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AN ASSESSMENT OF THE TARGET ORGAN DAMAGE AMONG PATIENTS OF RESISTANT HYPERTENSION- A CROSS SECTIONAL STUDY

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ABSTRACT

This study aimed to assess the distribution of target organ damage among the patients with Resistant hypertension. A Cross sectional study of a cohort of patients with resistant hypertension as defined by WHO-ISH Criteria was conducted. Patients' characteristics, history, physical examination and relevant investigations were done. Target organ damages was diagnosed and graded by standard criteria. Binomial test, chi square test were applied and the p value was computed to know the statistical significance of results obtained. A total of 233 patients were included in the study. 84.12% of the study population (196 patients) had evidence of cardiovascular system involvement, 42.92% had renal system involvement, and 27 patients (11.58%) had central nervous system involvement. The Least number of patients had evidence of ophthalmic (8.58%) and respiratory system (0.86%). This percentage doesn't add up to 100 as patients had multiple system involvement. Out of total target organs/system damaged in our study the most commonly effected system was cardiovascular system (56.81% of all target organs damaged) followed by renal (28.98%). Maximum number of patients (83) had left ventricular hypertrophy as evidenced by ECG or 2 D ECHO followed by 73 patients who had ischemic heart disease. Central nervous system involvement (7.83%) was seen in 27 patients.In conclusion , Heart and kidneys is the common target organs to be damaged in patients with resistant hypertension.

KEY WORDS - Resistant Hypertension, target organ damage

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INTRODUCTION

Hypertension prevalence is increasing worldwide with 972 million people (333 in economically developed and 639 million in economically developing countries like India suffering from hypertension).[1]Studies showed higher prevalence of hypertension in developing countries.[1,2]Resistant hypertension is primarily a systolic and age related problem. Pseudo resistance, poor compliance, inappropriate therapy, inadequate doses of antihypertensive drugs, cost and adverse effects of medication, complex drug regimens, failure of clinicians to fully realize the benefits of antihypertensive therapy, lack of patient education, use of exogenous medications, secondary causes of hypertension and lifestyle factors are important causes contributing to resistant hypertension. Patients whose hypertension is uncontrolled are more likely to have target-organ damage and a higher long-term cardiovascular risk than are patients whose blood pressure is controlled.[3]Randomized controlled trials including UKPDS, Hypertension Optimal Treatment (HOT) Trial, SHEP, the Syst-EUR, HOPE Study, LIFE, have demonstrated that adequate blood pressure (BP) control improves CVD outcomes, especially stroke, when aggressive BP targets are achieved.[4-11] Also, while the exact prevalence of resistant hypertension is unknown, clinical trials suggest that it is not rare, involving perhaps 20% to 30% of study participants.[12]An evaluation of health research output from India in 2002 indicated that less than 5% was in the 'public health sciences' and is grossly inadequate in relation to disease burdens and in terms of quality. Moreover, India is well on its way to being the hypertensive capital of the world besides holding the dubious title of diabetes capital[13]. There is a need for more analytical and experimental epidemiologic studies in the field of Hypertension especially resistant hypertension in India, the findings of which can be translated into health intervention strategies. So, we sought to investigate the distribution and extent of target organ damage in patients with resistant hypertension.

METHODS

Participants

A Cross sectional study spanning over a period of 2 years was done from June 2007 to June 2009 and total numbers of 223 resistant hypertensive patients were assessed in Kaushalya Medical Foundation Trust Hospital, a tertiary care center in Thane, India. The study was approved by Institutional Review Board of Kaushalya Medical Foundation Trust Hospital.Resistant hypertension was diagnosed by criteria as defined by WHO-ISH guidelines which defines as failure of concomitant use of three or more different antihypertensive drugs to lower B.P to less than 150/90 mmHg in patients with classical essential hypertension or to less than 150 mmHg in patients with isolated systolic hypertension or to less than 130/80 mmHg with diabetes and chronic renal disease.[14]

- Use of diuretics is recommended but not required.
- Doses of drugs should be optimal but not necessarily maximal.[14]
- High B.P controlled but with use of 4 or more agents is also considered under resistant hypertension.[14]

All the cases admitted to the hospital with BP >150/90; and diabetic and chronic renal disease patients with BP >130/80 in spite of administering 3 antihypertensive drugs were diagnosed as resistant hypertension and formed the study cohort.

