
Journal of
Diabetes Research & Clinical Metabolism
ISSN 2050-0866

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Original Open Access

Increased aldosterone in patients with metabolic syndrome; an additional risk factor

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Abstract

Background: Patients with metabolic syndrome (MSyn) are prone to increased cardiovascular morbidity and mortality, although the underlying mechanisms including plasma aldosterone (PA) are not yet fully known.

Aim: Evaluate the association of PA with the MSyn and each of its components.

Methods: 46 patients with MSyn and 25 healthy subjects as a control were subjected to measurements of BMI, waist circumference, office BP & HR, 24-hour BP monitoring, fasting blood sugar (FBS), lipid profile, serum sodium & potassium, serum insulin, insulin resistance calculation, plasma renin activity (PRA) and PA concentrations.

Results: PA concentrations, but not PRA, were significantly higher in MSyn patients (P 0.001, P 0.770 respectively).HR was significantly increased in MSyn patients compared to controls (P 0.024) .There were significant positive correlation between PA level and BMI, waist circumference, SBP, DBP, s.triglycerides, FBS and insulin resistance (r 0.947, P < 0.0001, r 0.829, P < 0.0001, r 0.885, P < 0.0001, r 0.831, P < 0.0001, r 0.611, P < 0.0001, r 0.851, P < 0.0001, r 0.712, P < 0.0001 respectively). A significant negative correlation was present between PA level and HDL-C (r - 0.443, P < 0.002). BMI & SBP were the only independent factors affecting PA level by regression analysis. In contrast to PRA, PA tended to increase with an increasing number of MSyn risk factors. In conclusion, PA is associated with MSyn and its components suggesting the link between aldosterone and several cardiovascular risk factors and this may address the possible beneficial effects of aldosterone blockade in those patients with MSyn.

Keywords: Metabolic syndrome, plasma aldosterone, plasma renin activity

Introduction

The metabolic syndrome (MSyn) represents a clustering of several cardiovascular risk factors, which include hypertension, dyslipidemia (low high-density lipoprotein (HDL) cholesterol and elevated triglycerides), abdominal obesity, glucose intolerance, and a proinflammatory and prothrombic state [1].

It is a cause for public health concern and its prevalence has increased over time. In the National Health and Nutrition Examination Survey (NHANES) cohort, the prevalence of MSyn between 1988 and 1994 was 29.2% and it reached 34.6% between 1999 and 2002 [2].

Patients with MSyn are associated with a 2-fold increase in cardiovascular outcomes and a 1.5-fold increase in all-cause mortality, although the underlying mechanisms responsible for these associations are not yet fully known [3].

Aldosterone is a mineralocorticoid hormone classically involved in sodium balance regulation. Many recent studies involve aldosterone in the pathogenesis of the cardiometabolic syndrome [2,4,5], although this relationship is complex and not well established, there is some evidence that different factors could act on it such as insulin resistance, renin-angiotensin-aldosterone system, oxidative stress, sodium retention and volume overload, increased sympathetic activity, levels of free fatty acids, or inflammatory cytokines and adipokines [5].

The aim of this study was to measure plasma aldosterone concentrations in patients with MSyn, and to evaluate its associations with each component of MSyn.

Subjects and methods

Patients

Forty six patients with MSyn were selected using a standard definition of the MSyn based on National Cholesterol Education Program-Adult Treatment Panel III (NCEP-ATP III) criteria [6].

Subjects with 3 or more of the following components were included in the study:

1) Waist circumference >102 cm in men and > 88 cm in women.
2) Triglycerides ≥150 mg/dl.
3) HDL-cholesterol < 40 mg/dl in men and < 50 mg/dl in women.
4) Ambulatory blood pressure ≥130/85 mmHg.
5) Fasting blood glucose ≥110 mg/dl.

Exclusion criteria were the presence of the following: Patients with more than stage-I HTN or on antihypertensive or lipid lowering medications, diabetes mellitus, known renal, hepatic, or immunologic disorders, obesity secondary to hypothyroidism

doi: 10.7243/2050-0866-2-17

or Cushing's disease, severe debilitating disease, malignancy and pregnancy or lactation.

