OPEN ACCESS
Freely Available Online

JOURNAL OF PREVENTIVE MEDICINE AND CARE
ISSN NO: 2474-3585

RESEARCH ARTICLE
DOI : 10.14302/issn.2474-3585.jpmc-14-540

One-Third of Patients With Type 2 Diabetes Mellitus Do Not Have Coronary Artery Calcification

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Abstract

Objective
Measuring coronary artery calcification (CAC) enables to optimize cardiovascular risk-stratification also in patients with type 2 diabetes mellitus (T2D), however the prevalence of CAC in randomly selected patients with T2D is uncertain. For this purpose we set out to examine and compare the occurrence of CAC in unselected T2D patients.

Design
A randomly selected cohort of 1825 individuals, men and women, either 50 or 60 years old, were invited to the screening study. Traditional risk factors were obtained and a non-contrast CT-scan was performed to assess the CAC score.

Results
A total of 1211 individuals participated, of whom 54 (4%) had T2D while 1157 (96%) were without diabetes. CAC was present in 62% of the patients with T2D versus 44% in those without (p=0.013). Also the prevalence of traditionally risk factors was high in patients with T2D as compared to subjects without T2D. When adjusting for age, gender, smoking, hypertension and hypercholesterolemia in multivariate logistic regression, T2D was not associated with presence of CAC (OR=1.0; 95% confidence interval 0.5 - 2.0, p=0.94).

Conclusions
One-third of patients with T2D did not have any CAC, and T2D per se was not associated to CAC.

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Citation: ML Tofterup, H Beck-Nielsen, O Gerke, K Egstrup, NPR Sand et al. (2015) One-Third of Patients With Type 2 Diabetes Mellitus Do Not Have Coronary Artery Calcification. Journal Of Preventive Medicine And Care - 1(1):1-8. https://doi.org/10.14302/issn.2474-3585.jpmc-14-540

Key words: Type 2 Diabetes Mellitus; atherosclerosis; coronary artery disease; risk assessment; cohort studies.
Short title: T2D and coronary artery calcification
Received : Jul 31, 2014; **Accepted** : Apr 27, 2015; **Published** : Jun 01, 2015;
Academic Editor: Haewon Byeon, Dept. of Speech Language Pathology & Audiology, Nambu University

Introduction

Cardiovascular disease (CVD) and especially ischemic heart disease (IHD) are the most common complications and the principal causes of death in patients with type 2 Diabetes mellitus (T2D). Over 60% of people with T2D develop CVD, a more severe and costly complication than retinopathy [1]. The incidence of T2D is expected to increase rapidly during the following years and a concomitant rise in morbidity and mortality due to CVD, especially IHD is expected [2]. Therefore, it is important to consider how to intercept and treat individuals with T2D in the future. To reduce the risk of CVD, statin therapy should be considered for all patients with diabetes [3]. However, it remains to be clarified whether patients can be stratified in subgroups who would benefit from a more aggressively preventive treatment algorithm, and who would do fine without. A tool for individualization of the risk of developing clinical symptoms of IHD would be preferable, since patients with diabetes often have blunted or atypical symptoms.

Coronary artery calcium (CAC) is a well-established marker for atherosclerosis, and measurement of CAC score predict future IHD, and all-cause mortality and provide a predictive power beyond standard risk factors in subjects without diabetes [4;5]. The presence of CAC in randomly selected patients with T2D is uncertain, but in selected patients the CAC score is elevated, and the score increases by the number of metabolic syndrome (MetS) risk factors [6]. Among patients with diabetes or MetS, the CAC score is correlated to a high annual rate of both CVD and IHD [7;8]. Indeed, CAC score measurements might optimize CVD risk stratification, and as a result, identify high risk subjects who could receive a more intensified risk modification regime, while in low risk subgroups a healthy lifestyle would be sufficient.

Consequently, the aim of this study was to assess the occurrence of CAC in unselected patients with T2D, and to identify a potential subgroup that might not benefit from intensified preventive medication.

