Title

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Journal

Journal of Diabetes and its Complications, 31(7)

ISSN

1056-8727

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Publication Date

2017-07-01

DOI

10.1016/j.jdiacomp.2017.03.013

Peer reviewed

Journal of Diabetes and Its Complications 31 (2017) 1096–1102

Contents lists available at ScienceDirect

Journal of Diabetes and Its Complications

journal homepage: WWW.JDCJOURNAL.COM

Diabetes and male sex are key risk factor correlates of the extent of coronary artery calcification: A Euro-CCAD study

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ARTICLE INFO

Article history:
Received 8 January 2017
Received in revised form 4 March 2017
Accepted 28 March 2017
Available online 31 March 2017

Keywords:
Coronary calcification extent
Risk factors
Diabetes
Gender
Hypertension

ABSTRACT

Background and Aims: Although much has been written about the conventional cardiovascular risk factor correlates of the extent of coronary artery calcification (CAC), few studies have been carried out on symptomatic patients. This paper assesses the potential ability of risk factors to associate with an increasing CAC score.

Methods: From the European Calcific Coronary Artery Disease (Euro-CCAD) cohort, we retrospectively investigated 6309 symptomatic patients, 62% male, from Denmark, France, Germany, Italy, Spain and the USA. All had conventional cardiovascular risk factor assessment and CT scanning for CAC scoring.

Results: Among all patients, male sex (OR = 4.85, $p < 0.001$) and diabetes (OR = 2.36, $p < 0.001$) were the most important risk factors of CAC extent, with age, hypertension, dyslipidemia and smoking also showing a relationship. Among patients with CAC, age, diabetes, hypertension and dyslipidemia were associated with an increasing CAC score in males and females, with diabetes being the strongest dichotomous risk factor ($p < 0.001$ for both). These results were echoed in quantile regression, where diabetes was consistently the most important correlate with CAC extent in every quantile in both males and females. To a lesser extent, hypertension and dyslipidemia were also associated in the high CAC quantiles and the low CAC quantiles respectively.

Conclusion: In addition to age and male sex in the total population, diabetes is the most important correlate of CAC extent in both sexes.

1. Introduction

Coronary artery calcification (CAC) is an independent predictor of cardiovascular (CV) events and all-cause mortality in both CV and renal patients[1,2] and is known as 'sub-clinical atherosclerosis' in asymptomatic individuals.[3] Severe CAC can cause hardening of the arteries (arteriosclerosis), which may result in exertional angina even in the absence of significant flow limiting lesions.[4] The conventional CV risk factors (hypertension, diabetes mellitus, dyslipidemia, family history of coronary artery disease (CAD), obesity and smoking), which have proved to be predictive of the estimated 10-year coronary event risk,[5] may also predict CAC. We have previously investigated the risk factor correlates of CAC presence and shown them to be principally dyslipidemia and diabetes in males and diabetes and smoking in females.[6] Although a few, such as Mayer et al.[7] and Mitsutake et al.,[8] have studied risk factors for CAC extent in symptomatic patients, their cohorts were relatively small. Using the 6309 symptomatic patients from the European Calcific Coronary Artery Disease (Euro-CCAD)

We declare that none of the authors have any financial or any other conflict of interest.

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http://dx.doi.org/10.1016/j.jdiacomp.2017.03.013
1056-8727/

study, an international platform established in 2009 in Umeå, Sweden, we intended to investigate correlates of CAC extent in a larger cohort and compare them with the correlates of CAC presence in the same cohort in a cross-sectional retrospective study.

2. Methods

Retrospective data were collected from seven heart centers in six countries on symptomatic patients with intermediate risk.[9] Some data were collected from registries. Patients may have typical or atypical angina symptoms; data allowing classification of chest pain as typical angina, atypical angina or non-cardiac chest pain as defined by Diamond[10] were not available although it was estimated that the majority had typical angina. Patients received a thorough clinical examination and assessment of conventional risk factors for CAD, together with coronary calcium scoring using the local CT protocol.

