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EVALUATION, RECOGNITION, MANAGEMENT AND TREATMENT OF RESISTANT HYPERTENSION

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ABSTRACT
High blood pressure is a major risk factor and better control can lead to prevention of 300,000 of the 1.5 million annual deaths from cardiovascular diseases in India. Epidemiological studies demonstrate that prevalence of hypertension is increasing rapidly in India. In the present study we found that prevalence of hypertension in Rawatsar city of Hanumangarh District of Rajasthan is increasing in men than women. We did not assess major dietary determinants of hypertension such as calorie intake, fat intake and sodium intake. Physical activity was also not accurately assessed in the study and these are study limitations. The choice of drug for the treatment of hypertension changes at short intervals. Drug utilization studies conducted at regular intervals help to guide the physician in prescribing drugs rationally. The present study was done to analyze the prescribing patterns of antihypertensive drugs in a North Indian hospital. A retrospective, cross sectional analysis of prescriptions of antihypertensive cases admitted in Medicine in-patient wards of civil hospital of Rawatsar was conducted. All the prescription files with diagnosis of essential hypertension were analyzed. Prescriptions for hypertension with other co-morbid conditions were also included. Frequency and proportions of utilization of antihypertensive medications were charted and figured. The most frequently prescribed in risk of hypertensive were: mono therapy (42.06%), (57.94%) of patients was on multiple drug therapy, the most favored fixed drug combination being diuretics with antihypertensive drug was (31.74%). The purpose of study was to examine the risk assessment of developing type 2 diabetes mellitus in patient resistant hypertensive patients. In the present study total 74 patient with essential hypertension of both sex with mean age 47.40±1.88 were recruited as per the inclusion criteria. Patients were segregated on the behalf of therapy they were using.

KEYWORDS: Hypertension, Prevalence, Prescription, Antihypertensive, Diabetes.

INTRODUCTION
Hypertension (HTN) or high blood pressure, sometimes called arterial hypertension, is a chronic medical condition in which the blood pressure in the arteries is elevated (Paul James, Suzanne Oparil et al 2014). Hypertension commonly defined as a sustained systolic blood pressure of 140 mm Hg or higher or a sustained diastolic blood pressure of 90 mm Hg. It is evidenced by numerous studies that untreated high blood pressure damages blood vessels, accelerates atherosclerosis and produces LVF Hypertrophy.

Hypertension, which affects over one billion adult's worldwide is a major risk factor for cardiovascular and renal diseases. Hypertension is the most common condition seen in primary care and leads to myocardial infarction, stroke, renal failure, and death if not detected early and treated appropriately.

Classification of blood pressure for adults by Institute for clinical system improvement (ICSI)

Classification of blood pressure for adults		
BP classification	**SBP mmHg**	**DBP mmHg**
Normal	<120	<80
Pre-hypertension	120-139	80-89
Stage 1 hypertension	140-159	90-99
Stage 2 hypertension	>160	or > 100

Type of hypertension

1. Primary hypertension
2. Secondary hypertension

1. Primary hypertension

About 95% of adults with high blood pressure have primary hypertension (sometimes called essential hypertension). The cause of primary hypertension is not known, although genetic and environmental factors that affect blood pressure regulation are now being studied. Environmental factors include excess intake of salt, obesity, and perhaps sedentary lifestyle. Some genetically related factors could include inappropriately high activity of the renin-angiotensinaldosterone system and the sympathetic nervous system and susceptibility to the effects of dietary salt on blood pressure. Another common cause of hypertension is stiffening of the aorta with increasing age. This causes hypertension referred to as isolated or predominant systolic hypertension characterized by high systolic pressures (often with normal diastolic pressures), which are found primarily in elderly people.

2. Secondary Hypertension

This pertains to the relatively small number of cases, about 5% of all hypertension, where the cause of the high blood pressure can be identified and sometimes treated. The main types of secondary hypertension are chronic kidney disease, renal artery stenosis, excessive aldosterone secretion, pheochromocytoma, and sleep apnea.