Control

Twenty five healthy, age-and sex-matched subjects were taken as a control group.

Methods

The study protocol was approved by the local ethic committee. All subjects gave written informed consent to participate in the study and the investigations conformed to the principles outlined in the Declaration of Helsinki [7].

All subjects were recommended to consume a diet with a normal amount of salt and were subjected to the followings:

Thorough history and clinical examination

Standardized anthropometric measurements included height, weight, body mass index (BMI), waist circumferences were done.

- Body weight and height were measured with the patient in light clothes without shoes to the nearest 0.5 kg and 0.5 cm.
- BMI was calculated by the formula: body weight (kg)/ height (m^2).
- Waist circumference was measured horizontally in quiet expiration, to the nearest 0.1 cm, directly on the landmarked skin with a flexible, inelastic measuring tape with a tension meter attached. The measure was taken at the highest point of the iliac crest [8,9].
- Blood pressure (BP) and heart rate were measured with the patient seated, after a 5-min rest period. Two BP measurements with a mercury sphygmomanometer were obtained at 5-min intervals, and then averaged.

Standard 12-lead resting electrocardiography (ECG)

Ambulatory BP monitoring (ABPM)

24-hour BP monitor was set in place using a continuous blood pressure device (model 90207-30, Spacelabs Inc, Redmond, WA, USA). The device was placed on the non-dominant upper limb of the patient and was programmed to record BP readings every 30 minutes during daytime and every 60 minutes during nighttime.

A satisfactory number of readings were obtained from all subjects in the study and mean 24-hour systolic BP, diastolic BP readings, and heart rate as well were then obtained.

Laboratory investigations

Samples collection

Fasting blood samples were collected while the patient was supine and had rested for 20 min and delivered into 2 tubes. Five ml of them was collected in K2EDTA-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 (PA) concentration. The rest of blood sample was collected in biochemical tube to obtain serum. The serum samples were obtained by centrifuging blood samples at 3000 rpm for 15 min. Serum was used for measurements of fasting glucose, lipid profile, serum electrolyte, and fasting serum insulin.

Biochemical Determinations

A. Fasting glucose and lipid profile were measured using enzymatic colorimetric methods (Cobas Integra 400, Roche Diagnostic, Mannheim, Germany).
B. Low-density lipoprotein cholesterol was calculated using Friedwald's formula [10]: LDL-C = Total Cholesterol - (Triglyceride/5 + HDL-C).
C. Serum Electrolyte measurements were carried out by ionselective electrodes using AVL 988 analyzer (Roche Diagnostics, Mannheim, Germany).
D. Serum insulin was measured by enzyme immunoassay using Medgenix-Ins-EASIA kit (BioSource, Belgium) [11].
E. Insulin resistance was calculated with the Homeostasis Model Assessment (HOMA). HOMA was calculated by the formula of Matthews *et al*., (1985) [12]. HOMA INDEX= Fasting glucose (mmol/l) X Fasting insulin (uU/ml)/ 22.5.
F. Plasma renin activity (PRA) was measured using commercially available solid phase radioimmunoassay kits supplied by Diagnostic Products Corporation (Los Angeles, CA, USA) according to the manufacture instructions [13].
G. Plasma aldosterone (PA) concentrations 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 [14].

Statistical analysis

Statistical analysis were performed using SPSS software version 15 (SPSS Inc. Chicago, IL). Data were expressed as means ± SD. Unpaired samples t test was used to compare the mean values in 2 groups. The relationships between variables were assessed using univariate linear regression analysis and Pearson's correlation coefficient. Spearman rank correlations were calculated between PA and PRA according to the number of risk factors. A P value <0.05 was accepted as having statistical significance [15].

Results

Our study included 46 subjects with MSyn and 25 healthy, age- and sex-matched subjects as a control group. Participants' clinical and laboratory data are presented in **Table 1** and **2**. There were significant higher levels of plasma aldosterone concentrations, but not plasma renin activity, in MSyn patients than controls and there was no significant difference between both groups regarding serum sodium and potassium. Average HR was significantly increased in MSyn patients compared to controls.

