Study of Serum Uric Acid in Essential Hypertension

Dr. Rohith Poondru Reddy [*] Dr. Naresh Monigari [**] Dr. Manjunath Hande[***]

[*]Senior Resident, Department of Cardiology, Kasturba Medical College, Manipal, India.
[**]Consultant physician, General Medicine, Life Line Hospitals, Karimnagar, Telangana, India.
[***]Professor and Head of Department, Department of General Medicine, Kasturba Medical College, Manipal, India.

***Abstract*- BACKGROUND:** Uric acid, which serves no biochemical function other than being an end product of purine metabolism, was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone. In 1797, a British chemist Wallaston detected uric acid in a tophus which was removed from his own ear. About 50 years later Alfred Baring Garrod, a British physician showed by chemical isolation that uric acid was abnormally high in gouty patients. In subsequent studies Garrod formulated a rational relationship between hyperuricemia and symptomatology of gouty patients.

Association between hypertension and hyperuricemia was recognized when a family with a unique and unfortunate pedigree attended Hammer Smith hospital in 1957. The father and six of the seven siblings had hyperuricemia, while the mother and all the siblings had hypertension[1]. This raised the question whether a raised serum uric acid was common in patients with hypertension.

METHODS:

- TYPE OF STUDY: This study was an age and sex matched prospective case control study. Matching for other confounding factors such as diet, alcohol and smoking was also done.
- STUDY PERIOD: The study was conducted during the period from September 2010 to September 2012 at Kasturba Hospital, Manipal.
- Institutional ethical committee clearance was obtained.

FINDINGS:

- Serum uric acid is significantly elevated in hypertensive as compared to normotensive individuals.
- Serum uric acid can be used probably as an early biochemical marker to determine the severity of hypertension as stage 2 hypertensive had more elevation in serum uric acid levels as compared to other hypertensive.
- The uric acid levels did not differ significantly between hypertensive with and without treatment.
- There is a considerable difference in the mean serum uric acid levels between stages 1, 2 and isolated systolic hypertension in the newly detected hypertensive but it is not of a linear correlation.

Thus serum uric acid estimation can be used for aiding in the diagnosis of essential hypertension as well as in assessment of the severity.

INTERPRETATION: Serum uric acid estimation can be used for aiding in the diagnosis of essential hypertension as well as in assessment of the severity.

FUNDING: None

I. INTRODUCTION

Uric acid, which serves no biochemical function other than being an end product of purine metabolism, was first discovered in 1776. A Swedish chemist Scheele isolated it from a urinary tract stone. In 1797, a British chemist Wallaston detected uric acid in a tophus which was removed from his own ear. About 50 years later Alfred Baring Garrod, a British physician showed by chemical isolation that uric acid was abnormally high in gouty patients. In subsequent studies Garrod formulated a rational relationship between hyperuricemia and symptomatology of gouty patients.

Association between hypertension and hyperuricemia was recognized when a family with a unique and unfortunate pedigree attended Hammer Smith hospital in 1957. The father and six of the seven siblings had hyperuricemia, while the mother and all the siblings had hypertension[1]. This raised the question whether a raised serum uric acid was common in patients with hypertension.

Raised serum uric acid has been reported to be associated with an increased risk of coronary heart disease and is commonly encountered with essential hypertension, even untreated hypertension, and type 2 diabetes, which are in turn associated with coronary heart disease. It is not known whether raised serum uric acid increases the risk of hypertension and type 2 diabetes independently of known risk factors such as age, obesity, alcohol consumption, and physical activity[2].

Hypertension is the third leading killer disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide[3]. The prevalence of hypertension is known to increase with age. Over 50% of individuals aged 60 to 69 and over 75% of those aged 70 years and older are affected. Recent Framingham Heart Study reported that lifetime risk of developing hypertension is approximately 90% for men and women who are normotensive at 55-65 years old and survived to the age of 80-85 years[4].

Studies have shown that BP is an independent risk factor for cardiovascular disease. This relationship is independent, consistent and continuous. Observations involving more than 1 million individuals have shown that death from both cardiovascular disease and stroke increases progressively and linearly from BP levels of as low as 115mm systolic and 75 mm diastolic upwards. The increased risks are present in all age groups ranging from 40 to 89 years old. For every increment of 20 mm hg systolic or 10mm diastolic there was a doubling of mortality from both ischemic heart disease and stroke[5].

Evidence also warrants greater attention to the importance of SBP as a major risk factor for cardiovascular disease. The rise in SBP continues throughout life, in contrast to DBP, which rises

until approximately 50 years age, tends to level off over the next decade, and may remain same or fall later in life. Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, CV mortality, and stroke and HF events[6, 7].

Definition

The best operational definition for hypertension is "the level at which the benefits (minus the risks and costs) of action exceed the risks and costs (minus the benefits) of inaction"[8].

Classification of Blood Pressure

Based on the seventh report of the Joint National Committee on prevention, detection, evaluation and treatment of high blood pressure (JNC 7 report) BP is classified into the following stages –

Table-1: Classification of Blood Pressure for adults > 18 years

BLOOD PRESSURE STAGING	SYSTOLIC BLOOD PRESSURE IN MM OF HG	DIASTOLIC BLOOD PRESSURE IN MM OF HG
NORMAL	<120	AND<80
PREHYPERTENSION	120-139	OR 80-89
STAGE 1 HYPERTENSION	140-159	OR 90-99
STAGE 2 HYPERTENSION	>160	OR >100
ISOLATED SYSTOLIC HYPERTENSION	>140	AND <89

In contrast with the classification provided in the JNC VI report, a new category designated prehypertension has been added and stages 2 and 3 have been combined[9].

Patients with prehypertension are at increased risk for progression to hypertension; those in the 130/80 to 139/89 mm hg BP range are at twice the risk to develop hypertension as those with lower values.[10]

Genetic Considerations

Essential hypertension is almost certainly a polygenic disorder, involving multiple genes, each having small effects on blood pressure[11].

Natural history of Untreated Hypertension

Both the rising SBP and falling DBP levels logically are associated with an increased risk for atherosclerotic vascular diseases. The resultant widening pulse pressures have been widely reported to be the best prognostic indicator of cardiovascular risk.

However, an analysis of data from one million adults in 61 prospective studies found that, for predicting mortality from both stroke and coronary disease, the SBP is slightly more informative than DBP and that pulse pressure is much less informative[12].

