A STUDY ON THE CORRELATION OF SERUM URIC ACID AND MICROALBUMINURIA IN PREHYPERTENSION

Dissertation Submitted for

MD Degree (Branch I) General Medicine

April 2011

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

Chennai – 600 032.

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CERTIFICATE

This is to certify that this dissertation titled "**A STUDY ON THE CORRELATION OF SERUM URIC ACID AND MICROALBUMINURIA IN PREHYPERTENSION"** submitted by **Dr.VAISHNAVI.S** to the faculty of General Medicine, The Tamilnadu Dr. M.G.R. Medical University, Chennai in partial fulfillment of the requirement for the award of MD degree Branch I General Medicine, is a bonafide research work carried out by her under our direct supervision and guidance.

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DECLARATION

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Place: Madurai **Dr.VAISHNAVI.S**

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ACKNOWLEDGEMENT

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

With deep sense of gratitude, I take this opportunity to express my regards and respect to my revered teacher and guide Prof. Dr. A.Ayyappan, Former Professor and Head, Department of Medicine, Madurai Medical College for his constant guidance, supervision and encouragement during the entire period of the study and also during my post graduate course. I shall always remember his constructive criticism and valuable advice which has created an everlasting light of inspiration in my life.

I express my sincere thanks to my present guide Prof.Dr.Bagialakshmi, Professor in Dept of Medicine, Madurai Medical college for her valuable guidance and support.

I am greatly indebted to my teachers Dr.Daniel.K.Moses., Dr.S.Vadivel murugan, Dr.Venkatraman, Dr.Premkumar, Dr.M.Natarajan, Dr.J.Sangumani, Dr.Giridhar Babu and Dr.Dharmaraj.

I am extremely thankful to my unit Assistant professors Dr.Amalraj, Dr.Gurunamasivayam and Dr.Ramesh for their constant encouragement, timely help and critical suggestions throughout the study and my entire course.

I profusely thank Biochemistry department for cooperation and support.

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

Dr.VAISHNAVI.S

ABBREVIATIONS

JNC	-	Joint national committee
PreHTN	-	Prehypertension
HTN	-	Hypertension
CVD	-	Cardiovascular Disease
CKD	-	Chronic Kidney Disease
CAD	-	Coronary Artery Disease
BMI	-	Body Mass Index
DM	-	Diabetes Mellitus
UAE	-	Urine Albumin Excretion
ACR	-	Albumin to Creatinine Ratio

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INTRODUCTION

The term "prehypertension" referring to those with blood pressure reading of 120-139mmHg systolic and 80-89mmHg diastolic, was first introduced when the JNC 7 was launched at the American Society of Hypertension annual scientific conference in 2003. It evoked tremendous discussions, amongst which were many objections to this new terminology. It was argued that this new definition of "illness" would impact an individual's employability, his life as well as medical insurance coverage and perhaps even labelling what was an otherwise healthy person into a sick one.

Nevertheless, this term was introduced as part of the categorization of hypertension because it was recognized that there is still an excess cardiovascular disease (CVD) risk at levels of blood pressure (BP) deemed previously to be "normal" or "high-normal". The rationale for this new term was to bring to the attention of doctors and the public the need for more strenuous efforts at prevention of hypertension.[52]

The prevalence of prehypertension is high and the progression to hypertension is also high.Prehypertension is also commonly associated with other CVD risk factors namely obesity, diabetes mellitus, dyslipidemia, and inflammatory markers, and evidence of organ damage for example, microalbuminuria, retinal arteriolar narrowing, increased carotid arterial intima-media thickness, left ventricular hypertrophy and coronary artery disease.

Eighty-five percent of prehypertensives have one other or more CVD risk factor compared to normotensives. A recent study has shown a reduction in the development of hypertension from prehypertension with the use of an angiotensin receptor blocker. Unfortunately to date, the impact of treatment of prehypertension on CVD outcome is still unknown except in those with high CVD risk like diabetes or established CVD,or CKD. However this does not mean that nothing can be done for those with prehypertension. The aim of managing prehypertension is to lower the BP, prevent progression to hypertension and to prevent BP related CVD deaths. Lifestyle changes can reduce BP and this by itself can lower CVD risk. Until more evidence about other modalities of treatment become available this is a sensible and cost-effective way to manage prehypertension.[52]

Several large epidemiological studies have reported that elevated serum uric acid level is associated with cardiovascular disease. Some investigators have suggested that uric acid plays a causal role in the development of cardiovascular disease, whereas others have concluded that uric acid merely reflects other concomitant risk factors, such as hypertension, insulin resistance, obesity, or lipid abnormality. The independent association of uric acid with cardiovascular disease appears to be stronger in persons with hypertension than in the general population.

Microalbuminuria is associated with an increased risk of cardiovascular morbidity in patients with diabetes,hypertension and in the general population.The amount of urinary albumin excretion is considered to be a reflection of generalized endothelial dysfunction associated with a variety of risk factors.Therefore, microalbuminuria is a useful biological marker for the identification of people who are at high risk for cardiovascular events and who require more intensive therapy.

The relationship between uric acid and microalbuminuria in healthy adults without other cardiovascular risk factors may help to clarify the role of uric acid in cardiovascular disease. In this study, we

observed that elevated serum uric acid level was associated with microalbuminuria among nondiabetic and nonhypertensive subjects without a history of cardiovascular disease or renal dysfunction and whose blood pressure was in the prehypertensive range.The relationship between blood pressure and blood pressure–related morbidity is continuous over the whole range of blood pressure. If hyperuricaemia has an independent association in target organ damage among hypertensive subjects, and perhaps in subjects with prehypertension, it must be linearly associated with microalbuminuria. Identifying this subset of prehypertensives with hyperuricaemia may further define their cardiovascular risk and in the future may benefit from blood pressure lowering therapy either by lifestyle modifications or even with pharmacological methods.

AIMS AND OBJECTIVES

1. To study the prevalence of hyperuricaemia in prehypertensive individuals.
2. To study the relationship between uric acid and microalbuminuria in prehypertensive adults.
3. To study if hyperuricemia has an independent role in target organ damage among prehypertensive subjects, as reflected by microalbuminuria.

REVIEWOF LITERATURE

HYPERTENSION- A BACKGROUND

The phenomenon of hypertension was first characterized at the turn of the past century, when Riva-Rocci developed the prototype of the modern sphygmomanometer and so allowed the routine measurement of BP.Korotkoff then perfected the sphygmomanometric technique by describing the sounds heard over the brachial artery as the pressure in the cuff is reduced. In general, the upper limits of normal BP in older persons have been considered to be a systolic value of 140 mm Hg and a diastolic value of 90 mm Hg. These figures may be adjusted downward for younger patients to the point that readings in excess of 120/80 mm Hg may be considered hypertensive. Clinically,hypertension might be defined as that level of blood pressure at which institution of therapy reduces blood pressure related morbidity and mortality.[1]

But population studies suggest that BP is a continuous variable, with no absolute dividing line between normal and abnormal values. This situation has resulted in an inevitable continuing debate over

borderline readings that focuses on whether people with such pressures are normal and on what, in fact, constitutes normalcy.[2]

Risks of death and disability associated with hypertension are increased only in a statistical sense; a large majority of patients with clearly elevated BP have normal longevity and health. Thus, hypertension is a physical sign and a risk factor to be assessed in conjunction with other physiologic and environmental factors.[2]

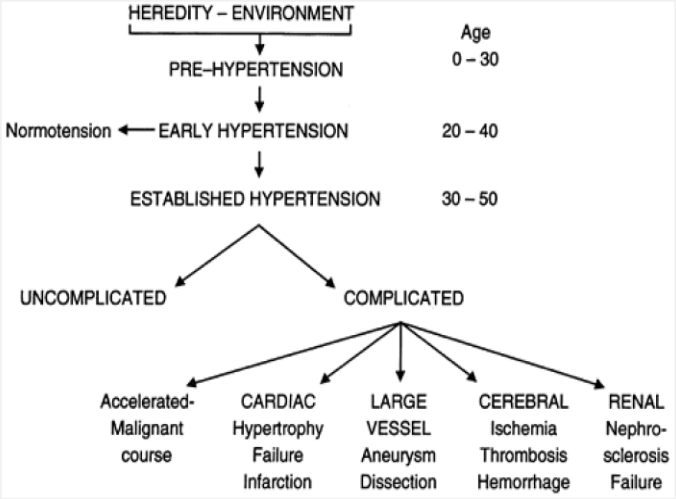


FIGURE 4-1 •Representation of the natural history of untreated essential hypertension.

PREHYPERTENSION- ORIGIN AND DEFINITION

The term 'prehypertension' was coined in 1939 in the context of early studies that linked high blood pressure recorded during physical examination for life insurance purposes to subsequent morbidity and mortality.60 years later, this term "prehypertension" was first introduced when the JNC 7 was launched at the American Society of Hypertension annual scientific conference in 2003.This new classification describes 'people with blood pressures between 120 and 139 mmHg systolic or between 80 and 89mmHg diastolic'.

Blood pressure Classification JNC-7-2003

	SBP mm Hg		**DBP mm Hg**
Normal	<120	and	<80
Prehypertension	120-139	or	80-89
Stage 1 Hypertension	140-159	or	90-99
Stage 2 Hypertension	≥ 160	or	≥100

The ‘new’ category between normal blood pressure and established hypertension includes a population at high risk for developing hypertension with its multifaceted complications and in which lifestyle modifications are needed.[3]

CONTROVERSIES IN THE NEW CLASSIFICATION:

KEY MESSAGES FROM JNC 7:

Blood pressure beyond 115/75mmHg, doubles CVD risk with each 20/10mmHg rise in BP. In 2003,the JNC 7 on hypertension unified the normal and high normal blood pressure categories into a single entity termed ‘prehypertension’. This change was based on evidence from the Framingham Heart Study that the chance of developing hypertension is higher in these “prehypertensive” patients than in those with optimal blood pressure(<120/80) at all ages.[4]

The European Society of Hypertension and European Society of Cardiology(ESH-ESC) guidelines for the management of arterial hypertension consider prehypertension to be categorized into

1.Normal blood pressure(SBP 120-129mmHg or DBP 80-84mmHg)

2.High normal blood pressure(SBP 130-139mmHg or DBP 85-89mmHg)

In 2007,ESH-ESC decided not to use the term ‘prehypertension’ for the following reasons

1.Even in Framingham Heart Study, the “risk of developing hypertension was definitely higher in patients with high normal blood pressure than in those with normal blood pressure”.

2.The word ‘prehypertension’ might create anxiety and lead to unnecessary consultation with the doctor.

