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ORIGINAL ARTICLE

Serum Adropin Level in Patients with Stable Coronary Artery Disease

Liang-Ping Zhao, MD [a,b], Wei-Ting Xu, MD [b], Li Wang, MD [b], Tao You, MD [b], Siew-Pang Chan, PhD [c,d,e], Xin Zhao, MD [a], Xiang-Jun Yang, PhD [a*]

[a]Department of Cardiology, The First Affiliated Hospital of Soochow University, PR China
[b]Department of Cardiology, The Second Affiliated Hospital of Soochow University, PR China
[c]Department of Medicine, Yong Loo Lin School of Medicine, National University of Singapore, Republic of Singapore
[d]Cardiovscular Research Institute, National University Heart Centre Singapore, National University Health System, Republic of Singapore
[e]Department of Mathematics & Statistics, Faculty of Science, Technology & Engineering, La Trobe University, Melbourne, Vic, Australia

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Objectives Adropin is a newly identified secreted protein implicated in the regulation of insulin sensitivity and vascular endothelial function. Recent studies have shown that lower serum adropin level is related to acute myocardial infarction and coronary atherosclerosis. The primary objective of this study was to ascertain the association of serum adropin level with stable coronary artery disease (SCAD).

Methods We prospectively recruited a cohort of patients with SCAD and similar sample size subjects without coronary artery disease as controls. Their serum adropin levels were measured, and the severity of coronary atherosclerosis in SCAD patients was quantified with the syntax score.

Results A total of 116 patients with SCAD and 116 control subjects without coronary artery disease were recruited. Patients with SCAD had lower serum adropin levels when compared with the controls (59.2±19.3 versus 70.0±18.2 pg/mL, P<0.001). The multiple logistic regression revealed that low serum adropin level was a significant predictor of SCAD (AOR 0.976, 95% CI 0.960–0.992; p=0.003). Through the gamma regression model, it was further revealed that serum adropin level is significantly associated with syntax score (coefficient: -0.134, 95% CI: -0.212– -0.056; p=0.001).

Conclusions Low serum adropin level is a significant predictor of SCAD. It is also associated with syntax score, thus indicating the close relationship between adropin and coronary atherosclerosis.

Keywords Adropin • Stable coronary artery disease • Syntax score • Insulin resistance • Predictor

Introduction

Adropin is a recently identified secretory protein that participates in the regulation of energy homeostasis and insulin response. It is encoded by the energy homeostasis associated gene (Enho) and expressed in the liver, brain and endothelial cells [1,2]. Animal studies have shown that adropin knockout mice exhibited dyslipidaemia and insulin resistance [3], and transgenic overexpression or systemic administration of adropin could attenuate insulin resistance and glucose intolerance in diet-induced obese mice [1]. A recent study also revealed that obese children had lower serum adropin levels than healthy counterparts, and lower adropin level was an independent predictor of nonalcoholic fatty liver disease in obese adolescents, thus suggesting the potential effects of adropin on lipid metabolic homeostasis [4].

Apart from the impact of adropin on body energy metabolism, there is also growing evidence that adropin is a marker

*Corresponding author at: Department of Cardiology, The First Affiliated Hospital of Soochow University, No 188, Shizi Street, Suzhou City, PR China 215006. Tel.: +86 051267780719; fax: +86 051267781712, Email: yang_xiangjun57@sina.com

of cardiovascular disorders. A laboratory test in vitro showed that adropin-treated endothelial cells presented with greater proliferation, migration, capillary-like tube formation and upregulation of the expression of endothelial nitric oxide synthase (eNOS) [2]. Celik's clinical study reported that patients with cardiac syndrome X had a lower serum adropin level than age-sex matched healthy subjects [5]. Coronary endothelial dysfunction contributing to the mechanisms of coronary microvascular dysfunction was suggested to be one of the potential pathogeneses for cardiac syndrome X [6,7]. A recent study with patients undergoing coronary artery bypass grafting showed that lower plasma adropin level was associated with late saphenous vein graft occlusion. This provided evidence that adropin had an effect on vascular atherosclerosis progression [8].

