LOW PREVALENCE OF SUBLIMINAL ATHEROSCLEROSIS IN ASYMPTOMATIC PATIENTS WITH TYPE 1 DIABETES MELLITUS IN A EUROPEAN MEDITERRANEAN POPULATION

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Short running title:
Subclinical atherosclerosis in patients with type 1 diabetes

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Abstract

Screening of cardiovascular disease in asymptomatic type 1 diabetes (type 1 diabetes) is a controversial issue.

Objective: To evaluate the presence of early carotid and coronary atherosclerosis in asymptomatic patients with type 1 diabetes with no history of ischemic heart disease.

Research Design and Methods: One hundred and fifty patients with type 1 diabetes (58% males; 38.6±8.1 years, 20.4±8.1 years of evolution; HbA\textsubscript{1c}: 8.1±2.3%; 52% non-smokers; 26% retinopathy; 9% microalbuminuria) and 50 non-diabetic controls age and sex matched were studied. Carotid ultrasonography to determine cIMT and the presence of atheroma plaques, and cardiac CT for calcium analysis and quantification (CACS) were performed.

Results: Most patients with type 1 diabetes and controls displayed a CACS of 0 (82% vs 92%). Patients with type 1 diabetes with CACS ≥1 were older and had higher HbA\textsubscript{1c} (44.5±5.1 vs. 36.7±8.1 years p<0.001 and 8.5±1.1 vs. 7.8±1.0% p<0.003, respectively), longer evolution of diabetes (25.4±9.2 vs. 19.3±7.4 years p<0.005) and mean cIMT (0.67±0.18mm. vs. 0.53±0.11mm. p<0.001) compared to patients with CACS of 0. Smoking (p<0.02), nephropathy (p<0.05), retinopathy (p<0.05) and male gender (p<0.03) were significantly and positively associated to CACS ≥1. Mean cIMT was significantly higher in patients with type 1 diabetes (0.55±0.14 vs. 0.48±0.14mm p<0.01) and 11% of them presented atheroma plaques (8% controls). Multivariant logistic regression analysis showed that c-IMT was related to CACS (beta=6.87, p<0.001).

Conclusions: A small percentage of patients with type 1 diabetes showed data suggestive of subclinical atherosclerosis. Universal screening of coronary disease in this population is not justified. Carotid ultrasonography maybe useful for screening in the subset of patients with cardiovascular risk factors and long disease evolution.
Introduction
Cardiovascular disease and especially coronary heart disease (CHD) is the leading cause of death in type 2 diabetes (1-3). Different studies have shown that changes in vascular structure, such as coronary intimal thickening, changes in arterial compliance and stiffness, and endothelial dysfunction also occur early in the course of type 1 diabetes, leading to an accelerated atherosclerosis (4,5).
Remarkably, type 1 diabetes is associated with even a higher CHD risk of at least a 10-fold increase compared to age matched non-diabetic subjects (6,7). Most of the clinical trials regarding prevention of CHD in diabetic persons have only included patients with type 2 diabetes and their conclusions have been applied to patients with type 1 diabetes. However, it is unclear whether asymptomatic patients with type 1 diabetes benefit from the current preventive treatment strategies for type 2 patients. Current guidelines do not recommend active screening of CHD and consider type 1 diabetes as a high-risk state only when microalbuminuria is present (8), even though microalbuminuria may not reflect reliably nephropathy (9).
Coronary artery calcium score (CACS) is a well-established index of atherosclerosis and is feasible to be performed in the clinical practice (10). CACS has been shown to predict both future CHD and all cause mortality in non-diabetic subjects (11,12). Type 2 diabetes is associated with higher CACS than general population, independently of other cardiovascular risk factors (13).
In the Pittsburgh Epidemiology of Diabetes Complication Study cohort, CACS was strongly correlated with CHD, particularly in men (14) but there is scarce information of CACS in asymptomatic type 1 diabetes. A positive relationship between glycemic control and CACS has been described by the Epidemiology of Diabetes Interventions and Complications study (EDIC) showing that intensive treatment is associated to lower CACS (15). Another study has also reported increased coronary calcification in women with type 1 diabetes compared to controls (16).
Additionally, increased common carotid artery (CCA) intima-media thickness (c-IMT) has been found to also be associated to diabetes mellitus in other chronic diseases where atherosclerosis is present (17).
Prediction and early diagnosis of CHD allows an appropriate intervention in the initial stages of the disease. Therefore, the aim of the present study was to evaluate the presence of early atherosclerosis in asymptomatic patients with type 1 diabetes with a lengthy evolution of the disease (more than 10 years) living in a Mediterranean country, with no previous history of ischemic heart disease.

