CORRELATION BETWEEN SERUM URIC ACID AND ESSENTIAL HYPERTENSION

Dissertation Submitted for

MD Degree (Branch I) General Medicine

March 2010

The Tamilnadu Dr.M.G.R.Medical University

Chennai – 600 032.

Madurai Medical College, Madurai

CERTIFICATE

This is to certify that this dissertation titled **"CORRELATION BETWEEN SERUM URIC ACID AND ESSENTIAL HYPERTENSION"** submitted by **DR.CHANDRASEKARAN.K** to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in partial fulfilment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

DR. V.T.PREMKUMAR, M.D.,
Professor of Medicine,
Chief, VI Medical Unit,
Department of Medicine,
Madurai Medical College,
Madurai

DR.A.AYYAPPAN, M.D.,
Professor and Head
Department of Medicine,
Madurai Medical College,
Madurai

DECLARATION

I, **Dr.CHANDRASEKARAN.K,** solemnly declare that the dissertation titled **"CORRELATION BETWEEN SERUM URIC ACID AND ESSENTIAL HYPERTENSION"** has been prepared by me. This is submitted to **The Tamil Nadu Dr. M.G.R. Medical University, Chennai,** in partial fulfilment of the regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

Date:14/12/2009 **DR.CHANDRASEKARAN.K**

ACKNOWLEDGEMENT

At the outset, I thank our Dean **Dr. S.M.SIVAKUMAR, M.S.,** for permitting me to use the facilities of Madurai Medical College and Government Rajaji Hospital to conduct this study.

I wish to express my respect and sincere gratitude to my beloved unit chief **Dr.V.T.PREMKUMAR, M.D.,** for his valuable guidance and encouragement throughout the study and also during my post graduate course. I owe my sincere thanks to him.

I express my special thanks to the department of biochemistry for the laboratory support provided.

I am greatly indebted to my beloved teachers, **Dr.A.Ayyapan M.D., Dr.MosesK.DanielMD,Dr.S.VadivelMuruganMD,Dr.D.D.Venkatraman, M.D., Dr. M.Muthiah M.D., Dr.M.Natarajan, M.D. and Dr.J.Sangmani, M.D.,** for their valuable advice and guidance throughout my postgraduate course.

My sincere thanks to my Assistant Professors **Dr.S.Maniappan M.D., Dr.D.Ganesapandian M.D., for** their constant encouragement, timely help

and critical suggestions throughout the study and also for making my stay in the unit both informative and pleasurable.

I profusely thank the Biochemistry Departments for their cooperation and support.

I extend my thanks to my family and friends have stood by me during my times of need. Their help and support have been invaluable to the study.

Finally, I thank all the patients, who form the most integral part of the work, were always kind and cooperative. I pray for their speedy recovery and place this study as a tribute to them.

Above all I thank the Lord Almighty for his kindness and benevolence.

CONTENTS

INTRODUCTION

Cardiovascular disease is an epidemic of modern society. Hypertension is the most common form of cardiovascular disease present in nearly 25% of adults and increases in prevalence with age. Cannon et al (1966) reported that hyperuricemia was observed in 25% of untreated hypertensive subjects, 50% of those on treatment, and 75% to 100% of those with malignant hypertension or renal dysfunction.

Frederick Akbar Mahomed observed that many hypertensive subjects came from gouty families, leading him to suggest uric acid as a causal factor in the blood pressure response. Haig, who proposed low purine diets as a means to prevent hypertension and vascular disease. The French academician, Henri Huchard, noted that renal arteriolosclerosis (the histological lesion of hypertension) was primarily observed in 3 groups: those with gout or lead poisoning or those with a diet enriched in fatty meat, all conditions associated with hyperuricemias.

Mazzali et al (2001) has demonstrated that hyperuricemic rats develop hypertension which is associated with preglomerular vascular disease. Prevention of the renal microvascular lesions during childhood might reduce the incidence of hypertension.

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, also found uric acid to predict the development of hypertension. Not only does uric acid predict the development of hypertension, but a recent study suggests that elevated uric acid is much more common in the new onset hypertensive patient than originally believed. In a study of new onset hypertension in adolescents, 89% of children with essential hypertension had a uric acid level >5.5 mg/dL versus 30% of secondary hypertension and 0% of white-coat hypertensive or control subjects. The relationship of uric acid to hypertension was independent of renal function or obesity and was strong and linear (r=0.8). Finally, pilot studies suggest that lowering uric acid in the new onset hypertensive subject can normalize blood pressure, although one must be cautious because no placebo group was included.

The baseline serum uric acid level is a durable marker of risk for the development of hypertension. The association is independent of elements of the metabolic syndrome, alcohol intake, and renal function**.** **(*Hypertension.* 2006; 48:1031.)**

The association of hyperuricemia with hypertension has long been recognized. It remains unresolved whether the association of hyperuricemia with hypertension is solely because of underlying renal and metabolic abnormalities. Decreased renal blood flow and decreased tubular secretion of uric acid have been associated with hyperuricemia in hypertension. Hyperinsulinemia secondary to insulin resistance may also contribute to the association of hyperuricemia with hypertension. Recent observations in experimental hyperuricemia suggest that uric acid may in fact have a pathogenic role in hypertension. Hyperuricemia induces hypertension in experimental animals that corrects with hypouricemic therapy.

This association was independent of age, body size, central adiposity, total cholesterol level, triglyceride level, smoking status and alcohol intake, and glucose level. These results demonstrate that the SUA level is a durable marker of risk for hypertension.

Here an attempt has been made to study the prevalence of elevated uric acid levels in essential hypertension and the correlation between elevated uric acid levels and hypertensive target organ damage.

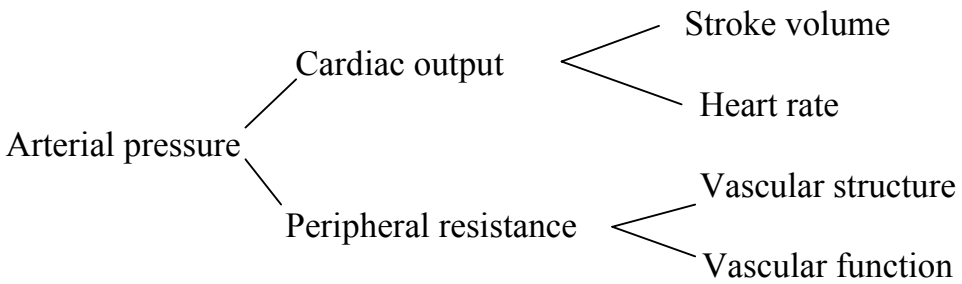
REVIEW OF LITERATURE

HYPERTENSION

Hypertension is the commonest cardiovascular disorder, posing a major public health challenge. The individual with of hypertension is 90%. The framingham Study have shown that hypertensive patients have a 4 fold increase in cerebrovascular accidents, as well as 6 fold increase in congestive Heart failure. When compared to Normotensive control subjects. It has been estimated that hypertension accounts for 6% of death world wide; of all hypertensive patients 90% have essential hypertension.

Definition:

Hypertension is defined as elevated arterial pressure that places patients at increased risk for target organ damage (TOD). According to JNC-VII report Hypertension defined as any one of the following. Systolic blood pressure > 140mmHg; Diastolic blood pressure > 90mm Hg and those taking anti hypertensive medications.



Classification:

JNC – VII included only adults aged 18 yrs and older, Definition and classification of hypertension refer to adults not taking anti hypertensive drugs and not actually ill, and based on the average of two or more reading on two or more occasions after initial screening.

Table: 1

Category	**Systolic B.P. (mm Hg)**		**Diastolic B.P. (mm Hg)**
Normal	<120	and	<80
Pre hypertension	120-139	or	80-99
Hypertension			
Stage I	140-159	or	100-109
Stage II	>160	or	>110

Prevalence:

In Framingham study, almost one half of the white sub-urban population had blood pressure >140/90 mm Hg.

In India as per study conducted by Gupta, et al (1977-78) the prevalence was 59.9 and 69.9 per 1000 is males and females respectively in the urban population and 35.5 and 35.9 per 1000 in males and females respectively in the rural population.

Determinants of arterial pressure:

Both environments and genetic factors may contribute to regional and racial variation of blood pressure and hypertension prevalence.

Diagnosis	Percentage
Essential Hypertension	>95%
Renal Hypertension	
Parenchymal	2-3%
Reno vascular	1-2%
Endocrine Hypertension	
Primary aldosteronism	0.3%
Cushing's syndrome	<0.1%
Pheochromocytoma	<0.1%
OCP Induced	2-3%
Miscellaneous	
Coarctation of aorta, PAN, Neurogenic and Drug Induced	1%

- No specific cause is known for >95% of hypertension and the condition is known as essential hypertension.

- The onset is usually between ages 25 and 55 years; it is uncommon before age 20 years.
- Secondary hypertension constitutes only 2-5% of total hypertensive population.

Mechanism of Essential Hypertension:

Genetic and Environment Predisposition:

In studies of twins and family members in which the degree of familial aggregation of blood pressure level is compared with closeness of genetic sharing, the genetic contributions have been estimated to range from 30% - 60%. (Harrap, 1994). Unquestionably environment plays some role and Harrap offers as a working model an interaction between genes and environment in which the average population pressure is determined by environment but the blood pressure rank within the distribution is decided by genes. Genetic abnormalities may be monogenic as in Liddle syndrome; glucocorticoid remediable aldosteronism and apparent mineralocorticoid excess (Luft, 1998) or involves polymorphism of genes involving Renin angiotension system (Staessen et al, 1999), Aldosterone system or adrenergic receptors.

Abnormal cardiovascular or renal development:

In normal cardiovascular system elasticity of the great arteries is matched to the resistance in the periphery to optimize large vessel pressure waves. In this way, myocardial oxygen consumption is minimized and coronary flow maximized.1.Elevated blood pressure later in life could arise from abnormal development of reduced aortic elasticity or reduced development of the microvascular network.2.Low birth weight as a consequence of fetal under nutrition is followed by an increased incidence of high blood pressure later in life (Law and Shiell, 1996).3.Brenner and Cherton hypothesized that a decreased number of nephrons from the intrauterine growth retardation could very well serve as a permanent irreparable defect that eventuates in hypertension (Brenner and Cherton, 1996).

Renal Retention and Excess of Dietary Sodium:

A considerable amount of circumstantial evidence supports a role for sodium in the genesis of hypertension. To induce hypertension some of that excess sodium must be retained by the kidneys. Such retention could arise in a number of ways.

- A decrease in the filtration surface by a congenital or acquired deficiency in nephron number or function (Brenner, 1992).

- A resetting of pressure - natriuresis relationship (Guyton, 1992).
- An acquired inhibitor of the sodium pumps (Noolfson et al, 1991).
- Nephron heterogenecity- presence of a subgroup of nephrons that is ischemic either from afferent arteriolar vasoconstriction or from an intrinsic narrowing of the lumen (Sealy et al, 1988).

Vascular Hypertrophy:

A number of factors increase peripheral resistance by both functional contraction and vascular remodeling and hypertrophy. Multiple vasoactive substances act as pressure-growth promoters resulting in both vascular contraction and hypertrophy, but perpetuation of hypertension involves hypertrophy. Lever and Harrap postulated (Lever, 1992) that primary hypertension has two mechanisms similar to secondary hypertension-(I) a growth promoting process in children ,(2) a self - perpetuating mechanism in adults.

Neurohumoral Causes of Essential Hypertension:

A large number of circulatory hormones may be involved in the development of hypertension which causes hypertension by vascular hypertrophy, capillary rarefaction and impaired micro vascular dilation (Pries, 1999).

A) Sympathetic Nervous Hyperactivity:

This is most apparent in younger persons with hypertension, who may exhibit tachycardia and an elevated cardiac output. However, correlations between plasma catecholamines and blood pressure are poor. Insensitivity of the baroreflexes may play a role in the genesis of adrenergic hyperactivity

B) Renin–angiotensin system activity:

Renin is secreted in response to a number of stimuli, including reduced renal perfusion pressure, diminished intravascular volume, circulating catecholamines, increased sympathetic nervous system activity, increased arteriolar stretch, and hypokalemia. Plasma renin levels are classified in relation to dietary sodium intake or urinary sodium excretion. Renin acts on angiotensinogen to cleave off the ten-amino-acid peptide angiotensin I. This peptide is then acted upon by angiotensin-converting enzyme (ACE) to create the eight-amino-acid peptide angiotensin II, a potent vasoconstrictor and a major stimulant of aldosterone release from the adrenal glands. The incidence of hypertension and its complications may be increased in individuals with the DD genotype of the allele coding for ACE. Despite the role of this system in the regulation of blood pressure, it probably does not play a central role in the pathogenesis of most primary (essential)

hypertension; only 10% of patients have high renin activity, whereas 60% have normal levels, and 30% have low levels. (Brenner, et al, 1973).

C) Hyperinsulinemia / Insulin resistance:

An association between hypertension and hyper insulinemia has been established not only in obese but also non obese hypertension (Liese et al, 1998). The Hyperinsulinemia of hypertension arises as a consequence of resistance to the effects of insulin on peripheral glucose utilization. Insulin has multiple pressor effects (Cardillo, et al, 1998) including activation of sympathetic activity, trophic action on vascular hypertrophy and increased renal sodium absorption. Normally The pressor effects are counteracted by insulin mediated increased synthesis of nitric oxide. In hypertension there is impairment in the insulin mediated increase in nitric oxide leading to rise in blood pressure.

Endothelial Dysfunction:

Endothelium is now known to be the source of multiple relaxing and contracting substances of which nitric oxide in an important vasodilator (Steinberg, et al, 1994). Hypertensive patients have been shown to have impaired nitric oxide mediated vasodilatory responses (Ruschitzka , et al, 1998).

Other Associated Conditions:

Hypertension is associated with other conditions like obesity, physical inactivity, sleep apnea, alcohol intake, smoking and hyperurcemia.

Complications of Untreated Hypertension:

Complications of hypertension are related either to sustained elevations of blood pressure, with consequent changes in the vasculature and heart, or to atherosclerosis that accompanies and is accelerated by long-standing hypertension. Most of the adverse outcomes in hypertension are associated with thrombosis rather than bleeding, possibly because increased vascular shear stress converts the normally anticoagulant endothelium to a prothrombotic state. If untreated, 50% of hypertensive patients die of coronary artery disease or congestive cardiac failure, about 33% of stroke and 10 - 15% of renal failure. The risk approximately doubles for each 6 mm Hg increase in diastolic blood pressure. A meta-analysis of nine major prospective studies shows a direct continuous and apparently independent association of diastolic BP with both coronary artery disease and stroke (Mac Mohan, et al 1990). However, target-organ damage varies markedly between individuals with similar levels of office hypertension; ambulatory pressures are superior to office

readings in the prediction of end-organ damage. The various target organ damage by hypertension is as follows.

