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Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study

Running title: Serum albumin and CAC progression

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ABSTRACT

OBJECTIVES This study evaluated the association between serum albumin levels and coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminemia at baseline.

DESIGN Observational cohort study

SETTING Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single ethnicity, multicenter, and observational registry were analyzed

PARTICIPANTS A total of 12344 Korean adults with baseline albumin level of ≥3.5 g/dL (51.7 ± 8.5 years; 84.3% male) were included. The median interscan period was 3.0 (2.0–4.8) years. All participants were stratified into three groups based on serum albumin tertile.

MAIN OUTCOMES MEASURES Association of serum albumin with the risk of CAC progression adjusted for relevant covariates was analyzed using logistic regression models. CAC progression was defined as a square root (√) transformed difference between the baseline and follow-up coronary artery calcium score (CACS) (Δ√transformed CACS) of ≥2.5. Annualized Δ√transformed CACS was defined as Δ√transformed CACS divided by inter-scan period.

RESULTS With increasing serum albumin tertiles, the annualized Δ√transformed CACS (I [lowest]: 0.16 (0−1.24) vs. II: 0 (0−1.09) vs. III [highest]: 0 (0−1.01)) and the incidence of CAC progression (I: 36.6% vs. II: 31.3% vs. III: 25.0%) were decreased despite higher prevalence of hypertension, diabetes, and hyperlipidemia (all P <0.05). Serum albumin levels were inversely related to the annualized Δ√transformed CACS and the risk of CAC progression among overall participants. This inverse association between serum albumin levels and the risk of CAC progression was consistently observed in baseline condition with CACS of 1–100 after adjusting for confounding factors.

CONCLUSIONS Serum albumin levels are inversely associated with CAC progression, especially in conditions with non-heavy CAC at baseline.

Key Words: albumin; atherosclerosis; coronary artery calcium score

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Longitudinal study with large sample size analyzing the data of multicenter and observational cohort registry
- Assessment of the association of serum albumin levels with coronary artery calcification (CAC) progression focusing on the baseline coronary artery calcium score
- Adjustment of traditional risk factors to evaluate independent relationship between serum albumin levels and the risk of CAC progression
- Difficulty in generalizing the results of current study because of the single-ethnicity participants

INTRODUCTION

Atherosclerotic coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide.[1] In asymptomatic populations, the coronary artery calcium score (CACS) has been used to stratify cardiovascular (CV) risk based on the evidence that the CACS provides strong prognostic information across age, sex, and ethnicity.[2–4] Moreover, the progression of coronary artery calcification (CAC) has additive prognostic values beyond traditional risk factors, particularly in the absence of heavy baseline CAC.[5,6] Thus, CACS determined using computed tomography (CT) has a substantial role in assessing CV risk for primary prevention.[7,8]

Albumin is a major protein accounting for more than half of the total serum composition. Previous studies have revealed that serum albumin has several physiological properties, including anti-oxidant, anti-inflammatory, and anti-platelet aggregation activities.[9–13] The normal range of serum albumin levels is defined to be within 3.5–5.5 g/dL in clinical practice. Recent evidence has suggested that low serum albumin levels are strongly associated with the increased risk of CHD and mortality beyond traditional risk factors.[14–17] However, data regarding the association between serum albumin levels and coronary atherosclerotic changes in asymptomatic adults are lacking. In addition, although previous studies have revealed that 1) the absence of CAC confers a low CV event risk[2,18] and 2) clinical risk factors are less predictive for the progression of coronary atherosclerosis compared to the baseline coronary plaque burden,[19] little is known regarding the association of serum albumin levels with the risk of CAC progression according to baseline CAC status. Therefore, the present study aimed to evaluate the association between serum albumin levels and the risk of CAC progression in an asymptomatic population of Korean adults without hypoalbuminemia at baseline.

METHODS

Study population and design

This study analyzed the data of Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single-ethnicity, multicenter, and observational registry with a self-referral setting for

asymptomatic subjects who underwent general health checkups at six healthcare centers in South Korea (Severance Cardiovascular Hospital; Samsung Medical Center; Seoul St. Mary's Hospital; Seoul National University Hospital; Seoul National University Bundang Hospital; Gangnam Heartscan Clinic). A total of 93,707 patients were enrolled in the registry between December 2012 and August 2016. Among these participants, 12353 who underwent at least two CAC scans with available serum albumin level data were identified. After excluding nine patients with hypoalbuminemia (serum albumin level <3.5 g/dL), 12344 were included in the present study. All data were obtained during visits to each healthcare center. Self-reported medical questionnaires were used to obtain information on medical histories. Information on the medical histories of hypertension, diabetes, hyperlipidemia, current smoking, and alcohol consumption status of each participant was systematically collected. Height, weight, and blood pressure were measured during healthcare center visits. Blood pressure was measured using an automatic manometer on the right arm after resting for at least 5 mins. Body mass index (BMI) was calculated as weight (kg)/height (m^2). All blood samples, including those for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, hemoglobin A1C (HbA1C), albumin, and creatinine were obtained after at least 8 h of fasting and analyzed. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, previous diagnosis of hypertension, or anti-hypertensive medication. Diabetes was defined as a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, a referral diagnosis of diabetes, or receiving anti-diabetic treatment. Hyperlipidemia was defined as a total cholesterol level of ≥240 mg/dL, a referral diagnosis of hyperlipidemia, or receiving anti-hyperlipidemic treatment. Obesity was defined as a BMI of ≥25.0 kg/m^2 following the Korean Society for the Study of Obesity Guidelines. Participants were categorized into three groups based on their serum albumin tertiles.

In this study, CACS was measured based on the scoring system previously described by Agatston et al.[20] The baseline CACS was divided into four groups: CACS of 0, 1–10, 11–100, and >100, respectively. The progression of CAC was defined as a difference ≥2.5 between the square roots (√) of

the baseline and follow-up CACS (Δ√transformed CACS),[5,21] considering interscan variability and the proportion of baseline CACS of 0 (56.2%). Annualized Δ√transformed CAC was defined as Δ√transformed CAC divided by interscan period. All computed tomography (CT) scans to assess CAC were obtained using >16-slice multidetector CT scanners (Siemens 16-slice Sensation [Siemens AG, Munich, Germany], Philips Brilliance 256 iCT [Philips Healthcare, Amsterdam, The Netherlands], Philips Brilliance 40 channel MDCT [Philips Healthcare], and GE 64-slice Lightspeed [GE Healthcare, Chicago, IL, USA]). Informed consent was obtained from all participants at each of centers. All methods were performed following relevant guidelines and regulations. The appropriate institutional review board of Severance Cardiovascular Hospital approved the study protocol (IRB No: 4-2014-0309).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or the median (interquartile range), and categorical variables are presented as absolute values and percentages. After checking the distribution status of independent variables, the one-way analysis of variance test or the Kruskal–Wallis test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables, as appropriate. Univariable regression analyses were performed to evaluate the relation of clinical variables with 1) annualized Δ√transformed CACS and 2) the risk of CAC progression. Subsequently, multiple logistic regression models were used to assess the association of serum albumin levels with the risk of CAC progression considering the baseline categorical CACS (Model 1, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, and alcohol consumption; Model 2, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine levels, baseline CACS, and interscan period). The forced entry method was used to enter the independent variables into the multiple regression models. All statistical analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$ in all analyses.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Baseline characteristics

Table 1 presents the baseline characteristics of the participants. The mean age of the participants was 51.7 ± 8.5 years, and 10,400 (84.3%) were men. The mean age decreased with increasing serum albumin tertiles. In contrast, the mean SBP, DBP, total cholesterol, triglyceride, LDL-C, fasting glucose, and HbA1C levels increased with increasing serum albumin levels. Similarly, the proportion of male sex and the prevalence of hypertension, diabetes, hyperlipidemia, and alcohol consumption increased with increasing serum albumin tertiles. Significant differences were not observed in the HDL-C and creatinine levels or in the prevalence of obesity and current smoking across the serum albumin tertiles.

