Endothelial Dysfunction and Intimal-Media Thickness in Relation to Cardiovascular Risk Factors in Patients Without Clinical Manifestations of Atherosclerosis

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Introduction. Endothelial dysfunction and increased intima-media thickness are early findings in the development of atherosclerosis that can be assessed non-invasively by echography. The aim of this study was to investigate endothelial function and intima-media thickness, and the relation between these processes and cardiovascular risk factors in patients without clinical atherosclerosis.

Patients and method. Fifty-two subjects were studied, 39 with one or more cardiovascular risk factors and 13 with none. Vascular echography was performed to analyze endothelium-dependent vascular dilatation in the brachial artery and intima-media thickness in the common carotid artery.

Results. Compared to patients without risk factors, patients with cardiovascular risk factors more frequently had impaired vascular dilatation after ischemia, 11.98 ± 4.61% vs 2.77 ± 2.57%, (*P*<.0.001; mean difference = 9.21%, 95% CI of the difference 6.33-12.07%) and a greater intima-media thickness, 0.085 ± 0.024% vs 0.057 ± 0.014 cm (*P* < 0.0001; mean difference = 0.028 cm, 95% CI of the difference, 0.017-0.04 cm).There was a significant negative correlation between intimal-media thickness and endothelial dysfunction (r = –0.357; *P*<0.01). Linear regression analysis showed that intima-media thickness was independently related to age and the presence of hypertension, while endothelial function was related only with the presence of hypertension, smoking, and hyperlipoproteinemia.

Conclusions. In patients without clinical atherosclerotic disease, cardiovascular risk factors were associated with impaired endothelial function and increased intima-media thickness. There was a negative correlation between endothelial-dependent vascular dilatation and intima-media thickness.

Key words: *Endothelial dysfunction. Intima-media thickness. Cardiovascular risk factors.*

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Asociación de la disfunción endotelial y el grosor mediointimal carotídeo con los factores de riesgo coronario en pacientes sin evidencia clínica de aterosclerosis

Introducción y objetivos. La disfunción endotelial y el aumento del grosor mediointimal carotídeo son fenómenos tempranos en el desarrollo de la aterosclerosis, que pueden estudiarse de forma incruenta por ecocardiografía. Se pretende analizar la función endotelial, el grosor mediointimal carotídeo y la correlación entre ambos parámetros con los factores de riesgo coronario en pacientes sin evidencia clínica de aterosclerosis.

Pacientes y método. Se incluyeron 52 sujetos, 13 sin ningún factor de riesgo coronario y 39 con al menos un factor de riesgo coronario. Se les realizó una medición ecocardiográfica de la vasodilatación dependiente del endotelio en la arteria braquial y del grosor mediointimal en la carótida común.

Resultados. En comparación con los sujetos sin factores de riesgo coronario, los pacientes con factores de riesgo presentaron una disminución de la vasodilatación dependiente del endotelio: 11,98 ± 4,61% frente a 2,77 ± 2,57%, (p < 0,0001; diferencia de medias del 9,21% con un IC del 95% de 6,33-12,07), y un aumento del grosor mediointimal carotídeo de 0,085 ± 0,024 cm frente a 0,057 ± 0,014 cm (p = 0,0002; diferencia de medias de 0,028 cm con un IC del 95% de 0,017-0,04). Se obtuvo una correlación estadísticamente significativa entre el grosor mediointimal carotídeo y la vasodilatación dependiente del endotelio (r = –0,357; p < 0,01). En el análisis de regresión lineal múltiple, el grosor mediointimal carotídeo dependía de la edad y de la presencia de hipertensión arterial, mientras que la vasodilatación dependiente del endotelio lo hacía de la presencia de hipertensión, tabaquismo y dislipemia.

Conclusiones. En pacientes sin evidencia clínica o complicaciones ateroscleróticas pero con factores de riesgo coronario, la función endotelial es peor y el grosor mediointimal carotídeo es mayor que en pacientes sin ellos. Además, existe una asociación lineal negativa entre la vasodilatación dependiente del endotelio y el grosor mediointimal.

