary disease was defined as stenotic lesions with 50% or greater reduction in the lumen diameter. In obese women without additional characteristics of the metabolic syndrome, only 25% exhibited anatomic coronary artery disease at cardiac catheterization. On the other hand, women with characteristics of the metabolic

Table 2
Effects of Estrogen on the Natural History of Atherosclerosis

Pre- and perimenopausal	Late postmenopausal
Fatty streaks → Fatty plaques →	Atherosclerotic plaques
→	Unstable plaques
↓ Recruitment of monocytes–macrophages, adhesion molecules	↑ Neovascularization
↓ Binding/accumulation of LDL	↑ Release of matrix metalloproteinase -2
↓ LDL oxidation	▶ Inflammation ?
↓ Smooth muscle cell proliferation	↓ Loss of endothelial response to estrogen
↑ Endothelial production of NO	▶ Thrombogenicity ?
Favorably influenced by adequate plasma concentrations of estrogen	Diminished beneficial or potentially unfavorable effects of initiating ERT treatment

syndrome and obesity revealed a 75% incidence of angiographic coronary atherosclerosis. This study provided evidence for the contribution of metabolic factors and obesity to the development of coronary atherosclerosis in women.

Hormonal and Vascular Mechanisms of Estrogen

Estrogen exerts both beneficial and adverse influences on the natural history of atherosclerosis (Table 2). Estrogenic benefits include inhibition of the LDL oxidation in the wall of the artery, decreased LDL binding to the vascular wall, reduction in the production of cellular adhesion molecules, inhibition of smooth muscle proliferation, and the restoration of endothelial function with resulting vasodilatation *(14)*. Estrogen also increases the HDL cholesterol and may cause elevation of the triglycerides. Potentially adverse affects of estrogen include inflammation, production of C-reactive protein, and the increased expression of matrix metalloproteinase, a proteolytic enzyme capable of dissolving collagen in the fibrous cap of the atheromatous plaque. The absence of estrogenic influence in the course of atherosclerosis can result in elevated cholesterol levels as well as loss of other cellular mechanisms such as vasodilatation. Laboratory studies have demonstrated methylation of the estrogen receptor gene can down-regulate estrogen receptors *(15)*. High cholesterol as well as the aging process increase the methylation process with reduction and eventual loss of estrogen receptors.

Coronary angiographic studies in postmenopausal women on estrogen have reported a decreased incidence of anatomic coronary disease when compared to nonusers of hormonal therapy. Sullivan et al. have reported in a 10-yr followup period that women remaining on hormonal replacement therapy had reduced development of atherosclerosis *(16)*. Hong and colleagues reported an 80% reduction in anatomic coronary disease in women with suspected myocardial ischemia compared to those not on replacement hormones *(17)*. Wenger and associates confirmed a lower incidence of anatomic coronary disease in postmenopausal women on hormonal therapy *(18)*. In this study, users of estrogen alone versus estrogen and progesterone both had a lower incidence of anatomic coronary disease, but women on estrogen alone exhibited the greatest benefit from development of the atherosclerotic process.

Another aspect of estrogenic influences on atherosclerosis is the timing of replacement hormone therapy after loss of ovarian function. Experimental studies in primates have documented the significance of timing of hormonal therapy after surgical removal of the ovaries *(19)*. In these studies, monkeys placed on either healthy or atherogenic diets, exhibited 70% and 50% inhibition of the atherosclerotic process, respectively, when estrogen replacement was immediately initiated after surgical removal of the ovaries. When hormonal therapy was delayed 2 yr after ovarian removal, no protection against the atherosclerotic process was observed. A 2-yr delay in primates is equivalent to a 6-yr delay in human subjects. These observations on the delay of estrogen replacement after loss of ovarian function are consistent with previous observations that women placed on hormonal therapy more than 6 yr after ovarian removal did not demonstrate restoration of bone mineral density *(20)*. Women placed on hormones up to 3 yr after removal of the ovaries restored bone mineral density to premenopausal levels.

The Heart and Estrogen/progestin Replacement Study (HERS) and the Women's Health Initiative (WHI) studies employed 0.625 mg conjugated equine estrogens (CEE), which may have exerted mixed protective and adverse affects of estrogen *(21,22)*. Two recent studies compared 0.625 mg to 0.3 mg CEE in postmenopausal women over 2 and 3 mo periods. In one study, patients received micronized progesterone with either 0.625 mg or 0.3 mg CEE for 2 mo. Low-dose CEE had comparable beneficial effects on lipids and endothelial vasodilatation but did not increase C-reactive protein or prothrombin fragments *(23)*. In the second study, after 3 mo, 0.625 mg CEE raised C-reactive protein, amyloid A, and interleukin-6, whereas low-dose 0.3 mg had no affect *(24)*. Low-dose CEE preserved endothelial function but eliminated the adverse affects of raising inflammatory markers. Thus, low-dose CEE can preserve lipid changes and endothelial function without provoking inflammatory and clotting mechanisms.

