Relations of serum aldosterone and microalbuminuria to left ventricular hypertrophy in patients with essential hypertension

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Abstract: ***Background:*** The identification of risk factors for the initiation of left ventricle hypertrophy (LVH), which is an independent risk factor for cardiovascular mortality and morbidity in hypertensive patients, is very important. The present study examined the role of aldosterone and microalbuminuria in LVH and geometry in patients with essential hypertension (EHT), and investigated the contribution of myocardial fibrosis to the process of LVH. ***Methods:*** The relationship of the plasma aldosterone concentration (PAC) to LVH and left ventricular (LV) geometry was investigated in 57 patients with EHT; mean age, 51 ± 10.2 years. Twenty-five had LVH. When evaluated according to the geometrical patterns of LVH, 14 patients had concentric LVH (CH), 11 had eccentric LVH (EH), and 12 had concentric remodeling. Twenty patients had normal left ventricle geometry. Two weeks after the cessation of antihypertensive medications, sodium, potassium, total protein and microalbumin in 24-hour urine samples and plasma aldosterone levels, plasma renin activity and serum procollagen type III amino-terminal peptide (PIIINP) were measured. ***Results:*** PAC of the patients with LVH was found to be significantly higher (23.0±5.6 versus 12.9±3.72 ng/dl, p=0.0001) than those without LVH. The difference between plasma renin activities was not statistically significant. Linear regression analysis revealed that plasma aldosterone level and age were independent parameters increasing left ventricle mass index (LVMI). PAC correlated with both LVMI (r=0.913, P=0.0001) and relative wall thickness (RWT: r=0.744, P=0.0001). In patients with LVH (LVMI ≥134 g/m^2), the serum concentration of PIIINP, a marker of myocardial fibrosis, correlated with RWT (r=0.422, p=0.001) and LVMI (r= 0.664, P=0.0001). The serum PIIINP concentration was significantly higher in the CH group than in the EH group (0.74±0.11 vs 0.66±0.19 ng/ml, respectively; p<0.05). Twenty-four hour urine microalbumin concentrations of the patients with LVH were found to be significantly higher (P=0.003) and positively correlated with LVMI and PAC (P=0.0001). ***Conclusions:*** Aldosterone may be involved in LVH and LV geometry, particularly in the development of CH. Myocardial fibrosis seems more strongly involved in the hypertrophic geometry of CH than with EH. A strong relation between microalbuminuria with aldosterone and LVMI was detected. The value of selective aldosterone blockers in preventing target organ damage awaits further investigations.

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Key Words: Aldosterone; Essential hypertension; Left ventricular hypertrophy; Left ventricular geometry; Procollagen type III amino-terminal peptide; Microalbuminuria.

Introduction:

Many patients with essential hypertension may present with overt or subclinical target organ damage (TOD) involving the heart, kidneys, central nervous system or retina at the time of their initial diagnosis. The cost effectiveness of BP reduction using drug therapy is greater in the presence of target organ abnormalities and/or co-morbidities. In this context, assessment of sub-clinical TOD has become the key element in evaluating hypertensive patients [(1)].

Left ventricular hypertrophy (LVH) represents an independent risk factor for cardiovascular mortality and morbidity in patients with hypertension (HT) [(2)]. In particular, concentric LVH is associated with a higher risk of cardiac arrhythmias, and even sudden death, and predicts the development of heart failure [(3)]. Hemodynamic load is strongly involved in the development of LVH in HT, but blood pressure and the degree of LVH do not necessarily correlate. The development of LVH is influenced by various neurohumoral factors; the renin-angiotensin system is thought to play an important role in the pathogenesis of LVH [(4)]. In morphological findings obtained from *in vivo* and *in vitro* studies, increased levels of aldosterone in the circulation were found to be related with the excessive accumulation of collagen

causing myocardial fibrosis [5]. However, it is not clear whether aldosterone plays an independent role in the development of hypertrophy in hypertensive patients [6,7].

Serum procollagen type III amino-terminal peptide (PIIINP), is formed during the conversion of procollagen type III to collagen type III and released into the blood, then cleared from the blood via hepatobiliary elimination. The serum concentration of PIIINP is used as a marker of collagen type III synthesis in various organs, including the liver under conditions of preserved bile excretion [2]. High serum levels of PIIINP gained attention as reflecting ongoing fibrosis in the heart [8].

Microalbuminuria (MA) is one of the earliest indications of kidney injury in patients with diabetes mellitus and hypertension and is associated with high incidence of cardiovascular morbidity [9,10,11].The National Kidney Foundation of the United States defines MA as urine albumin excretion of approximately 30-300 mg/day (20–200 µg/min) in at least two out of three consecutive samples of non-ketotic sterile urine or albumin creatinine ratio of 3–30 mg/mmol (30–300 mg/g) [12].

The association between MA and hypertension was described long time ago. A renewed interest in MA and essential hypertension occurred when several studies pointed out the importance of MA as a predictor of excess cardiovascular morbidity and mortality in non-diabetic hypertensive patients [13]. MA has proved to be highly specific in identifying patients with LVH and carotid atherosclerosis [9], because MA possibly reflects a state of increased renal endothelial permeability and is considered an early marker of diffuse endothelial dysfunction [14].

The aim of the present study was to investigate the relationship of aldosterone and microalbuminuria with LVH and different geometrical patterns of left ventricle that develop in hypertensive patients. In addition, the degree of ongoing fibrosis associated with various geometrical patterns of LVH was examined by assaying the serum PIIINP concentrations.

Subjects and Methods:

Patients

We enrolled 57 male patients with essential hypertension (EHT), randomly selected from the Out Patients Clinic of Specialized Medical Hospital, Mansoura University, with mean age, 51±10.2 years and 20 non-hypertensive normal male subjects of matched age and body weight as control group.

Patients with the following diseases were excluded from the study: secondary HT, coronary artery disease, valvular heart disease, atrial fibrillation, LV systolic dysfunction (LV ejection fraction; LVEF ≤50%), renal disorder (serum creatinine level ≥1.5 mg/dl) or electrolyte imbalance. Conditions associated with elevated serum concentrations of PIIINP were likewise excluded (liver disease, bone disease, malignant disease, diabetes mellitus, pulmonary fibrosis or collagen disease). All patients gave written informed consent to participate in the study and the investigations conformed to the principles outlined in the Declaration of Helsinki. The study protocol was approved by local ethics committee of the hospital.