Inclusion Criteria

1. Adult patients more than 18 years of age were included.
2. Patients with co-morbid conditions like diabetes mellitus, chronic renal disease having a blood pressure of more than 130/80 mm Hg in spite of taking 3 or more antihypertensive drugs.

Exclusion Criteria

1. All pregnant women.
2. Patients less than 18 years of age.
3. Patients who were unaware of their anti-hypertensive drugs.

4. Patients who were not admitted to the hospital.
5. Patients with a recent change in antihypertensive medications and their dosage (less than a month).[8]

Procedure

Medically relevant details including the primary condition for which the patient was admitted were noted. Additionally, an obstetric and menstrual history was taken in female patients.Patient's blood pressure was recorded in both arms with a properly calibrated mercury sphygmomanometer by the auscultatory method. An adequately sized cuff was used. Blood pressure was measured, with patient seated quietly for 5 minutes in a chair with feet resting on the ground or lying down according to standards set by Indian guidelines for management of hypertension.[15] A detailed drug history was taken with details also taken about drugs which may contribute to prevalence of resistant hypertension. Detailed questions were asked regarding use of antihypertensive drugs and their doses. Patients and their relatives were asked whether the drug was taken regularly and in the doses prescribed.A brief history and clinical examination was done to assess end organ damage and further investigations were done to assess the patients.

The investigations to which the patients were subjected are as follows

Complete blood count, Creatinine, Electrolytes, RBS/FBS/PLBS (Random blood sugar / Fasting blood sugar/ Post-prandial blood sugar), Urine routine, 2 D ECHO, ECG (Electrocardiogram).

Following tests were done in select patients based on history, physical examination and findings of ***basic investigations:***

- Liver function tests, Prothrombin time, Partial thromboplastin time
- BUN (Blood urea nitrogen).
- Serum Calcium, Phosphorus, Serum Uric acid.
- Erythrocyte Sedimentation Rate.
- CPK, CPK MB (Creatinine phosphokinase).
- Lipid profile, Glycosylated Hemoglobin.
- Serum Protein electrophoresis.
- Blood and/or Sputum Culture.
- X- ray chest, other relevant X-rays.
- Color Doppler of renal arteries
- Color Doppler of carotid arteries.
- Ultrasonography of abdomen and/or pelvis.
- CT Brain, CT abdomen, HRCT chest, MRI.
- Serum Ferritin, Serum Iron studies.
- Arterial blood gas analysis, Serum Bicarbonate.
- Intravenous pyelography.
- Few select patients were evaluated for secondary hypertension by tests like vanillylmandelic acid, serum cortisol, 24 hours urinary proteins, Calcitonin, Parathyroid hormone, SerumThyroglobulin, USG chest, Vitamin D3, T3, T4, TSH/ FT3, FT4, TSH, renal Doppler studies.

Fundoscopy was done by ophthalmic examination with dilatation in all patients. Hypertensive retinopathy was assessed as per Marcus Gunn classification[16] and diabetic retinopathy was assessed as per International Clinical Diabetic Retinopathy (DR) Disease Severity Scale.[17]To assess albuminuria dipstick testing was used. A one-cross positive (1+) on dipstick testing corresponds to a urine protein value of 300 mg/l; a two cross positive (2++) corresponds to a value 1000 mg/l; and a three-cross positive (3+++) corresponds to a value 5000 mg/l. Micro-albuminuria is defined as 30-300mg protein/24 hours (dipstick trace protein only).[18]CKD was defined as either: (1) reduced excretory function with aGFR < 60 mL/min/1.73 m2 (approximately corresponding to a creatinine of >1.5 mg/dL in men or >1.3 mg/dL in women); or (2) the presence of albuminuria (>300 mg/d or 200 mg/g creatinine).[19]

Statistical Analysis

Data collected was de-identified and computed for statistical analysis. Binomial test, chi square test were applied and the p value was computed to know the statistical significance of results obtained.

