Novel risk factors for peripheral arterial disease in young women

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Novel Risk Factors for Peripheral Arterial Disease in Young Women

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PURPOSE: To investigate traditional and novel risk factors (homocysteine and C-reactive protein levels, and exposure to infections) for peripheral arterial disease in young women.

SUBJECTS AND METHODS: In a multicenter, population-based, case-control study, 212 young women (mean [± SD] age, 48.2 ± 7.0 years) with peripheral arterial disease and 475 healthy control women (mean age, 45.5 ± 8.1 years) completed a standardized questionnaire and provided blood samples. Peripheral arterial disease was angiographically confirmed if a stenotic lesion (more than 50% reduction of the lumen) was present in at least one major peripheral artery. Hyperhomocysteinemia was defined as a nonfasting plasma homocysteine level exceeding the 90th percentile of the control group. History of infectious diseases was determined by questionnaire.

RESULTS: Elevated C-reactive protein levels were associated with an increased likelihood of peripheral arterial disease (odds ratio [OR] = 3.9; 95% confidence interval [CI]: 1.8 to 8.5 for women in the third quartile; OR = 3.1; 95% CI: 1.4 to 6.8 for women in the fourth quartile; both comparisons with women in the first quartile). Hyperhomocysteinemia was not associated with a significantly increased risk of peripheral arterial disease (OR = 1.6; 95% CI: 0.9 to 3.0). A history of chickenpox, shingles, mumps, pneumonia, chronic bronchitis, peptic ulcer, or periodontitis was independently related to peripheral arterial disease, with adjusted odds ratios varying from 1.7 (95% CI: 1.0 to 3.1) for mumps to 3.4 (95% CI: 1.5 to 7.7) for peptic ulcer. The risk of peripheral arterial disease increased with the number of these infections; exposure to five or more infections increased the odds 3.7-fold (95% CI: 1.7 to 8.2). This association was not affected by the level of C-reactive protein.

CONCLUSION: Our results do not support a strong relation between homocysteine and peripheral arterial disease in young women. However, an elevated C-reactive protein level and several types of symptomatic infection were associated with peripheral arterial disease. **Am J Med. 2002;113:462–467.** ©2002 by Excerpta Medica, Inc.

Previous reports have indicated that only 1% to 7% of patients with peripheral arterial disease are 50 years of age or younger (1) and that men are affected 10 times more often than women (2). Therefore, peripheral arterial disease is rare in young women, in whom little is known about its etiology. Indeed, only a few case series describe the conventional cardiovascular risk factors in young women with peripheral arterial disease (3–5).

Recently, several novel risk factors for peripheral arterial disease have been proposed, in particular, an elevated homocysteine level, chronic infections, and infection-related biomarkers, such as C-reactive protein level. Elevated C-reactive protein levels were a strong predictor of the risk of peripheral arterial disease in a cohort of U.S. male physicians (6,7). Elevated levels of total plasma homocysteine have been linked to oxidative damage of the vascular endothelium, proliferation of vascular smooth muscle cells, and lipid peroxidation. These reactions may accelerate atherogenesis, which could lead to peripheral arterial disease (8). In a follow-up study of 572 patients with coronary artery disease (9), infectious burden was related to peripheral arterial disease and carotid artery stenosis.

In this case-control study of young women, we studied the relation between novel risk factors (i.e., homocysteine and C-reactive protein levels, and previous infections) and peripheral arterial disease.

SUBJECTS AND METHODS

Study Design

Analyses were performed within the Risk of Arterial Thrombosis In relation to Oral contraceptives (RATIO) study, a multicenter, population-based, case-control study that was conducted between January 1990 and October 1995 to investigate the relation between oral contraceptive use and vascular diseases (stroke, myocardial infarction, and peripheral arterial disease) in young women in the Netherlands. In the first phase of the study, a standardized questionnaire was sent to all patients and control subjects (10). Later, all respondents were asked to participate in the second phase of the study. The group of

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patients with peripheral arterial disease was augmented with women referred between November 1995 and December 1999. In this phase, we asked all participants to provide blood samples and to complete a standardized questionnaire about previous infections. The patients who had not been included in the first phase of the study also received a questionnaire about cardiovascular risk factors and oral contraceptive use. The study protocols were approved by the ethics committees of all the participating hospitals, and informed consent was given by all participants.