Height, weight, body mass index (BMI), blood pressure, heart rate, the period they were aware of their hypertension and the medication they were using were recorded for each patient. BMI was calculated by the formula: body weight (kg)/ height (m^2). Blood pressure and heart rate were measured with the patient seated, after a 5-min rest period. Two measurements were obtained at 5-min intervals, and then averaged. The criteria for HT were: systolic blood pressure (SBP) ≥140 mmHg and diastolic blood pressure (DBP) ≥90 mmHg. In addition, blood and urine tests and echocardiography were performed within 2 weeks of the initial examination, while the patient was untreated.

Biochemical Determinations:

Prior to initiating the study, all antihypertensive medications were stopped for two weeks and the patients were recommended to consume a diet with a normal amount of salt. Ten patients who had uncontrolled elevations during the no medicated period were administered amlodipine since it would have the least effect on the measurements to be carried out. However, this medication was also stopped 48 hours before obtaining blood samples.

Fasting blood samples were collected while the patient was supine and had rested for 20 min and delivered into 2 tubes. Three ml of them was collected in K_2EDTA-containing tubes and the samples were centrifuged for 5 minutes at 3000 rpm at 4°C. Plasma was stored at -70°C until analysis of plasma renin activity (PRA) and plasma aldosterone concentration (PAC). The rest of blood sample collected in biochemical tube to obtain serum. The serum samples were obtained by centrifuging blood samples at 3000 rpm for 15 min at 4°C. Serum was stored at -70 °C until analysis of serum PIIINP, lipid profile, and electrolytes.

- Plasma renin activity (PRA) was measured using commercially available coat-A-count solid phase radioimmunoassay kits supplied by Diagnostic

Products Corporation (Los Angeles, CA, USA), according to the manufacture instructions [15].

- Plasma aldosterone concentrations (PAC) were measured using commercially available coat-A-count solid phase radioimmunoassay kits supplied by Diagnostic Products Corporation (Los Angeles, CA, USA), according to the manufacture instructions [16].

-Serum PIIINP concentrations were measured using commercially available immunoradiometric assay kits, (Riagnost PIIIP, CIS. Biointernational, Saclay, France), that employs monoclonal antibody to PIIINP [17].

At the same time, urine were collected for 24 hours, urine volume measured then 10 ml was stored in Falcon tubes at -70°C till assay of urine total protein, microalbumin and electrolyte. The patients were asked to avoid exercise prior to the urine collection.

- Electrolyte measurements were carried out by ion-selective electrodes using AVL 988 analyzer (Roche Diagnostics, Germany).

- Microalbuminuria (MA) was assessed using an immunoassay kit (Roche Diagnostics GmbH, Basel, Switzerland), according to the manufacture instructions.

Echocardiographic Measurement:

Comprehensive 2-dimensional echocardio-graphy was performed using an ESAOTE XP-10 with 2.5 MHz transducer (USA). Recordings were obtained at rest according to the recommendations of the American Society of Echocardiography [18]. Measurements included LV dimension at diastole (EDD), LV dimension at systole (ESD), interventricular septal thickness (IVST) and posterior wall thickness (PWT) and left atrium (LA) size at end-systole. LVEF was calculated in the parasternal long-axis view. LV mass was normalized for body surface area and expressed as the LV mass index (LVMI), which was calculated using Devereux's formula (1993) [19]: (LVMI =1.04 [(EDD + IVST +PWT) ^{3} – (EDD) ^{3}] –13.6). An LVMI value > 134 g/m^2 was taken as indicating LVH. The relative wall thickness (RWT) was calculated as PWT × 2/EDD and a value of more than 0.44 were accepted as indicating an increase [20]. Patients were divided into 4 groups according to their LV geometry [21]: N group, normal LVMI and RWT; concentric remodeling (CR) group, CR indicated by normal LVMI and increased RWT; eccentric hypertrophy (EH) group, EH indicated by increased LVMI and normal RWT; and concentric hypertrophy (CH) group, CH indicated by increased LVMI and RWT. In addition, pulse Doppler echocardiography was used to assess LV diastolic function. Peak velocities of the early diastolic filling wave (E wave) and atrial filling (A wave) were recorded and the E-to-A ratio (E/A) was calculated. Deceleration time (DcT) of the E wave was then determined.

Statistical Analysis:

Statistical analyses were performed using SPSS software (SPSS Inc. Chicago, IL). Data are expressed as means ± SD. Unpaired samples t test was used to compare the mean values in 2 groups and one-way ANOVA was used for groups of three or four. The relationships between variables were assessed using univariate linear regression analysis and Pearson's correlation coefficient. A P value <0.05 was accepted as having statistical significance.

Results:

Table (1): Compares the clinical and echocardiographic data of hypertensive patients and controls. The mean SBP, DBP, LVMI, IVST, PWT, RWT, EDD, LA, EF, mitral E/A ratio and DcT were significantly higher in HT patients compared to controls (P<0.05).

Table (2): Shows the laboratory data of the hypertensive patients and controls. There were significant higher levels of PAC, PRA and PIIINP in HT patients than controls (P<0.05). HT patients had high prevalence of MA (46.7%), with mean MA levels 44.3±13.7 mg/L (Figure 1).

Table (1): Clinical and echocardiographic data of hypertensive (HT) patients and controls

Parameters	***HT patients N=57***	***Controls N=20***	***P value***
Age (year)	51±10.2	50.9±7.9	0.960
Duration of HT (year)	6.1±3.8	--	--
Weight (Kg)	82.7±13.9	83.9±12.7	0.730
Height (cm)	164±21.1	166±23.2	0.740
BMI (Kg/m^2)	30.0±3.21	30.4±2.5	0.680
SBP (mmHg)	170.0±27.6	115±8.1	0.000
DBP (mmHg)	106±15.8	74.5±6.8	0.000
LVMI (g/m^2)	128.0±20.3	89.0±36.5	0.000
IVST(cm)	1.41±0.32	0.84±0.36	0.000
PWT (cm)	1.26±0.32	0.88±0.29	0.000
RWT	0.50±0.11	0.37±0.24	0.000

EDD (cm)	5.35±0.86	4.64±0.1.25	0.006
LA (cm)	3.74±0.77	3.26±0.73	0.018
EF (%)	61.1±10.1	66.3±12.1	0.066
Mitral E/A ratio	0.89±0.21	1.43±0.64	0.000
DcT (msn)	184.0±31.7	168±45.9	0.077

BMI= Body mass index, SBP= Systolic blood pressure, DBP= diastolic blood pressure, LVMI= LV mass index, IVST= Interventricular septal thickness, PWT= Posterior wall thickness, RWT= Relative wall thickness, EDD= LV dimension at diastole, LA= Left atrium size at end-systole, EF= LV ejection fraction, E/A= Early/atrial transmitral Doppler flow velocity, DcT= Deceleration time of early transmitral Doppler flow.

