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Femoral Intima-media Thickness, Risk Factors, and Markers of Inflammation in Cardiovascular Disease

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ABSTRACT

Introduction: The burden of coronary artery disease (CAD) and peripheral vascular pathologies caused by atherosclerosis is constantly increasing. There is continuous research aiming to develop new methods that can evaluate the extent of atherosclerotic disease in different vascular beds, thus estimating global risk. Similar to carotid artery thickness, which is an established marker for increased cardiovascular risk and cerebrovascular disease, femoral intima-media thickness (f-IMT) may have the same role in case of peripheral arterial involvement. The aim of the study was determine whether f-IMT, determined at the level of the superficial femoral artery, is related to traditional risk factors, markers of peripheral vascular atherosclerosis and inflammation. **Material and methods:** Forty-six patients with known cardiovascular disease were included in the study. Demographical data, cardiovascular history, and risk factors were assessed. We determined metabolic parameters (uric acid, fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides), renal function (creatinine and GFR), and inflammation status for all patients. Each patient underwent ultrasound examination of the superficial femoral artery, by which f-IMT was determined for right and left limbs. Ankle-brachial index was also calculated. Data from the low (f-IMT <0.75 mm) and high (f-IMT >0.75 mm) f-IMT groups were compared and correlation coefficients were determined in each groups for f-IMT in relation to the other parameters. **Results:** Mean age was 71.08 ± 9.78 years. 86.95% of the patients suffered from hypertension, 56.62% had coronary heart disease, and 21.73% had a history of stroke. More females had history of hypertension and CAD. The most prevalent cardiovascular risk factors were dyslipidemia (68.86%), diabetes (21.73%), and smoking (21.73%). There were significant differences between gender groups for total cholesterol levels (161.36 ± 25.04 mg/dL, 95%CI 150.26–172.47 in males vs. 201.33 ± 52.73 mg/dL, 95%CI 170.07–223.60 in females, p = 0.02), creatinine values (1.04 ± 0.22 mg/dL, 95%CI 0.94–1.14 for males vs. 0.91 ± 0.23 mg/dL, 95%CI 0.81–1.00 for females, p = 0.018), and left f-IMT (0.87 ± 0.18 mm, 95%CI 0.79–0.95 for males vs. 0.75 ± 0.10 mm, 95%CI 0.70–0.79 for females, p = 0.0049). In the group with low f-IMT, a significant, reverse correlation was established between f-IMT, uric acid (r = –0.483, p = 0.042), and right ABI (r = –730, p = 0.0006). In the group with high f-IMT, age (r = 0.408, p = 0.031), fasting glucose (r = 0.407, p = 0.034), total cholesterol (r = 0.429, p = 0.02), HDL-cholesterol (r = –0.56, p = 0.0019), triglycerides (r = 0.45, p = 0.01), hs-CRP (r = 0.45, p = 0.01), and left ABI (r = –0.71, p <0.0001) showed a significant correlation to f-IMT. **Conclusions:** Increased femoral intima-media thickness is related to age, cardiovascular risk factors, and markers of peripheral arterial disease. Patients with higher f-IMT have a more augmented inflammatory status. Based on these correlations, in patients with cardiovascular disease, f-IMT could become a marker for increased cardiovascular risk.

Keywords: peripheral artery disease, atherosclerosis, femoral intima-media thickness

INTRODUCTION

Cardiovascular disease caused by atherosclerosis is one of the most common causes of death globally.[1] Among a number of well-established biomarkers routinely used to assess the degree of cardiovascular risk, there is a constant need to introduce novel techniques that can assess the degree of atherosclerotic burden and are able to further stratify cardiovascular risk in different categories of patients, thus predicting future events. The relationship between vascular and biochemical markers of cardiovascular risk has been studied since the 1980's. Since then, studies have confirmed that arterial hypertension, glucose and lipid disorders all increase the incidence of cardiovascular disease. Also, evidence shows that atherosclerosis is a multi-vessel disease, and often, more than one cardiovascular disease is present in the same individual, with or without manifestations. Therefore, the obvious need to develop screening methods that could have a good predictive value for assessing cardiovascular diseases both on an individual and global level has emerged. These surrogate markers of atherosclerosis have become part of the routine assessment of patients' risk. Novel biomarkers are constantly emerging, many of them based on imagistic methods, whether traditional or cutting-edge. Besides the "traditional" screening for cardiovascular risk, consisting mostly of evaluating metabolic factors, smoking status, and presence of hypertensive disease, it is common practice to also determine the carotid intima-media thickness (c-IMT). There is evidence that this parameter is able to predict ischemic heart disease and coronary events and is recommended by current guidelines as a tool for stratification of global cardiovascular risk.[2–5]

