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Relation between homocysteine-to-adropin ratio and severity of coronary artery disease

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ABSTRACT

Purpose: This study aimed to uncover if homocysteine (Hcy) adropin balance expressed by homocysteine/adropin ratio (HAR) is related to severity of disease in coronary artery disease (CAD) patients.

Materials & Methods: The present cross-sectional study 50 consecutive patients with low/intermediate CAD severity and other 50 patients with severe CAD. Hcy and adropin levels were assessed using commercially available kits.

Results: Patients with low/moderate severity CAD expressed significantly lower HAR. According to HAR, all patients were classified into those with low HAR (<median) and high HAR (≥HAR). Comparison between these subgroups revealed that patients with low HAR had significantly lower number of affected vessels and lower SYNTAX score. Also, it was found that HAR is correlated with SYNTAX scores in all patients and in patients with severe CAD.

Conclusions: Hcy and adropin levels are interlinked, HAR can effectively distinguish severe from non-severe CAD.

Keywords: coronary artery disease, homocysteine, adropin, homocysteine/adropin ratio, SYNTAX score

INTRODUCTION

Coronary artery disease (CAD) remains one of the leading causes of mortality worldwide in spite of the magnificent progress achieved in diagnosis and management. Traditional risk factors for CAD include physical inactivity, hypertension, smoking, older age, obesity, physical inactivity and diabetes and dyslipidemia [1]. CAD is classically attributed to atherosclerosis and obstruction of epicardial coronary arteries. However, in patients with non-obstructive CAD, underlying microvascular pathology is suggested [2].

Multiple metabolic derangements had been linked to CAD. These include, among others, metabolic syndrome [3-5], dysfunctional lipid biology [6], impaired glucose homeostasis [7], disturbed carnitine metabolism [8], and hyperhomocysteinemia [9].

Homocysteine (Hcy) is an essential sulfur-containing amino acid produced during conversion of methionine to cysteine in the liver [10]. Altered Hcy metabolism is usually assessed using serum/plasma Hcy levels. However, many studies utilized combined metabolic ratios integrating Hcy with other biometabolic factors, e.g., methionine to Hcy ratio [11], urine Hcy/creatinine [12], and cysteine/Hcy [13].

Hyperhomocysteinemia is related to endothelial damage, atherosclerosis and CAD [14]. This condition may result from dietary vitamin B6 and/or folate deficiency [15]. Targeting Hcy metabolism was proposed as a new approach for person-tailored disease prevention, prognosis and management [16].

Adropin is a relatively new 76-amino acid-peptide hepatokine encoded by the energy balance gene *(enho)* and expressed primarily in the liver besides other tissues including pancreas, heart and vascular tissues [17]. Its roles in these tissues entail fatty acid metabolism, energy balance and glucose homeostasis [18]. Clinical data showed adropin levels are markedly diminished in variable inflammatory conditions expressing negative correlations with proinflammatory mediators [19]. Furthermore, growing body of evidence suggests a cardinal regulatory role of adropin in multiple cardiovascular pathologies [20].

Interestingly, it was reported inverse correlation between adropin and Hcy levels in CAD patients [21]. It is documented that the vasoprotective functions of adropin are primary related to its influence on nitric oxide (NO) synthesis [22]. Alongside, many studies highlighted the contribution of Hcy to

decreased NO production and impaired signaling in coronary microvasculature [23-26]. In this context, we aimed to uncover if Hcy adropin balance expressed as homocysteine/adropin ratio (HAR) is related to severity of disease in CAD patients.

MATERIALS & METHODS

The present cross-sectional study included 100 patients with CAD diagnosed according to recommended coronary angiography data. Patients comprised consecutive 50 patients with low/intermediate CAD severity and other 50 patients with severe CAD. CAD severity was categorized according to SYNTAX score. It is an angiographic grading tool for complexity and severity of CAD. Scores <33 indicates low/moderate severity while scores ≥33 indicates high severity disease [27]. Patients were excluded if they had malignant neoplasms, active infections, advanced hepatic or renal insufficiency. All participants provided full clinical history and had meticulous general and cardiac examination. Additional cardiac work up included 12 lead electrocardiogram and transthoracic echocardiography. Coronary angiography was performed and retrieved data were analyzed and interpreted by independent experienced cardiologists before calculation of SYNTAX score. Laboratory work up included complete lipid profile, serum uric acid and glycated hemoglobin (HbA1c). Hcy (Cat. No. E3292Hu) and adropin (Cat. No. E3231Hu) levels were assessed using commercially available kits (Bioassay Technology Laboratory Inc., Shanghai, China).

