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Review Article

A Systematic Review of Oxidative Stress Markers and Risk of Coronary Artery Calcification

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Abstract

Background: *Early diagnosis of atherosclerosis, particularly in its subclinical phase, is crucial for reducing mortality and morbidity associated with cardiovascular diseases. This study aims to investigate the relationship between oxidative stress markers and coronary artery calcification (CAC), enhancing our understanding of the pathophysiology of CAC.*

Methods: *In October 2022, we conducted a systematic search of the Web of Science, Scopus, PubMed, and Embase databases without language or time restrictions, screening a total of 557 records. We excluded studies involving animals, in vitro experiments, reviews, case reports, clinical trials, editorials, and clinical guidelines. Eligible human observational studies (cohort and cross-sectional) that examined the link between CAC and oxidative stress markers were included. The Newcastle-Ottawa Scale was employed to assess the quality of the included studies.*

Results: *Our systematic review encompassed 40 studies, all of which included both male and female participants, predominantly using cross-sectional designs. Participants included individuals at low, intermediate, or high risk of coronary artery disease, patients with type 2 diabetes, those with existing cardiovascular disease, and asymptomatic individuals. The studies investigated various oxidative stress markers, including serum uric acid and 8-isoprostane, both of which showed strong correlations with CAC incidence and severity.*

Conclusion: *Oxidative stress markers may positively correlate with CAC scores, indicating a potential avenue for identifying individuals at heightened risk. This review underscores the need for further studies to facilitate early diagnosis of cardiovascular complications and the establishment of novel pharmacological targets.*

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Introduction

Coronary artery disease (CAD) is a chronic condition with delayed onset of symptoms. This worldwide disease can gradually lead to death, if not appropriately managed. Hence, early diagnosis and efficient treatment are crucial to the patient's clinical outcome. Evidence suggests that inadequate monitoring will increase CAD prevalence in the general population within the next decade.[1] As a result, an appropriate and correct assessment of atherosclerosis in its subclinical stage is necessary for early intervention. For individuals who have an intermediate risk of myocardial infarction or cardiovascular death with no known cardiovascular disease (CVD), the European Society of Cardiology and the American Heart Association recommend considering the coronary artery calcification (CAC) score in the risk assessment process.[2] Some of the markers traditionally known as oxidative stress markers such as serum acid uric (UA), myeloperoxidase (MPO), serum gamma-glutamyl transferase (GGT), 8-isoprostane, 8 hydroxy 2' deoxyguanosine (8-OHdG), malondialdehyde (MDA), F2-isoprostane, and oxidized low-density lipoprotein (OX-LDL) can also influence CVD progression.

According to Drivelegka et al[2] (2020), higher serum UA levels have a significant nonlinear relationship with the presence of CAC in men but not in women Kiss et al[3] concluded that serum UA levels were associated with higher CAC scores in an asymptomatic population, and the third serum UA tertile was an independent predictor for high-risk CAC. Previous research has indicated that elevated MPO levels are linked to higher CAC scores and associated with an increased risk of CVD events.[4] On the other hand, a cross-sectional study recruiting 208 individuals free of coronary atherosclerosis failed to demonstrate an association between serum UA and CAC.[5] Ono et al[6] reported that the CAC score had a significant and independent association with urinary 8-isoprostane, and MDA-LDL/LDL levels in Japanese patients with type 2 diabetes.

Considering the role of CAC in the progression of CVD, it is beneficial to understand the relationship between oxidative stress markers and CAC. This understanding can help us identify new monitoring methods for CAC and, thus, increase the chance of early diagnosis and a better clinical outcome.

Methods

Search strategy

The present paper adheres to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement and is registered in the PROSPERO database (CRD42021245995). To identify eligible articles, we searched PubMed, Web of Sciences, Scopus, and Embase databases until October 2022 without any language or time restrictions. We employed MeSH terms, entry terms, or free texts as search keywords, encompassing coronary artery disease, cardiovascular diseases, oxidative stress, uric acid, pentosidine, isoprostanes, malondialdehyde, myeloperoxidase, oxidized low-density lipoprotein, 8 hydroxy 2' deoxyguanosine, oxysterols, reactive oxygen species, lipid peroxides, and coronary artery calcification. Furthermore, the bibliographies of relevant articles were also examined.

