Section: Biochemistry

Original Research Article

STUDY ON SERUM SALUSIN ALPHA - A NEGATIVE PREDICTIVE MARKER FOR SEVERITY OF CORONARY ARTERY DISEASE

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ABSTRACT

Background: Many cardiac biomarkers like Troponins, hsCRP and H-FABP are currently in use to identify and predict atherosclerotic events. But assessing the severity of coronary atherosclerosis is mainly dependent on imaging techniques like Coronary Angiography. Salusin-alpha is a recently investigated bioactive polypeptide secreted by cardiovascular system and involved in the origin of coronary atherosclerosis. Salusins have mitogenic effects on vascular smooth muscle cells and fibroblasts. They also play an important role in hemodynamic homeostasis. Salusins act by modulating the effects of ACAT-1 on cholesterol ester accumulation and macrophage foam cell formation. Salusin-alpha is anti-atherogenic and protective against cardiovascular diseases while salusin-beta is atherogenic. The aim is to estimate the level of serum salusin-alpha in patients with CAD as a marker for severity assessment. **Materials and Methods:** A case control study was conducted with 30 CAD patients planned for coronary angiography at department of Cardiology, Madurai Medical College and Hospital as Cases and 30 healthy individuals as Controls. Serum salusin-alpha was measured by ELISA. Sugar, urea, creatinine, liver enzymes, lipid profile, HbA1c and CRP were measured using standard kits. **Result:** Statistical Analysis was done by SPSS-20 software. Unpaired t-tests and linear regression were used. Serum salusin-alpha level was significantly reduced in patients with CAD ($p<0.0001$). Negative correlation was observed between the severity of CAD and serum salusin alpha levels. Mean salusin alpha value was found to be lowest in patients with triple vessel disease. **Conclusion:** Salusin alpha is a promising marker of severity in coronary artery disease.

INTRODUCTION

Coronary artery disease is the most common type of heart disease worldwide. According to CDC, about 5% adults aged 20 and older has CAD. One of the leading causes of mortality and a major global contributor to healthcare costs is coronary artery disease (CAD).[1,2] Diagnosis of CAD and assessment of its severity is therefore crucial.

A number of bioactive peptides, including cardiac troponin I and T, B-type natriuretic peptide (BNP), and C-reactive protein (CRP), have been shown to be significant cardiac biomarkers of independent diagnostic and/or prognostic significance. A family of recently identified bioactive peptides known as salusins was found using bioinformatics analysis of a whole cDNA library.[4,5] Shichiri et al. identified and characterised two highly similar isoforms of salusins, which they named salusin-α and salusin-β, respectively.[6,7] The predominant type of salusin seen in human plasma is salusin-α[8]. Previous research has shown that serum salusin-α levels were lower in patients with acute coronary syndrome (ACS),[4] and that in patients with essential hypertension, they are adversely linked with maximal intima-media thickness (IMT) and carotid atherosclerosis.[6]

Salusin-alpha and salusin-beta, are endogenous vasoactive peptides with respective lengths of 20 and 28 amino acids. These peptides are considered to be biosynthesized from preprosalusin, an alternative-splicing product of the torsion dystonia-related gene (TOR2A).[4] They are secreted by the cardiovascular system, central nervous system, and kidneys. Salusins, are highly expressed in endothelial and vascular smooth muscle cells.[3]

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Salusin alpha primarily affects the cardiovascular system with haemodynamic effects, which include reducing blood pressure and slowing heart rate. Salusins have been shown to promote development, induce hypertrophy, and block apoptosis in rat cardiomyocytes.[9,10] Salusin alpha is thought to be anti-atherogenic, but salusin beta is thought to have atherogenic properties. Recent research has revealed that salusin alpha is protective against cardiovascular diseases.[11]

The findings of multiple studies imply that in individuals referred for coronary angiography, the existence of coronary artery disease is correlated with the blood levels of biomarkers like high sensitive C-reactive protein, procalcitonin or BNP but not its severity.[12] Thus, the current research sought to measure serum salusin alpha levels in patients with coronary artery disease and to correlate levels with severity of atherosclerosis in coronary arteries based on coronary angiography.