There was significant positive correlation between PA level

doi: 10.7243/2050-0866-2-17

Table 1. Clinical parameters of metabolic syndrome patients and controls.

Parameter	MSyn Patients (n=46)	Controls (n=25)	P value
Age (year)	42.1 ± 9.40	40.90 ± 9.78	0.620
Gender (male/female)	20/26	10/15	0.327
Current smoking	24 (52.1%)	12 (48%)	0.247
Waist Circumference (cm)	108.0 ± 16.0	73.0 ± 5.48	<0.0001
BMI (kg/m^2)	32.5 ± 3.71	22.5 ± 2.12	<0.0001
Systolic blood pressure (mmHg)	156 ± 14.5	116 ± 8.16	<0.0001
Diastolic blood pressure (mmHg)	95.6 ± 9.0	75.8 ± 7.8	<0.0001
Heart rate *(BPM)*	98.7 ± 12.0	72.3 ± 6.9	0.024

Table 2. Laboratory parameters of metabolic syndrome patients and controls.

Parameters	MSyn Patients (n=46)	Controls (n=25)	P value
Fasting blood glucose (mg/dl)	114.0 ± 4.66	81.4 ± 8.01	<0.0001
Fasting insulin (mIu/ml)	14.8 ± 7.54	6.96 ± 2.31	<0.0001
Insulin resistance (HOMA-IR)	3.88 ± 1.94	1.42 ± 0.52	<0.0001
Serum potassium (mmol/l)	3.93 ± 0.46	3.84 ± 0.42	0.440
Serum sodium (mmol/l)	140.0 ± 6.71	138.0 ± 6.04	0.182
Total cholesterol (mg/dl)	197.0 ± 40.0	127.0 ± 29.8	<0.0001
HDL cholesterol (mg/dl)	40.4 ± 4.08	49.6 ± 5.14	<0.0001
LDL cholesterol (mg/dl)	119.0 ± 38.0	61.0 ± 27.8	<0.0001
Triglycerides (mg/dl)	187.0 ± 32.7	80.9 ± 21.3	<0.0001
Plasma aldosterone (ng/dl)	6.97 ± 2.49	5.11 ± 1.79	0.0016
Plasma renin activity (ng.ml-1.h-1)	0.87 ± 0.26	0.85 ± 0.22	0.770

and both BMI & waist circumference and between PA level and both systolic & diastolic blood pressure. A significant negative correlation was present between PA level and HDL-C but significant positive correlation was present between PA level and s.triglycerides. There was significant positive correlation between PA level and both fasting blood sugar & insulin resistance (**Figures 1A** to **1H**).

BMI & systolic blood pressure were the only independent factors affecting PA level by regression analysis (**Table 3**).

In contrast to PRA, PA tended to increase with an increasing number of MSyn risk factors (**Figure 2**).

Discussion

Although the role of renin and aldosterone in BP regulation is well known, and high BP is part of the MSyn, less is known about association of renin and aldosterone with the MSyn. Several observations suggest that plasma aldosterone (PA) plays a role in BP regulation in obesity [**16**,**17**].

In addition, several studies have reported an association between aldosterone and/or plasma renin activity (PRA) and blood lipids [**18**,**19**] and insulin resistance [**20**,**21**], which are components of the MSyn. In another words, there is still a conflict about the exact role of PA in the pathogenesis of MSyn and in spite that an activated renin–angiotensin–aldosterone system (RAAS) was found to be associated with cardiovascular risk factor clustering [**22**], no association was found between the MSyn and aldosterone or PRA in a recent TROPHY substudy [**21**].

The aim of this study was to evaluate the association of PA with the MSyn and each of its components.

In this study, PA was significantly increased in patients with MSyn compared to normal subjects and there was a significant positive correlation between PA and obesity parameters: BMI and waist circumference. BMI was the only independent parameter, together with SBP, affecting PA level in multiple regression analysis. It has been demonstrated that obese individuals have activation of the components of the RAAS [**23**].