Hypertension and Hyperuricemia:

Hyperuricemia is present in 25 – 50 % of individuals with untreated primary hypertension, about 5 times the frequency found in normotensive persons. Hyperuricemia reflects decreased renal blood flow presumably a reflection of nephrosclerosis[13].

Raised serum uric acid concentrations in the blood are commonly encountered in essential hypertension. Although the raised serum uric acid and episodes of gout are occasionally attributable to therapy, asymptomatic hyperuricemia not infrequently precedes the diagnosis and treatment of essential hypertension.

The hyperuricemia observed in untreated hypertension may reflect the decrease in renal blood flow and early hypertensive nephrosclerosis. However, antihypertensive drug regimens, especially those including diuretics, do confound the link between hypertension-associated morbidity and mortality.

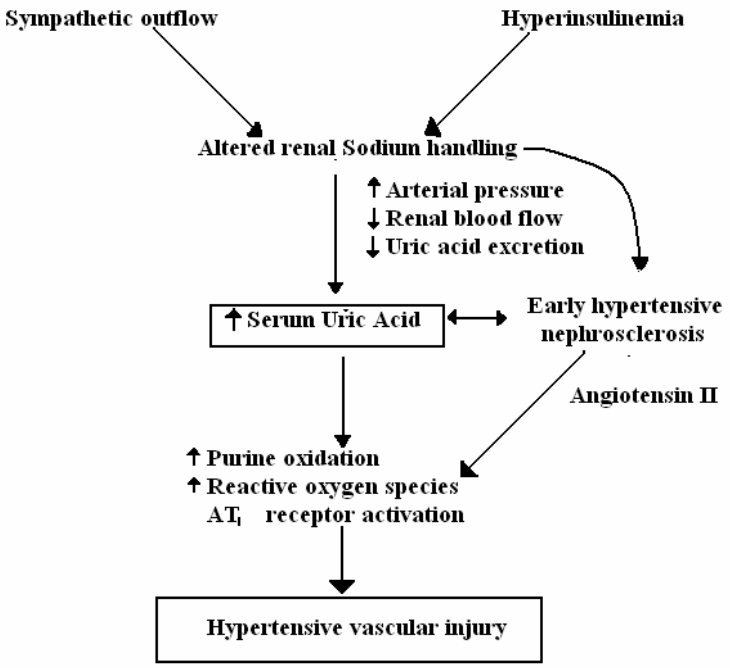
Epidemiological evidence to support the contention that uric acid is an independent risk factor for hypertension- associated morbidity can be gleaned from a recent multivariate analysis of 1988-94 data on 3900 hypertensive people from the public-use database of the US National Health and Nutrition Survey (NHANES III). It showed that raised serum uric acid was associated with significantly higher sex-adjusted risk of heart attack and stroke. Hypertensive people with raised serum uric acid had a significantly higher relative risk (RR) for both heart attack and stroke. The NHANES III data support the hypothesis that uric acid is an independent risk factor for hypertension-associated morbidity and mortality.

The renal handling of uric acid may provide a physiological clue to why hypertension-associated morbidity is closely linked to serum uric acid. It is well established that serum uric acid increases as arterial blood pressure rises and is associated with a reduction in renal blood flow.

High serum uric acid concentrations may increase serum sodium reabsorption at nephron sites proximal to the distal tubule, and it has been proposed that metabolic perturbations such as hyperinsulinaemia may mediate some of the effects of hypertension. (Figure 1)

Hyperuricaemia may represent the culmination a multi-metabolic syndrome in which insulin-mediated renal hemodynamic abnormalities lead to hypertensive renal damage. It seems safe to say that hyperuricaemia in hypertension may be an early indicator of hypertensive cardio renal disease, which is commonly associated with a multi-metabolic syndrome[14].

Figure 1: Interaction between renal pathophysiology of hyperuricemia and hypertension



Hyperuricemia:

Hyperuricemia may be defined as a plasma (or serum) urate concentration >420 umol/L (7.0 mg/dL). This definition is based on physicochemical, epidemiologic, and disease-related criteria. Physicochemically, hyperuricemia is the concentration of urate in the blood that exceeds the solubility limits of monosodium urate in plasma, 415 umol/L (6.8 mg/dL).

In epidemiologic studies, hyperuricemia is defined as the mean plus 2 standard deviations of values determined from a randomly selected healthy population. When measured in unselected individuals, 95% have serum urate concentrations <420 umol/L (7.0 mg/dL).

Finally, hyperuricemia can be defined in relation to the risk of disease. The risk of developing gouty arthritis or urolithiasis increases with urate levels >420 umol/L (7.0 mg/dL) and escalates in proportion to the degree of elevation. Hyperuricemia is present in between 2.0 and 13.2% of ambulatory adults and somewhat more frequently in hospitalized individuals[15].

Increased Serum Uric Acid in Hypertension:

The mechanisms underlying the increase in serum uric acid and its potential prognostic implications in patients with essential hypertension are still not completely known. Uric acid, a final product of purine metabolism, is 5% plasma protein bound, is freely filtered at the glomerulus as a function of renal blood flow, is 99% reabsorbed in the proximal tubule, secreted by the distal tubule, and subjected to considerable post secretory reabsorption. Fractional secretion of uric acid is about 7% to 10%. A direct association exists between serum uric acid and renal vascular resistance in subjects with essential hypertension[16].

Uric acid is also commonly associated with hypertension. It is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension. The increase in serum uric acid in hypertension may be due to the decrease in renal blood flow that accompanies the hypertensive state, since a low renal blood flow will stimulate urate reabsorption. Hypertension also results in microvascular disease, and this can lead to local tissue ischemia[17].

In addition to the release of lactate that blocks urate secretion in the proximal tubule, ischemia also results in increased uric acid synthesis. With ischemia, ATP is degraded to adenine and xanthine, and there is also increased generation of xanthine oxidase. The increased availability of substrate (xanthine) and enzyme (xanthine oxidase) results in increased uric acid generation as well as oxidant (O_2^-) formation. The finding that ischemia results in an increase in uric acid levels may also account for why uric acid is increased in preeclampsia and congestive heart failure[18].

Other factors may also contribute to why uric acid is associated with hypertension, including alcohol abuse, lead intoxication, obesity and insulin resistance, and diuretic use.

