RELATIONS OF SERUM ALDOSTERONE AND MICROALBUMINURIA TO LEFT VENTRICULAR HYPERTROPHY IN PATIENTS WITH ESSENTIAL HYPERTENSION

By

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ABSTRACT

Background : Left ventricular hypertrophy (LVH) is an independent risk factor for cardiovascular morbidity and mortality in hypertensive patients. The identification of risk factors for the initiation of LVH in patients with hypertension (HTN) is important including microalbuminununuria (MAU) and hyperaldosteronism.

Objectives : Evaluation of the relationship of MAU and plasma aldosterone to blood pressure (BP) and LVH in patients with essential HTN.

Subjects and Methods : Thirty male patients with essential HTN and 15 healthy subjects as a control group were subjected to thorough clinical examination, transthoracic echocardiography, lipid profile, serum potassium, serum aldosterone estimation. MAU was evaluated with dipstick Micral-II Test of fasting midstream morning urine on two successive days. Left ventricular mass index (LVMI) was calculated and values >134gm/m^2 were considered as LVH.

Results : Patients with LVMI >134 gm/m^2 had higher serum aldosterone, BMI, Interventricular septal

thickness (IVST),Posterior wall thickness (PWT) and Relative wall thickness (RWT). Serum aldosterone was significantly higher among the test hypertensive group and was positively correlated with LVMI, RWT, PWT, IVST, LVM and negatively correlated with LV diastolic dimensions. MAU was positively correlated with systolic BP, pulse pressure, BMI and LVMI and a strong relationship between MAU and serum aldosterone was detected.

Conclusion : Aldosterone is an important contributor to the development of LVH and hypertensive nephropathy and strong relation between microalbuminuria and aldosterone is detected. The value of selective aldosterone blockers in preventing target organ damage (TOD) awaits further investigation.

Introduction and aim of the work :

LVH is more than just an adaptive response to HTN as it predicts poor prognosis independently of BP control. HOPE and LIFE studies proved that LVH is a target for treatment above and beyond BP control [1]. LVH is associated with a markedly increased incidence of myocardial infarction (MI), heart failure (HF) or premature death [2,3].

Aldosterone is a potent mineralocorticoid that promotes sodium retention and elevation of arterial BP and cardiac hypertrophy. Within the myocardium, aldosterone acts via mineralocorticoid receptors to enhance extracellular matrix and collagen deposition [4].

Mottram et al. (2004) [5] reported that aldosterone is implicated in the genesis of myocardial fibrosis, hypertrophy and dysfunction and that aldosterone antagonists may be of value in improving myocardial function.

MAU is an integrated marker of TOD [6] and of increased cardiovascular (CV) morbidity and mortality even in non-diabetic hypertensive patients [7,8]. MAU has also proved to be highly specific in identifying patients with LVH and carotid atherosclerosis [9]. There is growing evi-

dence that MAU is an independent predictor of atherosclerosis and premature death in the general population [10].

Numerous clinical studies found an association between MAU and other CV risk factors, TOD and risk of cardiovascular disease (CVD) in clinical contexts different from diabetes mellitus DM and including HTN [11,12].

MAU is a useful, cost-effective marker of increased CV risk although still too often neglected in clinical practice [13].

The identification of risk factors for the initiation of LVH in hypertensive patients is important. The objectives of the present study was to identify the relationship of aldosterone and MAU to LVH in patients with essential HTN.

Although primary aldosteronism is a well recognized cause of secondary HTN, yet it is unknown whether serum aldosterone levels within the physiological range do influence the risk of HTN-TOD [14] and this was one of the goals of the present study. It was also aimed to identify whether MAU in essential HTN, is the victim or villain on LVH and its relation to the studied CV risk factors including aldosterone.

The availability of selective aldosterone antagonists that could improve myocardial dysfunctions and arrest the enhancing extracellular matrix, collagen deposition and fibrosis of hyperaldosteronism [15], and improving myocardial function in hypertensive heart disease [5] was one of the triggers to the present work.

