



Adropin- A Novel Biomarker of Heart Disease: A Systematic Review Article

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(Received 03 Feb 2016; accepted 10 Jul 2016)

Abstract

Background: Heart disease is one of the most common chronic disease and leading cause of morbidity and mortality worldwide. Adropin, a newly identified protein, is important for energy homeostasis and maintaining insulin sensitivity, and has been referred to as a novel regulator of endothelial cells. Endothelial dysfunction is a key early event in atherogenesis and onset of HD. Therefore, this review gives a systematic overview of studies investigating plasma adropin level in patient with heart disease.

Methods: Data carried out in PubMed, Scopus, Web of Science, Embase, Google scholar and MEDLINE, from the earliest available online indexing year through 2015. The search restricted to studies conducted in humans. The keyword search was adropin to apply in title, abstract and keywords. References lists of all original published articles were scanned to find additional eligible studies.

Results: Heart failure (HF), coronary atherosclerosis acute myocardial infarction and Cardiac Syndrome X (CSX) were type of heart disease acknowledged in this study. Majority of evidences introduced low adropin as an independent risk factor of heart disease. In a case-control study, the plasma level of adropin increased with the severity of HF.

Conclusion: Adropin may be a potential serum biomarker for early diagnosis of HD.

Keywords: Adropin, Heart, Endothelium, Systematic review

Introduction

Despite modern medical management, heart disease is still one of the most common chronic diseases and remains the leading cause of morbidity and mortality worldwide. Accurate diagnosis of HD improve prognosis through early treatment. Although, current strategy for prognosis of HD is good, however, are not enough to explain all coronary events. Therefore, researches for potential novel its risk factors and diagnostic criteria are requirement to be fulfilled (1-4).

Adropin is a recently identified protein encoded by the energy homeostasis-associated gene (Enho) identified during an investigation of obese

insulin resistant mice as a novel factor linking with metabolic homeostasis (5). Adropin appears to participate in the maintenance of energy homeostasis and insulin response, closely related to the development and progression of atherogenesis (5). Lower adropin level leads to endothelial impairment and dysfunction (6). Endothelial dysfunction is a key early event in atherogenesis and onset of HD (7). Furthermore, low serum adropin introduced as an independent predictor of clinically relevant coronary atherosclerosis (8). We hypothesized that adropin may have a potential role in the pathophysiology of HD.

The aim of this present study was to investigate the effects of adropin on HD through systematic review.

Material and Methods

Search strategy

We performed a systematic search of PubMed, Scopus, web of science, Embase, Google scholar and MEDLINE for studies examining the association between serum adropin levels and all type of heart disease. The keyword search was adropin to apply in title, abstract and keywords. The search strategies for the other databases were identical. The search was restricted to English article conducted in humans. The PRISMA 2009 guidelines for systematic review and meta-analysis were considered throughout the study. References lists of all original published articles were scanned to find additional eligible studies.

Study selection

The predetermined inclusion criteria were: 1) exposure introduced as serum adropin levels; 2) the outcome interest was all type of heart disease; 3) studies that conducted in adult population were not endocrine disorders. Studies were excluded if they were pregnant and lactating women or reviews, editorial, letters, meeting abstract and animal study. Studies screened independently by two investigators (SY, SS) based on the inclusion criteria with a low probability to exclude irrelevant abstract. Disagreements about inclusion of studies were settling after investigators expressed their opinion.

Overall, 220 abstracts were retrieved by searching in the electronic database. Of those, 151 abstracts were duplicated, 27 did not study coronary heart disease as interesting outcome (5, 9-34), 3 were editorial and review (35-37), 13 were non-human studies (6, 38-49), 8 were Meeting abstract (50-57) and 12 conducted in children, pregnant and lactating women (58-69). After final screening of full text, six articles were eligible to address in this systematic review (8, 70-74), which four of

those were case-control (8, 72-74) studies and 2 articles were cross-sectional studies (70, 71).

Data extraction

Two authors conducted independently data extraction using a pre-formatted spreadsheet. All data extracted we rescanned two times. If there were discrepancies, group consensus and consulted a third reviewer were used to reach a ensure accuracy of data. The data extracted included: study characteristics (authors, year of publication, study location, study design) the participants' age, number of allocated participants, serum adropin level, type of heart disease, adropin assessment method. The Newcastle-Ottawa scales, validated scale for non-randomized studies were applied to examine the quality of included evidences. This scale awards a maximum of nine points to each study.

Results

Table 1 exhibited detail of study and participants characterize. Heart failure (HF), coronary atherosclerosis acute myocardial infarction and Cardiac Syndrome X (CSX) were type of heart disease acknowledged in this study. All studies were conducted on both sex, two studies conducted in Turkey (70, 71), and four investigation were from China (8, 72-74).

There were significant differences in the plasma adropin level between heart disease patients with healthy participants. Majority of evidences introduced low adropin as an independent predictor of heart disease (8, 70, 71, 73, 74). In a case-control study, the plasma level of adropin increased with the severity of HF (control: 6.0 ± 0.3 ng/mL; HA functional Class II: 7.6 ± 0.4 ; HA functional Class III: 9.8 ± 0.5 ; HA functional Class IV: 12.4 ± 0.6 ng/mL ($P < 0.01$) (72). In a similar design, reported the stable angina pectoris (SAP) and acute myocardial infarction compare with control group have lower serum adropin (74).

Adropin could be a predictor serum biomarker of early diagnosis of AMI (74).

Table 1: Characteristic of studies that evaluated of adropin status in patient with coronary artery disease

Reference number	Number of participant	Age range (year)	measurements	Mean of BMI (kg/m ²)	Mean of adropin (ng/ml)
74	108 AMI patients, 114 stable angina pectoris (SAP) patients and 75 controls	AMI: 64.50 ± 10.53 SAP: 63.67 ± 11.18 Control: 60.40 ± 9.58	TC, TG, HDL, LDL, hs-CRP, proBNP, cTnT, Adropin, troponin I, ECG,	AMI: 25.07 SAP:25.12 Control:24.74	AMI: 2.19±1.61 SAP: 3.81±1.78 Control: 5.12±1.44
72	56 heart failure patients (HF) and 20 health person as control	HF:76.8 ± 7.6 Range 60-92 yr Control: mean age 72.4 ± 8.4 yr, range 57-82 yr	Fasting plasma glucose (FBG), lipids, creatinine (Cr), blood urea nitrogen (BUN), TC, TG, LDL, HDL, adropin, brain natriuretic peptide (BNP), tumor necrosis factor α (TNF- α) and interleukin 6 (IL-6)	Con-trol:24.2±0.07 NY-HAII:22.8±0.6 NY-HAIII:24.4±1.0 NY-HAIV:23.4±0.9	Control: 6±0.3 NYHAII: 7.6±0.4 NYHAIII: 9.8±0.5 NYHAIV:12.4±0.6
8	392 patients with suspected coronary artery disease	Non diabetic patient: 63.09±10.84 Diabetic patient: 63.2±9.88	Coronary angiograph, Fasting blood glucose (FBG), serum total cholesterol (TC), triglycerides (TG), low and high density lipoprotein cholesterol (LDL-C, HDL-C), creatinine and uric acid, HbA1c, hs-CRP, adropin	Non diabetic patient: 31.13 Diabetic patient: 34.44	Non diabetic patient: 5.53 Diabetic patient: 4.8
70	Thirty-eight patients with SVGD involving at least one graft (occluded group; 14 females, 24 males) and 42 patients with a patent saphenous vein graft (patent group; 15 females, 27 males)	occluded group: mean age 62.0 ± 9.7 yr patent group: 60.0 ± 12.0 yr	Coronary angiography, Adropin, Fasting plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, Low-density lipoprotein (LDL) cholesterol and triglyceride, CRP, blood pressure	occluded group: 26 ± 5.1 patent group: 25.3 ± 5.9	occluded group: 3.2±0.71 patent group: 4.9±1.51
71	86 consecutive Cardiac Syndrome X-diagnosed patients (CSX) and 86 age-sex matched healthy subjects	Cardiac Syndrome X: 54.8±9.2 Control: 52.7±8.5	Serum adropin levels, nitrite/nitrate Levels, exercise treadmill testing	Cardiac Syndrome X: 28.1±2.4 Control: 26.0±3.7	Cardiac Syndrome X: 1.7±0.8 Control: 3.4±1.8
73	116 patients with SCAD and 116 control subjects without coronary artery disease	patients with SCAD: 64.1±11.4 control: 62.8±12.6	BMI, Cholesterol, TG, LDL, HDL, Blood urea nitrogen, Creatinine, hs-CRP, FBS, insulin, adropin	patients with SCAD: 25.0±3.8 control: 23.9±3.5	patients with SCAD: 59.2±19.3 control: 70.0±18.2