These patients were collected from the following centers:

Denmark: 1015 patients from 2 centers
France: 547 patients
Germany: 351 patients
Italy: 3336 patients
Spain: 186 patients
USA: 874 patients

The inclusion criteria were exertional angina-like symptoms, whether typical or atypical, in patients who were at intermediate risk for CAD, and the angina was not explained by any other clinical finding.

The exclusion criteria for this study were:

- Acute coronary syndrome or recent cardiovascular event
- Stroke or transient ischemic attack
- Cardiac valve disease
- Atrial fibrillation
- Prior coronary intervention (percutaneous intervention or bypass graft surgery)
- Heart failure or previous decompensation
- Chronic kidney disease (creatinine >120 mmol/l)
- Parathyroid disease
- Pregnancy

Computed tomography scanning protocol

CT scanning for coronary calcification was undertaken with the patient in the supine position. The heart was localized by low-dose, low-resolution spiral CT imaging of the chest. High-resolution scanning of the heart was begun at the level of the bifurcation of the main pulmonary artery and proceeded caudally through the cardiac apex. Rotation and slice acquisition protocols were adopted according to individual scanners and local protocols. At least four contiguous pixels with a CT density ≥ 130 Hounsfield units were used to define an area of CAC. The total CAC score (CACS) was computed from all calcified lesions by means of the Agatston score, calculated by multiplying the area of each lesion by a density factor and then summing the individual lesion scores.[11] Analyses were performed using local protocols and workstations.[12]

Risk factor assessment

All centers used standard definitions for risk factors. Diabetes mellitus (DM) was defined as overnight fasting blood glucose ≥7 mmol/l (126 mg/dl), postprandial blood glucose ≥11.1 mmol/l (200 mg/dl) or use of insulin or oral hypoglycemic agents. Blood lipids were measured using standard enzymatic methods. Dyslipidemia (DL) was defined as total cholesterol >5.0 mmol/l (193 mg/dl), low density lipoprotein cholesterol >3.00 mmol/l (116 mg/dl) or use of lipid-lowering medication. Body mass index (BMI) was calculated using height and weight measurements, with BMI ≥30 kg/m^2 indicating obesity. Family history of premature CAD was noted if a male first-degree relative developed CAD aged <55 years or a female first-degree relative aged <65 years. Hypertension (HT) was defined according to the JNC-7 guidelines as systolic blood pressure ≥ 140 mm Hg, diastolic blood pressure ≥ 90 mm Hg and/or use of antihypertensive medication.[13] The patient was classified a smoker if they had smoked during the last month. A total risk factors score was created by counting 1 for each risk factor present, with the exception of age.

Statistical analysis

Quantitative data were presented as mean ± standard deviation (SD) and qualitative data were presented as frequencies. The CAC score was grouped as 0, 1–99, 100–399, 400–999, and ≥1000. Differences between groups were evaluated by ANOVA for parametric variables and by the chi-square test for categorical variables. A multivariate ordinal logistic regression analysis was used to elucidate the associations between risk factors and the severity of CAC, as represented by the different CAC score groups. In this analysis, the two highest CAC score groups were merged in order to fulfill the proportional odds assumption, which is a requirement for ordinal logistic regression. Finally, a quantile regression analysis was conducted to measure the effects of different risk factors on CAC extent, with age included as a co-variate. The CAC score was log-transformed ($\log_{10}$ CAC + 1). Quantile regression measures the relationship between the independent variable(s) and specific quantiles of the dependent variable (CAC extent). This gives an estimate of the change of the linear regression line in a specified quantile of the dependent variable in subjects with the risk factor, as compared to subjects without the risk factor. Thus, a comparison can be made how each quantile of CAC extent is affected by each of the risk factors, as reflected by a change in the magnitude of the regression coefficients at different quantiles. Standard errors for regression coefficients were obtained with the bootstrap method. A p-value of <0.05 was considered statistically significant. Statistical analyses were undertaken using SPSS for Windows software, version 21.0 (IBM Corporation, Armonk, NY, USA), except for the quantile regression analysis that was conducted using R v. 3.3.1 (2016, R Core Team, Vienna, Austria) and Matlab v. 2016a (Matworks Inc., Natick, MA).