Table (2): laboratory data of the hypertensive patients and controls

Parameters	***HT patients, N=57***	***Controls, N=20***	***P value***
Serum creatinine (mg/dl)	0.97±0.18	0.91±0.15	0.240
Serum potassium (meq/L)	3.93±0.46	3.84±0.42	0.441
Serum sodium (meq/L)	140±6.7	138±6.0	0.182
Serum Cholesterol (mg/dl)	208±33	141±23	0.000
Serum triglycerides (mg/dl)	112.0±30.7	89.2±22.6	0.003
HDL-C (mg/dl)	40.1±6.01	46.8±6.68	0.000
LDL-C (mg/dl)	145.0±33.0	76.4±24.0	0.000
Plasma aldosterone (ng/dl)	17.3±6.86	8.46±3.27	0.000
Plasma renin activity ($ng.ml^{-1}.h^{-1}$)	1.67±0.74	0.80±0.51	0.000
PIIINP (ng/ml)	0.61±0.18	0.35±0.07	0.000

Significant P: <0.05

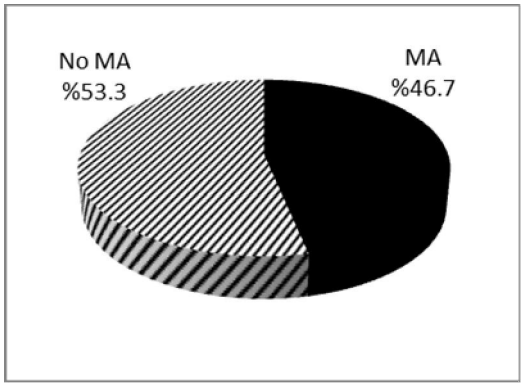

Figure (1): Prevalence of microalbuminuria in hypertensive patients

Of the 57 hypertensive patients participating in the study, 25 had LVH diagnosed echocar- diographically. When the patients were evaluated according to their left ventricle geometries, 14 patients had concentric LVH, 11 had eccentric LVH, and 12 had concentric remodeling. Twenty patients had normal left ventricle geometry. Twenty patients did not use any antihypertensive medications before, 6 were on beta-blockers, 7 were taking ACE inhibitors, 5 were receiving angiotensin II receptor blockers, 5 were on calcium antagonists, and 1 patient was receiving an alpha-blocker. Thirteen patients were receiving combined medical treatment.

When blood pressure levels were compared, the patients with LVH had higher SBP, compared to the patients without LVH (P=0.028), while no significant difference between DBP levels was found (P=0.670). The BMI of the patients with LVH was significantly higher than that of the patients without LVH (P=0.0001). The differences between the total cholesterol, triglyceride, HDL-C and LDL-C levels were not statistically significant (P>0.05). There was no statistically significant difference in duration of hypertension between patients with LVH and those without (6.8±3.2 versus 5.4±3.8) (*P*= 0.078) (Table 3).

The two-dimensional and Doppler echocardiographic parameters of the patients grouped according to LVH are presented in Table 3. Left ventricular ejection fraction did not show a statistically significant difference between the groups (*P*=0.077). The patients with LVH had significantly higher LVMI (P=0.0001). Diastolic functions of the patients with LVH were significantly disturbed. In patients with LVH, the mitral E wave deceleration times were statistically higher (P=0.046), and the mitral E/A ratios were significantly lower (P=0.001) (Table 3).

Patients with LVH had significantly higher 24-hour urine protein and microalbumin values than the patients without LVH (P=0.028 and P=0.003 respectively) in patients with LVH, plasma

aldosterone levels were higher than those without LVH (23.0 ± 5.6 versus 12.9 ± 3.72 ng/dl, *P*=0.0001), and the difference between plasma renin activity was not statistically different (1.87 ±0.72 versus 1.50 ± 0.73 $ng.ml^{-1}.h^{-1}$, P=0.062) (Table 4; Figure 2).

When a comparison was made according to geometrical remodeling of the left ventricle, the SBP levels of the patients with concentric LVH were statistically significantly greater than that of the patients with concentric remodeling (195.0±30.5 versus 157.8±14.8 mmHg, P=0.0001). There was no significant difference between DBP levels (106.4±16.3 versus 100.2±8.4 mmHg, P=0.510). BMI, duration of hypertension, and serum lipid levels did not exhibit significant differences between the groups (*P*>0.05). The LVMI, RWT, IVST and PWT of the patients with concentric LVH were statistically significantly higher than that of the patients with concentric remodeling (P=0.0001) (Table 5).

When the groups were compared according to the geometrical remodeling of the left ventricle, the patients with concentric LVH had significantly higher levels of plasma aldosterone (25.3±4.5 ng/dl) when compared to the patients with normal geometry (13.3±5.0 ng/dl) and to patients with concentric remodeling (14.5 ± 3.3 ng/dl) (P=0.0001). The plasma levels of aldosterone did not differ between patients having concentric hypertrophy and eccentric hypertrophy (P=0.053). The geometrical patterns of the left ventricle did not demonstrate significant differences with regards to plasma renin activity (P=0.612). The differences between the measured levels of 24-hour urinary microalbumin (P=0.543), sodium (P=0.771), and potassium (P=0.570) were not significant while urine protein levels were significantly higher in concentric LVH (Table 6).

Spearman's correlation showed positive correlations between PAC with PRA (r=0.672; p=0.0001), PIIINP (r=0.647; p=0.0001) and MA (r=0.694; p=0.0001) (figure 3). Also there were a positive significant correlations of MA with PRA (r=0.642; p=0.0001) and PIIINP (0.661; P=0.0001), in addition significant positive correlation was found also between PRA and PIIINP (r= 0.732; p=0.0001). Moreover, PAC, PRA, PIIINP and MA showed significant positive correlations with LVMI, IVST, RWT, EF, EDD and DcT while significant negative correlations were found with E/A ratio (p<0.05) (table 7; figure 4,5&6).

When independent parameters influencing LVMI were analyzed with linear regression analysis, there was a significant continuing relationship between LVMI and plasma aldosterone level and a significant relationship that was evolving with age (table 8).