A decrease in adropin level found in patients with CSX than control participants (1.7 ± 0.8 ng/mL and 3.4 ± 1.8 ng/mL, respectively; $P < 0.001$). Additionally, adropin was one of the predictor risk factors for CSX ($\beta = -0.104$, P -value = 0.005) (71). Patients with stable coronary artery disease (SCAD) had lower serum adropin levels compared to the controls (59.2 ± 19.3 versus 70.0 ± 18.2 pg/mL, $P < 0.001$).

Moreover, low serum adropin level was introduced as a predictor of SCAD (73). In a cross-sectional study, serum adropin was inversely associated with the score of severity of coronary atherosclerosis assessed by Gensini, Friesinger,

and SYNTAX scores. A decrease serum adropin indicated a negative independent predictor of coronary atherosclerosis (as SYNTAX score > 11) (8). In similar design study introduced lower serum adropin as an independent predictor of Saphenous Vein Graft Disease (SVG D) after coronary artery bypass grafting (OR = 0.558, 95% CI = 0.433-0.714, $P < 0.01$) (70).

Discussion

Adropin is a newly identified protein that its protective role on endothelial cells has been shown previously, and has been referred to as a novel

regulator of these cells (46). The key findings from the present review study were that there were significant differences in the plasma adropin level between patients with heart disease (AMI, SAP, atherosclerosis, Cardiac Syndrome X, occluded SVG) and control subjects. Furthermore, serum adropin inversely is associated with angiographic severity of coronary atherosclerosis. Serum adropin level may be referred to as a novel biomarker for evaluation and follow up in patients with HD.

Several mechanisms have been suggested to explain adropin effect in HD patients. Endothelial dysfunction has been introduced as main mechanism (75). The endothelium plays a crucial role in the maintenance of vascular homeostasis, and endothelial dysfunction contributes to the development and progression of cardiovascular diseases (71). Low adropin is associated with endothelial dysfunction (6, 13, 25). Furthermore, adropin can exert protective effects on the endothelial function (6).

Nitric oxide, a potent endogenous vasodilator formed in the endothelium by the endothelial isoform of eNOS, plays an important role in maintaining endothelial homeostasis (71). Nitric oxide furthermore inhibits monocytes and leukocytes adhesion to the endothelium, aggregation of platelets, oxidation of low density lipoprotein, and smooth muscle cell proliferation (76-79). Low levels of nitric oxide are associated with endothelial dysfunction. Adropin has a protective and regulator role on endothelial function (6). Adropin could enhance the expression of endothelial nitric oxide synthase (eNOS), responsible for the production of vascular nitric oxide, in the endothelium, so adropin deficiency is associated with reduced nitric oxide bioavailability in the endothelium (74, 80). Loss of NO bioavailability is a critical stage in formation of endothelial dysfunction that is an independent predictor of the onset of coronary artery disease (81). Patients with Cardiac Syndrome X, characterized by endothelial dysfunction, compared to healthy subjects had significantly lower adropin levels (71).

Besides, the reduced circulating adropin concentrations participates in metabolic disorders such

as insulin resistance (5, 13) related to the onset and progression of coronary atherosclerosis and increased incidence rate of cardiovascular events (82, 83).

C-reactive protein has been widely used for cardiovascular risk stratification (27-29). A negative correlation between adropin and hs-CRP levels was found (8). Atherosclerosis has been regarded as a chronic inflammatory disease, so adropin as a potential anti-inflammatory protein play an important role in the prevention of atherosclerosis (8).

However, plasma adropin levels were correlated positively with BMI and the severity of heart failure, which is in contrary to our results (72). Cardiac cachexia which characterized by weight loss, muscle wasting and cytokine activation frequently occurs in patients with advanced HF (84). Liver Enho expression decreases with either diet or genetically induced obesity (5). Besides, cardiac cachexia or wasting, which could reflect a decrease in visceral fat, may be result in the elevation of plasma adropin levels in patients with HF.

Conclusion

Adropin may serve as a potential biomarker for early diagnosis of and severity stratification HD.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

Acknowledgments

The research group thanks Dr. Mohammadreza Vafafor his contribution to our manuscript. The authors declare that there is no conflict of interests.

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