

Coronary artery calcium—a review article

Abstract

Coronary artery calcium represents a subclinical marker of atherosclerotic plaque burden in coronary artery disease. Coronary artery calcium detection has been in use for a long time to stratify the risk of coronary artery disease. This review talks about the pathogenesis, Chest X ray as a detection modalities of coronary artery calcium, and describe factors affecting coronary artery calcium. The purpose of this review is to provide a compiled knowledge of coronary artery calcium and provide directions for more research.

Keywords: coronary artery calcium, chest X rays, pathogenesis, factors, coronary artery disease

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Abbreviations: CAC, coronary artery calcium; CAD, coronary artery disease; AAC, abdominal aortic calcification; CT, computed tomography; CKD, chronic kidney disease; NE, norepinephrine; HAART, highly active antiretroviral therapy; ASCVD, atherosclerosis cardiovascular disease; NAFLD, non-alcoholic fatty liver disease; MESA, multiethnic study of atherosclerosis; LDL, low density lipoproteins; HRT, hormonal replacement therapy; ROS, reactive oxygen species; PPAR- γ , peroxisome proliferator activated receptor- γ ; ALP, alkaline phosphatase; SMC, smooth muscle cells; SHTC, second hand tobacco smoke; TNF, tumor necrosis factor; IL, interleukin; HDL, high density lipoproteins; VCAM, vascular cell adhesion molecule-1; ICAM, intracellular cell adhesion molecule-1; DECC, dual energy coronary calcium

Introduction

Coronary artery disease is the most common cardiovascular disease and is the leading cause of mortality worldwide. Early identification and intervention of coronary artery disease (CAD) and its risk factor decrease CAD related mortality by half.¹ Coronary artery calcium (CAC) deposits are a frequent component of atherosclerotic plaque² and are a subclinical marker of plaque burden in coronary artery diseases. CAC measurement by CT is a non-invasive method of quantifying the burden of coronary atherosclerosis, and it adds to the traditional method for risk stratification. CAC represents only one-fifth of total plaque content with the remaining four-fifth are the non-calcified plaque. However, the amount of coronary artery calcification and CAC score is strongly correlated to cardiovascular risk.³

Patients with a CAC score of 1-10 show a three-fold increased risk for coronary artery disease.⁴ Risk of mortality from cardiovascular disease increases with each fold increase in the risk of coronary artery calcium. Calcium score above 100 infers five folds' increase risk of mortality from cardiovascular diseases. Sizes and numbers of CAC deposits determine the type and prognosis of coronary artery disease. Plaques with many small calcium deposition foci are present in a patient with unstable coronary artery disease, and myocardial infarction. Whereas, plaques with few large calcium deposits are present in patients with the stable coronary artery disease.^{5,6} Small deposition of calcium increases the risk of plaque rupture especially at the edges whereas the risk of fracture decreases with extensive calcification.^{7,8}

CAC is often present in a low-risk patient of cardiovascular disease and absent in high-risk patients for cardiovascular disease.⁹ Early detection of CAC could improve the risk of cardiac diseases because CAC scanning leads to a healthy lifestyle, increase use of statins and aspirin based on elevated risk on CAC findings, and increase patient compliance to medication.^{10,11} This review summarizes the pathogenesis, factor affecting coronary artery calcium and the use of chest X rays as a new way of detecting coronary artery calcium. The purpose of this review is to provide a compiled knowledge of coronary artery calcium and provide directions for more research.

CAC and chest X rays

CT scan is the current modality of measuring CAC. CT scans have limitations of high cost and radiation dose. Recently, Di Wen et al developed and studied the use of dual-energy coronary calcium (DECC) processing method for CAC detection through dual energy chest radiograph, which provides low cost and radiation solution to CAC screening.¹² Before this study, Neves et al.¹³ reported a case of CAC detection in routine chest radiograph in a patient with the end-stage renal disease. These studies divert our attention towards the use of Chest X rays – dual energy or routine Chest X rays– for coronary artery calcium detection and demand more research in this regard.¹³ Correlation between CAC in Chest X-ray and CT scan should be studied so that X rays can be used to determine CAC score which would make a detection of CAC and cardiovascular risk cheaper.