Inclusion criteria

In the initial step, 2 independent researchers screened the articles based on their titles and abstracts. Studies involving animals, in-vitro experiments, review articles, case reports, clinical trials, editorials, and clinical guidelines were excluded. Conference articles were also not considered due to the unavailability of the required full texts. Patients with only CVD, type 2 diabetes, metabolic syndrome, and hypertension were allowed as comorbidities; studies involving patients with other comorbidities were excluded to reduce the risk of bias. The same 2 researchers then carefully examined the full texts of the relevant papers to determine their compatibility with the inclusion criteria. Any disagreements between the 2 authors were resolved through careful discussion or the intervention of a third researcher. The Population-Exposure-Outcome (PEO) template guided the formulation of the inclusion criteria. The study population consisted of CAD patients, while oxidative stress, identified by elevated oxidative stress markers such as serum UA, MPO, GGT, 8-isoprostane, 8-OHdG, MDA, F2-isoprostanes, OX-LDL, methionine sulfoxide, and 2-amino adipic acid (2-AAA), constituted the exposure. The primary outcome was CAC. We employed this PEO template to systematically analyze observational studies that explored the relationship between oxidative stress markers and CAC scores.

Data extraction and quality assessment

Data extraction was carried out independently by 2 researchers, who collected the following information from the included studies: author's last name, publication year, study population's country, sex, age, study design, follow-up duration (for cohort studies), study population and number of participants, effect sizes and risk estimates (odds ratios [ORs]) with their corresponding confidence intervals (CIs), and covariates in the multivariable model.

We utilized the Newcastle-Ottawa scale (NOS) for observational studies, including cohort, case-control, and cross-sectional studies, to evaluate the quality of the included studies. A score of ≥ 7 is regarded as an indicator of high quality according to the NOS scale. Due

to considerable heterogeneity among the articles in terms of study design and the variety of assessed oxidative stress markers, conducting a meta-analysis of the presented data was deemed impracticable.

Results

Results of the literature search

As depicted in Figure 1, 557 records were retrieved from Scopus, PubMed, Web of Science, and Embase databases. Among these, 304 duplicate articles were excluded, and 189 records were removed following the screening of titles and abstracts. After the assessment of the full texts of 64 records, 24 more articles were eliminated. Since no language restrictions were imposed, we also incorporated an article not written in English. Nonetheless, the full texts of 2 non-English articles could not be obtained despite contacting the authors.

General characteristics of the included studies

Among the 42 studies in this systematic review, the majority investigated the association between serum UA and CAC. All articles involved female and male participants, with most being cross-sectional in design. The study populations encompassed individuals with low, intermediate, or high risk of CAD, type 2 diabetes, patients with CVD, and asymptomatic individuals without known CVD. The relationship between oxidative stress markers and CAC was explained through OR, correlation coefficient, and β coefficient in all studies. A comprehensive overview of the studies' characteristics is provided in Table 1.

Association between oxidative stress markers and CAC

According to the results, 20 articles demonstrated a significant positive association between serum UA and CAC, comprising six prospective cohort studies and 14 cross-sectional studies.[2, 3, 7-25] In contrast, 5 studies, consisting of 1 cohort and 4 cross-sectional studies, revealed no statistically significant correlation between serum UA and CAC.[5, 26-30] Furthermore, a cross-sectional study by Sun et al[13] involving subjects with suspected CAD found a significant association between UA concentrations and CAC at the univariate analysis level; however, this relationship became insignificant upon further adjustment for major CVD covariates. Similarly, in a clinical study involving 6431 individuals without CAD, multivariate analysis revealed no significant relationship between serum UA and CAC incidence.[15] Six cohort studies, comprising