Palabras clave: *Disfunción endotelial. Grosor mediointimal. Factores de riesgo cardiovascular.*

ABBREVIATIONS

IMT: intima-media thickness.
EDV: endothelium-dependent vasodilation or flow-mediated dilatation.
NitroMV: nitroglycerine-mediated vasodilation or endothelium-independent vasodilation.
SD: standard deviation.

INTRODUCTION

Atherosclerosis is a systemic process. Recent studies have demonstrated a relationship between peripheral artery endothelial dysfunction and coronary disease.[1] In fact, endothelial dysfunction is considered an early event in the development of atherosclerosis, reflecting a functional change that occurs before the morphological changes.[2,3] One of the characteristic morphological changes of atherosclerosis is increased carotid intima-media thickness (IMT), and epidemiologic data have shown a clear correlation between this feature and cardiovascular disease.[4-6] In recent years, considerable interest has focused on analyzing the early indicators of atherosclerosis and determining their clinical usefulness; it has even been suggested that they could be future risk markers.[7]

Peripheral artery endothelial function and carotid IMT can both be studied by non-invasive techniques, such as echocardiography. Since endothelial dysfunction and increased IMT are interrelated, but indicative of different aspects of the atherosclerotic process, their early detection could have implications in highly directed, intense primary prevention. Some studies have related endothelial dysfunction and carotid IMT[8,9] in patients with demonstrated atherosclerosis or coronary disease. Nevertheless, to our knowledge, endothelial function and IMT, and the correlation between these two parameters, has not been investigated in patients with coronary risk factors, but no evidence of atherosclerotic disease. It would be expected that any changes in these parameters would be similar to those of patients with clinical atherosclerosis, but the value of the analysis does not lie in this outcome alone. Evidence of alterations in these two factors could provide a non-invasive method for early detection of an atherosclerotic process that will remain asymptomatic for many years before manifesting clinically, thereby providing a marker of this process with long-term prognostic value.

AIMS

The aim of this study is two-fold: *a)* to analyze whether peripheral endothelial function and carotid IMT are impared in patients with coronary risk factors and no clinical evidence of atherosclerosis or its complications, and *b)* to investigate the relationship between endothelial dysfunction and increased carotid IMT, and between these parameters and the risk factors present in these patients.

PATIENTS AND METHOD

The study included 52 patients with a mean age of 55.77 ± 14.96 years, equally distributed according to sex. The patients were referred from the outpatient clinic of our hospital cardiology department, after examination by the cardiologist. We selected patients presenting coronary risk factors and no symptoms of a cardiologic process or musculoskeletal chest pain. Those with a history or suspected diagnosis of atherosclerotic disease were excluded. Since the aim of the study was to apply non-invasive techniques in daily clinical practice, examinations with coronary angiography or arteriography to exclude asymptomatic atherosclerosis were not considered indicated; moreover, these tests were not considered relevant for the conclusions of the study. Among the 52 participants, 13 (25%), with a mean age of 44.92 ± 11.41 years and 53.8% men, had no coronary risk factors. The remaining 39 patients (75%), with a mean age of 59.38 ± 14.33 years and 48.7% men, had at least one coronary risk factor.

