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Original Article

Universal regulator adropin in patients with cardiorenal metabolic syndrome

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Abstract

The level of an adropin is a cytokine regulator of energy balance and metabolism of lipids and carbohydrates in the patients with the cardiorenal metabolic syndrome (CRMs) progression has not been precisely established. The purpose of the study was to determine adropin levels in different stages of CRMs and its correlations with other parameters. 70 patients with arterial hypertension stage 2, grade 2 were examined under the control of the University bioethics commission in compliance with the Helsinki Declaration of Human Rights. They were divided into 5 groups (G0, 1, 2, 3a, 3) depending on the stage of CRMs and glomerular filtration rate. The serum adropin level was determined by enzyme-linked immunosorbent assay. A body mass index, triglyceride-glucose index, and de Ritis index were calculated too. The results were statistically processed. Worsening of blood pressure control was accompanied by an increase in blood adropin level. The level of adropin did not depend on the stage of CRMs signifacantly. Adropin levels correlated with clinical metabolic parameters of obesity, triglycerides, glucose, triglyceride-glucose index, de Ritis index, blood pressure levels, left atrial size and left ventricular wall thickness in different way during kidney function decreasing. Adropin's correlations varied depending on the stage of CKMs, glomerular filtration rate, sex, age, and blood pressure control. The level of adropin did not depend on the stage of CRMs, but correlated differently with clinical and laboratory parameters.

Keywords: adropin, cardiorenal metabolic syndrome, stages, glomerular filtration rate, adropin correlations

Introduction

A new cytokine, adropin, was first identified in 2008. The peptide adropin consists of 76 aminoacid residues, has a cytoplasmic N-terminal and an extracellular C-terminal [1], and is synthesized mainly in the liver and brain from an energy homeostasis-associated protein [1, 2]. Adropin participates in the regulation of energy homeostasis, lipid and carbohydrate metabolism [1, 3], increases glucose oxidation and utilization, reduces insulin resistance.

In recent studies, adropinis considered to be a marker of chronic kidney damage in patients with diabetes mellitus [4]. However, adropin level in the conditions of the occurrence and progression of cardiorenal metabolic syndrome (CRMs) has not been precisely established. That's why our study of adropin level in patients with CRMs is relevant and necessary.

The purpose of the study was to determine adropin levels in different stages of cardiorenal metabolic syndrome and their correlations with clinical and laboratory parameters.

Material and methods

The cross-sectional observational study included 70 patients aged 40 to 75 with stage 2, grade 2 arterial hypertension and chronic heart failure of I-II functional classes. The study was approved by the Bioethics Committee of State Non-Profit Enterprise Danylo Halytsky Lviv National Medical University (protocol

No. 2 dated 21/02/2022), according to the principles of the Helsinki Declaration, European Convention on Human Rights and Biomedicine, and relevant laws of Ukraine. The patients were divided into 5 groups (G0, G1, G2, G3a, G3b) according to the stages of CRMs [5]. Comparative characteristics of patients by groups with different stages of CRMs are shown in Table 1. Patients with stage 1 CRMs were younger of age, but of maximum body weight. There were only men in the groups without a decrease in glomerular filtration rate (G0, G1), in other groups (G2, G3a, G3b) their number was 66.7%, 25.0%, 33.3%, respectively. According to hemodynamic parameters, stages and complications of hypertension, the groups were identical (Table 1).

In addition to the standard examination, serum adropin was quantified by immunoenzymatic analysis, reagents "Human ENHO (Adropin) ELISA kit (FineTest)" (China), norm up to 800 pg/ml. Body mass index (BMI), triglyceride-glucose index (TGGI), waist-to-height ratio, De Ritis index, glomerular filtration rate (GFR) according to MDRD were calculated.

Statistical processing was carried out using the "Statistica 6.0" program, the values are presented as the arithmetic mean with error (M±m). The correlation analysis was carried out according to Spearman-Pearson (r) method. The group differences were evaluated according to the t-criterion (Student). The level of significance was taken as $p<0.05$.