Baseline and changes of CAC according to the serum albumin tertiles

The median interscan period was 3.0 (2.0–4.8) years. During follow-up, the mean changes of √transformed CACS and annualized √transformed CACS were decreased with increasing serum albumin tertiles. The incidence of the CAC progression in overall participants was 30.6%; it significantly decreased with increasing serum albumin tertiles. The incidence of CAC progression at baseline CACS of 0, 1–10, 11–100, and >100 was 13.0%, 57.6%, 50.4%, and 52.6%, respectively; the progression of CAC was less observed with increasing serum albumin tertiles in all baseline CACS groups (**Table 2**).

Association between clinical variables and CAC changes

Univariable linear regression analysis showed that age, male sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine, and baseline CACS

were positively related to the annualized Δ √transformed CACS; in contrast, serum albumin levels were inversely related to the annualized Δ √transformed CACS. In univariable logistic regression analysis, age, male sex, hypertension, diabetes, hyperlipidemia, obesity, alcohol consumption, serum creatinine level, and baseline CACS were associated with an increased risk of progression of CAC. However, elevated serum albumin levels were associated with a decreased risk of progression of CAC (**Table 3**). The results of the subgroup analysis of the estimated risk of serum albumin levels for CAC progression are presented in **Figure 1**.

Serum albumin levels and CAC progression according to baseline CACS

In multiple logistic regression models, serum albumin levels were significantly associated with the decreased risk of CAC progression in overall participants. Multiple linear regression models regarding the association between serum albumin levels and the annualized Δ √transformed CACS with consecutive adjustment of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS showed the consistent results (**Supplementary table 1**). According to the categorical CACS at baseline, model 1 showed that serum albumin levels were consistently associated with the risk of CAC progression in participants with baseline CACS of 1–10, 11–100, and >100 except that of 0. In the model 2, the significant association between serum albumin levels and the risk of CAC progression was observed in participants with baseline CACS of 1–10 and 11–100 (**Table 4**).

DISCUSSION

The present study observed that the incidence of CAC progression significantly decreased with increasing serum albumin levels despite a positive relation between serum albumin levels and the prevalence of hypertension, diabetes, and hyperlipidemia in asymptomatic adults without hypoalbuminemia at baseline. An inverse association between serum albumin levels and the risk of progression of CAC was consistently observed after adjusting for confounding factors. Notably, no

significant association between serum albumin levels and the risk of progression of CAC was identified in participants with CACS of 0 as well as in those with CACS of >100 at baseline. These results suggest that high serum albumin levels have a protective effect for the progression of CAC in asymptomatic adults, particularly in those with non-heavy CAC at baseline.

Several studies have reported a positive association between serum albumin levels and metabolic risk factors, such as blood pressure, insulin resistance, and lipid profile.[22–26] A recent cohort study from the Kuopio Ischaemic Heart Disease population found a linear and positive association between serum albumin levels and type 2 diabetes but not improving diabetes risk prediction during a mean follow-up of 20.4 years.[27] Similar to the previous data reported by Danesh et al. in their cross-sectional investigation of individuals with no history of CHD,[25] we observed that serum albumin levels were positively associated with SBP, DBP, and triglyceride and LDL-C levels among our participants without hypoalbuminemia at baseline (**Supplementary Table 2**). Although the mechanistic pathways for this association between serum albumin and metabolic disorders are unclear, a higher intake of dietary protein reportedly contributes to the positive association between serum albumin levels and metabolic syndrome.[28] Interestingly, despite a positive relation of serum albumin levels with metabolic abnormalities, numerous studies have shown that serum albumin levels are inversely related to the prognosis with a cardioprotective effect.[14–17]

It is well-known that serum albumin has an essential blood anti-oxidant property as well as physiological activities including anti-inflammation and anti-platelet aggregation.[9–13, 29] Based on these findings, several studies have evaluated the relation between serum albumin levels and subclinical atherosclerosis. The National Heart, Lung, and Blood Institute Family Heart Study reported that lower serum albumin levels were not associated with an increased risk of prevalent carotid atherosclerosis in men or women among 2,072 participants.[30] However, Ishizaka et al. demonstrated somewhat different results that higher serum albumin levels were inversely associated with the prevalence of early carotid atherosclerosis, although they were positively associated with the prevalence of metabolic syndrome in 8142 Japanese individuals.[26] To our knowledge, there are no studies with a large sample size on the

effect of serum albumin levels on coronary atherosclerotic changes, particularly in conditions without hypoalbuminemia. In this study, we observed an independent and inverse association between serum albumin levels and the progression of CAC in 12,344 asymptomatic participants with normal range of serum albumin levels beyond traditional risk factors, particularly in those with non-heavy CAC. This finding suggests that serum albumin has anti-atherogenic effects, irrespective of its positive association with metabolic abnormalities. However, the superior utility of high serum albumin levels for improving CV risk prediction over and above traditional risk factors is questionable. Also, the present study could not evaluate the association of serum albumin levels with non-calcified plaques or vulnerable plaques in coronary arteries because this data is based on the evaluation of CACS performed in asymptomatic adult population. Further large-scale prospective investigations are required to confirm these issues.

The Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter substudy with a mean follow-up of 5.9 ± 1.2 years recently identified that further prognostic benefit was not offered by coronary CT angiography findings over CACS and traditional risk factors in 1,226 asymptomatic adults.[31] Blaha et al.[18] reported that the absence of CAC predicted survival, with 10-year event rates of approximately 1% in 44,052 consecutive asymptomatic patients referred for CAC testing during a mean follow-up of 5.6 ± 2.6 years. Similarly, the Multi-Ethnic Study of Atherosclerosis study found consistent results among 6,722 participants during a median follow-up of 3.8 years, irrespective of racial and ethnic differences.[2] In this study, despite the independent and inverse association between serum albumin levels and the progression of CAC in overall participants, this phenomenon was not observed in participants without CAC or those with heavy CAC at baseline. These results indicate that 1) the absence of CAC reflects a low CV risk status, which is less affected by serum albumin levels in asymptomatic populations and 2) it is hard to predict the progression of CAC using specific biomarkers in condition with heavy CAC at baseline as previous studies have suggested.[32,33]

This study had some limitations. First, this study was performed in a healthy population who voluntarily participated in the health check-ups, which may have resulted in a selection bias. Second, this was a retrospective study, which may have been influenced by unidentified confounders. Third,

data on the participants' physical activity were unavailable. Fourth, we could not control for the effects of medications for hypertension, diabetes, and hyperlipidemia on the progression of CAC because of the observational design. Fifth, a sample size of baseline CACS >100 was relatively small compared to that of other baseline categorical CACS. Finally, this study included only a Korean population, which may limit generalization. Nevertheless, this study is unique in that we evaluated the association between serum albumin levels and the risk of CAC progression after considering baseline CAC status in an asymptomatic Asian population with normal serum albumin levels.