The observation that an elevated uric acid is associated with subjects at cardiovascular risk may account for why hyperuricemia predicts the development of cardiovascular disease in the general population, in subjects with hypertension, and in subjects with preexisting cardiovascular disease. Hyperuricemia also predicts stroke in diabetic and nondiabetic subjects and predicts the development of hypertension and renal disease in the general population[19].

In these studies, uric acid may be simply "marking" subjects at increased cardiovascular and renal risk. Consistent with this hypothesis, many studies have found that uric acid is not an independent risk factor for cardiovascular disease after controlling for these other risk factors[20]. Hyperuricemia is therefore considered benign unless associated with gout or kidney stone.

Nevertheless, some studies find uric acid predictive for the development of cardiovascular disease, hypertension, and renal

disease despite controlling for associated risk factors. This raises the possibility that uric acid may have a pathogenic role in hypertension and cardiovascular disease. Indeed, recently soluble uric acid has been recognized to not be inert but rather to have several biological actions that could either be beneficial or detrimental to humans.

II. MATERIALS AND METHODS

- TYPE OF STUDY: This study was an age and sex matched prospective case control study. Matching for other confounding factors such as diet, alcohol and smoking was also done.
- STUDY PERIOD: The study was conducted during the period from September 2010 to September 2012 at Kasturba Hospital, Manipal.
- The study included a total of 142 patients of which 80 were cases (hypertensive) and 62 were controls (non hypertensive).
- Institutional ethical committee clearance was obtained.

Inclusion Criteria

1. Age > 18 yrs.
2. Newly detected patients of essential hypertension.
3. Patients with essential hypertension on treatment.

Exclusion Criteria

1. Patients with renal failure.
2. Patients on treatment with drugs altering uric acid levels such as thiazides, loop diuretics, pyrazinamide and allopurinol.
3. Lymphoproliferative or myeloproliferative disorders.
4. Secondary hypertension and pregnancy induced hypertension

III. METHODOLOGY

- The study included a total of 142 patients of which 80 were cases (hypertensive) and 62 were controls (non hypertensive).
- The patients were classified into the various stages of hypertension as per the JNC-7 mentioned in Table 1.
- Blood pressure has been recorded as the average of 2 or more readings at each of the 2 or more visits after initial screening.
- All the patients were subjected to relevant clinical examinations and laboratory investigations to look for secondary causes of hypertension.
- Essential hypertension is diagnosed in the absence of an identifiable cause.
- Hyperuricemia is defined as the serum uric acid >7.0 mg/dl in adult males, >6.0 mg/dl in adult females
- Serum uric acid levels are measured in the early morning venous blood sample after the patient is kept fasting for 12 hrs.
- Measurement of the serum uric acid was done by a chromatographic autoanalyser which absorbs light in the wavelength of 560 – 640 nm.

Reference Values for Serum Uric Acid levels -

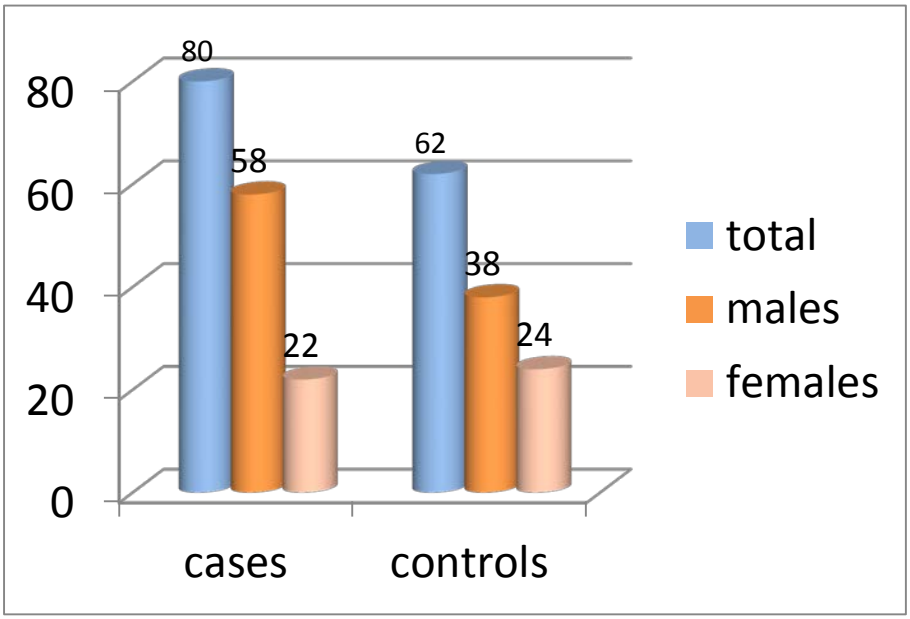
- In Males: 3.4 - 7.0 mg/dl, in females: 2.4 – 6.0 mg/dl.

OBSERVATIONS AND ANALYSIS:

- A total of 142 patients were studied during the period of 2 years from September 2010 to September 2012. This included 80 cases (hypertensive) and 62 controls (non hypertensive).
- Out of the 80 cases (hypertensive) 58 were males and 22 were females.

Out of the 62 controls (non hypertensive) 38 were males and 24 were females. (Figure 2)

Figure 2: Bar diagram representing the total number of cases and controls with sex wise distribution.



The range of the serum uric acid in cases was 1.40 to 11.30mg/dl. In hypertensive males it was found to be from 1.40 to 11.30 mg/dl and in hypertensive females it was found to be from 2.70 to 11.10 mg/dl. (Table 2)

Table 2: Range for uric acid in cases.

Total	**1.40 to 11.30 mg/dl**
Males	1.40 to 11.30 mg/dl
Females	2.70 to 11.10 mg/dl

The range of the serum uric acid in controls was 1.50 to 6.50 mg/dl. In Non-hypertensive males it was found to be from 1.50 to 6.50 mg/dl and in Non-hypertensive females it was found to be from 1.60 to 6.20 mg/dl. (Table 3)