PATIENTS AND METHODS

The present study comprised 30 male patients randomly selected from the outpatient clinic of Specialized Medical Hospital, Mansoura University with mean age 53±6.2 years, and 15 non-hypertensive normal male subjects of matched age and body weight as control group in the period from August 2004 to July 2005.

Complete medical history, physical examination, routine blood and urine analyses, and specific diagnostic procedures to exclude cases with secon-

dary HTN. Body weight (Kg) and height (meters) were recorded, and body mass index (BMI) was calculated.

Blood pressure was measured with the patient in the sitting position after a 5 minutes rest, with mercury sphygmomanometer. The mean of three measurements in the right arm was used. Phase V was the criterion for diastolic blood pressure. Hypertension was defined following the criteria of the Sixth Report of the Joint National Committee (1997) [16] for Prevention, Detection, Evaluation and Treatment of High Blood Pressure, as systolic blood pressure ≥ 140mmHg, &/or diastolic blood pressure ≥ 90 mmHg or when subjects were taking long term antihypertensive medication. Cessation of antihypertensive medication was the rule for about two weeks. Some of the included cases were never previously treated.

Exclusion criteria : Individuals with conditions that could influence left ventricular measures and/or affect serum aldosterone levels were not included. Cases with associated diabetes mellitus (DM), gross obesity (BMI ≥34), renal impairment (creatinine ≥2.2mg/dl) and resistant HTN were excluded. Also cases with previous history of MI or stroke and patients with valvular heart disease were not included.

ECHOCARDIOGRAPHIC MEASUREMENTS :

Two-dimensional echo-guided M-mode tracings using an ESAOTE XP-10 with 2.5 MHz transducer. Left ventricular internal end diastolic (EDD), end systolic dimensions (ESD), septal (IVST), posterior wall thickness (PWT), and the left atrium (LA) size at end-systole were measured using the leading-edge technique, according to the American Society of Echocardiography guidelines [17,18]. Mid-wall fractional shortening (MFS) was the index of ventricular systolic function accounting for the epicardial migration of the LV midwall during systolic myocardial contraction.

End-diastolic left ventricular wall thickness (LVWT) was calculated as

the sum of IVST and PWT; relative wall thickness (RWT) was computed as (IVST+PWT)/ EDD [19].

Left ventricular mass (LVM) was calculated from M mode echocardiograms according to the formula described by Devereux et al. (1993) [19]: Left ventricular mass M mode (g) = 0.8 (1.04 [EDD +SWth + PWth]^3 - EDD^3) + 0.6g.

Left ventricular mass was indexed to body surface area as left ventricular mass index in g/m^2 body surface area. Left ventricular hypertrophy by M mode criteria was considered when left ventricular mass index > 134 g/ m^2 body surface area in men (19).

BIOCHEMICAL MEASUREMENTS :

Fasting blood samples (3ml each) were withdrawn from patients and control subjects after resting in supine position for 60 minutes and delivered into plain tubes. The separated sera were aliquoted and kept frozen (-70 c) till analysis of serum cholesterol, triglycerides, LDL, and HDL using the respective kits supplied by Aumon, Germany, and serum aldosterone using coat-A-count solid phase radioimmunoassay [20]. The materials were supplied by diagnostic product corporation (DPCs). Serum potassium was assessed using electrolyte analyzer AVL 980, Switzerland.

The fasting midstream morning urine is tested for microalbuminuria using Micral-II test strips for the immunological semiquantitative determination of microalbuminuria. The screening result is positive when the reaction colour corresponding to 20mg/L (threshold value of microalbuminuria) or more on two successive occasions.

STATISTICAL ANALYSIS

All data were analyzed using a SPSS/PC statistical (SPSS Inc. Chicago, IL) package. Inter-group differences between continuous variables were assessed by two-tailed t-tests. Pearson correlation coefficient was used to study correlation between variables. Significance was considered when the P-value less than 0.05 at a confidence interval 95%.

