DE GRUYTER OPEN

DOI: 10.1515/folmed-2017-0066

ORIGINAL ARTICLE, MEDICINE

Relations of Apelin with Cardiac Remodeling in Patients with Hypertension and Type 2 Diabetes

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Received: 14 July 2016
Accepted: 24 June 2017
Published Online: 13 July 2017
Published: 30 March 2018

Key words: apelin, hypertension, type 2 diabetes, cardiac remodeling

Citation: Koval S, Iushko K, Starchenko T. Relations of apelin with cardiac remodeling in patients with hypertension and type 2 diabetes. Folia Med (Plovdiv) 2018; 60(1):117-23.

doi:10.1515/folmed-2017-0066

Background: The peptide apelin has antihypertensive and antidiabetic properties, but its role in the processes of cardiac remodeling in patients with hypertension and type 2 diabetes (T2D) is poorly understood.

Aim: The aim of the study was to investigate apelin levels in patients with hypertension and T2D and to determine its relations to heart structural parameters and types of cardiac remodeling.

Materials and methods: We examined 63 patients with hypertension and T2D. Investigation complex included physical examination, standard transthoracic echocardiography and determination of apelin serum levels by ELISA. Control group consisted of 16 volunteers.

Results: The apelin levels in patients were significantly lower than those in volunteers (0.882(0.788; 0.924) ng/ml versus 1.097(0.944; 1.171) ng/ml, $p<0.001$). Negative correlation relations of apelin with septal wall thickness ($r=-0.50$, $p<0.001$), posterior wall thickness ($r=-0.46$, $p<0.001$), left ventricle (LV) mass ($r=-0.39$, $p<0.01$), LV mass index ($r=-0.42$, $p<0.001$) and left atrium size ($r=-0.45$, $p<0.001$) were found. In patients with concentric remodeling of LV apelin levels were 0.918 (0.892; 0.984) ng/ml, with concentric LV hypertrophy – 0.855(0.722; 0.899) ng/ml, with eccentric LV hypertrophy – 0.884(0.856; 0.929) ng/ml ($p<0.05$, $p<0.001$, $p<0.001$ versus control, respectively). Patients with concentric LV hypertrophy had significantly lower apelin levels than patients with concentric remodeling of LV ($p<0.05$).

Conclusion: Patients with hypertension and T2D have significant reduction of apelin blood levels, which is accompanied by cardiac remodeling development primarily concentric LV hypertrophy and have negative correlation relations of apelin with heart structural parameters that characterize LV remodeling and left atrium size.

BACKGROUND

Hypertension and type 2 diabetes (T2D) are widespread diseases in the world. In the last years, a significant increase in the prevalence of the combination of these diseases has been observed. This combination increases the risk of cardiovascular complications by several times due to the mutually aggravating disease course and common target organ damage, including heart. Cardiac remodeling is inherent in patients with hypertension, accelerated by combination with T2D, including the development of hypertrophy of the left ventricle (LV), increasing the size of the left atrium (LA). Concentric LV hypertrophy (LVH) at the same time is one of the strongest predictors of cardiovascular (CV) risk. It is therefore important to search and explore new pathogenetic factors that affect the progression of both hypertension and T2D and are involved in the development of heart damage.[1]

One of these factors is apelin – the peptide capable of binding G protein-coupled receptor APJ and widely expressed in heart, lungs, kidneys, liver, adipose tissue, gastrointestinal tract, brain, adrenal glands, endothelium and human plasma. The gene of apelin encodes a 77 amino acid sequence called pre-pro-apelin. Upon cleavage by a family of endopeptidases pre-pro-apelin transforms in active forms, which are classified on the basis of the number of amino acids. Several active isoforms of apelin have been known - apelin-36, apelin-19, apelin-17, apelin-16, apelin-13, and apelin-12, which have similar biological activities.[2]

Endogenous peptide apelin is a functional antagonist of the renin-angiotensin system; it has powerful inotropic properties, is involved in the development of hypertension, reduces reperfusion destruction in myocardial infarction, shows vasodilatory properties, may change electrophysiological properties of the heart muscle, plays a role in the development of heart failure, renal lesions, atherosclerosis.[3-6] Also apelin influences carbohydrate metabolism, promotes glucose utilization, reduces insulin resistance.[7,8] At the same time data of apelin roles in the processes of cardiac remodeling in the patients with hypertension and T2D are very few.[9] Thus, the aim of the study was to investigate the levels of apelin in patients with hypertension and T2D and determine its relations to structural parameters of the heart and types of cardiac remodeling.

