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Keywords: atherosclerosis; carotid artery plaque; carotid intima media thickness; femoral artery plaque; femoral intima media thickness; short-term progression of atherosclerosis; ultrasound; vascular risk

*Article*

# Subclinical Atherosclerosis Progression in Low-Risk Middle-Aged Adults: Carotid Leads Femoral in IMT Increase but Not in Plaque Formation

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**Abstract:** This study investigated subclinical atherosclerosis progression in low-risk, middle-aged adults (N=141; mean age 49.6±4.7 years) using a 5-year ultrasound follow-up. We compared in-volvement of the carotid and femoral arteries. Methods: Clinical data, risk factors, and carotid/femoral intima-media thickness (IMT) and plaque presence were analyzed. Results: Cardiovascular risk factors and scores increased significantly at follow-up. Both carotid and femoral IMT increased ($p<0.001$) but remained within the normal range. While plaque prev-alence rose and was similar in both arteries (carotid: 4.8% to 17.9%, femoral: 3.6% to 17.7%, $p<0.001$ for both), the progression of plaque burden was greater in femorals. Notably, carotid IMT demonstrated a faster yearly progression rate compared to femoral IMT. The age- and sex-adjusted increase in IMT was also more frequent in the carotids (52.9% to 78.8%, $p<0.001$) compared to femorals (23.2% to 44.7%, $p<0.001$). Conclusions: This study demonstrates significant subclinical atherosclerosis progression in low-risk middle-aged adults during 5 years. Carotid arteries showed a faster progression rate and higher prevalence of increased age- and sex-adjusted IMT compared to the femoral arteries. However, plaque burden was similar in both territories, with greater progression in femorals. Identifying carotid and femoral atherosclerosis burden may be a valuable tool for risk stratification in this population.

**Keywords:** atherosclerosis; carotid artery plaque; carotid intima media thickness; femoral artery plaque; femoral intima media thickness; short-term progression of atherosclerosis; ultrasound; vascular risk.

## 1. Introduction

Atherosclerosis (ATS) burden is a strong risk for new cardiovascular (CV) events and is related to poor outcome after CV events [1]. A large proportion of the asymptomatic population stratified by various validated multivariable risk prediction tools is at low-to moderate CV disease (CVD) risk [2], with missed opportunities for early detec-tion and appropriate management of underlying ATS [3]. Identification of subclinical ATS is an important step in the management of patients in primary CVD prevention. There are several methods to evaluate the presence and progression of subclinical ATS [4,5]. Coronary artery calcification (CAC), carotid intima-media thickness (CIMT), carotid plaque and ankle-brachial index (ABI) were proposed as valuable markers of subclinical ATS and predictors of CV events [6], however, with not equal risk redefinition [7]. According to the current European guidelines, CAC scoring, or as alternative when CAC scoring is not feasible, plaque detection by carotid ultrasound (USG) may be considered to improve risk classification around treatment decision thresholds with IIb B level of evidence [8]. Since ATS is a global disease, the study of ATS requires a multimodal and multiterritorial approach. Several studies support the value of measuring subclinical ATS in multiple

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arterial territories for a more accurate CV risk stratification [9,10]. Subclinical ATS is highly prevalent in middle-aged asymptomatic population [11–13], in addition, clinical data documented extensive ATS in a substantial number of low-risk individuals [11]. Except for the preferentially screened carotid and coronary area, the iliofemoral arteries and abdominal aorta are also frequently affected. Results from the Progression of Early Subclinical Atherosclerosis Study (PESA) documented even higher prevalence of ATS plaque in the iliofemoral arteries, compared with the carotid, abdominal, and coronary arteries [11]. Identification of global atherosclerotic burden is a useful tool to identify patients at high CVD risk. There are limited numbers of studies comparing presence and progression of subclinical ATS in different arterial regions [14]. Ultrasound-based techniques are non-invasive, accessible, with quick measures, easy training, reduced cost, and no radiation [15], and so they are suitable for population screening. We aimed to study the short-time progression rate of carotid and femoral subclinical atherosclerosis in middle-aged, apparently healthy individuals and to evaluate their potential use in primary prevention.