Hypertensive patients were defined as those with a diagnosis of hypertension or under treatment with antihypertensive drugs for at least one year before entering the study and up to the time of writing. Dyslipidemic patients were defined as those with a diagnosis of dyslipidemia, documented serum cholesterol values above 250 mg/dL or low-density lipoprotein cholesterol (LDL-C) values above 160 mg/dL, or patients under treatment with lipid-lowering drugs. For the purpose of assessing well-established smoking habits, smokers were defined as persons smoking 10 or more cigarettes per day at least during the last year; light or sporadic smokers were excluded. Diabetes was defined according to the American Diabetes Association criteria.[10]

Coronary risk factors included were those considered to be modifiable, i.e., diabetes,

TABLE 1. **Distribution of relevant variables in the sample (I)**

	No.	%
Sex, male	26	50,0
Smoker	8	15,4
Hypercholesterolemia	18	34,6
Hypertensión	24	46,2
Known diabetes	5	9,6

TABLE 2. **Distribution of relevant variables in the sample (II)**

	Mean	DT	Minimum	Maximum
Age	55,77	14,96	26	79
Smoking history, years	2.88	8.56	0	40
No. of cigarettes	4.73	11.47	0	40
Total cholesterol	209.71	42.40	105	316
HDL cholesterol	56.35	17.38	31	129
LDL cholesterol	128.45	39.38	42	222
Triglyceride levels	125.79	105.76	38	770
Systolic BP	130.48	18.72	90	180
Diastolic BP	79.13	11.80	50	110
Baseline glucose level	99.04	26.99	56	233
Cardiovascular risk	11.82	12.65	10	45.20

SD indicates standard deviation; BP, blood pressure.

hypercholesterolemia, hypertension and smoking. A total of 13 patients (25%) had no coronary risk factors, 23 patients (44%) had one risk factor and 16 (31%) had more than one risk factor. Tables 1 and 2 summarize the distribution of the relevant cardiovascular variables in the sample.

Smokers consumed a mean of 30 ± 9.64 cigarettes per day and mean duration of the habit 24 ± 10.4 years. Among the 24 hypertensive patients, 29% were not receiving antihypertensive drugs. The drugs most frequently used in the treated patients were angiotensin-converting enzyme (ACE) inhibitors, diure-tics and ARA II (17.6% of patients each), followed by beta-blockers and doxazosin (11.7% of patients each), and amlodipine (6%). Drug combinations to control blood pressure were taken by 17.6% of patients. Mean duration of hypertension was 6 ± 5.2 years. The patients' usual systolic blood pressure was 151.42 ± 18.75 mm Hg and diastolic blood pressure was 88.92 ± 9.02 mm Hg. At the time of the study, systolic blood pressure was 144.38 ± 18.84 mm Hg and diastolic blood pressure was 82.71 ± 13.35 mm Hg. Among the 18 dyslipidemic patients, 11% were receiving treatment with statins, 28% were under dietary control, and 61% were untreated (80% of these had been recently diagnosed). The usual total cholesterol level of these patients was 270 ± 18.73 mg/dL. At the time of the study, total cholesterol was 243.8 ± 34.8 mg/dL, high-density lipoprotein cholesterol (HDL-C) was 50 ± 15.1 mg/dL and LDL-C was 164.7 ± 32.4 mg/dL. Three of the five diabetic patients were under dietary control and two were receiving oral antidiabetic medication; mean glucose concentration was 150.2 ± 51.3 mg/dL.

In order to quantify the patients' risk, independently of the number or type of risk factors present, we created a continuous quantitative variable using software for the calculation of cardiovascular risk. The program was based on the Framingham score and included the following factors: age, LDL-C, HDL-C and total cholesterol concentration, blood pressure values, diabetes and smoking.[11,12]

Clinical atherosclerotic disease was excluded in the participating patients by careful questioning and a meticulous physical examination performed by cardiology specialists, specifically directed towards detecting the signs and symptoms of cardiovascular disease. All patients presenting questionable symptoms that might be related with clinical atherosclerotic manifestations and all those with some past indication of the process, even without objective evidence, were excluded. All patients provided informed consent for the echocardiographic study of peripheral endothelial dysfunction and carotid IMT.

