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The association of hyperuricemia with hypertension has long been recognized with early investigators such as Frederick Mahomed, Alexander Haig, and Nathan Smith Davis, hypothesizing that uric acid might be a cause of hypertension or renal disease. Uric acid is thought to play a pathogenic role in hypertension mediated by several mechanisms such as inflammation, vascular smooth muscle cell proliferation in renal microcirculation, endothelial dysfunction and activation of the renin–angiotensin–aldosterone system. Furthermore, studies have shown that in overweight and obese subjects, hyperinsulinemia secondary to insulin resistance may enhance the reabsorption of uric acid and thus contribute to the association of hyperuricemia with hypertension. The increasing prevalence of hypertension and non-communicable diseases such as cardiovascular diseases will be the major causes of morbidity and mortality in developing countries, accounting for almost four times as many deaths as from communicable diseases warrant that individual risk factors of hypertension and the existence of any possible interaction between them as this will improve the efficiency of prevention strategies the results linking uric acid and hypertension are not entirely consistent.

Uric acid is a byproduct of purine metabolism produced in blood from endogenous purine (2/3) substances or from diet (1/3). Alcoholic and high-purine foods consumption, low water consumption and poorly exercising are contributing factors responsible for hyperuricemia. Its normal level in the body is <7 mg/dl in men and <6 mg/dl in women, based on the limits of solubility of the monosodium urate in serum at a temperature of 36.8°C. The amount of urate in the body is affected by the balance of its production and excretion. Conditions associated with urate overproduction and reduced renal excretion also cause hyperuricemia. Urate overproduction, which is the primary mechanism for hyperuricemia in 10 percent of the general population, is seen in conditions with high cellular turnover, genetic errors, and tumor lysis syndrome. Inefficient urate excretion, which accounts for 90 percent of cases of hyperuricemia, occurs in renal insufficiency of any cause and with certain medications. Hyperuricemia is a level of uric acid in the blood that is abnormally high. Men have a greater risk of developing hyperuricemia than women in all age groups, although the sex ratio tends to equalize with advancing age. Hyperuricemia is becoming
an increasing problem all over the world with a steady increase in its prevalence.\textsuperscript{14}

A randomized, placebo-controlled, double-blind, interventional study, which targeted young obese patients with prehypertension, demonstrated that an inhibitor of uric acid production (allopurinol) and an accelerator of uric acid excretion (probenecid) both lead to decreased blood pressure.\textsuperscript{15} A systematic review has studied data available in MEDLINE, Embase, and the Chinese Biomedical Literature Database, which also suggests that hyperuricemia could slightly increase the risk of cardiovascular diseases and diabetes in patients with hypertension.\textsuperscript{16}

A recently published retrospective observational study based on a registered database found that allopurinol use was associated with a significantly lower risk of both stroke (HR=0.50; 95\% CI, 0.32–0.80) and cardiac events.

Hyperuricemia often accompanies metabolic syndrome, hypertension, diabetes, dyslipidemia, chronic renal disease, and obesity, and the serum uric acid level is known to vary significantly depending on meals, lifestyle, gender, and previous use of diuretics.\textsuperscript{17}

Hyperuricemic patients with hypertension are more likely to have uncontrolled BP despite successful treatment with antihypertensive agents. In particular, the risk of uncontrolled BP related with hyperuricemia was prominent in hypertensive patients without metabolic syndrome. Uric acid levels need to be considered in strategies for BP control in hypertensive patients, even with good adherence to antihypertensive medications.\textsuperscript{18}

The article “Uric Acid and Hypertension” in this issue of the Journal highlights the increasing prevalence of Hyperuricemia in hypertensive and diabetic patients.

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3. Davis N. The cardiovascular and renal relations and manifestations of gout. \textit{JAMA} 1897; 29:261-262.


Eyes in Hypertension

R. R. Chaudhary

ABSTRACT
Eye health is the ignored subject. People only go to Ophthalmologist only when they feel difficulty in vision. The ocular effect of hypertension is caused from hypertension’s impact on the ocular vasculature. There may be ocular changes in an asymptomatic patient with hypertension. There may be acute and chronic hypertensive changes in the eyes, respectively, acute changes from malignant hypertension and chronic changes from long-term, systemic hypertension. The medical management for hypertensive optic complications includes evaluation of secondary causes, lifestyle changes and pharmacotherapy.

INTRODUCTION
“Eye” is the window to the world’s beauty. This world is full of scenic wonders, mesmerizing landscapes, enchanting people and charismatic views which we see through our eyes. Out of the five senses eyes are the most dominant one that enable us to enjoy the mystical beauty of this world. Visual impact is the highest on our minds. We follow the glamour stars with zeal, love the places that are beautiful and like the food that’s well placed. Eyes play a very important role in all these endeavors. But, are we paying complete attention towards the health of our eyes?

Eye health is the most ignored subject. People generally go to an Ophthalmologist only when they feel difficulty in seeing. Whereas there are many symptoms like repeated headaches, difficulty in focusing, dryness of eyes are also indicators that your eyes are not healthy and fine. Only vision correction with eyeglasses might not be good option. The cause can be much serious requiring through analysis and treatment.

ANATOMY
The ocular effects of hypertension arise from hypertension’s impact on the ocular vasculature.

Retinal arteries are micro arterioles with no internal elastic lamina or continuous muscular coat and its caliber is 100µm calibers. The changes in the luminal diameter of the arterioles are the most important component in regulating systemic arterial blood pressure. 50% decrease in the lumen results in a 16-fold increase in the pressure because the resistance of flow is equivalent to the fourth power of the diameter.¹

Retinal arterioles and capillaries exhibit autoregulatory mechanisms and tight junctions to maintain the blood-ocular barrier and are similar in anatomy to cerebral vessels. Choroidal arterioles and capillaries have fenestrations with no blood-ocular barrier and do not exhibit autoregulatory mechanisms. Optic nerve-head vessels exhibit autoregulatory mechanisms but an incompetent blood-ocular barrier as a result of the peripapillary choroidal vessels.

The retina, the choroid, and the optic nerve have vascular anatomic differences between each other so these anatomic regions respond differently to hypertension. They represent together the clinical picture of the ocular response to systemic hypertension.²

**HYPERTENSIVE VASCULAR CHANGES**

Systemic hypertension produces chronic changes resulting in atherosclerosis and arteriosclerosis predominate in the retina. The normal light reflex of the retinal vasculature is formed by the reflection from the interface between the blood column and vessel wall. Initially, the increased thickness of the vessel wall causes the reflex to be more diffuse and less bright.

Sclerosis and hyalinization when progress causes the reflex to be more diffuse and the retinal arterioles to become red-brown and this is known as copper wiring. Further progression of sclerosis of the retinal vasculature leads to increased optical density of the retinal blood vessel walls.

This phenomenon is known as sheathing of the vessels and visible on ophthalmoscopy. After the involvement of anterior surface, the entire vessel appears opaque (pipe-stem sheathing). Fluorescein angiography can demonstrate the patency of such vessels.

When wall is encircled by sheathing, a silver-wire vessel is produced. Diffuse vasospasm causes generalized attenuation of the arterioles, which occurs when a significant elevation of blood pressure has persisted for long period. A relationship between the narrowing of the caliber of the arteriole and the height of the diastolic pressure has been noted.

The narrowing of the arterioles is caused by increased intraluminal pressure either in the retinal arterioles or in the central artery of the retina. Focal narrowing occurs from spasm of local areas of the vascular musculature and edema in and around the vessel wall which can become permanent with fibrosis.

In arteriovenous nicking (the Gunn sign), impeded circulation results in a dilated or swollen vein peripheral to the crossing, causing hourglass constrictions on both sides of the crossing and aneurismal-like swellings. The arteriole and venous basement membranes are adherent with shared collagen fibers at the crossing points.

The crossing phenomenon is caused by thickening of the basement membrane and the media of the arteriole in hypertension which impinge on the vein. Sclerosis may shorten or elongate retinal arterioles, with the branches coming off at right angles. This change in length deflects the veins at the common sheath and changes the course of the vein (Salus sign).³

**Acute Hypertensive Retinal Changes (Hypertensive retinopathy)**

Changes in the retinal circulation in the acute phase of hypertension primarily involve the terminal arterioles rather than the main retinal arterioles. Main retinal arteriole changes are seen and recognized as a response to chronic systemic hypertension. First described by Hayreh, focal intraretinal periarteriolar transudates (FIPTs) are observed in malignant arterial hypertension. Consisting of small, white, focal, oval lesions deep in the retina, they are associated with major arteriole vessels and are among the earliest retinal lesions caused by malignant hypertension. Focal intraretinal periarteriolar transudates (FIPTs) may be related to dilation of terminal arterioles and the breakdown of autoregu-
latory mechanisms due to an acute, malignant increase in blood pressure.4

This results in the breakdown of the blood-retinal barrier, allowing transudation and accumulation of macromolecules. Focal intraretinal periarteriolar transudates (FIPTs) are not associated with capillary obliteration and are not cotton-wool spots. They are hyperfluorescent and leak on fluorescein angiography.

Fluffy, white lesions found at the level of the nerve fiber layer, inner retinal ischemic spots, also called cotton-wool spots, are located more commonly at the posterior pole and are related to the distribution of the radial peripapillary capillaries. These cotton-wool spots last approximately 3-6 weeks before fading away. Their fluorescein angiographic appearance is hypofluorescent due to nonperfusion and capillary dropout. Capillary obliteration results in the development of microaneurysms, shunt vessels, and collaterals.5

Hayreh noted that the development of blot retinal hemorrhages is neither an early nor a conspicuous finding associated with malignant hypertension.6

**Acute Hypertensive Choroidopathy**

The effects of hypertension on the choroid are related to the anatomic and functional differences found in the choroidal vasculature. Sympathetic innervation makes terminal arterioles more susceptible to vasoconstriction. Fenestrations in the capillaries and the consequent lack of a blood-ocular barrier allow free passage of macromolecules.

No autoregulation increase susceptibility to elevated perfusion pressures. Acute ischemic changes in the choriocapillaris and overlying retinal pigment epithelium result in acute, focal retinal pigment epithelium lesions. These focal, white spots at the level of the retinal pigment epithelium are similar to focal intraretinal periarteriolar transudates (FIPTs). Serous retinal detachments, which preferentially affect the macular region, cause neurosensory retinal detachments (NSRD) and cystoid macular edema. Ischemic damage to the retinal pigment epithelium leads to breakdown of the blood-retinal barrier.

Hayreh observed that the presence of neurosensory retinal detachments (NSRDs) was correlated to the degree of choroidal circulation disruption.

**Acute Hypertensive Optic Neuropathy**

Optic disc edema is a primary manifestation of hypertensive optic neuropathy. The blood supply to the optic nerve arrives via posterior ciliary arteries and peripapillary choroidal vessels. Vasoconstriction and choroidal ischemia in the setting of malignant hypertension result in optic disc edema and axoplasmic flow stasis.

**Chronic Hypertensive Retinal Changes**

Chronic hypertensive changes to the retina include the following:7

- Arteriolosclerosis – Localized or generalized narrowing of vessels.
- Copper wiring and silver wiring of arterioles as a result of arteriolosclerosis.
- Arteriovenous (AV) nicking as a result of arteriolosclerosis.
- Retinal hemorrhages.
- Nerve fiber layer losses.
- Increased vascular tortuosity.
- Remodeling changes due to capillary nonperfusion, such as shunt vessels and microaneurysms.

**Chronic Hypertensive Choroidal Changes**

- Retinal pigment epithelium changes include the development of diffuse pigmentary granularity and a moth-eaten appearance.
- Areas of retinal pigment epithelium clump and atrophy (Elschnig spots), forming from the focal acute white retinal pigment epithelium lesions. Triangular patches of atrophy result from the occlusion of a larger caliber choroidal vessel.
Chronic Hypertensive Optic Nerve Changes

- Optic disc pallor develops in chronic hypertension.
- Most patients are asymptomatic and commonly present with headaches and blurred visions.

Extravascular lesions of the retina include the following:

- Microaneurysms
- Retinal hemorrhages
- Retinal and macular edema
- Retinal lipid deposits
- Cotton-wool spots
- FIPT (focal intraretinal periarteriolar transudates).

The degree and the duration of hypertension are the primary determinants of hypertensive retinopathy. These changes are not unique for hypertension and may be seen in other diseases with vascular risk factors, such as diabetes. The retinopathy may also be more severe and more progressive when diabetes and hypertension are associated, other factors, such as hyperlipidemia, may make the retinopathy worse as well.

TREATMENT AND MANAGEMENT

Medical care for hypertensive optic complications involves evaluation of secondary causes and lifestyle changes and pharmacotherapy.

In the presence of hypertensive optic neuropathy, a rapid reduction of blood pressure may pose a risk of worsening ischemic damage to the optic nerve.

The optic nerve demonstrates autoregulation, so there is an adjustment in perfusion based on the elevated blood pressure.

A precipitous reduction in blood pressure will reduce perfusion to the optic nerve as a result of their autoregulatory changes, resulting in infarction of the optic nerve head.

Surgical management is indicated to address certain secondary causes of systemic hypertension.

CONCLUSION

1. Ocular changes can be the initial finding in an asymptomatic patient with hypertension.
2. In other instances, a symptomatic patient may be referred to an ophthalmologist for visual problems caused by hypertension.
3. Prompt and accurate diagnosis of hypertensive retinopathy, especially when associated with malignant hypertension, is necessary to avoid visual and systemic morbidity.
4. In addition, appropriate patient education regarding proper diet, exercise, and medication is crucial.

