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# Imaging Bioresorbable Vascular Scaffolds – at the Border between Science and Technology

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# PERCUTANEOUS CORONARY REVASCULARIZATION – FROM BALLOON TO BIORESORBABLE SCAFFOLDS

Coronary artery disease (CAD), in its various forms of clinical presentations, including acute coronary syndromes and stable CAD, continues to negatively impact the quality of life, mortality and morbidity, while concomitantly increasing healthcare costs. As the number of patients with CAD increases, the need for optimal revascularization strategies rises, both in the area of interventional cardiology and in coronary artery by-pass grafting techniques, which have substantially developed during the last decades.<sup>1</sup>

Percutaneous coronary revascularization techniques have undergone considerable progress in the last four decades, from the first use of balloon angioplasty, which provided a mechanical vascular patency but with a high risk of early recoil, to the introduction of the first metal stents that were able to provide better long-term results compared to balloon dilation. In spite of this, bare metal stents presented several disadvantages, including high rates of in-stent restenosis, therefore a need for an upgrade emerged that led to the development of drugeluting stents (DES). The main advantage of DES consisted in being coated with anti-proliferative pharmacological agents that inhibit neointimal proliferation, thus preventing restenosis. However, there were major concerns regarding the increased risk of late in-stent thrombosis which was higher in DES, meaning longer dual-antiplatelet therapy regimens, with their associated adverse effects.<sup>2–5</sup>

Newer-generation DES have been shown to present lower rates of late and very late thrombosis if associated with prolonged double-antiplatelet therapies. Their remaining main disadvantages include the failure to restore the native vascular motricity, architecture, and physiological function due to implantation of a rigid metallic cage-like structure at the site of the coronary lesion.<sup>6</sup> The development of bioresorbable vascular scaffolds (BVS) has revolutionized percutaneous coronary revascularization procedures, as they provide proper radial support



for early recoil prevention while releasing an anti-proliferative substance which delays neointimal hyperplasia and eventually resorbs, thus restoring the vascular function otherwise impaired by the presence of a metallic device within the coronary artery.<sup>6–9</sup>

# BIORESORBABLE VASCULAR SCAFFOLDS – PROS AND CONS

The short-term scaffolding of the arterial wall and the early healing and restoration of arterial wall motility seemed to overcome the limitations of BMS and DES. Promising early studies reported low restenosis rates, with major adverse cardiovascular event (MACE) rates around 3-6%, but the 5-year follow-up studies found a 11% MACE rate, with 7.8 to 12.5% binary restenosis rates.<sup>10,11</sup> In an Italian registry, Moscarella et al. investigated the use of BVS for BMS and DES restenosis with a median follow-up of 15 months and reported a 6.2% restenosis rate for BVS. The results of the large ABSORB III trial concluded that BVS were not inferior to third-generation everolimus-eluting stents (Xience, Abbott Vascular, Santa Clara, CA, USA), but they were associated with higher thrombosis rates (1.5% vs. 0.7%, p =0.13), leading to cessation of sales of this stent type on the European market.

# **IMAGING TECHNIQUES FOR BVS EVALUATION**

#### Invasive intracoronary imaging

Several imaging techniques have been used for the assessment of the safety, efficiency, and long-term follow-up of BVS. The follow-up studies used invasive imaging methods such as intravascular ultrasound (IVUS) and optical coherence tomography (OCT) for the assessment of procedural outcomes (under/overexpansion of the stent, dissection etc.), scaffold degradation, vascular healing response, vasomotion restoration, and for prediction of stent thrombosis. Both animal and human studies were conducted for the evaluation of BVS strut degradation, and follow-up studies proved that complete histological resorption of the stent struts takes up to 4 years. In a 2-year OCT follow-up study as many as 80% of the stent struts were still visible, which may explain the late or very late occurrence of thrombotic events, following the discontinuation of dual antiplatelet therapy in these patients.<sup>12</sup> The endothelial coverage of the struts has also been the subject of studies evaluating BVSs. Long-term follow-up studies also concluded that at the 2- or 3-year follow-up, 98 to 99% of the stent struts were covered by endothelium.13 OCT and IVUS studies also evaluated the luminal changes after BVS angioplasty. The implantation of BVS was associated with increased luminal area and dynamic changes in the follow-up period. The first 6 months were associated with a decrease in the mean and minimal luminal area, with significant increases from 6 months to 5 years due to the resorption of the stent struts and reduction (-14%) of the plaque area.<sup>10,12,14</sup>

#### Noninvasive imaging methods

With the emerging number of implanted BVS, there is an urging need for an accurate noninvasive imaging method for the evaluation of these scaffolds. Coronary computed to-mography angiography (CCTA) has already been proved as a liable imaging method for the analysis of both native and stented coronary arteries. In a recent study, Collet *et al.* assessed the accuracy of CCTA at 3 years after BVS implantation and established a 100% specificity and 80% sensitivity with area under the curve 0.88 (95% confidence interval 0.82 to 0.92) for stenoses greater than 50%, which were validated by quantitative coronary angiography and IVUS.<sup>15</sup>

In the current number of JIM, Ferent et al. published the results of a follow-up study, which included 30 patients, 1 to 2 years after BVS implantation using this emerging imaging method for the assessment of BVS. The study did not only target the evaluation of luminal volumes (100.8  $\pm$  33.68 mm<sup>3</sup> vs. 128.2  $\pm$  37.38 mm<sup>3</sup>, p = 0.01) and degree of stenosis (61.63% ± 12.6 vs. 23.41% ± 12.48, p < 0.0001) pre- and post-implantation, but also aimed higher by assessing the technical aspects of the implantation, which may be the key for avoidance of late or very late thrombotic events, which represent the main concern of these stent scaffolds. Furthermore, the workgroup analyzed plaque composition and demonstrated a significant decrease of the fibro-fatty tissue after BVS implantation (10.31%  $\pm$ 6.24 vs. 6.46%  $\pm$  6.14, p = 0.01) and regression of the vulnerability degree of coronary plaques (with significant decrease of low attenuation plaques [37.5% vs. 20.83%, p = 0.01] and significant increase of spotty calcifications after BVS implantation [66.66% vs. 79.16%, p = 0.05]).<sup>16,17</sup>

The result of this study aids in the understanding of vascular and plaque changes following BVS implantation and further enhances the role of CCTA in the evaluation of BVS. The authors succeeded to make a big step forward in order to validate CCTA as the method of choice for imaging-based follow-up of patients with BVS.

# CONFLICT OF INTEREST

Nothing to declare.

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**ORIGINAL RESEARCH** 



NUTRITION AND FOOD HYGIENE // CARDIOLOGY

# Adherence to the DASH-style Diet and the Presence of Cardiovascular Risk Factors in Adults from Tîrgu Mureş

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Received: June 27, 2018 Accepted: July 27, 2018

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#### ABSTRACT

Background: Adopting a healthy lifestyle, including a healthy diet, weight control, regular exercise, smoking cessation, and alcohol limitation, plays an important role in treating high blood pressure and cardiovascular and chronic diseases. Aim: This study aimed to investigate adherence to the DASH diet in relation to the occurrence of high blood pressure and chronic disease risk factors, in a group of people from Tîrgu Mureş. Material and methods: This was a cross-sectional study based on a food frequency and lifestyle questionnaire applied to a group of 2,010 people aged 15–92 years from Tîrgu Mureş. Results: Individuals over the age of 45 had higher DASH scores (Q4, Q5) compared to subjects younger than 40 years (Q1 and Q2, p <0.001). An important percentage (19.3%) of subjects who preferred a meat-based diet (Q3) had significantly larger abdominal circumference (mean 92.2  $\pm$  0.91 cm, p <0.001). An association between pure alcohol intake (mean 5.6 ± 0.43 g) and an unhealthy diet (Q1) was observed, compared to the average 1.7  $\pm$  19 g of alcohol consumed by subjects with a healthy diet (Q5), alcohol consumption decreasing with an increasing DASH score (p < 0.001). Conclusion: This study shows that individuals diagnosed with at least one cardiovascular risk factor had a higher adherence to the DASH diet than individuals with no cardiovascular risk factors, most likely due to the fact that diagnosed individuals had changed their eating behavior and lifestyle from the time of diagnosis, with a positive impact on treatment outcomes and quality of life.

Keywords: DASH diet, high blood pressure, cardiovascular risk factors, lifestyle

# INTRODUCTION

Globally, nearly 18 million people die annually due to cardiovascular (CV) disease, diabetes and hypertension being the major predisposing factors and representing the direct result of the obesity epidemic that has been doubling since the 1980s. In 2014, a WHO report indicated that there were more than 1.9 billion overweight people in the world, and over 600 million of them were obese. According to WHO statistics, in 2008, 18.1% of the population had obesity, 40.4% had high blood pressure (HBP), and in 2012, ischemic heart disease was the main cause of death, killing 54,500 people (21.4% of all deaths), followed by myocardial infarction (MI) with 45.4 thousand people, (17.8% of deaths), and high blood pressure, with a mortality of 11.3% (28.8 thousand persons).<sup>1</sup>

A remarkable progress in the analysis of CV risk factors was achieved by the INTERHEART study,<sup>2</sup> which assessed the importance of several cardiovascular risk factors and their association with the risk of acute myocardial infarction. Of these factors, six have been found to be significant in terms of prediction, including smoking, diabetes, high blood pressure, abdominal obesity, alcohol consumption, and low consumption of fruit and vegetables. But the most important conclusion of the above study was that the simultaneous presence of more than two risk factors explains 90% of major cardiac events, and the importance of diet and nutrition accounts for 50% of disease prevention interventions.<sup>2</sup>

The high prevalence of HBP (60%) is a major health problem in Europe, causing approximately 25% of MIs.<sup>3</sup> The value of blood pressure has been shown to be positively and continuously linked to the risk of developing several CV diseases, such as coronary heart disease, MI, and stroke, which can be prevented and treated. Applying therapy for HBP to risk levels below 140/90 mmHg is associated with a reduction in CV complications.<sup>4</sup>

Adopting lifestyle changes, including a healthy diet, weight control, regular exercise, smoking cessation, and alcohol limitation, plays an important role in treating HBP.<sup>5–10</sup> The DASH diet is a lifestyle approach to a healthy and balanced nutrition, developed by the National Heart Lung and Blood Institute and promoted by the American Heart Association, being recognized as a set of nutritional recommendations that was designed to help, treat, and prevent HBP.<sup>8–10</sup> This diet recommends focusing on a lower intake of saturated fat and cholesterol to help reduce blood pressure, and promotes an increased consumption of low fat and a balanced consumption of whole grains, fish, poultry, seafood, and oilseeds.<sup>5</sup>

Therefore, it is important to assess possible associations between a DASH-style diet adherence score and chronic disease risk factors. From our knowledge, no such study has been carried out in Romania, and we proposed to investigate the adherence of the population of Tîrgu Mureş to the DASH diet in the context of the presence of cardiovascular and chronic disease factors, in order to improve compliance with the cardiovascular treatment.

# MATERIALS AND METHODS

## Patient setting and population

This is a cross-sectional study based on a food frequency and lifestyle questionnaire applied to a group of 2,010 people aged 15–92 years from Tîrgu Mureş. The sampling was based on the systematic method (sampling step k = 5) by applying the initial cluster type in all districts of Tîrgu Mureş. Subsequently, a systematic sampling was applied, where starting from a main street, the fifth apartment building of the block or private house was chosen. For apartment buildings with 4 to 10 stories, one person from every third apartment was questioned. Data collection took place between May 2017 and July 2017, the time of the year when fruit and vegetable consumption is increased.

The interviews were conducted face to face, at the respondents' households, by trained interviewers, and had an average duration of 15 minutes, the subjects being informed of the purpose of the study, as well as the anonymity and confidentiality of their answers.

#### Dietary assessment

The questionnaire consisted of 106 questions related to anthropometric indicators, demographics, smoking status, lifestyle behavior, one-week food consumption estimation, and diagnosed chronic disease (ischemic cardiomyopathy, HBP, diabetes mellitus). Respondents were asked to refer to the frequency of a standard portion of a single serving over a week with 7 variants ranging from "not at all, or less than once/month" to a frequency of "2-3 times/ day". Total energy and nutrient intake was calculated by summing up energy and nutrients from all foods. We calculated the DASH score based on food and nutrients from the DASH diet,<sup>8,11</sup> focusing on 8 food groups: high intake of fruits, vegetables, nuts and legumes, whole grains, lowfat dairy products, and low intake of sodium, red and processed meats, and sweetened beverages.11,12 For each component of the questionnaire, we calculated the number of servings per day. Then, the obtained values were divided into five quintiles, and the average values of servings per each of the five quintiles are presented in a table. Quintiles values were turned into scores, using the following criteria: for fruits, vegetables, nuts and legumes, whole grains and low-fat dairy servings – Q1 = 1 point, Q2 = 2 points, Q3 =3 points, Q4 = 4 points, Q5 = 5 points; for sodium, red and processed meats, and sweetened beverages servings - Q1 = 5 points, Q2 = 4 points, Q3 = 3 points, Q4 = 4 points, Q5= 1 point (Table 1). We then summed up the component

scores to obtain an overall DASH score ranging from 10 to 40. For the consumption of healthy food groups, a higher score reflected a higher consumption of those food groups. These groups were rated on a scale of 1–5; participants in quintile 5 had the highest consumption and were scored 5. Less healthy food groups, where a lower consumption is recommended, were scored using a reverse scale. Participants from quintile 1 reported the lowest consumption and scored 5. Participants from quintile 5 had the highest DASH score and a good-quality diet (Table 1).

#### Anthropometric measurements

Body mass index (BMI, calculated as kg/m<sup>2</sup>) was derived from weight and height measured with a calibrated scale and a Kawe measure. Study subjects were included in the BMI classification as follows: underweight (BMI  $\leq 18.49$  kg/m<sup>2</sup>), normal weight (BMI = 18.50–24.99 kg/m<sup>2</sup>), overweight (BMI = 25.00–29.99 kg/m<sup>2</sup>), or obese (BMI  $\geq 30.00$  kg/m<sup>2</sup>). Waist circumference was measured using a Kawe measuring tape, and central obesity was defined as having a waist circumference  $\geq 94$  cm for men and  $\geq 80$  cm for women.<sup>13</sup>

Blood pressure was determined using a Beurer BM 85 digital blood pressure monitor, the subject being seated, and the right arm positioned at the heart level. Participants with a systolic pressure value  $\geq$ 140 mmHg and a diastolic pressure  $\geq$ 90 mmHg were classified as hypertensive subjects.<sup>4,8</sup>

#### Statistical analysis

The data was collected in an Excel database, and the statistical analysis was performed using the IBM SPSS program (Statistical Package for Social Sciences), Version 22.0 for Windows. The level of significance was considered 5%, and for comparisons of ordinal variables the Mann-Whitney and Kruskal-Wallis tests were applied. Chi-squared tests were used in tables with nominal/ordinal variables. A principal component analysis (PCA) was conducted on 49 items with orthogonal rotation (varimax). The Keiser-Meyer-Olkin measure verified the sampling adequacy for analysis, KMO = 0.77, which are above Keiser's criteria (>0.5). Bartlett's test of sfericity  $\chi^2(1176)=14716.6$ , p <0.001, indicated that the correlation between items was sufficiently large for PCA. An initial analysis was run to obtain eigenvalues for each component in the data. Fifteen components had eigenvalues over Keiser's criterion of 1 and in combination explained 53.7% of the variance. After inspecting the screen plot we decided to keep five components, which in combination would explain 21.5% of the variance (Table 2).

Table 2 shows factor loadings after rotation. The items that cluster on the same components suggest that component 1 represents a Mediterranean-like pattern, component 2 represents a pattern of consumption of meat and alcohol, component 3 represents a diet without meat, and component 4 includes fast-food eaters. Pattern 5 includes individuals who eat dairy.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. This study was approved by the Scientific Ethics Committee Board at the University of Medicine and Pharmacy of Tîrgu Mureş.

**TABLE 1.** Dietary food group intakes according to quintiles of Dietary Approaches to Stop High Blood Pressure related to the DASH diet score

Components of DASH score a,b	Quintiles DASH score				
	Q1 (n = 432)	Q2 (n = 450)	Q3 (n = 390)	Q4 (n = 391)	Q5 (n = 347)
Fruitsª (servings/day)	0.5746	0.7950	1.0358	1.2220	1.8153
Vegetablesª (servings/day)	0.8118	1.1540	1.4017	1.6436	2.4588
Nuts and legumes <sup>a</sup> (servings/day)	0.3778	0.4724	0.5780	0.7247	1.1140
Whole grainsª (servings/day)	0.6486	1.4518	2.2074	2.5903	3.3104
Low-fat dairyª (servings/day)	0.1060	0.1862	0.2704	0.3581	0.4926
Sodium <sup>b</sup> (mg/day)	3,681.09	2,868.23	2,593.77	2,225.04	1,746.56
Red and processed meat <sup>b</sup> (servings/day)	1.3036	0.9283	0.7653	0.5367	0.2753
Sweetened beverages <sup>b</sup> (servings/day)	0.5915	0.2718	0.1362	0.0701	0.0262

a. Scoring criteria: for fruits, vegetables, nuts and legumes, whole grains and low-fat dairy servings – Q1 = 1 point, Q2 = 2 points, Q3 = 3 points, Q4 = 4 points, Q5 = 5 points; for sodium, red and processed meats and sweetened beverages servings – Q1 = 5 points, Q2 = 4 points, Q3 = 3 points, Q4 = 4 points, Q5 = 1 point b. Higher quintiles represent higher intake; however, in constructing the DASH score, high intake and high quintiles received lower scores.

# TABLE 2. Diet patterns in relationship with DASH quintiles analysis – factor loadings after rotation

Food groups from the menu			Diet patterns		
	1	2	3	4	5
	Mediteranean- like	Diet with meat and alcohol	Diet without meat	Fast-food diet	Diary diet
Fresh vegetables	0.793				
Fresh green leaves vegetables	0.665				
Fresh fruits	0.653	-0.159	0.159		
Cooked food	0.529				
Home-made wine		0.745			
Spirits/liquor/brandy		0.718			
Beer		0.683		0.245	
Commerce wine		0.539		0.215	
Nuts/peanuts	0.247		0.721		
Seeds			0.688	0.212	
Dried fruits			0.501		
Soy beans and soy products			0.443		
Flakes/cereal/muesli		-0.168	0.356		
Sweet juices				0.641	
Energy drinks	-0.201			0.635	
Chips/fries				0.564	
Pizza	-0.188			0.430	
Salt cheese					0.660
Fermented salt cheese					0.643
Fresh cheese					0.532
Melted cheese					0.516
Fermented cheese					0.447
buttermilk/yogurt/kefir					0.378
Meat products – salami,bacon					
Meat products – ham					
Canned food products					
Mayonnaise	-0.180				
Fried meat products				0.332	
Pickles	0.276				
Pork meat		0.225		0.200	
Juice 25–50%				0.268	
Juice 100%			0.183		
Pre-cooked food products	-0.236			0.171	
Concentrated sweets					
Sweet dough					
Rice	0.159				
Mushrooms				-0.178	0.172
Pasta					
Beans/peas/lentils/chickpeas	0.156		0.243		
Fish					0.152
Beef					
Chicken	0.215		-0.326	0.267	
Mineral water					
Plain water			0.173		
Tap water					
Whole milk					
Eggs	0.242		-0.156		
Caffee					
Black/green tea			0.205		

Demographics	s/Parameters	Quintiles DASH score range					
		Q1 10–18	Q2 19–22	Q3 23–25	Q4 26–29	Q5 30–40	P for trend
		n = 432	n = 450	n = 390	n = <b>391</b>	n = 347	
Age (mean ± S	EM)	38.9 ± 0.77	43.9 ± 0.75	47.0 ± 0.85	46.1 ± 0.82	45.6 ± 0.82	<0.001
BMI (mean ± SI	EM)	25.1 ± 0.21	25.6 ± 0.22	$26.3 \pm 0.25$	$26.2 \pm 0.26$	25.4 ± 0.26	0.068
Abdominal circ	umference (mean ± SEM)	88.6 ± 0.83	89.2 ± 0.88	92.2 ± 0.91	$90.5 \pm 0.96$	86.2 ± 0.90	0.321
Systolic blood	pressure (mean ± SEM)	124.8 ± 1.17	126.6 ± 1.19	128.8 ± 1.13	127.4 ± 1.18	123.0 ± 0.99	0.562
Diastolic blood	pressure (mean ± SEM)	79.3 ± 0.71	81.4 ± 2.64	79.8 ± 0.74	79.1 ± 0.73	76.5 ± 0.59	0.094
Raw alcohol (m	iean ± SEM)	5.6 ± 0.43	3.9 ± 0.39	$3.8 \pm 0.41$	$2.8 \pm 0.33$	1.7 ± 0.19	<0.001
Total energy in	take, kcal	2001.7 ± 29.12	1755.6 ± 29.55	1739.1 ± 34.95	1676.3 ± 33.73	1741.9 ± 30.96	< 0.001
Gender, male (	%)	53.5%	36.4%	37.9%	30.4%	24.5%	<0.001
Education	less than 8 classes	8.1%	5.8%	5.9%	2.8%	2.6%	<0.001
level	secondary school	21.3%	18.0%	20.3%	22.8%	10.4%	
	high school studies	30.6%	32.9%	33.6%	28.1%	24.8%	
	post-graduate studies	8.3%	14.7%	11.3%	14.1%	17.3%	
	university studies	31.7%	28.7%	29.0%	32.2%	45.0%	
Marital status	married	49.5%	58.0%	63.8%	59.8%	59.7%	<0.001
	divorced	6.0%	7.1%	6.7%	8.7%	9.2%	
	single/ concubinage	39.1%	26.2%	20.0%	21.7%	22.2%	
	widower	5.3%	8.7%	9.5%	9.7%	8.9%	
History of	ischemic heart disease	4.4%	6.4%	9.2%	10.2%	5.8%	0.006
	obesity	5.8%	7.6%	11.0%	10.2%	5.8%	0.013
	diabetes mellitus	4.6%	4.4%	7.7%	9.7%	6.6%	0.010
	cancer	0.7%	0.9%	0.5%	1.0%	2.3%	0.135
	high blood pressure	13.7%	19.8%	24.9%	23.8%	19.3%	<0.001
	gastric pathology	5.1%	3.6%	4.6%	4.3%	2.9%	0.553
	osteoporosis	2.5%	4.9%	4.6%	4.1%	3.7%	0.438
	chronic hepatitis	1.4%	1.3%	2.6%	1.3%	0.9%	0.379
	neurological diseases	1.6%	0.9%	1.0%	2.3%	0.6%	0.225
Smoking	non-smoker	38.7%	46.4%	50.0%	54.7%	56.5%	<0.001
status	ex-smoker	18.1%	19.8%	23.1%	22.3%	24.8%	
	active smoker	43.3%	33.8%	26.9%	23.0%	18.7%	

TABLE 3. Distribution of demographic characteristics and risk factors of our sample in relationship with quintiles of DASH score range

# RESULTS

In the studied group, 62.8% (n = 1,263) of respondents were female, and the average age of the whole sample was 44.14  $\pm$  7.2 years (between 15 and 92 years). Almost one third of subjects have completed university studies (32.9%), followed by 30.2% who have just completed high school.