Table (3): Comparison between hypertensive cases with LVH (LVMI>134 gm/m^2) and those without LVH (LVMI<134 gm/m^2)

Parameters	***No LVH (N=32)***	***LVH (N=25)***	***P value***
Age (year)	50.2±9.8	51.9±10.8	0.550
BMI (kg/m^2)	28.44±3.56	33.5±2.87	0.0001
SBP (mmHg)	163±21.4	179±32.2	0.028
DBP (mmHg)	105±15.3	107±16.5	0.670
LVMI (g/m^2)	117.0±16.1	143.0±15.8	0.0001
IVST (cm)	1.21±0.14	1.68±0.29	0.0001
PWT (cm)	1.05±0.18	1.53±0.24	0.0001
RWT	0.41±0.004	0.61±0.003	0.0001
EDD (cm)	5.30±0.85	5.41±0.87	0.634
LA (cm)	3.66±0.80	3.84±0.73	0.400
EF (%)	59.0±10.3	63.8±9.35	0.077
Mitral E/A ratio	0.97±0.22	0.80±0.24	0.0017
DcT (msn)	175.5±28.3	190.0±28.9	0.046
Serum Cholesterol (mg/dl)	211±31.6	203.0±34.9	0.384
Serum triglycerides (mg/dl)	113.0±27.7	110.5±34.7	0.716
HDL-C (mg/dl)	41.0±6.34	39.0±5.48	0.211
LDL-C (mg/dl)	148.0±32.2	142.0±34.5	0.550

LVH= Left ventricular hypertrophy Significant P: <0.05

BMI= Body mass index, SBP= Systolic blood pressure, DBP= diastolic blood pressure, LVMI= LV mass index, IVST= Interventricular septal thickness, PWT= Posterior wall thickness, RWT= Relative wall thickness, EDD= LV dimension at diastole, LA= Left atrium size at end-systole, EF= LV ejection fraction, E/A= Early/atrial transmitral Doppler flow velocity, DcT= Deceleration time of early transmitral Doppler flow.

Table (4): Twenty–four hour urine finding, plasma aldosterone, renin activity and PIIINP in hypertensive cases with LVH and those without LVH

Parameter	*No LVH (N=32)*	*LVH (N=25)*	*P value*
24-hour urine:			
Protein (mg/day)	110.5±52.6	146.0±69.3	0.028
Microalbumin (mg/day)	39.7±12.5	50.3±13.2	0.0031
Sodium (mEq/L)	219.7±66.2	177.9±79.4	0.034
Potassium (mEq/L)	52.3±23.5	57.8±21.8	0.377
Plasma renin activity ($ng.ml^{-1}.h^{-1}$)	1.50±0.73	1.87±0.72	0.062
Plasma aldosterone (ng/dl)	12.9±3.72	23.0±5.6	0.0001
PIIINP (ng/ml)	0.55±0.16	0.67±0.17	0.0097

LVH= Left ventricular hypertrophyl; Significant P: <0.05

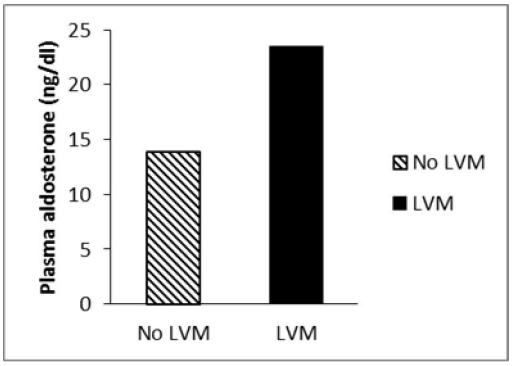

Figure (2): Plasma aldosterone in hypertensive cases with LVH and those without LVH hypertensive group

Table (5): Echocardiographic parameters according to ventricular Geometry

	Normal Geometry (n=20)	*Concentric Remodeling (n=12)*	*Eccentric LVH (n=11)*	*Concentric LVH (n=14)*
IVST (cm)	1.26±0.23	1.32±0.25	1.61±0.40	1.68±0.25**
PWT (cm)	1.05±0.19	1.30±0.28	1.31±0.35	1.59±0.23**
EDD (cm)	5.32±0.86	5.03±0.76	5.81±0.83	5.26±0.87
LVMI (g/m^2)	106.8±17.4	118.3±13.0	154.0±15.9	162.8±19.7**
RWT	0.42±0.02	0.59±0.02	0.45±0.01	0.62±0.02**
LVEF (%)	60±9.2	59.5±10.6	61.4±11.2	64.4±10.8
E/A	0.90±0.19	0.87±0.17	0.85±0.22	0.94±0.25
DcT (ms)	178±33.9	176±22.9	179±23	194±29.7

**P=0.0001 when compared with patients having normal geometry

LVMI= LV mass index, IVST= Interventricular septal thickness, PWT= Posterior wall thickness, RWT= Relative wall thickness, EDD= LV dimension at diastole, EF= LV ejection fraction, E/A= Early/atrial transmitral Doppler flow velocity, DcT= Deceleration time of early transmitral Doppler flow.

Table (6): Twenty–four hour urine finding, plasma aldosterone, renin activity and PIIINP values according to ventricular Geometry

	Normal Geometry (n=20)	***Concentric Remodeling (n=12)***	***Eccentric LVH (n=11)***	***Concentric LVH (n=14)***
24-hour urine:				
Protein (mg/day)	98.3±54.0	124.6±42.1	147.6±55.6	162.2±79.7
Microalbumin (mg/day)	41.1±13.2	45.4±13.8	47.3±13.8	46.8±15.1
Sodium (mEq/L)	203.7±57.1	208.5±107	180.2±81.5	185.3±82.8
Potassium (mEq/L)	50.8±24.0	55.6±25.2	53.6±17.4	62.3±22.2
Plasma renin activity ($ng.ml^{-1}.h^{-1}$)	1.58±0.78	1.56±0.74	1.66±0.65	1.92±0.77
Plasma aldosterone (ng/dl)	13.3±5.0	14.5±3.3	20.3±6.7	25.3±4.5$^{**,\#}$
PIIINP (ng/ml)	0.54±0.17	0.55±0.15	0.66±0.19	0.74±0.11$^{**,\#}$

**P=0.0001 when compared with patients having normal geometry

$^{\#}$P=0.0001 when compared with patients having concentric remodling

Table (7): Correlation of PAC, PRA, PIIINP and MA with SBP, DBP, BMI and echocardiographic findings in hypertensive patients

