Magnitude of Resistant Hypertension and Impact of Aldosterone to Renin Ratio In Resistant Hypertension

Basavanagowdappa H, Nikhil Basavanagowdappa, Ravikumar YS, Praveen Kulkarni[*], Devananda Devegowda

Department of General Medicine, JSS Medical College, JSS University, Shri Shivarathreeshwara Nagar, Bannimatap, Mysore, INDIA.

ABSTRACT

Background: Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialist. The magnitude of resistant hypertension is highly variable and is reported to be in the range of 12.8% to 25%. Increased incidences of elevated aldosterone levels have been implicated in difficult to manage hypertension. **Aim**: To estimate the magnitude and identifiable causes of resistant hypertension among on therapy hypertensive patients, and also to compare the aldosterone levels and aldoster one ren in ratio between resistant and controlled hypertensive conditions. **Subjects and Methods**: This Multistage, exploratory comparative study was conducted at JSS Hospital and Research Centre, Mysore, India for two years. 1537 adult hypertensive on antihypertensive drugs for a minimum of six months were included. Those who were on three or more antihypertensive medication with blood pressure not under control were defined as having resistant hypertension. **Results:** Prevalence of resistant hypertension was 16.13% (n=248). There was a marginal difference in the prevalence of resistant hypertension in male (51.2%, n=127) and females (48.8%, n=121). Renal diseases were the most common cause of resistant hypertension (n=103). Aldosterone Rennin Ratio >20 was significantly higher in resistant hypertensives without evident secondary cause compared to hypertensive's who were well controlled with less than three antihypertensive. **Conclusion:** Frequency of hyperal dosteronism with high ARR (Aldosterone to Renin Ratio) among resistant hypertensive's with no evident secondary cause for hypertension, probably suggestive of Primary hyperal dosteronism. This makes us to consider estimation of ARR in resistant hypertensive and also consider use of aldosterone antagonists as primary option for good control of Hypertension.

Key words: Resistant Hypertension, Renin, Aldoster one, Aldoster one renin ratio, Primary hyperal dosteronism.

Key message

1. Prevalence of resistant hypertension is variable. Prevalence of Primary hyperal dosteronism is higher in moderate than severe hypertensive. Excessive levels of Aldosterone plays an important role in development of resistance to anti-hypertensive.

2. The study helps to understand the magnitude of resistant hypertension in an Indian setting. It reinstates the importance of aldosterone in the patho physiology of resistant hypertension. ARR is an ideal and economical first step diagnostic method to assess primary hyperal dosteronism.

INTRODUCTION

Hypertension is a major public health problem. The incidence and prevalence of hypertension have been increasing at an alarming rate. Hypertension is one of the leading cause of vascular diseases. According to a WHO report published in 2012, the prevalence of hypertension in men and women over the age of 25 years is 23.1% and 22.6%, respectively. The number of people suffering from hypertension is projected to increase by another 60% by 2025.[1]

Irregular blood-pressure is known to increase the risk of myocardial infarction, stroke, heart failure, and renal failure. There is also a direct correlation with target-organ damage.[2] unfortunately; the targets achieved in blood pressure control are not more than 25% in most of the countries.

Resistant hypertension is a common clinical problem faced by both primary care clinicians and specialist.[3] the magnitude of resistant hypertension is highly variable and is reported to be in the range of 12.8% to 25%.[4]

Aldosterone is an important hormone associated with increasing blood pressure. Increased incidences of elevated aldosterone levels have been implicated in difficult to manage hypertension.[5] Patients suffering with resistant hypertension are often advised for numerous investigations except aldosterone levels. American Heart Association (AHA) has called for increased awareness of hyperal dosteronism among physicians and clinicians treating resistant hypertension.[6] Thus hyperal dosteronism might be a potentially reversible cause of resistant hypertension.[3] This

clinical condition can be targeted by a suitable drug regimen to achieve the target blood pressures. Screening for aldosterone levels in resistant hypertensive patients is a meaningful concept. The present study was designed to estimate the magnitude of resistant hypertension among on therapy hypertensive patients, and also to compare the aldosterone levels and ARR between resistant and controlled hypertensive conditions. Further, the present study was extended to explore the various identifiable causes of resistant hypertension.