MATERIALS AND METHODS

Study population

The study included 63 Caucasian patients with hypertension grades 2-3 combined with T2D who were admitted to the Department of Arterial Hypertension of Government Institution "L.T.Malaya Therapy National Institute of the NAMS of Ukraine", Kharkiv. Definition and classification of hypertension, stratification of patients by total cardiovascular risk was performed according to 2013 ESH/ESC Guidelines.[1] The T2D diagnosis was made according to 2013 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD.[10]

Inclusion criteria for the study were the age of patients: more than 18 years of age, presence of combination of hypertension with T2D, informed consent signed by the patient. Exclusion criteria were as follows: malignant hypertension, symptomatic hypertension, myocardial infarction and stroke in the patient's history, secondary insulin-dependent diabetes, severe heart failure and coronary heart disease, congenital heart disease, acute or chronic systemic inflammatory conditions, severe pulmonary, liver and kidney diseases, known or treated malignancies, pregnancy.

Age of the patients ranged from 40 to 70 years, median age 57 (50;64) years. Among men 32 patients (51%) were examined, among women 31 persons (49%) were examined. Duration of hypertension in patients was 15 (10;20) years, diabetes duration was 4 (1;6) years. Median level of systolic blood pressure was 180 (170;180) mmHg and diastolic blood pressure was 110 (100;120) mmHg. Grade 2 hypertension was in 28 patients (44%), grade 3 hypertension - in 35 patients (56%). Median level of glycated hemoglobin in patients with hypertension and T2D was 7.5% (7.1;7.8).

The control group consisted of 16 healthy volunteers (8 men and 8 women) who did not have history of any CV risk factors or illnesses. Its median age was 54.5 (49;58) years ($p>0.05$ in comparison with the patients).

Echocardiography

All subjects underwent standard trans-thoracic echocardiographic examination on the day of serum collection. The examinations were carried out using a "ULTIMA PA" echocardiography machine (RADMIR, Ukraine). All cardiac chamber measurements were made as suggested by the American Society of Echocardiography[11], including LV internal dimension at end diastole (LVIDd), septal wall thickness at end diastole (SWTd), posterior wall thickness at end-diastole (PWTd), left atrium (LA) anteroposterior linear dimension, diameter of the aortic root were measured using two-dimensional (2D), or M-mode images taken from parasternal long axis views of the heart. The LV ejection fraction (EF) was calculated using the LV volumes by the modified biplane Simpson's rule. LV mass (LVM) was calculated using the following formula:

$$LVM = 0.80\times(1.04\ [(LVIDd+PWTd+SWTd)^3 - (LVIDd)^3])+0.6\ g.$$

Body surface area (BSA) was calculated by the Dubois formula:

$$BSA = 0.007184\times height\ (cm)^{0.725}\times weight\ (kg)^{0.425}$$

LVM index was calculated by dividing the LVM by the BSA. LVH was estimated using thresholds of 95 g/m^2 for women and 115 g/m^2 for men.[1] Calculation of relative wall thickness (RWT) by the formula, (2×PWTd)/LVIDd, permits categorization of an increase in LV mass as either concentric (RWT≥0.42) or eccentric (RWT<0.42) LVH and allows identification of concentric remodeling (normal LV mass with increased RWT). Normal LV geometry was determined as normal LV mass with normal RWT.

Blood sampling

Blood samples were drawn in the early morning from the antecubital vein of each subject after an overnight fasting. Once drawn, the serum samples were centrifuged and immediately stored at -20°C prior to the analysis. Levels of apelin were measured

by enzyme-linked immunosorbent assay (ELISA), using ELISA kit of Phoenix Pharmaceuticals Inc, USA and automated ELISA assay system ImmunoChem – 2100 (HTI, USA) according to the manufacturer's instructions. Precision of inter and intra-assay variation were <10% and <15%, respectively. Minimal detectable concentration of apelin was 0.07 ng/ml, range of normality – 0-100 ng/ml, linear range – 0.07-0.9 ng/ml.

