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ORIGINAL ARTICLE

Primary aldosteronism among newly diagnosed and untreated hypertensive patients in a Swedish primary care area

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Abstract

Objective. To evaluate the prevalence of primary aldosteronism (PA) in newly diagnosed and untreated hypertensive patients in primary care using the aldosterone/renin ratio (ARR), and to assess clinical and biochemical characteristics in patients with high and normal ARR. *Design.* Patient survey study. *Setting and subjects.* A total of 200 consecutive patients with newly diagnosed and untreated hypertension from six primary health care centres in Sweden were included. *Main outcome measures.* ARR was calculated from serum aldosterone and plasma renin concentrations. The cut-off level for ARR was 65. Patients with an increased ARR were considered for confirmatory testing with the fludrocortisone suppression test (FST), followed by adrenal computed tomographic radiology (CT) and adrenal venous sampling (AVS). *Results.* Of 200 patients, 36 patients had an ARR $>$ 65. Of these 36 patients, 11 patients had an incomplete aldosterone inhibition during FST. Three patients were diagnosed with an aldosterone producing adenoma (APA) and eight with bilateral adrenal hyperplasia (BHA). Except for moderately lower level of P-K in patients with an ARR $>$ 65 and in patients with PA, there were no biochemical or clinical differences found among hypertensive patients with PA compared with patients without PA. *Conclusion.* Eleven of 200 evaluated patients (5.5%) were considered to have PA. The diagnosis of PA should therefore be considered in newly diagnosed hypertensive subjects and screening for the diagnosis is warranted.

Key Words: *Aldosterone, aldosterone to renin ratio, family practice, hypertension, primary aldosteronism, renin*

Hypertension affects up to 25% of the adult population in Sweden [1,2]. Primary aldosteronism (PA) is a common form of secondary hypertension, characterized by excessive aldosterone secretion and renin suppression, followed by hypertension, alkalosis and hypokalemia [3–6]. The latter is, however, not necessarily an integral element [3–6]. Resistant hypertension requiring more than three antihypertensive drugs, hypertension diagnosed at a young age, or family history of stroke at a young age are factors that suggest the possibility of PA [7]. PA arises from one or both adrenal glands. The two major subtypes are aldosterone producing adenoma (APA; 1/3 of the cases) and bilateral adrenal hyperplasia (BAH; 2/3 of the cases). APA is preferably treated by surgery while BHA is treated with aldosterone antagonists. The diagnosis thus enables tailored medical therapy or surgical intervention with possible cure [8].

PA has been considered a rare cause of hypertension [9] but recent studies suggest a prevalence of 5–10% [3,4,10–17]. Frequencies vary in different study populations and are increased in severe hypertension, especially at referral centres treating resistant hypertension [12]. Despite the fact that a number of studies have been carried out, the prevalence among primary care patients still remains uncertain. In a previous study [13] we confirmed an 8.5% prevalence of PA among 200 screened hypertensive patients in primary care. However, these patients had all been treated with antihypertensive medication for several years, which might have affected the attendance for screening, since only approximately 50% of invited subjects participated. Furthermore, it is known that a number of antihypertensive drugs alter the aldosterone to renin ratio (ARR); therefore withdrawal of medication is strongly suggested before screening [18].

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Primary aldosteronism (PA) is common in patients diagnosed with "essential hypertension" in specialized centres; however, reports on prevalence in primary care are few.

- Screening with the aldosterone to renin ratio followed by confirmatory testing showed that 5.5% of newly diagnosed and untreated hypertensive patients had PA.
- No particular clinical features could distinguish these patients from patients with essential hypertension.
- Screening for PA should always be performed in younger patients with newly diagnosed hypertension and in patients with resistant hypertension irrespective of potassium concentrations.

The aim of this study was to clarify the prevalence of PA by screening newly diagnosed and medically untreated hypertensive patients in primary care. Patients with a high ARR were referred for confirmatory testing. In addition, the study compared clinical and biochemical characteristics in patients with high or normal ARR.

Material and methods

Ethics

The Ethics Committee of the Faculty of Medicine, Lund University approved the study. After medical examination, and written and oral information, informed consent was obtained from all patients participating in the study.

