Section A-Research paper

CORONARY ARTERY CALCIFICATION: A REVIEW

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Abstract

Coronary artery calcification (CAC) is a quantifiable indicator of the presence of calcium deposits within the walls of the coronary arteries, which are responsible for the delivery of oxygen and nutrients to the heart. Numerous risk factors have been linked with coronary artery calcification (CAC), such as advanced age, male sex, tobacco use, hypertension, diabetes mellitus, and elevated serum cholesterol concentrations. Furthermore, the etiology of CAC involves both genetic and lifestyle determinants, including dietary habits and physical exercise.

The utilization of imaging modalities such as computed tomography (CT) has facilitated precise quantification of coronary artery calcium (CAC), thereby furnishing healthcare practitioners with a valuable means of evaluating cardiovascular risk in their patients. The present recommendations advise the utilization of coronary artery calcium (CAC) scoring in specific groups of patients, such as those with moderate cardiovascular risk, for the purpose of informing clinical judgments.

Although there is presently no designated therapy for coronary artery calcification (CAC), interventions that target the reduction of cardiovascular risk factors, such as smoking cessation, blood pressure regulation, and cholesterol-lowering therapies, have demonstrated efficacy in decelerating the advancement of CAC and mitigating the likelihood of cardiovascular incidents. Additional investigation is required to enhance comprehension of the involvement of coronary artery calcification in cardiovascular ailment and to formulate specific measures for its prevention and treatment.

Key words: Coronary artery calcification, cardiovascular disease, CT, heart attacks, cholesterol-lowering therapies

Introduction to CAC

The major cause of "cardiovascular disease (CVD)" is atherosclerosis, which frequently manifests as "coronary artery calcification (CAC)" (1). The development of plaques in the artery wall caused by atherosclerosis, a chronic inflammatory disease, narrows and obstructs the vessel lumen (2). A non-invasive imaging technology called "Computed Tomography (CT)" can be used to detect CAC, which has been found to be a very reliable predictor of future cardiac events (3).

The predictive significance of CAC for assessing cardiovascular risk has been shown in numerous studies (4, 5). Beyond conventional risk indicators such age, gender, smoking, blood pressure, and cholesterol levels, CAC has also been proven to offer additive predictive value (6). As a result, the CAC score is currently included in clinical practice recommendations for the assessment of cardiovascular risk (7).

Despite the rising acceptance of CAC as a useful tool for assessing cardiovascular risk, further investigation is still required to fully comprehend the biology of CAC and its connection to other atherosclerotic markers. Additionally, more research is required to determine the effectiveness of therapies designed to lower CAC and prevent cardiovascular events. In this review, we provide an overview of CAC, including its epidemiology, pathophysiology, risk factors, imaging techniques, and clinical implications. We also discuss the current evidence on interventions aimed at reducing CAC and preventing cardiovascular events. By summarizing the existing knowledge on CAC, this review aims to provide a comprehensive understanding of this important marker of cardiovascular disease.

Risk Factors for CAC

Multiple risk variables, including as the conventional cardiovascular risk factors, genes, and lifestyle factors, all have an impact on the complex process of CAC. Two of the most reliable risk variables for CAC are age and male gender (8,9). The promotion of oxidative stress, inflammation, and endothelial dysfunction by smoking has also been demonstrated to enhance the risk of CAC (10). Other recognized risk factors for CAC include hypertension, dyslipidemia, and diabetes mellitus (11–13).

The onset of CAC is also influenced by genetic factors. Independent of conventional risk variables, a family history of early CVD has been linked to a higher risk of CAC (14). Additionally, a number of genetic variations linked to an elevated risk of CAC have been discovered, including variations in genes related to lipid metabolism and inflammation (15). For instance, a variation in the PHACTR1 gene was found to be highly related with CAC in a genome-wide association study (16).

Diet and exercise habits are lifestyle factors that affect the risk of CAC. It has been demonstrated that a diet high in processed foods, sweets, and saturated and trans fats encourages the growth of CAC (16). The risk of CAC has, on the other hand, been linked to a diet high in fruits, vegetables, whole grains, and lean proteins (17). Regular exercise has also

been demonstrated to lower CAC risk by enhancing cardiovascular health and lowering inflammation (18).