Table 3Target Organ Damage

Heart • Left ventricular hypertrophy • Angina or prior myocardial infarction • Prior coronary revascularization • Heart failure
Brain • Stroke or transient ischemic attack
Chronic kidney disease
Peripheral arterial disease
Retinopathy

Overall Cardiovascular Risk:

The degree of risk from hypertension can be categorized with reasonable accuracy by taking into account

1. The level of Blood Pressure.
2. The biological nature of hypertension based on target organ damage.
3. The co-existence of other cardiovascular risk factors. (Jackson, et a11993)

The goal of anti-hypertensive therapy should not only be reduction of blood pressure but also treating other risk factors. The major cardiovascular risk factors indicated in JNC-7 report are:

- Hypertension
- Cigarette smoking
- Obesity
- Physical inactivity
- Dyslipidemia
- Diabetes mellitus
- Microalbuminuria or estimated GFR 60 < ml/min
- Age (> 55 for men,>65 for women)
- Family history of premature cardiovascular disease (<55 for men, <65 for women)

URIC ACID

Purines arise from metabolism of dietary and endogenous nucleic acids, and are degraded ultimately to uric acid in man, through the action of the enzyme xanthine oxidase Uric acid is a weak acid (pKa 5.8)

Purines

Nucleic acids (DNA, RNA) are made up of polynucleotide chain. These nucleotides are composed of purine or pyramidine bases. The various purine bases are: Adenine, Gaunine, Hypoxanthine and Xanthine.

Synthesis of Purines

Humans can synthesize purines from amphibolic intermediates. Purines are not dietarily essential. The purines are contributed by 3 sources:

- Denovo synthesis
- Dietary nucleic acids
- Cellular nucleic acid

Denovo Purine Synthesis

The atoms of purine ring are contributed by compounds including amino acids (aspartic acid, glycine and glutamine), CO2 and derivates of tetrahydrofolate. The purine ring is constructed by 11 step

process that results in, the formation of inosine mono phosphate (IMP). IMP can be converted to either adenosine monophosphate (AMP) or Guanine mono phosphate (GMP). The first step involves synthesis of phosphoribosyl pyrophosphate (PRPP). Next step involves synthesis of phosphoribosyl amine from PRPP and glutamine and is catalysed by the enzyme amido phosphoribosyl transferase. This is the rate limiting step in purine synthesis.

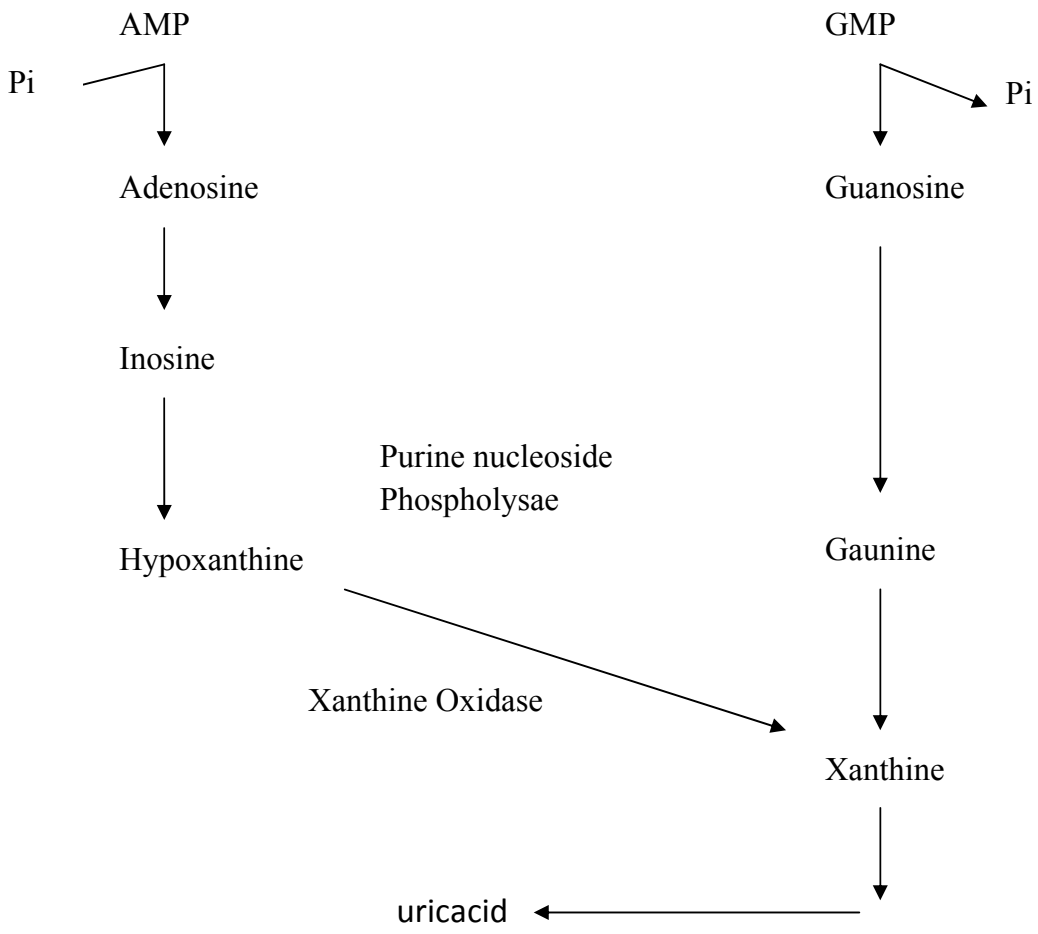
Salvage Pathway for Purines

All the purines are not degraded to uric acid. Purines that result from normal turnover of cellular nucleic acids can be reconverted to nucleotides and used by the body. Two enzymes Adenine phosphoribosyl transferase (APRT) and Hypoxanthine gaunine phosphoribosyl transferase (HGPRT) are involved. Deficiency of HGPRT causes Lesch-Nyhan syndrome

Uric Acid Metabolism

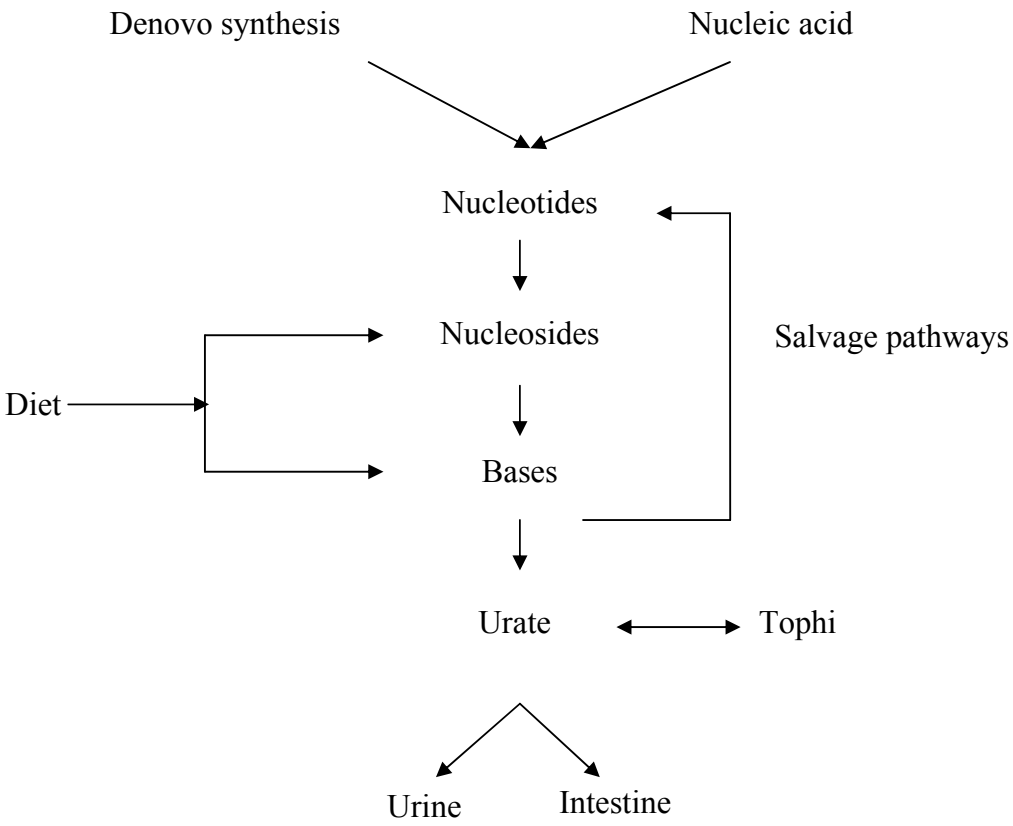
The total dynamic urate metabolic pool in the body is about 1200 mg expressed as uric acid of which denovo synthesis contributes about 300-600 mg and dietary purines contributes about 600-700 mg. Each day about 2/3 of the uric acid are excreted in the urine and 1/3 is destroyed by bacterial uricolysis in the gut.

Degradation of Purines - Production of Uric Acid



.

The total body urate pool



Urate anion is freely filtered at the renal glomerular and kidney handles urate by following

i. Glomurular filtration of 100% of the filtered load

ii. Proximal tubular absorption - of 99% of filtered load.

iii. Tubular secretion of about 50% of filtered load

iv. Post secretary reabsorption of about 40% of filtered load.

The net clearance of uric acid is around 10% of the filtered load and is in the range of 6 to 11 ml min/ 1.73 m^2.

Plasma Urate Levels:

As mentioned urates, the ionized forms of uric acid predominate in plasma extra cellular fluid and synovial fluid with approximately 98% existing as monosodium urate at PH 7.4.

Normal serum uric acid level in males ranges from3.1to 7mg/dl and in females from 2.5 to 5.6mg/dl.

Plasma is saturated with monosodium urate at a concentration of 415 micromol/L (6.8 mg/dl) at 37°C. At higher concentrations, plasma is therefore supersaturated, creating the potential for urate crystal precipitation. However, precipitation sometimes does not occur even at concentrations as high as 4800 μmol/L (80mg/dl), perhaps because of the presence of solubilizing substances in plasma.

Plasma urate levels rises at puberty with female values being lower than in men until menopause after when it gradually rises to male value. It decreases during pregnancy. Hyperuricemia is a characteristic and often an early feature of pre-eclampsia.

Extrinsic factors, particularly diet, plumbism, the prevalence of high ethanol intake in the community and diseases like malaria, thalassemia can affect plasma urate distribution in different populations. Epidemiological studies show significant variations in

plasma urate concentrations between different ethnic groups. For example, Polynesians have higher values than western Europeans and Americans. This illustrates the genetic, presumably, polygenic aspects in the control of serum uric acid. Other epidemiological studies emphasize the importance of environmental factors of purine, protein and alcohol intake. For example Gress and Zollner (1991) showed that the cumulated frequency of plasma urate rose from 6.2 mg/dL to about 9.0 mg/dl between 1962-1971 in association with improved nutritional state of Bovarian population.

The frequency distribution of plasma urate values based on asymptomatic population is only approximately gaussian, with an excess of higher values due to inclusion of some asymptomatic hyperuricaemic subjects. Ignoring the slight asymmetry of the frequency distribution and defining normality as the mean value $\pm$ 2SD above the mean, normal upper limit of 7.0 mg/dL (420 f.1moVL) for men and 6.0 mg/dL (360 f.1moVL) for women is widely adopted.

Hyperuricemia

Hyperuricemia can result from increased production or decreased excretion of uric acid or from a combination of the two processes. When sustained hyperuricemia exists, plasma and extra

cellular fluids are super saturated with respect to urate and total body urate is increased.

Physicochemically, hyperuricemia is the concentration of urate in the blood that exceeds the solutions limits of monosodium urate in plasma, 415 mol/l (6.8mg/dl). In epidemiological studies, hyperuricemia is defined as the mean plus 2 standard deviations of values determined from a randomly selected healthy population. Hyperuricemia is present between 2.0 and 13.2 % of ambulatory adults and some what more frequently in hospitalized individuals.

CLASSIFICATION OF HYPERURICEMIA:

Reduced renal excretion

1. An inherited defect in renal handling of urate.
2. Renal glomerular disease
3. Renal tubular dysfunction
    - Tubulointerstitial nephritis
    - Competition for tubule excreting mechanism (Lactic acidosis and keto acidosis)
    - Drugs (Diuretics, Pyrazinamide, Ethambutol etc.,)
4. Other conditions in which renal tubular dysfunction has been proposed are
    - Hypertension

- Sickle cell anemia
- Myxoedema
- Lead nephropathy

Increased-Uric acid production

- Dietary sources
- Hypoxanthine phosphoribosyl transferase deficiency
- Increased phosphoribosyl pyrophosphate activity
- Glycogen storage disorders
- Hereditary fructose intolerance
- Myeloproliferative diseases
- Chronic hemolytic anaemias
- Extensive psoriasis
- Gauchers disease

The following abnormalities are commonly associated with but not casually related to Hyperuricemia.

- Obesity
- Dyslipidemia (usually type 4 with increased VLDL and normal cholesterol)
- Hypertension
- Insulin resistance
- Ischemic heart disease

URIC ACID AND CARDIOVASCULAR DISEASE

Over recent years there has been renewed debate about the nature of the association between raised serum uric acid concentration and cardiovascular disease. Several large studies have identified the value, in populations, of serum uric acid concentration in predicting the risk of cardiovascular events, such as myocardial infarction. This has directed research towards the potential mechanisms by which uric acid might have direct or indirect effects on the cardiovascular system. It has been difficult to identify the specific role of elevated serum uric acid because of its association with established cardiovascular risk factors such as hypertension, diabetes mellitus, hyperlipidaemia and obesity.

Indeed, it is not even clear at this stage whether uric acid has a damaging or protective effect in these circumstances. Increased understanding of the mechanisms underlying these associations may allow a clearer interpretation of the importance of elevated serum uric acid concentrations, and the potential value of specific urate-lowering treatment of cardiovascular disease.

Nearly 120 years have elapsed since uric acid was first described as a potential factor in the development of cardiovascular disease

(Gerteler, et al 1951). Much but not all epidemiological research identifies hyperuricemia as an independent risk factor for the development of cardiovascular disease and renal disease, particularly in patients with hypertension or congestive heart failure and in women (Aldermen, 2002, Cohen, et al 1999, Freedman et al 1995).

Observational studies show that serum uric acid concentrations are higher in patients with established coronary heart disease compared with healthy controls. Elevated serum uric acid concentrations are also found in healthy offspring of parents with coronary artery disease, indicating a possible causal relationship.

However, hyperuricaemia is also associated with possible confounding factors including elevated serum triglyceride and cholesterol concentrations, blood glucose, fasting and post-carbohydrate plasma insulin concentrations, waist-hip ratio and body mass index. About one quarter of hypertensive patients has co-existent hyperuricaemia and, interestingly, asymptomatic hyperuricaemia predicts future development of hypertension, irrespective of renal function. (Q J Med 2000; 93: 707-713)

There are certain clinical clustering groups with increased cardiovascular risk, which have associated Hyperuricemia.

They are (Hayden, et al 2004)

- African American patient group
- Patient groups with excessive alcohol
- Hypertensive patient groups
- Non diabetic patient groups with accelerated atherosclerosis
- Congestive heart failure patient groups with ischemic cardiomyopathy.
- Metabolic syndrome patient groups (with hyper insulinemia, impaired glucose tolerance, obesity, dyslipidemia, and hypertension).
- Renal disease patient groups and
- Patients groups taking diuretics.

