SERUM URIC ACID LEVEL AND TARGET ORGAN DAMAGE IN ESSENTIAL HYPERTENSION

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I. INTRODUCTION

A number of studies have shown that serum uric acid (SUA) plays a role in the development of cardiovascular morbidity in the general population,[1-4] as well as in patients with hypertension, [5-7] type 2 diabetes,[8] and cardiac or vascular diseases.[9-12] A meta-analysis of data taken from 8 trials that were performed on hypertensive patients showed that each standard deviation (SD) increment in SUA entails an augmentation of cardiovascular risk that equals what is observed for similar changes in blood pressure or total cholesterol.[13] However, the independent role of SUA as a risk factor has been undergoing debate for years. In fact, mild hyperuricema is often a concomitant finding of obesity, lipid abnormalities, and insulin resistance, all of which are components of the metabolic syndrome (MS). Accordingly, in some studies on white as well as Asian populations, the direct relationship that is observed between uric acid and cardiovascular mortality weakens or disappears after adjusting for confounding factors.[14-16]

Several pathophysiological mechanisms linking SUA to cardiovascular damage at the cellular and tissue level have been proposed, including proliferation of vascular smooth muscle cells,[17] stimulation of the inflammatory pathway, [18] and possible prothrombotic effects mediated by platelet activation. [19] In addition, uric acid has proved to be an excellent

marker for tissue ischemia and endothelial dysfunction,[11,20] and it has been shown to play a role in the development of atherosclerotic lesions.[21]

The presence of subclinical hypertensive organ damage signals a condition of increased risk for cardiovascular and renal morbidity and mortality. Thus, the search for left ventricular hypertrophy (LVH), carotid atherosclerosis, and microalbuminuria, which likely reflect both the severity of blood pressure load and other nonhemodynamic risk factors, is currently recommended as part of global risk assessment.[22] Because the role of SUA in the development of cardiovascular disease is receiving growing attention, a better understanding of its relationship with subclinical hypertensive target organ damage(TOD) may help clarify the pathophysiological mechanism(s) underlying this association. The present study was therefore performed to evaluate the association between SUA levels and the presence of preclinical organ damage in newly or recently detected hypertensive patients.

II. AIM OF THE STUDY

The aim of this study is to evaluate the correlation between serum uric acid levels and the presence of preclinical target organ damage in hypertensive population.

Target organ damage is assessed by

a) Microalbuminuria,

b) Echocardiography,

c) Fundus examination.

III. REVIEW OF LITERATURE

Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. Hypertension is often associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors.[23]

MECHANISMS OF HYPERTENSION

1. INTRAVASCULAR VOLUME

The initial elevation of blood pressure in response to vascular volume expansion is related to an increase of cardiac output; however, over time, peripheral resistance increases and cardiac output reverts toward normal.

The mechanism for the "pressure-natriuresis" phenomenon may involve a subtle increase of glomerular filtration rate, decreased absorbing capacity of the renal tubules, and possibly hormonal factors such as atrial natriuretic factor.[23]

AUTONOMIC NERVOUS SYSTEM

The autonomic nervous system maintains cardiovascular homeostasis via pressure, volume and chemoreceptor signals. Adrenergic reflexes modulate blood pressure over the short term, and adrenergic function, in concert with hormonal and volume-related factors, contributes to the long-term regulation of arterial pressure.[23]

RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

The renin-angiotensin-aldosterone system(figure 1) contributes to the regulation of arterial pressure primarily via the vasoconstrictor properties of angiotensin II and the sodium-retaining properties of aldosterone. Angiotensin II is a potent pressor substance, the primary trophic factor for the secretion of aldosterone by the adrenal zona glomerulosa, and a potent mitogen stimulating vascular smooth-muscle cell and myocyte growth factor. Independent of its hemodynamic effects, Angiotensin II may play a role in the pathogenesis of atherosclerosis through a direct cellular action on the vessel wall.[23]

Aldosterone also has effects on nonepithelial targets. Independent of a potential effect on blood pressure, aldosterone may also play a role in cardiac hypertrophy and CHF.

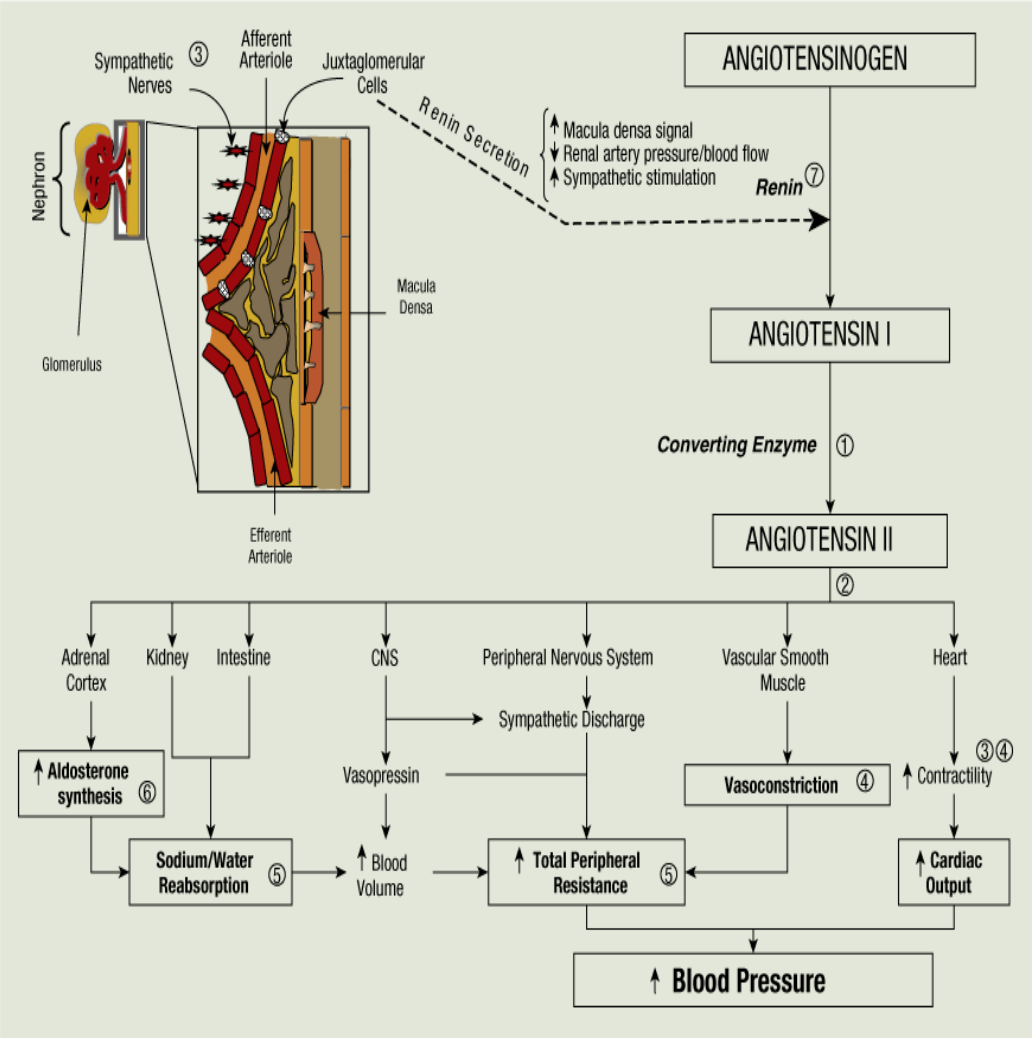


FIGURE 1 : Renin Angiotensin Aldosterone System.

Pathologic patterns of left ventricular geometry have also been associated with elevations of plasma aldosterone concentration in patients with essential hypertension, as well as in patients with primary aldosteronism.

PATHOLOGIC CONSEQUENCES OF HYPERTENSION

1. HEART

Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, diastolic dysfunction, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease and cardiac arrhythmias.

Diastolic dysfunction is an early consequent of hypertension- related heart disease and is exacerbated by left ventricular hypertrophy and ischemia.

2. BRAIN

Hypertension is an important risk factor for brain infarction and haemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years.[23]

Hypertension is also associated with impaired cognition in an aged population. Hypertensive encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Untreated hypertensive encephalopathy may progress to stupor, coma, seizures and death within hours.

3. KIDNEY

Hypertension is a risk factor for renal injury and ESRD. The increased risk associated with high blood pressure is graded, continuous, and present throughout the entire distribution of blood pressure above optimal. Renal risk appears to be more closely related to systolic than to diastolic blood pressure.

The atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic.

Clinically macroalbuminuria (random urine albumin/creatinine ratio > 300 mcg/mg or microalbuminuria (a random urine albumin / creatinine ratio 30-300 mcg/mg) are early markers of renal injury.[23]

4. PERIPHERAL ARTERIES

Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. The ankle-brachial index is a useful approach for evaluating Peripheral Arterial Disease and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood

pressure. An ankle-brachial index <0.90 is considered diagnostic of Peripheral Arterial Disease.

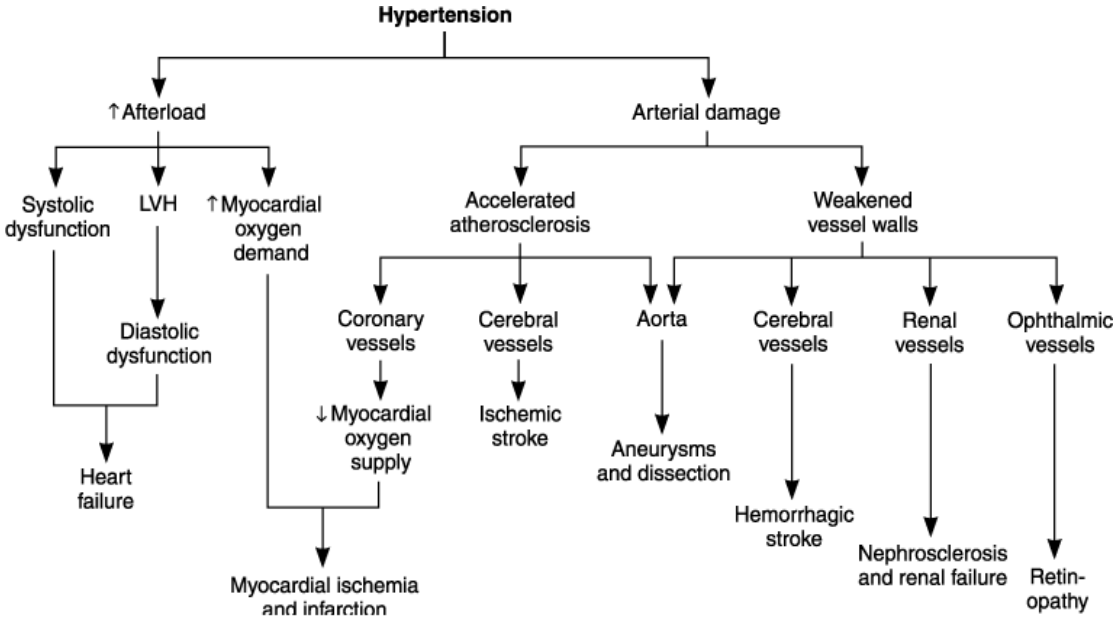


FIGURE 2 : Complications of Hypertension.