REFERENCES

Prevalence of Abnormal Blood Pressure Patterns in Normotensive Type 2 Diabetes Mellitus Patients Using Ambulatory Blood Pressure Monitoring (ABPM)

Ashwin Vijayakumar Nair, R Chandni, Shajit Sadanand, NK Thulaseedharan

BACKGROUND
Ambulatory blood pressure monitoring (ABPM) has now become the standard for detection of blood pressure. ABPM provides more accurate measurement of blood pressure and helps in detecting masked or white coat hypertension, ABPM has been found to be useful for predicting risk of cardiovascular morbidity and mortality.

Blood pressure variability (BPV), Morning blood pressure surge (MBPS) and Nocturnal non-dipping are the three parameters used to predict increased cardiovascular risk. BPV is the strongest indicator of cardiovascular disease (CVD) and for developing target organ damage in patients with diabetes or hypertension. We looked at diabetic patients with normal clinic BP to look for BPV, Non-dipping pattern and Morning blood pressure surge.

OBJECTIVES
1. Find the prevalence of blood pressure variability (BPV), nocturnal non-dipping, morning surge in patients without hypertension using ABPM.
2. To find a correlation between these ABPM parameters and BMI, HbA1c, LVH, Urine albumin excretion, diabetic retinopathy etc.

METHODS
70 diabetic patients coming to the OP department of Kozhikode medical college, and fulfilling the inclusion criteria were enrolled in study.

Inclusion criteria was kept as type 2 diabetes patient with clinical BP <140/90 and not on any anti-hypertensive drug. The duration of diabetes should be more than 5 years and patient should not have any symptoms or signs suggestive of macrovascular-complications of diabetes.

These patients’ physical examination and baseline investigations were done. They were put on ABPM for 24 hours and data collected. Diurnal index, morning surge, mean SBP, mean 24 hour blood pressure, 24 hour- weighted standard deviation were the main parameters calculated. Blood pressure variability was
defined as 24-hr weighted standard deviation of ≥ 10mm/hg.² Nocturnal non dipping was defined as less than 10% fall in night time mean blood pressure and morning blood pressure was defined as more than 20% rise in blood pressure 2 hours after rising when compared to night time average sleep.⁴⁵

The data was analysed using SPSS software version 20.0. All counts were expressed as percentage and chi-square test was applied to look for association of the categorical data.

RESULTS
70 patients were enrolled in the study, who had h/o type 2 DM for > 5 years and normal clinical blood pressure. There were total 38 males and 32 females in the study, average age was 51.02 years. Mean duration of diabetes was 9.6 years and mean HbA1c levels was 7.9%. Mean systolic blood pressure (SBP) was 118mm hg and mean diastolic blood pressure (DBP) was 69mm hg. Prevalence of BPV was 45.71% that is, 32 out of 70 subjects had 24 hr weighted SD ≥ 10mmhg. Prevalence of non-dipping of nocturnal BP was seen in 61.43% of our study subjects (41 out of 70 subjects), Morning surge was seen in 51.14% of study subjects (36 out of 70 subjects) (Figure 1, Table 1).

The relationship between U.ACR (urinary albumin creatinine ratio) and BPV was found to be statistically significant with a p value of less than 0.1, as 90.63% of patients with BPV had micro-albuminuria (Figure 2).
mass index) and BPV was also found to be statistically significant (p value <0.1), 90.83% of patients with BPV had a BMI of more than 23 (Figure 3). Other variables i.e age, sex, hbA1c, diabetic retinopathy, LVH on ecg, duration of diabetes and waist circumference did not yield significant correlation.

On analysis of variables with nocturnal non-dipping pattern, none of the variables had a significant correlation (Table 2). Morning blood pressure surge and BMI was found to be stastically significant with p value of <0.1, 91.6 of patient with morning blood pressure surge had a BMI > 23. Rest of the biochemical and physical parameters had no significant correlation.

<table>
<thead>
<tr>
<th>Table 1: Profile of patients with morning blood pressure surge</th>
<th>Numbers (%)</th>
<th>P value (&lt;0.1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>26 (72)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>10 (28)</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>26 (72)</td>
<td>0.12</td>
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<tr>
<td><strong>Overweight or obese</strong></td>
<td><strong>33 (91.6)</strong></td>
<td><strong>0.06</strong></td>
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<tr>
<td>hbA1c</td>
<td></td>
<td>0.35</td>
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<tr>
<td>&lt;7</td>
<td>11 (30.5)</td>
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</tr>
<tr>
<td>7-9</td>
<td>20 (55.5)</td>
<td></td>
</tr>
<tr>
<td>&gt;9</td>
<td>5 (14)</td>
<td></td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>20 (55.5)</td>
<td>0.48</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>20 (55.5)</td>
<td>0.12</td>
</tr>
<tr>
<td>5-10 years</td>
<td>19 (54)</td>
<td></td>
</tr>
<tr>
<td>11-20 years</td>
<td>14 (39)</td>
<td></td>
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<tr>
<td>&gt;20 years</td>
<td>3 (7)</td>
<td></td>
</tr>
<tr>
<td>LVH</td>
<td>1 (2)</td>
<td>0.96</td>
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<tr>
<td>Atheromatous plaque</td>
<td>3 (7)</td>
<td>0.22</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>16 (44)</td>
<td>0.56</td>
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<table>
<thead>
<tr>
<th>Table 2: Profile of patients with nocturnal non-dipping pattern</th>
<th>Numbers (%)</th>
<th>P value (&lt;0.1)</th>
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</thead>
<tbody>
<tr>
<td>Males</td>
<td>22 (51.16)</td>
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<tr>
<td>Females</td>
<td>21 (48.84)</td>
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<tr>
<td>Microalbuminuria</td>
<td>33 (76.74)</td>
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<tr>
<td>Overweight or obese</td>
<td>30 (42)</td>
<td>0.17</td>
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<tr>
<td>HbA1c</td>
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<td>0.49</td>
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<td>&lt;7</td>
<td>9 (20.93)</td>
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<td>7-9</td>
<td>27 (62.79)</td>
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<tr>
<td>&gt;9</td>
<td>7 (16.28)</td>
<td></td>
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<tr>
<td>Diabetic retinopathy</td>
<td>21 (49)</td>
<td>0.38</td>
</tr>
<tr>
<td>Duration of diabetes</td>
<td>21 (49)</td>
<td>0.40</td>
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<td>5-10 years</td>
<td>24 (55.8)</td>
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<td>11-20 years</td>
<td>16 (37.2)</td>
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<td>&gt;20 years</td>
<td>3 (7)</td>
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<tr>
<td>LVH</td>
<td>1 (4)</td>
<td>0.70</td>
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<tr>
<td>Atheromatous plaque</td>
<td>2 (6)</td>
<td>0.70</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>12 (28)</td>
<td>0.84</td>
</tr>
</tbody>
</table>

**DISCUSSION**

In our study, there was a significant prevalence of blood pressure variability (BPV), non-dipping nocturnal blood pressure (ND) and morning blood pressure surge (MBPS)-45.71%, 61.43% and 40% respectively. All the patients in our study were clinically normotensive with minimal duration of diabetes for 5 years. Hence, it’s interesting to note that without hypertension, diabetes itself results in abnormal blood pressure patterns that lead to increased future risk of cardiovascular morbidity and mortality. Blood pressure variability was found in 32 patients out of 70. These patients had a 24 hr weighted SD of ≥ 10mmhg, which suggested increased risk of TOD in these patients even without accompanying hypertension. As suggested by Bell et.al that BPV in diabetes patients could be a result of accelerated vascular ageing and decreased large vessel compliance. Also loss of baroreflex sensitivity secondary to diabetic autonomic neuropathy can lead to increased blood pressure variability. The correlation between BPV and urinary ACR was found to be statistically significant with 28 out of 32 patients having micro-albuminuria, which hasn’t been shown in previous studies. Lot of studies have shown correlation between microalbuminuria and nocturnal non-dipping but blood pressure variability hasn’t been shown. Whether BPV predisposes a patient to develop micro albuminuria or vice-versa is still not clear and debatable. BMI was also found to have significant correlation with 29 out of 32 patients having a BMI of more than 23 i.e. overweight. This implicit BMI as one of the causative factors that increases BPV and the
possible role of weight loss and diet modification to reduce BPV in diabetic patients. This was in contrast to Hermida et al.'s findings, in which they found BPV to be independent of BMI but correlated with waist circumference, whereas it’s vice versa in our study.

Nocturnal blood pressure is suggested to be the true BP without the environmental and emotional influences as seen in daytime BP. In our study we found that 41 out of 70 patients had a non-dipping or rising pattern of nocturnal blood pressure. Most of the studies have shown significantly increased risk of cardiovascular as well as all-cause mortality in such patients. It’s one of the most common blood pressure patterns in diabetes patients, as shown by Sadeghi et al. in which 92 patients out of 114 diabetes patients had a non-dipping pattern irrespective of blood pressure status. Urinary micro-albuminuria has been found to have a strong correlation with non-dipping status with the later found to be responsible for micro-albuminuria. But in our study 33 out of 41 patients had micro-albuminuria but this relation could not be proven statistically (p value > 0.1). Surprisingly, half of the patients with non-dipping pattern had duration of diabetes less than 10 years, therefore duration of diabetes did not influence non-dipping blood pattern. But the correlation could not be proved statistically. There was also no correlation between non-dipping status and parameters such as hbA1c levels, BMI, diabetic retinopathy or waist circumference.

The third abnormal blood pressure pattern that we studied was morning blood pressure surge (MBPS). It’s still the least understood of all the ABPM terms and blood pressure pattern. Still no consensus has been reached with respect to its definition. In our study we took it as >20% increase in mean waking up BP after 2 hours when compared to average night time BP. Using this definition we found that 36 out of 70 patients i.e. 51.14% of patients had MBPS. It’s pathogenesis could be explained by abnormal or surge in RAAS activation and increased sympathetic activity in diabetes patients, possibly secondary to autonomic dysfunction and hyperinsulinaemia. MBPS is associated with left ventricular hypertrophy, left ventricular diastolic dysfunction, myocardial ischemia and increased QTC and QTC dispersion. In diabetics, it is associated with albuminuria. In our study a strong correlation was found between BMI and MBPS, with 33 out of 36 patients having a BMI of more than 23 (overweight), therefore again re-emphasizing the role of weight loss and diet modification in prevention of cardiovascular morbidity and mortality. Other parameters such as micro-albuminuria, duration of diabetes, waist circumference, retinopathy, hbA1c levels, age, and gender did not show any correlation.

**CONCLUSION**

Hence, we concluded that BPV, non-dipping nocturnal BP and morning blood pressure surge can be present even without hypertension in diabetic patients, thereby contributing to increased CVD morbidity and mortality. The prevalence of these three abnormal blood pressure patterns was quite high in diabetic population than was expected. BMI was a significant factor contributing to increased risk of Blood pressure variability and morning blood pressure surge.

**REFERENCES**

Association of Preexisting Hypertension with the Morality in Patients with Systolic Heart Failure in Taiwan: The TSOC-HFrEF Registry

Fan-Chun Meng*a,c, Yi-Hwei Li*a, Gen-Min Lin*a,b,c,d, Chin-Sheng Lin*a, Shih-Ping Yang*a, Wei-Hsiang Lin*a,*

ABSTRACT

Purpose: To investigate the association of preexisting hypertension at admission with the morality in patients with systolic heart failure (HF).

Method: We prospectively investigated the association of preexisting hypertension with the mortality among 1351 patients with HF in Taiwan during an average 12 months (range: 8 months-18 months) follow-up period. A multivariate cox regression analysis for the overall cohort and a subgroup analysis by age were performed.

Results: After adjustment for all potential risk factors, the associations of preexisting hypertension with cardiovascular mortality were significantly reduced in the overall cohort and those aged less than 65 years (hazard ratios (HR): 0.53, 95% confidence intervals (CI): 0.33-0.84, and 0.28, 95% CI: 0.11-0.67, respectively). However, the associations with all-cause mortality were not significantly different in these two groups (HR: 0.77, 95% CI: 0.54-1.09, and 0.59, 95% CI: 0.32-1.07, respectively). Furthermore, the associations were all nonsignificant in the patients aged older than 65 years.

Conclusion: Preexisting hypertension have an inverse association with cardiovascular mortality/in the Asian patients with systolic HF, particularly for those with younger ages.

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Prevalence of Hyperuricemia in Indian patients with Type-2 Diabetes Mellitus and/or Hypertension

Siddharth Shah¹, Ramesh Dargad²

ABSTRACT

Introduction: Considering the growing incidence of type-2 diabetes mellitus (T2DM) and hypertension (HTN), and its potential link with serum uric acid levels (SUA), this study was conducted to assess the prevalence of hyperuricemia in Indian patients with T2DM, HTN, and both (T2DM+HT).

Methods: In this PAN – India study, subjects were categorized into normal, T2DM, HTN, and T2DM+HTN cohorts. Percentage of patients with hyperuricemia in all cohorts, clinico-epidemiological profile, mean SUA (mg/dl) levels, and the current management practices were assessed.

Results: Prevalence of hyperuricemia was higher amongst hypertensives (22.4%; OR: 1.88 [95% CI: 1.1039,3.2841]; p<0.05) compared to healthy subjects (13.3%). No statistically significant odds of having hyperuricemia were noted in T2DM (9.0%; OR: 1.55 [95% CI: 0.8241, 2.8794; p>0.05) and T2DM+HTN groups (18.7%; OR: 1.49 [95% CI: 0.8825, 2.6075]; p>0.05) versus healthy subjects. Additional analysis indicated a prevalence of 22% among prediabetics. Random blood glucose (p<0.0001) and mean HbA1c (p<0.0001) was higher amongst subjects with normal SUA vs. subjects with elevated SUA. Subjects with elevated SUA levels had higher odds of elevated triglycerides (p=0.009), and total cholesterol (p=0.0165). Furthermore, obese subjects had higher likelihood of having hyperuricemia (p=0.0002) compared to non-obese. About 19% patients were on concomitant medications.

