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The Study of Apelin-13 for the Assessment of Endothelial Dysfunction in Prehypertension and Hypertension Patients

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ABSTRACT

Background and aim: Hypertension is a leading global burden of deaths, coronary heart diseases, and stroke. Hypertension causes low-grade chronic systemic inflammation associated with endothelial dysfunction and vascular complications. The present study aimed to assess Apelin-13 levels in prehypertension and hypertension patients and find their association with oxidized low-density lipoprotein (LDL) and lipid profile.

Material and methods: Sixty prehypertension and 60 hypertension with the age group of 35 to 50 years were selected, and 60 healthy age-matched subjects were selected as controls. Beckman Colter's fully automated analyzer carried out serum apelin-13 and oxidized LDL estimated by enzyme-linked immunosorbent assay (ELISA) and other routine investigations.

Results: Apelin-13 levels were significantly increased in hypertensive patients compared to prehypertensive patients. A significant positive correlation was observed between apelin-13 and oxidized LDL and triglyceride levels. Further, there was no significance observed between other lipid profile parameters.

Conclusions: Apelin-13 is a vital factor for assessing endothelial dysfunction in hypertensive patients. Reduction of apelin-13 may be beneficial in preventing vascular complications and coronary heart diseases in hypertensive patients.

1. Introduction

The significant global burden of hypertension is a risk factor for cardiovascular morbidity and mortality. Per Current guidelines, hypertension is classified into isolated systolic (ISH), isolated diastolic (IDH), and systolic and diastolic combined hypertension.[1-3] The seventh Joint National Committee (JNC-7) report first reported prehypertension. Elevated blood pressure is due to a variety of risk factors, which among obesity is proven as closely interrelated to hypertension.[4] Studies reported that body mass index (BMI) and waist circumference (WC), fat accumulation, abnormal fat distribution, accumulation of subcutaneous adipose tissue and visceral adipose tissue, and dyslipidemias are seen in hypertension.[5-6] Apelin is a hormone peptide in adipose, cardiovascular, pulmonary, and cerebral tissues. Various active apelin peptides exist in 36, 17, and 13 amino acids, originating from preproproteins consisting of 77 amino acid residues.[7-8] So, apelin-13 has the highest activity of endogenous ligand for the G protein-coupled receptor apelin receptor (APJ) and plays an essential role in the cardiovascular system.[9] So we aimed to assess apelin-13 levels in prehypertension and hypertension patients compared with healthy controls and to find out their association with oxidized LDL and lipid profile parameters.

2. Material and methods

Sixty hypertensive and sixty prehypertensive patients of both sexes aged between 35-50 years, according to JNC-8 (Eighth Joint National Committee) guidelines, attending Government General Hospital attached to Siddhartha Medical College, Vijayawada, Andhra Pradesh, India, were selected for the present study. Diabetes mellitus, thyroid disorders, history of cardiovascular diseases, renal dysfunction, liver dysfunction, acute myocardial infarction, stroke, peripheral vascular disease, chronic alcoholics, smokers, pregnant women, and patients on antioxidant regimens are excluded from this study. Sixty healthy volunteers with age and sex match subjects were selected as controls. Informed consent was obtained from all the study subjects, and the Institutional Human Ethics Committee (IHEC- ECR\633\INST\AP\2014\RR-19)approved the study. Experiments were done by the Helsinki Declaration of 1975. Prehypertensive cases- the systolic blood pressure between 120 to 139 or diastolic blood pressure between 80 to 89. Hypertensive cases - systolic blood pressure greater than or equal to ⩾140) or diastolic blood pressure greater than or equal to ⩾90.

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Blood pressure measurement

According to JNC guidelines, blood pressure readings were taken with the patient's legs uncrossed while seated using a Mercury Sphygmomanometer (Diamond, Mumbai, India). After 5 minutes of rest in the sitting position, BP was measured on both arms, and the higher of the two was considered. The BP measurements were taken twice, and the average systolic and diastolic values were considered.

Biochemical analysis

Fasting blood samples were collected from the cases, healthy volunteers and centrifuged at 3000 rpm for 15 min. Routine laboratory investigations were performed immediately using a Beckman colter autoanalyzer, and aliquots were stored at −80 °C to further estimate serum apelin-13 and Ox-LDL levels. Routine investigations like glucose, Urea, Creatinine, Uric acid, Bilirubin, Total protein, Albumin, Globulin, Alanine aminotransferase, Aspartate aminotransferase, Alkaline phosphatase, serum cholesterol, triglycerides, HDL cholesterol, LDL cholesterol were assessed by standardized protocols. Serum apelin-13 and Ox –LDL was estimated by Enzyme-linked Immunosorbent Assay (ELISA).