	PAC		***PRA***		***PIIINP***		***MA***	
	r	***P***	***r***	***P***	***r***	***P***	***r***	***P***
SBP	0.179	0.182	0.078	0.564	0.172	0.201	0.132	0.327
DBP	0.307	0.023*	0.106	0.433	0.076	0.574	0.019	0.888
BMI	-0.383	0.057	-0.211	0.120	-0.079	0.657	-0.018	0.895
LVMI	0.913	0.000**	0.675	0.000**	0.664	0.000**	0.662	0.000**
IVST	0.816	0.000**	0.420	0.001**	0.477	0.000**	0.48	0.000**
PWT	0.010	0.939	0.02	0.833	0.042	0.755	0.224	0.093
RWT	0.744	0.000**	0.379	0.004**	0.422	0.001**	0.445	0.001**
EDD	0.336	0.011*	0.356	0.007**	0.271	0.041*	0.367	0.005**
LA	0.202	0.132	0.008	0.954	0.205	0.126	0.306	0.021*
EF	0.413	0.001**	0.277	0.037*	0.273	0.040*	0.396	0.002**
E/A ratio	-0.691	0.000**	-0.501	0.000**	-0.490	0.000**	-0.482	0.000**
DcT	0.679	0.000**	0.571	0.000**	0.602	0.000**	0.526	0.000**

*Correlation is significant at the 0.05 levels ** Correlation is significant at the 0.01 levels

Table (8): Linear regression analysis of the independent factors affecting LVMI

	Unstandardized Coefficients		***Standardized Coefficients***		
	B	Std. Error	Beta	***t***	**p**
PAC	2.434	0.252	0.817	9.648	0.000**
PRA	1.244	2.405	0.045	0.517	0.607
PIIINP	11.591	9.966	0.102	1.163	0.250
MA	0.003	0.123	0.002	0.026	0.979
SBP	-0.030	0.045	-0.040	-0.666	0.509
DBP	-0.092	0.077	-0.071	-1.188	0.241
BMI	0.283	0.196	0.154	1.529	0.117
Age	1.603	0.223	0.462	3.126	0.029*

Dependent Variable: LVMI

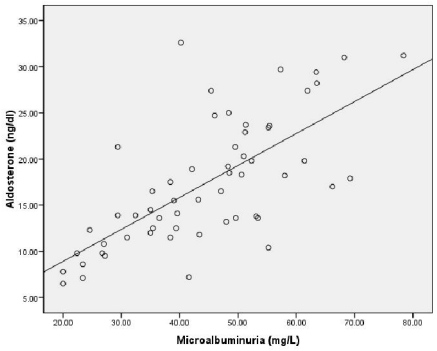

Figure (3): Positive correlation between aldosterone and microalbuminuria in hypertensive patients

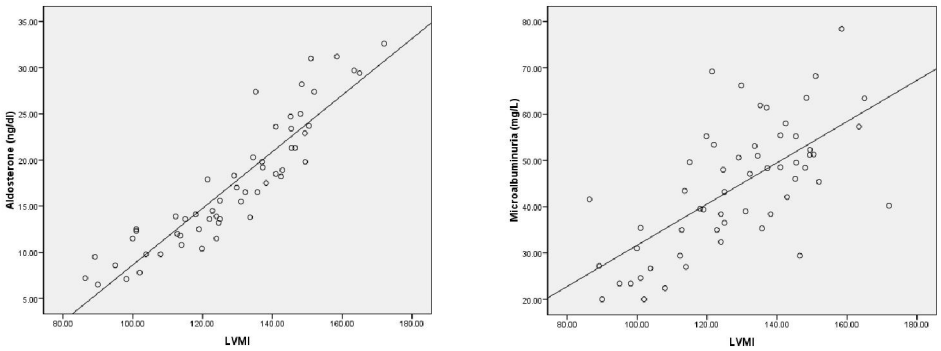

Figure (4): Correlation between LVMI with aldosterone and microalbuminuria in hypertensive patients

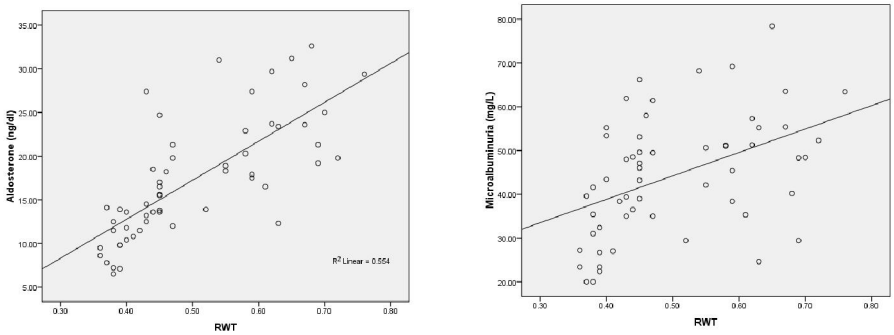

Figure (5): Correlation between RWT with aldosterone and microalbuminuria in hypertensive patients

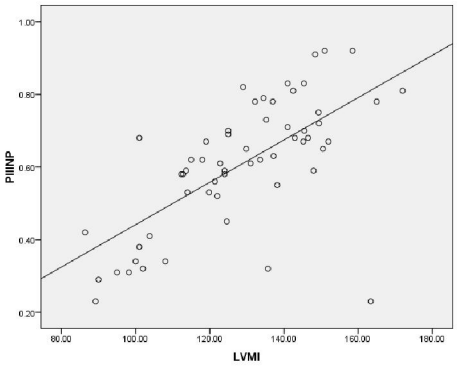

Figure (6): Correlation between LVMI with PIIINP in hypertensive patients

Discussion:

In hypertension, the major indicator of the degree of LVH is systolic blood pressure. Finding higher values of systolic blood pressure in our patients with LVH Than those without LVH (P=0.028) supports this. However, only 50% of the variances observed in left ventricular mass of hypertensive patients can be explained by the differences in systolic blood pressure and this is a very low rate [22]. The reason behind this is having several mechanisms responsible for the increase in cardiac mass. Non hemodynamic mechanisms such as the activities of the renin-angiotensin system and sympathetic nervous system might have an important role in the development of myocardial hypertrophy [7].

In the present study, plasma aldosterone levels were significantly higher in HT patients when compared to controls and was positively correlated with DBP (p= 0.023). Moreover, EHT patients with LVH, especially those with concentric hypertrophy, had higher levels of plasma aldosterone and that PAC was positively correlated with LVMI and RWT. These findings indicate the possibility that plasma aldosterone, is involved in the development of hypertensive cardiac hypertrophy and can cause increases in LV mass and concentric changes. These results in agreement with the results of Soylu et al., (2004) [7]; Vasan et al., (2004) [23]; Nakahara et al. (2007) [2] and (Gaddam et al., 2010) [24].