CONCLUSIONS

The current study observes that serum albumin levels have an independent and inverse association with the progression of CAC despite their positive relation with metabolic abnormalities in asymptomatic adults without hypoalbuminemia, particularly in those with non-heavy CAC at baseline. Considering the interaction between clinical variables and serum albumin levels regarding the risk of CAC progression in subgroup analysis, further prospective investigations to evaluate the significance of serum albumin levels for subclinical coronary atherosclerosis focusing on diabetes and hyperlipidemia should be necessary.

Contributiors

Study hypothesis and design: KBW and HJC. Data acquisitions: KBW, SYC, EJC, SHP, JS, HOJ, and HJC. Statistical analyses: KBW and HJC. Writing of the initial versions of the manuscript: KBW. Responsible for the overall content as the guarantor: HJC. All authors read, reviewed and provided feedback for the final manuscript.

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Competing interests

The authors declare no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and was approved by the appropriate institutional review board of Severance Cardiovascular Hospital (IRB No: 4-2014-0309). Participant consent is not required for the KOICA studies using purely observational data.

Data availability statement

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

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Table 1 Baseline characteristics

	Total (n = 12,344)	Tertiles of serum albumin			
		I (lowest) (n = 3,111) 3.5–4.2 g/dL	II (n = 5,241) 4.3–4.5 g/dL	III (highest) (n = 3,992) 4.6–5.5 g/dL	P
Age, years	51.7 ± 8.5	53.8 ± 8.5	52.1 ± 8.3	49.5 ± 8.3	<0.001
Male, n (%)	10400 (84.3)	2480 (79.7)	4382 (83.6)	3538 (88.6)	<0.001
SBP, mmHg	119.6 ± 15.0	117.3 ± 15.4	119.0 ± 15.1	122.1 ± 14.3	<0.001
DBP, mmHg	75.1 ± 10.6	73.2 ± 10.4	74.6 ± 10.6	77.1 ± 10.3	<0.001
BMI, kg/m^2	24.6 ± 2.8	24.5 ± 2.8	24.6 ± 2.7	24.6 ± 2.8	0.142
Hypertension	4024 (33.6)	961 (31.6)	1701 (33.6)	1362 (35.2)	0.007
Diabetes	1699 (13.8)	390 (12.5)	702 (13.4)	607 (15.2)	0.003
Hyperlipidemia	3459 (28.0)	777 (25.0)	1431 (27.3)	1251 (31.3)	<0.001
Obesity	5191 (42.2)	1285 (41.5)	2192 (42.0)	1714 (43.1)	0.362
Current smoking	3232 (28.5)	851 (29.6)	1341 (28.1)	1040 (28.2)	0.328
Alcohol consumption	7777 (81.3)	2145 (78.1)	3486 (81.9)	2146 (83.5)	<0.001
Total cholesterol, mg/dL	197.5 ± 34.0	190.9 ± 33.2	197.0 ± 32.8	203.3 ± 35.2	<0.001
Triglyceride, mg/dL	141.7 ± 89.3	133.2 ± 85.6	140.6 ± 85.2	149.7 ± 96.5	<0.001
HDL-C, mg/dL	53.3 ± 16.0	52.8 ± 14.2	53.4 ± 16.3	53.6 ± 16.7	0.102
LDL-C, mg/dL	122.0 ± 31.7	118.8 ± 30.4	122.2 ± 31.6	124.2 ± 32.7	<0.001
Fasting glucose, mg/dL	97.9 ± 20.4	95.7 ± 19.8	97.8 ± 20.7	99.6 ± 20.1	<0.001
HbA1C, %	5.68 ± 0.74	5.63 ± 0.74	5.66 ± 0.73	5.75 ± 0.74	<0.001
Creatinine, mg/dL	0.95 ± 0.17	0.95 ± 0.17	0.95 ± 0.17	0.95 ± 0.17	0.471
Albumin, g/dL	4.44 ± 0.27	4.10 ± 0.12	4.40 ± 0.08	4.75 ± 0.16	<0.001

Values are given as the mean ± standard deviation or number (%).

BMI, body mass index; DBP, diastolic blood pressure; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

384 **Table 2** Baseline and changes of CAC according to serum albumin tertiles

	Total (n = 12344)	Tertiles of serum albumin			
		I (lowest) (n = 3111) 3.5–4.2 g/dL	II (n = 5241) 4.3–4.5 g/dL	III (highest) (n = 3992) 4.6–5.5 g/dL	P
Baseline					
Categorical CACS					0.022
0	6937 (56.2)	1738 (55.9)	2930 (55.9)	2269 (56.8)	
1–10	1723 (14.0)	456 (14.7)	772 (14.7)	495 (12.4)	
11–100	2381 (19.3)	575 (18.5)	996 (19.0)	810 (20.3)	
>100	1303 (10.6)	342 (11.0)	543 (10.4)	418 (10.5)	
Follow-up					
Categorical CACS					<0.001
0	5771 (46.8)	1396 (44.9)	2391 (45.6)	1984 (49.7)	
1–10	1054 (8.5)	243 (7.8)	482 (9.2)	329 (8.2)	
11–100	2836 (23.0)	711 (22.9)	1212 (23.1)	913 (22.9)	
>100	2683 (21.7)	761 (24.5)	1156 (22.1)	766 (19.2)	
Δ √transformed CACS	0 (0−3.46)	0.39 (0−4.62)	0 (0−3.61)	0 (0−2.51)	<0.001
Annualized Δ √transformed CACS	0 (0−1.10)	0.16 (0−1.24)	0 (0−1.09)	0 (0−1.01)	<0.001
CAC progression, n (%)					
Overall	3780 (30.6)	1138 (36.6)	1643 (31.3)	999 (25.0)	<0.001
Categorical CACS at baseline					
0	902 (13.0)	271 (15.6)	401 (13.7)	230 (10.1)	<0.001
1–10	992 (57.6)	299 (65.6)	473 (61.3)	220 (44.4)	<0.001
11–100	1201 (50.4)	361 (62.8)	499 (50.1)	341 (42.1)	<0.001

>100	685 (52.6)	207 (60.5)	270 (49.7)	208 (49.8)	0.003

Values are given as the mean ± standard deviation, the median (interquartile range), or number (%).

CAC, coronary artery calcification; CACS, coronary artery calcium score.