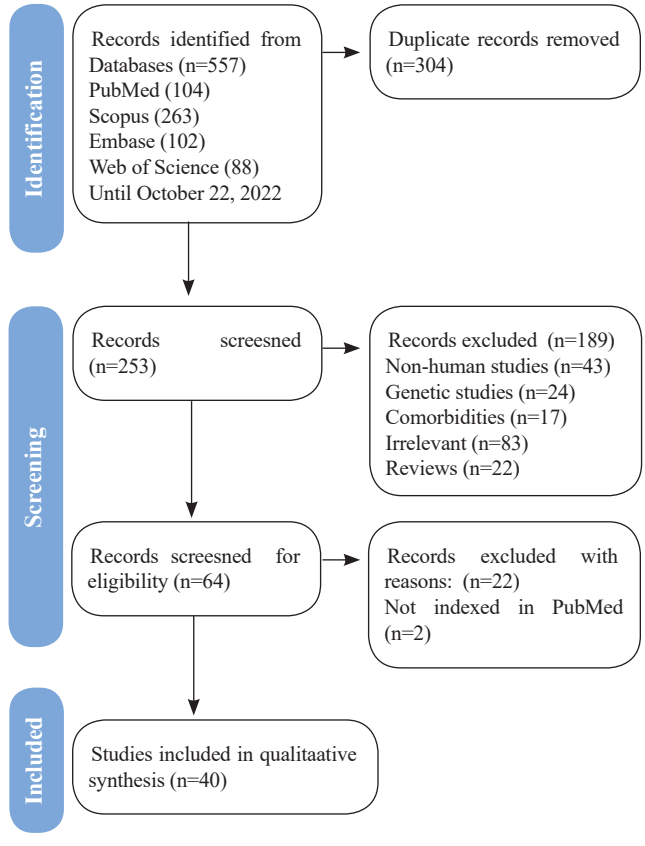

Figure 1. The image depicts the flowchart of the present study.

Table 1. Characteristics of the studies

Ref (y)	No.	Type of Study	Follow-up	Population	Biomarker	Result	Effect Size	Adjustment	Quality
Aslı İnc Atar[7] (2012)	442	Cross-sectional	-	Patients with low or intermediate risk of CAD	UA	A significant positive correlation was found between serum UA and the presence of CAC.	OR: 1.26 (1.04-1.54), 0.020	Age, sex, hypertension, smoking, fasting blood glucose, and the Framingham risk score	Good
Richard Y. Calvo[8] (2014)	368	Cohort	5 years	Postmenopausal women without known CVD	UA	A significant positive relationship was found between UA and CAC progression.	CAC severity correlations with UA: OR: 1.09 (95% CI: 0.92 -1.28), 0.335 CAC progression and UA: OR: 1.26 (95% CI: 1.02-1.56), 0.032	Age, diabetes, hypertension, statin use, visceral adiposity, and estrogen use	Moderate
Thais de A.Coutinho[9] (2007)	1107	Cross-sectional	-	Patients with the risk of CHD and yet no known CHD	UA	UA was significantly associated with CAC presence and quantity after adjustments for age and sex but not after further adjustments for CHD risk factors.	OR:1.04 (0.85–1.26), P value after adjustments for age, sex, and CHD risk factors=0.752 P value after adjustments for age and sex<0.001	Age, sex, and CHD risk factors (HDL, diabetes, smoking, systolic blood pressure, and BMI), serum creatinine, statin use, and hypertension pharmacotherapy	Good
Aramesh Saremi[40] (2017)	411	Cohort	10 years	Patients with type 2 diabetes	Methionine sulfoxide and 2-AAA	Specific advanced glycation end products and metabolic oxidation products were associated with the severity of subclinical atherosclerosis.	6.84±2.21, P<0.010	Age, duration of diabetes, prior CVD, history of hypertension, and smoking	Good
Myron Gross[41] (2005)	2850	Cross-sectional	-	Patients with CVD	F2-Isoprostaes	Plasma F2-isoprostane concentrations were strongly linked to CAC and were an independent predictor of the presence of CAC.	1.18(1.02-1.38), P<0.001	Age, race, sex, BMI (linear and quadratic plus all possible interactions of these with race and sex), clinical site, systolic blood pressure, use of blood pressure-lowering or cholesterol-lowering medications, antioxidant supplements, diabetes, impaired fasting glucose, current smoker, ex-smoker, HDL, LDL, TG, and C-reactive protein	Good
Eswar Krishnan [10] (2011)	2498	Cross-sectional	-	Subjects free of heart disease, diabetes, and renal impairment	UA	The UA concentration was directly correlated with the severity of CAC.	OR: 1.87 (1.19-2.93), P<0.001 Comparisons of the highest and lowest quartiles of UA	Age, sex, race, lipoproteins, TG, smoking, blood pressure, presence of metabolic syndrome, C-reactive protein, waist circumference, alcohol intake, creatinine, and serum albumin	Good

