Cardiology Journal
2012, Vol. 19, No. 4, pp. 402–407
10.5603/CJ.2012.0072

ISSN 1897–5593

VIA MEDICA

ORIGINAL ARTICLE

Traditional risk factors and coronary artery calcium in young adults

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Abstract

Background and methods: *362 symptomatic subjects of 45 years of age or younger were selected from a large database of around 4100 persons who underwent coronary artery calcium (CAC) scoring by means of a 64-multidetector computed tomography (MDCT). Amongst them, a group with the CAC > 0 Agatston units (n = 65) and a group with no detectable calcium (CAC = 0, n = 297) were compared in terms of risk factors presence. Risk factors considered were gender, body mass index, smoking habits, blood pressure level, blood lipids, presence of diabetes mellitus, family history of cardiovascular disease, and physical activity.*

Results: *The vast majority of subjects with a positive CAC were males (54, 83.1%) compared to those with a negative CAC (147, 49.5%, $p < 0.001$, χ^2). More frequent results of CAC > 0 were observed in obese subjects (38.5%* vs. *24.2%, $p < 0.05$), among smokers (41.5%* vs. *27.6%, $p < 0.05$). Presence of arterial hypertension coexisted with a more frequent CAC > 0 (76.9%* vs. *60.6%, $p < 0.05$). Also, the frequency of a positive CAC was significantly higher in patients with diabetes mellitus (10.8%), compared to those without diabetes mellitus (4.0%, $p < 0.05$). Effects of high lipids, family history, and physical activity were not observed. Accumulation of at least 4 risk factors was associated with more frequent positive CAC (26.0* vs. *15.9%, $p < 0.05$). Multivariate regression analysis showed that only male gender and presence of diabetes mellitus were independent predictors of a positive CAC in younger subjects ($F = 5.06$, $p < 0.001$, multiple $R = 0.321$).*

Conclusions: *Traditional risk factors, apart from gender and diabetes mellitus, do not seem to allow for distinguishing young persons with a premature coronary atherosclerosis. Therefore, CAC scoring might be considered justified in symptomatic young men with diabetes mellitus.* (Cardiol J 2012; 19, 4: 402–407)

Key words: coronary artery calcium, premature atherosclerosis, gender, risk factors, younger persons, diabetes mellitus

Introduction

Coronary artery calcium (CAC) determination is a noninvasive method of imaging of coronary atherosclerosis in asymptomatic subjects [1, 2]. Use of this method in relatively younger subjects is usually not advised as the global risk is aimed to be too low, being closely age-related, and not appropriate in terms of costs and benefits balance [3]. In a cohort of asymptomatic men aged 40–50 years, the

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Received: 16.10.2011 Accepted: 01.05.2012

Prospective Army Coronary Calcium Project (PACCs) participants, the CAC scoring has been found beneficial only in those with the Framingham risk score of more than 5% [4]. In a study of Wanahita et al. [5] on asymptomatic middle-aged police officers (mean age 42 years), the CAC 75 percentile was "zero" until 45 years of age. Also in symptomatic subjects, incremental value of CAC scoring was evidenced only in those aged far above 45 years [6]. At present there were no studies that addressed a relationship between traditional risk factors for coronary artery disease (CAD) and CAC in younger symptomatic subjects, thought the younger subjects with symptoms of angina or event myocardial infarction are not unusual in clinical practice. Importantly, within this subset of population, risk score prediction based on Framingham equation was found inadequate [7].

We aimed at examination of relationships between traditional risk factors for CAD and CAC scoring in order to determine whether a particular risk factor or their specific combination would help to indicate a need for CAC examination.

Methods

Study population

362 consecutive symptomatic subjects of 45 years of age or younger were selected retrospectivelly from a large dataset of above 4100 persons who underwent CAC scoring by means of a 64-multi-detector computed tomography (MDCT) between June 20th 2008 and October 12th 2011. Amongst them, the group with the CAC > 0 Agatston units [8] (n = 65) and the group with no detectable calcium (CAC = 0, n = 297) were compared in terms of traditional risk factors presence. They were referred for CAC scoring by discretion of their physicians because of symptoms, like exertion-provoked retrosternal chest pain, exertion dyspnea, atypical chest pain in subjects with risk factors' accumulation. In particular cases, a very high family risk had been considered by referring physician in spite of the presence of atypical chest pain, as well as a positive result of exercise testing. Exclusion criteria included very low CAD probability, age < 25 years, inability or refusal to sign consent, pregnancy or uncontrolled child-bearing potential, atrial fibrillation or frequent premature depolarizations precluding accurate ECG gating. The study was approved by the local institutional review board and received a waiver of patient consent [9].