3.This category is a highly differentiated one in practice, with the extremes consisting of patients in no need of any intervention as well as those with a very high –risk profile such as diabetes, chronic kidney disease, or hyperlipidemia for whom drug treatment is required. Hence, IHG(International Hypertension guidelines)does not recommend the use of the term ‘prehypertension’.

IS PREHYPERTENSION TERMINOLOGY JUSTIFIABLE?[5]

The impetus for creating the prehypertension blood pressure category came, at least in part, from a metaanalysis that included approximately 1 million individuals from 61 long term epidemiological studies.

In the Framingham Heart study, the progression rates to hypertension with optimal, normal and high normal blood pressure

were 5%,18% and 37% for the younger age groups(35-64yrs) and 16%,26% and 50% for the older(65 to 94yrs) over a 4 year period respectively.[6] People with prehypertension are more likely to be associated with hypercholesterolemia, obesity and diabetes mellitus than without it. It is associated with decreased life expectancy, increased hospitalizations and health care costs.

Increased Cardiovascular risk with prehypertension is smaller than the risk associated with diabetes(158% higher risk), but is greater than that that associated with smoking(34% higher risk).since smoking is pretty much unchallenged as a cardiovascular risk factor, perhaps prehypertension should be afforded the same acceptance. Hence, 'Prehypertension' terminology is justifiable.[7]

EPIDEMIOLOGY

The Third National Health and Nutrition examination survey (NHANES)1999–2000 reported that the overall prevalence of prehypertension in the US was 31%, higher in men than in women, and was higher in obese than in normal weight persons. On the basis of the NHANES 2005–2006 data, an estimated 25% of the US population

aged 20 years or older has prehypertension, including over 32 million men and 21 million women. [8]

Of the few Indian studies available, study done in urban Chennai, 2,007 people were studied , 951 (47.4%) had preHTN and 696 (34.7%) had HTN. PreHTN was found in 46.6% of the men and 49.8% of the women. PreHTN was prevalent in 47.4% of adults, and another 34.7% had hypertension (Stage I, 20%, and Stage II, 14.7%). In urban India less than 18% of adults have normal BP of less than 120/80. [9]

In North India, Data of study by Yadav et al[22] suggested that the prevalence of hypertension in the youngest age group (30-39 yr) was 13.7 per cent and increased to a peak of 64 per cent in the age group 60-69 yr, while prevalence of pre-hypertension was highest in the age group 30-39 yr that is 36%.[10]

ETIOLOGY OF PREHYPERTENSION:

Prehypertension is one step towards hypertension, hence the same factors are involved in both.

Risk factors associated are,[11]

1.Obesity

2.Male gender

3.Black race

4.Type 2 Diabetes mellitus

5.Impaired glucose tolerance

6.Metabolic syndrome

7.Dyslipidaemia

8.Smoking

Other factors being,

- Excess salt intake

  Mean intake: men- 4100mg ; women- 2750mg

- Reduced physical activity
- Inadequate fruits, vegetables and potassium intake.

PreHTN and CAD- PATHOPHYSIOLOGY:

Prehypertension is associated with subclinical cardiovascular disease, including both microvascular and macrovascular pathology.[12,13]

Accordingly, the Rotterdam study, a prospective, population based study with 1,900 participants found that individuals with prehypertension had significantly smaller arteriolar and venular diameters and arteriolar venular ratios than normotensive individuals, indicating the presence of microvascular damage.[14]

INFLAMMATORY MARKERS:

Elevated concentrations of C-reactive protein,Tumor necrosis factor-alpha,oxidized LDL,gamma glutamyl amyltransferase, microalbuminuria and other inflammatory markers are associated with high normal blood pressure.

Oxidative stress and PreHTN:

In ATTICA study, of 3041 men, preHTN was found to be inversely correlated with TAC(total oxidant capacity). PreHTN was found to be associated with 15% higher levels of Oxidized LDL when compared to normals and hence associated with atherosclerosis.

PreHTN and Insulin resistence:

Subjects with preHTN have clinical characteristics of the IR syndrome, and cannot handle oral glucose challenge as the normotensives.[15]

PreHTN and microalbuminuria:

Microalbuminuria, an organspecific manifestation of generalized endothelial dysfunction, that is associated with increased risk of cardiovascular disease – is more common in individuals with prehypertension than in those with normal blood pressure.

PreHTN and serum uric acid:

Serum uric acid was associated with PreHTN, as in established HTN and Atherosclerosis in Chinese adults independent of other metabolic risk factors.[16]

PreHTN and CKD:

First, increases in BP over time within the prehypertensive range are associated with morphological changes within the kidney as well as the behavior of the endothelium. Second, increases in albuminuria parallel BP increases and can antedate development of hypertension in Type I diabetes.[17]

Subclinical Atherosclerosis and PreHTN:

Individuals with prehypertension often have subclinical atherosclerosis, manifested by increased common carotid artery intima media thickness and increased calcium deposition in the coronary arteries.Serial observations, carried out as part of the Coronary artery risk Development in Young adults (CarDia)study, demonstrated that prehypertension, especially systolic prehypertension, before the age of 35 was significantly associated with coronary calcium in later life, even after adjusting for elevations in blood pressure after 35 years of age, other coronary risk factors and participant characteristics.[20]

PreHTN and Diastolic dysfunction:

Patients with PreHTN whose night time BP do not dip by 10%(non dippers) have more impaired diastolic dysfunction than patients with PreHTN who dip and are at higher risk of development of HTN with CV morbidity.[21]

To summarise,the excess CVD risk in prehypertension is due to subclinical atherosclerosis. Prehypertensives have

• increased coronary atherosclerosis

• increased carotid and brachial intima-media thickness, a surrogate for atherosclerosis

• elevated C-reactive proteins (CRP)

• elevated tumour necrosis factor-α (TNF-α)

• elevated serum homocysteine levels

• elevated oxidized LDLcholesterol

• microalbuminuria which is more common in prehypertension than normotension

• presence of other inflammatory markers like Interleukin, serum uric acid, etc

TREATMENT OF PREHYPERTENSION:

A major objective of JNC 7 in creating the prehypertensive classification of blood pressure was to provide a tool for the identification of individuals for whom early adoption of a healthy lifestyle could lower blood pressure and prevent progression to hypertension, with associated reductions in target organ damage and cardiovascular events. Lifestyle modifications, such as weight loss, dietary alterations and exercise, have been shown consistently in randomized,controlled trials to effectively lower blood pressure and are recommended for patients with prehypertension.[22,23,24,25]

Lifestyle modifications to prevent and manage hypertension

Modification	Recommendation	SBP reduction
Weight reduction	Aim for BMI 18.5-25 kg/m^2	5-20mmHg/10kg wt loss
Sodium intake	<100 mmol Na/6g Nacl (1¼ tsp salt)	2-8 mmHg
Physical exercise	Aerobic activity e.g. brisk walking 30-60 mins, minimum 3x/wk	4-9 mmHg
DASH Diet	Rich in fruit, vegetable and low-fat diary products	8-14 mmHg
Alcohol	2 units/day in men, 1 unit/day in women	2-4 mmHg

(DASH, Dietary Approaches to Stop Hypertenstion, SBP, systolic blood pressure)

Note: For over all cardiovascular mortality reduction, stop smoking. The effects of implememenTing these lifestyle modifications are dose- and time-dependent, and could be greater for some individuals.

LIFESTYLE MODIFICATIONS AND CAD:

In the PREMIER trial individuals with prehypertension or stage 1 hypertension were randomly assigned to receive multicomponent behavioral interventions with or without the DASH diet, or advice only.A followup study of the PREMIER trial demonstrated that multicomponent behavioral interventions with and without the DASH

diet produced significant reductions in the 10 year risk of coronary heart disease. [26]

PHARMACOLOGICAL TREATMENT:

Treatment of prehypertensive patients with antihypertensive agents in addition to nonpharmacological measures has been explored in clinical trials like TROPHY AND PHARAO TRIALS.

TROPHY TRIAL:

The trial of Preventing Hypertension (TROPHY) study tested whether pharmacological treatment with the angiotensin II receptor antagonist Candesartan cilexetil can prevent or delay the transition from prehypertension to stage 1 hypertension. 48 Participants with prehypertension were randomly assigned to receive candesartan cilexetil or placebo for 2 years, followed by 2 years of placebo for all participants. In addition, all participants received instructions for lifestyle modification.

1. Over a period of four years, nearly two thirds of the placebo group developed stage 1 hypertension requiring treatment.
2. In patients with prehypertension, 2 years of treatment with candesartan cilexitil 16 mg once a day:

- During the first 2 years, the risk of developing hypertension was reduced by 66.3% in the participants who received candesartan cilexetil compared with the placebo group; the magnitude of risk reduction decreased to 16% by year 4, but was still statistically different from placebo group.
- Substantially prolonged the hypertension-free period throughout the trial
- Was well tolerated; during the active treatment period serious adverse events in candesartan and placebo groups were infrequent and similar.

TROPHY provided the first demonstration that pharmacological treatment for patients with prehypertension is safe and atleast partially effective in reducing the risk of incident hypertension.

Even after TROPHY and PHARAO TRIALS, whether pharmacological management of blood pressure is a useful strategy for the management of prehypertension is a matter of debate.

Patients at high risk of cardiovascular events, such as those with diabetes mellitus, chronic kidney disease or coronary artery disease, clearly benefit from aggressive intervention, and pharmacological treatment should be administered to these patients if blood pressure exceeds 130/80 mmHg.

Cardiovascular risk and possible treatment of those prehypertensives with nontraditional risk factors like microalbuminuria, hyperuricaemia, raised CRP, dyslipidaemia has not been studied extensively till now. This study aims to explore this missing link.

MICROALBUMINURIA:

Microalbuminuria is defined as the excretion of 30 to 300mg of albumin per day in urine. It is not a different form or fraction of albumin but just a very small amount of albumin. Albumin molecule is relatively small and it is often the first protein to enter the urine after the kidney is damaged. The table below gives the values which constitute microalbuminuria. [27]

Category	24hr. collection (mg/24hr)	Timed collection (µg/min)	Spot collection Albumin Creatinine Ratio	
			µg/mg	mg/mmol
Normal	<30	<20	<30	<3.4
Micro albuminuria	>300	>200	>300	>33.9

MECHANISMS OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION

Increased UAE could be the consequence of an

1. augmented intraglomerular capillary pressure,

2.it could reflect the existence of intrinsic glomerular damage that causes changes in glomerular barrier filtration,

3.tubular alteration that impedes the normal reabsorption of filtered albumin.