Study population

The study population was recruited from six primary health care centres in Lund, Sweden. Consecutive patients, 75 years of age or younger, with newly diagnosed hypertension were invited to participate. The diagnosis of hypertension was confirmed by ambulatory 24-hour blood pressure measurement or by three high blood pressure records (>140/90). We recruited 200 patients: 115 women, age 24–75 and 85 men, age 21–75. Apart from hypertension there were four patients with diabetes mellitus, two medically treated. One patient had atrial fibrillation, two patients had TIA and one patient had stroke recorded in their medical history. Some 30 patients were documented with hyperlipidemia. There were no patients' records with heart failure or renal insufficiency in their medical history. None of the patients was on antihypertensive medication and all patients completed the study.

Study design

The patients' medical history was recorded, including heredity, current medication, and diseases. A physical examination of the patient was performed by the attending physician.

Handling of blood samples

Blood samples were centrifuged at room temperature. Plasma and serum were frozen at –20°C, with the exception of samples for sodium, potassium, and creatinine, which were analysed the same day on a routine auto-analyzer.

Biochemical methods

Blood samples for serum aldosterone concentration (SAC) and plasma renin concentration (PRC) were drawn in the morning with the patient seated and after 10 minutes' rest. The SAC and PRC were drawn twice, with a week in between the samples.

The SAC was determined with the DPC method (Aldosterone Coat-A-Count, DPC, California, USA). The total inter-assay variation (CV) was 8.7% and 8.9% at 90 and 725 pmol/L, respectively. The reference range in the morning was 110–860 pmol/L.

The PRC was determined with the direct method from Cis-Bio (Renin III generation, Cis-Bio, International France). The CV was 4.4% and 3.7% at 27 and 100 mIU/L, respectively. The reference range for morning samples was 4–64 mIU/L.

The plasma concentrations of creatinine, sodium, and potassium were determined with routine methods on Hitachi Modular P (Roche Diagnostics, Mannheim, Germany). The reference ranges for sodium was 136–146 mmol/L, for potassium 3.2–4.7 mmol/L and for creatinine 50–100 umol/L. The reference range for ARR with a morning sample is 4–65 pmol/mIU.

Confirmatory testing

Patients with one or two high ARR (>65 pmol/mIU) at screening were referred for a fludrocortisone suppression test (FST) at the department of endocrinology. A few patients who had very high blood pressure at diagnosis were treated by an alpha-blocking agent (doxacozin) or a calcium channel blocker (amlodipin), since these drugs have no or minor impact on the renin–angiotensin axis.

Fludrocortisone test

The rationale of the fludrocortisone suppression test is that the aldosterone secretion is insufficiently suppressed in primary aldosteronism (PA) [19,20]. Before the start of the FST the potassium level was controlled and adjusted if necessary. Over four days, 0.1 mg fludrocortisone was administered orally four times daily (at 08.00, 12.00, 16.00, 20.00 o'clock) and 500 mg sodium chloride was supplemented daily. The blood pressure was measured and blood samples for aldosterone and renin were drawn in the morning.

Additional diagnostic work-up

When the fludrocortisone suppression test had confirmed primary aldosteronism, computerized tomography (CT) of the adrenals was done, followed by adrenal venous sampling (AVS). The adrenal CT used 1.5 mm cuts, before and after the intravenous contrast. The detection rate of pathological findings on CT was 5 mm. AVS was done by sequential catheterization from the inguinal veins. Blood from the right and the left adrenal vein was analysed, comparing the concentrations of aldosterone and cortisol between the adrenal and peripheral veins [21]. For confirmation of an aldosterone producing adenoma the aldosterone/cortisol ratio should be >3 times higher on one side [21].

Statistics

Statistical analysis was performed using Stat-View for Windows, version 5.0.1 (SAS Institute Incorporation). For numeric data, the results are given as median (IQR) and for categorical data, as numbers and percentage if not stated otherwise. The Mann–Whitney U-test was used for numerical data when analysing differences between groups. For categorical data, the chi-squared test or Fisher's exact test was used when the expected frequency was less than five. A probability level of $p < 0.05$ was considered significant.

Results

Aldosterone to renin ratio (ARR) at screening

Of 200 patients, 36 patients (18%) had an ARR >65 (Figure 1). Compared with patients with an ARR <65, these 36 patients had lower potassium ($p = 0.002$), as well as higher serum aldosterone concentration (SAC) ($p < 0.0001$) and lower plasma renin concentration (PRC) ($p < 0.0001$) on both screening occasions (Table I). Otherwise, there were no significant differences in medical history, blood pressure, or biochemical variables studied between patients with normal or high ARR.