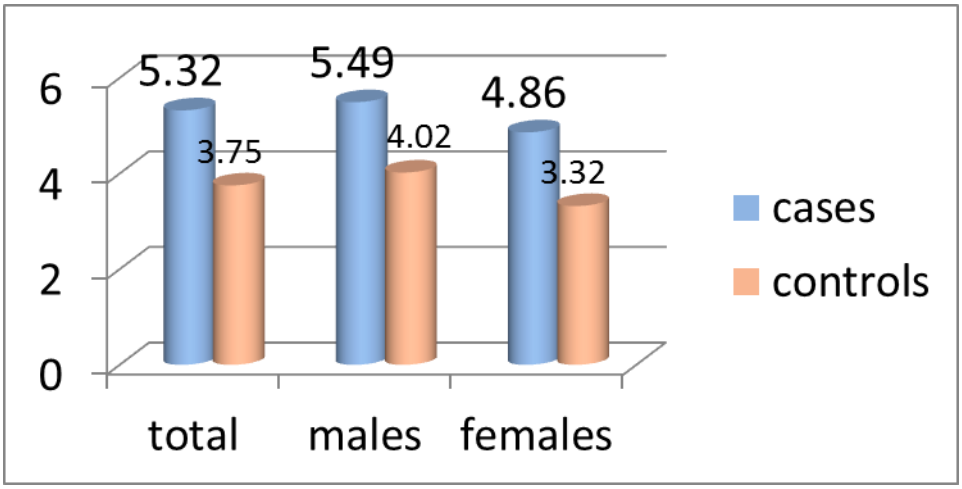
Table 3: Range for uric acid in controls

Total	**1.50 to 6.50 mg/dl**
Males	1.50 to 6.50 mg/dl
Females	1.60 to 6.20 mg/dl

The mean serum uric acid in cases (hypertensive) was 5.32 mg/dl and controls (non hypertensive) was 3.75 mg /dl. The mean serum uric acid in male cases and controls was 5.49 mg/dl and 4.02 mg/dl respectively. The mean serum uric acid in female cases and controls was 4.86 mg/dl and 3.32 mg/dl respectively. (Figure 3)

Data analysis by T-test , done to compare the mean serum uric acid values in hypertensive with that of non-hypertensive was proven to be significant with a p value of <0.001.

Figure 3: Bar diagram representing the mean serum uric acid levels in comparison to cases and controls with sex wise distribution



The cases were classified into the different stages as per the JNC-7 classification for hypertension. Known cases of hypertension, on treatment with a well-controlled blood pressure of <140/90 mm of hg were categorized under controlled hypertension.

Table 4: **Number of cases in different stages of hypertension with sex wise distribution.**

Out of the total 80 cases 14 were included under controlled hypertension, 26 under stage 1 hypertension, 31 under stage 2 hypertension and 9 under the isolated systolic hypertension category. (Table 4)

Stage	Males	Females	Total
Controlled hypertension	5.18 (3.80)	3.80 (1.32)	4.78(2.32)
Stage 1	4.32 (1.47)	4.60 (1.26)	4.42 (1.38)
Stage 2	6.75 (1.57)	5.83 (1.30)	6.57 (1.55)
Isolated systolic hypertension	4.12 (1.24)	5.10 (0.62)	4.44 (1.14)

The mean serum uric acid levels were found to be 4.78 (2.32) mg/dl, 4.42(1.38) mg/dl, 6.57(1.55) mg/dl and 4.44(1.44) mg/dl in controlled hypertension, stage 1 hypertension, stage 2 hypertension and isolated systolic hypertension respectively.(Table 5 and figure 4)

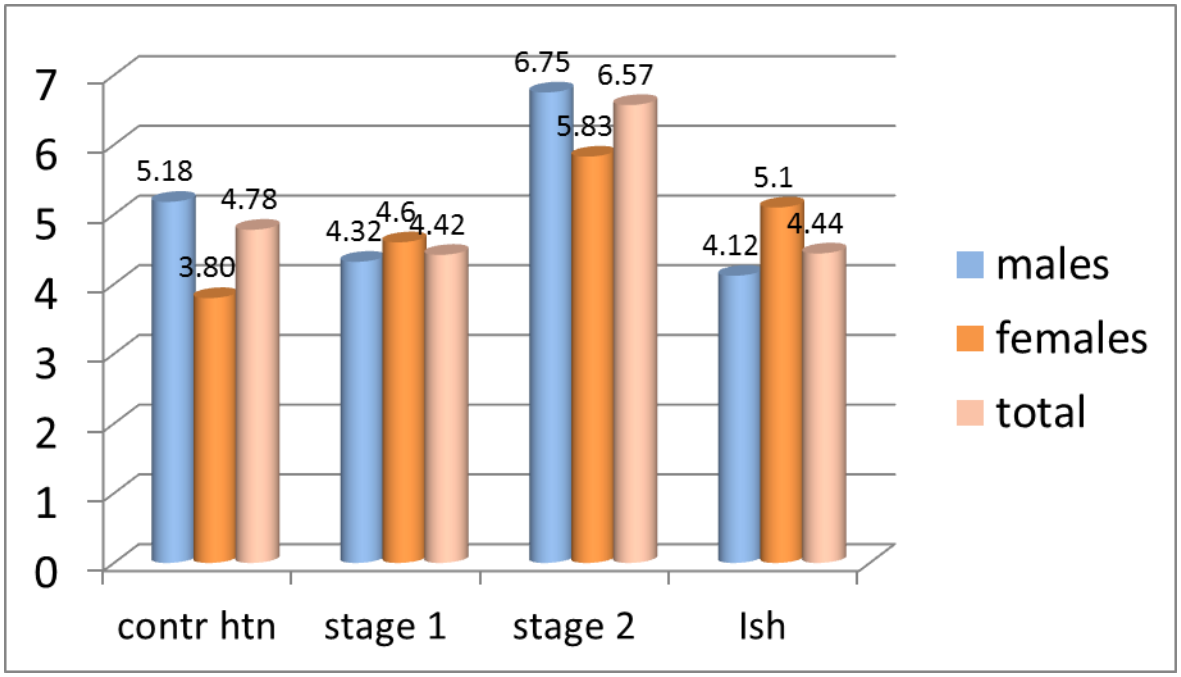
Data analysis done by one way Anova test showed significant difference between stage 2 hypertension with the stage 1 hypertensive, isolated systolic hypertensive and well controlled hypertensive with the p values of 0.001, 0.001 and 0.002 respectively.

*the values in the brackets ( ) indicate the standard deviation.

