Carotid Atherosclerosis in Premenopausal and Postmenopausal Women and Its Association With Risk Factors Measured After Menopause

Kim Sutton-Tyrrell, DrPH; Holly C. Lassila, DrPH; Elaine Meilahn, PhD; Clareann Bunker, PhD; Karen A. Matthews, PhD; Lewis H. Kuller, MD, DrPH

Background and Purpose—In women, symptoms of coronary artery disease are delayed by 10 to 15 years in comparison with men, most likely because of the protective effect of ovarian hormones. This report compares the prevalence and degree of carotid atherosclerosis between 292 premenopausal women and 294 women at 5 to 8 years after menopause.

Methods—Scans were performed in the same laboratory over the same time period for both groups. Intima-media thickness (IMT) was averaged across the common, bulb, and internal carotids. The plaque index summarized degree of focal plaque based on the size and number of plaques throughout both carotid systems.

Results—Mean IMT was 0.69 mm for premenopausal women and 0.77 mm for postmenopausal women (P<0.001). Prevalence of plaque was 25% among premenopausal women and 54% among postmenopausal women (P<0.001). In both premenopausal and postmenopausal women, risk factors measured before menopause were associated with carotid atherosclerosis. Premenopausal risk factors independently associated with IMT were higher pulse pressure (P<0.001), triglycerides (P=0.002), body mass index (P<0.001), and study group (a surrogate for both age and menopausal status; P<0.001). Premenopausal risk factors independently associated with focal plaque were ever smoking (P=0.002), higher pulse pressure (P=0.028), higher LDL (P=0.003), age at baseline (P=0.050), and study group (P<0.001).

Conclusions—Subclinical carotid atherosclerosis can be observed in middle-aged women. Risk factors measured before menopause are clearly associated with subclinical disease measured both concurrently and at 5 to 8 years after menopause. (Stroke. 1998;29:1116-1121.)

Key Words: atherosclerosis ■ carotid artery diseases ■ epidemiology ■ women

In women, manifest symptoms of coronary artery disease are delayed by approximately 10 to 15 years in comparison with men.1 The two major explanations for this are that women benefit from the protective effects of ovarian hormones, and men engage in more health-damaging behaviors.2 The risk of CHD clearly rises among postmenopausal women. This is true whether menopause is surgically induced3 or whether women undergo a natural menopause.4,5 Levels of LDL cholesterol and HDL cholesterol are primary determinants of the risk of atherosclerosis and heart attack among both men and women.6–8 However, the pattern of lipoprotein changes with age is markedly different in men and women. In men there is a fall in HDL cholesterol at the time of adolescence and a continued lower HDL cholesterol and its subfractions throughout life compared with women.9,10 In women, HDL increases at the time of adolescence and remains elevated in comparison with men. Furthermore, there are changes in lipids around the time of the menopause. The Healthy Women Study (HWS) found small but significant decreases in HDL cholesterol and a substantial increase in LDL cholesterol and total cholesterol at the time of the perimenopause.11 In addition, weight gain12 and increases in systolic blood pressure13 were notable as women aged in midlife.

Our previous work has documented the association between changing risk factors and carotid atherosclerosis in the HWS cohort.14 The prevalence of any focal plaque was surprisingly high (50%) in these women, despite a relatively young age (mean, 57 years). This report compares the prevalence and degree of carotid atherosclerosis between these women in the HWS who were scanned at 5 to 8 years after menopause and a group of premenopausal women participating in the Women’s Healthy Lifestyle Project (WHLP). In addition, the extent to which baseline premenopausal risk factors are associated with disease before menopause (WHLP) and 5 to 8 years after menopause (HWS) is evaluated.