3. Results

The overall Euro-CCAD cohort consists of data from 6309 symptomatic patients, among whom 600 (9.5%) had no risk factors, while among the 4177 patients with CAC, 7% had no risk factors. Table 1 describes the prevalence of individual risk factors categorized according to the CAC scores 0, 1–99, 100–399, 400–999 and ≥1000. Age and number of risk factors increased with the CAC score, as did the percentage of patients with HT, DL, and DM ($p < 0.001$ for all), while the percentage of patients with no risk factors decreased with increasing CAC score ($p < 0.001$). The percentage of patients with obesity, out of a reduced cohort of the 3680 patients in whom data were available, also increased with the CAC score ($p < 0.001$). The percentages of smokers and those with family history of CAD were not different among the CAC score groups.

Fig. 1 shows that when plotting the CAC score against number of risk factors, females with 0–6 risk factors have significantly less CAC than males ($p < 0.001$). The log transformed CAC score showed a nearly linear increase in CAC score with increasing number of risk factors in both males and females.

Fig. 2 demonstrates that as the number of risk factors increase, the proportion of patients in the lower CAC score ranges decreases, while the proportion with a higher CAC score generally increases ($p < 0.001$).

Table 1
Individual patient risk factors by CAC score category.

Risk factors	CACS = 0 (n = 2132)	CACS = 1–99 (n = 1728)	CACS = 100–399 (n = 1124)	CACS = 400–999 (n = 747)	CACS ≥ 1000 (n = 578)	p-Value
Age, years (6309), mean ± SD	54.3 ± 11.4	59.9 ± 10.8	64.3 ± 10.2	65.8 ± 9.4	68.2 ± 9.4	<0.001
Male sex (6309), %	47.0	64.0	68.5	78.0	77.9	<0.001
Hypertension (6287), %	44.1	58.2	63.7	68.2	72.6	<0.001
Diabetes (6278), %	7.2	11.6	17.4	20.9	30.4	<0.001
Dyslipidemia (6109), %	37.0	48.6	54.7	55.0	51.5	<0.001
Obesity (3680), %	17.3	21.8	19.3	23.4	27.8	<0.001
Smoking (6268), %	32.0	35.3	33.2	35.4	31.2	0.12
Family history of CAD (6084), %	46.7	46.4	43.9	42.6	41.9	0.09
Number of risk factors, mean ± SD	1.75 ± 1.16	2.10 ± 1.16	2.20 ± 1.19	2.31 ± 1.17	2.36 ± 1.26	<0.001
No risk factors, %	14.0	7.9	7.0	5.2	6.6	<0.001

CACS = coronary artery calcium score; CAD = coronary artery disease. Numbers in brackets correspond to the number of subjects without missing values. Number of risk factors = number of dichotomous risk factors present.

Table 2 shows the multivariate individual risk factor correlates of an increasing CAC score for patients without missing values of individual risk factors using ordinal regression analysis with subjects divided in different CAC score groups. In all patients, an increasing CAC score was strongly correlated with age and the other most important relationships were male sex (OR = 4.05, $p < 0.001$), DM (OR = 2.36, $p < 0.001$), HT, DL and smoking. In females, the most important risk factor for increasing CAC score was DM (OR = 2.59, $p < 0.001$) followed by smoking (OR = 2.06, $p < 0.001$), HT and age and in males age, HT, DM, DL, FH and smoking were associated, with DM being the most important (OR = 2.25, $p < 0.001$) followed by DL (OR = 1.73, $p < 0.001$). DL was not associated in females, whereas FH of CAD correlated only in males; obesity was not associated in any group.