Table 5: Mean uric acid levels in mg/dl of cases in different stages of hypertension

Stage	Males	Females	Total
Controlled hypertension	10	4	14
Stage 1	17	9	26
Stage 2	25	6	31
Isolated systolic hypertension	6	3	9

Figure 4: Bar diagram depicting the mean serum uric acid levels of cases in different stages of hypertension



In the total of 80 hypertensive, 41 of them were on treatment and 39 of them were not on treatment and the mean serum uric acid value was 4.98 (1.76) mg/dl and 5.67 (1.97) respectively. (Table 6)

Cases were classified as newly detected hypertensives if they were detected to have hypertension as per the standard blood pressure measurements for the first time or during the previous 14 days and not on any form of treatment

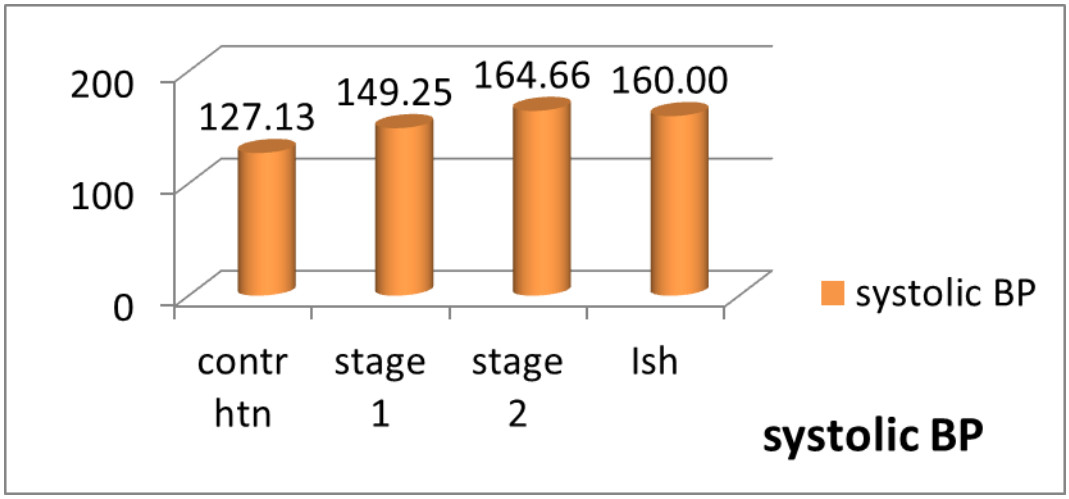
Table 6: **Comparison between hypertensive on and not on treatment**

Hypertensive	Total	Mean uric acid in mg/dl
On treatment	41	4.98 (1.76)
Newly detected and not on treatment	39	5.67 (1.97)

*values in the brackets ( ) indicate the standard deviation

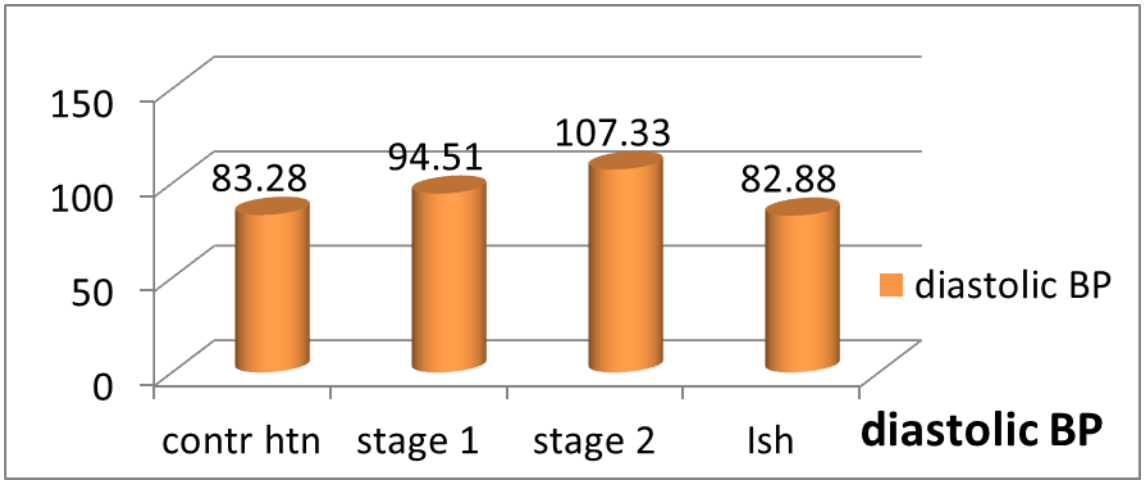
The mean systolic blood pressures recorded were 127.13 mm of hg, 149.25 mm of hg, 164.66 mm of hg and 160 mm of hg in the controlled hypertensive group, stage 1 hypertension, stage 2 hypertension and the isolated systolic hypertensive group respectively. (Figure 5)

Figure 5: Bar diagram depicting the mean systolic BP in different stages of hypertension



The mean diastolic blood pressures recorded were 83.28 mm of hg, 94.51 mm of hg, 107.33 mm of hg and 82.88 mm of hg in the controlled hypertensive group, stage 1 hypertension, stage 2 hypertension and the isolated systolic hypertensive group respectively. (Figure 6)

Figure 6: Bar diagram depicting the mean diastolic BP in different stages of hypertension



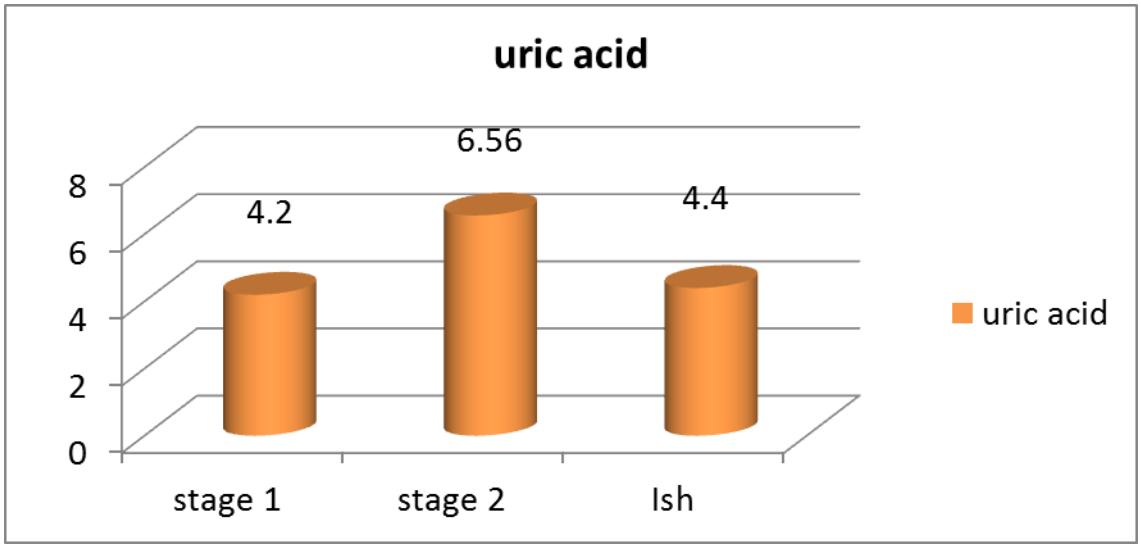
- The age group in cases (hypertensive) ranges from 19 yrs to 82 yrs .In males it ranges from 19 yrs to 81 yrs and females it ranges from 32 yrs to 82 yrs.
- The age group in controls (non hypertensives) ranges from 20 yrs to 81 yrs .In males it ranges from 20 yrs to 81 yrs and females it ranges from 26 yrs to 78 yrs
- The total number of newly detected hypertensives were 39 out of which 13 were diagnosed as stage 1 hypertension, 22 as stage 2 hypertension and 4 as isolated systolic hypertension.
- The mean of the serum uric acid was 4.20(1.37) mg/dl, 6.56(1.40) mg/dl and 4.40(1.40) in stage 1 hypertension, stage 2 hypertension and isolated systolic hypertension respectively, in newly diagnosed hypertensives. (Table 7 and figure 7)

