Adiponectin level in hypertension

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Received 14 January 2020
Revised 21 April 2020
Accepted 25 April 2020
Published 20 November 2020

Journal of Current Medical Research and Practice
2020, 5:389–394

Introduction
Adiponectin is a hormone, secreted mainly by adipocytes. Despite accumulating experimental evidence on the etiological role of adiponectin in hypertension (HTN), data on plasma adiponectin level and HTN in humans are inconsistent and dose–response relationship has not been established.

Aim
To estimate and evaluate the level of adiponectin in patients with different stages of HTN and evaluate the relationship between adiponectin level in hypertensive patients in the presence or absence of metabolic syndrome.

Patients and methods
This work was carried out at the Clinical Pathology and Cardiology Departments at Assiut University Hospital. It included two groups of individuals: 60 patients with primary HTN (the patient group) and 20 age-matched and sex-matched apparently healthy individuals (the control group).

Results
Plasma adiponectin level was significantly lower in patients with HTN in comparison to the control group. Adiponectin levels in patients with stage 2 HTN was statistically insignificantly higher than those with stage 1 HTN and the adiponectin level was statistically insignificantly higher in stage 1 hypertensive patients compared with prehypertensive patients. Adiponectin level was significantly lower in male hypertensive patients with metabolic syndrome in comparison to male hypertensive patients without metabolic syndrome. The predictive value of adiponectin for the occurrence of HTN was 2.63 ng/ml, with 90% sensitivity and 35% specificity; the area under the receiver operating characteristic curve was 0.65 and *P* value of 0.03.

Conclusion
The low level of plasma adiponectin is an independent predictive factor for HTN even with the presence or absence of metabolic syndrome.

Keywords:
adiponectin, hypertension, metabolic syndrome

J Curr Med Res Pract 5:389–394

2357-0121

Introduction

Hypertension (HTN) has been a well-recognized important risk factor for cardiovascular disease among adults causing a significant global disease burden [1]. It tends to cluster with metabolic risk factors and is considered one of the key features of the metabolic syndrome [2].

In recent years, metabolic syndrome and HTN are increasingly seen in the middle-aged and young populations. In these subpopulations, insulin resistance and overproduction of adipokines impair endothelial and heart function leading to early and accelerated cardiovascular aging [3].

Adipose tissue was considered a passive reservoir for energy storage, but now is viewed as an active endocrine organ secreting a variety of biologically active molecules including plasminogen activator inhibitor-1, tumor necrosis factor-α, resistin, leptin, interleukin 6, and adiponectin. Dysregulated production of these adipokines participates in the pathogenesis of obesity-associated metabolic syndrome [4].

Adiponectin is a hormone, secreted mainly from adipocytes. Its plasma level has been reported to be reduced in obese humans [5]. Adiponectin exerts insulin sensitizing and antiatherogenic effects, and hence a decrease in plasma adiponectin is causative for insulin resistance and atherosclerosis in obesity [4].

In endothelial cells, adiponectin activates the AMP kinase pathway, stimulating nitric oxide production, promoting anti-inflammatory macrophage phenotypes, and suppressing sympathetic nervous system [6].

Adiponectin is a vasoprotective agent acting via different mechanisms. It inhibits most atherosclerotic mechanisms, for example by suppressing tumor necrosis factor-α and thus reducing the adhesion of monocytes to endothelial cells, stymies proliferation of vascular

smooth muscles, and reduces the formation of foam cells by means of inhibition of oxidized low-density lipoprotein [7].

Despite accumulating experimental evidence on the etiological role of adiponectin in HTN, data on plasma adiponectin level and HTN in humans are inconsistent and response relationship has not been established [8].

Aim

To estimate and evaluate the level of adiponectin in patients with different stages of HTN and evaluate the relationship between adiponectin level in hypertensive patients in the presence or absence of metabolic syndrome.

Patients and methods

This study was carried out at the Clinical Pathology and Cardiology Departments at Assiut University Hospital over a period of 1-year duration from June 2016 to June 2017. It included two groups of patients: 60 patients with primary HTN (the patient group) and 20 age-matched and sex-matched apparently healthy individuals (the control group).