Patients with Peripheral Arterial Disease

Women were eligible if they had been referred to one of the collaborating hospitals between January 1, 1990, and December 31, 1999, with typical symptoms of intermittent claudication (cramping pain in the lower leg[s] during exercise) or with rest pain, nonhealing ulcers, or gangrene; were aged 18 to 49 years at the time of referral; had an angiographically confirmed diagnosis of peripheral arterial disease; and had given informed consent. Peripheral arterial disease was angiographically confirmed when a stenotic lesion causing more than 50% reduction of the lumen was present in at least one major peripheral artery (distal abdominal aorta, common iliac artery, internal and external iliac artery, femoral artery, popliteal artery, anterior and posterior tibial artery, or peroneal artery).

Of the 294 eligible patients, 24 (8%) could not be located. Of the 270 remaining patients, 212 (79%) agreed to complete the questionnaire about infections and to provide blood samples, including 113 (53%) who had also participated in the first phase of the study.

Control Subjects

In the first phase of the study, 925 population-based control women about the same age (5-year strata) as the patients were recruited by random digit dialing (10). In the second phase, 475 of these women completed the questionnaire about infections and provided blood samples. The most common reasons for refusal to participate in the second phase of the study were lack of time and fear of venipuncture.

Risk Factor Assessment

All patients and control women completed the same standardized questionnaire that asked about medication use and cardiovascular risk factors (smoking, body mass index, oral contraceptive use, history of hypertension, history of diabetes mellitus, and history of hypercholesterolemia). Blood pressure was measured semiautomatically (Omron*M1* OMRON Healthcare GmbH, Hamburg, Germany). Serum and plasma were stored at −80°C until processed. Serum total and high-density lipoprotein cholesterol, triglyceride, and glucose levels were measured with a clinical analyzer (Roche/Hitachi 747, Mannheim, Germany). Low-density lipoprotein cholesterol levels were calculated with the Friedewald equation.

Table 1. Characteristics of Women with Peripheral Arterial Disease and Controls

Characteristic	Peripheral Arterial Disease (n = 212)	Controls (n = 475)
	Number (%) or Mean ± SD	
Age (years)	48.2 ± 7.0	45.5 ± 8.1
Body mass index (kg/m^2)	26.3 ± 5.8	25.0 ± 4.3
Smoking		
Current	127 (60)	154 (32)
Former	74 (35)	158 (33)
Never	10 (5)	163 (34)
History of		
Hypercholesterolemia*	184 (88)	282 (58)
Diabetes mellitus†	28 (14)	5 (1)
Hypertension‡	122 (59)	116 (25)
Education		
Primary school or less	43 (21)	42 (9)
Secondary school	143 (70)	312 (66)
Higher education or university	18 (9)	118 (25)
Current oral contraceptive use	89 (42)	155 (33)
Blood pressure (mm Hg)		
Systolic	141 ± 23	130 ± 19
Diastolic	85 ± 12	83 ± 11
Glucose (mg/dL)§	114 ± 66	73 ± 25
Cholesterol (mg/dL)§	218 ± 53	207 ± 43
HDL cholesterol	50 ± 15	55 ± 13
LDL cholesterol	132 ± 53	126 ± 38
Cholesterol/HDL cholesterol ratio	4.9 ± 2.9	4.0 ± 1 3
Triglycerides (mg/dL)§	183 ± 97	132 ± 81