Statistical analysis

The data were analyzed with IBM SPSS Statistics version 19 (SPSS for Windows, Version 19.0., SPSS Inc., Chicago, IL, USA). The distribution of variables normality was tested with the Kolmogorov-Smirnov test. The quantitative data were presented using median as a measure of position and quartile, as a measure of dispersion. Continuous variables were defined as median (25 quartile; 75 quartile). The Mann-Whitney test was used to determine the differences between two groups. Kruskal-Wallis was used for abnormally distributed variables with more than 2 samples. The relationships between levels of apelin and other clinical indicators were examined using Spearman's correlation. A value of $p<0.05$ indicated a statistically significant result.

Ethics statement

The protocol of the study was carried out according to the principles of the Declaration of Helsinki and approved by local Ethics Committee (No 03.04.2012/10058).[12] Written informed consent was obtained from all the participants before enrolment.

RESULTS

The blood levels of apelin in all patients with hypertension and T2D were significantly lower than in healthy volunteers - 0.882 (0.788;0.924) ng/ml versus 1.097 (0.944;1.171) ng/ml, $p<0.001$ **(Fig. 1)**.

For Kruskal-Wallis test the levels of apelin were ranged in three different levels of concentrations – its concentration of more than 0.944 ng/ml (normal), its concentration within 0.832–0.944 ng/ml (less than normal) and its concentration of less than 0.832 ng/ml (significantly less than normal). Hearts indicators, which were evaluated are LVIDd, RWT, SWTd, PWTd, LVM, LVM index, LV geometry type, LV EF, LA anteroposterior linear dimension, diameter of the aortic root. We tested the hypothesis H0 - the three different apelin concentration ranges did not affect the value of the studied parameters in these samples. The test results showed significant effect of blood apelin levels on SWTd, PWTd, RWT, LVM, LVM index, LV geometry type and LA anteroposterior linear dimension in patients with hypertension and T2D **(Table 1)**.

Correlation analysis revealed that in patients with hypertension and T2D the apelin levels significantly negatively correlated with SWTd ($r=-0.50$, $p<0.001$), PWTd ($r=-0.46$, $p<0.001$), LVM ($r=-0.39$, $p<0.01$), LVM index ($r=-0.42$, $p<0.001$), LA anteroposterior linear dimension ($r=-0.45$, $p<0.001$) **(Table 2)**.

Among patients with hypertension and T2D concentric remodeling of LV was observed in 10 patients (16%), concentric LVH was observed in 29 patients (49%) and eccentric LVH was observed in 24 patients (38%). In each of these groups of patients the levels of apelin were lower than in control group: in patients with concentric remodeling of LV – 0.918 (0.892;0.984) ng/ml ($p<0.05$ – versus control), in patients with concentric LVH – 0.855 (0.722;0.899) ng/ml ($p<0.001$ – versus control), in patients with eccentric LVH – 0.884 (0.856;0.929) ng/ml, ($p<0.001$ - versus control). The patients with concentric LVH had significantly lower levels of apelin than the patients with concentric remodeling of LV, $p<0.05$ **(Table 3, Fig. 2)**.

DISCUSSION

Our findings about the basal levels of apelin in hypertensive patients with T2D are comparable to those of other authors. Numerous studies have shown that apelin levels are closely associated with reduced blood pressure in hypertensive patients and in patients with masked hypertension, and even with high normal blood pressure.[5,13-15] This allows to consider apelin as an important regulator of blood pressure and hypertension progression.

The data from the study suggests the importance of interactions of the processes of cardiac remodeling with apelin in patients with hypertension and T2D. Meanwhile, the patients have negative correlations of apelin levels with basic structural parameters of the heart, which characterize abnormal LV geometry. At the same time, the lowest apelin levels were observed in patients with concentric LVH, which is the strongest predictor of increased risk of cardiovascular incidences.[16,17] This suggests a protective influence of apelin on the processes of pathological LV remodeling.