Classification of patients

The patient group was classified according to the stage of HTN, based on JNC-7 as follows: pre-HTN stage (systolic blood pressure 120–139 or diastolic blood pressure 80–89), stage 1 HTN (systolic blood pressure 140–159 or diastolic blood pressure 90–99), stage 2 HTN(systolic blood pressure ≥160 or diastolic blood pressure ≥100).

According to the presence of metabolic syndrome, we identified the patients with metabolic syndrome-based ATP-III guidelines by the presence of HTN plus more than or equal to 2 of the following criteria: (a) serum triglyceride levels more than or equal to 150 mg/dl, (b) serum high-density lipoprotein (HDL) cholesterol less than 40 mg/dl in men and less than 50 mg/dl in women, (c) fasting plasma glucose more than or equal to 5.6 mmol/l, and (d) waist circumference more than 102 cm in men or more than 88 cm in women.

Approach to the patient

Patient evaluation

(1) Medical history and clinical examination:
Pulse and temperature measurement; chest, cardiac, and abdominal examinations, chest radiograph, and ECG.
(2) Blood pressure measurement:
Blood pressure taken as the mean of two reading measurements 2–3 min apart on the right arm with the forearm resting on the disk after the patient has been seated for about 10 min.
(3) Anthropometric measurements:
Measure body weight, height, BMI [weight (kg)/height (m^2)], and waist circumference.

Exclusion criteria

Children, adolescent, and patients with secondary HTN.

Sample collection, storage, and handling

A measure of 10 ml of venous blood was collected under complete aseptic conditions after fasting for 14 h and was divided into:

(1) 2 ml of venous blood was collected into an EDTA tube for complete blood count
(2) 8 ml was collected into plain tubes without anticoagulants
(a) Blood was allowed to clot for 15 min at 37°C and serum was separated by centrifugation at 3000 rpm for 10 min
(b) Separated serum was inspected to ensure it was clear and nonhemolyzed or lipemic
(c) Serum was divided into three aliquots, one of them used for routine laboratory investigations and the other two stored at −20°C till the time of assay of adiponectin level
(d) Random urinary samples were collected for urine analysis.

Laboratory investigations

Fasting serum glucose, kidney function, liver function tests, and lipid profile were done on Dimension RLMax. Complete blood picture was done on CELL-DYN (Abbott Diagnostic Division, USA) 3700-Abbott. Urine analysis was done using urinary dipstick strip test (ComboStik 10) and microscopic examination.

Special investigations

Serum adiponectin level was measured by human adiponectin, ADP ELISA kit, catalog number: KN1852Hu.

Principle of the adiponectin test:

Enzyme-linked immunosorbent assay was based on the sandwich immunoassay principle. The assay uses two highly specific monoclonal antibodies for the detection of the tested antigen; one antibody is

immobilized into the microplate and the other one is labeled to form a sandwich complex (antibody–antigen-labeled antibody). Absorbance is measured spectrophotometrically at 450 nm.

Statistical analysis

Data collected and analyzed by computer program SPSS, version 21 (SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean, SD and number, percentage. Analysis of variance test and c^2 were used to determine significance for categorical variable. Pearson's correlation test was used to determine correlation between variables. *P* value was considered significant if less than 0.05.

Ethical consideration

Formal consent was obtained from patients and controls. The study was approved by the Ethics Committee of Faculty of Medicine, Assiut University. IRB number is 17100950.

Results

There was statistically significant decrease in adiponectin level in the patient group compared with the control group (P = 0.04) (Table 1).

According to HTN stages, adiponectin level in patients with stages 1 and 2 HTN was statistically insignificantly higher than those with pre-HTN stage (P = 0.12) (Table 2).

There was statistically significant decrease in adiponectin levels in patients with and without metabolic syndrome compared with the control group (P = 0.03, 0.00, respectively) and no statistically significant difference in mean value of adiponectin between the patients with and without metabolic syndrome (P = 0.12) (Table 3).

