Age and gender are the strongest clinical correlates of prevalent coronary calcification (R1)

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Abstract

Objective: To determine which of the standard cardiovascular risk factors have the strongest associations with prevalent coronary artery calcification (CAC).

Study design and setting: A cross-sectional study of 6086 consecutive subjects who underwent electron beam computed tomography for CAC at a private, university-affiliated disease prevention center in San Diego, CA.

Results: The correlation between age and coronary calcium score in men (r = 0.463) was twice that of the next highest correlation (0.218) for percent body fat. A similar relationship was found for women (0.413 vs. 0.238). Calcium scores increased incrementally by age category in both men and women. This pattern of increase was not present for LDL cholesterol. Men and women over the age of 74 had highly elevated risks for the presence of any calcified coronary atherosclerosis compared to those under the age of 45 (OR [95% CI]: 11.08 [6.186–19.859] and 11.81 [6.718–20.746], respectively). Addition of the other traditional cardiovascular risk factors did not significantly increase the discriminatory power beyond that provided by age on ROC analysis.

Conclusion: Age and gender are significant independent clinical correlates of coronary calcium beyond that provided by the other risk factors. These results support the hypothesis that age is the predominant risk factor for coronary calcification.

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1. Introduction

Increasing age is a major, non-modifiable cardiovascular risk factor. Overall, the average age of first myocardial infarction (MI) is 65.8 in men and 70.4 in women. The incidence of coronary heart disease (CHD) increases from 7 per 1000 for individuals between the ages of 35 and 44–68 per 1000 for those above the age of 84. Eighty-four percent of people who die of coronary heart disease (CHD) are 65 or older [1]. The National Cholesterol Education Program (NCEP) states that men over the age of 45 and women over the age of 55 are at increased risk for coronary heart disease compared to their younger counterparts [2].

Calcification of atherosclerotic plaques begins as early as the second decade of life and continues to progress as the plaque matures [3]. This process occurs throughout all stages of atherosclerosis and is regulated in a fashion similar to bone formation [4]. That is, bone matrix proteins that activate and inhibit osteogenesis have been demonstrated in arterial walls containing atheromas. The inhibitors (matrix Gla protein, osteocalcin, and bone sialoprotein) seem to operate throughout the lifetime of the plaque whereas the activators (bone morphogenetic protein-2 and -4, osteopontin, and osteonectin) exert their effect preferentially during the more advanced stages of plaque development [5].

Histopathologic research has shown a high correlation between coronary calcification (CAC) and total atherosclerotic plaque burden [6]. These correlations (r = 0.90) have been shown to hold for all ages and for both sexes [7]. Although not considered the principle reason for plaque rupture, calcium has been detected histologically in 60–80% of coronary lesions that were determined to be the culprit lesion for sudden cardiac death [8]. Additionally, in some studies CAC has been associated with markers of inflammation linked to atherosclerosis [9].

Electron beam computed tomography (EBCT) is a reproducible [10], noninvasive screening procedure that can determine the extent of calcification in the coronary circulation. The degree of calcification is quantified by specialized computer software which calculates a coronary calcium score (CCS) [11]. The CCS is a measure of total coronary...
plaque burden [12] which has been found to be a powerful predictor of future coronary events in asymptomatic population-based studies with multivariable hazard ratios ranging from 4.5 to 10.5 [13–15]. In some studies EBCT has been shown to be superior to coronary angiographic measures in predicting subsequent cardiac endpoints such as cardiac death or nonfatal MI [16]. The sensitivity and specificity of the CCS for detecting greater than 50% stenosis have been estimated at 97% and 72%, [17] respectively, and CCS has a very high negative predictive value (99% in some studies) [18]. However, coronary calcium does suffer from a relatively low positive predictive value (5–14%) depending on the cutpoint used [19].

The purpose of this study was to determine the relative predictive ability of the traditional cardiovascular risk factors for the presence and extent of coronary calcium above that provided by age and gender. The relationship between risk factors and CCS has been conducted previously. However, these studies have either not conducted gender specific analyses [20] or have utilized restricted study populations [21–23] or age distributions [24] for analysis.

2. Methods

2.1. Subjects

From October 1999 to February 2002, 8101 consecutive patients who presented for preventive medicine services at a private, university affiliated disease prevention center in San Diego, CA, were eligible for inclusion in the study. Most patients were self referred or referred from their local doctors and were seeking preventive health information as a supplement to their routine medical care. Patients evaluated at the center more than once were included with their original study data only.

