ROLE OF CAROTID INTIMA-MEDIA THICKNESS FOR CARDIOVASCULAR RISK EVALUATION

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REZUMAT

Introducere: Riscul cardiovascular (RCV) este subestimat la un procent important din populație atunci când este evaluat apelând la metode convenționale de estimare cum este riscul SCORE. Ecografia carotidiană, prin măsurarea grosimii intimă-medie (GIM) carotidiană, este utilă în identificarea aterosclerozei subclinice și încadrarea astfel în clasa de RCV înalt. **Obiectivul studiului:** A fost evaluarea contribuției screening-ului grosimii intimă-medie carotidiană în redefinirea RCV la o populație de studiu asimptomatică încadrată în risc CV intermediar sau scăzut (risc SCORE 3-4% sau sub 3%). **Material și metode:** Ecografia carotidiană s-a efectuat la 142 subiecți cu risc CV SCORE mic sau intermediar. Depistarea la ecografia carotidiană a unei GIM crescute a permis reclasificarea pacienților în clasa de RCV înalt. **Rezultate:** RCV la lotul de studiu a fost mic la 40 (28,2 %) din pacienți și intermediar la 102 (71,8 %). GIM medie a fost de 0,65±0,14 mm. Rezultatele ecografiei carotidiene au reclasificat RCV la 39 (27,4%) pacienți. Reclasificarea s-a produs la 34 (33,3 %) subiecți cu RCV intermediar și la 5 (12,5%) subiecți din grupul cu RCV mic (p<0,05). Reclasificarea s-a asociat cu istoricul de hipertensiune arterială (p<0.001), tensiunea arterială sistolică crescută (p=0,001), vârsta (p<0,05), colesterolemia (p<0,05) și fumatul (p<0,05). **Concluzii:** Ecografia carotidiană este deosebit de utilă în medicina preventivă. GIM carotidiană îmbunătățește evaluarea RCV, identificând subiecții cu risc crescut, nedepistați prin evaluarea SCORE și contribuie astfel la instituirea unor strategii preventive mai agresive.

Cuvinte cheie: ateroscleroza subclinică, grosime intimă-medie carotidiană, reclasificarea riscului cardiovascular

ABSTRACT

Background: Conventional risk evaluation as SCORE underestimates the cardiovascular risk (CVR) in a significant proportion of population. Carotid artery ultrasonography, by measurement of carotid intima-media thickness (IMT) is useful in identifying subclinical atherosclerosis and placing an individual into high CVR class. The objective of the study was to establish the contribution of IMT screening to the improvement of CVR in a study population of asymptomatic adults at intermediate ore low CHD risk (SCORE risk 3-4% or under 3%). **Material and methods:** Carotid artery ultrasonography was effectuated in 142 subjects, with low or intermediate SCORE risk class. The detection of abnormal IMT reclassified the subjects to high CVR class. **Results:** The calculated CVR of the study population by SCORE charts was low risk in 40 (28.2%) patients and intermediate in 102 (71.8 %) individuals. Mean IMT was 0.65±0.14 mm. The results of the ultrasonography reclassified the risk class in 39 patients (27.4%). Reclassification occurred in 34 (33.3 %) patients of the intermediate CVR group and 5 (12.5%) patients of the low CVR group (p<0.05). Reclassification was connected to history of arterial hypertension (p<0.001), increased systolic blood pressure (p=0.001), age (p<0.05), cholesterol levels (p<0.05) and smoking (p<0.05). **Conclusions:** Carotid ultrasonography is an important investigation in preventive medicine. IMT improves risk classification, identifying high risk individuals, not detected by SCORE function and contributes to establish earlier and more aggressive CV preventive strategies.

Key Words: subclinical atherosclerosis, carotid intima-media thickness, cardiovascular risk reclassification

INTRODUCTION

Atherosclerosis and its complications are an important cause of morbidity and mortality in Romania and Europe. Cardiovascular risk (CVR) factors influences direct the atherosclerotic process. The evaluation and stratification of the cardiovascular risk is a daily clinical practice, based mainly on Framingham risk function and the European SCORE function, which integrates a part of the CVR factors of individuals, establishes the cardiovascular risk (low, intermediate and high) and the necessary preventive strategies.