**Subjects and Methods**

A group of 150 asymptomatic patients with type 1 diabetes followed in our outpatient clinic were consecutively recruited between 2010-2012. Inclusion criteria were aged between 20 and 50 years and an evolution disease of more than 10 years. Exclusion criteria included a previous history of clinical macrovascular or CHD. Current smoking and previously smoking condition for less than 5 years were included in the same category. A group of non-diabetic subjects matched for age, sex and smoking condition were recruited from the relatives, and staff from our hospital were also included in the control group. All patients were under intensive insulin treatment with 15% of them using pump devices.

The study was approved by the local ethics committee, in accordance with the Declaration of Helsinki; all participants gave their written informed consent prior to inclusion.

Demographic and clinical data, including age, sex, history of clinical macrovascular disease and microvascular diabetic complications, family history of early CHD in first degree relatives (defined as CHD occurring before age 55 years in men and before age 65 years in women) and medical treatment (antihypertensive agents, statins and acetylsalicylic acid) were recorded for all subjects. Body mass index was calculated as weight in kilograms divided by height per square meter.

Diabetic nephropathy was evaluated according to urinary albumin excretion. Normal urinary albumin excretion was considered below 30 mg/24 h, microalbuminuria from 30 to 299 mg/24 h and proteinuria above 300 mg/dl. These results were confirmed on at least two out of three consecutive determinations. Diabetic retinopathy was defined by fundus oculi performed by a specialized ophthalmologist.
**Biochemical measurements**

Blood samples were drawn by venipuncture at between 8.00 and 08.30 h. after overnight fast. Plasma glucose, total cholesterol, high density (HDL) and low density (LDL) lipoprotein cholesterol and triglycerides were measured by routine clinical chemistry immediately after extraction. HbA\textsubscript{1c} was measured in blood samples with EDTA by HPLC using a fully-automated Adams Menarini HI-AUTO A1c 8160 analyzer manufactured by Arkray (Kyoto, Japan) with an inter-assay coefficient of variation (CV) of 1.8 and 1.5% at HbA\textsubscript{1c} levels of 4.8 and 9.0% respectively (reference range: 4–5.8%). This method is a cation exchange HPLC method certified by the NGSP (National Glycohemoglobin Standardization Program) of traceability to the Diabetes Control and Complications Trial Reference (DCCT) Method. Mean HbA\textsubscript{1c} was calculated as an average of three determinations in the previous year before the inclusion in the study.

**Cardiac computed tomography protocol**

Multidetector cardiac CT (MSCT) was performed using a 16-slice high resolution CT ECG-gated, with retrospective reconstruction and with special attention to the coronary arteries (SOMATOM Sensation 16 and Syngo Calcium Scoring software for analysis and calcium calcification). CACS was identified as a dense area in the coronary artery exceeding the threshold of 130 Hounsfield units. A total Agatston score was determined for each patient. The results were expressed according to the classification previously described by Shaw et al (18). Scans were read by a single radiologist.

**Carotid ultrasonography**

Ultrasonographic images were acquired using high resolution B-mode ultrasound (Siemens Acuson Sequoia 512) with an electric linear array 13-5 MHz transducer. Acquisition, processing and storage of B-mode images were computer-assisted with the version of the software provided by the manufacturer. All measurements were performed by the same trained radiologist. The CCA segment was defined as the distal 1 cm of the CCA, immediately proximal to the onset of increased spatial separation of the walls of
the CCA. Both near and far walls of these arterial segments were scanned longitudinally and transversely to assess the presence of plaques. The protocol involved scanning of the CCA, carotid bifurcations and origins (first 2 cm.) of internal carotid arteries. The presence of carotid plaques was defined as focal echo structures encroaching into the arterial lumen of at least 0.5 mm or 50% of the surrounding c-IMT value, or when c-IMT was >1.5 mm as measured from the media–adventitia interface to the intima–lumen interface. Quantification of plaque thickness was made at the site of the maximum encroachment perpendicular to the vessel wall by measuring the distance between the media–adventitia interface and the lesion surface facing the lumen. CCA–IMT was measured in a longitudinal view at a site free of plaques along a 10 mm-long segment on the far wall of the CCA in agreement with the carotid IMT consensus (2004–2006) (19). Composite right and left c–IMT were calculated as the average of the four readings in each artery segment, and the mean of the left and right c–IMT measurements was used in the analysis.