Endothelial dysfunction was assessed with recently published guidelines.[7] Patients came to the examination without having eaten or smoked for at least 12 hours. The temperature in the examination room was kept constant for all patients. An ATL HDI 5000 echocardiography system equipped with a 12 MHz linear array transducer was used for all studies. After a ten-minute rest in decubitus position, the brachial artery was located between 3 and 5 cm above the cubital fold in a longitudinal plane, with an optimized program constant in gain and depth. When an optimum image had been obtained, the position was held with an external fixation device fixed to the patient's arm, and a baseline measurement of arterial diameter and flow velocity was acquired (mean of two measurements, with a least 5 points measured in each of them). The forearm was then compressed at 300 mm Hg for four minutes. Reactive hyperemia (change in flow velocity) was measured when compression was released, and the new arterial diameter and flow velocity were measured one minute later. The percent change between the diameter at release of compression (D_2) and the baseline diameter (D_1) is the so-called endothelium-dependent vasodilation (EDV). Thus:

$$EDV = (D_2\text{-}D_1)/D_1 \times 100$$

Ten minutes later, when the artery had returned to baseline, 300 mg of nitroglycerine (Solinitrina, Almirall Prodesfarma) was administered and four minutes later arterial dilatation was again measured. The percent change between the postnitroglycerine diameter (D_3) and the baseline value (D_1) is the so-called endothelium-independent vasodilation or nitroglycerine-mediated vasodilation (NitroMV). Thus:

$$\text{NitroMV} = (D_3\text{-}D_1)/D_1 \times 100$$

Measurement of carotid intima-media thickness

Based on the studies of Pignoli and Salonen,[13-15] a longitudinal scan of the right common carotid artery was recorded with the patient in supine position, using the ATL HDI 5000 system and a 12 MHz linear transducer. Once the image had been optimized, the bifurcation in the internal and external carotid was located and the echocardiograph zoom was deployed. Carotid IMT was measured between the bifurcation and one centimeter proximal to the bifurcation. At least five points were measured in the study segment and the entire sequence was performed twice to obtain the mean IMT of the right common carotid. The procedure was repeated in the left carotid and the two values were used to calculate the mean carotid value. Moreover, the maximum IMT in both carotids was recorded for subsequent analyses.

Statistics were performed with the SPSS software package (version 10.0). Quantitative values are expressed as mean and standard deviation, and discrete variables are expressed as frequencies. Comparison of continuous variables was carried out with the Student's t-test. Correlations between continuous variables were analyzed using Pearson's correlation coefficient. Normal distribution of the variables was determined with the Kolmogorov-Smirnov test. Multiple linear regression with backward elimination was used to assess the overall influence of coronary risk factors on the dependent variables EDV and IMT. Statistical significance was established at a *P*-value <.05. Collinearity of the model was assessed according to the criteria of Belsley.[16]

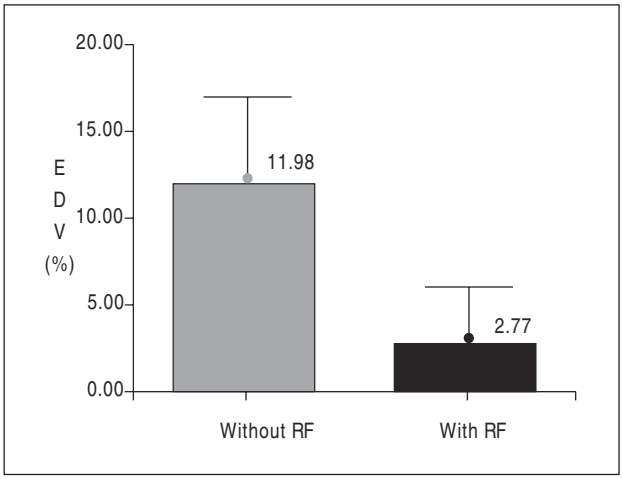

Fig. 1. Endothelial function results. Study of endothelial-dependent (or flow mediated) vasodilation (EDV) in patients with and without coronary risk factors. Values are expressed as mean ± SD.