DEFINING HYPERTENSION

From an epidemiologic perspective, there is no obvious level of blood pressure that defines hypertension. The multiple Risk Factor Intervention Trial (MRFIT), which included >350,000 male participants demonstrated a continuous and graded influence of both systolic and diastolic blood pressure on CHD mortality.

Cardiovascular disease risk doubles for every 20-mmHg increase in systolic and 10-mrnHg increase in diastolic pressure. Among older

individuals, systolic blood pressure and pulse pressure are more powerful predictors of cardiovascular disease than diastolic blood pressure.[23,24]

CRITERIA

Recommended criteria for a diagnosis of hypertension are average awake blood pressure ≥ 135/85 mmHg and asleep blood pressure ≥120/75 mmHg. These levels approximate a clinic blood pressure of **≥ 140/90 mm Hg.**[23,24]

Classification of Blood Pressure for Adults

Based on the seventh report of JOINT NATIONAL COMMITTEE on prevention, detection, evaluation and treatment of hypertension (JNC 7).

Table — I

JNC VII Classification

Blood Pressure Classification	Systolic, mmHg	Diastolic, mmHg
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 ≤90

ACCURATE BLOOD PRESSURE MEASUREMENT

The accurate measurement of BP is the sine qua non for successful management. The equipment whether aneroid, mercury or electronic, should be trained and regularly retrained in the standardized technique, and the patient must be properly prepared and positioned. The auscultatory method of BP measurement should be used.

Persons should be seated quietly for at least 5 minutes in a chair (rather than on an examination table), with feet on the floor, and arm supported at heart level. Caffeine, exercise and smoking should be avoided for at least 30 minutes prior to measurement. Measurement of BP in the standing position is indicated periodically, especially in those who report symptoms consistent with reduced BP on standing. An appropriately sized cuff (cuff bladder encircling at least 80% of the arm) should be used to ensure accuracy. At least two measurements should be made and the average recorded.

For manual determinations, palpated radial pulse obliteration pressure should be used to estimate SBP; the cuff should then be inflated 20 to 30 mm Hg above this level for the auscultatory determinations; the cuff deflation rate for auscultatory readings should be 2 mm Hg per second. SBP is the point at which the first of two or more korotkoff sounds is heard (onset of

phase I), and the disappearance of Korotkoff sound (onset of phase5) is used to define DBP.

In Certain conditions like Aortic Regurgitation, the diastolic BP will be 0 mm Hg and the appearance of muffled sound is taken as diastolic BP. Care should be taken while measuring BP in elderly patients as there will be auscultatory gap.

Recommendations for Follow-Up Based on Initial Blood Pressure Measurements for Adults without Acute End Organ Damage (JNC-7).

Initial Blood Pressure, mm Hg*	**Follow –Up Recommended**[+]
Normal	Recheck in 2 years
Prehypertension	Recheck in 1 Year
Stage 1 Hypertension	Confirm within 2 Months[#]
Stage 2 Hypertension	Evaluate or refer to source of care within 1 month.For those with higher pressures (eg.>180/110mm Hg) evaluate and treat immediately or within 1 week depending on clinical situation and complications.

* *If systolic and diastolic categories are different, follow recommendations for shorter time follow- up (e.g, 160/86 mm Hg should be evaluated or referred to source of care within 1 month)*

\+ *Modify the scheduling of follow up according to reliable information about past BP measurements, cardiovascular risk factors or target organ damage.*

\# *Provide advice about lifestyle modifications.*

The key messages of JNC- VII are : [24]

- In those older than age 50, systolic blood pressure of greater than 140 mm Hg is a more important cardiovascular disease (CVD) risk factor than diastolic BP.

- Beginning at 115/75 mm Hg, CVD risk doubles for each increment of 20/10 mm Hg.

- Those who are normotensive at 55 years of age will have a 90% life time risk of developing hypertension.

- Prehypertensive individuals require health promoting lifestyle modifications to prevent the progressive rise in blood pressure and Cardio-vascular disease.

- For uncomplicated hypertension, thiazide diuretic should be used in drug treatment for most patients, either alone or combined with drugs from other classes.

- Two or more antihypertensive drugs will be required to achieve goal BP (<140/90 mm Hg or <130 mm Hg) for patients with diabetes and chronic kidney disease.

- For patients whose BP is more than 20 mm Hg above the systolic BP goal or more than 10 mm above the diastolic BP goal, initiation of therapy using two agents, one of which usually will be a thiazide diuretic, should be considered.

CLINICAL DISORDERS OF HYPERTENSION

1. ESSENTIAL HYPERTENSION
2. METABOLIC SYNDROME
3. RENOVASULAR HYPERTENSION
4 PRIMARY ALDOSTERONISM
5. CUSHING'S SYNDROME
6. PHEOCHROMOCYTOMA
7. MISCELLANEOUS CAUSES OF HYPERTENSION

   Obstructive sleep apnea, Coarctation of the aorta, acromegaly, hypercalcemia, both hypo and hyper thyroidism.

8. MONOGENIC HYPERTENSION

ESSENTIAL HYPERTENSION

Essential hypertension tends to be familial and is likely to be the non-sequence of an interaction between environmental and genetic factors. The prevalence of essential hypertension increases with age. In the majority of patients with established hypertension, peripheral resistance is increased and cardiac output is normal or decreased; however, in younger patients with mild or labile hypertension, cardiac output may be increased and peripheral resistance may be normal.

High-renin patients may have a vasoconstrictor form of hypertension, whereas low renin patients may have a volume-dependent hypertension.[23]

URIC ACID METABOLISM

Uric acid is the final breakdown product of purine degradation in humans. Urates, the ionized forms of uric acid, predominate in plasma extracellular fluid and synovial fluid, with 98% existing as monosodium urate at pH 7.4.[25]

The pH of urine greatly influences the solubility of uric acid. Although purine nucleotides are synthesized and degraded in all tissues, urate is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine. Urate production varies with the purine content of the diet and the rates of purine biosynthesis, degradation, and salvage. Normally, two-third to three-fourth of urate is excreted by kidney, and most of the remainder is eliminated through the intestine.

METABOLISM

The kidneys clear urate from the plasma and maintain physiologic balance by utilizing specific organic anion transporters (OATs) including urate transporter 1 (URATI) and human uric acid transporter (hUAT). URATI and other OATs carry urate into the tubular cells from the apical side

of the lumen. Once inside the cell, urate must pass to the basolateral side of the lumen in a process controlled by the voltage-dependent carrier hUAT. Until recently, component model has been used to describe the renal handling of urate / uric acid. The methods are

(l) Glomerular filtration,

(2) Tubular reabsorption,

(3) Secretion, and

(4) Postsecretory reabsorption.

URAT1 is a novel transporter expressed at the apical brush border of the proximal nephron. . Uric acid compounds directly inhibit URAT1 on the apical side of the tubular cell (so called cis-inhibition).[25]

The total-body urate pool is the net result between urate production and excretion

Urate production is influenced by dietary intake of purines and the rates of de novo biosynthesis of purines from nonpurine precursors, nucleic acid turnover and salvaging phosphoribosyltransferase activities. The formed urate is normally excreted by urinary and intestinal routes. Hyperuricemia can be caused by increased production, decreased excretion, or a

combination of mechanisms. When hyperuricemia exists, urate can precipitate and deposit in tissues as tophi.

HYPERURICEMIA

Hyperuricemia is defined as a plasma (or serum) urate concentration > 6.0 mg/dl in females and > 7.0 mg/dl in males.[25,26,27]

CAUSES OF HYPERURICEMIA

Hyperuricemia may be classified as primary or secondary depending on whether the cause is innate or is the result of an acquired disorder.

However, it is more useful to classify hyperuricemia in relation to the underlying pathophysiology, i.e., whether it results from increased production, decreased excretion, or a combination of the two.

Classification of hyperuricemia by pathophysiology

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase Overactivity	Psoriasis	Alcohol
Hemolytic Processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine – rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (>2g/d)
Polycystic kidney	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
Down's syndrome	Cyclosporine	

Combined Mechanism		
Glucose -6- phosphatase deficiency	Fructose – 1 phosphate aldolase deficiency	Alcohol
		Shock

Note : HPRT, hypoxanthine phosphoribosyltransferase, PRPP, phosphoribosylpyrophosphate.

HISTORY OF URIC ACID AND HYPERTENSION

The concept that uric acid may be involved in hypertension is not a new one. In fact, in the paper published in 1879 that originally described essential hypertension, Frederick Akbar Mohamed noted that many of his subjects came from gouty families. He hypothesized that uric acid might be integral to the development of essential hypertension.[28]

Ten years later, this hypothesis re-emerged when Haig[29] proposed low-purine diets as a means to prevent hypertension and vascular disease. In 1909, the French academician Henri Huchard noted that renal arteriolosclerosis (the histologic lesion of hypertension) was observed in three groups: those with gout, those with lead poisoning, and those who have a diet enriched with fatty meat. All of these groups are associated with hyperuricemia.[30]

The association between elevated serum uric acid and hypertension was observed and reported repeatedly in the 1950s to 1980 but received relatively little sustained attention because of lack of a mechanistic explanation.[31-33]

Twenty-five to 40% of adult patients with hypertension have hyperuricemia (> 6.5 mg/dl), and this number increase dramatically when serum uric acid in the high-normal range is included.[34,35] In pre-eclampsia,

the correlation between elevated serum uric acid and hypertension is >70%.[36] Despite these observations, the lack of a causal mechanism led to mild elevations of serum uric acid being largely ignored in medial practice.

The strength of the relationship between uric acid level and hypertension decreases with increasing patient age and duration of hypertension, suggesting that uric acid may be most important in younger subjects with early-onset hypertension.[33]

Cross – sectional studies have consistently noted that more than a quarter of patients with untreated hypertension have elevated SUA.[34,37] SUA levels have also been associated cross–sectionally with BP[33,38,39] and longitudinally with hypertension incidence [42-44,47,48] and future increases in BP.[45]

MILD HYPERURICEMIA IN THE RAT, AN ANIMAL MODEL FOR ESSENTIAL HYPERTENSION

The study of mild hyperuricemia required an animal model before the lack of any mechanistic detail that had plagued the hypothesis over 100 years could be addressed.