Conventional scores as SCORE function underestimate the cardiovascular risk in a significant proportion of population.[1] Traditional coronary heart disease risk prediction schemes such as the Framingham risk although useful, do not adequately identify all individuals who experience an adverse coronary heart disease event. Therefore, additional tools, including biomarkers, genetic markers, and imaging markers, are being evaluated for their

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value in improving cardiovascular risk assessment. Carotid artery ultrasonography, by measurement of carotid intima-media thickness and detection of carotid plaques, is useful in identifying subclinical atherosclerosis and placing an individual into high CVR class.[2,3] Carotid intima-media thickness represents the sum of the thickness of the intima and media layers of the carotid artery. Because atherosclerosis is a subintimal process, IMT has become recognized as a surrogate imaging marker for assessing subclinical atherosclerosis. However, it must be noted that hypertension associated medial hypertrophy may be reflected in the IMT measurement as well.

Up to one third of the European adult population are subjects with an intermediate CVR, in whom the preventive measures are based on life style changes. But some of the subjects classified as low or intermediate risk present subclinical atherosclerosis, which detected in this stage, introduce the patients in the high CVR group that needs to benefit from a more aggressive management.[1]

A direct evaluation of the atherosclerotic carotid artery lesions, to identify high risk individuals, not detected by the CVR functions, can easily be made by high resolution B-mode ultrasonography. Ultrasound based IMT measurement is safe but has several challenges, including reproducibility and operator dependency. Quantifying the carotid IMT and by identification of carotid plaques, subclinical atherosclerosis can be detected and CVR stratification can be improved.[1] The actual guidelines for the use of IMT are determined by Mannheim Carotid IMT Consensus and the ASE Consensus Statement.[3,4]

Many studies have demonstrated that increased IMT is associated with risk of myocardial infarction, stroke and death.[5-8] The meta-analysis performed by Lorenz et al. and Roman et al. concluded that IMT is an important predictor of cardiovascular events.[8,9] Abnormal values of IMT, that indicate subclinical atherosclerosis, are considered those greater or equal to 75th percentile of the reference population, or values greater than 0.9 mm. By measurement of IMT carotid artery ultrasonography is useful in identifying subclinical atherosclerosis and placing an individual into a high CVR class.

OBJECTIVE

The aim of the study was to establish the contribution of IMT screening to the refining of CVR in a study population of asymptomatic adults at intermediate ore low CHD risk (SCORE risk 3-4%, or under 3%).

MATERIAL AND METHODS

Data were obtained from an ambulatory population sample of 526 patients, who voluntarily enrolled in the CVR screening at 12 general practitioners offices in Timis County, between 2010 and 2012. Ten year risk for cardiovascular disease (CVD) was obtained according to the SCORE charts for populations at high CVR, the cardiovascular risk recommended for Romania. (Fig. 1) The SCORE function classified the participants in low, intermediate and high risk classes, if their calculated risk was < 3%, 3-4% and respectively >5%. Patients with diabetes or cardiovascular disease (CVD) as coronary heart disease, revascularization procedures, stroke and peripheral arterial disease were classified as high risk.

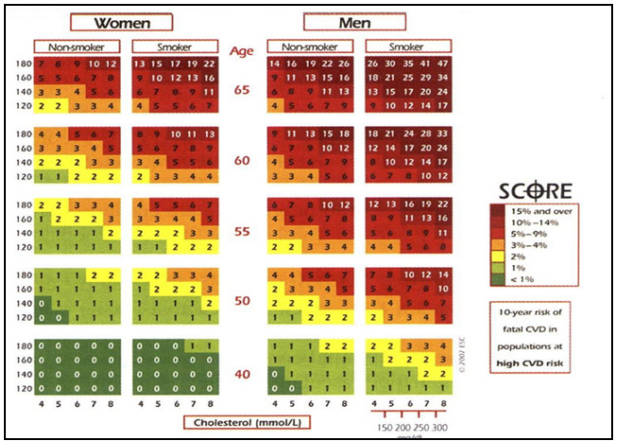

Figure 1. SCORE charts for high CVR countries, indicated for Romania.

three hundred seventy seven patients, 181(34.4%) were in the low CVR class and 196 (37.2%) in the intermediate CVR class. (Fig. 2) We excluded 149 (28.4%) patients of the total number of initial 526 enrolled subjects, because they were assessed in the high CVR class.