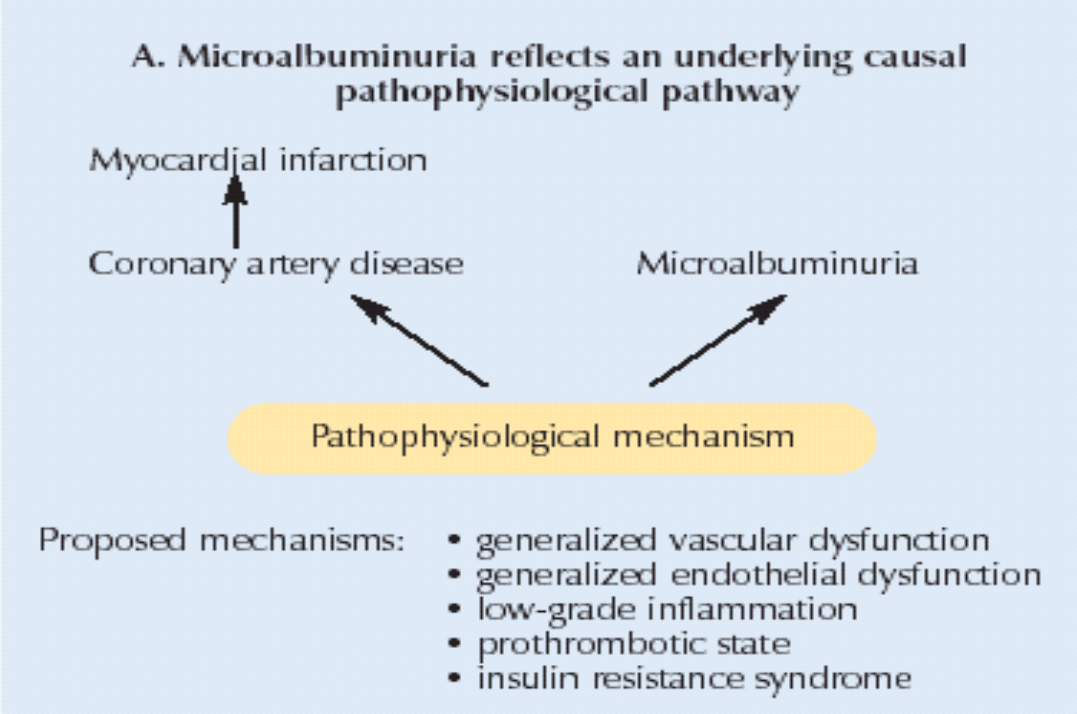
4.may represent the renal manifestation of generalized, genetically-conditioned vascular endothelial dysfunction that may underlie the link

between an increased UAE and an elevated risk for cardiovascular disease [31]

In favor of a significant role of elevated systemic blood pressure facilitating the transglomerular passage of albumin is the significant positive correlation found between office blood pressure levels and UAE by most groups[32,33,34].In this sense systolic blood pressure has been shown to be one of the most relevant determinants of microalbuminuria in the early stages of hypertensive disease. [35]On the other hand, higher levels of UAE have been described in those patients not exhibiting a nocturnal fall in blood pressure (non-dippers), indicating that a greater degree of renal involvement could be present in this particular group of patients. [36,37]

Some recent findings support an eventual relationship between microalbuminuria and endothelial dysfunction in hypertension that includes a positive correlation of UAE and circulating von Willebrand Factor antigen, Factor VII hyperactivity, fibrinogen and endothelial cell damage.[38]

MICROALBUMINURIA AS A RISK IN ESSENTIAL HYPERTENSION



In 1974 Parving et al reported the finding of elevated UAE levels in insufficiently treated essential hypertensives, which correlated significantly with blood pressure levels and the levels fell after blood pressure control.This finding has been amply confirmed and it is now recognized that microalbuminuria can be found in up to 40% of untreated hypertensive population. Prevalence of an elevated UAE increases with age, and with longer duration and a higher severity of hypertension[39]

Hypertensive target organ damage is more common in microalbuminuric patients. Patients with elevated UAE have higher left ventricular mass, a higher prevalence of hypertensive retinopathy, and an increased thickness and presence of plaques in the carotid artery. Furthermore, the presence of microalbuminuria in essential hypertensive patients has been interpreted as a marker of early intrarenal vascular dysfunction in essential hypertension .[40,41]

In summary, microalbuminuria is an independent predictor of cardiovascular morbidity and mortality in both men and women with essential hypertension. This could, in turn, be facilitated by the frequent association of an elevated urinary albumin excretion to a series of alterations, such as endothelial dysfunction, insulin resistance, altered lipid levels, higher body mass index, increased serum uric acid and salt-sensitivity. All these alterations could facilitate the accompanying risk for atherosclerosis, and it is a likely explanation for such an association between UAE and the risk of coronary heart disease. [45]

Clustering microalbuminuria with other cardiovascular risk factors contributes to considering that microalbuminuria in essential hypertension has a genetic origin.

Factors that cluster with microalbuminuria:

a. Insulin resistance

b. Central obesity

c. Metabolic syndrome

d. Low levels of high density lipoprotein cholesterol

e. High triglyceride levels

f. Systolic hypertension

g. Lack of nocturnal dip in blood pressure on 24 hour monitoring

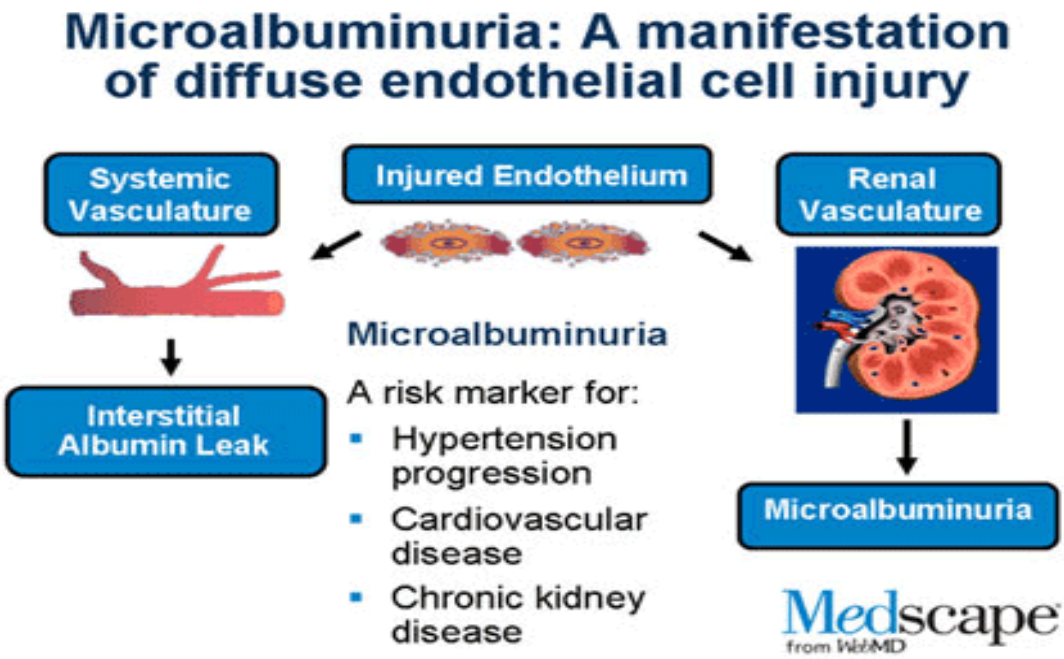
h. Salt sensitivity

i. Endothelial dysfunction

j. Hypercoagulability

k. Impaired fibrinolysis

l. Renal dysfunction



In conclusion, microalbuminuria seems to constitute a simple and accurate method to detect a hypertensive patient at a high risk for cardiovascular and probably renal damage.

PREHYPERTENSION AND MICROALBUMINURIA:

Prehypertension is associated with a number of nontraditional risk markers, all of which are associated with endothelial dysfunction, accelerated vascular aging, and increased CV risk. Some of these factors include microalbuminuria,C-reactive protein, serum tumor necrosis factor-α, amyloid A, endothelin-1, homocysteine, advanced glycation end products, and higher white blood cell counts. [46]

Microalbuminuria—an organ-specific manifestation of generalized endothelial dysfunction that is associated with increased risk of cardiovascular disease—is more common in individuals with prehypertension than in those with normal blood pressure.The appearance of albumin in the urine is a direct result of increased glomerular capillary permeability and serves as a marker for increased vascular permeability to proteins from other organs (for example, large arteries, heart and brain). Factors that confer a predisposition to microalbumin-uria, such as inflammation, oxidative stress and increased blood pressure, also have a role in the pathogenesis of microvascular and macrovascular disease. Thus, treatments that reduce microalbuminuria lower the risk of cardiovascular events.

Researchers from the Framingham Heart Study followed 1499 people without diabetes or hypertension to see whether microalbuminuria might predict blood pressure progression and incident hypertension.

After a mean of 2.9 years, 230 study subjects (15%) had developed hypertension, and 499 (33%) had progressed to worse BP categories as defined by standard guidelines. In multivariate analyses, the ratio of albumin to creatinine in the urine predicted incident

hypertension. Patients in the highest quartile of albumin/creatinine ratio at baseline had approximately double the risk for hypertension of those in the lowest quartile.

To summarize,it can be hypothesized that glomerular endothelial dysfunction, manifested as low-level microalbuminuria, is potentially both a precursor of essential hypertension and an indicator of patients at increased risk for BP progression, cardiovascular morbidity and mortality . Whether measuring microalbuminuria and instituting early intervention can change outcomes remains to be determined.

SERUM URIC ACID AND HYPERURICAEMIA:

Hyperuricemia may be *defined as a plasma (or serum) urate concentration >420 umol/L (7.0 mg/dL).* This definition is based on physicochemical, epidemiologic, and disease-related criteria. Physicochemically, hyperuricemia is the concentration of urate in the blood that exceeds the solubility limits of monosodium urate in plasma, 415 umol/L (6.8 mg/dL). In epidemiologic studies, hyperuricemia is defined as the mean plus 2 standard deviations of values determined from a randomly selected healthy population.