Table 3 Association of individual clinical factor with CAC changes

	Annualized Δ√transformed CAC			CAC progression	
	β	SE	*p*	OR (95% CI)	P
Age, pre-1 years increase	0.038	0.002	<0.001	1.071 (1.066−1.076)	<0.001
Male	0.472	0.043	<0.001	2.628 (2.312−2.987)	<0.001
Hypertension	0.514	0.034	<0.001	2.112 (1.948−2.289)	<0.001
Diabetes	0.639	0.046	<0.001	2.269 (2.044−2.518)	<0.001
Hyperlipidemia	0.329	0.035	<0.001	1.722 (1.585−1.870)	<0.001
Obesity	0.259	0.032	<0.001	1.529 (1.415−1.652)	<0.001
Current smoking	0.108	0.037	0.004	1.088 (0.997−1.188)	0.059
Alcohol consumption	0.099	0.049	0.045	1.218 (1.091−1.360)	<0.001
Creatinine, per-1 mg/dL increase	0.827	0.093	<0.001	4.051 (3.211−5.109)	<0.001
Albumin, per-1 g/dL increase	-0.288	0.058	<0.001	0.442 (0.383−0.510)	<0.001
Baseline CACS, per-1 unit	0.001	0.001	<0.001	1.002 (1.002−1.003)	<0.001

CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval;, OR, odds ratio.

Table 4 Serum albumin levels (per-1 g/dL increase) and the risk of CAC progression according to baseline CACS

	OR (95% CI)	P
Overall		
Model 1	0.583 (0.487−0.696)	<0.001
Model 2	0.578 (0.483−0.691)	<0.001
CACS 0		
Model 1	0.901 (0.649−1.252)	0.535
Model 2	1.051 (0.736−1.502)	0.784
CACS 1−10		
Model 1	0.220 (0.141−0.344)	<0.001
Model 2	0.392 (0.234−0.658)	<0.001
CACS 11−100		
Model 1	0.286 (0.199−0.409)	<0.001
Model 2	0.580 (0.381−0.883)	0.011
CACS >100		
Model 1	0.360 (0.224−0.579)	<0.001
Model 2	0.688 (0.404−1.170)	0.167

P values for interaction between serum albumin levels and categorical CACS was 0.142.

CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; OR, odds ratio.

Models:1 = adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, and alcohol consumption; 2 = adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine levels, baseline CACS, and interscan period.

Figure legend

Figure 1 Subgroup analysis for the association between serum albumin levels and the risk of CAC progression

Supplemental materials

Supplementary table 1 Multiple regression models for the association between serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC

Supplementary table 2 Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

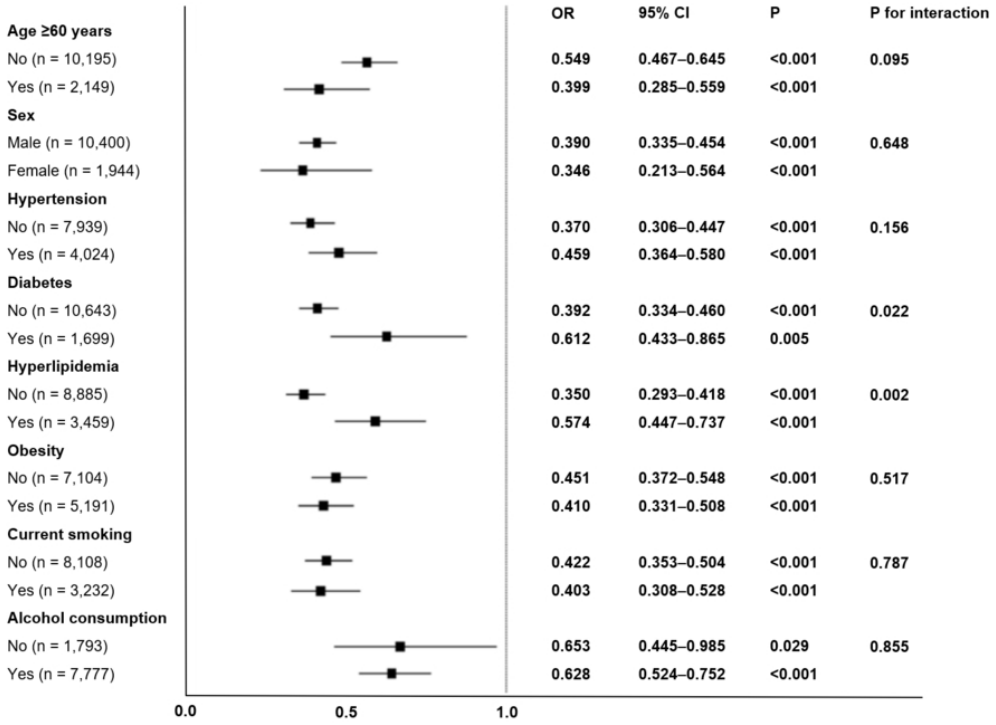

Figure 1

37x27mm (600 x 600 DPI)

Supplementary table 1 Multiple regression models for the association between serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC

	Annualized Δ√transformed CAC		
	β	SE	*p*
Model 1	-0.186	0.076	0.014
Model 2	-0.196	0.076	0.010

BMI, body mass index; CAC, coronary artery calcification; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Models:1 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption; 2 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS.

Supplementary table 2 Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

	Serum albumin levels		
Variables	β	SE	P
SBP, per 1-mmHg increase	0.002	0.001	<0.001
DBP, per 1-mmHg increase	0.004	0.001	<0.001
Triglyceride, per 1-mg/dL increase	0.001	0.001	<0.001
LDL-C, per 1-mg/dL increase	0.001	0.001	<0.001

DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

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Longitudinal assessment of serum albumin levels with the risk of coronary artery calcification progression in an asymptomatic population of Korean adults: An observational cohort study

Running title: Serum albumin and CAC progression

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ABSTRACT

Objectives This study evaluated the association between serum albumin levels and coronary artery calcification (CAC) progression in asymptomatic adults without hypoalbuminemia at baseline.

Design Observational cohort study

Setting Data from the Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single ethnicity, multicenter, and observational registry were analyzed.

Participants A total of 12344 Korean adults with baseline albumin level of ≥3.5 g/dL (51.7 ± 8.5 years; 84.3% male) were included. The median interscan period was 3.0 (2.0–4.8) years. All participants were stratified into three groups based on serum albumin tertile.

Primary and secondary outcome measures Association of serum albumin with the risk of CAC progression was analyzed using multivariate logistic regression models with adjustment of interscan period. CAC progression was defined as a square root (√) transformed difference between the baseline and follow-up coronary artery calcium score (CACS) (Δ√transformed CACS) of ≥2.5. Annualized Δ√transformed CACS was defined as Δ√transformed CACS divided by interscan period.

Results With increasing serum albumin tertiles, the annualized Δ√transformed CACS (I [lowest]: 0.16 (0−1.24) vs. II: 0 (0−1.09) vs. III [highest]: 0 (0−1.01)) and the incidence of CAC progression (I: 36.6% vs. II: 31.3% vs. III: 25.0%) were decreased despite higher prevalence of hypertension, diabetes, and hyperlipidemia (all P <0.05). Serum albumin levels were inversely related to the annualized Δ√transformed CACS and the risk of CAC progression among overall participants. After adjusting for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine levels, baseline CACS, and interscan period, this inverse association between serum albumin levels (per-1 g/dL increase) and the risk of CAC progression was consistently observed, especially in baseline CACS of 1–10 (odds ratio [OR]: 0.392, 95% confidence interval [CI]: 0.234−0.658) and 11–100 (OR: 0.580, 95% CI: 0.381−0.883) (all P <0.05).

Conclusions Serum albumin levels were inversely associated with the risk of CAC progression. This

phenomenon was predominantly observed in CACS of 1–100 at baseline.