Hypertension and c-IMT have long been linked. Intimal thickening of the carotid artery is considered a marker for end-organ damage in hypertension.[6] c-IMT has also the ability to predict major cardiovascular events and total mortality in patients with hypertension.[7] Based on the evidence regarding the importance of c-IMT, studies started focusing on the potential role of intima-media thickness measured at the femoral artery in assessing cardiovascular risk. A recent study reported an increased IMT both at the carotid and femoral arteries in a population suffering from hypertensive disease.[8] A good correlation has been demonstrated between the classical peripheral vascular marker, the ankle-brachial index (ABI) and femoral intima-media thickness (f-IMT) in a group of hypertensive patients.[9] There has been evidence of an association between IMT and hypertension from the early stages of the disease, emphasizing the importance of subclinical processes that lead to endothelial dysfunction and an accelerated atherosclerosis due to a decrease in arterial wall compliance.[10]

There is a difference between sexes in the degree of the influence of these risk factors: in men, c-IMT is more correlated with hypertension and diabetes; women have increased c-IMT also due to excess weight, as defined by increased abdominal circumference and body mass index. IMT increases with age in both genders.[11] The common nominator for the different atherogenic mechanisms is endothelial dysfunction. Endothelial dysfunction is induced by the so-called "traditional" risk factors, such as smoking and disturbances of the lipid and glucose metabolism. Intimal thickening of the arteries is one of the early signs of this process. Evidence suggests that inflammation also plays a key role in the development and progression of the atherosclerotic plaque.[12] Although a variety of markers of inflammation have been studied, C-reactive protein (CRP) exhibits most evidence in relationship with atherosclerosis. An increased level of hs-CRP predicts a higher risk for cardiovascular events.[13] Also, an association between CRP levels, c-IMT, and f-IMT has been reported among patients with chronic kidney disease.[14] Atherosclerotic plaque area in the femoral and carotid arteries is also influenced by levels of CRP and components of metabolic syndrome.[15]

The aim of the study was to demonstrate that femoral intima-media thickness, a novel imagistic marker of atherosclerosis, is correlated with the traditional cardiovascular risk factors and the markers of inflammation in patients with cardiovascular diseases.

MATERIAL AND METHODS

This was a single-center, prospective, observational study that included 46 patients with diagnosed cardiovascular disease, but without peripheral vascular involvement. Demographical data (age, sex, height, and weight), history of cardiovascular disease (coronary artery disease, hypertension, cerebrovascular disease), and cardiovascular risk history (dyslipidemia, diabetes, smoking habits) were recorded. The following laboratory parameters were measured using standard commercial assays: uric acid (UA), creatinine, total cholesterol, LDL-cholesterol, HDL-cholesterol, fasting glucose, triglycerides, and C-reactive protein. The ankle-brachial index was also determined by measuring systolic blood pressure at the brachial, dorsalis pedis, and posterior tibial arteries. The lowest value measured at the lower limb was divided with the brachial artery's systolic pressure value. Brachial artery blood pressures were measured by a calibrated OMRON M3 Intelli-

sense device (Omron Healthcare Europe, Hoofddorp, the Netherlands), and lower limb systolic measurements were made using a Bistos-BT-200 CW Doppler (Bistos Co. Ltd., Korea).

Glomerular filtration rate (GFR) was calculated according to the CKD-EPI creatinine 2009 Equation, using serum creatinine values and gender.

Cardiac disease (selection criteria for patient inclusion) was defined as one or more of the following: arterial hypertension, coronary heart disease, heart failure, mitral or aortic valvular disease, and atrial fibrillation or flutter with underlying structural disease.

Demographic data was self-reported by participants. Smoking habit was defined as affirmative response to the question "Are you currently smoking?", or if they admitted to smoking more than 100 cigarettes during their life, they were categorized as former smokers. Hypertension was defined as a systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg, reporting the use of blood pressure-lowering medication or documented diagnosis of arterial hypertension. History of ischemic heart disease included self-reported or documented history of CAD, the use of anti-ischemic medication, or ECG changes suggestive for myocardial ischemia – ST-segment depression/elevation or negative T waves in >2 leads. Criteria for cerebrovascular disease included self-reported or medically documented history of stroke. Dyslipidemia was defined as use of lipid-lowering medication, self-reported or documented history of high cholesterol or triglyceride levels. Diabetes criteria included fasting glucose >126 mg/dL, non-fasting glucose >200 mg/dL, history of diabetes, use of chronic antidiabetic medication or insulin. BMI >30 kg/m^2 was considered the threshold for obesity.