Our hypothesis about the positive cardiac role of apelin is confirmed by other authors. Experimental data demonstrated that chronic administration of apelin to mice reduces ventricular overload on hypertrophied hearts.[18] Another study has determined

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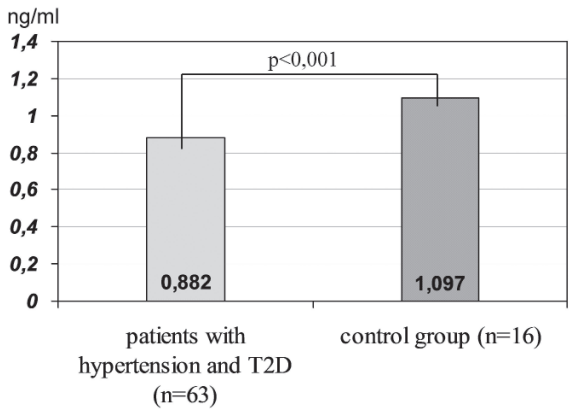

Figure 1. The apelin blood levels in patients with hypertension and T2D and control group.

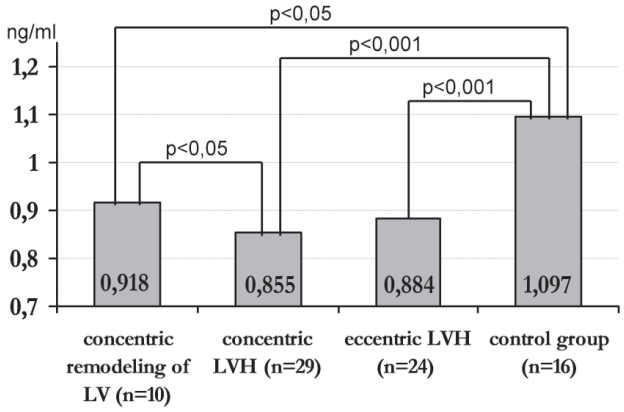

Figure 2. The apelin blood levels in patients with hypertension and T2D depending on LV remodeling and control group.

Table 1. Kruskal-Wallis test results

Heart indicators, n=63	χ^2	p
LVIDd	0.911	>0.05
RWT	8.459	<0.05
LVM	14.286	<0.01
LVM index	12.579	<0.01
LV geometry type	6.982	<0.05
LV EF	0.502	>0.05
SWTd	21.281	<0.001
PWTd	22.248	<0.001
LA anteroposterior linear dimension	20.604	<0.001
diameter of the aortic root	3.491	>0.05

LVIDd - left ventricle internal dimension at end diastole; RWT - relative wall thickness; SWTd - septal wall thickness at end diastole; PWTd - posterior wall thickness at end diastole; LVM - left ventricle mass; LV - left ventricle; EF - ejection fraction; LA - left atrium; n - numbers of patients

Table 2. The correlation of apelin with cardiac structural parameters

Heart indicators, n=63	r	*p*
SWTd	-0.50	<0.001
PWTd	-0.46	<0.001
LVM	-0.39	<0.01
LVM index	-0.42	<0.001
LA anteroposterior linear dimension	-0.45	<0.001

SWTd - septal wall thickness at end diastole; PWTd - posterior wall thickness at end diastole; LVM - left ventricle mass; LA - left atrium; n - numbers of patients

Table 3. Apelin blood levels depending on the type of cardiac remodeling and control group

Groups of patients and control	Number of observations	Levels of apelin, ng/ml	p, compared with the control group
Concentric remodeling of LV	10	0.918 (0.892;0.984)	<0.05
Concentric LVH	29	0.855 (0.722;0.899)*	<0.001
Eccentric LVH	24	0.884 (0.856;0.929)	<0.001
Control group	16	1.097 (0.944;1.171)	

LV - left ventricle; LVH - left ventricle hypertrophy
*- significant difference in comparison with the patients with concentric remodeling of LV, p<0.05.

the relation of apelin deficiency with the development of LVH in hypertensive patients. It was concluded that apelin may be used as a predictor for assessing the prevalence of LVH. Part of the study in vitro indicated a data about direct impact of apelin on the process of cardiomyocytes adaptation to hypertrophic incentives.[19] The application of apelin has protective effect on hypertrophied myocardium and its deficiency leads to hypertrophy of the LV.[20]

The results of our study may be indicative of involvement of apelin in the processes of pathological remodeling of the LA. Some studies have shown the reduction of apelin levels in patients with atrial fibrillation.[21] Some authors consider that apelin affects the electrophysiological characteristics of the heart muscle.[22] The reduction of its production may lead to the development of life-threatening arrhythmias, and its low level before cardioversion is a poor prognostic sign. Moreover, researchers have noted the dependence of the efficiency of antiarrhythmic therapy in these patients on baseline levels of this peptide.[23,24] One of the factors that affect the risk of developing atrial fibrillation, is a remodeling of the LA as an extension of its cavity.[11] The inverse relationship of apelin levels with LA size obtained in our study can contribute to the prediction of the risk of developing atrial fibrillation.