Key Words: albumin; atherosclerosis; coronary artery calcium score

STRENGTHS AND LIMITATIONS OF THIS STUDY

- Longitudinal study with large sample size analyzing the data of multicenter and observational cohort registry
- Assessment of the association of serum albumin levels with coronary artery calcification (CAC) progression focusing on the baseline coronary artery calcium score
- Adjustment of traditional risk factors to evaluate independent relationship between serum albumin levels and the risk of CAC progression
- Difficulty in generalizing the results of current study because of the single-ethnicity participants

INTRODUCTION

Atherosclerotic coronary heart disease (CHD) is a major cause of morbidity and mortality worldwide.[1] In asymptomatic populations, the coronary artery calcium score (CACS) has been used to stratify cardiovascular (CV) risk based on the evidence that the CACS provides strong prognostic information across age, sex, and ethnicity.[2–4] Moreover, the progression of coronary artery calcification (CAC) has additive prognostic values beyond traditional risk factors, particularly in the absence of heavy baseline CAC.[5,6] Thus, CACS determined using computed tomography (CT) has a substantial role in assessing CV risk for primary prevention.[7,8]

Albumin is a major protein accounting for more than half of the total serum composition. Previous studies have revealed that serum albumin has several physiological properties, including anti-oxidant, anti-inflammatory, and anti-platelet aggregation activities.[9–13] The normal range of serum albumin levels is defined to be within 3.5–5.5 g/dL in clinical practice. Recent evidence has suggested that low serum albumin levels are strongly associated with the increased risk of CHD and mortality beyond traditional risk factors.[14–17] However, data regarding the association between serum albumin levels and coronary atherosclerotic changes in asymptomatic adults are lacking. In addition, although previous studies have revealed that 1) the absence of CAC confers a low CV event risk[2,18] and 2) clinical risk factors are less predictive for the progression of coronary atherosclerosis compared to the baseline coronary plaque burden,[19] little is known regarding the association of serum albumin levels with the risk of CAC progression according to baseline CAC status. Therefore, the present study aimed to evaluate the association between serum albumin levels and the risk of CAC progression in an asymptomatic population of Korean adults without hypoalbuminemia at baseline.

METHODS

Study population and design

This study analyzed the data of Korea Initiatives on Coronary Artery Calcification (KOICA) which is a retrospective, single-ethnicity, multicenter, and observational registry with a self-referral setting for

asymptomatic subjects who underwent general health checkups at six healthcare centers in South Korea (Severance Cardiovascular Hospital; Samsung Medical Center; Seoul St. Mary's Hospital; Seoul National University Hospital; Seoul National University Bundang Hospital; Gangnam Heartscan Clinic). A total of 93914 patients were enrolled in the registry between 2003 and August 2017. Among these participants, 12353 who underwent at least two CAC scans with available serum albumin level data were identified. After excluding nine patients with hypoalbuminemia (serum albumin level <3.5 g/dL), 12344 were included in the present study. All data were obtained during visits to each healthcare center. Self-reported medical questionnaires were used to obtain information on medical histories. Information on the medical histories of hypertension, diabetes, hyperlipidemia, current smoking, and alcohol consumption status of each participant was systematically collected. Height, weight, and blood pressure were measured during healthcare center visits. Blood pressure was measured using an automatic manometer on the right arm after resting for at least 5 mins. Body mass index (BMI) was calculated as weight (kg)/height (m^2). All blood samples, including those for total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), glucose, hemoglobin A1C (HbA1C), albumin, and creatinine were obtained after at least 8 h of fasting and analyzed. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg, previous diagnosis of hypertension, or anti-hypertensive medication. Diabetes was defined as a fasting glucose level of ≥126 mg/dL, HbA1C level of ≥6.5%, a referral diagnosis of diabetes, or receiving anti-diabetic treatment. Hyperlipidemia was defined as a total cholesterol level of ≥240 mg/dL, a referral diagnosis of hyperlipidemia, or receiving anti-hyperlipidemic treatment. Obesity was defined as a BMI of ≥25.0 kg/m^2 following the Korean Society for the Study of Obesity Guidelines. Participants were categorized into three groups based on their serum albumin tertiles.

In this study, CACS was measured based on the scoring system previously described by Agatston et al.[20] The baseline CACS was divided into four groups: CACS of 0, 1–10, 11–100, and >100, respectively. The progression of CAC was defined as a difference ≥2.5 between the square roots (√) of

the baseline and follow-up CACS (Δ√transformed CACS),[5,21] considering interscan variability and the proportion of baseline CACS of 0 (56.2%). Annualized Δ√transformed CAC was defined as Δ√transformed CAC divided by interscan period. All computed tomography (CT) scans to assess CAC were obtained using >16-slice multidetector CT scanners (Siemens 16-slice Sensation [Siemens AG, Munich, Germany], Philips Brilliance 256 iCT [Philips Healthcare, Amsterdam, The Netherlands], Philips Brilliance 40 channel MDCT [Philips Healthcare], and GE 64-slice Lightspeed [GE Healthcare, Chicago, IL, USA]). The informed written consent for procedures was obtained from all participants at each of centers. All methods were performed following relevant guidelines and regulations. The appropriate institutional review board of Severance Cardiovascular Hospital approved the study protocol (IRB No: 4-2014-0309).

Statistical analysis

Continuous variables are expressed as the mean ± standard deviation or the median (interquartile range), and categorical variables are presented as absolute values and percentages. After checking the distribution status of independent variables, the one-way analysis of variance test or the Kruskal–Wallis test was used for continuous variables, and the χ^2 test or Fisher's exact test was used for categorical variables, as appropriate. Univariable regression analyses were performed to evaluate the relation of clinical variables with 1) annualized Δ√transformed CACS and 2) the risk of CAC progression. Subsequently, multiple logistic regression models were used to assess the association of serum albumin levels with the risk of CAC progression considering the baseline categorical CACS (Model 1, adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, and interscan period; Model 2, Model 1 + serum creatinine levels and baseline CACS). The forced entry method was used to enter the independent variables into the multivariable regression analysis. All statistical analyses were performed using R (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was set at $p < 0.05$ in all analyses.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Baseline characteristics

Table 1 presents the baseline characteristics of the participants. The mean age of the participants was 51.7 ± 8.5 years, and 10,400 (84.3%) were men. The mean age decreased with increasing serum albumin tertiles. In contrast, the mean SBP, DBP, total cholesterol, triglyceride, LDL-C, fasting glucose, and HbA1C levels increased with increasing serum albumin levels. Similarly, the proportion of male sex and the prevalence of hypertension, diabetes, hyperlipidemia, and alcohol consumption increased with increasing serum albumin tertiles. Significant differences were not observed in the HDL-C and creatinine levels or in the prevalence of obesity and current smoking across the serum albumin tertiles.

Baseline and changes of CAC according to the serum albumin tertiles

The median interscan period was 3.0 (2.0–4.8) years. During follow-up, the mean changes of √transformed CACS and annualized √transformed CACS were decreased with increasing serum albumin tertiles. The incidence of the CAC progression in overall participants was 30.6%; it significantly decreased with increasing serum albumin tertiles. The incidence of CAC progression at baseline CACS of 0, 1–10, 11–100, and >100 was 13.0%, 57.6%, 50.4%, and 52.6%, respectively; the progression of CAC was less observed with increasing serum albumin tertiles in all baseline CACS groups (**Table 2**).