## 2. Patients and Methods

The present study is an observational, prospective, real-life study in a target population of 400-450 apparently healthy subjects. Study subjects were 141 participants of Caucasian origin without established CVD, 56,7% women and 43,3% men, aged 49.6±4.7 years, who underwent baseline and 5-year follow-up (4.67±0.95 years) visit between February 2010 and October 2017. The study design has been reported elsewhere [13]. Briefly, males or females 35-55 years of age, non-diabetics, inhabitants of the East Slovak Region, with obtained written informed consent were included. Subjects with established CVD, European Systematic Coronary Risk Evaluation (SCORE) risk $\geq$5%, chronic kidney, respiratory or hepatic disorders, neoplasia, severe obesity (body mass index (BMI) >35 kg/m$^2$), alcoholism, non-compliance, pregnancy, as well as acute inflammatory disorders were excluded. Out of the target population, only 256 persons met the inclusion criteria, we excluded 69 patients. Finally, 187 individuals were enrolled into the study, 141 of them (75,4%) finished the follow-up. During follow-up, we observed one sudden cardiac death (0.53%), one suicidal death, and one nonfatal CV event (unstable angina pectoris). This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethical Committee of the L. Pasteur University Hospital in Košice (approval number 2020/EK/02018).

## 3. Data Collections and Statistics

### *3.1. Data Collection*

Participants were examined in the Outpatient Department of the 4th Clinic of Internal Medicine at L. Pasteur University Hospital in Košice, in the morning, under basal conditions. The examination itself consisted of the blood and urine collection for biochemical analysis, detection of morphological markers of subclinical ATS, interviews for medical history with the focus on classical risk factors (RFs) for ATS and current medications, measurements of body size, waist circumference and office blood pressure, determination of 10-year fatal and total CV risk (European SCORE) and resting 12-lead electrocardiogram recording. Blood and urine samples were analysed in the relevant subdivisions of the department of laboratory medicine at the same hospital. Metabolic parameters used in our work {fasting glucose, glycated haemoglobin (HbA1c), uric acid, serum total cholesterol (T-C), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides (TAG), serum creatinine} have been directly determined by standard laboratory tests; estimated glomerular filtration rate (eGFR) were calculated according to the Modification of Diet in Renal Disease (MDRD) formula [16]. The following values were considered pathological: creatinine > 90µmol/L, eGFR < 1.5mL/s/m$^2$, uric acid > 357/428µmol/L (males/females). Non-modifiable RFs for ATS as well as arterial hypertension (AH), dyslipoproteinemia (DLP), obesity/central obesity, diabetes mellitus (DM), impaired fasting glucose, metabolic syndrome (MetS) have been defined according to current

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recommendations [17,18]. Smoking status was characterized as current smoking ≥1cigarette/day. To estimate a person´s 10-year risk of CV death we used the SCORE chart for high-risk countries (low risk <1%/moderate risk ≥1% and <5%), total 10-year CV event risk was calculated by multiplying fatal risk (3x for men and 4x for women) [17]. The targeted dietary and pharmacological management of AH and DLP was satisfactory at the time of patient enrollment into the study. Based on personalized CV risk assessment, preventive measures (lifestyle modifications and/or pharmacological treatment) were recommended for each subject, to which they agreed. Adherence to instructions was regularly checked by family doctors and study investigators.

### *3.2. Morphological Markers of Subclinical Atherosclerosis*

#### 3.2.1. Carotid IMT and Plaque Assessment

Ultrasonography was performed by one experienced sonographer with acceptable intraobserver variability of measurements, blinded to subjects' health status and RFs. Details of the USG methodology and quality control have been reported previously [13,19]. CIMT and carotid plaque were defined according to the Mannheim consensus [20,21]. Bilateral carotid arteries were scanned using high-resolution B-mode USG (Philips HD 15) with the 7.5-MHz probe in real-time, at 5x magnification. IMT was defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface and was measured on distinct plaque-free segment of the common carotid artery (CCA) far wall, 1 cm from the flow divider, in the end-diastole, at its presumed maximum thickness. Examinations were made automatically. ATS plaque was defined as an endoluminal protrusion of at least 1.5 mm or a >50% focal thickening of the IMT relative to the adjacent wall segment. Plaque presence on both transverse and longitudinal planes was recorded in the CCA, bulb, internal (ICA) and external (ECA) carotid arteries. Generally, carotid plaques were stable, isoechogenic, with smooth surface and normal peak systolic velocity (PSV) at baseline and during follow-up. CCA parameters evaluated in our work: mean value of CIMT on the right, left (CIMTdx, sin), maximum value of CIMT right or left (CIMTmax), CIMT>0.9mm right or left (CIMTbilat>0.9), pathological mean right or left CIMT by age and sex (asCIMTbilat), i.e., in males/females on the left side: 31-40 years: >0.57/0.51 mm, 41–50 years: >0.61/0.57 mm, and over 50 years: >0.70/0.64 mm; on the right side: 31-40 years: >0.5/0.49 mm, 41-50 years: >0.57/0.53 mm, over 50 years: >0.62/0.59 mm [22,23], CCA-IMT progression (mm/year) and presence of carotid plaque.