The social-demographic characteristics of the studied group in correspondence with the DASH score quintiles are presented in Table 3. A share of 8.1% of the total respondents showed obesity, and 18.6% were overweight, the mean BMI being 25.7 kg/m<sup>2</sup> (min = 16.33 kg/m<sup>2</sup>, max = 54.69 kg/m<sup>2</sup>), abdominal circumference was characterized by an average of 89.4 cm in both sexes (36.5% had an abdominal circumference above the limit), and mean blood pressure was 126/79 mmHg (Table 2), 20.1% of the respondents having HBP.

The study group consisted of 58.3% healthy people and 41.7% people who reported chronic illnesses, among the most common being HBP (20.1%), ischemic heart disease (7.2%), and diabetes mellitus (6.5%).

Individuals over the age of 45 had higher DASH scores (Q4, Q5) than subjects under 40 years, which had Q1 and Q2, p <0.001. An important share (19.3%) of subjects who preferred a meat-based diet (Q3) had a significantly elevated abdominal circumference (mean =  $92.2 \pm 0.91$  cm, p <0.001).

An association between alcohol intake (mean =  $5.6 \pm 0.43$  g) and an unhealthy diet (corresponding to DASH score = 10-18) was recorded; compared to the average  $1.7 \pm 0.19$  g of alcohol consumed by subjects with a healthy diet (DASH score = 30-40), alcohol consumption decreased with an increasing DASH score, p <0.001. The



**FIGURE 1.** Adherence to the DASH diet style, individuals with cardiovascular risk vs. healthy individuals

highest caloric intake  $(2,001.7 \pm 29.32 \text{ kcal})$  was found in 53.5% of male respondents with an unhealthy diet (Q1), which also explained the increased BMI (overweight and obesity).

From respondents who follow a balanced dietary intake (Q5), 45% (p <0.001) declared that they have higher education levels, and 59.7% are married custodians (p <0.001). However, 63.8% of married people and 39.1% of unmarried or cohabiting relatives followed a less healthy diet (Q3). Of the non-smoker sample, 56.5% respected a balanced diet (Q5), p <0.001, compared to smokers, of which 43.3% associated a processed food menu (Q1).

Each diet pattern was statistically associated with lifestyle and demographic risk factors when comparing data between Q5 and Q1 (Table 3).

A total of 61.9% of subjects who scored an elevated DASH score (Q5) in the Mediterranean pattern were women over the age of 47 who consume >2,000 kcal/ day, with a DASH score of 26.2, as well as a high intake of healthy foods, vegetables, and legumes.

Patients diagnosed with at least one CV risk-related diagnosis had a higher median of DASH score, U = 363196, z = -4.03, p <0.001, r = 0.09, with a very small effect size (Figure 1), compared with healthy subjects.

#### DISCUSSIONS

Studies have shown that there is a link between increased chronic consumption of sodium and the occurrence of high blood pressure.<sup>3</sup> In Europe, about 70–75% of the total salt consumed is hidden in processed food or other food prod-

ucts that are not under consumer control, and the remaining 25–30% is added to meals at the table.<sup>3,14,15</sup> While overconsumption of salt is undoubtedly a worldwide problem, there is a growing concern in the European region, where a typical diet consists of high consumption of preserved meat, bread and cheese, high-salt foods, sugar, lipids, saturated fat, and cholesterol.<sup>3,16</sup> Research has found that limiting salt intake to less than 5 g/day (2,000 mg of sodium, one teaspoon of salt) is associated with a 17% reduction in the long-term risk of developing a CV disease.<sup>3,17</sup>

The DASH diet recommends a lower intake of sodium, sugars, and fats, as well as a lower intake of saturated fat and cholesterol to help reduce blood pressure. This diet also promotes a high consumption of vegetables, fruits, and low-fat diaries, as well as a balanced intake of whole grains, cereals, fish, and legumes.<sup>18–21</sup>

According to similar studies, adherence to the DASH diet has been shown to reduce the risk of developing coronary artery disease due to limited consumption of salt and saturated fats, which prevents HBP.<sup>11,22,23</sup>

For the analyzed population from Tîrgu Mureş, the profile of the top quintiles of DASH (Q4 and Q5) was as follows: older people, who consume less alcohol, have lower or normal caloric intake, are predominantly women, graduated university, are married, non-smokers, with a significantly higher prevalence than those in the lower quintiles. Subjects from Q3 have significantly higher values for BMI, abdominal circumference, and chronic disease history than those in the extreme quintiles.

Adherence to the DASH diet has been statistically associated with the presence of chronic diseases, except for cancer. Consumption of a DASH dietary pattern was not significantly associated with the BMI or abdominal circumference. The HBP cases were associated with the consumption of lower-than-healthy food products (Q3) in a proportion of 24.9%, and with a healthy lifestyle (Q5) in a share of 19.3%, compared to subjects who have an increased intake of processed foods (Q1), of which only 13.7% had HBP.

In this study, increased adherence to the DASH diet was associated with age over 45 years (p <0.001), a BMI >25 kg/m<sup>2</sup> (p <0.001), a lower frequency of males (p <0.001), married and non-smokers subjects (p <0.001), although other studies have shown that CV diseases are more prevalent among males.<sup>24</sup>

Lifestyle changes by community interventions that are focused on reducing the risk of CV diseases among the population of Tîrgu Mureş will have more effective outcomes with personalized therapy for the following risk profile: young men, smokers, and unmarried subjects, because in these individuals we identified a low adherence to the DASH diet.

Nutritional interventions should be applied in young subjects, at school (as a primary preventive measure), but also in patients with the above-mentioned profile and registered cardiovascular risk factors (even if there is no clear diagnosis) and in patients who already have a diagnosed cardiovascular disease, in order to improve their health status.

#### CONCLUSIONS

This research showed that individuals diagnosed with at least one cardiovascular risk factor had a higher adherence to the DASH diet, compared to individuals with no cardiovascular risk factors, most likely because diagnosed patients have changed their eating behavior and lifestyle from the time of diagnosis, with a positive impact on treatment outcomes and quality of life. Prospective cohort studies are required to confirm these findings.

# **CONFLICT OF INTEREST**

Nothing to declare.

#### ACKNOWLEDGEMENT

The present research is receiving funding from the University of Medicine and Pharmacy of Tîrgu Mureş, Romania, via governmental funds for PhD studies, contract number 13406/3/07.10.2015.

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**ORIGINAL RESEARCH** 



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

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Received: August 10, 2018 Accepted: September 1, 2018

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#### ABSTRACT

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

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

# INTRODUCTION

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

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

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

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

# **MATERIAL AND METHODS**

This was a single-center, prospective, observational study that included 46 patients with diagnosed cardiovascular disease, but without peripheral vascular involvement. Demographical data (age, sex, height, and weight), history of cardiovascular disease (coronary artery disease, hypertension, cerebrovascular disease), and cardiovascular risk history (dyslipidemia, diabetes, smoking habits) were recorded. The following laboratory parameters were measured using standard commercial assays: uric acid (UA), creatinine, total cholesterol, LDL-cholesterol, HDLcholesterol, fasting glucose, triglycerides, and C-reactive protein. The ankle-brachial index was also determined by measuring systolic blood pressure at the brachial, dorsalis pedis, and posterior tibial arteries. The lowest value measured at the lower limb was divided with the brachial artery's systolic pressure value. Brachial artery blood pressures were measured by a calibrated OMRON M3 Intellisense device (Omron Healthcare Europe, Hoofddorp, the Netherlands), and lower limb systolic measurements were made using a Bistos-BT-200 CW Doppler (Bistos Co. Ltd., Korea).

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

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

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

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

Each patient underwent ultrasound examination of the superficial femoral artery (SFA) (Aloka Prosound  $\alpha$ 10 device, Hitachi Aloka, Japan) with 7.5–10 MHz linear probe, by which intima-media thickness was determined, according to the Mannheim consensus.<sup>14–16</sup> Bilateral assessment of the arterial segment was performed, from the

bifurcation of the common femoral artery (CFA) into the superficial and profound femoral artery to Hunter's canal, where due to the anatomical characteristics of the vessel, accurate visualization is difficult. Measurements were made on two-dimensional longitudinal images at the far wall of the SFA. Intima-media thickness was defined as the distance between the leading edge of the first bright line of the far wall and the leading edge of the second bright line (the distance between the edge of adventitiamedia interface and intima-lumen interface). At least 3 measurements of IMT were made at minimum 5 cm distance between them, using the semi-automated software dedicated for c-IMT examinations. Mean IMT based on all measurements was calculated by the automated software. Segments with atherosclerotic plaques were defined as endoluminal thickening >1.5 mm or a 50% increase as compared to the adjacent segment. In the event that significant plaques were discovered, measurements were made in the vicinity of the area, on portions of the vessel without any lesions. Median f-IMT was calculated as the median value of left and right values. The highest value between mean left and right f-IMT was considered the maximum value.

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

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

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

# RESULTS

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

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

TABLE 1. Mean values of the examined parameters

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

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

#### Data distribution according to gender

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

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

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

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

There were no major differences between the two groups regarding CAD (66.66% vs. 53.57%), hypertension (88.88% vs. 85.71%), dyslipidemia (55.55% vs. 50%),

obesity (55.55% vs. 57.14%), and diabetes (22.22% vs. 28.57%). There were almost twice as many smokers in the group with increased f-IMT (11.11% vs. 21.42%), and patients with higher f-IMT had a higher incidence of stroke as well (11.11% vs. 25%).

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

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

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

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

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

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

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

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

## DISCUSSIONS

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

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

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

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

#### **Patient groups**

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

Although the median value of f-IMT in our study was 0.83 mm, we arbitrarily chose the cut-off value of 0.75 mm based on studies investigating carotid intima-me-

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



FIGURE 1. Cardiovascular comorbidities and risk factors in the groups with low and high f–IMT  $% \left( f_{1},f_{2},f_{3},f$ 



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

#### **Technical aspects of f-IMT evaluation**

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

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



FIGURE 3. Correlations between metabolic parameters and f–IMT in the group with high f–IMT  $% \left[ f_{\rm e}\right] =0.017$ 

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

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

#### Metabolic risk profile of the study population

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

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

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

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

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

# Markers of peripheral atherosclerosis and inflammation

As a subclinical process, inflammation in involved in the metabolic disturbances that precede manifest atherosclerosis. An increase in CRP indicates a pro-inflammatory status and is influenced by smoking, obesity, and age, factors also contributing to an accelerated atherosclerosis.<sup>36</sup> Even though a meta-analysis of studies concluded that CRP has a relatively moderate capacity of predicting CAD, still, in patient categories with a Framingham risk score between 10 and 20%, it is a good toll for risk stratification.<sup>37</sup> In patients with chronic kidney disease undergoing hemodialysis, CRP levels correlated with carotid and femoral intimamedia thickness.<sup>38</sup> The group with f-IMT >0.75 mm in our study also presented higher circulating CRP levels (r = 0.450, p = 0.01). This suggests that inflammation is a systemic process, but an aspect to be clarified is whether it is the promoter or the consequence of atherosclerosis. Shedding light on the mechanism that causes the inflammation atherosclerosis continuum could allow specific inhibition of the process and as such, reduce cardiovascular risk and prevent major cardiovascular events.

# Correlations between f-IMT and the ankle-brachial index

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

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

#### Study limitations

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

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

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

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

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

#### CONCLUSIONS

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

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

#### **CONFLICT OF INTEREST**

Nothing to declare.

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**ORIGINAL RESEARCH** 



CARDIOLOGY // CARDIOVASCULAR IMAGING

# CTA Evaluation of Bioresorbable Scaffolds versus Metallic Coronary Stents – a Feasibility Study

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#### **ARTICLE HISTORY**

Received: August 4, 2018 Accepted: September 10, 2018

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#### ABSTRACT

Background: Computed tomography angiography (CTA) presents important limits in in-stent restenosis (ISR) evaluation in case of metallic coronary stents, due to the artifacts determined by stent struts, which alter in-stent plaque analysis. In case of bioresorbable scaffolds, stent strut resorption allows accurate evaluation of the vessel wall. Aim of the study: This study aims to compare the feasibility of CTA as a follow-up imaging method for ISR diagnosis following elective PTCA procedures, between bioresorbable scaffolds and metallic coronary stents. Material and methods: We conducted a prospective, observational study on 73 patients with elective PTCA procedures in their medical history, in whom 113 stents were assessed via CTA in order to diagnose ISR. Based on stent type, the patients were divided into two groups: Group 1 - patients with bioresorbable vascular scaffolds (BVS) (n = 30); and Group 2 - patients with bare metal stents (BMS) (n = 43). Plague analysis was possible only in the BVS group with a post-processing research-dedicated software, Syngo.via Frontier, which identified plaque morphology and virtual histology composition. Results: After CTA evaluation, the BVS group presented a significantly higher incidence of severe coronary artery disease (CAD) (Group 1 – 73% vs. Group 2 – 30%, p <0.0001). The proximal part of the right coronary artery (RCA) presented a significantly higher percentage of metallic stents (14% BMS vs. 2% BVS, p = 0.0029). The comparative analysis of CTA sensibility for the visual evaluation of ISR identified a significantly higher percentage of diagnostic CT evaluations in the BVS group (Group 1 – 94% vs. Group 2 – 76.19%, p = 0.0006). CTA evaluation provided the most accurate results for the 3.0 and 3.5 mm devices. Regarding CTA sensibility for ISR diagnosis, the BVS group presented the smallest incidence of non-diagnostic CT evaluations. Conclusions: CTA evaluation of bioresorbable scaffolds is superior to metallic stent assessment, the latter being influenced by numerous sources of error dependent mainly on the presence of the metal structure.

Keywords: CTA, in-stent restenosis, bioresorbable scaffolds, metallic coronary stent

## INTRODUCTION

In the last decades, percutaneous coronary angioplasty has become one of the most common interventions for the treatment of coronary artery disease (CAD).<sup>1</sup> However, restenosis, occuring at the site of treated injuries, and the possible need for repeated revascularization are the main drawbacks encountered in interventional cardiology.<sup>2</sup> Restenosis represents a complex phenomenon that starts immediately after vessel barotrauma, induced by coronary angioplasty.<sup>3–5</sup> Based on the moment of occurrence, instent restenosis (ISR) can be classified in early ISR – due to elastic recoil and in-lumen axial plaque relocation, characterizes balloon angioplasty primarily, and late ISR – the consequence of thrombus reorganization, neointima formation, vascular remodeling, and resolution of the inflammatory process.

The need for adequate follow-up of patients undergoing coronary angioplasty emerged since the first angioplasty, performed more than 40 years ago.<sup>2</sup> After percutaneous coronary intervention (PCI), the patient falls into the category of patients that must be followed regularly, being at risk for stent occlusion by thrombosis or restenosis.6 The complete assessment of the type of occlusion is essential in order to choose the optimal revascularization strategy (DES vs. DEB). Thus, choosing an optimal imaging method to monitor stent permeability represents a priority in interventional cardiology. Identifying new, modern imaging techniques that can be applied as follow-up methods of implanted scaffolds represents an interest in interventional cardiology, knowing that the early identification of a significant restenosis simplifies the subsequent revascularization procedure.7

The CTA evaluation of metallic stents is based on contrast agent attenuation around the area of neointimal hyperplasia. However, this process presents major limitations due to metallic stent struts, which lead to significant artifacts and misinterpretations. Regarding post-implantation follow-up, bioresorbable scaffolds present the advantage of accurate evaluation via CTA in terms of luminal dimensions and plaque analysis. The accuracy and feasibility of multislice CTA in the evaluation of bioresorbable scaffolds, assessed in a multicentric study, may consolidate noninvasive imaging techniques as reference methods in this type of patient follow-up.<sup>8,9</sup>

CTA evaluation has become one of the most popular imaging techniques in cardiology, its relevance in vulnerable coronary plaque evaluation being widely accepted.<sup>10–14</sup> In a recent study, conducted on 238 patients enrolled in the ABSORB II trial with 258 coronary atherosclerotic lesions treated with bioresorbable scaffolds, subjects were evaluated via invasive angiography, intravascular ultrasound (IVUS), and CTA at the 3-year follow-up after PCI. After analyzing the results, CTA proved to have a similar diagnostic precision to conventional angiography in terms of identifying and quantifying the severity of ISR.<sup>15</sup>

In this regard, the accuracy of CTA evaluation represents another advantage of bioresorbable scaffolds in the interventional treatment of coronary atherosclerotic lesions.

#### OBJECTIVES

CTA presents important limitations in ISR evaluation in case of metallic coronary stents due to the artifacts determined by stent struts, which alter in-stent plaque analysis.

In case of bioresorbable scaffolds, stent strut resorption allows the accurate evaluation of the vessel wall. This study aims to analyze the utility of CTA in the follow-up evaluation of bioresorbable scaffolds versus metallic coronary stents, in order to diagnose ISR after PCI.

## **MATERIAL AND METHODS**

We conducted a prospective, observational study, which included 73 patients, treated by implanting one or more stents for coronary artery disease, in the CardioMed Medical Center Tîrgu Mureş, according to ESC guidelines, between January 2015 and March 2017. Based on stent type, the study subjects were divided into two groups: Group 1 – 30 patients with 50 implanted bioresorbable scaffolds (ABSORB 1.1/Abbott Vascular) and Group 2 – 43 patients with 63 metallic (MULTI-LINK ULTRA/Abbot Vascular, Tsunami Gold/Terumo, Guidant MULTI-LINK PLUS/ Abbot Vascular) and drug-eluting stents (Resolute Integrity/Medtronic, XIENCE/Abbot Vascular).

Patients with PTCA and stent placement in their medical history were included in this study. Other inclusion criteria were age over 18 years, BMI <40 kg/m<sup>2</sup>, signed written informed consent. Exclusion criteria were STelevation myocardial infarction or non-ST-elevation myocardial infarction as diagnosis of PCI indication, electric and hemodynamic instability at admission, allergy to iodine contrast material, indication for oral anticoagulation therapy à la longue, acute renal failure or terminal-stage chronic kidney disease, pregnancy or lactation, active malignancy/end-stage disease with life expectancy under 1 year, or refusal to provide written informed consent for study enrollment. Each patient underwent invasive angiography and CTA evaluation, between 12 and 24 months after PTCA, in order to evaluate the stent's degree of permeability. After PTCA, each subject performed the 1-, 6-, 12-, and 18-month follow-up visit with major adverse cardiovascular events (MACE) rate evaluation.

#### **CT** scanning protocol

Each CTA evaluation was performed using a 64- and 128-slice dual-source CT scanner (SOMATOM Definition, Siemens Healthcare) available in the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center of Tîrgu Mureş, with 64 detector rows  $\times$  0.5 mm and 128  $\times$  0.6 mm respectively, 330 ms rotation time, and a table feed of 0.2–0.4 mm per rotation.

