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Coronary artery calcium score in high-risk asymptomatic women in Saudi Arabia

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BACKGROUND AND OBJECTIVE: Coronary artery calcification (CAC) is indicated by calcium deposits in the coronary artery wall. Calcification is a component of atherosclerosis and coronary artery disease. Currently, there are no data on calcification in Saudi women at high risk of coronary artery disease. The aim of this study was to investigate the prevalence and percentiles of CAC score in high-risk asymptotic women in Saudi Arabia with comparison of age-specific CAC percentiles derived from la arge population-based published study in the United States.

DESIGN AND SETTING: Retrospective analysis of CAC scores (CACS) at a single tertiary care center.

METHODS. Between January 2011 and April 2015, women referred for CAC screening because of the presence of one or more CAD risk factors were enrolled in the study. CT scans were interpreted by an experienced radiographic technologist, and confirmed by a radiologist.

RESULTS: The study sample consisted of 918 women, mean (SD) age of 55 (11) years. All patients were asymptomatic and referred by their primary care physician or cardiologist for CAC screening because presence of one or more CAD risks factors. CAD risk factors included diabetes, hypertension, hypercholesterolemia, family history of CAD, and obesity. Baseline CAD risk factors were remarkably higher than in the US comparator group. CACS for 25th, 50th, 75th, and 90th percentiles were calculated. The 75th and 90th CACS percentiles in Saudi women were significantly higher than the US percentiles. Age and diabetes are the most independent predictor of severity of CAC.

LIMITATIONS: A potential bias due to sample collection because data was from a single tertiary care center, the study was retrospective and the sample size was small.

CONCLUSION: There are significantly higher CACS percentiles in Saudi women compared with international data. Application of available published percentiles to a local population is not applicable and underestimates the severity of subclinical atherosclerosis. A large local population-based study is warranted to establish local CACS percentiles for a better understanding CAD screening, diagnosis, and treatment.

Coronary artery calcification (CAC) is indicated by calcium deposits in the coronary artery wall. Calcification is a component of atherosclerosis and coronary artery disease (CAD).[1-5] CAC is quantified by either multidetector computed tomography (CT) or electron beam CT. Although there are several methods for calculating the CAC score, the Agatson method is most commonly used clinically.[6-9] There is a strong relationship between the amount of CAC and coronary plaques.[10,11] Moreover, it has been demonstrated that

CAC can be used to predict risk of coronary heart disease (CHD) in both symptomatic[12] and asymptomatic patients.[13,14] Data on racial differences in CAC are conflicting. Some studies have reported a lower prevalence of CAC in African Americans,[15] whereas others found no significant difference.[16] The current CAC data in people of Arabic descent is limited. A small study by Dakik et al[17] in a Lebanese population showed amounts of CAC equal to that in northern Americans despite a greater prevalence of CAD risk factors; however,

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these results have not been validated or reproduced by other studies in the region. Also, the sample size was small and was not compared with published data. Atherosclerotic disease, particularly CAD, is the leading cause of death worldwide and in Saudi Arabia in both men and women. The overall prevalence of CAD among women 45 years of age and older is 4.4%.[18] Therefore, the aim of this study was to investigate the prevalence and percentiles of CAC scores in high-risk asymptomatic women in Saudi Arabia by comparison of age specific CAC percentiles derived from a large population-based study in the US.[19]

PATIENTS AND METHODS

Study population

Between January 2011 and April 2015, women referred for CAC screening because of the presence of one or more CAD risk factors were enrolled in the study, which was conducted at King Faisal Specialist Hospital, a tertiary care center in Riyadh. CAD risk factors included a history of diabetes, hypercholesterolemia, hypertension, a history of smoking or a family history of CAD. A family history of CAD was defined as a history of myocardial infarction in a parent, grandparent, or sibling, angioplasty, stent placement, or coronary artery bypass grafting (CABG) at <65 years of age. A history of smoking was defined as a past or current use of cigarettes. Hypercholesterolemia was defined as a high cholesterol level of >200 mg/dL. Patients on current antihypertensive medication were considered hypertensive. A body mass index (BMI) was calculated as weight (kg) divided by height (m) squared, and obesity was defined according the WHO criteria,[20] as BMI >30 kg/m². The study was approved by an internal review board of the hospital.