Nakahara et al. (2007) [2] found that, the coexistence of arterial hypertension with high levels of aldosterone in the circulation was closely related to excessive collagen accumulation leading to myocardial fibrosis. Aldosterone is influential on myocardial tissue, especially non-myocyte cells (endothelial cells, cardiac fibroblasts) [7]. Non-myocyte cells are thought to be important in the development of pathological left ventricular hypertrophy. The synthesis of aldosterone is partially controlled by angiotensin-II and plasma levels of aldosterone are not always related to renin activity and angiotensin-II concentrations [25]. Increased levels of angiotensin-II in the circulation cannot by itself predict the fibrous tissue response. A study by Brilla and Weber (1992) [26] demonstrated that cardiac fibrosis in patients with left ventricular hypertrophy was

guided by aldosterone rather than angiotensin-II and renin. There is increasing evidence of the presence of a cardiac renin-angiotensin system with local aldosterone formation. Local aldosterone formation in the heart may contribute to the pathogenesis of cardiac hypertrophy [7]. Yamamoto, et al (2002) [27] had demonstrated that aldosterone is produced in the hypertensive human heart. Although cardiac aldosterone synthesis may be regulated by both the systemic and local renin-angiotensin system, the precise mechanisms for the induction of aldosterone in the hypertensive heart are not clear. Indeed, increased wall tension in the myocardium due to high blood pressure may be a main stimulus for activation of cardiac aldosterone production by way of the renin-angiotensin system in patients with hypertension. The amount of aldosterone produced by cardiac tissue is small compared with the amount of plasma aldosterone, suggesting that the biological function of cardiac aldosterone may be autocrine or paracrine [28]. However, cardiac aldosterone synthesis and its retention may be important for the pathogenesis of the hypertensive heart [2].

In our study, we found high PRA and positive correlation between PRA and LVMI in HT patients; however, the plasma levels of renin did not differ between different geometrical patterns of the left ventricle (P=0.610). In renovascular hypertension (high renin), the primarily identified geometrical pattern was concentric hypertrophy and there are studies demonstrating high levels of renin in EHT patients with concentric hypertrophy [29]. Furthermore, in several studies performed in patients with essential hypertension, different results have been observed with regards to the relationship between the renin-angiotensin system and the left ventricular mass. In research in which univariate analysis has been implemented, a significant relationship was found between PRA and left ventricular mass, yet this has not been possible in other studies. A possible explanation for this is that the relationship between renin and the left ventricle might be influenced by some cofactors. Age, blood pressure, sodium intake, plasma volume and levels of angiotensin II were positively correlated with LVMI, while inversely related to renin [7].

Primary aldosteronism is characterized by volume loading and when compared with renovascular hypertension, eccentric LVH is observed more frequently in primary aldosteronism [24]. In previous studies, aldosterone levels were found to be high in EHT patients with concentric hypertrophy as well, yet higher values were found in patients with concentric remodeling of the left ventricle and eccentric hypertrophy [29]. In our study, both in patients with eccentric and concentric hypertrophy, plasma aldosterone levels were observed to be higher, however; this only reached the limit of statistical significance in patients with concentric hypertrophy. When parameters such as

blood pressure, BMI, and age were added, the relationship between aldosterone and concentric hypertrophy still continued. Thus, we might speculate that there is an independent relationship between aldosterone and LVH (especially concentric hypertrophy). Independent of the effects of the factors increasing blood pressure, aldosterone might play a role in cardiac hypertrophy. Although eccentric LVH is more commonly seen in primary aldosteronism which is characterized by volume loading [24,30], etiology is multifactorial in cases of EHT and the geometry of the left ventricle might change depending on the degree of neurohumoral activity.

Diastolic dysfunction is identified more frequently in EHT with LVH. Correlations between PAC and impaired LV diastolic function have been described in EHT patients [7]. We investigated the relation of aldosterone with diastolic dysfunction and we found correlation between PAC and diastolic filling velocities of the left ventricle. Considering these findings together with the present results, leads to the following concepts. If the aldosterone-induced myocardial fibrosis progresses, impaired LV diastolic function and concentric hypertrophy appear. In such patients, activation of aldosterone receptors in the heart may be strongly potentiated, or aldosterone production in myocardial tissue may be accelerated. Further progression of myocardial fibrosis would gradually lead to impaired LV systolic function, followed by enlargement of the LV chamber, a decrease in the movement of the LV wall, and development of a state of hypertensive heart failure [2].

Several reports have suggested the possibility that aldosterone directly promotes myocardial hypertrophy and interstitial fibrosis by stimulating the synthesis of myocardial collagen and the proliferation of fibroblasts in experimental conditions [2]. Weber et al (1991) [31] used a hypertensive rat model and showed that aldosterone administration increased both blood pressure and interstitial and perivascular fibrosis, while co-administration of spironolactone, an aldosterone receptor antagonist, completely inhibited the development of fibrosis even at dosages that did not demonstrate an anti-hypertensive effect. In addition, aldosterone has been shown to increase extracellular matrix and collagen deposition in the myocardium by enhancing the expression of cardiac collagen type I and III genes [2].

PIIINP is released into the blood at the time of collagen synthesis, and has recently gained attention as a marker of ongoing tissue fibrosis in the cardiovascular organs [2]. Matoba et al (1998) [32] administered delapril hydrochloride, an ACE inhibitor, for 12 months to hypertensive patients with accompanying LVH and reported that serum PIIINP concentrations and LV mass were both reduced by this treatment. Sato et al (2002) [33] added spironolactone to an ACE inhibitor as drug therapy for EHT patients, and found that this combination significantly reduced both LVMI and the serum PIIINP concentration. In addition, Tsutamoto et al (2000) [34] performed cardiac catheterization to collect blood from the coronary sinus and aorta in chronic heart failure patients, which showed that the index of aldosterone incorporation into the heart correlated positively with LV end-diastolic volume and serum PIIINP concentration. Moreover, the Randomized Aldactone Evaluation Study (RALES) showed that the outcome in patients with severe chronic heart failure was strikingly improved when spironolactone was added to the treatment regimen [2]. Zannad et al (2000) [35] performed subanalysis of the RALES results and demonstrated that 6 months' administration of spironolactone brought about a significant decrease in serum PIIINP concentration compared with placebo, that outcome was better in the low-PIIINP-concentration group compared with the high concentration group. These reports suggest that aldosterone may be directly incorporated into cardiac tissue and is strongly involved in the development of remodeling of the LV.

