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What is This?

Slightly Elevated High-Sensitivity C-Reactive Protein (hsCRP) Concentrations Are Associated With Carotid Atherosclerosis in Women With Varying Degrees of Glucose Tolerance

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Abstract

We examined whether high-sensitivity C-reactive protein (hsCRP) ≥2.0 mg/L was associated with increased intima-media thickness (IMT), plaque burden, and plaque echolucency in carotid arteries. Women (n = 635) from a population sample of 64-year-old females with varying degrees of glucose tolerance underwent risk factor assessment, measurement of hsCRP, and ultrasound examinations of the carotid arteries. Participants with hsCRP levels ≥2.0 mg/L had elevated carotid bulb IMT independently of other cardiovascular risk factors compared with those with hsCRP <2.0 mg/L. The participants with plaques in the high-hsCRP group had larger total plaque area compared to those with plaque in the lower hsCRP group. Plaque echolucency did not differ between groups. High-sensitivity CRP levels ≥2.0 mg/L were accompanied by elevated IMT in the carotid bulbs independently of other cardiovascular risk factors. Total plaque area was larger among women with plaques in the high hsCRP group versus the lower hsCRP group.

Introduction

Inflammation plays a role in the development of atherosclerosis and several soluble markers of inflammation have been associated with the progression of atherosclerosis. In particular, the acute-phase C-reactive protein (CRP) has become a potential predictor of cardiovascular disease.[1-4] Another important element for cardiovascular disease is the metabolic syndrome,[5,6] and a well-known association exists between serum CRP levels and components of the metabolic syndrome such as central obesity, insulin resistance, impaired glucose tolerance, and hyperlipidemia.[7-9]

We and others have previously shown that common carotid artery (CCA) intima-media thickness (IMT) is associated with the established risk factors for cardiovascular disease, coronary atherosclerosis, and cardiovascular morbidity.[10-13] Furthermore, we showed that CRP is associated with future cardiovascular disease.[14] As reported in a recently published review, high-sensitivity CRP (hsCRP) is associated with increased IMT in carotid arteries in many but not all studies.[15]

The ultrasound technique allows for identification and measurement of plaques, and the occurrence of plaques is associated with an elevated risk of future cardiovascular disease.[16] Some studies have reported an association between hsCRP and occurrence of carotid atherosclerotic plaques[17,18] including 2 prospective studies.[18,19] However, most studies have not shown such an association.[20-26] Large plaque volume and low plaque density (measured by gray scale median [GSM] or visually evaluated) are both associated with increased cardiovascular risk.[16,27] As echolucent plaques have a high content of lipids and are associated with future cardiovascular events,[27] it has been suggested that such plaques are vulnerable and

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might be accompanied by elevated levels of circulating acute phase reactants.[17] In support of such a concept, hsCRP has been found to correlate negatively with carotid plaque fibrosis.[17]

Observational studies have resulted in suggested cut-off levels (eg, hsCRP ≥ 2.0 mg/mL), indicating increased risk.[28,29] Apparently healthy patients with hsCRP ≥ 2.0 mg/mL were randomized to rosuvastatin (20 mg daily) or placebo in the large, double-blind controlled Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial.[30] This study showed that rosuvastatin treatment resulted both in a lowering of hsCRP concentrations and in a 44% relative reduction in the primary cardiovascular end point.[31]

It is not clear whether a hsCRP cutoff level of ≥2.0 mg/L also relates to subclinical ultrasound-assessed atherosclerosis. In this study, we examine whether hsCRP ≥ 2.0 mg/L is associated with change in carotid IMT(C-IMT) independently of common cardiovascular risk factors and also with increased plaque burden in the carotid arteries, and increased occurrence of echolucent plaques in a population sample of postmenopausal women.