Limitations of the study

Our study has several limitations. The present study has the relatively small number of patients. There are no data about the relationships of apelin with parameters of diastolic function of the heart. Apelin levels were measured only once during hospitalization. Its levels and relations with cardiac parameters in response to different variants of antihypertensive treatment were not evaluated. We could not assess cardiac remodeling and cardiovascular events depending on basal apelin concentrations in long term period.

CONCLUSION

Significant reduction of apelin blood levels was found in patients with hypertension and T2D compared with healthy individuals. Reduced blood levels of apelin are accompanied by development of cardiac remodeling primarily concentric LV hypertrophy. Negative correlation of apelin with major heart structural parameters that characterize the LV remodeling and size of left atrium have been observed. The data allow us to consider apelin as an important prognostic marker of progression of hypertension with T2D, the development of pathological remodeling of the left ventricle and left atrium of the heart.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Взаимосвязь апелина с ремоделированием сердца у больных гипертонической болезнью с сахарным диабетом 2 типа

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Дата получения: 14 июля 2016
Дата приемки: 24 июня 2017
Дата онлайн публикации: 13 июля 2017
Дата публикации: 30 марта 2018

Ключевые слова: апелин, гипертония, диабет 2 типа, ремоделирование сердца

Образец цитирования: Koval S, Iushko K, Starchenko T. Relations of apelin with cardiac remodeling in patients with hypertension and type 2 diabetes. Folia Med (Plovdiv) 2018; 60(1):117-23.

doi:10.1515/folmed-2017-0066

Введение: Пептид апелин обладает антигипертензивными и антидиабетическими свойствами, но его роль в процессе ремоделирования сердца у больных с гипертонией и сахарным диабетом 2 типа (ДТ2) на данный момент не выяснена.

Цель: Целью настоящей работы является исследование уровней апелина у больных с гипертонией и ДТ2 и установление взаимосвязей со структурными параметрами сердца и типами ремоделирования сердца.

Методы: Нами было обследовано 63 больных с гипертонией и ДТ2. Исследовательский комплекс включал в себя физикальный осмотр, стандартную трансторакальную эхокардиографию и установление сывороточных уровней апелина при помощи метода ELISA. Контрольная группа состояла из 16 добровольцев.

Результаты: Уровни апелина у больных оказались в значительной степени более низкими по сравнению с показателями у добровольцев (0.882(0.788; 0.924) ng/ml и 1.097(0.944; 1.171) ng/ml, $p<0.001$) соответственно. Были установлены отрицательные корреляционные взаимосвязи апелина с толщиной стены межжелудочковой перегородки ($r=-0.50$, $p<0.001$), толщиной задней стены ($r=-0.46$, $p<0.001$), массой левого желудочка (ЛЖ) ($r=-0.39$, $p<0.01$), индексом массы ЛЖ ($r=-0.42$, $p<0.001$) и размером левого предсердия ($r=-0.45$, $p<0.001$). У больных с концентрическим ремоделированием ЛЖ уровни апелина составляли 0.918 (0.892; 0.984) ng/ml, с концентрической гипертрофией ЛЖ – 0.855(0.722; 0.899) ng/ml, с эксцентрической гипертрофией ЛЖ– 0.884(0.856; 0.929) ng/ml ($p<0.05$, $p<0.001$, $p<0.001$ соответственно по сравнению с контрольной группой). У больных с концентрической гипертрофией ЛЖ установлены сравнительно более низкие уровни апелина по сравнению с пациентами с концентрическим ремоделированием ЛЖ, $p<0.05$.

Заключение: У больных с гипертонией и ДТ2 установлено значительное понижение уровней апелина в крови, которое сопровождается развитием ремоделирования сердца - главным образом концентрической левожелудочковой гипертрофией и наличие отрицательных коррелятивных взаимосвязей апелина со структурными параметрами сердца, характерными для левожелудочкового ремоделирования и размера левого предсердия.