METHODS

Study Population

This multistage, exploratory comparative study was conducted in JSS Hospital and Research Centre, Mysore, India for a period of two years from October 2011 to September 2013.Study participants included were aged 18 and above as well as all those who were on anti-hypertensive medication for more than 6 months. Those subjects, whose blood pressure not under control with three anti-hypertensive or requiring more than three drugs for control of hypertension, were identified as resistant hypertensive. Patients were excluded if they were admitted with critical illness (Chronic liver disease, heart failure etc.) or if the patient was on aldosterone antagonists.

Informed consent was obtained from all the patients before recruiting in the present study. Ethical clearance for the present study was obtained

from the Institutional ethics committee of J.S.S. Medical College, Mysore, India.

Outcome measures

Data was collected in a pre-tested structured Performa. Consecutive hypertensive subjects were investigated for clinical and treatment related details. Blood pressure was measured for every subject in supine and standing posture, using standardised mercury sphygmomanometer. Anthropometric parameters such as weight (kilograms), height (centimetres) and waist circumference (centimetres) were gauged by standard techniques. The body mass index (BMI) was also derived from these details. Resistant hypertension was defined when more than three anti-hypertensive were required for the control of hypertension. In all resistant hypertensive patients, clinical examination was carried out to explore the secondary cause of hypertension. Blood urea, serum Creatinine, serum sodium, serum potassium, electrocardiogram, Ultra sonography of the abdomen with renal arterial Doppler study were carried out in all resistant hypertensive patients.

The patients with no specific investigational clue of hypertension were categorised as resistant hypertensive without secondary cause. Microsoft excel 2010 randomisation method was employed to select 45 such patients randomly. 45 age and sex matched controlled hypertensive patients were also selected for comparative analysis (Figure 1). Blood sample was collected in a plain vaccutainer after advising normal salt intake on the previous day. Subjects were made to rest in the sitting position for at least 30 minutes prior to phlebotomy. Serum was recovered using standard method. Pooled serum samples were used for the estimation of aldosterone and renin levels.

Estimation of Aldosterone

Aldosterone levels were estimated in the serum samples by ELISA (USCN Life Science Inc. USA) according to manufacturer's instruction and pilot standardisation. Briefly, 50μl serum followed by50μl of detection reagent A was added to each pre-coated well. Plates were incubated for one hour after uniform mixing. 100μl of detection reagent B was added to each well after thorough washing and kept for 30 minutes. 90 μl of substrate solution was added to each well after washing. 50 μl of stop solution was added after 25 minutes. Every incubation step was carried out at 37°C. Optical density was read immediately at 450 nm using a micro plate reader.

Estimation of Renin

Renin levels were estimated in the serum samples by ELISA (USCN Life Science Inc. USA) according to manufacturer's instruction and pilot standardization. Briefly, 100 μl serum sample was added to pre-coated well and incubated for two hours. 100 μl of detection reagent A was added to each well and incubated for one hour. 100 μl of detection reagent B was added and kept for another 30 minutes. 90 μl of substrate solution was added followed by 50 μl of stop solution after 25 minutes. Every incubation step was carried out at 37°C. Optical density was read immediately at 450 nm using a microplate reader.

The optical densities thus obtained were plotted on a graph obtained from the pilot standardisation and aldosterone and renin levels were calculated using Curve Expert Pro 2.01 software.

Statistical Analysis

The data was entered in Microsoft excel 2010 and analysed using SPSS version 20. Descriptive statistical measures like percentages, mean and standard deviations, median were applied. Inferential statistical test like independent sample t test was applied to test the difference between means. The differences were interpreted statistically significant at P<0.05

RESULTS

Demographic details

The present study recruited 1537 hypertensive patients ever visited JSS Hospital and research centre, Mysore, India from October 2011 to September 2013. Among 1537 hypertensive patients recruited in the present study 59% (n=908) were in the age group of 51-70 years and 52.5% (n=807) were males. Age wise distribution of hypertensive patients (Table 1) revealed the direct association of age with hypertension. 39% patients were on mono therapy, 34% on dual therapy, 18%on triple therapy, and nearly 9%were on four or more drugs. Nearly 60% patients were requiring two or more drugs while 27% patients were on three or more anti-hypertensive drugs.

Burden of resistant hypertension

Prevalence of resistant hypertension was 16.13% (n=248)among the study population. There was a marginal difference in the prevalence of resistant hypertension in male (51.2%, n=127) and female patients (48.8%, n=121). Out of the 248 resistant hypertensive patients screened, 54.8% (n=136) had evident secondary cause while 45.2% (n=112) had no obvious cause (Table 2a).

