Chapter 9
Print ISBN: 978-81-969497-2-3, eBook ISBN: 978-81-969497-9-2

B Flow Assessment of Femoral Artery as an Indicator for the Presence of Coronary Artery Disease in Individuals Undergoing Radionuclide Myocardial Perfusion Scintigraphy for the Evaluation of Chest Pain

Petar Avramovski [a*], Maja Avramovska [b], Zaklina Servini [c], Zorica Nikleski [d], Keti Veljanovska [c], Snezana Mihajlova [c], Kosta Sotiroski [e] and Aleksandar Sikole [f]

DOI: 10.9734/bpi/anums/v2/4200B

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/4200B

ABSTRACT

This study highlights about B flow assessment of femoral artery as an indicator for the presence of coronary artery disease in individuals undergoing radionuclide myocardial perfusion scintigraphy for the evaluation of chest pain. In the evaluation of patients with suspected coronary artery disease (CAD), the presence of the superficial femoral artery (SFA) plaque is more informative than a carotid plaque and at least as informative as coronary plaque in the identification of coronary death individuals. A total of 60 emergency room consecutive patients aged 59.2 ± 8.1 years that have been referred to our ambulatory of internal medicine for chest pain evaluation suggestive of ischemic heart disease with a normal or nondiagnostic electrocardiogram were included in

[a] Department of Internal Medicine, Clinical Hospital "D-r Trifun Panovski" - Bitola, High Medical School, University St. Kliment Ohridski, Bitola, North Macedonia.
[b] Department of Obstetrics and Gynecology, Clinical Hospital "D-r Trifun Panovski" - Bitola, North Macedonia.
[c] Department of Nuclear Medicine, Clinical Hospital "D-r Trifun Panovski" - Bitola, North Macedonia.
[d] Advanced Torrens University, Australia.
[e] Department of Statistics, Faculty of Economics, Prilep, University St. Kliment Ohridski, Bitola, North Macedonia.
[f] Department of Nephrology, Medical Faculty, University Ss. Cyril and Methodius, Skopje, North Macedonia.
**Corresponding author: E-mail: avramovski@gmail.com;*

the study. We found significant positive correlations between age and SFA plaque score (PS) (P = 0.0084), myocardial ischemia in rest and SFA PS (P <0.0001), and between transient ischemic dilation (TID) and SFA PS (P = 0.0069), too. The TID correlates only with myocardial ischemia in rest (P = 0.0022) and SFA PS (P = 0.0069). The results we got by the receiver operating characteristics (ROC) curve analysis with TID/without TID were the area under curve (0.704, P = 0.0038). The multiple regression analysis showed standardized coefficient β coefficients for SFA PS and TID (3.4577 and 1.9903, P < 0.001 and P = 0.0021), respectively. Proven correlative relationship of SFA atherosclerotic plaques and CAD using these two noninvasive methods gives us the ability to use B-flow as a screening method for triage of patients with chest pain before being sent to the assessment of coronary circulation with radionuclide MPS.

Keywords: Atherosclerotic plaque; B-flow; coronary artery disease; myocardial perfusion scintigraphy; superficial femoral artery.

1. INTRODUCTION

Atherosclerosis is the most common cause of coronary artery disease (CAD), carotid artery disease, and peripheral arterial disease including superficial femoral artery (SFA) disease [1]. It is a multifactorial systemic disease that affects the entire arterial tree, although some areas are more prone to lipid deposits than others. Moreover, the histopathological composition of the plaques differs, and the clinical manifestations are also different, depending on the location and structure of the atherosclerotic plaque [2]. Because atherosclerosis is considered a generalized disease, mainly manifested in the entire vasculature, an association between coronary and peripheral vascular disease has been well-established [2]. CAD is essentially connected with the development of atherosclerotic plaques along the course of coronary arteries, a phenomenon that is still poorly understood despite multiple pathophysiologic contributors [3]. In the evaluation of patients with suspected CAD, carotid artery intima–media wall thickness has been reported to be a useful marker for the presence of CAD, [4, 5] but the presence of the SFA plaque is more informative than a carotid plaque and at least as informative as coronary plaque in the identification of coronary death individuals. The SFA atherosclerosis is caused by its slower development and later occurrence of plaque compared with coronary and carotid atherosclerosis. That means that the presence of atherosclerotic plaque in the SFA is highly suggestive as a generalized susceptibility to atherosclerosis with even more advanced disease elsewhere [5]. The hazard ratio (HR) risk of SFA plaque is more predictable than HR risk of carotid plaques [6,7].

Advances in cardiovascular imaging have resulted in the development of multiple noninvasive techniques to evaluate myocardial perfusion and coronary anatomy. Computed tomography angiography (CTA) can directly visualize the presence of atherosclerosis but not the hemodynamic effect of lesions. Alternatively, myocardial perfusion scintigraphy (MPS) enables a physiological assessment, but it may underestimate the extent of atherosclerosis in patients with multivessel disease [8, 9]. Coronary angiography is the standard technique for assessing epicardial coronary anatomy and MPS is the standard technique for assessing myocardial perfusion. Although the anatomical extent of disease is best demonstrated by coronary angiography, MPS provides a complimentary assessment of its physiological significance and hence information on important features such as endothelial function, small vessel function, and collateralization, in addition to the hemodynamic significance of epicardial stenosis [10]. At the patients with suspected CAD, including those with equivocal chest pain or episodes of acute chest pain, detection of CAD is a fundamental step in the assessment of prognosis and the associated therapeutic decision-making process. A test that enables simultaneous evaluation of myocardial perfusion and function, such as MPS, is particularly appropriate [11].

B-flow imaging (BFI) as a newly discovered method is able to characterize the arterial wall and the local hemodynamic environmental factors likely responsible for the progression of carotid and femoral artery disease in humans [12]. This method can visualize real-time hemodynamic flow in relation to stationary tissue by high frame rate without blooming artifacts, with his higher spatial, transverse, and temporal resolution is superior to Doppler imaging. All of these results with a clearer definition of the vessel lumen and atherosclerotic plaque [13,14]. The superior method for the plaque scoring than maximum plaque height (MPH) scoring and total plaque area (TPA) scoring is total plaque score (TPS) defined as the sum of all plaque heights in bilateral SFA. In addition, their analysis supports the superiority of total PS to MPH and TPA in cardiovascular risk prediction [15,16].

Knowing the fact that there is a mutual association between atherosclerosis of the peripheral arteries and coronary atherosclerosis, we come up with idea to research atherosclerosis of SFA and CAD with two different techniques (B-flow and MPS, respectively), and to explore their mutual correlation. That way (after we have been previously established their mutual relation) in a simple, noninvasive way with B-flow on the SFA, we could establish the presence and the spread of the CAD in patients with chest pain in an indirect way.

2. METHODS

Study populations: A total of 60 emergency room consecutive patients aged 59.2 ± 8.1 years that have been referred to our ambulatory of internal medicine for chest pain evaluation suggestive of ischemic heart disease with a normal or nondiagnostic electrocardiogram were included in the study. They signed an informed consent, and the ethics committee of our institution approved the study, after a detailed description of the procedure was given. In this 6-month prospective study conducted on 29 males and 31 females, B-flow ultrasound estimation of SFA plaque and radionuclide MPS estimation for CAD was performed.

