



Association between serum adropin level and coronary artery disease: a systematic review and meta-analysis

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Background: Recent studies have found that adropin is associated with coronary artery disease (CAD). This meta-analysis sought to assess the relationship between serum adropin level and CAD.

Methods: Online databases including the Cochrane Library, PubMed, EMBase, Ovid, CBM, CNKI, VIP and WanFang Data were electronically searched for the clinical study concerning the relationship between serum adropin levels and CAD, including acute myocardial infarction (AMI), unstable angina pectoris (UAP), and stable angina pectoris (SAP). Two reviewers independently screened literature, extracted data and assessed methodological quality of included studies. Standard mean difference (SMD) with its 95% confidence interval (CI) was used as the effect size in this study. Then meta-analysis was performed using RevMan 5.2 software.

Results: A total of seven articles involved 945 participants were included. The results indicated that serum adropin level in CAD group was lower than healthy control group (SMD = -2.44, P=0.0008). In the subgroup analysis, the levels of serum adropin in AMI group (SMD = -2.96, P<0.00001), UAP group (SMD = -2.09, P=0.0001) and SAP group (SMD = -1.23, P=0.007) were also lower than that of healthy control.

Conclusions: Serum adropin level in patients with CAD was lower than healthy individuals, indicating that the decrease of adropin concentration might play an important role in the development of CAD.

Keywords: Adropin; coronary artery disease (CAD); meta-analysis

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Introduction

Coronary artery disease (CAD) is caused by atherosclerosis of the coronary arteries that leads to a restriction of blood flow to the heart (1). With the improvement of people's living standards and lifestyle changes, the morbidity and mortality of CAD increase year by year, which seriously threatens the health of human beings (2).

Adropin, a secreted protein consisting of 76 amino acids

with a molecular weight of 4,999.9 D, is encoded by energy balance related genes and is a new regulatory polypeptide involved in energy homeostasis (3,4). Some studies have found that adropin is associated with CAD, which can regulate lipid metabolism, improve insulin resistance, and protect vascular endothelial cell function and anti-inflammatory effect (5-7). However, the samples of these studies were quite small. Therefore, this study was performed to include related studies and systematically evaluated the

Table 1 PubMed search strategy

Search strategy
#1 "coronary disease OR coronary artery diseases OR coronary heart disease OR heart disease OR coronary"
#2 "Adropin"
#3 "Randomized Controlled Trial" [Publication Type]
#4 "Randomized Controlled Trial as Topic" [MeSH]
#5 "Random[Title]"
#6 "#1 AND #2 AND (#3 OR #4 OR #5)"

relationship between serum adropin levels and CAD.

Methods

Guidelines and searches

This meta-analysis followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement issued in 2009. Electronic databases, including the Cochrane Library, PubMed, Embase, Ovid, CBM, CNKI, VIP, WanFang Data databases were searched for relevant studies written in English or Chinese. The search terms include "adropin" "coronary disease" "coronary artery disease" "coronary heart disease", "coronary and heart disease". Take PubMed as an example, *Table 1* shows its specific search strategy.

Study selection

All eligible studies satisfying the following criteria were initially included in the analysis: (I) type of study randomized controlled trials, cohort studies, case-control studies, regardless of whether distributional or blinding; (II) research object patients diagnosed with CAD, acute myocardial infarction (AMI), unstable angina pectoris (UAP), stable angina pectoris (SAP), and CAD-free healthy people; (III) observe the indicator serum adropin levels. The exclusion criteria were: (I) severe cardiovascular and cerebrovascular diseases, severe respiratory diseases, liver or kidney organ dysfunction; (II) no data or data is obviously wrong; and (III) for repeated publications, only the most complete data are included.

Data extraction and quality assessment

All the enrolled studies were independently reviewed by two investigators and any disagreements in quality assessments

were resolved by discussion. Data extraction mainly include: (I) normal information, including title, first author's name, date of publication and source of documentation; (II) study object characteristics, including age, sex, blood lipids, liver and kidney function, adropin levels and so on; (III) observational indicators, including serum adropin level in the CAD group and control group. The methodology quality evaluation of the study was carried out in reference to Cochrane Handbook 5.1.0.

Statistical analysis

Meta-analysis was performed using RevMan 5.2 software provided by the Cochrane Collaboration. Standard mean difference (SMD) with its 95% confidence interval (CI) was used as the effect size in this study. Heterogeneity included in the study results was analyzed using the χ^2 test. To reduce the potential effect of statistical heterogeneity, random-effect model was chosen in this meta-analysis. Besides, subgroup analyzes are conducted to analyze the potential heterogeneity and characteristics in different patients.