All patients completed a detailed health history questionnaire just prior to undergoing the scanning procedure. Patients who were taking lipid altering medications or had a history of coronary heart disease related surgery (i.e. stent placement, coronary artery bypass graft) were excluded from the study. Exclusionary medications included 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, niacin, cholesterol therapies, fibrates and hormonal therapies. Individuals with a triglyceride value greater than 400 mg/dl were unable to be included in the study due to the inability to calculate low-density lipoprotein values using the Friedewald formula.

2.2. Imaging

All patients underwent imaging with an Imatron C-150 scanner. Images were obtained with 100-ms scan time. Using 3 mm slices starting at the level of the carina and proceeding to the level of the diaphragm, approximately 40–45 slices of the each subject’s heart were obtained. Tomographic imaging was electrocardiographically triggered at 40% or 65% of the R–R interval, depending on the subject’s heart rate. Coronary calcification was defined as a plaque of ≥2 pixels (area=0.67 mm²) with a density of ≥130 Hounsfield unites (HU). Quantitative calcium scores were calculated according to the method described by Agatston et al. [11]. Coronary calcium scoring was performed by either a physician or computed tomography technician with specific training for the methodology described above.

2.3. Laboratory

All patients underwent random serum lipid analysis using the Cholestec LDX® system. This analyzer has met the criteria set forth by the lipid standardization panel (LPS) for accuracy and precision of cholesterol measurements [25]. Capillary whole blood specimens were obtained by finger stick with the subject in the seated position using a 35-μl lithium heparin-coated capillary tube. Body mass index was calculated with the patient clothed without shoes and expressed in kg/m². Body fat measurement was conducted using the Omron™ HBF-300 body fat analyzer.

2.4. Statistical analysis

The outcome variable for this study was coronary calcium score. The primary predictor variable was age with covariates of gender, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), total cholesterol (TC), body mass index (BMI), percent body fat, diagnosis of hypertension or diabetes mellitus, current and past tobacco use and a history of premature coronary heart disease in first degree relative (parent or sibling). LDL-C, HDL-C, TC, age, body mass index and percent body fat were analyzed as continuous variables. The remaining predictor variables were dichotomized.

Attempts to transform the coronary calcium score using log transformation and other techniques failed to normalize the distribution of this variable. This was due to the large proportion of the sample that had a calcium score of zero and caused a large spike in the distribution, which is extremely resistant to transformation. Coronary calcium scores were therefore dichotomized (i.e. presence or absence of calcified plaque) for use in logistic regression.

Due to the highly skewed distribution of coronary calcium scores, median values and nonparametric methods for analyses were employed. Univariate associations for the continuous variables were calculated using the Spearman rank correlation. Comparison of group medians for categorical variables was conducted using the Wilcoxon rank sum test. Univariable logistic regression was conducted for all predictor variables. Variables that were significantly associated with the outcome at a p-value of less than or equal to 0.10 were included for multivariable analysis. Multivariable logistic regression was performed retaining variables that were significantly associated with CCS at a
p-value of < 0.05. Regression models were assessed using the Hosmer-Lemeshow goodness-of-fit test. Receiver operator characteristic (ROC) analysis was performed to determine the increase in predictive ability that was afforded by the cardiovascular risk factors in addition to age.

Analyses were performed on the entire cohort and then stratified by gender. A significance level of 0.05 was used for all analyses. All statistical analyses were conducted using SAS version 8.0® statistical package. The study protocol complies with the Declaration of Helsinki and was approved by the committee for protection of human subjects (CPHS) at San Diego State University who granted a waiver for written consent from the participants.

3. Results

After excluding those individuals who were on lipid altering medications or had a history of a coronary procedure that would interfere with the determination of coronary calcium, a total of 6086 subjects were available for analysis. Table 1 provides the characteristics of this sample. Ages ranged from 22 to 94. Non-Hispanic Whites comprised 88.7% of the sample while Asians accounted for 10.1%, Hispanics 8.8%, African Americans 1.1 and ‘Other’ 2.1%. Women were 38% of the cohort and on average had a higher total percent body fat compared to men. Men were slightly younger, had a lower HDL-C, a higher LDL-C and a higher BMI. The proportion of individuals diagnosed with hypertension or diabetes was similar for men and women. The distributions for smoking status and history of CHD in a first degree relative for the two groups were also similar.

Thirty-six percent of men and 55% of women were found to be free of coronary calcium. These proportions are similar to other populations studied on this topic [15,26]. The relative proportion of subjects without CAC decreased in both groups by increasing age category. For instance, this proportion decreased from 60% for men less than 45 years to 28% between the ages of 55–64 and to 14% in those 75 and older. In women these proportions decreased from 78% to 57% to 20%, respectively.