#### 3.2.2. Femoral IMT and Plaque Assessment

The literature diverges on the issue of the reference measurement site and methodology of IMT (especially in other than carotid area), even the pathological values of IMT in the carotid or femoral area are not uniform. Considering the need to use the same methodology, we proceeded with the assessment of subclinical ATS of the femoral artery as in the carotid area. The definition of IMT and plaque was identical for both arterial territories. Bilateral common femoral arteries (CFA) were scanned, femoral IMT (FIMT) was obtained 1-2 cm proximal from the bifurcation, on the far wall of CFA [24]. For the plaque presence, the CFA, the superficial and profundal femoral arteries were examined for a length of 3 cm (1.5 cm proximally and distally to the flow divider) [9]. CFA parameters evaluated in our work: mean value of FIMT on the right, left (FIMTdx, sin), maximum value of FIMT right or left (FIMTmax), FIMT>0.9mm right or left (FIMTbilat>0.9) [25], FIMT>1.1mm right or left (FIMTbilat>1.1) [24], pathological mean right or left FIMT by age and sex (asFIMTbilat), i.e., in white males/females 24-43 years: >0.75/0.64 mm [26], CFA-IMT progression (mm/year) and presence of femoral plaque.

### *3.3. Statistical Analysis*

Patient's data are summarized at baseline and at the end of follow-up and analysed by means of descriptive statistical methods. Continuous variables are shown in the tables in the form of arithmetic

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mean and standard deviation (SD), and the categorical variables as an absolute number and its relative representation (%) in the sample. Analysis of differences in the continuous clinical parameters investigated, including markers of subclinical ATS between patients at baseline and at follow-up visit was carried out using a paired samples t-test. A McNemar's test was used to compare the frequencies of categorical variables in time between paired samples. During the follow-up a progression rate of CIMT and FIMT was also calculated. A value of $p<0.05$ was considered statistically significant. The analyses were performed using the IBM SPSS 23.0 statistical software package (IBM Corp., Armonk, NY, USA).

## 4. Results

### *4.1. Characteristics of the Study Group*

Out of the study sample of 187 clinically healthy, non-diabetic, 35–55-year-old individuals (mean age 45,6±5 years at baseline) in the Eastern Slovak Region, 141 persons were checked after a follow-up of 4.67±0.95 years. Demographic, clinical and laboratory data at baseline and after follow-up are shown in Table 1.

**Table 1.** Comparison of mean values, standard deviations (SD) and changes (Δ) of continuous anthropometric, clinical and biochemical data at baseline and after follow-up assessed with paired t-test.

| Parameters | Baseline N=141 Mean (SD) | Follow-up N=141 Mean (SD) | Δ Mean (SD) | p |
|---|---|---|---|---|
| Age (yr) | 45.64 (5.02) | 49.64 ( 4.67) | 4.35 (1.6) | <0.001 |
| Waist circumference (cm) | 87.63 (13.07) | 92.33 ( 12.87) | 4 (5.39) | <0.001 |
| BMI (kg/m$^2$) | 25.28 (3.89) | 25.67 (4.55) | 0.38 (1.48) | 0.003 |
| Total cholesterol (mmol/L) | 5.47 (0.93) | 6.00 (1.09) | 0.48 (0.88) | <0.001 |
| LDL-C (mmol/L) | 3.24 (0.79) | 3.91 (0.83) | 0.63 (0.75) | <0.001 |
| HDL-C (mmol/L) | 1.5 ( 0.35) | 1.47 (0.36) | -0.01 (0.21) | NS |
| Triglycerides (mmol/L) | 1.26 (0.74) | 1.47 (0.86) | 0.15 (0.56) | 0.002 |
| Plasma glucose (mmol/L) | 5.01 (0.47) | 5.13 (0.49) | 0.11 (0.4) | 0.001 |
| HbA1c (IFCC) (mmol/mol) | 34.4 (3.6) | 32.4 (3.5) | -1.9 (3.4) | <0.001 |
| Uric acid (µmol/L) | 297.27 (80.09) | 312.16 (81.9) | 13.97 (45.31) | 0.001 |
| Creatinine (µmol/L) | 86.45 (10.64) | 71.36 (11.91) | -16.36 (5.63) | <0.001 |
| eGFR (mL/min/1.73m$^2$) | 70.2 (7.8) | 96.6 (11.4) | 26.4 (9.0) | <0.001 |