HYPERTENSION AND HYPERURICAEMIA:

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

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

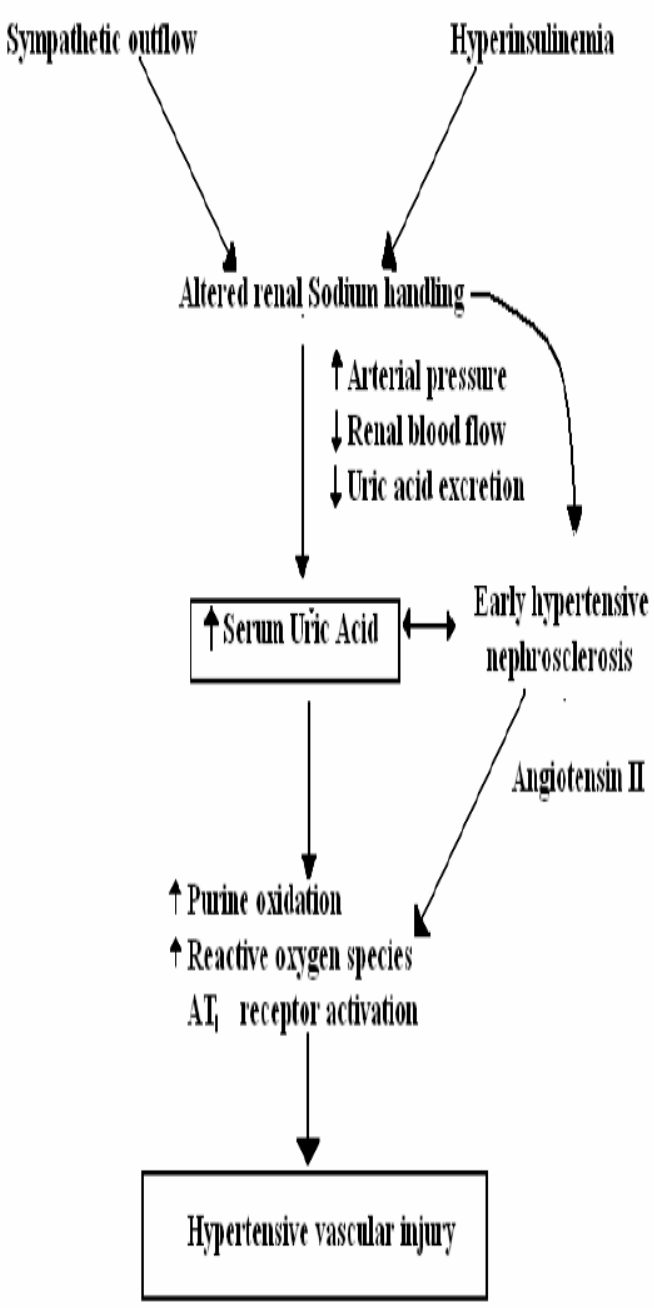
PROPOSED MECHANISMS OF URIC ACID MEDIATED HYPERTENSION:

1. METABOLIC SYNDROME AND RENAL HANDLING OF URIC ACID:

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

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

Hyperuricaemia may represent the culmination of a multimetabolic syndrome in which insulin-mediated renal haemodynamic abnormalities lead to hypertensive renal damage. It seems safe to say that hyperuricaemia in hypertension may be an early indicator of hypertensive cardiorenal disease, which is commonly associated with a multimetabolic syndrome.[48]


Sympathetic outflow
Hyperinsulinemia
Altered renal Sodium handling
↑ Arterial pressure
↓ Renal blood flow
↓ Uric acid excretion
↑ Serum Uric Acid
Early hypertensive nephrosclerosis
Angiotensin II
↑ Purine oxidation
↑ Reactive oxygen species
AT1 receptor activation
Hypertensive vascular injury

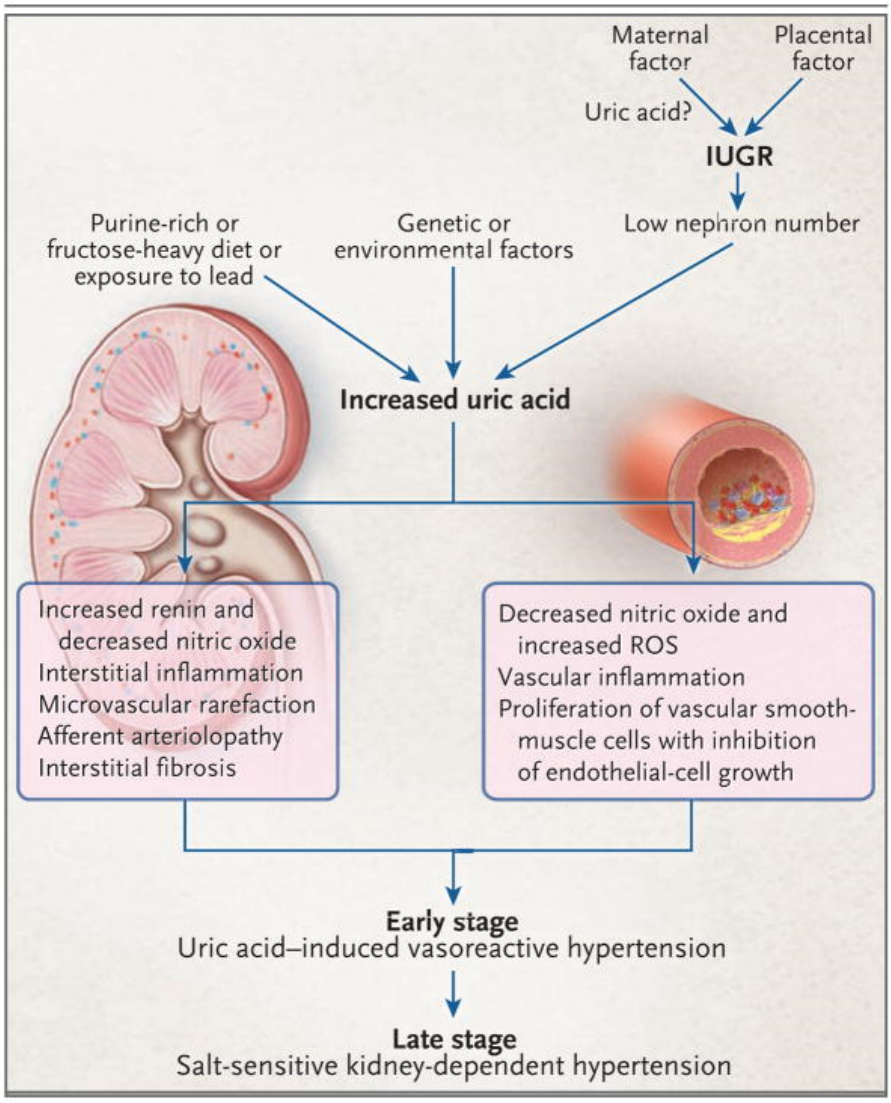
2.GENETIC POLYMORPHISMS:

It is also possible that genetic polymorphisms of transporters or enzymes involved in uric acid metabolism affect blood pressure, especially in younger subjects. For example, hypertension has been associated with polymorphisms of xanthine oxidoreductase. Solute carrier family 2, member 9 (SLC2A9) is a newly identified fructose and uric acid transporter in which several genetic polymorphisms have been identified that are associated with an increased risk of gout. [49]

3.DIET-LBW-URIC ACID- HYPERTENSION:

Excessive intake of fructose or purine-rich meats or exposure to low doses of lead may result in chronic hyperuricemia. Mothers with high uric acid levels that are the result of diet or conditions such as preexisting hypertension, obesity, or preeclampsia may transfer uric acid into the fetal circulation through the placenta, 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.[50]



SERUM URIC ACID-MICROALBUMINURIA-PREHYPERTENSION:

Our study is based on a study done in Division of Nephrology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea(2007) where they examined the cross-sectional association of serum uric acid level with microalbuminuria among 6771 subjects without diabetes or hypertension.Blood pressure was categorized as prehypertension (systolic blood pressure, 120 to 140 mm Hg or diastolic blood pressure, 80 to 90 mm Hg) and normotension (systolic blood pressure, <120 mm Hg and diastolic blood pressure, <80 mm Hg).

Microalbuminuria was found in 4.0% of normotensive subjects and in 7.9% of prehypertensive subjects.Prehypertensive subjects with microalbuminuria had higher uric acid level than those with normoalbuminuria. Increased serum uric acid level was an independent factor for microalbuminuria in the prehypertensive group. It is well known that microalbuminuria is associated with an increased risk for cardiovascular disease and might be an easily detectable marker for generalized vascular dysfunction. The findings of the study suggested that serum uric acid level can be a strong predictor of cardiovascular

disease when combined with elevated blood pressure (even mildly elevated). Endothelial dysfunction may be a possible pathway linking uric acid and cardiovascular disease.

Several studies have demonstrated that subjects with prehypertension are at increased cardiovascular risk and may already have evidence of end organ damage, such as impaired ventricular relaxation or microalbuminuria. However, there is no data to prove that pharmacological therapy in prehypertension improves outcomes. Drug therapy in >30% of the adult population would be prohibitively expensive and could cause side effects that would counteract any beneficial effects associated with the reduction in blood pressure. The Joint National Committee-7 report recommends antihypertensive drugs in patients with diabetes or chronic kidney disease as high-risk patients. This observational data imply that prehypertensive subjects with hyperuricemia may also be a high-risk group that could benefit from lowering blood pressure.

In summary, this study demonstrates a strong independent association between uric acid level and microalbuminuria in prehypertensive subjects without a history of cardiovascular disease or

decreased renal function. Although this particular study was unable to determine whether hyperuricemia has a causative effect, these findings suggest that hyperuricemia combined with prehypertension might be associated with an increased risk of cardiovascular disease. [52]

MATERIALS AND METHODS

SETTING:

Outpatient clinic of Government Rajaji Hospital, Madurai

DESIGN OF STUDY:

Analytical-cross sectional study

PERIOD OF STUDY:

Six months (March 2010-October 2010)

SAMPLE SIZE AND SELECTION OF STUDY SUBJECTS:

Hundred prehypertensive subjects(both newly and previously diagnosed) attending the outpatient clinic were included in this Analytical cross sectional study. This study group included males and females in the age group of 20-45years.

DETAILS OF STUDY SUBJECTS:

Blood pressure was recorded using sphygmonometer with standard cuff on 2 occasions 10min apart. Patients should have refrained from smoking or drinking tea or coffee for atleast 30min before measuring

BP. The higher of the two readings was taken as patient's blood pressure.

Patients' height and weight were measured and body mass index was calculated using the formula weight/height^2.Waist –hip ratio was measured.

Subjects with waist circumference>80cm (females) ,>90cm (males)(based on IDF criteria for Metabolic syndrome) were excluded from the study.

All the peripheral pulses were checked with special attention to femorals and carotids, to detect evidence of early atherosclerosis.An ocular fundus examination was done to detect hypertensive retinopathy.

All the subjects had routine urine analysis (albumin,sugar and deposits)done. Fasting and 2 hour postprandial blood sugar, serum urea, creatinine and fasting lipid profile were estimated.