Conclusion: Prevalence of hyperuricemia was found to be higher amongst hypertensives compared to normal subjects. A trend towards increasing prevalence of hyperuricemia was seen among prediabetics, patients with T2DM+HT and in subjects with co-morbidities like obesity and dyslipidemia. Interestingly, prediabetics were found to have a higher prevalence of hyperuricemia than patients with T2DM.
INTRODUCTION

Hyperuricemia is a condition characterized by elevated levels of serum uric acid (SUA), an end product of human purine metabolism.\(^1\) The serum level of UA is influenced by multiple factors such as exogenous ingestion, endogenous production by the liver, and renal excretion.\(^2\) Increased SUA above a specific threshold has been found to be associated with its tendency to form crystals, resulting in gout. The accumulation of crystals can in turn trigger complex inflammatory process, leading to increased neutrophil phagocytosis, consequential in the release of lysosomal enzymes and production of inflammatory chemokines.\(^3\)\(^,\)\(^4\) More recent evidence suggests that the pathological consequences of uric acid are not limited to local tissue damage (due to its insoluble, crystallized forms), but can cause a milieu of systemic inflammatory responses, that can ultimately cause metabolic and atherosclerotic diseases.\(^5\) However, more than two-thirds of hyperuricemic individuals remain asymptomatic.\(^5\)

Type-2 diabetes mellitus (T2DM) and hypertension (HTN) are two important public health challenges, and both are linked to increased risk of cardiovascular events.\(^6\)\(^-\)\(^8\) Hyperuricemia has recently emerged as an independent risk factor in the development of T2DM and HTN through several proposed mechanisms.\(^9\) Furthermore, SUA levels were observed to be positively associated with known risk factors for T2DM and HTN like triglyceride levels, total cholesterol, non-high density lipoprotein cholesterol (non-HDL) and negatively associated with fasting blood sugar (FBS), glycosylated haemoglobin (HbA1C) and HDL cholesterol.\(^6\)\(^-\)\(^8\) Data indicates a 2-phase mechanism for the development of hyperuricemic hypertension in which uric acid induces acute vasoconstriction by activation of renin-angiotensin system, followed by uric acid uptake into vascular smooth muscle cells, leading to cellular proliferation and secondary arteriolosclerosis that impairs pressure natriuresis.\(^10\)\(^,\)\(^11\) On the other hand, SUA has also been shown to be associated with oxidative stress and production of tumor necrosis factor-\(\alpha\), which are both related to the development of diabetes.\(^12\)\(^,\)\(^13\) Distribution of measured SUA levels and its predisposition to hyperuricemia associated conditions may vary significantly based on the factors such as race, ethnicity, gender etc., which may also be partially attributable to genetic differences.\(^14\)\(^-\)\(^16\) Furthermore, a recent report observed that the hypertensive patients with coexisting hyperuricemia were at a greater risk of uncontrolled HTN, in spite of good compliance with their antihypertensive treatment.\(^11\) Thus monitoring and management of hyperuricemia is very crucial in the effective management of patients with existing T2DM and HTN.

Hence considering the growing incidence of T2DM and HTN in India, and its potential link with SUA, it is imperative to understand the burden of hyperuricemia in these patients. Pharmacological and clinical management practices of hyperuricemia in India are also not known. Therefore, this Pan - India study was conducted to assess the prevalence of hyperuricemia in patients with T2DM, HTN, both (T2DM+HTN) and in healthy subjects in India. An attempt was also done to understand the association between SUA and CVD risk factors and the management practices of hyperuricemia in Indian real-life setting.

MATERIALS AND METHODS

Study design and Patient population

This cross-sectional, clinico-epidemiological, multicentric, PAN – India study was conducted at 25 centers across different geographical sites in India, between June and December 2017. Adults (≥18 years) with a diagnosis of T2DM and/or HT (established or newly diagnosed cases), attending the outpatient department of the private clinic or tertiary care setting were enrolled in this study. Individuals without T2DM and HTN visiting study sites were enrolled as healthy subjects/normal. Pregnant or lactating women, patient on drugs known to increase SUA, and those...
with ≥ grade-III chronic kidney disease or other major organ system involvement were excluded from this study.

The study protocol was approved by local independent ethics committees. The study was conducted in accordance with the principles of Declaration of Helsinki, International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines, and Indian regulatory guidelines (Indian Council of Medical Research and Indian GCP guidelines). All patients provided written consent in the patient authorization form to participate in the study.

**Laboratory Measurements**

Blood samples were measured at each hospital’s respective clinical laboratory department. Serum uric acid levels were measured by easy touch uric acid monitoring system. Random blood glucose (RBG) and HbA1c levels were measured by hexokinase method and high-performance liquid chromatography, respectively. Total cholesterol (TC), triglycerides (TG), HDL-cholesterol and LDL-cholesterol were measured by the enzymatic method.

**Study Definitions and Preferred cut-off values**

Subjects diagnosed with T2DM/HTN or both were categorized as patients and subjects without T2DM/HTN were categorized as healthy subjects/normal.

**Hyperuricemia:** SUA >7 mg/dL in men; >6 mg/dL in women

**Hypertension:** Systolic blood pressure (SBP) 140–159 mmHg; diastolic blood pressure (DBP) 90–99 mmHg

**Type-2 Diabetes Mellitus:** RBG ≥180 mg/dl; HbA1c ≥7%

**Dyslipidemia:** Total serum cholesterol ≥200 mg/dL; Serum triglyceride≥150 mg/dL

**Obesity:** Body Mass Index (BMI) ≥ 25 kg/m²

**Metabolic syndrome:** Based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III, the diagnosis of metabolic syndrome was made when ≥3 risk factors were present.

**Study Endpoints**

The primary endpoint was the percentage of patients with hyperuricemia among healthy subjects, patients with T2DM and/or HTN. Demographics, clinico-epidemiological profile, mean SUA level, complications, concomitant medication, association between various risk factors and hyperuricemia and the existing management practices for hyperuricemia were also assessed.

**Statistical methods**

**Sample size**

Assuming the prevalence of hyperuricemia to be 25% and 37% among patients with T2DM and HTN, respectively, approximately 323 patients with T2DM and 400 patients with HTN were planned to be enrolled to estimate the prevalence rate of hyperuricemia with an error margin of 5%, considering a 10% drop out rate. Assuming the prevalence of hyperuricemia to be 14% among healthy subjects, approximately 207 individuals were planned to be enrolled in this study to estimate the prevalence rate with an error margin of 5%, considering 10% drop out rate.

**Statistical analysis**

The statistical analysis was done using Statistical Analysis System® version 9.3 software. The continuous variables were summarized descriptively by mean, standard deviation, median and range (min-max). The categorical variables were described by frequencies and percentages. No missing data imputation was carried out. The statistical analyses were done using chi-square test and multivariate logistic regression at alpha level = 0.05. Chi Square test was used to evaluate the significance of the association between different categories; odds ratios (OR) were evaluated using multivariate logistic regression.
RESULTS

Subject population
A total of 1203 subjects were included in the study (T2DM: 322; HTN: 322; T2DM+HTN: 386; healthy subjects: 173). The mean age of the subjects was 52.0±14.0 years (18-94 years); 604 (50.2%) patients were men and 599 (49.8%) were women (Table 1). More than half of the subjects (62.8%) were moderately active with both vegetarian/non-vegetarian dietary habits (53.9%).

Mean duration of T2DM from diagnosis was 8±6.4 years; mean age at diagnosis was 48±11.6 years. Mean duration of HTN from diagnosis was 6.3±6.1years; mean age at diagnosis was 49.4 ±12.5years. Half of the subjects reported no complications due to T2DM (50.0%) and HTN (59.2%). About 19% subjects were on concomitant medications. The most commonly used concomitant medications were statins (5.4%), proton pump inhibitors (2.7%), vitamin B-12 (2.0%), thyroxine (1.7%), aspirin (1.4%) and clopidogrel (1.1%).

Demographic and clinical features of patients with and without hyperuricemia

Table 2 depicts the demographic and clinical features of patients with and without hyperuricemia. Majority of patients with hyperuricemia were in ≥40 years’ age group, and belonged to upper middle class.

Prevalence of hyperuricemia
Prevalence of hyperuricemia was higher amongst hypertensives (22.4%; OR: 1.88 [95% CI: 1.1039,3.2841]; p<0.05) compared to healthy subjects (13.3%). However, no statistically significant odds of having hyperuricemia were noted in T2DM (9.0%; OR: 1.55 [95% CI: 0.8241, 2.8794; p>0.05) and T2DM+HTN groups (18.7%; OR: 1.49 [95% CI: 0.8825, 2.6075]; p>0.05) versus healthy subjects. Additional analysis further indicated a prevalence of 22% among prediabetics.

Serum uric acid levels
Mean (±SD) SUA concentration in patients with T2DM, HTN, T2DM+HTN and healthy subjects are reported in Table 3A. Pair-wise comparison of mean SUA levels between patients with T2DM (p=0.0109), HTN (p<.0001) and T2DM+HTN groups (18.7%; OR: 1.49 [95% CI: 0.8825, 2.6075]; p>0.05) versus healthy subjects. Additional analysis further indicated a prevalence of 22% among prediabetics.

Cardiovascular risk factors in patients with hyperuricemia
Association between age and gender with hyperuricemia was non-significant among
Table 2: Demographic and clinical profile of patients with or without hyperuricemia

<table>
<thead>
<tr>
<th></th>
<th>T2DM With HU (N=29)</th>
<th>T2DM Without HU (N=293)</th>
<th>HTN With HU (N=72)</th>
<th>HTN Without HU (N=250)</th>
<th>T2DM+ HTN With HU (N=72)</th>
<th>T2DM+ HTN Without HU (N=314)</th>
<th>Healthy subjects With HU (N=23)</th>
<th>Healthy subjects Without HU (N=150)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;40</td>
<td>17.2%</td>
<td>13.3%</td>
<td>25.0%</td>
<td>18.8%</td>
<td>4.2%</td>
<td>6.7%</td>
<td>30.4%</td>
<td>60.7%</td>
</tr>
<tr>
<td>≥40</td>
<td>82.8%</td>
<td>86.7%</td>
<td>75.0%</td>
<td>81.2%</td>
<td>95.8%</td>
<td>93.3%</td>
<td>69.6%</td>
<td>39.3%</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>31.0%</td>
<td>48.1%</td>
<td>52.8%</td>
<td>54.8%</td>
<td>41.7%</td>
<td>52.5%</td>
<td>69.6%</td>
<td>45.3%</td>
</tr>
<tr>
<td>Women</td>
<td>69.0%</td>
<td>51.9%</td>
<td>47.2%</td>
<td>45.2%</td>
<td>58.3%</td>
<td>47.5%</td>
<td>30.4%</td>
<td>54.7%</td>
</tr>
<tr>
<td><strong>Socio-economic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>status</td>
<td>Score &lt;5 Lower Class</td>
<td>3.4%</td>
<td>4.8%</td>
<td>4.2%</td>
<td>4.8%</td>
<td>4.2%</td>
<td>4.8%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Score 5 – 10 Upper Lower Class</td>
<td>20.7%</td>
<td>25.6%</td>
<td>19.4%</td>
<td>18.8%</td>
<td>18.8%</td>
<td>31.9%</td>
<td>25.5%</td>
<td>17.4%</td>
</tr>
<tr>
<td>Score 11–15 Lower Middle Class</td>
<td>27.6%</td>
<td>21.8%</td>
<td>18.1%</td>
<td>23.6%</td>
<td>23.6%</td>
<td>18.1%</td>
<td>24.2%</td>
<td>13.0%</td>
</tr>
<tr>
<td>Score 16 – 25 Upper Middle Class</td>
<td>41.4%</td>
<td>37.5%</td>
<td>45.8%</td>
<td>42.0%</td>
<td>37.5%</td>
<td>36.0%</td>
<td>39.1%</td>
<td>46.0%</td>
</tr>
<tr>
<td>Score 26 to 29 Upper Class</td>
<td>6.9%</td>
<td>10.2%</td>
<td>12.5%</td>
<td>10.8%</td>
<td>8.3%</td>
<td>9.6%</td>
<td>30.4%</td>
<td>11.3%</td>
</tr>
<tr>
<td><strong>BMI (kg/m²), Mean (SD)</strong></td>
<td>29.18 (4.86)</td>
<td>26.73 (4.73)</td>
<td>28.49 (5.56)</td>
<td>26.48 (5.19)</td>
<td>27.89 (4.08)</td>
<td>27.32 (5.16)</td>
<td>27.52 (4.31)</td>
<td>25.41 (4.84)</td>
</tr>
<tr>
<td>Waist circumference (cms), Mean (SD)</td>
<td>85.07 (18.63)</td>
<td>86.48 (15.61)</td>
<td>84.62 (17.32)</td>
<td>85.94 (16.24)</td>
<td>87.41 (19.58)</td>
<td>88.70 (15.47)</td>
<td>87.47 (9.96)</td>
<td>82.62 (19.50)</td>
</tr>
<tr>
<td>WHR (cm), Mean (SD)</td>
<td>10.29 (27.18)</td>
<td>10.82 (27.13)</td>
<td>10.89 (27.95)</td>
<td>7.12 (22.06)</td>
<td>2.95 (13.13)</td>
<td>5.74 (19.60)</td>
<td>6.94 (22.47)</td>
<td>7.52 (23.00)</td>
</tr>
<tr>
<td>SBP, Mean (SD)</td>
<td>126.79 (12.43)</td>
<td>125.47 (9.48)</td>
<td>142.58 (18.70)</td>
<td>140.69 (18.81)</td>
<td>140.40 (15.91)</td>
<td>141.53 (16.97)</td>
<td>122.30 (8.90)</td>
<td>121.64 (8.24)</td>
</tr>
<tr>
<td>DBP, Mean (SD)</td>
<td>78.93 (6.75)</td>
<td>79.54 (6.40)</td>
<td>86.88 (11.60)</td>
<td>86.35 (11.23)</td>
<td>83.88 (9.28)</td>
<td>86.21 (9.66)</td>
<td>77.04 (5.12)</td>
<td>77.39 (6.64)</td>
</tr>
<tr>
<td><strong>Metabolic Syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presence</td>
<td>3.4%</td>
<td>0</td>
<td>9.7%</td>
<td>5.6%</td>
<td>15.3%</td>
<td>18.2%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Absence</td>
<td>96.6%</td>
<td>100%</td>
<td>90.3%</td>
<td>94.4%</td>
<td>84.7%</td>
<td>81.8%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

