Low Adiponectin Serum Level – Reduced Protective Effect on the Left Ventricular Wall Thickness

Kristina Selthofer-Relatić1, Radivoje Radić2, Aleksandar Včevar1, Robert Steiner1, Vedrana Vizjak1, Miroslav Šram1, Marija Tripolski1, Pašezada Kosović3, Ivica Bošnjak1 and Robert Selthofer2

1 »J. J. Strossmayer« University, Osijek University Hospital Center, Clinic of Internal Medicine, Osijek, Croatia
2 »J. J. Strossmayer« University, School of Medicine, Department of Anatomy, Osijek, Croatia
3 »J. J. Strossmayer« University, Osijek University Hospital Center, Department of Nuclear Medicine, Osijek, Croatia

ABSTRACT

Adiponectin, secreted by fat tissue, is down-regulated in obesity and may be involved in obesity-related disorders. It has anti-inflammatory, antiatherosclerotic and antidiabetic effect. Obesity is a strong predictor for hypertension and cardiovascular diseases. Recent studies showed that adiponectin level has important role in metabolic disorders, arterial hypertension and ischemic heart disease but its effect on left ventricular hypertrophy (LVH) has not been fully clarified. The aim of this research is to determine whether the protective effect of adiponectin against development of left ventricular hypertrophy is decreased in hypertensive overweight patients. The study included 61 adult, overweight hypertensive patients, with body mass index in range 25–30 kg/m². Patients had regular morning glucose serum values and regular creatinine level. They were divided into four groups, according to sex and the presence of LVH. There were 16 female and 15 male hypertensive patients with LVH and 15 female and 15 male hypertensive patients without LVH, who were a control group. Glucose profile, lipidogram, creatinine clearance and anthropometric measures were determined in all patients. Cardiovascular measurements were taken applying two-dimensional ultrasound. Adiponectin serum level was measured using enzyme immunoassay (ELISA). Results showed that adiponectin serum level was significantly lower in hypertensive, overweight females and males with LVH than in the control groups without LVH. Adiponectin serum level did not correlate significant with intraventricular or with posterior wall thickness of left ventricle. Hypoadiponectinemia presents part of neurohumoral, non-haemodynamic system who contributes to obesity-related hypertension and left ventricular hypertrophy development. Low adiponectin level together with others adipokines, cytokines and chemokines secreted by fat tissue could contribute to pathophysiologic changes of the myocardium via unknown molecular mechanisms yet.

Key words: adipokines, adiponectin, cardiovascular disease, hypertension, myocardial hypertrophy, obesity

Introduction

Adipose tissue is the biggest endocrine organ. Obesity is characterized by uncontrolled expansion of adipose tissue that secretes numbers of cytokines known as adipokynes1. It has autocrine, paracrine and endocrine functions2. Disregulation of that secretion leads to obesity-related disorders including metabolic syndrome3, diabetes, atherosclerosis, hypertension and cardiovascular diseases4. Adiponectin, known also as Acrp30, apM1, AdipoQ or GBP28, is an adipocytokine that is down-regulated in obesity. It exists in three different high-order complexes: high molecular weight form (HMW), low molecular weight form (hexamer) and trimetric form1. Critical mediators for adiponectin signaling are found in the skeletal muscles (ADIPOR1) and the liver (ADIPOR2)5. APPL1, an adaptor molecule, interacts with the intracellular fragment of AdipoR1. Expression of APPL1 is ubiquitous, which may reflect widespread relevance of adiponectin signaling in various tissues1. Research sho-
Adiponectin affects sympathetic nervous system activity via central regulation. Alterations in fat accumulation in intraabdominal organs, such as visceral adipose tissue and the liver, send afferent neuronal signals to the brain, leading to modulation of sympathetic tonus. In that way, these humoral and neuronal signaling pathways communicate with each other, causing changes in blood pressure and sympathetic nerve activity. Low adiponectin serum level leads to hypertension through endothelial dysfunction and NO decrease causing vasoconstriction and by overproduction of angiotensin II. Adiponectin can have important role in protection against cardiac hypertrophy in conditions of cardiac overload such as hypertension, hypertrophic cardiomyopathy and ischemic heart disease. Molecular basis linking obesity with cardiovascular diseases has not been fully clarified.