The scanning protocol involved a 4-6 h fasting period, avoidance of smoking, caffeine use, and intense physical exercises 24 h prior to the CT examination; a heart rate below 60 bpm during image acquisition, using a bradycardization protocol with Metoprolol 25-50 mg or Ivabradine 5 mg orally, 1 h prior to the CT scan. The scanning protocol was explained to each patient, the study subjects being instructed to follow audio instructions regarding respiration. The Ultravist 370 mg I/ml contrast agent (Bayer Healthcare, Germany) was administered through a peripheral venous catheter (16-22 G) placed in the antecubital vein, followed by 50 ml of 0.9% NaCl solution. The dose of the contrast agent was adjusted according to body weight and scan time, based on the formula: contrast agent volume (mL) = (scan time + 10)  $\times$  preset flow rate, at a flow rate of 5 mL/s, a tube voltage of 120 kV, and a tube current of 400 mAs.

The CT scanning protocol included a topography in antero-posterior and lateral incidence, in order to frame the acquisition territory from the base of the sternum to the apex of the heart. "Automatic bolus tracking" technique was used to detect the contrast reaching the descending aorta. The region of interest was placed in the descending aorta and the median region of the heart, and image acquisition was performed after the audio command of breathing, at 10 seconds after the beginning of contrast material injection.

#### CT image reconstruction and data analysis

Post-processing of CT acquisitions was performed using a dedicated software, Syngo.via Frontier with a Siemens workstation (Siemens AG, Erlangen, Germany) and QCTA RE (Medis, Leiden, Holland). In order to reconstruct images of the coronary arteries, cardiac cycles with minimal movement or frequency artefacts were selected. Stents were evaluated via curved multiplanar reconstructions, defining the following imagistic patterns:

- permeable stent without signs of neointimal hyperplasia: homogeneous opacification of the vascular lumen;
- permeable stent with insignificant neointimal hyperplasia: longitudinal attenuation of the contrast agent, with a lumen reduction <50%;
- significant ISR: longitudinal and transverse attenuation of the contrast agent, with a lumen reduction >50%;
- ISR with occlusion: complete lack of lumen opacity.

The analyzed stent was considered correctly evaluated if its lumen was visible in all its length and contrast attenuation was not significantly altered by artifacts caused by metals struts or motion. In the situation of getting a low-quality, blurry and unequally acquired image with a series of artifacts, the CT evaluation was considered nondiagnostic. Together with the stented coronary artery segment, 5 mm before and after the scaffold were evaluated with maximum intensity projection in order to define restenosis in the stent ends.

#### Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 software (GraphPad Software, Inc., San Diego, USA). A two-tailed p value of <0.05 was considered statistically significant. The D'Agostino Pearson normality test was used to test the normality of distribution of numerical data, continuous data was shown as mean  $\pm$  standard deviation and median respectively, and categorical variables were expressed as percentages and integer values. Pearson and Spearman coefficients were used for correlation analysis.

#### Ethics

This study was conducted according to the current revised edition of the Declaration of Helsinki. The study was performed under the approval of the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureş (approval no. 338/17.11.2017) and the Ethics Committee of the CardioMed Medical Center (approval no. 29/28.12.2017). Written informed consent was obtained from each patient.



**FIGURE 1.** CTA of the left anterior descending artery at 12 months after PTCA with 3 BVS and 1 DES – QAngio-CT RE post-processing software (Medis, Leiden, the Netherlands)

# RESULTS

#### General characteristics of the study population

General characteristics and the main cardiovascular risk factors in the two study groups are summarized in Table 1.

We found no significant differences regarding mean age in the study groups (Group  $1 - 65 \pm 7$  years vs. Group  $2 - 58.07 \pm 7.75$  years, p = 0.71). With regard to the incidence of cardiovascular risk factors, there were no statistically significant differences regarding the prevalence of diabetes mellitus (Group 1 – 38% vs. Group 2 – 20%, p = 0.56), male gender (Group 1 – 82% vs. Group 2 – 86.66%, p = 0.56), or chronic tobacco use (Group 1 – 40% vs. Group 2 – 43.33%, p = 1.0).

However, dyslipidemia had a higher incidence among patients from Group 1 (Group 1 - 73% vs. Group 2 - 30%, p <0.0001).

TABLE 1. Genera	I characteristics and	cardiovascular	risk factors
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	BMS, n	<b>BMS,</b> %	BVS, n	<b>BVS</b> , %	p value
Age (years)	65 ± 7	_	58.07 ± 7.75	_	0.71
Male gender	37	82%	26	86.66%	0.56
Body mass index (kg/m²)	23.7 ± 2.0	_	$24.5 \pm 2.3$	_	0.78
Diabetes mellitus	17	38%	6	20%	0.56
Dyslipidemia	33	73%	9	30%	< 0.0001
Chronic tobacco use	18	40%	13	43.33%	1.0
Diseased vessels					
1 vessel	26	60.46%	13	43.33%	0.0051
2 vessels	12	27.9%	8	26,66%	0.0051
3 vessels	5	11.62%	9	30%	0.0051

TABLE 2. Stent ty	pe and characteristics
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Model	Stent material	Strut thickness (µm)	Stent, n
BMS			
MULTI-LINK VISION/Abbott Vascular	Cobalt	81.28	2
Resolute Integrity DES/Medtronic	Cobalt	91.44	11
XIENCE PRO DES Everolimus/Abbott Vascular	Cobalt	81.28	28
Tsunami Gold BMS/Terumo Europe	Stainless steel	78.74	13
MULTI-LINK PLUS/Guidant	Stainless steel	55.88	9
BVS			
ABSORB Bioresorbable Vascular Scaffold 1.1, Abbott Vascular, Santa Clara, California	Poly-L-lactic acid	150	50

In terms of CAD severity, Group 1 presented a significantly higher incidence of severe atherosclerotic involvement (Group 1 - 11.62% vs. Group 2 - 30%, p <0.0051).

#### Characteristics of the implanted stents

The type and main characteristics of implanted stents are presented in Table 2.

Revascularized coronary segments with metallic and bioresorbable scaffolds are presented in Table 3.

Regarding the revascularized coronary segment, the proximal part of the right coronary artery (RCA) presented a significantly higher percentage of metallic stents compared to BVS (14% BMS vs. 2% BVS, p = 0.0029). The middle (9.52% BMS vs. 10% BVS, p = 1.0) and distal parts of the RCA (9.52% BMS vs. 4% BVS, p = 0.25) presented no significant differences in terms of the type of implanted device.

CTA performance in the evaluation of BVS vs. BMS

The comparative analysis of CTA sensitivity in terms of visual evaluation of ISR in the two study groups identified a significantly higher percentage of diagnostic CT evaluations in the BVS group (Group 1 - 94% vs. Group 2 - 76.19%, p = 0.0006). The diagnostic sensitivity analysis of CTA in ISR is presented in Table 4.

Plaque analysis was possible only in the BVS group with a post-processing research-dedicated software, Syngo.via Frontier, which identified the vulnerability markers presented in Table 5.

Patients from Group 1 presented in a greater percentage 1 (38.29%) or 2 (25.53%) vulnerability markers (Figure 2).

Morphological and virtual histology aspects of the analyzed coronary plaques in the BVS group are presented in Table 6.

Segment	BMS, n	<b>BMS</b> , %	BVS, n	<b>BVS</b> , %	p value
RCA proximal	9	14.29	1	2	0.0029
RCA mid	6	9.52	5	10	1.0
RCA distal	6	9.52	2	4	0.25
LAD proximal	9	14.29	11	22	0.66
LAD mid	14	22.22	13	26	0.61
LAD apical	1	1.59	2	4	0.36
LCX proximal	3	4.76	4	8	0.37
LCX mid	3	4.76	6	12	0.06
D1 proximal	6	9.52	3	6	0.59
D1 mid	0	0	1	2	_
MO1 proximal	3	4.76	0	0	_
MO2 mid	3	4.76	0	0	_
Intermediate	0	0	1	2	_
Left main	0	0	1	2	_
TOTAL	63	100	50	100	

TABLE 3. Stent location

	Diagno	Diagnostic CT		Non-diagnostic CT	
	n	%	n	%	
BVS	47	94	3	6	0.0006
BMS	48	76.19	15	23.8	0.0006

TABLE 4. ISR detection sensitivity of CTA

#### TABLE 5. CTA features of vulnerable plaques

	%
Positive remodeling	46.8
Spotty calcification	65.95
Napkin-ring	4.25
Low attenuation	19.14

In terms of significant hemodynamic ISR, CTA evaluation provides the most accurate results for the 3.0 and 3.5 mm devices. In 2.5 and 4.0 mm devices, the number of significant ISR diagnoses was zero. Regarding the sensitivity of CTA for ISR identification, the BVS group presented the smallest incidence of non-diagnostic CT evaluations (Figure 3).

#### DISCUSSIONS

Following the feasibility of CTA in diagnosing ISR in BMS vs. BVS as a primary endpoint, this study demonstrated a significant difference in the specificity of this imaging

**TABLE 6.** Plaque morphology and virtual histology composition- Group 1

	Mean value $\pm$ SD
Plaque length (mm)	17.45 ± 4.97
Stenosis (%)	22.37 ± 12.73
Eccentricity index	$0.43 \pm 0.26$
Remodeling index	1.03 ± 0.29
Vascular volume (mm³)	273.2 ± 87.42
Lumen volume (mm³)	119.8 ± 46.45
Plaque volume (mm³)	153.6 ± 65.0
Dense calcium (mm³)	17.48 ± 20.43
Dense calcium (%)	10.55 ± 11.92
Necrotic core (mm³)	136.4 ± 52.76
Necrotic core (%)	89.45 ± 11.92
Fibro-fatty (mm³)	11.07 ± 10.38
Fibro-fatty (%)	$6.83 \pm 5.66$
Fibrous (mm³)	125.1 ± 48.53
Fibrous (%)	82.56 ± 12.63
Calcium score – local	73.79 ± 80.19
Calcium score – target coronary artery	186.9 ± 207.5



FIGURE 2. Incidence of CTA markers of vulnerability

method, showing a higher accuracy for bioresorbable scaffolds compared with metallic coronary stents. The major advantage of BVS derives from its radiolucency properties. Moreover, the inclusion of the bioresorbable matrix in the vascular wall at 12–24 months after PTCA results in the loss of the initial mechanical resistance and lumen remodeling, with an increase in size.<sup>16</sup> Regarding metallic stents, it is a well-known fact that ISR is more common in small-diameter devices, the more so as the metallic struts are greater.

These findings are in line with data published by Oncel et al., which has shown that the visual CT analysis of 39 coronary stents, based on two independent radiologists, had a sensitivity of 89%, a specificity of 95%, and a positive predictive value of 90% compared to standard invasive angiography, these values being even much lower in case of devices with diameters below 2.75 mm.17 In a study conducted on 25 patients revascularized with metallic stents of 2.5 and 3.0 mm diameter, Rist et al. have shown that in this class of patients, the follow-up evaluation via CTA failed to detect the presence of asymptomatic intrastent occlusion in 17% of the cases.<sup>18</sup> However, another study, led by Graaf et al., using 320-slice CTA evaluation in 53 patients with 89 metallic stents in vessels with diameter under 3 mm and strut dimensions above 140 microns, demonstrated a reduced specificity of this method in assessing the incidence of ISR, due to significant reduction of image quality through metal artifacts.<sup>19</sup>

The most common causes for reconstruction errors in the CTA evaluation of metallic stents include the following: heart rate >65 bpm, which results in a larger number of cardiac cycles, a higher dose of irradiation in a time unit, and a loss of optimal spatial resolution due to motion artifacts, requiring the extension of acquisition over a larger number of cardiac cycles;<sup>20,21</sup> the so-called "blooming effect" of contrast reflection, which is more evident in small



FIGURE 3. A – ISR detection sensitivity of CTA in BMS of different dimensions; B – ISR detection sensitivity of CTA in BVS of different dimensions

diameter and large strut stents and is dimmed in stents with diameter above 3 mm;<sup>22,23</sup> stent composition: gold or gold-coated stents, as well as tantalum stents involve rough artifacts compared with steel or cobalt metallic stents.<sup>20</sup> Proximal stent distribution on LDA, LCX, or RCA allows a better visualization of contrast material in the lumen of the stent compared to more distal segments such as diagonal or obtuse marginal branches and distal LCX.<sup>23</sup>

A series of these technical obstacles disappear in bioresorbable scaffold reconstructions. Moreover, their diameter increases at 12–24 months after PTCA due to vascular remodeling as a result of matrix resorption and loss of rigidity, characteristic for these devices.

# CONCLUSIONS

The CTA evaluation of bioresorbable scaffolds is superior to metallic stent assessment, the latter being influenced by numerous sources of error dependent mainly on the presence of the metal structure. Noninvasive CT assessment is a fast and effective method compared to conventional invasive coronary evaluation, which is not a suitable screening technique due to the risks associated with the invasive nature of the procedure and the additional costs related to the need for post-interventional hospitalization for at least 24 hours.

# **CONFLICT OF INTEREST**

Nothing to declare.

#### ACKNOWLEDGEMENT

This research was supported via the research grant no. 103544/2016, contract number 26/01.09.2016, entitled

"Increasing the research capacity in the field of vulnerable plaque imaging, based on advanced nanoparticles, fusion imaging and computational simulation – PlaqueImage", financed by the Romanian Ministry of European Funds, the Romanian Government and the European Union.

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**ORIGINAL RESEARCH** 



# Malnutrition and Metabolic Changes in Patients with Type 2 Diabetes

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#### **ARTICLE HISTORY**

Received: August 19, 2018 Accepted: August 31, 2018

#### ABSTRACT

Background/Aim: In patients with type 2 diabetes (T2D), malnutrition has been recognized as a serious health problem mainly in hospitalized conditions, but there is little data regarding malnutrition outside hospital settings. The aim of this study was to evaluate the risk of malnutrition and associated metabolic changes in ambulatory patients with T2D. Material and methods: This analysis used data collected from 161 patients with T2D enrolled in a larger crosssectional study. Several anthropometric and metabolic parameters were obtained. Nutritional status was evaluated using the Controlling Nutritional Status (CONUT) score. Correlations between nutritional status and metabolic and anthropometric parameters of interest were examined. Results: Of all T2D patients, 29.8% had mild malnutrition (CONUT score 2-4). These patients presented lower triglyceride (124.8  $\pm$  42.3 mg/dL vs. 165.7  $\pm$  84.3 mg/dL, p <0.01) and LDL cholesterol concentrations ( $62.7 \pm 20.0 \text{ mg/dL}$  vs. 104.9  $\pm 30.6 \text{ mg/dL}$ , p <0.0001), higher leptin levels (10.2 [1.6–44.9] ng/mL vs. 7.3 [0.9–49.8] ng/mL, p < 0.05) and free leptin index (0.65 [0.04–2.88] vs. 0.36 [0.01–3.98], p <0.05) compared with patients with normal nutritional status. They also had higher total body adiposity. In patients with obesity, triglycerides levels were lower in those with mild malnutrition vs. those without malnutrition (mean difference: 27.26 mg/ dL, p <0.05). Serum C peptide/leptin ratio was higher in T2D patients with normal nutritional status without obesity, the differences being significant vs. the two groups with obesity (with or without malnutrition,  $0.71 \pm 0.53$ ,  $0.42 \pm 0.33$ , and  $0.49 \pm 0.68$ , respectively). HOMA-IR was lower in patients with normal nutritional status without obesity vs. those with obesity (mean difference: -0.7126, p <0.05), while in patients with mild malnutrition, HOMA-IR values were higher, but no differences were noted between the groups with or without obesity. Conclusion: In patients with T2D, malnutrition associated with lower triglycerides concentrations, even in the presence of obesity. Malnutrition and/or obesity associated with higher HOMA-IR, serum leptin levels and lower C peptide/leptin ratio.

Keywords: type 2 diabetes, malnutrition, metabolic parameters

# BACKGROUND

Malnutrition has emerged as a serious health issue, mainly in hospitalized patients, because it is associated with a poorer overall prognosis.<sup>1,2</sup> It occurs as a result of an inadequate diet with improper quantities and/or quality of nutri-
ents, malabsorption, or disease-related metabolic changes such as increased nutrient losses.<sup>3</sup> Malnutrition increases the risk of acute and chronic diseases, including osteoporosis or cardio-metabolic diseases, and alters the immune and muscular functions.<sup>4</sup> As a consequence, patients are at increased risk of infections or other complications such as impaired wound healing.<sup>5</sup> This might be particularly relevant for patients with type 2 diabetes (T2D), since they are already at increased risk of chronic complications due to hyperglycemia. In fact, both conditions can have serious health implications.

Some reports indicate that up to a third of T2D patients admitted to the hospital are malnourished, and this is associated with a longer hospitalization and a higher mortality risk.<sup>3,6</sup> On the other hand, diabetes has been identified as a risk factor for malnutrition in hospitalized patients.<sup>7</sup> However, there is little data regarding malnutrition in patients with T2D outside hospital facilities.

In this study we aimed to evaluate the risk of malnutrition and associated metabolic changes in ambulatory patients with T2D by using validated nutrition scores.

#### **MATERIAL AND METHODS**

#### Study population

This was an analysis of data obtained in a larger cross-sectional study that evaluated the role of leptin and leptin resistance in non-alcoholic fatty liver disease and in depression, in subjects with T2D. The study included adult patients with T2D, diagnosed according to the American Diabetes Association (ADA) criteria and older than 30 years of age.<sup>8</sup> Patients attended the Diabetes Outpatient Unit of the Emergency Clinical County Hospital of Tîrgu Mureş for regular checkups and were recruited in the study during 2017. Details regarding study participants, materials, and methods have been published previously.<sup>9</sup> The study was approved by the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureş, and all participants signed an informed consent before being enrolled.

Apart from demographic and clinical data (which included medical history, and measurement of blood pressure [BP] and pulse), several anthropometric parameters were also obtained by standard methods (weight, height, waist circumference, hip circumference, and four skinfolds that evaluated subcutaneous adipose tissue [subscapular, suprailiac, biceps, triceps]).

Several laboratory data were used in the analysis. Blood samples were collected after an overnight fast, in clot activator tubes (and aliquots stored at  $-80^{\circ}$ C for subsequent

analysis) and separately, on EDTA tubes for glycated hemoglobin (HbA1c) and complete blood count (CBC) analysis. The metabolic panel included blood glucose (measured by glucose-oxidase method), HbA1c (analyzed according to the DCCT-standardized and NGSP-certified [%] method, based on turbidimetric inhibition immunoassay), lipid profile (total cholesterol, high-density lipoprotein [HDL] cholesterol, triglycerides), C-peptide (measured by a competitive chemiluminescent enzyme immunoassay on Immulite 2000, Diagnostic Products Corporation, USA), serum leptin and soluble form of leptin receptor (sObR, measured by sandwich enzyme-linked immunosorbent assay [ELI-SA] on a DSX ELISA automated analyzer, Dynex Technologies, Inc. USA). Serum albumin was also measured on Cobas Integra 400 plus (Roche Diagnostic, Germany), together with HbA1c and lipids. The CBC was analyzed on a 5-differential hematology analyzer.

#### Calculations

Several metabolic and anthropometric parameters were calculated. Low-density lipoprotein (LDL) cholesterol concentrations were calculated with the Friedewald formula and the Free Leptin Index (FLI), basically an estimate of leptin resistance, by using the ratio of leptin and sObR values.<sup>10</sup> The Homeostasis Assessment Model (HOMA) calculator version 2.2.3 was used to estimate  $\beta$ -cell function (HOMA-B) and insulin resistance (HOMA-IR), by inputting fasting blood glucose and C-peptide values.<sup>11</sup> The waistto-hip ratio (WHR),  $\Sigma$ 4SF (the sum of 4 skinfolds), and the body mass index (BMI) were calculated. The percentage of body fat (BF) was estimated using the Durnin & Womersley and Siri equations.<sup>12</sup> The total body fat mass (TBFM) was calculated using the formula weight  $\times$  %BF/100, and the non-fat mass (NFM) by the difference between weight and TBFM. The daily resting energy expenditure (REE) was estimated using the Harris-Benedict formula.<sup>13</sup>

The nutritional status was evaluated with the widely used and validated Controlling Nutritional Status (CO-NUT) score, which employs a scoring system based on serum albumin levels, total cholesterol concentrations, and total lymphocyte count.<sup>14</sup> A total CONUT score of 0–1 points indicates a normal nutritional status, 2–4 points indicate mild malnutrition, 5–8 points are indicative of moderate malnutrition, while 9–12 points indicate severe malnutrition.<sup>14</sup> In addition, the Prognostic Nutritional Index (PNI) was calculated using the formula: 10 × serum albumin (g/dL) + 0.005 × total lymphocyte (count/µL).<sup>15</sup> A score of 38 or more is indicative of normal nutritional status and below 35 of severe malnutrition.<sup>15</sup>

# Statistical analysis

Descriptive statistics was calculated for all variables. They were expressed as mean  $\pm$  SD or median (min-max) (continuous variables) or as frequency (%) (categorical variables). Student's t-test, Mann-Whitney, ANOVA, or Kruskal-Wallis tests were used to compare means or medians between groups, and the Dunn or the Bonferroni posttests were employed to identify groups between which there were significant differences. Fisher's exact test was used for analysis of categorical variables. The correlations between variables were tested using Pearson's and Spearman's tests, respectively, and data are presented as r (95% confidence interval [CI]). The tests were two-tailed, and statistical significance was set at p <0.05. GraphPad InStat3 was employed for analysis.