HU = hyperuricemia; n = Number of subjects; S.D = Standard Deviation; Min. = Minimum; Max = Maximum; T2DM=Type 2 diabetes mellitus; Hypertension (HTN) = Systolic blood pressure (SBP) >130 mmHg/Diastolic blood pressure (DBP) >85 mmHg

patients in all three cohorts (T2DM, HTN, T2DM+ HTN); however, the association was significant in healthy subjects (age: p=0.0064; gender: p=0.0304). The association between BMI and hyperuricemia was found to be significant in the combined T2DM+ HTN group (p=0.0417) and in healthy subjects (p=0.0003). Other factors such as smoking, alcohol consumption and metabolic syndrome were not found to be associated with hyperuricemia in any of the cohorts. Furthermore, no association between severity and duration of disease (T2DM/HTN) with hyperuricemia was noted.

**Risk factors for hyperuricemia**

We carried out multivariate logistic regression analyses to evaluate the risk factors for hyperuricemia (Table 4). All the independent parameters were pooled into the analysis together and adjusted ORs were calculated. Overall, RBG (p<0.0001) and mean HbA1c (p<0.0001) was higher amongst subjects with normal SUA vs. subjects with elevated SUA.
Table 3A: Mean Serum Uric Acid Levels (mg/dl)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Median (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td>322</td>
<td>5.58 (1.52)</td>
<td>5.50 (2.20, 11.60)</td>
</tr>
<tr>
<td>T2DM</td>
<td>322</td>
<td>4.68 (1.31)</td>
<td>4.60 (1.20, 9.10)</td>
</tr>
<tr>
<td>Combined disease condition of T2DM + HTN</td>
<td>385</td>
<td>5.22 (1.51)</td>
<td>5.10 (1.30, 11.40)</td>
</tr>
</tbody>
</table>

*missing = 1 patient; n = Number of subjects; SD = Standard Deviation; Min = Minimum; Max = Maximum; HTN = Hypertension; T2DM = Type-2 diabetes mellitus

Table 3B: Pair-wise Comparison of Mean Serum Uric Acid (mg/dl)

<table>
<thead>
<tr>
<th>Condition</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Median (min, max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy Subjects</td>
<td>173</td>
<td>5.02 (1.50)</td>
<td>4.90 (1.60, 9.20)</td>
</tr>
<tr>
<td>HTN</td>
<td>322</td>
<td>5.58 (1.52)</td>
<td>5.50 (2.20, 11.60)</td>
</tr>
<tr>
<td>Healthy Subjects</td>
<td>173</td>
<td>5.02 (1.50)</td>
<td>4.90 (1.60, 9.20)</td>
</tr>
<tr>
<td>T2DM</td>
<td>322</td>
<td>4.68 (1.31)</td>
<td>4.60 (1.20, 9.10)</td>
</tr>
<tr>
<td>Healthy Subjects</td>
<td>173</td>
<td>5.02 (1.50)</td>
<td>4.90 (1.60, 9.20)</td>
</tr>
<tr>
<td>T2DM + HTN</td>
<td>385</td>
<td>5.22 (1.51)</td>
<td>5.10 (1.30, 11.40)</td>
</tr>
</tbody>
</table>

*p-value is calculated using two sample t-test; HTN = Hypertension, T2DM = Type 2 diabetes mellitus

Table 4: Multivariate Logistic Regression Model for Dependency of Hyperuricemia in Patients with T2DM, HTN, T2DM+HTN and Healthy Subjects

<table>
<thead>
<tr>
<th>Variable</th>
<th>Comparison</th>
<th>OR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;40/ ≥ 40 Years</td>
<td>0.827(0.552,1.240)</td>
<td>0.3588</td>
</tr>
<tr>
<td>BMI</td>
<td>Obese/Non obese</td>
<td>2.208(1.454,3.353)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Waist circumference</td>
<td>Men / Women</td>
<td>1.101(0.690,1.757)</td>
<td>0.6852</td>
</tr>
<tr>
<td>Smoking</td>
<td>Yes / No</td>
<td>0.851(0.240,3.017)</td>
<td>0.8032</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Yes / No</td>
<td>1.416(0.549,3.653)</td>
<td>0.4725</td>
</tr>
<tr>
<td>Severity of HTN</td>
<td>Stage 1 / Stage 2</td>
<td>0.716(0.347,1.477)</td>
<td>0.3657</td>
</tr>
<tr>
<td>RBG</td>
<td>RBG&lt;180 mg/dl / RBG ≥ 180 mg/dl</td>
<td>2.668(1.658,4.292)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>HbA1c</td>
<td>HbA1c&lt;7% / ≥ 7%</td>
<td>1.993(1.415,2.808)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Total serum cholesterol</td>
<td>&lt;200 mg/dL / ≥200 mg/dL</td>
<td>0.678(0.494,0.932)</td>
<td>0.0165</td>
</tr>
<tr>
<td>Serum triglyceride</td>
<td>&lt;150 mg/dL / ≥150 mg/dL</td>
<td>0.654(0.476,0.899)</td>
<td>0.0090</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Presence / Absence</td>
<td>0.358(0.180,0.713)</td>
<td>0.0035</td>
</tr>
<tr>
<td>Duration of T2DM</td>
<td>&lt; 5 years /≥ 5 years</td>
<td>1.236(0.771,1.981)</td>
<td>0.3797</td>
</tr>
<tr>
<td>Duration of Hypertension</td>
<td>&lt; 5 years /≥ 5 years</td>
<td>0.862(0.592,1.255)</td>
<td>0.4378</td>
</tr>
</tbody>
</table>

Subjects with elevated SUA levels had higher odds of elevated triglycerides (p=0.009) and total cholesterol (p=0.0165). Further, the results indicated that obese subjects had higher likelihood of having hyperuricemia (p=0.0002) compared to non-obese. No association between severity of disease (T2DM/HTN) and hyperuricemia was noted.

Management of hyperuricemia

No treatment was prescribed for hyperuricemia in majority of the patients (T2DM: 225 [69.88%]; HTN: 198 [61.49%]; T2DM+HTN: 242 [62.69%]; healthy subjects: 104 [60.12%]). The only pharmacological treatment prescribed was probenecid (n=1) in one patient with
T2DM, febuxostat (n=3) in three patients with HTN, allopurinol (n=1), febuxostat (n=1) and probenecid (n=1) in one patient each with T2DM+HTN and allopurinol (n=1) in one healthy subject. Data was missing for 96 (29.81%) patients with T2DM, 121 (37.58%) HTN patients, 141 (36.53%) patients with T2DM+HTN and 67 (38.73%) healthy subjects.

DISCUSSION

The results of the present study indicate that the prevalence of hyperuricemia in Indian patients with T2DM and HTN are 9.0% and 22.4%, respectively. The prevalence in patients with co-occurrence of T2DM and HTN was found to be 18.7%, while in healthy subjects, the prevalence was found to be 13.3%. Recently, many cross-sectional, cohort, and interventional studies have identified hyperuricemia as an independent risk factor for hypertension. It has been reported that the risk of developing HTN in patients with hyperuricemia for each mg/dl of uric acid above the normal value is about 13% - 15% (RR 51.15 [95% CI: 1.06-1.26]). In present study, higher prevalence of hyperuricemia was reported in subjects with HTN (22.4%) compared to healthy adults (13.3%). The results of this study are in line with the earlier published data. Mishra et al in a study in Indian patients with newly diagnosed essential hypertension reported a prevalence of 26%. However, in another randomized controlled trial of 2485 subjects, the prevalence of hyperuricemia in HTN was reported to be 10.7%. Yu F-N et al in a cross sectional study with 1730 subjects reported a prevalence of 17.45% among patients with HTN. Further, similar to the present study, other studies have also indicated a higher number of hyperuricemic subjects in hypertensive cases when compared to controls. Moreover, the association between hyperuricemia and HTN as compared to healthy subjects in the present study was found to be statistically significant (OR 1.87 [95% CI: 1.10-3.28]), indicating that hypertensive patients are 1.88 times more likely to incur hyperuricemia compared to healthy subjects.

The 3rd National Health and Nutrition Examination Survey reported the prevalence of diabetes to be 33.1% (95% CI, 28.8–41.4) in patients with gout. Also various studies conducted across the globe have reported that diabetes is associated with hyperuricemia. In a recent cross-sectional study conducted in 319 T2DM subjects in Ethiopia, the prevalence of hyperuricemia was reported to be 33.8% (n=106). Similarly, another multicentric hospital-based cross-sectional study conducted in 2,917 T2DM patients with central obesity in China reported prevalence of hyperuricemia to be 32.6%. However, in our study, the prevalence of hyperuricemia in subjects with T2DM (9%) was lower than the prevalence reported in the literature.

Further, an additional analysis was also done to evaluate the SUA levels in pre-diabetic population (along with T2DM patients). Interestingly, prediabetics were found to have a higher prevalence of hyperuricemia (22%) than patients with T2DM (OR 1.26 [95% CI: 0.5035-3.1514]). An earlier data has indicated a positive relationship between serum glucose and SUA concentrations up to about 8.0 mmol/l, with SUA levels decreasing at higher levels of glucose. This could be the one of the probable reason for the high prevalence of hyperuricemia noted in prediabetic population as compared to the diabetic population.

Wang et al in a study in Chinese population demonstrated that the prevalence of hyperuricemia in T2DM subjects with HbA1c <7% was significantly higher than in subjects with HbA1c ≥7% (p<0.001). The present study also revealed that the RBG (p<0.0001) and mean HbA1c (p<0.0001) was higher amongst subjects with normal SUA compared to subjects with elevated SUA (OR 1.993 [95%CI:1.415,2.808]). Obesity is considered as an independent risk factors of diabetes and in present study the mean BMI for T2DM subjects was found to be >25%.

It should be noted that the renal functions of study subjects were not evaluated in this study and hence it was not evident from the
results whether the elevated SUA in subjects were due to underlying renal pathology.

The mean uric acid level reported in this study was $4.7 \pm 1.0$ mg/dL, which was within the normal limits in all cohorts. Sujeet et al. (2014) in their study conducted in Himachal Pradesh in 118 hypertensive subjects reported a significant difference in mean SUA level between healthy subjects and patients with HTN ($p<.0001$) and T2DM ($p=0.01$).33 In the present study, SUA was found to be higher in HTN patients compared to healthy subjects, whereas it was higher in healthy subjects compared to T2DM patients. The serum uric acid levels in patients with T2DM+HTN was greater than healthy subjects but was not statistically significant ($p=0.1329$).

Hyperuricemia was frequently reported in patients either with cardiovascular disease or at a high risk of cardiovascular disease such as HTN, T2DM, coronary heart disease, peripheral vascular disease, heart failure, metabolic syndrome, and stroke.34,35 Hence in this study, an attempt was also done to assess the association between hyperuricemia and cardiovascular risk factors. Association between age and gender with hyperuricemia was not significant among patients in all three cohorts (T2DM, HTN, T2DM+HTN). However, higher age (>40 years) in healthy population was found to be a factor predisposing to higher odds of hyperuricemia. Similarly, a significant association was found between BMI and hyperuricemia in groups with combined condition of T2DM-HTN and healthy adults. Further, subjects with elevated SUA levels had higher odds of elevated triglycerides ($p=0.009$), and total cholesterol ($p=0.0165$). Other factors such as smoking, alcohol consumption and metabolic syndrome were not found to be associated with hyperuricemia in any of the cohorts.

Majority of the study population were not on any medication for the management of hyperuricemia. This study thus provides insights on the pharmacological management of hyperuricemia in India. Lifestyle changes such as changes in diet, reduction in alcohol intake, and exercise should be considered as an option in these patients to lower uric acid levels, in turn helping in the holistic management of hyperuricemia.

One of the limitation of this study is that there could be certain unmeasured confounding variables in a cross-sectional, observational study that might impact the investigation on causality. Also, the prevalence of hyperuricemia was evaluated in patients who reached out for the management of HTN/T2DM. However, asymptomatic nature of the disease coupled with a lack of awareness could have possibly understated the disease prevalence.

To conclude, prevalence of hyperuricemia was found to be higher amongst hypertensives compared to normal subjects. A trend towards increasing prevalence of hyperuricemia was seen among prediabetics, patients with T2DM+HTN and in subjects with co-morbidities like obesity and dyslipidemia. Interestingly, prediabetics were found to have a higher prevalence of hyperuricemia than patients with T2DM.

