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Carotid intima-media thickness and carotid plaque represent different adaptive responses to traditional cardiovascular risk factors

Liz Andréa Villela Baroncini *[,1], Lucimary de Castro Sylvestre [1], Roberto Pecoits Filho [1]

Pontifícia Universidade Católica do Paraná, Medical School, Health Sciences Postgraduate Program, Rua Imaculada Conceição 1155 — Bloco CCBS, CEP: 80215-901 Curitiba, Brazil

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ABSTRACT

Aim: To assess the effects of each traditional cardiovascular risk factor (hypertension, diabetes mellitus, dyslipidemia, and smoking), including the presence of coronary artery disease (CAD), on carotid intima-media thickness (CIMT) and to assess the degree of carotid plaque occurrence.
Methods: A total of 553 outpatients (216 men and 337 women; mean age 67.06 ± 12.44 years) who underwent a carotid artery ultrasound were screened for carotid plaque and CIMT measurements.
Results: The CIMT medians were higher in males ($P < .001$) and in patients with hypertension ($P < .001$). A linear increase occurred in mean CIMT of 0.0059 mm for each year of increase in age. The presence of plaque indicated a tendency to correlate with CIMT ($P = .067$). The presence of hypertension associated with diabetes ($P = .0061$; estimated difference 0.0494 mm) or dyslipidemia ($P = .0016$; estimated difference 0.0472 mm) or CAD ($P = .0043$; estimated difference 0.0527 mm) increased the mean CIMT measurements. The probability of plaque occurrence in carotid arteries is influenced by the age ($P < .001$) and is higher in patients with dyslipidemia ($P = .008$) and CAD ($P < .001$).
Conclusions: Hypertension is the strongest cardiovascular risk factor that increases CIMT, followed by age and male sex. Age and dyslipidemia increase the probability of carotid plaque. Increased CIMT and plaque could be present in the same patient caused by different risk factors and with independent effects on the artery wall and different clinical prognoses.

1. Introduction

Since 1986 when Pignoli et al. [1], in an in vitro study, concluded that B mode imaging represents a useful tool for detection and monitoring of changes in intimal + medial thickness and allows the evaluation of changes in the arterial wall in areas without localized plaques, carotid intima-media thickness (CIMT) measurements have been used in several observational and interventions studies [2–3]. The noninvasive nature of this approach became a recommendation for its use in the preclinical diagnosis and follow-up of patients with atherosclerosis. CIMT is widely used in clinical research for testing the value of new and emerging risk factors and for evaluation of the effects of various drugs on risk factor modifications [2]. CIMT is considered a reflection of multiple risk factors; however, primary contributors to intima-media thickening are age and hypertension, which do not necessarily reflect the atherosclerotic process [3–5]. The primary limitation of CIMT is its inability to distinguish lesions with a necrotic core considered a key indicator of significant plaque advancement and a recognized feature of lesion vulnerability [3]. CIMT and carotid plaque, although correlated, reflect different stages and aspects of atherosclerosis and have distinct determinants [6]. A hypertensive hypertrophic response of medial cells can be observed in early phases of atherosclerosis, while carotid plaque formation is often seen in later stages of atherosclerosis and may be caused by inflammation, oxidation, and endothelial dysfunction or smooth muscle cell proliferation, or both [7]. The objective of the present study was to assess the different effects of each traditional cardiovascular risk factor (hypertension, diabetes mellitus, dyslipidemia, and smoking), including also the presence of coronary artery disease (CAD) on CIMT and the presence of carotid plaque. The correlation between the presence of plaque and CIMT was also investigated.

2. Methods

2.1. Patients

The subjects were selected from a private cardiology clinic next to the ultrasound laboratory. All patients were under the care of a private cardiologist, who assessed the results of blood samples, collected from subjects after overnight fasting. The cardiologist used standard techniques

* Corresponding author.
E-mail address: lizandreabaroncini@hotmail.com (L.A.V. Baroncini).
[1] These authors take responsibility for all aspects of the reability and freedom from bias of the data presented and their discussed interpretation.

