УДК 616.12-008.331.1+616.379-008.641-074:577.175.85

INVESTIGATION OF PLASMA APELINLEVEL IN PATIENTS WITH ESSENTIAL HYPERTENSION CORRESPONDING TO THE TYPE OF OBESITY

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BMI as a measure of obesity is a good predictor of all-cause and cardiovascular mortality, cardiovascular mortality seems to be better predicted by abdominal or central obesity in addition to BMI.

Aim of the study: to investigate apelin's activity in patients with essential hypertension with obesity according to the type of obesity.

Materials and methods: 96 patients with essential hypertension were examined. Inquiring, inspection and laboratory investigations were provided.

Results: the average means of WC, BMI and apelin level in total group were significantly higher in comparing with control group. Patients were categorized into 4 cluster groups based on k-means according apelin and BMI data. No significance were in WC data between patients of 3rd and 4th clusters, but the opposite apelin activity was detected. In cluster 4, adipokine's activity was the lowest one from total amount of patients and in cluster 3 – the highest one. Patients of 4th cluster had pronounced carbohydrate disorders and dyslipiemia.

Summary: the increased level of peptide apelin in hypertensive patients with visceral type of obesity was detected. Overexpression of apelin in hypertensive patients with moderate abnormalities in lipid and carbohydrate metabolism is considered as compensatory reaction.

Key words: apelin, essential hypertension, obesity.

Obesity has been consistently associated with hypertension and increased cardiovascular risk. Based on population studies risk estimates indicate that at least two-thirds of the prevalence of hypertension can be directly attributed to obesity. Although BMI as a measure of obesity is a good predictor of all-cause and cardiovascular mortality, as recently described in two separate meta-analyses [1, 2], overall mortality and especially cardiovascular mortality seems to be better predicted by abdominal or central obesity in addition to BMI [3-5].

Obesity-related hypertension is commonly associated with further elements of the metabolic syndrome, such as hyperinsulinemia and glucose intolerance. In particular, one should be aware that diabetes *de novo* occurs in 2% of treated hypertensive patients per year [6].

It's well known that weight gain is associated with sustained inflammatory response with accompanied adipokine dysregulation which leads to chronic inflammation as well as insulin resistance. Chronic low-grade inflammation is thought to be the key parameter in the development of IR and T2DM. Apelin, a recently described adipokine, has been shown to have pro-inflammatory role with a close correlation demonstrated between apelin and TNFα levels, as well as other pro-inflammatory adipokines [7, 8, 9].

This highlights the importance of the site of deposition of adipose tissue in estimation of cardiovasculat risk in obese hypertensive patients.

Aim of the study: to investigate apelin'sactivity in patients with essential hypertension with obesity according to the type of obesity.

Materials and methods: 96 patients with EH were examined. Inquiring, inspection and laboratory investigations were provided according to the recommendations of Ukrainian Society of Cardiology and ESC/ESH recommendations 2007/2009 [10].The study was approved by local institutional review board committees, and all participants provided written informed consent. All subjects underwent measurements of height, weight at the baseline visit. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in meters (kg/m^2). Waist circumference (WC) was measured at the level of the umbilicus, using an unstretched tape meter, without any pressure to body surface over light clothing. Visceral obesity was estimated according to the ESC/ESH recommendations 2009 [10].

Three measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken using a standardized sphygmomanometer on the right arm, after a 15-minute rest in a sitting position; the average of the three measurements was used as subject's blood pressure.

A blood specimen was collected after overnight fasting into a tube with further centrifuging and freezing for investigations. Carbohydrate metabolism was evaluated on the basis of plasma glucose, insulin, glycated haemoglobin (HbA1c) that were measured as at fasting, as after 120 min of

standard glucose tolerance test (OGTT). For insulin measurements the laboratory set DRG® Insulin (DRG Instruments GmbH, Germany, Marburg) was used. Glucose and lipid profile (total cholesterol (TC), triglyceride (TG), high density lipoprotein-cholesterol levels (HDL-C)) were determined using standard biochemical methods.