RESULTS AND ANALYSIS

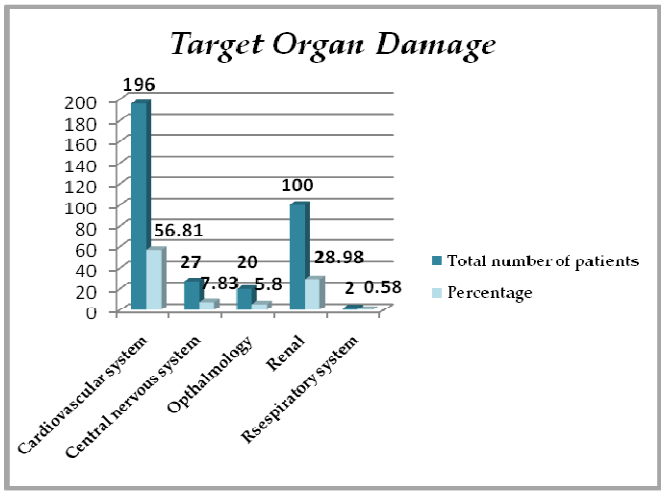
Table No: 1
Characteristics of study population

Age group	Percentage out of total female resistant hypertensive patients	Percentage out of total male resistant hypertensive patients	Percentage out of total resistant hypertensive patients
	F	M	
<30	1	3	4
	0.90%	2.50%	1.70%
31-40	3	6	9
	2.60%	5.00%	3.90%
41-50	14	17	31
	12.30%	14.30%	13.30%
51-60	32	31	63
	28.10%	26.10%	**27.00%**
61-70	30	32	62
	26.30%	26.90%	**26.60%**
71-80	29	23	52
	25.40%	19.30%	22.30%
81+	5	7	12
	4.40%	5.90%	5.20%
Total	114	119	233
	100.00%	100.00%	100.00%

Table No: 2
Target Organ Damage in Patients with Resistant Hypertension.

Target organ damage	Number of patients
Cardiovascular system	196
Left ventricular failure	12
Congestive cardiac failure	8
Unstable angina	6
Peripheral arterial disease	12
Left ventricular hypertrophy	83
Ischemic heart disease(IHD) 74, CABG done in 12 patients	74
Dialated cardiomyopathy	1
Central nervous system	27
Dementia	1
Transient ischemic attack	4
Multi infarct state	2
Intracerebral bleed	3
Cerebrovascular accident	17
Opthalmology	20
Hypertensive retinopathy	20
Renal	100
Chronic renal failure	100
Rsespiratory system	2
Pulmonary oedema	2

Figure 2
System wise Target organ damage in patients with resistant hypertension system.



84.12% of the study population (196 patients) had evidence of cardiovascular system involvement, 42.92% had renal system involvement, and 27 patients (11.58%) had central nervous system involvement. Least number of patients had evidence of ophthalmic (8.58%) and respiratory system (0.86%).This percentage doesn't add upto 100 as patients had multiple system involvement. Out of total target organs/system damaged in our study the most commonly effected system was cardiovascular system (56.81% of all target organs damaged) followed by renal (28.98%).Maximum number of patients (83) had left ventricular hypertrophy as evidenced by ECG or 2 D ECHO followed by 73 patients who had ischemic heart disease. Central nervous system involvement (7.83%) was seen in 27 patients.

Investigation Findings in Patients with Resistant Hypertension
Fundoscopy

Table No.3
Fundoscopic findings in patients with resistant hypertension.

Fundoscopic findings	Number of patients	Percentage of patients
Diabetic retinopathy	28	12.01
Hypertensive retinopathy	20	8.58
Normal	185	79.39

12.01% of patients had diabetic retinopathy followed by 8.58% having hypertensive retinopathy. 79.39% had normal fundoscopic findings. 50.64% patients (118 patients) had past H/O diabetes.

Table 4
Type of hypertensive retinopathy in the study cohort.

Hypertensive retinopathy	Number of patients
Grade I	5
Grade II	7
Grade III	5
Grade IV	3

25% of patients with hypertensive retinopathy each had grade I and grade III hypertensive retinopathy. 35% of patients had grade II hypertensive retinopathy. Hypertensive retinopathy was assessed as per Marcus Gunn classification of hypertensive retinopathy.[16]

Table 5
Comparison of fundoscopic findings in the study cohort.

Fundoscopic findings	Observed Number	Percentage	Expected Number	Residual	Chi square	df	P value
Diabetic retinopathy	28	12.01	77.7	-49.7	222.9	2	0 (Significant)
Hypertensive retinopathy	20	08.58	77.7	-57.7			
Normal	185	79.41	77.7	107.3			
Total	233	100					

Out of 233 patients, 28 (12.01%) of patients had diabetic retinopathy and 20 (8.58%) patients had hypertensive retinopathy. Application of chi-square test to the above data shows that there is a significant difference between the three parameters compared; i.e. number of patients with normal findings on fundoscopy is significantly higher than the number of patients with diabetic and hypertensive retinopathy.