Table 1 Adiponectin level in patients and control groups

Measurements	Patient group (*n*=60)	Control group (*n*=20)	*P*
Adiponectin (ng/ml)			0.04
Mean±SD	1.69±0.43	2.74±0.98	
Range	0.63-4.98	0.89-5.67	

P<0.05.

Table 2 Adiponectin level in different stages of hypertension

Stage of hypertension	Mean±SD	Range
Prehypertension (*n*=23)	1.26±0.48	0.63-2.8
Stage 1 (*n*=19)	1.57±0.28	0.69-4.98
Stage 2 (*n*=18)	2.35±0.33	0.63-3.9
P	0.12	

There was statistically significant decrease in adiponectin level in male patients with metabolic syndrome on comparing with those without metabolic syndrome (P = 0.02) and statistically insignificant decrease in serum adiponectin level in female patients with metabolic syndrome compared with those without metabolic syndrome (P = 0.52) (Table 4).

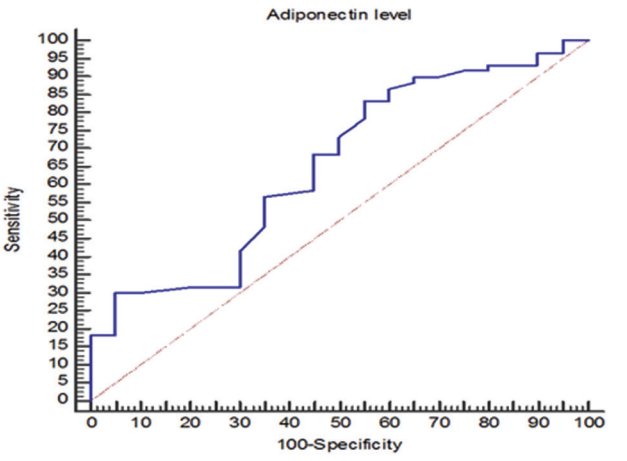
We used receiver operating characteristic (ROC) curve analysis to find the cutoff value of adiponectin for the prediction of HTN with the highest sensitivity and specificity. ROC curve analysis obtained a cutoff value of 2.63 ng/ml for serum adiponectin level for HTN (90% sensitivity and 35% specificity, area under the curve was 0.65, and P = 0.03) (Table 5 and Figure 1).

Of note in the present study, the frequency of control individuals with an adiponectin level of less than 2.63 ng/ml was significantly lower than those with an adiponectin level of more than 2.63 ng/ml; the frequency of hypertensive patients (regardless of having metabolic syndrome or not) with adiponectin levels of less than 2.63 ng/ml was significantly higher than those with an adiponectin level of more than 2.63 ng/ml (Table 6).

The presence of metabolic syndrome and low adiponectin level were independent factors for HTN (odds ratio = 2.11, 95% confidence interval = 1.2–4.97; P = 0.03 for metabolic syndrome and odds ratio = 3.78, 95% confidence interval = 6.09–9.04; P = 0.00 for low adiponectin level) (Table 7).

Since in the present study most hypertensive patients were taking B-blockers (65% of patients) and RAAS inhibitors group of therapy [angiotensin-converting enzyme inhibitors (18.4% of patients) – angiotensin receptor antagonist (5% of patients)], we make

Figure 1



Diagnostic accuracy of adiponectin level in the diagnosis of HTN by ROC curve. HTN, hypertension; ROC, receiver operating characteristic.

Table 3 Level of adiponectin based on the presence or absence of metabolic syndrome

	HTN patients with metabolic syndrome (*n*=24)		HTN patients without metabolic syndrome (*n*=36)		Control group (*n*=20)	
	Mean±SD	Range	Mean±SD	Range	Mean±SD	Range
Adiponectin (ng/ml)	2.02±0.37	0.63-3.89	1.46±0.98	0.64-4.89	2.74±0.98	0.89-5.67
P	*P*1=0.03		*P*2=0.00		*P*3=0.12	

HTN, hypertension. *P*1: *P* value between HTN patients with metabolic syndrome versus control group. *P*2: *P* value between HTN patients without metabolic syndrome versus control group. *P*3: *P* value between HTN patients with metabolic syndrome versus HTN patients without metabolic syndrome.