Classification of Antihypertensive drugs

1. **β-blockers:** Propranolol, Metoprolol, Atenolol, Sotalol, Nadolol, Pindolol, Esmolol, Acebutolol, Celiprolol, Nebivolol.
2. **β + α blockers:** Labetalol, Carvedilol.
3. **α – blockers:** Prazosin, Terazosin, Doxazosin, Phenoxybenzamine.
4. **Central sympatholytics:** Clonidine, Methyldopa.
5. **Ganglion blocker:** Trimethaphan.
6. **Diuretics**

I. **Thiazide:** Hydrochlorothiazide, Chlorthalidone, Indapamide
II. **High ceiling:** Furosemide, Torasemide
III. **K^+ sparing:** Spironolactone, Triamterene, Amiloride.

7. **Angiotensin converting enzyme inhibitor(ACE inhibitor):** Enalapril, Lisinopril, Ramipril
8. **Angiotensin receptor 1 blocker(ARB):** Losartan, Candesartan, Irbesartan, Telmisartan
9. **Ca^+ channel blocker(CCB)**: Verapamil, Diltiazem, Nifedipine, Amlodipine, Felodipine.
10. **Vasodilators**

I. **Arteriolar:** Hydralazine, Minoxidil, Diazoxide, Fenoldopam.
II. **Arteriolar Venous**: Sodium nitroprusside.

Others: Reserpine, Guanethidine

There is moderate evidence to support initiating drug treatment with an angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, calcium channel blocker, or thiazide-type diuretic in the nonblack hypertensive population, including those with diabetes. In the black hypertensive population, including those with diabetes, a calcium channel blocker or thiazide-type diuretic is recommended as initial therapy (Paul James, Suzanne Oparil et al 2014).The relation between the use of different classes of antihypertensive medications and the risk of incidence of type 2 diabetes is unclear.

Epidemiology of Hypertension

No communicable diseases (NCDs) accounted for 63% of global deaths in 2008 (36 million of 57 million), principally from cardiovascular diseases, diabetes, cancer and chronic respiratory diseases. Nearly 80% (28 million) of these deaths occurred in low- and middle-income countries. Addressing this burden is one of the major public health challenges facing all countries, regardless of their economic status. The general strategy to address NCDs using a public health approach is to focus on the risk factors of NCDs (WHO 2011).

As per the World Health Statistics 2012, of the estimated 57 million global deaths in 2008, 36 million (63%) were due to no communicable diseases (NCDs). The largest proportion of NCD deaths is caused by cardiovascular diseases (48%). In terms of attributable deaths, raised blood pressure is one of the leading behavioral and physiological risk factor to which 13% of global deaths are attributed. Hypertension is reported to be the fourth contributor to premature death in developed countries and the seventh in developing countries (Epidemiology of hypertension 2013).

The prevalence of hypertension in the late nineties and early twentieth century varied among different studies in India, ranging from 2-15% in Urban India and 2-8% in Rural India. (Epidemiology of hypertension 2013). As a follow up to the UN High-level meeting in September 2011, the World Health Organization (WHO) initiated a process of consultation to decide on a list of global indicators and voluntary targets for no communicable diseases. Based on extensive consultations, 25 indicators and nine targets have been agreed upon, which were submitted to the Sixty-sixth World Health Assembly for approval in May 2013. Three indicators and targets were directly relevant to hypertension (Table No.4.1). These were the age-adjusted prevalence of hypertension among adults, salt intake levels, and availability of diagnosis and medicines for hypertension at public and private health facilities (WHO 2011).

Indicator	Target
Age-standardized prevalence of raised blood pressure among persons aged 18+ years (defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg)	25% relative reduction in the prevalence of raised blood pressure or containment of the prevalence of raised blood pressure according to national circumstances
Availability and affordability of quality, safe and efficacious essential NCD medicines, including generics, and basic technologies in both public and private facilities	80% availability of affordable basic technologies and essential medicines, including generics, required to treat major NCDs in both public and private facilities
Age-standardized mean population intake of salt (sodium chloride) per day in grams in persons aged 18+ years	30% relative reduction in mean population intake of salt/sodium intake (WHO recommendation is less than 5 g of salt or 2 g of sodium per person per day)

Proposed Global Indicator and Targets for 2025 Related To Hypertension (WHO 2011) Control of the cardiovascular diseases will require modification of risk factors that have two characteristics. First, the risk factor must have high attributable risk or high prevalence or both, and secondly, most or all of the risks must be reversible cost-effectively. Blood pressure (BP) is directly associated with risks of several types of cardiovascular diseases, and the associations of BP with disease risk is continuous with large proportions of most populations having non-optimal blood pressure values. Moreover, most or all BP-related risks appear to be reversible within a few years with inexpensive interventions. In India cardiovascular diseases cause 1.5 million deaths annually. Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths. This fact is important because hypertension is a controllable disease and a 2 mm Hg population wide decrease in BP can prevent 151,000 stroke and 153,000 coronary heart disease deaths.