Results

Literature search results

At the beginning, 178 papers were found. These studies were screened layer by layer. Finally, there were seven studies included (8-14). The literature screening process and results are shown in *Figure 1*.

The basic characteristics of inclusion studies and methodological quality evaluation

The basic features of the study included in *Table 2*, the methodological quality evaluation results are attached.

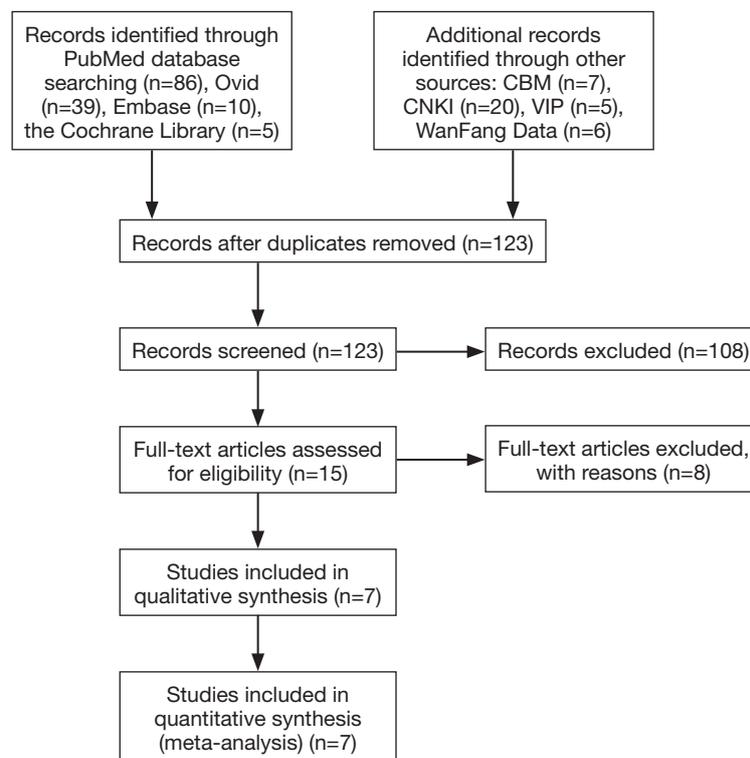


Figure 1 Literature screening process and results.

Meta-analysis results

Serum adropin levels in CAD group and control group

A total of seven studies were included (8-14). Meta-analysis of random effects model showed that serum adropin level in CAD group was lower than that in control group (SMD = -2.44, 95% CI: -3.87 to -1.01, P=0.0008) (Figure 2).

The levels of serum adropin in AMI group and control group

A total of five studies were included (9-13). Meta-analysis of random effects model showed that serum Adropin level in AMI group was lower than that in control group (SMD = -2.96, 95% CI: -4.11 to -1.81, P<0.00001) (Figure 3).

The levels of serum adropin in UAP group and control group

A total of three studies were included (8,10,12). Meta-analysis of random effects model showed that serum adropin level in UAP group was lower than that in control group (SMD = -2.09, 95% CI: -3.16 to -1.02, P=0.0001) (Figure 4).

The levels of serum adropin in SAP group and control group were compared

A total of two studies were included (8,13). Meta-analysis of random effects model showed that serum adropin level in SAP group was lower than that in control group (SMD = -1.23, 95% CI: -2.14 to -0.33, P=0.007) (Figure 5).

Quality evaluation

The study was biased using funnel charts and fail-safe number for evaluation. Funnel diagram was symmetrical, funnel-like, published bias is small. The fail-safe number of CAD is 2,981, high reliability. Based on the characteristics of the data collected, this study uses a one-by-one deletion of the included literature to conduct a sensitivity analysis to evaluate the impact of a single document on the overall outcome. This article analyzes the sensitivity of CAD and all subgroup. The results showed that there was no single document that could significantly influence the statistical results of original analysis and subgroup analysis. Indicating that the results excluded are less sensitive to the conclusion and the conclusion is more credible.