CT scanning protocol

Patients were scanned during a single breath-hold using a 64-slice Discovery CT750 HD scanner (GE Healthcare, Milwaukee, Wisconsin) with a customized protocol designed to minimize the administered radiation dose. All patients were scanned using a tube energy of 120 kVp in gated axial mode. The tube current was adjusted on the basis of the BMI to give adequate signal-to-noise ratio while minimizing the net current, using the empirically determined formula: tube current (mA)=11×BMI. The time of imaging during the cardiac cycle was adjusted on the basis of heart rate, imaging at 75% of the R-R interval for heart rate <75 beats/min, and at 50% of the R-R interval for heart rate >75 beats/min. The slice thickness was 2.5 mm, the gantry rotational period was 0.35 s, and the scan length was

adjusted from the scout images to encompass the entire heart. The median radiation dose–length product was 42 mGy·cm, which, using a conversion factor of 0.014 mSv/mGy·cm, corresponds to a median effective radiation dose of 0.59 mSv.[21]

Calcium scan interpretation

Foci of CAC were identified by both an experienced radiographic technologist, confirmed by a radiologist and scored using semiautomatic commercial software on an Advantage Workstation (GE Medical System, Waukesha, Wisconsin). The software calculated lesion-specific scores as the product of the area of each calcified focus and peak CT number (scored as 1 if 131 to 199 HU; 2 if 200 to 299 HU; 3 if 300 to 399 HU; and 4 if 400 HU or greater) according to the Agatson method6. These were summed across all lesions identified within left main, left anterior descending, left circumflex, and right coronary arteries to provide arterial-specific calcium scores, and across arteries to provide the total CAC score.

Table 1. Baseline demographic characteristics of study population (n=918).

Mean age (SD), years	55 (11)
Diabetes mellitus (%)	42
Hypertension%	62
Smoking %	2
Family history of CAD (%)	5
Hypercholesterolemia (%)	54
BMI>30/m² (%)	60

Table 2. Mean and SD of coronary artery calcium score per age group.

	Women		
		CAC score	
Age (years)	n	Mean	SD
<40	71	4	21
40-44	65	14	64
45-49	138	24	65
50-54	167	27	200
55-59	169	64	237
60-64	129	97	240
65-69	87	171	308
70-74	50	283	450
>74	42	342	648

Table 3. Coronary artery calcium score percentiles by age.

Age/years	P 25 US	P25 SA	P50 US	P50 SA	P75 US	P75 SA	P90 US	P90 SA
<40	0	0	0	0	1	0	3	0
40-44	0	0	0	0	1	0	4	2
45-49	0	0	0	0	2	0	22	13
50-54	0	0	0	0	5	0	55	124
55-59	0	0	0	0	23	35	121	165
60-64	0	0	0	2	57	93	193	317
65-69	1	0	1	15	145	209	410	653
70-74	3	6	3	85	210	314	631	1035
>74	9	10	9	99	241	355	709	1046

SA: Saudi Arabia
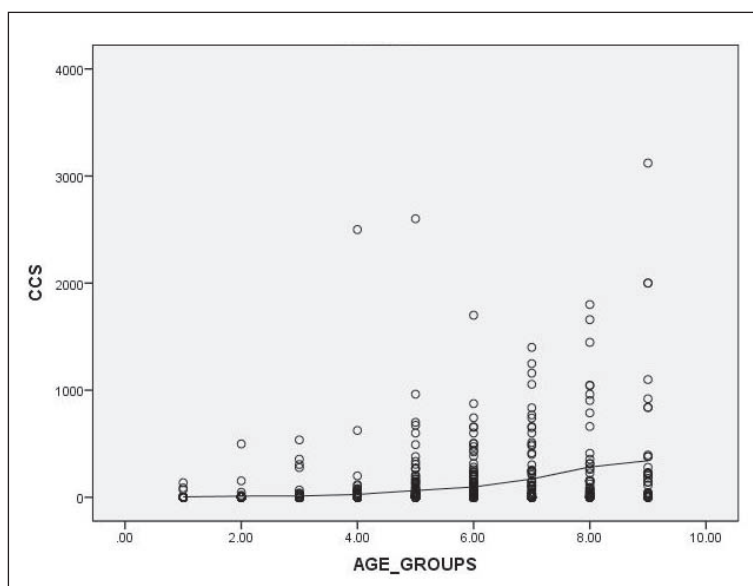
Figure 1. Coronary artery calcium score (CACS) by age group categories in years (1=<40; 2=40-44; 3=45-49, 4=50-54, 5=55-59, 6=60-64, 7=65-69, 8= 70-74, 9=>74).