Statistical analysis

Statistical analysis was carried out by using SPSS 25.0 software. Values expressed as mean ± standard deviation by t-test, p-value < 0.05 was considered statistically significant. The Pearson correlation test was used for correlation analysis.

3. Results

Table 1 Shows parameters like age, percentage of males, and females, body mass index, waist/Hip ratio, systolic BP, and diastolic BP. Body mass index, waist /Hip ratio, systolic BP, and diastolic BP were significantly increased in prehypertensive and hypertensive patients compared to controls. Also, there was significant changes were observed among prehypertensive and hypertensive patients.

Table 1. Comparison of general parameters like Age, BMI, W/H ratio, systolic and diastolic blood pressure in healthy volunteers, and Prehypertensive and Hypertensive cases.

Parameters	Controls (n=60)	Prehypertension patients (n=60)	Hypertension patients (n=60)
Age	39.9±4.2	40.1±.5.3	42.4±5.5
Body mass index (weight Kg/ height m^2)	24.2±1.5	29.8±1.4 [a*]	30.06±2.85 [a#,b*]
Waist/Hip ratio	0.92±0.06	0.95±0.08 [a#]	0.98±0.03 [b*,c#]
Systolic BP (mm Hg)	112.4±5.4	134.2±5.5 [a*]	189.0±18.1 [b*, c*]
Diastolic (mm Hg)	76.4±3.1	86.1±3.1 [a*]	108.8±9.6 [b*, c*]

Data are expressed as mean ±SD, *p<0.001, p<0.05 was considered statistically significant.
a= comparison between Controls and Prehypertension patients.
b=comparison between Controls and Hypertension patients.
c=comparison between Prehypertension and Hypertension patients.

Table 2 shows the fasting plasma glucose, lipid profile, Liver profile, renal profile, apelin-13, and OX- LDL levels. In this serum, cholesterol, triglycerides, and LDL-Cholesterol levels were significantly increased in hypertensive subjects compared with controls, and further significant variation between prehypertensive and hypertensive subjects. Decreased HDL cholesterol levels were observed in hypertensive patients compared to controls. Apelin-13 and Ox LDL levels were significantly increased in hypertensive patients compared to controls, and also significant difference was observed between prehypertensive and hypertensive patients.

Table 2. Comparison of fasting plasma glucose, Lipid profile, LFT, RFT, Apelin-13, and Ox LDL levels in controls, pre-hypertensive and Hypertensive patients.

Parameters	Controls (n=60)	Prehypertension Patients (n=60)	Hypertension Patients (n=60)
FPG(mg/dl)	85.5±10.8	88.3±10.8	89.1±13.4
Serum Cholesterol (mg/dl)	177.3±8.6	217.1±19.4 [a*]	240.7±16.7 [b*,c#]
Serum Triglycerides (mg/dl)	113.6±19.2	188.8±16.8 [a*]	179.9±20.6 [b*,c#]
HDL Cholesterol (mg/dl)	44.1±5.4	40.5±5.6 [a#]	37.3±6.7 [b*,c*]
LDL Cholesterol (mg/dl)	120.6±10.7	159.8±18.7 [a*]	157.1±16.9 [b*,c#]

Total Bilirubin(mg/dl)	0.78±0.09	0.8±0.05	0.83±0.07
Direct Bilirubin(mg/dl)	0.2±0.04	0.20±0.06	0.20±0.07
AST (IU/L)	28.6±3.5	29.8±8.2	29.3±7.6
ALT (IU/L)	29.4±3.9	30.5±5.7	30.5±5.7
ALP(IU/L)	98.6±14.1	101.2±16.7	100.2±12.9
Total Protein(gm/dl)	7.8±0.5	7.5±0.7	7.2±1.4
Albumin(gm/dl)	3.9±0.3	3.7±0.7	3.6±0.4
Globulin(gm/dl)	3.2±0.4	3.4±0.6	3.3±0.7
Serum Urea(mg/dl)	23.7±5.4	26.8±7.4	28.3±6.9
Serum Creatinine(mg/dl)	0.73 ±0.1	0.8±0.3	0.84±0.3
Apelin-13 (pg/ml)	250.3±24.9	298±32.3 [a*]	320±34.5[a*,b*]
OX-LDL (U/L)	84.5±10.26	107.5±9.4 [a*]	112±11.45 [a*,b*]

Data are expressed as mean ±SD, *p<0.001,#p<0.05 was considered statistically significant.
a= comparison between Control and Prehypertension subjects.
b=comparison between Control and Hypertension subjects.
c=comparison between Prehypertension and Hypertension subjects.