Methods

Study Cohort

The Danish Risk Score study (DanRisk) is a population-based survey studying the prevalence of CAC in a random sample of 1825 Danish men and women, 50 or 60 years of age [9]. The participants were selected by the Danish national Central Person Register in which all Danish citizens are registered. A total of 1257 (69%) accepted the invitation and were examined in one of the four regional centres (Odense, Esbjerg, Svendborg and Vejle). The protocol was approved by the Regional Scientific Ethical Committee of Southern Denmark (S-20080140), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from each participant.

Baseline Evaluation

On the day of examination, weight, height and waist circumference as well as blood glucose, lipids and hs-CPR were measured. Prior to the examination the participants were not fasting. If capillary blood glucose was ≥ 6.1 mmol/L, fasting plasma blood glucose was measured on a second day. After 5 minutes of supine rest, blood pressure was recorded three times. The last two values were averaged for further analyses.

Previous Disease and Current Medication

Prior to examination the participants filled out a questionnaire concerning medical conditions, current drug treatment, smoking habits and family history of CVD. Based on the self-reported medical history and the baseline evaluation, possible diseases were classified in subgroups: previous CVD, atrial fibrillation, heart valve disease, known or hitherto unknown diabetes, hypertension and hypercholesterolemia. Heart valve disease was defined as routinely follow-up with echocardiography for valve disease or prior heart valve surgery. Type 1 diabetes mellitus was defined as onset of diabetes in young age, and T2D as the use of antidiabetic medication, fasting plasma blood glucose level ≥ 7.0 mmol/L on two different days or a postprandial blood glucose level ≥ 11.1 mmol/L [10]. Antidiabetic treatment included any oral antidiabetic drug and/or insulin. Hypertension was defined as the use of antihypertensive drugs (angiotensin-converting enzyme inhibitors, angiotensin-receptor antagonist, calcium channel blockers, diuretics, β-blockers, α-blockers and centrally active antihypertensive drugs)

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and/or a blood pressure ≥ 140/90 mmHg at the time of study examination. Hypercholesterolemia was defined as the use of lipid-lowering agents, total cholesterol ≥ 5 mmol/L and / or LDL ≥ 3 mmol/L.

HeartScore

Using the HeartScore model [11], the 10-year risk of fatal cardiovascular events based on gender, age, smoking, systolic blood pressure, and total cholesterol was estimated. Increased risk was defined by a HeartScore > 5%.

Coronary artery calcification

A 64-slice non-contrast CT scan was performed as previously described [9]. To quantify the CAC score, the Agatston score [12] was calculated by experienced cardiologists, who were blinded to all patient data. Mean radiation dose was 1.2 mSv.

Statistics

Data were analysed and displayed descriptively according to their type, i.e., continuous data, and categorical data were summarized by means of descriptive statistics (arithmetic mean and standard deviation, median and range) and frequencies with corresponding percentages, respectively. The association between CAC and various demographic and clinical variables were assessed by means of multivariate logistic regression using three different cut-offs: 1) CAC present versus CAC absent (Agatston > 0 versus Agatston = 0) 2) moderate or high level of CAC present versus moderate or high level of CAC absent (Agatston ≥ 100 versus Agatston < 100), and 3) high level of CAC present versus high level of CAC absent (Agatston ≥ 400 versus Agatston < 400). In order to define potential explanatory variables of CAC, univariate logistic regressions were applied on all demographic and clinical variables available (sex, age, smoking status, T2D, hypertension, hypercholesterolemia, BMI, waist circumference, resting heart rate, family history, CRP). Statistically significant variables in the univariate analyses were included in a multivariate logistic regression model and highly correlated variables (according to Spearman's rank correlation coefficient) were not considered for inclusion (e.g. waist circumference was added to the multivariate model, whereas BMI was not). Exploratory testing of the association between two variables was done by means of Fisher's exact test. The significance level was 5%. All analyses were performed using SAS 9.1.3 (SAS Institute Inc., Cary, NC, USA) and Stata/MP 12.1 (StataCorp LP, College Station, Texas 77845 USA).

Results

A total of 1825 participants were invited, and 1257 (69%) accepted the screening project (Table 1). 1157 (95.5%) individuals were classified as previously healthy. Of these, 905 (74.7%) had a low and 252 (20.8%) a high HeartScore. Among patients with T2D, 41 had known T2D, and 13 prior unrecognised T2D.

