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ORIGINAL ARTICLE

Relation Between Adropin Levels and Hyperhomocysteinemia in Patients with Coronary Artery Disease

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Abstract

Background and aim: **Homocysteine and adropin effects on endothelial function are antagonistic. The current study aimed to evaluate the association between serum levels of adropin and homocysteine and the severity of coronary artery disease (CAD).**

Patients and methods: **This cross-sectional study included 86 patients subjected to coronary angiography with more than or equal to 50% stenosis in one or more coronary arteries. Serum adropin and homocysteine levels were estimated. The anatomical synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score was used to assess the severity of CAD.**

Results: **According to serum homocysteine levels, they were classified into patients with normal homocysteine levels (GI; $n = 54$) and patients with hyperhomocysteinemia (GII; $n = 32$). Comparison between the studied groups regarding clinical and laboratory findings revealed that GI patients had significantly shorter duration of diabetes (3.8 ± 5.3 vs. 8.2 ± 7.5 years, $P = 0.009$), higher serum triglycerides levels (204.7 ± 99.6 vs. 142.9 ± 55.6 mg/dl, $P = 0.002$), lower glycated hemoglobin levels (7.2 ± 1.6 vs. 8.2 ± 2.0%; $P = 0.013$), and significantly higher adropin levels (7.4 ± 2.5 vs. 1.6 ± 1.0, $P < 0.001$). Correlation analysis identified significant inverse correlation between adropin and homocysteine levels ($r = -0.89$, $P < 0.001$), synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score ($r = -0.97$, $P < 0.001$), and number of affected vessels.**

Conclusions: **Our findings suggest that adropin and homocysteine levels strongly correlate with the severity of CAD. Opposite to homocysteine, adropin may provide a protective effect against CAD.**

Keywords: Adropin, Coronary angiography, Coronary artery disease, Homocysteine, SYNTAX score

1. Introduction

Coronary artery disease (CAD) remains the main cause of mortality globally in spite of the significant progress achieved in prevention and management.[1] There is a consensus that the burden of the disease can be significantly reduced by modification of established risk factors and early identification of pathological changes.[2] In this context, pursuit of new biochemical markers that can early detect the progress of CAD is an essential element of the integrated management approach.[3–5]

Adropin is an endogenous bioactive molecule mainly found in the brain, heart, liver, and endothelial lining cells of the coronary arteries.[6] In addition to its anti-inflammatory characteristics, adropin has been found to protect vascular endothelial cells, improve insulin resistance, and regulate lipid metabolism.[7] Its endothelial protective role is probably mediated through upregulation of

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endothelial nitric oxide synthase, which has a proven involvement in the protection of endothelial cells.[8] In addition, a decreased serum adropin level has been linked to CAD, according to previously published trials.[9]

Homocysteine is sulfur-containing amino acid produced from methionine.[10] Hyperhomocysteinemia, defined as blood homocysteine levels exceeding 15 mol/l, is linked to calcified plaque, the severity of CAD, and associated mortality. Endothelial function and atherosclerosis progression are influenced in different ways by homocysteine and adropin. Accordingly, these two molecules may be linked.[9–11] However, the association between homocysteine and adropin is not well explored. Therefore, this study aimed to evaluate the association between adropin and serum homocysteine in patients with CAD, as well as the effect of both hormones on the severity of coronary artery atherosclerosis.

2. Patients and methods

The present cross-sectional study was conducted at Al-Zahraa University Hospital, Cairo, Egypt, in the period from June 2019 to June 2020. The study protocol was approved by the ethical committee of Faculty of Medicine, Al-Azhar University, and all included patients provided written informed consent before enrollment. The study included 86 patients with confirmed CAD on the basis of coronary angiography findings. Patients with malignant tumors, current microbial infections, severe hepatic insufficiency, or end-stage renal failure were excluded.