Table 7: Newly diagnosed hypertensives

	Stage 1 hypertension	Stage 2 hypertension	Isolated systolic hypertension
Total no.	13	22	4
Mean serum uric acid in mg/dl	4.20(1.37)	6.56(1.40)	4.40(1.40)

*the values in the brackets ( ) indicate the standard deviation

Figure 7: Bar diagram depicting the mean serum uric acid values of newly detected hypertensives in different stages of hypertension



IV. DISCUSSION

Elevated serum uric acid levels have been associated with an increased risk for cardiovascular disease. The potential mechanisms by which serum uric acid may directly affect cardiovascular risk include enhanced platelet aggregation and inflammatory activation of the endothelium[21].

In few studies, the association of serum uric acid with cardiovascular disease was uncertain after multivariate adjustment as in the Framingham Heart Study [10] and the ARIC study , but in others such as the study done by *verdecchia et al*[22] the association remained certain and significant.

Because elevated serum uric acid is correlated with several risk factors including renal dysfunction, hypertension, insulin resistance, hyper-homocystenemia and hyperlipidemia, it is debated whether serum uric acid is an independent cardiovascular risk factor.

In the present study the mean serum uric acid in the hypertensive group was 5.49 (1.86) mg/dl in males and 4.86

(1.47) mg /dl in females. On the other hand the mean serum uric acid level in the control group was 4.02 (1.09) mg/dl in males and 3.32 (1.196) mg/dl in females.

Data analysis by T-test, done to compare the mean serum uric acid values in hypertensive with that of non-hypertensive was proven to be significant with a p value of <0.001.

Data analysis by one way Anova test, was done to compare the mean serum uric acid and their significance between the different stages of hypertension and showed the following results

Non hypertensive and stage 1 hypertension p value of 0.337.

Non hypertensive and stage 2 hypertension p value of <0.001.

Non hypertensive and controlled hypertension p value of 0.116.

Non hypertensive and isolated systolic hypertension p value of 0.664.

Though the difference in serum uric acid levels were found to be more in other stages of hypertension as compared to the non-hypertensive, statistical significance was found only in stage 2 hypertensive when compared to non-hypertensive.

There was also significant difference noted between stage 2 of hypertension with the stage 1 hypertensive, isolated systolic hypertensive and well controlled hypertensive with the p values of 0.001, 0.001 and 0.002 respectively.

There is a considerable difference in the mean serum uric acid levels between stages 1, 2 and isolated systolic hypertension in the newly detected hypertensive but it is not of a linear correlation.

The mean serum uric acid levels in the hypertensive on treatment was 4.90 (1.97) mg/dl and those not on treatment was 5.67 (1.76) mg/dl with a p-value of 0.514.

Hence it appears that treatment of hypertension does not cause significant difference in the serum uric acid levels.

In the *PIUMA study* involving 1720 subjects who were followed up for 12 years *Verdechchia et al* has reported that in untreated subjects with essential hypertension, raised uric acid is a powerful risk marker for subsequent cardiovascular disease and all-cause mortality [22] .

Abdallah jeraiah et al In the study involving 49 known hypertensive (31 males and 18 females) and 16 healthy controls (without hypertension) reported serum uric acid levels from patients taken from various hospitals with hypertension increased significantly when compared with controls ($p < 0.001$). Male and female hypertensive patients had showed significant increase in serum uric acid levels when compared with controls ($p < 0.001$) [23].

Selby et al conducted a nested case-control study of 1,031 cases of essential hypertension and 1,031 persistently normotensive controls from the Kaiser Permanente Multiphasic Health Checkup cohort in Northern California adjusting for the risk factors, forced vital capacity (p less than 0.001), serum uric acid ($p = 0.003$), serum cholesterol ($p = 0.012$), and heart rate ($p = 0.014$) remained independently predictive for essential hypertension.

Uric acid remained positively related to risk (odds ratio, fifth vs. first quintile = 2.19, 95% Cl 1.20-3.98).Both forced vital capacity and serum uric acid are closely linked to development of hypertension and may be markers of susceptibility or intermediate steps in pathways leading to hypertension [24].

Fessel et al observed an elevation of systolic blood pressure in hyperuricemic patients but no elevation of diastolic blood pressure could be observed [25].

Myers et al reported some elevation of serum uric acid level in accordance with the increased blood pressure, but it was not a definite correlation [26].

*Zainab abdul razak et a*l in their study in Iraq featuring 20 cases and 15 controls had a mean serum uric acid value of 8.03(3.50) mg/dl in comparison to 4.32(1.07) mg/dl with a significant p value of <0.05.

The study showed that the serum levels of uric acid, CRP and total cholesterol were significantly higher in patients with hypertension than in healthy controls [27].

It certainly is possible that uric acid may be an earlier and more sensitive maker of decreased renal blood flow than serum creatinine. It has been recently suggested that since uric acid may play a role in the formation of free radicals and oxidative stress, the increased risk of hypertension in subjects with raised serum uric acid levels might be associated with this increased generation of free radicals.