The WHO age-standardized estimates of the prevalence of hypertension (systolic blood pressure ≥140 mmHg OR diastolic blood pressure ≥90 mmHg OR on medication) in countries of the South East Asia (SEA) Region in 2008. All countries uniformly show a high prevalence of hypertension in their populations and males have, in general, higher blood pressure levels in these countries. The figures shown in Table 2 are estimates and, for countries such as Bangladesh, Democratic People's Republic of Korea, Maldives, Nepal and Timor-Leste where no national information was available, data from other sources have been used. Myanmar and Indonesia seem to have the highest prevalence of hypertension in the Region.

Table No: 1.3 Estimate of Age Standardized Prevalence of Raised Blood Pressure in Adults 25+ Year in the Countries of the SEA Region 2008.

COUNTRY	MEN	WOMEN	BOTH
Bangladesh	39 (28.1–49.8)b	38.1 (26.6–49.7)	38.6 (30.8–46.5)
Bhutan	40.4 (31.1–49.3)	37.4 (28.7–46.7)	39.1 (32.7–45.5)
Democratic People's Republic of Korea	38.5 (27.0–49.8)	34.3 (22.3–46.2)	36.5 (27.9–44.8)
India	36 (29.7–41.8)	34.2 (28.6–39.9)	35.2 (30.9–35.2)
Indonesia	42.7 (35.3–49.9)	39.2 (32.5–46.0)	41.0 (35.9–45.8)
Maldives	41.5 (30.3–52.7)	35.1 (23.0–47.1)	38.4 (30.1–46.6)
Myanmar	44.3 (37.7–50.5)	39.8 (33.1–46.5)	42.0 (37.2–46.8)
Nepal	38.4 (27.0–49.2)	38.7 (26.9–50.4)	38.6 (30.2–46.7)
Sri Lanka	41.9 (34.0–38.2)	37.0 (29.4–44.6)	39.4 (33.8–44.6)
Thailand	37.0 (31.3–42.5)	31.6 (26.0–37.1)	34.2 (30.0–38.1)
Timor-Leste	39.7 (28.9–50.0)	35.2 (23.8–46.9)	37.5 (29.5–45.4)
SEAR	37.6 (32.6–42.4)	35.4 (30.9–39.8)	36.6 (33.1–39.8)
Global	40.8 (37.7–43.7)	36.0 (33.3–38.6)	38.4 (36.3–40.5)

a) Raised blood pressure defined as SBP ≥140 mmHg OR DBP ≥90 mmHg OR on medication
b) Figures in parentheses are 95% confidence intervals of the estimates (WHO 2009).

Table No 1.4: Recent Indian Hypertension Prevalence Studies in Urban Indian Subjects (Bp 140/90).

				Sample size		Prevalence	
References	**Years**	**Age group in years**	**Place**	**Men**	**Women**	**Men**	**women**
Gupta et al 1995	1995	20-75	Jaipur	1415	797	29.5	33.5
Joseph et al 2000	2000	20-89	Thiruvananthapuram	76	130	31.0	41.2
Anand et al 2000	2000	30-60	Mumbai	1521	141	34.1*	
Mohan et al 2007	2001	20-70	Chennai	518	657	21.1*	
Gupta et al 2007	2003	20-75	Jaipur	550	573	36.4	37.5
Gupta et al 2004	2004	18-60	Mumbai	40067	59522	43.8	44.5
Reddy et al 2006	2006	20-70	National	11829	8039	29.3	25.2

*Gender-specific data not available. (Gupta et al 2009)

This article summarizes epidemiology of hypertension in Hanumangarh district of Rajasthan India.

Resistant hypertension

Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic. Patients with resistant hypertension are at high risk for adverse cardiovascular events and are more likely than those with controlled hypertension to have a secondary cause, which is usually at least in part reversible.