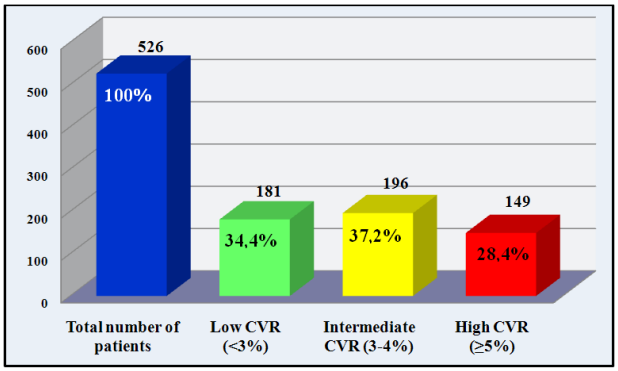

Figure 2. CV SCORE risk classes of the study population.

Three hundred fifty two patients (93.3%) answered a questionnaire, performed according to the European Guidelines of Cardiovascular Disease Prevention,

by which we obtained data about family history of cardiovascular disease, history of hypertension, hypercholesterolemia and smoking habits.[10-13] Blood pressure was measured with a calibrated mercury sphygmomanometer according to the JNC-7.[14] Laboratory data with total cholesterol and triglycerides were obtained from 285 patients (75.5%) of the low and intermediate CVR study groups. Of the 285 eligible participants (low and intermediate risk) with laboratory data, only 142 (37.6%) underwent the carotid ultrasonography for IMT measurement and carotid plaque assessment. (Fig. 3)

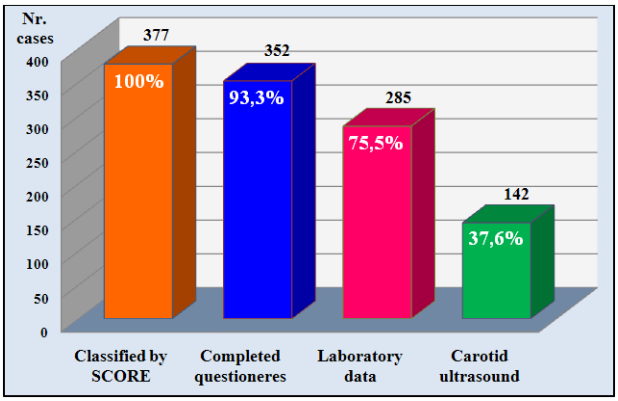

Figure 3. Evaluation methods of the low and intermediate CVR groups.

Carotid arteries were imaged with an ultrasound equipment Sonoscape SSI 8000 with high-resolution B-mode system and linear ultrasound transducer at frequencies of 7-13 MHz. Ultrasonography of the right and the left common carotid artery (CCA) was effectuated with the patient supine and with slight hyperextension of the neck (Mannheim Consensus).[3] The inner and outer walls of the carotid artery were scanned longitudinally to obtain a clear horizontal image. We examined a minimum of 10 mm length of both common carotids, 5 mm below the carotid bulb. (Fig. 4) The IMT was calculated as the distance from the leading edge of the first echogenic line to the leading edge of the second echogenic line of the CCA. The system was equipped with software that automatically identified the borders of the CCA and calculated IMT. (Fig. 5) The IMT value was defined as the average of the right and left CCA. Proper measurement of IMT was critical to its clinical use.

Plaque was defined as a focal wall thickening > 50% than the surrounding vessel wall or a focal region with the IMT >1.5 mm, protruding into the lumen, distinct from the adjacent boundary. As reference values for IMT, we used the value < and ≥ 0.9 mm. Subjects with a mean IMT ≥ 0.9 mm were considered as having subclinical atherosclerosis and reclassified to high CVR.

Figure 4. B-mode ultrasound scan of CCA. IMT is seen as a double echogenic line in the far wall.