Pathogenesis of CAC

Coronary artery calcium formation is an organized metabolic process which is similar to bone formation. Calcification occurs in both intima (atherosclerotic) as well as in media of coronary arteries. Inflammatory mediators and elevated lipid content within atherosclerosis are associated with intimal calcification whereas diabetes, advanced age and chronic kidney diseases (CKD) are associated with medial calcification.^{14,15}

Three common steps of coronary artery calcification are:

- Osteoblastic differentiation
- Bone-associated proteins formation
- Mineralization

Osteoblastic differentiation is the phenotypic transformation of smooth muscles of coronary arteries to osteoblast-like cells. Osteoblastic transformation occurs with the production of proinflammatory cytokines and high levels of calcium and phosphates.¹⁶ Pro-inflammatory cytokines and calcium and phosphates activate homeobox genes and Wnt signaling pathways which in turn activate runt related-transcription factors (Runx-2) and its downstream protein osterix. Both Runx-2 and osterix are critical transcription factors for osteoblastic differentiation and stimulate the production of bone associated protein formation. Runx-2 regulates the expression of osteocalcin, osteopontin, receptor activator of nuclear factor kappa b ligand (RANKL) and alkaline phosphatase (ALP). Whereas, osterix stimulates the production of osteopontin and alkaline phosphatase (ALP).^{17,18} Vascular smooth muscles also release matrix vesicles and apoptotic bodies which contain ALP and calcium and phosphorous. Alkaline phosphatase creates an environment for mineralization by hydrolyzing phosphate bonds. Osteocalcin is a marker of late differentiation of osteoblasts. Osteocalcin binds with hydroxyapatite with high affinity and causes hydroxyapatite calcification. As a result of all these vascular smooth muscles lose their contractile properties (smooth muscles 22 and α -SMA) and contribute in the mineralization of extracellular matrix environment and consequently calcification.^{19,20}

Calcification can also result from apoptotic bodies of smooth muscle cells (SMC) and macrophages. Calcification from SMC apoptosis appears microcalcification and calcifications from macrophages apoptosis appear as punctate calcifications. Microcalcification consists of necrotic core and surrounding collagenous matrix. Calcification starts from the outer rim which progressively involves collagenous matrix and necrotic core.²¹

Factors affecting coronary artery calcium

Factors that affect coronary artery calcification are

- a) Age
 - b) Gender
 - c) Race
 - d) Hyperlipidemia
 - e) Hypertension
 - f) Diabetes Mellitus
 - g) Tobacco Use/Cigarette smoking
 - h) Non -Alcoholic Fatty Liver Disease (NAFLD)
 - i) Drugs (Statins, HAART, Thiazolidinediones)
 - j) Abdominal Aortic Calcification (AAC)
 - k) Aortic unfolding
 - l) Hormones (catecholamine, cortisol, and dopamine)
 - m) Vitamin D Deficiency
- a) Age

Aging is a significant non-modifiable risk component for cardiovascular diseases, and it is associated with substantial functional and structural changes in the vascular system. Human age is related to an increase in incidence and magnitude of coronary artery calcium. Aging leads to the thickening of the intima of vessels, dilation of lumen and stiffening of the vessels.

The prevalence of CAC increases with age, and the highest prevalence is seen in men and women older than 70 years of age.²² For men and women, higher average and median total CAC scores were associated with increasing age even in asymptomatic individuals.²³

L.J. Shaw et al.,²⁴ showed in his study that there is a direct linear relationship between coronary artery calcium score and observed age. Score less than 10 resulted in the reduction in the observed age by ten years in adults who were above 70 years of age. Similarly, in younger patients, a calcium score of above 400 added as much as thirty years to their observed age.²⁴

Increasing coronary artery calcium was strongly associated with increased long-term mortality risk in both young and older age groups. Even older patients who have no or low coronary artery calcium scores had a significantly low risk of mortality compared to the general population.²⁵ Another study demonstrated that in determining the therapies for coronary artery disease (CAD) age and sex-based scores are clinically more useful than using the coronary artery score alone.²⁶

b) Gender

CAC is a strong independent predictor of CAD for both female and male patients. It is more common in men than women. CAC affects 90% of men and 67% of women older than 70 years of age. In a study done by Hoff et al.,²³ total CAC scores in men were higher than women with men demonstrating score equivalent to women who were 15 years older.²³ In the Multiethnic Study of Atherosclerosis (MESA) men had greater coronary calcium levels than women and the prevalence of CAC rose with age. A critical observation from this study is, Gender-specific arterial age would be higher in the women than men, which means that for a given CAC score, it has the worse prognosis for women than in men.²⁷