In the late 1990s, Johnson and Colleagues[46] developed a model using a pharmacologic inhibitor of urate oxidase, oxonic acid that allows the study

of sustained mild hyperuricemia. When fed 2% oxonic acid in their standard diet Sprague –Dawley rats have an increase of mean serum uric acid concentrations from 0.5 to 1.4 g/dl to 1.7 to 3.0 mg/dl. During a 7wk treatment period, systolic BP increases an average of 22 mm Hg. The increase in BP can be prevented entirely by the co-administration of the xanthine oxidase inhibitor allopurinol or by the uricosuric agent benziodarone, indicating linearly related to the rise in uric acid (r = 0.77).

Histologic evaluation of the renal tissue of the hyperuricemic hypertensive rats reveals an expansion of the vascular smooth muscle and narrowing of the lumina of the afferent arterioles. It is interesting that the development of arteriolosclerosis can be prevented using allopurinol to control uric acid levels; however, hydrochlorothiazide, which normalizes BP without lowering serum uric acid, does not prevent the development of arterioloscierosis, indicating that uric acid, not hypertension is the causative stimulus.[17,37]

These experimental results indicate that mild hyperuricemia induces renal inflammation, activation of the renin-angiotensin system, and downregulation of nitric oxide production, all of which are potentially important pathways that lead to uric acid-mediated hypertension. In short, mild hyperuricemia leads to an irreversible salt–sensitive hypertension over time.

Recent in vitro studies also have elucidated the possible mechanism of uric acid mediated arteriolosclerosis. Primary human vascular smooth muscle cells (HVSMC) are induced to proliferate by addition of uric acid to the growth medium in a dose-dependent manner.[49] The human smooth muscle cells express the urate-transport channel URATI as evidenced by both Northern and Western analyses. Consistent with this observation, cultured HVSMC rapidly take up C-urate, and blockade of this uptake by probenecid attenuates the uric acid-mediated induction of proliferation in a dose-dependent manner.[50] Signaling studies have revealed further the possible mechanism by which urate uptake leads to HVSMC proliferation.[49,51,52]

The effect of uric acid on vascular smooth muscle cells (VSMC)

Uric acid is taken up through the probenecid-sensitive urate-transport channel URATI. This leads to mitogen activated protein kinase activation and extracelluar signal–regulated kinase 1 and 2 (Erk ½) phosphorylation. In turn, transcription factors NF-β(nuclear transcription factor) and AP1 are activated leading to increased cyclo-oxygenase-2(COX-2) expression and activity. The COX-2 product Thromboxane A_2 mediates increased expression and elaboration of platelet derived growth factor (PDGF) and monocyte chemoattractant protein-1 (MCP-1), which induce VSMC proliferation and macrophage infiltration, respectively.[49,51,52]

REMNANT KIDNEY MODEL

Various studies have investigated the effect of uric acid on multiple mechanisms of progressive renal injury. In the remnant kidney models Hyperuricemic remnant kidney rats (caused by addition of 2% oxonic acid to their diets) had higher BP, greater proteinuria, and higher serum creatinine.[53,54] Addition of oxonic acid to cyclosporine treatment led to higher uric acid levels, more severe arteriolar hyalinosis, macrophage infiltration, and tubulointerstitial damage compared with rats that were treated with cyclosporine alone.[55] Furthermore treatment of cyclosporine-exposed rats with allopurinol improves GFR[55] and in human liver transplant patients who were receiving cyclosporine, treatment with allopurinol resulted in improved renal function.[56]

RECENT EPIDEMIOLOGY : A CHANGE IN PERSPECTIVE

Before 1990, only Khan et al.[42] had reported that an increased serum uric acid is an independent risk factor for hypertension; however, it had been noted that 25 to 40% of adults with hypertension have serum uric acid > 6.5 mg/ d1 and > 60% have a serum uric acid > 5.5 mg/dl[34,35] and that there was a linear relationship between serum uric acid and systolic BP.[57] Three reports indicated that serum uric acid is an independent risk factor for hypertension, were published in the 1990s [40,41,44] and five more were published in the past 4 years [43,45,58-60] including two in the first month of 2005. The recent evaluation of a subset of the Framingham Heart study found that serum uric acid level was an independent predictor of hypertension and BP progression over as little as 4yrs.[60]

Uric acid and essential hypertension in children

In adolescents, the association between elevated serum uric acid and the onset of essential hypertension is even more striking. The Moscow Children's Hypertension study found hyperuricemia (> 8.0mg/d1) in 9.5% of children with normal BP, 49% of children with border line hypertension and 73% of children with moderate and the severe hypertension.[61]

The Hungarian Children's Health Study followed all 17,624 children who were born in Budapest in 1964 for 13 yrs and found that significant risk

factor for the development of hypertension were elevated heart rate, early sexual maturity, and hyperuricemia.[62]

Gruskin [63] compared adolescents (13 to 18 yrs of age) who had essential hypertension with age matched healthy control subject and who had normal BP. The hypertensive children had both elevated serum uric acid (mean> 6.5 mg/d1)and higher peripheral renin activity.

Feig and Johnson observed that the mean serum uric acid level (±SD) in control subjects and children with white coat hypertension were nearly identical but slightly higher in secondary hypertension (4.3 ± 1.4 mg/dl, respectively; P = 0.80) but very high in children with primary hypertension (6.7 ± 1.3 mg/d1;P = 0.004). [54] There was a tight linear correlation between the serum uric acid levels and the systolic and diastolic BP in patients who were referred for evaluation of hypertension (r = 0.8 for systolic BP and r = 0.6 for diastolic BP).[39]

Among patient who were referred for evaluation of hypertension, a serum uric acid > 5.5 mg/d1 had an 89% positive predictive value for essential hypertension, whereas a serum uric acid level < 5.0 had a negative predictive value for essential hypertension of 96%. [39]

The results from both animal and human studies strongly implicate uric acid as a factor in the onset of essential hypertension and as a potential contributor to the progression of renal injury.

Evidence linking uric acid and hypertension

1. An elevated uric acid level consistently predicts the development of hypertension.[40-44]

2. An elevated uric acid level is observed in 25-60% of patients with untreated essential hypertension and in nearly 90% of adolescents with essential hypertension of recent onset.[39]

3. Raising the uric acid level in rodents results in hypertension with the clinical, hemodynamic, and histologic characteristics of hypertension.[46]

4. Reducing the uric acid level with xanthine oxidase inhibitors lowers blood pressure in adolescents with hypertension of recent onset.[64]

MECHANISM OF HYPERTENSION IN HYPERURICEMIA – RAT MODEL

Most mammals have a low serum uric acid level because of the presence of uricase, a hepatic enzyme that degrades uric acid to allantoin. However in humans the uricase gene is mutated resulting in uric acid levels that are both higher and less regulatable than in other mammals. Interestingly

when mild hyperuricemia was induced in rats by the administration of a uricase inhibitor, they became hypertensive .

Hypertension in this model was mediated by 2 mechanisms.

1. Uric acid induced renal vasoconstriction mediated by endothelial dysfunction with reduced NO levels and by activation of the renin-angiotensin system. This hypertension type is salt resistant in that it occurs even in the presence of a low salt diet, and it responds to lowering of uric acid.

2. Later however the hyperuricemia caused progressive renal microvascular disease (a lesion resembling arteriolosclerosis) and once sufficient narrowing of the arteriolar lumen occurs, a component of the hypertension become salt–driven; renal dependent and independent of uric acid levels.

The identification of biological mechanism by which uric acid could cause hypertension in humans has led to a renewed interest in the role of uric acid in hypertension. Indeed, there are now 10 studies that have examined whether an elevated uric acid level predicts the development of hypertension, and all found uric acid predictive.

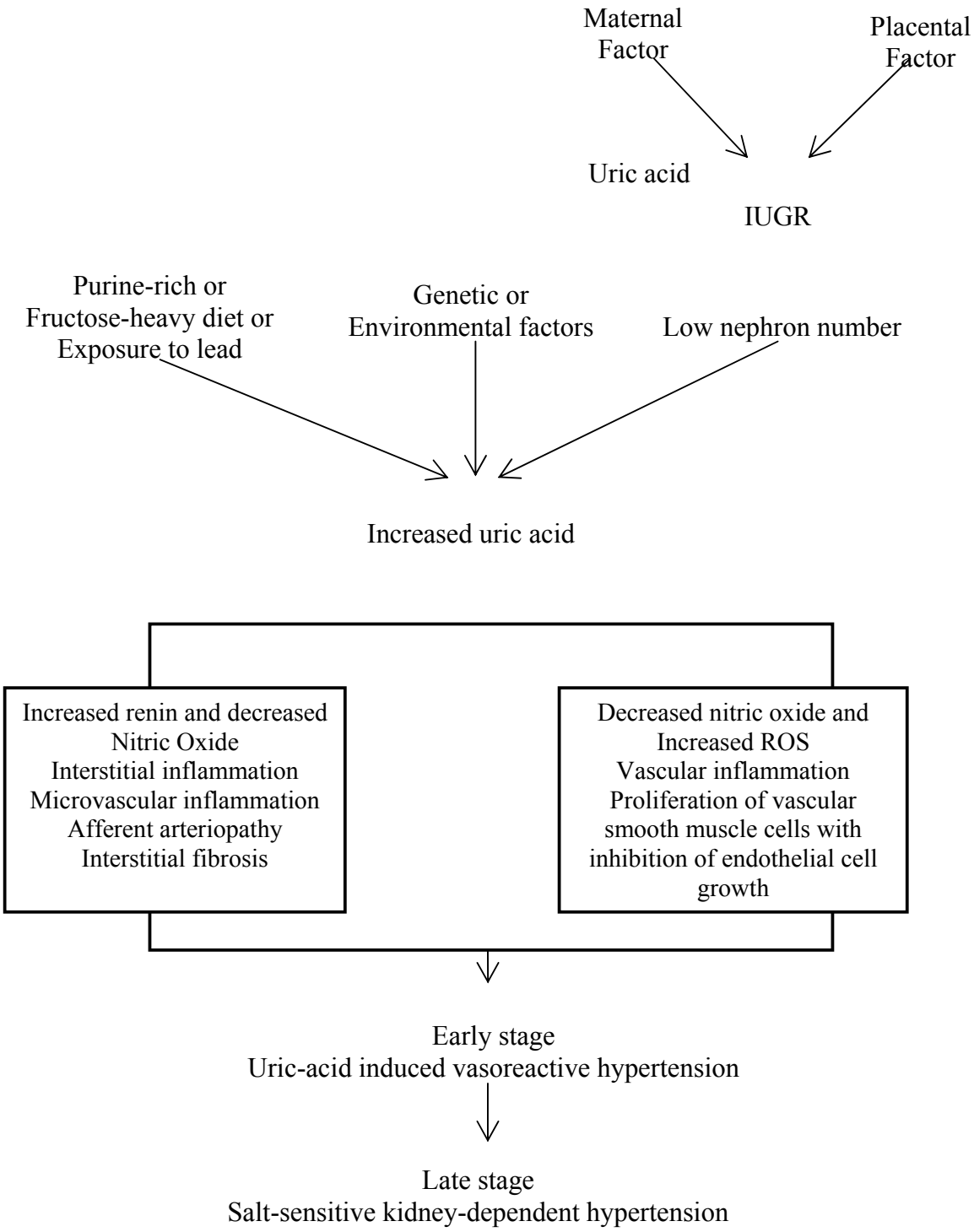
The Bogalusa Heart study, found that uric acid levels in childhood predict the development of diastolic hypertension 10 years later. The second

study, from the Framingham group[60],also found uric acid of hypertension. This latter study is all more remarkable as it was performed in an older population (mean age 50) which they first eliminated 25% of their subjects because they already had hypertension or gout, thereby removing a large proportion of their target population.