Data obtained from the present study were presented as number and percent, mean (M) and standard deviation (SD) or median and interquartile range (IQR). Comparative analysis was performed using Chi-square test for categorical data and t test or Mann-Whitney U test for numerical data as appropriate. Correlation analysis was achieved using Pearson's correlation coefficient. Receiver operator characteristic (ROC) curve analysis was used to determine diagnostic performance of investigated markers. All statistical operations were computed using SPSS version 26.0 with p-value less than 0.05 considered statistically significant.

RESULTS

The present study included 50 patients with low/moderate CAD and 50 patients with severe CAD. Patients included 53 males and 47 females with an age of 58.8±9.5 years (range: 42.0-77.0). Comparison between the studied groups regarding the clinical and laboratory data revealed that patients in the former group are significantly younger (55.2±9.8 vs. 62.3±7.8 years, p<0.001) with lower frequency of hypertension (48.0% vs. 90.0%, p<0.001), lower serum cholesterol levels (188.9±43.4 vs. 211.9±33.2 mg/dL, p=0.004), lower LDL levels (123.7±52.4 vs. 166.4±31.7 mg/dL, p<0.001) and lower uric acid levels (4.5±1.4 vs. 5.4±0.9 mg/dL, p<0.001). In addition, patients with low/moderate CAD expressed significantly lower Hcy levels (median [IQR]: 10.4 [7.1-24.9] vs. 28.0 [11.4-40.0] µmol/L, p<0.001) and higher adropin levels (median [IQR]: 17.8 [8.9-26.0] vs. 9.3 [5.3-17.6] pg/mL) and significantly higher lower HAR (median [IQR]: 0.90 [0.31-1.61] vs. 3.05 [1.36-5.94], p<0.001) (**Table 1**).

According to HAR, all patients were classified into those with low HAR (<median) and high HAR (≥HAR). Comparison between subgroups revealed that patients with low HAR had significantly lower cholesterol levels (178.1±35.2 vs. 222.8±31.5 mg/dL, p<0.001), lower triglycerides levels (164.4±55.9 vs. 210.4±71.2, p=0.001), lower LDL levels (126.2±52.9 vs. 164.0±34.1 mg/dL, p<0.001) higher HDL levels (38.2±4.7 vs. 35.7±5.1 mg/dL, p=0.014) and lower UA levels (4.7±1.1 vs. 5.2±1.3 mg/dL, p=0.02). They had significantly lower number of affected vessels (2.7±1.2 vs. 3.1±0.8, p=0.033) and lower SYNTAX score (20.5±12.3 vs. 32.1±10.7, p<0.001) (**Table 2**).

Table 1. Comparison between patients with low/intermediate & severe CAD regarding clinical & laboratory data