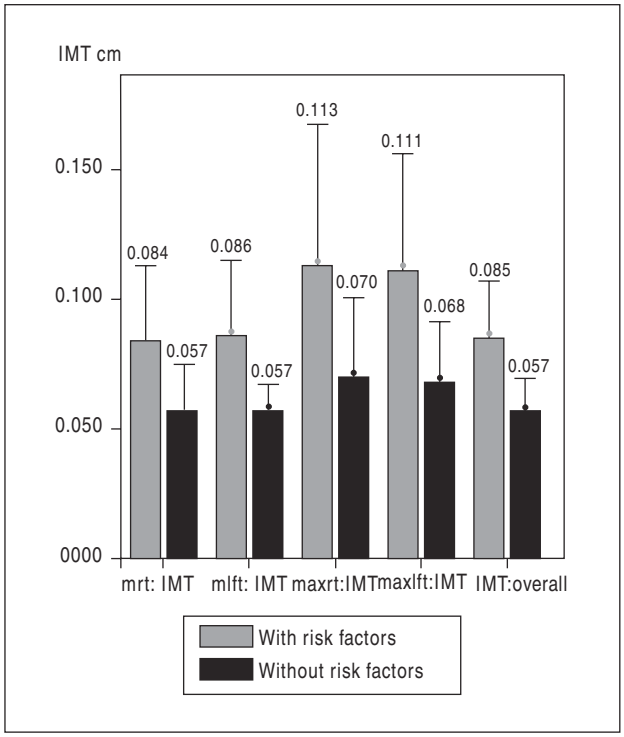

Fig. 2. Carotid intima-media thickness (IMT) in cm. Mean and maximum of each carotid, as well as overall mean in patients with or without cardiovascular risk factors. Values are expressed as mean ± SD in each subgroup.
Mrt indicates IMT of right carotid; mlft, IMT of left carotid; max rt, Maximum IMT of right carotid; max lft, maximum IMT of left carotid; IMT, overall of both carotids.

RESULTS

With a view to clinical utility, we considered risk factors as the presence of modifiable factors in the patient, i.e., smoking, hypercholesterolemia, hypertension and diabetes.

Analysis of endothelial function showed an almost four-fold greater EDV in the group of patients without risk factors than in those with at least one risk factor: 11.98% ± 4.61% vs 2.77% ± 2.57% (*P*<.0001; mean difference 9.21%; 95% CI of the difference, 6.33%-12.07%) (Figure 1). Nitroglycerine-mediated vasodilation was also significantly different between

TABLE 3. **Description of carotid media (cm) and endothelium-dependent vasodilation (EDV, %) in the sample**

	No.	Minimum	Maximum	Mean	SD
Carotid media	52	0.037	0.147	0.078	0.025
EDV	52	−3.087	19.960	5.075	5.113

EDV indicates endothelium-dependent vasodilation.

the two groups: 26.99% ± 9.08% vs 21.5% ± 6.28% (P<.03; mean difference 5.04%; 95% CI of the difference, 0.50%-9.58%).

Mean and maximum carotid IMT values were higher in the patients with risk factors than in those without. Mean carotid IMT in the group without risk factors was 0.057 ± 0.014 cm, versus 0.085 ± 0.024 cm in the group with risk factors (P<.0001; mean difference 0.028 cm; 95% CI of the difference, 0.017-0.04 cm) (Figure 2).