Table 4 Diagnostic accuracy of adiponectin level for the prediction of occurrence of hypertension

	Adiponectin (ng/ml)		*P*
	Mean±SD	Range	
Male patients with metabolic syndrome (*n*=11)	1.21±0.63	0.63-2.54	0.02
Male patients without metabolic syndrome (*n*=19)	3.01±0.32	0.67-4.83	
Female patients with metabolic syndrome (*n*=13)	1.28±0.59	0.95-4.98	0.52
Female patients without metabolic syndrome (*n*=17)	1.77±0.43	0.91-3.99	

P<0.05. *n*: number.

Table 5 Diagnostic accuracy of adiponectin level for the prediction of occurrence of hypertension

Diagnostic indices	Value
Sensitivity	90%
Specificity	35%
Positive predictive value	80.3%
Negative predictive value	53.8%
Cutoff point (ng/dl)	2.63
Area under the curve	0.65
P	0.03

comparison between these groups of antihypertensive drugs.

The mean value of adiponectin level in patients taken RAAS inhibitor drugs was statistically insignificantly low than those patients taken the B-blocker drug group ($P = 0.08$) (Table 8).

Discussion

The present study showed that serum adiponectin level was significantly lower in patients with HTN in comparison to the control group. This is in agreement with Brzeska *et al*. [7], Schillaci *et al*. [9], and Kou *et al*. [10]; they reported that the adiponectin concentration was significantly lower in patients with HTN than in normotensive persons. Low adiponectin levels may be one of the risk factors of arterial HTN, as adiponectin exerts anti-inflammatory action and prevents the formation of atherosclerotic plaque [7] Other studies found that adiponectin level showed nonstatistically significant difference between cases and controls [11,12].

The overall data indicate that discrepancies between the previous reports about plasma adiponectin levels in HTN may be related to the variability of other metabolic parameters in the study groups [13], small number of study group and sex-dependent differences in both groups [12], the effect of antihypertensive drugs intake, duration and stage of HTN.

As regards the adiponectin level in the different stages of HTN, the present study showed that the adiponectin level in patients with stage 2 HTN was statistically insignificantly higher than those with stage 1 HTN and the adiponectin level in patients with stage 1 HTN was statistically insignificantly higher than those with pre-HTN stage. This difference may be explained by the effect of antihypertensive drug intake. Some studies reported that renin–angiotensin system (RAS) blocking agents and B-blockers increase adiponectin levels with accompanying improvement in insulin sensitivity without affecting the degree of adiposity [14,15].

As regards the relation between adiponectin level and the presence of metabolic syndrome, the current study showed that adiponectin level showed statistically insignificant difference comparing hypertensive patients with metabolic syndrome with hypertensive patients without metabolic syndrome. Comparing female patients with metabolic syndrome with female patients without metabolic syndrome, the present study showed that adiponectin level was significantly lower in male hypertensive patients with metabolic syndrome in comparison to male hypertensive patients without metabolic syndrome. This is in agreement with Onat *et al*. [16], who reported that the low adiponectin level was found associated independently of all metabolic syndrome components only among men. Their study concluded that adiponectin concentrations may diverge among sexes regarding protection against cardiometabolic risk through anti-inflammatory or antioxidative function, men alone revealing significant dysfunction of anti-inflammatory and antioxidative

Table 6 Frequency of hypertension patients and control group based on cutoff point of adiponectin

Groups	Adiponectin level <2.63 ng/ml [*n* (%)]	Adiponectin level >2.63 ng/ml [*n* (%)]	*P*
HTN patient group (*n*=60)	42 (70)	18 (30)	0.03
HTN patients with metabolic syndrome (*n*=24)	19 (79.2)	5 (20.8)	0.02
HTN patients without metabolic syndrome (*n*=36)	23 (63.9)	13 (36.1)	0.02
Control group (*n*=20)	7 (35)	13 (65)	0.01

HTN, hypertension.