Remarks: BMI, body mass index; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; HbA1c, glycated hemoglobin; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; eGFR, estimated glomerular filtration rate; NS, statistically nonsignificant difference; N, number; SD, standard deviation; Δ, change; p, statistical significance; yr, years.

### *4.2. Risk Profile, Subclinical Carotid or Femoral Atherosclerosis Burden at Baseline and at Follow-Up*

Changes in the persons´ risk profile including analysed structural markers of subclinical ATS after 5 years are listed in Table 2. After follow-up we documented a significantly higher prevalence of modifiable RFs: DLP, central obesity, AH, as well as a corresponding increase of SCORE risk (1.2±1.61; $p < 0.001$) and number of RFs (3.72±5.82; $p < 0.05$). The mean values of CIMT right and left (0.62±0.10 mm; $p<0.001$, both) were significantly increased, but remained under the „cut off level of 0.9 mm" at follow-up. The increase in mean (0.07-0.08±0.12 mm) and maximum (0.07±0.13 mm) values of CIMT was significant. The mean and maximum values of IMT at baseline and at follow-up were almost identical at carotid and femoral sites (Table 2). The mean right and left CCA-IMT change/year was the same: 0.017± (0.027-0.029) mm. The FIMT progression was slower in comparison with CIMT, with the lowest rate for FIMTdx (right: 0.0085±0.035mm/year; left: 0.012±0.044 mm/year). The occurrence of CIMT>0.9 mm was rare (2.1%) and not significantly changed during the follow-up. In comparison with carotid region, the FIMT>0.9 mm was more frequent at the first and last visit, on the other hand,

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the presence of the other femoral IMT cut-off value, FIMT >1.1 mm, was similarly to carotid region, rare. However, the prevalence of asCIMTbilat was higher (78.8%) with greater increase (+25.9%) at the end of follow-up in comparison with the occurrence and increase rate of asFIMTbilat (44.7% and +21.5% resp.). Similar significant increase in the rate of carotid and femoral plaque burden was also observed (from 4.8% to 17.9% and 3.6% to 17.7% resp.; p< 0.001, both), but with higher progression in femorals (13.1% vs. 14.1%). Initially in 8.4% of subjects we found carotid or femoral plaque, at the end of the follow-up it was 26.9% (in 12 subjects' plaques were present in both, the carotid and femoral regions). If only the carotid area was examined, the ATS plaque on the femoral artery would be missed in approximately 9% of patients at the end of follow-up.

**Table 2.** Comparison of prevalence and mean values of cardiovascular risk factors and morphological markers of subclinical carotid/femoral atherosclerosis at baseline and after follow-up assessed with McNemar´s or paired t-test.