Table 3 shows the estimated coefficients of selected variables from age-adjusted quantile regression analysis at percentiles of 90%, 75%, 50%, 25% and 10%, as well as from regular linear regression, for those of the 4177 patients with CAC that did not have missing data regarding the presence/absence of each risk factor, which was between 2763 and 2901 males and 1219–1263 females (except for obesity: 1712 males and 699 females). Linear regression, which represents the effect of a risk factor on the average level, showed HT, DL and DM as correlates of CAC extent in both males and females, whereas smoking was associated only in females, and obesity and family history were associated only in males. Based on the magnitude of β, the strongest risk factor for CAC extent in males was DM ($\beta = 0.267$, $p < 0.001$) followed by DL ($\beta = 0.101$, $p < 0.001$). DM was also the strongest risk factor for CAC extent in females ($\beta = 0.336$, $p < 0.001$), followed by HT ($\beta = 0.134$, $p = 0.004$).

In quantile regression, which represents the effect of a risk factor on different CAC levels, HT was significantly associated with CAC extent in the 50% and 90% quantiles in males, and in the 50%–90% quantiles in females. DL was correlated with CAC extent in males in the 10%–50% quantiles (i.e., below the median) but in females it was associated only in the 50% and 90% quantiles. In contrast, DM was significantly associated with CAC extent at all quantile levels in both males and females, despite a slightly lower significance in the 10% and 25% quantiles in females. Smoking was a risk factor for CAC extent only at the 10% quantile in males but showed a closer relationship in females, with significance at the 10%, 25% and 90% quantiles. Family history for CAD was associated at the 50% and 75% quantiles only in males but not at any level in females. Finally, obesity modestly correlated with CAC extent at 50% and 90% quantile levels but the analysis could only be carried out in males. Based on the magnitude of β, DM is the most important correlate of CAC extent in every quantile in both males and females.

Fig. 3 shows the corresponding quantile regression lines for the principal risk factors HT, DL and DM in males and females, according to age. The distance between red and blue lines corresponds to the

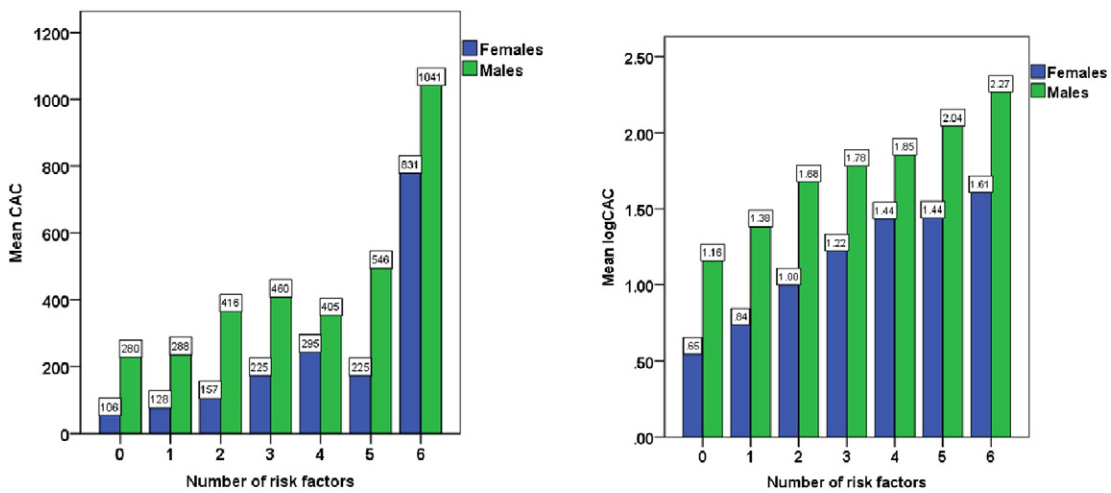

Fig. 1. Number of risk factors and the absolute CAC and log CAC score by sex.