Coronary artery calcium determination

CAC examinations were performed using a 64-raw MDCT scanner (Aquilion, Toshiba, Japan). Off-line reconstructions of the images were performed on Vitrea 2 workstations (software version 3.9.0.0, Vital Images, USA). Total and per-vessel (right coronary artery, left main coronary artery, left anterior descending branch and left circumflex branch) CAC burden was assessed by means of method of Agatston et al. [8]. Commercially available standardized reporting format for CAC scoring was used by all readers.

Coronary artery disease risk factors evaluation

In each subjects, body mass index (BMI, kg/m^2), smoking habits, systemic arterial blood pressure, lipids level, family risk and physical activity were noticed according to a clinical risk assessment protocol. Obese (BMI > 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) categories were distinguished. Smoking habit was categorized as current or former (anytime in the past) and never-smoking. Systemic arterial hypertension was recognized in subjects who had been diagnosed as hypertensive irrespective of the use of drugs or in whom two time measured blood pressure was 140/90 mm Hg or more. High lipids was diagnosed in subjects taking lipid lowering agents, or who had documented total cholesterol level of 200 mg/dL and above, or of triglyceride level 150 mg/dL and above, or both. Diabetes mellitus was recognized only in subjects who had been treated with insulin or oral agents. Family risk was considered positive if the first relatives died prematurely from cardiovascular death (including sudden cardiac death) or if the first relatives had suffered from the atherosclerosis-related cardiovascular diseases (infarction, stroke, peripheral artery disease, aortic aneurysm) below 55 years of age in males and 65 years in females. Physical inactivity was defined as no physical exercise during leisure time in not-heavy job workers. Otherwise, subjects were considered physically active.

Statistical analysis

Quantitative data are presented as means ± ± 1 standard deviation or median and interquartile range, depending on their distribution. Qualitative data are presented as numbers or proportions. Student t-test was used to compare normally distributed parametric data, and Kruskal-Wallis test for non-parametric comparisons. Distributions were

Table 1. Characteristic of groups of young persons with regard to total coronary artery calcium (CAC) scoring.

Parameter	CAC > 0 (n = 65)	CAC = 0 (n = 297)	P[#]
Age (years)*	40.1 ± 4.0	39.2 ± 4.9	NS[‡]
Gender (male)	54 (83.1%)	147 (49.5%)	< 0.001
Body mass index [kg/m^2]*	28.5 ± 6.0	27.1 ± 5.1	< 0.05
Obesity	25 (38.5%)	72 (24.2%)	< 0.05
Smoking	27 (41.5%)	82 (27.6%)	< 0.05
Hypertension	50 (76.9%)	180 (60.6%)	< 0.05
Hyperlipidemia	32 (49.2%)	124 (41.8%)	NS
Diabetes mellitus	7 (10.8%)	12 (4.0%)	< 0.05
Positive family risk	35 (53.9%)	154 (51.9%)	NS
Physical inactivity	40 (61.5%)	169 (56.9%)	NS
Sum of risk factors (RF)	2.94 ± 1.01	2.43 ± 1.17	< 0.01
Sum of RFs + obesity	3.32 ± 1.15	2.67 ± 1.28	< 0.001

*means ± 1 standard deviation, #χ^2 test, ‡ t-Student test

Table 2. Proportion of positive coronary artery calcium scoring in relation to gender and risk factors' presence.

