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Characteristics of Coronary Lesions in Small Vessel Disease Treated with Elective Stenting in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Background: The incidence of diabetes mellitus (DM) has suffered a dramatic increase and is a serious worldwide issue. Diabetes causes microvascular and macrovascular complications including coronary artery disease (CAD) that ultimately contributes to a high rate of cardiovascular morbidity and mortality. **Study aim:** The aim of this study was to assess the factors associated with the atherosclerotic involvement of small coronary arteries as compared to large vessel disease, in patients with type 2 diabetes mellitus undergoing percutaneous stent coronary angioplasty. **Material and methods:** Thirty-one patients who underwent Multislice 64 CT assessment of coronary lesions and stent implantation at the level of the significant coronary lesion were included in the study. CT-based Calcium Score was determined in all patients. Group 1 included patients with coronary lesions located on a vessel with a reference diameter above 3 mm (n = 24) and Group 2 included patients with a coronary lesion located on a vessel with a reference diameter below 3 mm (n = 7). **Results:** The mean age of the study population was 62.25 ± 2.59 years in Group 1 and 64.28 ± 9.18 years in Group 2. Female gender was recorded in 38% of cases in Group 1 and in 14% of cases in Group 2. The left ventricular ejection fraction was below 45% in 13% of cases in Group 1 and in 29% of patients in Group 2. Bioabsorbable stents were implanted in 57% of coronary arteries suffering from small vessel disease, compared to 4% in the rest of the coronary arteries (p = 0.005). The Calcium Score was 552.45 ± 545.79 (95% CI: 354.41–694.64) in Group 1 compared to 1387 ± 1830.3 (95% CI: 305.85–3079.9) (p = 0.014). **Conclusions:** The location of the atherosclerotic process at the level of the small coronary arteries is associated with a significantly higher Calcium Score at the level of the coronary tree, and with a higher rate of bioabsorbable stent implantation.

Keywords: diabetes, small vessel disease, coronary atherosclerosis, Calcium Score, bioresorbable scaffolds

INTRODUCTION

The incidence of diabetes mellitus (DM) has suffered a dramatic increase and is a serious worldwide issue.[1] Diabetes causes microvascular and macrovascular complications, including coronary artery disease (CAD) that ultimately contributes to a high rate of cardiovascular morbidity and mortality.[2,3] Diabetes is strongly associated with microvascular and macrovascular complications, such as nephropathy, retinopathy, neuropathy, or atherosclerotic diseases located on peripheral, coronary or carotid arteries. Anatomical, structural, and functional changes leading to multi-organ dysfunction is also included in the group of diabetes-associated vascular alterations. Persistent elevated levels of blood sugar could play a major role in the initiation of diabetic vascular complications through many structural and metabolic disturbances, which include: production of advanced glycation end-products (AGE), elevated production of reactive oxygen species, abnormal activation of signaling cascades.[4]

Elevated free fatty acids, hyperglycemia, insulin resistance and increased amounts of circulating end-glycosylated serum products are the principle factors involved in the accelerated atherosclerotic process that is observed in type 2 DM patients.

In diabetic patients the coronary arteries are described as diffusely atherosclerotic with more distal involvement, small and prone to acute coronary events.[5]

Nicholls reported that IVUS lumen volumes were smaller in diabetic patients compared to those in non-diabetic patients. The most common factors described in association with angiographically small coronary arteries were:

a) Arteries that have a large atherosclerotic burden;
b) Anatomically small arteries that are distal in location, non-dominant, and supply limited amounts of myocardium;
c) Arteries with negative remodeling.[5]

In diabetic patients, CAD is usually detected in an advanced stage, while the asymptomatic stages remain unfortunately undetected.[6]

Many analytical scores such as Syntax, Extent, and Vessel, were developed in order to analyze the severity of coronary atherosclerosis. These scores are useful especially for the estimation of the progression of atherosclerosis, and are very important in deciding the means of coronary interventions.[7]

The adverse macrovascular consequences of DM are usually easily recognized.[8] Patients with diabetes mellitus are developing a very fast and progressive form of atherosclerosis which requires revascularization and also, in these patients, the rate of restenosis is significantly higher.

New techniques for the interventional treatment of coronary artery disease are continuously in development.

