Serum Adiponectin Level as a Biomarker of Coronary Artery Calcification and Severe Coronary Lesions

La concentración sérica de adiponectina como biomarcador de calcificación arterial coronaria y lesiones coronarias graves

To the Editor,

Coronary artery calcification (CAC) is an independent risk factor for coronary atherosclerosis and belongs to the type VII category on Stary's classification.[1] Because CAC strongly predicts adverse cardiovascular events, and coronary disease is a major cause of death, the problem is of obvious clinical importance. Despite the heterogeneous extent of calcification among atherosclerotic patients, CAC can be easily and noninvasively quantified by cardiac computed tomography (CCT).[2] Little information is available, however, on the underlying mechanisms of plaque calcification.

Plasma adiponectin appears to exert cardioprotective effects, showing differences in both genders–probably influenced by testosterone levels–and distinct pathological conditions. Low adiponectin levels seem to be associated with CAC progression and susceptibility to plaque rupture, although the paradoxical role of adiponectin depending on the type of patients is increasingly debated.[3]

To highlight the role of adiponectin and testosterone in CAC and coronary lesions, we recruited stable ambulatory patients undergoing CCT for chest pain of possible coronary origin.

Blood samples were obtained (immediately before performing CCT) by venepuncture in overnight fasting conditions. The samples underwent standard processing and researchers performed a blind analysis. Serum testosterone (detection limit 0.025 ng/mL, 8.4% interassay variation) and adiponectin (detection limit 0.195 ng/mL, 8.6% interassay variation) levels were respectively determined by electrochemiluminescence (Roche) and by enzyme-linked immunosorbent assay (R&D Systems). Calcium score was determined using 64-slice CT (General Electric Healthcare). The total calcium content was quantified by a standardized protocol based on the Agatston score ($\geq$400 Hounsfield units indicated a high calcification score). Severe lesions (stenosis$\geq$70% in 1 of the main coronary arteries) were assessed by coronary angiography. The statistical analysis was performed using SPSS 15.0 for Windows.

We prospectively included 139 patients, aged 58.5 (11.4) years; 46.8% were males. A total of 17.3% of the patients had a high calcification score and 18.7% had severe coronary lesions (Table 1). A receiver operating characteristic (ROC) curve was calculated and a higher calcium score was associated with lower adiponectin levels but the predictive value for adiponectin was modest (c-statistic=0.65; 95% confidence interval [95%CI], 0.53-0.77; *P*=.021), the optimal cut-off being 8418 μg/mL, with a positive predictive value of 31% and a negative predictive value of 93%. Univariate analysis also showed that age and diabetes mellitus were associated with calcium score. After adjustment for confounding factors in the multivariate analysis (those presenting *P*-values<.15 in the univariate analysis), age, low adiponectin levels and high testosterone levels were independently associated with the calcification score.

Additionally, adiponectin levels modestly predicted the presence of severe coronary lesion (c-statistic=0.68; 95%CI, 0.57-0.79, *P*=.004) in the ROC curve with an optimal cut-off of 8005 μg/mL, a positive predictive value of 32% and a negative predictive value of 90%. In addition to well-recognized atherosclerosis risk factors such as smoking and diabetes mellitus, high testosterone levels, male gender and high CAC were also significantly associated with severe coronary lesions in the univariate analysis. Only low adiponectin levels, high CAC and high testosterone concentrations remained as independent variables predicting severe coronary lesions after the multivariate analysis was performed (including variables with *P*-values of<.15 in the univariate analysis) (Table 2). Notably, high testosterone levels were independently associated with severe coronary lesions, even after adjusting for clinical and demographic features, including the category of gender. In addition, adiponectin levels were negatively correlated with serum testosterone levels.

However, the inclusion of adiponectin to the integrated discrimination improvement (IDI) index and ROC curve calculations failed to produce statistical improvement within the model for the calcium score *P*=.061 or for severe angiographic lesions (*P*=.056).

Our data are in agreement with previous reports performed in asymptomatic patients with subclinical coronary artery disease in whom CAC progression was associated with low circulating adiponectin levels.[4] We established a cut-off point for serum adiponectin levels, with concentrations below this cut-off may indicate both CAC (<8418 μg/mL) and severe coronary lesions (<8005 μg/mL). Importantly, we found a strong association between among high CAC score and the presence of severe coronary lesions, supporting previous data on calcification in the atherosclerotic process. Moreover, the data on the protective or deleterious role of testosterone in coronary disease are conflicting and strong evidence indicates that testosterone suppresses adiponectin production.[5] The association data also suggest that testosterone may increase coronary lesion severity, probably by reducing circulating adiponectin levels. Thus, testosterone-reduced adiponectin levels may lead to CAC development and subsequently increase coronary lesion severity.