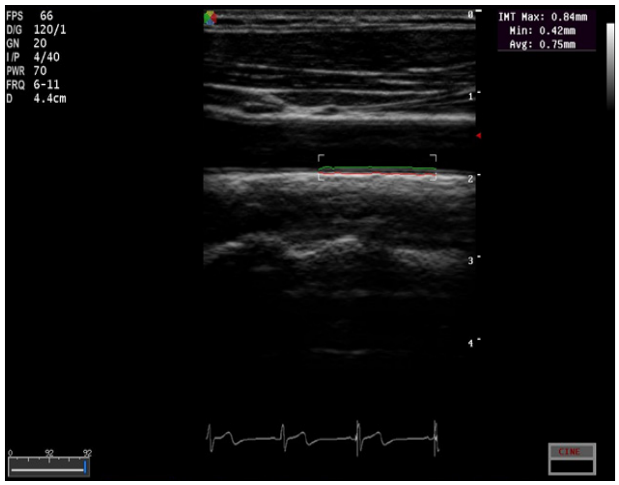

Figure 5. IMT automatic measurement.

Statistical analysis

The study data were expressed as mean ± (SD) for continuous variables and as frequencies or percentages for categorical variables. Differences in mean values were assessed using t-test. Categorical variables were compared using chi-square tests. Linear regression analysis was used to determine the relationships between continuous variables Comparisons were considered significant in the presence of a P value < 0.05. All statistical analyses were performed using the Software Stata 9.2.

RESULTS

One hundred forty two patients, aged between 40 and 72 years, with low or intermediate CVR underwent carotid ultrasonography for IMT assessment and carotid plaques detection. The study population characteristics are described in Table 1.

The mean age of the study group was 55.8 ± 9.6 years, the minimum age was 40 years and the oldest patient had 72 years. The mean height was 166.1 ± 11.6 cm, with a minimum of 152 cm and a maximum

of 198 cm. The mean weight was 75.9 ± 12.8 kg, with a minimum of 45 kg and a maximum of 112 kg. The mean systolic blood pressure was 142.1 ± 12.3 mm Hg, with a minimum of 65 mm Hg and a maximum of 108 mm Hg. The mean diastolic blood pressure was 84.75 ± 7.5 mm Hg with a minimum of 65 mm Hg and a maximum of 115 mm Hg. Mean total cholesterol level was 230.5 ± 42.1 mg/dl, with a minimum of 160 mg/dl and a maximum of 335 mg/dl. The mean triglycerides values were 186.4 ± 60.9 mg/dl, with a minimum of 90 mg/dl and a maximum of 428 mg/dl. Fifty two patients of the study group (36.6%) were smokers. A history of hypertension was present at 49 (34.5%) and a history of hypercholesterolemia at 52 (36.6%) patients.

Table 1. General baseline characteristics of the study population (n = 142).

Characteristics	Mean values/percentages
Age (years)	55.8 ± 9.6
Height (cm)	166.1 ± 11.6
Weight (kg)	75.9 ± 12.8
SBP (mmHg)	142.1 ± 12.3
DBP (mmHg)	84.7 ± 7.5
Cholesterol (mg/dl)	230.5 ± 42.1
Triglycerides (mg/dl)	186.4 ± 60.9
Gender (%)	Male 45.7 %, Female 54.2 %
Smokers (%)	36.6% (52)
History of hypertension (%)	34.5% (49)
History of hypercholesterolemia (%)	36.6% (52)

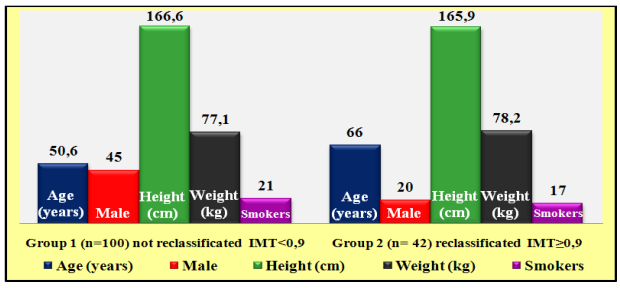

Figure 6. Comparison of the two study groups general characteristics.