Drug-eluting stents (DES) in diabetic patients reduce considerably the need for repeated revascularization compared with bare-metal stents (BMS). In case of diabetes, there is an increased risk for adverse clinical events after percutaneous coronary intervention (PCI) with DES. The newer generations of DES generally have shown a better long-term outcome compared with first-generation DES.[8]

Bioresorbable vascular scaffolds (BVS) are a novelty in the treatment of CAD, providing transient vessel support and drug delivery to the vessel wall.[8] Bioresorbable stents (BRS) are useful in the acute revascularization of coronary artery lesions and show reasonably low rates of target lesion revascularisation (TLR) and major adverse cardiac events. Plaque stabilization and sealing caused by BRS-induced remodeling was revealed by multiple imaging analyses, although the clinical impact needs further assessment. No foreign body remains in the vessel in the long term, because of BRS degradation. Stent thrombosis risks are potentially reduced or eliminated, depending on the duration of the resorbtion. This risk may be reduced, because BRS are dissolved, especially in the case of long or complex lesions and diffuse artery disease, when several would be implanted simultaneously. DES have been shown to have an incomplete endothelization, after as long as 40 months post-implantation.[8] BRS coating is degradable, not durable, and this way stent thrombosis stimulation is absent. Optical coherence tomography (OCT) and intravascular ultrasound examinations display late lumen enlargement in numerous cases with the BVS and BRS.[9]

The Coronary Artery Calcium (CAC) Score, measured by Coronary Computed Tomography Angiography (CCTA) is an independent predictor of coronary heart disease risk, and consequently may help in deciding how aggressively to pursue cholesterol-lowering, anti-platelet therapy and other primary prevention strategies.[10]

The aim of this study was to assess the factors associated with the atherosclerotic involvement of small coronary arteries as compared to large vessel disease, in patients with type 2 diabetes mellitus undergoing percutaneous stent coronary angioplasty.

MATERIAL AND METHODS

Study design

From January 2015 to December 2015, 31 type 2 diabetic patients aged >18 years, with coronary artery disease (acute or chronic), having a stenosis of at least 50% by vi-

sual assessment, who underwent CT coronary angiography and percutaneous coronary intervention (PCI) were enrolled in this retrospective study.

The analyzed variables were: age, gender, cardiovascular risk factors, the presence of multi-vessel coronary disease, left ventricular ejection fraction, the Calcium Score, the type of stent that was implanted (DES, BMS, bioresorbable scaffolds). The data was collected from the medical discharge papers, from echocardiographic reports, computed tomography results and laboratory analysis results. According to the size of the stented vessel, the study population was divided into 2 groups. The first group included patients with coronary lesions located in vessels with a reference diameter larger than 3 mm (n = 24 patients), while the second group included patients with coronary lesions located in vessels with a reference diameter below 3 mm (n = 7).

The study has been carried out in accordance with the code of ethics of the World Medical Association's Declaration of Helsinki. All patients gave written informed consent, and the ethics committee of the Cardio Med Medical Center, the center where the study was conducted, approved the study protocol.

Stent procedure

Before coronary catheterization, the general laboratory tests were evaluated. Patients received antiplatelet therapy (Aspirin) before the procedure, while during the procedure, repeated intravenous heparin boluses were administered.

Using the general technique, with pre-dilatation followed by the implantation of the stent/scaffold and post-dilatation, we performed the coronary interventions. The standard stents and the sirolimus-eluting stents (available in 8 mm and 18 mm diameters, and 2.5 mm, 3.0 mm, and 3.5 mm diameters respectively) were identical in appearance. Patients received dual antiplatelet therapy with Clopidogrel (75 mg/day) and Aspirin (75 mg/day) for nine months after the intervention. Patients were followed-up at 1, 3, 6, 9 and 12 months after stent implantation.

Angiographic analysis

CCTA was performed, and the Calcium Score was assessed. The applied procedure consists in CCTA examination (64 MDCT Siemens), focused on the coronary arteries, completed by dynamic administration (5 ml/s) of 100 ml non-ionic contrast substance (Iopamiro 370), followed by the administration of 100 ml of saline solution, using a right antecubital venous line. According to standard protocols, a Calcium Score (CaS) of zero was considered to indicate the absence of CAD, a CaS between 1 and 10 minimal evidence of coronary artery disease, a CaS between 11 and 100 mild evidence of CAD, a CaS between 101 and 400 moderate evidence of coronary artery disease and a CaS above 400 extensive atherosclerotic CAD.