The present study found that the serum PIIINP concentration was high and significantly correlated with RWT and LVMI in the combined LVH group (EH + CH group). Moreover, the serum PIIINP concentration was significantly higher in the CH group than in the EH group. These findings suggest that the development of interstitial fibrosis is more strongly involved in CH than in EH, and that aldosterone likely influences the development of fibrosis. Taniguchi et al (2006) [36] reported that the addition of spironolactone significantly reduced LVMI only in the concentric LV hypertrophy subgroup of hypertensive patients during angiotensin II receptor blocker treatment.

Another finding obtained in our study was that EHT patients with LVH had higher levels of microalbumin excretion in 24-hour urine samples compared to those without LVH (P=0.003). There was also a significant positive correlation between MA with LVMI and RWT. However, results regarding the relationships between MA and geometric pattern of LV did not showed statistically significant difference between the 4 groups of HT patients. Similarly, in the previous studies, high urinary microalbumin excretion by hypertensive patients was found to be in correlation with electrocardiographic LVH and the risk of myocardial infarction [37]. Also, similar to the report of Busari et

al. (2010) [12] which showed that MA was independently associated with ECG abnormalities such as ECG LVH, QTc prolongation and ventricular arrhythmias in adult non-diabetic Nigerians with hypertension. Moreover, Bulatov et al. (2001) [38] found linear correlation between LVMI and albumin excretion rate. Assadi (2008) [13] found that MA and C-reactive protein (CRP) levels are predictors of increased risk for LVH and the strength of association between LVH and CRP is comparable to that of MA in children and adolescents with essential HT nephropathy.

The pathogenic mechanisms leading to the development of MA are not yet fully known: blood pressure load and increased systemic vascular permeability, possibly due to early endothelial damage, seem to play a major role [39]. MA itself has been recognized as a sign of hypertensive target organ damage and since it reflects the influence of so many clinically relevant parameters, it can rightly be considered an integrated marker of cardiovascular risk, a unique feature among the several available prognostic predictors for stratifying risk in hypertensive patients. Effective antihypertensive treatment, especially with drugs counteracting the renin angiotensin system, has been found to reduce urinary albumin excretion. More recently, regression from microalbuminuria to normoalbuminuria has been associated with an amelioration of cardiovascular outcome, regardless of achieved blood pressure levels and type of drug [13].

In the present study, MA showed significant positive correlation with plasma aldosterone, this is in agreement with Baldoncini (1999) [40] and could suggest an important role for aldosterone in the pathogenesis of renal impairment in HT patients due to impaired vascular reactivity. Also, our results are coinciding with those of Smilde et al. (2005) [41] who found that subjects with mild renal impairment have substantially higher risk of LVH than those without renal dysfunction.

Conclusion:

Aldosterone may be involved in LVH and LV geometry, particularly in the development of concentric hypertrophy. Myocardial fibrosis seems more strongly involved in the hypertrophic geometry of CH than with EH. Also, the role of combined aldosterone and microalbuminuria on LVH was illustrated. The determination of MA is recommended in the initial work-up of subjects with EHT. The value of selective aldosterone antagonists on kidney, CV dysfunction awaits wide studies.

References:

1- Hitha B, Pappachan JM, Pillai HB, Sujathan P, Ramakrishna CD, Jayaprakash K and Raihanathul Misiriya KJ: Microalbuminuria in patients with essential hypertension and its relationship to target organ damage: an Indian experience. Saudi J Kidney Dis Transpl, 2008; 19: 411-9.

2- Nakahara T, Takata Y, Hirayama Y, Asano K, Adachi H, Shiokawa G, Sumi T, Ogawa and Yamashina A: Left Ventricular Hypertrophy and Geometry in Untreated Essential Hypertension is Associated With Blood Levels of Aldosterone and Procollagen Type III Amino-Terminal Peptide. Circ J, 2007; 71: 716 – 721.

3- Sharp A and Mayet J: Regression of left ventricular hypertrophy; hoping for a longer life. J Renin Angiotensin Aldosterone Syst, 2002; 3: 141-144.

4- Slight SH, Joseph J, Ganjam VK and Weber KT: Extra adrenal mineralocorticoids and cardiovascular tissue. J Mol Cell Cardiol, 1999; 31: 1175-1184.

5- Brilla CG: Aldosterone and myocardial fibrosis in heart failure. Hypertension, 2000; 25: 299 – 306.

6- Iwashima Y, Horio T, Kuroda S, Takishita S and Kawano Y: Influence of plasma aldosterone on left ventricular geometry and diastolic function in treated essential hypertension. Hypertens Res, 2002; 25: 49-56.

7- Soylu A, Temizhan A, Duzenli MA, Sokmen G, Koylu O and Telli H: The influence of aldosterone on the development of left ventricular geometry and hypertrophy in patients with essential hypertension. Jpn Heart J, 2004; 45: 807-821.

8- Robert V, Silvestre JS, Charlemagne D, Sabri A, Trouve P, Wassef M, et al.: Biological determinants of aldosterone-induced cardiac fibrosis in rats. Hypertension, 1995; 26: 971 – 978.

9- Schrader J, Luders S, Kulschewski A, et al: Microalbuminuria and tubular proteinuria as risk predictors of cardiovascular morbidity and mortality in essential hypertension: final results of a prospective long-term study (MARPLE Study). J Hypertens, 2006; 24: 541-548.

10- Rayner B: Importance of modulating the renin-angiotensin system in preventing renal complications of hypertension. Saudi J Kidney Dis Transpl, 2006; 17: 469-480.

11- Barratt J and Topham P: Urine proteomics: the present and future of measuring urinary protein components in disease. CMAJ, 2007; 177: 361-368.

12- Busari O, Opadijo G, Olarewaju T, Omotoso A and Jimoh A: Electrocardiographic correlates of microalbuminuria in adult Nigerians with essential hypertension. Cardiology Journal, 2010; 17(3): 281–287.

13- Assadi F: Relation of Left Ventricular Hypertrophy to Microalbuminuria and C - reactive protein in Children and Adolescents with Essential Hypertension. Pediatric Cardiology, 2008; 29(3): 580-584.

14- Cottone S, Mule G, Nardi E, et al: Microalbuminuria and early endothelial activation in essential hypertension. J Hum Hypertens, 2007; 21: 167-172.