On the other hand, weight loss studies demonstrated a significant reduction in aldosterone levels together with renin and angiotensin II, following even moderate weight loss, suggesting the involvement of an increased RAAS activity in the development of obesity hypertension [**16**,**24**]. Even in normotensive overweight subjects ,compared to lean normotensives, Twenty-four hour urinary aldosterone secretion was elevated [**25**].

PA levels were significantly elevated in MSyn patients, but PRA was not, in our study and in the study of Kidambi *et al.,* 2007 [**26**] as well. This may reflect a mild variant of primary aldosteronism supports the hypothesis of factors released from fat cells directly or indirectly stimulating aldosterone secretion. In another words, dysfunctional adipose tissue can secrete aldosterone independently from renin stimulation [**27**].

In our study, heart rate was significantly increased in patients with MSyn compared to normal subjects; may be a marker of absolute or relative sympathetic overactivity. Some reports showed that MSyn is associated with autonomic dysfunction [**28**], moreover, elevated heart rate has been shown to precede the development of the MSyn [**29**]. Another study showed that high resting heart rate clusters with other cardiovascular risk factors, such as hypertension, diabetes, and hypertriglyceridemia [**30**].

Concordant with many studies [**19**,**31**,**32**], our study demonstrated a positive correlation between PA levels and s.triglycerides and a negative correlation between PA levels and high-density lipoprotein (HDL) cholesterol. Some authers [**19**] demonstrated that patients with the highest aldosterone levels showed the lowest HDL levels. However,