RESULTS

Table (1) Clinical and laboratory data of the test group. All were males with mean age 53±6.2y with BMI 30.46±4.11, SBP 162±12.4 mmHg, DBP 99.6±4.7 mmHg, serum cholesterol was on the high normal levels (203±42.9 ml/dl), serum triglycerides level were 111.80±57.5 mg/dl, high density lipoprotein (HDL-C) 38.06±6.99 mg/dl, LDL-C 143.7±48.1 mg/dl, the mean MAU was 38.66±29.21 mg/L, while the serum aldosterone level was 17.71±8.58 ng/dl.

Table (2) Echocardiographic data of the test group shows that the mean LVMI was 124.53±48.64 gm/m^2, IVST was of average normal & PWT were higher than axerage normal the mean EF% was within the average normal range (64.4±10.78)

Table (3) Comparative analysis of serum aldosterone concentration in hypertensive versus control group. The mean serum aldosterone of the hypertensive group was more than double (17.71±8.58 ng/dl) the level detected in the control group (8.46±3.27 ng/dl) (P<0.001).

Table (4) Correlation of serum aldosterone concentration with blood pressure, pulse pressure, BMI and echocardiographic findings. Serum aldosterone revealed a significant positive correlation with diastolic blood pressure, IVST, LVMI and was negatively correlated with left ventricular end diastolic dimension (LVEDD).

Table (5) Comparison between hypertensive cases with LVH and those with no LVH. 12 cases with evidence of LVH (LVMI >134 gm/m^2) have a significant differences as regards BMI, IVST, PWT, RWT, LVWT and serum aldosterone level (P<0.001), the mean serum aldosterone among cases with LVH was 23.47±7.24 ng/dl while its level among cases with no LVH was less (13.87±7.25 ng/dl).

Table (6) and Figure (4) show the prevalence of MAU among hypertensive cases was 46.7%.

Table (7) show that MAU has a significant positive correlation with

SBP, pulse pressure, BMI, LVMI and serum aldosterone.

Figure (1) shows that serum aldosterone is significantly higher in hypertensive cases than in normotensive control subjects.

Figure (2) shows that serum aldosterone is significantly higher in hypertensive cases with LVH than in those without LVH.

Figure (3) shows that there is a significant positive correlation of microalbuminuria with serum aldosterone in hypertensive patients.

Table (1): Clinical and laboratory data of the test group:

Parameter	Mean	± SD
Age (year)	53	6.2
Weight (Kg)	83.46	13.28
Height (m)	165.	11.42
BMI (kg/m^2)	30.46	4.11
Systolic blood pressure (mmHg)	162.0	12.4
Diastolic blood pressure (mmHg)	99.66	4.7
Serum creatinine (mg/dL)	0.9	0.1
Serum potassium (meq/L)	3.8	0.1
Serum sodium (meq/L)	140	1.0
Serum cholesterol (mg/dL)	203.73	42.90
Serum triglycerides (mg/dL)	111.80	57.53
HDL-C (mg/dL)	38.06	6.99
LDL-C (mg/dL)	143.73	48.14
Microalbuminuria (mg/L)	38.66	29.21
Serum aldosterone (ng/dl)	17.71	8.58

Table (2): Echocardiographic data of the test group:

Parameter	Mean	± SD
LVMI (g/m2)	124.53	48.64
IVST (mm)	1.41	0.36
PWT (mm)	1.29	0.33
LVWT	2.69	0.68
RWT	0.49	0.13
EDD (mm)	5.38	0.44
LA (mm)	3.70	0.52
EF (%)	64.40	10.78

Table (3): Comparative analysis of serum aldosterone concentration in hypertensive versus control group:

	Hypertensive group (n=30)	Control group (n=15)	t	P value
Serum aldosterone (ng/dl)	17.71 8.58	8.46 3.27	4.01	<0.0001***

Table (4): Correlation of serum aldosterone concentration with blood pressure, pulse pressure, BMI and echocardiographic findings

	Aldosterone r	P
Systolic blood pressure	0.310	0.096
Diastolic blood pressure	0.414	0.023*
BMI	-0.383	0.057
Pulse pressure	0.186	0.324
IVST	0.281	0.048*
PWT	0.279	0.047*
RWT	0.49	0.01*
LVMI	0.561	0.021*
LVWT	0.540	0.036*
LVEDD	-0.361	0.01*