| Parameter | Baseline N=187/141 Mean (SD) | Follow-up N=141 Mean (SD) | Δ Mean (SD) | p |
|---|---|---|---|---|
| Risk age (N/ %) | 41/ 21.9 | 65/ 46.1 | 24/ 24.2 | NS** |
| Sex (male) (N/ %) | 75/ 40.1 | 61/ 43.3 | -14/ 3.2 | NS** |
| Positive family history (N/ %) | 33/ 17.8 | 31/ 22.1 | -2/ 4.3 | NS** |
| DLP (N/ %) | 132/ 71 | 126/ 89.4 | -6/ 18.4 | <0.001** |
| AH (N/ %) | 48/ 25.8 | 54/ 38.6 | 6/ 12.8 | <0.001** |
| Duration of AH (years) | 0.78 (2.12) | 2.1 (4.57) | 1.32/ (2.45) | <0.001* |
| Smoking (N/ %) | 38/ 20.3 | 28/ 19.9 | -10/ -0.4 | NS** |
| MetS (N/ %) | 31/ 16.8 | 40/ 28.4 | 9/ 11.6 | NS** |
| Central obesity (N/ %) | 105/ 57.4 | 103/ 74.6 | -2/ 17.2 | <0.001** |
| SCORE fatal | 0.57 (0.93) | 1.16 (1.56) | 0.59/ (0.63) | <0.001* |
| SCORE total | 1.81 (2.70) | 3.71 (4.72) | 1.9/ (2.02) | <0.001* |
| Number of RFs | 2.61 (1.63) | 3.78 (6.06) | 1.17/ (4.43) | <0.027* |
| Treatment of DLP (N/%) | 12/ 6.4 | 12/ 8.5 | 0/ 2.1 | NS** |
| CIMT sin (mm) | 0.54 (0.09) | 0.62 (0.10) | 0.08 /(0.11) | <0.001* |
| CIMT dx (mm) | 0.54 (0.09) | 0.62 (0.10) | 0.08 /(0.12) | <0.001* |
| CIMT max (mm) | 0.67 (0.11) | 0.74 (0.11) | 0.07 /(0.12) | <0.001* |
| CIMT bilat 0.9 mm (N/ %) | 2/ 1.1 | 3/ 2.1 | 1/ 1.0 | NS** |
| asCIMT bilat (N/ %) | 99/ 52.9 | 111/ 78.8 | 12/ 25.9 | <0.001** |
| Carotid plaque (N/ %) | 9/ 4.8 | 25/ 17.9 | 16/ 13.1 | <0.001** |
| FIMT sin (mm) | 0.56 (0.13) | 0.64 (0.14) | 0.08/(0.17) | <0.001* |
| FIMT dx (mm) | 0.56 (0.14) | 0.63 (0.15) | 0.07/(0.15) | <0.001* |
| FIMT max (mm) | 0.70 (0.15) | 0.79 (0.17) | 0.09/(0.18) | <0.001* |
| FIMT bilat >0.9 (N/ %) | 7/ 5.1 | 16 / 11.4 | 9/6.3 | NS** |
| FIMT bilat >1.1 (N/ %) | 3/2.2 | 4 / 2.9 | 1/0.7 | NS** |
| asFIMT bilat (N/ %) | 32 / 23.2 | 63/ 44.7 | 31/21.5 | <0.001** |
| Femoral plaque (N/ %) | 5/3.6 | 25/ 17.7 | 20/14.1 | <0.001** |

Remarks: DLP, dyslipoproteinemia; AH, arterial hypertension; MetS, metabolic syndrome; RFs, risk factors; CIMT or FIMT: dx/sin/max, mean common carotid or femoral artery intima-media thickness: right/left/maxium value; CIMT or FIMT bilat >0.9 mm, common carotid or femoral artery intima-media thickness >0.9 mm bilaterally; FIMT bilat >1.1 mm, common femoral artery intima-media thickness >1.1 mm bilaterally; asCIMT or FIMT bilat, pathological common carotid or femoral artery intima-media thickness by age and sex on the right or left; SD, standard deviation; NS, statistically nonsignificant difference; N, number; p, statistical significance; *, paired t-test; **, McNemar´s test; Δ, change, difference. In paired t-test (N= 141 at baseline and follow-up), in McNemar´s test (N=187 at baseline and N=141 at follow-up).

## 5. Discussion

Early detection of subclinical ATS has received increased attention in CVD prevention in the last decades. Clinical studies on subclinical ATS are heterogeneous, performed mostly in elderly populations. Less data is available in younger "low risk" populations using multiple phenotypes across multiple arterial sites. Examination of different arterial segments may complement each other

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in the evaluation of the presence and extent of ATS and in the modification of CV risk [27]. There are also limited numbers of studies comparing progression of subclinical ATS in different regions [14] with impact on the timing of population screening.