Risk associated with Diuretic therapy in resistant hypertension

Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.There are many medications available for the treatment of high blood pressure (hypertension), but finding the right one for a specific patient can be challenging. Previous research has suggested that different class of antihypertensive agents may increase the risk of type II diabetes mellitus. So the present study is designed to study the risk assessment of developing type II diabetes mellitus In resistant hypertensive patients in the population of Rawatsar city Hanumangarh district.

MATERIAL AND METHODS

Retrospective Study

The retrospective study was conducted during the period of Feb 2016 to Dec 2016, during which data on all patients visited the outdoor patients department and indoor patient department of the hospital was collected. Collected retrospective data suggested that a sufficient number of patients were available to conduct further study.

Prospective study

Total 74 Hypertensive patients were recruited for the prospective Study as per Following Inclusion Criteria. And Among these 74 recruited patients Further 20 resistant Hypertensive patients Who Were Using Diuretics Therapy along with other Antihypertensive drugs patients were followed up.

Selection criteria for subjects

Inclusion Criteria

- *Age*: 20 Year- 80 Years,
- *Genders*: Both
- According to JNC 7 an average seated home DBP > 85 mmHg and home SBP < 180 mmHg. Subjects must also have an average seated (> 5 minutes) clinic DBP between 90 mmHg and 110 mmHg and SBP < 180 mmHg
- BMI: normal range < 18.5 >24.9 kg/m^2
- Patient diagnosed with Resistent hypertension.
- Drugs: combination therapy (more than two drugs) along with one of the drug should be diuretics .

Exclusion Criteria

- Secondary hypertension
- Patient using monotherapy
- Known cardiovascular disease (including history of angina pectoris, heart failure presence of a cardiac pacemaker, history of myocardial infarction or revascularization procedure, or cerebrovascular disease, including stroke and TIA),
- Diabetes mellitus (Type 1 or 2)
- Primary renal disease
- Pregnancy or lactation
- Current treatment with NSAIDS, COX2-inhibitors, oral contraceptives or estrogen,X

The subjects will be followed up for 6 months for monitoring of blood glucose, lipid profile **Total** Cholesterol, HDL- Cholesterol and Triglycerides at the starting of study and at ending of study. During the follow up period blood pressure was monitored on monthly basis.

Ethical consideration:

The study design was approved by institutional ethics committee and all patients were informed about the aim of study and were included in the study after verbal and written consent.

Informed consent

For the protection of subjects a legally effective informed consent of the subject was obtained providing specific information about the study to subjects in a

manner comprehensive to them. The consent has two parts (a) an information seat describing the research and the nature of the participant's involvement in it and (b) a certificate of consent attesting to the participants consents. The format of informed consent is as follows.

Laboratory measurement

1) Anthropometric measurements

BMI of all 74 enrolled patients were recorded body weight was measured(to the nearest 0.5 kg) with the subjects standing motionless on the weighing scale, feet about 15 cm apart and equally distributing weight on both limbs with minimum clothes and no footwear Height was measured to the nearest 0.5 cm with the subjects standing in erect position using anthropometric rod BMI was calculated as per standard formula kg/m^2. (**Snehlata et al 2003**).

Measurement of blood pressure

Blood pressure was measured by auscultator method with use of a stethoscope and a sphygmomanometer. An inflatable cuff was placed around the upper left arm, at the same vertical height as the heart measurement was made in rest in a seating Position (JNC 7).

Blood sample collection and storage

The sample (5ml) was collected in sterile ethylene demine tetra acetate (EDTA) coated tube (2.5 mmole as an anticoagulant)

Measurement of blood sugar

Blood glucose of the patients was monitored at the starting of therapy and after 6 months of drug therapy by (GOD POD method) Dubois et al., (1956).

Measurment of Lipid Profile

Estimation of lipid profile, Total Cholesterol, HDL and Triglycerides was done by phosphotungstic Acid Method.

Biostatical Interpretation

All data was analyzed by using Student t-Test $P<0.05$ was considered as level of significance.

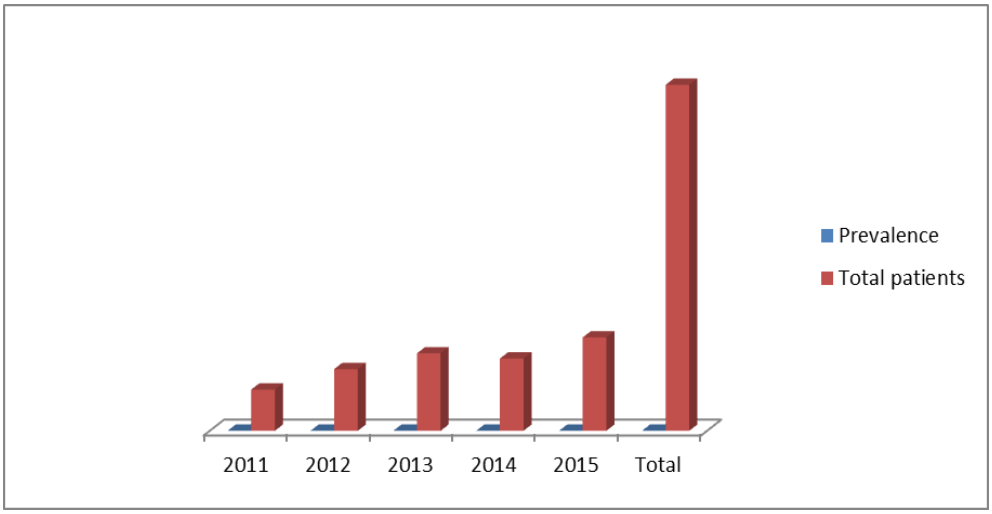
RESULT AND DISCUSSION

Retrospective Study

In the year 2011 total visited patients were 83829 and among these 383were hypertensive patients. Prevalence of hypertension in 2011 was 0.457%. In the year 2012 total visited patients were 125314 and hypertensive patients were 588. Prevalence of hypertension in 2012 was 0.469%. In the year 2013 total visited patients were 157416 and hypertensive patients were 1689. Prevalence of hypertension in 2013 was 1.073%%. In the year 2014 total visited patients were 146707 and hypertensive patients were 1410. Prevalence of hypertension in 2014 was 0.961%. In the year 2015 total visited patients were 189688 and hypertensive patients were 1833. Prevalence of hypertension in 2015 were 0.966%.. The present study showed that overall prevalence of hypertension has increased.

Retrospective Study

YEAR	TOTAL PATIENTS	TOTAL PATIENTS OF HYPERTENSION	PREVALENCE
2011	83829	383	**0.457%**
2012	125314	588	**0.469 %**
2013	157416	1689	**1.073 %**
2014	146707	1410	**0.961 %**
2015	189688	1833	**0.966 %**
Total	702954	5903	**0.840%**



Retrospective Study

Prescription pattern

Among 31 hypertensive patient 8 were using monotherapy and 23were using combination therapy. Among 23 patient were using combination therapy 16 were using 2 drugs. And 7 were using more than 2 drugs. Among patient using combination of 3 drugs 6 patient are using amlodipine, 4 patients are using AT Receptor blocker and 3 patients are using β-blocker.

Prescription pattern

THERAPY	NUMBER
Mono	8
Combination of 2 drugs	16
Combination of 3 drugs	7

Anthropometric

From 74 patients diagnose with hypertension avg BMI was 21.60±0.37. from the 74 patient 13(17.56%) were using alcohol smoker were 10 (13.51%) and 8 patient were diagnosed for hypertension along with other disorder. Among hypertensive patient male BMI 21.93±0.49 Female BMI was 23.23±1.17. table no. 3 showing anthropometric parameter of hypertensive patients.