MATERIALS AND METHODS

Study design and participants: A case control study was conducted during Febrauary 2023 - Jan 2024 at Madurai Medical College and Hospital, Madurai. Informed consent was obtained from all patients. All procedures concerning patients were permitted by the Institutional Ethical Committee. Controls (N=30) were healthy individuals with no other organic disease based on their clinical history and routine investigations with normal range of HbA1c. Cases (N=30) were CAD patients planned for coronary angiography at department of Cardiology, Madurai Medical College and Hospital. Inclusion criteria were CAD patients with age 18-65 years and planned for coronary angiography. Exclusion criteria were patients with recent acute coronary syndrome or who underwent procedures like coronary artery bypass surgery, percutaneous coronary intervention, patients with Valvular heart disease /pericarditis/pericardial effusion, patients with advanced hepatic and renal disease, or those who are not willing to participate. All study participants were explained about the study protocol.

Sample collection: For the study, 5ml of venous blood sample was collected in plain tube from all the study participants. Serum was separated after centrifuging the sample at 3000rpm for 10 minutes and the following investigations were performed.

Biochemical estimation: Sugar was estimated by GOD POD method, urea was estimated by GLDH-urease method, creatinine by Jaffe's Method, total cholesterol by CHOD-PAP method, triglycerides by Glycerol-3-Phosphate oxidase method, HDL by Phosphotungstic Acid method, total protein by Biuret method, albumin by Bromocresol green method. CRP and HbA1c by immunoturbidimetric method using ERBA XL1000 fully automated analyzer

Salusin alpha estimation: Serum salusin alpha was measured by commercially available enzyme linked immunosorbent assay (ELISA) kit by krishgenbiosystems.

ELISA assay was Sandwich-ELISA principle, with a biotin labelled antibody, a assay range of 78 to 5000 pg/ml and a sensitivity of 46 pg/ml

Assessment of CAD severity: Coronary angiography was performed for all patients and they were classified into three groups based on the presence of single vessel occlusion, double vessel occlusion or triple vessel occlusions

Data analysis: Statistical Analysis was done by SPSS-20 software; Continuous data has been expressed as Mean and Standard Deviation. Unpaired t test was used to compare the mean value of biochemical parameters between controls and cases. Simple linear regression was used for finding the correlation of salusin alpha with biochemical parameters like sugar, urea, creatinine, AST, Total cholesterol, Triglycerides, HDL and LDL. p value less than 0.05 was considered statistically significant.

RESULTS

Baseline biochemical characteristics: Serum Salusin alpha, sugar, urea, creatinine, liver enzymes, lipid profile, HbA1c and CRP were estimated in controls and cases. In case group, there were 19 males and 11 females. Control group constituited 10 males and 20 females. Mean age in case group was 56.07±9.41 years and in control group 25.17±4.21 years.

Biochemical parameters of cases and controls are given in [Table 1]. Patients with CAD had significantly higher LDL, Total cholesterol, TGL levels and higher CRP levels compared to controls.

As given in Fig 1, the mean blood sugar level in cases (145.1±75.09 mg/dl) was higher compared to controls (101.3±9.37 mg/dl) and the difference was statistically significant ($p=0.00024$ $p<0.05$). As per, Fig 2, there was statistically significant high level of HbA1c in cases (5.81±1.64%) compared to controls (4.21±0.45%) ($p=0.0001$ <0.05). Lipid profile data is shown in Fig 3-6. Total Cholesterol level of CAD cases was 190±66.39 mg/dl and that of controls was 149.77±29.96 mg/dl and the difference was statistically significant ($p=0.0037$). Triglyceride level of cases was 170.97±64.64 mg/dl and that of controls was 114.5±28.04 mg/dl and the difference was statistically significant ($p<0.0001$). LDL level of cases was (110.03±37.03 mg/dl) and that of controls was (82.77±20.61 mg/dl) and the difference was statistically significant ($p<0.0008$). The difference in HDL level was not statistically significant in cases(37.9±9.09 mg/dl) compared to controls (37.37±5.74 mg/dl) ($p=0.7881$).

As per Fig 7, the mean CRP level in patients with CAD was 18.84±15.98 mg/dl which is significantly

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high in comparison with CRP of controls (2.83±1.2 mg/dl) (p<0.0001).