Subjects and Methods

Healthy Women Study
The HWS was initiated to study the changes in risk factors occurring in women as they go through the menopause. Beginning in 1983, 541...
premenopausal women aged 42 to 50 years, living in Pittsburgh, Pa, were recruited. Eligible women had diastolic blood pressures <100 mm Hg, were free from chronic disease requiring medication (including blood pressure medication), were not taking hormone replacement therapy, and were menstruating within 3 months of the baseline examination. These women were followed until they ceased cycling and/or used hormone replacement therapy in combination for 12 months, at which time they were considered postmenopausal and reevaluated. Evaluations were also done at 2, 5, and 8 years after menopause. Carotid ultrasound was performed at either the 5-year (49%) or 8-year (51%) clinic visit. Women were scanned consecutively as they returned for their clinic visits. An evaluation of baseline characteristics between the 292 participants presented here and the full cohort of 541 participants revealed no significant differences in baseline characteristics.

The Women’s Healthy Lifestyle Project

The WHLP was initiated to determine whether a vigorous intervention consisting of a low-fat, low-cholesterol diet, weight loss or prevention of weight gain, and increased exercise can prevent a rise in LDL cholesterol during the menopause. From 1991 to 1994, 535 premenopausal women aged 44 to 50 years were recruited. Eligible women had diastolic blood pressures <95 mm Hg, were free from chronic disease requiring medication (including lipid-lowering agents, insulin, thyroid, antihypertensive or psychotropic medications), were not taking hormone replacement therapy, and were menstruating within 3 months of the baseline examination. Women were randomly assigned to active intervention or a corresponding control group. All women were followed annually for 5 years. Women underwent carotid ultrasound exams while they were premenopausal, an average of 1 year after study entry. Women were scanned consecutively as they returned for their clinic visits. An evaluation of baseline characteristics between the 292 participants presented here and the full cohort of 535 participants revealed no significant differences in baseline characteristics.

Although the entry criteria for the HWS and WHLP cohorts were quite similar, the WHLP had additional exclusion criteria. BMI was required to be between 20 and 34, fasting glucose <140 mg/dL, LDL cholesterol between 80 and 160 mg/dL, and total cholesterol between 140 and 260 mg/dL. All participants signed informed consent, which was approved by the University of Pittsburgh Institutional Review Board.

Clinic Visits

Baseline clinic visits for the HWS and WHLP cohorts were similar and included height, weight, blood pressure, and a fasting blood draw for determination of insulin, glucose, and lipoproteins. Laboratory assays were measured at a central laboratory located at the University of Pittsburgh Graduate School of Public Health. This laboratory adheres to the quality control standards recommended by the Centers for Disease Control and the National Heart, Lung, and Blood Institute. Standard assays were used to measure total serum cholesterol, total HDL cholesterol, and triglycerides. LDL cholesterol was estimated with the use of the Friedewald equation. Serum glucose was determined by enzymatic assay, and plasma insulin concentration was measured by radioimmunoassay. Blood pressures were measured twice with the use of standard criteria and a random-zero sphygmomanometer, and the results were averaged. Similar data were collected at visits 5 and 8 years after menopause in the HWS.

Carotid Ultrasound Protocol

Carotid ultrasound was performed in the same laboratory by the same personnel over approximately the same period for both cohorts of women. A Toshiba SSA-270A scanner equipped with a 5-MHz linear array imaging probe was used. Sonographers scanned the right and left common carotid artery, the carotid bulb, and the first 1.5 cm of the internal and external carotid arteries. For each location, the sonographer imaged the vessel in multiple planes and then focused on the interfaces required to measure IMT as well as any areas of focal plaque. The best images were digitized for later scoring.