**FUNDING**

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**CONFLICT OF INTEREST**

This work was supported by Abbott Healthcare Private Limited. All other authors have declared and confirmed that there is no conflict of interest with respect to the authored article.

**REFERENCES**


Impact of Coronary Artery Disease on Augmentation Index as Measured by Estimated Central Blood Pressure: A Case Control Study in Asian Indians

Kamal H. Sharmaa,*, Neha Sharmab, Komal Shaha, Sachin Patila

ABSTRACT

Aims: We compared various components of blood pressure and arterial stiffness of healthy control with those of coronary artery disease (CAD) patients using BP+ machine™.

Methods: In this prospective, case-control study, total 585 individuals of both the genders were enrolled. The study population consisted of 277 controls (healthy siblings of diseased subjects not having CAD - group A) and 308 CAD patients (group B). Age and sex adjusted regression and receiver operative curve (ROC) analysis was performed to assess the strength of association of these parameters.

Results: We found that mean systolic blood pressure (SBP) (137.14 ±22.49 vs. 129.26 ±19.86), central isystolic blood pressure (CSBP) (130.78±21.89 vs. 117.53±17.98), augmentation index (AI) (108.55 ±44.98 vs. 49.38 ±21.03) and pulse rate variability (98.82 ±231.09 vs. 82.86±208.77) were significantly (p < 0.05) higher in CAD population as compared to healthy counterparts. Left ventricular contractibility as measured by dP/dt was significantly lower in CAD patients. All these parameters were significantly abnormal in CAD as compared to healthy control population irrespective of the gender of the patient except for SBP in females. Both - odds ratio (1.108; 95% CI: 1.081-1.135; p<0.0001) and ROC analysis (AUC: 0.937; 95% CI: 0.919-0.956; p<0.0001) showed AI as the strongest predictor of CAD, closely followed by CSBP.

Conclusion: Central aortic blood pressure parameters such as AI and CSBP measured non-invasively with BP+ machine could be the effective predictors of CAD in Asian Indians.

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Prescribing Patterns and Real-world Effectiveness of Antihypertensive Therapy: A Prospective Multicenter Registry in India

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ABSTRACT

Aim: Elevated blood pressure (BP) is a leading risk factor for global disease burden. We conducted a pan-India registry to obtain real-life data on antihypertensive pharmacotherapy and its short-term effectiveness and safety.

Methodology: This observational, multicenter, non-interventional, openlabel registry was conducted at 67 urban centers. Enrolled population included patients with Stage 1, Stage 2, or uncontrolled hypertension (HTN) per the Joint National Committee 7 criteria who received antihypertensive treatment as part of routine care; they were followed up for 4-6 weeks. We analyzed data using Statistical Package for the Social Sciences, version 23.

Results: Of the 1376 patients enrolled, 35.2% had Stage 1, 21.6% had Stage 2, and 43.2% had uncontrolled HTN; 74% of the patients had other comorbid conditions. Angiotensin II receptor blocker (ARB) monotherapy (37.6%) or ARB+calcium channel blocker (CCB) combination therapy (15.7%) was most frequently prescribed: Stage 1 (55.9%; 6.4%), Stage 2 (33.0%; 17.8%), and uncontrolled HTN (25.1%; 22.2%). The mean reduction in sitting BP was 17-26.1mmHg systolic and 9.6-11.7mmHg diastolic with ARB monotherapy and 22-32mmHg systolic and 11.5-14.9mmHg diastolic with ARB+ Beta Blockers (BB). Of the 1376 patients, 558 (40.5%) achieved the BP goal (<140/90mmHg). Compliance was high and no adverse drug reactions were reported.

Conclusions: In this Indian registry, 40.5% of the enrolled patients achieved the BP goal within 4-6 weeks of follow-up duration. Indian practitioners prefer ARB as monotherapy followed by ARB+CCB or ARB+BB for HTN management.
INTRODUCTION

Hypertension (HTN) manifested by sustained increased blood pressure (BP) is a key modifiable risk factor for cardiovascular disease (CVD) development and stroke, and is the second leading cause for renal impairment-related mortality and morbidity. In 2008, an estimated 1 billion adults had HTN; in 2025, an estimated 1.56 billion adults will have CVD and HTN. In 2010, elevated BP caused 9.4 million deaths worldwide and it was the leading single risk factor for global disease burden. Other risk factors included high body mass index, high fasting plasma glucose, high total cholesterol, and low bone mineral density. The complications of HTN are directly responsible for >50% of deaths due to CVD.

Approximately 20% of the Indian population was suffering from HTN in 2005. According to the World Health Organization’s estimations, in 2008, 32.5% of the Indian population had elevated BP. Every fourth individual in India ≥18 years has elevated BP, and the prevalence has increased by 10% from 2010 to 2014. An estimated 213.5 million Indians will have HTN by 2025. The prevalence of HTN in urban and rural Indians is 33% and 25%. Hypertension causes about 57% of stroke-related deaths and 24% of coronary heart disease-related deaths in India. Despite the challenges posed by HTN, studies in India have suggested poor awareness, treatment, and control of HTN in both rural and urban populations. Hypertension control can prevent mortality and morbidity associated with HTN and its complications; antihypertensive drugs are prescribed mainly to reduce the morbidity and mortality.

Several international and national guidelines on the classification and management of HTN serve as reference for HTN management in clinical practice. The Association of Physicians of India published the Indian Hypertension Guidelines III in 2013. The Eighth Joint National Committee (JNC 8) guidelines published in 2014 and the American College of Cardiology (ACC) and American Heart Association guidelines published in 2017 are the most recent guidelines for HTN management. Per the JNC 8 guidelines, pharmacological treatment should be initiated in adults <60 years if BP is >140/90mmHg or in elderly patients >60 years if BP is >150/90mmHg. In case of comorbidities such as diabetes or chronic kidney disease (CKD), the target BP in adults >18 years is 140/90mmHg. Per the ACC guidelines, normal BP is defined as <120/80mmHg; elevated BP is 120-129/<80mmHg; HTN Stage 1 is 130-139/80-89mmHg, and HTN Stage 2 is ≥140/≥90mmHg. The target BP in patients with diabetes or CKD is <130/80mmHg. The first-line therapy in HTN management includes angiotensin II receptor blockers (ARBs), angiotensin-converting enzyme inhibitors (ACEIs), calcium channel blockers (CCBs), and thiazide diuretics alone or in combination. Beta blockers (BBs) can be used in the management of HTN with coronary artery disease or restricted heart function. The drug classes of choice for HTN management in patients with diabetes are ACEIs, ARBs, CCBs, or diuretics; those in patients with CKD are ACEIs or ARBs. Despite the availability of several antihypertensive agents from different pharmacological classes, achieving BP control to the recommended target levels is challenging. A study reported the superiority of combination therapy in the first 16 weeks (phase 1), by margins of almost 8 and 10mmHg, compared with initial monotherapy.

Although HTN exerts a substantial public health burden on cardiovascular health status and healthcare systems, real-life data on the prescribing patterns and effect of BP-controlling drugs in India are scarce. We conducted a Pan-India registry to evaluate the current treatment practices and epidemiology and comorbidities in patients with HTN. Follow-up data were analyzed for the short-term effectiveness and safety of antihypertensive therapy.
METHODS

Study Design

This was an observational, multicenter, non-interventional, open-label registry conducted in patients with HTN at 67 urban centers between July 2017 and February 2018. After obtaining approval from the Institutional Review Boards/Institutional Ethics Committees, the study was conducted in compliance with the protocol and all relevant regulatory guidelines.

Patients received antihypertensive treatment as part of routine care and according to the local prescribing information(s). Data originated from the physicians’ routine practice during scheduled clinic visits with no additional diagnostic procedures beyond standard care. The observation period was 4-6 weeks.

Study Population

Adult patients (18-65 years) with newly established diagnosis of HTN or HTN that remained uncontrolled even after treatment with antihypertensive drugs, who were prescribed antihypertensive treatment as part of routine patient care, and who consented to data collection were enrolled. Elderly patients >65 years were also enrolled and were reported as protocol deviations. Pregnant or lactating women and individuals requiring hospitalization for any cause were excluded. Patients were classified using the JNC 7 criteria as having Stage 1 (systolic BP [SBP] 140-159mmHg or diastolic BP [DBP] 90-99mmHg), Stage 2 (SBP ≥160mmHg or DBP ≥100mmHg), or uncontrolled HTN (despite being on antihypertensive medications, these patients did not achieve the target BP of <140/90mmHg in patients without diabetes or <130/80mmHg in patients with diabetes).

Data Collection

Data collected at baseline visit included demographics, HTN history, comorbidity burden, relevant medical history, vital signs, antihypertensive and other concomitant medication use, and adverse drug reactions (ADRs). Patients were followed up for 4-6 weeks for the effectiveness of antihypertensive therapy, assessed by changes in mean sitting SBP and mean sitting DBP from baseline. Blood pressure was measured per the clinician’s practice. Safety assessments included physician monitoring and recording of incidence of all adverse events (AEs) and serious adverse events (SAEs).

Statistical Analysis

Summary statistics for quantitative variables included the number of observations (n), arithmetic mean, standard deviation (SD), minimum, maximum, and median. Qualitative variables were presented with absolute and relative frequencies. Key quantitative variables were presented with two-sided 95% confidence intervals and p values for changes across time (baseline to follow-up), using Student’s t-test; p<0.05 was considered statistically significant. Statistical analyses were performed using Statistical Package for the Social Sciences, version 23.

RESULTS

Demographic and Clinical Profile

Of the 1376 patients enrolled, 1366 (99.3%) completed the study (followed up at 4-6 weeks); remaining 10 (0.7%) patients were lost to followup. Table 1 summarizes the demographic and clinical characteristics of patients. The mean (±SD) age of patients was 52.9 (±9.6) years with a baseline sitting BP of 159.2 (±14.9)/96.3 (±9.2) mmHg. Most patients (43.2%) had uncontrolled HTN, followed by Stage 1 (35.2%) and Stage 2 (21.6%). Three-fourths of the patients reported cardiovascular risk factors: diabetes (48.1%), dyslipidemia (41.2%), and ischemic heart disease (15.1%). Metformin use was reported in 30.0% of patients, followed by glimepiride (15.4%) and teneligliptin (5.7%). Rosuvastatin use was reported in 27.6% of patients, followed by atorvastatin (15.8%).
Antihypertensive Therapy

Prior Therapy in Uncontrolled HTN

At baseline, all patients with uncontrolled HTN were taking antihypertensive medications, with ARBs as the most frequently used monotherapy (33.8%), followed by CCBs (16.5%). Beta blockers, ACEIs, diuretics, or alpha blockers were prescribed to <10% of patients. Among patients receiving combination therapy, the most common therapies were BB+CCB (7.7%) and ARB+CCB (7.6%), followed by ARB+diuretics (6.2%) and ARB+BB (5.2%). Combination therapy with >2 drugs was rare. Furthermore, 21% of patients in this group were taking telmisartan.

Current Prescription Practice in All Patients

Angiotensin II receptor blockers as monotherapy (37.6%) or dual therapy (36.7%) in combination with other antihypertensive drugs were most commonly prescribed (Table 1, Figure 1). Angiotensin II receptor blocker monotherapy was prescribed in all stages of HTN: Stage 1 (55.9%), Stage 2 (33.0%),
and uncontrolled (25.1%). The most frequently prescribed 2-drug therapy was ARB+CCB (15.7%); the 3-drug combination therapy was ARB+BB+CCB (4.1%). For patients with diabetes or dyslipidemia, ARB monotherapy was prescribed most frequently, followed by combination therapy with ARB+CCB and ARB+BB+CCB (Figure 1). In this subgroup of patients, monotherapy with telmisartan or azilsartan was the most common, followed by combination therapy with azilsartan plus amlodipine.

**Treatment Switch (Uncontrolled HTN Group)**

Among the 594 patients with uncontrolled HTN, a switch from monotherapy to another monotherapy drug was prescribed for 110 (18.7%) patients: to azilsartan in 80 (13.5%), to telmisartan in 11 (1.9%), to amlodipine in 7 (1.1%), and to cilnidipine in 6 (1%). A total of 208 (34.9%) patients on monotherapy switched to combination therapy, whereas 52 (8.8%) patients switched from combination therapy to monotherapy. Furthermore, 27.9% of patients receiving combination therapy switched to another combination therapy. Sixty-two (10.4%) patients continued with the earlier treatment during this period; however, the dose of their initial treatment was changed during the course of the study (Figure 2).

**Effectiveness**

Treatment with 4-6 weeks of ARB as monotherapy or ARB+BB or ARB+CCB combination therapy showed clinically significant (p<0.001) mean reductions in BP from baseline in all HTN stages (Table 2). The mean reduction in sitting BP was 17 to 26.1mmHg systolic and 9.6 to 11.7mmHg diastolic with ARB monotherapy and 22 to 32mmHg systolic and 11.5 to 14.9mmHg diastolic with ARB+BB. Of the 1376 patients, 558 (40.5%) achieved the BP goal (<140/90mmHg).

A paired samples t-test was conducted to compare the BP and pulse in patients with
Stage 1, Stage 2, or uncontrolled HTN at baseline and follow-up visits. A significant (p=0.000) reduction was observed in the mean vital sign scores at the follow-up visit compared with that at the baseline visit for most of the comparisons.

Overall, 87.9% of patients were compliant with their medication regimen. Reasons for nonadherence in 12.1% of patients were multifactorial and difficult to identify.

**Safety**

None of the patients who were followed up reported any ADRs, SAEs, or deaths. Data were missing for the 10 patients who were lost to followup.