Creatinine

Table 6
Comparison of resistant hypertensive patients with a creatinine of <=1.5 or >1.5.

Creatinine	Number of patients	Observed Proportion	Test Proportion	P value (by binomial patients)
<= 1.5	139	0.597	0.5	.004(a)
> 1.5	94	0.403		(Significant)
	233	1		

94 patients (40.3%) of the study cohort had a creatinine of more than 1.5.Above table shows that there was a significant difference between the two groups, i.ecreatinine<=1.5 and creatinine>1.5

Lipid profile

A strong, graded relation between raised serum cholesterol and coronary artery disease is seen with total cholesterol values above normal.[20]

Table 7
Lipid profile analysis in patients with resistant hypertension.

Lipid profile	Number of patients	Percentage of patients
Normal	80	78.4
Abnormal	22	21.6
Total	102	100

Lipid profile analysis was done in 102 patients. 22 patients out of 102 patients, showed that 21.6% had an abnormal lipid profile as per National Institutes of Health guidelines.[21, 22]

Table 8
Albuminuria in patients with resistant hypertension.

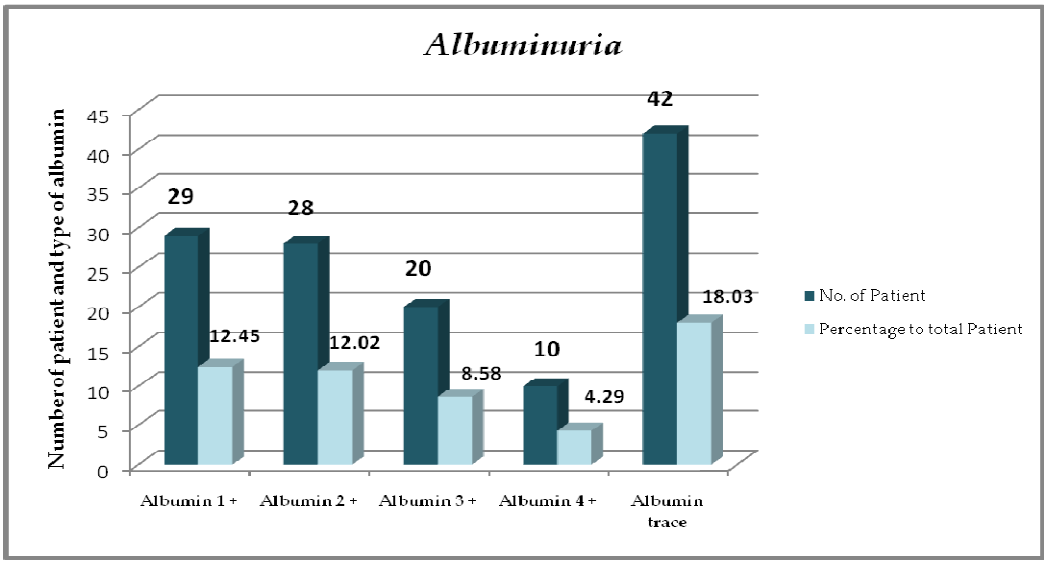


Table 9
Comparison of patients with and without albuminuria in the study cohort.

Category	Number	Observed Proportion	Test Proportion	P value (by binomial test)
Albuminuria	129	0.55	0.5	.116(a) (Not significant)
Nonalbuminuria	104	0.45		
Total	233	1		

129 patients (55.36%) had albuminuria. 42 patients (18.03%) had trace albumin followed by 12.45% patients having 1+ albumin. Almost the same number of people (12.02%) had 2+ albumin. Application of binomial test shows that number of patients without albuminuria on urine analysis is almost the same as number of patients having albuminuria. A one-cross positive (1+) on dipstick testing corresponds to a urine protein value of 300 mg/l; a two cross positive (2++) corresponds to a value 1000 mg/l; and a three-cross positive (3+++) corresponds to a value 5000 mg/l. Microalbuminuria is defined as 30-300mg protein/24 hours (dipstick trace protein only).[18]

Table 10
Comparison of albuminuria and microalbuminuria in patients with resistant hypertension.