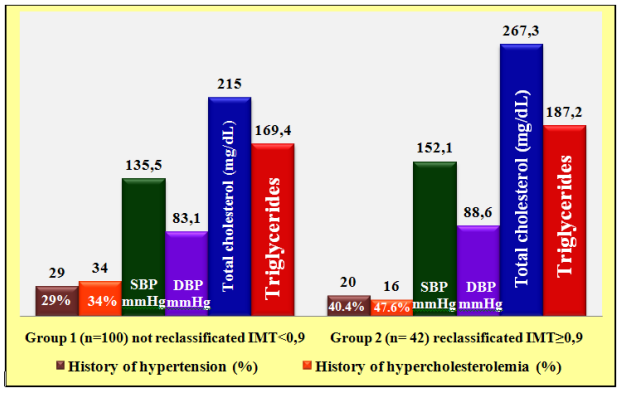

Figure 7. Comparison of the two study groups risk factors.

The calculated CVR class of the study population using SCORE charts was low risk class in 40 (28.2%) patients and intermediate risk class in 102 (71.8%). Depending on the values of IMT, the study population was divided into two groups. Group 1 included subjects with IMT < 0.9 mm, not reclassified by carotid ultrasonography. Group 2 included subjects with IMT ≥ 0.9, reclassified into high CVR class by carotid ultrasonography. Baseline characteristics of the two study groups are presented in Table 2. (Figs. 6,7)

Mean IMT was 0.65 ± 0.14 mm. Intermediate CVR subjects had higher values of IMT than subjects with low CVR (0.77 ± 0.14 mm vs. 0.59 ± 0.11 mm. Carotid plaque was found in 15 (10.5%) patients, being more frequent in the intermediate CVR group than in the low CVR group: 13 (12.7%) vs. 2 (5%). (Fig. 8)

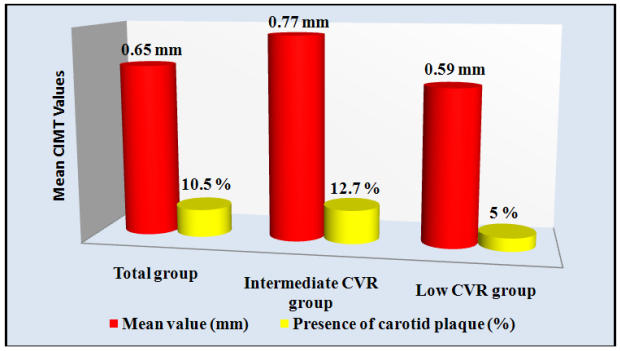

Figure 8. Mean IMT and presence of plaques in the study groups.

The results of the ultrasonography reclassified the risk of 39 patients (27.4%). Reclassification occurred in 34 (33.3 %) patients of the intermediate CVR group and in 5 (12.5%) patients of the low CVR group. (Table 3) Reclassification was connected to history of arterial hypertension (p<0.001), increased systolic blood pressure (p=0.001), age (p<0.005), cholesterol levels (p<0.05) and smoking (p<0.05).

Table 3. Cardiovascular reclassification distribution (n = 142).

SCORE CV risk		Reclassification of CVR after IMT	No. (%)
Low CVR	n = 40 (28.2%)	Low	35 (87.5%)
		High	5 (12.5%)
Intermediate CVR	n = 102 (71.8%)	Intermediate	68 (66.6%)
		High	34 (33.3%)

Exemplifications of cases in which IMT measurement reclassified the cardiovascular risk of patients and in which normal IMT at ultrasonographic examination maintained the patient in the SCORE risk class, are presented in Figures 9-14.

Table 2. Baseline characteristics of the study groups.

Baseline characteristics	**Group 1** (n = 100) Not reclassified IMT < 0.9 mm	**Group 2** (n = 42) Reclassified IMT ≥ 0.9 mm	**P value**
Mean IMT (mm)	0.67 ± 0.1	0.95 ± 0.07	–
Age (years)	50.6 ± 9.7	66.0 ± 7.4	P < 0.05
Male (%)	45% (45)	47.6% (20)	NS
Height (cm)	166.6 ± 10.1	165.9 ± 8.5	NS
Weight (kg)	77.1 ± 13.3	78.2 ± 12.7	NS
Smokers (%)	21% (21)	40.4% (17)	P < 0.05
History of hypertension (%)	29% (29)	47.6% (20)	P < 0.001
History of hypercholesterolemia (%)	34% (34)	38% (16)	NS
SBP (mmHg)	135.5 ± 10.9	152.1 ± 10.5	P = 0.001
DBP (mmHg)	83.1 ± 7.3	88.6 ± 6.5	NS
Total cholesterol (mg/dl)	215.0 ± 34.4	267.3 ± 36.7	P < 0.05
Triglycerides (mg/dl)	169.4 ± 41.0	187.2 ± 51.4	NS

Figure 9. Carotid ultrasound in patient with intermediate SCORE risk, normal IMT, not reclassified.