Table 7 Multivariate regression analysis for predictors of hypertension in the current study

	OR	95% CI	*P*
Age	1.11	2-6.09	0.55
Sex	0.87	3.06-4.55	0.45
Metabolic syndrome	2.11	**1.2-4.97**	0.03
Low adiponectin level	3.78	**6.09-9.04**	0.00
Hyperlipidemia	1.01	0.09-3.92	0.08

P value was significant if less than 0.05. *The bold values refer to that we are 95% confident that the larger population^s value or risk lies within the limit of the CI of the selected sample. *The lower limit of CI must be 1 or more to be significant. *odd ratio refer to relative risk. *Odd ratio must be between the lower and upper limit of CI and not equal 1 to be significant.

Table 8 Level of adiponectin based on the type of antihypertensive agents

Antihypertensive agents	Mean±SD	Range
B-blockers (*n*=39)	1.82±0.84	0.63-4.98
RAAS inhibitors (*n*=14)	1.06±0.31	0.63-2.88
P	0.08	

P value was significant if less than 0.05.

action of adiponectin and HDL independent of obesity. This dysfunction may underlie also the association of adiponectin levels with metabolic syndrome in men to be independent of the metabolic syndrome components. In women, the existing reciprocal relationship between normal anti-inflammatory adiponectin and HDL functions and proinflammatory state leads to no association independent of metabolic syndrome components. An additional explanation would implicate that sex mattered in the anti-inflammatory functions of plasma fibrinogen independently predicted metabolic syndrome prospectively in men, in contradistinction to women and, hence, was considered likely one of its components [17].

In the current study we found that normal individuals with adiponectin levels of less than 2.63 ng/ml will be suspected to develop HTN (the predictive value of adiponectin for the occurrence of HTN was 2.63 ng/ml, with 90% sensitivity and 35% specificity, area under the ROC curve was 0.65 and $P = 0.03$). As regards the control group in the present study, the frequency of controls with adiponectin levels of less than 2.63 ng/ml was significantly lower than those with adiponectin levels of more than 2.63 ng/ml. As regards the patient group in the present study, the frequency of hypertensive patients (regardless of having metabolic syndrome or not) with an adiponectin level of less than 2.63 ng/ml was significantly higher than those with an adiponectin level of more than 2.63 ng/ml.

The present study showed that adiponectin level in patients taken RAAS inhibitor drugs was statistically insignificantly low than those patients taken the B-blocker drug group. Other studies suggested that RAS blockers improved plasma adiponectin levels more significantly than amlodipine, doxazosin, and metoprolol regimens. Plasma adiponectin levels increased parallel to the improvement in insulin resistance and reduction in the inflammatory activity; RAS blockade increases serum adiponectin concentrations with improvement in insulin sensitivity; nebivolol and metoprolol show similar reductions in blood pressures but differ in their effects on plasma adiponectin levels. It is not clear whether the increase in adiponectin levels is related to the antihypertensive or the metabolic effects of various regimens [13]. Other studies show that Nebivolol (a new B-blocker), in contrast to metoprolol, improved oxidative stress, insulin sensitivity, and increased adiponectin levels in hypertensive patients [14,15]. Several studies with different antihypertensive regimens have shown that plasma adiponectin levels increase along with the reduction of blood pressure [14].

Conclusion

Low level of plasma adiponectin is an independent predictive factor for HTN even with the presence or absence of metabolic syndrome.

Adiponectin has a role in the initiation and development of HTN, not in the progression of the stages of HTN.

Adiponectin level is not sex related; however, male metabolic hypertensive patients have significantly lower adiponectin levels compared with male nonmetabolic hypertensive patients and this significant difference is not present in female sex.

The predictive value of adiponectin in hypertensive patients in this study was 2.63 ng/ml, so normal individuals with an adiponectin level of less than 2.63 ng/ml will be suspected to develop HTN.

These facts together with the promising results of experimental studies suggest that the possibility of adiponectin replacement might become a new pharmacological approach to the treatment of HTN and atherosclerosis and prevention of cardiovascular diseases.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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