Each of these clustering groups has metabolic mechanisms that may help to explain which serum uric acid may be elevated. In addition to the recurring finding of an elevated tension of Oxidative - redox stress and reactive oxygen species in many of the groups is the importance of the metabolic syndrome and insulin resistance.

Uric Acid in Hypertension:

Hypertension is strongly associated with hyperuricemia. Cannon et al (1966) reported that hyperuricemia was observed in 25% of untreated hypertensive subjects, 50% of those on treatment, and 75% to 100% of those with malignant hypertension or renal dysfunction

Potential mechanisms involved with the association of Hyperuricemia and hypertension include the following

1. Decreased renal blood flow (decreased GFR) stimulating urate absorption (Mersserli, et al, 1980).
2. Microvascular (capillary) disease resulting in local tissue ischemia (Puig, Ruilope, 1999)
3. Ischemia with associated increased lactate production that blocks urate secretion in the proximal tubule and increased uric acid synthesis due to increased RNA – DNA breakdown and increased purine metabolism.
4. Ischemia induces increased xanthine oxidase production.

Other factors which may contribute are alcohol abuse (Ramsay, 1979), lead intoxication, obesity and insulin resistance (Galvan et al, 1995) and diuretic use. **(*Hypertension. 2005; 45:18.)***

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. Further studies showed that the hypertension in this model was mediated by 2 mechanisms.

The first mechanism resulted from 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.Later, however, the hyperuricemia causes progressive renal microvascular disease (a lesion resembling arteriolosclerosis), and once sufficient narrowing of the arteriolar lumen occurs, a component of the hypertension becomes salt-driven, renal-dependent, and independent of uric acid levels.

Finally, further studies demonstrated that this microvascular disease resulted from direct effects of uric acid, in that the urate was shown to enter into the vascular smooth muscle cell where it caused cell proliferation, activated the local renin-angiotensin system, and

stimulated the production of various inflammatory mediators including CRP and monocyte chemoattractant protein-1.

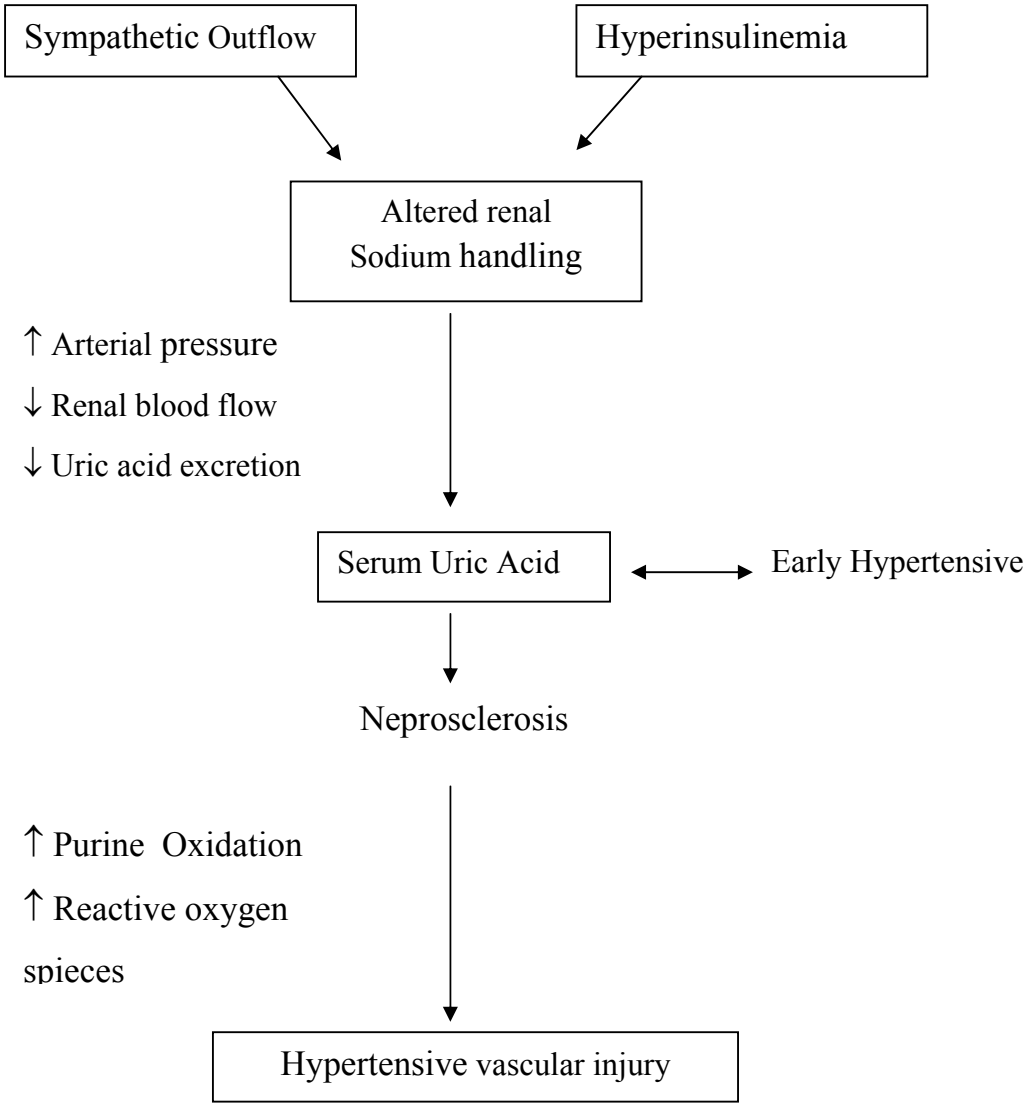
Mild hyperuricemia causes hypertension and renal injury in the rat via a crystal-independent mechanism, with stimulation of the renin-angiotensin system and inhibition of neuronal NO synthase.(Marilda Mazzali et al ;*Hypertension.* 2001;38:1101.)

It is also possible that metabolic perturbations like Hyperinsulinemia or sympathetic activity may produce alterations in renal sodium handling, leading to increased arterial pressure, decreased renal blood flow and decreased uric acid secretion. This in turn, increases purine oxidation, which results in increased reactive oxygen radicle, subsequent vascular injury and reduced nitric oxide.

Hyperuricemia and Renal Injury

Renal injury occurs in Hyperuricemic rats, consisting of afferent arteriolopathy, mild tubulo interstitial fibrosis, glomerular hypertrophy and eventually, glomerulosclerosis and albuminuria. The renal changes are prevented if serum uric acid is maintained in the normal range with allopurinol. Increased serum uric acid has been found to predict the

development of renal insufficiency in individuals with normal function (Johnson, et al, 2003).



(Adapted from ward, Lancer 1998)

Uric acid as a marker of insulin resistance

Insulin resistance syndromes result in attenuation of insulin-mediated glucose utilization and confer a substantial increase in cardiovascular risk, through activation of several pathways including the sympathetic nervous system. Elevated serum uric acid is consistent feature of the insulin resistance syndromes, which are also characterized by elevated plasma insulin level (fasting and post-carbohydrate), blood glucose concentration, and serum triglyceride concentration, and raised body mass index and waist-hip ratio.

Insulin has a physiological action on renal tubules, causing reduced sodium and uric acid clearance. Despite blunting of the action of insulin on glucose metabolism, sensitivity to the renal effects persists. Because plasma insulin concentration is characteristically elevated, hyperuricaemia may arise as a consequence of enhanced renal insulin activity. Elevated serum uric acid concentrations predict subsequent development of diabetes mellitus and hypertension, even in the presence of normal creatinine clearance and plasma glucose concentrations, and therefore may be a subtle, early marker of peripheral insulin resistance syndromes.

Thus a link between elevated serum uric acid concentration and cardiovascular disease may arise through its non-causal relationship with insulin resistance syndromes, where cardiovascular risk is mediated by other factors.

Hyperuricemia has been associated with increasing body mass index (BMI). Bedir A et aI, have recently described the role of leptin as possibly being a regulator of serum uric acid levels in humans.

Uric Acid as One of the Multiple Injurious Stimuli To The Endothelium of the Arterial Vessel Wall and Capillary:

The upper 1/3 of the normal physiologic - homeostatic range (> 4 mg /dl) and abnormal elevations (> 6.5 or 7 mg /dl in men and> 6.0 mg/dl in women) in serum uric acid definitely should be considered as one of the multiple injurious stimuli to the arterial vessel wall and capillary, which may contribute to endothelial dysfunction and vessel wall remodeling through oxidative redox stress. (Hayden, 2002; Fang, Alderman 2000).

Uric Acid as Antioxidant:

An important observation was that uric acid may function as an ANTIOXIDANT, and possibly one of the most important antioxidants in plasma. Urate can scavenge superoxide, hydroxyl radical and 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. Uric acid can block this. Recently Hink et al (Ulrich Hink et aI, 2002) reported that uric acid may also prevent the degradation of extracellular superoxide dismutase (SOD3) an enzyme critical in maintaining endothelial function. SOD3 removes reactive oxygen spieces and thus helps in maintaining Nitric Oxide levels. Normally SOD3 is inactivated in the presence of H202 but uric acid blocks SOD inactivation and regenerates SOD3.

The simple concept that elevated serum uric acid in patients with cardiovascular disease and hypertension may reflect a compensatory mechanism to counter oxidative stress in intriguing. However this does not explain why higher serum uric acid levels in patients are generally associated with worse outcomes (Johnson, ET al2003).

An Antioxidant – Pro oxidant Urate Redox Shuttle:

Antioxidants may become prooxidants in certain situations (Bagnati, et. a1.1999; Patternson et al 2003). Hayden et al proposes the existence of an antioxidant pro oxidant redox shuttle in the vascular milieu of atherosclerotic macrovessel intima.

Serum Uric Acid in the early stages of the atherosclerosis process is known to act as an antioxidant (Nyyssonen, et al. 1997)

However, later in the atherosclerotic process when uric acid levels are known to be elevated (in the upper 1/3 of normal range more than 4mg/dl and outside of the normal range > 6 mg /dl in females and 6.5 - 7 mg/dl in males), this previously antioxidant paradoixcally becomes pro oxidant. This urate redox shuttle seems to rely on its surrounding environment - the accelerated atherosclerotic vulnerable plaque in the intima, which is acidic depleted of local antioxidants, with an increase in the oxidative stress, all those makes uric acid a pro oxidant.

Endothelial Dysfunction:

The endothelium is an elegant symphony responsible for the synthetics and secretion of several biologically active molecules. It is responsive for the regulation of vascular tone, inflammation, lipid metabolism, vessel growth, endothelial matrix remodelling and modulation of coagulation and fibrinolysis. One particular enzyme system seems to act as the maestro: The endothelial nitric oxide systhase (e NOS) enzyme and its omnipotent product: Endothelial Nitric oxide (e NO).

This endothelial nitric oxide synthase (e NOS) enzyme reaction is of utmost importance in maintaining endothelial function. When this enzyme system uncouples, the endothelium becomes a net producer of

superoxide and reactive oxygen spieces instead of net production of nitric oxide.

The antioxidant pro oxidant urate redox is one of the causes of uncoupling of this enzyme system.

Uric Acid, Vascular Smooth Muscle Proliferation and Inflammation:

Uric acid stimulates rat smooth muscle cell proliferation in vitro. Uric acids enters smooth muscle cell by organs transporters. Inside the smooth muscle all it activates specific mitrogen activated protein kinases (Erk ½) with denovo induction of cyclo oxygenase - 2 (Cox - 2), local thromboxane formation and with upregulation of platelet derived growth factor - A (PDGF-A) and C chain and PDGF alpha - receptor mRNA)

Soluable uric acid is also pro inflammatory Uric acid stimulates synthesis of monocyte chomoattractant protein - 1 (MCP - 1) in rat vascular smooth muscle cell and by activating P 38 MAP Kinase and the nuclear transcription factors NF - KB. MCP-l is a chemokine that is important in vascular disease and atherosclerosis. Soluable uric acid also stimulates the production of interleukin -1 Beta, interleukin-6 and tumour factor (TNF).

Elevations of uric acid> 4mg/dl should be considered a "red flag" in those patients at risk for cardiovascular diseases and should alert the clinician to strive to utilize a global risk reduction program to reduce the complications of the atherogenic process (Melvin R Hayden 2004).

AIMS AND OBJECTIVES

1. To study the level of uric acid in patients with essential hypertension

2. To identify whether any association exists between ages, sex, body mass index, smoking, diabetes and target organ damage and the presence of elevated serum uric acid.

MATERIALS AND METHODS

Setting	Government Rajaji Hospital and Madurai Medical College, Madurai.
Collaborative Department	Department of Biochemistry, Madurai Medical College, Madurai
Study design	Cross sectional study
Period of Study	March2009 to august2009
Sample Size	225 cases
Ethical committee approval	The Present project was approved by the ethical committee
Conflict of interest Financial Support	NIL NIL

Inclusion Criteria:

- Patients with Essential hypertension
- Patients whose ages were above 25 years were included
- Both sexes were included.

Exclusion Criteria:

- Individuals below 25 years were excluded
- Patients with renal failure
- Pregnancy
- Patients with secondary hypertension.
- Patients who were on long-term diuretics.
- Patients who were regular consumer of alcohol.
- Patients who were on anti metabolite and chemotherapy

Controls

Subject whose ages were above 25 years and had normal blood pressure and who met the above exclusion criterion.

Consent

The study group thus identified by the above criteria (inclusion and exclusion criteria) was first instructed about the nature of the study. Willing participants were taken up after getting a written informed consent from them.

Materials

Thus a total of 150 cases that satisfied the inclusion and exclusion criteria above were taken up for subsequent study. 75 age and sex matched subjects were kept as control.

Limitations

1. In this study, both newly detected as well as known cases of essential hypertension that were on treatment were included in the study.
2. The study population included patients with essential hypertension both with and without target organ damage and other cardiovascular risk factors but without renal failure.
3. Diagnosis of peripheral vascular disease was made on clinical examination only. Doppler study was not performed in every case due to technical limitation.
4. Only serum uric acid levels were analyzed. Urinary urate excretion and urate clearance was not done.

Methods

Selected Socio-demographic, clinical and laboratory data were elicited from the patients and controls and recorded in a proforma (enclosed in Annexure -Annexure-I)

I. Socio-demographic data

- Age
- Sex

II. Clinical data

- Body mass index
- Systolic and diastolic blood pressure

- Cardiovascular risk factors
- Clinical examination

III. Laboratory data

- **Blood Urea** Estimation done manually by using Diacetyl monoxime (DAM) technique.
- **Serum creatinine** Estimation was done using COBAS auto analyzer
- **Serum uric acid** Enzymatic method (semi auto analyzer)

Principle:

Uric acid is converted by uricase to allantoin and hydrogen peroxide in the presence of peroxidase (POD) oxidises the chromogen to a red coloured compound which is read at 500 mm.