The patients with previous history of percutaneous coronary intervention or myocardial infarction (MI), cerebrovascular disease, cardiomyopathy, cardiac surgery, multiple myeloma, organ transplantation, atrial fibrillation, aortic stenosis, renal insufficiency, New York Heart Association Class III or IV heart failure, and body mass index (BMI) over 40 were not eligible. Demographic and clinical data were collected from the patient's chart and included age, height, weight, history of diabetes mellitus, hypertension, smoking habit, lipid profile, and the diseases mentioned above, which might affect the progression of atherosclerosis.

Assessment of B-flow superficial femoral artery ultrasonography: The BFI of both SFA was performed with ultrasound scanner (General Electric Logiq 7) equipped with a linear array transducer with central frequency of 10 MHz.

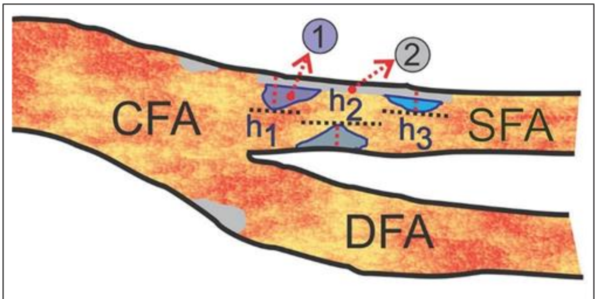
To evaluate the SFA, the patient lies supine with the leg in slight external rotation. We performer longitudinal scan at groin and we continued distally. In front of the hip joint, we have detected the part of the femoral artery located proximally to the arising of the deep femoral artery (DFA), which is called the common femoral artery (CFA). In continuation of the CFA, distally from the DFA bifurcation, the proximal part of SFA was appeared. A 90° imaging angle was used to identify and assess atherosclerotic plaque composition [8].

The simplest way of scoring plaques is to make the sum of all plaque height for SFA on the right and the left side. We imaged and scored the SFA only, because it is the most common site of lower extremity atherosclerosis and because it supplies calf muscle, which is typically symptomatic in peripheral artery disease [17]. The basic principle of scoring SFA plaques is shown in Fig. 1, based on a previously validated system of plaque scoring [18].

The sum of all plaque height for SFA, we calculated, for example, TPS1 of left SFA (h1 + h2 + h3 +... hn or 2.8 mm + 3.0 mm + 2.1 mm) summed with the TPS_2 of right SFA (h1 + h2 + h3 + h4 +... hn or 1.2 mm + 2.3 mm + 2.7 mm + 1.4 mm) gives a TPS = TPS1 + TPS2 = 7.9 + 7.6 = 15.5. The TPS is not expressed in millimeters (like measured plaque height) but in no name unit. A focal intima-media thickening ≥1.1 mm was designated as plaque.

Assessment of radionuclide myocardial perfusion scintigraphy: Myocardial perfusion imaging utilizes an intravenously administered radiopharmaceutical to depict the distribution of nutritional blood flow in the myocardium [18]. The MPS has a key role in a clinical decision-making algorithm for determining the most appropriate management of patients presenting with acute chest pain [11]. Investigation of the patients was done on Gamma spect MEDISO (MEDISO GmbH Schiewenhügel 7 Laer 48366 Germany, [software package InterView™ XP]) with a radiotracer of sestamibi labiliased Tc-99m-sestamibi. Perfusion imaging is useful to identify areas of relatively or reduced myocardial blood flow associated with ischemia or scar. The distribution of perfusion following radiopharmaceutical injection can be assessed at rest, cardiovascular stress, or both. The study was done as one stress-rest study. The stress was done using pharmaceutical stressor dipyridamole to perform an examination of patients with chest pains episode [19]. Authentic MPS scan with Tc-99m-sestamibi in a 56 years old male patient with chest pain is presented in Fig. 2.

Patients were been fasting before rest myocardial perfusion imaging for at least 4 h. We used a dipyridamole as pharmacologic stress to create coronary hyperemia. We used 1 day, rest and dipyridamole stress imaging protocol with the consecutive administration of 555 and 925 MBq derived unit of radioactivity, respectively.



CFA, Common Femoral Artery; **SFA**, Superficial Femoral artery; **DFA**, Deep Femoral Artery;
***1** - plaque; **2** - intima-media thickening.*

Fig. 1. Measurement of the superficial femoral artery plaque score

The MEDISO software provides to us results for ejection fraction (EF%), end diastolic volume (EDV mL), end systolic volume (ESV mL) in rest and stress, and transient ischemic dilatation (TID) determined from stress and rest ventricular volumes. TID ratio is calculated dividing stress by rest LV volumes. TID is present when the ratio falls above a “normal” limit that has ranged from 1.22 to 1.36 in various studies. It is a more sensitive and specific marker for multivessel CAD than other common markers during stress testing [20]. Heston and Sigg found that TID is a sensitive and specific marker for multivessel CAD [21,22].

Statistical analysis: Statistical data were analyzed using MedCalc for Windows, version 13.0.6.0. (MedCalc Software, Ostend, Belgium). We expressed the results as mean ± standard deviation (SD).

Pearson’s correlations were calculated to explore the relationship between left ventricular EF and SFA plaques (to estimate the strength and direction of their relationship), and between SFA PS and other variables, as appropriate. Simple linear regression analysis was performed to assess the association between dependent and independent variables, to create the equation of linear regression, and to draw the scatter diagram. We conducted a multiple backward regression analysis to determine the effect on the dependent variable (myocardial ischemia in rest) of variations in one of the independent variables (SFA PS, TID, EF in rest, ESV, and EDV), while the other independent variables were fixed. Receiver operating characteristics (ROC) curve analysis assessed distinction between patients with or without TID to find an appropriate sensitivity/specificity pair in dependent of SFA PS.

3. RESULTS

Demographics and bivariate analysis: Patients' demographics, clinical, and Bivariate Pearson's characteristics determined of the study, presented as mean ± SD or number (%) are shown in Table 1. The range column of continuous variables and column of Pearson's *r* and *P* value are presented too.

Pearson's product-moment correlation coefficients (r) indicated significant positive correlations between age and SFA PS (r = 0.337, P = 0.0084), myocardial ischemia in rest and SFA PS (r = 0.830 P < 0.0001) and between TID and SFA PS (r = 0.345, P = 0.0069), too. Significant positive correlation between age and SFA PS, we found even in the relatively young participants (age ≤50 years, r = 0.513, P = 0.029). Pearson's r revealed significant inverse correlations between SFA PS and EDV (in rest and stress, r = −0.429, P = 0.0006 and r = −0.402, P = 0.0014, respectively), SFA PS and ESV (in rest and stress, r = −0.523, P < 0.0001 and r = −0.537, P < 0.0001, respectively), and between SFA PS and myocardial EF (MEF) (in rest and stress, r = −0.399, P < 0.0016 and r = −0.597, P < 0.0001, respectively). Other demographic and clinical biomarkers (gender, BMI, hypertension, diabetes, smoking, and myocardial ischemia in rest) do not indicated significant correlation with SFA PS (P > 0.05).