Salusin alpha levels: [Table 2] and Figure 8], show the comparison between serum Salusin alpha levels in controls and cases. the mean value of salusin alpha level in patients with CAD was 236.37±189.31pg/ml. the mean value of salusin alpha level in controls was 420.69± 141.21pg/ml. Statistically significant decrease of salusin alpha values was observed in patients with CAD than in controls.

Relationship of serum Salusin alpha levels with CAD severity: A comparison was made between Salusin Alpha levels of the patients in each group divided with respect to coronary Angiogram as triple vessel disease, double vessel disease and single vessel disease [Table 3 and Figure 9]. Mean salusin alpha value in single vessel disease was 332.15±227.77 pg/ml, in double vessel disease was 217.68±105.47 pg/ml and in triple vessel disease mean value was 63.11±21.63 pg/ml.

Statistically significant difference in salusin alpha values were observed between these three group of patients (p=0.0001). Lowest mean salusin alpha values were recorded in patients with triple vessel disease. Decreasing pattern of salusin alpha level was noted from single vessel disease to triple vessel disease.

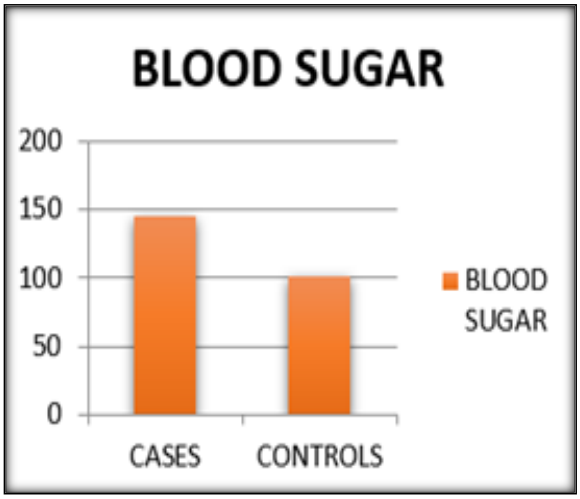

Figure 1: Blood sugar in cases and controls

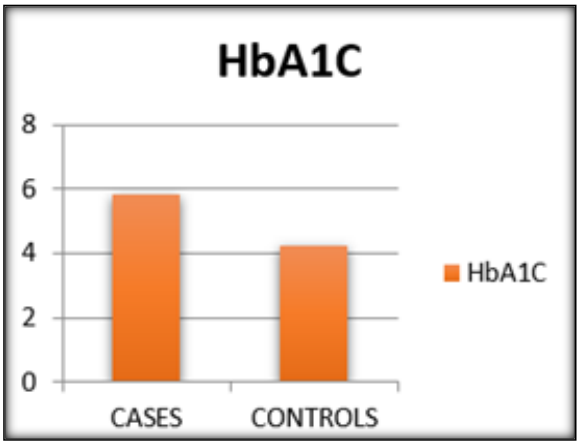

Figure 2: HbA1c levels in cases and controls

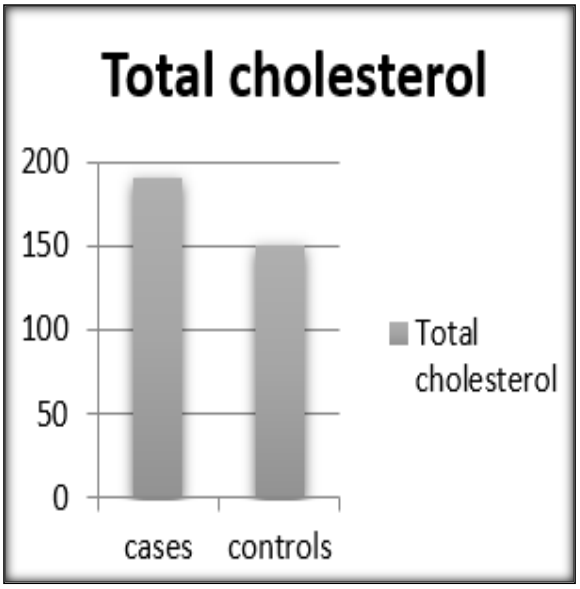

Figure 3: Total cholesterol in cases and controls

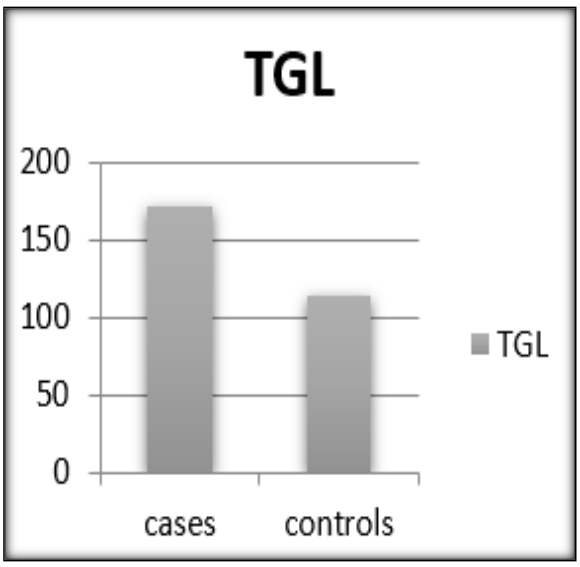

Figure 4: TGL in cases and controls

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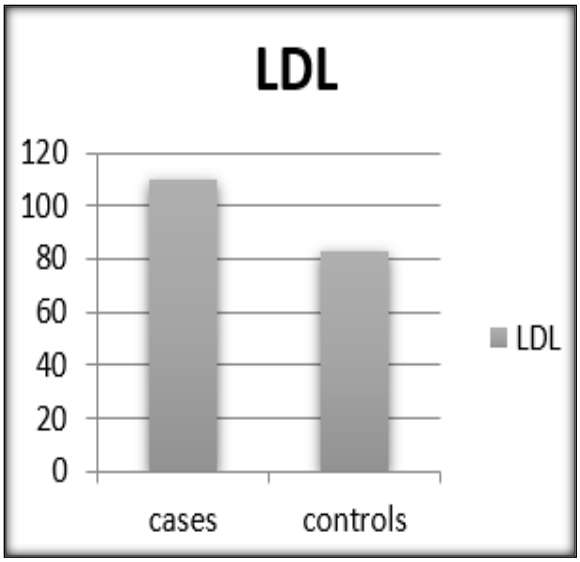