GFR was estimated by the Abbreviated Modification of Diet in Renal Disease Study Equation, that is

GFR (mL/min/1.73 m^2) = 186 x $(Pcr)^{-1.154}$ x $(age)^{-0.203}$ x (0.742 if female) ,where Cr is creatinine and GFR expressed as ml/min/1.73m^2.

A 12 lead electrocardiogram and chest X-ray were also taken. Hypertension was defined as systolic blood pressure of >140 mm Hg, diastolic blood pressure of >90 mm Hg, or use of antihypertensive drugs, including diuretics. Study subjects were classified into 1 of the 2 nonhypertensive blood pressure categories according to the criteria of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure and the International Society of Hypertension: Prehypertension (systolic blood pressure of 120 to 140 mm Hg or diastolic blood pressure of 80 to 90 mm Hg) and Normotension (systolic blood pressure >120 mm Hg and diastolic blood pressure >80 mm Hg).

All the patients were instructed to report with early morning urine sample for Albumin creatinine ratio measurements. Serum uric acid levels were measured for all patients.

EXCLUSION CRITERIA:

1.Hypertension(defined by JNC 7 criteria)

2.Diabetes Mellitus

3.History of Cardiovascular disease or cerebrovascular accidents

4.Microalbuminuria detected by dipstick(trace-3+)

5.Febrile patients

6.Patients with UTI

7.Patients on ACE inhibitors

8.Metabolic syndrome based on IDF(International Diabetes foundation) criteria.

ALBUMIN TO CREATININE RATIO(ACR) ESTIMATION:

All patients were asked to report with early morning urine sample. Spot urine collection was used for determination of Albumin creatinine ratio.

MICROALBUMINURIA ESTIMATION:

Various methods to detect microalbuminuria:

METHOD	DURATION	TIME OF ASSAY
Single radio immune diffusion (Manini 1965)	1.25mg/ml	1 day
Electro immune assay (Laurel 1966)	5mg/1	4-6hrs
Immuno turbidimetric assay (teppor 1982)	5mg/1	20-30min
Radio immuno assay (Keen and	6.2mcg/1	1-2days

Chlouvervakis, 1963)		
ELISA (Filding 1983)	250mcg/1	12-18min
Fluoresecent immuno assay (Chavers 1984)	500mg	4-6 hrs
Latex agglutinates immune nephelometry (Vasquez 1984)	750mcg/1	6hrs
Immuno chemical semi quantia dipstic (MICRAL)	20-300mg./1	5sec-5min

In our study,modified immunoturbimetric assay known as 'turbilatex' test was used to measure microalbuminuria.

Microalbumin-turbilatex is a quantitative turbidimetric test for the measurement of microalbumin in human urine.

Latex particles coated with specific antibodies,anti-human albumin are agglutinated when mixed with samples containing micoralbumin. The agglutination causes an absorbance change, dependent upon the microalbumin contents of the patient sample that can be quantified by comparison from a calibrator of known microalbumin concentration.

CREATININE:

Technology: Jaffe method-Rate blanked and compensated

Method : photometry

REFERANCE VALUES:

To define microalbuminuria in random urine specimens, we used the ACR cutoff values of 30 to 300 mg/g for both men and women were used. Subjects with an ACR<30mg/g were defined as having normoalbuminuria; those with ACR >300 mg/g were defined as having overt proteinuria.

SERUM URIC ACID ESTIMATION:

PRINCIPLE:

The principle for the determination of Serum Uric Levels was devised by Trivedi and Kabasakalian with a modified Trinder peroxidase method using TBHB.

URIC ACID + O_2 + H_2O $\xrightarrow{\text{Uricase}}$ Allantoin + CO2 + H_2O_2

H_2O_2 + 4- AAP + TBHB $\xrightarrow{\text{Peroxidase}}$ Quinoneimine + H_2O

The intensity of chromogen (Quinoneimine) formed is proportional to the uric acid concentration in the sample when measured at 510 nm (510 -550nm).

REFERANCE VALUES SERUM URIC ACID LEVELS:

In Males : 3.4 - 7.0 mg/dl

In females : 2.4 - 6.0 mg/dl

Hyperuricemia was defined as serum uric acid level of >7.0mg/dl for men and >6.0mg/dl for women.

RESULTS AND OBSERVATIONS

AGE DISTRIBUTION:

A total of 100 cases between the age group of 20-45 years were studied. The maximum number of cases34(34%) were in the 41-45 year category. The next large number of cases31(31%) were in the 36-40year category, followed by 31-35yr category with 16cases,26-30yr category with 14 cases and 21-26yr category with least number of cases that is 5(5%)cases.

	Frequency	Percent
21-25	**5**	**5.0**
26-30	**14**	**16.0**
31-35	**16**	**14.0**
36-40	**31**	**31.0**
40+	**34**	**34.0**
Total	**100**	**100.0**

SEX DISTRIBUTION AMONG PREHYPERTENSIVES:

Sex	Percent
Male	**47%**
Female	**53%**

Among total of 100 cases studied,47% were males and 53% were females.

BMI DISTRIBUTION:

BMI Cat	Percentage
<18.00	1.0
18.00 – 24.99	87.0
25.00 – 29.99	12.0
>30	0

Of the total of 100 cases, maximum number of cases (87%) were in 18-24.99 category (normal). 12 cases were in 25-29.99 category (overweight) others were in <18 category. none were in >30(obesity).

SMOKING AMONG PREHYPERTENSIVES:

	Frequency	**Percent**
Absent	**23**	**48.9**
Present	**24**	**51.1**
Total	**47**	**100.0**

Among the 47 male subjects, 24(48.9%) were smokers and 23(51%) were non smokers. All female subjects studied were non smokers.

ALCOHOL CONSUMPTION AMONG PREHYPERTENSIVES :

	Frequency	**Percent**
Absent	31	66.0
Present	16	34.0
Total	47	100.0

Among 47 male subjects studied, 16(34%) were alchoholics and 31(66%) were non alchoholics. All female subjects were non alchoholics.

DISTRIBUTION OF BLOOD PRESSURE:

Category	Percent
Normal	**60**
High-normal	**40**

1. Normal blood pressure (SBP 120-129mmHg or DBP 80-84mmHg)

2. High normal blood pressure SBP 130-139mmHg or DBP 85-89mmHg)

Of the total 100 cases studied, 60 cases belonged to 'normal' category and 40 cases belonged to 'high normal' category based on The European Society of Hypertension and European Society of Cardiology (ESH-ESC) classification of prehypertension.

BLOOD PRESSURE AND MICROALBUMINURIA:

			Microalbuminuria		
			Absent	**Present**	
Blood pressure	120 - 129	Count	37	23	60
		Percent	61.7%	38.3%	100.0%
	130-139	Count	26	14	40
		Percent	65.0%	35.0%	100.0%
Total		Count	63	37	100
		Percent	63.0%	37.0%	100.0%

Of the total 100 cases studied, prevalence of microalbuminuria in prehypertension was 37%. In the 'normal' blood pressure category (120-129mmHg systolic), prevalence of microalbuminuria was 38.3%. In the 'high normal' category (130-139mmHg systolic), prevalence of microalbuminuria was 35%.

SIGNIFICANCE OF MICROALBUMINURIA IN PREHYPERTENSION:

Pearson Chi-square test	Value	Df	Asymp. Sig. (2sided)
Person Chi-Square	.114		1 .735

Pearson Chi-square test shows asymptotic significance of 0.735.hence, there is no correlation between microalbuminuria and prehypertension in our study.

BLOOD PRESSURE AND HYPERURICAEMIA-MALES

FREQUENCY TABLE

Males		**<=7.00**	**>7.00**	
	120-129	15	9	24
	130-139	13	10	23
	Total	28	19	47

PERCENTAGES

Males		**<=7.00**	**>7.00**
	120-129	62.5	37.5
	130-139	56.5	43.5
	Total	59.6	40.4

BLOOD PRESSURE AND HYPERURICAEMIA:

Of the total 47 male subjects, 40.4%(19) had hyperuricaemia. In the 'normal' blood pressure category, 37.5%(9) had hyperuricaemia. In the 'high normal' blood pressure category,43.5%(10) had hyperuricaemia.

RELATION BETWEEN BLOOD PRESSURE AND URIC ACID:

Pearson Chi-square test shows asymptotic significance value of 0.676.Hence, this association seems to be due to chance and there is no relation between blood pressure and hyperuricaemia in males in our study.

BLOOD PRESSURE AND URIC ACID - FEMALES

FREQUENCY TABLE

Females		<=6.00	>6.00	
	120-129	23	13	36
Freq	130-139	11	6	17
	Total	34	19	53

PERCENTAGES

Females		<=6.00	>6.00
	120-129	63.9	36.1
Percent	130-139	64.7	35.3
	Total	64.2	35.8

BLOOD PRESSURE AND HYPERURICAEMIA-FEMALES:

Of the total 53 female subjects studied,35.8%(19) had hyperuricaemia.In the ‘normal’ blood pressure category,36.1%(13) had hyperuricaemia.In the ‘high normal’ blood pressure category,35.3%(6) had hyperuricaemia.

RELATION BETWEEN BLOOD PRESSURE AND HYPERURICAEMIA:

Pearson Chi-square test showed a asymptotic significance value of 0.954. Hence, there is no correlation between blood pressure and hyperuricaemia in our study.

MICROALBUMINURIA AND URIC ACID-MALES:

			<= 7.00	<7	
ACR	Normoalbuminuria	Count	20	7	27
		Percent	74.1%	25.9%	100.0%
	Microalbuminuria	Count	8	12	20
		Percent	40.0%	60.0%	100.0%
Total		Count	28	19	47
		Percent	59.6%	40.4%	100.0%

HYPERURICAEMIA IN PREHYPERTENSIVES WITH MICROALBUMINURIA-MALES:

Of the total 47 prehypertensive subjects(males) studied 20 had microalbuminuria and 27 had normoalbuminuria.

Of the total 47 prehypertensive subjects(males) studied 40.4%(19) had hyperuricaemia.

Prevalence of hyperuricaemia in subjects with normoalbuminuria.

Of the 27 prehypertensive subjects(males) with normoalbuminuria, 25.9%(7) had hyperuricaemia.

Prevalence of hyperuricaemia in subjects with microalbuminuria.

Of the 20 prehypertensive subjects (males) with microalbuminuria, 60%(12) had hyperuricaemia.

THE FINAL OUTCOME

RELATION OF HYPERURICAEMIA WITH MICROALBUMINURIA IN PREHYPERTENSIVE SUBJECTS:

Odd Ratio : 4.29

	Value	**df**	**Asymp. Sig. (2-sided)**
Pearson Chi-Square	5.539[a]	1	.019

Pearson Chi-square test shows that asymtotic significance value is 0.019.