The description of overall carotid media values and

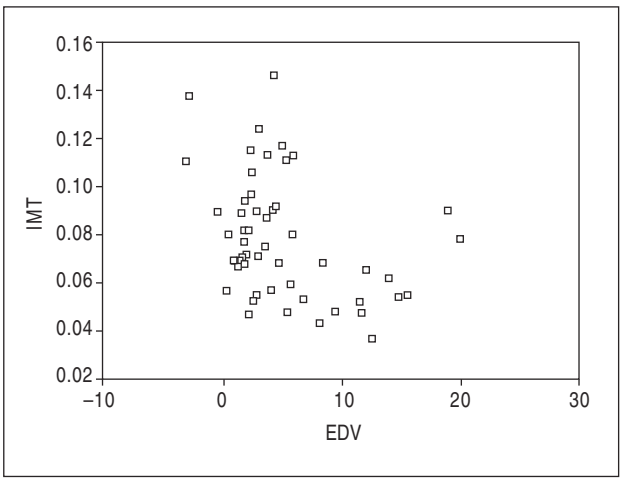

Fig. 3. Correlation between intima-media thickness (IMT) and endothelial-dependent vasodilation (EDV). Negative EDV values probably represent an absence of arterial vasodilation in addition to some variation between the pre- and post-occlusion measurement with the cuff.

TABLE 4. **Description of endothelium-dependent vasodilation (EDV, %) according to modifiable risk factors and sex**

	No.	Mean	SD	*P*
Sex				.782
Woman	26	4.88	5.06	
Man	26	5.27	5.25	
Smoking				.636
No	44	5.22	5.38	
Yes	8	4.28	3.47	
Hypercholesterolemia				.000
No	34	6.82	5.36	
Yes	18	1.78	2.27	
Hypertension				.001
No	28	7.09	6.05	
Yes	24	2.72	2.07	
Diabetes				.046
No	47	5.26	5.34	
Yes	5	3.32	1.16	

TABLA 5. **Descripción del GMI (cm) según factores de riesgo modificables y sexo**

	n	Media (cm)	DT	*P*
Sexo				0,505
Mujer	26	0,081	0,208	
Varón	26	0,076	0,030	
Tabaquismo				0,067
No	44	0,081	0,026	
Sí	8	0,063	0,016	
Hipercolesterolemia				0,028
No	34	0,073	0,026	
Sí	18	0,089	0,022	
Hipertensión				0,000
No	28	0,065	0,018	
Sí	24	0,094	0,024	
Diabetes				0,048
No	47	0,076	0,024	
Sí	5	0,100	0,029	

TABLE 6. **Multiple linear regression models of the variables: endothelium-dependent vasodilation (EDV) and carotid intima-media thickness (IMT)**

			95% CI	
	Coefficient	*P*	Lower limit	Upper limit
EDV[a]				
Constant	9.952	.000	8.070	11.834
Hypercholesterolemia	–5.560	.000	–7.927	–3.193
Smoking	–5.086	.003	–8.314	–1.858
Hypertension	–4.701	.000	–6.943	–2.459
IMT[b]				
Constant	0.019	.051	0.000	0.038
Hypertension	0.016	.006	0.005	0.027
Age	0.001	.000	0.001	0.001

[a]R=0.631; R^2=0.40. The model explains 40% of the variability of EDV.
[b]R=0.755; R^2=0.57. The model explains 57% of the variability of IMT.

dependent vasodilation flow values in our series is summarized in Table 3. Results of the EDV and IMT analyses according to the individual modifiable risk factors and sex and are shown in Tables 4 and 5, respectively.

A statistically significant inverse linear correlation was found between IMT and endothelial function, with a Pearson coefficient of r=-0.357 (*P*<.01). As the EDV worsened, there was a proportional increase in IMT (Figure 3).

The overall effect of coronary risk factors on the independent variables EDV and IMT was analyzed using a linear multiple regression model with backward elimination. The maximum model included five independent variables (usually one variable is chosen for every ten cases) selected for their clinical importance. Four modifiable risk factors were included: hypertension, smoking, dyslipidemia and diabetes mellitus, as well as the factor, age, which had a homogeneous distribution in the sample. The variables predicting EDV in the regression model were hypertension, smoking and dyslipidemia. The only variables predicting IMT were age and hypertension. The final regression models are summarized in Table 6.

DISCUSSION

Endothelial function was found to be poorer and IMT values were higher in patients with coronary risk factors. These two parameters showed an inverse correlation.