Table 2 The basic features of the included studies

Study	Country	Number CAD/ Control	Age, years CAD/ Control	Male, % CAD/ Control	Hypertension, % CAD/ Control	Diabetes, % CAD/ Control	Smoking, % CAD/ Control	TC (mmol/L) CAD/ Control	TG (mmol/L) CAD/ Control	HDL (mmol/L) CAD/ Control	LDL (mmol/L) CAD/ Control	CRP (mg/L) CAD/ Control	Adropin (μ g/L) (CAD/ Control)	Techno NOS	
Du 2015 (8)	China	90/80	63.55/56.2	61.1/65	54/54	49/21	43/37	5.56/4.45	1.61/1.53	1.15/1.19	2.59/2.63	NA	52.18/92.51	ELISA	7
Erfem 2017 (9)	Turkey	35/29	62.94/58.90	65.7/72.4	NA	37.1/24.1	48.6/27.6	5.16/4.56	1.97/1.66	1.23/1.51	3.07/2.55	4.02/1.58	2.36/3.69	ELISA	8
Mu 2014 (10)	China	33/30	59.4/59.3	54.54/43.33	72.72/30	57.58/16.67	60.60/36.67	4.33/3.06	1.85/1.37	1.05/1.32	3.49/1.95	12.75/6.21	1.91/3.19	ELISA	7
Qi 2015 (11)	China	90/40	NA	67.78/75	NA	NA	NA	4.63/3.15	1.95/1.49	0.89/1.26	3.87/1.99	NA	3.15/7.49	ELISA	6
Xu 2016 (12)	China	53/50	59.2/59.9	54.72/54	56.60/56	15.09/16	28.30/32	4.36/3.81	1.79/1.79	1.05/1.12	3.14/2.27	NA	0.03/0.06	ELISA	7
Yu 2014 (13)	China	108/75	64.50/60.40	57.41/52	NA	NA	37.04/29.33	4.62/4.16	1.77/1.50	0.92/1.04	2.80/2.32	1.68/0.88	2.19/5.12	ELISA	6
Zhao 2015 (14)	China	116/116	64.1/62.8	74.1/75.0	65.5/68.1	18.1/16.4	48.3/44.8	4.3/4.5	1.5/1.6	1.0/1.2	2.6/2.6	7.6/4.9	0.07/0.06	ELISA	7

CAD, coronary heart disease group; Control, healthy control group; NA, not acquired; ELISA, Enzyme linked immunosorbent assay; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; CRP, C-reactive protein.

Discussion

We are the first meta-analysis of the relationship between adropin and CAD so far in the world. A total of 7 case-control studies were included in this meta-analysis (8-14), including 525 CAD patients and 420 healthy controls. The results of meta-analysis showed that the levels of serum adropin in patients with CAD, AMI, UAP and SAP were significantly lower than those in healthy controls.

CAD is the most common cardiovascular disease, with high morbidity and mortality, serious threat to human health, and coronary atherosclerosis is its pathogenesis. It is generally believed that endothelial dysfunction, vascular inflammation and lipid metabolism disorder are the more important cause of CAD (15). Vascular endothelial cells are a barrier between the blood and the blood vessel wall can produce endothelin, nitric oxide, prevent thrombosis and platelet adhesion (16). The damage of vascular endothelial cells is a key factor in the early stage of atherosclerosis, and is also an important link in the early stage of coronary atherosclerosis and acute coronary syndrome (17). Inflammatory factors play an important role in the process of coronary atherosclerosis. Studies have shown that IL-6, C-reactive protein, interleukin 10 and other inflammatory cytokines expression in patients with CAD was significantly increased, and closely related to the severity of the disease (18-20).

Adropin is a newly discovered endogenous bioactive substance that is mainly expressed in the heart, brain, liver and coronary endothelial cells (21). Adropin is involved in regulating lipid metabolism, improving insulin resistance, protecting vascular endothelial cells, and anti-inflammatory effects (4-6). Adropin can increase the endothelial nitric oxide synthase expression, which has a certain endothelial cell protection potential (22). Circulating low levels of adropin are associated with endothelial dysfunction (23); decreased serum adropin levels weaken endothelial protection and may cause or accelerate atherosclerosis. Therefore, consider the level of adropin and CAD may have a certain relationship. In the 33 CAD patients and 30 healthy controls, serum adropin was detected by ELISA. The level of serum adropin in CAD group (1.91 ng/mL) was lower than that in healthy controls (3.19 ng/mL) (10). Yu *et al.* also found that serum adropin levels in CAD patients were lower than those of healthy controls (13). However, due to the small number of patients involved in the current literature, the quality of the literature is not high. In this study, meta-analysis was used to evaluate the