Patients exhibiting signs of acute infections (increased leucocyte or granulocyte count and/or clinical signs and symptoms of respiratory/gastrointestinal/urinary infection, cutaneous ulcers etc.) were excluded from the study. Also, patients with a history of chronic inflammatory condition (e.g., autoimmune diseases, active neoplasia etc.) were not included. History of peripheral arterial disease, defined as documented arterial pathology, interventional or surgical revascularization procedures of the lower limbs, and/or symptoms of intermittent claudication were also an exclusion criteria.

Each patient underwent ultrasound examination of the superficial femoral artery (SFA) (Aloka Prosound α 10 device, Hitachi Aloka, Japan) with 7.5–10 MHz linear probe, by which intima-media thickness was determined, according to the Mannheim consensus.[14–16] Bilateral assessment of the arterial segment was performed, from the bifurcation of the common femoral artery (CFA) into the superficial and profound femoral artery to Hunter's canal, where due to the anatomical characteristics of the vessel, accurate visualization is difficult. Measurements were made on two-dimensional longitudinal images at the far wall of the SFA. Intima-media thickness was defined as the distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line (the distance between the edge of adventitia-media interface and intima-lumen interface). At least 3 measurements of IMT were made at minimum 5 cm distance between them, using the semi-automated software dedicated for c-IMT examinations. Mean IMT based on all measurements was calculated by the automated software. Segments with atherosclerotic plaques were defined as endoluminal thickening >1.5 mm or a 50% increase as compared to the adjacent segment. In the event that significant plaques were discovered, measurements were made in the vicinity of the area, on portions of the vessel without any lesions. Median f-IMT was calculated as the median value of left and right values. The highest value between mean left and right f-IMT was considered the maximum value.

Participants were divided into two groups. Differences between the two sexes were evaluated. Another division of the patients was made based on the arbitrary f-IMT cut-off value of 0.75 mm. The first group comprised 18 patients with f-IMT <0.75 mm, the second group included 28 patients with f-IMT >0.75 mm.

All variable data were checked for normality. Continuous variables were presented as mean ± SD. Continuous data were analyzed using the Mann-Whitney test and unpaired t-test. Categorical variables were expressed as numbers and percentages. Categorical data were compared using Fischer's exact test. Univariable relationships between variables and the calcium score were assessed with the Pearson correlation coefficient (r).

All phases of the study were carried out according to the principles outlined in the code of ethics of the World Medical Association's Declaration of Helsinki. Patients consented to participating in the study, and the study protocol was approved by the ethics committee of the center where the study was conducted.

RESULTS

Mean age was 71.08 ± 9.78 years. Distribution of sexes was proportioned (48.82% male, 52.17% female). Overall, 86.95% of participants were hypertensive, 56.62% had coronary heart disease, and 21.73% had suffered a stroke.

TABLE 1. Mean values of the examined parameters

Parameter	Mean ± SD	95% confidence interval
Total cholesterol (mg/dL)	182.21 ± 46.57	162.07–202.36
LDL–cholesterol (mg/dL)	95.91 ± 28.94	83.39–108.43
HDL–cholesterol (mg/dL)	45.64 ± 9.86	41.38–49.91
Triglyceride (mg/dL)	119.13 ± 50.10	97.46 ± 140.80
Fasting glucose (mg/dL)	107.13 ± 36.25	91.45–122.81
Creatinine (mg/dL)	0.97 ± 0.24	0.64–0.93
GFR (ml/min/1.73 m^2)	69.47 ± 17.24	62.02–76.93
Uric acid (mg/dL)	7.07 ± 1.76	6.30–7.83
hsCRP (mg/L)	1.29 ±1.37	0.69–1.89
Right f–IMT (mm)	0.85 ± 0.20	0.76–0.94
Left f–IMT (mm)	0.81 ± 0.16	0.85–1.14
Right ABI	1.17 ± 0.35	
Left ABI	1.03 ± 0.34	

The most prevalent cardiovascular risk factors were dyslipidemia (68.86%), diabetes (21.73%), and smoking (21.73%).

Mean values of patients' metabolic profile, ABI, and f-IMT are summarized in Table 1.

Data distribution according to gender

Differences of parameters according to gender are shown in Table 2. Significant differences were noted regarding total cholesterol levels (161.36 ± 25.04 mg/dL, 95%CI 150.26–172.47 in males vs. 201.33 ± 52.73 mg/dL, 95%CI 170.07–223.60 in females, p = 0.02), creatinine values (1.04 ± 0.22 mg/dL, 95%CI 0.94–1.14 for males vs. 0.91 ± 0.23 mg/dL, 95%CI 0.81–1.00 for females, p = 0.018), left f-IMT (0.87 ±0.18 mm, 95%CI 0.79–0.95 for males, 0.75 ± 0.10 mm, 95%CI 0.70–0.79 for females, p = 0.0049).