Resistant hypertensive patients without secondary causes were categorised according to their age and gender (Table 2b). 86.6% (n=97) of the patients were above 50 years of age. Evidently, maximum prevalence of resistant hypertension was in the age group of 61-70 years. The prevalence was marginally higher among female (40.7%, 22/54) in comparison to male resistant hypertensive patients (32.8%, 19/58) in this age group.

Various secondary causes among resistant hypertensive patients were evaluated and are presented in Table 3. It is evident that renal diseases were among the most common secondary cause (75.7%, n=103), followed by drug induced factors (14%, n=19). Obstructive sleep apnoea and hyperthyroidism were other notable secondary causes.

Anthropometric Investigations

Anthro pometric parameters among controlled and resistant hypertensive male and female patients are described in Table 4. Mean age was found to be significantly (P<0.05) higher among resistant hypertension in comparison to well controlled hypertension in both male and female patients. No significant variation in age was observed in the gender wise comparison. Only a marginal higher age was observed in female resistant hypertensive patients. Data presented in Table 4, also notify that the mean duration of hypertension, body weight, BMI and waist circumference were significantly (P<0.05) higher in resistant hypertensive patients as compared to controlled hypertensive patients in both male and female subjects. However, among resistant hypertensive patients, BMI and waist circumference was significantly (P<0.01) higher in females when compared to male patients.

Co-morbidity

Occurrence of diabetes as co-morbidity was investigated in hypertensive patients (Table 5). The incidence of diabetes was notably (P<0.01) higher among resistant hypertensive patients (35.1%, 87/248) as compared to the controlled hypertensive patients (29.6%, 382/1289). Diabetes was as frequent as 40.1% in resistant hypertensive patients without evident secondary cause as compared to 30.9% in patients with known secondary cause of hypertension.

Aldosterone Renin Ratioand Serum Aldosterone levels

37.78% (17/45) of the resistant hypertensive patients had an aldosterone to renin ratio (ARR) of more than 20, whileonly one patient was having ARR>20 among controlled hypertensive patients. Serum aldosterone

Table 1: Age and Sex wise distribution of study subjects

Age group (years)	Male	Female	Total
18-30	6	12	18
31-40	42	42	84
41-50	130	140	270
51-60	225	224	449
61-70	230	229	459
>70	174	102	276
Total	807	730	1537

Table 2a: Magnitude of resistant hypertension

Subject Categories	Male	Female	Total
HTN*	807	730	1537
Resistant HTN	127	121	248
Resistant HTN with evident secondary cause	69	67	136
Resistant HTN without evident secondary cause	58	54	112

*HTN: Hypertensive patients.

Table 2b: Age and gender distribution of resistant hypertensive patients without secondary cause

Age group (years)	Male	Female	Total
31-40	1	3	4
41-50	8	3	11
51-60	13	16	29
61-70	19	22	41
>70	17	10	27
Total	58	54	112

Table 3: Secondary causes of hypertension among resistant hypertensive patients

Secondary Cause	Number	Percentage
Renal diseases	103	75.7
Drug induced	19	13.9
Obstructive sleep apnoea	5	3.7
Hyperthyroidism	5	3.7
Renal artery stenosis	2	1.5
Phaeo chromocytoma	1	0.7
Intracranial tumour	1	0.7

Table 4: Sex wise comparison of various quantitative parameters among controlled and resistant hypertensives

Parameter	Male			Female		
	Controlled HTN (n=23)	Resistant HTN (n=23)	P	Controlled HTN (n=22)	Resistant HTN (n=22)	P
Age (Years)	58.5 ± 11.2	62.2 ± 8.8	0.04	58.1 ± 10.8	63.6 ± 9.4	0.05
Duration of HTN	9.5 ± 7.0	12.1 ± 7.4	0.03	8.5 ± 6.8	11.5 ± 6.7	0.04
Body weight (Kg)	66.2 ± 10.3	74.1 ± 13.5	0.001	62.8 ± 10.9	72.7 ± 11.6	0.001
BMI (Kg/m²)	24.7 ± 5.9	28.12 ± 5.7	0.01	25.7 ± 5.1	30.25 ± 5.8	0.01
Waist circumference	84.5 ± 13.8	87.5 ± 9.1	0.01	89.8 ± 12.5	92.8 ± 10.5	0.01

*HTN: Hypertension.

**Table 5:** Distribution of diabetics in hypertensive patients

Subject Categories	Male	Female	Total
Controlled HTN	226	156	382
Resistant HTN with evident secondary cause	22	20	42
Resistant HTN without evident secondary cause	22	23	45

*HTN: Hypertensive patients.