Risk factor	Present			Absent			P[#]
Gender	All	Males	Females	All	Males	Females	
Obesity	25.8*	32.4*	10.3	15.1	24.1***	6.1	< 0.05
Smoking	24.8*	34.7†,***	5.4	15.0	22.5***	7.3	< 0.05
Hypertension	21.7*	30.0***	8.9	11.4	19.7**	4.2	< 0.05
Hyperlipidemia	20.5	29.2**	9.0	16.0	25.0***	5.3	NS
Diabetes mellitus	36.8*	75.0 ‡,**	9.1	16.9	24.9***	6.7	< 0.05
Positive family risk	18.5	26.9***	7.4	17.3	26.9***	6.3	NS
Physical inactivity	19.1	28.8***	8.2	16.3	24.4**	4.8	NS

*p < 0.05, **p < 0.01, ***p < 0.001, males *vs.* females, ‡p < 0.01; †p < 0.1 presence *vs.* absence in males, #χ^2 test

quantified by means of χ^2 test. Multivariate regression analysis was used to determine independent predictors of the CAC presence. Statistical package was used (Statistica 8.0, StatSoft Inc. Tulsa, OK, USA). The p-value < 0.05 was considered significant.

Results

In total, a positive CAC (CAC > 0) was found in a substantial proportion of young symptomatic persons (65/362, 17.9%). Male gender, obesity, smoking, hypertension and diabetes mellitus were more frequent among young subjects with a positive CAC score. Family risk, physical inactivity and high lipids were not found to be associated with the presence of calcified lesions (Table 1).

The proportion of a positive CAC was significantly higher in males (26.9%, 54/201) compared to females (6.8%, 11/161, p < 0.001, χ^2). The predominance of males among CAC positive persons within any category of risk factors' presence was statistically significant (Table 2). Among males, the only significant difference was found for the presence of diabetes mellitus, while there was a tendency toward more frequent CAC > 0 in current/past smokers (Table 2). In fact, the CAC was positive in all four males who were smokers and diabetes mellitus (100%, 4/4), while in 2 out of 4 diabetes mellitus who were non-smokers. The association of certain risk factors combination and a positive CAC in males is presented in the Figure 1.

Accumulation of risk factors was found to be related with the proportion of CAC scoring, being highest in males and more than 3 risk factors, and lowest in females with 3 or less risk factors' presence (Fig. 2).

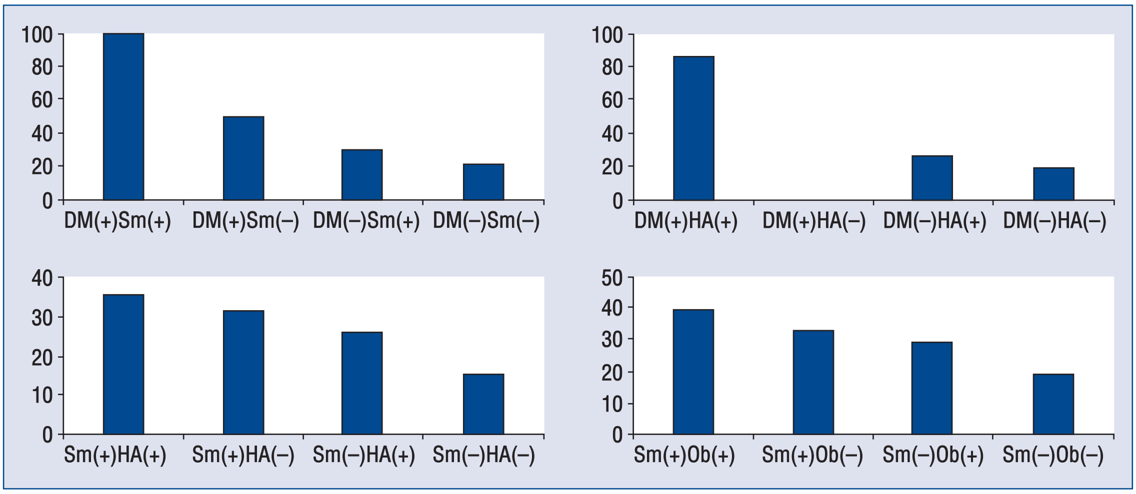

Figure 1. Frequency of a positive coronary artery calcium in males with various risk factors' co-existence. There was a trend toward highest proportions in patients who had at least two of these factors that could reach 35–100%, while ranged between 15–20% among males without these factors; DM — diabetes mellitus; Sm — smoking (current/ /past); HA — systemic arterial hypertension; Ob — obesity; (+) present; (–) absent.