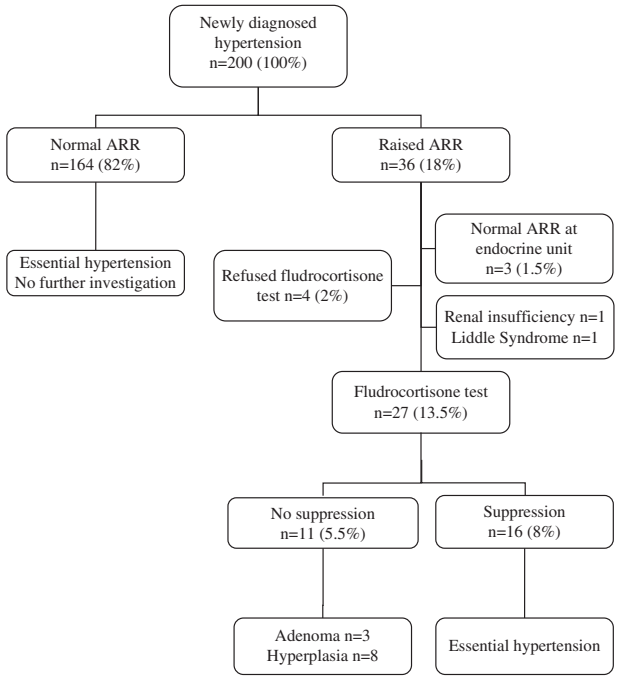

Figure 1. Flow diagram of patients with newly diagnosed hypertension screened with the aldosterone to renin ratio (ARR).

Confirmatory testing

All 36 patients with an aldosterone to renin ratio > 65 were referred for further evaluation. However, four patients abstained from further testing, one patient was diagnosed with renal failure and one patient with Liddle's syndrome, and thus they were not eligible for the fludrocortisone suppression test. Furthermore, an increased aldosterone to renin ratio was not

Table I. Clinical and biochemical variables in patients screened for PA with a raised ARR and a normal ARR.

Variables	Ratio > 65 n = 36 (IQR)	Ratio < 65 n = 164 (IQR)	p-value
Heredity (n)	11 (31%)	72 (44%)	0.14
Systolic BP (mmHg)	160 (20)	160 (20)	0.93
Diastolic BP (mmHg)	95 (10)	95 (14)	0.47
S-Na^+ (mmol/L)	141 (3)	141 (3)	0.66
S-K^+ (mmol/L)	3.8 (0.3)	4.0 (0.4)	0.002
Creatinine (umol/L)	70 (16)	72 (18)	0.27
SAC 1 (pmol/L)	354 (148)	204 (182)	< 0.0001
SAC 2 (pmol/L)	330 (136)	207 (178)	< 0.0001
PRC 1 (mIU/L)	4.0 (2.2)	12 (8.5)	< 0.0001
PRC 2 (mIU/L)	3.6 (2.8)	11.0 (8.2)	< 0.0001
Age (years)	58 (8)	60 (18)	0.29
Gender (m/f)	12/24	79/92	0.24

confirmed in three patients. Therefore, the fludrocortisone suppression test was performed in 27 patients of whom 11 showed incomplete suppression (see Figure 1).

There were no significant differences in medical history, blood pressure, or measured biochemical variables between patients with a positive or negative fludrocortisone suppression test (Table II).

Radiology and adrenal venous sampling (AVS)

Computer adrenal tomography (CT) and adrenal venous sampling (AVS) were done in all patients with a positive FST. Six CT scans were normal and two had bilateral adrenal enlargement. Three CT scans showed an adenoma (see Figure 1), and AVS confirmed lateralization of aldosterone secretion in two patients.

Summary of outcome

Eleven of 200 evaluated patients (5.5%) had incomplete suppression with fludrocortisone. Three patients were diagnosed with aldosterone producing adenoma (APA) and eight patients with bilateral adrenal hyperplasia (BAH) (see Figure 1). All patients with BAH and one patient with an APA were treated medically with spironolactone. Two patients with APA were operated on by unilateral laparoscopic adrenalectomy, confirming an APA.