Because of the prevalence and socioeconomic importance of atherosclerosis, a great deal of effort is centered on its primary prevention and risk markers. Numerous studies in recent years have focused on the measurement of phenomena related to the development of atherosclerosis, such as carotid intima-media thickness, with non-invasive techniques such as echocardiography. The study of peripheral artery endothelial function shows promise as an even earlier marker of atherosclerosis than the anatomic changes associated with this disease.

Endothelial dysfunction is defined as a functional deterioration of the endothelium characterized by vasospasm, vasoconstriction, alterations in coagulation mechanisms and fibrinolysis, and increased vascular proliferation.[17] Endothelial dysfunction has been related with coronary risk factors,[18] and decreased EDV has been seen even in early stages in patients with hypercholesterolemia and hypertension,[19] smokers[20,21] and diabetics.[22] Several studies have investigated the relationship between coronary disease and endothelial function. A significant decrease in EDV was found in patients with angiographically proven coronary disease as compared to persons without this condition. Endothelial dysfunction, defined as EDV≤4.5%, proved to have a sensitivity of 71%, a specificity of 81% and positive predictive value of 95% for coronary disease.[23] The results obtained with our patients, in which the eight smokers in the series showed EDV values of 4.27% ± 3.47%, are very similar to those found in an early risk factor study, in which EDV was 11% ± 2% in controls and 4% ± 2% in smokers.[21]

Maximum carotid IMT has been shown to be related to systolic blood pressure, diabetes, LDL-C concentration, smoking and a family history of ischemic heart disease.[14] Depending on age, IMT ranges from 0.7 to 1.5 mm, although values higher than 1 mm are gene-rally considered to be abnormal.[15] Intima-media thickness increases by 0.01 to 0.02 mm with each year of life.[24] The presence of increased carotid IMT and the existence of stenotic or non-stenotic carotid plaque is associated with a three-fold increase in the relative risk of experiencing an acute

myocardial infarction. Moreover each 0.11 mm increase in IMT is associated with an 11% increase in the risk of infarction.[15] In the Rotterdam study, an IMT greater than 0.89 mm was associated with atherosclerosis of the lower limbs and it was concluded that carotid IMT is a predictor of generalized atherosclerosis.[25] In a large prospective study among the young adult population of Iowa, carotid IMT was found to be related to proximal calcification of the coronary arteries, as measured by positron emission tomography, and to the presence of coronary risk factors, indicating that IMT could be useful for identifying young adults with early atherosclerotic changes.[26] Despite the differences in the po-pulations included and the study designs, our results are in keeping with those of classic studies on this subject.[14,24]

Two studies have correlated carotid IMT with peripheral artery endothelial function.[8,9] In one of them, coronary arteriography was used to investigate these two parameters in patients with clinically suspected coronary disease. A reduction in EDV was found in the group with angiographically significant lesions as compared to those without lesions. Moreover, a trend toward increased carotid IMT was found in the coronary disease patients. An EDV value ≤4.5% predicted coronary disease with a sensitivity of 71% and a specificity of 81%, and carotid IMT demonstrated a positive correlation with the extent of coronary disease.[8] The other study was more similar in design to ours, comparing EDV and IMT in 34 men with demonstrated atherosclerosis and 33 men without atherosclerosis, but with coronary risk factors. Once again, higher IMT values and poorer endothelial function were found in the atherosclerotic group. The results obtained in the asymptomatic group with risk factors (IMT 0.91 ± 0.03 mm and EDV 5.1 ± 0.6%) are very similar to those found in our risk factor group. The authors also reported a negative correlation between IMT and EDV.[9]