# RESULTS

Data from 161 patients with T2D was analyzed and classified as having normal nutritional status (CONUT score 0–1 points) (70.2%) or mild malnutrition (CONUT score 2–4 points) (29.8%). No patient presented a CONUT score  $\geq$ 5 points. There were no differences with regards to age (63.4 ± 8.0 years vs. 65.9 ± 6.6 years), gender distribution (66.4% vs. 72.9% females) and diabetes duration (6.0

[0.0–21.0] years vs. 5.5 [0.0–27.0] years) between the two groups (p: NS for all). Their BP values (129.7  $\pm$  14.1/76.0  $\pm$  9.7 mmHg vs. 128.7  $\pm$  16.3/73.4  $\pm$  9.5 mmHg) and their pulse (74.7  $\pm$  11.5 b/min vs. 73.0  $\pm$  10.1 b/min) were similar (p: NS for all). The group with mild malnutrition according to the CONUT score also had significantly lower PNI values (52.3  $\pm$  4.5 vs. 55.0  $\pm$  3.6, p <0.0001).

## Metabolic data

The CONUT score correlated negatively with LDL cholesterol concentrations (-0.78, 95%CI -0.84 to -0.71, p <0.0001), triglycerides (-0.24, 95%CI -0.39 to -0.08, p <0.01) (Figure 1A), HDL cholesterol (-0.23, 95%CI -0.37 to -0.07, p <0.01), and C peptide/leptin ratio (-0.16, 95%CI -0.31 to 0.001, p <0.05) and positively with leptin (0.21, 95%CI 0.05 to 0.36, p <0.01), FLI (0.23, 95%CI 0.08 to 0.38, p <0.01), HOMA-B (0.17, 95%CI 0.02 to 0.33, p <0.05).

The correlations of PNI with metabolic markers were additionally studied in order to verify the results. The PNI score correlated positively with triglycerides (0.28, 95%CI 0.12 to 0.42, p <0.001) and negatively with leptin levels (-0.19, 95%CI -0.34 to -0.03, p <0.05) and FLI (-0.17, 95%CI -0.32 to -0.01, p <0.05).

TABLE 1. Metabolic parameters in patients with T2D with or without mild malnutrition

	CONUT score 0–1 (normal nutrition status) (n = 113)	CONUT score 2–4 (mild malnutrition) (n = 48)	p value
HbA1c (%)	6.4 (5.2–12.4)	6.5 (5.1–9.7)	NS
Fasting blood glucose (mg/dL)	138 (64–297)	136 (84–267)	NS
Total cholesterol (mg/dL)	175.7 (140.0–326.5)	128.1 (91.7–200.6)	< 0.0001
HDL cholesterol (mg/dL)	46.9 ± 13.0 44.5 (24.0-81.7)	43.5 ± 9.7 41.6 (27.2–66.0)	NS
Triglycerides (mg/dL)	165.7 ± 84.3 143.6 (47.7–434.9)	124.8 ± 42.3 119.8 (56.7–234.3)	<0.01
LDL cholesterol (mg/dL)	104.9 ± 30.6 99.7 (53.3–217.7)	62.7 ± 20.0 61.0 (27.5 –12.1)	<0.0001
C-peptide (ng/mL)	2.89 ± 1.34 2.67 (0.33–6.52)	3.17 ± 1.71 2.96 (0.29–7.06)	NS
HOMA-B (%)	70.5 ± 31.1	83.3 ± 38.5	< 0.05
HOMA-IR	2.52 ± 1.19 2.38 (0.45–5.92)	2.65 ± 1.42 2.4 (0.43–6.06)	NS
Leptin (ng/mL)	7.3 (0.9–49.8)	10.2 (1.6-44.9)	< 0.05
FLI	0.36 (0.01–3.98)	0.65 (0.04-2.88)	< 0.05
C-peptide/leptin ratio	2.91 (0.40-27.11)	3.40 (0.31-20.81)	NS
REE (kcal/day)	1,052.3 ± 198.1 1,080.2 (598.4–1,673.0)	1,121.9 ± 204.1 1,111.2 (592.6–1,821.8)	<0.05

FLI – free leptin index; REE – resting energy expenditure. Data are presented as mean ± SD and/or median (min-max)



FIGURE 1. CONUT score correlations with serum triglyceride levels (A) and total body fat mass (TBFM) (B). Data is presented as r (95%CI).

There were no significant differences between the two CONUT groups with regards to fasting blood glucose, HbA1c, or HDL cholesterol levels, but triglycerides and LDL cholesterol concentrations were lower in the mild malnutrition group (124.8  $\pm$  42.3 mg/dL vs. 165.7  $\pm$  84.3 mg/dL, p <0.01 and 62.7 ± 20.0 mg/dL vs. 104.9 ± 30.6 mg/dL, p <0.0001, respectively) (Table 1, Figure 2A). Additionally, although there were no significant differences between C-peptide concentrations  $(2.89 \pm 1.34 \text{ ng/mL vs.})$  $3.17 \pm 1.71$  ng/mL, p: NS), patients with mild malnutrition had higher HOMA-B values, as well as higher leptin (Figure 2B) and FLI values, indicative of higher leptin resistance (Table 1). However, when C-peptide values were divided with leptin values, the difference was no longer significant (p: NS) (Table 1). The two groups presented similar insulin resistance (HOMA-IR).

## Anthropometric data

The CONUT score correlated positively with weight (0.18, 95%CI 0.02 to 0.33, p <0.05), BMI (0.23, 95%CI 0.08 to 0.38, p <0.01), waist (0.26, 95%CI 0.11 to 0.41, p <0.001), hip circumference (0.23, 95%CI 0.07 to 0.37, p <0.01), %BF (0.16, 95%CI 0.004 to 0.31, p <0.05), TBFM (0.24, 95%CI 0.08 to 0.38, p <0.01) (Figure 1B), and  $\Sigma$ 4SF (0.19, 95%CI 0.04 to 0.34, p <0.05). The PNI correlated negatively only with the hip circumference (-0.17, 95%CI -0.32 to -0.01, p <0.05).

Although the total body weight and NFM were similar between the two groups, contrary to our expectations, T2D patients with mild malnutrition had higher BMI values ( $34.1 \pm 4.8 \text{ kg/m}^2 \text{ vs.} 32.2 \pm 5.0 \text{ kg/m}^2$ , p <0.01) (Figure 2C) and a higher proportion of them presented obesity

TABLE 2.	Anthropometric	parameters in	patients with	1 T2D with	or without m	ild malnutrition
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	CONUT score 0–1 (normal nutrition status) (n = 113)	CONUT score 2–4 (mild malnutrition) (n = 48)	p value
Weight (kg)	80.5 (55.5–136.5)	85.7 (62.0–157.0)	NS
BMI (kg/m²)	32.2 ± 5.0 31.8 (21.7–49.5)	34.2 ± 4.8 33.2 (25.8–49.6)	<0.01
Waist circumference (cm)	105.5 ± 11.1	109.8 ± 11.3	<0.05
Hip circumference (cm)	107.1 ± 9.0 106.0 (91.5–142.0)	110.4 ± 9.0 109.0 (97.0–142.0)	<0.05
WHR	0.98 ± 0.07	$0.99 \pm 0.06$	NS
%BF	41.4 (14.1–51.6)	42.3 (22.3–47.8)	NS
TBFM (kg)	31.4 ± 9.8	34.8 ± 8.4	<0.05
NFM (kg)	47.3 (34.8–83.5)	49.5 (35.9–102.4)	NS
Σ4SF (mm)	97.1 ± 28.4	104.8 ± 22.7	NS

 $BMI - body mass index; WHR - waist-to-hip ratio; %BF - % body fat; TBFM - total body fat mass; NFM - non-fat mass, <math>\Sigma$ 4SF - sum of four skinfolds Data are presented as mean  $\pm$  SD and/or median (min-max).



FIGURE 2. Serum triglyceride concentrations (A), serum leptin concentrations (B), and BMI (C) in patients with T2D with or without mild malnutrition. Data are presented as mean ± SE.

(87.5% vs. 60.2%, p <0.001). T2D patients with mild malnutrition had higher body adiposity (TBFM, waist and hip circumferences, p <0.05 for all) (Table 2).

# The impact of malnutrition and obesity on metabolic and anthropometric parameters

In order to better discern the impact of obesity and malnutrition on metabolic changes, we have further divided the two CONUT groups according to the presence of obesity (BMI < or  $\geq$  30 kg/m<sup>2</sup>) and have delineated four subgroups: normal nutritional status without obesity (Group 1) or with obesity (Group 2), and mild malnutrition without obesity (Group 3) or with obesity (Group 4).

There was a significant difference in triglyceride values between the four groups (p < 0.05, Table 3). Patients with obesity without malnutrition had significantly higher triglyceride concentrations than those with obesity

TABLE 3.	Metabolic and anthropometric variables in	T2D patients with/without obe	esity and with/without mild malnutritio	n, respectively

	Group 1 CONUT score 0–1 BMI <30 kg/m <sup>2</sup> (n = 45)	Group 2 CONUT score 0–1 BMI ≥30 kg/m² (n = 68)	Group 3 CONUT score 2–4 BMI <30 kg/m <sup>2</sup> (n = 6)	Group 4 CONUT score 2–4 BMI ≥30 kg/m² (n = 42)	p value
HbA1c (%)	6.3 (5.2–12.4)	6.5 (5.3–10.3)	6.0 (5.4–6.5)	6.5 (5.1–9.7)	NS
Fasting blood glucose (mg/dL)	138.0 (64.0–297.0)	138.5 (99.0–289.0)	128.5 (84.0–165.0)	136.0 (88.0–267.0)	NS
Triglycerides (mg/dL)	121.1 (47.7–434.8)	156.5 (65.1–375.5)*	98.4 (69.8–184.2)	120.4 (56.7–234.3)*	0.01
HDL cholesterol (mg/dL)	$49.6 \pm 14.4$	45.1 ± 11.8	40.1 ± 7.9	44.0 ± 9.9	NS
LDL cholesterol (mg/dL)	109.4 ± 28.5 <sup>\$\$</sup>	101.9 ± 31.8**	79.5 ± 24.8	60.5 ± 18.4 <sup>\$\$**</sup>	<0.0001
Leptin (ng/ml)	5.1 ± 3.7 3.8 (0.9–18.4)¶¶\$\$	11.6 ± 7.9 10.9 (2.3–49.8) <sup>11</sup>	9.2 ± 9.6 7.0 (1.6–27.5)	12.1 ± 7.9 10.4 (1.7–44.9) <sup>\$\$</sup>	<0.0001
FLI	0.24 ± 0.22 0.15 (0.01–1.18) <sup>¶¶\$\$</sup>	0.72 ± 0.6 0.58 (0.06-2.98)¶^^	0.25 ± 0.25 0.17 (0.04–0.69)^#	0.78 ± 0.6 0.71 (0.09–2.88) <sup>\$\$#</sup>	<0.0001
C peptide (ng/ml)	2.39 ± 1.11	3.22 ± 1.391	$3.01 \pm 1.80$	3.19 ± 1.73	<0.05
НОМА-В (%)	60.6 ± 26.0\$\$	77.0 ± 32.5	84.3 ± 21.6	83.2 ± 40.5 <sup>\$\$</sup>	<0.01
HOMA-IR	2.08 ± 0.991	2.80 ± 1.231	2.55 ± 1.52	2.67 ± 1.43	<0.05
C peptide/leptin ratio	0.71 ± 0.53 0.60 (0.06–2.49) <sup>1\$</sup>	0.42 ± 0.33 0.28 (0.04-1.4) <sup>¶</sup>	0.53 ± 0.41 0.47 (0.09–1.21)	0.49 ± 0.68 0.29 (0.05–3.19) <sup>\$</sup>	<0.01
REE (kcal/day)	913.5 ± 161.3 <sup>¶¶\$\$</sup>	1,144.2 ± 164.4¶^^	895.9 ± 162.8^^##	1,154.2 ± 189.7 <sup>\$\$##</sup>	<0.0001
Waist circumference (cm)	97.3 ± 7.0 <sup>11\$\$</sup>	110.9 ± 10.0 11^	97.8 ± 7.6^#	111.6 ± 10.8 <sup>\$\$#</sup>	<0.0001
Hip circumference (cm)	100.5 ± 5.111\$\$	111.5 ± 8.311^	100.0 ± 3.2^#	111.9 ± 8.6 <sup>\$\$#</sup>	<0.0001
TBFM (kg)	24.6 ± 6.211\$	35.9 ± 9.211^	25.1 ± 5.0^#	36.2 ± 7.9 <sup>\$\$#</sup>	<0.0001
NFM (kg)	44.6 (34.8–68.2)1	47.8 (40.2-83.5)1	42.5 (35.9–66.6)	49.8 (39.5–102.4)	<0.01
%BF	37.9 (14.1–45.5)***	43.1 (21.7–51.6)**	40.8 (22.3-42.2)	42.6 (24.0-47.8)\$\$	<0.0001
Σ4SF (mm)	$78.8 \pm 20.6^{11}$	109.2 ± 26.411^	82.8 ± 15.9^	107.9 ± 21.8 <sup>\$\$</sup>	<0.0001

FLI – free leptin index; REE – resting energy expenditure; %BF – % body fat; TBFM – total body fat mass; NFM – non-fat mass; 24SF – sum of four skinfolds. Data are presented as mean ± SD and/ or median (min-max).

Group 2 vs. Group 4: p < 0.05; \*\* Group 2 vs. Group 2 vs. Group 4: p < 0.001; \*\$ Group 1 vs. Group 4: p < 0.001; \*\$ Group 1 vs. Group 2 vs. Group 2 vs. Group 3: p < 0.05; \* Group 3 vs. Group 4: p < 0.05; <sup>1</sup> Group 1 vs. Group 2: p <0.05; <sup>\$</sup> Group 1 vs. Group 4: p <0.01; <sup>##</sup> Group 3 vs. Group 4: p <0.01; <sup>^^</sup> Group 2 vs. Group 2: p <0.01



**FIGURE 3.** Differences in triglyceride concentrations (**A**), C-peptide/leptin ratio (**B**), HOMA-IR (**C**), and C-peptide (**D**) values in the four groups of patients with T2D: Group 1 – without malnutrition and without obesity; Group 2 – without malnutrition and with obesity; Group 3 – with mild malnutrition and without obesity; Group 4 – with mild malnutrition and with obesity. Data are presented as mean  $\pm$  SE.

and mild malnutrition (mean difference: 27.26 mg/dL, p < 0.05) (Figure 3A). There were also significant differences between the four groups with regards to FLI and several anthropometric parameters (Table 3), but this mostly reflected the presence of obesity. Serum leptin levels and HOMA-B were lower in T2D patients with normal nutritional status without obesity, while the C-peptide/ leptin ratio was higher, the differences being significant vs. groups 2 and 4 (with obesity) (Table 3, Figure 3B). Serum C-peptide concentrations and HOMA-IR were lower in T2D patients with normal nutritional status without obesity vs. those with obesity (mean difference: -26.749 ng/ mL and -0.7126, respectively, p <0.05 for both), indicating higher insulin resistance in this group (Group 2), while in patients with mild malnutrition, the respective values were higher, but no differences were noted between the groups with or without obesity (Group 3 vs. Group 4) (Table 3, Figure 3C and 3D).

## DISCUSSION

This study evaluated the nutritional status of adult ambulatory patients with T2D by using the CONUT score, an index that reflects the immune function and nutritional status of the body and that has been mainly used in cardiovascular, hepatic, and oncologic diseases so far.

The first finding of this study was that about a third of outpatients with T2D have mild malnutrition. Other studies also indicated an increased prevalence of malnutrition and malnutrition risk in patients with T2D, mainly elderly inpatients.<sup>3,16,17</sup> The causes may be multiple. Advanced age or the presence of chronic complications, mainly diabetic nephropathy, have been shown to be associated with malnutrition.<sup>17,18</sup> T2D patients with diabetic nephropathy/ chronic kidney disease (CKD) may follow a diet with decreased protein intake as part of their disease management and on the other hand, CKD associates with elevated protein catabolism and protein malnutrition.<sup>19,20</sup>

Another observation in this analysis was that malnutrition was present even in patients with obesity. Usually, malnutrition is associated with underweight/weight loss, but certain features of malnutrition can occur even in subjects with higher BMI. One of the studies mentioned above indicated that 15% of malnourished T2D patients were obese.<sup>17</sup> Although at first sight this might be surprising, in fact, obesity and malnutrition are not reciprocally exclusive. A study in a large population of critically ill adults has demonstrated that obese patients with malnutrition had poorer outcomes than obese patients without malnutrition.<sup>21</sup> In fact, it has been recognized that poor diets may provide sufficient energy to meet or even exceed the needs, but may lack the quality required for an optimal health status, and may associate with subclinical nutrient deficiencies.<sup>22</sup> Actually, excessive body fat may hide sarcopenia and/or altered immune function and induce false clinical judgment. Moreover, obesity and diabetes may be associated with micronutrient deficiencies, such as thiamine, vitamin D, zinc, chromium etc., that play a role in glucose metabolism, insulin secretion, and signaling pathways.<sup>23</sup> Therefore, T2D patients with obesity should be evaluated for malnutrition as well.

We found that T2D patients with malnutrition had significantly lower triglycerides, even in the presence of obesity. Another study in elderly hypertensive subjects that used the CONUT scoring system to evaluate the nutritional status reported similar results: triglyceride concentrations decreased with malnutrition severity.<sup>24</sup> In both studies, patients with malnutrition also had lower LDL cholesterol levels.<sup>24</sup> It could be argued however, that since the CONUT score uses total cholesterol values as a parameter for scoring, the findings could be biased. In a different study that evaluated the nutritional status of patients with acute myocardial infarction by using the PNI, the authors similarly reported that patients with malnutrition had lower levels of serum triglycerides.<sup>25</sup> The causes are not entirely clear, but it is possible that in malnutrition there is an impairment in the body's ability to mobilize substrates, including triglycerides, and/or substrate malabsorption.

In addition, we found that patients with mild malnutrition had higher HOMA-B, serum leptin concentrations and leptin resistance, but this could be related to higher body adiposity observed in this group. In order to decipher the role of obesity, the data was further analyzed according to both malnutrition and obesity status. In T2D patients with normal nutritional status, obesity was associated with higher insulin resistance, serum C-peptide, and leptin levels, and lower C-peptide/leptin ratio. Patients with mild malnutrition had higher values of HOMA-IR, serum C-peptide, and leptin concentrations, and lower C peptide/leptin ratio, but there were no significant differences between those with and without obesity, suggesting that malnutrition per se may be associated with these changes. Animal data showed that chronic malnutrition is associated with insulin resistance, both through receptor and post-receptor defects.<sup>26,27</sup> There is limited data in humans in this regard.

The study had several limitations. First, it was a single center evaluation, with relatively low number of patients with mild malnutrition (mainly the subgroup without obesity). Moreover, no patient presented more severe degrees of malnutrition, which would have been helpful to better understand the metabolic changes associated with this condition. Second, it was a cross-sectional study, and the collection of prospective data would certainly add value. Third, perhaps different methods of nutritional assessment should be further employed in order to validate the results.

## CONCLUSIONS

According to our results, in T2D patients, malnutrition is associated with lower triglyceride levels, even in the presence of obesity, and malnutrition and/or obesity is associated with higher HOMA-IR and serum leptin levels, and lower C peptide/leptin ratio.

## **CONFLICT OF INTEREST**

Nothing to declare.

## ACKNOWLEDGEMENTS

This work was supported by the University of Medicine and Pharmacy of Tîrgu Mureş Internal Research Grant (number 275/2/11.01.2017).

The laboratory analyses were done with the technical support of the Center for Advanced Medical and Pharmaceutical Research, University of Medicine and Pharmacy of Tîrgu Mureş, Romania.

The authors thank Liliana Demian, Adina Huţanu, Ştefan Barbu, Mirela Pasztor, and Maria Mureşan for their valuable technical assistance.

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**ORIGINAL RESEARCH** 

PROSTHODONTICS // ORAL AND MAXILLOFACIAL SURGERY

# Knowledge and Attitude of Dentists Regarding Patients Undergoing Bisphosphonate Treatment: a Comparative Questionnaire

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#### **ARTICLE HISTORY**

Received: June 12, 2018 Accepted: July 28, 2018

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## ABSTRACT

Background: Osteonecrosis of the jaw is an uncommon but serious complication related to oral and intravenous bisphosphonate (BP) therapy. Its pathogenesis is not well understood, and there are no universal protocols accepted to treat it. The **aim** of our study was to use the same guestionnaire as four years ago to evaluate the awareness of dentists in Tîrgu Mures regarding the dental treatments that can be applied in patients on BP therapy, and to assess how their knowledge on the subject has evolved over these years. Material and method: We used the same questionnaire-based study as four years ago among dentists in Tîrgu Mures, raising important issues such as: is the patient asked about current or previous treatments with BPs, do they perform surgical treatment in these patients, do they know under what conditions they can perform this treatment, or do they deem it necessary to contact the prescriber before surgical treatment. Results: One-hundred twenty questionnaires were returned. The majority of respondents (n = 113, 94.2%) included the question regarding the use of BPs in their medical records. Of all respondents, 48 (40%) perform dental or surgical treatments on patients undergoing BP therapy, 68 (56.7%) do not perform dental or surgical treatments on these patients, and four of the respondents (3.3%) did not know the answer. One hundred (83.3%) respondents always contact the prescriber prior to surgery in these patients, regardless of how BPs are administered. Conclusions: According to the findings of the present study, many of the respondent doctors have heard about BPs and their complications, but they are not aware of the fundamental concepts of bisphosphonate-related osteonecrosis of the jaw prevention and treatment protocols. In the absence of appropriate protocols, the quality of life of these patients is compromised.