Low density lipoprotein-cholesterol was calculated (LDL-C) with W.T. Friedewald formula [11]:LDL-C= TC—(HDL-C + TG / 2,22),where TG / 2,22 is very low density lipoprotein-cholesterol.

Index of atherogenity (IA) was calculated according A. M. Klimov fomula [12]:

IA = (TC — HDL-C) / HDL-C 2

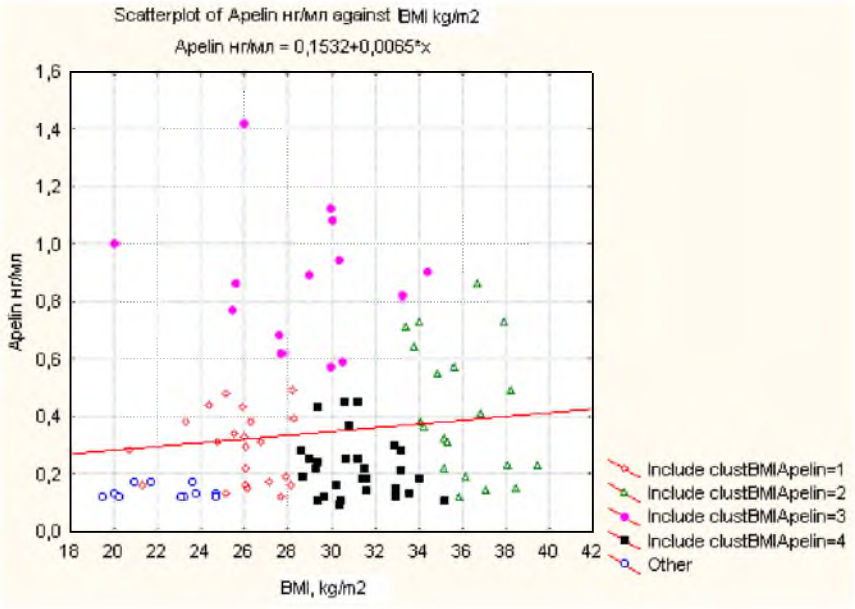
Apelin was estimated in blood plasma using ELISA technique (Phoenix, USA).

Statistical representation of the results is median (Me) and inter-quartile range. All patients were categorized according to cluster analysis using k-means using apelin and BMI means. Difference between groups was calculated using Kruskal-Wallis test. A p value of less than 0.05 was considered to be statistically significant.

Results

Comparing with control group the average means of BMI and apelin level in total group (96 pts) were significantly higher: 30,47 (27,70; 33,70) kg/m² and 0,28 (0,16; 0,48) ng/ml respectively. In comparing control group: BMI – 21,23 (18,96; 23,12) kg/m²and apelin – 0,12 (0,10; 0,15) ng/ml. 77,1 % of hypertensive patients had visceral obesity.

To find out the interrelations of obesity, adipose tissue location and expression of adipokineapelin, all patients were categorized into 4 cluster groups based on k-means according apelin and BMI data (see pic. 1).



Picture 1. Clustering of results according apelin and BMI data

There were 23 pts. with EH In the 1st cluster of 40-71 age, Me – 63,0y.o.; 13 females and 10 males. 34,7% of the patients had visceral obesity. The 2nd cluster consists of 22 pts. With EH of 35-72 age, Me – 60,5y.o.; 12 females and 10 males. And 95,4% from the group had abdominal type of obesity. 3rd cluster includes 14 pts. with EH of 54-74 age, Me – 61,5 y.o.; 8 females and 6 males. 85,7% of the patients had abdominal distribution of adipose tissue. In the 4th cluster there were 37 pts of 30-72 age, Me – 58,0y.o. 89,1% of the patients had visceral type of obesity.