PROPOSED MECHANISM FOR URIC ACID MEDIATED HYPERTENSION IN HUMANS [27]

Excessive intake of fructose or purine-rich meats or exposure to low does of lead may result in chronic hyperuricemia. Mothers with high uric acid that are the result of diet or conditions such as pre-existing hypertension, obesity, or preeclampsia may transfer uric acid through the placenta to the fetus, which may ultimately contribute to intrauterine growth retardation (IUGR) and a reduction in nephron number. Among babies born with a low nephron number, hyperuricemia may develop in childhood because of genetic or environmental factors. Chronic hyperuricemia would stimulate the renin-angiotensin system and inhibit release of endothelial nitric oxide contributing to renal vasoconstriction and possibly increasing blood pressure. Persistent renal vasoconstriction may contribute to arteriolosclerosis and the development of salt sensitive hypertension , even if the hyperuricemia is corrected.

PROPOSED MECHANISM FOR URIC ACID MEDIATED HYPERTENSION IN HUMANS



Uric Acid as an Antioxidant : A Protective Factor in Cardiovascular Disease ?

An important observation was that uric acid might function as an antioxidant, and possibly one of the most important antioxidants in plasma.[70,72,73] Urate (the soluble form of uric acid in the blood) can scavenge superoxide, hydroxyl radical the singlet oxygen and can chelate transition metals. Peroxynitrite is a particularly toxic product formed by the reaction of superoxide anion with nitric oxide that can injure cells by nitrosylating the tyrosine residues (nitrotyrosine formation) of proteins. Uric acid can also block this reaction.[67]

Recently, Hink et al[68] reported that uric acid might also prevent the degradation of extra cellular superoxide dismutase (SOD3), an enzyme critical in maintaining endothelial and vascular function. SOD3 is an extracellular enzyme that catalyzes the reaction of superoxide anion (o_2^-) to hydrogen peroxide (H_2O_2) . The removal of O_2 by SOD3 prevents the reaction and inactivation by O_2^- of the important endothelial vasodilator, nitric oxide(NO).SOD3, by removing O_2, therefore helps to maintain NO levels and maintain endothelial function. Normally SOD3 is inactivated in the presence of H_2O_2, suggesting a feedback inactivation of the enzyme. However uric acid blocks SOD inactivation by H_2O_2 by regenerating SOD3

with the production of a urate radical. This latter radical although potentially a pro-oxidant, has been found to be markedly less reactive than classic oxidants and can be rapidly regenerated back to urate in the presence of ascorbate.[69]

Ames et al[70] hypothesized that the uricase mutation occurred during early hominoid evolution because the antioxidant action of uric acid may have provided an evolutionary advantage and that this may have accounted for the greater longevity of humans and the great apes compared with most other primates. The increase in serum uric acid in subjects with cardiovascular disease might therefore reflect a compensatory mechanism to counter the oxidative stress that occurs in these conditions. [71] However this does not readily explain why higher uric acid levels in patients with cardiovascular disease are generally associated with worse outcomes.

IV.MATERIALS AND METHODS

The study was conducted in 100 patients attending Government Royapettah Hospital Medicine Out Patient Department during the period from January 2009 to September 2010.The study was a cross-sectional study. The study group consisted of patients who fit into the criteria noted below. Written informed consent was obtained from all patients after explaining to them about the physical examination and investigation procedures that they will have to undergo during the study period. Ethical Committee approval was obtained for the study.

A) INCLUSION CRITERIA:

1) Newly detected hypertensive patients.
2) Patients giving written consent for participating in the study.

B) EXCLUSION CRITERIA:

1) Age > 70 years.
2) Hypertension duration > 6 months.
3) Diabetes Mellitus.
4) Congestive cardiac failure.
5) Chronic Kidney Disease.
6) Patients on diuretics, ACE inhibitors, AT receptor antagonists.
7) Secondary hypertension.

8) Patients fulfilling the ATP III criteria for Metabolic syndrome.

9) Malignancy and lymphoproliferative disorders.

10) Patients in hypertensive emergency.

11) Patients with cerebrovascular disease.

Definition of Metabolic syndrome

NCEP : ATP III 2001.

There or more of the following:

1. Central obesity

   Waist circumference > 102 cm (M) > 88 cm (F)

2. Hypertriglyceridemia

   Triglycerides ≥ 150 mg / dl or specific medication.

3. Low HDL cholesterol : < 40 mg/dl (M) and < 50 mg / dl (F) or specific medication.

4. Hypertension : Blood pressure ≥ 130 mm Hg systolic BP or ≥ 85 mm Hg diastolic BP or specific medication.

5. Fasting plasma glucose ≥ 100 mg/dl or specific medication or previously diagnosed type 2 diabetes.

Three patients were lost to follow up, two had diastolic dysfunction in ECHO, one had increased renal parenchymal echoes in USG abdomen.

A written informed consent was obtained from all patients. History regarding the duration of hypertension, the medications being taken, co-existing medical problems, and symptomatology suggestive of ischemic heart disease, transient ischemic attacks and that of renal involvement were documented. A detailed history of smoking (pack years / smoking index) and alcoholism (number of alcohol units per week was recorded; 1 alcohol unit = 300 ml of beer, 100 ml of wine, or 30ml of liquor) was obtained. A family history of type 2 diabetes mellitus, systemic hypertension, cardiovascular and renal disease was noted. An overall clinical examination was done to exclude major co-morbidities. Examination of the heart and the peripheral pulses including the carotids were made. Abdominal examination was done to look for renal bruit. Central nervous system was examined to rule out focal neurological deficits.

The blood pressure was measured at the time of enrollment. The average of their BP recorded in the last 6 months, if present was noted. With the patients in a seated position and after a 5-minute rest, BP was measured on the right arm and on the left arm with a mercury sphygmomanometer (cuff size 12.5 x 40 cm). The systolic pressure and diastolic pressure were

read to the nearest 2 mm Hg. Hypertension was defined according to JNC VII guidelines.

The presence, type, and extent of hypertensive retinopathy was investigated in a darkened room and under pupil dilatation. Direct ophthalmoscopy was carried out with an ophthalmoscope. The first arteriovenous crossing at least one disc diameter from the disc in each quadrant was selected and assessed for the presence of focal arteriolar narrowing, haemorrhages, exudates, and papilledema. Retinal lesions were classified according to the Keith-Wagner-Barker classification.

BMI was calculated with the following formula:

$$\textbf{BMI = weight (kg) / height}^2\textbf{(m}^2\textbf{).}$$

Waist circumference was measured as per ATP III guidelines. The standard laboratory testing for blood glucose, urea, serum creatinine, potassium was done. Serum lipid profile was done for all patients. These blood investigations were done with semi auto analyzer Merck 300. Urine was examined for protein and screened under the microscope for deposits. A baseline standard 12 lead ECG was taken. Left ventricular hypertrophy was calculated using the Romhilt-Estes scoring system (RE score) as shown below.:

Largest R/S wave in limb leads > 20mm or S wave in V1/V2 or R wave in V5/V6 > 30 mm	3
Strain Pattern (without digoxin)	3
Left atrial enlargement	3
Left axis deviation	2
QRS duration > 0.09 sec.	1
Intrinsicoid deflection > 0.05 sec.	1

A score greater than five was taken to indicate left ventricular hypertrophy.

Microalbuminuria :

All patients were subjected to a spot early morning urine sampling for microalbuminuria. The test was carried out by Immunoturbidometry. Microalbuminuria was present when urine albumin excretion was 30-300 mcg/mg creatinine.

Echocardiogram :

Echocardiograms were obtained at rest with patients supine in the left lateral position, using standard parasternal and apical views. LV mass was derived using the formula described by Devereux and associates:

LV mass (grams) = 0.80 x 1.04 [(VSTd+LVIDd+PWTd)^3- (LVIDd)^3]+0.6

- VSTd is ventricular septal thickness at end diastole
- LVIDd is LV internal dimension at end diastole
- PWTd is LV posterior wall thickness at end diastole

LV mass was corrected for height$^{2.7}$ (LVMI), and expressed in units of grams / meter (g /m$^{2.7}$). The presence of left ventricular hypertrophy was defined for LVMI > 51 g/m$^{2.7}$ in either gender[74].

Serum Uric Acid levels (SUA) :

Serum uric acid was calculated using the enzymatic calorimetric test with the normal range for adult males being 3.6 – 7 mg/dl and for adult females being 2.3 – 6.1 mg/dl. Hyperuricemia was defined as SUA > 7 mg/dl in males and SUA > 6 mg/dl in females.

Statistical analysis :

All the datas in our study were analysed with SPSS software. The statistical analysis was done using chi-square and two sample T test.