Keywords: osteonecrosis, jaw, bisphosphonates, surgery, quality of life

# INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is an uncommon but serious complication, reported for the first time by Marx in 2003.<sup>1</sup> BRONJ is defined as necrotic bone exposed in the maxillofacial region for at least eight weeks with no signs of healing in patients treated with bisphosphonates (BPs) and without head and neck radiation therapy in the present or the past.<sup>2</sup> BPs are used in the treatment of Paget's disease, multiple myeloma, as well as osteolytic lesions associated with bony metastases and is the most prescribed therapy against osteoporotic pathology.

Due to the fact that BPs are not metabolized and accumulate in the bone, the osteoclastic activity is interrupted by other inhibitors, such as denosumab and bevacizumab, and under conditions of bone trauma, the osteonecrosis of the jaw is likely to be triggered. The uncontrolled therapeutic effect of monoclonal antibodies and BPs in reducing osteoclast function may lead to osteonecrosis when a critical limit of at least 50% of the total cell mass is reached.<sup>3</sup>

Various studies attempted to elucidate why BP treatment complications, such as inhibition of angiogenesis and apoptosis of osteoclasts, inhibition of bone remodeling and bone turnover, inflammation, infection, or the vast variety of microorganisms in the oral flora, occur only at the level of the oral cavity.<sup>4–10</sup>

The actual incidence of BRONJ is uncertain; it depends on treatment indication, sample size, and the studied population, and varies from 0.028% to 18.6%.<sup>11,12</sup>

Administering BPs via the intravenous route has a higher risk of developing BRONJ, although oral treatment longer than three years may also increase this risk.<sup>2</sup>

A frequent trigger factor is represented by dentoalveolar procedures in patients undergoing intravenous BP treatment. They are at least seven times more likely to develop osteonecrosis of the jaw than those who underwent intravenous BP treatment but are not subject to dentoalveolar surgery.<sup>13</sup>

Our study is focused on BRONJ, although other medications (denosumab, bevacizumab, cabozantinib, sunitinib) have also been associated with jaw osteonecrosis in 2014 by the special committee of American Association of Oral and Maxillofacial Surgeons (AAOMS), who called this condition medication-related osteonecrosis of the jaw (MRONJ).<sup>14</sup>

In 2014, we carried out a questionnaire-based study among dentists in Tîrgu Mureş.<sup>15</sup> At present, in June 2018, we intended to use the same questionnaire and assess how the dentists' knowledge regarding dental treatments in patients with current or previous BP therapy has evolved over these four years.

## **MATERIAL AND METHOD**

In June 2018, we carried out a questionnaire-based study among dentists in Tîrgu Mureş. The questionnaire consisted of the same 13 questions included in the previous study, conducted in 2014.

A total of 26 questionnaires were handed personally to clinicians within the Faculty of Dentistry of Tîrgu Mureş, and the others were sent to dental practitioners using social networks. The respondents were dentists, residents, and specialists, who were asked to choose one of the answers for every question. We asked whether the respondents were residents or medical specialists in a branch of dentistry. We also asked whether they had knowledge about BPs and whether they deem it necessary to ask their patients about current or previous BP treatments.

We considered it important to ask whether the respondents knew that they performed dental treatments/dentoalveolar surgery in patients who are/were treated with BPs and whether they know under what conditions they can perform tooth extractions or other dentoalveolar surgical treatments in patients treated with BPs.

An important aspect of the questionnaire was whether the respondents contacted the prescriber before performing a tooth extraction or dentoalveolar surgical treatment on a patient.

Statistical analysis was not carried out, as it was considered that it would not be helpful due to the large number of variants.

## RESULTS

The questionnaires were completed and returned by 120 respondent clinicians. The results are presented and compared with those from the 2014 study in Table 1.

## DISCUSSIONS

In the last years, the number of BRONJ cases reported in the literature has increased.<sup>16–19</sup> As far as we know, no study has been conducted in Romania yet to investigate the degree of dentists' knowledge about BRONJ.

The present study was developed in order to evaluate the awareness of dentists in Tîrgu Mureş using the same questionnaire we used four years ago, and to determine whether their knowledge regarding BRONJ has improved in these four years.

No.	Question	Answers	Responses from 2014, 70 respon- dents	Responses from 2018, 120 respon- dents
1.	For how long have you been practicing dentistry?	a) less than three years b) three-six years c) more than six years	a) 27.14% b) 32.86% c) 40%	a) 35% b) 26.66% c) 38.34%
2.	Are you a resident doctor in a branch of den- tistry?	<ul><li>a) no</li><li>b) resident in dentoalveolar surgery/maxillofacial surgery</li><li>c) other branches, please specify</li></ul>	a) 77.14% b) 7.14% c) 15.72%	a) 90% b) 4.17% c) 5.83%
3.	Do you have a specialty in a branch of den- tistry?	<ul><li>a) no</li><li>b) specialty in dentoalveolar surgery/maxillofa- cial surgery</li><li>c) other branches, please specify</li></ul>	a) 47.37% b) 15.79% c) 36.84%	a) 69.17% b) 13.33% c) 17.5%
4.	Have you heard about bisphosphonate treat- ment?	a) no b) yes	a) 17.14% b) 82.86%	a) 3.33% b) 96.67%
5.	Do you know in which pathology/pathologies is this treatment recommended?	a) no b) yes, please specify	a) 25.71% b) 74.29%	a) 5.83% b) 94.17%
6.	Do you ask about treatments with bisphospho- nates while completing the patient's medical history?	a) no b) yes c) not relevant in dentistry practice	a) 38.57% b) 60% c) 1.43%	a) 5.83% b) 94.17% c) 0%
7.	Have you performed dental treatments/ dento- alveolar surgery on a patient who was under/ has received bisphosphonate treatment?	a) no b) yes c) I do not know	a) 42.85% b) 34.29% c) 22.86%	a) 56.67% b) 40% c) 3.33%
8.	Do you know whether complications of bisphosphonate treatment occur only in the oral cavity or in other parts of the body as well?	a) no b) yes	a) 41.43% b) 58.57%	a) 20.83% b) 79.17%
9.	Do you know what kind of manifestations occur in the oral cavity after treatment with bisphos- phonates?	a) no b) yes	a) 25.71% b) 74.29%	a) 15.83% b) 84.17%
10.	Do you know under what conditions you can perform tooth extractions or other dentoalveo- lar surgical treatments on patients treated with bisphosphonates?	a) no b) yes c) not relevant in dentistry practice	a) 48.57% b) 50% c) 1.43%	a) 11.67% b) 85% c) 3.33%
11.	Do you contact the prescriber before surgery in a patient that needs a tooth extraction or other dentoalveolar surgery and is under bisphos- phonate treatment?	a) no b) yes c) not relevant in dentistry practice	a) 12.86% b) 85.71% c) 1.43%	a) 10% b) 86.67% c) 3.33%
12.	Do you think there are differences between the complications that occur after treatment with bisphosphonates administered intravenously or orally?	a) no b) yes	a) 40% b) 60%	a) 34.17% b) 65.83%
13.	Do you contact the prescriber before surgery in a patient who needs a tooth extraction or other dentoalveolar surgery and is under bisphos- phonate treatment administered intravenously or orally?	<ul> <li>a) I do not contact the prescriber</li> <li>b) I contact the prescriber only in case of oral administration</li> <li>c) I contact the prescriber only in case of intravenous administration</li> <li>d) I always contact the prescriber</li> </ul>	a) 12.86% b) 0% c) 4.28% d) 82.86%	a) 11.67% b) 0% c) 5% d) 83.33%

#### TABLE 1. Comparison between questionnaire response distribution in 2018 vs. 2014

The majority of respondents (38.34%) had a dental practice for more than six years, and most of them (96.67%) heard about BP therapy, representing a 13.81% increase compared to the responses received in 2014. Regarding the pathologies recommended to be treated with BPs, most of the respondents (15.7%) mentioned osteoporosis, 5.8% bone tumors, 4.1% bone metastases, and 1.65% mentioned chemotherapy. None of the respondents were aware of the use of BPs in the treatment of Paget's disease. In the 2014 study, 5.81% knew about Paget's disease and multiple myeloma, and they recognized osteoporosis as the main pathology to benefit from these drugs in a higher

percentage (55.82%). None of the dentists who responded to the questionnaire in 2014 and 2018 knew about the usage of BPs in the treatment of malignant hypercalcemia and osteogenesis imperfecta. Dentists should know the mechanism of action of BPs due to their adverse effects: bone turnover is reduced, and the function of osteoclasts is inhibited, which leads to the reduction of bone remodeling.<sup>2,20</sup> The consequent necrosis of bone cells appears due to the inhibition of angiogenesis, another mechanism of action of BPs.<sup>2,5,14</sup> The dentists' knowledge will influence the attention given to the patient, the way they draw up the patients' medical file, whether they ask about or recognize the medication. The majority of the respondents (94.17%) ask about a possible treatment with BPs while completing the patients' medical history. This is a step forward for the early identification of possible complications, especially as there is a significant increase from the 2014 questionnaire, where only 60% of the respondents had this question in their anamnesis.

In question number seven, a small percentage (3.33%) of respondents did not know if they performed surgical or dental treatments in patients who are/were treated with BPs. This percentage decreased compared to 22.86% obtained in the 2014 questionnaire.

A percentage of 20.83% said they do not know if BP treatment complications occur only in the mouth. Dentists should be aware of the manifestations of BRONJ and their preferred area of occurence. BRONJ is more common in the posterior mandible than the maxilla, in a ratio of  $2:1.^2$ 

It is critical for dentists to be prepared to treat these patients appropriately. Dentoalveolar surgeries represent the main local risk factors for BRONJ, especially tooth extraction acts as a trigger point in the development of BRONJ. Periodontal diseases and denture use are also considered potential risk factors.<sup>2,14</sup>

Our study revealed that 11.67% of the respondents do not know under what conditions they can perform tooth extractions or other dentoalveolar surgical treatments on patients treated with BPs, and 3.33% considered the subject is not relevant for dentistry practice.

Besides dental procedures, BRONJ is related to trauma to the mouth caused by incorrectly adjusted prostheses, oral infection, poor oral hygiene, diabetes, and smoking.<sup>9,21-24</sup>

The percentage of respondents who contact the prescribing physician before carrying out a tooth extraction or other dentoalveolar surgery in a patient with BP treatment was similar in 2014 and 2018, 85.71% and 86.67% respectively. About one-third of the respondents, 34.17%, said there is no difference between the oral or intravenous administration of BPs, but according to studies, the route of administration affects the skeleton differently. Oral BPs are poorly absorbed and present less than one percent of bioavailability, whereas BPs administered intravenously have maximum bioavailability.<sup>25</sup>

A large part of respondents, 100 from a total of 120 (83.33%), answered that they always contact the prescriber before dentoalveolar surgery in patients treated with BPs. The result is similar to the one from the 2014 questionnaire (82.86%). The percentage of those who never contact the prescriber before dental surgery has decreased only slightly, from 12.86% in 2014 to 11.67% in 2018, and due to these unsupervised procedures, the patients' quality of life is compromised.

#### CONCLUSIONS

According to the findings of the present study, many of the respondent dentists have heard about BPs and related complications, but they are not aware of the fundamental concepts of BRONJ prevention and treatment protocols. Despite the limited size of the studied sample, the data are enough to affirm that the dentists' knowledge about BRONJ and the treatment of patients undergoing BP therapy improved over four years, but there are still many unknowns. The literature reveals many unknowns in the pathogenesis of the disease, and universal protocols are not established. Without appropriate protocols for prevention and treatment, the patients' quality of life is affected. Dentists should be more prepared regarding the treatment of these patients and they should be aware that conservative attitudes are the most suitable for patients with a history of BP treatment. A complete medical history of the patient must be recorded carefully, and the treatment should be analyzed after contacting the prescriber. Therefore, practical initiatives, such as lectures and workshops at conferences, or even flyers, should be taken seriously, to help strengthen knowledge in this domain. Preventing or minimizing the occurrence of BRONJ must be known among doctors who prescribe BPs, such as oncologists, endocrinologists, hematologists (referring patients to the dentist before starting a BP treatment), but to the same extent by maxillofacial surgeons or dentists whom the patient are addressing.

## **CONFLICT OF INTEREST**

The authors declare no conflict of interests.

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**ORIGINAL RESEARCH** 



RHEUMATOLOGY // CARDIOLOGY

# Impact of Pulmonary Arterial Hypertension on Left Ventricular Function – a Comparative Study between Scleroderma and Coronary Artery Disease

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#### **ARTICLE HISTORY**

Received: August 7, 2018 Accepted: September 3, 2018

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## ABSTRACT

Background: The impact of pulmonary arterial hypertension (PAH) on left ventricular performance in patients with scleroderma is still unknown. This study aims to perform a comparative echocardiographic analysis of left ventricular function between two different etiological varieties of PAH, namely PAH caused by systemic sclerosis as a representative of systemic inflammatory diseases and PAH caused by myocardial ischemia. Material and method: We conducted a prospective observational study on 82 patients, of which 36 were with documented PAH, with the systolic pressure in the pulmonary artery above 35 mmHg, and 46 were patients with normal pulmonary artery pressure. The study population was divided into two groups, based on the etiology of PAH: group 1 included patients diagnosed with scleroderma (n = 48); group 2 included patients with coronary artery disease (n = 35). Patients from each group were divided into two subgroups based on the diagnosis of PAH: subgroup 1A – subjects with scleroderma and associated PAH (n = 20); subgroup 1B - subjects with scleroderma without PAH (n = 28); subgroup 2A – ischemic patients with associated PAH (n = 16); and subgroup 2B – patients with ischemic disease without PAH (n = 19). Results: A significant difference between LVEF values in patients with PAH versus those without PAH in the ischemic group (p = 0.023) was recorded. Compared to scleroderma subjects, ischemic patients presented significantly lower values of LVEF in both PAH and non-PAH subgroups (p <0.0001 and p <0.0001, respectively). Linear regression analysis between sPAP and LVEF revealed a significant negative correlation only for the ischemia group (r = -0.52, p = 0.001) and the scleroderma 2B subgroup (r = -0.51, p = 0.04). Tissue Doppler analysis of left ventricular function revealed a significant impact of PAH on left ventricular diastolic performance in the ischemic group. Conclusions: Compared to patients with coronary artery disease, those with scleroderma present a less pronounced deterioration of LVEF in response to pulmonary arterial hypertension.

Keywords: pulmonary arterial hypertension, scleroderma, LVEF, coronary artery disease

## INTRODUCTION

Pulmonary arterial hypertension (PAH), defined as an increase in the average pulmonary artery pressure above 25 mmHg, is triggered and maintained by a series of pathological changes based on vascular remodeling and vasoconstriction resulting from inflammatory phenomena and fibrosis, all of which ultimately result in increased pulmonary vascular resistance.<sup>1</sup> A number of studies have advocated for the inflammatory pathogenesis of this pathology, identifying proinflammatory cytokines such as interleukins, alpha tumor necrosis factor, and certain antibodies as promoters of PAH.<sup>2,3</sup>

The vascular remodeling process, invariably followed by increased pressure in the right side of the heart, ultimately leads to a series of constant changes in the right cavities, characterized by the appearance of right atrial remodeling, right ventricular hypertrophy, and tricuspid regurgitation. The association of this condition with myocardial ischemia or ventricular fibrosis leads to the development of right heart failure. Therefore, PAH resulting from the remodeling of distal pulmonary vessels leads invariably to death caused by advanced right heart failure.

Clinically, the PAH patient is generally oligosymptomatic until later stages, presenting progressive fatigue and progressive dyspnea or palpitations, which are unspecific and often overlooked. Symptoms that should raise alarm signals are syncope caused by exertion, or angina occurring as a result of left ventricular insufficiency. Clinical examinations identify in most cases the signs caused by increased pressure in the right cavities: low pulse pressure, painful hepatomegaly associated with hepatojugular reflux, turgescent jugular veins, ascites, and peripheral edema.<sup>4,5</sup>

The World Health Organization (WHO) classifies PAH in 5 etiological subgroups, as follows: subgroup 1 – idiopathic or familial PAH; subgroup 2 – PAH caused by left heart failure (systolic, diastolic or valvular); subgroup 3 – PAH caused by respiratory diseases evolving with pulmonary fibrosis, including bronchial asthma, pulmonary emphysema, chronic obstructive bronchopneumonia; subgroup 4 – PAH caused by chronic pulmonary thromboembolism; subgroup 5 – unclear or multifactorial pathogenetic mechanisms.<sup>6</sup> At the same time, a pulmonary etiology has been described in the literature, caused by left ventricular insufficiency, as the main cause for most cases of PAH.<sup>7</sup>

PAH is a frequent complication of several systemic autoimmune disorders such as scleroderma, studies showing that approximately 8–12% of patients with systemic sclerosis develop different degrees of PAH during the course of the disease.<sup>8–10</sup> Furthermore, the resulting PAH is associated with a significantly higher rate of complications and death compared to patients with other etiological forms of PAH, including those with idiopathic PAH.<sup>11–13</sup> PAH in scleroderma occurs as a consequence of the progressive remodeling of distal lung vessels. Progression mechanisms are incompletely known, but common precursors are considered to be represented by endothelial inflammation and dysfunction, which ultimately determines a progressive increase in pulmonary vascular resistance and pulmonary arterial pressure, leading to pressure overload in the right chambers.<sup>14</sup>

Left heart failure caused by ischemic coronary artery disease (CAD) is characterized by increased influx pressures in the left cavities, either due to alteration of the diastolic function or due to mitral valve insufficiency, which in turn causes post-capillary pulmonary hypertension or venous hypertension. This complex pathogenetic mechanism leads to dysfunction of the vascular endothelium and pulmonary vascular remodeling, which will inevitably lead to changes similar to those seen in patients with primary arterial pulmonary hypertension.<sup>15–17</sup> The impairment of left ventricle systolic function in patients with scleroderma is a controversial issue in the literature, several studies identifying a reduced number of subjects with decreased left ventricular contractility.<sup>18</sup> However, the left myocardium is frequently characterized by piecemeal fibrosis, secondary to both ischemia and immune inflammatory phenomena, which invariably leads to the alteration of diastolic function and, to some extent, also influences the systolic performance of the left heart.<sup>19,20</sup> Regarding the alteration of diastolic function in myocardial ischemia, it is known that it leads to the alteration of myocardial relaxation, which is reversible by myocardial revascularization in the initial phase, but becomes permanent in the post-myocardial infarction phase, when an altered relaxation pattern appears in relation to the ventricular remodeling processes.<sup>21</sup>

This study aims to perform a comparative echocardiographic analysis of left ventricular function between two different etiological varieties of PAH, namely PAH caused by systemic sclerosis as a representative of systemic inflammatory diseases and PAH caused by myocardial ischemia.

## **MATERIAL AND METHOD**

We conducted a prospective observational study on 82 patients, of which 36 were patients with documented PAH, with a systolic pressure in the pulmonary artery above 35 mmHg, and 46 were patients with normal pulmonary artery pressure.

All patients were examined by 2D, Doppler, and tissue Doppler transthoracic echocardiography, and the following parameters were assessed: (a) for left heart cavities: left ventricular ejection fraction (LVEF), left atrium diameter, LV end-systolic/diastolic diameter, E/A ratio, DT, tissue Doppler (e' septal and e' lateral); (b) for right heart cavities: systolic pulmonary artery pressure (sPAP). Images were obtained from parasternal, apex, and subcostal views. The noninvasive assessment of sPAP was determined based on the peak velocity of the continuous Doppler tricuspid regurgitation wave, followed by the Bernoulli equation and adding the estimated right atrial pressure. Valvular regurgitation was evaluated using the Doppler color function. The LVEF was evaluated using the Simpson formula based on two-dimensional LV images during systole and diastole from apical views of 4 and 2 chambers. Mitral valve flow assessment was performed to quantify the following parameters: maximum velocity of early diastolic filling (E), maximum velocity of late diastolic filling by atrial contraction (A), and deceleration time of the E wave (DT). Tissue Doppler analysis was performed at the level of the mitral annulus, from apical 4 chambers view, to assess early diastolic velocity at the lateral ring (E' lateral) and early septal diastolic velocity (E' septal). All measurement values were obtained as an average of more than 3 heart cycles. All echocardiographic examinations were performed with a Vivid E9 echocardiographic equipment (General Electric Vingmed Ultrasound, Horten, Norway).

Statistical analysis was performed using the GraphPad Prism 7 software. To test the distribution of numerical data, the D'Agostino Pearson normality test was used; numerical data was expressed as mean  $\pm$  standard or median deviation when appropriate, and qualitative data was expressed as numerical value and percentage. The Spearman or Pearson coefficient was used to illustrate linear correlation and regression analysis. The t test was used for the analysis of the two groups regarding non-pair continuous variables. The specific variables were compared using the chi-square test, and a p value below 0.05 was considered statistically significant.