	All patients (n=100)	Low/intermediate CAD (n=50)	Severe CAD (n=50)	p-value
Age (years), M±SD	58.8±9.5	55.2±9.8	62.3±7.8	<0.001
Male/female, n	53/47	25/25	28/22	0.690
Body mass index (kg/m^2), M±SD	31.7±5.4	33.0±6.4	30.3±3.9	0.013
Family history of CAD, n (%)	38 (38.0)	17 (34.0)	21 (42.0)	0.410
Comorbidities, n (%)				
Hypertension	69 (69.0)	24 (48.0)	45 (90.0)	<0.001
Diabetes mellitus	47 (47.0)	20 (40.0)	27 (54.0)	0.160
Smoking	51 (51.0)	26 (52.0)	25 (50.0)	0.840
Laboratory data, M±SD/median (IQR)				
Cholesterol (mg/dL)	200.4±40.1	188.9±43.4	211.9±33.2	0.004
Triglycerides (mg/dL)	187.4±67.8	181.7±70.5	193.0±65.2	0.410
Low-density lipoprotein (mg/dL)	145.0±48.2	123.7±52.4	166.4±31.7	<0.001
High-density lipoprotein (mg/dL)	37.0±5.0	37.6±4.3	36.4±5.6	0.230
Uric acid (mg/dL)	5.0±1.3	4.5±1.4	5.4±0.9	<0.001
HbA1c (%)	7.1±1.5	6.8±1.2	7.4±1.7	0.057
Homocysteine (µmol/L)	17.1 (8.3-31.9)	10.4 (7.1-24.9)	28.0 (11.4-40.0)	<0.001
Adropin (pg/mL)	14.3 (6.1-21.6)	17.8 (8.9-26.0)	9.3 (5.3-17.6)	0.001
HAR	1.59 (0.60-3.66)	0.90 (0.31-1.61)	3.05 (1.36-5.94)	<0.001
HAR≥median	50 (50.0)	13 (26.0)	37 (74.0)	<0.001
Left ventricular ejection fraction (%)	57.6±9.5	59.1±10.1	56.1±8.6	0.120
Affected vessels n (%)				
Left main	34 (34.0)	10 (20.0)	24 (48.0)	0.005
Left anterior descending	93 (93.0)	43 (86.0)	50 (100.0)	0.006
Left circumflex artery	83 (83.0)	33 (66.0)	50 (100.0)	<0.001
Right coronary artery	79 (79.0)	29 (58.0)	50 (100.0)	<0.001
Number of affected vessels, M±SD	2.9±1.0	2.4±1.1	3.5±0.5	<0.001

Table 2. Comparison between patients with low & high HAR regarding clinical & laboratory data

	Low HAR (n=50)	High HAR (n=50)	p-value
Age (years), M±SD	57.2±10.3	60.3±8.4	0.110
Male/female n	27/23	26/24	0.840
BMI (kg/m^2), M±SD	32.3±6.1	31.0±4.6	0.230
Family history of CAD, n (%)	18 (36.0)	20 (40.0)	0.680
Comorbidities, n (%)			
Hypertension	31 (62.0)	38 (76.0)	0.130
Diabetes mellitus	21 (42.0)	26 (52.0)	0.320
Smoking	23 (46.0)	28 (56.0)	0.320
Laboratory data			
Cholesterol (mg/dL)	178.1±35.2	222.8±31.5	<0.001
Triglycerides (mg/dL)	164.4±55.9	210.4±71.2	0.001
Low-density lipoprotein (mg/dL)	126.2±52.9	164.0±34.1	<0.001
High-density lipoprotein (mg/dL)	38.2±4.7	35.7±5.1	0.014
Uric acid (mg/dL)	4.7±1.1	5.2±1.3	0.020
HbA1c (%)	6.9±1.3	7.3±1.6	0.140
Homocysteine (µmol/L)	9.1 (6.7-15.4)	31.5 (17.9-40.3)	<0.001
Adropin (pg/ml)	21.6 (15.1-31.0)	6.9 (4.5-12.8)	<0.001
Left ventricular ejection fraction (%)	57.3±10.3	57.9±8.7	0.760
Affected vessels, n (%)			
Left main	18 (36.0)	16 (32.0)	0.670
Left anterior descending	44 (88.0)	49 (98.0)	0.050
Left circumflex artery	37 (74.0)	46 (92.0)	0.017
Right coronary artery	34 (68.0)	45 (90.0)	0.007
Number of affected vessels, M±SD	2.7±1.2	3.1±0.8	0.033
SYNTAX score	20.5±12.3	32.1±10.7	<0.001