Results

It was stated that the level of adropin had a very wide range of fluctuations – from 231 to 1318 pg/ml, making an average of 778.47±35.62 pg/ml among all patients. Regardless of the presence or absence of CRMs, the concentration of adropin was inversely correlated with the levels of systolic and diastolic blood pressures ($r=-0.25$; $r=-0.26$, both $p<0.05$). Thus, the deterioration of arterial hypertension control was accompanied by an increase in the level of adropin in blood.

According to the level of GFR, the examined patients were divided into persons with normal values (G0+G1; n=11) and those with a decrease in GFR (G2+3a+3b; n=59). It was found that under the conditions of a decrease in GFR, the concentration of adropin was slightly higher, but the difference did not reach the level of significance (797.98±38.49 *vs*. 771.45±99.53 pg/ml, $p>0.05$). However, under the conditions of the presence of CRMs with a decrease in GFR, an increase in the amount of adropin can be considered unfavorable, which was significantly correlated with the amount of glucose ($r=0.28$; $p<0.05$) and the value of TGGI ($r=0.39$; $p<0.01$).

According to correlation analysis, fasting glucose levels in these patients correlated with hip circumference ($r=0.37$; $p<0.05$), waist-to-hip ratio ($r=-0.30$; $p<0.05$), left atrial size ($r=0.34$; $p<0.05$), left ventricular posterior wall thickness ($r=0.27$; $p=0.06$), and TGGI correlated with triglyceride content ($r=0.51$; $p<0.01$) and the De Ritis index ($r=-0.32$; $p<0.05$). Hence, it can be asserted that indirectly through carbohydrate metabolism under conditions of reduced renal function, an increase in adropin is accompanied by hyperglycemia, hypertriglyceridemia, femoral obesity, cardiac geometry abnormalities with diastolic dysfunction and left ventricular hypertrophy, and hepatic steatosis with a decrease in the De Ritis index.

Determining the level of adropin depending on the stage of CRMs showed that no dependence was detected. Thus, the level of adropin was 817.50±194.82 pg/ml in G0 patients; 745.14±121.60 pg/ml in G1; 797.61±54.15 pg/ml in G2; 796.80±56.76 pg/ml in G3a; 741.67±152.22 pg/ml in G3v; all $p>0.05$. Its amount

Table 1: Comparative characteristics of patients in groups with different stages of CRMs.

Indicator	G0, n=4	G1, n=7	G2, n=33	G3a, n=20	G3b, n=6
Age, years	58.75±5.15[1]	51.43±4.62[2, 3]	59.18±1.54[4]	69.90±1.10[1, 2, 4]	66.50±2.17[3]
Gender (m.-1,f.-2)	1.00±0.00[5, 6, 7]	1.00±0.00[8, 9, 10]	1.33±0.08[5, 8, 11]	1.75±0.10[6, 9, 11]	1.67±0.21[7, 10]
Height, cm	172.75±2.02[12]	172.29±1.75[13]	172.21±1.22[14]	165.00±1.65[12, 13, 14]	168.00±3.39
Body weight, kg	76.75±2.29[15, 16, 17]	93.43±3.20[15]	92.88±2.46[16]	86.80±2.82[17]	91.17±7.38
Heart rate per minute	79.50±0.50	76.57±3.72	76.51±2.02	78.40±2.30	80.17±4.90
SBP*, mm Hg	152.50±4.79	160.00±5.34	154.24±1.77	156.50±3.86	155.00±8.47
DBP*, mm Hg	92.50±4.79	97.86±1.49	96.21±1.32	89.50±1.77	95.00±2.24

Note: [1–17] – $p<0.05$; SBP* – systolic blood pressure; DBP* – diastolic blood pressure.

did not correlate with indicators of kidney function (creatinine, GFR, proteinuria).