Materials and Methods

Patients

The research included 61 adult patients. They were divided into four groups according to the existence of left ventricular hypertrophy (LVH): there were 16 female patients with LVH and 15 male patients with LVH. In the control groups there were 15 females and 15 males without LVH. In all patients body mass index (BMI) was in range 25–30 kg/m². All patients were hospitalized on Department for Cardiovascular medicine because of first myocardial infarction. According to their medical records they had personal history of essential hypertension for at least five years. All patients had second degree of arterial hypertension pursuant to European society of hypertension/European society of cardiology 2007. guidelines for the management of arterial hypertension. The presence of secondary hypertension was excluded in all patients.

Exclusion criteria for the study were glucose intolerance, diabetes mellitus, increased creatinine level in the morning serum, valvular heart disease and left ventricular ejection fraction below 50%. All women were postmenopausal and possible effect of estrogen was excluded.

All patients were all without early and late acute complications after myocardial infarction as arrhythmias, pericarditis, heart failure, cardiogenic shock. They were discharged from hospital fourteen days after acute event in a stable condition.

They were treated with nitrates, beta blockers, ACE inhibitors and aspirins. According to recent studies, ACE inhibitors and selective beta blockers increase plasma adiponectin levels while there is very little evidence to suggest direct effect of aspirin on adipocytes.

Patient’s history, clinical examination, electrocardiography, X-ray of the thorax, biochemical blood analysis, adiponectin level and two-dimensional echocardiography were taken for each patient. All patients gave their written informed consent. The study was approved by ethical committees of our institutions.

Anthropometric measurements

Weight and height were measured by standard techniques. The most common methods for diagnosing overweight and obesity are based on BMI (kg/m²). Body mass index was calculated as body weight divided by height squared. Waist end hips circumference was taken by tape measure. Waist circumference was measured at the umbilical level, in the middle between the lowest rib and the iliac crest. Hip circumference was measured at the trochanter level.

Biochemical blood analysis

Blood glucose level, serum creatinine level and lipogram were measured in all patients. Blood samples for biochemical analysis were taken in the morning, on an empty stomach. All patients had normal blood glucose values, measured five times during hospitalization. Also, they all had regular creatinine serum level. Cholesterol, triglyceride, LDL, HDL were measured before hypolipemic therapy. Creatinine clearance was calculated using Cockcroft-Gault equation.

Cardiovascular determinations

In all patients a 12-lead ECG was performed two times a day to monitor coronary heart disease stabilization. Also, X-ray of the thorax was taken to evaluate the left ventricular enlargement.

Echocardiographic determinations were obtained by two-dimensional ultrasound Siemens Acuson CV 70 with cardiologic probe P4-2. During the examinations patients were lying in the left lateral position. Intraventricular septum (IVS) and posterior wall thickness (PWT) of the left ventricle were determined by M-mode technique. Ejection fraction was measured by Simpson Bi-plane method, and all the patients had normal value, which is 50% or higher.

Echocardiographic measurements were taken according to Textbook of Clinical Echocardiography by Otto (3rd edition, Elsevier Sounders 2004), where the referent value defining LVH in both sexes was 12 mm or more. The data were classified into two groups, regarding IVS and PWT. Both patients with LVH and patients without LVH were examined.
Determination of adiponectin in serum

Blood samples for adiponectin were taken from all subjects between 7 and 7:30 a.m. on the twelfth day after myocardial infarction, on an empty stomach. Total circulating adiponectin serum level was measured using enzyme immunoassay for quantitative determination of human adiponectin, ELISA KAPME09, IN VITRO DIAGNOSTIC USE, Biosource Europe S.A, Nivelles, Belgium. Majority of clinical studies involving adiponectin and human diseases only describe the relationship between total circulating levels of adiponectin. Use of asays measuring total levels of adiponectin in large clinical studies remains a legitimate approach6.

Statistical methods

Data are presented as mean±SD. All statistical tests were two-sided and carried out to a significance level (P) of 0.05. Statistical analysis were done by non-parametric Mann-Whitney test was used for statistical analysis of adiponectin distribution in hypertensive patients with and without LVH. Spearman method was used to assess univariate relations. The value p<0.05 was considered statistically significant. Data were prepared for analysis in Microsoft Excel 2003. Statistical analysis was made by SPSS 15.0 for Windows Evaluation Version and Statistica 7.1.

Results

All patients were adults with similar build and regular blood glucose and serum creatinine levels. Demographic, anthropometric, biochemical and echocardiographic data for all groups of patients are given in Table 1. All subjects were hypertensive males and females and they were divided into four groups according to sex and presence of LVH. First two groups were males and females with LVH and control groups were males and females without LVH. LVH is characterized by intraventricular wall thickness, as the most significant indicator of LVH, and by posterior wall thickness. Ejection fraction (EF) was preserved in all patients, above 50%.