In both men and women, age showed the largest correlation with CCS (Table 2). For both genders, the next largest correlations were found for percent body fat, HDL-C and then BMI. Adjustment for age did not change the order of these correlations in women (data not shown) but did cause a decrease in the correlation for percent body fat (r = 0.067). This adjustment in men resulted in the percent body fat correlation also decreasing significantly (r = 0.036) while the correlation for LDL-C increased to 0.048. The age-adjusted correlations for HDL-C and BMI in men were similar to their unadjusted values (r = 0.072 and 0.049, respectively).

The median calcium scores for men and women were 15.5 [IQR: 0–118.5] and 0.0 [0–51.8], respectively. Fig. 1 shows the median coronary calcium scores per age level. As can be seen, men show evidence of calcium at an earlier age

![Fig. 1. Distribution of coronary calcium by age.](image-url)
than women (45–54 vs. 65–74, respectively) and have larger amounts of calcified plaque at all ages except less than 45 where both groups do not exhibit any plaque. The median calcium score for women under the age of 55 has previously been found to be zero in a study of a large cohort with the next higher age group (55–59) having a median score of 1 [27]. For men, median calcium scores were not significantly different for the LDL-C or the total cholesterol levels while women displayed either minimal or no calcified plaque for these variables (Table 3). There were significant differences with respect to HDL-C levels in both men and women where individuals with an HDL-C less than 40 mg/dL had higher median calcium scores. For both genders, having a diagnosis of hypertension or diabetes was significantly associated with a larger amount of coronary calcium. This finding was especially pronounced in men. There were no significant differences by smoking category in both groups except for former male smokers (median CCS: 64.3 vs. 8.0, respectively). On subanalysis, former smokers were found to be significantly older but not otherwise significantly different with respect to percent with a diagnosis of hypertension or diabetes, LDL or HDL cholesterol levels, BMI or percent body fat.

### Table 4
Final multivariable logistic regression modelsa

<table>
<thead>
<tr>
<th>Variable</th>
<th>Women, odds ratio</th>
<th>95% CIb</th>
<th>Men, Odds ratio</th>
<th>95% CIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age category</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;45 years</td>
<td>1.00</td>
<td></td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>45–54 years</td>
<td>1.39, 0.91–1.91</td>
<td>1.74</td>
<td>1.37–2.21</td>
<td></td>
</tr>
<tr>
<td>55–64 years</td>
<td>2.30, 1.60–3.32</td>
<td>4.02</td>
<td>3.11–5.20</td>
<td></td>
</tr>
<tr>
<td>65–74 years</td>
<td>6.18, 4.10–9.32</td>
<td>7.57</td>
<td>5.39–10.63</td>
<td></td>
</tr>
<tr>
<td>≥75 years</td>
<td>11.81, 6.72–20.75</td>
<td>11.08</td>
<td>6.19–19.86</td>
<td></td>
</tr>
<tr>
<td>LDL-C (10 mg/dL)</td>
<td>1.05, 1.01–1.08</td>
<td>1.07</td>
<td>1.04–1.09</td>
<td></td>
</tr>
<tr>
<td>HDL-C (5 mg/dL)</td>
<td>0.92, 0.89–0.95</td>
<td>0.93</td>
<td>0.90–0.96</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>2.94, 1.22–7.10</td>
<td>2.65</td>
<td>1.34–5.22</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.56, 1.17–2.08</td>
<td>2.14</td>
<td>1.67–2.75</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>1.77, 1.18–2.64</td>
<td>1.57</td>
<td>1.13–2.18</td>
<td></td>
</tr>
<tr>
<td>Former smoking</td>
<td>1.72, 1.34–2.20</td>
<td>1.65</td>
<td>1.35–2.02</td>
<td></td>
</tr>
</tbody>
</table>

a Including only significant variables at p < 0.05.  

In the final multivariable logistic regression model for the entire sample, men had 2.52 higher odds for the presence of coronary calcification than women after adjustment for the other cardiovascular risk factors. In both men and women, a 5-year increase in age was associated with a 43% and 41% increase in risk, respectively, for the presence of coronary calcification. Results of the multivariable logistic regression analysis using age strata are provided in Table 4. There was nearly a doubling of risk of CAC for each decade in both genders. This risk was greater than 11-fold for both men and women in the age categories greater than 74 years compared to less than 45 (p < 0.001). Only the age group from 45 to 54 in women did not attain statistical significance for the presence of calcified plaque (p = 0.08). Notably, men had larger odds ratios for all age categories except for the over 74 group.