*Use of lipid-lowering medication or cholesterol level ≥193 mg/dL.
†Use of a blood-glucose–lowering medication or (nonfasting) glucose level ≥198 mg/dL
‡Use of antihypertensive drugs, systolic blood pressure ≥160 mm Hg, or diastolic blood pressure ≥95 mm Hg
§To convert total cholesterol, LDL cholesterol, and HDL cholesterol from mg/dL to mmol/L, multiply by 0.0259 To convert triglycerides from mg/dL to mmol/L, multiply by 0 0113 To convert glucose from mg/dL to mmol/L, multiply by 0 05551.
HDL = high-density lipoprotein, LDL = low-density lipoprotein

Information about a history of infectious diseases (infectious mononucleosis, chickenpox, shingles, fever blister, mumps, hepatitis A or B, pneumonia, bronchitis, peptic ulcer, periodontitis, and gingivitis) was obtained by questionnaire. Total plasma homocysteine levels were measured by high-pressure liquid chromatography (11), and includes the sum of free and bound forms of homocysteine, homocystine, and homocysteine-cysteine mixed disulfide. Plasma C-reactive protein level was measured using an enzyme immunoassay (C-reactive protein EAI HS; Kordia, Leusden, The Netherlands). All mea-

Table 2. Associations between Common Infections and Risk of Peripheral Arterial Disease in Young Women

Infection	Peripheral Arterial Disease	Controls	Unadjusted	Adjusted for Age, Smoking, and Education	Multiply Adjusted*
	Number (%)		Odds Ratio (95% Confidence Interval)		
Infectious mononucleosis	8 (4)	25 (5)	0 7 (0 3–1 6)	1 1 (0 5–2 8)	1 7 (0 6–4 4)
Chickenpox†	125 (91)	304 (89)	1 2 (0 6–2 3)	1 9 (0 9–3 9)	3 1 (1 3–7 7)
Shingles	30 (14)	34 (7)	2 1 (1 3–3 5)	2 1 (1 2–3 8)	2 6 (1 3–5 1)
Fever blister	90 (44)	176 (38)	1 3 (0 9–1 8)	1 1 (0 7–1 6)	1 1 (0 7–1 7)
Mumps†	91 (69)	192 (59)	1 5 (1 0–2 4)	1 5 (0 9–2 4)	1 7 (1 0–3 1)
Hepatitis A	6 (3)	9 (2)	1 5 (0 5–4 3)	1 6 (0 5–5 0)	1 5 (0 4–6 2)
Hepatitis B	3 (1)	2 (0)	3 4 (0 6–20)	2 2 (0 3–14)	3 0 (0 3–29)
Pneumonia	55 (26)	68 (15)	2 1 (1 4–3 1)	1 9 (1 2–3 0)	1 9 (1 2–3 3)
Bronchitis	71 (35)	107 (24)	1 8 (1 2–2 5)	1 7 (1 2–2 6)	1 8 (1 1–3 0)
Peptic ulcer	27 (14)	15 (3)	4 6 (2 4–8 9)	3 0 (1 5–6 3)	3 4 (1 5–7 7)
Periodontitis‡	31 (23)	33 (8)	3 4 (2 0–5 9)	3 6 (2 0–6 7)	3 0 (1 4–6 3)
Gingivitis‡	31 (23)	67 (17)	1 5 (1 0–2 5)	1 8 (1 0–3 0)	1 2 (0 6–2 2)

*Adjusted for age, body mass index smoking hypercholesterolemia, diabetes mellitus, hypertension education, oral contraceptive use, and C reac tive protein and homocysteine levels

†Women who answered ' yes ' or no were included in the analyses

‡Only women without dentures were asked about periodontitis and gingivitis

surements were performed without knowledge of case or control status

Definition of Risk Factors

A history of infection was defined as a "yes" answer to the question concerned The answers "no" and "I don't know" were classified as "not exposed to infection" for all infections except chickenpox and mumps Women who had answered "I don't know" on these two variables were excluded from the analyses Hyperhomocysteinemia was defined as a nonfasting plasma total homocysteine level exceeding the 90th percentile of the control group (≥2 16 mg/L)