Compared with patients with essential hypertension, patients with primary aldosteronism had lower potassium ($p = 0.003$), higher SAC ($p < 0.005$), and lower PRC ($p < 0.001$) on both screening occasions (Table III). The overlapping of potassium between the two groups of patients was, however, considerable (Figure 2). Otherwise, there were no significant differences in medical history, blood pressure, or biochemical variables between patients with essential hypertension and primary aldosteronism (Table III).

Table II. Clinical and biochemical variables in patients with a positive and a negative fludrocortisone suppression test (FST).

Variables	Positive fludrocortisone suppression test n = 11 (IQR)	Negative fludrocortisone suppression test n = 16 (IQR)	p-value
Heredity (n)	4 (36%)	7 (44%)	0.67
Systolic BP (mmHg)	165 (28)	160 (20)	0.44
Diastolic BP (mmHg)	100 (8)	92 (12)	0.47
S-K^+ (mmol/L)	3.7 (0.5)	3.8 (0.2)	0.32
Creatinine (umol/L)	70 (14)	76 (10)	0.13
Age (years)	46 (22)	58 (7)	0.22
Gender (m/f)	6/5	7/9	0.58

Table III. Clinical and biochemical variables in patients with PA and patients with essential hypertension.

Variables	PA n = 11 (IQR)	Essential hypertension n = 189 (IQR)	p-value
Heredity (n)	4 (57%)	79 (72%)	0.72
Systolic BP (mmHg)	165 (28)	160 (20	0.72
Diastolic BP (mmHg)	100 (8)	95 (12)	0.11
S-Na^+ (mmol/L)	143 (4)	141 (3)	0.27
S-K^+ (mmol/L)	3.7 (0.5)	4.0 (0.4)	0.003
Creatinine (umol/L)	70 (14)	72 (17)	0.25
SAC 1 (pmol/L)	327 (240)	237 (212)	< 0.005
SAC 2 (pmol/L)	356 (199)	231 (200)	< 0.003
PRC 1 (mIU/L)	4.0 (2.2)	10 (9.0)	< 0.0001
PRC 2 (mIU/L)	2.9 (2.9)	10.0 (9.6)	< 0.0001
Age (years)	46 (22)	60 (17)	0.07
Gender (m/f)	6/5	78/111	0.39

Discussion

This study confirms a high prevalence of primary aldosteronism (PA) in an unselected newly diagnosed group of hypertensive patients. The strength of this investigation, compared with study populations from tertiary units, is that the patients were unselected and better reflect the hypertensive population. The patients were screened without medication that could disturb the aldosterone–renin–angiotensin system. Two sets of aldosterone to renin ratio (ARR) tests were performed and patients with an ARR >65 were further investigated with the fludrocortisone suppression test (FST) for aldosterone autonomy.

The present high frequency of PA is in accordance with the reported 5–10% prevalence of PA in studies from specialized centres [12,15] and our earlier study [13]. However, in our previous study the frequency was somewhat higher, i.e. 8.5%, probably because these patients were well-known hypertensives who had been on treatment for several years,

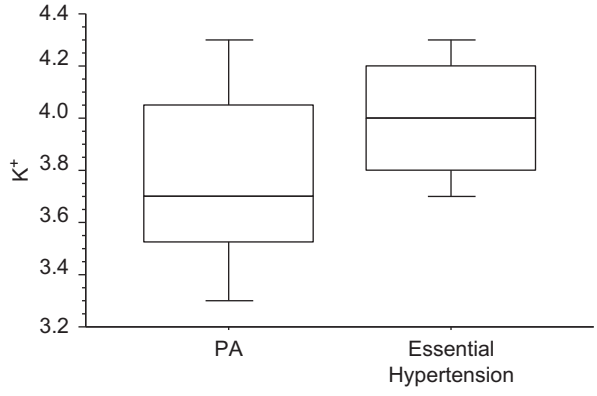

Figure 2. Box plot analysis of the value of plasma potassium (mmol/L) in patients with PA and in patients with essential hypertension, p between mean values = 0.003.

which might have biased the result. Nevertheless, PA is one of the most frequent causes of secondary hypertension [4,17]. Since it is a potentially curable disease and associated with a high rate of cardiovascular complications [22,23], it is important not to miss the diagnosis of PA. Removal of an aldosterone producing adenoma (APA) or unilateral autonomous hyperplasia (IHA) corrects hyperaldosteronism and cures or significantly decreases hypertension and cardiovascular alterations [23]. Therefore, early diagnostic efforts are warranted.