Association between clinical variables and CAC changes

Univariable linear regression analysis showed that age, male sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, serum creatinine, and baseline CACS

were positively related to the annualized Δ √transformed CACS; in contrast, serum albumin levels were inversely related to the annualized Δ √transformed CACS. In univariable logistic regression analysis, age, male sex, hypertension, diabetes, hyperlipidemia, obesity, alcohol consumption, serum creatinine level, and baseline CACS were associated with an increased risk of progression of CAC. The results regarding the risk of CAC progression related to glucose, triglyceride, HDL-C, and LDL-C are present in **Supplementary table 1.** Elevated serum albumin levels were associated with a decreased risk of progression of CAC (**Table 3**). The results of the subgroup analysis of the estimated risk of serum albumin levels for CAC progression are presented in **Figure 1**.

Serum albumin levels and CAC progression according to baseline CACS

In multiple logistic regression models, serum albumin levels were significantly associated with the decreased risk of CAC progression in overall participants. Multiple linear regression models regarding the association between serum albumin levels and the annualized Δ √transformed CACS with consecutive adjustment of age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS showed consistent results (**Supplementary table 2**). According to the categorical CACS at baseline, model 1 showed that serum albumin levels (per-1 g/dL increase) were consistently associated with the risk of CAC progression in participants with baseline CACS of 1–10 (odds ratio [OR]: 0.396, 95% confidence interval [CI]: 0.237−0.662; P <0.001) and 11–100 (OR: 0.603, 95% CI: 0.397−0.915; P = 0.018). In model 2, this association was consistently observed in participants with baseline CACS of 1–10 (OR: 0.392, 95% CI: 0.234−0.658; P <0.001) and 11–100 (OR: 0.580, 95% CI: 0.381−0.883; P = 0.011) (**Table 4**).

DISCUSSION

The present study observed that the incidence of CAC progression significantly decreased with increasing serum albumin levels despite a positive relation between serum albumin levels and the prevalence of hypertension, diabetes, and hyperlipidemia in asymptomatic adults without

hypoalbuminemia at baseline. An inverse association between serum albumin levels and the risk of progression of CAC was consistently observed after adjusting for confounding factors. Notably, no significant association between serum albumin levels and the risk of progression of CAC was identified in participants with CACS of 0 as well as in those with CACS of >100 at baseline. These results suggest that high serum albumin levels have a protective effect for the progression of CAC in asymptomatic adults, particularly in those with CACS of 1–100 at baseline.

Several studies have reported a positive association between serum albumin levels and metabolic risk factors, such as blood pressure, insulin resistance, and lipid profile.[22–26] A recent cohort study from the Kuopio Ischaemic Heart Disease population found a linear and positive association between serum albumin levels and type 2 diabetes but not improving diabetes risk prediction during a mean follow-up of 20.4 years.[27] Similar to the previous data reported by Danesh et al. in their cross-sectional investigation of individuals with no history of CHD,[25] we observed that serum albumin levels were positively associated with SBP, DBP, and triglyceride and LDL-C levels among our participants without hypoalbuminemia at baseline (**Supplementary Table 3**). Although the mechanistic pathways for this association between serum albumin and metabolic disorders are unclear, a higher intake of dietary protein reportedly contributes to the positive association between serum albumin levels and metabolic syndrome.[28] Interestingly, despite a positive relation of serum albumin levels with metabolic abnormalities, numerous studies have shown that serum albumin levels are inversely related to the prognosis with a cardioprotective effect.[14–17]

It is well-known that serum albumin has an essential blood anti-oxidant property as well as physiological activities including anti-inflammation and anti-platelet aggregation.[9–13, 29] Based on these findings, several studies have evaluated the relation between serum albumin levels and subclinical atherosclerosis. The NHLBI (National Heart, Lung, and Blood Institute) Family Heart Study reported that lower serum albumin levels were not associated with an increased risk of prevalent carotid atherosclerosis in men or women among 2,072 participants.[30] However, Ishizaka et al. demonstrated somewhat different results that higher serum albumin levels were inversely associated with the

prevalence of early carotid atherosclerosis, although they were positively associated with the prevalence of metabolic syndrome in 8142 Japanese individuals.[26] To our knowledge, there are no studies with a large sample size on the effect of serum albumin levels on coronary atherosclerotic changes, particularly in conditions without hypoalbuminemia. In this study, we observed an independent and inverse association between serum albumin levels and the progression of CAC in 12,344 asymptomatic participants with normal range of serum albumin levels beyond traditional risk factors, particularly in those with baseline CACS of 1–100. This finding suggests that serum albumin has anti-atherogenic effects, irrespective of its positive association with metabolic abnormalities. However, the superior utility of high serum albumin levels for improving CV risk prediction over and above traditional risk factors is questionable. Also, the present study could not evaluate the association of serum albumin levels with non-calcified plaques or vulnerable plaques in coronary arteries because this data is based on the evaluation of CACS performed in asymptomatic adult population. Further large-scale prospective investigations are required to confirm these issues.

The CONFRIM (Coronary CT Angiography Evaluation For Clinical Outcomes: An International Multicenter) substudy with a mean follow-up of 5.9 ± 1.2 years recently identified that further prognostic benefit was not offered by coronary CT angiography findings over CACS and traditional risk factors in 1,226 asymptomatic adults.[31] Blaha et al.[18] reported that the absence of CAC predicted survival, with 10-year event rates of approximately 1% in 44,052 consecutive asymptomatic patients referred for CAC testing during a mean follow-up of 5.6 ± 2.6 years. Similarly, the MESA (Multi-Ethnic Study of Atherosclerosis) study found consistent results among 6,722 participants during a median follow-up of 3.8 years, irrespective of racial and ethnic differences.[2] In this study, despite the independent and inverse association between serum albumin levels and the progression of CAC in overall participants, this phenomenon was not observed in participants without CAC or those with CACS >100 at baseline. These results indicate that 1) the absence of CAC reflects a low CV risk status, which is less affected by serum albumin levels in asymptomatic populations and 2) it is hard to predict the progression of CAC using specific biomarkers in condition with CACS of >100 at baseline alike

previous KOICA studies have suggested.[32,33]

The strength of this study is that the risk of CAC progression is assessed in asymptomatic adult population without heavy CAC at baseline. The proportion of CACS >400 was only 2.6% in the present study. According to the HNR (Heinz Nixdorf Recall) study,[6] repeat CT scans after 5 years provided the readjustment of risk attributable to the increased risk in baseline CACS <400. However, although a high CV risk was present in baseline CACS more than 400, additional evaluation of CACS could not add the prognostic value in this condition. Additionally, the PARADIGM (Progression of AtheRosclerotic PlAque DetermIned by Computed TomoGraphic Angiography Imaging) registry, baseline coronary plaque burden was the most important factor, when compared with clinical and laboratory factors, in identifying patients at the risk of rapid plaque progression.[19] These findings emphasize the significance of early detecting both the presence of subclinical coronary atherosclerosis and its progression.