In one study the mean age of males with CAC was 62 years, as compared to the mean age of 51 years for men with a CAC score of zero. But comparatively females with zero CAC scores, the mean age was 56, and those who have CAC had a mean age of 66 years.²⁸ In many other studies, it is also noted that females with coronary artery calcium usually had a history of hypertension and a family history of heart diseases. Moreover, females who used hormone replacement therapy (HRT) after menopause, there was a strong association with long-term Hormonal replacement therapy and lower CAC scores as compared to the females who had never used HRT. This negative association between HRT and CAC was linear with the duration of HRT and evident in all age groups of women.²⁹

c) Race

CAC is also related with race. The prevalence of CAC is the lowest in African American.³⁰ The Multiethnic Study of Atherosclerosis (MESA) by McClelland et al. demonstrated that white females had the highest percentiles of the CAC distribution as compared to Hispanic women who had the lowest but in the oldest age group, Chinese women had the lowest percentile values.

In case of males, white males had the highest CAC values as compared to Hispanics who although had lower values than the white males but had high CAC values than black males in younger age group. Chinese man showed the lowest percentiles in the older age group.²⁷ Overall, White had the highest values of CAC as compared to other ethnicities.

d) Hyperlipidemia

Atherosclerosis is an inflammatory lesion which starts in early life as a fatty streak and is followed by deposition of fats and other inflammatory cells resulting in a plaque formation. Coronary artery calcification occurs when atherosclerosis is already present resulting in further narrowing of the vessels. This whole process is accelerated in the presence of dyslipidemia or hyperlipidemia.

In asymptomatic patients, hypercholesterolemia, total and low-density lipoprotein cholesterol, is independently associated with CAC.^{2,31} Many studies revealed a strong positive association of hyperlipidemia, particularly low-density lipoprotein (LDL) cholesterol, with coronary artery calcification. O' Brien et al.,³² observed that the presence of lipoprotein in aortic valves leads to microscopic calcium deposition.³² Presence of isolated vascular smooth muscle cells (VSMCs) in the lipid core during the formation of atherogenic plaque results in calcium deposition.³³ LDL cholesterol also promotes calcification of VSMCs due to lipid peroxidation.³⁴ There is a direct relation of LDL cholesterol and prevalence of CAC while HDL is inversely related.^{35,36}

Other studies have also demonstrated a close association between lipids and calcification in atherosclerotic lesion.^{37,38} The composition of coronary artery plaque is 20% calcium and 80% atherosclerosis, that is why CAC is also considered as a marker of coronary atherosclerosis.^{39,40}

CAC can be affected by the duration as well as the severity of cholesterol exposure as seen in the study by Hoeg et al.⁴¹ They observed that LDL levels greater than 130mg/dl lead to rapid progression of coronary artery calcification. Bild et al.,⁴² found that LDL cholesterol more strongly correlated with coronary artery calcium levels as compared to age, smoking, blood pressure and fasting insulin levels. Lipid lowering medications which leads to the low levels of LDL and other cholesterol lipids can halt the progression of calcification in coronary arteries as discussed below.

e) Hypertension

The probability of calcium detection increases in patients with the history of hypertension.² Presence of CAC also predict the risk of hypertension and intense preventive efforts should be made in-patient with CAC. Shared cardiovascular risk factors (e.g., Diabetes, hyperlipidemia, and obesity) explain the relationship between CAC and hypertension.⁴³ CAC can also guide the initiation and intensification of anti-hypertensive therapy especially in a person with systolic blood pressure between 120-159mmHg and atherosclerosis cardiovascular disease risk (ASCVD) in between 5-15%. People with CAC=0 would be likely to benefit from traditional SBP treatment goal of 140 mmHg whereas people with CAC score >100 would probably be helped most from intensive SBP goal of 120 mmHg. [43] Hypertension aggravates the atherosclerotic process through arterial wall trauma and contributes to the development of coronary artery calcification.²