Methods

Study Outline

The Diabetes and Impaired glucose tolerance in Women and Atherosclerosis (DIWA) study is based on screening 64-year-old women in Gothenburg, Sweden, to identify those with diabetes and impaired glucose tolerance.[32] From the screened cohort of 2595 women, a subgroup of 638 women underwent ultrasound examination of the carotid arteries. All clinical and laboratory examinations were performed as previously described.[32,33] From the subgroup of 638 women, 3 women had missing blood sample values for hsCRP and were not included. Predictors of cardiovascular disease assessed in the current study included smoking (assessed as cigarette years and smoking status), anthropometric data, serum concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, apolipoproteins A-I (Apo A-I) and B (Apo B), Apo B/Apo A-I ratio, lipoprotein (a) (Lp(a)), blood glucose, HbA1c, blood pressure, and heart rate. Systolic and diastolic blood pressures were assessed in supine patients at rest. Heart rate was assessed using electrocardiogram (ECG). The study was approved by the regional ethics committee and all participating individualss gave their informed consent.

Biochemistry

Capillary blood glucose was analyzed without delay using a glucose oxidase technique (HemoCue AB, Ängelholm, Sweden). Venous blood samples were drawn after an overnight fast to obtain serum lipids and HbA1c. Cholesterol and triglyceride levels were determined by enzymatic techniques (Thermo Clinical Labsystems, Espoo, Finland). High-density lipoprotein was determined after precipitation of apoliprotein B-containing lipoproteins with magnesium sulphate and dextran sulphate (Thermo Clinical Labsystems). Low-density lipoprotein was calculated as described by Friedewald et al.[34] HbA1c was determined with high-pressure chromatography on a Mono S HR 5/5 column (Amersham Biosciences, Piscataway, New Jersey, and Pharmacia, Uppsala, Sweden). High-sensitivity CRP was measured at the Wallenberg Laboratory by an ultrasensitive method using particle-enhanced immunoturbidimetry (Orion Diagnostica, Espoo, Finland) and the coefficient of variation was 3.4%.

Ultrasound Examination

Examinations were performed with an ultrasound scanner equipped with a linear 8L5-MHz transducer (Sequoia 512, Siemens, Mountain View, California). An ECG signal (lead II) was simultaneously recorded to synchronize image capture to the peak of the R wave to minimize variability during the cardiac cycle. The left and right carotid arteries were scanned at the level of the bifurcation, and the images used to measure IMT were recorded from the far wall in the CCA and the carotid bulb from the real-motion image loop (real-time images). To identify and record the occurrence of atherosclerotic plaques, carotid arteries were scanned from the distal part of the CCA to 10 mm into the external and internal carotid arteries. A sequence of real-time images was captured and saved digitally from the position yielding the best visibility of the plaque (ie, the largest cross-sectional area in a longitudinal transaxial view, as judged visually). We measured IMT and plaque characteristics according to the definitions we previously used,[35] which largely supports the American Society of Echocardiography (ASE) consensus.[36] From the real-motion loop, an R-wave-triggered longitudinal image for each plaque was saved digitally.

For IMT measurements and plaque classification purposes, the ultrasound image was converted to an 8-bit gray-scale image (bitmap). As described previously by our group, the software allows measurements of IMT and lumen diameter (LD) using an automatic border detection with an option to make manual corrections by the user.[35] This semiautomated method to measure IMT is associated with a low coefficient of variation.[37] A composite measure of IMT was also calculated as the mean IMT of the CCA and carotid artery bulb. Cross-sectional area for the CCA was calculated as the difference between the total area inside the adventitia and the lumen area: $\pi (LD_{mean}/2 + IMT_{mean})^2 - \pi (LD_{mean}/2)^2$.

Plaque echogenicity was assessed by (1) visual classification, using the Gray-Weale method[38] and (2) using a new software, Semi-Automatic Method to Evaluate Echogenicity (SAMEE) described previously by our group.[39] SAMEE presents values for GSM and percentage white (PW). Percentage white is a new feature describing the percentage of plaque pixels above an adaptive intensity threshold that takes into account image echogenicity and noise. For participants with multiple plaques, we calculated the average GSM and average PW (the average of GSM and PW values from all plaques in each participant, respectively).[39]

Statistical Analyses

The cohort was divided into 2 groups, hsCRP <2.0 mg/L and hsCRP $\geq$2.0 mg/L for statistical analyses. Results are presented as means $\pm$ standard deviation or number and percentage unless otherwise indicated. Categorical data were analyzed by Fishers exact test and chi-square test. Mann-Whitney U tests were used for comparison of continuous variables. A well-known problem is the co-variability between risk factors related to hsCRP and carotid IMT. To reduce the number of variables included in the multiple regression analysis, a correlation matrix was used to select the most representative variable, that is, the variable with the highest correlation coefficient with both carotid IMT and hsCRP for each of the risk factor clusters representing obesity and glucose/insulin metabolism, respectively. Regarding lipoproteins, Apo B/Apo A-I ratio was included in the multivariate analysis because it is known to mirror both proatherogenic and antiatherogenic lipoproteins in the circulation.[40] For the regression analyses, skewed variables were log transformed. However, to obtain measured values, additional analyses with the same adjustment was performed not log transforming the IMT variable. Two-tailed P < .05 was considered significant.