Statistical analysis

Frequencies, means and standard deviation (SD) were used to describe the baseline characteristics of the study sample. For comparison with published literature, subjects were divided according to age categories (<40, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74 and >74 years old). Descriptive statistics were calculated for CACS and results were expressed as mean (SD) and percentiles (25th, 50th, 75th and 90th). Multiple linear regression was carried out with CACS as the dependent variable and baseline CAD risk factors as independent variables. The Statistical Package for the Social Sciences (SPSS 20.0) was used for all computations (SPSS, Inc.). A P value <.05 was considered significant.

RESULTS

The study sample consisted of 918 women, mean age 55 (11) years. All patients were asymptomatic and referred by their primary care physician or cardiologist for CAC screening because of the presence of one or more CAD risks factors. CAD risk factors included diabetes, hypertension, hypercholesterolemia, a family history of CAD, and obesity. Baseline CAD risk factors are listed in **Table 1**. **Table 2** provides the size of the study population, mean and standard deviation and CACS for 25th, 50th, 75th, and 90th percentiles. **Table 3** compares CACS percentiles between the US and Saudi Arabia. CACS percentiles for all Saudi women were significantly higher than US percentiles. **Table 4** shows that age and diabetes were significantly associated with CACS by multivariate analysis. The CACS distribution based on age showed a strong relationship between age and severity of CACS (**Figure 1**). **Figures 2 and 3** show CACS 50th and 90th percentiles in the US and Saudi Arabia.

DISCUSSION

The main finding of our study is the presence of strong association between conventional risk factors of CAD with CACS. The 75th and 90th percentiles were statistically higher for Saudi Arabia compared with the US. The greatest potential for CAC detection is as a marker for CAD prognosis in asymptomatic women, which goes beyond the prognostic information supplied by conventional CAD risk factors. A number of studies primarily composed of men reported that the presence of severity of CAC has independent and in-
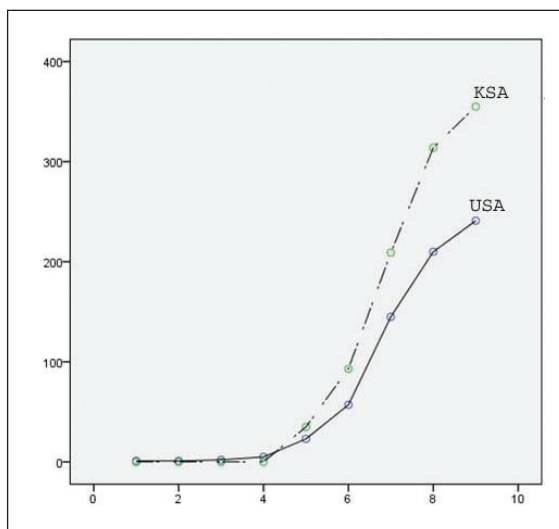
Figure 2. CACS 50th and 90th percentiles in the United States.
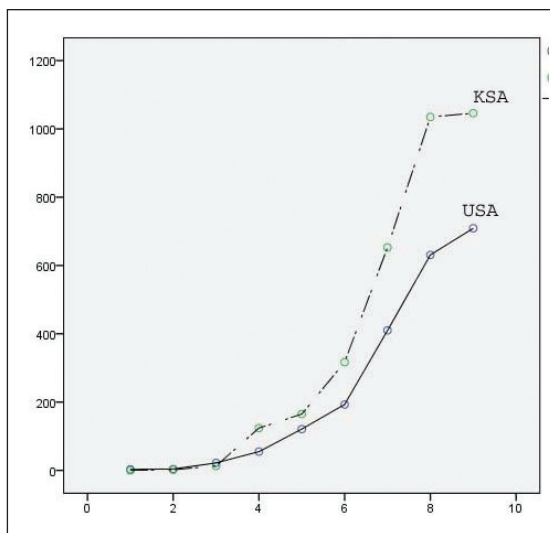
Figure 3. CACS 50th and 90th percentiles in Saudi Arabia.

cremental value added to clinical and historical data in the estimation of death and non-fatal myocardial infarction.[22] To our knowledge, our study is the first study investigating CAC in women in Saudi Arabia. In general, the role of CAC in CAD is not yet investigated in the region. A previous study in Saudi Arabia conducted by Fathala et al,[23] indicated a strong association between severity of CAC and ischemic myocardial perfusion in women. Asymptomatic women with one or more CAD risk factors and moderate to severe CAC had more than 50% of ischemic myocardial perfusion.