Figure 5: LDL in cases and controls

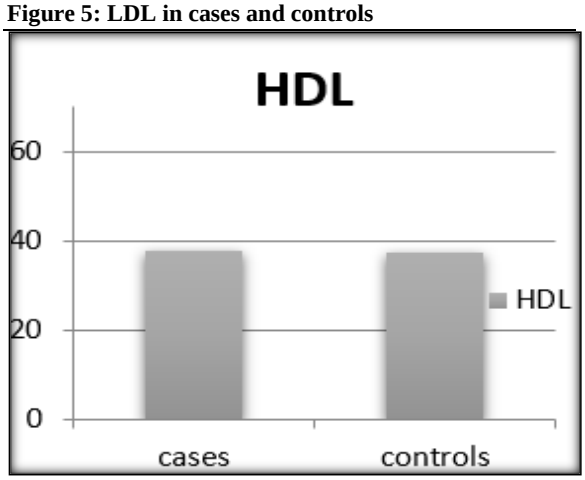

Figure 6: HDL in cases and controls

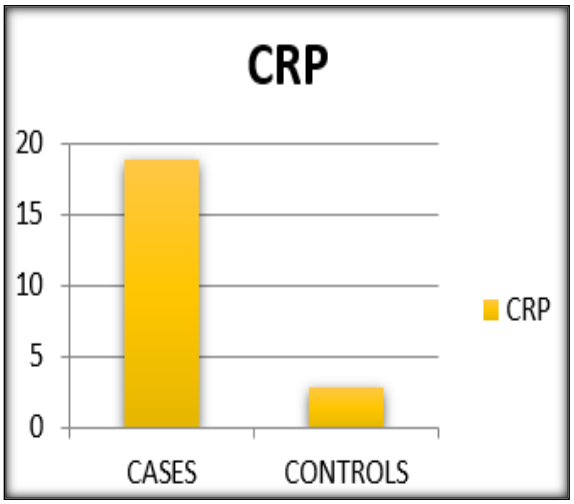

Figure 7: CRP levels in cases and controls

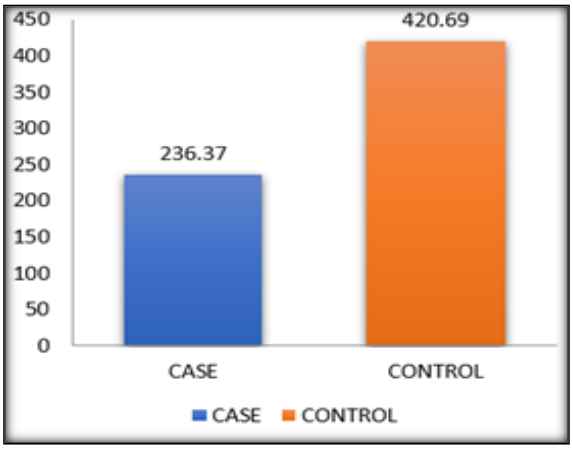

Figure 8: Serum salusin alpha level in cases and controls

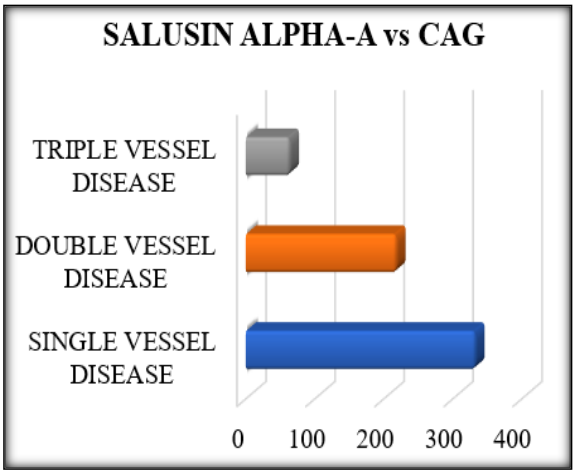

Figure 9: Salusin levels in 3 groups of CAD

Table 1: Comparison of biochemical parameters in cases and controls

Biochemical parameter	Cases	Controls	p value
Blood sugar (mg/dl)	145.1±75.09	101.3±9.37	0.0024
HbA1c (%)	5.81±1.64	4.21±0.45	<0.0001
Total cholesterol (mg/dl)	190±66.39	149.77±29.96	0.0037
Triglyceride (mg/dl)	170.97±64.64	114.5±28.04	<0.0001
LDL (mg/dl)	110.03±37.03	82.77±20.61	<0.0008
HDL (mg/dl)	37.9±9.09	37.37±5.74	0.7881
SGOT (U/L)	33.6±15.69	28.13±5.53	0.0769

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Urea (mg/dl)	27.97±10.6	28.87±4.23	0.0008
Creatinine (mg/dl)	0.92±0.24	0.64±018	0.0008
CRP (mg/dl)	18.84±15.98	2.83±1.2	<0.0001

Table 2: Comparison of salusin levels in cases and controls

Salusin alpha (pg/ml)	Mean	SD	p Value	t Value	95% CI
Case	236.37	189.31	0.0001	4.84	98.0071 to 270.6329
Control	420.69	141.21			

Table 3: Comparison of salusin levels in 3 groups of CAD

CAD category	Salusin alpha (pg/ml)		P Value	Df Value
	Mean	SD		