Women who smoked were categorized as current, former, or never Body mass index was calculated as kg/m^2 Education was defined as the highest level of education attained primary school, secondary school, or higher education/university Current oral contraceptive use was defined as use within 1 month before the date of completion of the questionnaire A history of diabetes mellitus was defined by the use of glucose-lowering medication or a (nonfasting) serum glucose level ≥198 mg/dL A history of hypercholesterolemia was defined by the use of cholesterol-lowering medication or a serum total cholesterol level ≥193 mg/dL A history of hypertension was defined by use of antihypertensive drugs, a systolic blood pressure ≥160 mm Hg, or a diastolic blood pressure ≥95 mm Hg

Statistical Analysis

The crude and the adjusted odds ratios (OR) and 95% confidence intervals (CI), as estimates for the relative risk of peripheral arterial disease, were calculated The cumulative number of infections was categorized into three subgroups low (zero to one infection, reference group), intermediate (two to four infections), and high (five or more infections) The relation between C-reactive protein and homocysteine levels and peripheral arterial disease was assessed by calculating the risk by quartiles

Odds ratios were first adjusted for age, smoking (current, former, never), and education (low, middle, high) They were then adjusted for cardiovascular risk factors, including age, smoking (current, former, never), body mass index, history of hypertension (yes, no), hypercholesterolemia (yes, no), diabetes mellitus (yes, no), education (low, middle, high), current oral contraceptive use (yes, no), C-reactive protein and homocysteine levels, and infectious burden (low, intermediate, high)

To evaluate whether infectious burden and C-reactive protein levels contribute jointly to the risk of peripheral arterial disease, an analysis was performed in subjects with a C-reactive protein level above and below the median value of the control group A multiplicative interaction term was added to the logistic model to test for a statistically significant interaction

RESULTS

All traditional risk factors for atherosclerosis were more common in patients with peripheral arterial disease than in control subjects (Table 1) Patients reported a history of more of the common infections than did the control subjects, with the exception of infectious mononucleosis (Table 2) The unadjusted odds ratios in women who had been exposed to shingles, mumps, pneumonia, chronic bronchitis, peptic ulcer, periodontitis, or gingivitis were

Table 3. Associations among C-Reactive Protein Level, Homocysteine Level, and the Cumulative Number of Common Infections with Peripheral Arterial Disease in Women

Risk Factor	Peripheral Arterial Disease	Controls	Unadjusted	Adjusted for Age, Smoking, and Education	Multiply Adjusted*
	Number (%)		Odds Ratio (95% Confidence Interval)		
C-Reactive protein quartiles (levels in mg/L)†					
I: ≤0.5	16 (8)	118 (25)	1	1	1
II: 0.6–1.3	26 (12)	115 (25)	1.7 (0.9–3.3)	1.8 (0.8–3.7)	1.5 (0.7–3 6)
III· 1 4–5.0	82 (39)	116 (25)	5.2 (2.9–9.4)	5 4 (2.8–10.7)	3.9 (1.8–8.5)
IV: ≥5.1	88 (41)	115 (25)	5.6 (3.1–10)	5.3 (2.7–10)	3.1 (1.4–6 8)
Homocysteine quartiles (levels in mg/L)†					
I: ≤1 35	52 (25)	118 (25)	1	1	1
II: 1.36–1.58	48 (24)	119 (25)	0.9 (0.6–1.5)	0.8 (0.5–1.4)	0.5 (0.3–0 9)
III: 1.59–1.86	35 (17)	114 (25)	0.7 (0.4–1 2)	0.7 (0.4–1.2)	0.5 (0.3–1 0)
IV: ≥1.87	69 (34)	117 (25)	1.3 (0.9–2.1)	1.2 (0.7–1.9)	0.8 (0.4–1 4)
Hyperhomocysteinemia‡	45 (22)	46 (10)	2.6 (1.7–4.1)	1.9 (1.2–3 1)	1.6 (0.9–3.0)
Cumulative number of infections§					
0 or 1	51 (24)	163 (35)	1	1	1
2 to 4	136 (64)	283 (60)	1.5 (1 1–2.2)	1.8 (1.2–2.7)	2 0 (1.2–3.2)
≥5	25 (12)	26 (6)	3.1 (1.6–5 8)	3.0 (1.5–6.0)	3.7 (1.7–8.2)

*Adjusted for age, body mass index, smoking, hypercholesterolemia, diabetes mellitus, hypertension, education, oral contraceptive use, C-reactive protein and homocysteine levels, and cumulative number of infections

†Quartiles based on levels in the control group.