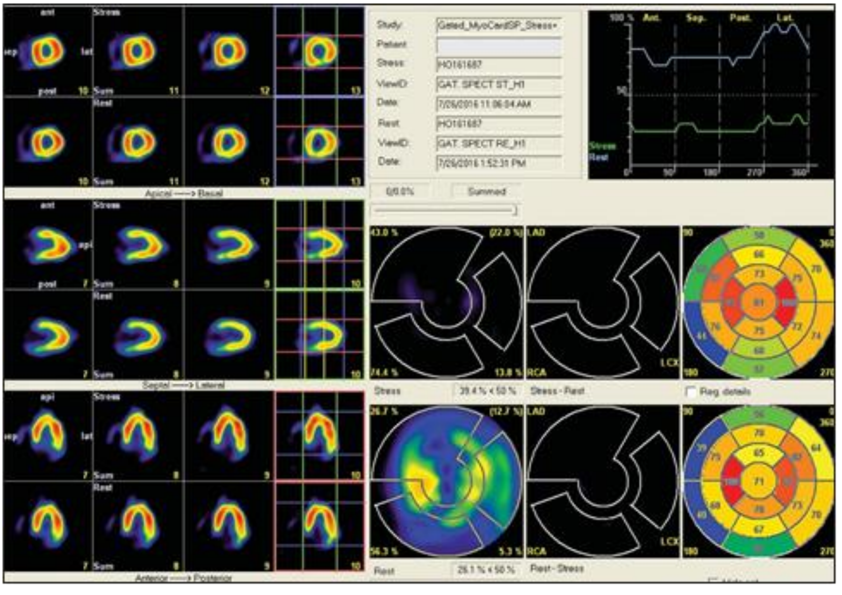


Fig. 2. Myocardial perfusion scan (stress and rest) with Tc-99m-sestamibi

Table 1. Demographic, clinical, and bivariate characteristics of the patients studied

Characteristics	Values	Range	SFA PS(Pearson's *r*, *P*)
Gender, male, *n* (%)	29 (48.3)	/	0.119, 0.365
Age (years)	59.2±8.1	38-78	0.337, 0.0084
BMI (kg/m2)	26.23±3.52	19.31-35.48	0.144, 0.272
Hypertension, *n* (%)	14 (23.3)	/	0.199, 0.127
Diabetes, *n* (%)	11 (18.3)	/	0.194, 0.138
Smokers, *n* (%)	25 (41.7)	/	0.145, 0.267
SFA PS	2.82±2.10	0.5-10.2	/
EDV in rest (mL)	82.63±39.53	26-268	−0.429, 0.0006
EDV in stress (mL)	81.82±42.30	12-262	−0.402, 0.0014
ESV in rest (mL)	36.61±32.11	15-197	−0.523, <0.0001
ESV in stress (mL)	38.31±33.06	16-196	−0.537, <0.0001
MEF in rest (%)	63.85±14.13	26-97	−0.399, 0.0016
MEF in stress (%)	60.01±13.53	25-87	−0.597, <0.0001
Ischemia in rest (%)	5.6±9.29	0-36	0.830, <0.0001
Ischemia in stress (%)	2.0±4.08	0-18	0.083, 0.530
TID	1.053±0.133	0.84-1.37	0.345, 0.0069

Values are presented as mean ± SD, n (number) or (percent %). Statistically significant values in bold. SFA PS: Superficial femoral artery plaque score; EDV: End diastolic volume; ESV: End systolic volume; MEF: Myocardial ejection fraction; TID: Transient ischemic dilation; SD: Standard deviation; BMI: Body mass index

There were no statistically significant differences between EDV in rest and EDV in stress ($P = 0.9139$, test statistics $t = -0.108$); ESV in rest and ESV in stress ($P = 0.7756$, test statistics $t = 0.286$). There was statistically significant difference between myocardial ischemia in rest and myocardial ischemia in stress ($P = 0.0069$, test statistics $t = -2.748$). There was statistically significant difference between MEF in rest (MEFR) and MEF in stress ($P = 0.0065$, test statistics $t = -2.823$). We found a strong inverse correlation between SFA PS and MEF in stress ($P < 0.0001$, $r = -0.5967$).

There were 22 patients with TID. TID values >1.18 in men and >1.22 in women were considered abnormal. The TID correlate only with myocardial ischemia in rest ($r = 0.387$, $P = 0.0022$) and SFA PS ($r = 0.345$, $P = 0.0069$), calculated by Pearson product-moment correlation coefficient (two-tailed probability).

Descriptive and linear regression analysis: The strength and direction of the linear relationship between pairs of continuous variables (MEFR and SFA PS) we measured by bivariate Pearson correlation. There is inverse correlation between MEFR and SFA PS ($r = -0.398$, $P = 0.0016$). The mean value and SD of the MEFR (63.85 ± 14.13%) and SFAPS (2.82 ± 2.10) are presented by box and whisker plots in Fig. 3.

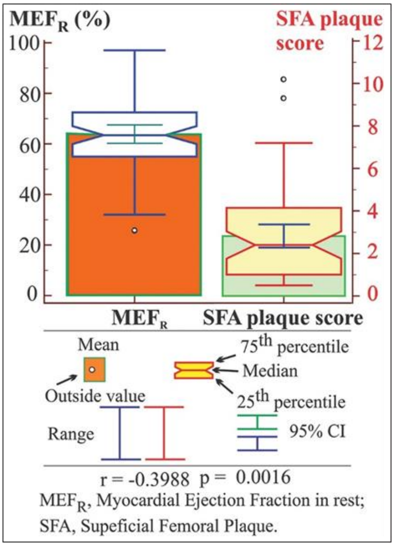


Fig. 3. Box and whisker plots of the mean, range, median, 25th and 75th percentiles, range and 95% confidence interval for myocardial ejection fraction and superficial femoral artery plaque

Fig. 4 shows a scatter plot of MEFR and SFA PS. There was an inverse association between these variables. This scatter plot displayed the data from each of 60 patients, presented as a collection of small blue colored circle, determining the SFA PS. Each point had the value of one variable (SFA PS) determining the position on the horizontal axis (X) and the value of the other variable (MEFR) determining the position on the vertical axis (Y). The linear regression line calculated by the equation ($y = 71.4116 – 2.6798\ x$) and plotted with the red solid line, shows an inverse (negative) correlation between SFA PS and MEFR. The 95% confidence interval (CI) curve and prediction interval curve are presented by blue dashed line and green dash-dot line, respectively.

Receiver operating characteristics curve: We used receiver operating characteristics (ROC) curve as a graphical plot that illustrates the performance of binary classifier system (TID is presented, equal to 1; TID is no presented, equal to 0). In a ROC curve, the true positive rate (sensitivity) is plotted in function of the false positive rate (100 - specificity) for different cutoff points of a parameter. The accuracy of the test depends on how well the test separates the group being tested into those with and without the disease (TID) in question. Accuracy is measured by the area under the ROC curve [Fig. 5].