All patients were subjected to full medical history analysis and clinical examination with particular emphasis on risk factors of CAD. Routine laboratory tests were performed. These included glycated hemoglobin, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, and total cholesterol. Commercially available quantitative sandwich enzyme immunoassay kits were used for assessment of homocysteine and adropin (Bioassay Technology Laboratory Inc., Shanghai, China; Catalog numbers; E3292Hu and E3231Hu, respectively). Homocysteine levels were measured in nmol/ml, whereas adropin levels were measured in ng/l. Hyperhomocysteinemia was defined as homocysteine levels more than 15 μmol/l.

For cardiac evaluation, 12-lead ECG was done. Transthoracic echocardiography was performed in all patients using the E–9 GE system, Horton-Norway with multifrequency (2.5–3.5 MHz) matrix probe M3S. All captured echo pictures and loops are displayed alongside a simultaneous ECG physio signal. All imaging and loops of at least three cardiac cycles were recorded, saved digitally, and retrieved for offline analysis on echo PAC software, version 201 for GE vivid E9. American Society of Echocardiography standards were followed in every step of the testing.[12]

Standard femoral or radial methods were used to perform coronary angiography in all patients. The angiographic data were analyzed by well-experienced blinded interventional cardiologists. The synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) score was determined using a computer program and was used assess the severity of CAD.[13]

Analysis of the collected data was done using the Statistical Package for the Social Sciences (SPSS) program (IBM Inc., Chicago, Illinois, USA), version 16 for Windows. The central tendency (means) and dispersion (SD) of quantitative data, as well as the number and percentage of qualitative data, were calculated. Student *t*-test and the Mann–Whitney *U* test were used to compare both groups in terms of parametric and nonparametric data, respectively. To assess the difference between the two qualitative variables, we used the χ^2 test. In addition, the Pearson correlation coefficient was done to test the association between parametric variables and Spearman's correlation coefficient when dealing with nonparametric ones. *P* value of less than 0.05 was considered significant.

3. Results

The present study included 86 patients with CAD. They comprised 46 (53.5%) males and 40 (46.5%) females. According to serum homocysteine levels, they were classified into patients with normal homocysteine levels (GI; $n = 54$) and patients with hyperhomocysteinemia (GII; $n = 32$). Comparison between the studied groups regarding clinical and laboratory findings revealed that GI patients had significantly shorter duration of diabetes (3.8 ± 5.3 vs. 8.2 ± 7.5 years, $P = 0.009$), higher serum triglycerides levels (204.7 ± 99.6 vs. 142.9 ± 55.6 mg/dl, $P = 0.002$), lower glycated hemoglobin levels (7.2 ± 1.6 vs. 8.2 ± 2.0%, $P = 0.013$), and significantly higher adropin levels (7.4 ± 2.5 vs. 1.6 ± 1.0, $P < 0.001$) (Table 1).

No statistically significant differences were found between the studied groups regarding echocardiographic findings (Table 2). Angiographic evaluation revealed that GII patients had significantly higher frequency of multiple-vessel affection (75.0 vs. 25.9%, $P < 0.001$). Moreover, GII patients had

Table 1. Clinical and laboratory findings in the studied groups.

	Group I ($N = 54$)	Group II ($N = 32$)	P value
Age (years)	52.6 ± 8.5	55.7 ± 8.9	0.11
Male/female (N)	28/26	18/14	0.69
BMI (kg/m^2)	31.8 ± 6.4	32.6 ± 5.7	0.58
Smoking [n (%)]	30 (55.6)	16 (50.0)	0.62
Hypertension [n (%)]	26 (48.1)	18 (56.2)	0.47
Diabetes [n (%)]	28 (51.9)	22 (68.8)	0.13
Duration of diabetes (years)	3.8 ± 5.3	8.2 ± 7.5	0.009
Insulin use [n (%)]	14 (25.9)	14 (43.8)	0.09
Family history of IHD [n (%)]	22 (40.7)	12 (37.5)	0.77
Cholesterol (mg/dl)	166.5 ± 46.4	169.9 ± 60.9	0.77
Triglycerides (mg/dl)	204.7 ± 99.6	142.9 ± 55.6	0.002
HDL (mg/dl)	36.6 ± 6.3	36.2 ± 5.7	0.77
LDL (mg/dl)	97.2 ± 50.0	111.0 ± 44.4	0.2
VLDL (mg/dl)	49.6 ± 22.2	40.4 ± 17.6	0.29
HbA1C %	7.2 ± 1.6	8.1 ± 2.0	0.013
Adropin (pg/ml)	7.4 ± 2.5	1.6 ± 1.0	<0.001

HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; IHD, family history of ischemic heart disease; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

significantly higher SYNTAX scores (27.7 ± 7.7 vs. 8.6 ± 4.3, $P < 0.001$) (Table 2).

Regarding the relation between adropin levels and clinical data, it was shown that diabetic patients had significantly lower adropin levels when compared with nondiabetics (4.2 ± 2.9 vs. 6.7 ± 3.8 pg/ml, $P < 0.001$). In addition, diabetic patients had significantly higher homocysteine levels when compared with nondiabetics (17.18 ± 8.72 vs. 14.09 ± 9.35, $P = 0.035$).

Table 2. Echocardiographic and angiographic findings in the studied groups.

	Group I ($N = 54$)	Group II ($N = 32$)	P value
Echocardiographic findings (mean ± SD)			
LVEDd (mm)	43.2 ± 18.9	44.5 ± 21.2	0.78
LVESd (mm)	28.9 ± 13.3	29.8 ± 15.7	0.76
FS %	33.3 ± 8.5	31.7 ± 8.0	0.39
EF m-mode %	59.1 ± 11.8	58.3 ± 11.8	0.75
EF 2D %	50.1 ± 11.3	49.7 ± 13.1	0.88
LA (mm)	39.4 ± 6.6	38.6 ± 4.3	0.54
E velocity (m/s)	0.76 ± 0.19	0.73 ± 0.26	0.54
A velocity (m/s)	0.69 ± 0.20	0.73 ± 0.22	0.43
E/A	1.22 ± 0.50	1.06 ± 0.46	0.14
Sm (cm/s)	6.20 ± 1.97	6.10 ± 1.8	0.82
Em (cm/s)	7.68 ± 2.79	7.13 ± 1.61	0.31
Am (m/s)	8.33 ± 2.89	8.25 ± 2.23	0.89
Number of affected vessels [n (%)]			
Single vessel	26 (48.1)	2 (6.2)	<0.001
Two vessels	14 (25.9)	6 (18.8)	
Multiple vessels	14 (25.9)	24 (75.0)	
SYNTAX score (mean ± SD)	8.6 ± 4.3	27.7 ± 7.7	<0.001

A velocity, A wave velocity; Am, myocardial segmental velocity during late diastole; E velocity, E wave velocity; E/Em, transmitral to basal septal myocardial early diastolic velocity ratio; E/A, early to late diastolic transmitral flow velocity; Sm, peak systolic velocity at myocardial segments; EF, ejection fraction; Em, myocardial segmental velocity during early diastole; FS, fractional shortening; LA, left atrium; LVEDd, left ventricular end-diastolic diameter; LVESd, left ventricular end-systolic diameter; SYNTAX, synergy between percutaneous coronary intervention with taxus and cardiac surgery.

Correlation analysis identified a significant inverse correlation between adropin and homocysteine levels ($r = -0.89$, $P < 0.001$) (Fig. 1), SYNTAX score ($r = -0.97$, $P < 0.001$) (Fig. 2), and number of affected vessels ($r = -0.72$, $P < 0.001$).

4. Discussion

The current study noted that patients with CAD with hyperhomocysteinemia had significantly lower adropin levels when compared with their counterparts with normal homocysteine levels. Moreover, an inverse correlation was found between homocysteine and adropin levels. Similar relation between the two markers was observed by other studies. In their work on 170 patients with CAD, Zhao et al.[14] could also identify a similar relation between adropin and homocysteine levels.