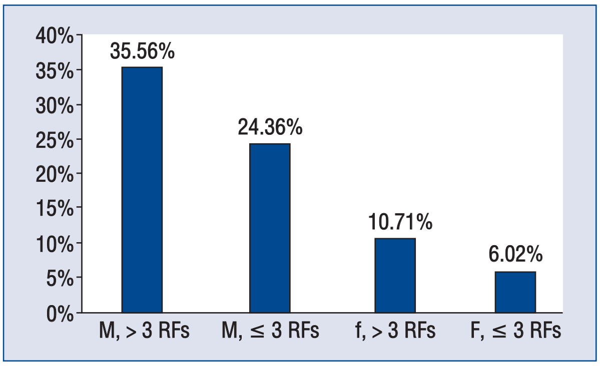

Figure 2. Frequency of a positive coronary artery calcium scoring in respect to gender (M — male, F — female) and risk factors (RFs) accumulation.

In a group of patients with a positive CAC scoring, the analysis of risk factors distribution in respect to extend of calcified lesions revealed that neither risk factor was associated with a more diffused coronary calcifications (Table 3).

Multivariate analysis showed that in the examined population of subjects aged 45 years or less, two factors, gender and diabetes mellitus were associated with the presence of calcified lesions (Fig. 3).

Discussion

There are several interesting findings of our study. First, we found that in relatively young symp-

Table 3. Distribution of calcified lesions in coronary artery calcium (CAC)-positive symptomatic young subjects.

Parameter	1 vessel (n = 38)	2 vessels (n = 15)	3 or more vessels (n = 12)	P#
Age (years)*	39 (37, 43)	41 (40, 43)	41 (40.5, 44)	NS‡
Gender (male	31 (81.6%)	13 (86.7%)	10 (83.3%)	NS
Body mass index [kg/m^2]*	28.1 (23.2, 30.9)	29.8 (24.1, 31.0)	28.4 (24.6, 30.0)	NS‡
Obesity	13 (34.2%)	7 (46.7%)	5 (41.7%)	NS
Smokers	16 (42.1%)	4 (26.7%)	7 (58.3%)	NS
Hypertension	29 (76.3%)	13 (86.7%)	8 (66.7%)	NS
Hyperlipidemia	16 (42.1%)	10 (66.7%)	6 (50%)	NS
Diabetes mellitus	2 (5.3%)	3 (20.0%)	2 (16.7%)	NS
Positive family risk	22 (57.9%)	6 (40.0%)	7 (58.3%)	NS
Physical inactivity	21 (55.3%)	11 (73.3%)	8 (66.7%)	NS

*median (25%, 75% percentile values), #χ^2 test, ‡ Kruskal-Wallis test

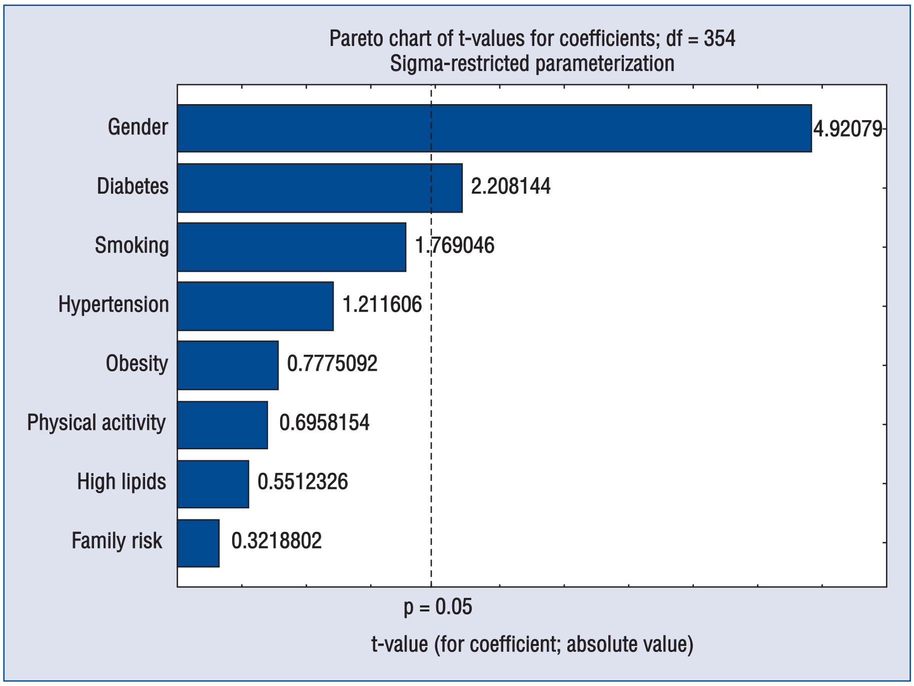

Figure 3. Independent effects of analyzed risk factors on the presence of a positive coronary artery calcium scoring in younger subjects, as resulted from multivariate regression analysis. Age has not been included in the model (a priori).