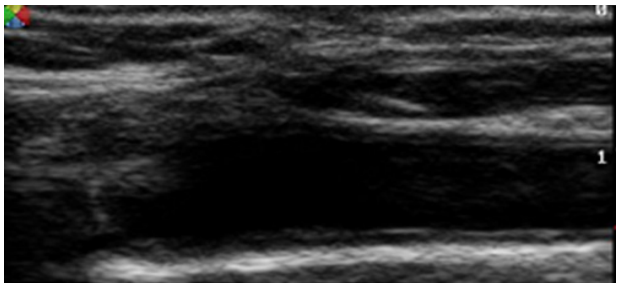

Figure 10. Carotid ultrasound in a case reclassified to high CVR by thickened IMT.

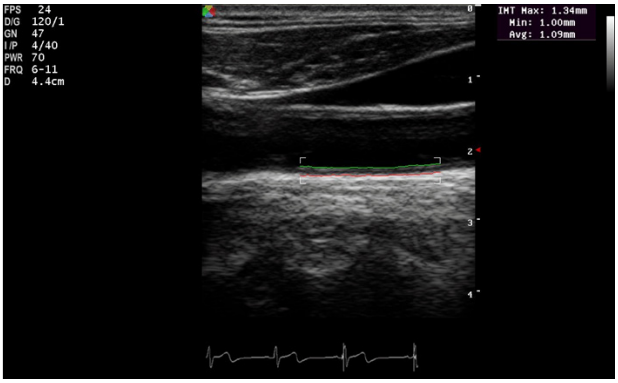

Figure 11. Average IMT of 1.09 mm changed SCORE risk (from intermediate to high CVR).

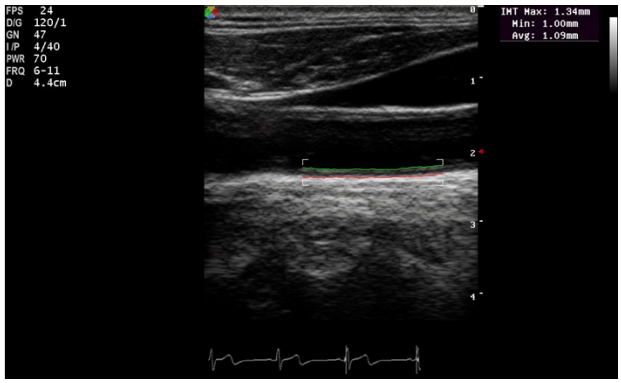

Figure 12. Detection of pathological IMT and carotid bulbus atherosclerotic plaques.

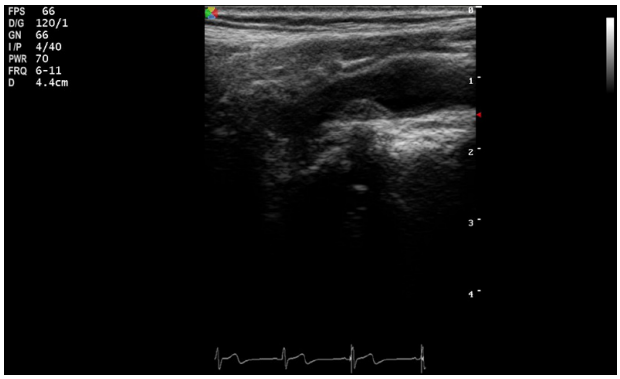

Figure 13. Detection of carotid plaque at a case classified at intermediate risk with SCORE.