In our 5-year prospective study, in clinically healthy, 35–55-year-old, nondiabetic, predominantly non-hypertensive individuals, without known CVD, with low-to moderate calculated fatal risk SCORE, the increase in mean and maximum values of CIMT and FIMT was significant, with almost identical CIMT and FIMT values. The yearly progression rate of IMT was slower in femoral region in comparison with the carotids. IMT>0.9mm (previously identified as hypertension-mediated organ damage) was 5x more frequent in femoral region in comparison with the carotids. On the other hand, the occurrence of FIMT >1.1mm (predictive value of CIMT>0.9mm) [24] was as low, as CIMT>0.9mm. The presence of age- and sex-adjusted abnormal mean CIMT and FIMT was surprisingly high (mainly carotid) and compared to the beginning of the study, the prevalence was significantly higher by 25.9%. Similarly, a relatively high and similar prevalence of carotid (17.9%) and femoral (17.7%) plaque burden was documented at the end of follow-up, with a more pronounced progression during the follow-up in femoral region.

### *5.1. Risk Profile*

The risk profile of our study group is comparable with the literature [12,28], and was commented in our previous study [13]. Obesity and DLP were increased due to the fact, that we followed central obesity and tighter cut-offs for DLP. In the large on-going PESA study with enrollment of participants without CVD, with no exclusion of diabetics, the study group had a better risk profile in term of DLP (40.9%) and obesity (13.3%), but the proportion of lipid-lowering therapy was similar (6.6%) [29].

### *5.2. CIMT and FIMT Progression*

Increased CIMT represents subclinical vascular disease and CVD risk marker [30,31], may be related to intimal and/or medial hypertrophy, and may be an adaptive response to changes. Increased CIMT is related to (not clearly synonymous with) subclinical ATS due to similar alterations in the progression of both processes [30]. The initiation, progression and expression of ATS lesions are mainly artery-related [32]. Shared common risk factors have different impact in different arterial territories [33,34]. Autopsy studies revealed, that in different vascular segments there is no uniform involvement of ATS [35]. ATS plaques in different segments of the arterial tree have similar cell types, but their relative numbers and amount of connective tissue and lipids can vary considerably [36]. Twin studies also reported a heritable component on carotid and femoral IMT [37–39]. Like carotid, femoral artery wall morphology is correlated with subclinical ATS [40], is associated with CAC score (CACS) [10], and is an independent predictor of future CV events [41–45]. Some studies have reported that ATS changes are more advanced in the femoral artery than carotid artery [46,47], another ones revealed that IMT of femoral artery is a better indicator of extent and severity of coronary artery ATS than in carotid arteries [48,49]. Examination of various arterial segments may complement each other in the evaluation of the extent of ATS [27]. The majority of studies have assessed only common carotid artery IMT, USG of femoral arteries for CV risk modification has not become a part of the routine, moreover, comparative data from the presence and dynamics of vascular target organ damage phenotypes in carotid and femoral arterial segments are scarce [47].

A systematic review reported the mean CIMT between 0.62-1.07 mm, and CIMTmax between 0.78-1.8 mm in low-to-intermediate risk individuals aged 60±7.6 years [50]. In the PESA study, with a comparable mean age of study population, similar to our results [13] the mean CIMT value was 0.59 mm [11,29]. The varying progression rate of the mean CCA-IMT was published in different population-based studies, ranged between 0.0038-0.060 mm/year [51,52], other studies detected comparable progression rate to ours [53,54]. A mildly higher rate of CCA-IMT (0.025 mm/year) was observed in the large Atherosclerosis Risk in Communities (ARIC) Study [55], lower progression rate of the CCA-IMT was documented in the Carotid Atherosclerosis Progression Study (CAPS) (0.001 mm/year) [28].

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For CVD risk assessment, instead of normative values (i.e. pathological IMT>0.9 mm, reflecting primarily ATS at the carotid bifurcation and hypertension mediated hypertrophy at the level of CCA), carotid USG imaging and measurements should follow protocols with CIMT values in percentiles by age, sex, race/ethnicity and mostly also by side [22,23,56]. In comparison with previous data [12,57], the occurrence of CIMT>0.9 mm was rare in our study and not significantly changed after 5-year follow up [13]. Similarly to us, CIMT>0.9 mm was detected in 1% of participants in the PESA study [11,29]. In contrast, there was a 36.7% incidence of CIMT>0.9mm reported by Mitu et al. among apparently healthy individuals, classified mainly in high-risk SCORE [12] and an incidence of 34% was reported by Novo et al. in an older study group, with a relatively high prevalence of diabetics and hypertensives [57].