Anthropometric study

Prospective study

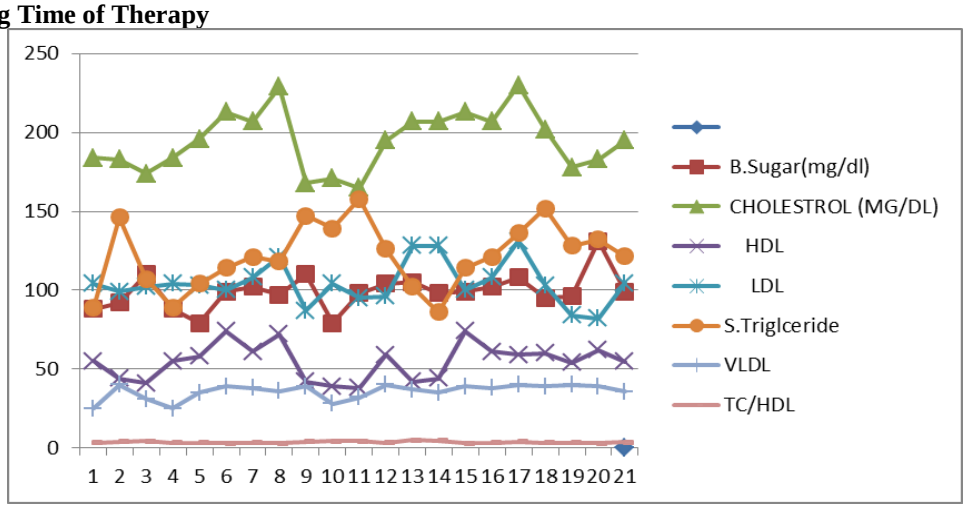
During Feb 2016 to Dec. 2016 Total from 31 Resistant Hypertensive Patient Using Combination of 3 Anti hypertensive agent 20 patients were using diuretics along with other combination of anti hypertensive agent.

N	20
Age	42.7±9.55
Male	20
Female	0
BMI	21.43±4.79
Alcohal	6(1.2%)
Smoker	5 (1.0%)
Hypertension with other disorders	0
Hypertensive male BMI	21.43±4.79
HYPERTENTION FEMALE BMI	0

Prospective study

B.Sugar (mg/dl)	CHOLESTROL (MG/DL)	HDL	LDL	S.Triglceride	VLDL	TC/HDL	LDL/HDL
88	184	55	104	89	25	3.35	2.23
92	183	44	99	146	40	4.16	4.5
110	174	41	102	107	31	4.24	3.78
88	184	55	104	89	25	3.35	2.2
79	196	58	103	104	35	3.38	2.75
99	213	74	100	114	39	2.88	2.6
102	207	61	108	121	38	3.3	3.11
97	229	72	121	118	36	3.18	2.5
110	168	42	87	147	39	4	4.64
79	171	39	104	139	28	4.38	3.59
98	165	38	95	158	32	4.34	4.21
104	195	59	96	126	40	3.31	3.39
105	207	42	128	102	37	4.93	4.44
98	207	44	128	86	35	4.7	3.97
99	213	74	100	114	39	2.88	2.63
102	207	61	108	121	38	3.39	3.11
108	230	59	131	136	40	3.9	3.39
95	202	60	103	152	39	3.37	3.25
96	178	54	84	128	40	3.3	3.7
131	183	62	82	132	39	2.95	3.14
99	194.8	54.7	104.35	121.45	35.75	3.6645	3.3565