tomatic subjects the abnormal CAC (any positive scoring) could be detected in a substantial proportion of persons (approximately 1/5th). This proportion cannot be compared to majority of existed data, since younger subjects (either asymptomatic or symptomatic) are commonly excluded from CAC scoring studies. However, in some studies in young persons an overall proportion of CAC-positive subjects was similar, irrespective of symptomatic status [7, 10, 11].

Second, we confirmed the association between the premature atherosclerosis and male gender also in younger persons. Such an association is well documented in previous studies, irrespective of age range and race-homogeneity [11, 12].

Third, we found that weights of association of various risk factors with a positive CAC scoring differed between males and females. We found that the extension of coronary atherosclerosis was not related to the presence of certain risk factor, despite it was suggested that premature atherosclerosis is associated with genetically-determined metabolic imprint [12, 13], however, detailed examination of the profile of the relatives could not actually be performed.

Our observation about more frequent CAC-positive results in obese persons, especially males, is in agreement with a previous report about association of increased BMI and CAC scoring in the Framigham population [4].

The mentioned results and observations were obtained despite a small number of females and subjects with diabetes mellitus. The gender-related bias in fact represents a real world, especially in a subset of young subjects [14]. Moreover, taking into account the differences in gender-associated risk, the results of our study indicate that population-based studies might not be appropriate if males and females are considered jointly. Therefore, separate studies in females are still necessary to be performed. Also, a relatively high proportion of subjects with a positive family history also introduced a bias, however, it indicated that in young symptomatic persons this factor had been considered especially important by supervising physicians.

Our study was undertaken in a homogeneous population of Caucasians. Therefore, comparisons with results of reports based on studies from racially-heterogeneous population do not seem to be justified. Also, reference values of CAC that may come from studies in asymptomatic subjects cannot be reliably ascertained in our population. As various geographical regions demonstrate different prevalence of atherosclerosis-related diseases, our data can be considered only in regions with a relatively high prevalence of CAD.

The results of our study indicate that in males, CAC scoring might be justified in certain subsets (like diabetics, smokers, obese with hypertension). Otherwise, evidence for a subclinical atherosclerosis might be sporadic [15]. Also, CAC scoring in young females seems to be unjustified, as only in a very small proportion a positive CAC score could be detected. However, as a relative risk might be substantially higher in smoking females, one should consider CAC scoring if symptoms and results of others measures for ischemia are impressive. One has to keep in mind that in some young symptomatic subjects a lack of evidence of coronary calcified lesions does not necessarily exclude the presence of atherosclerotic plaques [15] with a subset of smoking females have been identified as bearing a higher risk for non-calcified coronary lesions [16]. As the number of younger females with a positive CAC score was actually limited, the sex-related difference requires confirmation in a much larger population.

As we did not quantify the severity of a certain risk factor, we cannot exclude that in certain circumstances, an effect of a high level (concentration) of risk factor (i.e. malignant hypertension, familial hypercholesterolemia, a history of premature death in many keens etc.) would be grater than that accounted from simplified categorization. Also, other risk factors, like socio-economic status, or psychosocial factors, as well as newer measures of CAD risk (i.e. inflammation markers), have not been controlled in our study. Thus, CAC scoring might be considered justified even if only one, well documented risk factor is present, irrespective of age and gender. Also, as we relied on self-reporting data on risk factors, a re-evaluation on basis of measured factors might bring into a more accurate conclusion. However, such approach in not unusual in literature [17]. We are also aware that established risk factors' related formulae (like EuroSCORE) or CAD probability equations (like Diamond-Forrester) cannot be simply adopted in our study, since they had been drawn from much older populations.

Conclusions

We concluded that traditional risk factors, apart from gender and diabetes mellitus, do not seem to allow for distinguishing young persons with a premature coronary atherosclerosis. Therefore, CAC scoring might be considered justified in symptomatic young men with diabetes mellitus.

Conflict of interest: none declared

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