This study had some limitations. First, this study was performed in asymptomatic adult population who voluntarily participated in the health check-ups, which may have resulted in a selection bias. Second, this was a retrospective study, which may have been influenced by unidentified confounders. Third, data on the participants' physical activity was unavailable. Fourth, we could not control the effects of medications for hypertension, diabetes, and hyperlipidemia on the progression of CAC because of the observational design. Fifth, the sample size of baseline CACS >100 was relatively small compared to that of other baseline categorical CACS. Sixth, different CT scanners were used among the participating centers; however, all participants were examined using the same CT scanner with identical ECG-triggering method during the initial and follow-up image acquisitions. Also, CAC progression was defined with the SQRT method, considering interscan variability in the present study.[5,21] Seventh, the present study did not perform the variability analysis based on the strong evidence regarding variability and reproducibility of CACS measurement.[21,34,35] Eighth, we only evaluated the association of the baseline serum albumin levels with CAC progression; any consecutive serum albumin changes during follow-up were not confirmed. Finally, this study included only a Korean population, which may limit generalization. Nevertheless, this study is unique in that we evaluated the association

between serum albumin levels and the risk of CAC progression after considering baseline CAC status in an asymptomatic Asian population with normal serum albumin levels.

CONCLUSIONS

The current study observes that serum albumin levels have an independent and inverse association with the progression of CAC despite their positive relation with metabolic abnormalities in asymptomatic adults without hypoalbuminemia, particularly in those with CACS of 1–100 at baseline. Considering the interaction between clinical variables and serum albumin levels regarding the risk of CAC progression in subgroup analysis, further prospective investigations to evaluate the significance of serum albumin levels for subclinical coronary atherosclerosis focusing on diabetes and hyperlipidemia should be necessary.

Contributiors

Study hypothesis and design: KBW and HJC. Data acquisitions: KBW, SYC, EJC, SHP, JS, HOJ, and HJC. Statistical analyses: KBW and HJC. Writing of the initial versions of the manuscript: KBW. Responsible for the overall content as the guarantor: HJC. All authors read, reviewed and provided feedback for the final manuscript.

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Competing interests

The authors declare no competing interests.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Ethics approval

This study involves human participants and was approved by the appropriate institutional review board of Severance Cardiovascular Hospital (IRB No: 4-2014-0309).

Data availability statement

The datasets used and analyzed in the current study are available from the corresponding author upon reasonable request.

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Table 1 Baseline characteristics

	Total (n = 12,344)	Tertiles of serum albumin			
		I (lowest) (n = 3,111) 3.5–4.2 g/dL	II (n = 5,241) 4.3–4.5 g/dL	III (highest) (n = 3,992) 4.6–5.5 g/dL	P
Age, years	51.7 ± 8.5	53.8 ± 8.5	52.1 ± 8.3	49.5 ± 8.3	<0.001
Male, n (%)	10,400 (84.3)	2,480 (79.7)	4,382 (83.6)	3,538 (88.6)	<0.001
SBP, mmHg	119.6 ± 15.0	117.3 ± 15.4	119.0 ± 15.1	122.1 ± 14.3	<0.001
DBP, mmHg	75.1 ± 10.6	73.2 ± 10.4	74.6 ± 10.6	77.1 ± 10.3	<0.001
BMI, kg/m^2	24.6 ± 2.8	24.5 ± 2.8	24.6 ± 2.7	24.6 ± 2.8	0.142
Hypertension	4,024 (33.6)	961 (31.6)	1,701 (33.6)	1,362 (35.2)	0.007
Diabetes	1,699 (13.8)	390 (12.5)	702 (13.4)	607 (15.2)	0.003
Hyperlipidemia	3,459 (28.0)	777 (25.0)	1,431 (27.3)	1251 (31.3)	<0.001
Obesity	5,191 (42.2)	1,285 (41.5)	2,192 (42.0)	1,714 (43.1)	0.362
Current smoking	3,232 (28.5)	851 (29.6)	1,341 (28.1)	1,040 (28.2)	0.328
Alcohol consumption	7,777 (81.3)	2,145 (78.1)	3,486 (81.9)	2,146 (83.5)	<0.001
Total cholesterol, mg/dL	197.5 ± 34.0	190.9 ± 33.2	197.0 ± 32.8	203.3 ± 35.2	<0.001
Triglyceride, mg/dL	141.7 ± 89.3	133.2 ± 85.6	140.6 ± 85.2	149.7 ± 96.5	<0.001
HDL-C, mg/dL	53.3 ± 16.0	52.8 ± 14.2	53.4 ± 16.3	53.6 ± 16.7	0.102
LDL-C, mg/dL	122.0 ± 31.7	118.8 ± 30.4	122.2 ± 31.6	124.2 ± 32.7	<0.001
Fasting glucose, mg/dL	97.9 ± 20.4	95.7 ± 19.8	97.8 ± 20.7	99.6 ± 20.1	<0.001
HbA1C, %	5.68 ± 0.74	5.63 ± 0.74	5.66 ± 0.73	5.75 ± 0.74	<0.001
Creatinine, mg/dL	0.95 ± 0.17	0.95 ± 0.17	0.95 ± 0.17	0.95 ± 0.17	0.471
Albumin, g/dL	4.44 ± 0.27	4.10 ± 0.12	4.40 ± 0.08	4.75 ± 0.16	<0.001

Values are given as the mean ± standard deviation or number (%).

BMI, body mass index; DBP, diastolic blood pressure; HbA1C, hemoglobin A1C; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

413 **Table 2** Baseline and changes of CAC according to serum albumin tertiles

	Total (n = 12,344)	Tertiles of serum albumin			
		I (lowest) (n = 3,111) 3.5–4.2 g/dL	II (n = 5,241) 4.3–4.5 g/dL	III (highest) (n = 3,992) 4.6–5.5 g/dL	P
Baseline					
Categorical CACS					0.022
0	6,937 (56.2)	1,738 (55.9)	2,930 (55.9)	2,269 (56.8)	
1–10	1,723 (14.0)	456 (14.7)	772 (14.7)	495 (12.4)	
11–100	2,381 (19.3)	575 (18.5)	996 (19.0)	810 (20.3)	
>100	1,303 (10.6)	342 (11.0)	543 (10.4)	418 (10.5)	
Follow-up					
Categorical CACS					<0.001
0	5,771 (46.8)	1,396 (44.9)	2,391 (45.6)	1,984 (49.7)	
1–10	1054 (8.5)	243 (7.8)	482 (9.2)	329 (8.2)	
11–100	2,836 (23.0)	711 (22.9)	1,212 (23.1)	913 (22.9)	
>100	2,683 (21.7)	761 (24.5)	1,156 (22.1)	766 (19.2)	
Δ √transformed CACS	0 (0−3.46)	0.39 (0−4.62)	0 (0−3.61)	0 (0−2.51)	<0.001
Annualized Δ √transformed CACS	0 (0−1.10)	0.16 (0−1.24)	0 (0−1.09)	0 (0−1.01)	<0.001
CAC progression, n (%)					
Overall	3,780 (30.6)	1,138 (36.6)	1,643 (31.3)	999 (25.0)	<0.001
Categorical CACS at baseline					
0	902 (13.0)	271 (15.6)	401 (13.7)	230 (10.1)	<0.001
1–10	992 (57.6)	299 (65.6)	473 (61.3)	220 (44.4)	<0.001
11–100	1201 (50.4)	361 (62.8)	499 (50.1)	341 (42.1)	<0.001

>100	685 (52.6)	207 (60.5)	270 (49.7)	208 (49.8)	0.003

Values are given as the median (interquartile range), or number (%).