The 95% CI curve, ROC curve, and diagonal line are presented by green dashed line, blue line with red points, and thin red line, respectively. The area under the ROC curve (area under curve [AUC]) is a measure of how well a parameter can distinguish between the two diagnostic groups (with TID/without TID). Each point on the ROC curve represented a sensitivity/specificity pair corresponding to a particular threshold (SFA PS in the detection of TID). The results we got by the ROC curve analysis were as follows: AUC (0.704), Z statistic (2.891), significance level (P = 0.0038), sensitivity (73.9%), and specificity (59.5%). The SFA PS cutoff point where the parts of sensitivity/specificity points were the highest was 2.5. Due to the small number of participants, CI of sensitivity and specificity was too wide (51.6 - 89.8/42.1 - 75.2).

Linear and nonlinear regression analysis: Linear and nonlinear regression line with nonlinear scatter plot of Myocardial Ischemia in Rest (MIA) and SFA PS are shown in Fig. 6. This figure shows a strong significant correlation between two variables presented as scatter plot, a graph of plotted points (blue and yellow) that shows the relationship between two sets of data. Linear regression line plotted with red dashed line and nonlinear regression curve plotted by blue solid line, both show a positive correlation between MIR and SFA PS. The blue and yellow circles are distributed in accommodation of mutual dependence of the variables and thus are displayed above and below the blue ascending curve of the nonlinear dependence.

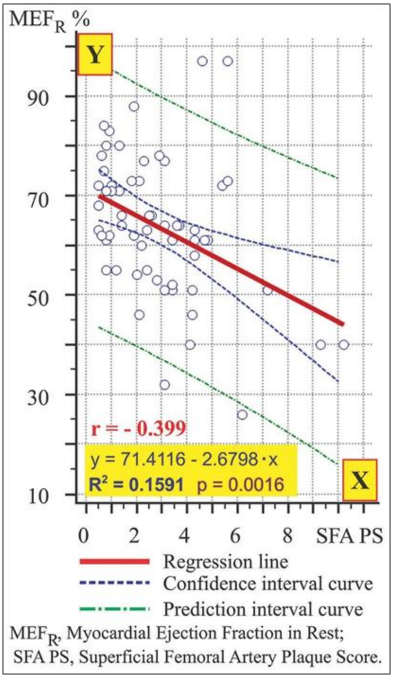


Fig. 4. Scatter plot of superficial femoral artery plaques score and myocardial ejection fraction in rest

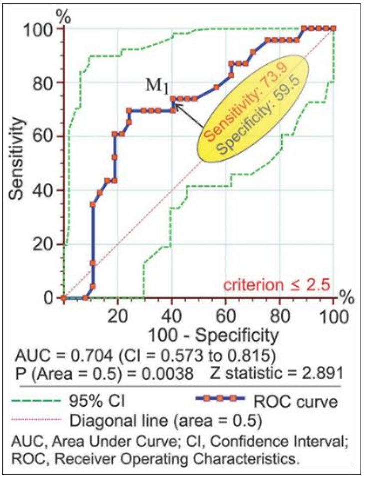


Fig. 5. Receiver operating characteristics for superficial femoral artery plaque score as a marker for transient ischemic dilation

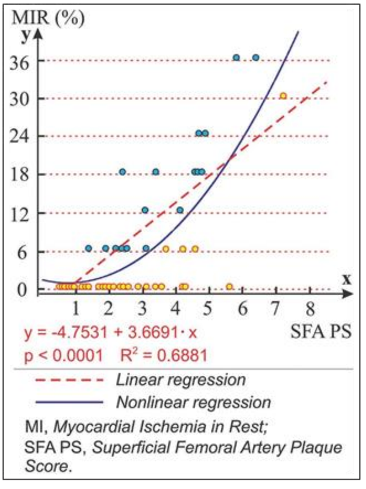


Fig. 6. Scatter plot of superficial femoral artery plaques score and myocardial infarction in rest

Multiple regression analysis: Assessments (standardized coefficient β [βst]), standard error of βst, *t*, *P* value (*P*), and variance inflation factor (VIF) of the independent predictor SFA PS or determinant TID for increasing of myocardial ischemia in rest after backward multiple regression analysis are shown in Table 2.

The VIF measures how much the variance of the estimated regression coefficient is inflated as compared to when the predictor variables (SFA PS) are not linearly related. In our case of the regression model (VIF <2), there was no problem of multicollinearity.

The *P* followed the order of statistical significance: SFA PS (<0.0001) and TID (0.0021). There was a positive correlation (positive value of βst coefficient) between the MI in rest and SFA PS. This means that any increase in the SFA PS results in an increased MI in rest. There was no statistical significance of βst coefficients expressed by *P* for EF in rest, ESV in rest, EDV in rest and diabetes. These variables were not included in the model because their high value of $P >$ 0.3. The coefficient of determination *R*2 (0.7062) showed that 70.62% of the total variability was explained with the linear relation between MI in rest and SFA PS accompanied by other determinants, or that 70.62% from MI in rest was dependent on SFA PS as the predictor and other determinants (TID, EF in rest, ESV in rest, EDV in rest, and diabetes).

4. DISCUSSION

To the best of our knowledge, this is the first prospective longitudinal study that investigates the relationship between SFA plaques and the spread of CAD in sixty patients with chest pain using two noninvasive methods: B-flow ultrasonography and radionuclide MPS, respectively. Several studies estimated B-flow femoral atherosclerotic plaques and MPS imaging for detection of CAD, both like each study itself. We did not found a study that brings together B-flow and MPS imaging in one integrated study. Selective search on "Google scholar" with the abbreviated term "b-flow myocardial perfusion imaging" or "b-flow femoral artery" yielded zero reference. The most of the references independently studied femoral or CAD, but there are no studies, which make a comparison between them.

The aim of our study was to determine the correlation between CAD and SFA PS and to estimate the extent of coronary disease based on the atherosclerotic plaques widespread of the SFA. We found a significant positive correlation between SFA PS and age in the elderly, but even in the relatively young participants (≤50 years), too. The morphostructural atherosclerotic changes in arterial wall are present before the clinical manifestation of cardiovascular disease, especially in diseases states such as hypertension, diabetes, and end-stage renal disease [22, 23]. The relatively small number of the participants with these diseases in our study does not give statistically significant results of a correlation between SFA PS and hypertension, diabetes, and another demographic data such as BMI, gender, and smoking. Even studies with a larger number of participants (n = 1007) showed that hypertensive disease itself had only a minimal effect on atherosclerotic changes in femoral arteries [24,25]. They investigated and concluded that hypertensive disease has a greater impact on changes in the aorta than the changes in the femoral arteries [26,24].