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to determine serum glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides. The decision to perform a carotid artery study was made exclusively by the private cardiologist. A total of 553 consecutive outpatients (216 men and 337 women; mean age 67.06 ± 12.44 years) who underwent a carotid artery ultrasound were screened for carotid plaque and CIMT measurement, during a period of 6 months. There were no exclusion criteria. Before the study, the ultrasonographist collected information on demographic characteristics and risk factors for each patient according to the report from the private cardiologist. Patients were asked about the presence of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, and current smoking habit. Hypertension was defined as a history of treated hypertension or the presence of systolic BP ≥ 140 mm Hg or diastolic BP ≥ 90 mm Hg as measured by the private cardiologist. Smoking history was coded as never or current smoker. Subjects were classified as having diabetes when treated for insulin-dependent or non-insulin-dependent diabetes or having elevated fasting glucose levels (≥126 mg/dL). The use of lipid-lowering drugs or the presence of total cholesterol >200 mg/dL, HDL-cholesterol <40 mg/dL, LDL-cholesterol >100 mg/dL or triglycerides >150 mg/dL was recorded. No patient at the present study had a history of stroke or transient ischemic attack and no patient complained of intermittent claudication suggesting peripheral arterial disease. A history of myocardial infarction, angioplasty, or coronary artery by-pass surgery was recorded and a positive CAD history was defined as the presence of any of these diseases in conjunction with the evaluation report from the private cardiologist. Local Institutional ethical committee approval was obtained for the study. Informed consent was obtained from each patient and the study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

2.2. Ultrasound measurements

Measurements were made with a high-resolution B-mode ultrasonography (Philips Medical Systems' HD11 platform) with a broadband width linear array transducer L 3–12 MHz. Sonography and readings were carried out by trained certified sonographers. On longitudinal 2D ultrasound images of the carotid artery, the near wall and the far wall are displayed as 2 echogenic lines (the adventitia and intima) that are separated by the hypoechoic media. The distance between the leading edge of the first bright line of the far wall (lumen-intima interface) and the leading edge of the second bright line (media-adventitia interface) is defined as the CIMT. Measurements of CIMT were taken manually on the distal 10 mm of both right and left common carotid arteries in the far wall. Five determinations were conducted on each side and the average measurement was used for the CIMT, according to Brazilian Cardiovascular Imaging Department Task Force for Carotid Ultrasound [8]. An artery was classified as being affected by plaque if there was a focal wall thickening at least 50% greater than that of the surrounding vessel wall or a localized region with CIMT greater than 1.5 mm that did not uniformly involve the whole left or right carotid artery with or without a flow disturbance. The vascular ultrasonographist identified plaques in common, internal and external carotids at the time of ultrasound measurement. The presence of plaque was coded as yes or no; however, the degree of stenosis has not been taken into account in the present study.

2.3. Statistical analysis

Categorical variables are expressed as percentages and continuous variables are expressed as mean ± SD, with a 95% confidence interval (CI) and a significance level of 5%. Multiple linear regression analysis was used to assess the effects of each cardiovascular risk factor (hypertension, diabetes mellitus, smoking, dyslipidemia, and CAD) and the presence of plaque on CIMT. Age and sex were used as control variables. The chi-square test with Yates correction was used to correlate each risk factor and the presence of plaque. The logistic regression model was used to assess all variables with respect to the presence of plaque. Statistical significance was indicated by a value of $P < .05$. Analyses were performed using IBM SPSS v.20.0 computer software.

3. Results

A total of 553 patients were analyzed. Patients' baseline characteristics are provided in Table 1. At least one risk factor was found in 450 (174 men; 67.6 ± 11.7 years) patients; 103 patients (41 men; 64.6 ± 15.1 years) had no risk factors. Carotid plaque was present in 119 (21.5%) patients: 107 (19.3%) patients with at least one risk factor and 12 (2.1%) patients without risk factors (Table 1). The corrected coefficient of determination was equal to 0.34, indicating that 34% of changes in CIMT were explained by the variables included in the model. The CIMT medians were higher in males and in patients with hypertension. There was a linear increase in mean CIMT of 0.0059 mm for each year increase in age. An interesting result indicates that 25.33% of the variations of CIMT are explained by the age of the individual, excluding the effect of sex, hypertension, diabetes, dyslipidemia, smoking, CAD, and the presence of plaque. Diabetes, dyslipidemia, CAD, and smoking did not influence the CIMT measurements in the present study. The presence of plaque indicated a tendency to influence the CIMT measurements (Table 2). However, there was a significant difference between the effects of hypertension on CIMT and the effects of diabetes, dyslipidemia, and CAD. The presence of hypertension associated with diabetes ($P = .0061$; estimated difference 0.0494 mm) or dyslipidemia ($P = .0016$; estimated difference 0.0472 mm) or CAD ($P = .0043$; estimated difference 0.0527 mm) increases the mean CIMT measurements. Hypertension did not influence CIMT when associated with plaque ($P = .2891$) or current smoking ($P = .1103$). The probability of plaque occurrence on carotid arteries is influenced by age and is higher in patients with dyslipidemia and CAD and had a tendency to be higher in patients who were current smokers. Hypertension and diabetes did not cause an increase in the presence of plaque in the present study (Table 3).