Trained readers measured the mean IMT across 1-cm segments of the near and far walls of the distal common carotid artery and the far wall of the carotid bulb and the internal carotid artery on both right and left sides. Measures from each location were then averaged to produce an overall measure of IMT. A computerized reading program developed for the Cardiovascular Health Study and modified in Pittsburgh was used. Readers also scored the ultrasound images for plaque in the proximal common, distal common, carotid bulb, internal carotid, and external carotid. Plaque was defined as a distinct area protruding into the vessel lumen with ≥50% greater thickness than surrounding areas. For each segment, the degree of plaque was graded as follows: 0 = no plaque; 1 = one small plaque <30% of vessel diameter; 2 = one medium plaque between 30% and 50% of the vessel diameter or multiple small plaques; and 3 = one large plaque >50% of the vessel plaque or multiple plaques with at least one medium plaque. The grades were summed across right and left carotid arteries to create an overall measure of extent of focal plaque termed the plaque index. The plaque index has been used as a measure of focal plaque for a number of years and has been found to be a valid and reproducible measure of carotid atherosclerosis in a number of populations. Sonographers responsible for the scoring of the scans were unaware of the study hypotheses or baseline characteristics of the women.

Reproducibility of IMT and the plaque index was assessed in five women who underwent two ultrasound examinations within 1 week. Each time, the women were scanned by two separate sonographers, and each scan was scored by two readers. When we accounted for both sonographer and reader variation, the intraclass correlation was 0.86 for IMT and 0.96 for the plaque index.

Statistical Methods

Descriptive statistics including measures of central tendency and dispersion were computed for continuous variables. The distributions of IMT were markedly skewed for both HWS and WHLP populations, and therefore Spearman correlations were used to describe the relationship between continuous risk factors and IMT. An inverse exponential transformation was performed to normalize the IMT distribution, and linear regression was used to evaluate factors independently associated with IMT. Models were run for each population separately and then both populations combined.

The plaque index was divided into three groups: those without plaque (plaque index = 0), those with minimal plaque (plaque index 1 to 2), and those with higher levels of plaque (plaque index ≥ 3). ANOVA was used to evaluate the association between continuous risk factors and IMT. An inverse exponential transformation was performed to normalize the IMT distribution, and linear regression was used to evaluate factors independently associated with any focal plaque. Logistic regression was used to evaluate risk factors independently associated with any focal plaque. Models were constructed for each group separately and then combined.

Results

Prevalence of Carotid Atherosclerosis

Mean IMT was 0.69 mm (median, 0.68 mm) for the premenopausal (WHLP) women and 0.77 mm (median, 0.74 mm) for the postmenopausal (HWS) women (P<0.001) (Figure 1). Previous literature reporting results in middle-aged women suggests that an IMT ≥0.75 mm can be considered high.
The percentage of women with IMT values $\geq 0.75$ mm was 16.1% for premenopausal women and 44.9% for postmenopausal women ($P<0.001$). The prevalence of any focal plaque was 25% among the premenopausal women and 54% among the postmenopausal women ($P<0.001$) (Figure 2), and the median plaque index values were 0 and 1 for the premenopausal and postmenopausal women, respectively ($P<0.001$). Among premenopausal women, there was no association between carotid atherosclerosis and WHLP intervention arm.

**Premenopausal Risk Factors of Premenopausal and Postmenopausal Cohorts**

Carotid ultrasound data are available for 292 premenopausal WHLP participants and 294 postmenopausal HWS participants. Baseline characteristics measured before menopause for both groups were compared (Table 1). While the mean age at baseline (study entry) was 47 years for both groups, the HWS cohort was on average 4 months older than the WHLP cohort. This difference was small, but it did reach statistical significance ($P=0.03$). Blood pressure and lipid values for both groups were well within the normal range. Systolic blood pressure was similar between the two cohorts, but diastolic blood pressure was higher among the HWS cohort, and therefore pulse pressure was higher for the WHLP cohort. Total cholesterol was similar for the two groups, but WHLP women had lower HDL and higher LDL levels than HWS women. Smoking history was similar between groups, with 50% of both groups having ever smoked and 12% to 14% current smokers. BMI was similar for both groups, but the WHLP cohort had a higher mean insulin level than the HWS cohort. Thus, there were some differences between the cohorts, probably as a result of the exclusion criteria for WHLP.