Uric acid + 2H2O + O2 $\xrightarrow{\text{Uricase}}$ Allantoin + CO2 + H202

2H202 + 4 Aminoantipyrine + $\xrightarrow{\text{DHBS POD}}$ Red quinolone + H2O+ HCI (DHBS - 3, 5 - Dichloro - 2 - Hydroxy benzene sulphonic acid).

DEFINITIONS USED IN THE PRESENT STUDY

1) Essential Hypertension

According to the JNC- VII report, Hypertension is defined as systolic blood pressure of 140mm Hg and above and or diastolic blood pressure of 90 and above. In newly detected cases it was the mean of 3 relaxed, seated right arm readings. The diagnosis that the hypertension is essential and not secondary was made on the over all clinical impression only. Laboratory investigations to rule out secondary causes were not done in each case.

2) Hyperuricemia

Hyperuricemia is defined as serum uric acid levels> 7mg/dl in males and >6mg/dl in females.

3) Over weight / Obesity.

- Over weight - Body mass index of ≥ 23
- Obesity - Body mass index> 25 (York et al)

4) Diabetes Mellitus

- Already a known case of diabetes mellitus on treatment
- Fasting plasma glucose ≥126mg/dl
- Two hour plasma glucose ≥ 200mg/dl
- Symptoms of diabetes plus random blood glucose ≥ 200mg/dl

5) Left ventricular hypertrophy

Based on electrocardiographic findings satisfying either Sokolon-Lyon criteria or Cornell voltye criteria (Sokolan, Lyon, 1949) (Casale, et al, 1987)

6) Hypertensive retinopathy

Based on Keith-Wagner-Barker grading

Grade I- attenuation of arteries.

Grade II-arterio-venous nipping.

Grade III-with hemorrhage and exudates.

Grade IV-with papiledema.

RESULTS

This study group included total number of 225 subjects. Among these 225 subjects, 150 were cases (hypertensives) and 75 were controls (normotensives).

ANALYSIS OF CASES AND CONTROLS WITH RESPECT OF TO THE AGE

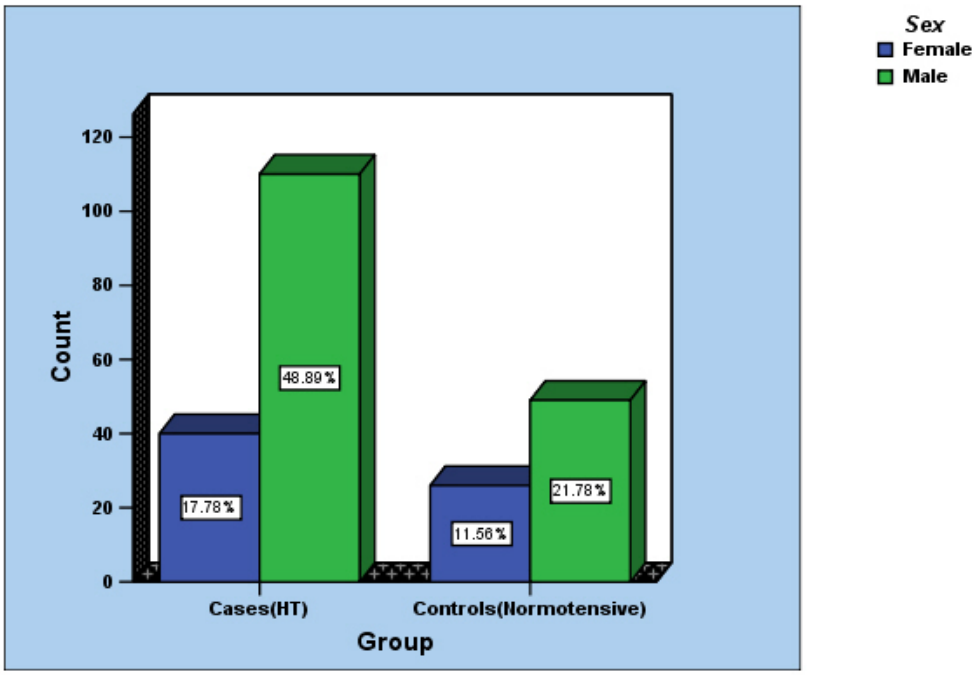
Table 1 Distribution of age among cases and controls

GROUP	NO.	AGE		T TEST P VALUE
		MEAN	S.D	
CASES	150	54.57	12.438	0.128
CONTROLS	75	52.13	9.820	

The age of the subjects in this study group ranged from 26 to 79 years. The mean and standard deviation of age for cases and controls were 54.57 ±12.438 and 52.13 ±9.82 respectively.

There was no significant (p value = 0.128) difference in the age composition of those with and without hypertension in this study. Hence elevated serum uric acid among cases and controls was independent of age.

Sex Distribution Among The Study Groups



SEX DISTRIBUTION IN THE STUDY POPULATION

Table 2 Distribution of study population in relation to gender

SEX	CASES		CONTROLS	
	No	PERCENTAGE	No.	PERCENTAGE
MALE	110	73.3	49	65.3
FEMALE	40	26.7	26	34.7
TOTAL	150	100	75	100

Among the 150 cases studied, there were 110 males and 40 females. Among the 75 controls, there were 49 males and 26 females. In the study population, 69.2% of males were hypertensives, while in females 60.6% were hypertensives.

There was no significant (P-value= 0.139) difference in the sex distribution among cases and controls.

ANALYSIS OF CASES AND CONTROLS WITH RESPECT TO BODY MASS INDEX (BMI)

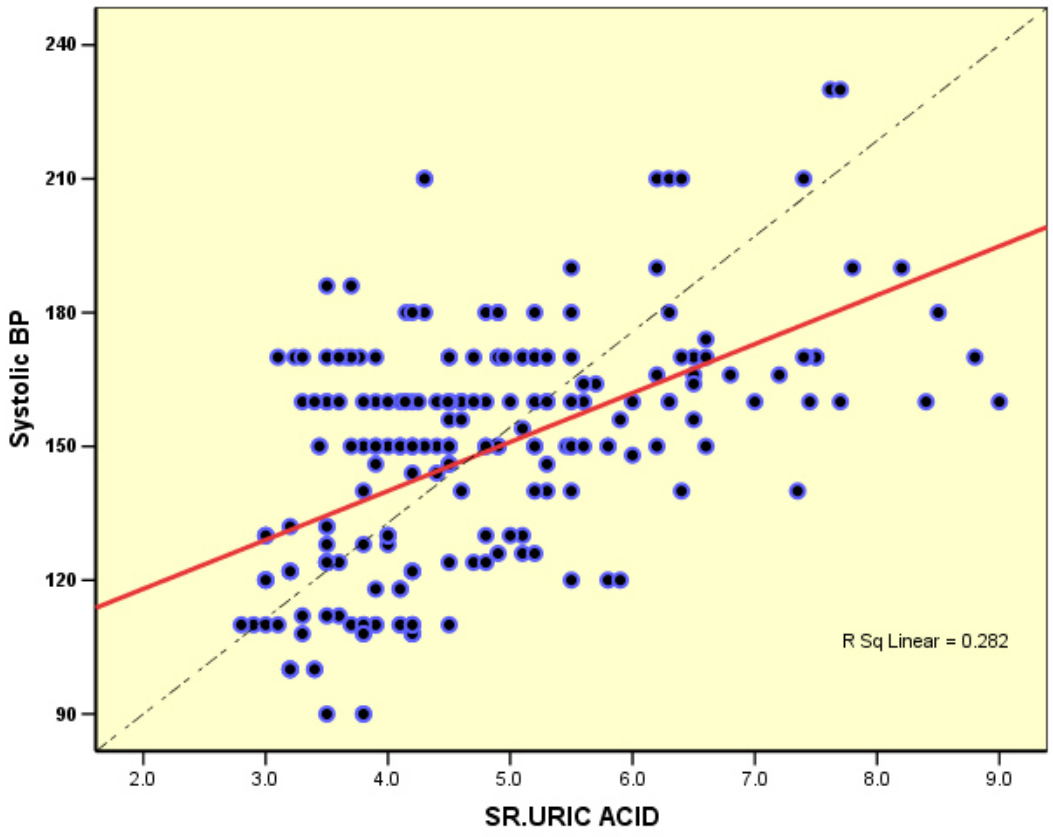
Table 3 BMI Distributions In The Study Population

BMI	CASES		CONTROLS		T TEST (P VALUE)
	NO	%	NO	%	
< 23	74	49.3	44	58.7	
≥23	76	50.7	31	41.3	
TOTAL	150	100	75	100	0.063
MEAN	23.404		22.416		
S.D.	3.9589		1.9555		

The mean and standard deviation of BMI for cases and controls were 23.4±3.96 and 22.42±1.96 respectively. 30% of cases were obese while in the control group it was 12%.

The difference in Body Mass Index between cases and controls were statistically not significant (p-0.063).

SYSTOLIC BP IN RELATION TO SERUM URIC ACID IN STUDY GROUP



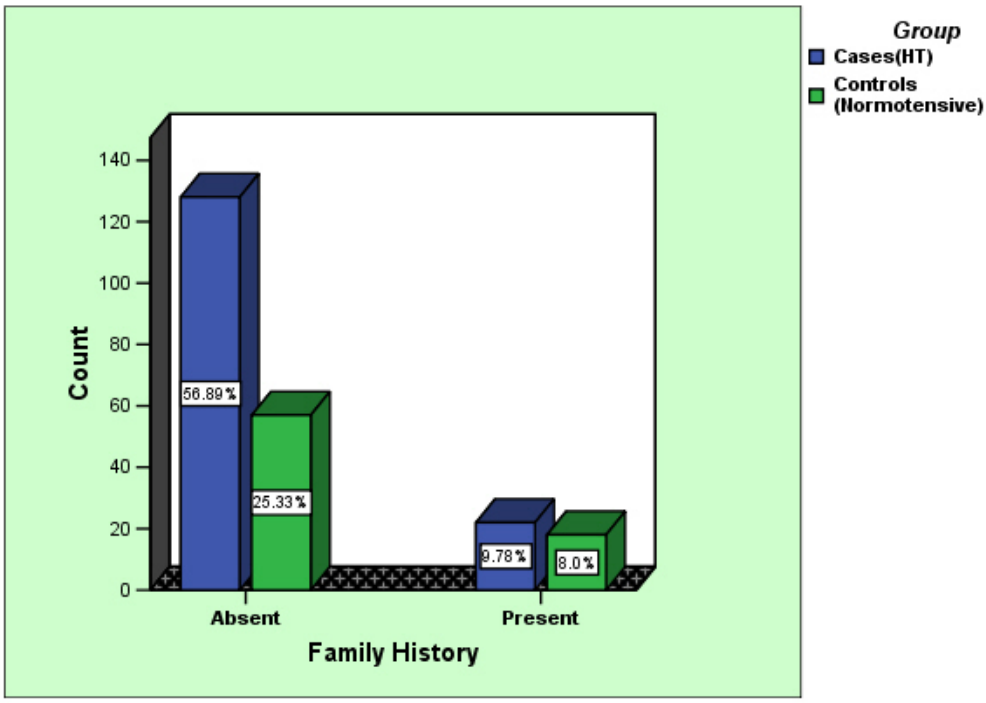
BLOOD PRESSURE DISTRIBUTION AMONG CASES AND CONTROLS

Table 4 Distribution of systolic and diastolic BP among study group

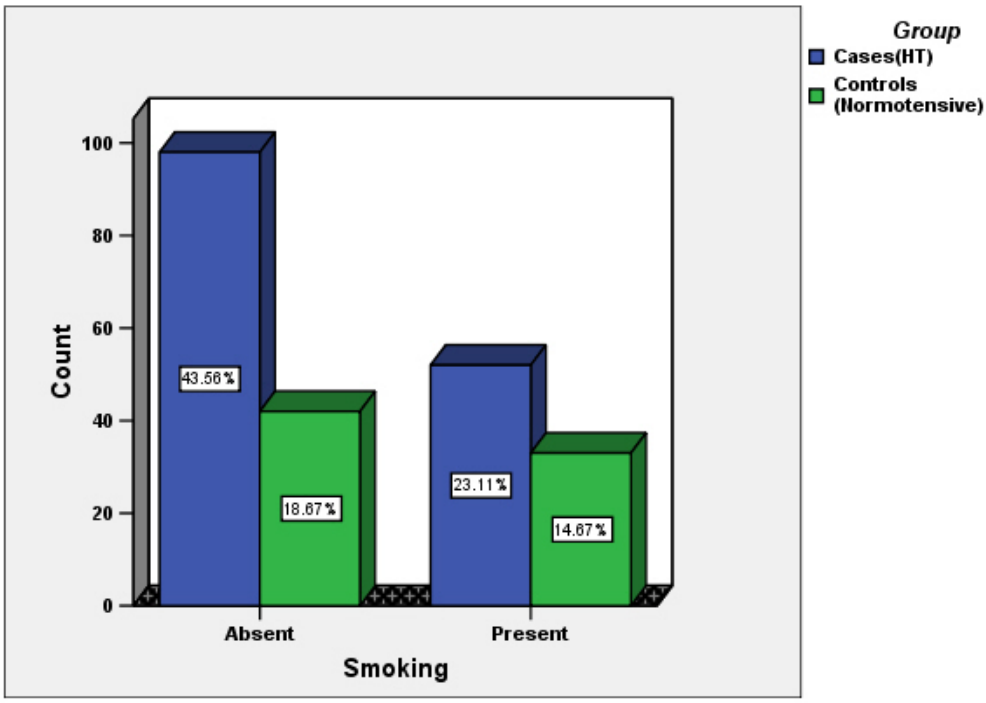
Blood Pressure	Group	No	Mean	S.D
SYSTOLIC BP	CASES	150	163.87	16.916
	CONTROLS	75	116.72	10.819
DIASTOLIC BP	CASES	150	101.68	8.954
	CONTROLS	75	75.36	7.656
PULSE PRESSURE	CASES	150	62.1867	13.69534
	CONTROLS	75	41.3600	10.43466

The mean and standard deviation of systolic and diastolic BP in cases were 163.87±16.92 and 101.68±8.95 respectively.

