Impact of diabetes mellitus on the dimensions of normal atherosclerosis-free coronary arteries

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Kardiol Pol. 2021; 79 (5): 566–568; DOI: 10.33963/KP.15941

Received: February 8, 2021

Revision accepted: March 22, 2021

Published online: March 26, 2021

INTRODUCTION

In diabetic patients the coronary arteries appear angiographically smaller [1–5]. This is typically seen in the reference segments and may influence stent size selection. The possible explanations for this appearance in diabetics include: (1) more diffuse disease, (2) less pronounced remodeling, or (3) authentically smaller vessel size. The aim of our study was to use coronary computed tomography angiography (CCTA) in order to compare the dimensions of normal coronary arteries in patients with and without diabetes mellitus.

METHODS

The current study is a subgroup analysis of a larger study focused on the anatomy of normal coronary arteries [6]. The study conduct complied with the Helsinki Declaration and was performed with agreement of institutional review board. Written consent was not required due to the retrospective character of the study. Demographic characteristics and patient risk factors were collected retrospectively by hospital chart review. The risk factor definitions have been described previously [6]. Patients with diabetes mellitus were case-control matched in a 1:3 ratio with non-diabetics, exactly according to sex and coronary dominance pattern and within 0.1 m^2 maximal allowance of freedom for body surface area (BSA) calculated with the Du-Bois formula [7].

In all patients CCTA was performed after administration of sublingual nitroglycerin (0.8 mg). If necessary, intravenous boluses of metoprolol were given to reduce heart rate below 75 bpm. The CCTA studies were performed with the use of a dual-source computed tomography scanner (Somatom Definiton; Siemens Healthcare, Forchheim, Germany) as described previously [6].

The normal coronary artery was defined by CCTA as free of any calcification and detectable atherosclerosis. CCTA measurements were performed by a single reader at a dedicated workstation (Syngovia software, Siemens, Forchheim, Germany). The coronary artery dominance pattern and segmentation were defined according to the SYNTAX study criteria [8]. The distal coronary segments were excluded from the analysis. Lumen diameters (LD) and lumen areas (LA) were measured in all coronary segments. Mean values were computed using minimal and maximal dimension and then were used for the analyses.

The statistical analyses were performed with MedCalc 9.3.8.0 (MedCalc, Marierkerke, Belgium). The categorical data are presented as numbers and percentages and analyzed with the χ^2 test. The Shapiro-Wilk test was performed to assess the normality of data distribution. Continuous variables are presented as mean and standard deviation and compared with the t-test, or in the case of non-parametric distribution median with first and third quartile and compared with the Mann–Whitney U test. The Spearman test was used for the correlation analysis.

RESULTS AND DISCUSSION

The population of 201 consecutive subjects without CCTA-detected coronary atherosclerosis was described previously in an article focused on the influence of sex and coronary artery dominance pattern on the coronary segments dimensions [6]. Overall, in the cur-

rent sub-analysis, there were 14 (7%) diabetic patients (4 males, mean [SD] age 58 [6] years) and 42 matched control subjects (12 males, mean [SD] age 51 [12] years). All diabetic patients had type 2 diabetes and were on oral antidiabetic medication (8 patients treated with metformin, 1 patient with glyclaside, 2 patients with inhibitors of dipeptidyl peptidase-4), except for 2 patients treated with insulin and 1 patient with newly diagnosed diabetes with diet-controlled disease. The median duration of diagnosed diabetes was 5.5 years (Q1 = 2; Q3 = 9 years). Diabetic patients were older (58 [6] years vs 51 [12] years; $P = 0.046$), more often had arterial hypertension (100% vs 62%; $P = 0.005$), and their mean (SD) body mass index was higher (31.9 [5.6] kg/m^2 vs 27.9 [3.3] kg/m^2; $P = 0.002$). There were no differences in any coronary segments with regards to the LA or LD comparing the two groups (Table 1). We did not find any correlation between the duration of diabetes and coronary dimensions including the left main coronary artery LA (r = -0.2; $P = 0.48$) and LD (r = -0.3; $P = 0.38$) and proximal right coronary artery LA (r = -0.5; $P = 0.13$) and LD (r = -0.5; $P = 0.16$).

Interobserver variability for appropriate measurements was reported previously [6].

The main finding of our study is that diabetes mellitus *per se* does not influence the dimensions of coronary arteries in the absence of atherosclerosis.

The coronary arteries in diabetics with coronary artery disease (CAD) appear angiographically smaller than in CAD patients without diabetes [1–5]. By excluding any influence of diabetes mellitus on non-atherosclerotic coronary artery dimensions, the most probable explanations for this finding are either more diffuse atherosclerosis in diabetics or impairment of compensatory remodeling.

Coronary angiography can identify reduction of lumen size, but cannot explain its pathophysiological background. Moseri et al. [1] found that angiographically normal coronary arteries in diabetic patients were smaller as compared with matched controls. The authors claimed that their findings represented the earliest phase of CAD. However, invasive angiography cannot exclude mild atherosclerotic lesions that can be identified by CCTA.

Coronary stenoses develop either due to plaque accumulation that outstrips the capacity of the coronary artery to adapt (limitation of positive remodeling) or due to inadequate or negative vessel remodeling with limited plaque accumulation. These two processes can be visualized with intravascular ultrasound (IVUS) studies or non-invasively with CCTA. Vavuranakis et al. [5] showed with IVUS that compensatory vessel response to atherosclerosis is impaired in diabetic patients which may explain earlier and accelerated disease progression. Jansen et al. [4] found blunted remodeling response to atherosclerosis accumulation in reference segments of diabetic subjects. A pooled analysis of 5 prospective IVUS studies showed inadequate compensatory remodeling in diabetics, especially insulin-dependent subjects [9]. Typically, the development of type 2 diabetes mellitus is proceeded by several years of hyperinsulinemia [10]. Moreover, the diagnosis of type 2 diabetes is usually delayed by 2 years and 7% of patients are unaware of the disease for up to 7 years [11]. In response to insulin, the smooth muscle proliferates; and the amount of fibrous tissue increases which together with endothelial dysfunction may impact the ability of the arterial wall to expand [12]. However, it has been unclear whether negative remodeling (i.e. vessel shrinkage) in diabetic patients may occur independently and prior to the plaque accumulation. The results of the current study of diabetic patients without any plaque accumulation suggest that negative remodeling does proceed the plaque formation

Table 1. Comparison of lumen area and diameter in diabetic and control subjects

Segment	Diabetic group (n = 14)	Control group (n = 42)	*P* value
LMCA LA, mm^2, median (IQR)	21.7 (19.6–27.1)	21.3 (17.4–28.3)	0.64
LMCA LD, mm, mean (IQR)	5.4 (0.6)	5.3 (0.8)	0.60
Prox LAD LA, mm^2, median (IQR)	11.8 (10.1–13,9)	11.5 (9.8-14.4)	0.81
Prox LAD LD, mm, median (IQR)	3.9 (3.6–4.2)	3.9 (3.6–4.3)	0.87
Mid LAD LA, mm^2, mean (SD)	7.3 (2.5)	6.9 (2.1)	0.53
Mid LAD LD, mm, mean (SD)	2.9 (0.5)	2.9 (0.5)	0.57
OM LA, mm^2 median, (IQR)	3.6 (2.9–4.0)	2.9 (2.4–3.9)	0.19
OM LD, mm, mean (SD)	2.0 (0.3)	1.8 (0.3)	0.14
IM LA, mm^2, median (IQR)	2.0 (1.9–4.2)	3.3 (2.2–4.1)	0.33
IM LD, mm, median (IQR)	1.5 (1.4–2.1)	1.9 (1.6–2.1)	0.31
Prox LCX LA, mm^2, mean (SD)	12.6 (4.2)	10.4 (4.1)	0.09
Prox LCX LD, mm, mean (SD)	3.9 (0.7)	3.6 (0.7)	0.09
Mid LCX LA, mm^2, mean (SD)	12.9 (4.3)	10.7 (4.1)	0.44
Mid LCX LD, mm, mean (SD)	4.0 (0.7)	3.7 (0.7)	0.45
Prox RCA LA, mm^2, mean (SD)	13.1 (4.6)	12.5 (4.2)	0.66
Prox RCA LD, mm, mean (SD)	4.0 (0.6)	3.9 (0.7)	0.68
Mid RCA LA, mm^2, mean (SD)	11.1 (4.9)	9.4 (4.1)	0.20
Mid RCA LD, mm, mean (SD)	3.7 (0.9)	3.4 (0.8)	0.26

Abbreviations: IM, intermediate artery; LA, lumen area; LAD, left anterior descending coronary artery; LCx, left circumflex coronary artery; LD, lumen diameter; LMCA, left main coronary artery; mid, middle; OM, obtuse marginal branch; IQR, interquartile range; prox, proximal; RCA, right coronary artery; SD, standard deviation

and that the reduction of luminal diameters only begins with the start of plaque accumulation.

All the diabetics and control patients routinely received sublingual nitroglycerin prior to CCTA. It is possible that the size of coronary arteries in diabetic patients was smaller at baseline, due to lower levels of nitric oxide mediated vasodilation (i.e.. endothelial dysfunction) [13].

The current study has some limitations. The study is retrospective, and the population is small. However, diabetes is one of the strongest risk factors of the CAD and the diabetic patients with coronary tree virtually free from atherosclerosis are not common. The median duration of diabetes was 5.5 years. However, as stated above the pre-diabetic state and even undiagnosed diabetes could have been present for much longer period.

Article information

Conflict of interest: None declared.

How to cite: Skowroński J, Mintz GS, Michałowska I, et al. Impact of diabetes mellitus on the dimensions of normal atherosclerosis-free coronary arteries. Kardiol Pol. 2021; 79(5): 566–568, doi: 10.33963/KP.15941.

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