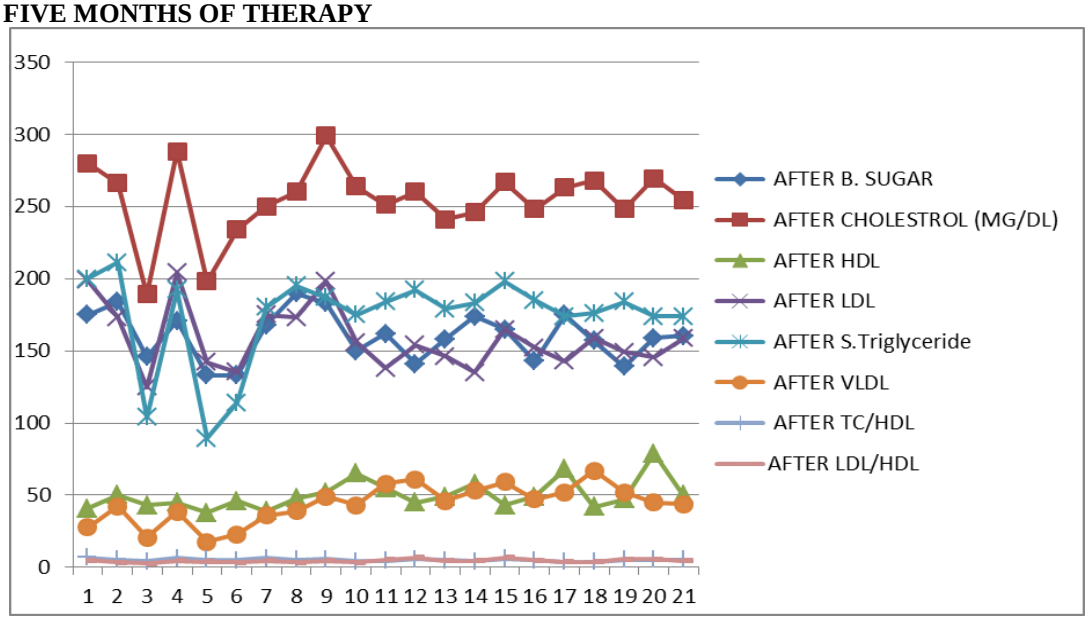
At the starting Time of Therapy



At the starting Time of Therapy

AFTER B. SUGAR (MG/DL)	AFTER CHOLESTROL (MG/DL)	AFTER HDL	AFTER LDL	AFTER S.Triglyceride	AFTER VLDL	AFTER TC/HDL	AFTER LDL/HDL
175	280	41	199	200	27.8	6.82	4.85
184	266	50	173	211	42.2	5.32	3.47
145.9	189	43	125	104	20.8	4.3	2.9
171	288	45	204	192	38.4	6.4	4.54
133	198	38	142.2	89.4	17.8	5.2	3.7
133	234	46	135.2	114	22.8	5	3.5
168	250	39	175	180	36	6.41	4.48
190	260	48	173	195	39	5.41	3.6
183	299	52	198	187	49	5.75	4.71
150	264	65	156	175	43	4.06	3.3
162	251	55	138	184	58	4.56	5.27
141	260	45	154	192	61	5.78	6.77
158	241	49	146	179	46	4.92	4.69
174	246	58	135	183	53	4.24	4.56
165	267	43	165	198	59	6.21	6.86
143	248	49	152	185	47	5.06	4.79
174.9	263	68	143	174	52	3.87	3.82
157	267.8	42	158.8	176	67	3.87	3.82
139	248	47	149	184	52	5.28	5.53
159	269.4	78.9	145.5	174	45	5.28	5.53
160.29	254.46	50.095	158.335	173.82	43.84	5.187	4.5345

AFTER FIVE MONTHS OF THERAPY



AFTER FIVE MONTHS OF THERAPY

Comparison between Clinical Data at the starting of therapy and after Five month of therapy:-

In the end of study after 5 month clinical data of Resistant hypertensive patients was compared with the data at the time of starting of therapy, Blood glucose, Cholestrol, HDL, LDL, S. Triglyceride, VLDL a significant difference was observed. as observed data shows a significant difference in Blood Glucose level after 5 months of antihypertensive therapy showed that use of diuretic agent may be responsible for metabolic disturbance patient of resistant hypertension.

Comparison Between At the Stating Time of Therapy and After Five Months of Therapy.

Clinical Parameter	At The starting of Therapy	After 5 month of Therapy	P value
Blood sugar	99±22.14	160.±35.85	<0.0001****
CHOLESTROL (MG/DL)	194.8±43.4	254.46±57.57	<0.0001****
HDL	54.7±12.23	50.09±35.42	0.218ns
LDL	104.35±23.34	158.33±35.42	<0.0001****
S.Triglceride	21.45±27.14	173.82±38.88	<0.0001****
VLDL	35.75±7.99	43.84±9.98	0.0066**
TC/HDL	3.66±.81	5.18±1.15	<0.0001****
LDL/HDL	3.33±0.74	4.53±1.01	0.0005***

(Mean ±SEM, ns –non significant, *-significant, ** -very significant, *** -extremely significant)

CONCLUSION

From the current retrospective study carried out at Rawatsar, Distt Hanumangarh it can be concluded that there is an increasing trend in the prevalence of hypertension as it is evident that number of hypertensive patients has increased to 8.94 % in the year 2014. A slight decrease in the number of patients suffering from hypertension as compared to the year 2015 is insignificant.From the prospective study of Resistant hypertension is defined as blood pressure that remains above goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic Studies observe the pharmacological treatment of antihypertensive drugs like beta adrenergic drug, calcium channel blocker, diuretics and ACE inhibitor may worsen the insulin resistance and associated with metabolic abnormalities in lipid and carbohydrate metabolism and contribute to the type-2 diabetes mellitus In the present study we also observed similar results as significant difference in Blood Glucose level after 5 months of antihypertensive therapy was also observed by us.

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