Serum adiponectin level determination in patients at low cardiovascular risk could help their management as biomarker of

Table 1
Baseline and Demographic Characteristics of the 139 Included Patients

Age, years	58.5±11.4
Male sex	65 (46.8)
Hypertension	102 (73.5)
Diabetes mellitus	31 (22.7)
Hypercholesterolemia	68 (50.0)
Smoking	28 (21.2)
Body mass index, kg/m^2	28.27 [25.95-31.94]
Creatinine, mg/dL	0.86 [0.72-1.00]
Creatinine clearance, mL/min	95.98 [77.68-121.38]
HDL-C, mg/dL	49.5±18.6
LDL-C, mg/dL	117.6±37.7
Triglycerides, mg/dL	117.0 [85.5-156.5]
Coronary calcification score (Agatston Score)	23 [0-197]
High calcification score	24 [17.3]
Severe coronary lesions	26 [18.7]
Adiponectin, μg/mL	9.445 [5.441-17.587]
Testosterone, ng/mL	0.97 [0.17-3.28]

HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol.
Data are expressed as no. (%), mean±standard deviation, or median [interquartile range].

Table 2
Association of the Calcification Score (Linear Regression Analysis) and Severe Coronary Lesions (Stenosis >70% in 1 of the Main Coronary Arteries; Logistic Analysis, Conditional Mode) With Clinical Features

	Calcification score						Severe coronary lesions			
	Univariate analysis			Multivariate analysis			Univariate analysis		Multivariate analysis	
Condition	B	95%CI	*P*	B	95%CI	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
Age	9.16	2.48 to 15.84	**.008**	10.49	3.39 to 17.60	**.004**	1.01 (0.97-1.05)	.567		
Male sex	−124.18	−278.99 to 30.63	.115	29.08	−157.01 to 215.17	.758	6.59 (2.31-18.75)	<**.001**	2.77 (0.48 to 16.15)	.111
HT	139.02	−37.29 to 315.34	.121	7.24	−182.24 to 196.71	.940	1.70 (0.59-4.90)	.325		
DM	213.89	28.66 to 399.11	**.024**	130.25	−57.34 to 317.83	.172	2.68 (1.07-4.73)	**.036**	3.71 (0.94 to 14.67)	.084
DLP	72.84	−84.68 to 230.36	.362				1.55 (0.65-3.67)	.321		
Smoking	−43.70	−176.16 to 88.77	.515				2.29 (1.21-4.32)	**.011**	1.74 (0.66 to 4.45)	.219
Testosterone 4th Q[a]	147.78	−46.31 to 341.876	.134	191.31	4.58 to 378.05	**.045**	3.60 (1.41-9.20)	**.008**	10.44 (2.42 to 45.05)	**.002**
Low Acrp30 levels[b]	−244.25	−396.849 to −91.659	**.002**	−284.90	−475.58 to −94.21	**.004**	4.04 (1.64-9.93)	**.002**	6.98 (1.84 to 26.50)	**.004**
High calcification score[c]							21.00 (7.22-61.11)	<**.001**	28.67 (7.33 to 112.19)	<**.001**

95%CI, 95% confidence interval; Acrp, adipocyte complement-related protein, adiponectin; B, unstandardized coefficient; DLP, dyslipidemia defined as low-density lipoprotein-cholesterol level >130 mg/dL or patient under lipid-lowering therapy; DM, diabetes mellitus; HT, hypertension; OR, odds ratio; Q, quartile.
[a] The association study was performed including testosterone level as a qualitative variable: The 4th quartile was compared with the other 3 quartiles in each gender category.
[b] Low Acrp levels is a qualitative variable. The association study was performed by comparing levels above and below the cut-off point for calcification (<8418 μg/mL) or severe coronary lesion (<8005 μg/mL) in each case.
[c] A high calcification score is a qualitative variable. The association study was performed by comparing levels above and below the cut-off point for a high calcium score (≥400 in the Agatston score).

subclinical atherosclerosis. Since it is easy to validate, such determination could be evaluated as a plausible alternative to the expensive recommendation proposed in the SHAPE (Screening for Heart Attack Prevention and Education) study[6] for noninvasive and generalized screening for asymptomatic subclinical atherosclerosis. Nonetheless, we assessed a cohort–based study and therefore our results might be specific to the patient population included and their management. Moreover, despite the statistical significance found, we consider that the limited sample size could have led to bias in our results. ROC curves with or without adiponectin and the IDI index did not show statistical improvement for the model including adiponectin. Consequently, larger cohorts and different populations are needed to validate the present findings. We are aware that more research including larger series of patients could be useful in daily clinical practice.

We conclude that low adiponectin levels, high testosterone levels and aging are associated with CAC severity in stable ambulatory patients undergoing CCT for chest pain of possible coronary origin. Additionally, CAC, low adiponectin levels, testosterone levels and smoking seem to be associated with the severity of coronary lesions.

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CONFLICTS OF INTEREST

None declared.

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