Regarding history of cardiovascular diseases, female participants had a higher incidence of hypertension (81.81% in males vs. 91.66% in females) and CAD (36.36% in males vs. 75% in females), while men had a higher incidence of stroke (27.27% in males vs. 16.66% in females).

Obesity, dyslipidemia, and diabetes were more prevalent in women (58.33% vs. 45.45%, 75% vs. 45.45% and 33.33% vs. 18.18%, respectively). There were more smokers among men (45.45% vs. 0%).

Characteristics of patient groups with low vs. high f-IMT

There were no major differences between the two groups regarding CAD (66.66% vs. 53.57%), hypertension (88.88% vs. 85.71%), dyslipidemia (55.55% vs. 50%), obesity (55.55% vs. 57.14%), and diabetes (22.22% vs. 28.57%). There were almost twice as many smokers in the group with increased f-IMT (11.11% vs. 21.42%), and patients with higher f-IMT had a higher incidence of stroke as well (11.11% vs. 25%).

Age, gender, biochemical and inflammatory parameters showed no significant differences between the two groups.

There were statistically significant differences between right, left f-IMT (p <0.0001, p = 0.0007), and left ABI (p = 0.0034).

Correlations between f-IMT, demographic and biochemical parameters, and peripheral vascular markers

A significant, reverse correlation was established between uric acid and f-IMT in the group with f-IMT <0.75 mm (r = –0.483, p = 0.0042). Among the patients with f-IMT >0.75 mm, there was a significant correlation of f-IMT with age (r = 0.408, p = 0.031), fasting glucose levels (r = 0.407, p = 0.034), total cholesterol (r = 0.429, p = 0.02), and serum triglycerides (r = 0.454, p = 0.01). Results are shown in Table 3.

Maximum f-IMT was significantly, reversely correlated with right ABI in the group with f-IMT <0.75 mm (r = –730, p = 0.0006), maintained also upon univariate regression analysis (p = 0.001). Other parameters showed no significant associations with f-IMT determined at either side – right or left.

In the group with f-IMT >0.75 mm, significant associations were detected between f-IMT and ABI (r = –0.718, p <0.001 for correlation and p = 0.04 for regression) and fIMT vs. hs-CRP (r = 0.450, p = 0.01).

TABLE 2. Distribution of metabolic and inflammatory risk factors and vascular parameters according to gender

Parameter	Male n = 22	Female n = 24	p value
Total cholesterol (mg/dL)			
Mean ± SD	161.36 ± 25.04	201.33 ± 52.73	0.02
95% confidence interval	150.26–172.47	170.07–223.60	
LDL–cholesterol (mg/dL)			
Mean ± SD	88.34 ± 21.81	102.85 ± 32.61	0.13
95% confidence interval	78.67–98.01	88.77–117.58	
HDL–cholesterol (mg/dL)			
Mean ± SD	45.92 ± 11.55	45.92 ± 8.50	0.70
95% confidence interval	40.40–50.29	42.33–49.51	
Triglyceride (mg/dL)			
Mean ± SD	117.63 ±46.05	120.5 ± 53.49	0.66
95% confidence interval	97.21–138.06	97.90–143.09	
Fasting glucose (mg/dL)			
Mean ± SD	116.54 ± 48.63	98.5 ± 13.83	0.10
95% confidence interval	94.97–138.11	92.65–104.34	
Creatinine (mg/dL)			
Mean ± SD	1.04 ± 0.22	0.91 ± 0.23	0.018
95% confidence interval	0.94–1.14	0.81–1.00	
GFR (ml/min/1.73 m^2)			
Mean ± SD	74.18 ± 17.85	65.16 ± 15.40	0.11
95% confidence interval	66.26–82.09	58.66–71.67	
Uric acid (mg/dL)			
Mean ± SD	8.11 ± 0.91	6.11 ± 1.79	<0.0001
95% confidence interval	7.70–8.51	5.35–6.87	
hsCRP (mg/L)			
Mean ± SD	1.58 ± 0.90	1.02 ± 1.65	0.0075
95% confidence interval	1.18–1.98	0.33–1.7	
Right f–IMT (mm)			
Mean ± SD	0.85 ± 0.20	0.85 ± 0.22	0.76
95% confidence interval	0.77–0.93	0.76–0.95	
Left f–IMT (mm)			
Mean ± SD	0.87 ±0.18	0.75 ± 0.10	0.0049
95% confidence interval	0.79–0.95	0.70–0.79	
Right ABI			
Mean ± SD	1.20 ± 0.46	1.15 ± 0.20	0.76
Left ABI			
Mean ± SD	0.98 ± 0.35	1.07 ± 0.19	0.20

DISCUSSIONS

The results of the study revealed that in patients with cardiovascular diseases, there is a significant correlation between femoral intima-media thickness, inflammatory processes, and markers of cardiovascular risk. Patients who exhibited higher values of f-IMT had also higher plasma glucose, cholesterol, triglyceride, and hs-CRP levels. Also, those with lower ankle-brachial index showed increased intimal thickening. These results suggest that f-IMT could become a reliable predictor of global cardiovascular risk and could also indicate peripheral arterial disease in asymptomatic patients suffering from other cardiovascular comorbidities. The significant correlation between hs-CRP as a marker of inflammation and f-IMT in the category with increased f-IMT confirms that pro-inflammatory factors that lead to endothelial dysfunction are involved in the atherosclerotic process. There are few studies involving the measurement of intima-media thickness at the femoral arteries, and most of them determine IMT at the common femoral artery. Many of them use both carotid and femoral measurements as basis of comparison with cardiovascular risk profile, major cardiovascular events, or markers of inflammation. In a

TABLE 3. Correlations between risk factors and f–IMT in the two groups

Parameter	f–IMT < 0.75 mm n = 18	f–IMT > 0.75 mm n = 28
Age (years)	r = 0.22, p = 0.35	r = 0.40, p = 0.03
Total cholesterol (mg/dL)	r = –0.29, p = 0.23	r = 0.42, p = 0.02
LDL–cholesterol (mg/dL)	r = 0.19, p = 0.43	r = 0.007, p = 0.69
HDL–cholesterol (mg/dL)	r = 0.31, p = 0.19	r = –0.56, p = 0.0019
Triglyceride (mg/dL)	r = –0.35, p = 0.14	r = 0.45, p = 0.01
Fasting glucose (mg/dL)	r = 0.04, p = 0,86	r = 0.40, p = 0.03
Creatinine (mg/dL)	r = 0.30, p = 0.21	r = 0.14, p = 0.46
GFR (ml/min/1.73 m^2)	r = –0.11, p = 0.64	r = –0.31, p = 0.10
Uric acid (mg/dL)	r = –0.48, p = 0.04	r = 0.32, p = 0.09
hsCRP (mg/L)	r = –0.5316, p>0.99	r = 0.45, p = 0.01
Right ABI	r = –0.7303, p = 0.0006	r = –0.17, p = 0.37
Left ABI	r = 0.60, p = 0.007	r = –0.71, p<0.0001

group of non-smoker males without known cardiovascular pathology, there were significant associations between the components of metabolic syndrome – hypertension, dyslipidemia, hyperinsulinemia and abdominal obesity – and femoral intima-media thickness.[17]

Patient groups

In our study, patients were divided into two groups based on f-IMT values. The first group included 18 patients with f-IMT <0.75 mm and the second group comprised 28 patients with f-IMT >0.75 mm.

Although the median value of f-IMT in our study was 0.83 mm, we arbitrarily chose the cut-off value of 0.75 mm based on studies investigating carotid intima-media thickness and results of other studies involving the measurement of f-IMT. In a study led by Godoi, which included both carotid and femoral measurements, the mean value of f-IMT was 0.74 ± 0.3 mm in the control group, even though the cut-off value was set at 0.8 mm. The value of 0.7 mm was used when calculating the sensitivity (72.5%) and specificity (46%) of the test.[18] Lucatelli and associates reported 0.73 mm as the median value of f-IMT for CFA in a study involving individuals with no cardiovascular disease, but noticed an increase with age and the presence of risk factors.[19] Another study investigating the predictive value of f-IMT for cardiovascular events in patients with stable CAD, median values of f-IMT were 0.78 ± 0.26 mm in men and 0.71 ± 0.29 mm in women.[20]

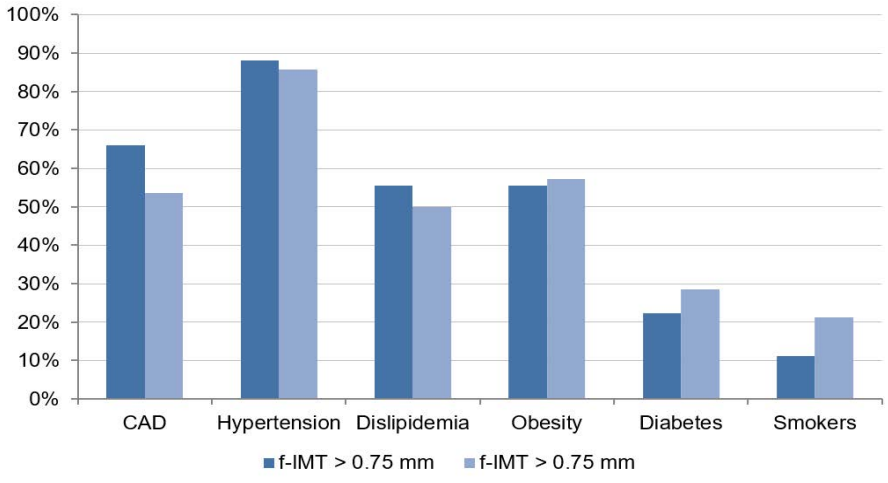

FIGURE 1. Cardiovascular comorbidities and risk factors in the groups with low and high f–IMT