	Number of patients	Observed Proportion	Test Proportion	P value by binomial test
Albuminuria	87	0.67	0.5	.000(a) (Significant)
Microalbuminuria	42	0.33		
Total	129	1		

Application of binomial test to the above table shows that there is a significant difference between number of patients with albuminuria and microalbuminuria among all the patients who show albumin in their urine analysis. Number of patients having albuminuria is significantly higher (67.44%) then the number of patients with microalbuminuria (32.56%). 42 patients (18.03%) had trace albumin or microalbuminuria followed by 12.45% patients having 1+ albumin. Almost the same number of people (12.02%) had 2+ albumin.

2 D ECHO

Left ventricular hypertrophy

2 D ECHO was done in 145 patients of the study cohort.

Table 11
2D ECHO findings in patients with resistant hypertension.

2 D ECHO findings	Number of patients in whom 2 D echo was done	Percentage of patients
LVH	44	30.35
IHD	27	18.62
Normal	32	22.06
Others	42	28.97
Total	145	100

Out of 145 patients with resistant hypertension in whom 2 D ECHO was done, 30.35% of patients showed evidence of left ventricular hypertrophy. 18.62% patients had evidence of ischemic heart disease. 22.06% patients had a normal 2 D ECHO finding.

DISCUSSION

In our study 84.12% of the total study population gave evidence of cardiovascular system involvement however patients had multiple system involvement. In our study also the most commonly effected system was cardiovascular system (56.81% of all target organs damaged) (Refering figure 2). Application of binomial test to the above data indicates that number of patients with CVS target organ damage was significantly higher than the number of patients with other end organ damage (Referring table 2 and Figure 2). Hence there is a need to adequately prevent and treat cardiovascular risk factors like hyperlipidemia, diabetes, hypertension, obesity, LVH, albuminuria. Patients should be encouraged to adopt healthier lifestyles. Left ventricular hypertrophy is a common effect of hypertension and a strong independent predictor of future cardiovascularevents.[23] In an analysis of Framingham study data, the next strongest predictors after age of lack of systolic blood pressure control were the presence of LVH and obesity (body mass index [BMI] >30 kg/m^2).[24]Maximum number of patients (83) out of the ones with cardiovascular system involvement had left ventricular hypertrophy as evidenced by ECG or 2 D ECHO. 74 patients out of total of 233 (31.75%) had ischemic heart disease(IHD).CABG was done in 12 of these patients indicating extensive IHD. 20 patients out of 233 had history of heart failure. Next most commonly effected system was renal (28.98% of all target organs damaged). 42.92% of the total study population had renal system involvement.Progression of renal disease and its association with hypertension and diabetes is shown by the Prospective studies collaboration and the JNC-7 report(The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure).[25, 26]The age-related loss of renal function by 1-2 ml/min/year is proportional to BP level, and the rate of GFR deterioration can accelerate to 4–8 ml/min per year if SBP remains uncontrolled.[27]The strongest predictor of treatment resistance was having CKD (Chronic kidney disease) as defined by a serum creatinine of >1.5 in ALLHAT trial.[28]NHANES III data shows that 70 percent of people with elevated creatinine values have hypertension and hypertension is difficult to control in these patients.[29] CVD is the most common cause of death in individuals with CKD, and CKD is an independent risk factor for CVD as per JNC-7 findings.[30] Findings of the United Kingdom Transient Ischemic Attack Collaborative Group[31], ALLHAT trial (the Antihypertensive and Lipid-Lowering and Treatment to Prevent Heart Attack Trial) [28,] HOPE trial (Heart Outcomes Prevention Evaluation trial) [32],Fagan et al[33], HOT (Hypertension optimum treatment) study group[34] and Goldstein et al[35] showed the association of stroke with hypertension and blood pressure. The risk of clinical complications of cerebrovascular disease including ischemic stroke, hemorrhagic stroke, and dementia increases as a function of BP levels. The incidence of ischemic or hemorrhagic stroke is reduced substantially by treatment of hypertension as per the JNC-7 study group.[26]Prospective studies collaboration group showed that for