Of the 54 participants with T2D, the Agatston score was missing in two due to inadequate scan quality (severe obesity) or claustrophobia, while of the 1157 healthy participants, the Agatston score was missing in four participants. Among patients with T2D the prevalence of men, 60 years old, smokers, hypertension and hypercholesterolemia were 50%, 58%, 33%, 69% and

Table 1 - Description of the study population

Invited subjects			1825
Included			**1242**
CVD		31	
Previous AMI	15		
Previous stroke	14		
Peripheral atherosclerosis	2		
Known T2D		41	
Newly diagnosed TD2		13	
Previously healthy		1157	
Excluded			**15**
T1D		5	
Atrial fibrillation		9	
Previous valve surgery		1	
Non-responders			568

CVD; cardiovascular disease. AMI; acute myocardial infarction. T2D; Type 2 diabetes mellitus. T1D: type 1 diabetes mellitus. Numbers given in n.

83% respectively, while 47%, 49%, 25%, 49% and 76% for subjects without (Table 2).

Participants with known CVD had significantly higher Agatston scores than those without (p<0.0001), with a median CAC score of 141U versus 11U and 0U among patients with T2D and healthy participants. Previously diagnosed T2D (n=40) had a non-significant higher median CAC score than newly diagnosed T2D (n=12) (16U and 4U, respectively). Compared to subjects without diabetes, CAC was significant more prevalent in those with T2D (62% versus 44%; p=0.013). Participants with T2D had Agatston scores comparable to those with a high HeartScore (prevalence of calcification 62% versus 68%, p=0.34, and severe calcification (Agatston score ≥ 400) 10% versus 12%, p=0.22). Lipid-lowering treatment was more common among subjects with T2D as opposed to those with a high HeartScore (54% and 12%, respectively), and accordingly mean total-cholesterol value was lower (4.8 mmol/L and 5.9 mmol/L, respectively). While 59% of the T2D patients with CAC (19 of 32 patients) received lipid-

Table 2. Baseline characteristics of the study sample.

	Known CVD		Diabetes		Non Diabetic	
	n = 31		n = 54		N = 1157	
Age (years)	58.8 ± 3.6		56.6 ± 4.8		55.3 ± 5.0	
Gender (Male)	23	(75)	27	(50)	546	(47)
Family history	7	(23)	14	(26)	268	(23)
Active smoking	12	(39)	18	(33)	288	(25)
Former smoking	14	(45)	17	(31)	387	(33)
BMI (kg/m3)	29 ± 5.5		32 ± 6.5		27 ± 4.6	
Known hypertension	23	(75)	26	(48)	225	(19)
New discovered hyperten-sion	0	(0)	11	(20)	336	(29)
Hypercholesterolemia	27	(90)	45	(83)	884	(76)
Systolic blood pressure (mmHg)	139 ± 20.0		138 ± 21.4		136 ± 22.8	
Diastolic blood pressure (mmHg)	84 ± 10.2		81 ± 10.8		82 ± 10.7	
Total cholesterol (mmol/l)	4.5 ± 1.0		4.8 ± 1.1		5.5 ± 1.02	
LDL-C (mmol/l)	2.4 ± 0.9		2.7 ± 0.9		3.3 ± 0.9	
HDL-C (mmol/l)	1.4 ± 0.5		1.2 ± 0.4		1.5 ± 0.5	
Triglycerides (mmol/l)	1.9 ± 1.1		2.5 ± 1.6		1.5 ± 1.01	
CRP	3.4 ± 5.0		3.8 ± 3.0		2.9 ± 5.0	
CAC						
Mean (U)	526 ± 867		240 ± 716		80 ± 261	
Median (U)	141	(0-3050)	11	(0-4473)	0	(0-4220)
CAC-score categories						
0 U	5	(16)	20	(38)	647	(56)
> 0 U	26	(84)	32	(62)	506	(44)
1-9 U	5	(16)	5	(10)	146	(13)
10-99 U	4	(15)	14	(26)	199	(17)
100-399 U	9	(28)	9	(17)	102	(9)
≥ 400 U	8	(26)	5	(10)	59	(5)

Values are n (%) or mean ±SD. CVD; cardiovascular disease. CAC; Coronary artery calcification

lowering medication, this was the case for 45% (9 of 20 patients) of the T2D patients without CAC.