Comparing our results to a large population based study in the US,[19] the CACS reported in our study were significantly higher compared with those in the US. There are several explanations for these findings, most importantly that our patients are considered at higher risk compared to published data. In our subjects, the prevalence of diabetes, hypertension, hypercholesterolemia, and obesity is 42%, 62%, 54%, and 60%, respectively. Obviously, the prevalence of CAD risk factors in our patients is remarkably higher compared with North Americans. The prevalence of hypertension (26%)[24] and diabetes (22%) are higher in Saudi Arabia.[25] Generally, CAD is multifactorial and other etiologies could explain this major difference in CACS among the two groups. In addition to higher CAD risk factors, genetic factors have not been yet well characterized, and there are other environmental factors, life style factors, dietary habits, and lack of physical exercise.

Using multivariate analysis, the age and presence of diabetes were the only predictors of severity

of CAC. It is well known that conventional risk factors do correlate with CACS,[26] even though CACS is superior to conventional risk factors in predicting outcome. Postmenopausal women (majority of our study population) are a striking example of the inability of conventional risk factors analysis to predict the presence or absence of atherosclerosis. A prior study showed no difference in any lipid parameters or in the Framingham risk score between post-menopausal women with and without calcified plaques.[27] Most recently, a multicenter and multicountry registry showed that CT angiography provides incremental prognostic utility for prediction of mortality and nonfatal myocardial infarction for asymptomatic individuals with moderately high CACS, but not for lower or higher CACS.[28]

Study limitations
Several factors may affect interpretation of the results of this study. First, the data was obtained from a single tertiary care center with a high prevalence of CAD risk factors; therefore, a potential bias due to sample collection might have had an adverse effect on the validity of the result. Secondly, questionnaire-based demographics was not obtained from the patients as the study was retrospective. Third, the study sample was relatively small compared with published data; a large sample study in the future is warranted to overcome this limitation.

CONCLUSION
This was the first population-based study of CACS in women in Saudi Arabia. CACS percentiles were

significantly higher when compared with international data. The application of available published percentiles to a local population was not applicable and underestimates the severity of subclinical atherosclerosis. Convectional risk-factor analysis is not an optimum strategy to identify women at risk for CAD. CACS may have a major impact on CAD risk stratification, prevention, and treatment of CAD, a leading cause of death in females. A large local population-based study is warranted to establish local CACS percentiles for a better understanding CAD diagnosis, prevention and treatment.

REFERENCES

1. Blankenhorn DH, Stern D. Calcification of the coronary arteries. Am J Roentgenol Radium Ther Nucl Med.1959;81:772-7.
2. Beadenkopf WG, Daoud AS, Love BM. Calcification in the coronary arteries and its relationshio to arteriosclerosis and myocardial infarction. Am J Roentgenol Radium Ther Nucl Med. 1964;92:865-71
3. Warburton RK, Tampas JP, Soule AB, Taylor HC 3rd. Coronary artery calcification: Its relationship to coronary artery stenosis and myocardial infarction. Radiology. 1968;91:109-15
4. Frink RJ, Achor RW, Brown AL Jr, Kincaid OW, Brandenburg RO. Significance of calcification of the coronary arteries. Am J Cardiol. 1970;26:241-7.
5. Rifkin RD, Parisi AF, Folland E. Coronary calcification in the diagnosis of coronary artery disease. Am J Cardiol. 1979;44:141-7.
6. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15:827-32.
7. Becker CR, Kleffel T, Crispin A, Knez A, Young J, Schoepf UJ, et al. Coronary artery calcium measurement: agreement of multirow detector and electron beam CT. AJR Am J Roentgenol. 2001;176:1295-8.
8. Hoffmann U, Brady TJ, Muller J. Cardiology patient page. Use of new imaging techniques to screen for coronary artery disease. Circulation. 2003;108:e50-3
9. Qian Z, Anderson H, Marvasty I, Akram K, Vazquez G, Rinehart S, Voros S. Lesion- and vessel-specific coronary artery calcium scores are superior to whole-heart Agatston and volume scores in the diagnosis of obstructive coronary artery disease. J Cardiovasc Comput Tomogr. 2010;4:391-9
10. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation. 1995;92:2157-62.