Table 3 shows the Pearson correlation analysis between apelin-13 and Ox LDL, Cholesterol, TGL, HDL, LDL, BMI, Waist /Hip ratio, Systolic BP and Diastolic BP. Apelin-13 shows a significant positive correlation with OX LDl, TGL, LDL, and BMI in both (prehypertensive and hypertensive patients). Further, apelin-13 shows a significant positive correlation with waist /Hip ratio and systolic and diastolic BP in hypertensive patients.

Table 3. Correlation between Apelin -13 and measured parameters in Prehypertensive and Hypertensive patients.

Parameters	Prehypertension (Correlation Coefficient-r)	Hypertension (Correlation Coefficient-r)
Ox-LDL	0.393*	0.463**
Cholesterol	0.287	0.343*
TGL	0.392**	0.427**
HDL	-0.190	-0.262
LDL	0.427**	0.523**
BMI	0.278*	0.326*
Waist /Hip ratio	0.267	0.319*
Systolic BP	0.145	0.311*
Diastolic BP	0.124	0.367**

*Correlation is significant at the 0.05 level (2-tailed).
**Correlation is significant at the 0.01 level (2-tailed).

4. Discussion

Hypertension is due to various causes, in that most patients do not recognize the exact etiology. The interaction of environmental, genetic, endocrine, humoral, hemodynamic, anatomical, and neural factors plays a role in hypertension.[10-11] The present study shows a significant change between BMI and W/H ratio in prehypertensive and hypertensive patients. The high-calorie fat diets are immediately stored in fat cells, which aggravates to increase in body weight and girth as they are deposited in adipose tissue and diversify the fat distribution. Obesity and fat accumulation will influence lipid profile parameters like cholesterol, LDL, and triglyceride levels (dyslipidemias).[12-14] In the present study, we observed significantly increased apelin-13 levels in hypertensive patients compared with controls, and also, there was significant variation between prehypertensive and hypertensive patients. Apelin is a fat factor in adipose tissues. Experimental animal studies reported that apelin increases cardiac contractility and reduces ventricular preload and afterload in rats with failing hearts. Studies also reported that apelin-13 protects the heart against ischemia-reperfusion injury by inhibiting Endoplasmic reticulum stress.[15-16] In addition to the protective role of apelin in heart failure, it has also been reported that apelin induces nitric oxide-dependent vasodilation in humans.[17, 18] Li L et al. and Tempel D et al. Have reported that apelin-13 may modulate endogenous stem cell function after acute myocardial injury.[19, 20] Fukushima et al., in 2010, reported that olmesartan, an angiotensin II receptor antagonist, as a treatment for hypertension in rats with heart failure, also found that apelin can be involved in the regulation of the endothelial nitric oxide synthase (eNOS) pathway.[21] Apelin-13 also has a cytoprotective effect against methylglyoxal (MGO), a glycolytic metabolite-induced endothelial apoptosis via regulation of the AMP-activated protein kinase (AMPK) activating pathway.[22] Our study also observed apelin-13 significant positive correlation with diastolic blood pressure, TGL, LDL, and OX-LDL levels. Apelin is an endogenous ligand for angiotensin type 1 receptor-associated protein, and it counteracts the effects of angiotensin-converting enzyme (ACE)-angiotensin (Ang)-II-angiotensin II type 1 receptor angiotensin converting enzyme-2 (ACE2) under many physiological and pathological conditions.[23-25] Apelin infusion improves pulmonary vascular hemodynamics in experimental studies of Pulmonary arterial hypertension, which may translate into benefits for patients with pulmonary arterial hypertension by reducing pulmonary vascular resistance (PVR) and increasing cardiac output.[26, 27] So dyslipidemias, obesity, and genetic and environmental primary risk factors for hypertension lead to endothelial dysfunction. Apelin-13 levels may aggravate in hypertensive cases to encounter the axis and prevent cardiovascular complications in the early stages. So regular monitoring of apelin-13 may be beneficial to assess endothelial dysfunction in hypertensive patients.

Limitations

The limitation of the present study is considered to be sample size is less, and large cohort studies are required to confirm it.

5. Conclusion

Apelin-13 is a vital factor for assessing endothelial dysfunction in hypertensive patients. Regular monitoring and reduction of apelin-13 may be beneficial to prevent early stages of vascular complications and coronary heart diseases in hypertensive patients.

Conflict of Interest

The authors declared that there is no conflict of interest.

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