Several observations support this concept of free radical mediated inhibition of endothelium dependent vasodilation. An antioxidant deficiency in diet which produces hyperuricemia, contributes to the etiology of hypertension, and the antioxidant drugs also show a blood pressure lowering effect in both diabetic and hypertensive patients[28].

Three possible conclusions can be drawn from the association of hypertension with raised serum uric acid levels. Hypertension may arise as a result of hyperuricemia, hypertension can cause hyperuricemia and the duration and severity of hypertension is related directly to the serum uric acid levels.

In gouty patients without advanced tophi, however renal failure and hypertension are rare. In a group of 80 patient's attending the Hammersmith hospital gout clinic only 2 were hypertensive. In a study of gouty patients of Northern India by *Kumar et al* they found that only one out of 30 patients had hypertension[29].

Fessel et al showed no appreciable loss of renal function in 112 patients with gout as compared to normal subjects followed up for 12 years[25].

In a study by *Lawrence E Ramsay* there was no evidence that hyperuricemia had a deleterious effect on renal function[30].
Canon et al considered that an impairment of renal function will raise the serum uric acid levels more commonly than an increased serum uric acid will cause renal damage[31].

Hence it is unlikely that hypertension arises as a result of raised serum uric acid levels, but the possibility that uric acid which plays a role in the formation of free radicals and oxidative stress, the increased risk of hypertension in subjects with raised serum uric acid levels might be associated with this increased generation of free radicals. Hence the fact that raised serum uric acid levels can lead to Hypertension cannot be entirely ruled out.
As to the possibility that Hypertension can cause hyperuricemia, it is thought that hyperuricemia can result from either overproduction of uric acid or from under excretion of uric acid.
Overproduction of uric acid can be measured by the rate of incorporation of acid precursors such as Glycine labeled N 15, into the uric acid pool. Such a study carried out in 4 hypertensive

patients with raised serum uric acid levels did not show any overproduction of uric acid.

In the study of *Breckenridge* [1] excretion of uric acid and uric acid clearance were lower in all hypertensive patients than in the normal group. When the uric acid clearance was expressed per 100ml of glomerular filtrate, there was no significant difference between normal subjects and hypertensive patients who had normal serum uric acid levels, but the difference between those 2 groups and the hyperuricemic hypertensive was significant and they suggested a renal tubular abnormality in the handling of uric acid, the nature of the abnormality which was not clear.

Later *Messerli et al* showed that hyperuricemia in hypertensive is due to early renal vascular involvement, namely nephrosclerosis [28]. Serum uric acid rises because of impaired renal tubular function, which is the main site of regulation of serum uric acid due to nephrosclerosis. *Tykarski* in his study showed that serum uric acid levels in hypertensives are due to impaired tubular secretion of urate [32].

In the *present study* incidence and severity of elevated serum uric acid levels between cases and controls correlated significantly with the severity of hypertension. This correlated with both the Kinsey [33] and Breckenridge [1]studies, but according to *Cannon et al* [31] severity of hypertension had no relation to serum uric acid levels. Our study agrees with the study of *Tykarski et al* in that there is a positive correlation between serum uric acid and severity of hypertension[32] as per the stages but it is not of a linear correlation.

Breckenridge in his study showed an increasing incidence of hyperuricemia as the diastolic BP increased in his study, but there was no tendency for hyperuricemia to occur, only with patients with more severe hypertension [1].

The PIUMA study demonstrates a strong independent association between serum uric acid levels and CV risk in initially untreated and asymptomatic adult subjects with essential hypertension, but it is unable to answer the question of whether serum uric acid exerts direct toxic effects. As extensively reviewed by *Puig and Ruilope*, [34] both uric acid and superoxide radicals are produced for the effect of xanthine oxidase in the late phase of purine metabolism. Superoxide radicals, which may cause tissue and vascular damage, [35] are increased in subjects with essential hypertension.[36] It would be important to clarify whether such increase is due, at least in part, to enhanced xanthine oxidase activity and whether inhibition of this enzyme by allopurinol may reduce CV risk .[37]

In our study it was found that there is definite relation in serum uric acid levels between hypertensive patients and normotensive patients and there is a directly proportional relation in the levels of serum uric acid in relation to the severity of hypertension, though it is not of a linear correlation. Also it was found that there was no significant difference in the levels of serum uric acid in hypertensive on treatment as compared to those not on treatment.

Hence the possibility of serum uric acid acting by the production of free radicals and causing oxidative stress leading to hypertension and whether the duration and severity of hypertension lead to renal dysfunction in the form of nephrosclerosis leading to higher levels of serum uric acid has to be considered as various other studies have also shown to have a positive relation in the serum uric acid levels and hypertension.

V. CONCLUSION

Thus based on the study carried out we can conclude that

1. Serum uric acid is significantly elevated in hypertensive as compared to normotensive individuals.
2. Serum uric acid can be used probably as an early biochemical marker to determine the severity of hypertension as stage 2 hypertensive had more elevation in serum uric acid levels as compared to other hypertensive.
3. The uric acid levels did not differ significantly between hypertensive with and without treatment.
4. There is a considerable difference in the mean serum uric acid levels between stages 1, 2 and isolated systolic hypertension in the newly detected hypertensive but it is not of a linear correlation.
5. Thus serum uric acid estimation can be used for aiding in the diagnosis of essential hypertension as well as in assessment of the severity.

REFERENCES

[1] A. Breckenridge “Hypertension and Hyperuricemia” The Lancet 1966: 287; 15-18.

[2] Frohlich ED “Uric acid: A risk factor for coronary heart disease.” JAMA 1993; 270:378-379.

[3] World Health report 2002. Reducing Risks and Promoting Healthy Life Geneva, Switzerland: World Health Organization; 2002: 7, 58. http://www.who.int/whr/2002.

[4] Vasan R S, Beiser A, Sheshadri S, et al. “Residual lifetime risk for developing hypertension in middle-aged women and men: The Framingham Heart Study.” JAMA 2002; 287:1003-1010.

[5] Lewington S, Clerk R, Qizilbash N, et al. “ A meta-analysis of individual data for 1 million adults in 61 prospective studies”. Prospective Studies Collaboration. Lancet 2002:360:1903-1913.

[6] SHEP Cooperative Research Group. “Prevention of Stroke by antihypertensive drug treatment in older patients with isolated systolic hypertension, Final results of the Systolic Hypertension in the Elderly Program (SHEP)”. JAMA 1991; 265:3255-3264.