The baseline characteristics of EH duration, blood pressure data, anthropometric measurements, results of carbohydrate and lipid pool investigation are shown in Table 1.

Table 1

Results of inquiring, anthropometric measurements, laboratory and instrumental investigations data in patients with essential hypertension according to clusters distribution

Groups / Means	1 Cluster, 23 pts with EH	2 Cluster, 22 pts with EH	3 Cluster, 14 pts with EH	4 Cluster, 37 pts with EH	Kruskal-Wallis ANOVA; Median Test
Duration of EH, years	8,0 (5,0;12,0)	10,0 (6,0;13,0)	11,5 (5,0; 13,0	12,0 (6,0; 17,0)	p>0,05
SBP, mm Hg	160 (150;180)	180 (160;185)	166 (160;180)	160 (150;165)	p<0,05
DBP, mm Hg	90 (90;100)	100 (90;100)	99 (89;100)	95 (90;100)	p>0,05
BMI, kg/m^2	26,09 (25,15;27,15)	35,82 (34,92;37,12)	29,50 (26,00;30,40)	31,21 (29,70;32,89)	p<0,05
WC, cm	88,00 (84,10;96,00)	111,20 (106,10;120,20)	100,50 (95,00;106,40)	102,00 (94,00;112,50)	p<0,05
HC, cm	99,00 (97,00;104,10)	122,00 (113,00;125,10)	108,50 (103,00;112,40)	110,00 (105,00;112,00)	p<0,05
Apelin, ng/ml	0,29 (0,16; 0,38)	0,37 (0,23; 0,64)	0,87 (0,68; 1,00)	0,18 (0,14; 0,25)	p<0,01
IL-6, pg/ml	13,35 (8,77; 19,63)	9,81 (8,79; 11,82)	8,95 (7,62; 26,00)	13,47 (10,00; 15,64)	p>0,05
TC, mmol/l	5,21 (4,63; 5,60)	4,95 (4,02; 4,90)	5,47 (4,29; 6,00)	5,49 (4,98; 6,30)	p<0,05
TG, mmol/l	1,52 (1,11; 2,67)	1,45 (0,83; 2,39)	1,12 (0,80; 1,98)	1,62 (1,11; 2,73)	p>0,05
HDL-C,mmol/l	1,23 (0,88; 1,28)	1,20 (0,74; 1,35)	1,12 (0,69; 1,33)	0,76 (0,73; 1,05)	p<0,05
LDL-C,mmol/l	3,29 (2,29; 3,61)	2,89 (1,91; 3,57)	3,41 (2,51; 4,91)	3,70 (3,44; 4,74)	p<0,05
VLDL-C, mmol/l	0,66 (0.50; 1,21)	0,58 (0,38; 1,09)	0,50 (0,36; 0,89)	0,77 (0,50; 1,24)	p>0,05
IA	3,24 (2,70; 5,64)	3,32 (2,27; 5,54)	2,80 (2,28; 7,24)	5,31 (4,15; 7,02)	p<0,01
FPG, mmol/l	5,51 (4,73; 6,65)	5,21 (4,90; 7,20)	6,51 (5,62; 9,55)	6,90 (5,99; 8,25)	p<0,05
2h OGGT glucose, mmo/l	5,96 (5,66; 6,59)	6,48 (6,32; 7,09)	5,57 (5,42; 5,72)	7,13 (6,48; 8,04)	p<0,05
FI, mmol/l	20,58 (12,47; 26,18)	19,78 (11,74; 23,22)	26,5 (18,96; 34,03)	24,62 (14,10; 29,87)	p>0,05
2h OGGT insuline, mmo/l	55,65 (43,68; 59,38)	67,69 (57,14; 69,18)	42,87 (40,22; 45,53)	68,81 (54,48; 80,29)	p<0,01
HOMA	5,09 (2,19; 6,90)	4,65 (2,66; 6,65)	7,38 (4,44; 13,65)	7,02 (4,51; 9,53)	p<0,05
HbA1c	7,00 (4,90; 8,00)	7,15 (6,90; 7,90)	5,70 (4,77; 9,20)	7,35 (5,30; 8,10)	p>0,05