Table 2. Multiple backward regression analysis of determinants of myocardial ischemia in rest

	Multiple regression (backward)				
Dependent Y			**Myocardial ischemia in rest**		
Coefficient of determination $R2$			0.7062		
$R2$-adjusted			0.6904		
Residual SD			5.1741		
	Regression equation				
Independent variables	**Coefficient β standardized**	**SE**	***t***	***P***	**VIF**
SFA PS	3.4577	0.3517	9.833	<0.0001	1.205
TID	1.9903	0.6177	3.222	0.0021	1.021

Variables not included in the model: EF in rest, ESV in rest, EDV in rest and diabetes. SE: Standard error; SFA PS: Superficial femoral artery plaque score; VIF: Variance inflation factor; TID: Transient ischemic dilation; BMI: Body mass index; EF: Ejection fraction; ESV: End systolic volume; EDV: End diastolic volume; SD: Standard deviation

We found a strong significant inverse correlation (P < 0.0001) between SFA PS and MEF (in rest and stress) and SFA PS and ESV (in rest and stress) and a weaker significant inverse correlation between SFA PS and EDV (in rest and stress). We found a strong significant positive correlation between SFA PS and myocardial ischemia in rest, and between SFA PS and TID, but not in ischemia in stress. After backward multiple regression, the analysis only MIR (as the dependent variable) remains with strong correlation with independent variables SFA PS and TID. The TID index is significantly greater in patients with a greater number of occluded coronary vessels [26, 27]. Many studies reported that TID is present in 8%–37% of patients, depending on the patient population, stress modality, radioisotope, test protocol, and TID threshold criteria [27, 28]. The results from our study correlate with those results, we found 22/60 (36.66%) patients with TID according to standard threshold criteria (TID >1.18 for male and 1.22 for female). The main reason for this relatively large percentage of TID presence is the nature of our study population, patients with clinically expressed symptoms of impaired coronary circulation, chest pain.

Because TID is more sensitive and specific marker for multivessel CAD than other common markers during stress testing; in our study, we gave importance due to TID as the main biomarker for prediction of cardiac event. The patients with TID are more likely to have a cardiac event (nonfatal MI or cardiac death) then those without TID. TID is a parameter that is useful to detect extensive and balanced CAD in patients with normal myocardial perfusion [20,24]. Both MEF (in rest and stress) and MIR are mutually correlates, each with himself and with SFA PS. We did not find a study that examines the correlation of the MEF and SFA atherosclerotic plaque. We found an inverse correlation; the SFA plaque spread as peripheral vascular disease has 15.9% impact on MEF reducing (the residual impact on the reduction of MEF attributed to other factors).

All of the above-mentioned myocardial hemodynamic markers obtained by MPS (EDV, ESV, MEF, myocardial ischemia, and TID) determine myocardial ischemia, and they are in a significant correlation with SFA regarding the extent of PS. Watching this mutual correlation, we got an idea for the assessment of CAD and consecutive myocardial ischemia through the extent of femoral plaques estimated by B-flow. We estimate a spread of atherosclerosis in the SFA because the superficial femoral and popliteal arteries are the vessels most commonly affected by the atherosclerotic process [25]. Peripheral arterial disease often coexists with other manifestations of the systemic atherosclerotic process, including CAD (myocardial ischemia) and cerebrovascular disease [24,25]. A number of studies have established the importance of SFA plaque assessment to prognosis the myocardial ischemia and risk of cardiovascular event. Their study suggests that evaluation of SFA plaque echogenicity by B-mode ultrasound may help to identify patients exposed to higher cardiovascular risk who may benefit from additional diagnostic and therapeutic strategies [29, 30, 31]. We found by multiple regression analysis a strong positive correlation between MIR and SFA PS, and between MIR and TID.

The results of our study suggest that TID is useful to separate patients with extensive myocardial ischemia from those without ischemia. Therefore, we correlated the results of ischemic patients with the SFA PS results. We found by linear regression analysis that 68.81% of the myocardial ischemia changes were the result of SFA PS value changes, and the remaining from the total variability between MIR and SFA PS were not explained (31.19% of myocardial ischemia were dependent of other factors, which not covered with regression model).

Starting from the fact that the process of atherosclerosis, the peripheral blood vessel changes (SFA PS) and the coronary circulation (MIR) that goes with it, are nonlinear processes during the aging, to present the mutual dependence of both variables, We decided to use a nonlinear process for the first time. We presented both regression curves on one scatter plot for a bigger perspicuity when comparing them. The ascending angle of the blue nonlinear curve is significantly more expressed then the ascending angle of the red dashed linear regression line. Anyway, to prove their mutual correlation, it is irrelevant if we used the linear or nonlinear model of regression, it is evident and statistically significant that the femoral arteries (expressed through SFA PS) is instep followed by CAD (expressed through myocardial ischemia and TID). The advantage of the nonlinear regression analysis is in the upward sloping of the curve which is more expressed, so it includes in counting the patients with early atherosclerotic changes also. This way, the detection of early, silent myocardial ischemia met in younger patients is improved.

However, it is obvious those above-mentioned three clinical biomarkers: MIR, TID, and SFA PS are the main carriers of mutual influences in the process of atherosclerosis that determines how the process of peripheral atherosclerosis on coronary disease does. TID serves as an accurate marker for extensive multivessel CAD; it is clinically useful diagnostic tool. It is easy to assess and is most useful when integrated with other clinical information (MIR, SFA PS, and MEF) and interpretation of MPS and B-flow for detection of CAD.

We found by ROC curve analysis that SFA PS is strong prognostic tool for detecting of TID because his AUC value of 0.704 which is a measure of how well SFA PS can distinguish the patients with chest pain (whether or not have CAD expressed by TID/without TID state).

Considering the relatively high sensitivity (95%) and specificity (60%) of TID method in the detection of CAD, we reaffirm the importance of SFA PS to establish the TID and hence the importance of SFA PS in detecting of CAD [18,28]. Thus, the high diagnostic value of SFA PS and TID and their high mutual correlation allow us to estimate the CAD by determining the extent of plaque in the SFA. The carotid and femoral plaques are early signs of silent coronary disease even in the absence of systemic atherosclerosis, demonstrated by another studies that a significant correlation with the left main coronary atheroma, as assessed by intravascular ultrasound [30, 31,32, 33]. It is evident that coronary vascular bed and all of the listed vascular sites (femoral, carotid, and aortic) are under the influence of the process of systemic atherosclerosis.

None of the vascular territories is spared from the unstoppable incremental progress generalized atherosclerosis [8]. Early detection of femoral plaque by B-flow, much before than a flow-limiting stenosis develops, has the potential to improve the sensitivity of predictable value of atherosclerotic plaque in cardiovascular event. Some clinical observations suggest that ultrasound screening for plaque presence or aggregate ultrasound based PSs may be more sensitive than the ankle-brachial index in the detection of high-risk individuals [34, 35].

Study limitations: The basic disadvantages of this study originate from imaging techniques for the detection and estimation of CAD and atherosclerosis of SFA. We learned from comparative studies that CTA is a superior imaging technique (gold standard) for detection and volume assessment of atherosclerotic plaques in the peripheral arteries. Therefore, due to the good match of B-flow and 64-row multidetector CTA (excellent correlation, r = 0.88, CI = 0.77–0.93) and in the absence of CTA, we do not consider the use of B-flow instead CTA as a certain limitation. Another limitation is the use of MPS instead of CT coronary angiography, which qualifies as an excellent initial test to exclude the presence of CAD. On the other hand, the quantification of inducible ischemia by MPI enhances our ability to identify the optimal therapeutic approach: Medical therapy versus possible revascularization [30]. Thelast limitation of our study stems from several artifacts and interpretation pitfalls that can potentially compromise MPI, related to the patient, the equipment, or the technologist and the interpreting physician.