‡Defined as plasma total homocysteine levels exceeding the 90th percentile of the control range (≥2 16 mg/L) To convert homocysteine from mg/L to μmol/L, multiply by 7 397.

§Includes infectious mononucleosis, chickenpox, shingles, fever blister, mumps, hepatitis A and B, pneumonia, chronic bronchitis, peptic ulcer, periodontitis, and gingivitis

statistically significant and varied between 1.5 (95% CI: 1.0 to 2.4) for mumps to 4.6 (95% CI: 2.4 to 8.9) for peptic ulcer. Adjustment for age, smoking, and education did not significantly affect these odds ratios; the risk associated with peptic ulcer decreased the most, to 3.0 (95% CI: 1.5 to 6.3). Adjustment for other risk factors did not cause substantial changes in these odds ratios, except perhaps for gingivitis (Table 2).

The risk of peripheral arterial disease in women with a C-reactive protein level in the highest two quartiles was increased substantially in both unadjusted and adjusted models (Table 3). In contrast, elevated homocysteine levels were not associated with peripheral arterial disease (Table 3). Hyperhomocysteinemia was associated with an increased risk of peripheral arterial disease, but not after adjustment for cardiovascular risk factors (Table 3).

The risk of peripheral arterial disease increased with the cumulative number of infections (Table 3). Level of C-reactive protein did not affect this relation (Table 4).

DISCUSSION

We evaluated novel risk factors (C-reactive protein and homocysteine levels, and symptomatic infections) for peripheral arterial disease in this case-control study of young women. A C-reactive protein level in the highest two quartiles increased the risk of peripheral arterial disease more than threefold, independently of all other risk factors. In contrast, homocysteine level was not independently related to peripheral arterial disease. Symptomatic infections (chickenpox, shingles, mumps, pneumonia, chronic bronchitis, peptic ulcer, and periodontitis) and the infectious burden were independent risk factors for peripheral arterial disease.

Most previous case-control studies have reported an association between homocysteine level and cardiovascular risk (12). A meta-analysis including more than 4000 patients reported an increased risk of coronary artery disease (OR = 1.7; 95% CI: 1.5 to 1.9), cerebrovascular disease (OR = 2.5; 95% CI: 2.0 to 3.0), and peripheral arterial disease (OR = 6.8; 95% CI: 2.9 to 15.8) in patients with increased levels of homocysteine (13). However, not all studies have reported unequivocal evidence that homocysteine is associated with vascular disease (7,14). For instance, a nested case-control analysis within a cohort of 14,916 initially healthy U.S. male physicians showed no significant relation between homocysteine and peripheral arterial disease (7). It has been suggested that the case-control studies may have made insufficient adjustments for confounding factors, and that a high homocys-

Table 4. Associations among C-Reactive Protein Level, Cumulative Number of Infections, and Peripheral Arterial Disease