Left ventricular ejection fraction (LVEF) was determined using echocardiographic examination.

Statistical analysis

Statistical analysis was performed using the GraphPad InStat3 statistical software. The baseline characteristics, laboratory data and angiographic characteristics were analyzed for significant differences between the two groups. Continuous variables are expressed as mean values and categorical variables are presented as proportions (%).

Differences between groups were considered to be significant at a p value of <0.05.

RESULTS

Patient demographics

Characteristics of the study population are summarised in Table 1. The mean age of the study population was 62.25 ± 2.59 years in Group 1 and 64.28 ± 9.18 years in Group 2 (p = 0.72).

There were no significant differences between the two groups regarding the number of patients over 65 years. In the first group 46% of patients, and in the second group 29% of patients were over 65 years (p = 0.6). Furthermore, 53.91% of patients were between the age 50 and 65 years in Group 1 and 71.43% in Group 2. In case of patients with coronary lesions located on vessels with a diameter below 3 mm, the age ranged between 50 and 65 years.

Regarding gender, there were 38% women in Group 1 and 14% in Group 2 (p = 0.31) (Figure 1).

The rate of smokers was 8% in the first group and 29% in the second group, the differences was not statistically significant (p = 0.21).

Predictors of the extent of coronary artery atherosclerosis

The mean cholesterol value was 189 mg/dl in the group of patients with coronary lesions on a vessel with diameter >3 mm and 160 mg/dl in the group of patients with coronary lesion on a vessels with a diameter <3 mm (p = 0.43).

TABLE 1. Characteristics of the study groups

	Group 1 Diameter >3 mm		Group 2 Diameter <3 mm		p value
	n = 24	%	n = 7	%	
Mean age	62.25		64.28		ns
Aged >65 years	11	45%	2	28%	0.6
Aged <50 years	2	8%	0	0%	ns
Female gender	9	37%	1	14%	0.31
Smokers	2	8.3%	2	28%	0.21
Mean total cholesterol (mg/dl)	188.9		159.8		0.43
Three-vessel CAD	2	8%	0	0%	1.00
Mean LVEF	53.9		49.28		0.39
LVEF <45%	3	12.5%	2	28%	0.39
Ca Scoring	552.54		1387		0.014
No. of patients with DES	15	62.5%	4	57.1%	1
No. of patients with BRS	1	4%	2	28%	0.1
No. of patients with BMS	9	37.5%	1	14.2%	0.3
No. of DES/coronary artery	18	75%	7	10%	0.29
No. of BRS /coronary artery	1	4.1%	4	57.1%	0.005
No. of BMS /coronary artery	9	37.5%	1	14.2%	0.31

Regarding the multi-vessel coronary artery disease, there were no statistically significant differences between the 2 groups (8% vs. 0%, p = 1.00).

There were no statistically significant differences between the study groups in respect to the mean value of LVEF; the mean value of LVEF was 54 ± 2.24 in Group 1 and 49 ± 7.04 in Group 2. The number of patients with EF below 45% was 13% in the first group and 29% in the second group, the differences between the two groups being insignificant (Figure 2).

Patients with coronary lesions located on vessels with a reference diameter below 3 mm showed to have a higher calcium score (CaS 1387 ± 1830.3), compared with patients with lesions located on a vessel with reference diameter above 3 mm (CaS 552 ± 545.79) and the results were statistically significant (p = 0.014) (Figure 3).

Types of stents implanted in the coronary arteries

Analysis of the percentage of bare metal stents per coronary artery and drug eluting stent per coronary artery in diabetic patients showed that the differences did not reach statistical significance. The rate of DES implantation was 75% in Group 1, compared to 10% in Group 2 (p = 0.29). The number of bioresorbable scaffolds per coronary artery was 4% in the first group and 57% in the