Ref (y)	No.	Type of Study	Follow-up	Population	Biomarker	Result	Effect Size	Adjustment	Quality
Raul D. Santos[11] (2007)	371	Cross-sectional	-	Non-diabetic white men asymptomatic for CHD	UA	A higher UA level was independently associated with the presence and severity of CAC in white men, especially in those with metabolic syndrome.	High vs normal UA levels with CAC in the overall sample: 1.81 (1.03–3.16), P=0.040 With increasing CAC severity: 1.77 (1.06–2.95), P=0.027 In subjects with MS, the presence of any CAC: 3.47(1.26-9.53), 0.010 with increasing levels of CAC: 2.74 (1.15-6.50),0.020	Age, systolic blood pressure, waist circumference, HDL, TG, glucose, smoking status, physical activity, white blood cell count, and metabolic syndrome.	Good
Nathan D. Wong[4] (2009)	1302	Retrospective cohort	3.8 years	Asymptomatic individuals without known CVD	MPO	Higher levels of MPO had a trend for higher CAC scores in patients with higher levels of MPO, though the association was nonsignificant.	-	-	Good
Panagiota Drivelegka[2] (2020)	1040	Cross-sectional (patients from a pilot study [SCAPIS])	-	Subjects without CVD or hyperuricemia	UA	Higher levels of UA were significantly associated with CAC in men, but not in women.	Men: OR: 2.30 (1.20–4.40), P=0.010 Women: OR: 1.00 (0.50–2.00), P=0.960	Age, smoking, BMI, GFR, diabetes, dyslipidemia, hypertension, hs-CRP, physical activity level, and educational level	Moderate
Loretta Zsuzsa Kiss[3] (2018)	281	Cross-sectional	-	Asymptomatic individuals (without a CVD history)	UA	UA was significantly associated with severe CAC and, hence, acted as a predictor.	OR: 5.17 (1.48-18.03), P=0.010	Age, sex, and risk factors with the first UA tercile as the reference category	Good
Tuhina Neogi[26] (2011)	2412	Cross-sectional	-	White adult individuals with no CVD	UA	UA was not associated with CAC.	Men:OR:0.90 (0.48–1.67), P=0.500 Women: OR:0.87 (0.43–1.74), P=0.700	Age, BMI, smoking, alcohol intake, educational level, low-dose aspirin use, hypertension and its treatments (including diuretics), diabetes and its treatments, and renal insufficiency	Moderate
Yujiao Sun[13] (2014)	1116	Cross-sectional	-	Patients with suspected CAD	UA	Higher levels of UA were significantly associated with higher CAC scores. This association was no longer applicable after adjustments.	Univariate: OR: 1.00 (95% Cl: 1.00-1.00), P<0.001 Multivariate: OR:1.00 (0.99-1.00), P=0.205	Age, male sex, BMI, smoking, family history of CAD, hypertension, diabetes, LDL, HDL, TG, UA, and creatinine	Moderate

Ref (y)	No.	Type of Study	Follow-up	Population	Biomarker	Result	Effect Size	Adjustment	Quality
Zhengyun Zhang[14] (2011)	3010	Cross-sectional	-	Patients with no chronic diseases	UA	Serum UA levels were independently associated with CAC.	Before adjustments: OR:1.09 (1.00-1.19), P=0.030 After adjustments: OR: 1.11 (1.00-1.23), P=0.042	Age, weight, hypertension, hypercholesterolemia, hypertriglyceridemia, low HDL-C, metabolic syndrome, hs-CRP, serum creatinine, liver function, statin treatment, smoking status, and alcohol intake	Good
Magdalna Kwaśniewska[32] (2016)	62	Prospective cohort	25 years	Asymptomatic men without chronic diseases and with a constant level of physical activity	OX-LDL	OX-LDL was not significantly correlated with CAC.	-	-	Moderate
Doo-Ho Lim[15] (2019)	6431	Cross-sectional	-	Asymptomatic adults with no previous history of CAD	UA	UA levels were significantly associated with CAC scores. However, the association became nonsignificant after adjustments for CVD risk factors.	Before adjustments: OR: 2.05 (1.74–2.41), P<0.001 After adjustments: OR:1.19 (0.97–1.46), P=0.090	Age, sex, obesity, diabetes mellitus, hypertension, hyperlipidemia, current smoking, family history of CAD, and hs-CRP	Good
H. Wang[16] (2013)	3964	Prospective cohort (the CARDIA study)	10 years	-	UA	During years 15 to 25, the baseline UA concentration was positively associated with CAC.	HR: 2.07 (1.66– 2.58), P<0.001	At 15 years of age: race, educational level, smoking status, physical activity, and average intakes of total calories, and alcohol intake At 0–7 years of age: protein	Good
Paulo H. Harada[27] (2019)	3753	Cross-sectional (the ELSA-Brazil)	-	Adults with no CVD or chronic diseases	UA	UA was not associated with CAC scores of >0 or CAC scores.	UA associations with CAC (CAC>0): OR: 1.14 (0.84, 1.56), P=0.500 Adjusted CAC scores for UA: OR: 1.91 (1.45–2.46), P=0.700	Age, sex, race, family history of CAD, alcohol intake, smoking, physical activity, waist circumference, diabetes, hypertension, HDL, and TG	Good
Asli I. Atar[25] (2013)	270	Cross-sectional	-	Patients without known CHD who had a low-intermediate risk for CHD	UA GGT	Serum UA and GGT levels were significantly correlated with CAC and CHD risk factors.	UA: OR: 1.40 (1.10–1.78), P=0.006 GGT: OR: 1.03 (1.00–1.06), P=0.030	Established CVD risk factors	Moderate