11. Virmani R, Kolodgie FD, Burke AP, Finn AV, Gold HK, Tulenko TN, et al. Atherosclerotic plaque progression and vulnerability to rupture: angiogenesis as a source of intraplaque hemorrhage. Arterioscler Thromb Vasc Biol. 2005;25:2054-61
12. Detrano R, Hsiai T, Wang S, Puentes G, Fallavollita J, Shields P, et al. Prognostic value of coronary calcification and angiographic stenoses in patients undergoing coronary angiography. J Am Coll Cardiol. 1996;27:285-90.
13. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. J Am Coll Cardiol. 2000;36:1253-60.
14. Raggi P, Callister TQ, Cooil B, He ZX, Lippolis NJ, Russo DJ, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron-beam computed tomography. Circulation. 2000;101:850-5.
15. Newman AB, Naydeck BL, Whittle J, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Racial differences in coronary artery calcification in older adults. Arterioscler Thromb Vasc Biol. 2002;22:424-30.
16. Khurana C, Rosenbaum CG, Howard BV, Adams-Campbell LL, Detrano RC, Klouj A, Hsia J. Coronary artery calcification in black women and white women. Am Heart J. 2003;145:724-9.
17. Dakik HA, Skouri HN, Mehio-Sibai A, Sibai T, Alam S, Sawaya J, et al. Prevalence of coronary artery calcium among asymptomatic men and women in a developing country: comparison with the USA data. Atherosclerosis. 2005;183:141-5.
18. Al-Nozha MM, Arafah MR, Al-Mazrou YY, Al-Maatouq MA, Khan NB, Khalil MZ, et al. Coronary artery disease in Saudi Arabia. Saudi Med J. 2004;25:1165-71.
19. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol. 2001;87:1335-9.
20. WHO. Obesity: preventing and managing the

global epidemic. Report of a WHO consultation on obesity, June 1997.
21. Halliburton SS, Abbara S, Chen MY, Gentry R, Mahesh M, Raff GL, et al. SCCT guidelines on radiation dose and dose-optimization strategies in cardiovascular CT. J Cardiovasc Comput Tomogr. 2011;5:198-224.
22. Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. Radiology. 2003;228:826-33.
23. Fathala A, Al Amer A, Shukri M, Abouzied MM, Alsugair A. The relationship between coronary artery calcification and myocardial perfusion in asymptomatic women. Ann Saudi Med. 2012;32:378-83.
24. Al-Nozha MM, Abdullah M, Arafah MR, Khalil MZ, Khan NB, Al-Mazrou YY, et al. Hypertension in Saudi Arabia. Saudi Med J. 2007;28:77-84.
25. Al-Nozha MM, Al-Maatouq MA, Al-Mazrou YY, Al-Harthi SS, Arafah MR, Khalil MZ, et al. Diabetes mellitus in Saudi Arabia. Saudi Med J. 2004;11:1603-10.
26. Kuller LH, Matthews KA, Sutton-Tyrrell K, Edmundowicz D, Bunker CH. Coronary and aortic calcification among women 8 years after menopause and their premenopausal risk factors : the healthy women study. Arterioscler Thromb Vasc Biol. 1999;19:2189-98.
27. Hecht HS, Superko HR, Smith LK, mccolgan BP. Relation of coronary artery calcium identified by electron beam tomography to serum lipoprotein levels and implications for treatment. Am J Cardiol. 2001;87:406-12
28. Cho I, Chang HJ, Ó Hartaigh B, Shin S, Sung JM, Lin FY, et al. Incremental prognostic utility of coronary CT angiography for asymptomatic patients based upon extent and severity of coronary artery calcium: results from the coronary CT Angiography evaluation For Clinical Outcomes international Multicenter (CONFIRM) study. Eur Heart J. 2015;36:501-8.