Results showed that adiponectin serum levels were statistically significantly lower in hypertensive females with left ventricular hypertrophy than in females without LVH (p=0.009). Also, hypertensive males with left ventricular hypertrophy had statistically significantly lower adiponectin level than males without LVH (p=0.035) (Figure 1).

Serum adiponectin level did not have significant negative correlation with intraventricular wall thickness in females with LVH (p=0.790) as well as with posterior wall thickness of the LV (p=0.803). Also, in males with left ventricular hypertrophy there was no statistically significant negative correlation between adiponectin serum level and intraventricular wall thickness (p=0.649)

| TABLE 1 | DEMOGRAPHIC, ANTHROPOMETRIC, BIOCHEMICAL AND ECHOCARDIOGRAPHIC DATA |
|-------------|-----------------|-----------------|-----------------|-----------------|
|             | Hypertensive males with LVH | Hypertensive females with LVH | Hypertensive males without LVH | Hypertensive females without LVH |
| n            | 15               | 16               | 15               | 15               |
| Age, years (range) | 56±9             | 68±8             | 57±9             | 60±8             |
| Weight (kg)  | 81.60±9.08      | 73.50±8.91      | 80.8±8.89       | 68.73±5.68       |
| BMI (kg/m²)  | 26.56±1.48      | 27.41±2.07      | 26.46±1.83      | 26.50±1.80       |
| Wc (cm)      | 101.13±6.23     | 96.06±6.90      | 98.2±8.58       | 89.26±8.81       |
| Hc (cm)      | 101.40±4.26     | 101.69±5.87     | 99±7.69         | 97.93±6.76       |
| Bg (mmol/L)  | 5.33±0.80       | 5.54±0.75       | 5.66±0.66       | 5.75±0.48        |
| Serum creatinine (µmol/L) | 79.93±14.72 | 72.56±14.62 | 76.53±10.37 | 74.86±10.61 |
| Cc (mL/min)  | 103.96±20.29    | 92.77±26.24     | 108.67±19.44    | 92.24±22.62     |
| Cholesterol (mmol/L) | 5.15±1.82 | 5.81±1.35 | 5.38±1.11 | 5.38±1.50 |
| Triglycerides (mmol/L) | 1.99±0.99 | 1.86±0.83 | 2.07±1.59 | 1.82±0.814 |
| LDL (mmol/L) | 3.26±1.11 | 3.35±0.96 | 3.34±1.10 | 3.07±1.40 |
| HDL (mmol/L) | 1.02±0.13 | 1.22±0.62 | 1.11±0.34 | 1.20±0.33 |
| Adiponectin level (µg/mL) | 7.952±4.852 | 11.029±4.579 | 15.227±14.239 | 23.248±13.727 |
| IVS (mm)     | 14.73±1.67      | 14.19±1.94      | 10.53±0.64      | 10.267±0.799     |
| PWT (mm)     | 12.87±0.83      | 12.69±0.70      | 9.33±0.9        | 9.06±0.79        |
| EF (%)       | 57.67±7.37      | 58.06±6.90      | 58±7.04         | 60.8±6.51        |

Mean±SD, unless otherwise stated

LVH – left ventricle hypertrophy, BMI – body mass index, Wc – waist circumference, Hc – hips circumference, Bg – blood glucose, Cc – creatinine clearance, IVS –intraventricular septum, PWT – posterior wall thickness, EF – ejection fraction
Discussion and Conclusion

Hemodynamic factors have been thus far known to cause development of arterial hypertension and left ventricular hypertrophy. However, it has been discovered that neurohumoral, non-hemodynamic factors are also significant in development of LVH, which offers new possibilities in both prevention and treatment.

This research presents the effect of adiponectin on development of left ventricular hypertrophy in patients with hypertension and obesity, in other words the influence of neurohumoral system on development of LVH. Most studies up to the present have studied the role of adiponectin in metabolic disorders, arterial hypertension and coronary heart disease. This research included normoglycemic persons who were overweight, with BMI in range 25–30 kg/m² in order to determine the role of adiponectin and its serum level in patients who were not excessively obese. In our opinion patients’ therapy did not have significant influence on the results of this study taking into consideration that all the patients included in the study received only short-term therapy.

According to recent studies, adiponectin level can predict improvement of cardiac damage and function 7 days after myocardial infarction. This means that when the samples were taken to determine adiponectin level in our study, twelve days after coronary incident, there was no evidence that it can influence on adiponectin level.