Ref (y)	No.	Type of Study	Follow-up	Population	Biomarker	Result	Effect Size	Adjustment	Quality
A. E. Berezin[17] (2013)	126	Cohort	-	Subjects asymptomatic for CAD	UA	UA was significantly associated with CAC.	OR: 1.42 (1.20–1.82), P<0.001 HR: 1.12 (1.01–1.52), P<0.001	Osteopontin, osteoprotegerin, type 2 diabetes mellitus, TC, and demographic variables (age and sex)	Moderate
Lu Q. Chen[35] (2011)	3294	Cross-sectional	-	The Dallas Heart Study	MPO	MPO was not associated with CAC after adjustments for conventional risk factors.	OR: 0.84 (0.61, 1.17)	Age, sex, race/ethnicity, BMI, diabetes, current smoking, hypertension, hypercholesterolemia, and low HDL	Good
Søren Zöga Diederichsen[28] (2017)	1006	Prospective cohort	5 years	Asymptomatic subjects	UA	Urate was not associated with CAC.	IRR, 2.05 (0.30–13.90), P=0.500	Sex, age, diabetes, hypertension, dyslipidemia, and smoking (and the baseline CAC score where applicable)	Good
Chagai Grossman[18] (2014)	663	Cross-sectional		Asymptomatic patients	UA	Elevated serum UA levels were significantly associated with CAC.	OR: 1.84 (1.10–3.07), P=0.020	Age, sex, hypertension, estimated GFR, BMI, diabetes mellitus, and hyperlipidemia	Good
Ji Eun Jun[19] (2018)	4461	Retrospective cohort	4.1 years	Participants without a CVD history who had no or minimal CAC scores in their first examination (CAC<10)	UA	Elevated UA levels were significantly associated with an increased risk of future CAC.	HR: 5.93 (2.88-12.19), P<0.001	Age, sex, BMI, systolic blood pressure, TG, HDL, LDL, GFR, use of antihypertensive medication, use of lipid-lowering drugs, use of aspirin, current smoking, and diabetes	Good
Hyunwook Kim[20] (2017)	4188	Cross-sectional	-	Individuals without prior CAD or urate-deposition disease	UA	Serum UA levels were positively and independently associated with CAC scores.	B: 0.116, SE: 0.03, P=0.001	Age, sex, diabetes mellitus, hypertension, ever smoking, systolic blood pressure, BMI, CRP, WBC, hemoglobin, GFR, TG, HDL, and LDL	Moderate
Mitsutaka Ono [6] (2014)	163	Cross-sectional	-	Patients with type 2 diabetes	Urinary 8-isoprostane, 8-OHdG, and MDA-LDL cholesterol	A significant association was found between CAC and urinary 8-isoprostane and also MDA-LDL-C/LDL-C. However, no significant association existed between the urinary 8-OHdG and the CAC score.	CAC>400 AU: Urinary 8-isoprostane: OR: 2.54 (1.03–6.32), P=0.040 MDA-LDL-C/LDL-C-C: OR: 2.62 (1.07-6.40), P=0.035	Age (median), sex, BMI, HbA1c (median), urinary 8-isoprostane (median), urinary 8-OHdG (median), and MDA-LDL/LDL-C (median)	Moderate