**Premenopausal Risk Factors Associated With IMT**

For both groups of women, risk factors measured before menopause were evaluated for their association with carotid atherosclerosis. In univariate analysis (Table 2), premenopausal factors significantly associated with greater IMT measured before menopause (WHLP) were older age, lower HDL, and higher LDL, triglycerides, insulin, BMI, and systolic and diastolic blood pressures. Premenopausal factors significantly associated with IMT measured after menopause (HWS) were higher cholesterol, lower HDL, and higher LDL, triglycerides, glucose, insulin, BMI, systolic blood pressure, and pulse pressure. Interestingly, pulse pressure measured before menopause was not associated with IMT among premenopausal women but was strongly associated with IMT in postmenopausal women.

Because many of these variables are highly correlated, linear regression was used to determine the independent associations of premenopausal risk factors with IMT. Among premenopausal women, these were higher BMI ($P=0.004$) and higher systolic blood pressure ($P=0.004$), with the model explaining 28% of the variation in IMT. After we controlled for these two factors, other variables were no longer significantly associated with IMT. Among postmenopausal women, independent associations with IMT were higher pulse pressure ($P<0.001$), higher triglycerides ($P=0.003$), and greater BMI ($P=0.04$), with the model explaining 39% of the variation in IMT. When both premenopausal and postmenopausal groups were combined, independent associations with IMT were higher pulse pressure ($P<0.001$), higher triglycer-
TABLE 2. Univariate Associations Between Risk Factors Measured Before Menopause and Carotid IMT Measured Before (WHLP) and After Menopause (HWS)

<table>
<thead>
<tr>
<th></th>
<th>Before Menopause (WHLP) (n=292)</th>
<th>5–8 years After Menopause (HWS) (n=294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spearman Correlation Coefficient</td>
<td>P</td>
<td>Spearman Correlation Coefficient</td>
</tr>
<tr>
<td>Age</td>
<td>0.12 0.02</td>
<td>0.07 0.12</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>0.08 0.09</td>
<td>0.09 0.07</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.14 &lt;0.01</td>
<td>-0.19 &lt;0.01</td>
</tr>
<tr>
<td>LDL</td>
<td>0.10 0.05</td>
<td>0.12 &lt;0.01</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>0.15 0.01</td>
<td>0.22 &lt;0.01</td>
</tr>
<tr>
<td>Glucose</td>
<td>0.06 0.15</td>
<td>0.13 0.01</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.10 0.04</td>
<td>0.17 &lt;0.01</td>
</tr>
<tr>
<td>BMI</td>
<td>0.23 &lt;0.01</td>
<td>0.21 &lt;0.01</td>
</tr>
<tr>
<td>Systolic BP</td>
<td>0.19 &lt;0.01</td>
<td>0.27 &lt;0.01</td>
</tr>
<tr>
<td>Diastolic</td>
<td>0.21 &lt;0.01</td>
<td>0.09 0.06</td>
</tr>
<tr>
<td>Pulse pressure</td>
<td>0.07 0.13</td>
<td>0.26 &lt;0.01</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.

In multivariate analysis (Table 4), premenopausal risk factors independently associated with plaque in premenopausal women were smoking (P=0.042) and systolic blood pressure (P=0.030). For postmenopausal women, important premenopausal factors appear to be smoking (P=0.014), pulse pressure (P=0.044), and LDL cholesterol (P=0.001). When the two groups were combined, premenopausal risk factors independently associated with plaque were smoking (P=0.002), pulse pressure (P=0.028), LDL (P=0.003), age at baseline (P=0.050), and study group (WHLP versus HWS; P<0.001). In this model, women at 5 years after menopause had 4.1 times greater odds of having plaque than premenopausal women (95% confidence interval, 2.6 to 6.4). This odds ratio rises to 5.3 for women at 8 years after menopause (95% interval, 3.2 to 8.6). These odds ratios represent the risk associated with both menopause and time (increased age) since menopause.