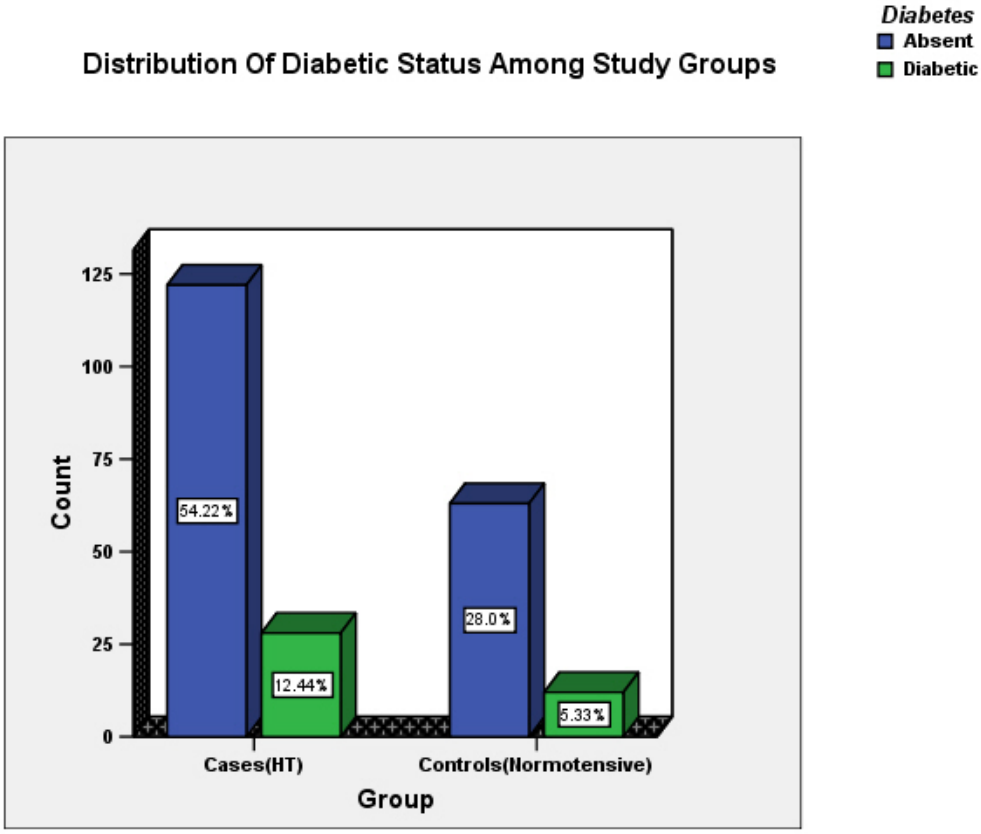
Distribution Of Family History Study Population



Distribution Of Smoking Among The Study Population



Distribution Of Diabetic Status Among Study Groups



DISTRIBUTION OF CASES AND CONTROLS IN RELATION TO CARDIOVASCULAR RISK FACTORS

In this study population family history of cardiovascular disease, smoking and diabetes mellitus were equally prevalent in both cases and controls.

Table 5 Distribution of study population in relation to cardiovascular risk factors.

		CASES		CONTROLS		P VALUE
		COUNTS	%	COUNTS	%	
FAMILY H/O	YES	22	14.7	18	24	0.184
	NO	128	85.3	57	76	
SMOKING H/O	YES	52	34.7	33	44	0.173
	NO	98	65.3	42	56	
DIABETIC H/O	YES	28	18.7	12	16	0.622
	NO	122	81.3	63	84	

There was no statistical significance between cases and controls in relation to family history of cardiovascular disease, smoking and diabetes.

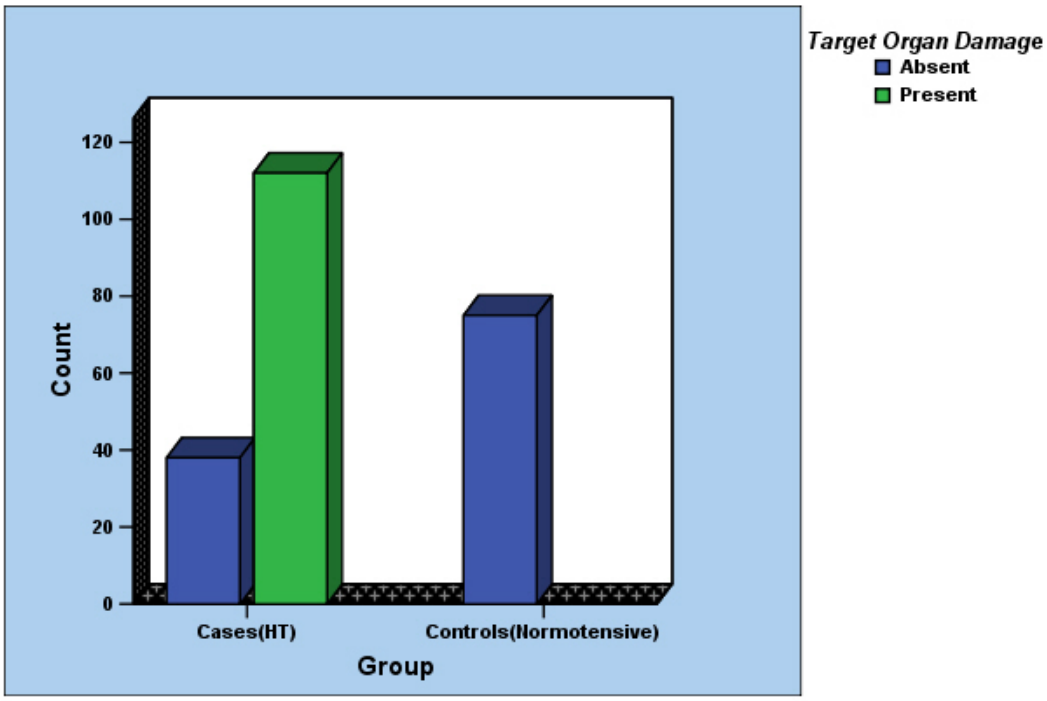
Distribution of cases and controls in relation to blood sugar,urea and serum Creatinine.

Table 6 Distribution of study population in relation to blood parameters

		NO.	MEAN	SD	P
BL.SUGAR	CASES	150	105.25	37.920	
	CONTROLS	75	101.15	17.620	0.374
BL.UREA	CASES	150	29.04	5.601	
	CONTROLS	75	28.11	4.072	0.201
SR.CREAT	CASES	150	0.947	0.2113	
	CONTROLS	75	0.923	0.1538	0.370

There was no statistical significance in distribution of cases and controls in relation to Blood sugar, urea and serum creatinine.

Distribution Of Target Organ Damage Among The Study Groups



ANALYSIS OF CASES IN RELATION TO TARGET ORGAN DAMAGE (TOD)

The details of prevalence of target organ damage (TOD) - Left ventricular hypertrophy (LVH), Coronary artery disease (CAD), Congestive cardiac failure (CCF), Cerebrovascular accident/Transient ischemic attack (CVA/TIA), Peripheral arterial disease (PAD) and Hypertensive retinopathy.

Table 7 Distribution of cases in relation to TOD

TOD		Cases	
		No.	Percentage
LVH	Present	22	14.7
	Absent	128	85.3
CAD	Present	53	35.3
	Absent	97	64.7
CCF	Present	22	14.7
	Absent	128	85.3
CVA/TIA	Present	24	16
	Absent	126	84
PAD	Present	4	2.7
	Absent	146	97.3
Retinopathy	NIL	87	58
	Grade I	37	24.7
	Grade II	24	16
	Grade III	2	1.3

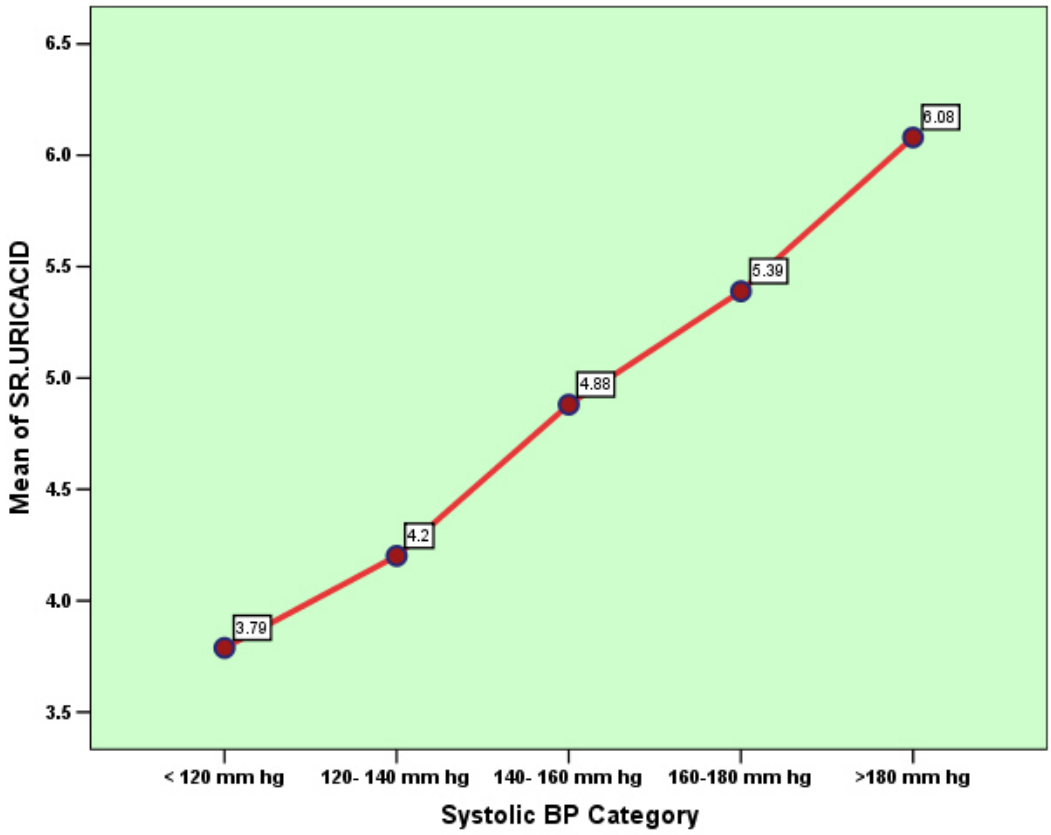
Among 150 cases, LVH was present in 22 cases, CAD was present in 53 cases, CCF was present in 22 cases, CVA/TIA was present in 24 cases, PAD was present in 4 cases and Hypertensive Retinopathy was present in 63cases.

Table 8 Distribution of serum uric acid among study population

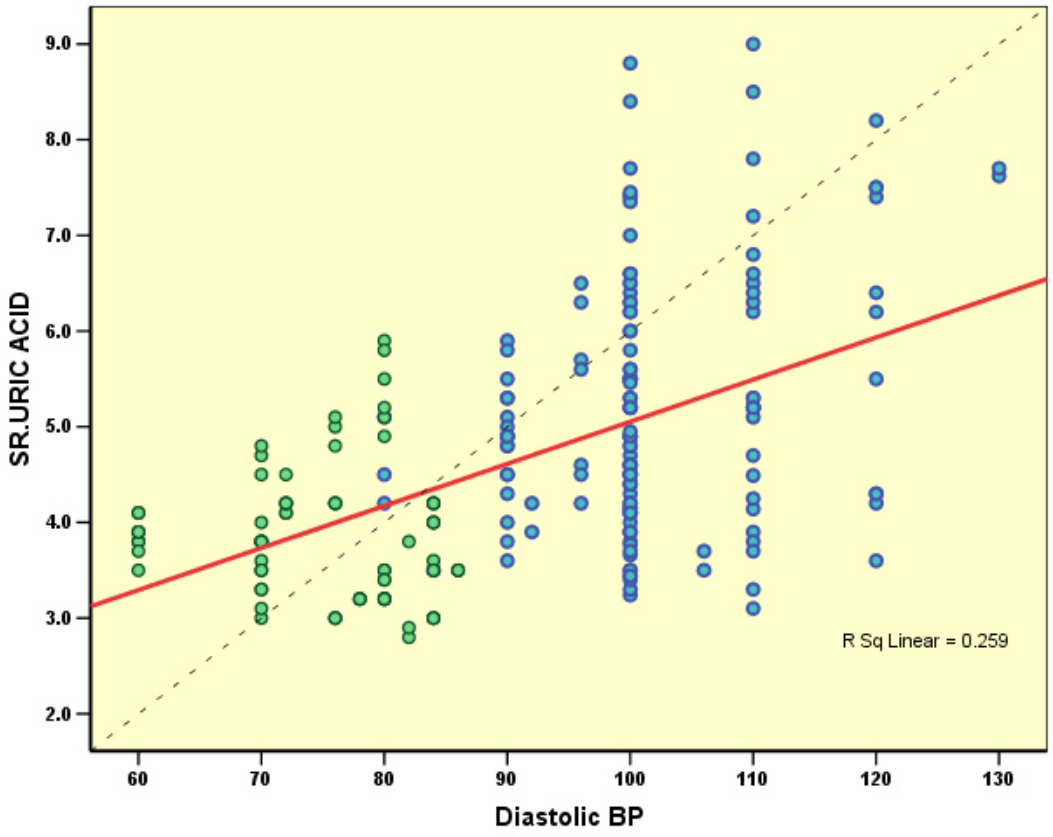
	Group	No.	Mean	SD	P-value
SR.URIC ACID	CASES	150	5.185	1.3104	0.0001
	CONTROLS	75	3.853	0.7006	

Serum uric acid in cases varied from 3.1mg% to 9mg% and in the control from 2.8mg% to 5.9mg%. The mean and standard deviation of serum uric acid among cases were 5.185±1.31 while in control it was 3.853±0.7 respectively. This table clearly shows that the serum uric acid level was significantly influenced by systemic hypertension.

SERUM URIC ACID IN RELATION TO SYSTOLIC BP IN STUDY GROUP



SERUM URIC ACID IN RELATION TO DIASTIOLIC BP IN STUDY GROUP



DISTRIBUTION OF CASES AND CONTROLS IN RELATION TO HYPERURICEMIA

Table 9 Comparisons of mean uric acid levels among the cases and controls

URICEMIC STATUS		N	MEAN	STD. DEVIATION	P VALUE
NORMAL	CASES	129	4.790	0.8982	0.0001
	CONTROLS	75	3.853	0.7006	
HYPER URICEMIA	CASES	21	7.611	0.6654	
	CONTROLS	0(A)	-	-	-

(A) - T CANNOT BE COMPUTED BECAUSE AT LEAST ONE OF THE GROUPS IS EMPTY.

Hyperuricemia is defined as serum uric acid levels >7mg/dl in males and >6mg/dl in female. 21 cases had hyperuricemia while none of the controls had hyperuricemia. Mean and SD of hyperuricemia in cases 7.6±0.67. Hyperuricemia was present in 14%of hypertensives.

This table clearly shows hyperuricemia was statistically significant in hypertensives when compared to normotensives.