Our suggestions for the procedural development of the future studies of this type are

1. Use magnetic resonance angiography (MRA) or CTA for providing qualitative diagnostic information of the lower-extremity arteries
2. Use coronary MRA with high temporal resolution visualization of the entire coronary arterial tree.

5. CONCLUSION

The current study’s finding suggests that detection of SFA plaques assessed by B-flow ultrasound as a simple, reproducible and noninvasive method for evaluation of regional arteries provides us with a reasonable prediction on the spread of CAD in patients with chest pain, detected by radionuclide MPS. Proven correlative relationship of SFA atherosclerotic plaques and CAD using these two noninvasive methods gives us the ability to use B-flow as a screening method for triage of patients with chest pain before being sent to the assessment of coronary circulation with radionuclide MPS. The associative connection between these two vascular beds (femoral and coronary) is applicable in the inverse direction, too: referral of patients with proven CAD to B-flow assessment for potential atherosclerosis of SFA.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Naghavi M, Falk E, Hecht HS, Jamieson MJ, Kaul S, Berman D, et al. From vulnerable plaque to vulnerable patient – Part III: Executive summary of the Screening for Heart Attack Prevention and Education (SHAPE) Task Force report. Am J Cardiol. 2006;98:2H-15H.
2. Achim A, Péter OÁ, Cocoi M, Serban A, Mot S, Dadarlat-Pop A, NemesA, Ruzsa Z. Correlation between coronary artery disease with other arterial systems: similar, albeit separate, underlying pathophysiologic mechanisms. Journal of Cardiovascular Development and Disease. 2023;10(5):210.
3. Blacher J, Pannier B, Guerin AP, Marchais SJ, Safar ME, London GM, et al. Carotid arterial stiffness as a predictor of cardiovascular and all-cause mortality in end-stage renal disease. Hypertension 1998;32:570-4.
4. Kallikazaros I, Tsioufis C, Sideris S, Stefanadis C, Toutouzas P. Carotid artery disease as a marker for the presence of severe coronary artery disease in patients evaluated for chest pain. Stroke 1999;30:1002-7.
5. Geroulakos G, O'Gorman DJ, Kalodiki E, Sheridan DJ, Nicolaides AN. The carotid intima-media thickness as a marker of the presence of severe symptomatic coronary artery disease. Eur. Heart J. 1994;15:781-5.
6. Siljanovski S, Avramovski P. Carotid artery wall changes as a prognostic indicator of coronary artery disease. Maced J of Med Sci. 2009;2:137-40.
7. Dalager S, Falk E, Kristensen IB, Paaske WP. Plaque in superficial femoral arteries indicates generalized atherosclerosis and vulnerability to coronary death: An autopsy study. J Vasc Surg. 2008;47:296-302.
8. Avramovski P, Avramovska M, Sikole A. B-flow imaging estimation of carotid and femoral atherosclerotic plaques: Vessel walls rheological damage or strong predictor of cardiovascular mortality in chronic dialysis patients. Int Urol Nephrol. 2016;48:1713-20.
9. Blankstein R, Di Carli MF. Integration of coronary anatomy and myocardial perfusion imaging. Nat Rev Cardiol2010;7:226-36.
10. Underwood SR, Anagnostopoulos C, Cerqueira M, Ell PJ, Flint EJ, Harbinson M, et al. Myocardial perfusion scintigraphy: The evidence. Eur J Nucl Med Mol Imaging. 2004;31:261-91.
11. Machecourt J, Vanzetto G. Myocardial perfusion imaging for the detection of coronary artery disease in patients with known or suspected disease. Eur Heart J Suppl. 2001;3 Suppl F: F2-4.
12. Weskott HP. B-flow – A new method for detecting blood flow. Ultraschall Med. 2000;21:59-65.
13. Tola M, Yurdakul M, Cumhur T. Combined use of color duplex ultrasonography and B-flow imaging for evaluation of patients with carotid artery stenosis. AJNR Am J Neuroradiol. 2004;25:1856-60.

14. Henri P, Tranquart F. B-flow ultrasonographic imaging of circulating blood. J Radiol. 2000;81:465-7.
15. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. ArteriosclerThromb. 1991;11:1245-9.
16. Held C, Hjemdahl P, Eriksson SV, Björkander I, Forslund L, Rehnqvist N, et al. Prognostic implications of intima-media thickness and plaques in the carotid and femoral arteries in patients with stable angina pectoris. Eur Heart J. 2001;22:62-72.
17. Hyvärinen S. Arteriographic findings of claudication patients. Ann Clin Res 1984;16 Suppl 41:1-45. Ikeda N, Kogame N, Iijima R, Nakamura M, Sugi K. Carotid artery intima-media thickness and plaque score can predict the SYNTAX score. Eur Heart J 2012;33:113-9.
18. Elhendy A, Bax JJ, Poldermans D. Dobutamine stress myocardial perfusion imaging in coronary artery disease. J Nucl Med 2002;43:1634-46.
19. Strauss HW, Miller DD, Wittry MD, Cerqueira MD, Garcia EV, Iskandrian AS, et al. Procedure guideline for myocardial perfusion imaging 3.3. J Nucl Med Technol. 2008;36:155-61.
20. Weiss AT, Berman DS, Lew AS, Nielsen J, Potkin B, Swan HJ, et al. Transient ischemic dilation of the left ventricle on stress thallium-201 scintigraphy: A marker of severe and extensive coronary artery disease. J Am Coll Cardiol. 1987;9:752-9.
21. Heston TF, Sigg DM. Quantifying transient ischemic dilation using gated SPECT. J Nucl Med. 2005;46:1990-6.
22. Halligan WT, Morris PB, Schoepf UJ, Mischen BT, Spearman JV, Spears JR, et al. Transient ischemic dilation of the left ventricle on SPECT: Correlation with findings at coronary CT angiography. J Nucl Med. 2014;55:917-22.
23. McLaughlin MG, Danias PG. Transient ischemic dilation: A powerful diagnostic and prognostic finding of stress myocardial perfusion imaging. J NuclCardiol. 2002;9:663–667.
24. Päivänsalo MJ, Merikanto J, Jerkkola T, Savolainen MJ, Rantala AO, Kauma H, et al. Effect of hypertension and risk factors on diameters of abdominal aorta and common iliac and femoral arteries in middle-aged hypertensive and control subjects: A cross-sectional systematic study with duplex ultrasound. Atherosclerosis. 2000;153:99-106.
25. Bestetti A, Di Leo C, Alessi A, Triulzi A, Tagliabue L, Tarolo GL. Post-stress end-systolic left ventricular dilation: a marker of endocardial post-ischemic stunning. Nucl Med Commun. 2001;22:685–693.
26. Jani B, Rajkumar C. Ageing and vascular ageing. Postgrad Med J. 2006;82:357-62.
27. Rajala U, Laakso M, Päivänsalo M, Suramo I, Keinänen-Kiukaanniemi S. Blood pressure and atherosclerotic plaques in carotid, aortic and femoral arteries in elderly finns with diabetes mellitus or impaired glucose tolerance. J Hum Hypertens2005;19:85-91.