Discussion

These data suggest that the prevalence of subclinical carotid atherosclerosis in relatively young women is high both before and after menopause. Slightly lower levels of carotid atherosclerosis have been reported in other studies, and this may be due to differences in population characteristics and definitions of disease. In the Atherosclerosis Risk in Communities (ARIC) study, among women aged 45 to 54 years, the mean IMT was found to be 0.65 mm for premenopausal women and 0.66 mm for postmenopausal women.27 However, women who had been postmenopausal for 5 years or more had a mean IMT of 0.75 mm. Prevalence rates of carotid plaque in the ARIC study were 18% to 23% in women aged 45 to 64 years.28 This is similar to a 19% prevalence of plaque in a French study of women 45 to 54 years found an IMT of ≥0.75 mm in 30.4% of women.29 These authors found a prevalence of plaque of only 8% because the definition of plaque required more advanced disease and the internal carotid artery was not included in the examination. Exact

In multivariate analysis (Table 4), premenopausal risk factors independently associated with plaque in premenopausal women were smoking (P=0.042) and systolic blood pressure (P=0.030). For postmenopausal women, important premenopausal factors appear to be smoking (P=0.014), pulse pressure (P=0.044), and LDL cholesterol (P=0.001). When the two groups were combined, premenopausal risk factors independently associated with plaque were smoking (P=0.002), pulse pressure (P=0.028), LDL (P=0.003), age at baseline (P=0.050), and study group (WHLP versus HWS; P<0.001). In this model, women at 5 years after menopause had 4.1 times greater odds of having plaque than premenopausal women (95% confidence interval, 2.6 to 6.4). This odds ratio rises to 5.3 for women at 8 years after menopause (95% interval, 3.2 to 8.6). These odds ratios represent the risk associated with both menopause and time (increased age) since menopause.

Premenopausal Risk Factors Associated With Focal Plaque

Among premenopausal women, those with higher levels of plaque had higher systolic and diastolic blood pressure. Among postmenopausal women, significant associations were seen with cholesterol, LDL, and blood pressure. Compared with premenopausal women, systolic blood pressure was less strongly associated with plaque, and pulse pressure was more strongly associated with plaque.

TABLE 3. Mean Risk Factors Measured Before Menopause by Plaque Index

<table>
<thead>
<tr>
<th></th>
<th>Women Evaluated Before Menopause (WHLP) (n=292)</th>
<th>Women Evaluated After Menopause (HWS) (n=294)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.80 47.30 47.80 0.04</td>
<td>47.10 47.30 47.80 0.19</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>4.87 4.93 5.26 0.06</td>
<td>4.62 4.87 5.09 0.01</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.50 1.47 1.59 0.45</td>
<td>1.60 1.55 1.48 0.15</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>2.99 2.99 3.24 0.28</td>
<td>2.64 2.90 3.06 0.01</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>0.78 0.89 0.66 0.19</td>
<td>0.66 0.79 0.97 0.01</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.40 5.40 5.60 0.26</td>
<td>4.80 4.80 4.90 0.13</td>
</tr>
<tr>
<td>Insulin (nmol/L)</td>
<td>95.60 105.70 92.70 0.40</td>
<td>56.50 54.40 67.00 0.19</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.80 25.10 26.00 0.36</td>
<td>24.30 24.20 25.40 0.30</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>108.20 110.20 120.70 &lt;0.01</td>
<td>108.50 108.90 111.80 0.02</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>66.40 67.90 73.50 &lt;0.01</td>
<td>71.30 72.70 12.00 0.40</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>41.80 42.30 47.20 0.11</td>
<td>35.20 36.20 39.80 &lt;0.01</td>
</tr>
</tbody>
</table>

BP indicates blood pressure.
comparisons are difficult because data are not routinely reported by menopausal status.

The data reported here suggest that premenopausal risk factors are associated with subclinical atherosclerosis both before menopause and at 5 to 8 years after menopause. Postmenopausal women had four to five times the odds of plaque compared with premenopausal women. While some of this difference is likely due to the difference in age at time of scan between the two cohorts, the magnitude of the difference suggests that menopausal status is a key factor. Because of the close association between age and menopause, the true independent effects of each may not be able to be elucidated. This issue will be more thoroughly evaluated in a prospective manner when the WHLP cohort can undergo a postmenopausal carotid evaluation.