**DISCUSSION**

This panIndia registry demonstrates that ARB as monotherapy or ARB+BB or ARB+CCB combination therapy in a real-life setting significantly reduced BP within 6 weeks of treatment from baseline in patients with HTN. The study population included patients with comorbid diabetes or dyslipidemia. Although our study reports the short-term effects of antihypertensive therapy, the initial period of 4-6 weeks is critical for titrating therapy and monitoring compliance. At baseline, 43.2% of the study population had uncontrolled HTN despite being on antihypertensive therapy; this finding is alarming and highlights the challenge of achieving target BP.

Most HTN registries have not reported the proportion of patients attaining recommended BP goals; mean reductions in BP have been the primary endpoint of interest. In our study, 40.5% of enrolled patients with Stage 1, Stage 2, or uncontrolled HTN achieved the target BP goal of <140/90mmHg. The mean BP in all HTN groups showed a significant reduction after most hypertensive treatment regimens. Our results are comparable with those obtained from other countries. Half of the total group in an Australian registry and about twothirds of the population in an African study achieved target BP goals. Our study shows male preponderance (60.2%); a cross-sectional study conducted between 2013 and 2014 reported a high burden of uncontrolled HTN in elderly Indian men.

<table>
<thead>
<tr>
<th>FromMono</th>
<th>FromCombo</th>
<th>No change</th>
</tr>
</thead>
<tbody>
<tr>
<td>34.90%</td>
<td>27.80%</td>
<td>10.40%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ToMono</th>
<th>ToCombo</th>
</tr>
</thead>
<tbody>
<tr>
<td>18.70%</td>
<td>8.80%</td>
</tr>
</tbody>
</table>

Fig. 2: Switch in Antihypertensive Treatment in Patients With Uncontrolled Hypertension; FromCombo: from any combination therapy; FromMono: from any monotherapy; ToCombo: to any combination therapy; ToMono: to any monotherapy; N=594 patients with uncontrolled hypertension.
Table 2: Effect of Angiotensin Receptor Blocker Monotherapy and Combination Therapy on Systolic and Diastolic Blood Pressure

<table>
<thead>
<tr>
<th>Therapy</th>
<th>HTN Class</th>
<th>Number of Patients</th>
<th>Mean (±SD) Baseline SBP/DBP (mmHg)</th>
<th>Mean Followup SBP/DBP (mmHg)</th>
<th>Mean Change (mmHg)</th>
<th>Mean Baseline Pulse (bpm)</th>
<th>Mean Followup Pulse (bpm)</th>
<th>Mean Change (bpm)</th>
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</thead>
<tbody>
<tr>
<td>ARB monotherapy</td>
<td>Stage 1</td>
<td>269</td>
<td>150.6 (10.8)/92.2 (6.7)</td>
<td>133.6 (10.2)/82.6 (5.3)</td>
<td>-17.0/-9.6</td>
<td>79.3 (7.7)</td>
<td>76.0 (95.0)</td>
<td>-3.3</td>
</tr>
<tr>
<td></td>
<td>Stage 2</td>
<td>96</td>
<td>165.1 (13.1)/98.1 (10.2)</td>
<td>139.0 (11.2)/85.4 (5.8)</td>
<td>-26.1/-12.7</td>
<td>83.8 (7.7)</td>
<td>78.6 (95.3)</td>
<td>-5.1</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled</td>
<td>148</td>
<td>160.0 (16.3)/98.0 (9.4)</td>
<td>136.9 (11.7)/86.3 (7.9)</td>
<td>-23.1/-11.7</td>
<td>83.2 (7.2)</td>
<td>78.2 (5.2)</td>
<td>-5.0</td>
</tr>
<tr>
<td>ARB+CCB</td>
<td>Stage 1</td>
<td>31</td>
<td>152.5 (8.9)/95.6 (8.1)</td>
<td>133.6 (9.9)/86.7 (6.5)</td>
<td>-18.9/-8.9</td>
<td>85.8 (7.4)</td>
<td>79.3 (7.3)</td>
<td>-6.5</td>
</tr>
<tr>
<td></td>
<td>Stage 2</td>
<td>52</td>
<td>167.5 (11.0)/100.5 (8.5)</td>
<td>138.3 (9.8)/88.0 (7.1)</td>
<td>-29.2/-12.5</td>
<td>85.8 (5.8)</td>
<td>79.0 (6.8)</td>
<td>-6.8</td>
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<tr>
<td></td>
<td>Uncontrolled</td>
<td>130</td>
<td>166.4 (15.1)/98.4 (7.2)</td>
<td>139.2 (12.3)/86.0 (6.7)</td>
<td>-27.2/-12.4</td>
<td>85.0 (6.8)</td>
<td>78.6 (5.5)</td>
<td>-6.4</td>
</tr>
<tr>
<td>ARB+BB</td>
<td>Stage 1</td>
<td>45</td>
<td>154.0 (13.3)/94.2 (7.3)</td>
<td>127.0 (14.4)/81.7 (4.0)</td>
<td>-27.0/-12.5</td>
<td>84.7 (8.1)</td>
<td>79.2 (6.7)</td>
<td>-5.5</td>
</tr>
<tr>
<td></td>
<td>Stage 2</td>
<td>43</td>
<td>168.7 (9.5)/98.5 (8.4)</td>
<td>136.6 (12.0)/83.6 (5.2)</td>
<td>-32.0/-14.9</td>
<td>85.6 (11.1)</td>
<td>76.1 (5.4)</td>
<td>-9.5</td>
</tr>
<tr>
<td></td>
<td>Uncontrolled</td>
<td>59</td>
<td>162.5 (13.3)/97.9 (8.4)</td>
<td>140.0 (10.1)/86.4 (5.6)</td>
<td>-22.5/-11.5</td>
<td>87.4 (11.1)</td>
<td>77.4 (5.3)</td>
<td>-9.9</td>
</tr>
</tbody>
</table>

ARB: angiotensin receptor blocker; BB: beta blocker; CCB: calcium channel blocker; DBP: diastolic blood pressure; HTN: hypertension; SBP: systolic blood pressure; SD: standard deviation

Analyzed using Student t-test.

Significant p<0.001 unless otherwise mentioned.

Most patients with uncontrolled HTN were switched to other drugs of the same class or other classes and only 10% of patients continued treatment with earlier drugs with dose adjustments. Azilsartan was the drug of choice when treatment was switched from monotherapy to another monotherapy. Treatment switch to combination therapy was the most preferred option (35%), and 18.5% of patients switched to another monotherapy (same or other class). Treatment switch from combination therapy to monotherapy was observed in 8.8% of patients. A retrospective study reported a switching rate of 38.5% in Southern India. Treatment switch is common when BP does not remain stable with the current prescription. The JNC 8 guidelines recommend that if the target BP is not reached within 1 month after initiating therapy, the dosage of the initial medication should be increased, or a second medication should be added. In a study, response to initial combination therapy was uniform and at least 5mmHg greater than that seen with monotherapy in adults 18-79 years old with BP >150/95mmHg. Angiotensin II receptor blockers were the most commonly prescribed class (37.6%). Very few patients were prescribed CCBs (4.1%) and BBs (1.3%). Dual therapies with ARB were also equally preferred in almost 32.5% (ARB+CCB, 15.7%; ARB+BB, 10.7%; and ARB+diuretics, 6.1%). This finding highlights the clinical confidence of initial prescribing or switching to combination drugs, which is also recommended by recent guidelines. A study confirmed that physicians commonly prescribe a combination of two or three
drugs to achieve target BP. A patient survey showed that switching to combination antihypertensive drugs improves patient adherence and satisfaction. Diuretics were not routinely prescribed in our study, possibly because of the perceived lack of tolerance and reported AE profile when prescribed in larger doses. Although diuretics are recommended by the European Society of Cardiology/European Society of Hypertension guidelines and the British Hypertension Society, their role as first-line or even second-line drugs is being questioned as newer, more effective, safer antihypertensive drugs are available. Diuretics are safe at low doses; however, they do not show the same effectiveness with comorbidities. The safety of diuretics at low doses was proved in patients with diabetes and hypertension; however, the effectiveness has not been clearly established. A 5-year cohort study involving 250,851 patients showed that thiazide diuretics had the most marked increase in switching rate. Newer antihypertensive drugs such as selective imidazoline receptor antagonists like moxonidine have been used in case of HTN resistance and renal failure.

The effectiveness of the antihypertensive therapy was assessed by measuring the reduction in BP. In our study, when ARBs were prescribed as monotherapy, the percentage mean reduction was 11.3% to 15.8% for SBP and 10.4% to 12.9% for DBP. When ARBs were prescribed as combination therapy, the reduction was 5.8% to 19.0% for SBP and 9.3% to 15.1% for DBP. Worldwide, HTN treatment strategies have varied widely regarding the initial drug of choice from diuretics to ACEIs, CCBs, ARBs, from monotherapy to low-dose combination single pill therapy. The JNC 8 criteria mention the BP goal as ≤140/90 mmHg in the general population <60 years without diabetes or kidney disease, or in all age groups with diabetes but no kidney disease. In our study, 40.5% of enrolled patients achieved the target BP goal (<140/90 mmHg). In a systematic review and metaanalysis of prevalence, awareness, and control of HTN, only ~10% of rural Indians and ~25% of urban Indians with HTN managed to control BP. Initial drugs of choice are ACEIs, ARBs, diuretics, and CCBs. In our study, ARBs were the most frequently prescribed; ACEIs were prescribed to only 0.3% of patients. Bharatia et al reported ARBs to be the most preferred agent as monotherapy (70.6%) and the most common component of dual (ARB+CCB) and triple (ARB+CCB+diuretics) combination therapies. Azilsartan was effective in reducing BP when used alone or in combination in patients with diabetes or renal failure.

With the rational use of antihypertensive therapy, the targeted BP goals can be achieved. What is needed is the awareness of HTN as a modifiable factor, which, when under control, can prevent the development of life-threatening cardiovascular and renal complications.

Three-fourths of the study population had a history of at least one major cardiovascular risk: 48.1% of patients had diabetes, 41.2% had dyslipidemia, and 15.1% had ischemic heart disease. Geldsetzer et al (2018) reported the crude prevalence of diabetes and HTN in India as 7.5% (95% confidence interval [CI], 7.3%-7.7%) and 25.3% (95% CI, 25.0%-25.6%). The high coprevalence of HTN and diabetes found in this study is concerning as India is ill-reputed for being the “diabetes capital of the world.” The alarming numbers being projected for these diseases in the coming years stress the need for health education and lifestyle modification in Indians.

Another important factor for treatment effects is compliance to antihypertensive therapy in the initial treatment periods, which was 87.9% in this study. True compliance gets reported only from real-world observational studies. Most (93.5%) Indian physicians believe that noncompliance is majorly responsible for uncontrolled HTN. Poor treatment adherence, mostly in the rural setting, was common in patients with HTN because of the presence of a symptom-free period. In a longitudinal study conducted in an urban city in India, patients changed or discontinued treatment because of lack of efficacy
and adverse effects, such as dizziness, edema, cough, and rash.\textsuperscript{34} No ADRs were reported in our study. The safety and efficacy of the currently used antihypertensive drugs is well proven. Our study proves their effectiveness and tolerability in patients with comorbidities and on concomitant medications in the initial treatment phase.

Our study limitations include its observational study design and a short follow-up period of 46 weeks. New diagnosis of HTN coupled with a short followup may also have led to higher compliance. A record of symptoms for which the patients visited the physicians would have provided information about patients’ awareness regarding HTN. Subgroup analysis with age, body mass index, HTN duration, and gender would have proven useful. The real-life setting did not allow comparative efficacy and safety of different drugs. A record of whether the patients were counseled for lifestyle modifications, and whether they followed it, even for the short followup period, would have generated data regarding the importance of treating the risk factors for HTN and their role in achieving BP goals.

Ours is an observational registry with a fairly large sample size, high retention rate, and data obtained from across various geographical locations; therefore, the results are relevant to the clinical practice setting in urban India. Our study confirms that prescribing trends are rational and are per the existing guidelines. However, long-term studies will be required to evaluate drug prescription patterns, patients’ adherence to treatment, reasons for non-adherence, and the effect of comorbidities on BP control.

CONCLUSION
HTN management remains a challenge that requires special and supervised attention. Indian practitioners prefer ARB as monotherapy followed by ARB+CCB or ARB+BB for HTN management. Our results show that 40.5% of enrolled patients achieved the BP goal within 46 weeks of treatment.

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INTRODUCTION
Hypertension (HT) is a leading non-communicable public health problem and the morbidity and mortality associated with it is considerably high worldwide. World Health Organization (WHO) defined hypertension as “a humanitarian tragedy on a planetary scale.” It is estimated that due to hypertension up to 7 million people die prematurely and around 64 million disability adjusted life years (DALY) are lost.

In a recent data from WHO, the prevalence of hypertension was found to be 23% in Indian adults while in western countries (Europe) it was found to be as high as 40%. This high blood pressure puts the population at an excessive risk of stroke (hemorrhagic and ischemic), heart failure, acute coronary syndromes and chronic kidney disease (CKD). As per American Heart Association and National Institute of Health update on heart diseases and stroke, from 2001 to 2011, the death rate attributable to high blood pressure has increased by 13.2%, and the actual number of deaths rose to 39.3%. As per WHO the ten leading causes of disease burdening the world are perinatal disorders, lower respiratory tract infections, ischemic heart diseases, stroke, HIV/AIDS, diarrheal disease, depression, chronic obstructive pulmonary disease (COPD), malaria and tuberculosis. Between the year 1990 and 2001 there was up to 20% worldwide decrease in mortality due to communicable disease, similarly there was also reduction in mortality due to perinatal and maternal causes. Now non-communicable diseases have become the leading cause of death and disease burden, and as per recent data the NCD global burden has risen to 50%.