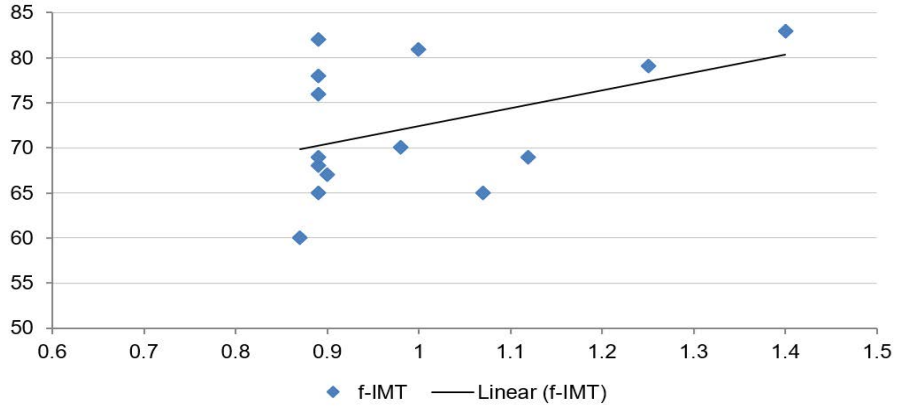

FIGURE 2. Correlation between age and f–IMT in the group with high f–IMT

Technical aspects of f-IMT evaluation

A good correlation between f-IMT and c-IMT has been reported by other studies.[21] Although the majority of studies use the common femoral artery as the site for measuring the intima-media thickness of the lower limb arteries, results of the assessment of carotid arteries can be extrapolated to underline the usefulness of examining different segments of the femoral arterial axis. In carotid arteries, each segment presented different correlations with cardiovascular risk factors. Both common and superficial carotid artery IMT increased with age and presented differences according to gender; while CCA-IMT variations were more influenced by systolic arterial pressure, increase in internal carotid artery IMT was associated with smoking. The same study demonstrated an independent correlation of arterial wall IMT with the Framingham risk score.[22] In the Rotterdam study, both common and internal carotid artery IMT had a good predictive role for the incidence of acute myocardial infarction.[23]

In ultrasound evaluations, the superficial femoral artery is easier to visualize than the common femoral artery, because direct examination of the latter can be impaired by excess adipose tissue, the presence of enlarged lymph nodes, intestinal content due to inguinal or femoral hernias, or anatomical variants, e.g. a high bifurcation. Due to its relatively superficial and long trajectory, the SFA allows proper examination of a segment in which far-wall measurement of IMT is possible (extrapolating recommendations for carotid artery examinations, where far-wall measurement of IMT is preferred). Also, the potential presence of atherosclerotic plaques which can impair measurements can be avoided in the SFA by choosing an

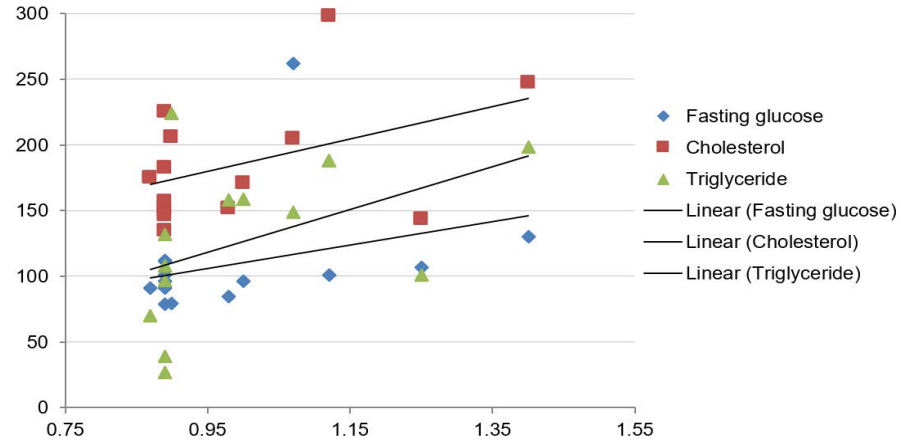

FIGURE 3. Correlations between metabolic parameters and f–IMT in the group with high f–IMT

adjacent, "healthy" segment. Series of measurements can also be made, which contribute to the accuracy of mean IMT values. One of the pitfalls of SFA examination is the difficulty of examining the portion in Hunter's canal, where anatomical and hemodynamical aspects can represent a challenge even for experimented examiners. Increased turbulence is also the reason why this segment is the elective locus for the development of atherosclerotic plaques, because of increased shear stress and intermittent muscular compression. Because these characteristics can influence IMT, we chose not to include this segment in our study.