SEX DISTRIBUTION OF SERUM URIC ACID IN STUDY POPULATION

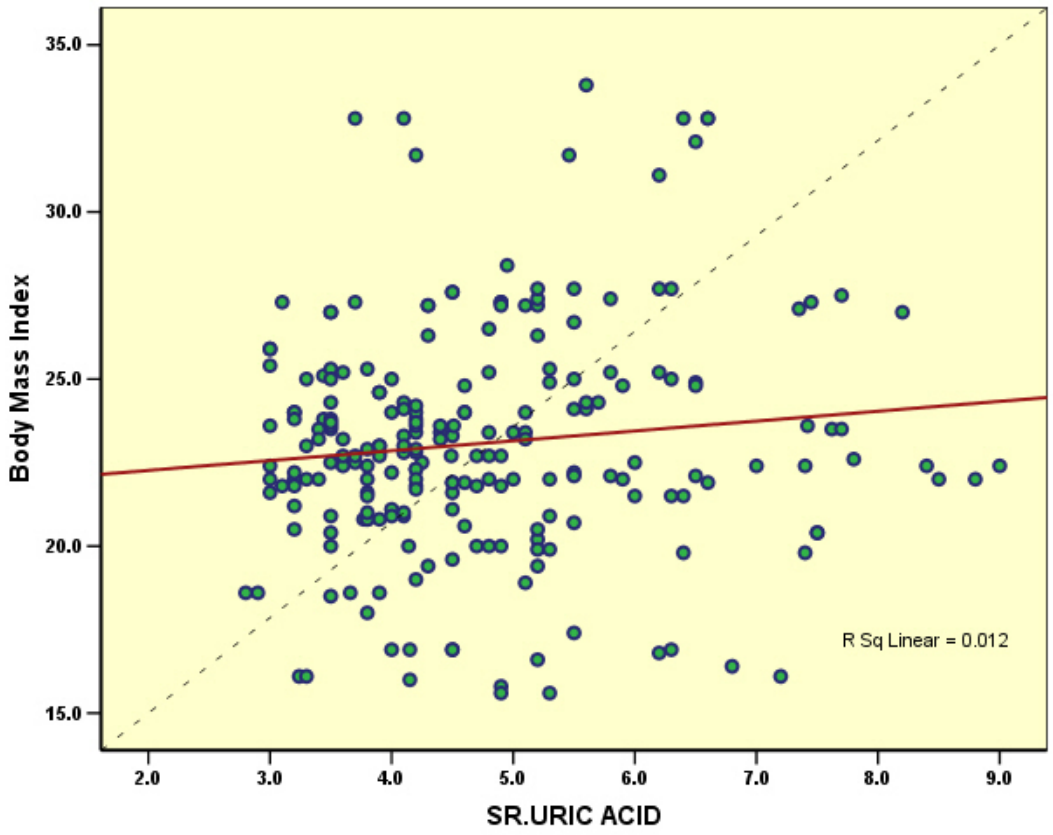
Table 10 Comparision Of Uric Acid Levels Amongs the Study Groups

GROUP	SEX	N	SR URIC ACID		P VALUE
			MEAN	SD	
CASES	FEMALES	40	5.047	1.2643	0.438
	MALES	110	5.236	1.3289	
CONTROLS	FEMALES	26	3.700	0.5741	0.169
	MALES	49	3.935	0.7521	

The mean serum uric acid level in hypertensive males and females were 5.24±1.33 and 5.05±1.26 respectively.

Even though the mean serum uric acid level was higher in hypertensive males when compared to hypertensive females it was not statistically significant.

SERUM URIC ACID IN RELATION TO BMI IN STUDY GROUP



SERUM URIC ACID IN RELATION TO BODY MASS INDEX

In the study population, BMI <23 was seen in 74 cases among 118 subjects, and the mean serum uric acid level was 5.16±1.4. BMI ≥23 was seen in 76 cases among 107 subjects and and the mean serum uric acid level was 5.2±1.18.

Table No-11: Relationship Between BMI and Uric Acid Level in cases and controls

	Study group	Serum uric acid			Cases	Serum uric acid		
BMI	No.	Mean	S.D	PVALUE	No.	Mean	S.D	pVALUE
<23	118	4.73	1.37	0.917	74	5.18	1.4	0.925
≥23	107	4.75	1.24		76	5.2	1.18	

This table shows Body Mass Index was not significantly influencing the serum uric acid.

Table 12 Serum uric acid Levels in relation to smokers in study population

			H/o Smoking	
			Absent	**Present**
Serum Uric Acid	Normal	Count	124	79
		Percentage	88.6	92.9
	Hyperuricemia	Count	16	6
		Percentage	11.4	7.1

Chi Square test : p= 0.108

		Serum uric acid		
H/o smoking	No.	Mean	S.D.	pValue
YES	85	4.77	1.27	0.873
NO	140	4.73	1.33	

This table showed smoking did not influence serum uric acid level significantly.

Hyperuricemia was present in 7.1% of smokers in study population. The mean serum uric acid level of smokers in study population was 4.77 ±1.3 when compared to non smoker 4.73±1.33.

Table 13 Serum uric acid levels in Diabetes Mellitus among study population

			H/o Smoking	
			Absent	**Present**
Serum Uric Acid	Normal	Count	169	34
		Percentage	91.4	85
	Hyperuricemia	Count	16	6
		Percentage	8.6	15

Chi Square test : p=0.288

Table 14 Serum uric acid levels in Diabetes Mellitus among study population

		Serum uric acid		
H/o smoking	No.	Mean	S.D.	pValue
YES	40	4.85	1.35	0.573
NO	185	4.72	1.3	

Hyperuricemia was present in 15% of Diabetics in study population. The mean serum uric acid level of Diabetics in study population was 4.85±1.3.

This table showed Diabetes did not influence serum uric acid level significantly.

Serum uric acid level in relation to Target Organ Damage (TOD)

The mean values and standard deviation of target organ damage which was present in cases were shown in table below.

Table 15 Serum uric acid level in relation to target organ damage.

TOD		No.	Mean	S.D.	P-value
LVH	YES	22	5.29	1.34	0.635
	NO	128	5.14	1.29	
CAD	YES	53	5.56	0.02	0.01
	NO	97	4.98	0.01	
CCF	YES	22	5.85	1.57	0.0965
	NO	128	5.18	1.22	
CVA/TIA	YES	24	4.73	1.13	0.064
	NO	126	5.27	1.33	
Retinopathy	YES	63	4.97	1.13	0.075
	NO	87	4.56	1.28	

Coronary arterial disease was seen in 53 hypertensive individuals. The mean serum uric acid level in cases with CAD was 5.56±0.02 while it was 4.98±0.01 among the cases without CAD. There was significant difference noticed among the cases with and without CAD (P-value 0.01).

There was no significant difference noticed among the cases with and without other target organ damages like LVH, CCF, CVA, and RETINOPATHY.

Peripheral arterial disease was seen in 4 hypertensive individuals only. The mean serum uric acid level in cases with PAD was 7.26±0.6 while it was 5.23±1.29 among the cases without PAD.

Serum uric acid level in hypertensive subjects with and without Target Organ Damage (TOD).

Table 16 Serum uric acid level in cases with/without TOD

TOD	No	Mean	S.D	P-value
Present	112	5.21	1.41	0.701
Absent	38	5.114	0.93	

The mean serum uric acid level in hypertensive subjects with and without TOD was 5.21±1.4 and 5.114±0.93 respectively. The serum uric acid level in cases with and without target organ damage was not statistically significant (P-value 0.701)

Discussion

Hypertension is the most common form of cardiovascular disease which is present in nearly 25% of adults and the prevalence increases with age. Hypertension is strongly associated with hyperuricemia (Hayden, 2004). Cannon et al (1966) reported that hyperuricemia was observed in 25% of untreated hypertension or renal dysfunction.

In the study the relation between serum uric acid level and hypertension was analyzed. Previous strong epidemiological data had linked serum uric acid level and hypertension (Cannon et al 1966, Kinsley et al, 1961, Klein et al, 1973) and experimental animal data suggested hyperuricemia causes hypertension (Mazzali et al 2001, Sanchezs et al 2002, Watanable, 2002).

Among the 150 cases of hypertension, hyperuricemia was seen in 21 cases, which is account for 14% of cases. Cannon et al 1966 showed a prevalence of hyperuricemia in 25% of untreated hypertensive cases. But in our study many of the cases were on treatment which might have affected the results.

The experimental studies further showed that hyperuricemia caused preglomerular vascular disease via BP independent pathway (Mazzali et al 2001) and once vascular disease was established, the hypertension was driven

by kidney and lowering uric acid level was no longer protective (Watanable, 2002)

The observation from the Framingham study revealed that the correlation of uric acid level with blood pressure was attenuated in the study population as they aged is consistent with these data. (Source : Feig and Johnson 2003).

Various studies have linked the development of hypertension with hyperuricemia. The Olivetti heart study (Joss et al, 1994) has shown an independent positive association between serum uric acid and development of hypertension. Selby, et al, (1990) have concluded in their study that both forced vital capacity and serum uric acid were closely linked to the development of hypertension.

Feig and Johnson et al (2003) found that serum uric acid was elevated in 89% of children with essential hypertension. He concluded that serum uric acid level directly correlated with blood pressure in untreated children and that a serum uric acid level of >5.5mg% in an adolescent being evaluated for hypertension strongly suggests essential hypertension.

The mean age for cases in this study is 54.57 years. This might explain the lower prevalence of hyperuricemia when compared with Feig and Johnson et al study (2003).

The mean serum uric acid level in male is 5.24±1.33 while in female it is 5.05±1.26 and the difference is not statistically significant. This is in contrast with the study done by Ketker et al (1979) in which they have shown that the serum uric acid level was more in males when compared to females.

In this study serum uric acid do not correlate with Body Mass Index. The mean serum uric acid level in hypertensive with BMI<23 and BMI≥23 are 5.175mg/dl and 5.195mg/dl and the difference is not statistically significant. Shobha Kelker et al and Healey have shown in their study that there was no significant correlation between serum uric acid level and obesity.

The serum uric acid level is significantly higher in hypertensives when compared to normotensive subjects. The mean serum uric acid level in cases is 5.185mg/dl while in the control it is 3.85mg/dl. This is consistent with other studies, which has shown serum uric acid is elevated in hypertension.

In a review article by Hayden et al (2004) it was noted that elevation of serum uric acid level >4mg/dl should be considered as a **red flag** in those cases with risk for cardiovascular disease. In this study 82%of hypertensive has serum uric acid level >4mg/dl, while in controls 36% of subjects have serum uric acid level >4mg/dl. In these subjects the clinician

should strive to utilize global risk reduction programme to reduce the complications of atherogenic process. The details in relation to this study are shown in the table given below.

Table 17 Distribution cases and controls in relation to high risk serum uric acid:

Serum uric acid	Cases		Controls		P-value
	No.	%	No.	%	
≤4mg/dl	27	18	48	64	0.0001
>4mg/dl	123	82	27	36	

The association of serum uric acid with cardiovascular disease has been appreciated for nearly half a century (Gertler et al, 1951). However, its role as a cardiovascular risk factor remains controversial. The Framingham heart study concluded that uric acid does not have a causal role in the development on coronary heart disease and death from other cardiovascular disease. In an epidemiologic follow up study an association between serum uric acid and cardiovascular disease was shown (Fredman et al). The recent PIUMA study also concluded that raised serum uric acid is a powerful risk factor for subsequent cardiovascular disease and all cause mortality (PaolaVerdecchia,et al,2000).

A large body of evidence links uric acid with the metabolic syndrome of insulin resistance, obesity, hypertension and dyslipidemia.Cappuccio et al reported an association of hyperuricemia with increased renal tubular sodium reabsorption, thus providing a link with hyperuricemia, hypertension and hyperinsulinemia. However there is no significant association between serum uric acid level and diabetic in this study. Smoking which is also a cardiovascular risk factor does not significantly influence serum uric acid level in the present study. (Hypertension. 2005; 45:991-996)

Overall, patients with target organ damage had significantly higher levels of serum uric acid as compared with those without it. But in our study, the serum uric acid level in cases with and without target organ damage is not statistically significant (P-value0.701).

Hyperuricemia is more pronounced in hypertensives complicated by PAD and is associated with worse functional status of the peripheral circulation (Atherosclerosis.2003 may; 168(1):163-8)

In our study, peripheral arterial disease is seen in 4 hypertensive individuals only. The mean serum uric acid level in cases with PAD is 7.26±0.6 while it is 5.23±1.29 among the cases without PAD.

Adenosine synthesis and release are up regulated in response to hypoxia and tissue ischemia. The adenosine is rapidly degraded by endothelium to uric acid. Therefore hyperuricemia is considered as a marker of underlying tissue ischemia (Waring et al2000).

The Subjects with altered Coronary Flow Rate (CFR) had significantly higher SUA levels compared with those with normal CFR These results support a role for SUA level as an independent marker of target organ damage in hypertension (Mustafa Caliskan, Dogan Erdogan et al).

Serum uric acid levels are independently and significantly associated with risk of cardiovascular mortality (JAMA. 2000; 283:2404-2410).

In our study, coronary arterial disease is seen in 53 hypertensive individuals. The mean serum uric acid level in cases with CAD is 5.56±0.02 while it is 4.98±0.01 among the cases without CAD. There is significant difference noticed among the cases with and without CAD (Pvalue- 0.01).

Hyperuricemia, a known correlate of oxidative stress, is a marker for adverse prognosis among individuals with heart failure. Hyperuricemia is a novel, independent risk factor for heart failure in a group of young general community dwellers. This has implications for development of preventive strategies for heart failure **(**Circulation: Heart Failure. 2009; 2:556-562)

As there are controversies with reference to elevated uric acid as an independent risk factor for cardiovascular disease, it is suggested to carry out similar prospective studies among newly detected hypertensive population and follow them to ascertain truth.

CONCLUSION

1. Hyperuricemia (>7mg/dl in males and >6mg/dl in females) is found in 14% of hypertensives while none of the normotensives had hyperuricemia.

2. Serum uric acid level is significantly elevated in Essential hypertension.

3. There is no correlation between serum uric acid with age, gender, body mass index, smoking, and Diabetes.

4. Serum uric acid level is significantly elevated in cases with coronary artery disease /peripheral arterial disease as compared to those with other target organ damage.

5. In this study, 82% of hypertensive population having Serum uric acid level >4mg/dl which is now considered as a red flag in those with risk factor for cardiovascular disease.

BIBLIOGRAPHY

1. Agamah ES, Srinivasan SR, Webber LS, Berenson GS. Serum uric acid and its relation to cardiovascular disease risk factors in children and young adults from a biracial community: the Bogalusa Heart Study. J Lab Clin Med1991; **118**:241–9. 4. Emmerson BT. The management of gout. N Engl J Med1996; **334**:445–515. Steele TH. Hyperuricemic nephropathies. Nephron1999; **81** (Suppl. 1):45–9.
2. Alderman MH, Cohen H, Madhavan S, Kivlighn S. Serum uric acid and cardiovascular events in successfully treated hypertensive patients. Hypertension1999; **34**:144–50
3. Alper AB, Chen W, Yau L, Srinivasan S, Hamm LL, Berenson G. Childhood uric acid predicts adult blood pressure: The Bogalusa Heart Study. *Hypertension.* 2005; 45: 34–38.
4. Anker SD, Leyva F, Poole-Wilson PA, Kox WJ, Stevenson JC, Coats AJ. Relation between serum uric acid and lower limb blood flow in patients with chronic heart failure. Heart1997; **78**:39–43.
5. Beard JT. Serum uric acid and coronary heart disease. Am Heart J1983; **106**:397–400.