Table (5): Comparison between hypertensive cases with LVH (i.e. LVMI> 134 gm/m^2) and those with no LVH (i.e. LVMI< 134 gm/m^2) :

Parameter	No LVH: LVMI <134(gm/m^2) (n=18)	LVH: LVMI >134 (gm/m^2) (n=12)	P value
Age (year)	52.22± 6.82	54.50± 5.31	NS
Serum aldosterone (ng/dl)	13.87± 7.25	23.47± 7.24	0.001**
BMI (kg/m^2)	28.44± 3.56	33.50± 2.87	0.0001***
SBP (mmHg)	161.11± 12.07	163.33± 13.37	NS
DBP (mmHg)	100.0± 5.94	99.16± 1.94	NS
IVST (mm)	1.19± 0.19	1.78± 0.18	0.0001***
PWT (mm)	1.08± 0.14	1.61± 0.26	0.0001***
RWT	0.40±0.0004	0.62	0.0001***
LV wall thickness	2.22± 0.33	3.39± 0.41	0.0001***
EDD (mm)	5.35± 0.54	5.41± 0.22	NS
LA (mm)	3.65± 0.59	3.78± 0.40	NS
MFS (%)	30.33± 7.42	31.83± 7.14	NS
Ejection fraction (%)	58.55± 11.53	63.16± 9.35	NS
S. cholesterol (mg/dL)	212.88± 51.74	190.0±19.28	NS
S. triglycerides (mg/dL)	103.33± 54.46	124.5±62.04	NS
HDL-C (mg/dL)	37.88± 8.49	38.33± 4.16	NS
LDL-C (mg/dL)	154.22±56.71	128.0± 26.28	NS

Table (6): Prevalence of microalbuminuria in the hypertensive group:

	N	%
Cases with microalbuminuria	14	46.7
Cases without microalbuminuria	16	53.3

Table (7): Correlation of microalbuminuria to some studied parameters:

	Microalbuminuria	
	r	P
Age	N.S.	0.10
SBP	0.34	**0.02***
DBP	0.13	N.S.
LVMI	0.18	**0.048***
BMI	-0.30	**0.041***
Pulse pressure	0.389	**0.01***
Aldosterone	0.423	**0.003****
Total cholesterol	0.025	N.S.
Serum triglycerides	N.S.	-0.20
HDL-C	-.0126	N.S.
LDL-C	-0.59	N.S.

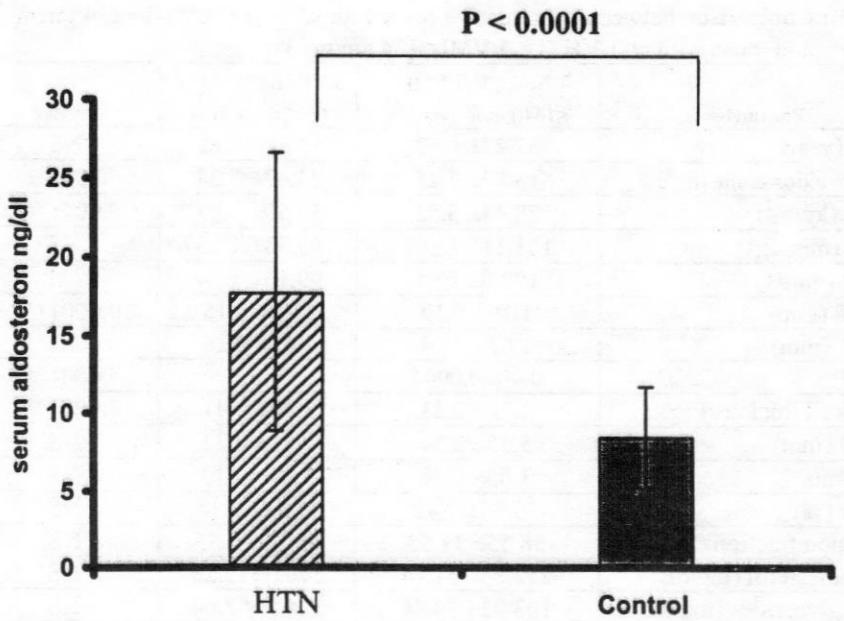

Figure (1): Comparison of serum aldosterone in the hypertensive and the control group