However, among patients with missing CRMs (G0), serum adropin concentrations decreased proportionally with the body mass index increases (r=-0.98; p<0.05). In patients with preserved functional capacity of kidneys, but with stage 1 of CRMs the level of adropin decreased as diastolic blood pressure increased, which has been proved by adverse correlation (r=-0.77; p<0.05).

On the other hand, among patients with stage 2 CRMs adropin content correlated with TGGI (r=0.51; p<0.05), left ventricular ejection fraction (r=-0.50; p<0.01), and diastolic pressure (r=-0.358; p=0.06). That why an increase of adropin was more likely to be unfavorable. In patients with stage 3a CRMs, adropin content was inversely associated with systolic pressure (r=-0.58; p<0.05), and only among persons with stage 3b, the amount of adropin increased with age (r=0.87; p<0.05).

Morever, some differences have been found when gender was taken into account. Thus, among women with reduced GFR (G2+3a+3b), adropin levels were inversely correlated with BMI, waist and hip circumference, waist-to-height ratio, De Ritis index, and directly correlated with fasting glucose and TGGI values. Among men with reduced GFR, adropin had inverse correlations with triglyceride levels and TGGI (Figure 1).

Thus, it has been stated that the deterioration of hypertension control was accompanied by an increase in the level of adropin. The correlations of adropin with clinical and laboratory parameters of patients varied in accordance with the stage of CRMs, GFR, gender, age and hypertension control.