Results

Patient Characteristics

High-sensitivity CRP $\geq$2.0 mg/L was associated with elevated body mass index (BMI), higher levels of waist circumference, diastolic blood pressure, heart rate, and higher serum concentrations of triglycerides, Apo B, and a higher Apo B/Apo A-I ratio (Table 1). Diabetes, treatment with antidiabetic drugs, and impaired glucose tolerance were more common in the high-hsCRP group, which was also characterized by higher concentrations of fasting blood glucose, HbA1c, and fasting plasma insulin (Table 1) compared with the low hsCRP group.

Carotid Intima-Media Thickness and hsCRP

Only women having IMT measurements in both the bulb and the CCA (n = 559) were included in these analyses. High-sensitivity CRP $\geq$2.0 mg/L was associated with increased IMT in the CCA and in the carotid bulb, both for mean and maximum values (Table 2). Consequently, the carotid IMT composite (IMT comp) was increased in the high-hsCRP group and the common carotid cross-sectional area was larger in the high-hsCRP group. There was no difference in LD between the two hsCRP groups.

Among the ultrasound IMT measurements, carotid IMT $comp_{max}$, carotid bulb IMT_{mean}, carotid bulb IMT_{max}, and common carotid IMT_{max} showed the highest correlations with hsCRP ($r = .15, r = .15, r = .14, r = .12$, all Ps < .01) and were chosen for subsequent multivariate analysis. Among obesity variables, waist circumference showed the highest correlations with hsCRP and carotid $IMTcomp_{max}$ ($r = .45$ and $r = .19$, respectively, all Ps < .01) compared with BMI. Plasma insulin concentrations showed higher correlations with hsCRP and carotid $IMTcomp_{max}$ ($r = .33, r = .17$, both Ps < .01) than

HbA1c or fasting blood glucose. Serum Apo B/Apo A-I ratio showed correlations with both hsCRP and carotid $IMTcomp_{max}$ ($r = .22, P$ < .01; $r = .10, P$ < .05). Correlations with both hsCRP and measures of carotid IMT were not observed for cigarette years, blood pressure, or heart rate.

As shown in Tables 2 and 3, $IMTcomp_{max}$, carotid bulb IMT_{mean}, carotid bulb IMT_{max}, and common carotid IMT_{max} were increased in the group with high hsCRP compared with the group with low hsCRP. After adjustment for glucose tolerance group, log waist circumference, Apo B/Apo A-I ratio, and log plasma insulin, hsCRP$\geq$ 2.0 mg/L remained significantly associated with increased carotid bulb IMT_{max}, carotid bulb IMT_{mean}, and carotid $IMTcomp_{max}$ but not with common carotid IMT_{max}. Furthermore, when carotid bulb IMT_{max} was not log transformed after the same adjustment as described previously, carotid bulb IMT_{max} was 0.15 mm larger in the high hsCRP group compared with the low hsCRP group (95% confidence interval [CI] 0.05-0.26 mm].

Carotid Plaque and hsCRP

All women with ultrasound examination and blood sample values for hsCRP were included (n = 635). Comparisons between the low and high hsCRP groups did not reveal any differences in the number of women with or without plaques (158 [41%] vs 105 [42%], respectively, ns), nor in the mean number of plaques observed (0.64 $\pm$ 0.94 vs 0.71 $\pm$ 1.0, respectively, ns), nor mean plaque area (10.9 $\pm$ 19.6 vs 14.4 $\pm$ 25.5 mm^2, respectively, ns).