537 of the 1211 participants without CVD had coronary calcification, 174 had moderate or severe calcification (Agatston score ≥100), and 64 demonstrated severe calcification (Agatston score ≥400). Adjusting for covariates in multivariate logistic regression, known risk factors including male gender, aged 60 years, active smoking and hypercholesterolemia were significantly associated with the presence and extent of coronary calcification (Table 3), while T2D was not. Excluding hypercholesterolemia from the multivariate regression, T2D continued to be without association to presence and extent of CAC (data not shown).

Table 3: Odds ratios for the presence of different levels of CAC

	CAC > 0 (n=537)			CAC > 99 (n=174)			CAC > 399 (n=64)		
	OR	95% CI	P value	OR	95% CI	P value	OR	95% CI	P value
Male	3.2	2.5 – 4.2	<0.0001	3.7	2.5 – 5.4	<0.0001	3.7	2.0 – 6.9	<0.0001
Hypercholesterolemia	2.9	1.9 – 4.4	<0.0001	2.5	1.6 – 3.9	<0.0001	2.9	1.6 – 5.5	0.0007
Aged 60 years	2.2	1.7 – 2.9	<0.0001	3.7	2.5 – 5.6	<0.0001	6.5	3.0 – 14.1	<0.0001
Active smoking	1.9	1.4 – 2.5	<0.0001	2.0	1.3 – 2.9	0.0005	2.3	1.3 – 4.1	0.003
Hypertension	1.3	0.99 – 1.7	0.06	1.4	0.98 – 2.1	0.07	1.7	0.9 – 3.1	0.11
T2D	1.0	0.5 – 2.0	0.94	1.2	0.6 – 2.5	0.61	1.0	0.3 – 2.8	0.93
Resting pulse	1.0	0.99 – 1.02	0.35	1.02	1.001 – 1.03	0.03	1.02	0.99 – 1.04	0.06
Waist length	1.0	0.99 – 1.01	0.78	0.99	0.98 – 1.009	0.43	1.0	0.98 – 1.02	0.95

CAC; Coronary artery calcification. OR; odds ratio. CI; confidence interval. T2D: Type 2 diabetes mellitus.

Discussion

We studied the prevalence of CAC in patients with T2D and found that more than one third of these did not have coronary calcification. CAC was more frequent in T2D compared to subjects without diabetes, but T2D per se was not associated to CAC. These data may challenge the European recommendation that all patients with T2D have an increased CVD risk, and should be treated accordingly [13].

It is well known that patients with T2D are at increased risk of developing IHD, and several studies have demonstrated a two times higher CVD risk in patients with diabetes compared to those without [14;15]. These observations have lead to the conclusion, that asymptomatic patients with T2D have the same risk of myocardial infarction as patients with a prior myocardial infarction. Thus T2D has been proposed to be an IHD equivalent, and patients with diabetes should preferably receive intensive primary preventive therapy. Opposed to our study, one earlier study did also suggest that the CAC score in patients with T2D is similar to that of patients with established CVD [16]. However, these data were obtained from a selected population of patients with known diabetes for several years and consequently with a potential higher CAC score than patients with newly discovered diabetes. In our study both subjects with known and newly diagnosed T2D were enrolled, and we found a significantly higher CAC score in patients with established CVD compared to patients with T2D. A more balanced interpretation of the prognostic impact of T2D is supported by the results of a large meta-analysis, showing that patients with diabetes but no prior myocardial infarction have a 43% lower risk of developing IHD compared with patients with previous infarction but without diabetes [17]. This is in concordance with the recent MESA study by Malik et al [8], where individuals with T2D or MetS were found to have a low risk of developing IHD or CVD when CAC was not increased, and thereby questioning whether T2D per se is a coronary risk equivalent. The MESA study also showed that CAC added incrementally to the predictive value of both IHD and CVD events in those with T2D or MetS as well as those with none of these conditions. The above is in concordance with our study; when adjusting for covariates in multivariate logistic regression, T2D

was not associated with presence or extent of CAC. Thus T2D per se might not be an IHD risk equivalent.