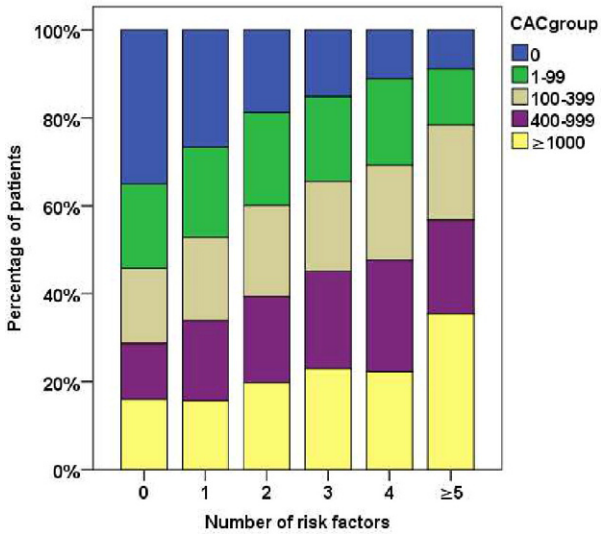

Fig. 2. Number of risk factors and the proportion of patients in each CAC score group.

magnitude of β in Table 3. In addition to age being clearly a strong risk factor, the figures show that HT is mainly important for high CAC (≥50% quantile), while DL is mainly important for males with lower levels of CAC (≤50% quantile) but for females the importance of DL is more evenly distributed. For DM, the distance between red and blue lines is greater than for the other risk factors, indicating the higher β from Table 3.

4. Discussion

Summary of findings

Among 6309 symptomatic patients, 9.5% of the total and 7% of those with CAC had no risk factors. With the exception of smoking and family history of CAD, the prevalence of all risk factors increased with the CAC score, although the proportion of patients with no risk factors decreased. The number of risk factors increased fairly uniformly with the CAC score. In ordinal logistic regression, age, male sex, DM, HT, DL and smoking were associated with an increasing CAC score in the patient cohort as a whole, with the most important being male sex and DM. The same risk factors were correlated in males, with the addition of FH of CAD, while in females only age, HT, DM and smoking were associated. DM was the most important risk factor in males and females and hence DM is the most important CV risk factor for increasing CAC irrespective of sex.

Among the 4177 patients with CAC, logistic regression analysis showed HT, DL and DM to be correlates of CAC extent in both males and females, whereas smoking was associated only in females, and obesity and family history were associated only in males. DM was the strongest risk factor in both sexes. In quantile regression, DM was consistently the most important risk factor at all levels of CAC extent in both males and females. HT was correlated in both sexes but only at or above the median, whereas DL was correlated at or below the median in males but at or above the median in females. Smoking showed a stronger relationship in females than males but family history of CAD and obesity were modestly associated only in males. In

Table 3
Quantile regression of different risk factors for CAC extent with correction for age, including regression coefficients from regular linear regression (LR).