6. Bengtsson C, Lapidus L, Stendahl C, Waldenstrom J. Hyperuricaemia and risk of cardiovascular disease and overall death. A 12-year follow-up of participants in the population study of women in Gothenburg, Sweden. Acta Med Scand1988; **224**:549–55.
7. Bonora E, Targher G, Zenere MB, Saggiani F, Cacciatori V, Tosi F, Travia D, Zenti MG, Branzi P, Santi L, Muggeo M. Relationship of uric acid concentration to cardiovascular risk factors in young men. Role of obesity and central fat distribution. The Verona Young Men Atherosclerosis Risk Factors Study. Int J Obes Relat Metab Disord1996; **20**:975–80.
8. Boogaerts MA, Hammerschmidt DE, Roelant C, Verwilghen RL, Jacob HS. Mechanisms of vascular damage in gout and oxalosis: crystal induced, granulocyte mediated, endothelial injury. Thromb Haemost1983; **50**:576–80.
9. Bulpitt CJ. Serum uric acid in hypertensive subjects. *Brit Heart J.* 1975; 37: 1210–1215.
10. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *N Engl J Med.* 1966; 275: 457–464.

11. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med1999; **131**:7–13.

12. Dobson A. Is raised serum uric acid a cause of cardiovascular disease or death? Lancet1999; **354**:1578.

13. Duff GW, Atkins E, Malawista SE. The fever of gout: urate crystals activate endogenous pyrogen production from human and rabbit mononuclear phagocytes. Trans Assoc Am Physicians1983; **96**:234–45.

14. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA.* 1991; 266: 3008–3011

15. Feig DI, Johnson RJ. Hyperuricemia in childhood essential hypertension. *Hypertension.* 2003; 42: 247–252.

16. Ferro CJ, Webb DJ. Endothelial dysfunction and hypertension. Drugs1997, **53**(Suppl. 1): 30–41.

17. Haffner SM, Miettinen H, Gaskill SP, Stern MP. Metabolic precursors of hypertension. The San Antonio Heart Study. *Arch Intern Med.* 1996; 156: 1994–2001

18. Hunt SC, Stephenson SH, Hopkins PN, Williams RR. Predictors of an increased risk of future hypertension in Utah. A screening analysis. *Hypertension.* 1991; 17: 969–976

19. Hutton CW, Collins AJ, Chambers RE, Whicher J, Dieppe PA. Systemic response to local urate crystal induced inflammation in man: a possible model to study the acute phase response. Ann Rheum Dis1985; **44**:533–6.

20. Iribarren C, Folsom AR, Eckfeldt JH, McGovern PG, Nieto FJ. Correlates of uric acid and its association with asymptomatic carotid atherosclerosis: the ARIC Study. Atherosclerosis Risk in Communities. Ann Epidemiol1996; **6**:331–40.

21. Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, Tuttle KR, Rodriguez-Iturbe B, Herrera-Acosta J, Mazzali M. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease. *Hypertension.* 2003; 41: 1183–1190.

22. Jossa F, Farinaro E, Panico S, Krogh V, Celentano E, Galasso R, Mancini M, Trevisan M. Serum uric acid and hypertension: the Olivetti heart study. *J Hum Hypertens.* 1994; 8: 677–681.

23. Kahn HA, Medalie JH, Neufeld HN, Riss E, Goldbourt U. The incidence of hypertension and associated factors: the Israel ischemic heart disease study. *Am Heart J.* 1972; 84: 171–182

24. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L, Johnson RJ. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. *Hypertension.* 2003; 41: 1287–1293

25. Klein R, Klein BE, Cornoni JC, Maready J, Cassel JC, Tryoler HA. Serum uric acid. Its relationship to coronary heart disease risk factors and cardiovascular disease, Evans County, Georgia. *Arch Intern Med.* 1973; 132: 401–410.

26. Kohn PM, Prozan GB. Hyperuricemia: relationship to hypercholesterolemia and acute myocardial infarction. JAMA1959; **170**:1909–15.

27. Kroll K, Bukowski TR, Schwartz LM, Knoepfler D, Bassingthwaighte JB. Capillary endothelial transport of uric acid in guinea pig heart. Am J Physiol1992, **262**:H420-H431.

28. Lee J, Sparrow D, Vokonas PS, Landsberg L, Weiss ST. Uric acid and coronary heart disease risk: evidence for a role of uric acid in the obesity-insulin resistance syndrome. The Normative Aging Study. *Am J Epidemiol.* 1995; 142: 288–294

29. Lehto S, Niskanen L, Ronnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. Stroke1998; **29**:635–9.

30. Leyva F, Anker SD, Godsland IF, Teixeira M, Hellewell PG, Kox WJ, Poole-Wilson PA, Coats AJ. Uric acid in chronic heart failure: a marker of chronic inflammation. Eur Heart J1998; **19**:1814–22.

31. Liese AD, Hense HW, Lowel H, Doring A, Tietze M, Keil U. Association of serum uric acid with all-cause and cardiovascular disease mortality and incident myocardial infarction in the MONICA Augsburg cohort. World Health Organization Monitoring Trends and Determinants in Cardiovascular Diseases. Epidemiology1999; **10**:391–7.

32. Masuo K, Kawaguchi H, Mikami H, Ogihara T, Tuck ML. Serum uric acid and plasma norepinephrine concentrations predict subsequent weight gain and blood pressure elevation. *Hypertension.* 2003; 42: 474–480

33. Mazzali M, Hughes J, Kim YG, Jefferson JA, Kang DH, Gordon KL, Lan HY, Kivlighn S, Johnson RJ. Elevated uric acid increases blood pressure in the rat by a novel crystal-independent mechanism. *Hypertension.* 2001; 38: 1101–1106. 38. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S,

Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. *Am J Physiol Renal Physiol.* 2002; 282: F991–F997.

34. Mercuro G, Vitale C, Cerquetani E, Zoncu S, Deidda M, Fini M, Rosano GM. Effect of hyperuricemia upon endothelial function in patients at increased cardiovascular risk. *Am J Cardiol.* 2004; 94: 932–935

35. Messerli FH, Frohlich ED, Dreslinski GR, Suarez DH, Aristimuno GG. Serum uric acid in essential hypertension: an indicator of renal vascular involvement. *Ann Intern Med.* 1980; 93: 817–821.

36. Muscelli E, Natali A, Bianchi S, Bigazzi R, Galvan AQ, Sironi AM, Frascerra S, Ciociaro D, Ferrannini E. Effect of insulin on renal sodium and uric acid handling in essential hypertension. Am J Hypertens1996; **9**:746.

37. Nagahama K, Inoue T, Iseki K, Touma T, Kinjo K, Ohya Y, Takishita S. Hyperuricemia as a predictor of hypertension in a screened cohort in Okinawa, Japan. *Hypertens Res.* 2004; 27: 835–841.

38. Nakagawa T, Mazzali M, Kang DH, Kanellis J, Watanabe S, Sanchez-Lozada LG, Rodriguez-Iturbe B, Herrera-Acosta J, Johnson RJ. Hyperuricemia causes glomerular hypertrophy in the rat. *Am J Nephrol.* 2003; 23: 2–7.

39. Nakanishi N, Okamoto M, Yoshida H, Matsuo Y, Suzuki K, Tatara K. Serum uric acid and risk for development of hypertension and impaired fasting glucose or Type II diabetes in Japanese male office workers. *Eur J Epidemiol.* 2003; 18: 523–530.

40. Perlstein TS, Gumieniak O, Hopkins PN, Murphey LJ, Brown NJ, Williams GH, Hollenberg NK, Fisher ND. Uric acid and the state of the intrarenal renin-angiotensin system in humans. *Kidney Int.* 2004; 66: 1465–1470.

41. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E. Effect of insulin on uric acid excretion in humans. *Am J Physiol.* 1995; 268: E1–E5

42. Raatikainen MJ, Peuhkurinen KJ, Hassinen IE. Contribution of endothelium and cardiomyocytes to hypoxia-induced adenosine release. J Mol Cell Cardiol1994; **26**:1069–80.

43. Reunanen A, Takkunen H, Knekt P, Aromaa A. Hyperuricemia as a risk factor for cardiovascular mortality. Acta Med Scand Suppl1982; **668**:49–59.

44. Sánchez-Lozada LG, Tapia E, Santamaria J, Avila-Casado C, Soto V, Nepomuceno T, Rodriguez-Iturbe B, Johnson RJ, Herrera-Acosta J. Mild hyperuricemia induces vasoconstriction and maintains glomerular hypertension in normal and remnant kidney rats. *Kidney Int.* 2004.

45. Selby JV, Friedman GD, Quesenberry CPJ. Precursors of essential hypertension: pulmonary function, heart rate, uric acid, serum cholesterol, and other serum chemistries. Am J Epidemiol1990; **131**:1017–27

46. Short RA, Tuttle KR. Clinical evidence for the influence of uric acid on hypertension, cardiovascular disease, and kidney disease: a statistical modeling perspective. *Semin Nephrol.* 2005; 25: 25–31

47. Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis.* 2006; 47: 51–59.

48. Skinner KA, White CR, Patel R, Tan S, Barnes S, Kirk M, Darley-Usmar V, Parks DA. Nitrosation of uric acid by peroxynitrite. Formation of a vasoactive nitric oxide donor. J Biol Chem1998; **273**:24491–7.

49. Sundström J, Sullivan L, D'Agostino RB, Levy D, Kannel WB, Vasan RS. Relations of serum uric aid to longitudinal blood pressure tracking and hypertension incidence in the Framingham Heart Study. *Hypertension.* 2005; 45: 28–33.

50. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K. Serum uric acid and the risk for hypertension and type 2 diabetes in

Japanese men: The Osaka Health Survey. *J Hypertens.* 2001; 19: 1209–1215.

51. The Coronary Drug Project Research Group. Serum uric acid: its association with other risk factors and with mortality in coronary heart disease. J Chron Dis1976; **29**:557–69.
52. Torun M, Yardim S, Simsek B, Burgaz S. Serum uric acid levels in cardiovascular diseases. J Clin Pharm Ther1998; **23**:25–9.
53. Tykarski A. Evaluation of renal handling of uric acid in essential hypertension: hyperuricemia related to decreased urate secretion. Nephron1991; **59**:364–8.
54. Vaccarino V, Krunholz HM. Risk factors for cardiovascular disease: one down, many more to evaluate. *Ann Int Med.* 1999; 131: 62–63.
55. Vallance P. Nitric oxide in the human cardiovascular system- SKB lecture 1997. Br J Clin Pharmacol1998; **45**:433–9.
56. Wannamethee SG, Shaper AG, Whincup PH. Serum urate and the risk of major coronary heart disease events. Heart1997; **78**:147–53.
57. Ward H. Uric acid as an independent risk factor in the treatment of hypertension. Lancet1998, **352**:670–1.

PROFORMA

NAME: AGE: SEX: IP/OP No:

BMI:

COMPLAINTS:

PAST HISTORY:

DIABETES MELLITUS:

CAD:

CVA/TIA:

HISTORY OF SMOKING:

FAMILY HISTORY:

EXAMINATION:

BLOOD PRESSURE: ALL PERIPHERAL PULSES:

CCF:

CVA/TIA: FUNDUS:

INVESTIGATIONS:

ECG:

BL.SUGAR: BL.UREA: SR.CREATININE:

SR.URIC ACID:

ABBREVIATIONS

BMI:Body Mass Index.

S.B.P:Systolic blood pressure.

D.B.P:Diastolic blood pressure.

FAMILY.H: Family history.

DM:Diabetes mellitus.

LVH:Left ventricular hypertrophy.

CAD:Coronary artery disease.

CCF:Congestive cardiac failure.

CVA:Cerbrovascular accident.

TIA:Transient ischemic attack.

PAD:Peripheral arterial disease.

RETINO:Retinopathy.

RBS:Random blood sugar.

BL.UREA:Blood urea.

S.CREAT:Serum creatinine.

SUA:Serum uric acid.

MASTER CHART-CASES

S.No.	AGE	SEX	B.M.I	S.B.P	D.B.P	FAMILY.H	SMOKING	DM	LVH	CAD	CCF	CVA/TIA	PAD	RETINO	RBS.	B.UREA	S.CREAT	SUA
1	61	F	31.7	160	100	NO	NO	NO	NO	YES	NO	NO	NO	II	71	40	0.7	4.2
2	52	F	21.1	150	90	NO	NO	NO	NO	NO	NO	NO	NO	NIL	89	30	0.9	4
3	55	M	17.4	160	100	NO	YES	NO	NO	NO	NO	YES	NO	II	96	30	1.4	5.5
4	46	F	27.6	150	100	NO	NO	NO	NO	YES	NO	NO	NO	NIL	108	20	0.8	4.5
5	41	M	16.6	160	110	NO	YES	NO	NO	NO	NO	YES	NO	I	90	23	1.1	5.2
6	44	M	22.7	160	110	YES	YES	NO	NO	NO	YES	NO	NO	NIL	95	26	0.9	4.7
7	47	M	16.8	210	110	NO	YES	NO	NO	YES	NO	NO	NO	III	120	40	1.4	6.2
8	59	M	25.3	170	84	YES	NO	NO	NO	YES	NO	NO	NO	NIL	118	36	1.1	3.5
9	63	M	26.5	150	90	NO	YES	NO	NO	YES	NO	NO	NO	NIL	88	30	1.1	4.8
10	55	M	23.6	170	100	NO	NO	YES	NO	YES	YES	NO	YES	II	170	40	0.8	7.42
11	51	M	20.5	170	110	NO	YES	NO	NO	NO	NO	YES	NO	NIL	77	28	1	5.2
12	59	M	24.1	190	120	NO	NO	NO	NO	NO	NO	NO	NO	I	89	32	1.1	5.5
13	48	M	19.9	160	100	YES	NO	NO	NO	NO	NO	YES	NO	NIL	110	22	0.7	5.3
14	30	M	21.8	170	100	NO	YES	NO	NO	NO	NO	NO	NO	I	112	24	0.9	4.7
15	40	M	22.4	160	120	NO	NO	NO	NO	NO	NO	YES	NO	NIL	98	18	0.9	3.6
16	62	M	25.2	150	100	NO	YES	NO	NO	NO	NO	NO	NO	NIL	105	30	1	4.8
17	59	M	24.8	160	100	NO	YES	YES	NO	NO	YES	NO	NO	I	162	26	1.1	4.6
18	60	M	23.6	160	100	NO	NO	YES	NO	NO	NO	NO	NO	NIL	180	30	0.8	4.4
19	48	M	22.1	164	100	YES	YES	NO	NO	YES	NO	NO	NO	NIL	77	24	0.9	6.5
20	33	M	21.9	146	90	NO	YES	NO	NO	NO	YES	NO	NO	I	125	40	1	4.5
21	74	M	27.5	160	100	NO	NO	NO	NO	NO	NO	NO	NO	I	74	20	0.9	7.7
22	55	M	32.8	170	110	NO	YES	YES	YES	YES	NO	NO	NO	NIL	203	30	0.8	6.4
23	70	M	23.3	150	100	NO	NO	NO	YES	YES	NO	NO	NO	II	68	19	0.7	4.1
24	54	M	24	160	100	YES	YES	YES	YES	NO	NO	NO	NO	I	179	30	0.7	4.6
25	26	M	27.4	150	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	90	26	0.8	5.8