Ref (y)	No.	Type of Study	Follow-up	Population	Biomarker	Result	Effect Size	Adjustment	Quality
Rehan Malik[5] (2016)	208	Cross-sectional	-	Patients without coronary atherosclerosis, cerebrovascular, or perivascular diseases	UA	Serum UA was not associated with CAC.	CAC=0-400: OR: 3.01 (0.67, 13.58), P=0.382 CAC>400: OR: 0.79 (0.28, 2.20), P=0.988	Sex, BMI, systolic and diastolic blood pressure, antihypertensive treatment, diabetes, use of oral hypoglycemic agents, TC, HDL, LDL, TG, and creatinine clearance	Moderate
Antonio E. Pesaro[31] (2018)	130	Cross-sectional	-	Patients with CAC (without CAD)	OX-LDL	OX-LDL was not significantly associated with CAC.	Univariate analysis: OR: 1.19 (0.99; 1.44), P=0.070 Multivariate analysis: OR: 1.27 (0.95; 1.71), P=0.110	Age, sex, hypertension, diabetes, treatment with statins, and LDL levels	Good
Mahmoud M. Ramadan [32] (2008)	177	Cross-sectional	-	Asymptomatic subjects with intermediate risk for CAD	OX-LDL	OX-LDL was not significantly associated with CAC.	-	Sex and BMI	Moderate
Jamal S. Rana[36] (2012)	1286	Cohort	4.1±0.4 years	Asymptomatic participants with no known CVD	MPO	The CAC score correlation with the MPO level was nonsignificant.	HR: 0.80 (0.60–1.20), P=0.340	The Framingham Risk Score	Moderate
Joseph Shemesh[22] (2004)	446	Retrospective cohort	3.8±0.4 years	High-risk asymptomatic hypertensive patients	UA	A significant correlation was found between UA levels and CAC scores.	-	-	Moderate
D Vaidya[34] (2011)	997	Cross-sectional	-	Subjects free of clinical CVD at baseline	OX-LDL	TC and OX-LDL were jointly associated with CAC prevalence.	Relative prevalence/1 log-unit greater OX-LDL: 1.14 [1.04–1.25]	Race, sex, age, current smoking, and metabolic syndrome	Good
H.S. Cho[39] (2015)	1520	Cross-sectional	-	Patients with no CVD, cerebrovascular disease, or chronic liver or kidney dysfunction	GGT	GGT levels were positively associated with a CAC score of >100.	GGT: OR: 1.35 (1.05-1.73) TB: OR: 0.67 (0.52-0.87)	Age, waist circumference, hypertension, smoking (except in women), alcohol consumption, estimated GFR, hyperlipidemia, diabetes, insulin resistance, and fatty liver	Good
Yun Kyung Cho[37] (2015)	1246	Cohort	3.0 (2.1–3.8) years	Asymptomatic middle-aged subjects	GGT	High serum GGT was independently and significantly associated with CAC progression.	OR:1.85 (9% CI: 1.14-3.00), P=0.006	Age, sex, BMI, smoking, drinking,exercise, hypertension, diabetes, systolic blood pressure, the baseline CAC score, the follow-up interval, TG, HDL, LDL, and hs-CRP	Moderate

Ref (y)	No.	Type of Study	Follow-up	Population	Biomarker	Result	Effect Size	Adjustment	Quality
Akın Dayan[21] (2012)	128	Cohort	36.6±3.3 months	Type 2 diabetic patients asymptomatic for CVD	UA	CAC scores showed a statistically positive correlation with UA.	Multiple linear regression analysis: b=0.129 (0.00-0.25), P=0.030	-	Moderate
Li Gang[38] (2014)	326	Cohort	20±4 months	Patients with type 2 diabetes with no CVD symptoms	GGT	GGT activity was significantly correlated with CAC progression.	OR: 1.08 (1.05-1.11), P<0.010	Age, sex, blood pressure, BMI, smoking, diabetes, LDL-C, HbA1C, pulse pressure, CRP, UA, and HDL	Moderate
Trine R. Larsen[29] (2017)	1016	Cross-sectional	-	Random asymptomatic middle-aged individuals	UA	UA levels were not correlated with CAC severity after adjustments for usual risk factors.	OR: 1.19 (0.98-1.44), P=0.080	Age, sex, smoking, hypertension, and hypercholesterolemia	Low
Shoichi Ehara[33] (2008)	83	Cross-sectional	-	34 patients with acute MI and 49 patients with stable angina	OX-LDL	There was no significant correlation between plasma OX-LDL levels and CAC.	r=0.067, P=0.550	-	Moderate
Youngmi Eun [23] (2021)	617	Cross-sectional	-	Participants without diabetes, hypertension, CAD, or stroke	UA GGT	GGT and UA were significantly associated with CAC.	univariate logistic regression: UA: OR: 2.23 (1.07-1.41), P=0.003 GGT: OR: 1.00 (1.00-1.01), P=0.030	-	Good
Cecilia Castro-Diehl[42] (2021)	890	Cross-sectional	-	The Framingham Offspring Study	F2-isoprostane	F2-isoprostane was not significantly associated with CAC.	OR: 0.06 (-0.10– 0.22), P=0.40	Age, sex, BMI, systolic blood pressure, hypertension pharmacotherapy, diabetes, current smoking status, and TC/HDL	Good
Beilei Wang[24] (2021)	478	Cross-sectional	-	Patients with suspected CHD	UA	UA was a risk factor for calcification.	OR:1.00 (1.00~1.00), P=0.020	Age, hypertension, fasting blood glucose, and metformin levels	Good