A closer analysis of the women with plaques showed that women in the high hsCRP group had a larger mean plaque area than women in the low hsCRP group with plaque (Table 4). Interestingly, further examination of the high and low hsCRP groups with plaques showed that there was a significant difference in waist circumference, plasma insulin, and Apo B/Apo A-I ratio (Table 4). No other variables showed a significant difference (data not shown). After adjustment for waist circumference, log plasma insulin, and Apo B/Apo A-I, hsCRP levels $\geq$ 2.0 mg/L still remained significantly associated with a larger log median total plaque area (β: 0.109, 95 % CI 0.017-0.20). When the median total plaque area was not log transformed, and after the same adjustment described previously, the median total plaque area was 7.73 mm^2 larger in the high hsCRP group compared with the low hsCRP group (95% CI 0.50-14.95 mm^2, P: .04).

There were no significant differences between low- and high-hsCRP groups in either PW or GSM as evaluated by SAMEE (Table 4). When examining the number of echolucent plaques per participant using the classification according to Gray-Weale,[38] no significant difference was observed between the low and high hsCRP groups (Table 4).

Discussion

We found in our cross-sectional study of 64-year-old women that hsCRP $\geq$2.0 mg/L was significantly associated with a larger

Table 1. Demographics and Clinical Data in the two Groups With hsCRP < 2.0 and ≥ 2.0 mg/L, Respectively[a]

Variable	hsCRP < 2.0 mg/L, n = 386	hsCRP ≥ 2.0 mg/L, n = 249	P
hsCRP,[b] mg/L	0.80 (0.45-1.25)	4.12 (2.65-6.25)	NA
Age,[c] yrs	64.5 (0.3)	64.5 (0.3)	NS
Weight,[d] kg	70.9 (11)	80.4 (14)	<.001
Height,[d] m	164 (6)	164 (5)	NS
BMI,[d] kg/m^2	26.3 (3.8)	30.1 (4.9)	<.001
Hip circumference,[d] cm	103 (8)	110 (10)	<.001
Waist circumference,[d] cm	89 (10)	99 (12)	<.001
WHR[d]	0.87 (0.07)	0.90 (0.06)	<.001
Systolic BP,[c] mmHg	138 (20)	140 (19)	NS
Diastolic BP,[c] mmHg	77 (9)	78 (10)	.04
Heart rate,[c] bpm	64 (10)	67 (11)	<.001
Smoking habits			NS[4]
Current smoker, n (%)	74 (19)	56 (23)	
Previous smoker, n (%)	134 (35)	86 (35)	
Never smoked, n (%)	171 (44)	104 (42)	
Cigarette years	300 (121-500)	308 (100-597)	NS
Clinical chemistry			
Total cholesterol, mmol/L	5.82 (1.06)	5.81 (1.05)	NS
HDL, mmol/L	1.70 (0.43)	1.53 (0.44)	<.001
LDL, mmol/L	3.51 (0.98)	3.52 (1.00)	NS
Triglycerides,[b] mmol/L	1.16 (0.91-1.66)	1.50 (1.09-2.12)	<.001
Apo A-I, g/L	1.59 (0.26)	1.54 (0.27)	.006
Apo B, g/L	1.11 (0.27)	1.19 (0.28)	.001
Apo B/Apo A-I	0.72 (0.21)	0.79 (0.22)	<.001
Lp(a),[b] g/L	0.234 (0.149-0.559)	0.262 (0.157-0.262)	NS
HbA1c,[b] %	4.60 (4.40-5.10)	4.80 (4.50-5.40)	.003
B-glucose,[b] mmol/L	5.20 (4.75-5.95)	5.50 (4.80-6.60)	.004
Plasma insulin,[b] pmol/L	39.9 (26.9-58.2)	59.1 (36.2-92.5)	<.001
Medical history/new findings			
Myocardial infarction, n (%)	9 (2)	6 (2)	NS[e]
Stroke, n (%)	9 (2)	6 (2)	NS[e]
Hypertension			
Earlier known hypertension, n (%)	99 (26)	84 (34)	NS[e]
Newly detected hypertension,[f] n (%)	46 (12)	37 (15)	NS[e]
Prevalence of diabetes and glucose tolerance group			.011[e]
Diabetes, n (%)	128 (34)	101 (41)	−
IGT,[g] n (%)	123 (32)	85 (34)	−
NGT,[g] n (%)	130 (34)	60 (24)	−
Medical treatment			
Statin therapy, n (%)	46 (12)	38 (15)	NS[e]
Fibrate therapy, n (%)	4 (1)	3 (1)	NS[e]
Insulin therapy, n (%)	17 (4)	12 (5)	NS[e]
Oral antidiabetic therapy, n (%)	27 (7)	35 (14)	.005[e]
Glitazone therapy, n (%)	8 (2)	4 (2)	NS[e]
Family history			
Overweight, n (%)	96 (25)	65 (26)	NS[e]
Atherosclerotic disease,[h] n (%)	188 (49)	121 (49)	NS[e]
Diabetes, n (%)	98 (25)	66 (26)	NS[e]