doi: 10.7243/2050-0866-2-17

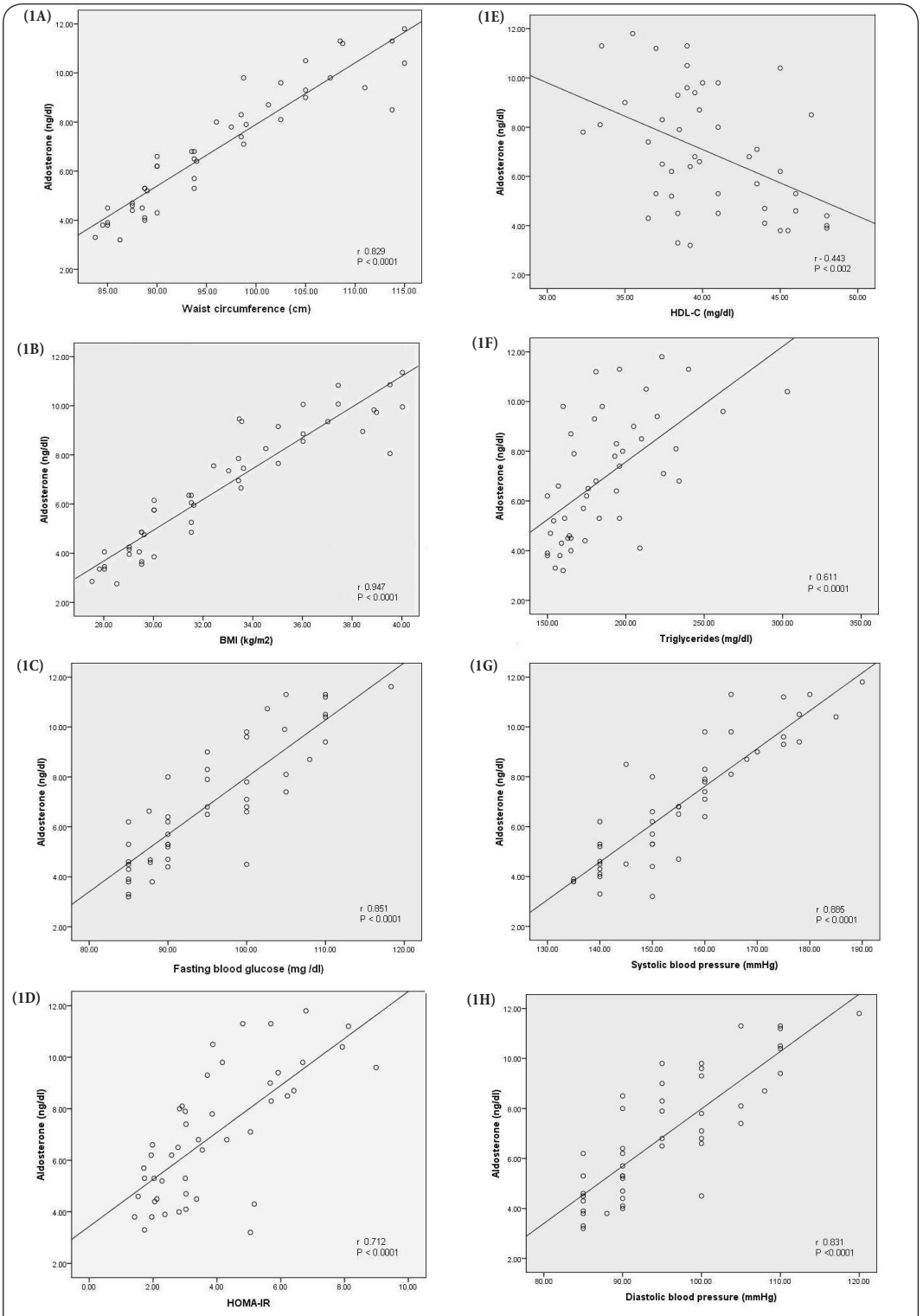

Figure 1A. Correlation between plasma aldosterone level and waist circumference.
1B. Correlation between plasma aldosterone level and body mass index (BMI).
1C. Correlation between plasma aldosterone level and fasting blood glucose.
1D. Correlation between plasma aldosterone level and insulin resistance (IR).
1E. Correlation between plasma aldosterone level and high density lipoprotein-cholesterol (HDL).
1F. Correlation between plasma aldosterone level and S.triglycerides.
1G. Correlation between plasma aldosterone level and systolic blood pressure.
1H. Correlation between plasma aldosterone level and diastolic blood pressure.

doi: 10.7243/2050-0866-2-17

Table 3. Linear regression analysis of the independent factors affecting plasma aldosterone secretion in MSyn patients.

	b ± SE	t	P	Sig
Age	.007 ± .014	.504	.618	*NS*
WC	.000 ± .020	-.016	.987	*NS*
FBG	.014± .067	.212	.833	*NS*
FI	-.006 ± .010	-.603	.551	*NS*
Cholesterol	.018 ± .017	1.042	.305	*NS*
Triglycerides	-.011± .008	-1.329	.193	*NS*
HDL-C	-.051 ± .047	-1.106	.277	*NS*
LDL-C	-.017 ± .016	-1.074	.291	*NS*
HOMA-IR	-.003 ± .128	-.022	.983	*NS*
PRA	-.850 ± .637	-1.334	.192	*NS*
SBP	.048 ± .021	2.309	.028	*S*
DBP	.025 ± .028	.892	.379	*NS*
BMI	.456 ± .121	3.773	.001	*S*

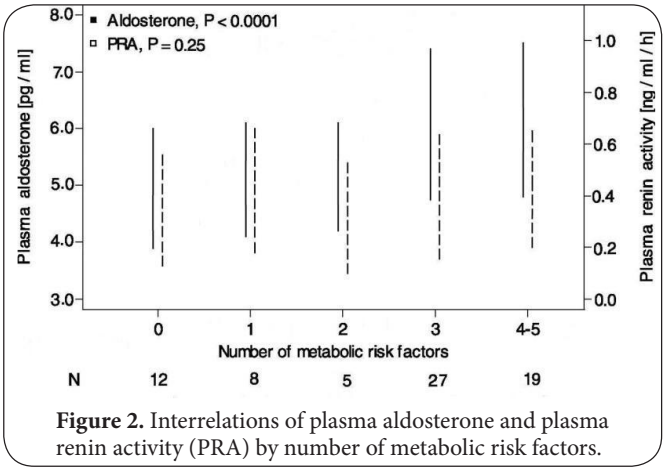

Figure 2. Interrelations of plasma aldosterone and plasma renin activity (PRA) by number of metabolic risk factors.