So, the association between hyperuricaemia with an (odd ratio 4.29) with microalbuminuria in prehypertension (males) is significant.

HYPERURICAEMIA IN PREHYPERTENSIVES WITH MICROALBUMINURIA-FEMALES:

			Uric Acid		Total
			<=6.00	>6	
ACR	Normoalbuminuria	Count	27	9	36
		Percent	75.0%	25.0%	100.0%
	Microalbuminuria	Count	7	10	17
		Percent	41.2%	58.8%	100.0%
Total		Count	34	19	53
		Percent	64.2%	35.8%	100.0%

Odd Ratio : 4.29

Of the total 53 prehypertensive subjects(females) studied,36 had normoalbuminuria and 17 had microalbuminuria.

Of the total 53 prehypertensive subjects(females) studied,35.8%(19) had hyperuricaemia.

Prevalence of hyperuricaemia in subjects with normoalbuminuria:

Of the total 36 prehypertensive subjects(females) with normoalbuminuria,25%(9) had hyperuricaemia.

Prevalence of hyperuricaemia in subjects with microalbuminuria:

Of the total 17 prehypertensive subjects(females) with microalbuminuria 58.8% had hyperuricaemia. **Odd Ratio : 4.29**

THE FINAL OUTCOME:

RELATION OF HYPERURICAEMIA WITH MICROALBUMINURIA IN PREHYPERTENSIVE SUBJECTS:

	Value	df	Asymp. Sig. (2-sided)
Pearson Chi-Square	5.744[a]	1	.017

Pearson Chi-square test shows that asymptotic significance value is 0.017.

So, the association between hyperuricaemia with an (Odds ratio 4.29) with microalbuminuria in prehypertension (males) is significant.

DISCUSSION AND COMPARATIVE ANALYSIS

Cardiovascular disease (CVD) risk is a continuum across blood pressure. The term prehypertension was introduced because it is now recognized that blood pressure readings between what is deemed optimal and hypertension is associated with increased CVD risk.

When JNC VII introduced a new category of blood pressure (BP), so-called prehypertension, for those with 120-139/80-89 mm Hg, the purpose of this new category was to identify the individuals with increased risk of cardiovascular events because of elevated blood pressure, an increased burden of other risk factors such as obesity, diabetes mellitus, dyslipidemia, and inflammatory markers, and evidence of organ damage for example, microalbuminuria, retinal arteriolar narrowing, increased carotid arterial intima-media thickness, left ventricular hypertrophy and coronary artery disease. More importantly, to define this subset of people in whom an early intervention can reduce the risks of developing hypertension and a cardiovascular event.

FRAMINGHAM STUDY, ATTICA STUDY, Women's health initiative(WHI) study uniformly associate prehypertension with subclinical cardiovascular disease, including both microvascular and macrovascular pathology.[12,13]

Although several studies have previously shown the association between hyperuricemia and microalbuminuria in hypertensive patients, its relationship in subjects without hypertension,especially prehypertension is unknown.

In this study, we demonstrated the relationship between serum uric acid level and microalbuminuria in persons with prehypertension.

In our study, a total of 100 cases between the age group of 20-45 years were studied. The maximum number of cases34(34%) were in the 41-45 year category. This pattern was slightly different from the large scale study done by Yadav et al where prevalence of prehypertension was highest in the 31-39yr category(36%).

Comorbid conditions for cardiovascular risk in our patients included,

- Smoking

Among the 47 male subjects,24(48.9%) were smokers and 23(51%) were non smokers. All female subjects studied were non smokers.

- Alchohol consumption:

Among 47 male subjects studied,16(34%) were alchoholics and 31(66%) were non alchoholics. All female subjects were non alchoholics.

As studied by Norman M.Kaplan, smoking can be an independent risk factor for prehypertension, microalbuminuria and cardiovascular morbidity. Smoking by causing polycythaemia, can by itself be associated with hyperuricaemia.

Study done by Sabharwal et al, showed increased prevalence of microalbuminuria in smokers and alchoholics, reflecting their cardiovascular risk.

- BMI

Of the total of 100 cases, maximum number of cases(87%) were in 18-24 category(normal).12 cases were in 25-29.99 category(overweight) others were in <18 category. none were in >30(obesity).

Obesity, dyslipidemia and metabolic syndrome are factors which cluster with microalbuminuria and hyperuricaemia. Patients with metabolic syndrome were excluded from this study, as hyperuricaemia may represent the culmination of a multimetabolic syndrome in which insulin-mediated renal haemodynamic abnormalities lead to hypertensive renal damage.

- Microalbuminuria in prehypertension:

  Of the total 100 cases studied, prevalence of microalbuminuria in prehypertension was 37%.

It has been suggested that microalbuminuria may represent the renal manifestation of generalized, genetically-conditioned vascular endothelial dysfunction that may underlie the link between an increased urine albumin excretion and an elevated risk for cardiovascular disease. In this sense, it has been described that microalbuminuria is associated with a decreased size- and charge-selectivity of the glomerular vessel wall in clinically healthy subjects, and is an independent marker of systemic transvascular albumin leakiness. Furthermore, atherosclerotic vascular disease is associated with renal and systemic transvascular leakiness for albumin.

A cross sectional study done in Renal unit, Massachusetts general hospital, Boston concluded that 'High-normal BP is significantly associated with microalbuminuria compared with optimal BP and may be a biomarker of the increased cardiovascular risk observed in this population'(odds ratio [OR], 2.13; 95% confidence interval [CI], 1.51 to 3.01).

A 10-year follow-up analysis of all subjects with untreated arterial hypertension or borderline hypertension identified within the World Health Organization (WHO) Multinational Monitoring of Trends and Determinants in Cardiovascular Disease (MONICA) study in Denmark, 1983 and 1984 concluded that microalbuminuria confers a 4-fold increased risk of ischemic heart disease among hypertensive or borderline hypertensive subjects.

It is safe to conclude that microalbuminuria is a established risk factor for both subclinical and overt cardiovascular disease. Hence, this particular study utilizes microalbuminuria as a parameter to assess subjects at increased cardiovascular risk.

HYPERURICAEMIA AND PREHYPERTENSION:

Of the total 47 male subjects,40.4%(19) had hyperuricaemia. In the ’normal’ blood pressure category,37.5%(9) had hyperuricaemia.In the ‘high normal’ blood pressure category,43.5%(10) had hyperuricaemia.

Of the total 53 female subjects studied,35.8%(19) had hyperuricaemia.In the ‘normal’ blood pressure category,36.1%(13) had hyperuricaemia. In the ‘high normal’ blood pressure category,35.3%(6) had hyperuricaemia.

The relationship between serum uric acid and hypertension has been studied extensively since 1970s. Ramsay (1979) in his study of 73 men with untreated hypertension had with raised serum uric acid levels (25%) 46. Messerli et al (1980) had an incidence of 72 % raised serum uric acid in their study population of 39 established hypertensives.Messerli and Frohlich et al hypothesized that the frequent presence of hyperuricemia in hypertensive patients reflects underlying renal dysfunction or reduced renal perfusion.

Three possible conclusions can be drawn from the association of hypertension with raised serum uric acid levels. Hypertension may arise as a result of hyperuricemia, hypertension can cause

hyperuricemia and the duration and severity of hypertension is related directly to the Serum uric acid levels.

But, the relationship between serum uric acid,prehypertension and its cardiovascular risk is almost unknown. The Korean study done in Samsung Medical center on which our present study is based is one of the few studies in this direction.

RELATION BETWEEN HYPERURICAEMIA AND MICROALBUMINURIA:

Of the 27 prehypertensive subjects (males) with normoalbuminuria,25.9%(7) had hyperuricaemia.Of the 20 prehypertensive subjects(males) with microalbuminuria,60%(12) had hyperuricaemia.(Odds ratio 4.29)

Of the total 36 prehypertensive subjects(females) with normoalbuminuria,25%(9) had hyperuricaemia.Of the total 17 prehypertensive subjects(females) with microalbuminuria 58.8% had hyperuricaemia.(Odds ratio 4.29)

In both males and female prehypertensive subjects,those with microalbuminuria had higher uric acid levels than those with normoalbuminuria and this relation was statistically significant.(men p value-0.019,women p value-0.017,odds ratio 4.29)

In the study done in Samsung medical center, Seoul, Korea by Jung Eun Lee et al, Prehypertensive subjects with microalbuminuria had higher uric acid level than those with normoalbuminuria (men, 387[68] mmol/L versus 371 [69] mmol/L; *P*_0.017; women 286 [56] mmol/L versus 262 [54] mmol/L; *P*_0.006). In the normotensive group, serum uric acid quartile did not show the independent association with microalbuminuria. The independent relationship between serum uric acid level and microalbuminuria was confirmed by the results of multiple logistic regression analyses . In the prehypertensive group, after adjustment for other cardiovascular risk factors (age, BMI, smoking status, serum glucose,low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, CRP, fibrinogen, and GFR), upper uric acid quartiles were associated with a higher risk of microalbuminuria for both men (*P*_0.004 for trend) and women (*P*_0.025 for trend). Compared with the lowest quartile, the highest

uric acid quartile entailed >2 times greater risk for microalbuminuria in both men (odds ratio, 2.12; 95% CI, 1.16 to 3.87) and women (odds ratio, 3.36; 95% CI, 1.17 to 9.69). In the normotensive group, serum uric acid quartile was not an independent factor for microalbuminuria.

This study demonstrates a strong independent association between uric acid level and microalbuminuria in prehypertensive subjects without a history of cardiovascular disease or decreased renal function. It is well known that microalbuminuria is associated with an increased risk for cardiovascular disease and might be an easily detectable marker for generalized vascular dysfunction. Although we are unable to determine whether serum uric acid has a causative role in hypertension or prehypertension, the findings of the study suggest that serum uric acid level can be a strong predictor of cardiovascular disease when combined with elevated blood pressure (even mildly elevated).Endothelial dysfunction may be a possible pathway linking uric acid and cardiovascular disease.[52]

Several studies have demonstrated that subjects with prehypertension are at increased cardiovascular risk and may already have evidence of end organ damage, such as impaired ventricular relaxation or microalbuminuria. However, there is no data to prove that

pharmacological therapy in prehypertension improves outcomes. Drug therapy in >30% of the adult population would be prohibitively expensive and could cause side effects that would counteract any beneficial effects associated with the reduction in blood pressure. The Joint National Committee-7 report recommends antihypertensive drugs in patients with diabetes or chronic kidney disease as high-risk patients. Our observational data imply that prehypertensive subjects with hyperuricemia may also be a high-risk group that could benefit from lowering blood pressure by both lifestyle modifications and pharmacological methods.[52]

LIMITATIONS OF THE STUDY:

1. This was a cross-sectional study; therefore, we were unable to examine the impact of hyperuricemia over time.

2.Normotensives were not examined, hence multiple regression analysis could not be done to confirm the independent association between hyperuricaemia and cardiovascular risk in prehypertension.