Abbreviations: BMI, body mass index; WHR, waist−hip ratio; BP, blood pressure; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; B-glucose, blood glucose; Apo, apolipoprotein; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; NA, not analyzed; NS, nonsignificant.
[a] Data are mean and standard deviation (SD) unless otherwise stated.
[b] Median (Percentile 25-75).
[c] At (date of) ultrasound examination.
[d] Mean value of screening and ultrasound measurements.
[e] Chi-square for independence.
[f] Systolic BP >160 mmHg and/or diastolic BP >90 mmHg mean values.
[h] Diagnosed after 2 OGTTs.
[g] Mother and/or father had myocardial infarction or stroke.

Table 2. Intima-Media Thickness and Lumen Diameter in the two Groups With hsCRP < 2.0 and ≥ 2.0 mg/L, respectively[a]

Variable	hsCRP <2.0 mg/L, n = 352	hsCRP ≥2.0 mg/L, n = 207	*P* Value
Carotid artery bulb			
Carotid bulb IMT$_{mean}$, mm	0.95 (0.83-1.11)	1.03 (0.87-1.29)	<.0001
Carotid bulb IMT$_{max}$, mm	1.26 (1.12-1.52)	1.41 (1.15-1.90)	.001
CCA			
CCA IMT$_{mean}$, mm	0.83 (0.75-0.93)	0.85 (0.77-0.98)	.041
CCA IMT$_{max}$, mm	0.92 (0.83-1.04)	0.95 (0.87-1.07)	.009
Lumen diameter, mm	5.91 (5.75-6.28)	5.99 (5.65-6.41)	NS
CCA Cross-sectional area, mm^2	17.3 (15.28-20.72)	18.6 (16.13-21.96)	.009
Composite (CCA + bulb)/2			
Carotid composite$_{mean}$, mm	0.90 (0.80-1.02)	0.94 (0.83-1.12)	.001
Carotid composite$_{max}$, mm	1.11 (0.99-1.28)	1.17 (1.10-1.45)	.001

Abbreviations: CCA, common carotid artery; hsCRP, high-sensitivity C-reactive protein; IMT, intima media thickness; NS, nonsignificant.
[a] Data are median and interquartile range (percentile 25-75).

IMT of the carotid bulb, independent of other cardiovascular risk factors compared with women with hsCRP below 2.0 mg/L. Furthermore, in women with carotid plaques, those with hsCRP levels ≥2.0 mg/L had significant larger total plaque area compared to those with levels below 2.0 mg/L independent of other cardiovascular risk factors. There were no differences between the high and low hsCRP groups with respect to plaque echogenicity.

We observed that hsCRP levels ≥2.0 mg/L were accompanied by increased IMT in the bulb, measured as either mean or maximum thickness, after adjustment for cardiovascular risk factors. This difference was not observed in CCA. The maximum carotid bulb IMT was significantly larger in the high hsCRP group even after adjustment for risk factors associated with both IMT and hsCRP. This finding is important to address for two reasons. First, it is well known that the predilection site for development of atherosclerosis is the carotid bulb. This is related to the flow conditions in the carotid bifurcation.[41-43] Our laboratory has previously reported that carotid bulb IMT, but not CCA IMT, is associated with coronary atherosclerosis.[44] Hence, the carotid bulb (or internal carotid artery) rather than the CCA is a part of the artery exhibiting atherosclerotic changes as expressed in enlargement of the intima-media complex.