Table 3. Correlations between HAR & clinical & laboratory data in studied groups

	All patients		Low/intermediate CAD		Severe CAD	
	r	p-value	r	p-value	r	p-value
Age	0.210	0.034	0.040	0.800	-0.020	0.090
Body mass index	-0.130	0.200	-0.100	0.480	-0.030	0.850
Cholesterol	0.460	<0.001	0.410	0.003	0.300	0.031
Triglycerides	0.280	0.006	0.210	0.140	0.110	0.440
Low-density lipoprotein	0.270	0.007	0.066	0.650	0.140	0.340
High-density lipoprotein	-0.310	0.002	-0.180	0.190	-0.300	0.035
Uric acid	0.190	0.062	0.030	0.840	-0.120	0.410
HbA1c	0.110	0.260	0.120	0.430	-0.062	0.670
Homocysteine	0.700	<0.001	0.670	<0.001	0.570	<0.001
Adropin	-0.820	<0.001	-0.750	<0.001	-0.820	<0.001
Left ventricular ejection fraction	-0.019	0.860	0.110	0.470	0.030	0.830
Number of affected vessels	0.140	0.160	-0.050	0.720	-0.150	0.290
SYNTAX score	0.500	<0.001	0.270	0.061	0.320	0.027

Table 4. Performance of homocysteine, adropin, & HAR for detection of severe CAD

	Cut-off	AUC (95% CI)	p-value	SEN	SPEC
Homocysteine	≥30.8	0.73 (0.63-0.83)	<0.001	46.0%	90.0%
Adropin	≤14.5	0.69 (0.59-0.79)	0.001	46.0%	62.0%
HAR	≥2.24	0.78 (0.69-0.87)	<0.001	62.0%	92.0%

Note. SEN: Sensitivity & SPEC: Specifity

Correlation analysis identified significant correlations between HAR and lipid profile parameters in all patients and in patients with low/intermediate and severe CAD. Also, it was found that HAR is correlated with SYNTAX scores in all patients (r=0.50, p<0.001) and in patients with severe CAD (r=0.32, p=0.027) (**Table 3**).

ROC curve analysis showed that HAR had a sensitivity and specificity of 62.0% and 92.0% for detection of severe CAD in comparison to sensitivity and specificity of 46.0% and 90.0% for Hcy and 46.0% and 62.0% for adropin (**Table 4**, **Figure 1**, **Figure 2**, and **Figure 3**).

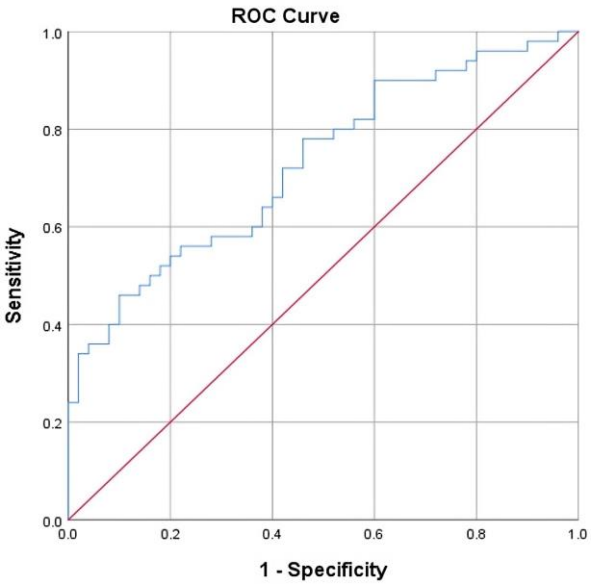

Figure 1. ROC curve for homocysteine & severity of CAD (Source: Authors' own elaboration)

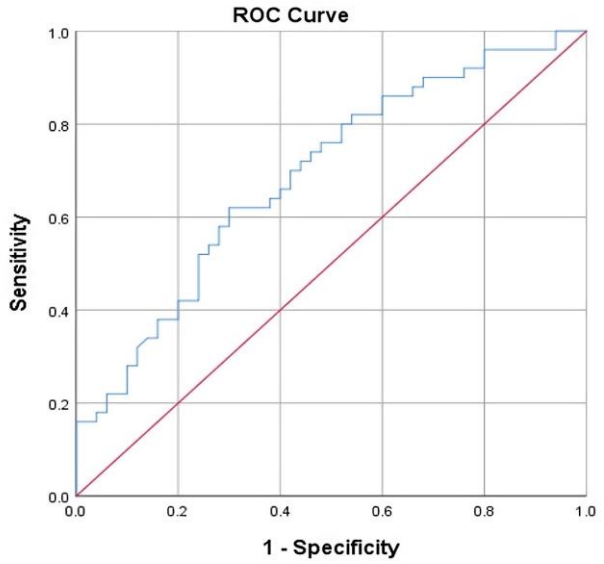

Figure 2. ROC curve for adropin & severity of CAD (Source: Authors' own elaboration)

