Subclinical Coronary Artery Disease in Patients with Type 1 Diabetes Mellitus Undergoing Hemodialysis

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Summary
Background: In patients with type 1 diabetes mellitus, atherosclerosis occurs earlier in life and coronary artery disease (CAD) constitutes the major cause of death.

Objective: Evaluate the prevalence and anatomic characteristics of coronary artery disease (CAD) in type 1 diabetic patients with chronic renal failure undergoing hemodialysis.

Methods: This is a descriptive study of 20 patients with type 1 diabetes mellitus undergoing hemodialysis without known CAD. CAD was assessed by quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS). QCA was performed in all lesions ≥30%, visually. All proximal 18-mm segments of the coronary arteries were analyzed by IVUS. All other coronary segments with stenosis ≥30% were also analyzed.

Results: Angiography detected 29 lesions ≥30% in 15 patients (75%). Eleven (55%) of the lesions were ≥50% and 10 (50%) ≥70%. Thirteen patients had all 3 major arteries interrogated by IVUS. Atherosclerosis was present in all patients and in all 5 proximal 8-mm segments analyzed. The mean vessel diameter of these segments was significantly larger at the IVUS than at the QCA, for all vessels. IVUS images of 25 (86.2%) of the 29 lesions ≥30% were obtained. Fibrotic plaques were common (48%) and 60% had intermediate vessel remodeling.

Conclusion: CAD was present in all vessels of all type 1 diabetic patients undergoing hemodialysis. These findings are in agreement with other autopsy, angiography and IVUS studies. Additionally, they indicate the need for additional epidemiological and imaging studies to better understand and treat such a complex and serious clinical condition affecting young people. (Arq Bras Cardiol 2009;93():4-9)

Key words: Coronary artery disease; diabetes mellitus, type 1; ultrasonography, interventional; renal insufficiency, chronic.

Introduction
In patients with type 1 diabetes mellitus, atherosclerosis occurs earlier in life and coronary artery disease (CAD) constitutes the major cause of death1. By the age of 55 years, the cumulative mortality rate due to CAD has been reported to be 30 to 40%2, which is much higher than the overall mortality rate of 4% in non-diabetic subjects. In fact, in type 1 diabetic patients, the mortality risk by CAD is increased 4 to 9 fold in men and 4 to 29 fold in women1. This risk is even higher when proteinuria or renal failure is present3-8. Tuomilehto et al5 followed 5,148 type 1 diabetic patients for more than 10 years and found that once chronic renal failure occurs, CAD develops earlier and much more often5.

Despite growing epidemiological and clinical interest, very few studies have been currently undertaken to characterize CAD in these individuals9-11, in opposition to type 2 diabetic patients. The present study was designed to evaluate the prevalence, the qualitative and quantitative characteristics of CAD in type 1 diabetic patients with chronic renal failure undergoing hemodialysis.

Methods
Patients with type 1 diabetes mellitus undergoing hemodialysis without known CAD were prospectively included in this descriptive and observational study. All patients underwent biochemical and standard hematomical work-up. Cardiovascular assessment included electrocardiogram, Doppler-echocardiogram and an ischemic test.

The study protocol was approved by the Ethics Committee of the Federal University of Sao Paulo and written informed consent was obtained from all participants.

Quantitative coronary angiography and intravascular ultrasound analysis
Nitroglycerin (300 µg) was given immediately before angiograms and intravascular ultrasound (IVUS) interrogations.

Visual analysis of coronary angiograms was performed by two experienced angiographists. Percent diameter stenosis of lesions was estimated and patients were classified as having...
normal arteries, lesions < 30% or lesions ≥ 30%. Quantitative coronary angiography (QCA) was performed in all lesions ≥ 30% using an automated edge detection algorithm (QCA CMS System, MEDIS Medical Imaging Systems, Leiden, Netherlands). Lesion length, minimal lumen diameter, reference diameter and percent diameter stenosis were measured at these sites.

IVUS imaging was performed using mechanical systems (Clear View or Galaxy, Boston Scientific, Sunnyvale, CA, USA) consisting of 30-MHz ultrasound catheters with a 0.5 mm/s motorized pull-back system. IVUS recording was initiated at the most distal segment of each vessel with diameter greater than 2 mm. Accordingly, at least half of the total vessel length was studied. The S-VHS recorded tape was used for offline measurements using dedicated IVUS analysis software (QIVA, Pie Medical, Netherlands). For this analysis, the most proximal 18-mm segment of the major coronary arteries was arbitrarily selected. Additionally, all other segments in the coronary tree presenting stenosis ≥ 30% at the angiography were analyzed.

The following measurements were performed at the proximal 18-mm coronary segments: vessel, lumen and plaque cross-sectional areas (CSA) and maximum plaque thickness, at every millimeter. Based on these measurements, vessel, lumen and plaque volumes were calculated. Minimal lumen CSA was also obtained. Atherosclerotic plaques were considered present when intimal thickness exceeded 0.3 mm. The axial distribution of the plaque along each of these coronary segments was assessed by calculating its coefficient of variation, by dividing the mean plaque CSA by the standard deviation of the plaque CSA.