Similarly to our results [13] the 75th percentile of the CCA-IMT distribution was established at 0.58 and 0.59 mm in healthy females and males without CV RFs, over 40 years of age [58,59]. In a recent study of an apparently healthy population aged 57.7±10.4 years, without exclusion of diabetics, the distribution of pathological CIMT>0.74 mm (75th percentile) was 25.96% (lower than in our study), but it followed a higher cut-off level in comparison with us [60].The prevalence of CIMT>75th percentile for the patient's age, sex and race/ethnicity was approximately 12% across the Framingham Heart Study, but at intermediate Framingham risk score (FRS), 22–58% of patients had increased CIMT [61]. However, no data are available on the progression rate of pathological age- and sex-adjusted CIMT in the literature.

Very similar to our mean FIMT values were found by Deparion et al. [62] in healthy subjects aged 20-60 years, without CV RFs: 0.543±0.063 mm and 0.562±0.074 mm for women and men resp. The estimated increase per year was less than in our study, (0.0031 mmm for men and 0.0012 for women), probably because the fact, that they screened subjects without CV RFs, in our study the presence of RFs was not an exclusion criterion. In some studies the mean CFA IMT was higher than in our: in size and risk profile similar study to our, regardless of sex, the FIMT was 0.80±0.2mm [47]; in another one the FIMT was 0.72/0.73mm (left/ right), probably due to the effect of older age and presence of DM [63]. A bit higher value of mean FIMT (0.64mm females /0.75mm males) was measured in healthy participants of the Bogalusa Heart Study (71% white, aged 24–43 years), but only single measurement of the left common femoral artery was provided [26]. The population based French (low-risk country) AXA Study (Sex and Topographic Differences in Associations Between Large-Artery Wall Thickness and Coronary Risk Profile in a French Working Cohort) in subjects (employees of an insurance company AXA, Paris La Défense, France) aged 17-65 years, with no exclusion of CVD and CV RFs, documented mean FIMT 0.43±0.06 mm for women and 0,50±0.11mm for men (thinner than FIMT in our study) with progression rate 0.003 and 0.005mm/year for women and men, resp. [64]. The Asclepios Study in apparently healthy population aged 35-55 years without exclusion of DM documented thinner FIMT than in our cohort in females (0.49 mm) but not in males [25] (due to thickened femoral IMT measurement site, incorrectly classified as plaque, however, we did not evaluate separately IMT for females and males).

FIMT>0.9mm, age and sex adjusted pathological FIMT occurrence have received less attention to date in the literature. Langlois et al. found the maximal FIMT 0.59 (0.51–0.70) mm in females and 0.71 (0.60–0.87) mm in males [25], which is similar to our results, even though we did not determine FIMT separately for men and women, but the presence of age- and sex-adjusted FIMT. In the same cohort, [25] with no exclusion of DM, 26,3% of subjects had FIMT>0.9mm, more than in our study.

Rietzschel et al. in a population of 156 apparently healthy normotensive Caucasian volunteers between 18 and 65 years revealed, similarly to us, identical right common femoral and carotid mean IMT (0.52 mm) [65]. In above mentioned studies [47,63] the mean and maximal femoral IMT were greater than the mean and maximal carotid IMT. In accordance with us, the CIMT was greater in other studies [25,26], also the progression rate was higher for CIMT than for FIMT in the AXA study and in the study conducted by Markus [64,66].

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*5.3. Carotid and Femoral Plaque Progression*

Carotid IMT and plaque are markers for measuring ATS burden and strongly associated with vascular RFs and the incidence of CV events [31]. ATS progression predicts CV events [67]. The occurrence of carotid plaques is variable in the general population and might be explained by age, CV RFs and geographical influence [12]. According to a systematic review [50], the occurrence of plaque in asymptomatic, low-to-intermediate risk cohorts, with different age and risk profile was an average of 35%. Some studies [12,57,60,68] in comparison to our results, reported a higher prevalence of carotid plaque (40%, 25%, 34%, 78%, resp.) probably due to the enrollment of older subjects. Studies with asymptomatic, middle-aged individuals documented higher occurrence of carotid plaques (29.3% in subjects with risk SCORE <5% [12], 31% in the PESA Study [29]). In the Refine study among 50–69-year-old participants, after a 4.2-year follow-up, in those patients without plaque at the first visit, the rate of plaque burden was 29.7%, which is a higher progression than in our study, but in a population with worse risk profile, with no exclusion of CVD [54]. Similar to our data, 20.5% of subjects developed new carotid artery plaques during a 5-year follow-up in a community in Taiwan (older subjects, no exclusion of DM) [53].