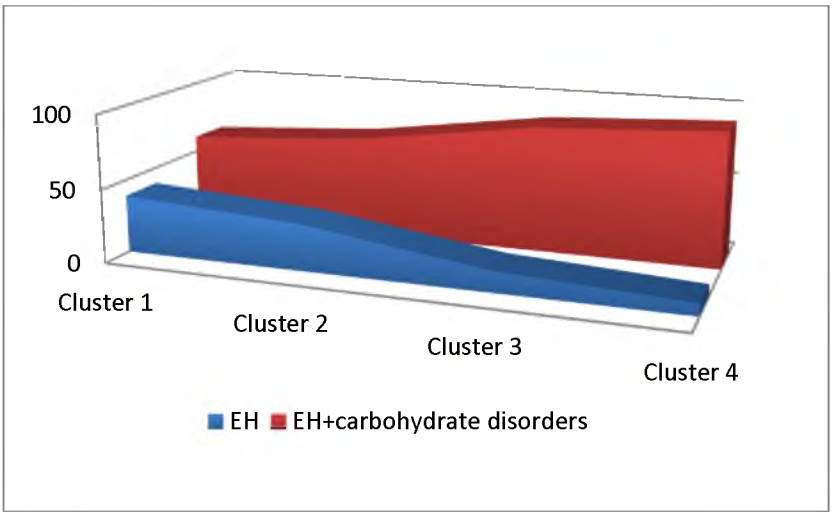
Data is described by median and inter-quartile range.

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; BMI, body mass index; WC, waist circumference; HC, hips circumference; IL-6, interleukine-6;TC, total cholesterol; TG, triglyceride; HDL-C, high density lipoprotein-cholesterol; LDL-C, low density lipoprotein-cholesterol; VLDL-C, very low density lipoprotein-cholesterol; IA, index of atherogenity; FPG, fasting plasma glucose. OGGT, oral glucose tolerance test.

Patients in 1st and 2nd clusters had opposite meanings of WC, HC and BMI. But, patients of the 1st cluster had the lowest WC and BMI and also the shortest duration of the disease. It was accompanied with not very pronounced changes in lipid profile, carbohydrate pool and moderate expression of IL-6 and apelin. Comparing with patients of 1st cluster hypertensive obese patients of 2nd cluster had longer anamnesis of EH, dyslipidemia, more pronounced dysglicemia, hypercytokinemia that was accompanied by highest WC, BMI, SAP and DAP and increased level of apelin.

In patients of 3rd and 4th clusters there was no significant difference in BMI data,but there was opposite apelin activity.Level of adipokine in patients of 3rd cluster was 3-fold higher than in other groups. In cluster 4, adipokine's activity was the lowest one from total amount of patients and in cluster 3 – the highest one. Both groups had similar and longest duration of EH in the whole group. Analysis of the instrumental and laboratory investigations have shown higher levels of SAP and DAP in patients of 3rd cluster in comparing with 4th. On the background of the lowest in the group level of apelin, patients of 4th cluster had significant and highest levels of TC, TG, LDL-C, VLDL-C; lowest data of HDL-C and increasing of IA, almost 2-fold in comparing with patients of other clusters. The most pronounced carbohydrate disorders were common for the patients of 4th cluster. Levels of fasting glucose, post OGTT glucose and insulin, HbA1c, index HOMA were the highest in patients of 4th cluster comparing with other patients with EH. Pronounced hypercytokinemia was established in patients of 4th cluster.

Distribution of the patients according to dysglicemia in each cluster (see pic.2) we found out that, the smallest percentage of accompanied carbohydrate disorders 60,8% was in hypertensive patients of 1st cluster. In the 2nd cluster there was 68,4% patients with EH and dysglicemia. Patients of 3d and 4th clusters had hypertension and comorbid carbohydrate pool abnormalities in 85,6% and 91,8% correspondingly.