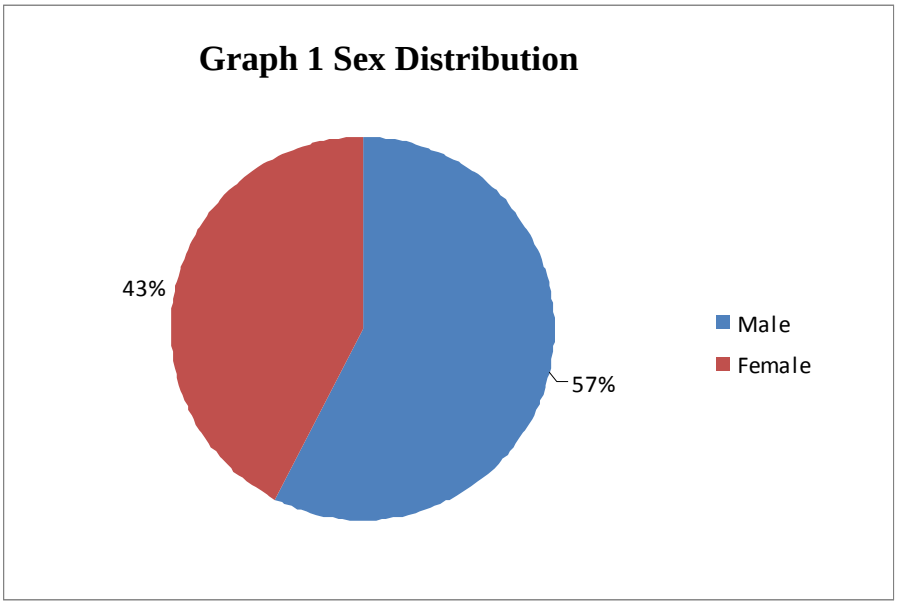
V. RESULTS

1. Age Distribution :

Age Group	Numbers
≤ 35	20
36 – 45	36
46 – 55	20
≥ 56	18

2. Sex Distribution :

Sex	Numbers (%)
Male	54 (57.4%)
Female	40 (42.6%)

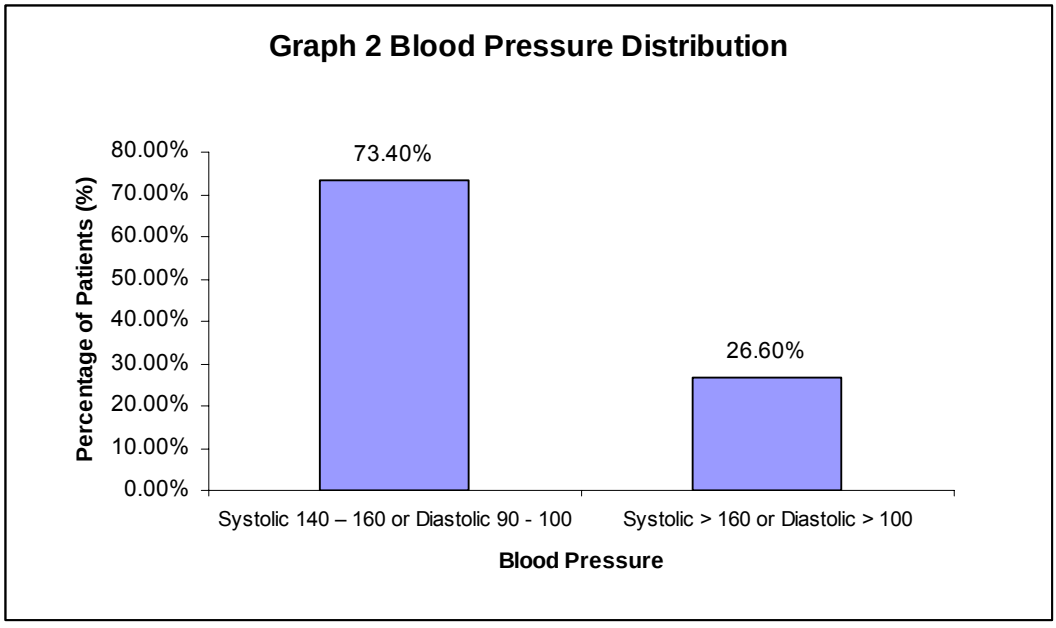


3. Menopausal Status :

Menopausal State	Numbers (%)
Attained Menopause	16 (40%)
Not Attained Menopause	24 (60%)

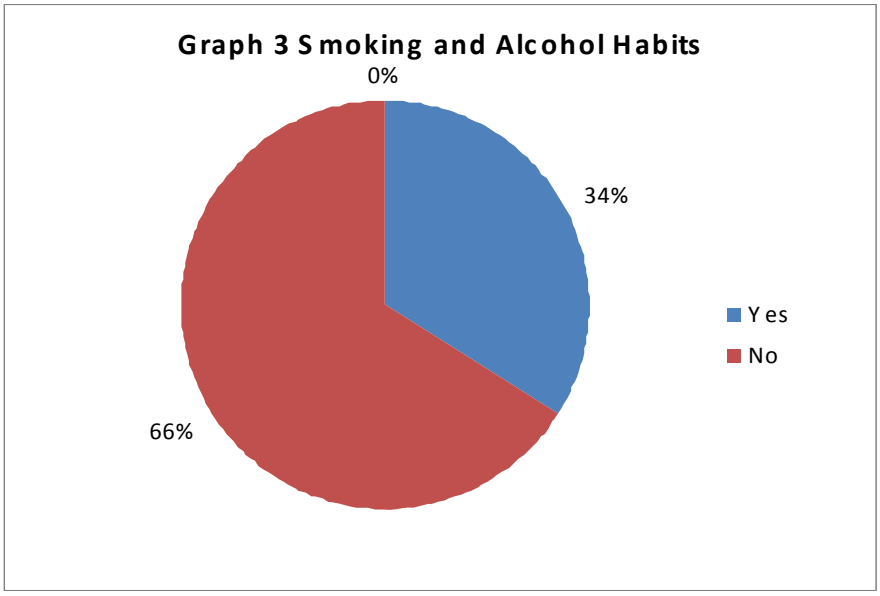
4. Blood Pressure Distribution :

Average Blood Pressure	Numbers (%)
Systolic 140 – 160 or Diastolic 90 - 100	69 (73.4%)
Systolic > 160 or Diastolic > 100	25 (26.6%)



5. Smoking or Alcohol Habits :

Habits	Numbers (%)
Yes	32 (34%)
No	62 (66%)
Smokers only	9 (0.1%)
Alcoholics only	11 (11.7%)
Both	12 (12.8%)



6. Family History of SHT / DM / CHD :

Family History	Numbers (%)
Positive	40 (42.5%)
Negative	54 (57.5%)

7. Body Mass Index Distribution :

Characteristics	Numbers (%)
BMI (mean)	24.175
BMI (range)	21.6 - 29.14
BMI (25 – 30) Overweight	23 (24.5%)

8. Waist Circumference Distribution :

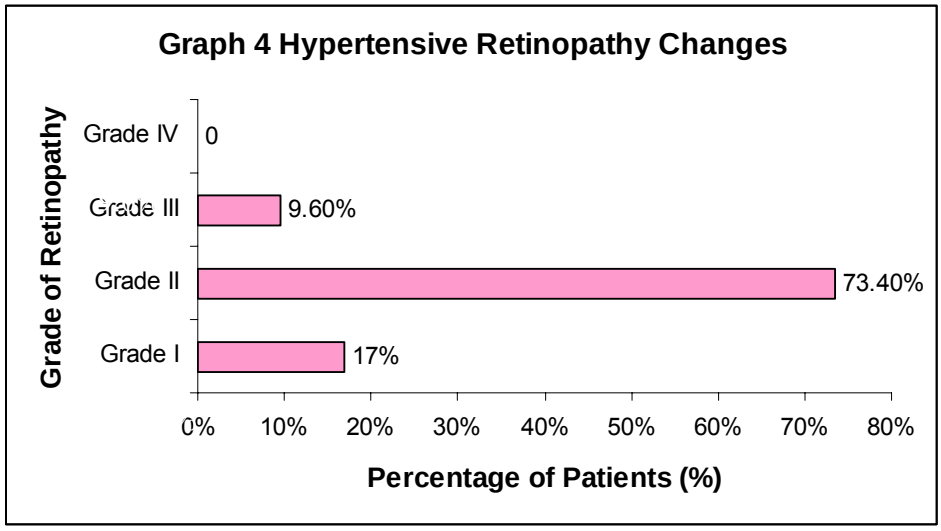
Characteristics	Numbers (%)
Waist Circumference (mean)	89.09 cm
Waist Circumference (range)	80 – 106 cm
Waist Circumference > 90 cm (males)	35 (64.8% of males)
Waist Circumference > 80 cm (Females)	34 (85% of females)

9. Lipid Distribution :

Characteristics	Distribution
Total Cholesterol (mean)	195.11
Total Cholesterol (range)	150 – 234
HDL Cholesterol (mean)	47.28 mg/dl
HDL Cholesterol (range)	36-56

10. Hypertensive retinal changes :

Keith Wagner grading	Numbers (%)
Grade I	16 (17%)
Grade II	69 (73.4%)
Grade III	9 (9.6%)
Grade IV	0



11. ECG evidence of left ventricular hypertrophy :

Romhilt Estes Score	Numbers (%)
< = 5	83 (88.3%)
> 5	11 (11.7%)

12. Microalbuminuria :

Characteristics	Numbers (%)
Microalbuminuria present	27 (28.7%)

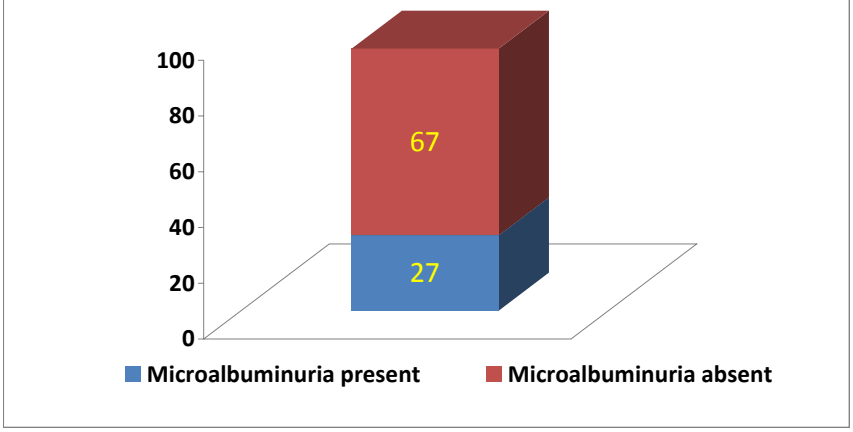
13. Left Ventricular Mass Index Distribution :

Characteristics	Numbers (%)
LV mass index (mean)	51 ± 0.503
LV mass index (range)	40 – 65
LV mass index > 51 (left ventricular hypertrophy)	48 (51.1%)
LV mass index ≤ 51	46 (48.9%)

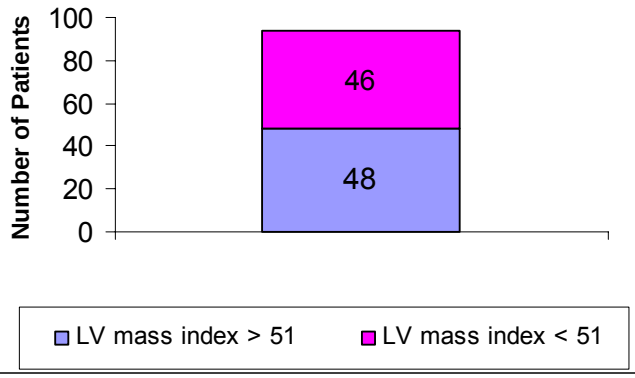
14. Serum Uric Acid Distribution :