At the segments selected for analysis for the presence of stenosis ≥ 30%, the lumen, vessel and plaque CSA were measured at the site with the minimum lumen CSA. Plaque burden was calculated as: (plaque CSA / vessel CSA at the lesion site) x 100. Proximal and distal reference sites were defined as those cross-sections with the least amount of disease and largest lumen within 10 mm of the lesion boundary. At these sites, vessel and lumen CSA were measured. The averaged lumen CSA of the proximal and distal reference was considered the reference lumen CSA. The lumen area stenosis was calculated as: [(reference lumen CSA minus lumen CSA at the lesion site / reference lumen CSA) x 100]. Vessel remodeling was determined based on the following definition: adaptive remodeling was considered to be present when vessel CSA at the lesion site was larger than vessel CSA at the proximal reference; constrictive remodeling was considered to be present when vessel CSA at the lesion site was smaller than vessel CSA at the distal reference and intermediate remodeling was present when vessel CSA at the lesion site was intermediate between vessel CSA at the proximal and distal references. A remodeling index was calculated as vessel CSA at the lesion site divided by vessel CSA at the proximal reference. At the lesion site, plaque composition was classified as soft, fibrotic or fibrocalcific, according to its characteristics. QCA and IVUS measurements were performed at the Core Laboratory of Hospital Israelita Albert Einstein (São Paulo, Brazil).

**Statistical analysis**

Quantitative data are presented as the mean value ± SD and qualitative data are presented as frequencies.

To study the association of the presence of stenosis ≥ 30% with age and duration of type 1 diabetes, the Student’s t test was applied. The same test was used to compare mean vessel diameter of the proximal 18-mm at the IVUS and angiography.

The search for an association between plaque maximum thickness and plaque volume in the most proximal 18-mm segments of the coronary arteries and age, serum cholesterol, body mass index, hemodialysis duration, and diabetes duration was carried out by calculating Pearson’s linear correlation coefficient.

All significance tests were two-tailed, and p values < 0.05 were considered significant.

**Results**

**Study population**

From February to November 2003, 20 patients were recruited for the study. Demographic and clinical data are depicted in Table 1. Only two patients (10%) presented myocardial ischemia at the functional tests.

**Angiographic analysis**

Visual assessment of the coronary angiograms detected 29 lesions ≥ 30% in 15 (75%) patients [1.93 ± 1.03 lesions per patient (Table 2)]. Eleven (55%) of them had lesions ≥ 50% and 10 (50%) had lesions ≥ 70%. One patient presented a proximal left anterior descending (LAD) artery occlusion. One of the patients with a positive ischemic test had stenosis in all three vessels [LAD: 50%, left circumflex (LCX): 80% and right coronary artery (RCA): 40%]. The other one presented stenosis in two vessels (LAD: 70% and RCA: 50%).

**Intravascular ultrasound analysis**

IVUS imaging of the most proximal 18-mm segments of at least one of the major coronary arteries was obtained from all patients. Thirteen patients had all 3 major arteries interrogated, 5 patients had 2 and 2 patients had only one. Atherosclerosis was present in all patients and in all 51 most proximal 18-mm segments analyzed (18 LAD, 18 LCX and 15 RCA). These segments presented...
abundant and diffusely distributed atherosclerosis (Fig. 1). In 9 (17.6%) segments, minimal lumen CSA was ≤ 4 mm². Plaque volume, maximum plaque thickness, minimal lumen CSA, and axial coefficient of variation of the plaque area for these segments are shown in Table 3.

The mean vessel diameter of the proximal segments was significantly larger at the IVUS than at the QCA, in all vessels: [18 LAD segments: 4.24 ± 0.45 vs. 3.30 ± 0.59 (p<0.001)]; [18 LCX segments: 3.64 ± 0.60 vs. 3.20 ± 0.56 (p=0.04)]; [15 RCA segments: 4.35 ± 0.56 vs. 3.82 ± 0.56 (p=0.01)].

IVUS images of 25 (86.2%) of the 29 lesions ≥ 30% were obtained. Fibrotic plaques were the most common (48%) and the majority presented intermediate vessel remodeling (60%). Plaque characteristics, plaque burden, lumen area stenosis and minimal lumen CSA of these lesions are shown in Table 3.

Age and diabetes duration were related to greater plaque thickness, plaque volume and the presence of lesions ≥ 30% (Fig. 2).

Discussion

The most remarkable finding of this study was the diffuse vessel involvement and the large amount of atherosclerosis identified at the IVUS in this selected population of type 1 diabetic patients with end-stage renal disease (ESRD). We verified a relatively uniform plaque distribution along all the most proximal 18-mm segments, as shown by the low plaque area axial coefficient of variation (33.6 ± 10%). Additionally, plaque quantification in these segments demonstrated the existence of large plaque masses by both the axially corrected plaque volume (4.6 ± 2.4 mm³/mm) and maximum intimal thickness (1.49 ± 0.71 mm).