C-Reactive Protein Level*	Cumulative Number of Infections†	Peripheral Arterial Disease	Controls	Unadjusted	Adjusted for Age, Smoking, and Education	Multiply Adjusted‡
		Number (%)		Odds Ratio (95% Confidence Interval)		
Low	0 or 1	9 (4)	83 (18)	1	1	1
High	0 or 1	42 (20)	76 (17)	3.9 (2.0–7.6)	4.1 (1.8–9.4)	3.9 (1.5–10)
Low	2 to 4	26 (12)	139 (30)	1.5 (0.8–3.0)	1.7 (0.7–3.9)	2.5 (0.9–6 9)
High	2 to 4	110 (52)	137 (30)	5.7 (3.1–11)	7.4 (3.4–16)	6.9 (2.8–17)
Low	≥5	7 (3)	11 (2)	5.3 (1.9–15)	5.0 (1.4–17)	8.2 (1.9–35)
High	≥5	18 (9)	15 (3)	7.0 (2.9–17)	9.4 (3.3–26)	10.2 (3 1–34)

*Divided into above or below the median value (1 3 mg/L) in the control group

†Includes infectious mononucleosis, chickenpox, shingles, fever blister, mumps, hepatitis A and B, pneumonia, chronic bronchitis, peptic ulcer, periodontitis, and gingivitis.

‡Adjusted for age, smoking, body mass index, hypercholesterolemia, diabetes mellitus, hypertension, oral contraceptive use, and homocysteine level There was no evidence of an interaction between C-reactive protein levels, number of infections, and peripheral arterial disease ($P > 0$ 10).

teine level may be a consequence rather than a cause of vascular disease.

Few studies have analyzed the relation between clinical symptoms as indicators of infection and vascular disease. In one cohort study, symptoms of chronic respiratory infections predicted the risk of coronary events independently of known cardiovascular risk factors (15). In contrast, two prospective studies reported no relation between self-reported periodontal disease and coronary artery disease (16,17). However, other studies that involved dental examination have found an increased risk of coronary artery disease in people with periodontal disease (18–21).

Epidemiological studies on the relation between infection and atherosclerosis have mainly used antibody titers against microorganisms to assess exposure status, instead of a history of clinical symptoms (22,23). The advantage of the latter approach is that clinical symptoms may be associated with the extent of the inflammatory reaction caused by the infection (24). Because infections are thought to influence atherogenesis by causing an inflammatory response, infections that cause mild or no clinical symptoms might not be related to atherogenesis.

We found that the number of self-reported infections was related to the risk of peripheral arterial disease in young women. Perhaps each infection evokes an inflammatory response that triggers the same common pathway of cellular reactions that eventually affect the vascular endothelium. Other studies have shown that greater pathogen burden is related to the risk of coronary artery disease (9,25,26). In one study, for example, people exposed to at least one chronic infection had a fourfold risk of developing subclinical atherosclerosis in the next 5 years (25).

We found a significant and independent relation between elevated C-reactive protein levels and peripheral arterial disease, consistent with results in men (6,7). The mechanisms responsible for this association are uncertain, but C-reactive protein induces the expression of adhesion molecules in human endothelial cells (7,26). Liuzzo et al. suggested that increased levels of C-reactive protein are a marker of hyperresponsiveness of the inflammatory system (27).

A potential limitation of our study is that we measured nonfasting levels of homocysteine. Other studies, however, have shown that the plasma total homocysteine level is influenced only modestly by food intake (breakfast) (28). Other potential sources of bias are recall bias and self-report of information about risk factors and infections. Adjustment for potential confounders was done in two steps. First, odds ratios were adjusted for age, smoking, and education, and then for other vascular risk factors. This allowed us to evaluate the effects of different adjustments. Another approach would have been to adjust for only those confounders that are related to peripheral arterial disease and the factor of interest. Potential confounding variables such as age, body mass index, and C-reactive protein and homocysteine levels were entered in the multivariate models as continuous variables, whereas smoking, socioeconomic status, oral contraceptive use, and diabetes, hypertension, and hypercholesterolemia were entered as categorical variables. We chose to adjust for diabetes, hypertension, and hypercholesterolemia, instead of the glucose or cholesterol level or the actual blood pressure, because many women were being treated for these risk factors.

In conclusion, the results of our study do not support a strong relation between homocysteine levels and peripheral arterial disease in young women in The Netherlands. However, elevated C-reactive protein levels were associated with peripheral arterial disease, as was infectious burden.

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