The associations between premenopausal risk factors and carotid atherosclerosis were similar regardless of whether disease was measured before or after menopause. Important variables were blood pressure, lipid values, and smoking. A number of studies have shown carotid atherosclerosis to be associated with blood pressure parameters, lipid levels, and smoking in both men and women. The degree of atherosclerosis as measured by wall thickness and plaque is likely a function of both the levels of risk factors and the duration of exposure to these levels. The loss of the protective effects of estrogen with menopause in combination with these lifestyle changes may occur as a result of subclinical disease. As mentioned above, the other factor operating here is age. As the vessels age, they may also become more susceptible to increasing risk factors and decreasing estrogen.

Of particular interest are the blood pressure parameters. For both IMT and plaque, premenopausal systolic blood pressure is more strongly associated with disease before menopause, while premenopausal pulse pressure is more strongly associated with disease 5 to 8 years after menopause. An increase in pulse pressure accompanies the structural changes that occur with age, including fragmentation and degeneration of elastin, increases in collagen, and a thickening of the arterial wall. Arterial stiffening occurs at different rates for different individuals and can be viewed as a process of biological aging of the vascular system. It is possible that pulse pressure measured before menopause predicts the degree to which systolic blood pressure rises after menopause or the degree to which the central arteries stiffen. The women with wider pulse pressures before menopause may be those whose vessels are beginning to show the effects of age.

The WHLP has shown that women are receptive to a preventive approach to CHD risk reduction and can be successful in making initial positive lifestyle changes. Long-term follow-up of these women will determine whether these lifestyle changes can be maintained and, if so, whether this has an effect on atherosclerotic disease measures. While prevention of risk factor changes with menopause is an important approach, this study suggests that premenopausal risk factors are important as well.

Clearly, the precursors of clinically important atherosclerotic vascular disease are present among premenopausal women. While the risk of clinical CHD among these relatively young women is very low, the progression of vascular disease will lead to more serious disease in their later years. This is supported by the fact that CHD is the leading cause of morbidity and mortality among postmenopausal women. The risk factors for carotid disease are similar to risk factors for clinical disease for both men and women. Effective methods to control most of these risk factors are available. Preventing the progression of vascular disease among these perimenopausal women would be more advantageous than focusing on very expensive and less successful approaches to treating CHD among older women. Early identification of women with subclinical disease may allow early modification of risk factors and ultimately prevent or delay the onset of clinical CHD.

In conclusion, subclinical carotid atherosclerosis can be observed in middle-aged women, and there are fairly dramatic differences in disease prevalence between women before menopause and women at 5 and 8 years after menopause. Risk factors measured before menopause are clearly associated with subclinical disease measured 5 to 8 years after menopause. Risk factor modification aimed at young to middle-aged women is a logical step in the prevention of

### Table 4. Premenopausal Risk Factors Associated With Focal Plaque

<table>
<thead>
<tr>
<th></th>
<th>Women Evaluated Before Menopause (WHLP) (n = 292)</th>
<th>Women Evaluated 5–8 Years After Menopause (HWS) (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Age at baseline (5-year increment)</td>
<td>1.91</td>
<td>0.94–3.9</td>
</tr>
<tr>
<td>Ever smoking</td>
<td>1.78</td>
<td>1.02–3.11</td>
</tr>
<tr>
<td>Systolic BP (10-mm Hg increment)</td>
<td>1.26</td>
<td>1.02–1.56</td>
</tr>
<tr>
<td>Pulse pressure (10-mm Hg increment)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>LDL (0.65-mmol/L increment = 25 mg/dL)</td>
<td>1.06</td>
<td>0.77–1.46</td>
</tr>
</tbody>
</table>

OR indicates odds ratio; CI, confidence interval; and BP, blood pressure.
atherosclerosis that develops as the beneficial effects of estrogen are lost in later years.

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