Characteristics	Numbers (%)
Serum Uric Acid Levels (mean)	5.89
Serum Uric Acid Levels (range)	3 – 8.2
Uric acid > 6 (females)	12 (30% of females)
Uric acid > 7 (males)	17 (31.5% of males)

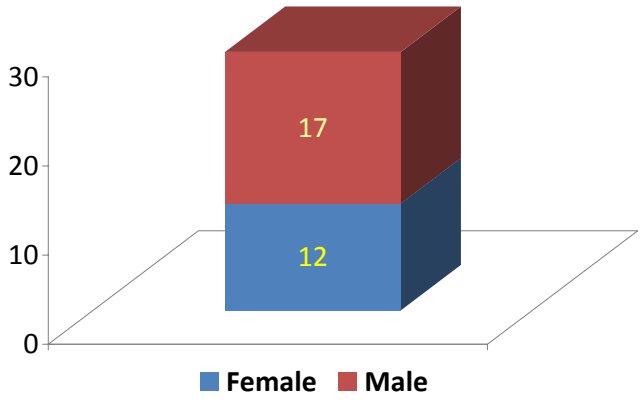
Graph 5. Prevalence of Microalbuminuria



Graph 6 Prevalence of LVH



Graph 7. Prevalence of Hyperuricemia



CORRELATION OF URIC ACID LEVELS WITH VARIOUS PARAMETERS

TABLE 1 : CORRELATION OF AGE AND URIC ACID

	URIC ACID	N	Mean	Std. Deviation	Std. Error Mean
AGE	HIGH	29	47.07	10.166	1.888
	NORMAL	65	43.58	9.639	1.196

			URIC ACID		
			NORMAL	HIGH	Total
AGE GROUP	≤ 35	Count	14	6	20
		% within URIC ACID	21.5%	20.7%	21.3%
		% of Total	14.9%	6.4%	21.3%
	36-45	Count	29	7	36
		% within URIC ACID	44.6%	24.1%	38.3%
		% of Total	30.9%	7.4%	38.3%
	46-55	Count	11	9	20
		% within URIC ACID	16.9%	31.0%	21.3%
		% of Total	11.7%	9.6%	21.3%
	≥ 56	Count	11	7	18
		% within URIC ACID	16.9%	24.1%	19.1%
		% of Total	11.7%	7.4%	19.1%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

P= 0.201 NOT SIGNIFICANT.

TABLE 2: CORRELATION OF SEX AND URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
SEX	F	Count	28	12	40
		% within URIC ACID	43.1%	41.4%	42.6%
		% of Total	29.8%	12.8%	42.6%
	M	Count	37	17	54
		% within URIC ACID	56.9%	58.6%	57.4%
		% of Total	39.4%	18.1%	57.4%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

P= 0.878 NOT SIGNIFICANT.

TABLE 3: CORRELATION OF MENOPAUSE AND URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
MENOPAUSE	NO	Count	17	7	24
		% within URIC ACID	60%	58.3%	
		% of Total	42.5	17.5%	60%
	YES	Count	11	5	16
		% within URIC ACID	40%	41.66%	
		% of Total	27.5%	12.5%	40%
	Total	Count	28	12	40
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	70%	30%	100.0%

P= 0.8327 NOT SIGNIFICANT.

Age, Sex, Menopausal Status did not correlate significantly with uric acid.

TABLE 4: CORRELATION OF SMOKING WITH URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
SMOKING	Absent	Count	54	19	73
		% within URIC ACID	83.1%	65.5%	77.7%
		% of Total	57.4%	20.2%	77.7%
	Present	Count	11	10	21
		% within URIC ACID	16.9%	34.5%	22.3%
		% of Total	11.7%	10.6%	22.3%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%

P= 0.059 NOT SIGNIFICANT.

TABLE 5 :CORRELATION OF ALCOHOL WITH URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
ALCOHOL	Absent	Count	52	19	71
		% within URIC ACID	80.0%	65.5%	75.5%
		% of Total	55.3%	20.2%	75.5%
	Present	Count	13	10	23
		% within URIC ACID	20.0%	34.5%	24.5%
		% of Total	13.8%	10.6%	24.5%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

P= 0.131 NOT SIGNIFICANT.

Smoking and Alcoholism did not correlate significantly with uric acid.

TABLE 6 : CORRELATION OF BLOOD PRESSURE WITH URIC ACID

	URIC ACID	N	Mean	Std. Deviation	Std. Error Mean
SYSTOLIC BLOOD PRESSURE	HIGH	29	158.48	11.028	2.048
	NORMAL	65	154.43	9.556	1.185
DIASTOLIC BLOOD PRESSURE	HIGH	29	96.14	6.717	1.247
	NORMAL	65	94.95	5.636	.699

SYST. BP P= 0.160

DIAS. BP P= 0.337 BOTH NOT SIGNIFICANT.

TABLE 7 : CORRELATION OF BMI WITH URICACID

	URIC ACID	N	Mean	Std. Deviation	Std. Error Mean
BMI	HIGH	29	23.90	1.231	.229
	NORMAL	65	24.45	1.818	.225

P= 0.142 NOT SIGNIFICANT.

TABLE 8 : CORRELATION OF WAIST CIRCUMFERENCE WITH URIC ACID

	URIC ACID	N	Mean	Std. Deviation	Std. Error Mean
WAIST	HIGH	29	89.14	6.463	1.200
	NORMAL	65	89.05	5.914	.733

P= 0.951 NOT SIGNIFICANT.

TABLE 9 : CORRELATION OF TOTAL CHOLESTEROL WITH URIC ACID

	URIC ACID	N	Mean	Std. Deviation	Std. Error Mean
TOTAL CHOLESTEROL	HIGH	29	194.97	23.603	4.383
	NORMAL	65	195.25	20.588	2.554

P= 0.954 NOT SIGNIFICANT.

TABLE 10 : CORRELATION OF TGL WITH URIC ACID

	URIC ACID	N	Mean	Std. Deviation	Std. Error Mean
TGL	HIGH	29	145.66	13.468	2.501
	NORMAL	65	146.46	15.478	1.920

P= 0.809 NOT SIGNIFICANT.

SBP, DBP, BMI, waist circumference, Total Cholesterol, TGL did not correlate significantly with uric acid.

TABLE 10 : CORRELATION OF ECG WITH URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
ECG	LVH (–)	Count	59	21	80
		% within URIC ACID	90.8%	72.4%	85.1%
		% of Total	62.8%	22.3%	85.1%
	LVH (+)	Count	6	8	14
		% within URIC ACID	9.2%	27.6%	14.9%
		% of Total	6.4%	8.5%	14.9%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

P=0.021 SIGNIFICANT.

TABLE 11 : CORRELATION OF LVMI WITH URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
LVMI	≤ 51	Count	43	3	46
		% within URIC ACID	66.2%	10.3%	48.9%
		% of Total	45.7%	3.2%	48.9%
	> 51	Count	22	26	48
		% within URIC ACID	33.8%	89.7%	51.1%
		% of Total	23.4%	27.7%	51.1%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

P < 0.001 SIGNIFICANT

TABLE 12 : CORRELATION OF MICROALBUMINURIA WITH URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
MICRO	Absent	Count	61	6	67
		% within URIC ACID	93.8%	20.7%	71.3%
		% of Total	64.9%	6.4%	71.3%
	Present	Count	4	23	27
		% within URIC ACID	6.2%	79.3%	28.7%
		% of Total	4.3%	24.5%	28.7%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

P < 0.001 SIGNIFICANT.

ECG, LVMI, Microalbuminuria correlate significantly with uric acid.

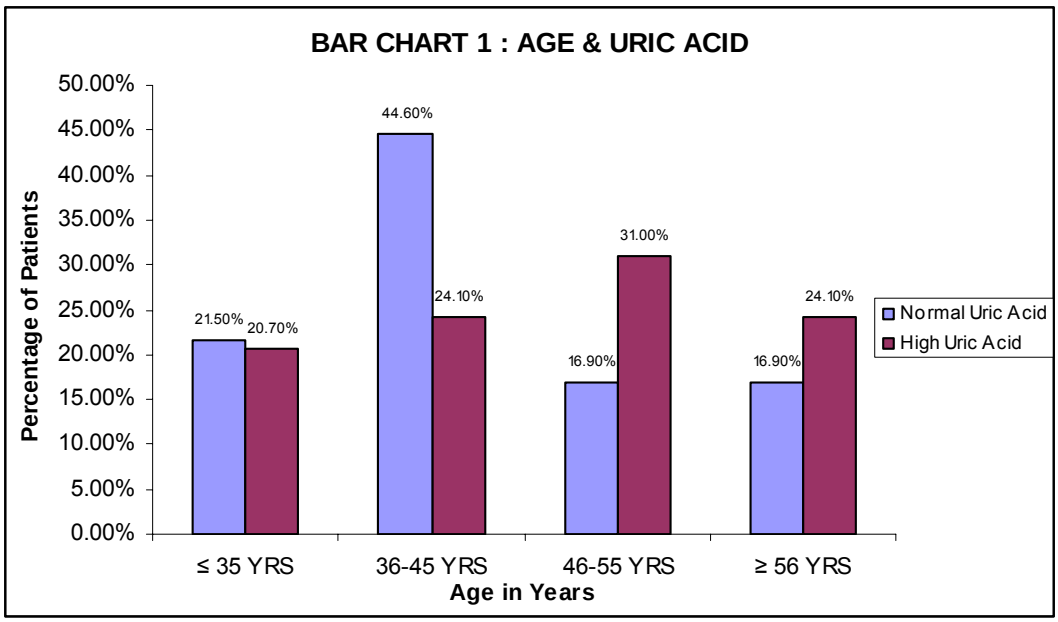
TABLE 13 : CORRELATION OF RETINOPATHY WITH URIC ACID

			URIC ACID		
			NORMAL	HIGH	Total
KW	1	Count	14	2	16
		% within URIC ACID	21.5%	6.9%	17.0%
		% of Total	14.9%	2.1%	17.0%
	2	Count	45	24	69
		% within URIC ACID	69.2%	82.8%	73.4%
		% of Total	47.9%	25.5%	73.4%
	3	Count	6	3	9
		% within URIC ACID	9.2%	10.3%	9.6%
		% of Total	6.4%	3.2%	9.6%
	Total	Count	65	29	94
		% within URIC ACID	100.0%	100.0%	100.0%
		% of Total	69.1%	30.9%	100.0%