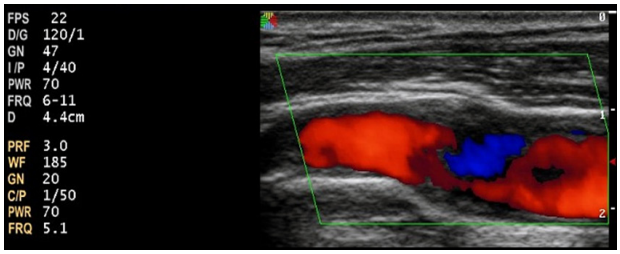

Figure 14. Carotid atherosclerotic plaques and IMT over 0.9 mm at a reclassified case.

DISCUSSIONS

Normal values of IMT are considered 0.4 – 0.89 mm. IMT increases with age with 0.01 mm/ year. Values are greater in man than women and in the left common carotid artery (LCCA) than in the right common carotid artery (RCCA). IMT is related to classical risk factors of atherosclerosis as hyperlipidemia, diabetes, hypertension and smoking. IMT has also non atherosclerotic mediators as age related sclerosis and pressure overload.

IMT and Cardiovascular Risk Factors

IMT values and progression has been associated with age (linear increasing), gender, race (blacks have greater IMT than whites, who in turn have greater IMT than Hispanics), hypertension, smoking, diabetes in longitudinal studies, SBP, body mass index, waist-to-hip ratio, fasting glucose, insulin, mean hemoglobin A1C levels (supporting a link between diabetes and arterial wall thickening).

The association of IMT with lipid parameters: HDL-cholesterol levels have an inverse association with IMT. Elevated LDL-cholesterol, lipoprotein(a) levels are associated with thicker IMT and its progression. Lovastatin, atorvastatin and rosuvastatin therapy were shown to reverse IMT progression, being associated with LDL-C reduction and with decreased CVD events. Homocysteine and C-reactive protein have been found to be weakly linked with IMT.

IMT and Incidence of CVD Events

Several large epidemiologic studies have examined the association between cardiovascular events and IMT measures. For an absolute carotid IMT difference of 0.1 mm, the future risk of myocardial infarction (MI) increases by 10% to 15% and stroke risk by 13% to 18%.

In the Atherosclerosis Risk in Communities Study (ARIC), increased IMT was prospectively associated with increased risk of CHD, respectively with a 13% increase of hazard ratio for MI per 0.1 mm increase IMT of CCA, adjusted for age and gender.[11]

In the Kuospio Ischemic Heart Disease (KIHD) Risk Factor Study made on 1288 finish men, IMT≥1 mm at baseline was associated with increased risk of MI.[8]

In the study of Matthias W. Lorenz et al., the authors pointed out that IMT is a strong predictor for father CV events.[8] The relative risk per IMT difference was slightly higher for the endpoints of stroke than MI.

An important percentage of subjects who present subclinical atherosclerosis are not detected by the actual CVR functions, as SCORE charts.[8-10] By detecting subclinical atherosclerosis, the risk evaluation and stratification can be improved by high-resolution B-mode carotid ultrasonography, particularly in patients having an intermediate or low SCORE CVR. The literature review presents studies that mainly used the IMT in the assessment of the Framingham risk function, rather than that of the SCORE function.[2,12,14,15]

Bard et al. selected from a sample of 200 subjects 95 individuals with intermediate CVR and measured the IMT.[16] Of these subjects, 22% presented an abnormal IMT and were so reclassified as having a high CVR. In the study of Stein et al., the IMT was calculated in 82 individuals with no diabetes or CVD.[15] Of the study patients, 35.7% with intermediate CVR, according to Framingham function, were reclassified to high CVR. Reclassification was associated with increased SBP, cholesterol levels and smoking.

Baldassarre et al. made a 5-year prospective study on dyslipidemic subjects.[10] At the beginning of the study IMT was performed. The study group was divided in two groups: the first with low or intermediate CV risk consisted of 242 subjects and the second group with high Framingham CVR class consisting of 44 subjects. The study demonstrated that subjects with an abnormal IMT and intermediate Framingham risk had a CVR similar to those subjects with high Framingham CVR class.