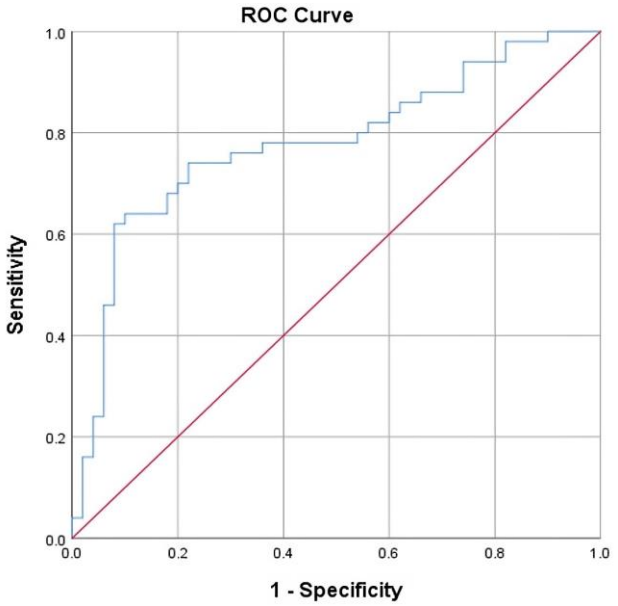

Figure 3. ROC curve for HAR & severity of CAD (Source: Authors' own elaboration)

DISCUSSION

The present study showed that HAR combining Hcy and adropin expression levels can effectively distinguish low/intermediate from severe CAD with adequate correlation with lipid profile parameters and SYNTAX score, which is a novel finding to the best of our knowledge. Our findings are supported by the conclusions of [21], which investigated Hcy and adropin levels in CAD patients. In their work, Hcy levels were inversely correlated adropin levels, which in turn was inversely correlated with SYNTAX score. However, their study did not integrate the two markers as one ratio.

Our findings may give an insight into the complimentary roles both adropin and Hcy play in the so-called liver heart axis. Being primarily synthesized in the liver, it's probable that dysfunctional hepatic biosynthesis of any of them is reflected on the other. This indication is supported by our data. While both markers generally show inverse correlation, those with low HAR show either simultaneously elevated or low levels of both markers. While regulation of NO synthesis system appears to be crucial in the inter-relation between the two markers, exact mechanisms linking Hcy and adropin remain to be elucidated. Data derived from epidemiological studies support a proposed association between non-alcoholic fatty liver disease and CAD. This association is probably mediated through this axis, which entails a complex signaling network of cardiomyokines, hepatokines and adipokines [28].

Noteworthy, anti-atherosclerosis effects of adropin are not only mediated through its effect on NO system. Adropin also suppresses monocyte-endothelial cell adhesion and smooth muscle cell proliferation [29]. It was noted that protects against hepatic injury through Nrf2 mediated antioxidant capacity [30].

CONCLUSIONS

Conclusions of the present study may have therapeutic implications. It was noted that adropin treatment restored cardiac glucose oxidation in pre-diabetic obese mice [31]. Moreover, it was found that adropin-based dual treatment enhances the therapeutic potential of mesenchymal stem cells in rat myocardial infarction [32].

In conclusion, the present study suggested that Hcy and adropin levels are interlinked, HAR can effectively distinguish severe from non-severe CAD. However, these conclusions may be limited by the relatively small sample size. In addition, the study is of cross-sectional design and lacks prognostic implications. Moreover, many patients are elderly and Hcy level changes with aging.

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Ethical statement: The authors stated that the study protocol was approved by Ethical Committee of October 6 University. Written informed consents were obtained from all participants.

Declaration of interest: No conflict of interest is declared by authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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