every 20 mmHg systolic or 10 mmHg diastolic increase in BP, there is a doubling of mortality from both IHD and stroke.[36]Hypertension has been reported to be responsible for 57 per cent of all stroke deaths and 24 percent of all cardiovascular deaths in East Asians.Lowering blood pressure under 140/85 mm Hg reduces the RR of stroke by 43% and it is postulated that 10 mm reduction in systolic pressure (SBP) would result in 28% reduction in risk of recurrent stroke.[37]This is well borne out by recent studies like HOPE study, PROGRESS study (Perindopril Protection against Recurrent Stroke Study) and LIFE study (Losartan intervention for endpoint reduction in hypertension study).[38,10,39]27 patients out of a study cohort of 233 (11.58%) had evidence of central nervous system (CNS) involvement. It formed 7.83% of the total target organ damage in our study.The UKPDS (UK Prospective Diabetes Study Group) study group has shown a significant association of systolic blood pressure with diabetic retinopathy in Type 2 diabetic subjects.[4] Similar findings are seen in other studies by Wong et al[40] and Klein et al.[41]Diabetic subjects with a systolic blood pressure ≥140 mmHg were 2.8 times more likely to develop retinopathy as compared to diabetic subjects with systolic blood pressure <125 mmHg.[4]The Framingham Eye Study found a prevalence of less than 1 percent of hypertensive retinopathy among participants.[42]Prevalence rates ranged from 2 to 15 percent for various signs of retinopathy in other studies.[43, 44, 45]Two studies indicate that the incidence of various signs of retinopathy over a period of five to seven years ranges from6 to 10 percent as per Klein et al [41]and Van Leiden et al.[46]Prevalence hypertensive retinopathy in this study is 8.58%. Of all the patients with hypertensive retinopathy, grade I and grade III hypertensive retinopathy was present in 25% of patients each. 35% had grade III and 15% had grade IV hypertensive retinopathy. Use of retinal photographs instead of the traditional method of clinical opthalmoscopy as employed in this study can give a greater prevalence of hypertensive retinopathy.[40.]Patients with hypertensive retinopathy need greater vigilance in treatment of hypertension and cardiovascular risk factors. Rajeev guptaet al[47] in the Jaipur heart watch study showed an age-adjusted prevalence of hypercholesterolemiato be 28.5% in males and 27.8% in females. In this study 22 patients out of 102 patients (21.6%) in whom lipid profile was done had an abnormal lipid profile as per National Institutes of Health guidelines. CVD risk exhibits a continuous relationship with albuminuria; the presence of microalbuminuria confers a 50 percent increase in risk and the presence of macroalbuminuria, a 350 percent increase.[48]In the Modification of Diet and Renal Disease (MDRD) Study, individuals with proteinuria had slower rates of progression to ESRD if their SBP values were <130 mmHg.[49]Albuminuria and microalbuminuria are commoner in patients with severe hypertension, advanced target organ damage, or a non-dipping profile on ambulatory monitoring as per Jafferet al.[49]Microalbuminuria occurs in 11% to 40% of persons with hypertension, the prevalence increasing with age and the duration of hypertension as studied by Rossa et al.[50]Albuminuria is an independent risk factor for cardiovascular disease.[48,49]Evidence of albuminuria and microalbuminuria was shown by 55.36% of the study cohort. Of these patients 18.03% had microalbuminuriaand significantly higher number 37.33% had macroalbuminuria. This could be due to the fact that the study population has patients with difficult to control, long term hypertension.Number of patients having albuminuria is significantly higher (67.44%) then the number of patients with microalbuminuria (32.56%) in all the patients who had a positive urine dipstick test (Referring table 11).There is no significant difference in the number of patients with or without albuminuria (referring table 10). Regular screening for proteinuria in patients with hypertension may identify those patients in the early stages of renal decline and progression to CKD and cardiovascular morbidity and mortality can be lessened with timely interventions.

As per Sandoziet al[51] 28% had associated DM whereas in our study 50.64% of the population gave a history of having

diabetes.There are some limitations of our study. Although the population was generally similar in age and gender,our study did not take into account the other comorbid conditions and family history and smoking history of the patients, all of which have been shown to have predictive value in target organ damage. Moreover, it is single centered study but this study will give enormous scope for further evaluation with multi-centered study design. Important strengths of this study are the inclusion and exclusion restrictive criteria of selected patients to aid in standardized observation. For example, patients who were unaware of their anti-hypertensive drugs and patients with a recent change in antihypertensive medications and their dosage (less than a month)[8]were excluded from the study cohort.

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