**Statistical methods**

Continuous variables were expressed as mean SD or median (interquartile range) and categorical variables as frequency and/or percentage. Differences between groups were tested by the Student’s t-test or the non-parametric Mann–Whitney U test, where appropriate. A p value less than 0.05 was considered statistically significant. Categorical variables were compared with a \( \chi^2 \) test. Separate multivariate regression analyses with backward elimination were performed, correcting for all baseline clinical characteristics including as confounders age, male sex, BMI, smoking, positive family history of CHD, dyslipidemia, hypertension, mean HbA\(_{1c}\) to identify independent predictors of each coronary atherosclerosis variable on MSCT. All statistical analyses were performed using the Statistical Package for Social Science (SPSS, Chicago, IL, USA) for personal computers, version 12.0 (SPSS).
Results
The clinical characteristics of the 150 patients and the 50 controls are shown in Table 1. All patients had normal creatinine levels and a glomerular filtration rate over 60 ml/min.

CACS
CACS results are shown in Table 2. A high proportion of subjects in both controls and patients displayed a CACS of 0 (92% vs 82%), and the differences between groups were not statistically significant. For all patients, mean and median CACS were 19.5 ± 102 and <1 respectively. When a CACS of moderate severity of >100 was considered, it was found only in a low proportion of type 1 diabetes (6/150, 4%). When patients were categorized using a lower CACS of ≥1, those showing values higher of this cut-off had significantly higher age and a longer duration of the disease compared with patients with a CACS of 0 (Figure 1A). There were more men than women with CACS≥1 (p<0.02). In relation to metabolic control patients with CACS ≥1 also showed significantly higher HbA1c (Figure 1B).

Thirteen out of the 150 patients (9%) patients presented nephropathy and 10 of them also retinopathy. Eight of the 13 patients with nephropathy had a CACS of 0 and 5 of them >50 (with values of 58, 99, 227, 523, 1062). All these 5 patients also presented proliferative retinopathy. The highest CACS (1062) was found in a type 1 diabetes patient, female, 47 years old, current smoker and with a positive family history of CHD (Supplementary Figure 1).

Carotid ultrasonography
Patients with type 1 diabetes showed a significantly higher c-IMT compared to control group (0.55±0.14 vs. 0.48±0.14 mm., p<0.01). A low proportion of subjects in both groups presented atheroma plaques (16 patients and 4 control subjects, 11 vs. 8%), in all cases conditioning stenosis of less than 50%.

Patients with nephropathy showed a higher c-IMT compared to patients without nephropathy (0.59±0.14 vs. 0.54±0.14 mm., p<0.08). There were no differences regarding to c-IMT in relation to retinopathy.
Patients with type 1 diabetes with plaques had a significantly higher HbA$_{1c}$ and c-IMT (Figure 1C) compared to those patients without plaques. Four out of the sixteen patients with plaques (25%) presented retinopathy and only one patient had both proliferative retinopathy and nephropathy.

**Associations between study variables**

When univariate correlation analyses were performed in diabetic subjects, we found that previous and active smoking habit ($p<0.02$), nephropathy ($p<0.05$), retinopathy ($p<0.05$) and male gender ($p<0.03$) were significantly and positively associated to CACS $\geq 1$ ($p<0.01$ and $p<0.004$). No relationships were found regarding family history of CHD. The presence of carotid plaques was only associated to smoking condition ($p<0.02$) but not with the rest of study variables. Those patients with type 1 diabetes with a CACS $\geq 1$ showed a significantly higher c-IMT compared with patients with a CACS of 0 (Figure 1B). A positive correlation was found between values of CACS and c-IMT ($r_s 0.36$ $p<0.001$).

A multivariant logistic regression analysis was performed in type 1 diabetes group in order to identify those factors influencing independently CACS, including all variables that showed a statistically significant association in the univariate analysis. The step forward methodology was applied including the following variables: age, gender, duration of disease, smoking status, HbA1c, retinopathy, nephropathy, treatment for hypertension, statin use, CHD family history and aspirin treatment. After elimination of confounders, the final model included the following covariates: duration of diabetes, statins treatment and c-IMT ($R^2 =0.44$). In all the models generated, we found that c-IMT was related to the CACS (beta=6.87, $p<0.001$), duration of diabetes (beta=0.09, $p<0.008$) and statin treatment (beta=1.43 $p<0.02$).

**Discussion**

Most clinical guidelines do not recommend active screening in apparently healthy patients with type 1 diabetes (20-22), but a debate regarding this has been ongoing for years. In our study we found that a small percentage of type 1 diabetic individuals who had been diagnosed more than 10 years previously,
presented data suggestive of subclinical atherosclerosis. Most of our patients displayed a CACS of 0, slightly lower than in the control group. Only a very low 4% of patients showed a CACS over 100, suggesting moderate or significant calcification, with most of them also presenting associated microvascular complications. Moreover, c-IMT information was quite concordant to CACS data.

Few studies on CACS measurement in asymptomatic type 1 diabetes population have been made (15,16, 23-25). Data concerning Mediterranean population are even more scarce and our results clearly differ from previously published reports that showed higher CACS in comparison to our findings (see table 3). In those studies, patients were younger but with a higher HbA1c, (24) or the prevalence of hypertension and dyslipidemia was higher (25) than in our cohort. The EDIC cohort follow-up showed a loss of protective effect assigned to women and that intensive glucose treatment was also associated to a better CACS (15). Other studies by Colhoun (16) and Dabelea (23) displayed a smaller proportion of patients with CACS of 0 than our study despite that mean age and duration of type 1 diabetes were similar. Long duration of disease and the presence of autonomic cardiovascular neuropathy is also associated to high CACS (26). None of our patients presented clinical signs of dysautonomia, although no specific procedures were performed to rule it out.

In the present study, patients with type 1 diabetes showed a higher c-IMT when compared to the control population but there were no differences in the presence of plaques. Our patients did not show a particular metabolic instability, neither was hypoglycaemia severe, or very frequent. However metabolic instability may also worsen c-IMT and for this reason, another study performed in Spain with such patients presented a higher c-IMT compared to our cohort (27).

The fact that our cohort is living in a geographical area with a low prevalence of CHD (28-30) may have influenced our findings. This general population background with specific dietary factors such as Mediterranean life style, may be of importance, especially when comparing with Northern European diets.
Actually, a recent randomized controlled intervention trial conducted in population from our region showed that a Mediterranean diet reduced the incidence of major cardiovascular events (31). Finally, the genetic background of the cohort was also relevant as there was a low CHD family history.

In addition, and possibly of much importance, it has to be taken into account that our patients with type 1 diabetes have all been treated in the era of universal intensive glycemic treatment -15% were under pump treatment-, as well as the use of cardiovascular protective drugs immediately when indicated following international guidelines. Therefore, our data on CACS are very close to those found in the intensive arm of the EDIC cohort (15). This intensive glycemic treatment could have a positive impact in the prevention of cardiovascular disease as well as better control of blood pressure and lipids in the current era of diabetes management.

In summary, our data indicate that a small percentage of patients with type 1 diabetes living in Catalonia with a mean of 20 years disease duration showed data suggestive of subclinical atherosclerosis. For this reason, universal screening of coronary disease in this Mediterranean type 1 diabetes population is not justified. CACS is expensive and our data support that alternative and cheaper techniques which are readily available in the clinical practice such as carotid ultrasonography, may be useful for CHD screening in patients with type 1 diabetes when associated classic cardiovascular risk factors, microvascular complications or very long disease duration are present. In this subset of subjects, as CHD mortality is higher than expected, attention should be given to detecting macrovascular disease in the same way as is done for microvascular disease, provided that the screening procedure is sufficiently robust.

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E.A. researched data, contributed to discussion, wrote the manuscript, and reviewed/edited the manuscript. E.S., M.L.G., N.A., S.P., E.P., J.R. I.S. and B.S. researched data and reviewed the manuscript. D.M. and M.P. contributed to discussion and reviewed/edited the manuscript.

There is no conflict of interest regarding to this work.

Dr. M. Puig-Domingo is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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18- Shaw Lj, Raggi P, Schisterman E, Berman DS, Callister TC. Prognostic value of cardiac risk factors and coronary artery calcium screening for all cause mortality. Radiology 2003;228: 826-33


on the gender difference in coronary artery calcification: a role for insulin resistance? The Coronary Artery Calcification in Type 1 Diabetes (CACTI) Study. Diabetes 2003; 52: 2833-2839


Table 1. Basal characteristics of patients with type 1 diabetes and control group