CAC has been established as a reliable non-invasive marker of coronary atherosclerosis [18], and CAC scoring improves risk stratification, discrimination, and reclassification above and beyond traditional risk factor categories in subject without diabetes [4;5]. A high HeartScore has been associated with a high CAC score [19], and also in individuals at low expected risk according to HeartScore, traditional risk factors predict CAC progression in the short term with good discrimination and calibration [20]. In subjects with T2D, Qu et al found increased risk and high CAC scores. However, compared to subjects without diabetes the prognostic power of the CAC score was lower in those with T2D [15]. Unfortunately, the screening strategy in this study only included high risk subjects with a high proportion of patients with diabetes compared with the general population. In our study, subjects with T2D had higher CAC score than subjects without diabetes, and 38% did not have CAC. This is in accordance with a review by Elkeles [21]. They found that 23% of T2D subjects had a low CAC score and were at low risk for CVD. Raggi et al concluded that measurement of CAC score predicted all-cause mortality as effectively in those with T2D as in those without. In fact, subjects with zero CAC score had the same prognosis irrespectively of the presence of T2D [22]. Also, Shemesh et al have demonstrated that the risk of developing CVD in patients with T2D and concurrent arterial hypertension but no CAC is lower than in subjects with CAC but no diabetes [23]. Finally, the Predict study concluded that CAC score strongly predicts CVD in asymptomatic patients with T2D [24]. A doubling of the CAC score was associated with a 32% increase in risk of CVD including strokes.

Atherosclerosis is accelerated in patients with T2D, and often they do have CVD in more than one vascular territory [25]. Progression of calcification may provide insight into atherogenesis, development and treatment of CVD. Thus, a very important question to be answered is when to perform the CAC scan and which frequency is required to determine CAC progression. In subjects without diabetes, CAC progression is found to add incremental value in predicting all-cause mortality, but not in individuals with a baseline CAC score of zero [18]. Measurement of CAC progression as a non-invasive predictor of future clinical events in patients with diabetes has yet to be determined, but Wong et al recently concluded that increased progression of CAC in patients with diabetes or MetS could predict future CVD events [7]. Also, persons with T2D had an increased incidence and absolute progression of CAC compared with individuals without. In the VADT-study, neither intensive glycemic control nor standard risk factors did influence the CAC progression [26]. This study only investigated patients with long lasting T2D and not patients with newly discovered T2D. Interestingly, in a recent follow-up accelerated calcification was associated with more frequent statin use in T2D patients with advanced atherosclerosis [27].

Absence of coronary calcification does not exclude atherosclerosis and even obstructive coronary artery disease in high risk individuals as well as subjects with diabetes [28]. In the future a contract-enhanced CT coronary angiography (CTCA) might become a valuable tool for visualizing both silent vulnerable non-calcified plaques and calcified plaques and thereby predict the true plaque burden.

Limitations

Only 69% of invited subjects accepted screening. Therefore, it may be argued that our study does not represent a truly random population sample, since people who agree to participate may be selected and healthier than the general population. However, the participation rate in our study is high, when compared with earlier studies. The presence of CAC indicates atherosclerosis of the coronary arteries, but absence of CAC does not exclude atherosclerosis, since atherosclerotic coronary arteries do not necessarily show calcification. Thus, CAC is solely a pseudo marker, meaning that the measurements do not detect incipient atherosclerosis such as fatty streaks and lipid deposits, which are common in patients with diabetes. Glycated haemoglobin has now been accepted as a criterion for the diagnosis of diabetes, but at the time of the screening fasting plasma blood glucose level was applied, and therefore glycated haemoglobin was not measured. Our data does not include the duration of T2D, and thereby not revealing a possible relationship between T2D duration and CAC score.

Conclusion

There is a wide range of CVD risk in patients with T2D. In this study, more than one-third did not have any coronary calcification. This observation suggests that also in patients with T2D individual treatment should be considered.

Acknowledgements

We are indebted to the dedicated staff at the Department of Cardiology and Nuclear Medicine, Odense University Hospital, the Department of Cardiology, Vejle Hospital, the Department of Cardiology and Radiology, SVS Esbjerg, and the Department of Cardiology and Radiology, Svendborg Hospital.

Source of Funding: This work was supported by Region Syddanmark and Odense University Hospital both Denmark.

Conflict of Interest: None

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