This study was conducted in accordance with the revised version of the Helsinki Declaration. The study was conducted under the approval of the Ethics Commission of SCJU Tîrgu Mureş No. 17345/09.07.2018. Written informed consent was obtained from each patient prior to enrolment.

The study population was divided into two groups, based on the etiology of PAH: group 1 included patients diagnosed with scleroderma (n = 48); group 2 included patients diagnosed with CAD (n = 35). Patients of each group were divided into two subgroups based on the diagnosis of PAH: subgroup 1A – subjects with scleroderma associated with PAH (n = 20); subgroup 1B – subjects with scleroderma without PAH (n = 28); subgroup 2A – ischemic patients with associated PAH (n = 16); and subgroup 2B – patients with ischemic disease without PAH (n = 19).

## RESULTS

#### General characteristics of the study population

From 82 study patients, 48 presented scleroderma (58.53%), and 35 (42.68%) presented CAD. In total, 36 patients were diagnosed with PAH, of which 20 (subgroup 1A – 41.66%) with scleroderma and 16 (subgroup 2A – 45.71%) with myocardial ischemia. There were no significant differences between groups regarding the body mass index (BMI, p =0.8), or chronic tobacco use (p = 0.7). However, patients in the first group presented a significantly higher number of female subjects (p = 0.001) and a higher mean age (p =0.009) compared to group 2 (Table 1).

## LVEF and PAH

We found no statistically significant differences between the subgroups of scleroderma patients in terms of LVEF (p = 0.2182). However, there was a significant difference between LVEF values in patients with PAH versus those without PAH in the ischemic group (p = 0.023) (Figure 1). Moreover, when compared to subjects with scleroderma, ischemic patients presented significantly lower values of LVEF in both the PAH and the non-PAH subgroups (p<0.0001 and p <0.0001, respectively) (Figure 2). Linear regression analysis between sPAP and LVEF revealed a significant negative correlation only for the ischemia group (r = -0.52, p = 0.001) and the scleroderma 2B subgroup (r = -0.51, p = 0.04) (Table 2).

#### **Tissue Doppler analysis of left ventricular function**

Regarding the results of tissue Doppler measurements, a significant negative correlation was obtained between the

TABLE 1. Ge	eneral chara	cteristics	of the	study	population
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	Scleroderma	CAD	p value
Age (years)	49.7 ± 6.4	57.5 ± 5.3	0.009
Female gender	67%	37%	0.001
BMI	24.7	25.6	0.8
Smoking	40%	45%	0.7



FIGURE 1. LVEF in patients with PAH vs. patients without PAH in the scleroderma group (A) and in the ischemic group (B)



FIGURE 2. LVEF in the scleroderma group vs. the ischemic group in patients with PAH (A) and without PAH (B)

septal E' value and the sPAP value for the main group of ischemic patients (r = -0.52, p = 0.0013). In the ischemic group, we found a negative correlation between the septal E' value and the sPAP (r = -0.44, p = 0.08) for the PAH subgroup and a positive correlation (r = 0.08, p = 0.85) for the 2B subgroup, both without statistical significance.

**TABLE 2.** Correlations between sPAP and LVEF in the studygroups and subgroups

Group	r	p value
Scleroderma	O.11	0.43
Ischemia	-0.52	0.001
Scleroderma and PAH	-0.26	0.15
Scleroderma without PAH	-0.51	0.04
Ischemia and PAH	-0.45	0.08
Ischemia without PAH	-0.37	O.11

Among patients with scleroderma, a weak positive correlation between E' lateral and sPAP was obtained for both the main group (r = 0.04, p = 0.85) and subgroup 1B (r = 0.03, p = 0.89). In contrast, scleroderma and PAH patients showed a poor negative correlation between sPAP and septal E', with no statistical significance (r = -0.09, p = 0.6) (Figure 3).

#### Analysis of left ventricular diastolic function

Regarding the correlations between the E/A ratio and sPAP, only the subgroup of ischemic PAH patients showed a statistically significant positive correlation (r = 0.48, p = 0.05). Neither the main group of ischemic patients (r = 0.21, p = 0.21), nor the subgroup of patients without PAH (r = -0.34, p = 0.15) showed any significant correlations. Among the patients with scleroderma, no significant correlations were found between the E/A ratio and sPAP for the main group



**FIGURE 3.** Correlation between tissue Doppler indexes (E` septal and E` lateral) and PAPs in the study groups. **A** – correlation between E' septal value and the sPAP in patients with scleroderma; **B** – correlation between E' septal value and the sPAP in patients with coronary artery disease; **C** – correlation between E' lateral value and the sPAP in patients diagnosed with coronary artery disease; **E** – correlation between E' septal value and the sPAP in patients diagnosed with coronary artery disease; **E** – correlation between E' septal value and the sPAP in patients with SS(+) PAH(+); **F** – correlation between E' septal value and the sPAP in patients with SS(+) PAH(-); **G** – correlation between E' lateral value and the sPAP in patients with SS(+) PAH(-); **H** – correlation between E' lateral value and the sPAP in patients with SS(+) PAH(-); **I** – correlation between E' septal value and the sPAP in patients with Isch(+) PAH(-); **K** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **K** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **K** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **K** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' lateral value and the sPAP in patients with Isch(+) PAH(-); **L** – correlation between E' later

(r = 0.23, p = 0.12), or for the subgroups (r = 0.20, p = 0.29) – subgroup 1B; r = -0.44, p = 0.08) (Figure 4).

Concerning the E-wave DT, the patients from the scleroderma group did not present any significant correlations with sPAP in the main group (r = -0.23, p = 0.13), neither in the subgroups with (r = 0.20, p = 0.49) or without PAH (r = 0.14, p = 0.46). Patients in the ischemic group showed a negative correlation between DT and sPAP (r = -0.25, p = 0.17), a positive correlation in the two subgroups: with PAH (r = 0.09, p = 0.73) and without PAH (r = 0.01, p = 0.95), but without reaching the statistical threshold. Following the comparison of the mean DT value, a statistically significant difference was obtained between the study subgroups (subgroup 1A 175 ± 11, subgroup 1B 208 ± 10, subgroup 2A 190 ± 4, subgroup 2B 190 ± 3, p = 0.01) (Figure 5).

#### DISCUSSIONS

The purpose of this study was to evaluate systolic and diastolic ventricular function in scleroderma patients compared to those with ischemic heart disease. In this respect, we compared left ventricular systolic and diastolic function for two disorders involving different pathophysiological mechanisms. Myocardial ischemia episodes are common in the development of scleroderma, not due to epicardial coronary artery stenosis, but to microvascular dysfunction, since vascular lesions specific to scleroderma lead to a major alteration of the microcirculation.<sup>22,23</sup> Moreover, we attempted a comparative analysis between subgroups with and without PAH in each of the main study groups, since beyond the impact of PAH on the structure of the heart and independent of it, myocardial damage is well-



**FIGURE 4.** Correlation between the E/A index and PAPs in the study groups. **A** – patients with scleroderma; **B** – patients with coronary artery disease; **C** – patient with SS(+) PAH(+); **D** – patients with SS(+) PAH(–); **E** – patients with lsch(+) PAH(+); **F** – patients with lsch(+) PAH(–)

known both for ischemic patients and for those diagnosed with scleroderma.

The impairment of LVEF in patients with scleroderma is still a controversial issue in the literature, studies identifying a low percentage of subjects with impaired ventricular contractility.<sup>24</sup> About 40% of patients with scleroderma show relaxation disorders.<sup>25</sup> The results of this study revealed, as expected, a significantly more depressed ejection fraction among ischemic patients. A lower LV systolic function was observed in ischemic subjects, both when comparing the two large groups and the subgroups of the study. Ischemic subjects with PAH had the most depressed LVEF, followed by ischemic patients without PAH. There was also a significant difference among patients with scleroderma, where the associated PAH included a significant impairment of LV systolic performance. In addition, the same type of correlation was present for patients with non-PAH scleroderma, indicating that beyond the depreciating impact of PAH on LVEF, intrinsic myocardial dysfunction in scleroderma plays an important role in left ventricular systolic function.

It is known that myocardial ischemia leads to the alteration of the myocardial relaxation process, which is reversible in the early phases by restoring normal myocardial flow.<sup>15–17</sup> Diastolic dysfunction occurs from the first moments of myocardial ischemia, characterized by a specific



**FIGURE 5.** Comparative analysis of the mean DT values across the study subgroup

pattern of altered relaxation, whereas in the post-myocardial infarction phase, the same dysfunctional LV pattern is correlated with the myocardial remodeling processes.<sup>16</sup> In a patient diagnosed with scleroderma, diastolic dysfunction is common,<sup>26</sup> being correlated with the duration of the illness.<sup>27</sup> However, it is only identified in a minority of these patients, being underestimated in most studies conducted among subjects with systemic scleroderma.<sup>28</sup> One of the largest studies on LV diastolic function has identified distal dysfunction by echocardiographic evaluation in 50% of patients with scleroderma compared to 23% of patients from the control group.<sup>26</sup>

The present study identified the presence of altered relaxation-type diastolic dysfunction based on E' lateral and E' medial mitral valve Doppler tissue indexes in both subjects with scleroderma and subjects with ischemia. Additionally, an important negative correlation was identified between sPAP values and both indices of diastolic dysfunction for the group of ischemic patients. Mene *et al.* indicated Doppler tissue echocardiography parameters as valuable markers in identifying myocardial damage in patients with asymptomatic scleroderma.<sup>29</sup> The evaluation of diastolic dysfunction in patients with scleroderma in particular is clinically important, Yiu *et al.* demonstrating that the subtle diastolic dysfunction of the LV evaluated by tissue Doppler is correlated with a very low capacity and rhythm disorders in patients with scleroderma.<sup>30</sup>

An echocardiographic control study conducted by Meune *et al.* on 100 patients with scleroderma confirmed the increased frequency of diastolic dysfunction in patients with systemic sclerosis versus the control group; however, in patients with PAH associated with systemic sclerosis, elevated sPAP values involve a more pronounced distal alteration of the LV.<sup>31</sup> Our study identified the same negative correlation for the E/A ratio used as an indicator of LV diastolic function among patients with scleroderma and PAH. Furthermore, E DT evaluation identified significantly lower values for subjects with scleroderma and associated PAH, leading to the diagnosis of altered relaxation diastolic dysfunction.

## CONCLUSIONS

Scleroderma, by intrinsic myocardial damage, can lead to the alteration of LV function even in the absence of PAH. Patients with PAH present a higher proportion of diastolic dysfunction both in case of associated CAD and scleroderma. However, PAH severity, assessed by the mean sPAP, correlates well with the severity of diastolic dysfunction in ischemic patients, quantified by tissue Doppler echocardiography. Compared to patients with coronary artery disease, those with scleroderma present a less pronounced deterioration of LVEF in response to PAH.

## **CONFLICT OF INTEREST**

Nothing to disclose.

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**ORIGINAL RESEARCH** 



GYNECOLOGY // SURGERY

# Laparoscopic Versus Conventional Open Surgery for the Treatment of Bilateral Inguinal Hernias

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Received: June 27, 2018 Accepted: July 30, 2018

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#### ABSTRACT

Objective: To evaluate and compare laparoscopic and conventional open procedures for bilateral inguinal hernia surgical repair, using clinical, intraoperative, and postoperative criteria. Methods: Forty-three patients with bilateral inquinal hernia were included in a retrospective study, between 2014–2017. All patients underwent conventional open or laparoscopic bilateral hernioplasty, and were divided into two groups: a conventional open group (COG) and a laparoscopy group (LG). Clinical, intraoperative, and postoperative outcomes were reviewed. **Results:** In the laparoscopic hernioplasty group, there was a significantly shorter hospitalization period (p = 0.026), less postoperative pain (p = 0.03), and a prompt return to work (p = 0.026) and p = 0.026). 0.043) compared to the conventional open procedure. On the other hand, patients who underwent hernioplasty with the Progrip-type synthetic mesh developed a lower pain score, an earlier return to work, and a quick start to normal physical activities in comparison with other mesh types used for the treatment of bilateral inguinal hernias. For patients who underwent conventional open procedure, there was a significantly shorter operating time (p = 0.042). Conclusion: Laparoscopic bilateral inguinal hernioplasty is a time-consuming and technically demanding procedure. However, the current study underlines the benefits of this type of surgery. This technique presents comparable clinical, intraoperative, and postoperative results with the conventional open surgery.

Keywords: bilateral inguinal hernia, laparoscopic, hernioplasty, ProGrip, chronic pain

# INTRODUCTION

Nowadays, despite the rare occurrence of bilateral inguinal hernias in medical practice, they are encountered in about 15–20% of patients with inguinal hernia. There are still discussions regarding the treatment of bilateral hernias, whether surgery should be performed in one, or two stages. A simultaneous surgical intervention seems to be more beneficial from every point of view, requiring only one hospital admission, as well as fast anesthesia and postoperative recovery. In the medical literature, only sporadic studies have compared laparoscopic surgery with conventional open procedures for the treatment of bilateral inguinal hernias. Recent studies have shown that the laparoscopic procedure can be a feasible alternative to conventional open surgery.<sup>1-10</sup> The aim of this study was to compare the open conventional procedure with laparoscopic surgery in patients diagnosed with bilateral inguinal hernia.

## **MATERIAL AND METHODS**

This retrospective study was conducted between 2014 and 2017, and followed 43 patients diagnosed with bilateral inguinal hernia at the Second Surgery Clinic of the Emergency Clinical County Hospital from Tîrgu Mureş. All study subjects underwent bilateral inguinal hernia surgical repair. Based on the surgical approach, patients were selected and divided in two groups: a laparoscopy group (LG), which included 16 patients, and a conventional open group (COG) with 27 patients. In patients belonging to the LG, the surgery was performed according to the transabdominal preperitoneal procedure (TAPP) in all cases. Conventional open surgery was performed following the Lichtenstein or tension-free mesh plug techniques. In order to compare the two types of surgeries, clinical, intraoperative, and postoperative criteria were evaluated. From the clinical perspective, the patient groups were analyzed and compared based on gender, age, and type of hernia. For surgical assessment, the type of surgical procedure, type of applied mesh, duration of surgery and hospitalization period, complications, and hernia recurrence were analyzed. Postoperatively, the acquired pain score, the existence of chronic postoperative pain syndrome, the time until returning to work and to normal physical activities were compared. Furthermore, the correlations between the type of surgical mesh and postoperative outcomes following the mentioned criteria: pain score, return to work, restart of physical activities were evaluated. The chronic postoperative pain syndrome and pain score were assessed applying the PainDetect Questionnaire. Data assembled from existing medical records for all patients included in this study was introduced and organized in Microsoft Excel. Statistical analysis of the parameters was performed using GraphPad InStat software, and the statistical significance of the study was set at a value of p <0.05 with a 95% confidence.

#### RESULTS

The study followed 43 patients with bilateral inguinal hernia hospitalized in the Second Surgery Clinic of Tîrgu Mureş, between 2014 and 2017. The assessed clinical and surgical criteria are presented in Table 1 and Figure 1.

The distribution of patients by gender showed a majority of male patients for both study groups, 93.75% for the LG and 92.5% for the COG. The mean age in the LG was 43.8 years, while in the COG it was 63.4 years. A total of 16 patients underwent laparoscopic hernioplasty, while 27 patients benefited from a conventional open approach.

Laparoscopic surgery was performed using the TAPP procedure for all patients, while for open hernioplasty mostly the Lichtenstein (63%), but also tension-free mesh

	Laparoscopy Group (LG)	Conventional Open Group (COG)
Number of patients	16 (37.20%)	27 (62.97%)
Gender		
Male	15 (93.75%)	25 (92.5%)
Female	1 (6.25%)	2 (7.5%)
Average age (years)	43.8	63.4
Surgical procedure		
Lichtenstein procedure	-	17 (63%)
Tension-free mesh plug procedure	-	10 (37%)
TAPP procedure	16 (100%)	-
Mesh type		
Prolene mesh	-	27 (100%)
Parietex mesh	9 (56.25%)	_
ProGrip mesh	7 (43.75)	_

Laparoscopic hernioplasty



Right side Left side



FIGURE 1. Types of hernias and surgical approach

plug (37%) techniques were used. Different mesh types were used to perform inguinal hernia repair: Prolene, Parietex, and ProGrip synthetic mesh. For open surgery, Prolene surgical meshes were used in all 27 cases. During laparoscopic hernioplasties, Parietex meshes were used in 9 (56.25%) cases and Progrip meshes in 7 (43.75%) cases.

Regarding the types of hernias, we found a majority of external oblique hernias in both groups, totaling 54 hernias, followed by direct hernias in 29 cases. Complex hernias (simultaneous external oblique and direct hernia) occured in only 3 cases.

The statistical analysis of data regarding intraoperative and postoperative outcomes in the two groups is presented in Table 2. We observed that the duration of surgery was significantly longer for patients who underwent laparoscopic hernioplasty compared to the open procedure (p = 0.017). The average hospital stay was significantly shorter for the LG (3.43 days) compared to the COG (4.29 days) (p = 0.030). Postoperative complications existed in 2 cases from the LG (one case of surgical wound infection, and in one patient we observed a remaining palpable nodule in the surgical wound area), while in the COG there was a single complication, paresthesia surrounding the surgical wound in 1 case. Recurrence occured in only 1 case for each type of procedure. Postoperative pain was significantly higher in patients in the COG (p = 0.035). Chronic postoperative pain syndrome was present in 2 cases in the COG and in

	Laparoscopy Group (LG) n = 16	Conventional Open Group (COG) n=27	p value
Surgical intervention and immediate post	operative recovery		
Duration of surgery (minutes)	83.12	73.14	0.017
Hospital stay (days)	3.43	4.29	0.030
Complications	2	1	NS
Recurrence and postoperative pain			
Number of recurrences	1	1	NS
Pain score (mean)	4.87	7.03	0.035
Chronic postoperative pain syndrome	1	2	NS
Time until return to normal activity			
Return to work (weeks)	2.43	3.85	0.036
Restart of physical activities (weeks)	5.3	6.2	NS

#### TABLE 2. Intraoperative and postoperative outcomes

only 1 patient in the LG. Patients who underwent laparoscopic bilateral inguinal hernia repair returned to work significantly earlier than patients in which the surgery was performed through a conventional procedure (p = 0.036). Furthermore, patients undergoing laparoscopic surgery resumed their physical activities earlier (5.3 weeks) compared to patients who were submitted to open surgery (6.2 weeks).

Table 3 presents the influence of mesh type on postoperative outcomes. The ProGrip mesh resulted in a lower pain score, an earlier return to work, and a quicker start of physical activity, in comparison with other mesh types used in the treatment of bilateral inguinal hernia.

# DISCUSSIONS

The surgical treatment of bilateral inguinal hernias remains a matter of debate in many studies, the main questions being whether to carry out a single- or a two-staged operation, or if the surgical intervention should be through a conventional open approach or a minimally invasive procedure. This study focuses on the evaluation of the two surgical strategies, the major objective being a reflection on the advantages of minimally invasive surgery. When evaluating the duration of surgery, we observed that there was a significantly longer operation time for patients in the laparoscopic group, other authors reporting similar results.<sup>3,7,10-12</sup> Furthermore, we observed a significantly shorter hospital stay in case of patients who underwent laparoscopic hernioplasty. These data are in accordance with other authors' reports.<sup>1,2,5,10,12,13</sup> Data concerning postoperative complications and recurrence showed similar results for conventional open and laparoscopic procedures, recent studies publishing close results.1-3,5,8,10,12,13,15 Postoperative pain was significantly lower for patients in the laparoscopic group, similar results being found in other studies.<sup>1–3, 7,10,11,12,14</sup> Also, we observed that patients who underwent laparoscopic surgery returned earlier to work and started physical activity (sports) earlier. Other studies reported comparable results.<sup>10-12,14</sup> Comparing the surgical mesh types used for hernioplasty showed clear benefits for the ProGrip mesh appliance. The self-fixating mesh produced lower postoperative pain, earlier return to work, and earlier start of physical activity. Recent studies showed similar results.16

Mesh type	Number	Pain Score	Start of work (weeks)	Start of sports/ physical activity (weeks)
Prolene	27 (62.79%)	6.92	3.7	6.22
Parietex	9 (20.93%)	5.33	2.44	5.55
ProGrip	7 (16.27%)	4.28	2.42	5.14

## CONCLUSIONS

Although the minimally invasive technique requires a longer learning curve and a significant number of cases in order to achieve the maximum potential in repairing a bilateral inguinal hernia, the laparoscopic aproach has proven major benefits for this type of surgical cases. The procedure allows a single surgical repair of both defects without additional incisions and offers better or at least similar results in comparison to the conventional open procedure. The present study shows that laparoscopic repair is a feasible choice for bilateral inguinal hernia, resulting in less postoperative pain, shorter hospital stay, earlier return to work and physical activities, and also similar recurrence rates with the conventional open procedure.

## **CONFLICT OF INTEREST**

The authors declare no conflict of interests.