According to data obtained up to the present, some studies have shown that adiponectin inhibits hypertrophic, extracellular signal-regulated kinase (ERK) in myocardium through activating AMP-activated protein kinase (AMPK) and is beneficial in the setting of pathological cardiac remodeling and acute cardiac injury. Also, research in mice has shown that adiponectin protects against overload-induced and adrenergically induced cardiac myocyte hypertrophy. Obesity-related hypertension in patients with hypoadiponectinemia develops through endothelial dysfunction (low NO level, increased TNF-α, increased C-reactive protein), increased rennin-angiotensin...
system activity and sympathetic nervous system overactivity (increased heart rate and peripheral vascular resistance) 1.

According to acquired knowledge on local production of adiponectin and its receptors in the myocardium, which has been obtained mostly in experimental studies, it is possible to assume that neurohumoral system represented by adipocytokines, and in our study by adiponectin, is a crucial part of a complex system that influences the function and pathophysiologic processes of the heart.

We proved significant difference between serum level of adiponectin in hypertensive patients with marked LVH in comparison to hypertensive patients without LVH. Hypoadiponectinemia, in the group of males and females with LVH, presents part of non-haemodynamic system who influence on obesity-related hypertension development and has part in the myocardial hypertrophy development via unknown mechanisms yet. Low adiponectin level could mean: lost of anti-inflammatory and antiatherogenic effect on the vascular endothel – leading to systemic hypertension and increased cardiomyocytes hypertrophic signal – leading to myocardial hypertrophy. Haemodynamic and non-haemodynamic factors (hypoadiponectinemia together with disregulation of other pro-inflammatory and proatherogenic adipokines, cytokines and chemokines secreted by fat tissue) contribute to pathophyslogic changes of the myocardium (Figure 4). Present results and hypothesis need to be proved by future investigations on molecular mechanisms level.

REFERENCES

K. Selthofer-Relatić

»J. J. Strossmayer« University, Osijek University Hospital Center, Clinic of Internal Medicine, J. Huttlera 4, 31000 Osijek, Croatia
e-mail: kristina.selthofer@os.t-com.hr

SNIŽENA SERUMSKA KONCENTRACIJA ADIPONEKTINA – REDUCIRAN PROTEKTIVNI UČINAK NA DEBLJINU STIJENKI LIJEVE KLIJETKE

SAŽETAK

Stanje pretilosti karakterizirano je sniženom koncentracijom adiponektina koja može utjecati na razvoj bolesti povezanih s debljinom. Adiponektin posjeduje antiinflamatorni, antitrošklerotski i antihipergišetni učinak, a debljina je direktno povezana s razvojem hipertenzije i kardiovaskularnih bolesti. Najnovije studije pokazuju da adiponektin ima važnu ulogu u razvoju metaboličkih poremećaja, arterijske hipertenzije i koronarne bolesti, no učinak na razvoj hiper- trofije lijeve klijetke (HLK) još nije razjašnjen. Cilj istraživanja je utvrditi da li protektivni učinak adiponektina je smanjen u procesu razvoja hipertrofije lijeve klijetke kod hipertoničara s prekomjernom tjelesnom težinom. U studiju je uključen 61 hipertoničar s ITM 25–30 kg/m2. Pacijenti su imali uredne vrijednosti glukoze u serumu natašte i koncentracije kreatinina. Podijeljeni su u četiri skupine, prema spolu i prisutnosti HLM: 15 muškaraca i 16 žena bez HLM s koncentracijama kreatinina. Podijeljeni su u četiri skupine, prema spolu i prisutnosti HLM: 15 muškaraca i 16 žena bez HLM, te 16 žena s HLM. Koncentracija glukoze i kreatinina, lipidogram i antropometrijska mjere- nja učinjena su svim ispitanim. Kardiovaskularna mjerenja učinjena su dvodimenzionalnim ultrazvukom. Koncentracija adiponektina određena je enzimatskim immunoassay testom (ELISA). Rezultati su pokazali da je koncentracija adiponektina u serumu značajno niža kod hipertenzivnih muškaraca i žena s HLM u odnosu na kontrolne skupine bez HLM. Koncentracija adiponektina kod hipertensijskih muškaraca i žena s HLM. Niska koncentracija adiponektina zajedno s drugim adipokinima, citokinima i kemokinima sintetiziranim u masnom tkivu pridonosi patofiziološkim promjenama miokarda putem još nerazjašnjenih molekularnih mehanizama.

791