15- Carilloa BA, Beutela A, Mirandolab DA, Vidonho AF, Furukawab L, Casarinic D, Camposa RR, Dolnikoffa MS, Heimannb JC and Bergamaschid CT: Differential sympathetic and angiotensinergic responses in rats

submitted to low- or high-salt diet. Regulatory Peptides, 2007; 140 (1-2): 5-11.
16- Brown NJ, Nakamura S, Ma L, Nakamura I, Donnert E, Freeman M, Vaughan DE and Fogo AB: Aldosterone modulates plasminogen activator inhibitor-1 and glomerulosclerosis in vivo. Kidney International, 2000; 58: 1219–1227. doi:10.1046/j.1523-1755.2000.00277.
17- Ihara A, Kawamoto T, Matsumoto K, Kawamoto J, Katayama A, Yoshitatsu M, Izutani H and Ihara K: Relationship between hemostatic markers and circulating biochemical markers of collagen metabolism in patients with aortic aneurysm. Pathophysiol Haemost Thromb, 2003; 33:221–224. doi: 10.1159/000081512.
18- Devereux RB, Lutas EM, Casale PN, Kligfield P, Eisenberg R, Hammond IW, et al.: Standardizat- ion of M-mode echocardiographic left ventricular anatomic measurements. J Am Coll Cardiol, 1984; 4:1222 – 1230.
19- Devereux RB, Koren MJ, De Simone P, Okin N and Kingfield P: Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. Eur Heart J, 1993; 14: 8-15.
20- Savage DD, Garrison RJ, Kannel WB, Levy D, Anderson SJ, Stokes J, et al.: The spectrum of left ventricular hypertrophy in a general population sample: The Framingham study. Circulation, 1987; 75:2 6 – 33.
21- Koren MJ, Devereux RB, Casale PN, Savage DD and Laragh JH: Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. Ann Intern Med, 1991; 114: 345 – 352.
22- Leenen FH and Harmsen E: Antihypertensive drugs and cardiac trophic mechanisms. J Cardiovasc Pharmacol, 1991; 17: 50-57.
23- Vasan RS, Evans JC, Larson MG, Wilson PWF, Meigs JB, Rifai N, et al: Serum aldosterone and the incidence of hypertension in non-hypertensive persons. N Engl J Med, 2004; 351: 33 – 41.
24- Gaddam K, Corros C, Pimenta E, Ahmed M, Denney T, Aban I, Inusah S, Gupta H, Lloyd SG, Oparil S, Husain A, Dell'Italia LJ and Calhoun DA: Rapid reversal of left ventricular hypertrophy and intracardiac volume overload in patients with resistant hypertension and hyperaldosteronism. Hypertension, 2010; 55:1137-1142.
25- Schmieder RE, Langenfeld MR, Friedrich A, Schobel HP, Gatzka CD and Weihprecht H: Angiotensin II related to sodium excretion modulates left ventricular structure in human essential hypertension. Circulation, 1996; 94:1304-1309.
26- Brilla CG and Weber KT: Reactive and reparative myocardial fibrosis in arterial hypertension in the rat. Cardiovasc Res, 1992; 26: 671-677.
27- Yamamoto N, Yasue H, Mizuno Y, et al.: Aldosterone is produced from ventricles in patients with essential hypertension. Hypertension, 2002; 39: 958-962.
28- Mizuno Y, Yasue H, Yoshimura M, Hararda E, Fujii H, Nakamura S, et al.: Adrenocorticotropic hormone is produced in the ventricle of patients with essential hypertension. J Hypertens, 2005; 23: 41-416.
29- Muscholl MW, Schunkert H, Muders F, et al.: Neurohormonal activity and left ventricular geometry in patients with essential arterial hypertension. Am Heart J, 1998; 135: 58-66.
30- Umpierrez GE, Cantey P, Smiley D, Palacio A, Temponi D, Luster K and Chapman A: Primary aldosteronism in diabetic subjects with resistant hypertension. Diabetes Care, 2007; 30: 1699–1703.
31- Weber KT and Brilla CG: Pathological hypertrophy and cardiac interstitium: Fibrosis and renin-angiotensin-aldosterone system. Circulation, 1991; 83: 1849 – 1865.
32- Matoba M, Asaji T, Matsui S and Takekoshi N: Long-term effect of delapril hydrochloride on procollagen type III amino-terminal peptide, left ventricular mass and left ventricular function in hypertensive patients. Jpn Circ J, 1998; 62: 900 – 902.
33- Sato A, Hayashi M and Saruta T: Relative long-term effects of spironolactone in conjunction with an angiotensin-converting enzyme inhibitor on left ventricular mass and diastolic function in patients with essential hypertension. Hypertens Res, 2002; 25: 837 – 842.
34- Tsutamoto T, Wada A, Maeda K, Mabuchi N, Hayashi M, Tsutsui T, et al.: Spironolactone inhibits the transcardiac extraction of aldosterone in patients with congestive heart failure. J Am Coll Cardiol, 2000; 36: 838 – 844.
35- Zannad F, Alla F, Dousset B, Perez A and Pitt B: Limitation of excessive extracellular matrix turnover may contribute to survival benefit of spironolactone therapy in patients with congestive heart failure: Insights from the Randomized Aldactone Evaluation Study (RALES). Circulation, 2000; 102: 2700 -2706.
36- Taniguchi I, Kawai M, Date T, Yoshida S, Seki S, Taniguchi M, et al.: Effect of spironolactone during an angiotensin II receptor blocker treatment on the lef ventricular mass reduction in hypertensive patients with concentric left ventricular hypertrophy. Circ J, 2006; 70:995-1000.
37- Duka I and Bakris G: Influence of microalbuminuria in achieving blood pressure goals. Curr Opin Nephrol Hypertens, 2008; 17(5):457-463.
38- Bulatov V, Stenehjem A and Os I: Left ventricular mass assessed by electrocardiography and albumin excretion rate as a continuum in untreated essential hypertension. J Hypert, 2001; 19(8): 1473-1478.
39- Lieb W, Mayer B, Stritzke J, et al.: Association of low grade urinary albumin excretion with left ventricular hypertrophy in the general population: the MONICA/KORA Augsburg Echocardiographic substudy. Nephrol Dial Transplan, 2006; 21(10): 2780-2787.
40- Baldoncini R: High plasma renin activity is combined with elevated urinary albumin excretion in essential hypertension. Kid Intr, 1999; 56: 1499-504.
41- Smilde TD, Asselbergs FW, Hillege HL, Voors AA, Kors JA, et al.: Mild renal dysfunction is associated with electrocardiographic left ventricular hypertrophy. Am J Hypertens, 2005; 18: 342-347.

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