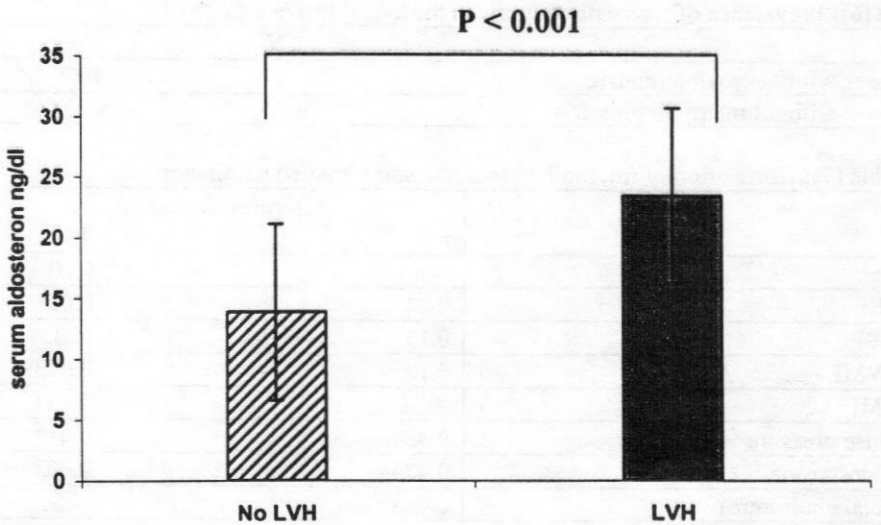

Figure (2): Comparison of serum aldosterone in cases with LVH and those without LVH

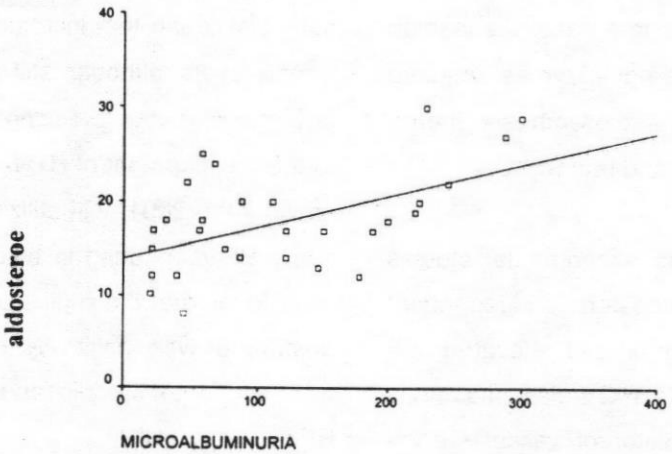

Figure (3): Correlation of microalbuminuria with serum aldosterone in hypertensive patients.

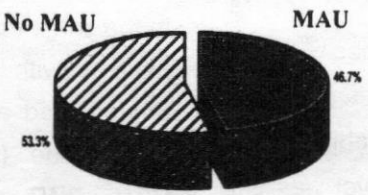

Figure (4): Prevalence of microalbuminuria in hypertensive patients

DISCUSSION

Williams and Williams in the 50th anniversary (2003) [21] stated that aldosterone acts in a paracrine fashion in tissues having enzymes required for aldosterone biosynthesis (heart, blood vessels and brain).

Clinical and experimental studies indicate that aldosterone independent of angiotensin-II and elevated BP may play a role in CV diseases and is a critical mediator of vascular damage [22,23,24,].

This vascular damage is possibly via increasing vascular smooth hypertrophy, generation of reactive oxygen species, inhibition of norepinephrine uptake, upregulation of angiotensin-II receptors and stimulation of several growth factors and cytokines [25].

