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Novel Heuristic Parameters in Coronary Artery Disease Prevention and Treatment

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Abstract

There are many factors associated with the incidence and progression of coronary artery disease. Still, the exact mechanisms and pathophysiology remain unclear. The pathophysiology of atherosclerosis remains an enigma, though some basic mechanisms are known. Some risk factors associated with clinical conditions appear protective based on clinical experience. The factors include chronic obstructive lung disease, chronic liver diseases, cataract formation, and chronic renal failure, where the incidence and progression are slower. However, additional mechanisms, such as hypoxic-ischemic growth factors, including downstream vascular endothelial growth factors (VEGF) and insulin-like growth factors (IGF-1), serum estrogen levels, dystrophic calcification mechanisms, and parathyroid hormone- or calcium-related metabolism through 1,25-dihydroxycholecalciferol, could also play a role in the etiopathogenesis. Understanding and application of the underlying pathophysiology and mechanisms can be highly productive for the prevention, progression, and further treatment of coronary artery disease, as well as for future research.

Keywords: Coronary artery disease, Angiogenesis, Hypoxia, Parathormone, Estrogen

Main text

Many factors influence the onset and incidence of coronary artery disease. Apart from the conventional risk factors, numerous other factors influence the occurrence of coronary artery disease. Some of the factors are unexplained and, though not subtle, possibly play a role in the incidence and progression of coronary artery disease. In the heuristic assessment of these factors, some could include chronic respiratory disorders, chronic liver disease, cataract formation, and chronic kidney disease. The underlying mechanisms could include hypoxia and hypoxic-ischemic growth factors, estrogen and

vascular endothelial growth factors, dystrophic calcification mechanisms, and parathyroid hormones or associated mechanisms, respectively. Though coronary artery calcifications are associated with a higher incidence of coronary artery disease and progression, the concept is not well studied, especially in its association with cardiovascular mortality.

The association of cataract and cardiovascular disorders have not been studied in depth, though many studies have shown a higher association of cataract with cardiovascular diseases.[1,2] In a study, there were no changes in mortality associated with the presence of cataract,[3] and in another study, the cardiovascular mortality was reduced in patients undergoing cataract surgery.[4] However, this is a slightly different parameter compared to the incidence of cataract. Chronic liver diseases are associated with higher levels of estrogen, and estrogen is known to prevent the occurrence of coronary diseases in premenopausal women.[5] Estrogen is also associated with less calcification in coronary vessels.[6,7]

Secondary hyperparathyroidism, as seen in chronic renal diseases[8] and occasionally hypoparathyroidism[9] are associated with coronary artery disorders. According to the author, the progression of coronary artery disease after onset is usually slower than that of other general parameters. This must be studied by matching on propensity scores between patients with chronic kidney disease and those without, though it is difficult to study head-on because of the complexity of comorbidities and illness severity. Published studies indicate a higher mortality and cardiovascular morbidity in chronic kidney disease patients. [10] Spotty calcifications are more associated with vulnerable plaque than dense calcification.[11] Calcification of coronary arteries is seen in chronic renal disease, due to hypercalcemia, hyperphosphatemia, inflammation, and amyloid deposits. This process extends to calcified vulnerable plaque.[12] Dense coronary calcifications are often difficult to treat and, at times, require atherectomy or rotablator devices during coronary angioplasty.

Parathyroid hormone is known to have pro-angiogenic and bone-forming properties by enhancing VEGF-mediated actions and endothelial stimulation. This phenomenon is well-studied in bone regeneration, fracture healing, and radiation-induced hypocellularity.[13] It enhances circulatory VEGF levels and increases pro-angiogenic effects by altering Ang-1/Ang-2 activity. Its effect on cardiac angiogenesis remains poorly studied.[14,15]

Chronic calcific coronary diseases can be associated with the formation of coronary collaterals, and the underlying coronary capillary circulation cannot be studied easily. Estrogen per se is associated with fewer coronary events in females in premenopausal women, but due to the thrombotic phenomenon and malignancy potential, it cannot be used as a therapy for preventive purposes in the postmenopausal age group. Instead, estrogen-associated molecules, such as digoxin at very low doses, can enhance benefits. Similarly, calcification-inducing mechanisms can be triggered to induce dystrophic calcifications in a graded or therapeutic manner using parathyroid hormone, vitamin D, or its derivatives.