CAD, Coronary artery disease; UA, Uric acid; CAC, Coronary artery calcification; MI, Myocardial infarction; OR, Odds ratio; CVD, Cardiovascular disease; CHD, Coronary heart disease; BMI, Body mass index; HDL, High-density lipoprotein-cholesterol; LDL, Low-density lipoprotein-cholesterol; TG, Triglycerides; TC, Total cholesterol; TB, Total bilirubin; hs-CRP, Highly sensitive C-reactive protein; GFR, Glomerular filtration rate; HR, Hazard ratio; MPO, Myeloperoxidase; OX-LDL, Oxidized low-density lipoprotein; 2-AAA, 2-amino adipic acid; GGT, Gamma-glutamyl transferase; 8-OHdG, 8 hydroxy 2' deoxyguanosine;

13,553 individuals with a mean follow-up of 25.95 years, demonstrated a significant association between UA and CAC. Nevertheless, a prospective cohort study by Diederichsen et al[28] (2017), involving 1006 asymptomatic individuals, found no statistically significant data supporting this association. Subgroup analysis of 444 subjects with confirmed CAC at baseline showed that these patients had increased levels of triglyceride, LDL, creatinine, and UA compared with subjects without CAC at baseline. Overall, 5 cross-sectional clinical studies found insignificant associations between high CAC scores and OX-LDL.[30-33] However, Vaidya et al[34] reported that although neither total cholesterol nor OX-LDL was individually associated with CAC prevalence, the association between OX-LDL and CAC prevalence remained significant after adjusting for traditional CVD risk factors but not total cholesterol. Notably, no association was found between OX-LDL and the magnitude of calcification.

Our review identified 3 studies, consisting of 2 cohort studies and 1 cross-sectional study, that explored MPO as an oxidative stress marker, demonstrating a nonsignificant relationship with abnormal CAC.[1, 4, 35, 36] In contrast, 2 cross-sectional and 2 cohort studies revealed a significant correlation between GGT activity and CAC prevalence.[23, 25, 37, 38] Cho et al[39] demonstrated a positive correlation between GGT and CAC. According to cross-sectional analyses, other oxidative stress markers, such as MDA and 8-isoprostane, exhibited independent relationships with CAC. Moreover, a cohort study indicated significant associations between methionine sulfoxide, 2-AAA, and CAC subclinical atherosclerosis.[6, 40, 41] Still, no significant association was found with 8-OHdG.[6] A study involving 2850 subjects with CVD demonstrated that individuals with higher levels of F2-isoprostane had an 18% increased risk of CAC after adjusting for major CVD covariates.[41] In contrast, a recent study by Castro-Diehl et al,[42] involving 890 participants, found no significant association between F2-isoprostanes and CAC.

Discussion

Given the crucial role of oxidative stress markers in CAD pathogenesis, this systematic review aimed to explore the correlation between oxidative stress markers and CAC, a recognized predictor of CAD.

Based on the findings from cohort studies, we observed positive associations between UA, GGT, and CAC. Furthermore, a strong correlation between methionine sulfoxide, 2-AAA, and subclinical atherosclerosis has been suggested.

Although an increasing trend was observed for higher CAC scores in subjects with elevated MPO levels, adjusting for major CVD covariates revealed a trivial association between MPO concentrations and increased CAC levels.[4] Notably, no direct relationship between CAC and total bilirubin was found. In a cohort study of 2588 individuals, multivariate analysis showed no significant association between MPO and CAC development.[4, 35] Consistent with these findings, a cross-sectional study by Chen et al,[34] involving 3294 participants, reported similar results. On the other hand, the majority of cross-sectional studies indicated no positive association between OX-LDL and CAC.[30-33] Limited information is available on the association between other oxidative stress indicators and CAC as a marker of subclinical atherosclerosis. Significant positive associations were observed between MDA, 8-isoprostane, and CAC incidence, while no significant relationship was found between 8-OHdG and CAC.