4. Discussion

The main finding of the present study is that CIMT and carotid plaque are influenced differently by traditional cardiovascular risk factors. Hypertension is the risk factor that most increases the CIMT measurements alone and when associated with diabetes, dyslipidemia, and CAD, while dyslipidemia and CAD increase the probability of carotid plaque occurrence. Age influences both CIMT and plaque, and male sex increases CIMT values, but not plaque occurrence. Although intima-media thickness is considered a marker of hypertrophy of intima and media layers of the artery wall, it is not synonymous with atherosclerosis [9–10]. Actually, CIMT and atherosclerosis share common underlying mechanisms for both disease initiation and progression. Pathological intimal thickness is characterized as the formation of lipid pools in the

Table 1
Patient's baseline characteristics.

Patients with risk factors (N/%)	450 (81.3%)
Sex (M/F)	174/276
Age (y ± SD)	67.6 ± 11.7
Carotid plaque (N/%)	107 (23.8)
History of hypertension (N/%)	333 (74)
History of dyslipidemia (N/%)	249 (55.3)
History of diabetes mellitus (N/%)	100 (22.2)
Cardiovascular history (N/%)	71 (15.7)
Current smoking (N/%)	65 (14.4)
Patients without risk factors (N/%)	103 (18.62)
Sex (M/F)	41/62
Age (y ± SD)	64.6 ± 15.1
Carotid plaque (N/%)	12 (11.6)

Table 2
Influence of cardiovascular risk factors on carotid intima-media thickness values according to multiple linear regression analysis.

Variable	Parameters	95% CI	*P* value
Intercept	0.3059		<.001
Sex	0.0280	0.0082–0.0478	.0057
Age	0.0059	0.0050–0.0067	< .001
Hypertension	0.0391	0.0190–0.0592	< .001
Plaque	0.0224	−0.0430–0.0158	.0670
Current smoking	0.0095	0.0201–0.0390	.5293
Diabetes	−0.0103	0.0358–0.0151	.4251
Dyslipidemia	−0.0081	−0.0273–0.0112	.4109
CAD	−0.0136	−0.0430–0.0158	.3636

absence of a necrotic core that is a marker of plaque advancement [3]. Therefore, most investigators do not consider adaptive intimal thickening as representative of an atherosclerotic disease process. CIMT assessed by B-mode ultrasound cannot distinguish between intima plus media layer hypertrophy (which is not considered atherosclerosis) from plaque initiation. Previous studies [11–13] indicate that CIMT increases with age, and the present study verified that 25.33% of the variations of CIMT are explained by the age of the individual excluding the effect of sex, hypertension, diabetes, dyslipidemia, and smoking. Although CIMT has been proposed as a quantitative index of atherosclerosis, patients' age should be taken into account. The normal range and abnormal value and the risk factors associated with CIMT might vary considerably between different populations and sexes [13–16]. Despite these facts, CIMT by itself is a marker of generalized atherosclerosis, and, for example, the relation between intima-media thickness and stroke is independent of plaque [17]. In support of these findings, the present study demonstrates that the presence of plaque is not strongly correlated with CIMT values. In other words, both pathological features (increased CIMT and plaque) could be present in the same patient but caused by different risk factors and with independent effects on the artery wall and with different clinical prognostic factors. Studies observed that foam cell lesions, considered types I and II atherosclerosis, are present in the third decade of life at the carotid bifurcation and are gradually replaced by lipid core plaques (types IV and V) in the following decades [18]. In these initial stages where foam cells are found only in the intima layer, without fibrous tissue, CIMT may or may not progress to more advanced lesions, depending on the presence of cardiovascular risk factors, the medical therapy received by the patient, and genetic influences [18–19]. The present study based on a population between the fifth and seventh decades of life shows the presence of carotid plaque in just 21.5% of the subjects. The majority (78.5%) had no carotid plaque identified by the B-mode ultrasound, which could justify why CIMT is not a good predictor of cardiovascular events when compared to coronary calcification that has long been known also to occur as a part of the atherosclerotic process [20–24]. CIMT might just represent an adaptive response of the arterial wall to age and hypertension, the major risk factors in this study population. The absence of carotid plaque (an established atherosclerotic lesion) does not exclude the probability of the presence of atherosclerotic plaques in other vascular territories. But, on the contrary, the presence of carotid plaque had a higher diagnostic accuracy for the prediction for future CAD events [25–26]. The presence of hypertension significantly increases CIMT values due to a hypertrophy of the media layer of the vessel wall [27], but the formation of carotid plaque is most strongly related to blood lipid levels as indicated by the study of Gardener et al. [28]. Hypertension alone or in association with other cardiovascular risk factors causes a significant increase in CIMT [4,29–31], and besides the fact that it is considered a major cardiovascular risk factor, in the present study, hypertension did not contribute to the occurrence of plaque. This finding is corroborated in other studies [32–34] that found no correlation between the presence of hypertension and the occurrence of atherosclerotic plaques. However, the presence of hypertension could accelerate plaque vulnerability provoking intraplaque hemorrhage and rupture [35]. Although CIMT and plaque share the effect of atherosclerotic risk factors, they have different natural histories, patterns of risk factors, and prediction of vascular events [27]. To corroborate these findings, the present study found 12 (2.1%) patients with carotid plaque but no traditional identifiable cardiovascular risk factor. Another interesting finding of the present study is that diabetes mellitus, dyslipidemia, CAD, and smoking did not influence the CIMT measurements.