these patients also presented with the highest BMI suggesting that fat tissue, and not aldosterone, per se, might have caused the derangement in the lipid metabolism. Bochud *et al.,* [31] showed a negative association between plasma aldosterone levels and HDL cholesterol levels in MSyn patients, regardless of all of the other MSyn components. However, a Framingham Heart Study subanalysis with higher subject numbers (2891subjects) did not show a direct correlation between aldosterone and low HDL cholesterol [32]. Therefore, a possible causative relation between aldosterone and lipid metabolism needs to be investigated further.

Again, SBP was the only independent parameter, together with BMI, affecting PA level in multiple regression analysis and systolic& diastolic BP were significantly correlated with PA level. The implication of aldosterone in the pathogenesis of arterial hypertension is supported by a vast body of evidence from experimental and clinical studies [13,33,34]. Serum aldosterone levels were significantly associated with an elevation of blood pressure in a significant number (1688) of normotensive participants in the Framingham Study, indicating that increased plasma aldosterone levels within the physiological range predispose toward the development of arterial hypertension [34].

Parameters of impaired glucose homeostasis such as fasting plasma glucose, insulin resistance,and insulin levels were significantly affected in patients with MSyn and there were significant correlation between PA level and both insulin resistance and fasting blood glucose. Many observational studies have suggested direct associations between aldosterone levels and parameters of impaired glucose homeostasis in patients with [21,26] and without the MSyn [19]. Besides its classic actions, aldosterone and mineralocorticoid receptor activation affect glucose metabolism, inducing insulin resistance through various mechanisms that involve oxidative stress, inflammation, and downregulation of proteins involved in insulin signaling pathways [35]. However, no conclusive evidence that establishes aldosterone as an independent risk factor for the development of diabetes mellitus and whether aldosterone, per se, on the one hand or elevated blood pressure on the other hand, as a concomitant component of the MSyn with a possible consequence of elevated aldosterone levels is the causative factor for impaired glucose homeostasis [36].

Inspite of missing salt loading or suppression tests to confirm the presence of 1ry aldosteronism, we supposed that our patients lack this abnormality in the presence of normal s.potassium, stage-1 hypertension at most, and the non-significant difference between both controls and MSyn patients regarding PRA. There was a strong relation between PA, but not PRA, with the numbers of risk factors. In conclusion, PA is associated with MSyn and its components, although an association does not necessarily imply a cause-effect relationship.These findings reinforce previous observations suggesting that aldosterone is associated with several cardiovascular risk factors. Additional studies are needed to determine the role of aldosterone in causing metabolic dysfunction and to address the possible beneficial effects of aldosterone blockade in MSyn patients.

List of abbreviations

BMI: Body Mass Index
BP :Blood Pressure
DBP: Diastolic Blood Pressure
FBG: Fasting Blood Glucose
FI: Fasting Insulin
HDL-C: High Density Lipoprotein Cholesterol
HOMA-IR: HOmeostasis Model Assessment–Insulin Resistance
HR: Heart Rate
LDL-C: Low Density Lipoprotein Cholesterol
MSyn: Metabolic Syndrome
PRA: Plasma Renin Activity
PA: Plasma Aldosterone
SBP: Systolic Blood Pressure
WC: Waist Circumference

Competing interests
The authors declare that they have no competing interests.

Publication history
Received: 08-Feb-2013 Revised: 04-Mar-2013
Accepted: 06-Mar-2013 Published: 29-Mar-2013

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Citation:
Abdou M, AbdElGawad M S and Mohamed S A: **Increased aldosterone in patients with metabolic syndrome; an additional risk factor**. *Journal of Diabetes Research and Clinical Metabolism* 2013, **2**:17.
http://dx.doi.org/10.7243/2050-0866-2-17