[7] Staessen JA, Thijis L, Fagard R et al. “ Predicting cardiovascular risk using conventional vs. ambulatory blood pressure in older patients with systolic hypertension”. JAMA 1999; 282:539-546.

[8] Norman M Kaplan, Braunwald’s textbook of Cardiovascular Medicine 9th edition, “Systemic Hypertension: Mechanism and Diagnosis”; Elsevier Saunders 37:962.

[9] Aram V. Chobanian, George L. Bakris. “ The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure” JAMA, 2003, May 21,vol 289; 2561-2562.

[10] Vasan RS, Larson MG, Leip EP et al “ Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study” Lancet 2001; 358: 1682-1686.

[11] Luft FC “Hypertension as a complex genetic trait” Seminar in Nephrology, 2002 22:115.

[12] Prospective Studies Collaboration: “Age specific relevance of usual blood pressure to vascular mortality: A Meta analysis of individual data for 1 million adults in 61 prospective studies” Lancet 2002, 360; 1903.

[13] Norman M Kaplan, Braunwald’s textbook of Cardiovascular Medicine 9th edition “Systemic Hypertension: Mechanism and Diagnosis.” Elsevier Saunders 37:935-972.

[14] Harry J. Ward, “Uric Acid as an independent risk factor in the treatment of hypertension” The Lancet 1998:352:670-671.

[15] Robert L. Wortmann “Disorders of Purine and Pyrimidine Metabolism” Harrison’s Principles of Internal Medicine 18th edition, Mc-Gram Hill, 3182-3185.

[16] Richard J. Johnson; Duk-Hee Kang; Daniel Feig; Salah Kivlighn; John Kanellis et al: "Is There a Pathogenetic Role for Uric Acid in Hypertension and Cardiovascular and Renal Disease?" Hypertension. 2003;41:1183.

[17] Puig JG, Ruilope LM. "Uric acid as a cardiovascular risk factor in arterial hypertension." Journal of Hypertension. 1999; 17:869–872.

[18] Leyva F, Anker S, Swan JW, Godsland IF, et al. "Serum uric acid as an index of impaired oxidative metabolism in chronic heart failure." European Heart Journal. 1997; 8: 858–865.

[19] Iseki K, Oshiro S, Tozawa M, et al. "Significance of hyperuricemia on the early detection of renal failure in a cohort of screened subjects." Hypertension Res. 2001; 24: 691–697.

[20] Vaccarino V, Krunholz HM. "Risk factors for cardiovascular disease: one down, many more to evaluate." Annuls of Internal Medicine. 1999; 131: 62–63.

[21] "Systemic Hypertension: Mechanism and Diagnosis." Elsevier Saunders 37:962.

[22] Paolo Verdecchia; Giuseppe Schillaci; GianPaolo Reboldi; et al. "Relation Between Serum Uric Acid and Risk of Cardiovascular Disease in Essential Hypertension: The PIUMA Study "Hypertension. 2000; 36:1072.

[23] Uric acid levels in patients with hypertension in benghazi by abdalla jarari et al Libyan journal of medical research, vol 6, no 2, 2009.

[24] Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries Selby JV, Friedman GD, Quesenberry CP Jr :Source Division of Research, Kaiser Permanente Medical Care Program, Oakland, CA 94611.

[25] Fessel WJ "Renal outcomes of gout and hyperuricemia" American journal of medicine 1979, 67: 74 - 82.

[26] Myers, Jacques BC, Ginsberg MH. "The role of cell surface proteins in platelet stimulation by monosodium urate crystals" Arthritis Rheumatology 1982;25: 508-521.

[27] Uric Acid and Endothelial Dysfunction in Essential Hypertension by Zainab Abdul Razak Al- Sharifi, Halla G. Al-Gebouri: Karbala J. Med. Vol.3, No.3,4, Dec, 2010.

[28] Messerli FH, Frohlich ED, Dreslinski GR, et al. "Serum Uric Acid in Essential Hypertension: an indicator of renal vascular involvement" Annuls of Internal Medicine 1980; 93:817-821.

[29] Kumar A., Singh YN, Malaviya AN, et al. "Clinical profile, therapeutic approach and outcome of gouty arthritis in northern India" Journal of Association of Physicians of India, June 1990, 38(6); 400-402.

[30] Ramsay L "Hyperuricemia in hypertension, role of alcohol" British Medical Journal, 1979, 1: 653-654.

[31] Canon P.J., Stason W.B., Demartini F.E., et al. " Hyperuricemia in primary and renal hypertension" New England Journal of Medicine 1966;275:457-464.

[32] Tykarski A. "Evaluation of renal handling of uric acid in essential hypertension; hyperuricemia related to decreased urate secretion" Nephrology 1991, 59(3); 364-368.

[33] Kinsey D., Walther R., Wise HS and Smithwick R. "Incidence of hyperuricemia in 400 hypertensive patients" Circulation, 1961, 24:972.

[34] Puig JG, Ruilope LM. "Uric acid as a cardiovascular risk factor in arterial hypertension." Journal of Hypertension. 1999; 17:869–872.

[35] McCord JM. "Oxygen-derived free radicals in postischemic tissue injury". New England Journal of Medicine. 1985; 312:159–163.

[36] Lacy F, O'Connor DT, Schmid-Schoenbein GW. "Elevation in plasma hydrogen peroxide in hypertensive and normotensive subjects at genetic risk for hypertension". Journal of Hypertension. 1998; 16:292–303.

[37] Yuki Taniguchi, Tomoshige Hayashi, Kei Tsumura, et al.: "Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey" Journal of Hypertension 2001; 19:1209-1215.

AUTHORS

First Author – Dr. Rohith Poondru, Senior Resident, Dept of cardiology, Kasturba medical college, Manipal, India. E-mail: poondrurohith@gmail.com.
Second Author – Dr. Naresh Monigari, Consultant physician, Lifeline hospitals, Karimnagar, Telangana, India. E-mail: medico.ktya@gmail.com
Third Author –Dr. Manjunath Hande, Professor and head of Department, Dept of General Medicine, Kasturba medical college, Manipal, India. E.mail: manjunath.hande@manipal.edu.

Correspondence Author – Dr. Rohith Poondru, Senior Resident, Dept of cardiology, Kasturba medical college, Manipal, India. E-mail: poondrurohith@gmail.com

Contributors:
1) Dr. Rohith Poondru
2) Dr. Naresh Monigari
3) Dr. Manjunath Hande