

population.¹⁰ This study provides relevant data, but we feel that a prospective study in Spain is still required to clarify the true value of carotid IMT measurement in the field of cardiovascular prevention in our general population.

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Predictors of Carotid Intima-media Thickness

Predictores del grosor íntima-media carotídeo

To the Editor,

We have read the interesting report of Grau et al.¹ on reference values for carotid intima-media thickness in the Spanish population and their association with cardiovascular risk factors. In their study, involving 3161 patients of both sexes, the authors found that the major predictors of carotid intima-media thickness were age and pulse pressure, as well as smoking in men and high-density lipoprotein cholesterol in women.

Aging is accompanied by atherosclerosis, which explains why age is predictive of the carotid intima-media thickness; as the authors point out,¹ the association of smoking in men is explained by the higher prevalence of this habit in male patients (24.2%).

The predictive nature of high-density lipoprotein cholesterol exclusively in women can be explained by the effect of 2 confounding variables that are not considered in the study: abdominal obesity and menopausal status. In men, fat is most commonly deposited in the abdominal region, a phenomenon referred to as android obesity, which is associated with increased insulin resistance.

In insulin resistance, the flow of fatty acids from the visceral fat to the liver is enhanced, resulting in triglyceride accumulation (hepatic steatosis) and an increase in very low-density lipoprotein synthesis. The increase in plasma lipoproteins due to their enhanced formation in the liver raises serum triglyceride levels, a process favored by the reduced activity of lipoprotein lipase, an insulin-dependent endothelial enzyme.²

Hypertriglyceridemia affects the pattern of other lipoproteins by increasing the activity of cholesteryl ester transfer protein, which augments the triglyceride content of high-density lipoproteins particles and the cholesterol ester concentration in very low-density lipoprotein particles.³ Ultimately, low-density lipoproteins become small and dense, allowing them to pass through the vascular endothelium and form atheromatous plaques; in addition, these lipoproteins are taken up preferentially by macrophage scavenger receptors, enabling them to evade the normal mechanisms for their elimination by means of low-density lipoprotein receptors. Triglyceride-rich high-density lipoproteins particles are more easily eliminated by hepatic lipase, which reduces serum high-density lipoprotein cholesterol concentrations.

Another factor that could influence the negative association between high-density lipoprotein cholesterol and carotid intima-media thickness in women is menopausal status.⁴ During menopause, there are profound metabolic and hormonal changes due to a loss of ovarian function and a reduction in circulating estrogen levels. These changes contribute, among other effects, to fat distribution in the abdominal region, increased insulin resistance, and the resulting dyslipidemia. If the prevalence of menopause in the sample analyzed had not been high,¹ the presence of these disorders would have been less marked, which partially explains the higher high-density lipoprotein cholesterol concentrations in women and the negative association with the carotid intima-media thickness observed in this group.

Another factor that could contribute to dyslipidemia and favor atherosclerosis is the chronic low-grade inflammation that accompanies abdominal obesity. Visceral adipose tissue is an important source of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor- α , and high blood

concentrations of these proteins favor the inflammatory process and promote insulin resistance.⁵

We suggest that Grau et al.¹ include measurement of abdominal circumference as an indicator of abdominal obesity, take into account menopausal status in women, and determine low-density lipoprotein cholesterol and triglyceride levels. As demonstrated in a number of studies,⁶ these variables are easy to determine noninvasively and are useful. Despite the questions raised in the present article, we consider the work carried out by these authors to be excellent.

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Carotid Intima-media Thickness in the Spanish Population: Reference Ranges and Association With Cardiovascular Risk Factors. Response to Related Letters

Grosor íntima-media carotídeo en población española: valores de referencia y asociación con factores de riesgo cardiovascular. Respuesta a cartas relacionadas

To the Editor,

We appreciate the comments of Cordero et al. and of Miguel-Soca et al. regarding our article “Carotid Intima-media Thickness in the Spanish Population: Reference Ranges and Association With Cardiovascular Risk Factors”.¹ Although we share most of their views, as can be understood from our article, we would like to provide certain data that we have been asked to present and which complement some of the opinions expressed in the “Letters to the Editor”.

Measurement of carotid intima-media thickness (IMT) has been increasingly employed in the last 2 decades. This measure is easily reproducible and an increase in thickness is associated with the prevalence of cardiovascular risk factors. Moreover, carotid IMT has been shown to have a constant and gradual association with the risk of cardiovascular events. The American Heart Association has pointed out that carotid IMT measurement improves the prediction of prognosis in individuals with intermediate risk classified according to the Framingham equation.^{2,3} As Cordero et al. state, the utility of carotid IMT measurement in the context of atherosclerotic disease in general remains to be clarified. To respond to this question and to determine the independent predictive value of carotid IMT and its utility in the reclassification of individuals at intermediate risk, we are presently following a population-based cohort whose baseline carotid IMT values were used in our article published in the *Revista Española de Cardiología*.¹

In response to the request of Miguel-Soca et al., we wish to point out that, although we collected data on low-density lipoprotein cholesterol, triglycerides, and waist circumference, this information was not included in the original article for reasons of space. To respond to the Letter by Miguel-Soca et al. we have adjusted multivariate models to determine the association of the mean IMT of the common carotid artery and of all the segments of the carotid artery with these 3 risk factors. These models were adjusted in a way similar to that described in the original article (adjustment

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variables: age, smoking, diabetes mellitus, pulse pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and abdominal circumference), although, in this case, total cholesterol and body mass index were not considered due to problems with collinearity.

Abdominal circumference is the only risk factor of the 3 considered that was found to have a significant association with the mean IMT of the common carotid artery in both women and men (coefficient=0.01 [$P=.015$] and coefficient=0.01 [$P=.017$], respectively). On the other hand, the increase of 10 mg/dL in LDL-C was significantly associated with the mean IMT in the 3 carotid artery segments in women and men (coefficient=0.03 [$P=.005$] and coefficient=0.03 [$P=.006$], respectively). Triglyceride levels showed no significant association with any of the carotid IMT measurements considered.

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