In the present study (table 3 & fig. 1), serum aldosterone level was significantly higher in the hypertensive group when compared to the normotensive age, BMI matched, control group (P<0.0001) and was positively correlated with diastolic blood pressunt (DBP) (P<0.02) (table 4). Ramarchandran et al. (2004) [23] (during their follow up of non-hypertensive subjects) found that increased aldosterone levels, although still within the physiologic range predisposed them to the development of HTN. Areg and co-workers (2001) [24] utilizing ambulatory BP monitoring in black Americans found that the supine plasma aldosterone was positively correlated with nocturnal systolic and diastolic BP.

In this study, serum aldosterone was significantly correlated to DBP and there was a positive correlation with IVST (P<0.04), RWT (P=0.01), PWT (P=0.047), LVWT (P=0.03) and LVMI (P=0.02) and a negative correlation with LVEDD (P=0.01) (table 4). In the same manner, the hypertensive patients with LVH (i.e. LVMI > 134 gm/m^2) had a higher level of serum aldosterone (P<0.001), BMI, IVST, PWT, RWT and LVWT)P<0.0001) when compared with those without LVH. These results are confirmatory to those of Heribert et al. (1997) [26] and Ahmet et al. (2004) [27]. Heribert et al. (1997) [26] and Soylu et al.

(2004) [28] had found that the serum aldosterone was strongly related to septal and posterior wall thickness. Ahmet and coworkers [27], Soylu et al. (2004) [28] found the highest plasma aldosterone concentration were in cases of essential HTN with the concentric type of LVH.

Ramarchandran et al. (2004) [23] concluded that increased aldosterone levels even within the physiologic range predispose to development of HTN. However, the present results are not in agreement with Vasan et al. (2004) [29] who found significant positive relation of serum aldosterone to LVWT and RWT only in women. The studied cases were all males (tables 1& 4).

Aldosterone influence LV remodeling independent of its impact on systemic BP [30] and this is achieved via different effects on collagen synthesis and fibroblast proliferation [4], endothelial dysfunction, autonomic dysfunction [31,32].

In the present study, the prevalence of MAU in the hypertensive patient was 46.7% (tables 6 & fig. 4). This is somewhat higher than that reported by previous studies [33,34] where the prevalence ranges between 4 to 46%. This could be due to the huge intra-individual variability in urinary albumin excretion rate, the discrepancies of techniques of measurement and the wide range of MAU (30-300 mg/24 hs). The BMI of the studied group was 30.46±4.11 (table 1) could explain the higher prevalence of MAU in our hypertensive group.

Lieb et al. (2006) [35] found that at general population level, even low grade albuminuria is associated with LVH and the conventional urinary albumin threshold of MAU (30 mg/day) may be too conservative and end organ damage (LVH) is observed with increased frequency at much lower level.

In the present study, MAU showed significant positive correlation with serum aldosterone (P=0.003) (table 7 & fig. 3) and this is in agreement with

Baldoncini et al. (1999) [36] and could suggest an important role for aldosterone in the pathogenesis of renal impairment in hypertensive patients.

Our results are coinciding with those of Smilde et al. (2005) [37] who found that subjects with mild renal impairment have substantially higher risk of LVH than those without renal dysfunction.

The positive correlation of MAU with SBP, pulse pressure, BMI are confirmatory to many previous studies [38,39]. We agree with Verdecchia and Reboldi (2004) [12] who suggest the routine estimation of MAU in the initial work-up of subjects with HTN.

There was no significant correlation between MAU and plasma lipoprotein (table 7). This is in contrast to previous studies [40,41] which may be due to small sample size in our study.

The significant positive correlation of MAU with LVMI (table 7) is also confirmatory to previous studies [10,34,42,43]. Bulatov et al. (2001) [44] had found linear correlation between LVM assessed by ECG and albumin excretion rate.

SUMMARY AND CONCLUSION

The role of combined MAU and hyperaldosterone on LVH and CV events was illustrated. The determination of MAU is recommended in the initial work-up of subject with HTN even non diabetics. The value of selective aldosterone antagonists on kidney, CV dysfunction awaits wide scale studies.

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