There is a slight difference in the genesis of ATS plaques in CCA and CFA, supported by pathology [36], biochemical studies [25], different distribution of plaques in carotid and femoral sites [36], as well as by significant side-difference in IMT of CFA but not of CCA , underlining a possible role of local geometry in the development of ATS [69]. However, this side difference was not observed by Lucatelli at al. [63] by us not even in carotid area.

Although ATS is considered a generalized disease process, the extent of ATS and its underlying risk factors differ among arterial sites [70], confirmed by autopsy studies [35]. It has been shown that ATS lesions are more frequent and advanced in femoral arteries than in carotid arteries independent of increasing number of risk factors [71–73]. ATS in femoral arteries occurred earlier than carotid arteries [72] and femoral artery is more susceptible to the atherogenic influence of risk factors [73].

In our study the occurrence of carotid plaque was slightly higher than femoral plaque, mainly at baseline, the difference practically disappeared at the end of follow-up due to higher progression rate in femoral region. Generally, high plaque frequency was documented among participants aged 45–64 years, with 17.5% diabetics, in study conducted by Yerly at al. [74]: 73.4 % of participants had $\geq$1 plaque (defined as IMT $\geq$1.2 mm) at carotid level and 67.5 % at femoral level. In contrast, among healthy adults (subpopulation of international twin study), aged 20-78 years, with 4.1% presence of DM, with higher prevalence of smokers, the plaque prevalence was significantly higher in the CFA compared to the CCA (40.7% vs 30.4%), the progression rate was not followed [63]. Among PESA participants, plaques were most common in the iliofemorals (44%), followed by the carotids (31%) aorta (25%) and coronary arteries (18%). Interestingly, among participants with low Framingham Heart Study (FHS) 10-year risk, subclinical disease at all was detected in 58% (higher than in our study, but in mul-titerritorial location). Nearly 60% of those, with CACS=0, had plaques at other vascular sites implying, that in low-risk sample, the absence of CAC does not necessarily indicate that a participant is disease free [11]. In the large Asklepios Study cohort of asymp-tomatic subjects aged 35 to 55 years without exclusion of DM/impaired fasting glucose (21.4%) the occurrence of carotid and femoral plaque was generally high, 43.6% in ca-rotid and 54.9% in femoral region [25]. In the Cafes-Cave 10-year, prospective study with 10 000 healthy, low risk individuals without AH, DM and DLP, aged 35-65 years, 10.8% of study population had ATS plaque either at the femoral, or carotid level (less than in our study, but their study population was free of 3 main modifiable RFs). Moreover, the authors documented a difference in morphology between carotid and femoral arteries: in 51% of subjects the carotid was the most advanced artery and in 52.4% the right (carotid or femoral) arteries were more advanced than the left [9]. We observed almost the same prevalence on both arterial sites but did not evaluate side difference.

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## 6. Limitations

Limitations of our study are a small study group and lower response rate (75%). Moreover, the lack of methodological standardization, measurement difficulties and publication bias make it difficult to compare our results with other studies. In addition, there are limited data focusing on the comparison of subclinical ATS progression in-corporating 2 peripheral arterial sites concurrently in similarly selected subjects and using markers. Due to these limitations, there is a need for cautious interpretation of our results. Additional research in a larger sample of asymptomatic individuals is needed to quantify the impact of imaging in different arterial territories for subclinical ATS in CV risk management before applying them in clinical practice.

## 7. Conclusions

In middle-aged, non-diabetic, low-to moderate CV risk individuals, during a short follow-up, a relatively high prevalence and significant progression of subclinical carotid and femoral ATS was detected by standardized ultrasound techniques, expressed mainly as the presence of plaque and age- and sex-adjusted increase of IMT. Carotid arteries showed a faster progression rate and higher prevalence of increased age- and sex-adjusted IMT compared to the femoral arteries. However, plaque burden was similar in both territories, with higher progression rate in femorals. The high prevalence, short-term different dynamics of subclinical ATS in the carotid and femoral regions (between 45 and 50 years of patients' age), may underline the rationale for carotid and femoral ATS screening and optimal timing for personalized CV risk stratification in middle-aged subjects with low-to moderate calculated CV risk, especially in those over 50 years old with several RFs.

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