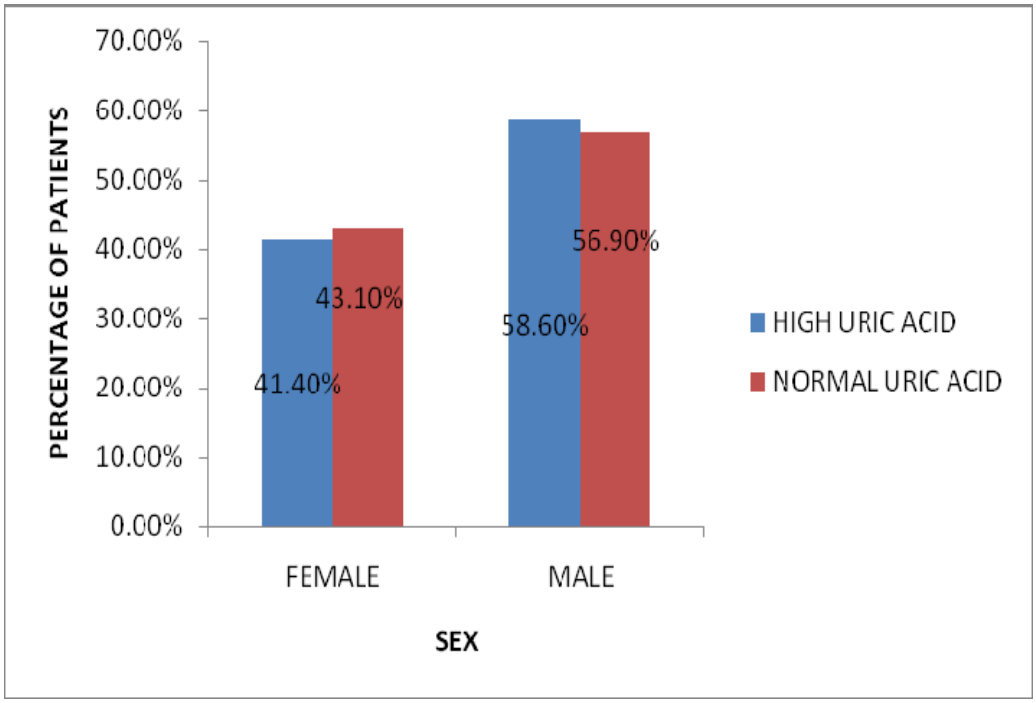
P= 0.217 NOT SIGNIFICANT.

Hypertensive retinopathy did not correlate significantly with uric acid.

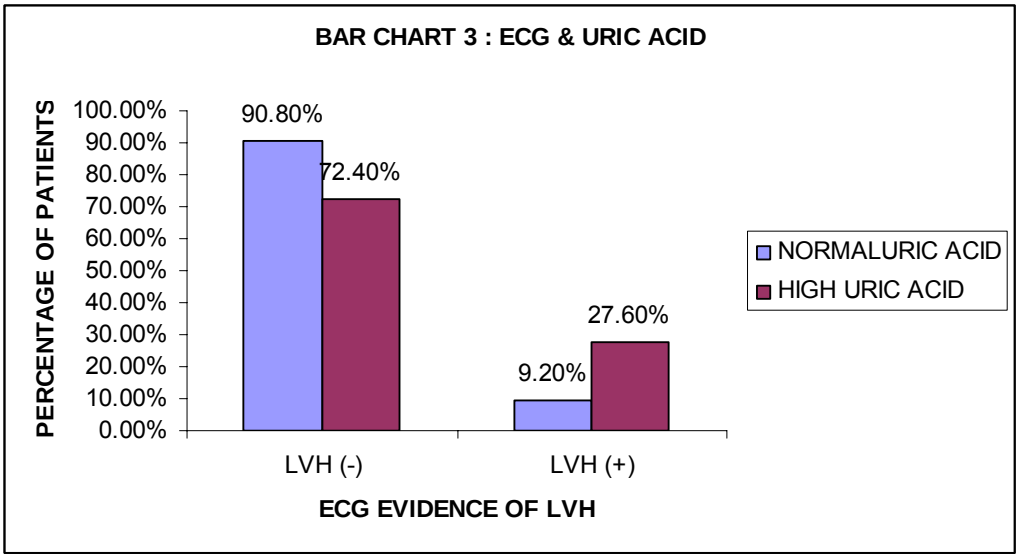
BAR CHART 1 : AGE & URIC ACID



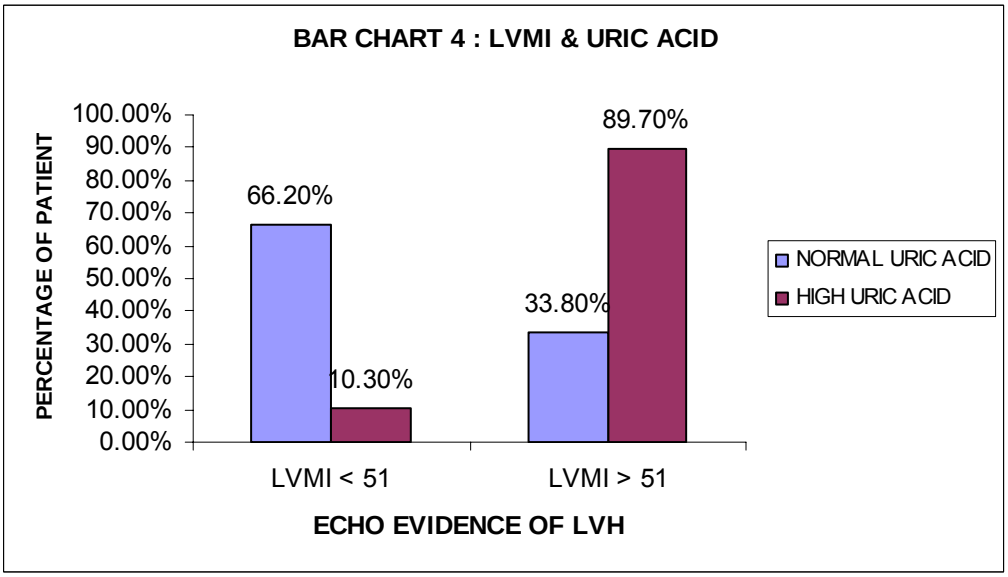
BAR CHART 2 : SEX & URIC ACID



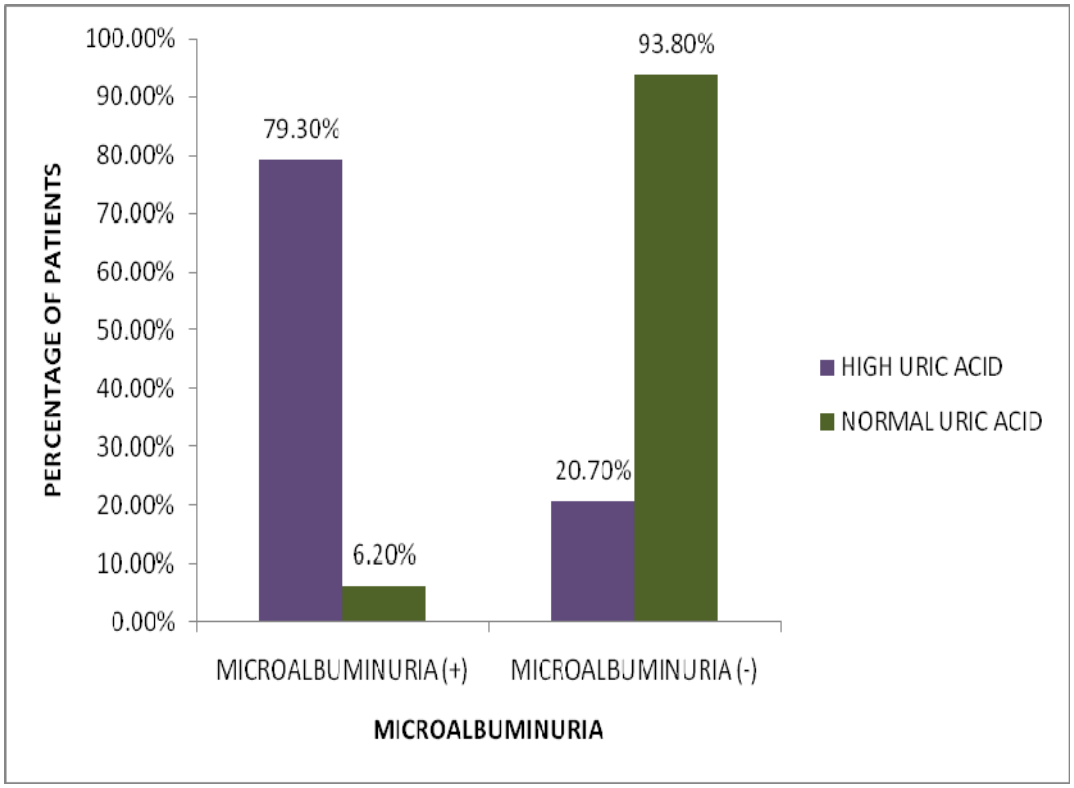
BAR CHART 3 : ECG & URIC ACID



BAR CHART 4 : LVMI AND URIC ACID



BAR CHART 5 : MICROALBUMINURIA & URIC ACID



VI. DISCUSSION

Our study demonstrates that serum uric acid levels are associated with preclinical TOD, namely LVH and microalbuminuria, in newly detected hypertensive patients. Similarly, there are few studies done on association between serum uric acid levels and presence and degree of target organ damage in essential hypertension. We will compare our study with two other studies namely an Italian study done by Francesca Viazzi et al [65,66] and another study done by C Tsioufis, D Chatsis[75] in Athens university. Similar studies have not been undertaken in our country.