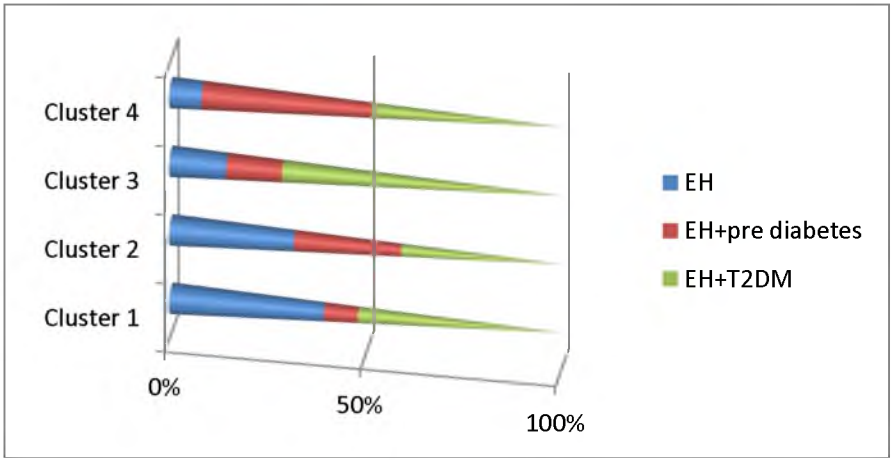
Picture 2. Essential hypertension and percentage of accompanied dysglycemia in clusters

There is an evidence that exogenous apelin reduces the peak plasma glucose concentration after a glucose load by increasing glucose turnover through insulin-dependent and -independent pathways. Apelin-deficient animal models have reduced insulin sensitivity and this can be corrected by the administration of exogenous apelin[13].

Conversely, exogenous apelin reduces the peak plasma glucose concentration following a glucose load by increasing glucose turnover and this effect is preserved in insulin-resistant animal strains. The exact cellular mechanisms leading to increased glucose uptake are incompletely understood. Apelin increases glucose uptake through phosphorylation of components of insulin-dependent pathways, such as Akt, although increased glucose uptake is still observed in the presence of inhibition of this pathway suggesting both insulin-dependent and -independent pathways [14].

As clusterization of the hypertensive patients according to the BMI and apelin activity showed peculiarities of carbohydrate metabolism that is connected with adipokine expression, we also analyzed amount of the patients with co-morbid state in each cluster (see pic.3).

So, there were 60,9% of patients with co-morbid state in 1st cluster, 68,8% – in 2nd cluster, 85,7% – in 3rd and 94,6% – in 4th. Particularly the amoun of hypertensive patients with pre diabetes state in 1st cluster – 8,79%, in 2nd – 27,3%, 3rd – 14,3%, in 4th cluster – 43,2%.



Picture 3. Distribution of the patients in the clusters according to co-morbid state

Analysis of apelin's interrelations in total group showed significant correlations with WC (R=0,23, p<0,05) and parameters of carbohydrate pool. Positive correlations of apelin were found: with fasting insulin (R=0,29, p<0,05), -post OGTT glucose and insulin levels (R=0,39 and R=0,41 respectively, p<0,05), -HOMA index (R=0,24, p<0,05) and HbA1c (R=0,24, p<0,05).

WC in total group correlates with fasting glucose and insulin (R=0,32 and R=0,46 respectively, p<0,05), -post OGTT glucose and insulin levels (R=0,65 and R=0,46 respectively, p<0,05), -HOMA index (R=0,43, p<0,05) and HbA1c (R=0,32, p<0,05).

In patients of cluster 1 the significant correlation of apelin and HbA1c was estimated (R=0,53, p<0,05). In patients of 2nd and 4th clusters significant negative correlations of apelin with BMI were detected (R=-0,72 and R=-0,41 respectively, p<0,05). In patients of cluster 3 the significant correlation of apelin and WC was estimated (R=0,54, p<0,05).