There is an ongoing debate as to which ultrasound-assessed measure of carotid IMT should be used in observational and intervention studies. In the recent consensus statement from the American Society of Echocardiography, it is concluded that mean-maximum values are more sensitive to change but could also be less reproducible, but that maximum values are an alternative if there is a local expertise.[36] The method used for measuring IMT in this study has been used in our laboratory since 1991,[35] and several articles regarding method and evaluation has been published from our group showing acceptable reproducibility.[35,37] The composite measure that is an average of IMT in the CCA and bulb regions has been used in several studies.[45-48]

In a large meta-analysis, CRP concentrations had continuous associations with coronary heart disease, ischemic stroke, and vascular mortality. Data showed that associations with ischemic vascular disease depended considerably on conventional risk factors and other markers of inflammation.[49]

Table 3. Differences Between the High and Low hsCRP Groups in IMT in the CCA and Carotid Bulb, and the Means of These two Measurements (Composite IMT) in 64-year-old Women

Log Values	Differences Between the Groups With hsCRP ≥ 2.0 mg/L and hsCRP < 2.0.mg/L	
	Unadjusted (mean [95 % confidence interval])	Adjusted[a] (mean [95 % confidence interval])
Carotid bulb IMT$_{mean}$	0.039 (0.019-0.059)[d]	0.029 (0.007-0.052)[b]
Carotid bulb IMT$_{max}$	0.045 (0.022-0.067)[d]	0.037 (0.011-0.062)[c]
CCA IMT$_{mean}$	0.014 (0.001-0.027)[b]	0.00 (−0.014-0.015)
CCA IMT$_{max}$	0.016 (0.003-0.030)[b]	0.00 (−0.013-0.017)
Carotid composite$_{mean}$	0.026 (0.011-0.042)[c]	0.015(−0.002-0.032)
Carotid composite$_{max}$	0.032 (0.015-0.049)[d]	0.022 (0.003-0.041)[b]

Abbreviations: CCA, common carotid artery; hsCRP, high-sensitivity C-reactive protein; IMT, intima-media thickness.
[a] Adjusted for glucose tolerance group (diabetes, impaired, and normal glucose tolerance), log waist circumference, serum apolipoprotein B/A-I, and log plasma insulin.
[b] *P* < .05.
[c] *P* < .01.
[d] *P* < .001.

No other study has been identified that relates the hsCRP ≥2.0 mg/L threshold to carotid IMT and plaque occurrence. A recent review examined the association between serum hsCRP levels and carotid IMT.[15] They identified 65 groups within 54 studies that represented healthy participants, population samples, patients with vascular risk factors, and those with overt cardiovascular disease. C-reactive protein was independently associated with carotid IMT in 20 of 59 groups, after adjustment for factors that covariate. Significant positive associations between hsCRP and carotid IMT were more common among men than among women. The carotid IMT measures comprised a mixture of assessments from the CCA.

However, in the current study we found a significant univariate correlation between all measurements of IMT and

Table 4. Characteristics of 64-year-old Women With Carotid Artery Plaques, and CRP ≥2.0 mg/L or CRP <2.0 mg/L

Variable	hsCRP <2.0 mg/L, n = 158	hsCRP ≥2.0 mg/L, n = 105	*P* Value
hsCRP, mg/L	0.86 (0.52-1.28)	4.10 (2.71-5.90)	NA
Waist circumference,[a] cm; mean (SD)	89 (±10)	99 (±12)	<.001
Plasma insulin, pmol/L; median (IQR)	40.0 (26.1-57.4)	54.9 (34.5-91.7)	<.001
ApoB/ApoA-I, mean (SD)	0.70 (±0.18)	0.81 (±0.23)	<.001
Total plaque area/participant (participants with plaque), mm²; median (IQR)	19.4 (10.7-34.6)	25.8 (13.8-42.9)	.014
Percentage echolucent plaque/participant (Gray-Weale), mean (SD)	88 (±24)	91 (±20)	NS
Average gray scale median, median (IQR)	52.8 (40.4-62.4)	49.0 (38.0-59.0)	NS
Average percentage white, median (IQR)	37.6 (24.0-47.4)	34.3 (24.2-45.5)	NS

Abbreviations: PW, percentage white; GSM, gray-scale median; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range (shown as percentile 25-75); NA, not analyzed; N.S, nonsignificant; SD, standard deviation.
[a] Mean value of screening and ultrasound measurements.

hsCRP. After adjustment for glucose tolerance group, waist circumference, plasma insulin, and Apo B/Apo A-I ratio, this correlation remained for maximum carotid bulb, mean carotid bulb, and maximum composite carotid IMT.