IA. Comparative Descriptive statistics (Age; Sex)

Parameters	Italian Study (n=425)	Athens Study (n=842)	Current Study (n=94)
Sex : Male	265	407	54
Female	160	435	40
Age (yrs)	47 ± 9	52.94 ± 11.57	45.3 ± 9.9
Premenopausal (nos.)	NA	NA	24
Postmenopausal (nos.)	NA	NA	16

IB. Comparative Descriptive statistics (family history, smoking, BMI, lipid profile)

Parameters	Italian Study (n=425)	Athens Study (n=842)	Current Study (n=94)
Family history (%)	52	NA	42.5
Smokers (%)	NA	31.1	22.3
Alcohol (%)	NA	NA	24.5
BMI (kg/m^2)	26.4 ± 3.6	28.51 ± 4.09	24.17 ± 1.52
Total Cholesterol (mg/dl)	211.13 ± 1.11	222.14 ± 40.46	195.11 ± 22.09
HDL Cholesterol (mg/dl)	52.97 ± 0.36	48.36 ± 9.67	47.28 ± 4.65

The average age of patients in our study was 45.3 ,which was comparable to the Italian study. In the Athens study the average age was 52.94, a little higher than our study. Our study also demarcated the female population into the premenopausal and the postmenopausal groups to study if there existed any significant correlation with SUA values with menopause but there was none. A positive family history in the Italian study was slightly higher when compared to our study. This could be due to the lack awareness and accessibility of pre-symptomatic health screening as well as lack of knowledge regarding the symptomatology of various cardiovascular, renal events in our population. About 22.3% of the study population were smokers in our study where as it was around 31.1% in Athens study. The BMI among

our study population was lower when compared with the other two study populations. This could probably be explained by the high prevalence of malnutrition, modified life style and food habits in our country. The mean total cholesterol was highest in the Athens study group, followed by the Italian study population. Further the HDL cholesterol was highest among the Italian study group. The prevalence of metabolic syndrome in the Italian study group was 21%. In our study, patients were selected such that they don't fall into the criteria for metabolic syndrome according to ATP III guidelines. But the individual components of metabolic syndrome were not compared in our study.

IC. Comparative Descriptive statistics :

Parameters	**Italian Study (n=425)**	**Athens Study (n=842)**	**Current Study (2010)**
Uric acid (mg/dl)	5.14 ± 0.13	5.1 ± 0.1	5.4 ± 1.57
LVH - ECG evidence (%)	13%	NA	14.9
LV mass index	52 ± 2.8	53 ± 0.7	51 ± 0.503
LVH – ECHO evidence (%)	43%	36.2%	51.1

The mean uric acid levels were comparable among all three population. Electrocardiographic evidence of LVH was found in 14.9% in our study, while echocardiographic evidence was present in 51.1%. The figures are

slightly higher when compared with the Italian study(43%). In the Athens study group, the ECHO evidence of LVH was found in 36.2%. The mean LV mass index was comparable between all three populations.

II. Comparative Descriptive statistics :

Parameters	Italian Study (n=425)	Athens Study (n=842)	Current Study (2010)
Age	Not Sig.*	Not Sig.	Not Sig.
Gender	NA	Not Sig.	Not Sig.
SBP	Not Sig.	P < 0.05	Not Sig.
BMI	P=0.003	P < 0.05	P = 0.142
Total Cholesterol	Not Sig.	NA	Not Sig.
Microalbuminuria	P = 0.02	P < 0.001	P < 0.001
LV mass index	P = 0.002	P < 0.05	P < 0.001

* Not Sig. – Not Significant.

Serum uric acid values were correlated with various variables that affected the target organ damage in hypertensive population. In all the three study groups, age and sex did not have any significant effect on the uric acid levels. Among the Athens study group, there was a positive correlation between SBP and serum uric acid values where as in our study and Italian study, the correlation of SBP and serum uric acid levels was not significant. However we will have to emphasize the fact that target organ dysfunction primarily depends on adequacy of blood pressure control. This has been emphasized by previous studies by Francesca et al.[68] The role of increased

pulse pressure in the context of cardiovascular risk assessment and stratification is currently receiving growing attention. Furthermore, elevated pulse pressure values, measured both in office and by 24-hr ambulatory monitoring, have been linked to the presence of sub-clinical cardiovascular damage, i.e. left ventricular hypertrophy, increased carotid wall thickness and microalbuminuria as well as to structural changes in peripheral vasculature. It has been suggested that high pulse pressure levels reflect the degree of stiffness of the arterial tree, regardless of whether they are caused by increased systolic blood pressure (SBP) and/or reduced diastolic blood pressure (DBP).

In our study, it has been noted that serum uric acid levels did not correlate significantly with BMI, total cholesterol, waist circumference suggesting SUA as an independent marker of cardiovascular and renal abnormalities. Similarly in the Italian study, total cholesterol did not correlate significantly with serum uric acid. But BMI correlated significantly with serum uric acid values in both Italian and Athens study.

Further in our study there was a significant correlation of serum uric acid levels with target organ dysfunction such as microalbuminuria, LV mass index but not with hypertensive retinal changes. These findings were similar to the Italian study, which also reported a strong association between serum uric acid levels and pre-clinical organ dysfunction. In the Athens

study, there was a significant correlation with SUA values and microalbuminuria. But when comparing LVH(+) group with LVH(-) one, although a trend for higher values of microalbuminuria was noted, there was no significant correlation with SUA values.

In studies it was observed that the degree of blood pressure control had a negative correlation with the waist circumference. Insulin resistance can explain this relation and in the context of primary hypertension, mild hyperuricemia is often a feature of insulin resistance and the metabolic syndrome. The current study however did not show any correlation between the metabolic syndrome components (waist circumference, dyslipidemia) and uric acid levels. However a formal comparison was not done between patients who had metabolic syndrome and those who did not, as we have excluded patients fitting into metabolic syndrome. The results suggested that uric acid might be implicated in the early pathogenetic stages of cardiovascular damage. They also provide a pathophysiological rationale to at least partly account for the association of uric acid to cardiovascular events and mortality in hypertensive patients. In fact, sub clinical TOD represents an intermediate step between exposure to risk factors and occurrence of overt cardiovascular disease and has previously been shown to be a strong predictor of major events.

Several mechanisms have been proposed to account for the association between SUA and cardiovascular and renal abnormalities, and include: (1) increased uric acid production to counteract oxidative stress and endothelial damage in the context of the atherosclerotic process (2) the severity of hypertension itself; and (3) a subtle reduction in glomerular filtration rate leading to impaired renal uric acid clearance. The issue of mild hyperuricemia and cardiovascular disease has been getting more and more attention since anti-hypertensive agents were shown to possibly induce subtle but significant changes in uric acid, which could have an impact on their ability to provide cardiovascular and renal protection. In conclusion the present study showed that increased SUA was a marker of preclinical TOD in a population of patients with primary hypertension.

VII. SUMMARY

- Age, sex, menopausal state did not have any effect on serum uric acid levels.
- Alcohol and smoking habits did not influence the serum uric acid values significantly.
- Family history of diabetes, hypertension and coronary artery disease were not associated significantly with serum uric acid values.
- Systolic and diastolic blood pressures had no significant influence on serum uric acid values.
- BMI, waist circumference, total cholesterol, TGL, HDL did not correlate significantly with serum uric acid values.
- Uric acid values correlated significantly with target organ indices such as electrocardiographic and echocardiographic evidence of LVH, microalbuminuria.
- Uric acid values did not correlate significantly with hypertensive retinal changes.

VIII. CONCLUSION

The role of serum uric acid as an independent risk factor for cardiovascular and renal morbidity is controversial. However studies have shown that SUA is often elevated in hypertension and can indicate impaired renal function even before development of proteinuria.[76,77] The present study aimed to evaluate the correlation between SUA levels and the presence of pre-clinical target organ damage in hypertensive population. 100 patients with newly or recently detected hypertension were studied and assessed for target organ damage indices. SUA levels correlated significantly with target organ damage indices such as LVMI and microalbuminuria but not with hypertensive retinal changes. Further we will have to note that even after excluding patients with metabolic syndrome, SUA correlated significantly with TOD suggesting that serum uric acid may be a predictor of cardiovascular and renal morbidity in hypertensive patients. However further studies have to be done to confirm the role of SUA as a predictor of target organ damage.

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PROFORMA

NAME : AGE: SEX: O.P. NO:

OCCUPATION: ADDRESS:

HISTORY : - Headache - Breathlessness

- Giddiness - Palpitation

- Chest pain - Edema legs

PAST HISTORY :

1) HT-YES/NO DURATION : Rx DETAILS

2) DM-YES/NO DURATION : Rx DETAILS

3) CKD- YES/NO DURATION : Rx DETAILS

4) CCF- YES/NO DURATION : Rx DETAILS

DRUG HISTORY : YES/NO CVA - YES/NO GOUT- YES/NO

CAD-YES/NO MALIGNANCY : YES/NO

THYROID DISORDER - YES/NO

PERSONAL HISTORY :

DIET : SALT RESTRICTED : YES/NO

SMOKING : YES/NO ALCOHOL : YES/NO

TOBACCO : YES/NO

GENERAL EXAMINATIONS :

HT : WT: BMI: WAIST CIRCUM.

ANAEMIA

CYANOSIS

CLUBBING

PEDAL EDEMA

ICTERUS

GENERALISED LYMPHADENOPATHY

THYROID

VITALS : PR

BP - LEFT ARM RIGHT ARM

1.

2.

MEAN :

Higher of the mean:

SYSTEMIC EXAMINATION :

CVS:

RS :

ABD:

CNS:

FUNDUS EXAMINATION :

INVESTIGATIONS :

1. COMPLETE HAEMOGRAM
2. URINE – ALBUMIN
   SUGAR
   DEPOSITS
3. FASTING BLOOD SUGAR -
4. BLOOD UREA -
5. SERUM CREATININE -
6. SERUM URIC ACID -
7. LIPID PROFILE - TOTAL CHOLESTROL
   TRIGLYCERIDES
   HDL
   LDL
   VLDL
8. LIVER FUNCTION TEST SERUM BILIRUBIN
   TRANSAMINASES,
   ALKALINE PHOSPHATASE
   SERUM ALBUMIN AND
   GLOBULIN
9. THYROID FUNCTION TESTS - T3, T4, TSH
10. ECG
11. ECHO

ABBREVIATIONS

BP	-	Blood Pressure.
SBP	-	Systolic Blood Pressure.
DBP	-	Diastolic Blood Pressure.
HT	-	Hypertension.
SUA	-	Serum Uric Acid.
SD	-	Standard Deviation.
MS	-	Metabolic Syndrome.
TOD	-	Target Organ Damage.
BMI	-	Body Mass Index.
CHD	-	Coronary Heart Disease.
CHF	-	Congestive Heart Failure.
ECHO	-	Echocardiography.
USG	-	Ultrasonogram.
NCEP	-	National Cholesterol Education Program.
ATP	-	Adult Treatment Panel.
LVMI	-	Left ventricular myocardial index.
LVH	-	Left ventricular hypertrophy.
ECG	-	Electrocardiography.
RE Score	-	Romhilt Estes Score.

KW	-	Keith-Wagner-Barker Staging.
ESRD	-	End Stage Renal Disease.
JNC	-	Joint National Committee.
CVD	-	Cardiovascular disease.
GFR	-	Glomerular Filtration Rate.
IUGR	-	Intrauterine Growth Retardation.
ROS	-	Reactive Oxygen Species.
SOD	-	Superoxide Dismutase.
ACE	-	Angiotensin-converting enzyme.
AT	-	Angiotensin.
LV	-	Left Ventricle.
HDL	-	High Density Lipoprotein.
TGL	-	Triglyceride.
NA	-	Not Available.