Table 6: Aldosterone levels in resistant and controlled hypertensive patients

Parameter	Controlled HTN (n=45)	Resistant HTN without evident secondary cause (n=45)	P
Serum Aldosterone (ng/dl)	22.67 ± 14.2	91.76 ± 75.94	0.001

*HTN: Hypertensive patients.
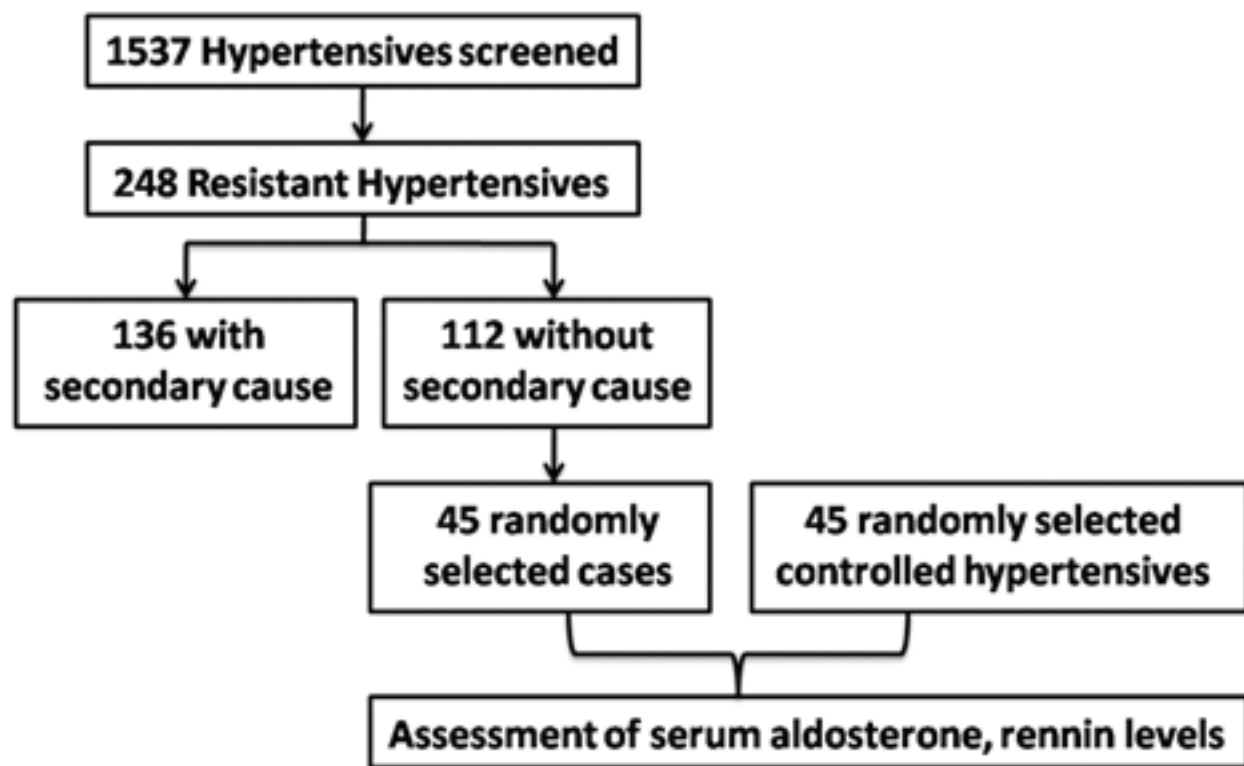
Figure 1: Descriptive summary of the study.

levels were significantly (P<0.001) higher in resistant hypertensive patients without evident secondary cause as compared to resistant hypertensive patients with known secondary cause (Table 6). Occurrence of ARR>20 was significantly higher in resistant hypertensive patients.

DISCUSSION

Prevalence of hypertension in general population is on the rise globally, including India. The individuals with definable resistant hypertension need to be evaluated to rule out secondary cause and look into other hidden conditions like primary hyperal dosteronism, which may not be clinically evident. This cross sectional comparative study was under taken during October 2011 to September 2013.