There is a discrepancy between our finding that hsCRP ≥2.0 mg/L was associated with increased carotid bulb IMT but not in plaque burden in the entire diabetic cohort. Among women with plaques, those with hsCRP ≥2.0 mg/L had significant larger total plaque area independent of other cardiovascular risk factors compared to those with low hsCRP levels. This discrepancy is probably explained by the fact that plaque examinations may be less precise than IMT measurements, which constitute a continuous variable not including the zero level. Previously published studies that have examined associations between hsCRP and carotid plaque occurrence show inconsistent results. In a cross-sectional analysis, the large Tromsø cohort study did not show that CRP was elevated in individuals with carotid plaques compared with those without.[26] Blackburn et al showed a relationship between hsCRP and the formation of advanced plaques, but only in males.[20] More recent studies confirm that elevated CRP is associated with increased plaque formation in men, but not in women.[23-25] However, in our previous studies, no significant correlation was observed between hsCRP and subclinical atherosclerosis in carotid arteries of healthy males.[21]

A prospective analysis from the Rotterdam study showed independent and graded associations of CRP with carotid plaque progression during a 6.4-year follow-up.[19] Smaller studies performed in patients with hypertension,[50] cardiovascular risk factors,[18] and carotid artery stenosis[17] have reported that CRP was associated with increased carotid plaque burden.

We and others have presented data indicating that echolucent carotid plaques are associated with increased risk of cardiovascular disease.[27,51] We hypothesized in the current study that elevated hsCRP was related to increased occurrence of echolucent plaques as measured by GSM, PW,[39] and quantification of echolucent plaques classified visually according to Gray-Weale.[38] We could not verify this hypothesis, as there were no differences between the high and low hsCRP group regarding these variables. Literature shows a slightly

contradicting image regarding echogenicity and biomarkers. A previously published study has shown that the acute-phase reactant orosmucoid is associated with echolucent carotid plaques and that histopathologically assessed fibrosis of carotid plaques shows an inverse correlation with GSM.[17] Other studies have failed to show an association between carotid plaque echolucency and hsCRP concentrations.[26,52] It remains unknown whether echolucency in asymptomatic plaques is related to atherogenic properties such as rate of plaque development, size, or persistence over time.

Previous observational studies have indicated that hsCRP levels ≥2.0 mg/L is associated with medium- and high-risk cardiovascular disease.[28,53] In the large prospective cardiovascular health study (CHS), CRP correlated weakly with carotid IMT and carotid plaque severity.[54,55]

Many studies have shown that statins reduce hsCRP levels[31,56] and progression rates of C-IMT.[57,58] Furthermore, some studies have indicated that statins also reduce carotid plaque volume.[59,60] However, little is known about how echolucency of the plaque is affected, but Kadoglou et al have shown that intensive treatment with atorvastatin increases GSM in patients with carotid stenosis.[61]

One limitation of the current study is that we only examined 64-year-old women who had been screened for diabetes and impaired glucose tolerance. This can also be viewed as a strength, however, as we reduce the introduction of significant biological variables (eg, age and sex). Women with impaired glucose tolerance and diabetes are of particular interest, as the incidence of diabetes increases steeply in this age category and these phenotypes are typically accompanied by a very strong relative increase in cardiovascular risk in women, resulting in an absolute risk that is similar to that among men at the same age.[62]

Our interpretation of the current results, taken in the context of available data from previous studies, is that hsCRP levels (mg/L) are associated with increased C-IMT in 64-year-old women with varying degrees of glucose tolerance and that this association is independent of several other important cardiovascular risk factors. Plaque abundance was not increased in women with hsCRP levels ≥2.0 mg/L, although total plaque

area was significantly larger among women with plaques in the high-hsCRP group. We found no evidence that elevated hsCRP is accompanied by a high proportion of echolucent plaques as an indication of plaque vulnerability. The contribution of the current study to the accumulating body of data relating hsCRP to atherosclerotic disease is that the hsCRP cutoff value used in the JUPITER study is also associated with prevalent subclinical ultrasound-assessed atherosclerosis in a population-based cohort of women.

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