Table 2 - Angiographic data

<table>
<thead>
<tr>
<th>CAD Prevalence (n: 20 patients)</th>
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<tr>
<td>Lesions &lt; 30%*</td>
<td>5 (25%)</td>
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<tr>
<td>30-49%*, n (%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>50-69%*, n (%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>≥ 70%*, n (%)</td>
<td>10 (50%)</td>
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<th>Lesion Severity and QCA (n: 29 lesions)</th>
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<tr>
<td>30-49%*, n</td>
<td>11 (38%)</td>
</tr>
<tr>
<td>50-69%*, n</td>
<td>6 (20%)</td>
</tr>
<tr>
<td>≥ 70%*, n</td>
<td>12 (42%)</td>
</tr>
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</table>

| Reference Diameter, mm                | 2.88 ± 0.78 |
| Minimal Lumen Diameter, mm            | 1.64 ± 0.51 |
| Diameter stenosis, %                  | 45 ± 13     |
| Lesion length, mm                     | 9.6 ± 13.3  |

<table>
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<tr>
<th>Lesion location (n=29)</th>
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<tr>
<td>Proximal LAD: 4 (14%)</td>
<td>Proximal LCX: 2 (7%) Proximal RCA: 3 (10%)</td>
</tr>
<tr>
<td>Mid LAD: 11 (38%)</td>
<td>Mid LCX: 4 (14%) Mid RCA: 4 (14%)</td>
</tr>
<tr>
<td>Distal LAD: 0 (0%)</td>
<td>Distal LCX: 0 (0%) Distal RCA: 1 (3%)</td>
</tr>
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* Visual analysis; QCA - quantitative coronary angiography; LAD - left anterior descending artery; LCX - left circumflex artery; RCA - right coronary artery.

The development of atherothrombosis in the presence of nephropathy has been attributed to several mechanisms, including hypertension, dyslipidemia, and abnormalities...
Figure 2 - A - Age according to the presence or absence of lesion ≥ 30% (p=0.003); B - Duration of type 1 diabetes according to the presence or absence of lesion ≥ 30% (p=0.03); C - Correlation between age and plaque maximum thickness. Pearson's linear coefficient = 0.71 (CI = 0.39–0.87); D - Correlation between age and plaque volume. Pearson's linear coefficient = 0.68 (CI = 0.34–0.86); E - Correlation between duration of type 1 diabetes and plaque maximum thickness. Pearson's linear coefficient = 0.79 (CI = 0.53–0.91); F - Correlation between duration of type 1 diabetes and plaque volume. Pearson's linear coefficient = 0.77 (CI = 0.51–0.90).

Based on the angiographic parameters, the high prevalence of significant lesions replicated the findings we had previously.
Importantly, our study showed the predominance of atherosclerotic lesions with characteristics of stability, represented by their fibrotic composition with negative or intermediate remodeling. However, even considering the lower percentage of potentially vulnerable plaques (lipidic composition with positive remodeling), the enormous amount of disease makes it a frequent finding in the coronary tree of type 1 diabetic patients with ESRD, which may explain the high rates of adverse events in this population.

When correlating clinical variables with coronary atherosclerosis, we observed that age and diabetes duration were related to greater plaque thickness, plaque volume and the presence of lesions ≥ 30%. We did not find any correlation between coronary atherosclerosis and serum cholesterol, smoking, body mass index, and the hemodialysis procedure. For a few of these variables, the lack of correlation might be due to beta error. In another study, a 1% increase in mean HbA1c over 18 years implied in a 6.4% increase in plaque burden, 15 mg increase in total cholesterol implied in 10% increase in plaque burden and a 10-year increase in age implied in a 16.2% increase in plaque burden.

It is known that the angiography underestimates vessel diameter and atherosclerosis extent when compared with IVUS, and there are three predictors for this discrepancy: vessel diameter by angiography < 3 mm, proximal segments and diabetes, presumably type 2. Our study is the first to address this issue in type 1 diabetic patients.

Magnetic resonance imaging and computed tomography (through the evaluation of coronary artery calcium content) can identify subclinical CAD. The calcium score has been used to evaluate the prevalence and prognosis of CAD in type 1 diabetic patients. However, in patients with ESRD, the association between coronary calcium and coronary atherosclerosis is less well established.

Currently, a better CAD characterization in type 1 diabetic patients with ESRD undergoing hemodialysis has become more important, in view of the increasingly availability of simultaneous pancreas-kidney transplantation. This modern treatment may improve cardiovascular outcome in these patients. In fact, it has been reported that CAD progression is reduced based on the results of angiography performed before transplantation and four years later.

This study has two main limitations: the small sample size, and the lack of information regarding long-term glycemic control.

**Conclusion**

In summary, subclinical CAD is present in all vessels of all type 1 diabetic patients undergoing hemodialysis. It indicates the need for additional epidemiological and imaging studies to better understand and treat such a complex and serious clinical condition affecting young people.

**Potential Conflict of Interest**

No potential conflict of interest relevant to this article was reported.

**Sources of Funding**

There were no external funding sources for this study.

**Study Association**

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References