CACS quantile	Males			Females		
	β	SE	*p* Value	β	SE	*p* Value
Hypertension						
90%	0.14	0.04	<0.001	0.160	0.073	0.03
75%	0.050	0.03	0.11	0.209	0.063	0.001
50%	0.096	0.046	0.04	0.179	0.058	0.002
25%	0.058	0.053	0.27	0.050	0.073	0.50
10%	0.043	0.066	0.52	0.036	0.092	0.70
LR	0.062	0.031	0.04	0.134	0.046	0.004
Dyslipidemia						
90%	0.003	0.040	0.94	0.124	0.045	0.006
75%	0.029	0.030	0.33	0.076	0.059	0.20
50%	0.106	0.043	0.01	0.120	0.057	0.03
25%	0.197	0.048	<0.001	0.135	0.077	0.08
10%	0.216	0.059	<0.001	0.083	0.090	0.36
LR	0.101	0.03	<0.001	0.103	0.043	0.02
Diabetes mellitus						
90%	0.212	0.033	<0.001	0.296	0.601	<0.001
75%	0.230	0.043	<0.001	0.388	0.052	<0.001
50%	0.303	0.044	<0.001	0.433	0.077	<0.001
25%	0.288	0.073	<0.001	0.261	0.104	0.01
10%	0.221	0.089	<0.001	0.303	0.124	0.02
LR	0.267	0.038	<0.001	0.336	0.055	<0.001
Smoking						
90%	−0.057	0.036	0.12	0.108	0.052	0.04
75%	0.018	0.031	0.56	0.118	0.065	0.07
50%	0.080	0.042	0.06	0.086	0.070	0.22
25%	0.071	0.054	0.19	0.220	0.066	0.001
10%	0.155	0.068	0.02	0.272	0.083	0.001
LR	0.055	0.030	0.07	0.125	0.049	0.01
Family history						
90%	0.035	0.039	0.36	−0.093	0.055	0.09
75%	0.060	0.029	0.04	−0.108	0.059	0.07
50%	0.116	0.044	0.009	−0.056	0.060	0.35
25%	0.054	0.054	0.31	0.038	0.077	0.62
10%	0.053	0.068	0.43	0.091	0.081	0.26
LR	0.059	0.030	0.05	−0.022	0.045	0.61
Obesity						
90%	0.159	0.042	<0.001			
75%	0.099	0.052	0.06			
50%	0.035	0.002	<0.001			
25%	0.123	0.081	0.13			
10%	0.109	0.113	0.34			
LR	0.099	0.045	0.03	−0.011	0.073	0.88

Only subjects with CAC > 0 were included in the analysis. SE = standard error; CACS = CAC score.

Table 2
Multivariate correlates of CAC extent.

Risk factors	All patients (n = 3594)		Females (n = 1296)		Males (n = 2298)	
	OR (CI)	*p*-Value	OR (CI)	*p*-Value	OR (CI)	*p*-Value
Age	1.09 (1.09–1.10)	<0.001	1.10 (1.08–1.11)	<0.001	1.09 (1.09–1.10)	<0.001
Male sex	4.05 (3.51–4.67)	<0.001				
Hypertension	1.58 (1.37–1.81)	<0.001	1.44 (1.14–1.83)	0.003	1.65 (1.39–1.95)	<0.001
Diabetes	2.36 (1.95–2.85)	<0.001	2.59 (1.88–3.57)	<0.001	2.25 (1.78–2.84)	<0.001
Dyslipidemia	1.53 (1.35–1.74)	<0.001	1.12 (0.97–1.50)	0.09	1.73 (1.48–2.03)	<0.001
Obesity	1.12 (0.96–1.32)	0.15	1.15 (0.87–1.52)	0.33	1.10 (0.91–1.33)	0.32
Family history of CAD	1.12 (0.98–1.27)	0.09	0.94 (0.75–1.17)	0.57	1.24 (1.05–1.45)	0.009
Smoking	1.48 (1.28–1.71)	<0.001	2.06 (1.56–2.73)	<0.001	1.31 (1.10–1.55)	0.002

CAD = coronary artery disease; OR = odds ratio; CI = 95% confidence interval for OR.