Principal findings

The present study showed a clear trend of increase in hypertension from second to seventh decade, and the gender bias was insignificant until the age of 70 years. However there was significant male preponderance after 70 years of age. Similar involvement of age and sex in hypertension was reported by Framingham Heart study (ALLHAT study).[7]

Disease burden

The magnitude of resistant hypertension, in hypertensive population, is highly variable and has been reported to be in the range of 12.8 to 25%.[4] Resistant hypertensive cases (16.1%), reported in the present study lie well within this range. In literature, the prevalence was reported to

be 12.8%[4] and 25% .[3] this difference in prevalence could be attributed to ethnic, regional, cultural and therapeutic variations. Chronic kidney disease was found to be the most common secondary cause of hypertension in this study, resulting from various renal disorders. 112 among the resistant hypertensive patients did not have any clinical, or laboratory evidence of secondary cause.

Age and resistant hypertension

Age is one of the important risk factor in the development of resistant hypertension. The present study showed the evidence of increasing age associated with higher incidences of resistant hypertension. Similar evidences had been reported in previously published studies.[3,8]

Duration and resistant hypertension

The mean duration of hypertension in male resistant hypertensive patients was 12.1 years while in female resistant hypertensive patients it was 10.5 years. Similar observation was reported by Lloyd *et al.*[8] this study mentioned higher risk of developing resistant hypertension with longer duration of hypertension. The mean duration of hypertension in resistant hypertensive patients in that study was 11 years which is close to 11.3 years as found in the present study.

Anthropometric parameters and Co-morbidity

All the 3 anthropometric parameters studied *i.e.* Weight, height and BMI were significantly higher in resistant hypertensive patients as compared to controlled hypertensive patients. The BMI suggested that controlled hypertensive patients were in the range of overweight whereas resistant hypertensive patients fell in obese category. Female resistant hypertensive's had a much higher BMI than their counterparts. Similar observations were reported in ALLHAT study.[7] Framingham heart study[9] also revealed similar facts. These observations were instrumental in indicating that higher body weight, BMI and waist circumferences are definite risk factors for resistant hypertension. The present study showed higher prevalence of resistant hypertension among diabetics. Similar findings were reported in a previous published study.[10] Also, 40% incidence of diabetes was reported in a previously published study in resistant hypertensive patients which was close to 35.1% incidence rate observed in the present study.

ARR and resistant hypertension

One of the first studies mention 12% incidence of hyperaldosteronism in referred patients of severe hypertension.[5] Mosso *et al*[11] had screened more than 600 hypertensive patients for primary hyperal dosteronism. Overall, 6.1% of subjects were confirmed to have primary hyperal dosteronism. The prevalence, moreover, increased progressively with increasing severity of hypertension. The incidence of hyperal dosteronism has been reported in the range of 13-23% in resistant hypertensive patients.[11] ARRhas been used as the primary screening tool in the diagnosis of primary aldosteronism.[12] this test has a high sensitivity and a high negative predictive value. It is considered as positive if the ratio is higher than 20 when aldosterone is measured in ng/dl and renin is measured in ng/ml/h. ARR cut off of 20 is a better predictive value for resistant hypertension because increasing the cut off to 50 decreases the sensitivity of the test.[11-14]

In the present study 17 out of 45 resistant hypertensive patients had an ARR more than 20, while only one patient crossed this cut off out of 45 controlled hypertensive patients. This incidence of 37.7% was significantly higher than previously reported 12%[5] and 23%.[14] Higher incidence of ARR in the present study could be attributed to either the higher number of diabetics in the study subgroup or/and other factors like ethnicity, cultural, and geographical variations.

Strength and weakness of the study

Resistant hypertensive patients are at higher risk of developing severe co-morbidities such as Ischemic heart disease, cerebral and coronary events. Hyperaldosteronism are also involved in complications related to persistent intravascular volume expansion.[15] Present study was instrumental in assessing the magnitude of resistant hypertensive patients. The secondary causes were also investigated and renal diseases were found to have the significant contribution as a secondary cause of hypertension. The levels of aldosterone and renin were investigated in resistant hypertensive patients without evident secondary cause of hypertension. The ARR was found to be the useful criterion for identifying the resistant hypertension patients and to take therapeutic decisions. However, the ARR was not correlated with the therapeutic response after administering aldosterone antagonist in resistant patients.

CONCLUSION

Increasing age, duration of hypertension, BMI, waist circumference and co-existent diabetes were seen to be common risk factors associated with resistant hypertension. The mean aldosterone levels were four times higher in resistant hypertensive patients than controlled hypertensive patients.Since secondary causes were not evident in many of the resistant hypertensive patients; primary hyperaldosteronism might have a significant contribution in developing resistant hypertension. In the present study significant number of resistant hypertensive patients showed ARR>20. This observation points towards the clinical significance of considering the estimation of ARR in resistant hypertensive patients. Present study may also suggest the use of aldosterone antagonists as a primary option to achieve good control of hypertension.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST

No conflict of interest.