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**ORIGINAL RESEARCH** 



CARDIOLOGY // CARDIOVASCULAR IMAGING

# CTA Assessment of Coronary Atherosclerotic Plaque Evolution after BVS Implantation – a Follow-up Study

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Received: August 15, 2018 Accepted: September 6, 2018

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#### ABSTRACT

Background: Computed tomography angiography (CTA) occupies an important place in the evaluation of coronary atherosclerotic lesions, both before and after the implantation of bioresorbable stents (BVS), providing an accurate assessment of the treated lesions. Aim of the study: This study aims the prospective follow-up of atherosclerotic plaques electively treated with BVS implantation via CTA evaluation in terms of morphological and virtual histology aspects. Material and methods: This is a prospective observational study which enrolled 30 patients electively treated with BVS implantation, in whom CTA was performed after PTCA in order to assess the morphological and virtual histology aspects of coronary plaques. In order to evaluate the impact determined by pre- and post-implantation procedures, statistical analysis was performed among 6 subgroups. Results: After BVS implantation, a significant reduction was observed in terms of stenosis % (61.63  $\pm$  12.63% in subgroup 1A vs. 24.41  $\pm$  12.48% in subgroup 1B, p <0.0001) and eccentricity index (0.46  $\pm$  0.24 in subgroup 1A vs. 0.43  $\pm$  0.24 in subgroup 1B, p <0.0001). In terms of plaque components, there were significant differences with regard to lipid volume and lipid % (20.07  $\pm$  15.67 mm<sup>3</sup> in subgroup 1A vs. 11.05  $\pm$  10.83 mm<sup>3</sup> in subgroup 1B, p = 0.01), which presented a significant reduction after BVS implantation. The calcium score evaluated locally ( $82.97 \pm 107.5$  in subgroup 1A vs.  $96.54 \pm 85.73$  in subgroup 1B, p = 0.25) and on the target coronary artery (148.2  $\pm$  222.3 in subgroup 1A vs. 206.6  $\pm$  224.0 in subgroup 1B, p = 0.10), as well as the total calcium score (377.6  $\pm$  459.5 in subgroup 1A vs. 529.5  $\pm$  512.9 in subgroup 1B, p = 0.32), presented no significant differences when compared with and without post-dilatation lesions. As far as CT vulnerability markers are concerned, the study groups presented significant differences only in terms of spotty calcifications (66.66% in subgroup 1A vs. 79.16% in subgroup 1B, p = 0.05) and low attenuation (37.5% in subgroup 1A vs. 20.83% in subgroup 1B, p = 0.01). **Conclusions:** Following the analysis of coronary artery plagues after the implantation of BVS, significant changes were noted both in the morphology of the atherosclerotic plaques treated with these devices and in the lumen and coronary wall.

Keywords: bioresorbable stent, CTA, elective treatment, coronary artery plaque

## INTRODUCTION

Coronary computed tomography angiography (CTA) occupies an important place in the evaluation of coronary atherosclerotic lesions, both before and after the implantation of coronary bioresorbable vascular scaffolds (BVS).<sup>1</sup> This noninvasive examination, still more used as a complementary examination in patients with coronary artery disease next to invasive coronary angiography, offers major benefits in tracking bioresorbable stents.

Having the advantage of radiolucency and resorption over time, a BVS can be accurately evaluated with CTA after implantation, thus opening up a new era in the followup methods of these devices.<sup>2,3</sup>

Due to the possibility of evaluating BVS through coronary CTA, it is feasible to analyze the plaques and their structure through a post-processing software, dedicated to the analysis of atherosclerotic plaque composition, enabling the concurrent analysis of vulnerability characteristics as well as of the information related to the lumen and walls of the coronary arteries.<sup>4</sup> Details of plaque composition before stenting and its morphological characteristics under the implanted BVS can be obtained after the post-processing of CTA-acquired images.<sup>5–8</sup> A detailed analysis is obtained with the help of virtual histology, using a color code for the different components of the plaque: white for calcium, red for the necrotic core, light green for the fibrolipidic core, dark green for fibrous tissue. The final results are available in absolute values or as a proportion in the plaque.<sup>9,10</sup>

The implantation of bioresorbable stents requires a careful lesion assessment to determine the need for and extent of lesion preparation, and to select the size and length of the device. The use of conventional imaging as well as preand post-procedural intracoronary imaging techniques is encouraged to optimize the implantation and the subsequent monitoring of the device.<sup>11</sup>

Given their structure and mechanical properties, compared to the pharmacologically-treated metallic stents, bioresorbable scaffolds require a meticulous evaluation of the lesion and also the frequent use of pre- and post-dilatation. As a result, the duration of the procedure and the use of contrast substance increases.

It is recommended to dilate the lesion with a noncompliant balloon before BVS implantation, by targeting balloons with a diameter corresponding to the estimated diameter of the reference vessel. Orthogonal angiographic projections are required for viewing the entire expansion of the balloon, otherwise it is necessary to use other preparation techniques before implanting the BVS.<sup>12</sup> As a technical notion, pre-dilatation should be performed with a balloon of a size that is appropriate for the vascular diameter (ratio of 1:1). BVS should not be implanted in lesions that present suboptimal results after pre-treatment. If pre-dilatation results are not satisfactory, implantation of the bioresorbable stent will cause incomplete expansion associated with an increased risk for restenosis or in-stent thrombosis.<sup>13</sup>

Post-dilatation with a non-compliant high-pressure balloon should be performed routinely with a balloon diameter that exceeds the diameter of the device with a maximum of 0.5 mm. The expansive limit of the bioresorbable scaffold is 0.5 mm above the nominal diameter. A 3.2 mm bioresorbable stent should not be dilated above 3.5 mm, which is the size when the stent struts are prone to fracture. If the stent struts rupture, they will lead to subsequent complications that pose a potential cause of concern.<sup>12</sup>

Magnesium alloy bioresorbable stents present high radial force, which could expose it to fractures during expansion.<sup>14</sup> Although the radial force of bioresorbable stents has been reported to be comparable to that of metallic stents, this holds true if the bioresorbable stent is expanded within the limits of its size. If the bioresorbable stent is expanded beyond its size, it can lose its radial force and possibly fracture.<sup>15</sup>

The topic of implantation methodology and subsequent follow-up of bioresorbable scaffolds is still largely discussed in the field of interventional cardiology. Therefore, this study aims the prospectively follow-up patients with significant coronary atherosclerotic plaques who have been treated electively with BVS implantation, via coronary CTA evaluation.

## MATERIALS AND METHODS

We performed a prospective observational study, which included 30 patients with stable and unstable angina, who underwent elective BVS implantation for significant coronary atherosclerotic lesions in the CardioMed Medical Center between January 2015 and March 2017. Data regarding the patients' medical history and clinical examination were collected, and the patients presented at 1, 6, or 12 months for follow-up visits.

Other inclusion criteria were age over 18 years, BMI <40 kg/m<sup>2</sup>, signed written informed consent given by the patient. Exclusion criteria included STEMI or non-STE-MI diagnosis, electric and hemodynamic instability at admission, known allergy for contrast agent, indication for long-term anticoagulant treatment, chronic kidney disease stage 4 or 5, end-stage disease with life expectancy below 1 year.



**FIGURE 1.** CTA of diagonal coronary artery 12 months after PTCA with BVS – no significant stenosis between BVS markers

All patients underwent CTA evaluation 12 to 24 months after PTCA in order to assess the morphological and virtual histology aspects of the coronary plaques. CTA was performed before and after BVS implantation for 16 patients and only after BVS implantation for 14 of the study subjects. In total, 48 coronary plaques were analyzed.

In order to evaluate the impact determined by the preand post-implantation procedures on the structure and morphology of the coronary artery, statistical analysis was performed in 2 subgroups, as follows:

- subgroup 1 pre-implantation lesions (n = 48)
- subgroup 2 post-implantation lesions (n = 48)



**FIGURE 2.** CTA of diagonal artery 12 months after PTCA with BVS, post-processed image with Syngo.via Frontier (Siemens AG, Erlangen, Germany) – no significant stenosis between BVS markers.



**FIGURE 3.** 128-slice CTA. Left anterior descending artery with critical stenosis in the third segment, before implantation of BVS

Vessel:	LAD 🤜			
Component	Vol. [mm³]	Plaque Ratio [%]	AHA Segments:	
🖻 Vessel	278.53			
Lumen	101.22			
⊡- Plaque	177.31	100.0	5 6 7 8	
Calcified	29.91	16.8	9 10 11 12	
⊡ Non-Calcifie	ed 147.40	83.2	13 14 15 16	
···· Lipid Ri	ch 4.88	2.8		
Fibrotie	142.52	80.4	Napkin Ring Sign	
Length of plaque segm	ient [mm]:	18.4		
2D Measurements		Accept current		
Min. Luminal Area (mm	1²]: 0.04	Stenosis Grade [%]: 35.23		
Remodeling Index:	1.13	Eccentricity	Index: 0.35	
Threshold Presets:	120 kV 🗸 🔻	+ -	B 🤹	
TO (HU): -100 🚔	T1 (HU): 30 🗲	T2 (HU): 400 🚝	T3 (HU): 950 🚔	
20 10 -200 0 -200 0 200 0 200 0 200 0 200 10 -200 0 200 10 -200 0 200 10 -200 -20	90;950) ibliounge (1934), service 1 ) 800 1000 1200 1400 Fhreshold Evaluation Mode	1600 1800		

FIGURE 4. Coronary plaque analysis platform – Syngo.via Frontier software

## **CT** scanning protocol

CTA evaluations were performed in the Laboratory of Advanced Research in Cardiac Multimodal Imaging of the Cardio Med Medical Center of Tîrgu Mureş, with a 64- and 128-slice dual-source CT (SOMATOM Definition, Siemens Healthcare), with the following technical characteristics:  $64 \times 0.5$  mm and  $128 \times 0.6$  mm detector rows, 330 ms rotation time, and a table feed of 0.2–0.4 mm per rotation.

Optimization of the CT scanning protocol consisted in a fasting period of 5–24 h prior to CT examination, avoidance of smoking, caffeine use or physical exercises before CT scanning. During CT image acquisition, a heart rate <60 bpm was obtained with the oral titrated administration of Metoprolol or Ivabradine 1 h prior to the CT scan.

#### **Reconstruction of CT images and data analysis**

CT image post-processing was performed with a dedicated research software, Syngo.via Frontier, using a Siemens workstation (Siemens AG, Erlangen, Germany). Figure 1 presents a coronary angiographic 128-slice CT scan, Figure 2 presents a detailed analysis of a coronary plaque and the BVS, and Figure 3 presents a critical stenosis of the left anterior descending artery before implantation of the BVS.

## **Plaque structure**

A coronary plaque analysis platform was used to assess morphology and plaque composition (Figure 4). Plaque structure was evaluated according to the CT density of its main components: lipids (-100-30 HU), fibrotic tissue (30-400 HU) and calcifications (400-950 HU).

#### Statistical analysis

Statistical analysis was performed using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Continuous variables were compared using Student's t-test for paired data or the Wilcoxon test when appropriate, and categorical data were compared using the Chi-square test. The statistical significance of the study was set at an alpha of 0.05.

## **Ethical approval**

This study was carried out in accordance with the World Medical Association's Declaration of Helsinki. All patients gave written informed consent, and the study protocol was approved by the Ethics Committee of the University of Medicine and Pharmacy of Tîrgu Mureş (approval no. 338/17.11.2017) and the Ethics Committee of CardioMed Medical Center (approval no. 29/28.12.2017).

# RESULTS

#### General characteristics of the study population

The mean age of study population was  $58.35 \pm 7.79$  years, and 20% of the study subjects were over 65 years. With regard to gender distribution, 86.66% of the subjects were males (n = 26).

General characteristics of the study population and their cardiovascular risk factors are presented in Table 1. In terms of left ventricular dysfunction incidence, 70% of the subjects presented a left ventricular ejection fraction <55%, 63.33% were enrolled with a diagnosis of stable angina, and 36.67% were diagnosed with unstable angina.

After coronary CT evaluation, 43.33% of the subjects presented coronary artery disease (CAD) with lesions in a single vessel, 30% were diagnosed with 2-vessel disease, and 26.66% presented severe 3-vessel disease. From the treated lesions, pre-dilatation was performed in 80% of cases, while post-dilatation was carried out in 26.66% of cases.

#### Post-implantation CT analysis of coronary plaques

Morphological and virtual histology aspects of the analyzed coronary plaques after BVS implantation are presented in Table 2.

After BVS implantation, a significant reduction was observed in the degree of stenosis ( $61.63 \pm 12.63\%$  in subgroup 1 vs. 24.41  $\pm$  12.48% in subgroup 2, p <0.0001) (Figure 5A) and the eccentricity index ( $0.46 \pm 0.24$  in subgroup 1 vs.  $0.43 \pm 0.24$  in subgroup 2, p <0.0001) (Figure 5B).

TABLE 1. General characteristics and cardiovascular risk factors

	Mean value ± SD	%
Age, years	58.35 ± 7.79	
Age >65 years	6	20
Male gender	26	86.66
Female gender	4	13.43
EF <55%	21	70
Hypertension	25	80.64
Creatinine clearance	73.55 ± 18.12	
Diabetes Mellitus	6	20
Dyslipidemia 10 33		33.33
History of AMI	10	33.33

TABLE 2.	Morphological	and virtual histol	ogy aspects o	f analyzed	coronary plaques
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	Pre-BVS Mean value ± SD (95% CI)	Post-BVS Mean value ± SD (95% CI)	p value
Plaque length (mm)	18.69 ± 2.73 (17.54–19.85)	18.91 ± 2.87 (17.7–20.12)	0.64
% stenosis	61.63 ± 12.63 (52.02-66.69)	23.41 ± 12.48 (18.14–28.68)	< 0.0001
Eccentricity index	0.46 ± 0.24 (0.36–0.57)	0.43 ± 0.24 (0.33–0.53)	< 0.0001
Remodeling index	1.04 ± 0.2 (0.95–1.13)	1.09 ± 0.3 (0.96–1.21)	0.71
Vascular volume (mm3)	277.7 ± 86.36 (241.3–314.2)	283.7 ± 72.24 (253.2–314.2)	0.79
Lumen volume (mm3)	100.8 ± 33.68 (86.53–115.0)	128.2 ± 37.38 (112.4–144.0)	0.01
Dense calcium (mm3)	13.59 ± 17.36 (6.26–20.92)	16.07 ± 19.0 (8.0–24.09)	0.45
Dense calcium (%)	6.72 ± 7.79 (3.43–10.02)	8.98 ± 9.0 (5.15-12.82)	0.25
Necrotic core (mm3)	169.8 ± 63.7 (142.9–196.7)	143.6 ± 53.62 (121.0–166.2)	0.12
Necrotic core (%)	93.27 ± 7.79 (89.98–96.56)	91.0 ± 9.0 (87.17–94.84)	0.25
Fibro-fatty (mm3)	20.07 ± 15.67 (13.46-26.69)	11.05 ± 10.83 (6.47–15.62)	0.01
Fibro-fatty (%)	10.31 ± 6.24 (7.67–12.95)	6.46 ± 6.14 (4.05–9.24)	0.01
Fibrous (mm3)	114.8 ± 59.62 (119.6–170.0)	132.6 ± 50.97 (111.0–154.1)	0.44
Fibrous (%)	82.97 ± 7.74 (79.69–86.24)	84.26 ± 10.73 (79.73–88.79)	0.63
Calcium score – local	82.97 ± 107.5 (37.57–128.4)	96.54 ± 85.73 (60.34–132.7)	0.25
Calcium score – target coronary artery	148.2 ± 222.3 (54.37–242.1)	207.6 ± 224.0 (113.0-302.2)	0.10

In terms of plaque components, there were no significant differences between subgroup 1 and subgroup 2 regarding to the calcified volume (13.59 ± 17.36 mm<sup>3</sup> in subgroup 1 vs. 16.07 ± 19.0 mm<sup>3</sup> in subgroup 2, p = 0.45), % calcified ( $6.72 \pm 7.79$  in subgroup 1 vs.  $8.98 \pm 9.0$  in subgroup 2, p = 0.25), necrotic core volume ( $169.8 \pm 63.7$  mm<sup>3</sup> in subgroup 1 vs. 143.6 ± 53.62 mm<sup>3</sup> in subgroup 2, p = 0.12), necrotic core % ( $93.27 \pm 7.79$  in subgroup 1 vs.  $91.0 \pm 9.0$  in subgroup 2, p = 0.25), fibrotic volume ( $114.8 \pm 59.62$  mm<sup>3</sup> in subgroup 1 vs.  $132.6 \pm 50.97$  mm<sup>3</sup> in subgroup 2, p = 0.44), or fibrotic % ( $82.97 \pm 7.74$  in subgroup 1 vs.  $84.26 \pm 10.73$  in subgroup 2, p = 0.63), except for lipid volume and lipid % ( $20.07 \pm 15.67$  mm<sup>3</sup> in subgroup 1 vs.  $11.05 \pm 10.83$  mm<sup>3</sup> in subgroup 2, p = 0.01) which presented a significant reduction after BVS implantation (Figure 6).

Regarding the calcium score evaluated locally (82.97  $\pm$  107.5 in subgroup 1 vs. 96.54  $\pm$  85.73 in subgroup 2, p = 0.25), at the level of the target coronary artery (148.2  $\pm$  222.3 in subgroup 1 vs. 206.6  $\pm$  224.0 in subgroup 2, p = 0.10), and the total calcium score (377.6  $\pm$  459.5 in subgroup 1 vs. 529.5  $\pm$  512.9 in subgroup 2, p = 0.32), there were no significant differences when comparing lesions with versus without post-dilatation (Figure 7).

Table 3 presents the comparative analysis between the pre- and post-BVS implantation aspects of the CTA evaluation combined with the image post-processing analysis in terms of CT vulnerability markers of the analyzed coronary plaques.

Regarding CT vulnerability markers, the study groups presented significant differences only in terms of spotty



FIGURE 5. A - % stenosis mean value pre- and post-BVS implantation; B - Eccentricity index pre- and post-BVS implantation



FIGURE 6. A – Calcified volume (mm<sup>3</sup>); B – Necrotic core volume (mm<sup>3</sup>); C – Fibrotic volume (mm<sup>3</sup>); D – Lipid volume (mm<sup>3</sup>)

calcifications (66.66% in subgroup 1 vs. 79.16% in subgroup 2, p = 0.05) and low attenuation (37.5% in subgroup 1 vs. 20.83% in subgroup 2, p = 0.01) (Figure 8).

# DISCUSSIONS

Given that coronary atherosclerotic plaques, treated by implantation of bioresorbable scaffolds, can also be evaluated after the procedure using a noninvasive method, this could lead to the routine evaluation of these devices through coronary CT angiography. This way, the coronary CT angiography evaluation of BVS can highlight certain complications that may occur over time.<sup>16,17</sup>

The CTA evaluation of BVS is possible due to the special advantages of these structures, namely polymer resorption over time. All patients included in this study underwent BVS implantation, with a composition based on polymers. Regarding the radiological advantages, the radiotransparency of the device is worth mentioning, which facilitates the acquisition of coronary CT angiography, as well as subsequent image post-processing.<sup>17–20</sup>

The post-processing software dedicated to the detailed

analysis of atherosclerotic plaque components enabled the analysis of important elements for a percutaneous procedure.

Another crucial element in a successful revascularization treatment using bioresorbable stents is the careful analysis of the target lesion. This thorough analysis, corroborated with noninvasive pre-interventional CT imaging, can contribute to the best revascularization approach of the atherosclerotic lesions.

Pre-dilatation techniques, implantation of the device, and its subsequent optimization by post-dilatation were elements evaluated in this study. When the first BVS had been implanted, there were no precise guidelines related to these procedural aspects; nevertheless, we monitored these aspects in this study. Although statistically significant differences were not obtained, differences in absolute values were observed for multiple parameters such as stenosis % (CT performed 12 to 24 months postimplantation showed less procedural stenosis in patients with pre-dilatation); the eccentricity index, the remodeling index, vascular volume, plaque volume, and necrotic core were lower among these patients. Following the in-



FIGURE 7. A – Local calcium score; B – Target lesion calcium score; C – Total calcium score

tervention, stent lumen was larger in patients with predilatation.

Regarding patients who underwent post-dilatation of the bioresorbable stent versus patients without post-dilatation, except for statistically significant differences in vascular volume and lumen volume, differences in absolute stent-stenosis values were observed, which were lower in stents that have been post-dilated.

No randomized trials with specific, mandatory, predefined implantation techniques have been completed, based on the PSP concept (pre-dilation, dimensioning, and post-dilatation of the bioresorbable stent).<sup>21</sup> In this re-

#### TABLE 3. CT vulnerability markers

	Pre-BVS (%)	Post-BVS (%)	p value
Positive remodeling	45.83	58.33	0.08
Spotty calcifications	66.66	79.16	0.05
Napkin-Ring sign	0	4.16	-
Low attenuation	37.5	20.83	0.01

spect, the evaluation of these procedures can lead to new ideas, improvement, and mandatory implementation of certain specific techniques in the treatment of coronary atherosclerotic lesions with bioresorbable stents. It is recommended that the stents be implanted by trained and experienced operators in interventional cardiology.<sup>22–24</sup>

### CONCLUSIONS

During the analysis of coronary artery plaques after the implantation of bioresorbable scaffolds with noninvasive CT imaging techniques, significant changes were noted both in the morphology of the atherosclerotic plaques treated with these devices and in the lumen and coronary wall. The assessment of coronary atherosclerotic plaques and bioresorbable scaffolds via coronary CT angiography could become a novel follow-up method for these cases.