Single Vessel Disease	332.15	227.77	0.0001	15.84
Double Vessel Disease	217.68	105.47		
Triple Vessel Disease	63.11	21.63		

Correlation of salusin with clinical parameters: There was a negative correlation of parameters like age, male sex, higher blood sugar, CRP, total cholesterol, triglyceride and LDL with salusin alpha value.

Table 4: Comparison between salusin alpha and the variables shown by simple linear regression

Variables	Simple linear Regression		
	OR	95% CI	p VALUE
Age	-4.66	-8.25to-3.29	0.001
Male	45.73	52.32-235.42	0.003
Blood Sugar	-2.59	-1.89 to -0.24	0.012
Urea	1.28	-2.21 to 10.07	0.205
Creatinine	-1.46	-330.32 to 52.27	0.151
HbA1c	-1.94	-66.08 to 0.97	0.057
CRP	-3.49	-9 to _2.43	0.001
Total Cholesterol	-2.33	-1.88 to -0.14	0.023
Triglyceride	-2.62	-1.91 to -0.25	0.011
LDL	-2.8	-3.43 to -0.57	0.007
HDL	0.92	-3.56 to 9.58	0.362
SGOT	-1.93	-7.93 to 0.15	0.059

DISCUSSION

Biomarkers of coronary atherosclerosis that can be readily assayed from blood or other body fluids and also useful in reflecting the severity of CAD are critical in effective application of secondary prevention strategies to reduce the cardiac mortality and morbidity, instead of solely depending on imaging studies for grading of CAD severity which requires skilled manpower and consumes much time. Serum salusin alpha serves such a purpose.