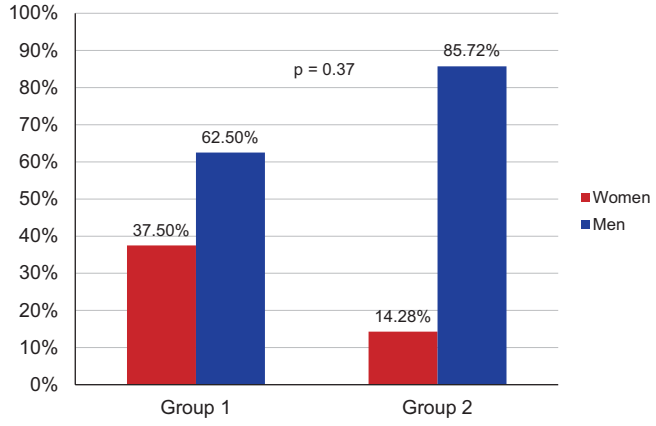

FIGURE 1. Gender distribution in the study groups

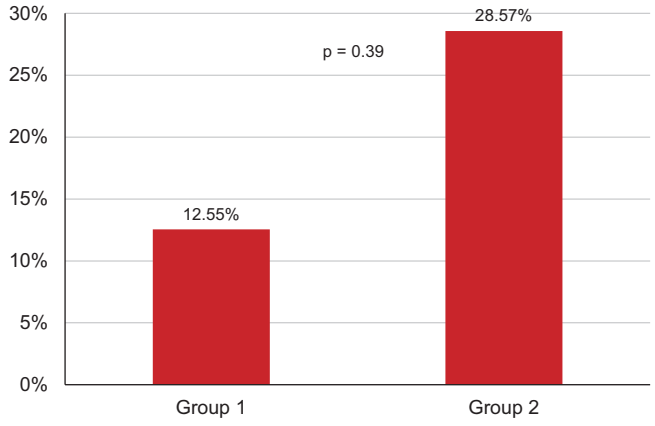

FIGURE 2. Patients with LVEF below 45%

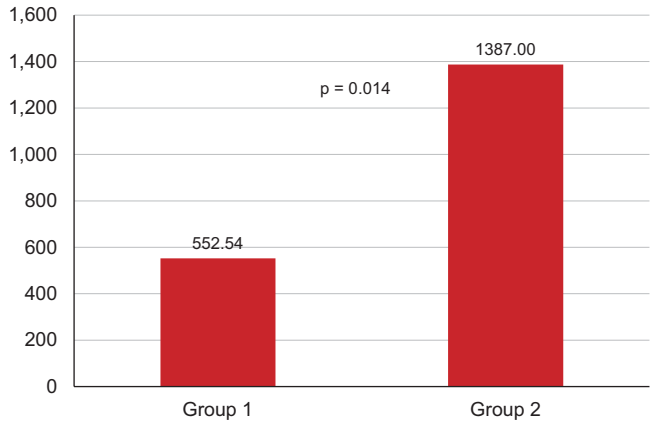

FIGURE 3. Coronary Calcium Score assessed by CCTA in the study groups

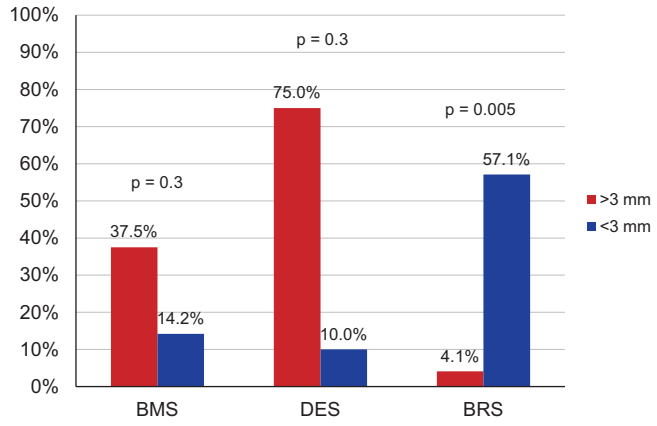

FIGURE 4. Stent types in the study groups. BMS = bare metal stent, DES = drug eluting stent, BRS = bioresorbable stent

second group, the difference being statistically significant (p = 0.005) (Figure 4).

DISCUSSIONS

In this study, we compared the rate of elective implantation of stents in the coronary arteries with the diameter of the vessel and with the Calcium Score. Bioresorbable stents have a higher rate of implantation in the area of the coronary tree with a diameter below 3 mm, probably because the restenosis rate associated with standard stents is higher in diabetic patients.

Diabetes is a predictor of restenosis after angioplasty and coronary stenting. Several studies have reported restenosis rates of 47% to 71% in diabetics.[4]

In diabetic patients, there is an exaggerated tissue proliferation in stented lesions. In diabetes there is an association between the hormonal and vascular abnormalities, which promotes smooth muscle cell proliferation after vascular injury.[4]

The pattern of post-interventional restenosis differs in case of sirolimus-eluting stents: restenotic lesions in standard stents were diffuse, while in the sirolimus-eluting stents they were focalized.[11]

Bioresorbable scaffolds determine a successful acute revascularization of coronary artery lesions and indicate low rates of major adverse cardiac events during early follow-up. Multiple imaging analyses show a beneficial plaque stabilization.