Table 3
Probability of occurrence of plaque, according to each risk factor.

Variable		Without plaque (N/%)	With plaque (N/%)	*P*	OR (CI 95%)
Hypertension	No	180 (81.08%)	42 (18.92%)		
	Yes	243 (72.97%)	90 (27.03%)	.908	0.97 (0.6–1.57)
Diabetes	No	356 (78.24%)	99 (21.76%)		
	Yes	67 (67.00%)	33 (33.00%)	.253	1.38 (0.8–2.38)
Smoking	No	372 (75.92%)	118 (24.08%)		
	Yes	51 (78.46%)	14 (21.54%)	.087	1.85 (0.91–3.77)
Dyslipidemia	No	240 (78.69%)	65 (21.31%)		
	Yes	183 (73.2%)	67 (26.8%)	.008	1.84 (1.17–2.88)
CAD	No	382 (78.93%)	102 (21.07%)		
	Yes	41 (57.75%)	30 (42.25%)	<.001	3.14 (1.76–5.62)
Age				<.001	1.11 (1.08–1.13)
Sex				.731	1.09 (0.68–1.75)

4.1. Study limitations

The present study has some important limitations identified as (a) lack of important clinical data; (b) renal control; (c) adopted method for CIMT measurement and (d) lack of total atherosclerotic burden assessment. In regard to lack of data, the medical therapy received by the patients and the time course and treatment of their disease, mainly diabetes and hypertension, were not provided [36]. However, only 15% of subjects in the present study presented CAD according to a private cardiologist's report and no patient had a history of stroke or intermittent claudication suggestive of more advanced macrovascular disease observed in diabetic patients. Moreover, according to previous studies, subjects presented multiple risk factors, which made it difficult to establish whether an increase in pathological events could be correlated with the degree of CIMT or with the number and type of risk factors present. The influence of the traditional vascular risk factors on the arterial hyperplasia was not clearly established as well [37]. Most of subjects in the present study presented more than one risk factor and received more than one medical therapy. Assessment of the effect of each medical therapy on each risk factor as well as of the effect the prescribed medication on CIMT was not performed. Additionally, the effect of various antihypertensive drugs on carotid intima-media thickness (CIMT) produced conflicting results [38]. The second limitation addresses the investigation of the renal function which was not performed [39]; however, there were no patients on maintenance dialysis treatment in the present study. Third, the method used to measure CIMT was manual, subject to intra- and inter-observer variability. Finally, the total atherosclerotic burden (sum of the total plaque area) and plaque morphology were also not taken into consideration; only the presence or absence of carotid plaque was considered.

5. Conclusions

CIMT and carotid plaque have different influences than traditional cardiovascular risk factors have. Hypertension is the strongest cardiovascular risk factor that increases CIMT, followed by age and male sex, compared to diabetes mellitus, dyslipidemia, and smoking. The presence of dyslipidemia and CAD increases the probability of carotid plaque. The presence of plaque indicated a tendency to correlate with CIMT. Increased CIMT and plaque could be present in the same patient

caused by different risk factors and having independent effects on the artery wall and different clinical prognostic outcomes.

6. Perspectives

According to the data from the present study, patients with dyslipidemia and CAD had an increased probability of having carotid plaque. Hypertension alone or in the presence of diabetes, dyslipidemia or CAD increases CIMT, but not the probability of carotid plaque. The current imaging methods do not adequately distinguish carotid intimal hyperplasia from initial lipid core. There is no current evidence to suggest that CIMT may progress to atherosclerotic plaque. Further diagnostic imaging methods should be capable of distinguishing the adaptive arterial intima-media hypertrophy from initial atherosclerosis lesion, mainly in the presence of hypertension alone.

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Conflicts of interest

None.

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