In a model including age only, the area under the curve (AUC) for the ROC analysis in men was 71.4%. Inclusion of the other NCEP risk factors (LDL-C, HDL-C, family history of premature CHD, smoking status, diagnoses of hypertension and diagnosis of diabetes) increased this area to only 74%. Likewise, in women the AUC for age only was 71.7% and increased to 73.8% with the inclusion of NCEP risk factors. For men and women respectively, the areas were 52.9% and 55.4% for LDL-C, 55.0% and 58.5% for HDL-C, 55.5% and 54.2% for hypertension and 51.5% and 51.3% for diabetes mellitus.

### 4. Discussion

Consistent with results previously published on this population [28], this study demonstrates that age and gender are significant independent clinical correlates of coronary calcification as measured by EBCT and that the contribution of these variables in the prediction of the presence and extent of CCS is substantially greater than the other cardiovascular risk factors. Specifically, the correlation between age and coronary calcium was twice that of the next largest
correlation while multivariable logistic regression analysis revealed an insignificant effect of the cardiovascular risk factors on the relationship between these two variables. Furthermore, there was a definite gradient for calcified atheromatous disease and increasing age categories. These results were further substantiated by the ROC analyses which revealed only minimal increases in discriminatory power when the “non-age” risk factors were included in the models.

The results of this study are similar to other CAC research focusing on the major cardiovascular risk factors. Feuerstein et al. [29] found that the magnitude of the CCS was strongly associated with age and male gender in 3263 active duty, dependent and retired military subjects. Raggi et al. [20] studied 245 subjects between the ages of 39 and 84 and found age, gender and lipoprotein (a) to be significant predictors of coronary artery calcification on multivariable analysis. Hoff et al. [24] conducted a cross-sectional study on over 30,000 asymptomatic subjects between the ages of 30 and 90. In this study, age greater than 55 years was the strongest predictor for the presence of any detectable CAC and was associated with an odds ratio of 3.6 in men and 2.8 in women using multivariable logistic regression which controlled for the NCEP risk factors. Our results indicate that the risk associated with increasing age can be further stratified. For example, in men the risk for CAC is 6.0 and 12.6 times higher for those between the ages of 65 and 74 and ≥ 75 respectively, compared to those under the age of 45. In women, the odds ratios for the same age comparisons were 7.44 and 10.26.

Despite the results of this and other studies on the subject, it is important interpret these findings within the context of study design. Since these studies have in large part been exclusively cross-sectional in nature, the longitudinal impact of changes in traditional risk factors over time may be diminished. For example, the aging process has been associated with increases total cholesterol until the 7th decade of life after which time it begins to decrease [30]. Similarly, women have on average higher HDL cholesterol levels than men until menopause. Subsequently, HDL decreases significantly with the distribution resembling but remaining higher than that seen in men [31]. These factors may contribute to the relatively small impact these risk factors have on predicting coronary calcium scores from a cross-sectional perspective. Age on the other hand is a reflection of the cumulative exposure to all atherogenic risk factors [32].

On average, subjects in this study who had either hypertension or diabetes mellitus had dramatically higher calcium scores. The odds for the presence of coronary calcium was over 2 1/2 times higher for diabetics while there was a 56–114% increase in this risk for subjects with hypertension. Wong et al. have previously shown a gradient for increasing risk in individuals with metabolic syndrome (40%) and then diabetes (67%) for the presence of coronary calcium [26]. Furthermore, ambulatory diastolic (but not systolic) BP during active and inactive periods has been shown to be a statistically significant additional predictor of the probability of having CAC (OR ~ 1.4) [33].

Novel risk factors are currently being studied that may help explain the relative lack of discriminatory power of the traditional cardiovascular risk factors for CAC. Atherosclerosis is now considered an inflammatory disease [34] with markers such as C-reactive protein (CRP) [35], fibrinogen [36] and homocysteine [37] being implicated in the process. The Framingham study has recently reported significant correlations between CRP and coronary calcification in 321 men and women where CRP levels were determined 4–7 years prior to EBCT imaging [9].

Potential limitations of this study include survivor bias where individuals with vulnerable plaques may have died prior to being enrolled in the study or having a scan for coronary calcium. This could overestimate the association of CAC to the atherosclerotic process. Additionally, the sample for this project was composed mostly of self-referred patients which may limit the generalizability of the results. These individuals tend to be from higher socioeconomic status and more concerned with health related issues and therefore are probably engaged in more preventive health strategies. These factors may have led to the underestimation of the influence of the traditional risk factors on coronary calcification since the prevalence of diseases such as diabetes [38] and hypertension [1] are lower in this population compared to community samples. The Multi-Ethnic Study on Atherosclerosis (MESA) is examining measures of subclinical atherosclerosis such as coronary calcium in a ethnically diverse multi-center community sample that should provided further insight into the relationship between NCEP risk factors and coronary calcification [39].

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