28. Kinoshita N, Sugihara H, Adachi Y, Nakamura T, Azuma A, Kohno Y, et al. Assessment of transient left ventricular dilatation on rest and exercise on tc-99m tetrofosmin myocardial Spect. Clin Nucl Med. 2002;27:34-9.
29. Marcassa C, Galli M, Baroffio C, Campini R, Giannuzzi P. Transient left ventricular dilation at quantitative stress-rest sestamibi tomography: Clinical, electrocardiographic, and angiographic correlates. J NuclCardiol. 1999;6:397-405.
30. Abidov A, Bax JJ, Hayes SW, et al. Transient ischemic dilation ratio of the left ventricle is a significant predictor of future cardiac events in patients with otherwise normal myocardial perfusion SPECT. J Am Coll Cardiol. 2003;42:1818–1825.
31. Bertomeu V, Morillas P, Gonzalez-Juanatey JR, Quiles J, Guindo J, Soria F, et al. Prevalence and prognostic influence of peripheral arterial disease in patients ≥40 years old admitted into hospital following an acute coronary event. Eur J VascEndovasc Surg. 2008;36:189-96.
32. Schiano V, Sirico G, Giugliano G, Laurenzano E, Brevetti L, Perrino C, et al. Femoral plaque echogenicity and cardiovascular risk in claudicants. JACC Cardiovasc Imaging. 2012;5:348-57.
33. Katz JS, Ruisi M, Giedd KN, Rachko M. Assessment of transient ischemic dilation (TID) ratio in gated SPECT myocardial perfusion imaging (MPI) using regadenoson, a new agent for pharmacologic stress testing. J NuclCardiol. 2012;19:727-34.
34. Ogata T, Yasaka M, Yamagishi M, Seguchi O, Nagatsuka K, Minematsu K, et al. Atherosclerosis found on carotid ultrasonography is associated with atherosclerosis on coronary intravascular ultrasonography. J Ultrasound Med.2005;24:469-74.
35. Chatzizisis YS, Coskun AU, Jonas M, Endothelial shear stress in the natural history of coronary atherosclerosis and vascular remodeling: Molecular, cellular, and vascular behavior. J. Am. Coll. Cardiol. 2007;49:2379–2393.

Biography of author(s)

Petar Avramovski
Department of Internal Medicine, Clinical Hospital "D-r Trifun Panovski" - Bitola, High Medical School, University St. Kliment Ohridski, Bitola, North Macedonia.

He was born in 1962 in Bitola. He graduated from the Medical Faculty – Skopje in 1986 and specialised in Internal Medicine in 1993. He completed his education in echo tomography acquired from the University “Diukitz”, Erasmus University in Rotterdam in 1988, abdominal Doppler from the “Queen Joanna”- Sofia, 2000 and echocardiography Doppler from the same University hospital in 2001. He became Primarius in 2005 and obtained his Master's degree in Doppler ultrasonography with a thesis entitled “The significance of changes in Doppler hepatic arterial flow volume and hepatic perfusion index in the detection of liver metastases” in December 2008, mentored by Prof. Metodija Neskovski. His doctoral dissertation entitled “Pulse wave velocity–a marker of cardiovascular morbidity and mortality in hemodialysis patients” which he defended in April 2014 and obtained an MD PhD degree, mentored by Professor Aleksandar Sikole. He is the author of 90 and co-author of 35 papers and a regular collaborator to the Emiter, an indexed scientific journal. He has been a member of the Macedonian Scientific Association-Bitola since 2009. He is currently working as a doctor, a specialist in the internal department at the Clinical Hospital, Bitola and a professor at the Faculty of Veterinary and Higher Medical School in Bitola, until 2019. He published a paper with the co-author Peter in “The Lancet” (Ebiomedicine), a journal with the highest 96th percentile. He is a student educator of medical students. His manuscripts have received more than 306 cited. He is a verified manuscript drat reviewer with more than 380 reviews. His ORCID number is 0000-0003-2816-3365.

Maja Avramovska
Department of Obstetrics and Gynecology, Clinical Hospital "D-r Trifun Panovski" - Bitola, North Macedonia.

She was born in 1988 in Bitola, Republic of North Macedonia. She graduated from the Medical Faculty - Skopje with an average grade of 9.34. After receiving a work license on 01.10.2013, she enrolled in a private specialization in gynecology and obstetrics. On October 10, 2018, she successfully passed the specialist exam, as the first trainee of the generation of 2013-2014 and acquired the title of specialist in gynecology and obstetrics. In the academic year 2016-2017, she enrolled in the third cycle (doctoral) studies at the Medical Faculty in Skopje, School for Doctoral Studies, UKIM. On 02.06.20231, she defended her doctoral dissertation titled “Thyroid status in pregnancy and its impact on neonatal outcome” and she earned a Ph.D. in clinical medicine, obstetrics, and gynecology.

Since 2018, she has been employed at the gynecological and obstetric department in the Clinical Hospital Bitola, where she is involved in the professional-applicative work of the department. She was head of the ObGyn Department from November, 2023 to May, 2023. Since December 2020, she has been elected Coordinator of the Executive Board for Perinatal Network Units, Bitola, Republic of North Macedonia, for the implementation of the Master Plan for Perinatal Protection, Ministry of Health. She has published 7 papers and co-authored 22 scientific papers in the field of gynecology and obstetrics, of which 2 scientific papers in international journals with impact factor, part of the scientific base Pubmed and Web of Science. She participated in an International scientific project named Evaluation of Tireoglobulin as an innovative biomarker for iodine status in pregnant women (EUthyroid), the first pan-European initiative. The main objective of the project was to investigate the iodine intake of the European population, which was successfully finished at the University Clinic of Obstetrics and Gynecology – Skopje.

She is a co-author of the manuscript published in the American Journal "The Lancet" (Ebiomedicine), a journal with the highest 96th percentile. Her Research Gate profile showed 213 points of Research interest score and 67 citations. Since 2023, She has been a member of the UKLO science network, from the University St.KlimentOhridski, Bitola, Republic of North Macedonia. Her ORCID ID is 0000-0003-1129-1205.

ZaKlina Servini
Department of Nuclear Medicine, Clinical Hospital "D-r Trifun Panovski" - Bitola, North Macedonia.