Genes implicated in calcium signaling, inflammation, and lipid metabolism were among the unique genetic loci connected to CAC by Mightyman et al.'s genome-wide association study (GWAS) (19). Additionally, genetic variations in genes implicated in the regulation and metabolism of vitamin D have been linked to CAC in other GWAS investigations (20,21).

Environmental elements like air pollution may potentially contribute to the development of CAC in addition to hereditary causes. According to studies, air pollution from traffic and fine particulate matter (PM2.5) exposure increases the risk of CAC and other cardiovascular events (22,23).

Overall, it is essential to have a better understanding of the various risk factors that might lead to CAC in order to identify people who are at a high risk of having CVD and to create effective preventative and treatment plans.

Pathogenesis of CAC

CAC is a complex process involving several biological pathways, including inflammation, oxidative stress, and vascular calcification (24). One of the key drivers of CAC is inflammation, which promotes the recruitment of immune cells to the arterial wall and the release of cytokines and other inflammatory mediators that contribute to plaque formation and calcification (25). Oxidative stress, which results from an imbalance between reactive oxygen species and antioxidants, can also promote CAC by inducing endothelial dysfunction and vascular inflammation (26). Finally, vascular calcification, which involves the deposition of calcium phosphate crystals in the arterial wall, can lead to the development of calcified plaques and stiffening of the arterial wall (27).

Several molecular pathways have been implicated in the pathogenesis of CAC. For instance, the "nuclear factor-kappa B (NF-κB)" pathway, which regulates the expression of genes involved in inflammation and cell survival, has been shown to promote CAC in animal models (28). The Wnt signaling pathway, which plays a critical role in bone formation and remodeling, has also been implicated in the development of vascular calcification and CAC (29). Other factors, such as matrix metalloproteinases, advanced glycation end products, and microRNAs, have also been implicated in the pathogenesis of CAC (30-32).

Diagnostic Methods for CAC

The accurate detection and quantification of CAC are essential for risk stratification and the management of cardiovascular disease. Several imaging modalities have been developed for the diagnosis of CAC, including CT and "*Electron Beam Tomography* (EBT)". These techniques are non-invasive and provide high-resolution images of the coronary arteries, allowing for the detection and quantification of CAC (4).

"CT angiography (CTA)" is another imaging modality that can be used to diagnose CAC. CTA allows for the visualization of the coronary arteries and the detection of luminal stenosis, as well as the assessment of CAC burden (33). However, CTA is associated with higher radiation exposure and contrast agent administration, which limits its use in certain patient populations (34).

In addition to imaging techniques, several biomarkers have been investigated for the diagnosis of CAC. These include serum markers of inflammation, such as "*High-Sensitivity C-Reactive Protein* (hs-CRP)", and markers of oxidative stress, such as "*Oxidized Low-Density Lipoprotein* (ox-LDL)" (35,36). Overall, imaging techniques such as CT and EBT remain the gold standard for the diagnosis and quantification of CAC. Future research may focus on developing novel imaging techniques or biomarkers for the early detection and management of CAC.

Clinical Significance of CAC

Future cardiovascular events, such as myocardial infarction and stroke, are well predicted by CAC. It has been demonstrated that the presence and severity of CAC correlate with the seriousness of coronary artery disease and total CV risk (37). The chance of dying from any cause is likewise enhanced by CAC (38).

Several guidelines have endorsed the use of CAC scoring in clinical practice. Individuals at an intermediate risk of cardiovascular disease can benefit most from CAC scoring because it can help to hone risk estimates and direct treatment choices (39).

Monitoring the success of treatment can also benefit from CAC scoring. For instance, research has demonstrated that statin medication can lessen cardiovascular events and decrease the advancement of CAC in people with existing coronary artery disease (40). CAC scoring can be used to monitor changes in CAC load over time and assess how well a therapy is working.

Despite the fact that CAC scoring has been shown to be an effective tool for risk stratification and therapy selection, it is crucial to consider the particular needs and preferences of each patient. Age, sex, and comorbidities can affect the appropriate use of preventive medications and the interpretation of CAC scores (41). In general, CAC scoring is a useful tool for determining the best course of treatment for specific patient populations and assessing cardiovascular risk. Current studies may help to improve the practical application of CAC assessment and advance cardiovascular results.