In the study of Wyman et al., made on 327 individuals with no diabetes or CVD, 41.6% individuals presented abnormal IMT and 58% carotid plaques. The abnormal IMT was associated to age, male gender and carotid plaque. The high percentage of abnormal IMT detected in this study is explained by the fact that high-risk subjects were not excluded, as CVR stratification was not made. Grewal et al. found that 23% of 752 low-risk individuals had an abnormal IMT, that was associated to high SBP, female gender and apolipoprotein B.[17] To explain that female gender is a factor associated to abnormal IMT, we must take in consideration that in this study participated more than twice as many women as men. According to the Framingham scores, most of the young females are considered at low CV risk.

Lester et al. determined IMT in 86 low-risk individuals, according to Framingham.[18] Abnormal IMT was found in 13% of the study population.

Juvent et al., in a study on 409 subjects with dyslipidemia, classified according to the Framingham function into low or intermediate CVR three hundred and sixty seven individuals.[19] After IMT determination, 193 (52.5%) were reclassified into high CVR group. This study presents the highest percentage of reclassification that is explained by the

use of abnormal IMT or carotid plaque presence as reclassifying criteria.

It is recognized that the presence of carotid plaques is associated with higher values of IMT and higher incidence of cardiovascular events.[15-18] In our study, we found more carotid plaques in the intermediate CVR group than in the low CVR group. Many studies demonstrated discordance between the CVR detected by SCORE or Framingham functions and the direct demonstration by ultrasonography of an advanced subclinical atherosclerosis. This discordance can be explained by the fact that the CVR functions do not include all the risk factors involved in atherosclerosis. By means of carotid ultrasound and calculating IMT, we can observe the consequences of all the factors involved in atherogenesis, those included by the CVR functions and not, as individual CVR factors that have a genetic base, those that are dependent on environmental factors, homocysteine levels and so on.

Recommendations for IMT measurement from Current Guidelines

The ASE Consensus Statement, the National Cholesterol Education Program, the Screening for Heart Attack Prevention , the Education Task Force and the International Panel on Man-agement of Familial Hypercholesterolemia recommend for a better cardiovascular stratification the use of IMT in individuals with intermediate CVR.[2,4,12]

The ASE task force recommend IMT screening as class IIA level (a reasonable or probably recommended strategy) based on B level evidence (ie, studies on limited populations).

American College of Cardiology (ACC)/ American Heart Association (AHA) guidelines on assessment of cardiovascular risk in adults recommend IMT:

- In patients who may benefit from the screening (asymptomatic adults, classified as intermediate CHD risk, without CHD or CHD equivalent);

- In patients with following features (ASE Consensus Statement):

  - Family history of premature CHD in a first-degree relative (men < 55 years old, women < 65 years old);

  - Age < 60 years with a severe single risk factor, not otherwise on pharmacotherapy;

  - Women < 60 years old with two or more CHD risk factors.

Detection of abnormal IMT by ultrasound determines often a change in treatment plans, by initiation of early and a more aggressive CV preventive strategies, with additional aspirin therapy and increase of statins, until LDL cholesterol is below targets. The adherence of the patient to changes in lifestyle, weight control, BP control and statin therapy is better after the identification and communication of data about an abnormal IMT and presence of atherosclerotic plaques.

Limitations

The findings of the study are observational, prospective, that include IMT as part of the CVR evaluation. Another limitation of the study is that we had no IMT reference values for Romanian population, for reclassification we didn't the recommended IMT values greater than 75 percentiles of the reference values, but the IMT < or ≥ than 0.9 mm. The main purpose of this study was to evaluate the use of IMT in CVR assessment and for this reason we did not reclassify subjects with carotid plaques. Future studies, that evaluate the preventive interventions of reclassified individuals, in order to decrease in evolution future cardiovascular events, needs to be conducted.

CONCLUSIONS

Carotid ultrasonography has become useful for monitoring carotid atherosclerosis, prediction of CVD risk and management of preventive strategies. IMT has the potential to be widely adopted as a clinical tool for physician offices, as it is a quick, safe, non invasive, cost effective and a reliable screening tool for subclinical atherosclerosis. In our study the values of IMT measurements were directly associated with history of hypertension, increased SPB, cholesterol, age and smoking. IMT improves CV risk assessment in patients at intermediate or low CVD risk, identifying high risk individuals that are not detected by the SCORE function and contributes to the establishment of earlier and more aggressive CV preventive strategies.

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