In the present study, the results show that PA cannot be recognized from clinical characteristics or routine laboratory tests. In order to diagnose PA, the family practitioner should incorporate the ARR screening as a diagnostic tool. This study shows that it is possible for doctors in primary care to use the ARR to identify possible cases of PA. Several of the patients in the present study with confirmed PA had normokalemia. This clearly implies that hypokalemia is an insensitive screening test for PA [19]. Another important finding is the high percentage of false positive ARR results, which is in line with previous reports showing that 30–50% of patients with a high ARR do not have PA [20,24,25]. To avoid a high number of false-positive screened cases, the combination of increased ratio and high aldosterone levels has been suggested [26]. Furthermore, possibly two or more samples should be analysed before referring the patient for confirmatory testing, which is necessary for accurate diagnosis.

Using ARR for screening, it is also important to avoid false-negative results, which may conceal PA. Patients with negative results are not further investigated in most centres, nor was this done in the present investigation. Cut-off values for ARR vary among centres. It is still possible that the cut-off value for ARR was too high in this context, with the potential consequence that mild forms of PA may not have been detected. However, using a cut-off based on samples from healthy subjects analysed at the local laboratory should be the best possible way to avoid this.

The results from the present study suggest that the ARR could be used as a screening tool for PA in newly diagnosed patients with hypertension, although the possibility to diagnose patients can be expected to be higher in selected patient groups. When performed, measurement of ARR in all hypertensive individuals, followed by FST in patients with an ARR >65 to confirm or exclude PA, and computed tomography (CT) and adrenal vein sampling (AVS) to determine the subtype, can result in the detection of significant numbers of patients with specifically treatable or curable hypertension.

Finally, there is a need for guidelines based on standardized and simple tests for PA screening in primary health care. A national screening programme for PA among hypertensive patients could potentially be justified in light of the present results, and the beneficial outcome of surgical and medical treatment of PA [27,28]. Particular attention should be paid to newly discovered hypertension, especially in younger patients.

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Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

[1] Jönsson B. Cost benefit of treating hypertension. J Hum Hypertens 1994;12:65–70.
[2] Johannesson M. The cost-effectiveness of hypertension treatment in Sweden: An analysis of the criteria for intervention and choice of drug treatment. J Hum Hypertens 1999;10:23–6.
[3] Stowasser M, Gordon RD. Primary aldosteronism. Best Pract Res Clin Endocrinol Metab 2003;17:591–605.
[4] Young WF Jr. Primary aldosteronism: A common and curable form of hypertension. Cardiol Rev 1999;7:207–14.
[5] Stowasser M, Gordon RD. Primary aldosteronism: From genesis to genetics. Trends Endocrinolol Metab 2003;14:310–7.
[6] Young WF. Primary aldosteronism: Renaissance of a syndrome. Clin Endocrinolol 2007;66:607–18.
[7] Funder JW, Carey RM, Fardella C, Gomez-Sanchez CE, Mantero F, Stowasser M, et al. Case detection, diagnosis and treatment of patients with primary aldosteronism: An endocrine society clinical practice guideline. J Clin Endocrinolo Metab 2008;93:3266–81.
[8] Mattson C, Young WF jr. Primary aldosteronism: Diagnostic and treatment strategies. Nat Clin Pract Nephrol 2006; 2:198–208.
[9] Conn JW. Primary aldosteronism, a new clinical entity. J Lab Clin Med 1955;45:661–4.