One of the advantages of femoral IMT examinations is that cardiac cycle variations seem to influence the measurements less than at the carotid arteries. This could also influence the process of vascular remodeling. A study conducted by Layne, comparing variations of c-IMT and f-IMT during the cardiac cycle, demonstrated that the variations at the femoral site do not reach the threshold for statistical significance and as such, can be considered more reliable.[24] Femoral intima-media measurements are also more reproducible than those of the carotid arteries.[25]

Metabolic risk profile of the study population

It is a well-known fact that age is associated with an acceleration of atherosclerosis, and the prevalence of peripheral arterial disease is increased in the elderly.[26] The results of our study are in line with this information, as there was a significant correlation between an increase in age and f-IMT in the group with f-IMT >0.75 mm.

Our study established a significant correlation between f-IMT >0.75 mm and total cholesterol, HDL-cholesterol, and triglyceride levels that have not been demonstrated in the group with f-IMT <0.75 mm. This can be an important indicator of the contribution of metabolic factors to the progression of atherosclerosis.

Glucose metabolism disorders cause an acceleration of atherosclerosis. A number of studies have confirmed that IMT thickening and higher glucose levels are related.[27,28] Our results confirm these findings based on the fact that in the group with f-IMT >0.75 mm, there was a significant correlation between IMT and fasting glucose. ($r = 0.407$, $p = 0.03$). The endothelial dysfunction induced by diabetes plays a significant role in accelerated atherosclerosis that can lead to intimal proliferation, but it has to be stated that glucose metabolism disorders also contribute to the thickening of media, and current imagistic techniques cannot distinguish between intimal and medial alterations of the arterial wall, although different pathogenic mechanism may be involved in their development.

In our study, we established a significant correlation between f-IMT, total cholesterol, and HDL-cholesterol ($r = 0.429$, $p = 0.02$ and $r = -0.561$, $p = 0.001$ respectively). This confirms the well-known fact that dyslipidemia has a strong influence on atherogenesis.[29] Similarly to our results, studies report that high HDL-cholesterol levels decrease cardiovascular risk and are inversely correlated with f-IMT.[30] Increased levels of triglycerides were reported to contribute to f-IMT thickening in overweight patients, according to the study published by Genoud and assoc., which is in trend with our results, where similar significant associations have been found ($r = 0.454$, $p = 0.001$ for triglycerides vs. f-IMT).

An interesting finding in our data was the reverse correlation between f-IMT and uric acid in the group with f-IMT <0.75 mm ($r = -0.0048$, $p = 0.042$). UA is the final product of purine metabolism and has both anti-oxidant, as well as pro-oxidant properties. It is presumed that the pro-oxidant effect is dependent of increased serum concentrations, due to its capacity to decrease the bioavailability of nitric oxide secreted by the endothelium. This leads to an auto-catalytic cascade that increases oxidative stress and further reduces nitric oxide levels. Even though, compared to other factors, UA has been attributed importance in risk-reducing strategies, it can be considered a metabolic-cardiovascular risk factor, since there is convincing evidence that it contributes to glucose and lipid metabolism disorders.[31–34] In our study, mean levels of UA were lower in the group with f-IMT <0.75 mm, comparable to normal serum levels, and we attribute the reverse correlation to its antioxidant effect. This information seems the more plausible, as in the same group, levels of hs-CRP were also lower and showed no significant association with f-IMT, suggesting that their inflammatory status was not increased. Still, studies show that extremely low or high serum concentrations of UA have a strong pro-oxidative effect.[35]

Markers of peripheral atherosclerosis and inflammation

As a subclinical process, inflammation in involved in the metabolic disturbances that precede manifest atherosclerosis. An increase in CRP indicates a pro-inflammatory status and is influenced by smoking, obesity, and age, factors also contributing to an accelerated atherosclerosis.[36] Even though a meta-analysis of studies concluded that CRP has a relatively moderate capacity of predicting CAD, still, in

patient categories with a Framingham risk score between 10 and 20%, it is a good toll for risk stratification.[37] In patients with chronic kidney disease undergoing hemodialysis, CRP levels correlated with carotid and femoral intima-media thickness.[38] The group with f-IMT >0.75 mm in our study also presented higher circulating CRP levels ($r = 0.450$, $p = 0.01$). This suggests that inflammation is a systemic process, but an aspect to be clarified is whether it is the promoter or the consequence of atherosclerosis. Shedding light on the mechanism that causes the inflammation-atherosclerosis continuum could allow specific inhibition of the process and as such, reduce cardiovascular risk and prevent major cardiovascular events.