Oxidative stress is recognized as an early contributor to the development of various diseases, including atherosclerosis, and circulating levels of oxidative stress markers have been suggested as potential predictors of cardiovascular events.[43] The overall evidence from this study highlights the significant role of oxidative stress indicators, particularly UA, in the incidence and progression of subclinical atherosclerosis and CAD. Currently, the precise role of UA in atherosclerosis remains unclear. Nonetheless, multiple studies have demonstrated UA's role as an antioxidant in the body, potentially exerting a protective effect against atherosclerosis. In contrast, some studies have indicated that elevated UA levels can cause oxidative stress and endothelial dysfunction.[15, 44, 45] The mechanisms linking serum UA to vascular impairment involve increased vascular muscle proliferation, enhanced production of monocyte chemoattractant protein-1, and elevated platelet-derived growth factor levels, ultimately leading to atherosclerosis and endothelial calcification.[13, 46] In a cross-sectional study, Lim et al[15] examined 6431 patients and found a significant association between CAC and serum UA levels, although this correlation became insignificant after adjusting for cardiovascular risk factors. In a cohort study, Wang et al[16] investigated 3964 individuals and observed that higher serum UA concentration was correlated with CAC progression, indicating an increased risk of subclinical atherosclerosis. Additionally, a cohort study by Grossman et al[18] demonstrated a strong association between serum UA levels and CAC.

Uric acid has dual effects on atherosclerosis pathophysiology, necessitating further clinical studies to reach a definitive conclusion. The majority of cohort studies with large populations in our systematic review revealed a positive association between serum UA and CAC. Conversely, studies that showed a negative association had low to moderate quality, and most were cross-sectional. Since cross-sectional studies cannot establish causality, it can be assumed that a positive association between UA and CAC is more likely. However, additional research is required to confirm this association.

MPO is an enzymatic catalyst that initiates LDL peroxidation and foam cell formation, leading to endothelial impairment and biochemical instability. Moreover, MPO oxidizes apoA1 in HDL and depletes nitric oxide (NO), causing vasoconstriction and damage.[35, 47, 48] Wong et al[4] conducted a retrospective cohort study involving 1302 adults without CAD and found that although increased MPO levels showed a trend toward elevated subclinical atherosclerosis grade and higher CAC levels, the association became nonsignificant after adjusting for CVD covariates. In contrast, a multi-ethnic population-based study by Chen et al[35] revealed no association between MPO and CAC in a multivariate model adjusted for age, sex, race/ethnicity, body mass index, diabetes, smoking, hypertension, hypercholesterolemia, and low HDL. However, the study demonstrated an association between MPO and aortic wall thickness and aortic plaques.

F2-isoprostane is a product of arachidonic acid oxidation in various tissues and is regarded as an indicator of systemic oxidative damage. According to a study by Gross et al,[41] the plasma F2-isoprostane concentration is an independent predictor of CAC presence. Still, contradictory results were reported by Castro-Diehl et al.[42]

There is limited information on the correlation between CAC and other potential oxidative stress markers such as methionine sulfoxide, 2-AAA, F2-isoprostane, urinary 8-isoprostane, and 8-OHdG. Although short-lived oxidation species are highly reactive against biological molecules, 2-AAA, as a final product of metal-catalyzed oxidation of lysine with an extended half-life, can be considered a potential oxidative stress factor.[49] Further evidence is needed to confirm the association between oxidative stress factors and identifying individuals at high risk of abnormal CAC scores as an indicator of subclinical atherosclerosis. This information would provide useful targets for pharmacological interventions.

However, this study has some limitations, including the use of observational studies, which may increase the possibility of bias, and differences in methodological design that could affect the results. Future high-quality studies with larger populations are required to validate these findings. Researchers should also consider the presence of confounding variables and adjust their study designs accordingly to obtain more accurate results. The evidence from various studies exhibited significant variation in aims and design, which substantially hindered data pooling.

Conclusion

Our study indicates that oxidative stress markers, specifically uric acid and GGT, positively correlate with CAC scores. Further high-quality prospective cohort studies are needed to validate these results. The findings of this review could provide clinical evidence for future studies investigating oxidative stress markers as predictors of CAC burden.

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