f) Diabetes mellitus

Studies have shown link between CAC and diabetes mellitus. Wong et al. found a relationship between impaired fasting glucose, untreated and treated diabetes mellitus (type 2) and coronary artery calcification.² The mechanism of CAC development due to high blood glucose include the production of advanced glycation end products

due to elevated blood glucose levels. These advanced glycation end products may cause deposition of calcium in pericytes in coronary vessels which cause coronary artery calcification.⁴⁴ Coronary artery calcium score can also be used to detect atherosclerosis in type 1 diabetic, and it can guide anti-atherosclerotic therapy in type 1 diabetics as well.⁴⁵ Intensive glycemic control in people with type 1 diabetes slows coronary artery calcium progression.⁴⁶

g) Tobacco use/cigarette smoking

Tobacco use doubles the deposition of calcium in coronary arteries in both men and women.⁴⁷ Smoking causes coronary artery atherosclerosis, and it exerts multiplicative effects on coronary artery atherosclerosis along with other risk factors such as hyperlipidemia, hypertension, and diabetes. The number of cigarettes smoked per day and duration of smoking correlates with coronary artery disease development. Smoking modifies the mechanism of vascular calcification by increasing LDL cholesterol and decreasing HDL cholesterol.⁴⁸ Smoking also causes endothelial dysfunction and activates the sympathetic nervous system. Endothelial dysfunction leads to vascular inflammation, cell proliferation, and thrombosis. The levels of adhesion molecules (both sVCAM or an ICAM) rises in plasma, and smoking can also decrease the production of nitric oxide which is a notorious antithrombotic molecule.^{49,50}

Besides direct smoking, second-hand smoking is positively correlated with coronary artery calcium regardless of the other risk factor. The significant dose-response relationship exists between second-hand tobacco smoking and CAC. Increasing SHTS associated with an increase in the extent of CAC. Second smoke cause platelet activation, endothelial dysfunction, and arterial stiffness. All these things can contribute to the development of coronary artery calcification.⁵¹⁻⁵³

h) Non-alcoholic fatty liver disease (NAFLD)

Nonalcoholic fatty liver disease (NAFLD) - one of the disorders of metabolic syndrome – is studied to be associated with subclinical atherosclerosis.⁵⁴ NAFLD is an independent risk factor for coronary artery atherosclerosis and hence coronary artery calcification.⁵⁵

There are several mechanisms through which NAFLD cause subclinical atherosclerosis and coronary artery calcification. NAFLD can create pro-inflammatory conditions in the body which increase the production of reactive oxygen species. Inflammation and reactive oxygen species are atherogenic. ROS induce the production of TNF- α and IL-6 which augment atherosclerosis.⁵⁶ Moreover, serum adiponectin levels decrease in the NAFLD which possess antiatherogenic and anti-inflammatory properties. Adiponectin has been studied to be inversely associated with coronary artery calcification.^{55,57}

i) Drugs

Statins: Statins use and healthy lifestyle changes are linked to the presence and extent of coronary artery calcium. Statin may induce, promote the progression of coronary artery calcification.⁴⁷ but prevent new coronary artery calcium deposition. It increases the density of calcification by removing lipids from calcified plaques and stabilizes them. Statins improve clinical outcome of atherosclerotic disease by eliminating noncalcified plaques and maintaining calcified plaques. Due to the variable relation of CAC with statins, CAC cannot be used to follow up on lipid-lowering drug intervention.⁵⁴

HAART: Mortality due to HIV has been significantly declined since the advent of Highly active antiretroviral therapy (HAART).⁵⁸ HAART especially protease inhibitors have been studied to increase subclinical atherosclerosis and coronary artery calcification. Studies have shown higher rates of coronary artery calcification in HIV patients on HAART therapy as compared to HIV not taking HAART.⁵⁹ The possible explanation is that HAART therapy cause hyperlipidemia, insulin resistance, and lipodystrophy which can contribute to coronary artery calcification.⁶⁰