CAC, coronary artery calcification; CACS, coronary artery calcium score.

Table 3 Association of individual clinical factor with CAC changes

	Annualized Δ√transformed CAC			CAC progression	
	β	SE	*p*	OR (95% CI)	P
Age, pre-1 years increase	0.038	0.002	<0.001	1.071 (1.066−1.076)	<0.001
Male	0.472	0.043	<0.001	2.628 (2.312−2.987)	<0.001
Hypertension	0.514	0.034	<0.001	2.112 (1.948−2.289)	<0.001
Diabetes	0.639	0.046	<0.001	2.269 (2.044−2.518)	<0.001
Hyperlipidemia	0.329	0.035	<0.001	1.722 (1.585−1.870)	<0.001
Obesity	0.259	0.032	<0.001	1.529 (1.415−1.652)	<0.001
Current smoking	0.108	0.037	0.004	1.088 (0.997−1.188)	0.059
Alcohol consumption	0.099	0.049	0.045	1.218 (1.091−1.360)	<0.001
Creatinine, per-1 mg/dL increase	0.827	0.093	<0.001	4.051 (3.211−5.109)	<0.001
Albumin, per-1 g/dL increase	-0.288	0.058	<0.001	0.442 (0.383−0.510)	<0.001
Baseline CACS, per-1 unit increase	0.001	0.001	<0.001	1.002 (1.002−1.003)	<0.001

CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; OR, odds ratio.

Table 4 Serum albumin levels (per-1 g/dL increase) and the risk of CAC progression according to baseline CACS

	OR (95% CI)	P
Overall		
Model 1	0.813 (0.671−0.985)	<0.034
Model 2	0.822 (0.677−0.997)	<0.046
CACS 0		
Model 1	1.001 (0.702−1.426)	0.997
Model 2	1.051 (0.736−1.502)	0.784
CACS 1−10		
Model 1	0.396 (0.237−0.662)	<0.001
Model 2	0.392 (0.234−0.658)	<0.001
CACS 11−100		
Model 1	0.603 (0.397−0.915)	0.018
Model 2	0.580 (0.381−0.883)	0.011
CACS >100		
Model 1	0.696 (0.409−1.182)	0.179
Model 2	0.688 (0.404−1.170)	0.167

P values for interaction between serum albumin levels and categorical CACS was 0.142.

CAC, coronary artery calcification; CACS, coronary artery calcium score; CI, confidence interval; OR, odds ratio. Models:1 = adjusted for age, sex, hypertension, diabetes, hyperlipidemia, obesity, current smoking, alcohol consumption, and interscan period; 2 = Model 1 + adjusted for serum creatinine levels and baseline CACS.

Figure legend

Figure 1 Subgroup analysis for the association between serum albumin levels (per-1 g/dL increase) and the risk of CAC progression

Supplemental materials

Supplementary table 1 Univariable linear regression analysis for the risk of CAC progression related to the levels of glucose, triglyceride, HDL-C, and LDL-C

Supplementary table 2 Multiple regression models for the association between serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC

Supplementary table 3 Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

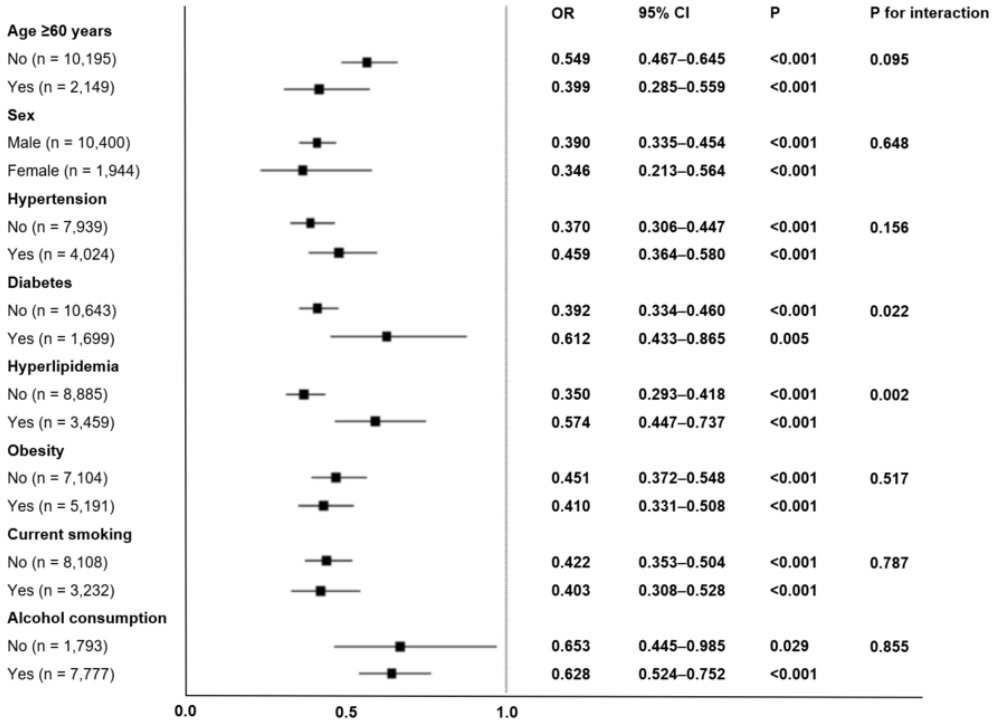

Figure 1

37x27mm (600 x 600 DPI)

Supplementary table 1 Univariable linear regression analysis for the risk of CAC progression related to the levels of glucose, triglyceride, HDL-C, and LDL-C

	CAC progression		
Variables	OR	95% CI	P
Glucose, per 1-mg/dL increase	1.013	1.011−1.015	<0.001
Triglyceride, per 1-mg/dL increase	1.002	1.002−1.003	<0.001
HDL-C, per 1-mg/dL increase	0.994	0.992−0.997	<0.001
LDL-C, per 1-mg/dL increase	1.005	1.003−1.006	<0.001

CAC, coronary artery calcification; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio.

Supplementary table 2 Multiple regression models for the association between serum albumin levels (per-1 g/dL increase) and the annualized Δ√transformed CAC

	Annualized Δ√transformed CAC		
	β	SE	*p*
Model 1	-0.186	0.076	0.014
Model 2	-0.196	0.076	0.010

BMI, body mass index; CAC, coronary artery calcification; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

Models:1 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption; 2 = adjusted for age, sex, SBP, fasting glucose, triglyceride, LDL-C, BMI, current smoking, and alcohol consumption, serum creatinine levels, and baseline CACS.

Supplementary table 3 Univariable linear regression analysis for the association of serum albumin levels (per-1 g/dL increase) with and clinical variables

	Serum albumin levels		
Variables	β	SE	P
SBP, per 1-mmHg increase	0.002	0.001	<0.001
DBP, per 1-mmHg increase	0.004	0.001	<0.001
Triglyceride, per 1-mg/dL increase	0.001	0.001	<0.001
LDL-C, per 1-mg/dL increase	0.001	0.001	<0.001

DBP, diastolic blood pressure; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure.