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

Authors: Jarosław Skowroński, Gary S. Mintz, Ilona Michałowska, Emilia Szudejko, Min Jae Cha, Cezary Kępka, Mariusz Kruk, Jacek Kwieciński, Łukasz Kalińczuk, Zbigniew Chmielak, Adam Witkowski, Michał Ciszewski, Sang-Wook Kim, Jerzy Pręgowski

Article type: Short communication

Received: February 8, 2021.

Accepted: March 22, 2021.

Published online: March 26, 2021.

ISSN: 0022-9032

e-ISSN: 1897-4279

This is an Open Access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives 4.0 International License (CC BY-NC-ND 4.0), allowing third parties to download articles and share them with others, provided the original work is properly cited, not changed in any way, distributed under the same license, and used for noncommercial purposes only. For commercial use, please contact the journal office at kardiologiapolaska@ptkardio.pl.
Impact of diabetes mellitus on the dimensions of normal, atherosclerosis-free coronary arteries

Jarosław Skowroński a, Gary S. Mintz b, Ilona Michałowska a, Emilia Szudejko a, Min Jae Cha c, Cezary Kępka a, Mariusz Kruk a, Jacek Kwieciński a, Łukasz Kalińczuk a, Zbigniew Chmielak a, Adam Witkowski a, Michał Ciszewski a, Sang-Wook Kim c, Jerzy Pręgowski a

a National Institute of Cardiology, Warsaw, Poland.
b Cardiovascular Research Foundation, New York, United States of America.
c Chung-Ang University Hospital, College of Medicine, Chung-Ang University, Seoul, Korea.

Short title: Impact of diabetes mellitus on the coronary tree

Corresponding author

Jarosław Skowroński, MD, PhD
National Institute of Cardiology, Alpejska 42 St., 04-628 Warsaw, Poland
E-mail: jskowronski@ikard.pl
Phone number: + 48 22 3434127, Fax number: + 48 22 3434506

Conflict of interest: none declared.
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) truly smaller vessel size. The aim of our study was to use coronary computed tomography angiography (CCTA) 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 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 m² maximal allowance of freedom for body surface area (BSA) calculated by 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 beats/min. The CCTA studies were performed with the use of a dual-source computed tomography scanner (Somatom Definiton; Siemens Healthcare, Forchheim, Germany) as described before [6].

The normal coronary artery was defined by CCTA as lack of any calcification and absence of 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 analysed with the chi-square 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 manuscript focused on the influence of sex and coronary artery dominance pattern on the coronary segments dimensions [6]. Overall in current sub-analysis, there were 14 diabetic patients (7%) (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] BMI 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 angiography 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. found that angiographically normal coronary arteries in diabetic patients were smaller as compared with matched controls [1]. 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. showed with IVUS that compensatory vessel response to atherosclerosis is impaired in diabetic patients which may explain earlier and accelerated disease progression [5]. Jansen et al. found blunted remodeling response to atherosclerosis
accumulation in reference segments of diabetic subjects [4]. A pooled analysis of five 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 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 (ie. 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 prediabetic state and even undiagnosed diabetes could have been present for much longer period.
References:


<table>
<thead>
<tr>
<th>Segment</th>
<th>Diabetic group (n = 14)</th>
<th>Control group (n = 42)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LMCA LA, mm² (Q1;Q3)</td>
<td>21.7 (19.6;27.1)</td>
<td>21.3 (17.4;28.3)</td>
<td>0.64</td>
</tr>
<tr>
<td>LMCA LD, mm (SD)</td>
<td>5.4 (0.6)</td>
<td>5.3 (0.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>prox LAD LA, mm² (Q1;Q3)</td>
<td>11.8 (10.1;13.9)</td>
<td>11.5 (9.8-14.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>prox LAD LD, mm (Q1;Q3)</td>
<td>3.9 (3.6;4.2)</td>
<td>3.9 (3.6;4.3)</td>
<td>0.87</td>
</tr>
<tr>
<td>mid LAD LA, mm² (SD)</td>
<td>7.3 (2.5)</td>
<td>6.9 (2.1)</td>
<td>0.53</td>
</tr>
<tr>
<td>mid LAD LD, mm (SD)</td>
<td>2.9 (0.5)</td>
<td>2.9 (0.5)</td>
<td>0.57</td>
</tr>
<tr>
<td>OM LA, mm² (Q1;Q3)</td>
<td>3.6 (2.9;4.0)</td>
<td>2.9 (2.4;3.9)</td>
<td>0.19</td>
</tr>
<tr>
<td>OM LD, mm (SD)</td>
<td>2.0 (0.3)</td>
<td>1.8 (0.3)</td>
<td>0.14</td>
</tr>
<tr>
<td>IM LA, mm² (Q1;Q3)</td>
<td>2.0 (1.9;4.2)</td>
<td>3.3 (2.2;4.1)</td>
<td>0.33</td>
</tr>
<tr>
<td>IM LD, mm (Q1;Q3)</td>
<td>1.5 (1.4;2.1)</td>
<td>1.9 (1.6;2.1)</td>
<td>0.31</td>
</tr>
<tr>
<td>prox LCX LA, mm² (SD)</td>
<td>12.6 (4.2)</td>
<td>10.4 (4.1)</td>
<td>0.09</td>
</tr>
<tr>
<td>prox LCX LD, mm (SD)</td>
<td>3.9 (0.7)</td>
<td>3.6 (0.7)</td>
<td>0.09</td>
</tr>
<tr>
<td>mid LCX LA, mm² (SD)</td>
<td>12.9 (4.3)</td>
<td>10.7 (4.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>mid LCX LD, mm (SD)</td>
<td>4.0 (0.7)</td>
<td>3.7 (0.7)</td>
<td>0.45</td>
</tr>
<tr>
<td>prox RCA LA, mm² (SD)</td>
<td>13.1 (4.6)</td>
<td>12.5 (4.2)</td>
<td>0.66</td>
</tr>
<tr>
<td>prox RCA LD, mm (SD)</td>
<td>4.0 (0.6)</td>
<td>3.9 (0.7)</td>
<td>0.68</td>
</tr>
<tr>
<td>mid RCA LA, mm² (SD)</td>
<td>11.1 (4.9)</td>
<td>9.4 (4.1)</td>
<td>0.20</td>
</tr>
<tr>
<td>mid RCA LD, mm (SD)</td>
<td>3.7 (0.9)</td>
<td>3.4 (0.8)</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Abbreviations: IM-intermediate artery, LA-lumen area, LAD-left anterior descending coronary artery, LCX-ramus circumflex of left coronary artery, LD-lumen diameter, LMCA-left main coronary artery, OM-obtuse marginal branch, Q1;Q3-first quartile; third quartile, RCA-right coronary artery, SD-standard deviation.

Continuous data are presented as either mean (SD) or median (Q1;Q3), the latter in the case of nonparametric distribution.