26	64	M	22.5	186	106	NO	NO	NO	NO	NO	NO	YES	NO	NIL	115	26	0.9	3.7
27	55	M	27.7	190	120	NO	NO	NO	YES	NO	NO	NO	NO	II	104	40	1	6.2
28	65	F	16.4	166	110	NO	NO	NO	NO	NO	NO	NO	NO	I	79	24	0.8	6.8
29	40	F	24.3	164	96	NO	NO	NO	NO	NO	NO	NO	NO	NIL	92	30	0.9	5.7
30	42	F	20.7	150	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	78	24	0.8	5.5
31	50	F	19.4	180	100	NO	NO	NO	NO	NO	NO	YES	NO	NIL	87	22	0.7	4.3
32	26	M	24.8	156	90	NO	NO	NO	NO	NO	NO	NO	NO	NIL	70	30	1	5.9
33	30	M	22.5	148	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	74	24	0.9	6
34	62	M	25.2	150	90	NO	NO	NO	NO	NO	NO	NO	NO	NIL	88	24	0.8	5.8
35	63	M	31.1	150	100	NO	YES	NO	NO	NO	NO	NO	NO	NIL	106	28	1	6.2
36	55	M	21.5	140	100	NO	NO	NO	NO	YES	NO	NO	NO	NIL	96	30	0.8	6.4
37	63	M	25	180	100	YES	NO	NO	NO	YES	NO	NO	NO	I	114	24	1	5.5
38	74	M	22.8	150	92	NO	NO	NO	NO	YES	NO	NO	NO	NIL	109	26	0.7	3.9
39	60	M	27.2	170	110	NO	YES	NO	NO	YES	NO	NO	NO	I	83	32	0.8	5.2
40	70	M	32.8	150	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	117	28	0.7	4.1
41	67	M	24.6	160	100	NO	YES	NO	NO	NO	NO	NO	NO	NIL	73	28	1	3.9
42	55	M	23.4	170	80	NO	NO	NO	NO	NO	NO	NO	NO	NIL	99	30	1.1	5.1
43	51	F	27.3	170	90	NO	NO	NO	NO	NO	NO	NO	NO	II	101	29	0.9	4.9
44	40	F	22.4	160	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	65	24	0.9	7
45	63	F	26.7	150	90	NO	NO	NO	NO	NO	NO	NO	NO	NIL	82	30	1.1	5.5
46	48	M	22	170	100	NO	YES	NO	NO	YES	YES	NO	NO	NIL	110	28	1	8.8
47	45	F	24.9	166	96	NO	NO	YES	NO	NO	NO	NO	NO	I	167	30	0.9	6.5
48	30	M	22.4	160	100	YES	NO	NO	NO	YES	NO	NO	NO	NIL	94	26	0.7	8.4
49	47	M	21.6	156	96	NO	NO	NO	NO	NO	NO	NO	NO	NIL	101	20	0.8	4.5
50	28	F	27.1	140	100	NO	NO	YES	NO	YES	NO	NO	NO	NIL	217	32	0.7	7.35
51	56	M	15.8	180	100	NO	YES	NO	YES	NO	NO	NO	NO	II	66	40	1.5	4.9
52	63	M	22.7	180	100	YES	NO	NO	NO	YES	NO	YES	NO	I	74	34	1.3	4.8
53	60	F	16.9	170	80	NO	NO	NO	NO	YES	YES	YES	NO	I	67	28	0.7	4.5
54	48	M	20.4	170	120	NO	YES	NO	NO	YES	YES	NO	NO	II	73	30	0.7	7.5
55	39	M	25.3	146	90	YES	NO	YES	NO	YES	NO	NO	NO	II	69	29	1.2	5.3
56	66	M	22.2	140	100	NO	YES	NO	YES	YES	YES	NO	NO	I	83	32	1.4	5.5

57	48	M	20.8	150	110	NO	NO	YES	NO	NO	NO	NO	NO	NIL	134	24	0.8	3.9
58	65	M	23.5	230	130	NO	YES	NO	YES	NO	NO	YES	NO	II	72	26	0.8	7.62
59	79	M	19.8	210	120	NO	NO	NO	YES	NO	YES	NO	YES	NIL	70	38	1.5	7.4
60	49	M	21.9	140	100	NO	YES	NO	NO	YES	NO	NO	NO	NIL	69	30	1.3	4.6
61	60	M	22.8	150	100	NO	YES	YES	NO	YES	YES	NO	NO	NIL	220	26	1	4.1
62	60	F	27.2	210	120	YES	NO	NO	YES	NO	NO	YES	NO	I	145	40	1.3	4.3
63	45	F	33.8	150	100	NO	NO	YES	NO	YES	YES	NO	NO	NIL	180	34	1	5.6
64	62	F	23.2	144	100	NO	NO	YES	NO	NO	NO	NO	NO	NIL	185	32	0.8	4.4
65	38	M	23.4	160	90	NO	YES	YES	NO	YES	NO	NO	NO	NIL	112	26	0.9	4.8
66	54	F	27.3	170	110	NO	NO	YES	YES	NO	NO	NO	NO	NIL	172	24	0.8	3.1
67	61	M	22	160	100	NO	YES	NO	NO	NO	NO	YES	NO	I	96	25	0.9	3.3
68	65	M	28.4	170	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	79	40	1	4.95
69	70	M	16.1	170	100	NO	NO	NO	NO	YES	NO	NO	NO	NIL	83	35	1.1	3.24
70	49	F	24.3	160	100	NO	NO	NO	NO	NO	NO	NO	NO	I	69	19	0.6	4.1
71	65	M	18.6	170	100	NO	YES	NO	NO	NO	NO	NO	NO	II	95	24	0.9	3.66
72	67	M	16.9	180	100	YES	NO	NO	YES	NO	NO	NO	NO	NIL	87	21	1	4.15
73	56	F	23.8	150	100	NO	NO	NO	NO	NO	NO	NO	NO	I	72	20	0.8	3.44
74	53	M	20.8	170	100	NO	NO	NO	NO	NO	NO	NO	NO	II	83	39	1.3	3.77
75	45	F	25.1	150	100	NO	NO	NO	NO	YES	NO	NO	NO	I	78	29	0.8	3.44
76	64	F	31.7	150	100	NO	NO	NO	NO	YES	NO	NO	NO	II	66	40	0.7	5.46
77	48	F	22.5	160	110	NO	NO	NO	NO	NO	NO	NO	NO	NIL	104	26	0.8	4.25
78	50	F	20	160	110	NO	NO	NO	NO	NO	NO	NO	NO	NIL	80	30	0.9	4.14
79	65	M	16	160	100	NO	YES	NO	NO	NO	NO	YES	NO	II	94	33	1.3	4.15
80	43	F	27.6	150	100	NO	NO	NO	NO	YES	NO	NO	NO	NIL	104	19	0.9	4.5
81	40	M	15.6	160	110	NO	YES	NO	NO	NO	NO	YES	NO	I	88	23	1.1	5.3
82	42	M	22.7	160	110	YES	YES	NO	NO	NO	YES	NO	NO	NIL	93	26	1	4.49
83	45	M	16.9	210	110	NO	YES	NO	NO	YES	NO	NO	NO	III	118	40	1.2	6.3
84	64	M	25.2	170	90	YES	NO	NO	NO	YES	NO	NO	NO	NIL	119	36	1.4	3.6
85	60	M	26.3	150	90	NO	YES	NO	NO	YES	NO	NO	NO	NIL	86	30	1.1	4.3
86	56	M	22.6	190	110	NO	NO	YES	NO	YES	YES	NO	YES	II	170	40	0.6	7.8
87	52	M	20.9	170	90	NO	YES	NO	NO	NO	NO	YES	NO	NIL	76	28	0.9	5.3

88	60	M	24.1	160	100	NO	NO	NO	NO	NO	NO	NO	NO	I	88	32	1.2	5.6
89	46	M	19.9	150	100	YES	NO	NO	NO	NO	NO	YES	NO	NIL	108	22	0.7	5.2
90	30	M	21.8	170	100	NO	YES	NO	NO	NO	NO	NO	NO	I	112	24	1.1	4.9
91	40	M	22.4	140	110	NO	NO	NO	NO	NO	NO	YES	NO	NIL	96	18	0.9	3.8
92	65	M	27.2	150	100	NO	YES	NO	NO	NO	NO	NO	NO	NIL	82	30	1	4.9
93	58	M	24	160	100	NO	YES	YES	NO	NO	YES	NO	NO	I	162	26	1.1	4.6
94	60	M	23.6	160	100	NO	NO	YES	NO	NO	NO	NO	NO	NIL	180	30	0.8	4.51
95	48	M	21.9	170	100	YES	YES	NO	NO	YES	NO	NO	NO	NIL	72	24	0.9	6.6
96	39	M	22.3	144	96	NO	YES	NO	NO	NO	YES	NO	NO	I	126	37	1	4.2
97	73	M	27.3	160	100	NO	NO	NO	NO	NO	NO	NO	NO	I	72	22	0.9	7.45
98	55	M	32.8	150	100	NO	YES	YES	YES	YES	NO	NO	NO	NIL	208	30	0.8	6.6
99	70	M	23.3	146	100	NO	NO	NO	YES	YES	NO	NO	NO	II	60	25	0.7	4.5
100	54	M	23.4	150	100	YES	YES	YES	YES	NO	NO	NO	NO	I	180	35	0.7	4.4
101	28	M	27.4	150	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	80	20	0.8	5.2
102	64	M	22.5	186	106	NO	NO	NO	NO	NO	NO	YES	NO	NIL	113	26	0.9	3.5
103	55	M	27.7	160	100	NO	NO	NO	YES	NO	NO	NO	NO	II	100	39	1	6.3
104	65	F	16.1	166	110	NO	NO	NO	NO	NO	NO	NO	NO	I	81	25	0.8	7.2
105	41	F	24.3	164	96	NO	NO	NO	NO	NO	NO	NO	NO	NIL	72	29	0.9	5.6
106	45	F	20.2	140	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	70	24	0.8	5.2
107	50	F	19	180	120	NO	NO	NO	NO	NO	NO	YES	NO	NIL	87	22	0.7	4.2
108	27	M	24.8	156	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	65	31	1	6.5
109	30	M	21.5	160	96	NO	NO	NO	NO	NO	NO	NO	NO	NIL	74	29	0.9	6.3
110	62	M	25.2	166	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	88	23	0.8	6.2
111	63	M	32.1	170	110	NO	YES	NO	NO	NO	NO	NO	NO	NIL	106	27	1	6.5
112	55	M	21.5	160	100	NO	NO	NO	NO	YES	NO	NO	NO	NIL	96	30	0.8	6
113	63	M	25	180	100	YES	NO	NO	NO	YES	NO	NO	NO	I	112	25	1	6.3
114	74	M	22.8	150	92	NO	NO	NO	NO	YES	NO	NO	NO	NIL	108	27	0.7	4.2
115	60	M	27.2	170	110	NO	YES	NO	NO	YES	NO	NO	NO	I	80	35	0.8	5.1
116	42	M	32.8	150	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	116	30	0.7	3.7
117	61	M	24.6	146	100	NO	YES	NO	NO	NO	NO	NO	NO	NIL	72	27	1	3.9
118	55	M	23.4	150	80	NO	NO	NO	NO	NO	NO	NO	NO	NIL	92	36	1.1	4.2
119	51	F	27.3	150	90	NO	NO	NO	NO	NO	NO	NO	NO	II	108	29	0.9	4.9

120	40	F	22.4	170	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	66	24	0.9	7.4
121	63	F	27.7	170	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	75	33	1.1	5.2
122	48	M	22	180	110	NO	YES	NO	NO	YES	YES	NO	NO	NIL	117	28	1	8.5
123	45	F	24.9	140	100	NO	NO	YES	NO	NO	NO	NO	NO	I	166	32	0.9	5.3
124	30	M	22.4	160	110	YES	NO	NO	NO	YES	NO	NO	NO	NIL	76	29	1	9
125	56	M	20.6	156	96	NO	NO	NO	NO	NO	NO	NO	NO	NIL	118	28	0.8	4.6
126	29	F	27	190	120	NO	NO	YES	NO	YES	NO	NO	NO	NIL	220	25	0.7	8.2
127	57	M	15.6	150	90	NO	YES	NO	YES	NO	NO	NO	NO	II	69	40	1.5	4.9
128	63	M	22.7	180	100	YES	NO	NO	NO	YES	NO	YES	NO	I	75	34	1.3	4.9
129	60	F	16.9	170	90	NO	NO	NO	NO	YES	YES	YES	NO	I	88	30	0.7	4.5
130	47	M	20.4	170	120	NO	YES	NO	NO	YES	YES	NO	NO	II	78	26	0.9	7.5
131	53	M	26.3	180	110	YES	NO	YES	NO	YES	NO	NO	NO	II	80	31	1.2	5.2
132	66	M	22	170	110	NO	YES	NO	YES	YES	YES	NO	NO	I	78	34	1.4	5.3
133	48	M	20.8	160	100	NO	NO	YES	NO	NO	NO	NO	NO	NIL	125	27	0.5	3.8
134	65	M	23.5	230	130	NO	YES	NO	YES	NO	NO	YES	NO	II	83	29	0.8	7.7
135	72	M	19.8	210	120	NO	NO	NO	YES	NO	YES	NO	YES	NIL	90	37	1.5	6.4
136	49	M	21.9	150	100	NO	YES	NO	NO	YES	NO	NO	NO	NIL	80	30	1.4	4.5
137	60	M	22.3	150	100	NO	YES	YES	NO	YES	YES	NO	NO	NIL	205	30	1	4.2
138	59	F	27.2	210	120	YES	NO	NO	YES	NO	NO	YES	NO	I	144	36	1.3	4.3
139	47	F	32.8	174	110	NO	NO	YES	NO	YES	YES	NO	NO	NIL	179	28	1	6.6
140	62	F	23.2	154	90	NO	NO	YES	NO	NO	NO	NO	NO	NIL	190	34	0.6	5.1
141	39	M	23.4	160	90	NO	YES	YES	NO	YES	NO	NO	NO	NIL	115	28	1.1	5
142	55	F	27.3	170	110	NO	NO	YES	YES	NO	NO	NO	NO	NIL	175	32	0.8	3.7
143	61	F	22	160	100	NO	YES	NO	NO	NO	NO	YES	NO	I	116	27	0.9	3.4
144	62	M	27.7	170	100	NO	NO	NO	NO	NO	NO	NO	NO	NIL	96	35	1	5.5
145	70	M	16.1	170	110	NO	NO	NO	NO	YES	NO	NO	NO	NIL	81	34	0.9	3.3
146	49	F	24.3	160	100	NO	NO	NO	NO	NO	NO	NO	NO	I	112	29	1	3.5
147	65	M	18.6	170	100	NO	YES	NO	NO	NO	NO	NO	NO	II	96	25	0.8	3.9
148	68	M	16.9	160	100	YES	NO	NO	YES	NO	NO	NO	NO	NIL	85	26	1.1	4
149	57	F	23.8	160	100	NO	NO	NO	NO	NO	NO	NO	NO	I	88	25	0.7	3.5
150	52	M	20.8	150	90	NO	NO	NO	NO	NO	NO	NO	NO	II	110	42	1.2	3.8