## CONFLICT OF INTEREST

Nothing to declare.



FIGURE 8. A - Spotty calcifications; B - Low attenuation; C - Positive remodeling; D - Napkin-ring sign

# ACKNOWLEDGEMENT

This research was supported via the research grant no. 103544/2016, contract number 26/01.09.2016, entitled "Increasing the research capacity in the field of vulnerable plaque imaging, based on advanced nanoparticles, fusion imaging and computational simulation – PlaqueImage", financed by the Romanian Ministry of European Funds, the Romanian Government and the European Union.

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#### **ORIGINAL RESEARCH**

MEDICAL INFORMATICS // PUBLIC HEALTH

# Widely Accepted Credibility Criteria for Online Health-related Information Are Not Correlated with Content Quality of Stroke Webpages in Two Languages of Central and Eastern European Countries

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Received: August 3, 2018 Accepted: August 16, 2018

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#### ABSTRACT

Background: Finding accurate health-related information on the Internet may be a real challenge for users lacking the critical skills necessary to assess the validity of online content, even if they browse websites that are compliant with credibility criteria. The aim of the study was to check whether an overall high website credibility or compliance to any of the individual criteria for credibility are correlated/associated with a higher quality of health-related information on a sample of Romanian and Hungarian stroke-related websites. Methods: The crosssectional study included a sample of 50 websites presenting stroke for the general population in Romanian and Hungarian language. The websites' compliance with 12 widely recognized credibility criteria, and the completeness and accuracy of the stroke-related articles found on the respective sites were systematically assessed by two independent evaluators applying a common evaluation procedure. Results: The mean value of the credibility score was 4.3 points (95% CI: 3.9-4.8), the mean value of the completeness score was 4.8 points (95% CI: 4.2-5.5), and the mean value of the accuracy score was 6.6 points (95% CI: 6.3-6.8). Correlation coefficients between the credibility score and completeness/accuracy score did not reach statistical significance (Spearman rho = 0.038, p = 0.793 and Spearman rho = 0.156, p = 0.278, respectively). With a few exceptions, the t-tests for independent sample comparison have shown no significant differences between websites that complied and those that did not comply with each individual credibility criterion. Conclusions: The mean credibility score of the Romanian and Hungarian stroke-related websites was poor and it was not correlated with neither completeness nor accuracy of the information displayed on the respective pages. With a few, practically irrelevant exceptions, compliance with individual credibility criteria was not associated with higher content quality on the investigated sample.

Keywords: stroke, credibility criteria, proxy quality indicators, health-related internet, consumer health
# INTRODUCTION

The Internet abounds in more or less scientifically validated health-related information.<sup>1</sup> Finding accurate healthrelated information on the Internet may be a real challenge for users lacking the critical skills necessary to assess the validity of online content.<sup>2</sup> To address this issue, several expert initiatives from Europe and North America have proposed lists of proxy quality indicators to help users in finding reliable health-related websites by indirectly estimating the scientific quality of the medical information based on more friendly cues.<sup>1,3</sup>

The Health on the Net Foundation (HON) is a nongovernmental organization founded to encourage the dissemination of quality health information for patients and professionals, and the general public. The eight principles proposed by HON to improve health information available on the internet include: authority (medical advice to be provided only by medical professionals); complementarity (the information provided should support, not replace the patient-doctor relationship); privacy (users' personal information should be confidential); attribution and date (the source of information and the date of publication should be displayed); justifiability (claims regarding benefits of any treatment should be supported with adequate evidence); transparency (website owners should provide contact information); financial disclosure (website funding should be clearly identified); advertising policy (advertising as a source of funding should be explicitly disclosed, and advertising should be differentiated from other information).<sup>4</sup> These quality indicators are known under various labels such as 'credibility', 'general' and 'ethical' criteria. Similar or more complex consumer health orientation principles and tools were developed and promoted by the European Council (the eEurope2002 initiative)<sup>5</sup>, the Department of Public Health and Primary Care at Oxford University (the DISCERN Project),6 the American Medical Association (the Silberg criteria),<sup>7</sup> and other medical or public entities. The core assumption of these initiatives is that "credibility constitutes the 'premier criterion' for evaluating online health information",<sup>2</sup> but it's validity is hardly supported by the body of existing evidence in the field of consumer health.<sup>8,9</sup> Nevertheless, online credibility or quality criteria continue to be promoted, raising the possibility of users being persuaded to falsely believe that websites with a high compliance with credibility criteria must be scientifically accurate as well.

Considering that poor-quality medical information may have adverse consequences for patients' decisions, particularly with regard to critical conditions such as stroke,<sup>10,11</sup> the objective of this study was to test whether an overall high website credibility or compliance with any of the individual criteria for credibility are correlated/associated with a higher quality of health-related information on a sample of Romanian and Hungarian stroke-related websites.

# MATERIAL AND METHODS

The cross-sectional study included a sample of 50 websites presenting stroke for the general population in Romanian and Hungarian language. Google searches were performed using "accident vascular cerebral" (Romanian for stroke) and "stroke" as search terms in April 2018. The links listed on the search engine's results page were checked for eligibility based on a set of inclusion and exclusion criteria, saved in a local database, and evaluated following a rigorous methodology. The websites' compliance with 12 widely recognized credibility criteria, and the completeness and accuracy of the stroke-related articles found on the respective sites were systematically assessed by two independent evaluators applying a common evaluation procedure. The exact steps and assessment methods are described in detail in previously published papers by Nădăşan *et al.*<sup>12,13</sup>

Credibility, completeness, and accuracy scores were calculated and reported on a decimal scale. Scores ranging from 0 to 2 points were characterized as very poor, from 2.1 to 4 as poor, from 4.1 to 6 as average, from 6.1 to 8 as good, and from 8.1 to 10 as very good. Compliance with the 12 individual credibility criteria was calculated as percentage. Compliance was considered very poor from 0 to 20%, poor from 21 to 40%, average from 41 to 60%, good from 61 to 80%, and very good from 81 to 100%. The t-test for independent samples was applied to check whether websites complying with each individual credibility criteria had higher quality ratings, and depending on the normality of the data. Pearson or Spearman correlation tests were applied to test the correlation between the credibility score on one hand and the completeness and accuracy scores on the other. All statistical analyses were performed in SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). The threshold value for statistical significance was set at  $\alpha = 0.05$ .

# RESULTS

Descriptive statistics of the 50 websites included in the sample are presented in Table 1.

The mean value of the credibility score was 4.3 points (95% CI: 3.9–4.8), the mean value of the completeness score was 4.8 points (95% CI: 4.2–5.5), and the mean value of the accuracy score was 6.6 points (95% CI: 6.3–6.8).

General characteristics		n	%
Site ownership	Foundation, NGOs	5	10
	Health care provider	15	30
	Commercial company	21	42
	Not identifiable	9	18
Main goal of the site	Educational	33	66
	Commercial	17	34
Site format	Medical or general web-portal	23	46
	Electronic publication	11	22
	Online shop	16	32
Medical paradigm of the site	Conventional medicine	36	72
	Alternative or mixed approach	14	28

TABLE 1. General characteristics of the websites included in the sample



FIGURE 1. Stroke-related websites' compliance with credibility criteria

The websites' compliance with each of the examined credibility criteria is represented in Figure 1.

The results of the t-test for independent samples regarding the differences in quality scores of the websites complying vs. not-complying with each of the individual credibility criteria are presented in Table 2.

Correlation statistics between credibility scores on one hand and completeness and accuracy scores on the other hand are presented in Table 3, both for the sample as a whole (N = 50) and for the two language sub-samples separately.

# DISCUSSIONS

The credibility of the stroke-related information on Romanian and Hungarian websites was poor (4.3 points) and was consistent with the results of previously published studies about the credibility of Romanian health-related websites.<sup>14,15</sup> This low level of compliance with accepted credibility criteria might indicate that site owners are not aware of the ethical expectations regarding health-related websites or might not be motivated to comply with them. While compliance was very good or good with certain criteria (providing contact information, displaying the owner's name and address, the mission statement, and the confidentiality declaration), some of the crucially important criteria for medical websites (mentioning the author's name and credentials, referencing the sources of the information, and displaying the date of the last update) were poorly observed or almost totally ignored.

Overall, we found no significant differences between websites that complied and those that did not comply with each individual credibility criterion as far as completeness and accuracy of the stroke-related information on Roma**TABLE 2.** Completeness and accuracy scores of compliant vs. non-compliant websites by individual credibility criterion (full sample, N = 50)

Credibility criteria	Compliance	Completeness score (mean)	p value	Accuracy score (mean)	p value
Owner name and address	No	5.5	0.245	6.1	0.049*
	Yes	4.6		6.7	
Mission statement	No	5.3	0.325	6.5	0.878
	Yes	4.6		6.6	
Consultation disclaimer	No	4.4	0.070	6.4	0.204
	Yes	5.7		6.8	
Disclosure of funding	No	4.8	0.778	6.6	0.486
	Yes	5.0		6.4	
Disclosure of commercial interest	No	4.9	0.903	6.4	0.179
	Yes	4.8		6.9	
Confidentiality statement	No	4.7	0.830	6.2	0.047*
	Yes	4.9		6.7	
Providing contact mechanism	No	6.3	0.258	5.7	0.095
	Yes	4.7		6.6	
Authorship disclosure	No	4.8	0.907	6.5	0.486
	Yes	4.9		6.7	
Referencing sources	No	4.7	0.529	6.6	0.455
	Yes	5.2		6.4	
Displaying publication date	No	4.8	0.892	6.9	0.012**
	Yes	4.9		6.2	
Displaying date of last update	No	4.7	0.054*	6.5	0.765
	Yes	7.3		6.7	
Quality procedure statement	No	4.7	0.282	6.3	0.054*
		6.0		7.4	

\* p values with marginally statistical significance; \*\* p values with statistical significance

nian and Hungarian websites are concerned. Although the analysis revealed one statistically significant difference (displaying publication date, p = 0.012) and three more criteria with marginally significant p values (owner's name and address, p = 0.049; confidentiality statement, p = 0.047; and quality procedure statement, p = 0.054), their practical significance remains uncertain because the dif-

ferences in quality ratings were small and, at best, may be considered as indicators of a relative superiority but not as predictors of good or very good completeness or accuracy scores. Furthermore, the present study has shown that credibility scores did not correlate with completeness/accuracy scores on the examined Romanian and Hungarian stroke-related websites. This finding suggests that compli-

**TABLE 3.** Correlation statistics showing the relationship between site credibility and content quality scores of the Romanian and Hungarian stroke-related websites

Sample/Variables	Spearman's/Pearson's rho	p value
Full sample (N = 50)		
Credibility vs. Completeness Score	0.038	0.793
Credibility vs. Accuracy Score	0.156	0.278
Romanian language sub-sample (N = 25)		
Credibility vs. Completeness Score	0.056	0.789
Credibility vs. Accuracy Score	0.236	0.256
Hungarian language sub-sample (N = 25)		
Credibility vs. Completeness Score	0.327	0.110
Credibility vs. Accuracy Score	-0.125	0.550

ance with credibility criteria may not be a true indicator of the quality of medical information. This observation has important practical implications because credibility criteria have been promoted by several expert bodies as a simple and dependable method, which enables users with no specific training in science or medicine to identify accurate and trustworthy online health-related information sources. If, as implied by our study, compliance with credibility criteria is not a reliable predictor of scientific accuracy of health-related information, then, consumer health experts should stop recommending credibility criteria as a tool to detect accurate health information.

These findings are in line with the conclusions of several studies that have investigated the relationship between credibility and content quality on samples that included websites addressing other medical topics both in Romanian,12,13,16,17 as well as in English.3,18,19 In one of the earliest studies that tested the association of credibility and content quality on English-language health-related websites, Griffiths and Christensen have found that none of the content quality measures correlated with the JAMA-Silberg accountability score.<sup>18</sup> In a more comprehensive study including 121 websites presenting information on five common health topics, Kunst et al. have discovered that website credibility criteria have only a weak or at best moderate correlation with the accuracy of information and concluded that apparently credible websites may not necessarily provide more accurate information.<sup>19</sup> A meta-analysis of English-language websites on various topics such as social phobia, bipolar disorders, pathological gambling, cannabis, alcohol and cocaine addiction, has failed to show the HON label as a predictor of good content quality websites, suggesting that the HON credibility criteria are more related to the ethical dimension of online health communication than to the scientific quality of the information conveyed.8 The authors of another study examining the quality of information about prehospital care of venomous snake bites on the English internet consider that the observed lack of correlation between the accuracy of the information and two credibility indicators (HON and JAMA) represents a reason of concern, since online health-seekers relying on these tools may be exposed to potentially harmful misinformation.9

## **Strengths and limitations**

To the best of our knowledge, this is the first study assessing the association of credibility criteria with the quality of stroke-related information for users of Romanian and Hungarian websites. The results of the study bring an addition to the debate surrounding reliability/unreliability of some widely known indirect predictors of online healthrelated information quality by reporting results based on the assessment of a new topic in Central and Eastern European languages.

The main limitations of the study consist in some constraints intrinsic to internet research that may have a sensible impact on the replicability of the results (search results are highly dependent on the choice of search engine, search terms, time of the query etc.). The influence of the evaluators' biases was proactively addressed by: selecting medical doctors or medical students as evaluators, providing the evaluators with detailed instructions regarding the evaluation procedures, performing two independent assessments of the websites' content, systematically checking the interrater agreement, and performing a third, consensus evaluation whenever was necessary. The use of Google as the only search engine in our study may be regarded as a limitation, but considering that up to 97% of Romanians use Google as their search engine, this methodological decision should not be of concern.<sup>20</sup> Even if the sample of included sites is small, this should not be taken as a limitation, because the majority of users access only websites included on the first page of the Google search results.<sup>21</sup> Finally, since our study included only a sample of Romanian and Hungarian websites about stroke, the results cannot be extrapolated to other medical topics or other languages.

# CONCLUSIONS

The mean credibility score of the Romanian and Hungarian stroke-related websites was poor and it was not correlated with neither completeness nor accuracy of the information on the respective webpages. With a few, practically irrelevant exceptions, compliance with individual credibility criteria was not associated with higher content quality on the investigated sample.

# ACKNOWLEDGEMENTS

We thank Sorin Săndulache MD, PhD, neurologist at Colentina Hospital, Bucharest, Romania for his valuable input in the development of the quality benchmark for the strokerelated websites. Also, we thank Dalma Kasza, medical student at the University of Medicine and Pharmacy of Tîrgu Mureş, Romania, for her contribution to data acquisition.

# CONFLICT OF INTEREST

Nothing to declare.

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**CLINICAL UPDATE** 



DERMATOLOGY // PATHOLOGY

# 70% Trichloroacetic Acid in the Treatment of Facial Sebaceous Hyperplasia

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#### **ARTICLE HISTORY**

Received: June 1, 2018 Accepted: July 29, 2018

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# ABSTRACT

The present paper highlights the usefulness of 70% trichloroacetic acid in treating sebaceous hyperplasia in elderly patients. Esthetics are an important issue, and different therapeutic modalities can be used, such as systemic isotretinoin, surgical excision, electrocautery, cryosurgery, topical photodynamic therapy and laser, but all these methods are expansive and invasive procedures that may result in scars, which are more extensive than the original lesions.

Keywords: 70% trichloroacetic acid, sebaceous hyperplasia, treatment

Sebaceous hyperplasia is a common benign proliferation of the sebaceous glands in middle-aged and elderly people. The clinical picture is striking and with great esthetic impact. Soft yellow papules with central umbilication are noticed not only on the face (particularly on the forehead, cheeks, and nose), but also on the genitalia, areola, and chest. Although they are known as senile sebaceous hyperplasia due to predominance in the elderly, nowadays sebaceous hyperplasia has been observed in middle-aged and even young women. In the majority of cases, the evolution is progressive, over several years, with crops of new lesions while the older ones become larger, umbilicated, and may discharge sebum from the center. No spontaneous clinical involution has been noted.

Sebaceous hyperplasia lesions can have variable morphological distribution: diffuse, unique large form, linear or zosteriform distribution, or along Blaschko's lines. In daily practice, most cases show a diffuse facial distribution of sebaceous hyperplasia papules.

Skin biopsy is not necessary every time; the diagnosis is usually clinical, although a histological report would confirm a lobular array of well-differentiated



**FIGURE 1. A** – Adult sebaceous hyperplasia; **B** – The same patient with frosting of the skin during application of 70% trichloroacetic acid (third application); **C** – Close view of the frontal area of the same patient after 6 months of treatment

mature sebaceous lobules. In the pathologist's view on microscopic examination, sebaceous hyperplasia is defined only if at least 4 sebaceous lobules are attached to the infundibulum of the pilosebaceous unit, and sebocytes are filled with lipids.

The explanation why some individuals are predisposed to develop sebaceous hyperplasia is not completely understood, although different etiopathogenic factors have been incriminated such as natural aging, prolonged exposure to UV radiation, genetic predisposition. Presenile (or premature) diffuse familial sebaceous hyperplasia is a rare disorder in adolescents with family traits.

Molecular data support the hypothesis that the sporadic form may be a benign neoplasm instead of sebaceous hyperplasia; a pathogenic role of the EGFR-RAS-MAPK pathway has been demonstrated in sporadic sebaceous gland hyperplasia.<sup>1</sup>

During recent years, reports of other factors inducing sebaceous hyperplasia have been published. Cyclosporine administered in organ transplant recipients, especially renal transplant, was associated with the development of multiple sebaceous hyperplasia treated with oral isotretinoin. Additionally, sebaceous hyperplasia was reported in immune-suppressed organ transplant recipients in 16% of cases.

Various treatment methods have been attempted during the last decades, such as electrodessication, light lasers, applications of acids and photodynamic therapy, with different results and with the risk of scars and residual hyperpigmentation. Moreover, these methods are costly and difficult to access for patients. Oral isotretinoin is welldocumented in treating sebaceous hyperplasia; its action is based on inhibiting the size and function of sebaceous glands, but encumbered by serious side effects and recurrences upon discontinuation.

Monthly application of 70% trichloroacetic acid (TCA) for 5 consecutive months on the forehead of a 67-year-old woman diagnosed with sebaceous hyperplasia proved to

be a valuable therapeutic option in our daily practice, with no side effects. Close follow-up of the patient showed no recurrence; new papules were treated in a similar way with positive results (Figure 1, panels A–C).

Based on these results, the method was applied to other patients with the same good tolerability and outcome. No laboratory investigations or other examinations were necessary during the topical treatment. Between sessions, an emollient cream with high UV protection index and avoidance of sun exposure were recommended.

According to the definition, TCA is a chemical peel that induces exfoliation of the skin. Initially, it was used for the cosmetic improvement of photo aging; subsequently, it became a versatile topical agent with a wide spectrum of clinical indications, exceeding its cosmetic purposes. In different concentrations with or without other ingredients, TCA was used in diverse pathologies, for example: striae rubra, plantar callus and warts, cutaneous leishmaniasis scars, for chemocauterization of small tracheocutaneous fistula, cervical intraepithelial neoplasia (CIN), acne, pyogenic granulomas in children, sebaceous hyperplasia.<sup>2</sup>

TCA is very caustic and should be handled with care. At a concentration of 70%, it acts as a deep peel at the level of mid reticular dermis.<sup>3</sup> A short contact produces the coagulation of epidermal and dermal proteins, as well as the necrosis of collagen from the upper reticular dermis.<sup>4</sup>

The necrotic layers are replaced with "seemingly normal skin" due to re-epithelization from the surrounding islets of keratinocytes and from skin appendages.<sup>5</sup>

TCA is a self-neutralizing peel, no systemic absorption has been reported, and patients do not complain of pain and/or pruritus. A burning sensation is sometimes described, but for a short period of time.

In conclusion, chemical cauterization with 70% TCA is a safe, easy-to-perform, non-expansive, and effective method for the treatment of sebaceous hyperplasia in patients to whom other methods are inaccessible.

# **CONFLICT OF INTEREST**

Nothing to declare.

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Editorials should address either a particular topic that is currently of interest in the field of interdisciplinary medicine or to an article which is published in the same issue of the journal. The number of references should not exceed twenty-five in total.

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**Style and spelling:** Authors, whose first language is not English, are requested to have their manuscripts checked carefully, preferably by an English native-speaker, before submission, to expedite the review process.

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- Acknowledgements, Competing Interests, Funding, and all other required statements.
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# Reference to an article

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# Reference to a book

2. Nichols WW, Rourke MF. Aging, High Blood Pressure and Disease in Human. 3rd ed. London/Melbourne: Lea and Febiger; 1990.

# Reference to a chapter in a book

3. Nichols WW, O'Rourke MF. Aging, high blood pressure and disease in humans. In: Arnold E, ed. McDonald's Blood Flow in Arteries: Theoretical, Experimental and Clinical Principles. 3rd ed. London/Melbourne/Auckland: Lea and Febiger, 1990; p. 398-420.

# Reference to a webpage

4. Panteghini M. Recommendations on use of biochemical markers in acute coronary syndrome: IFCC proposals. eJIFCC 14. http://www.ifcc.org/ejifcc/ vol14no2/1402062003014n.htm (28 May 2004)

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