Today we have more than hundred drugs available to treat hypertension, either alone or in combinations. In spite of this notable progress in drug development, millions of hypertensive patients still continue to have BP levels far above the desirable target values based on their cardiovascular risk and co-morbid conditions. Present estimates for uncontrolled hypertension in general populations suggest that up to 30%–40% of the patients have BP levels above their optimal target.

In spite of much recent advancement in diagnosis and management of hypertension, we are not able to control hypertension. We are facing number of issues from availability of proper calibrated BP equipments to availability of many confusing varied guidelines by different groups and regions, which are at time difficult for general practitioner to interpret and follow. Important issues and challenges are shown in Table 1; we need to...
address these issues in future for achieving our target of controlling high BP and decreasing cardiovascular mortality.

1. Blood Pressure Measurement

Mercury sphygmomanometer has been considered to be the ‘Gold Standard’ among BP measuring devices from which treatment recommendations were developed since early 80’s. However, mercury is a potent human neurotoxin and therefore its use has been banned. In present time, majority of the physicians use either aneroid sphygmomanometer or oscillometric battery operated BP devices. The battery-operated oscilloscope has become very popular for home based self-monitoring of BP. There are several advantages associated with these oscillometric devices. These battery operated BP instrument are popular with physicians, patients and their home care givers. The advantage of oscilloscope BP instruments includes ease of use, economical, easier to read and interpret the digital reading compared to aneroid needle, and also availability of memory function in some of the higher-end instruments comes handy in keeping previous records. The World health organization also recommended its use in resource-limited settings considering its low cost and limited need for trained man power. They also reduce terminal digit preference, viewer bias and reduce white coat hypertension. However, in present time, the majority of oscillometric devices are sold in the market without any rigorous validation or check.[4] Since the algorithms to calculates the diastolic pressure and systolic pressure from the measured mean are proprietary are proprietary in nature, each model must be authorized separately before being promoted. The digital oscilloscope BP instruments are still not validated for use in elderly population, diabetes patient, pregnant females and in patient with arrhythmias. Therefore its use should be with caution in patient with these condition and there is urgent need for further trials in these group of patients to show there consistency in BP recording. The following agencies are authorized to issue standardization and validation certificates according to region of instruments: USFDA/ European CE or British standard Institute (BSI). In Indian Bureau of Indian Standard (BIS) or ISO is commonly used.

Once a sphygmomanometer is procured by a medical facility, it needs to be calibrated regularly, to avoid faulty reading. The WHO recommends annual or six monthly calibrations of mechanical BP instruments by the users as de-calibrated device may give faulty reading and lead to mismanagement. In a study of private and public hospitals of Sao Paolo (Brazil), calibration of aneroid manometer was tested against mercury manometer between year 2009 and 2010. The instrument was considered out of calibration when the differences in reading between test and control instrument were 4 mmHg or more. The study found that 56.2% of manometers were not calibrated. It was also observed that in 70.2% cases, no periodic evaluation was done. There were significant number of equipment with aged/damaged rubber extension, leaking valve and manometer not pointing to zero during rest. The calibration technique involves testing pressure readings between a standard
pressure meter, which could either be a digital pressure gauge or a mercury sphygmomanometer, and a test device, using a Y-connector to the cuff, which is wrapped around a rigid cylinder. As to possible replacement of aneroid for mercury devices, recent articles stated that when aneroid devices were calibrated and maintained suitably, they performed equally or even better than the mercury counterparts.4

In most instances physicians take single BP reading and rarely follow the ideal method of BP measurement. Ideally whenever possible, BP should be measured with patient relaxed and seated with his arm outstretched and supported. Two readings should be taken; if the average is 140/90 mmHg or more, an additional reading should be taken at the end of the consultation for confirmation. BP should be measured in both arms initially, and the arm with the higher reading should be used for future measurements.6 Physicians may not be able to follow ideal method due to heavy patient load in their clinics or sometime, it may be due to their ignorance of knowing the ideal method.

2. Patient Awareness

Adherence to medication is fundamental to controlling hypertension; non-adherence could result in hypertensive complications. Research has shown that there is a gradual rise in disease burden of heart failure, myocardial infarction and stroke in hypertensive patients. Family members are the key stakeholders in the hypertension management system. Family members are involved in shaping the lifestyle of the patients. Health education programs about hypertension should involve the community in general and family members of the hypertensive patients in specific. The monetary status of the patient can affect hypertension management in various ways. In some parts, non-adherence to medication is due to a low economic status resulting in difficulties to cover the costs of drugs. In addition to the individual and community level barriers, problems related to public health and services also play a major role in creating awareness among the general population. The media and health promotion materials are essential dimensions to encourage disease prevention and management. Empowering families and community with adequate information about hypertension and its management and continuous government support with medications could help overcome the challenge of non-adherence.

3. Multiplicity of guidelines

Despite favorable developments in hypertension treatment and control, the high occurrence of uncontrolled hypertension, particularly among geriatric age groups remains a challenge. Guidelines for hypertension in elderly are consensus reports developed by hypertension experts. Undoubtedly, provision of up-to-date material and guidelines for hypertension has contributed to enhanced high BP control and reduced death rates, secondary to reduced cardiovascular diseases mortality. Not unexpectedly, guidelines change over time, based on new information, evidence and increased availability of more effective antihypertensive agents. According to a recent report, most guidelines used today, suffer from shortcomings in development.7

In contrast to the National Institute of Health’s historical involvement in directing the JNC reports; Canadian and European guidelines have been guided by professional bodies, rather than by funding agencies. Both Canadians and European approaches have been more rational than the JNC reports in their approaches to guideline development, in terms of the frequency of reports and a willingness to revisit earlier recommendations, flexibility of the recommendations for clinical care.
and emphasis on implementation of current discrepant strategies. The suggestion by different professional groups highlights the inconvenience of translating science into a public policy.\textsuperscript{7-9} Although critical assessment of current science may expose ambiguities and uncertainties, conflicting references may confuse the physicians and possibly undermine the credibility of all recommendations. From a clinical viewpoint, the primary failure to achieve hypertension control may be associated with the failure of both providers and patients to implement recommendations rather than to the guidelines themselves. Guidelines presently serve as a key educational function, however they should not be considered as strict prescriptions for action but serve to allow the healthcare provider to make learned clinical judgments regarding the treatment of patients.\textsuperscript{10}

4. Hypertension with comorbidities

Hypertension is closely associated with a number of comorbidities notable among them are diabetes mellitus (DM), obesity, metabolic syndrome, chronic kidney disease (CKD) among others. Hypertension in these special populations with co-morbidities presents with unique challenge to the physicians. Elderly patients are unique to this group, as they are more susceptible to target organ damage therefore stringent targets for blood pressure control have been set up in some clinical guidelines. Patients with these comorbidities are more likely to require combination therapy, yet physicians are often hesitant to adjust the number and doses of medications to achieve target blood pressure. All available anti-hypertensive are equally efficient in controlling BP over 24 hours while some may exacerbate underlying metabolic abnormalities.

- Hypertension in Diabetes Mellitus type 2

There is a strong association between hypertension and diabetes, 15 out of 100 hypertensive patients have concomitant diabetes.\textsuperscript{8} This strong association, with their cumulative risk for renal damage and cardiovascular disease (CVD), makes aggressive control of blood pressure important in diabetic hypertensive. This is reflected in guideline, as diabetic patients has been recommended aggressive BP target of 130/80 mm.\textsuperscript{7} Diabetic patients in particular need effective 24-hour BP control, and antihypertensive medications should not exacerbate underlying metabolic abnormalities. Thiazide/thiazide-like diuretics and beta blocker drugs should not be used as the first-line therapy because they may worsen insulin resistance. Renin Angiotensin Aldosterone System (RAAS) blockers, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are recommended because of their superiority in slowing diabetic nephropathy. The new direct renin inhibitor Aliskiren may offer additional reno-protective effects when added to recommended treatment with losartan and optimal antihypertensive therapy.\textsuperscript{9}

- Hypertension in Elderly:

India is in a transition phase of demography. There has been a marked increase in the number of elderly population between 1991 and 2001. Recent projection estimates that by the year 2050, the geriatric population in India would rise to about 324 million. The effective and safe management of hypertension in elderly cohort is both critical and challenging, first to improve patient outcomes and secondly to reduce health care costs. This can be accomplished by using present guidelines and targeted approach to geriatric
principles of treatment. A higher Target of initial systolic BP (SBP) 150 mm Hg, and a diastolic BP (DBP) 90 mm Hg in late elderly or frail patient instead of 140/90 mmHg is a prudent approach as suggested by various guidelines. Evidence indicates that numerous classes of antihypertensive drugs are effective in stopping CVS events, but considering effectiveness and best side effect profile, a long-acting dihydropyridine- calcium channel blocker (CCB) should be preferred first. Angiotension converting enzyme-inhibitor (ACE-I) should be used if there is comorbid diabetes, ischemic heart disease, or CKD. Presence of concomitant cardiac illness should decide the individualization of the treatment in elderly.11

• Hypertension in CKD

Hypertension and chronic kidney disease are closely linked with an overlapping and intermingled cause and effect relationship. Deteriorations in kidney function are typically associated with the rise in blood pressure (BP) and sustained elevations in BP hasten the decline in kidney function. Salt sensitivity is especially marked in hypertensive CKD. Impairment of BP dipping during sleep and exaggerated hypertensive response to dietary salt restrictions, all highlight the importance of salt in patients with CKD.9 Non dipping of BP at night in CKD patients can also lead to poor BP control and may mandate night time dosing of antihypertensive medication. Chronic kidney disease itself can lead to BP drugs resistance; however any patient who remains uncontrolled on optimum doses of three different antihypertensive medication classes, which includes a diuretic, should undergo an evaluation for a secondary hypertension. In addition to the well-established use of an ACE-I or angiotensin receptor blocker (ARB), the dietary salt restriction and appropriate diuretic therapy, sum up the HT treatment in patients with CKD. Use of above drugs may not be possible in advanced CKD due to risk of increasing azotemia, drugs like beta blockers and calcium channel blockers (CCB) may be need to be introduced. Drugs that decrease the sympathetic outflow such as clonidine and alpha blockers (prazosin) have been successfully used in advanced CKD.

5. Secondary and Resistant Hypertension including Hyperaldosteronism

Resistant hypertension is defined as blood pressure that remains above the goal despite concurrent use of three antihypertensive agents of different classes, one of which should be a diuretic.12 Secondary Hypertension is due to a secondary medical condition and needs to be differentiated from essential or primary HT. It is the secondary causes of HT, which most commonly lead to resistant hypertension. Undiagnosed forms of secondary hypertension are likely to substantially contribute to the ongoing epidemic of uncontrolled hypertension. Thus, a considerable proportion of these patients now mislabeled as “essential hypertension,” this group of patient’s blood pressure can be controlled or cured, once the secondary cause of HT is taken care off. Special mention among the causes of secondary HT, and hence resistant hypertension is primary hyperaldosteronism as it is the most common endocrine cause and also probably the most under diagnosed and under-treated, cause of hypertension.12-13 As a result many patients who could be cured, are unnecessarily get exposed to antihypertensive medicines for their complete lifetime. At the same time, they remain exposed to an excess risk of cardiovascular events. Numerous reasons can account for this ominous situation. The still
prevalent, albeit wrong, perception that primary aldosteronism is exceptionally rare is the first of them. The second reason may be due to the fact that the diagnostic workup is too complex for primary health care center (PHC), where most of the HT patients get diagnosed and treated. The development of simplified diagnostic algorithms based on novel biomarkers or making simple algorithm for general physicians to understand is therefore, a key challenge for the hypertension expert and specialists. These algorithms could then be used to screen these patients at PHC level, leading to a more aimed treatment with resulting improved BP control.

6. Genomics and Hypertension
Genetic cause of hypertension has been a major topic of research for many researchers for past 2-3 decades, some impressive studies to know the inheritance pattern and associations of hypertension with specific genes has been discovered. Genetic location of few monogenic hypersensitive disease like Familial Hyperaldosteronism (FH)-1 (GRA), Liddle’s syndrome, Gordon syndrome and more recently FH-3 has been documented. Even when association of BP with genetic variants was identified, the relative risk of hypertension in the individual carrying the variants was miniscule. Therefore, the impact of these studies on clinical practice has been negligible. A key challenge for the future is therefore to improve the stratification of the hypertensive patients not only for gender, age, and/or BP values but also for traits that can better lend themselves for the genetic analysis. While the vision of uncovering new targets for pharmacologic intervention and of creating novel agents for individualized treatment glimmers tantalizingly distant. Much closer to application would be to use the genetic information, to know how these genetic variations affect the efficacy of drugs, and to guide prescribing decisions for agents currently in the market.

7. Other Challenges (white coat, masked hypertension)
When Blood pressure is high at office but not in the home, the condition so-called is “masked hypertension,” the diagnosis is very challenging to make. Although it can occur at any age, it is more common in older men and women. White coat hypertension is the result of an exaggerated white coat effect of physician, which may be a conditioned anxiety response. Masked and situational hypertension known as “white coat hypertension” must be considered in this situation. Home and office BP measurements as well a 24-hour ambulatory BP monitoring may be helpful in diagnosing this condition and help in avoiding unnecessary drug treatment which may be harmful too.