REFERENCES

1. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. *Lancet.* 2005;365(9455): 217-23. http://dx.doi.org/10.1016/S0140-6736(05)70151-3.

2. Lip G, Target Y. organ damage and the prothrombotic state in hypertension. *Hypertension.* 2000;36(6):975-7. http://dx.doi.org/10.1161/01.HYP.36.6.975; PMid:11116110.

3. Calhoun DA, Jones D, Textor S, Goff DC, Murphy TP, Toto RD *et al.* Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. *Hypertension.* 2008;51(6):1403-19. http://dx.doi.org/10.1161/HYPERTENSIONAHA.108.189141; PMid:18391085.

4. Persell SD. Prevalence of resistant hypertension in the United States, 2003-2008. *Hypertension.* 2011;57(6):1076-80. http://dx.doi.org/10.1161/HYPERTENSIONAHA.111.170308; PMid:21502568.

5. Gordon, RD, Stowasser M, Tunny TJ, Klemm SA, Rutherford JC. High incidence of primary aldosteronism in 199 patients referred with hypertension. Clin Exp Pharmacol Physiol. 1994;21:315-8. http://dx.doi.org/10.1111/j.1440-1681.1994.tb02519.x; PMid:7923898.

6. Sarafidis, P. A.; Bakris, G. L. Resistant hypertension: an overview of evaluation and treatment. J Am Coll Cardiol. 2008;52:1749-57. http://dx.doi.org/10.1016/j.jacc.2008.08.036; PMid:19022154.

7. Cushman WC, Ford CE, Cutler JA, Margolis KL, Davis BR, Grimm RH *et al.* Success and predictors of blood pressure control in diverse North American settings: the antihypertensive and lipid-lowering treatment to prevent heart attack trial (ALLHAT). J Clin Hypertens (Greenwich) 2002;4:393-404. http://

dx.doi.org/10.1111/j.1524-6175.2002.02045.x.

8. Lloyd-Jones, D. M.; Evans, J. C.; Larson, M. G.; O'Donnell, C. J.; Roccella, E. J.; Levy, D. Differential control of systolic and diastolic blood pressure : factors associated with lack of blood pressure control in the community. Hypertension. 2000;36:594-9. http://dx.doi.org/10.1161/01.HYP.36.4.594; PMid:11040241.

9. Chobanian, A. V.; Bakris, G. L.; Black, H. R.; Cushman, W. C.; Green, L. A.; Izzo, J. L., *et al*. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42:1206-52. http://dx.doi.org/10.1161/01.HYP.0000107251.49515.c2; PMid:14656957.

10. Umpierrez GE, Cantey P, Smiley D, Palacio, A. Temponi, D. Luster, K., et al. Primary aldosteronism in diabetic subjects with resistant hypertension. Diabetes Care. 2007;30:1699-703. http://dx.doi.org/10.2337/dc07-0031; PMid:17429062.

11. Mosso L, Carvajal C, Gonzalez A, Barraza A, Avila F, Montero J *et al*. Primary aldosteronism and hypertensive disease. Hypertension. 2003;42(2):161-5.

http://dx.doi.org/10.1161/01.HYP.0000079505.25750.11; PMid:12796282.

12. Calhoun DA, Izzo Jr, Sica DA, Black HR. Management of hyperaldosteronism and hypercortisolism. In Hypertension Primer: The Essentials of High Blood Pressure: Basic Science, Population Science, and Clinical Management, 4 Ed.; Lippincott Williams & Wilkins: Philadelphia, 2008; pp 564-567.

13. Beevers G, Lip GY, O'Brien E, ABC of hypertension: The pathophysiology of hypertension. BMJ. 2001;322(7291):912-6. http://dx.doi.org/10.1136/bmj. 322.7291.912; PMid:11302910 PMCid:PMC1120075.

14. Calhoun, D. A. Is there an unrecognized epidemic of primary aldosteronism? Pro. Hypertension. 2007;50:447-53. http://dx.doi.org/10.1161/HYPERTENSIO-NAHA.106.086116; PMid:17679651.

15. Acelajado, M. C.; Calhoun, D. A. Aldosteronism and resistant hypertension. Int J Hypertens. 2011;2011:1-7. http://dx.doi.org/10.4061/2011/837817 PMid:21331160 PMCid:PMC3034938.