In addition, our study recognized an inverse correlation between adropin levels and CAD severity as assessed by SYNTAX score. This result is consistent with the conclusions of Zheng et al.,[15] who reported significantly lower serum adropin levels in patients with CAD compared with healthy individuals. Compared with patients with NSTEMI and low SYNTAX scores, patients with NSTEMI and high SYNTAX scores had significantly lower adropin serum levels. Likewise, Ertem et al.[16] concluded that adropin may be used as an alternative blood sample value for predicting the severity of CAD.

Interestingly, the current study noted that diabetic patients with CAD expressed significantly lower levels of serum adropin when compared with nondiabetic patients. This finding is in harmony

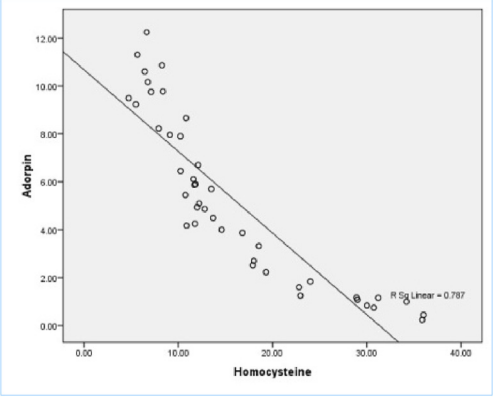

Fig. 1. Correlation between adropin level and homocysteine level.

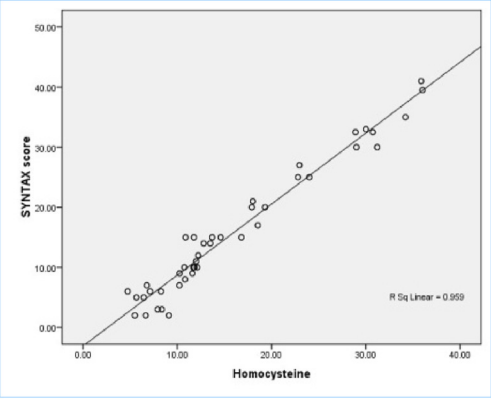

Fig. 2. Correlation between adropin level and SYNTAX score.

with previous reports. In the study of Wei et al.,[17] the authors found an inverse relation between adropin levels and risk of atherosclerotic plaque in diabetic patients. Moreover, Jurrissen et al.[18] noted that low adropin levels are associated with arterial stiffening in obese and diabetic patients.

Although the exact mechanisms involved in the protective role of adropin against atherosclerotic changes and CAD remain elusive, many theories were proposed. It was suggested that adropin has the ability to inhibit vascular smooth cell osteogenic differentiation, a pathway in which tyrosine protein kinase JAK2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) signaling pathway played a key role.[19] In addition, it was found that good coronary collateral circulation in chronic coronary syndrome was linked to elevated adropin levels.[20]

Findings of the present study may have therapeutic implications. For example, a study by Davoodi et al.[21] showed that increasing adropin levels in diabetic patients by high-intensity interval training was associated with marked vasodilatation and lowering of blood pressure through increased production of nitric oxide. Moreover, it was noted that elastic band resistance training was associated with elevated adropin levels and improved cardiometabolic factors in elderly.[22]

4.1. Conclusion

Our findings suggest that adropin and homocysteine levels strongly correlate with the severity of CAD. Opposite to homocysteine, adropin may provide a protective effect against CAD.

Conflict of interest

There are no conflicts of interest.

Acknowledgements

Authors' contributions: B.M.A.H. and O.H.A.E.: collected the data, performed data analysis, and prepared the manuscript. I.H.A.: performed the study design and searched for literature. M.K.A.E.: perform the laboratory analysis. H.N.M.: performed editing of the manuscript. All authors have read and approved the final manuscript.

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