Bioresorbable scaffolds present the capability of dissolving themselves, this way no foreign body remains in the vessel in the long term. This process can facilitate the return of vessel motility properties, late expansive remodeling and late luminal enlargement.[12]

Stent thrombosis risks are potentially reduced or eliminated, but this process is happening late, depending on resorbtion duration.[13] Knowing that BRS dissolve, this risk may be reduced, especially in long or complex lesions and diffuse coronary atherosclerotic disease. Also, the permanent complete side-branch occlusion risk could be prevented.[14]

When a patient receives a drug-eluting stent, there is a reduced neointimal tissue growth and neoatherosclerosis occuring in time within the stent. Chronic inflammation, as reaction to a permanent metal implant, triggers stent thrombosis in case of DES implantation. BRS coating is degradable, not durable, and the stimulus for stent thrombosis is absent in this case.[13]

At the same time, bioresorbable stents reduce bleeding complications, a particularly important fact in the elderly, who are at the greatest risk of bleeding.[15]

For patients with BRS, the use of non-invasive imaging techniques such as computed tomography angiography or magnetic resonance imaging for follow-up is indicated. Metallic stents can cause a blooming effect with these techniques, making the interpretation more difficult. Bioresorbable scaffolds do not restrict the use of CT or magnetic resonance imaging because they are non-metallic.[16]

Optical coherence tomography and intravascular ultrasound examinations show late lumen enlargement in numerous patients with the Absorb BVS.[13]

The mechanical flexibility of some BRS initially maintains the original vessel geometry better than rigid metal stents; a minor bad position can be resolved by BRS self-correction.[17]

Bioresorbable stents have a role in the reduction of adverse events, such as infarction or reocclusion. Drug elution and scaffolding are temporary options, and are pro-

vided by the device only until the vessel has healed, this way no foreign material such as non-endothelialized struts and drug polymers can persist in the long term.[12]

The implantation of these new stents might allow surgeons to carry out anastomoses of coronary artery bypass grafts at distal segments, and if the patients need multiple interventions, there will be no interference with previously implanted DES, because side branches can sometimes be especially difficult to re-cross the lesion.[13]

BRS seem attractive for the treatment of in-stent restenosis. They provide short-term scaffolding, ensure drug delivery, and do not affect vessel diameter with another metal layer, comparable with drug-eluting balloons.[18]

At the moment, several possible benefits of BRS are hypothetical or only demonstrated in animal testing, an example is the impact of restoring vasomotion, as shown by data derived from a small, non-randomized study investigating patients with stable coronary artery disease and *de novo* lesions.[13]

A large number of cross-sectional studies have recognized that patients with diabetes have a higher prevalence and extent of coronary calcium level than non-diabetic patients. There is less information available about the utility of coronary calcium as a predictor of risk in diabetic patients.[19]

Coronary calcium predicted all-cause mortality in diabetics referred for coronary CT scanning, as found by Raggi *et al*. They also found that diabetic patients have a higher risk for mortality associated with a given degree of calcium than the non-diabetic patients.[20]

In diabetes, multi-vessel coronary atherosclerosis is frequently present before ischemic symptoms occur and before treatment is instituted.[21]

Computed tomography shows that diabetes-affected individuals have a high level of calcification in their vascular beds, reported as the Coronary Artery Calcium Score, being a significant cardiovascular disease burden.[22]

A recent study reveals that coronary Ca scoring may be superior to other techniques for the determination of cardiovascular risk factors and for predicting the evolution in uncomplicated, stable, type 2 diabetes patients.[19]

Diabetic patients without a history of coronary calcification have a survival rate similar to non-diabetic patients during 5 years of follow-up.[20] These results suggest that the Coronary Calcium Score might be useful for further short-term risk stratification in diabetic patients.[19]

CONCLUSIONS

The location of the atherosclerotic process at the level of small coronary arteries is associated with a significantly higher Calcium Score at the level of the coronary tree, and with a higher rate of bioabsorbable stent implantation.

CONFLICT OF INTEREST

Nothing to declare.

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