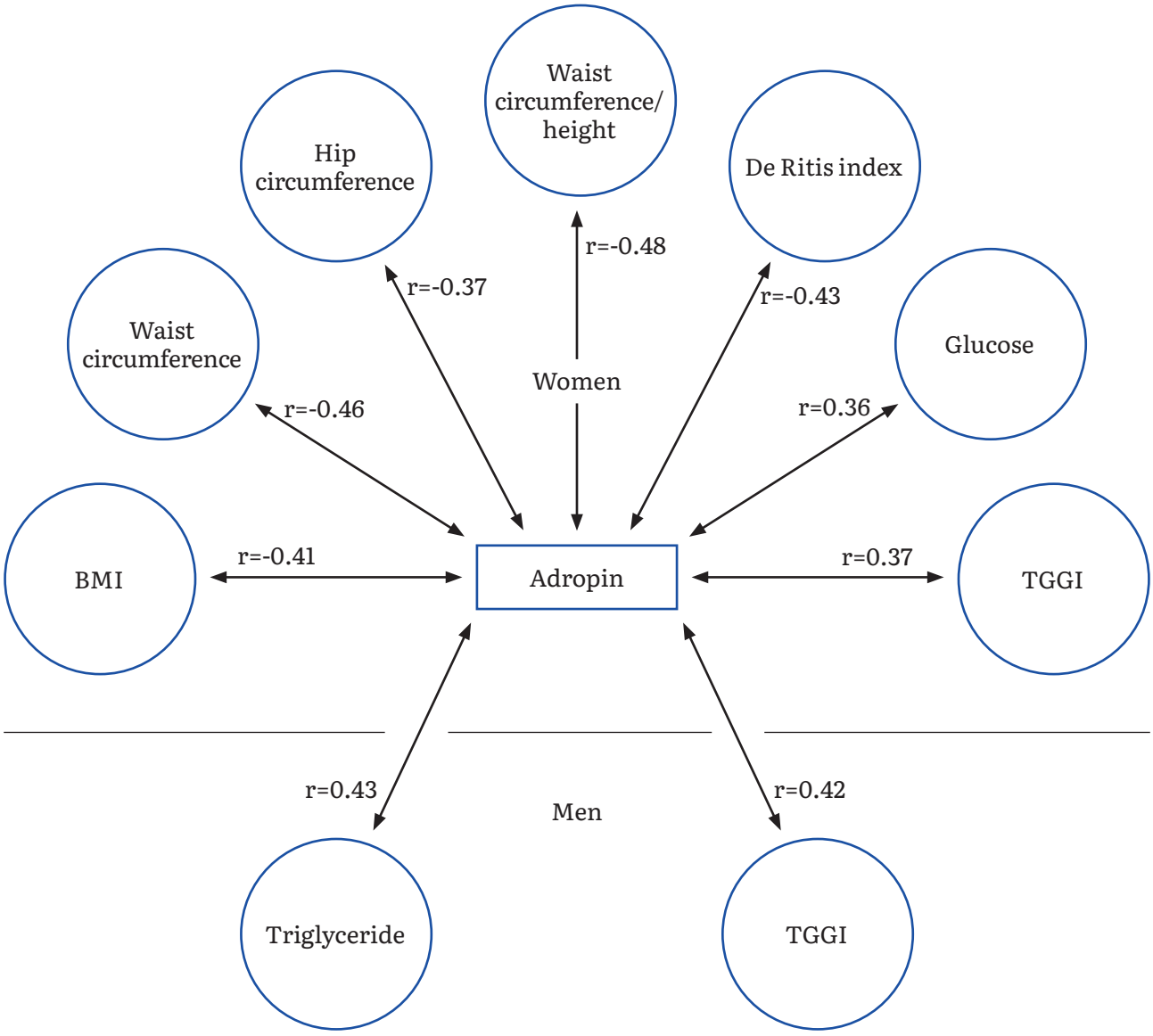

Figure 1: Significant and approximate correlations of adropine content in women and men with reduced GFR.

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Discussion

Our finding out an increase in adropin content with worsening the control of arterial hypertension corresponds to the results of previous studies [6]. Similar correlations of adropin with blood pressure levels were described in an experiment on mice, when pressures and adropin levels were simultaneously reduced as the result of regular training [7]. However, in patients with arterial hypertension who trained intensively, on the contrary, an increase in adropin and a decrease in blood pressure were noted [8], which requires further research. The ambiguity of data on the content of adropin under the conditions of metabolic syndrome was also noted by other researchers [9].

Regarding the role of adropin in the development and progression of kidney damage, the main studies so far have concerned patients with diabetic nephropathy and final-stage chronic kidney disease (CKD). It is described that the content of adropin was significantly reduced among those patients with CKD who required hemodialysis [10]. In an experiment on mice, adropin levels under CKD conditions were lower than those in animals without CKD and in animals with CKD treated with captopril [11]. Modern studies consider adropin as a marker of chronic kidney damage in patients with diabetes, even after excluding the effects of such factors as age, sex, BMI, creatinine level, microalbuminuria, use of statins and NDTG-2 inhibitors [4]. The increase in adropin under the conditions of diabetic CKD can be a compensatory response to oxidative stress and inflammation. Thus, it acts as a counterbalance to elevated markers of inflammation. At early stages of CKD, adropin is reduced, while in the terminal stages it increases, which is explained by the development of adropin resistance [4].

The mediated correlations of adropin content due to glucose with heart geometry parameters emphasize the scientific opinion that adropin is currently being studied as a biological marker of cardiovascular lesions in patients with CKD [12]. Thus, the adropin level of 304 pg/ml can be a threshold for the diagnosis of cardiovascular lesions with a specificity of 46.4% and a sensitivity of 84.4% [13].

Conclusion

Deterioration of hypertension control was accompanied by an increase in blood adropin content. The level of adropin did not depend on the stage of cardiorenal metabolic syndrome. Under the conditions of CRMs presence with a decrease in GFR, the level of adropin correlated with clinical metabolic parameters of obesity, triglyceride, glucose, TGGI, De Ritis index, blood pressure levels, left atrial size, and left ventricular wall thickness. Correlations varied in accordance with the stage of CRMs, GFR, gender, age and hypertension control.

Conflict of interest

The authors declare no conflict of interest.

Ethics approval

The approval for this study was obtained from the Ethics Committee of the Danylo Halytsky Lviv National Medical University (Approval ID: 417).

Consent to participate

Written informed consent was obtained from all the participants.

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