Cataracts can be associated with cardiovascular morbidity.[1] However, the progression and mortality reasons are still not clear in the literature. Runx2 and SOX9 are some of the common

transcription factors associated with cataract and coronary calcification. TNF-α and other cytokines are also associated with this common pathway of coronary and cataract calcification. Though the incidence of coronary artery disease could be higher, the coronary events and mortality tend to be lower in the observations of the author, especially in diabetes patients.

Some observations suggest that coronary artery calcification may be beneficial in chronic stable angina, whereas less or no calcification is more commonly associated with plaque rupture and myocardial infarction.[12,16-20] Especially, the calcium density is associated with the protective effect.[12] Intense physical activity is paradoxically associated with higher calcification.[21]

Many published studies show an increased association between chronic obstructive lung disease (COPD) and coronary artery disease.[22,23] However, in the experience of the author, an inverse correlation is observed between COPD and coronary artery disease manifestation and progression. The incidence of coronary artery disease is lower in people living at high altitudes, and a reduction in coronary artery disease mortality of about 30% has been observed in people living at altitudes of 1000-2000 m.[24]

Interestingly, in the observation of the author, digital clubbing is also associated with less severe coronary artery disease, though this is a 'superficial' observation. In clubbing, there is a proliferation of nail bed capillaries; possibly, the same mechanism that underlies coronary collateral or capillary network formation underlies this superficial observation. The real challenge lies in quantifying the collateral or capillary network using current investigative modalities.

Hypoxic-ischemic growth factor (HIF-α) is a master regulator of oxygen homeostasis and causes downstream signalling pathways involving vascular endothelial growth factors, erythropoietin, insulin-like growth factors (IGF-1), etc.[25] These factors are actively involved in hypoxic tissue adaptation, cell survival, and collateral formation. It is also known to activate the PI3K/Akt signalling pathway. There is also a lack of convincing evidence that frequent exacerbations of COPD are associated with acute coronary events.[23] HIF-α activates VEGF-A in the tissues and activates sprouting angiogenesis.[26]

However, the concepts are in the early stages, and some are counterintuitive and based on the author's long-term clinical observations. Further rigorous research, both in vitro and in vivo, is required to assess the benefits of these parameters relative to the incidence of acute coronary events or cardiovascular mortality. These parameters can be readily applied therapeutically in clinical practice if the research outcomes are suggestive.

Potential clinical and experimental application

The clinical application of these concepts could be interesting, though they need wide, rigorous testing in vitro and in vivo. Graded hypoxic chamber therapy, by slowly reducing tissue oxygen concentration and daily exposure to a monitored low-oxygen environment, can mimic a physical exercise or COPD milieu and be a useful method in orchestrating benefits. This can induce graded,

controlled hypoxia at the cellular level and, in turn, induce the formation of capillary/collateral connections. High doses of vitamin D and parathyroid hormone administration can induce calcifications and stabilise the coronary artery plaques. Estrogen, or estrogens that are impeded or modified, and molecules like digoxin and resveratrol can be studied in the progression of atherosclerosis. Since thrombotic events are a concern with estrogens, progesterone or its derivatives could be an alternative molecule. These molecules are currently not used in refractory angina.

Conclusion

There is potential for novel methods identified through clinical observations across various clinical scenarios to be tested in research for application in the prevention and treatment of coronary artery disease and its progression.

Author contributions

MCA conceived the idea and wrote the paper. The concepts written were the authors' own.

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