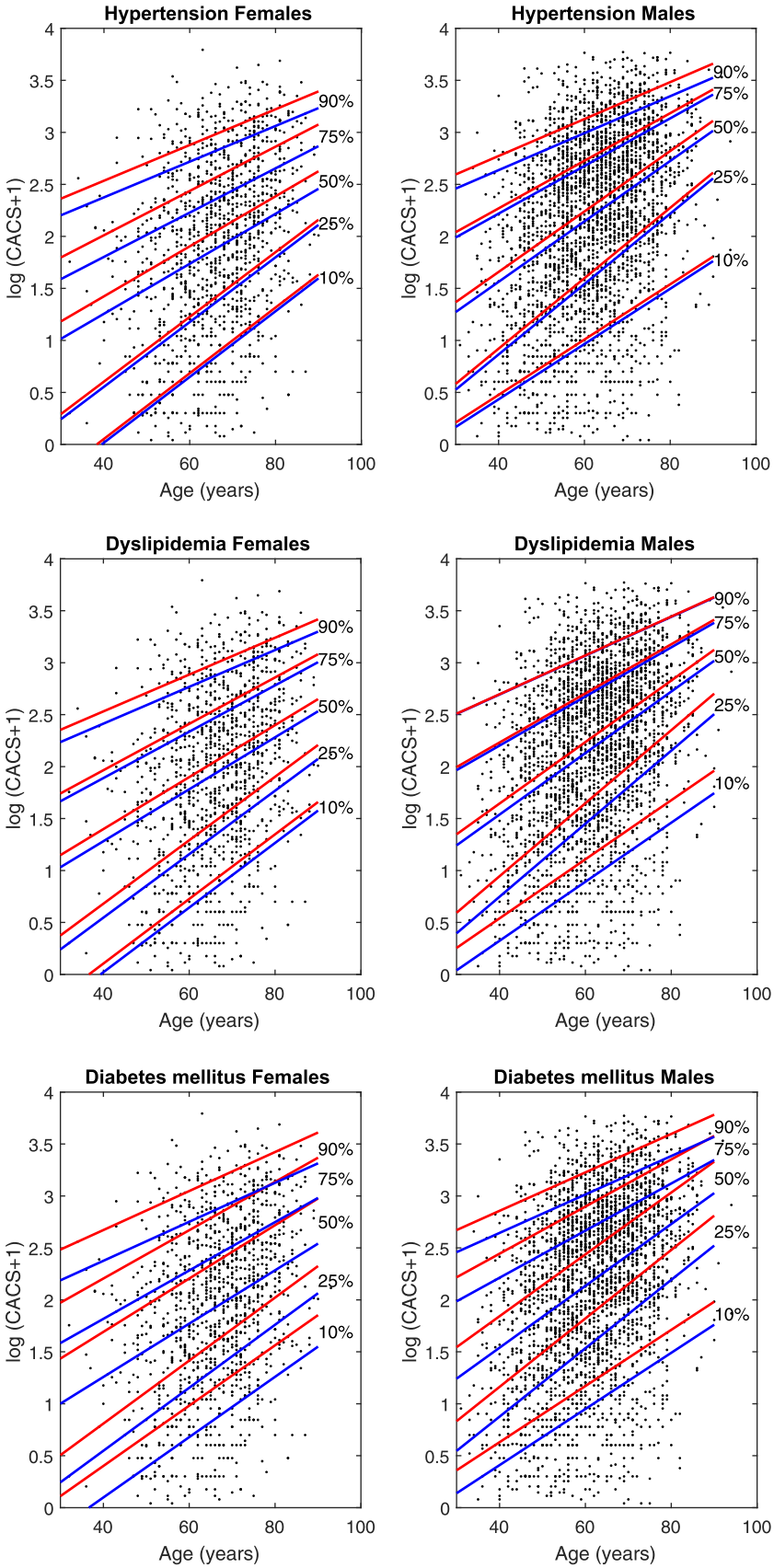

Fig. 3. Quantile regression lines for hypertension, dyslipidemia and diabetes by age and sex. For each quantile, the distance between the linear regression line for patients with the risk factor present (red lines) and patients without the risk factor (blue lines) corresponds to the β in Table 3.

summary, the correlates for CAC extent using all patients and the correlates using only patients with CAC both show DM to be the most important risk factor, with male sex being the most important correlate in all patients.