Thiazolidinediones: Thiazolidinediones are one of the oral hypoglycemic drugs which are prescribed for the management of type II diabetes. Thiazolidinediones are agonists of peroxisome proliferator receptor activator- γ (PPAR- γ).⁶¹ Evidence shows the protective effect of PPAR- γ in vascular calcification. Woldt et al.,⁶² observed increased vascular calcification in nuclear receptor PPAR γ deleted mice.⁶² More research is needed to study the effect of thiazolidinediones on CAC.

j) Abdominal aortic calcification (AAC)

Abdominal aortic calcification (AAC) can predict the initiation and progression of CAC. Many studies have shown the association between AAC and CAC. Onuma et al.,⁴⁷ found AAC as an independent predictor of CAC development and progression.⁴⁷ Wilson et al.,⁶³ demonstrated AAC as a marker of subclinical atherosclerosis. Patient with incidental detection of AAC should be considered high risk for coronary artery disease and should be evaluated for cardiovascular risk factors.⁶³

k) Aortic unfolding

Aortic unfolding is a radiologic finding which is usually seen on chest radiograph. It reflects dilatation, widening, and shortened curvature of the aortic arch. Aortic unfolding - independent of traditional risk factors—is studied to be positively associated with CAC.⁶⁴ Aortic unfolding finding on chest radiograph should be used as an indication for detection of subclinical atherosclerosis and measurement of coronary artery calcium. More research should be done on the relationship of CAC with aortic unfolding to use aortic unfolding as an indication of CAC detection and predictor of cardiovascular risks.

l) Hormones (norepinephrine, cortisol, and dopamine)

Studies have shown the relationship of CAC with hormones and vasoactive substances. Cortisol and norepinephrine showed the positive correlation with CAC. Zipursky et al.,³⁰ observed the higher blood levels of cortisol and Nor-epinephrine were associated with a higher prevalence of coronary artery calcium.³⁰

Psychological stress, low-income status, depression, and anxiety increase catecholamine's levels in the blood. Norepinephrine contributes to atherosclerosis by causing vasoconstriction, hypertension, insulin resistance, inflammation, and thrombosis.³⁰

The Varied relationship exists between dopamine blood levels and CAC. Some studies have shown a positive correlation of dopamine levels with CAC, and some have demonstrated negative correlation of CAC with dopamine levels.^{30,65} Studies have also shown a positive and a negative association of dopamine blood levels with hypertension which is another risk factor for CAC.^{66,67} Dopamine exerts its cardioprotective effect and prevent coronary artery calcium formation

by inhibiting the norepinephrine release, reducing pancreatic insulin production and by decreasing the activity of lymphocytes.³⁰

m) Vitamin D deficiency

Vitamin D is an essential micronutrient,⁶⁸ which besides its action on mineral metabolism also exert pleiotropic effects on the cardiovascular system.⁶⁹ Vitamin D deficiency is found in 1 billion people, worldwide.⁷⁰ Vitamin D deficiency increases the risks of CAD and cardiovascular mortality.⁷¹ Vitamin D deficiency especially lower vitamin D levels anticipate coronary artery calcification.⁷¹

Vitamin D receptors have been found in vascular smooth muscle cells. Presence of vitamin D receptors on vascular cells depicts the significance of vitamin D deficiency in causing coronary artery disease and coronary artery calcification.⁷² A higher rate of hypovitaminosis D in patients with coronary artery disease, a higher rate of hypertension and diabetes away from equator⁷³ and roles of vitamin D deficiency in the development of diabetes^{74–76} hypertension⁷⁷ and metabolic syndrome⁷⁸ -risk factors of coronary artery disease—provide evidences for the role of vitamin D deficiency in cardiovascular disease and coronary artery calcification. Cardiovascular disease is also one of the most common causes of mortality in conditions causing hypovitaminosis D e.g., Chronic kidney disease and primary hyperparathyroidism.^{79,80}

Vitamin D regulates various physiological and pathological process, which play an essential role in all stages of atherosclerosis.⁸¹ Vitamin D regulates serum calcium levels and influence factors which are the common causes of coronary artery atherosclerosis. Presence of vitamin D metabolite receptors on vascular endothelial and smooth muscles increase the uptake of calcium via enhancing the expression of Ca-ATPase. Calcium entry in vascular smooth muscles can contribute to coronary artery calcification.⁷²

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Conflict of interest

The author declares that there is no conflict of interest.

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