Correlations between f-IMT and the ankle-brachial index

The results of our study demonstrated a significant, reverse correlation between f-IMT and the well-established biomarker of peripheral vascular involvement, the ankle-brachial index ($r = -0.7303$, $p = 0.0006$ for right ABI in the group with f-IMT < 0.75 mm and $r = -0.7183$, $p < 0.01$ for left ABI in the group with f-IMT >0.75 mm). This confirms that there is an association between different methods of assessing the degree of lower limb atherosclerosis and that f-IMT may be considered as a new tool to assess peripheral vascular involvement. Similar associations regarding c-IMT were described by Winckler and associates.[39] Ultrasound examinations may have a higher sensibility than ABI for detecting atherosclerosis of the lower limb according to results published in a study led by Flanigan.[40] More advanced imagistic methods have also confirmed these findings, an angiographic magnetic resonance study reporting a good correlation between the ABI and local atherosclerotic burden.[41]

An unusual finding of our study was the different associations of left and right ABI with f-IMT (significant for right ABI vs. f-IMT in the group with low f-IMT vs. left ABI in the group with high f-IMT). We attributed these results to the fact that unilateral stenosis of the peripheral arteries is more common than bilateral lesions, due to the random nature of the atherosclerotic process. Similar results were reported in another study, where significant differences were noted in the distribution of stenotic lesions in right or left sides of different arterial segments.[42] It may be assumed that local anatomic and/or hemodynamic characteristics (the influence of aortic pulsations or distention of the left renal artery) contribute to local vascular endothelial function and result in different degrees of atherosclerotic involvement.

Study limitations

Our research made efforts to include a variety of aspects of atherosclerotic disease, regarding personal history as well as biochemical and imagistic parameters. Still, the study has a few limitations. First of all, although it comprised a considerable number of participants, a larger patient cohort may have allowed extrapolating results to a larger scale. Even though strong correlations between f-IMT and lipid markers have been demonstrated, the use of apolipoprotein (a) could have been useful as well, as there is evidence that suggests that it is associated with an increased risk for CAD and PAD. Measuring apo(a) might yield additional information about the cardiovascular risk of those with increased f-IMT and could contribute to a better risk stratification in this category.[43–45] Regarding markers of inflammation, a number of publications underlined their utility as markers of risk for PAD.[46–48] Based on this information, other components of the pentraxin class, such as pentraxin-3 or levels of matrix metalloproteinase, cellular adhesion molecules, interleukin-1 or interleukin-6 levels could have been added to the inflammatory panel to further investigate the relationship between inflammation, imagistic markers, and atherosclerosis.

The study population consisted of patients with cardiovascular comorbidities. Because of this, it would have been useful to determine surrogate markers of organ damage such as carotid intima-media thickness and left ventricular ejection fraction. The potential correlations between femoral parameters and these well-established markers of atherosclerosis may have contributed to the evaluation of the capacity of f-IMT to become a surrogate marker of peripheral vascular disease caused by atherosclerosis.

Another aspect to be considered is the effect of medication on the progression of atherosclerosis in patients with cardiovascular disease. There is evidence that the use of ACE inhibitors and statins can lead to plaque regression and as such, are firmly recommended by guidelines for the prevention of major cardiovascular events.[49–51] Comparing the degree of intimal thickening in the femoral artery in relationship with statin and ACE use could help confirm that atherosclerosis of the lower limb is also influenced by these standard therapies.

In order to confirm the predictive role of f-IMT in cardiovascular events, follow-up studies need to be conducted, which can demonstrate that femoral intimal thickening is correlated with the incidence of peripheral or coronary embolic events.

All these limitations of the study also open up new perspectives in the research regarding f-IMT and could become the basis of new studies.

CONCLUSIONS

In our study, femoral intima media thickness measured at the superficial femoral artery significantly correlated with fasting plasma glucose, total cholesterol, serum triglyceride, and C-reactive protein levels. Associations between f-IMT and the surrogate marker of peripheral vascular involvement – the ankle-brachial index were demonstrated. All these data bring further evidence to support the fact that atherosclerosis is a multifactorial disease. It affects multiple arterial sites and it is the consequence of a complex process that implies the existence of endothelial dysfunction induced by lipid and glucose metabolism disorders and is influenced by inflammation.

The relationship between f-IMT and ABI is in favor of the assumption that f-IMT could become, similarly to c-IMT, a marker of cardiovascular risk and a surrogate marker of cardiovascular events in a population with high cardiovascular risk or overt cardiovascular disease.

CONFLICT OF INTEREST

Nothing to declare.

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