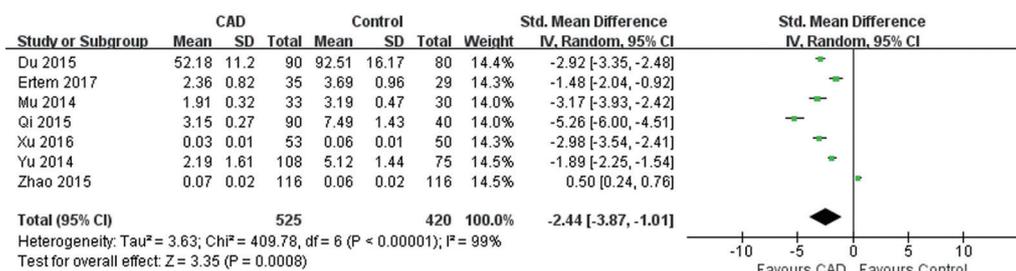


Figure 2 Serum adropin levels in CAD group and control group were compared. CAD, coronary artery disease.

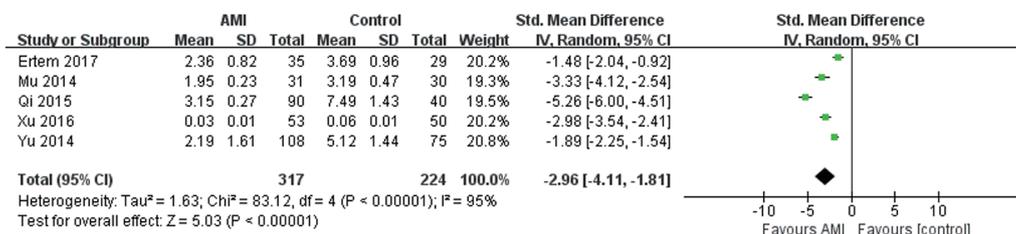


Figure 3 The levels of serum Adropin in AMI group and control group were compared. AMI, acute myocardial infarction.

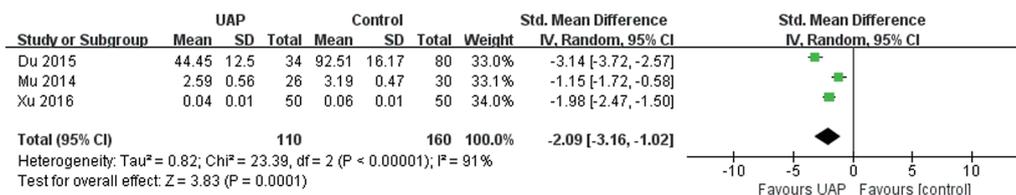


Figure 4 The levels of serum adropin in UAP group and control group were compared. UAP, unstable angina pectoris.

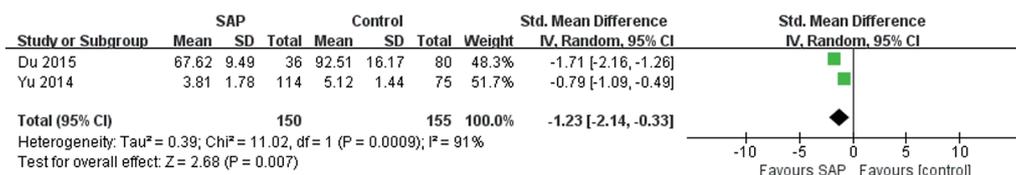


Figure 5 The levels of serum adropin in SAP group and control group were compared. SAP, stable angina pectoris.

relationship between serum adropin level and CAD in a comprehensive and systematic way, further demonstrating that serum adropin levels in CAD patients were lower than those in healthy controls. This study brings together outstanding papers published by core journals both at home and abroad, screened the selected documents strictly, selected more articles, large sample size and high credibility.

This meta-analysis also has some limitations: (I) the quality of meta-analysis is based on the quality of the

research, and the quality of this meta-analysis is relatively general; (II) the number of included studies is relatively inadequate and the sample size is relatively small, so the statistical power of this meta-analysis is relatively inadequate; (III) meta-analysis is based on a summary of past research literature, and may expand the sample size and improve the credibility of the conclusion, but also may accumulate the bias of the corresponding original document.

Conclusions

In summary, serum adropin levels in patients with CAD were significantly lower, suggesting that serum Adropin levels may be associated with the pathogenesis of CAD. However, due to the limited number of included studies and the small number of cases, the above conclusion still needs more high-quality research to be verified.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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