The development of atherosclerosis is influenced by abnormalities in cellular cholesterol balance in subendothelial macrophages. Intracellular free cholesterol level is largely deposited by the uptake of acetylated low-density lipoprotein (acetyl-LDL) via scavenger receptor class A (SR-A). Since excessive accumulation of free cholesterol is toxic for cells, free cholesterol must either be removed through efflux to extracellular acceptors, such as HDL, or esterified to cholesterol ester (CE) inside the cell by the microsomal enzyme acyl-coenzyme A:cholesterol acyltransferase-1 (ACAT-1). ACAT-1 promotes CE accumulation in macrophages, thereby contributing to foam cell formation, a hallmark of early atherosclerosis.[13-15]

Studies have revealed that salusins modulate human macrophage foam cell formation by decreasing the activity of ACAT-1. Salusin also reduces the expression of ACAT-1 gene in macrophages, so that cholesterol ester accumulation inside the cell is greatly reduced. Hence the conversion of macrophages to foam cell is retarded. Salusins were identified and extensively studied by Takuya Watanabe et al.[4]

They reported significant decrease in CE accumulation in Human Monocyte-Derived Macrophages on incubation with acetyl LDL and salusin alpha in cell culture, when compared to the macrophages incubated with acetyl LDL alone. They also found that salusin alpha decreased ACAT-1 expression in these cells in a concentration and time-dependent manner. Thus salusin alpha plays a preventive role against atherosclerosis.[16]

In our study, serum salusin alpha levels are significantly lower in CAD patients than in non-CAD patients. Our results are similar to the study performed by Du and colleagues. They investigated the relationship between serum salusin-α levels and the severity of coronary artery disease (CAD) by recruiting 91 controls and 172 CAD patients.[17] They showed that, in comparison to controls, serum salusin alpha levels in CAD patients were considerably lower. Serum salusin alpha levels were shown to be significantly lower in angiographically proven CAD patients, such as angina pectoris and Acute Coronary Syndrome(ACS) than healthy volunteers by Watanabe et al.[16]

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In our study we also observed that salusin alpha levels were significantly lower in patients with triple-vessel disease than those with double vessel disease and single-vessel disease. Our results are in accordance with the observations of Watanabe et al. they also reported lowest levels of salusin alpha in patients with triple vessel disease and inversely correlated salusin levels with the severity of atherosclerotic lesions on coronary arteriography among ACS patients.[4] Du et al. noted independent and negative correlation of serum salusin alpha levels with the severity of CAD given by Coronary Angiographic Index score(CAI score).[17]

In this study, CRP levels were high in CAD patients and negatively correlated with salusin levels. High CRP levels were shown to be independently associated with angiographically confirmed CAD patients by Auer et al.[12]

In a research done by Yılmaz et al., a significantly negative moderate connection was observed between salusin alpha levels and subjects with high PCE and SCORE2 cardiovascular risk scores (developed by American Heart Association and European Society of Cardiology) and this suggests that salusin alpha can have a prominent role in cardiovascular risk stratification also.[18]

To summarize, CAD patients had significantly lower serum salusin alpha levels compared to those without CAD. Moreover, serum salusin alpha levels were negatively correlated with severity of CAD. These findings indicated that salusin alpha is a reliable biomarker for detecting the development and progression of CAD.

CONCLUSION

The results of the study support the cardiovascular protective role of salusin alpha. Salusin alpha may be regarded as a promising biomarker for coronary atherosclerosis in both diagnosis and severity assessment. It might also be a potential marker for evaluating future CAD risk and a therapeutic target for the prevention of cardiovascular atherosclerotic disorders. Salusin-based treatments could emerge as a new line of therapy against atherosclerosis and its related diseases.

Limitations: The limitation of the study is small sample size and other cardiac bio markers like Troponins, hsCRP, Lp(a) were not measured. Large cohort studies are needed to confirm the clinical values of salusin alpha in different levels of CAD severity.

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