Plasma apelin level in hypertensive patients of 1st cluster without estimated co-morbid state correlates with post OGTT insulin level (R=0,77, p<0,05). In 2nd cluster apelin correlates with HbA1c (R=0,75, p<0,05) in patients with EH without carbohydrate abnormalities. Analysis of adipokine activity in patients of 2nd cluster according to the carbohydrate disorders showed positive correlation of apelin with WC and BMI in hypertensive patients with pre diabetes (R=0,81 and R=0,64 respectively, p<0,05), but in the same cluster in hypertensive patients with accompanied T2DM apelin negatively correlate with BMI (R=-0,72, p<0,05). In patients of 4th cluster with EH and pre diabetes apelin correlates with SAP (R=0,63, p<0,05); weight (R=0,64, p<0,05); TC (R=-0,60, p<0,05); HDL-C (R=0,68, p<0,05); LDL-C (R=-0,79, p<0,05); IA (R=-0,57, p<0,05); post OGTT glucose (R=0,66, p<0,05). Also there was negative correlation of IL-6 with apelin in patients of 4th cluster with pre diabetes (R=-0,73, p<0,05).

Interestingly, Li L. et al. have showed that plasma apelin concentrations are reduced in patients with newly diagnosed type 2 diabetes mellitus but increased in obese non-diabetic individuals [15]. This may suggest that the initial increase in apelin seen in obesity serves to delay the development of type 2 diabetes mellitus by preserving glycaemic control.

Conclusion:

1. Apelin plasma level is increased in patients with essential hypertension and visceral type of obesity.
2. Visceral type of obesity is associated with expression of the peptide and accompanied with dyslipidemia and carbohydrate metabolism disturbances.
3. Pronounced pro-inflammatory state, dyslipidemia with high atherogene index, dysglicemia, hyperinsulinemia in patients with essential hypertension and visceral type of obesity are accompanied with decreasing of apelin level and negative correlation of waist circumference and BMI with peptide.
4. Overexpression of apelin in hypertensive patients with moderate abnormalities in lipid and carbohydrate metabolism is considered as compensatory reaction.
5. Increasing of plasma apelin level in obesity may play protective role by delaying the development of type 2 diabetes mellitus.

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ИССЛЕДОВАНИЕ ПЛАЗМЕННОГО СОДЕРЖАНИЯ АПЕЛИНА У БОЛЬНЫХ ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНЬЮ В ЗАВИСИМОСТИ ОТ ТИПА ОЖИРЕНИЯ

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Индекс массы тела (ИМТ) – известный предиктор не только кардиоваскулярной смертности. Абдоминальное ожирение, дополнительно к ИМТ, являются более весомыми маркерами прогноза сердечно-сосудистой смертности.

Цель исследования: изучение активности апелина у больных гипертонической болезнью в зависимости от типа ожирения.

Материал и методы: 96 пациентов с гипертонической болезнью были обследованы. Опрос, осмотр, лабораторные методы исследования были использованы.

Результаты: средние значения объема талии, ИМТ и апелина в целой выборке были значительно выше показателей группы контроля. Пациенты были разделены на кластеры с использованием k-значений апелина и ИМТ. Достоверных различий в ОТ между пациентами 3 и 4 кластера не выявлено, но установлена противоположная активность апелина. В 4 кластере уровень апелина был наименьшим в целой группе больных, а в кластере 3 – наивысший. У пациентов 4 кластера выявлены наиболее выраженные нарушения углеводного обмена и дислипидемия.

Выводы: установлено достоверное повышение уровня пептида апелина у больных гипертонической болезнью с абдоминальным ожирением. Гиперэкспрессия апелина у больных гипертонической болезнью с умеренными нарушениями липидного и углеводного метаболизма является компенсаторной реакцией.

Ключевые слова: апелин, гипертоническая болезнь, ожирение.