Moreover, lower serum adropin level was significantly associated with acute myocardial infarction onset [9], as well as being a significant predictor of angiographic coronary atherosclerosis [10]. However, there is a shortage of published evidence evaluating the relationship between adropin and stable coronary artery disease (SCAD) to date. In this exploratory study, we investigated the serum adropin levels of a cohort of patients with and without SCAD, and sought to ascertain the association of adropin with SCAD.

Methods

Study Design and Subjects

This was a prospective observational study conducted in an Asian country. We recruited consecutive patients hospitalised at the Second Affiliated Hospital of Soochow University China for the diagnosis and management of SCAD. All of the recruited patients had undergone coronary angiography, and only patients who were found to have $\geq$50% stenosis in at least one coronary artery were deemed eligible. The controls included subjects who were referred to Department of Cardiology for investigation, and were found to have no coronary disease according to the results of the coronary angiography or 64-slice CT angiography. Patients with acute coronary syndrome, severe heart failure (NYHA $\geq$ grade 3), end stage renal failure, current microbial infections and malignant tumour were excluded. Details about the study protocol were explained to the recruited patients and informed consent was obtained. The study protocol was approved by the Medical Ethics Committee of the Second Affiliated Hospital of Soochow University China.

Collection of Demographic and Clinical Data

The demographic and clinical characteristics of the study patients were collected from hospital case records. These included age, gender, cigarette smoking status and medical history (e.g., hypertension, diabetes mellitus). Patients' height and weight in light clothing were measured, and the body mass index (kg/m^2) was calculated as weight (kilogram) divided by the square of height in metres (square metres). Syntax score of the patients with SCAD was calculated according to the guideline of the Syntax Steering Committee and Boston Scientific Corporation, which has been validated for use to assess the severity of coronary atherosclerosis [11].

Biochemical Investigations

Samples of venous blood were collected after overnight fasting, and stored at –80 °C prior to analyses. Serum adropin level was measured using a commercial ELISA kit (JRDUN Biotechnogy, Shanghai, China). High sensitivity C-reactive protein (hsCRP) level was measured using a high-sensitivity ELISA kit (Orion Diagnostica, Espoo, Finland). Fasting plasma glucose was measured with the hexokinase method and insulin concentration was assessed using radioimmunoassay techniques. Blood urea nitrogen, creatinine, and serum lipid profiles (including triglyceride, total cholesterol, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol) were assessed using standard methods. Insulin resistance index was expressed by the homeostasis model assessment for insulin resistance (HOMA-IR) calculated from [fasting plasma glucose (mmol/L)$\times$fasting plasma insulin (mU/L)] / 22.5 [12].

Statistical Analyses

Exploratory data analysis involving quantitative and qualitative (nominal and ordinal) was performed with independent-sample t tests (or its nonparametric counterpart, Wilcoxon-Mann-Whitney tests, if the data were skewed) and chi-squared tests, respectively. In the following confirmatory analyses based on the generalised linear modelling (GLM) framework, tow regression models were applied: a) binary logistic regression for identifying which risk factors were associated with SCAD and b) gamma regression for ascertaining the relationship between adropin and syntax score in patients with SCAD, while considering other covariates. The final models were chosen based on a backward elimination procedure. Their goodness-of-fit, interpretability and all possible merits were considered. Analysed with SPSS 17.0 for Windows (SPSS Inc, Illinois, U.S.A.) and Stata MP 13 (Stata Corporation, Texas, U.S.A), all statistical tests were conducted at 5% level of significance.

Results

Demographic and Clinical Characteristics

Between January 2011 and December 2012, 116 consecutive patients with SCAD including stable angina and asymptomatic myocardial ischaemia were successfully recruited in this study. In the same period, we recruited 116 controls who were referred to Cardiology for investigation and were found to have no coronary artery disease. Patients' demographic and clinical characteristics are presented in Table 1. Among the total of 232 study patients, the overall serum adropin level was 64.6$\pm$19.5 pg/mL. Serum adropin level was significantly