Our aim was to assess IMT changes, endothelial function and the correlation between these parameters in patients with no history or clinical evidence of atherosclerosis or its complications. These parameters have a clear role as indicators of incipient atherosclerotic injury in the symptomatic risk population, but their use in asymptomatic patients could also be of value by providing a means for even earlier recognition of atherosclerotic disease and intensifying the control of modifiable risk factors. The present study, which includes patients without clinical symptoms of atherosclerosis, provides additional information on the spectrum of endothelial function deterioration: the process can occur in healthy individuals, some degree is seen in persons with one or several risk factors, and finally, there is progression to clinical atherosclerosis. The results obtained for endothelial dysfunction are highly consistent with those of previous studies, even with the existing differences in the criteria for patient selection. Intima-media thickness also shows a progressive increase along these stages. Also in keeping with a previous study, we found an inverse correlation between EDV and IMT, in which the poorer the peripheral artery endothelial function, the more advanced was carotid artery atherosclerosis. Using published cut-offs that define endothelial dysfunction as EDV<4.5%[23] and carotid thickening as IMT>1 mm,[15] 90% of patients in our sample with IMT>1 mm showed endothelial dysfunction. Although not demonstrable with the findings and methods used in this study, endothelial dysfunction might logically be considered an earlier phenomenon than increased IMT.

One limitation of this study is the difference in age between patients with coronary risk factors and those without. Taking into account this age difference, the linear regression analysis for EDV showed that hypertension, smoking and dyslipidemia had an effect on EDV, but age did not. These results concur with those of an early study, in which endothelial function was found to appear at early ages and showed a stronger relationship with risk factors than age.[21] Nevertheless, age has an important influence on IMT, as seen in our study. Multiple linear regression demonstrated that hypertension was also related with IMT, regardless of age, and that the proportional increase in IMT with age could not, in itself, explain the considerable differences between the groups. There were no differences according to sex, and the presence of diabetes showed little significance, probably because of the small number of diabetic patients in our sample.

A great deal of interest is centered on determining the clinical usefulness of the study of carotid IMT and endothelial dysfunction. It has been proposed that endothelial dysfunction could be considered another risk factor and a preclinical marker of cardiovascular disease.[27] Various studies have suggested that coronary endothelial dysfunction is an independent predictor of cardiovascular events.[28,29] Several ongoing studies, including the Framingham study and the Cardiovascular Health Study, will determine whether brachial artery endothelial dysfunction can be used to identify patients at risk of experiencing cardiac, cerebral or peripheral vascular disease. This will allow detection of early phases of atherosclerosis in children and young people, and facilitate its prevention. It is also known[7] that endothelial dysfunction regresses

with modification and treatment of the risk factors; thus, measurement of this parameter could be used as a marker of the response to a specific treatment or intervention.

Keeping in mind the aforementioned limitations, we conclude that endothelial function is poorer and carotid IMT is greater in patients with risk factors and no clinical signs of atherosclerotic disease than in patients with no risk factors. Intima-media thickness increases with age. As peripheral artery endothelial function worsens, increasingly more significant pre-atherosclerotic changes are seen in the carotid (greater IMT). Finally, we found a negative linear association between EDV and the patients' cardiovascular risk, and a positive association between carotid media thickness and cardiovascular risk.

What information does this study provide? Though EDV and IMT have been extensively investigated in atherosclerotic patients, the novel aspects of this study lie in the clinical application of non-invasive techniques to show that both endothelial function and carotid thickness can be altered in persons without atherosclerotic disease. Second, non-invasive screening of pre-atherosclerotic lesions in patients typically seen in the cardiology consulting room could be highly relevant in the control of risk factors. A person with similar levels of hypercholesterolemia as another, but with endothelial dysfunction or increased carotid IMT, would probably have a comparatively higher risk of developing future cardiovascular events. In coming years, the study of these parameters could become highly useful for early, non-invasive detection of atherosclerosis and for follow-up of primary prevention treatment, with important social and economic repercussions.

Although further study is needed, our data suggest that non-invasive measurement of endothelial function and IMT are interrelated techniques that probably assess the same atherosclerotic process from difference viewpoints (functional and anatomic, respectively) allowing early, non-invasive assessment of cardiovascular risk in patients with asymptomatic risk factors.

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