Treatment and Prevention of CAC

Changes in lifestyle, drugs, and invasive procedures are all used in the treatment and prevention of CAC. A good diet, consistent exercise, and quitting smoking are examples of lifestyle changes that have been demonstrated to delay the advancement of CAC (42).

Aspirin, statins, and blood pressure-lowering drugs have all been investigated for their potential to slow the course of CAC (43).

The most popular treatment for delaying the advancement of CAC is statin therapy, and numerous clinical studies have shown that it is effective in lowering cardiovascular events in those with existing coronary artery disease (40). Although its role in primary prevention is less obvious, aspirin has also been investigated for its capacity to slow CAC progression (44). ACE inhibitors and angiotensin receptor blockers, which lower blood pressure, have also been proven to slow the course of CAC (45).

Invasive methods like "*Percutaneous Coronary Intervention* (PCI)" and "*Coronary Artery Bypass Grafting* (CABG)" can also be used to treat CAC in select patients. PCI is typically reserved for patients with focal lesions causing significant stenosis, while CABG may be considered for patients with diffuse multivessel disease (46).

Managing cardiovascular risk factors like hypertension, diabetes, dyslipidemia, and smoking can prevent CAC. CAC can be prevented by diet and exercise (47). Early detection and treatment of CAC may also slow its progression and lower cardiovascular event risk. The treatment and prevention of CAC involve a multifaceted approach, including lifestyle modifications, medications, and invasive procedures. Early detection and management of cardiovascular risk factors are also critical in preventing the progression of CAC and reducing the risk of future cardiovascular events.

Future Directions in CAC Research

There remain several areas of research that require further investigation. One area of future research is the identification of novel biomarkers for the early detection and risk stratification of CAC (48).

Advanced imaging techniques such as "*Positron Emission Tomography* (PET)" and MRI have also shown promise in detecting early-stage CAC and it is possible that they may play a role in the monitoring of disease progression and the evaluation of treatment response (49). Additionally, the development of artificial intelligence and machine learning algorithms for the analysis of CAC imaging data may improve diagnostic accuracy and facilitate risk stratification (50).

Another area of future research is the development of targeted therapies for CAC. While current therapies such as statins and blood pressure-lowering medications have been shown to slow the progression of CAC, they do not target the underlying molecular mechanisms driving disease progression (27). Novel therapies targeting these mechanisms, such as the regulation of vascular calcification pathways, may hold promise for the prevention and treatment of CAC (51).

Finally, the role of genetic factors in the pathogenesis and progression of CAC remains poorly understood, and further research in this area may shed light on novel therapeutic targets (52).

The future research in CAC should focus on the identification of novel biomarkers, the development of advanced imaging techniques, the use of artificial intelligence and machine learning algorithms for risk stratification, the development of targeted therapies, and the investigation of genetic factors driving disease progression.

Conclusion and Implications for Practice

CAC is a prevalent observation among individuals with CVD and has been linked to a heightened likelihood of experiencing unfavorable cardiovascular outcomes. The etiology of CAC is complex, involving multiple factors. However, certain risk factors that can be modified, such as smoking, hypertension, and dyslipidemia, have been identified. This underscores the significance of implementing intensive risk factor modification strategies in patients who are at high risk (53).

The present diagnostic techniques, namely coronary artery calcium scoring and computed tomography angiography, exhibit potential in identifying and supervising CAC. As a result, a few clinical practice guidelines have suggested their application in specific patients (54).

In terms of treatment and prevention, current therapies such as statins and blood pressure-lowering medications have been shown to slow the progression of CAC, highlighting the importance of aggressive medical therapy in high-risk patients (55). Additionally, lifestyle modifications such as exercise, dietary changes, and smoking cessation may also have a role in reducing CAC burden (56).

The implications for practice are clear - clinicians should be vigilant in identifying patients at high risk for CAC, aggressively manage modifiable risk factors, and utilize appropriate diagnostic and therapeutic strategies to decrease the risk of adverse cardiovascular events.

While there remain several areas of future research in CAC, including the development of novel biomarkers and targeted therapies, the current state of knowledge provides ample opportunity for clinicians to take proactive steps to reduce the burden of this common and serious cardiovascular disease.

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