CONCLUSION
The issue of correct blood pressure measurement by standard method, by a standardized and validated sphygmomanometer is important for diagnosis and management of hypertension. Similarly it is also essential that physicians or hospital administration should get all sphygmomanometer annual checked and calibrated to avoid faulty BP reading. Appropriate antihypertensive drug therapy with healthy lifestyle, regular exercise and low salt intake are essential for optimum BP control. The challenges of secondary hypertension, masked hypertension and resistant hypertension can be taken care by good clinical history, examination and keeping high clinical suspicion in appropriate cases. The various hypertension guidelines may also help in knowing the drug and target of treatment. The guidelines should be simplified with the general practitioner in mind, instead of “by the specialist and for the specialist approach”. In spite of so many issues and challenges the future of hypertension management appears to be bright, with advancement of scientific technology
and development of genetic research for personalized medicine according to genetic makeup.

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Alpha Blockers: Role in Hypertension

Dilip A. Kirpalani

TYPES OF ALPHA RECEPTORS
Alpha Receptors exist on peripheral sympathetic nerve terminals and are of 2 types:- Alpha 1 and Alpha 2. Alpha 1 Receptors exist postsynaptically and are divided into 3 highly homologous subtypes, namely, Alpha 1A, Alpha 1B and Alpha 1D. The function of these receptors include causation of vasoconstriction, smooth muscle contraction of internal urethral sphincter, contraction of sphincters in gastrointestinal tract, increased secretion from sweat and salivary glands, relaxation of smooth muscles of gut and pupillary dilatation.

The Alpha 2 Receptors are typically situated presynaptically but can also occur postsynaptically and have 3 subtypes, namely, Alpha 2A, Alpha 2B and Alpha 2C. The function of these receptors include inhibition of neurotransmitter release, decrease in central sympathetic outflow, decrease in insulin release and increased platelet aggregation.

ALPHA BLOCKERS IN HYPERTENSION
Alpha Receptor Antagonist drugs are broadly classified into non-selective and selective (Figure 1). The non-selective Alpha Blockers such as Phentolamine and Phenoxybenzamine are used only in the treatment of Pheochromocytoma. They are not used in the management of Chronic Hypertension as they have major side effects such as Orthostatic Hypotension and Tachycardia as a result of their non-selectivity. Amongst the selective Alpha Blockers, the Alpha 1 Blockers such as Prazosin, Terazosin, and Doxazosin have a role to play in the management of Chronic Hypertension mainly as third line and fourth line agents being added on.

Another group of drugs used in the management of Chronic Hypertension are Presynaptic Alpha 2 Receptor Agonists such as Clonidine and Moxonidine, as agonism of the Presynaptic Alpha 2 Receptor causes a reduction in central sympathetic outflow.

Inhibitors of Alpha 2 Receptor will actually cause an increase in Blood Pressure and this group of drugs, of which Yohimbine is an example, were used in the past for treatment of Orthostatic Hypotension.

ALPHA 1 RECEPTOR ANTAGONISTS IN TREATMENT OF BLOOD PRESSURE
Alpha 1 Receptor Antagonists reduce Blood Pressure by decreasing Peripheral Vascular Resistance. They do so by acting on Alpha 1 Receptors (primarily Alpha 1B subtype of Alpha 1 Receptor) on vascular smooth muscle and thereby cause a reduction in vasoconstriction. They prevent the pressor effects of usual doses of Alpha Agonists on the vascular smooth muscle, hence causing vasodilatation. Their main side effect therefore, is causation of Orthostatic Hypotension.

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Selective Alpha 1 Blockers which are used in clinical practice today for treatment of Hypertension are Doxazosin, Prazosin and Terazosin. Doxazosin has a longer half life of 22 hours and the dose is 4 mg to 16 mg per day in one or two divided doses. The major adverse event is Orthostatic Hypotension, which may be severe after the first few doses but is otherwise uncommon (First Dose Phenomenon).

Prazosin has a short half life of 3 hours, bioavailability of 50% and the dose is 5 mg to 20 mg per day in 2 to 3 divided doses. It causes little or no reflex tachycardia.

Terazosin has a high bioavailability, a half life of 9 to 12 hours and the dose is 5 mg to 20 mg per day in one or two divided doses.

Selective Alpha 1 blockers such as Prazosin and Terazosin are considered drugs of choice in male hypertensives who also have Benign Prostatic Hyperplasia as these drugs also relax the smooth muscle in the prostate gland and those in the urinary bladder neck.

**Fig. 1: Classification of Alpha Blockers**

Selective Alpha 1 Receptor Antagonists are excellent drugs in the management of Chronic Hypertension with a good tolerability profile. The TOMHS study and the GATES study showed that Doxazosin is a very potent antihypertensive.

In the ASOCIA study, which was a short study but involving over 3500 patients, it was shown that target BP was achieved in 61% of patients at 16 weeks with Doxazosin used as an add on therapy, versus placebo. In this study, there was an average 15% fall in pulse pressure and an average 19% fall in rate pressure product amongst the subjects after adding on Doxazosin, thereby reducing resting myocardial oxygen demand.

The pleiotropic benefits of Alpha 1 Receptor Antagonists are many; namely, decrease in Total and LDL Cholesterol, improvement in insulin sensitivity, improvement in endothelial function and thereby reduction in arterial stiffness and lastly, recovery of spontaneous baroreflex sensitivity and short-term heart rate variability. They are the drugs of choice in elderly males with Hypertension and Benign Prostatic Hyperplasia, as they are known to cause relaxation of smooth muscle in bladder neck, prostatic capsule and prostatic urethra.

In CKD patients, when GFR is < 45 mL/min, and hyperkalaemia can be a major problem...
with increasing doses of Renin Angiotensin System blocker, the Alpha Blocker becomes a great add on drug to bring the BP down to target, especially when 3 or more antihypertensive agents are required for BP control, as is the case in large number of CKD patients. This is because Alpha Blockers neither alter serum Potassium nor do they have a direct effect on GFR.

**PRECAUTIONS WITH THE USE OF ALPHA 1 RECEPTOR ANTAGONISTS**

The one situation where we need to be cautious with the use of Alpha Blockers, is the elderly patients, as this group of drugs is notorious to cause postural hypotension. Hence, in this subset of patients, the Alpha Blocker must be started at a very low dose, preferably at night time, with a very gradual up titration of dose and the patient should be instructed to get up very gradually from a recumbent position.

We also need to bear in mind, that checking of supine and standing BP must be done in any patient who is on an Alpha 1 Receptor Antagonist.

**ALPHA BLOCKERS OTHER THAN SELECTIVE ALPHA 1 RECEPTOR ANTAGONISTS**

Labetolol is a combined Alpha and Beta Blocker which is very useful in treatment of Hypertension during pregnancy. It is also used parenterally in the treatment of Hypertensive Urgencies and Emergencies.

Carvedilol, another combined Alpha and Beta Blocker, although relatively weak in its antihypertensive potency, is used in treatment of Cardiac Failure.

**PRESYNAPATIC ALPHA 2 AGONISTS**

Clonidine and Moxonidine, though not Blockers of Alpha Receptors, deserve a mention here.

They are Presynaptic Alpha 2 Receptor Agonists and act as Antihypertensives by reducing central sympathetic outflow. Moxonidine has a very Selective Agonistic action at the Imidazoline 1 Receptor in the Rostral Ventrolateral Medulla (RVLM) and hence causes much lesser side effects such as sedation, compared to Clonidine. Both, Moxonidine and Clonidine are emerging as useful add on agents in treatment of difficult to treat Hypertension.

**CONCLUSIONS**

Alpha 1 Receptor Antagonists have been superseded by Calcium Channel Blockers, Diuretics and Blockers of the Renin Angiotensin System, as a first choice drug in treatment of Hypertension. Add on therapy is usually indicated in most patients in the natural history of Hypertension.

Alpha 1 Receptor Antagonists provide a definite third line or fourth line agent for BP control, particularly in Resistant Hypertension and difficult to treat Hypertension, more so if Aldosterone Antagonist is contraindicated due to Hyperkalaemia. Apart from being lipid neutral and glucose neutral, Alpha 1 Receptor Antagonists have many other Pleotropic benefits such as improvement in endothelial function.

Hypertension Guidelines, worldwide, which are not yet endorsing Alpha 1 Receptor Antagonists in a major way, must mention it as an add on option in difficult to treat Hypertension and should even mention it as a first line or second line Antihypertensive agent in a select group of hypertensives, namely, elderly males with Benign Prostatic Hyperplasia.

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“Assay that Made Me Walk”; A Case of Secondary Hypertension

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ABSTRACT
Endocrine hypertension is emerging as a major cause for secondary hypertension. We report a 31-year-old-male with acute onset paraparesis without sensory or sphincter disturbances and severe hypokalaemia. He was managed as hypokalaemic periodic paralysis; and improved with parenteral K⁺. On investigating for secondary hypertension, his CECT adrenal glands were normal, but had elevated serum aldosterone (36.9 ng/dl), low plasma renin (0.64 ng/dl) assays, with a high aldosterone to renin ratio highly suggestive of idiopathic primary hyperaldosteronism. Hyperaldosteronism once considered rare, now contributes to nearly 15% of all secondary hypertension; most diagnosed by adrenal imaging. Idiopathic primary hyperaldosteronism is characterised by hypertension, hypokalemia, normal adrenals and high serum aldosterone.

INTRODUCTION
Hypertension is associated with high vascular morbidity and mortality. Secondary hypertension accounts only to a small fraction of all hypertensions in clinical practice. The advancements in assays and imaging have made endocrine hypertension easily identifiable as cause for secondary hypertension. Though thought to be rare, endocrine hypertension forms a major component of secondary hypertension.

CASE REPORT
We report a 31-year-old-male presenting with acute onset paraparesis with no sensory or sphincter disturbances. His pulse was 100bpm; BP was 200/150mmHg; afebrile, with no features of meningeal irritation or raised intracranial hypertension. On examination he had normal cranial nerves; hypotonia, weak proximal muscles (3/5) and sluggish reflexes in lower limbs; flexor plantar response and normal sensory system.

Investigations showed S. K⁺ -1.9mEq/l, normal RFT and other electrolytes; normal blood counts, ESR, thyroid and liver function tests, elevated urine K⁺, sonography -normal kidneys and adrenals; ECG and 2D-ECHO showed left ventricular hypertrophy.
Provisional diagnosis of hypokalemic periodic paralysis was entertained; and parenteral K+ correction was initiated. But, ‘why hypertension?’ need to be answered. We could control the potassium and hypertension with parenteral plus oral potassium and oral prazosin respectively; with remarkable improvement in muscle power. CECT abdomen did not reveal adrenal hyperplasia (Figure 1), however the high serum aldosterone (36.9 ng/dl), low plasma renin (0.64 ng/dl) assays, and the resultant high aldosterone to renin ratio clinched the diagnosis of idiopathic primary Hyperaldosteronism. After 5 days of starting spironolactone his potassium levels and BP normalised.

DISCUSSION
Endocrine hypertension constitutes 5-10% of cases of secondary hypertension. Primary hyperaldosteronism is one of the major causes of endocrine hypertension, now contributes to nearly 15% of all secondary hypertension. Classical presentation of Primary hyperaldosteronism is with resistant hypertension and hypokalemia causing muscle weakness (Figure 2). Aldosterone is the primary mineralocorticoid secreted by the Adrenal Cortex. Aldosterone increases Sodium reabsorption and potassium secretion. In Primary Hyperaldosteronism, adrenal glands produce high aldosterone which leads to depletion of potassium and regain sodium. It is essential to differentiate primary hyperaldosteronism from Secondary hyperaldosteronism. Primary hyperaldosteronism is caused by defect of the adrenal glands resulting in aldosterone excess, where as secondary Hyperaldosteronism, is usually due to enhanced activity of renin in response to inadequate renal perfusion and hypotension. Most individuals with primary hyperaldosteronism have bilateral adrenal hyperplasia (idiopathic hyperaldosteronism).

Idiopathic Primary Hyperaldosteronism involves bilateral adrenal glands. Primary hyperaldosteronism is mostly diagnosed by adrenal imaging, blood investigations might reveal elevated plasma aldosterone concentration and reduced plasma renin activity. Ratio between plasma aldosterone and plasma renin activity is useful screening test and the ratio >30:1 with elevated plasma aldosterone (>20 ng/dL) has sensitivity of 90% and specificity of 91% for diagnosing Hyperaldosteronism. Idiopathic primary hyperaldosteronism is characterised by hypertension, hypokalemia, normal adrenals and high serum aldosterone.
CONCLUSION
It is prudent for a clinician to identify possible endocrine secondary hypertension in young with judicious investigations, so as to prevent complications. Hyperaldosteronism should be suspected in patients who present with low serum potassium levels and Resistant Hypertension. Hyperaldosteronism if not treated can lead to increased risk of cardiovascular events. Hyperaldosteronism can be treated with mineralocorticoid antagonists or adrenalectomy. Patient initially was reluctant to undergo the expensive assays, but he realised that “Assay made him walk”.

REFERENCES

Fig. 2: Hyperaldosteronism: Symptoms
Presents...

Rosuvastatin range

Specially designed for Indians

Roseday® - 5/10/20/40
Rosuvastatin 5/10/20/40 mg

Roseday® F5/F10/F20
Rosuvastatin 5/10/20 mg + Fumed Sodium Forte 181 mg

Roseday® A10/A10Forte
Rosuvastatin 10 mg + Aspirin 75/150 mg

Ref: # Data on file
USV Joins hands with World Hypertension League

Target
Target to Reduce the Burden of Hypertension in India

Tazloc®
Telmisartan Tablets 20/40/80 mg

Clinical ASCVD or estimated 10 years CVD risk >10%

Tazloc®-AM
Telmisartan 40/80 mg + Amlodipine 5 mg