Comparison with other studies investigating CAC extent

Other studies investigating risk factors independently associated with CAC extent in symptomatic patients include Mayer et al.[7] who found that in 877 males, age, HT, DL and family history of CAD were correlated with severe CAC assessed angiographically, while obesity, DM and smoking were not correlated. Similarly, Mitsutake et al.[8] found that in 535 patients age, male sex and HT were associated with CAC extent, while DL and DM were not associated but Tanaka et al.[14] found that age, male sex, HT, DM were associated in 1363 patients, while obesity, smoking and DL were not. Additionally, using a cut-off of ≥400, Lai et al.[15] found that in 210 patients, none of the conventional CV risk factors correlated with a higher CAC score. Our patient group of 6309 was considerably larger than the cohort size in any of these studies but there is little agreement either between these studies or with our findings, except to demonstrate the importance of age and male sex.

Comparison with correlates of CAC presence in the same cohort

Our earlier study of the risk factor for CAC presence in the 6309 patients from the Euro-CCAD cohort found that the most important were DL and DM in males and DM and smoking in females.[6] This compares well with our present results using the cohort as a whole, which found that DM was the most important risk factor for CAC extent in males and females. When studying only the 4177 patients with CAC, we found a similar correspondence between the strong risk factors in males although there was a divergence among females. Although DM remained the most important risk factor among females, this was followed by HT rather than smoking, although smoking was correlated. Consequently, we can conclude that among males the strongest risk factors for CAC presence and extent are DM and DL (with DM being stronger for CAC extent and DL for CAC presence), while the most important risk factor among females is DM for both CAC presence and extent.

Findings interpretation

Our results highlight the important relationship between DM and coronary calcification, irrespective of sex and the presence of other risk factors. This consistent relationship between diabetes and CAC extent, irrespective of age and sex, may reflect a form of diabetic angiopathy rather than simply the conventional atherosclerosis pathology. The generally accepted pathophysiological mechanism is microcirculation pathology, known among diabetics, not only involving the coronary arteries but also other arterial systems. As for the CAC extent, it may be explained on the basis of a natural healing process of such arteriopathy or as a result of the medications these individuals are taking.

Limitations

We relied on the risk factor assessments by the investigating centers rather than by our own core lab, but we believe that they should be substantially accurate. Data on whether the patients had typical or atypical angina and the duration of risk factors were not available and might have had a bearing on their correlation. Patients with typical angina would invariably have been sent for an invasive angiogram, whereas those receiving CTCA are likely to have had atypical angina, The lack of difference in the risk factor association for CAC beyond a score of 100 was not analyzed in this study as it was not part of the objective. Despite the lack of data for obesity in all patients, analysis of those with data did not demonstrate any correlation for obesity. There are likely to be additional confounding factors, for example serum uric acid,[16] lipoprotein (a)[17] and diet.[18] Although large studies such as the Multiethnic Study of Atherosclerosis (MESA),[19] the Heinz Nixdorf Recall study (HNR)[12] and DanRisk[20] have reported relationships between risk factors and CAC, we believe that direct comparison with our finding cannot be justified, as these cohorts were population-based with asymptomatic subjects, whereas ours were symptomatic patients. The slight difference in the prevalence of patients with CAC in the elderly compared to prevalence in asymptomatic population studies could be explained on the basis of selection bias.

Clinical implications

Regardless of the pathophysiological mechanism behind this association, the findings strengthen the role of determining the extent of CAC among diabetics, particularly when symptomatic. It has previously been documented that severe and extensive calcification could contribute to patients' limiting symptoms, irrespective of the presence of significant stenosis. Thus, our findings strengthen this argument and establish the vital place of CAC assessment in the routine management of older symptomatic patients with DM.

5. Conclusion

In this cohort of symptomatic patients with CAC, age, DM, HT, DL and number of risk factors correlated with an increasing CAC score in both sexes, with DM being the most important dichotomous risk factor in every quantile in both sexes. A small proportion of patients with CAC had no risk factors, while some of those with risk factors had zero CAC. These findings support the important role of CAC assessment in the management of symptomatic patients, particularly diabetics.

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