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<thead>
<tr>
<th></th>
<th>Type 1 diabetes</th>
<th>Control</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>150</td>
<td>50</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>38.6±8.1</td>
<td>38.1±7.2</td>
</tr>
<tr>
<td>Sex (male/female %)</td>
<td>58/42</td>
<td>56/44</td>
</tr>
<tr>
<td>Evolution type 1 diabetes (yr)</td>
<td>20.4±8.1</td>
<td>----</td>
</tr>
<tr>
<td>Family history CHD (%)</td>
<td>20</td>
<td>22</td>
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<tr>
<td>Body mass index (kg/m²)</td>
<td>25.1±3.6</td>
<td>25.3±4.3</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>117.3±13.5</td>
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</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>70.9±7.7</td>
<td>----</td>
</tr>
<tr>
<td>Retinopathy (%)</td>
<td>26</td>
<td>----</td>
</tr>
<tr>
<td>Nephropathy (%)</td>
<td>9</td>
<td>----</td>
</tr>
<tr>
<td>HbA₁c (%), mmol/mol</td>
<td>8.1±2.3 (64.89±11.48)</td>
<td>----</td>
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<tr>
<td>Total cholesterol (mg/dl)</td>
<td>182.7±25.1</td>
<td>191.1±34.1</td>
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<tr>
<td>HDL (mg/dl)</td>
<td>60.3±15.1</td>
<td>61.8±16.6</td>
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<tr>
<td>LDL (mg/dl)</td>
<td>105.3±21.9</td>
<td>111.3±33.5</td>
</tr>
<tr>
<td>Smoke (% yes/no)</td>
<td>48/52</td>
<td>42/58</td>
</tr>
<tr>
<td>Statins (%)</td>
<td>21</td>
<td>----</td>
</tr>
<tr>
<td>Antihypertensive (%)</td>
<td>15</td>
<td>----</td>
</tr>
<tr>
<td>Acetylsalicylic acid (%)</td>
<td>16</td>
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</table>
Table 2. CACS results

<table>
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<tr>
<th>Score Level</th>
<th>Type 1 diabetes</th>
<th>Control</th>
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<tbody>
<tr>
<td>Score 0: No plaques (very low risk)</td>
<td>123 (82%)</td>
<td>46 (92%)</td>
</tr>
<tr>
<td>Score 1-10: Minimal plaques (low risk)</td>
<td>12 (8%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Score 11-100: Mild calcification (moderate risk)</td>
<td>9 (6%)</td>
<td>2 (4%)</td>
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<tr>
<td>Score 101-400: Moderate calcification (high risk)</td>
<td>4 (2.6%)</td>
<td>1 (2%)</td>
</tr>
<tr>
<td>Score &gt;400: Significant calcification (very high risk)</td>
<td>2 (1.3%)</td>
<td>0</td>
</tr>
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Table 3. CACS in asymptomatic patients with type 1 diabetes

<table>
<thead>
<tr>
<th></th>
<th>Cleary et al. (12)</th>
<th>Colhoun et al. (13)</th>
<th>Dabelea et al. (24)</th>
<th>Salem et al. (25)</th>
<th>Djaberi et al. (26)</th>
<th>Present study</th>
</tr>
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<tbody>
<tr>
<td>n</td>
<td>1205 Int/Conv *</td>
<td>199</td>
<td>656</td>
<td>60</td>
<td>65</td>
<td>150</td>
</tr>
<tr>
<td>Mean age (years)</td>
<td>43</td>
<td>38</td>
<td>37</td>
<td>16</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Evolution type 1 diabetes (yr)</td>
<td>21</td>
<td>24</td>
<td>23</td>
<td>12</td>
<td>23</td>
<td>20</td>
</tr>
<tr>
<td>Retinopathy/nephropathy (%)</td>
<td>50</td>
<td>---</td>
<td>---</td>
<td>30/63</td>
<td>---</td>
<td>26/9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9</td>
<td>8.6</td>
<td>7.8</td>
<td>9.7</td>
<td>7.6</td>
<td>8.1</td>
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<tr>
<td>Hypertension/dyslipidemia (%)</td>
<td>29/30</td>
<td>21/---</td>
<td>14/---</td>
<td>---</td>
<td>49/63</td>
<td>15/21</td>
</tr>
<tr>
<td>Mean CACS</td>
<td>--- †</td>
<td>--- †</td>
<td>--- †</td>
<td>44</td>
<td>217</td>
<td>19</td>
</tr>
<tr>
<td>CACS=0 (% total)</td>
<td>78/70</td>
<td>---</td>
<td>---</td>
<td>80</td>
<td>---</td>
<td>82</td>
</tr>
<tr>
<td>(% men/women)</td>
<td>---</td>
<td>48/53</td>
<td>52/72</td>
<td>---</td>
<td>---</td>
<td>67/91</td>
</tr>
</tbody>
</table>

* Int: Intensive treatment /Conv: Conventional treatment
† In these studies CACS was reported categorized as 0 or > 0
Figure 1.

A. Association of CACS with age and type 1 diabetes evolution
B. Association of CACS with metabolic control and carotid ecography
C. Association of carotid plaques with metabolic control and c-IMT
Supplementary Figure 1.
CACS in a patient with type 1 diabetes and calcifications in the three main coronary arteries
CACS in a patient with type 1 diabetes and calcifications in the three main coronary arteries

254x190mm (96 x 96 DPI)