She was born in 1964 in Bitola, Republic of North Macedonia. She worked as a general practice medicine doctor from August 1991 to May 1994. She completed her degree with a specialisation in internal medicine from December 2001 to December 2005. She completed her Master's degree in May 2002. She became a cardiologist in her specialisation from 2011 to 2013. She studied at Bresha (Italy) for myocardial perfusion scintigraphy (MPS). She participated as an active member in 2 studies "A phase 3b, Randomized, Double-blind, Placebo-controlled study to evaluate the efficacy and safety of TRC101 in Delaying Chronic Kidney Disease progression Subject with Metabolic acidosis", and "A phase 2, Randomized, Double-blind, Placebo-controlled study to evaluate the efficacy and safety of GDC-0068 (AKT INHIBITOR), MCN/AER#: AER2721038". Now, she is working as a cardiologist and MPS nuclear interpretation in Clinical Hospital-Bitola, North Macedonia.

Zorica Nikleski
Advanced Torrens University, Australia.

She is a native of North Macedonia and has lived in Sydney, Australia, since 2017. She currently works as a Public Health Officer and Health and Service Manager in Occupational Health (Allied Health) in a medico-legal clinic in Sydney, Australia. She was the first student from the University of Veterinary Medicine in Bitola, who completed the degree in 5 years and 3 months with an estimated grade record of 94%. She won the Award for Best Business Idea from the "University of Kliment Ohridski" Bitola, Republic of Macedonia. She was also awarded "The Most Famous Person in Bitola in 2012". She decided to pursue her dream of being part of academic research. Her passion and interest in research were supported by her highly respected mentor Dr Petar Avramovski. While studying for the Master of Public Health Advanced in Australia, one of the best healthcare systems in the World, she identified the gaps that the Macedonian healthcare system faces as a developing country. She was the main author of the study titled "Bone Mineral Density Treatment and Prevention Program in North Macedonia" conducted in 2019. Also, she is a co-author in 5 internationally recognized academic publications. Her ORCID ID is 0000-0001-9859-9493. The skills and knowledge that she gained during her Master's studies and research experience are making a high impact on international health research, and are of great benefit for further development and improvement of Macedonian health outcomes.

Keti Veljanovska
Department of Nuclear Medicine, Clinical Hospital "D-r Trifun Panovski" - Bitola, North Macedonia.

She was born on June 17th, 1967 in Bitola, Republic of North Macedonia.

Research interests: Her research interests include the medical field, nuclear medicine, and psychology.

University education: She completed her medical doctorate at the University of St. Kiril and Metodij Skopje, in 1991. She completed her specialization in Nuclear Medicine at the University of St. Kiril and Metodij in 2008.

Work experience: She has worked as a Family doctor in Bitola, Republic of North Macedonia from 1996 to 2008, as a specialist in Nuclear Medicine at the Clinical Hospital Dr Trifun Panovski, Bitola, Republic of North Macedonia since 2008 and as the Head of the department of Nuclear Medicine, Clinical Hospital Dr Trifun Panovski, Bitola, Republic of North Macedonia since 2021.

Professional certificates: She has earned three professional certificates including "Sentinel lymph node scintigraphy" from the University Acibadem Maslak, Istanbul, Republic of Türkiye, "SPECT-CT, PET-CT and Radionuclide Therapy" from the University Cerrahpasa, Istanbul, Republic of Türkiye and "Fine needle aspiration biopsy of the thyroid gland" from the University St. Kiril and Metodij, Skopje, Republic of North Macedonia.

Kosta Sotiroski
Department of Statistics, Faculty of Economics, Prilep, University St. Kliment Ohridski, Bitola, North Macedonia.

He was born on June 8, 1963, in Krusevo, R. Macedonia.

Research Interests: His areas of interest include business statistics, business informatics and university education. He completed his PhD in Economics at the Faculty of Economics, Prilep, in 1998 and his MSc in Economics at the Faculty of Economics, Prilep, Republic of Macedonia in 1993.

Scientific and professional activities: He did first cycle studies - Professor of Statistics for Economists, ERP systems, Second cycle studies- Professor of Methodology of scientific research work, E-business Management, Econometrics, Faculty of Economics - Prilep, University “St. Kliment Ohridski”- Bitola; and Third cycle - doctoral studies- Big Data technologies, Exploratory data analysis and data mining, Faculty of Economics - Prilep, University “St. Kliment Ohridski”- Bitola, Republic of Macedonia. He is the Head of the Department of Business Informatics and a member of the University Senate, University “St. Kliment Ohridski”- Bitola, Republic of Macedonia.

Study visits: His three important study visits include the University of Ghent-Belgium, 2002; the University of Macedonia, Thessaloniki-Greece, 2005 and 2008; and the University of Udine, Italy, 2009.
Publications: He published a statistics textbook in 2004 and a business informatics textbook in 2010.

Participation in projects: He was a part of 4 important projects including-

- TEMPUS JEP 15041/2000-European integration in the field of higher education;
- TEMPUS JEP 18046-2003 Management and Business education in computer studies;
- EU Cards Project: Regional Development, Trans-Border Cooperation and The European Union Factor; Interreg III A/Phare Cards;
- Tempus Joint European Project 41077 2006 Joint Master for South-East Europe in Economics and Management Science Program.

Aleksandar Sikole
Department of Nephrology, Medical Faculty, University Ss. Cyril and Methodius, Skopje, North Macedonia.

He was born on January 30, 1954, in Skopje and died on March 24, 2021, after having acutely suffered from severe brain cancer. He graduated from the Medical Faculty of University Kiril i Metodij of Skopje and received an MD degree in 1980. His further education at the Health Department of Skopje in the Emergency Unit was dedicated to internal medicine with a focus on nephrology. He joined the Department of Nephrology, Medical Faculty, Skopje in the unit for dialysis and renal transplantation in 1986. The early 1990s were the time when the situation of dialysis patients was greatly improved due to the availability of recombinant "erythropoietin" and it had a large impact on the "quality of life" of kidney patients. Later in 1994, he obtained a PhD degree with a thesis entitled "The effect of erythropoietin therapy on the heart and bone marrow of patients on maintenance haemodialysis". In 2001, he was elected Associate Professor of Internal Medicine at the University Hospital of Nephrology, Faculty of Medicine, Ss Cyril and Methodius University. Apart from EPO and anaemia, other highly valued scientific contributions came from him. Clinical investigations and publications on hypertension, cardiomyopathy, renal osteodystrophy, infection with Hepatitis C, diabetes, AGE-proteins and uraemic toxins in uraemia showed his multifaceted interest and experience in clinical nephrology. As a collaborator of Dr. Christos Stathakis who later served as President of the Balkan City Association for Nephrology, Transplantation and Artificial Organs (BANTAO), he was an active member of the BANTAO organisation. His ORCID number was 0000-0003-0323-7241.

DISCLAIMER
This chapter is an extended version of the article published by the same author(s) in the following journal.
World J Nucl Med, 18: 396-405, 2019. DOI: 10.4103/wjnm.WJNM_74_18

Peer-Review History:
This chapter was reviewed by following the Advanced Open Peer Review policy. This chapter was thoroughly checked to prevent plagiarism. As per editorial policy, a minimum of two peer-reviewers reviewed the manuscript. After review and revision of the manuscript, the Book Editor approved the manuscript for final publication. Peer review comments, comments of the editor(s), etc. are available here: https://peerreviewarchive.com/review-history/4200B