Clinical Trials

Over 20 observational studies with hormonal therapy in postmenopausal women reported a 30–50% reduction in the incidence of coronary artery disease *(25–27)*. In over 90% of these reports hormonal therapy was initiated for

Table 3
Baseline Characteristics
NHS vs WHI

	NHS	WHI
Mean age or age range at enrollment (yr)	30–55	63
BMI (mean)	25.1 kg/m^2	28.5 kg/m^2
Aspirin users	43.9 %	19.1 %
HRT regimen	Unopposed or sequential	Continuous–combined
Menopausal symptoms (flushing)	Predominant	Uncommon

control of menopausal symptoms and the usual agent was CEE. Recent prospective randomized trials, notably the HERS and the WHI, failed to observe cardiovascular benefits with hormonal therapy in postmenopausal women. In the first 2 yr after randomization in these trials, women assigned to the hormonal replacement arm exhibited a significant increase in cardiovascular events compared to the placebo group. These studies resulted in recommendations that hormonal therapy should not be initiated for the primary prevention of coronary artery disease in women. Additional randomized studies have also failed to show benefit in postmenopausal women with coronary disease receiving hormonal therapy.

An important consideration in analyzing these trials is the characteristics of the participants. Comparison of the randomized trials to previous studies revealed significant differences in the patient characteristics. The Nurses Health Study (NHS) was a prospective observational trial of a 121,964 nurses followed for up to 20 yr *(28)*. Women were 30–55 yr when hormonal therapy was initiated for treatment of menopausal symptoms (Table 3). In the Women's Health Initiative participants ranged in age from 50 to 79 yr with an average of 63 yr. When compared to participants in the Women's Health Initiative, women in the Nurses Health Study had a lower body weight. Women with menopausal symptoms were excluded from participation in the WHI trial, whereas menopausal symptoms were the usual indication for initiating hormonal therapy in the Nurses Health Study. Participants in the Nurses Health Study and other observational trials have been characterized as healthier, younger, and more highly motivated individuals for lifestyle changes as compared to the WHI trial with older individuals, higher incidence of obesity, and coronary risk factors. Differences in patient characteristics as well as timing of hormonal replacement therapy likely contributed to the disparate results of these observational and randomized trials.

Timing with hormonal replacement therapy appears to be an important factor, because women receiving estrogen within 6 yr after loss of ovarian function in these trials exhibited a reduction in cardiovascular events, whereas the older women with established coronary disease failed to demonstrate cardiovascular benefits and exhibited a small increase in vascular complications. A recent analysis of the WHI trial in women ages 50–59 yr identified individuals describing hot flushes at the time of study entry *(29)*. When these women were further analyzed, those receiving hormonal therapy had the same number of cardiovascular events as the women in the placebo group. This observation supports the potential benefit of early administration of hormonal therapy.

Treatment

Strategies for slowing the atherosclerotic process in pre- and postmenopausal women include lifestyle modification, smoking cessation, weight control, and regular exercise. Both the WHI trial as well as studies on the metabolic syndrome have demonstrated the contribution of obesity to the acceleration of atherosclerosis. Weight reduction can lower blood pressure, reduce plasma lipids, lower blood sugar, and diminish levels of C-reactive protein.

Exercise is an important aspect of lifestyle modification, and recommendations have varied from walking 20–30 min a day to more vigorous programs. Benefits from regular exercise include not only the cardiovascular influences but also forms of stress relaxation. Emphasis should be placed on the frequency of modest exercise rather than infrequent extensive exercise workouts. Although studied in men with coronary artery disease, a recent study compared regular exercise to angioplasty as treatment for patients with angiographic coronary artery disease *(30)*. After 1 yr, individuals assigned to the exercise arm of the study without angioplasty experienced significantly fewer ischemic events than those undergoing coronary angioplasty. The form of exercise employed in this study was 30 min a day on a stationary bicycle.

In women with angiographic or clinical evidence of coronary artery disease, standard measures should include the use of proven therapies such as statin drugs, beta-blockers, aspirin, and the angiotensin converting enzyme inhibitors for hypertension. These drugs have been shown to reduce the incidence of myocardial infarction in clinical trials.