[10] Lim PO, Brennan G, Shiels P. Unexpectedly high prevalence of primary hyper-aldosteronism in a hypertensive population in Dundee. J Endocrinol 1998;156:22.
[11] Lim PO, Rodgers P, Cardale K, Watson AD, MacDonald TM. Potentially high prevalence of primary hyperaldosteronism in a primary-care population. Lancet 1999;353:40.
[12] Mulatero P, Stowasser M, Loh KC, Fardella CE, Gordon RD, Mosso L, et al. Increased diagnosis of primary aldosteronism, including surgically correctable forms, in centres from five continents. J Clin Endocrinolo Metab 2004;89:1045–50.
[13] Westerdahl C, Bergenfelz A, Isaksson A, Wihl A, Nerbrand C, Valdemarsson S. High frequency of primary aldosteronism among hypertensive patients from a primary care area in Sweden. Scand J Prim Health Care 2006;24:154–9.
[14] Gordon RD, Stowasser M. Primary aldosteronism: The case for screening. Nat Clin Pract Nephrol 2007;3:582–3.
[15] Stowasser M, Gordon RD, Gunasekera TG, Cowley DC, Ward G, Smithers BM. High rate of detection of primary aldosteronism, including surgically treatable forms, after "non selective" screening of hypertensive patients. J Hypertens 2003;2:2149–57.
[16] Fogari R, Preti P, Zoppi A, Rinaldi A, Fogari E, Mugellini A. Prevalence of primary aldosteronism in unselected hypertensives: A prospective study based on the use of an aldosterone/renin ratio as a screening test. Hypertens Rev 2007;30:111–17.
[17] Anis AY, White WB, Mansoor GA. Hyperaldosteronsim is a common cause of secondary hypertension missed by primary care physicians and associated with normokalemia. Am J Hypertens 1998;11:199A.
[18] Seifarth C, Trenkel S, Schobel H, Hahn EG, Hensen J. Influence of antihypertensive medication on aldosterone and renin concentration in differential diagnosis of essential hypertension and primary aldosteronism. Clin Endocrinol 2002;57:457–65.
[19] Rossi GP, Rossi E, Pavan E, Rosati N, Zecchel R, Semplicini A, et al. Screening for primary aldosteronsism with a logistic multivariate discriminant analysis. Clin endocrinol (Oxf.) 1998;49:713–23.
[20] Mulatero P, Dluhy RG, Giachetti G, Boscaro M, Veglio F, Stewart PM. Diagnosis of primary aldosteronism: From screening to subtype differentiation. Trends Endocrinol Metab 2005;16:114–9.
[21] Doppman J, Gill J. Hyperaldosteronism: Sampling adrenal veins. Radiology 1996;198: 309–12.
[22] Milliez P, Girerd X, Plouin PF, Blacher J, Safar ME, Mourad JJ. Evidence for an increased rate of cardiovascular events in patients with primary aldosteronism. J Am Coll Cardiol 2005;45:1243–8.
[23] Catena C, Colussi G, Nadalini E, Chiuch A, Baroselli S, Lapenna R, Sechi LA. Cardiovascular outcomes in patients with primary aldosteronism after treatment. Arch Intern Med 2008;168:80–5.
[24] Mosso L, Carvajal C, González A, Barraza A, Avila F, Montero J, Huete A, et al. Primary aldosteronism and hypertensive disease. Hypertension 2003;42:161–5.
[25] Stowasser M, Gordon RD. Primary aldosteronism: Careful investigation is essential and rewarding. Molecular Cellular Endocrinolol 2004;217:33–9.
[26] Seiler L, Rump L, Schulte-Mönting J, Slawik M, Borm K, Pavenstädt H, et al. Diagnosis of primary aldosteronism: Value of different screening parameters and influence of antihypertensive drugs. Eur J Endocrinol 2004;150:329–37.
[27] Hennings J, Andreasson S, Botling J, Hägg A, Sundin A, Hellman P. Long-term effects of surgical correction of adrenal hyperplasia and adenoma causing primary aldosteronism. Langenbeck's Arch Surg 2009;395:133–7.
[28] Campagnacci R, Crosta F, De Sanctis A, Baldarelli M, Giacchetti G, Paganini AM, et al. Long-term results of laparoscopic adrenalectomy for primary aldosteronism. J Endocrinol Invest 2009;32:57–62.
[29] Nishikawa T, Saito J, Omura M. Prevalence of primary aldosteronism: Should we screen for primary aldosteronism before treating hypertensive patients with medication? Endocrine J 2006;10:1507–19.
[30] Montoni VM, Young W Jr. Use of plasma aldosterone concentration-to-plasma renin activity ratio as a screening test for primary aldosteronism: A systematic review of literature. Endocrionol Metab Clin Am 2002;31:619–32.
[31] Rossi GP, Pessina, Heagerty AM, Primary aldosteronism: An update on screening, diagnosis and treatment. J Hypertens 2008;26:613–21.
[32] Mulatero P, Monticone S, Bertello C, Tizzani D, Iannaccone A, Crudo V, Veglio F. Evaluation of primary aldosteronism. Curr Opin Endocrinol Diabetes Obes 2010b;17:188–93.