Hormonal therapy is currently recommended for control of menopausal flushes and treatment of osteoporosis. These benefits have been confirmed in clinical trials and are included in the current labeling of available forms of estrogen. The majority of these trials used CEE with or without progestin and a standard dose of 0.625 mg of CEE. Recent studies in postmenopausal women have reported that low-dose CEE 0.3 mg preserves the lipid benefits and endothelial function without elevating C-reactive protein and other clotting abnormalities when compared to the higher dose of 0.625 mg. Low-dose estrogen may not only control symptoms of flushes and slow osteoporosis but may also provide lipid and vascular benefits without contributing to

the inflammatory and clotting mechanisms observed with higher-dose estrogen.

Although beneficial effects of estrogen probably result from early administration after loss of ovarian function, the exposure of advanced atherosclerosis to estrogen may have deleterious effects. Estrogen has recently been applied directly to atheromatous plaques during coronary angioplasty *(31)*. Drug-eluting stents have been developed to retard fibrosis and thrombosis after coronary angioplasty. Since estrogen can reduce smooth muscle migration and proliferation as well as restore endothelial function and vasodilatation, estrogen-eluting stents have been reported to reduce restenosis at 6 mo and ischemic events at 1 yr. There may be a role for estrogen in advanced atherosclerotic disease with its beneficial influence on vascular and endothelial mechanisms.

In multiple randomized trials in men and women, statin drugs have been shown to reduce heart attacks and deaths from myocardial infarctions by 30–45%. In the AF/CAPS/TEX/CAP study, women were included who possessed few cardiovascular risk factors but exhibited low HDL cholesterol values *(32)*. Over a 5-yr followup in this randomized study, women experienced the same beneficial reduction in cardiovascular events and mortality as men. In a subgroup analysis from the HERS trial, women assigned to the hormonal arm who were simultaneously taking a statin drug did not exhibit an increase in cardiovascular events when compared to the placebo arm *(33)*. Thus, the addition of a statin drug to a female wishing to continue hormonal therapy for lifestyle benefits may protect against cardiovascular complications.

Unresolved Questions

A major unresolved question in estrogen therapy is the role in primary prevention of coronary atherosclerosis. Primary prevention would involve the treatment of females without clinical manifestations of coronary artery disease. The recently reported randomized studies of older women with angiographic evidence or clinical evidence of coronary disease is considered to be a secondary rather than a primary prevention trial. The question remains whether hormonal therapy may be beneficial in slowing atherosclerotic progression in postmenopausal females who have not experienced a heart attack or clinical manifestations of coronary artery disease.

Another important consideration is the dose of estrogen replacement therapy, particularly since many of the observational and randomized trials administered high-dose 0.625 mg CEE. Recent studies suggest that lower-dose 0.3 mg may preserve the lipid and vascular benefits without disturbing inflammatory and clotting mechanisms. Both the dose as well as route of administration for either oral or transdermal forms are important, because circulation of estrogen through the liver has been shown to increase the production of C-reactive protein, but transdermal application avoids hepatic circulation.

The role of progestins in combination with estrogen and its influence on atherosclerosis requires continued experimental and clinical study. Progestin counteracts the lipid and vascular benefits of estrogen and the type of progestin as well as the dose will be important in future clinical trials. Wenger observed that estrogen alone had more favorable angiographic benefits than the combination of estrogen and progestin.

Finally, newly developed agents such as the selective estrogen receptor modulators require clinical trials to determine vascular protection against advancing atherosclerosis. Lower dose, newer agents, earlier replacement, and statin drugs as well as drug eluting estrogen stents may all contribute to slowing the atherosclerotic process in women.

Conclusions

1. Increased awareness, recognition, and diagnosis of heart disease in women are needed.
2. Lifestyle changes are beneficial and essential in postmenopausal females.
3. Hormonal therapy in coronary atherosclerosis remains unsettled. Observational studies suggest that early hormonal replacement in younger women can reduce cardiovascular disease by 30–50%, whereas use in older women failed to show a cardiovascular benefit.
4. Hormonal therapy initiated within 6 yr after loss of ovarian function may slow the atherosclerotic process.
5. Continued use of hormonal therapy for osteoporosis as well as quality of life should consider addition of a statin drug to prevent cardiovascular complications.
6. Low-dose hormonal therapy, earlier administration, newer agents, statin drugs, and estrogen eluting vascular stents may potentially slow the atherosclerotic process in women.

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