FUTURE AREAS OF RESEARCH:

1.Prospective studies to study the actual cardiovascular events and risk in prehypertensive subjects with hyperuricaemia are needed to to prove this association.

2.Hyperuricaemia in prehypertension and hypertension-a cause or effect?

This has to addressed by studies which may include pharmacological treatment of prehypertensive subjects with hyperuricaemia either with antihypertensives or uric acid lowering drugs.

CONCLUSION

The following conclusions were derived from the study,

1.Prehypertension clusters with other cardiovascular risk factors like smoking, alchoholism, dyslipidemia ,microalbuminuria and hyperuricaemia.

2.Hyperuricaemia is an independent risk factor for microalbuminuria and thereby cardiovascular risk in prehypertension.

3. Urinary albumin excretion rate can be used as an immediate end point to evaluate the outcome of lowering the uric acid level in future investigations, and this will help draw a conclusion regarding its relation with cardiovascular disease.

4.As per JNC 7,pharmacological treatment is recommended for prehypertension, only if associated with diabetes,chronic kidney disease,microalbuminuria,etc ,this study suggests that the subset of patients with hyperuricaemia can also be regarded as a high risk group who could benefit from blood pressure lowering therapy.

SUMMARY

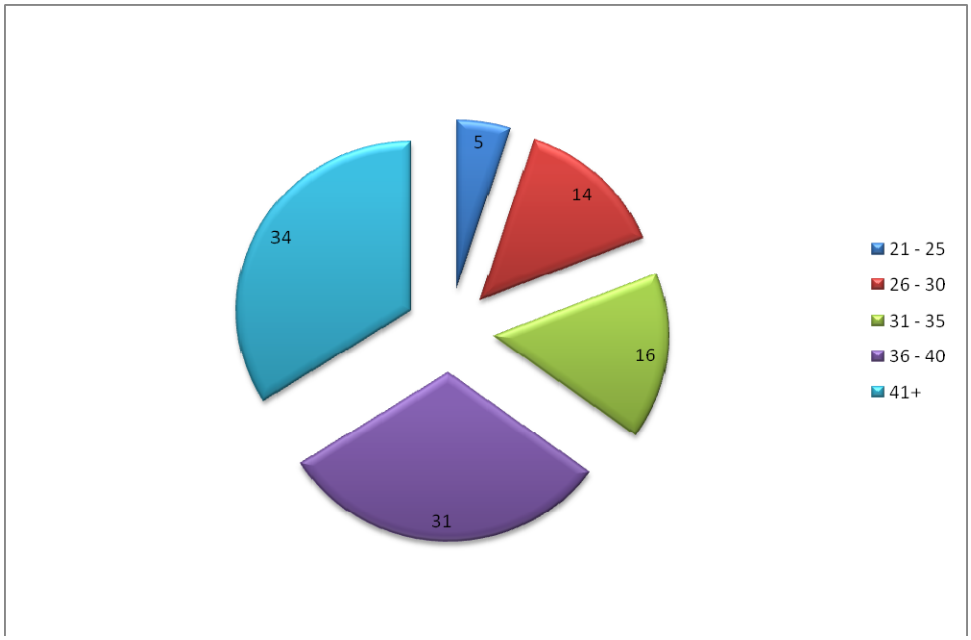
This study **"CORRELATION BETWEEN SERUM URIC ACID AND MICROALBUMINURIA IN PREHYPERTENSION"** was carried out in Govt. Rajaji Hospital, Madurai Medical College, Madurai from March 2010 to October 2010.

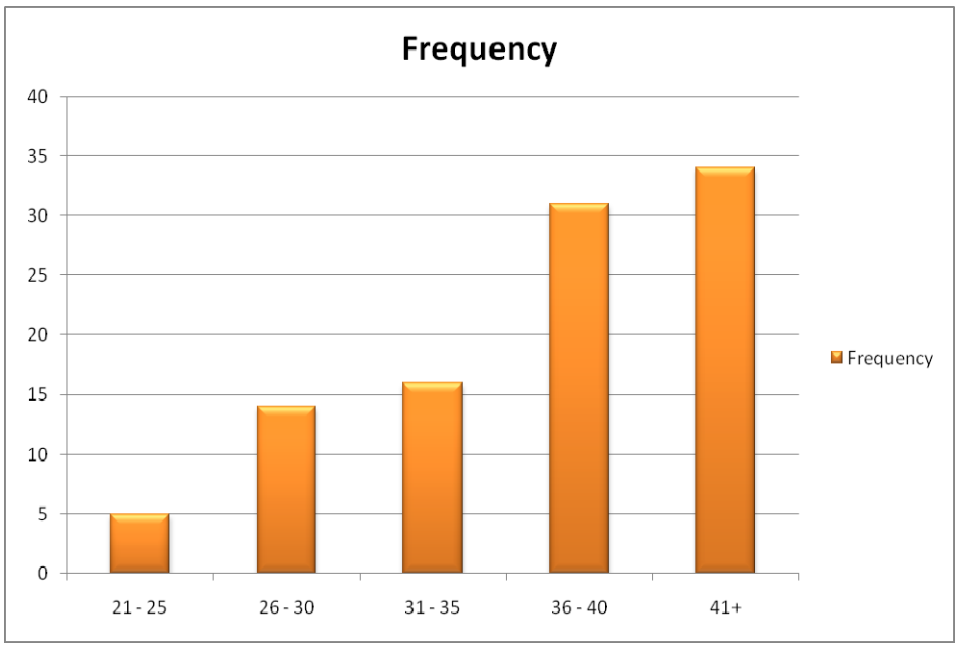
100 cases of prehypertension in the age group of 20-45years were studied during this period.Male subjects-43% and females-57%. Hyperuricaemia was found to be strongly associated with microalbuminuria in prehypertensive subjects.

Increased uric acid level in a prehypertensive group should be considered as a risk factor for cardiovascular disease.

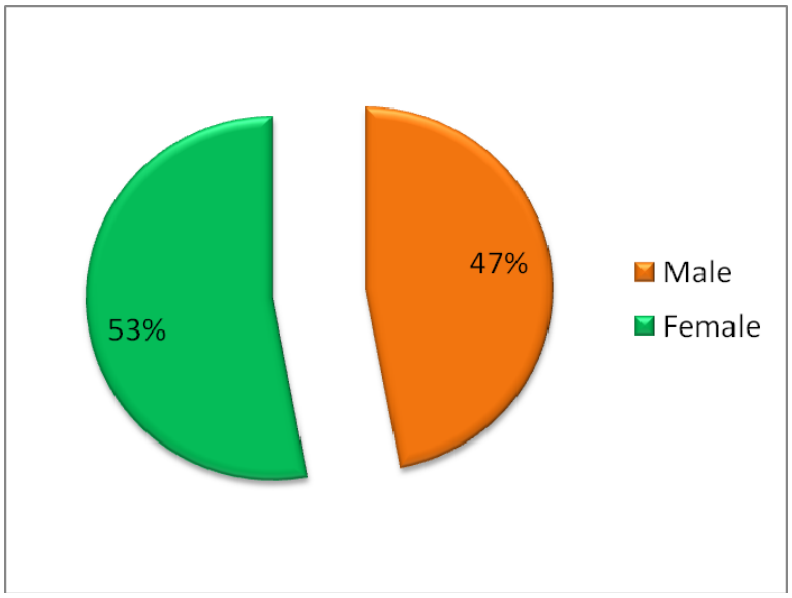
RESULTS AND OBSERVATIONS

AGE DISTRIBUTION IN PREHYPERTENSION:

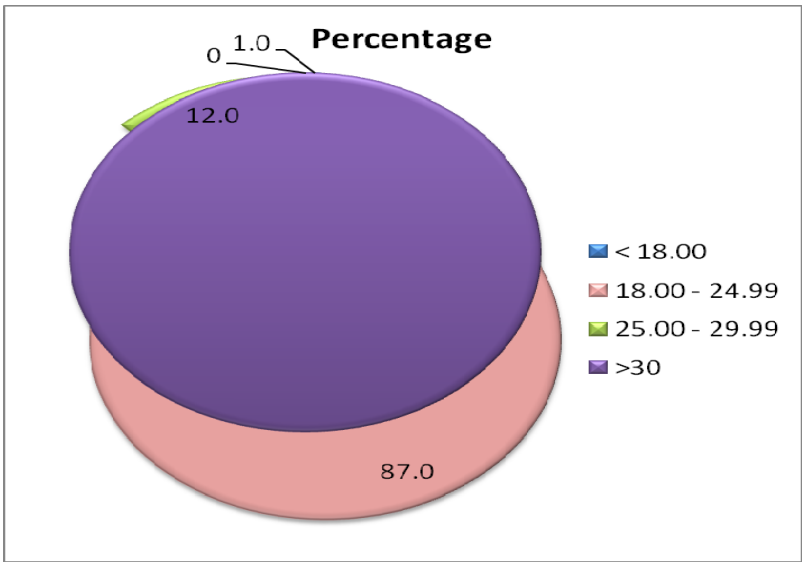




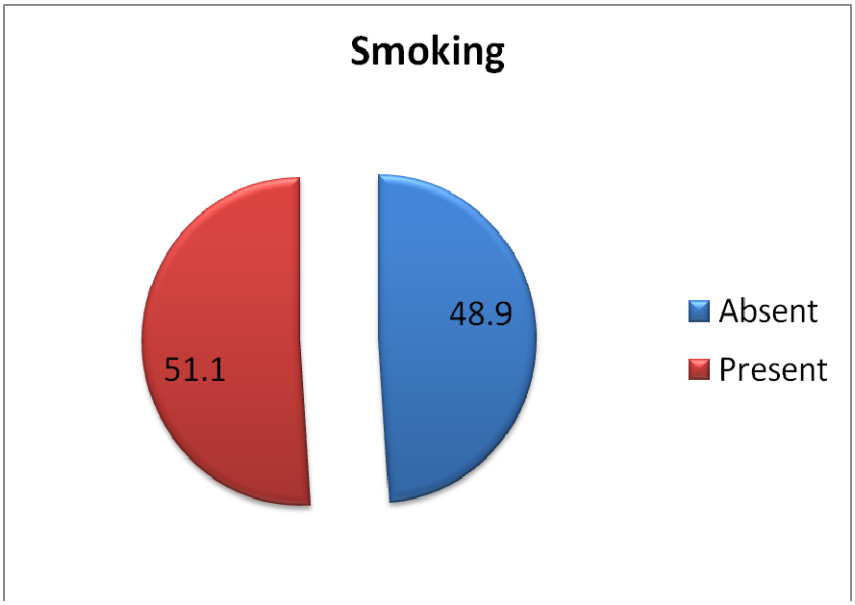
SEX DISTRIBUTION AMONG PREHYPERTENSION:



BMI DISTRIBUTION:



SMOKING AMONG PREHYPERTENSIVES:



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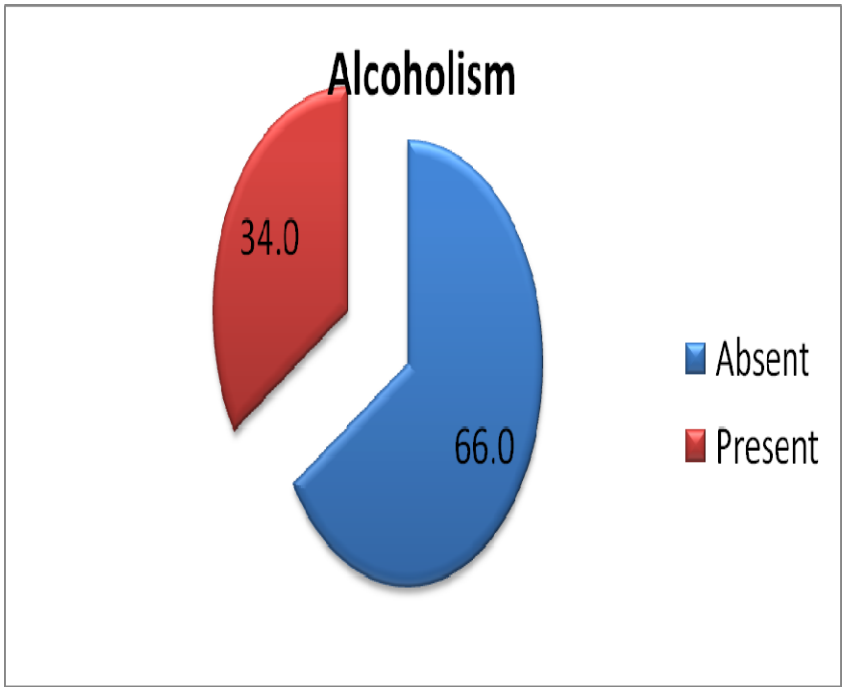
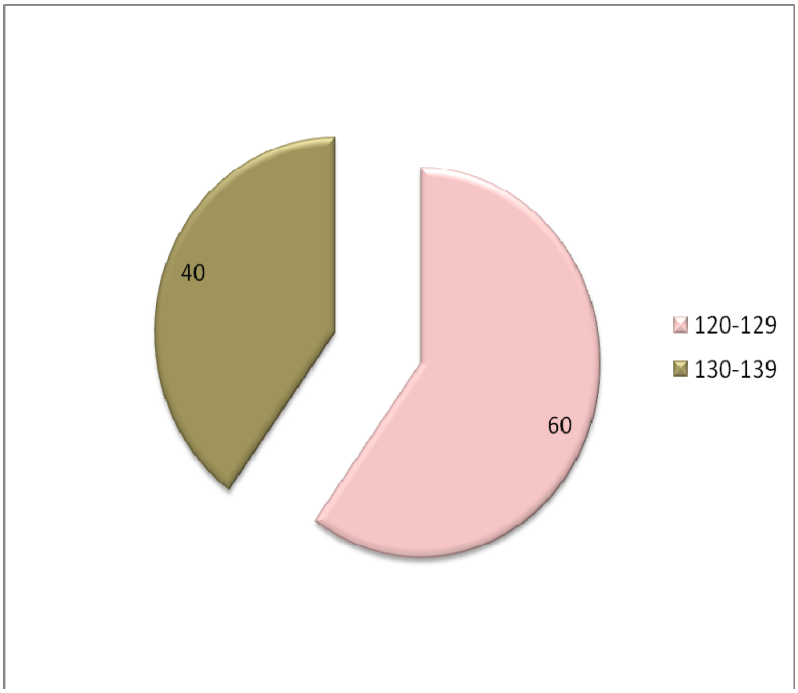
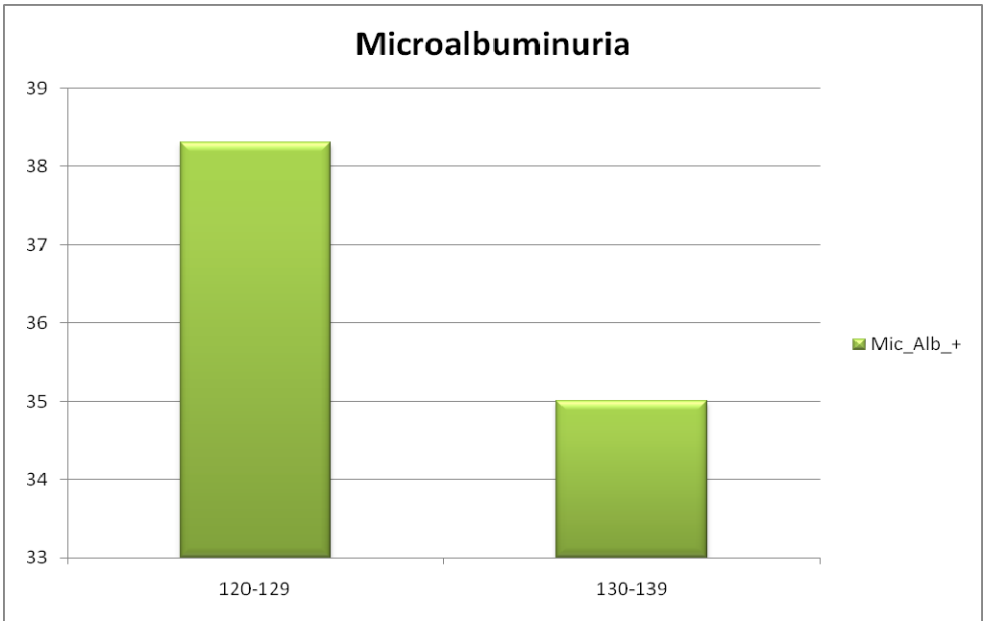


DISTRIBUTION OF BLOOD PRESSURE:

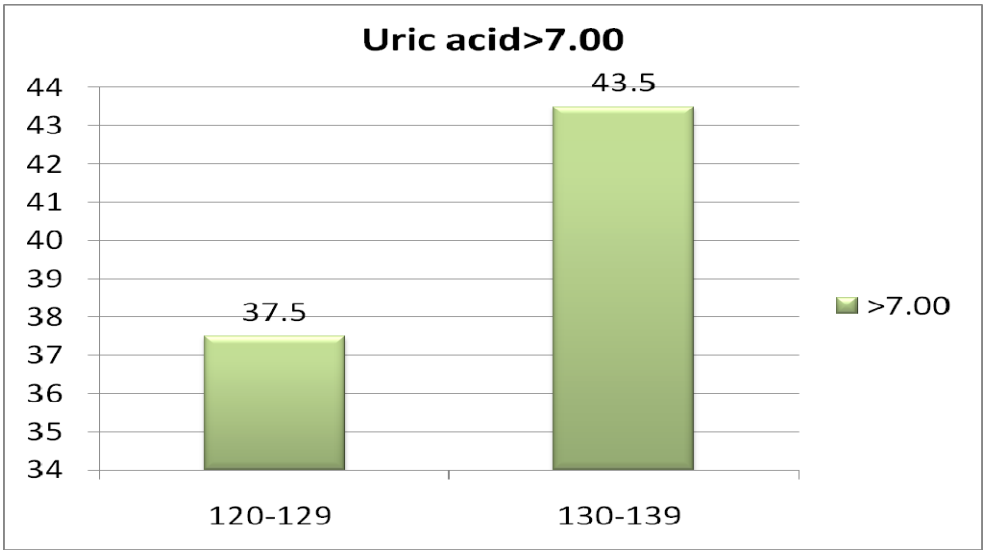


BLOOD PRESSURE AND MICROALBUMINURIA:

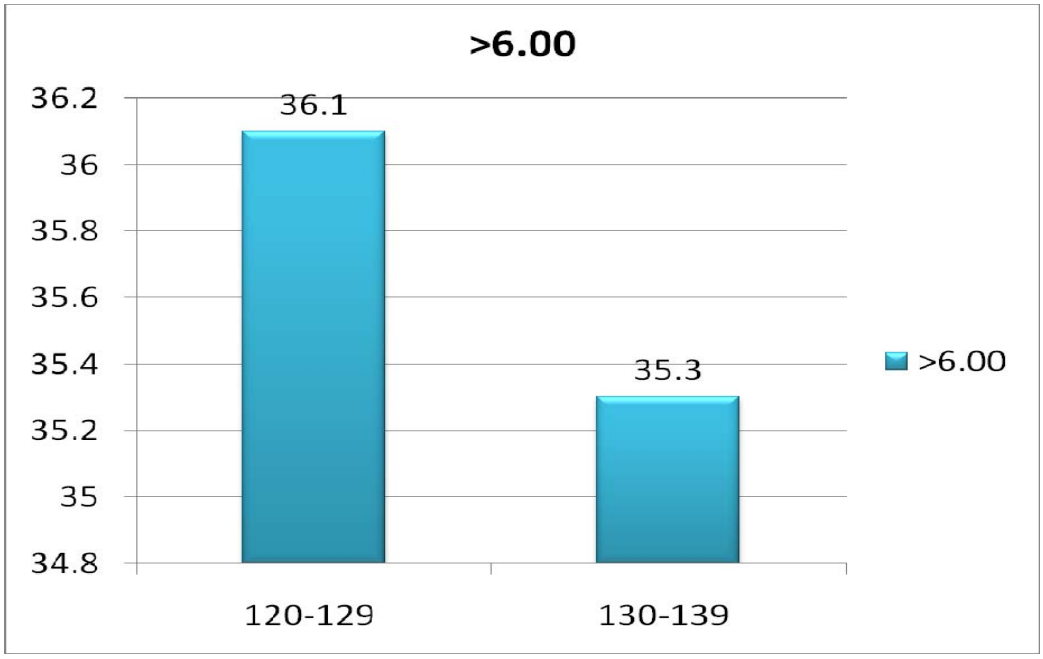


BLOOD PRESSURE AND HYPERURICAEMIA-

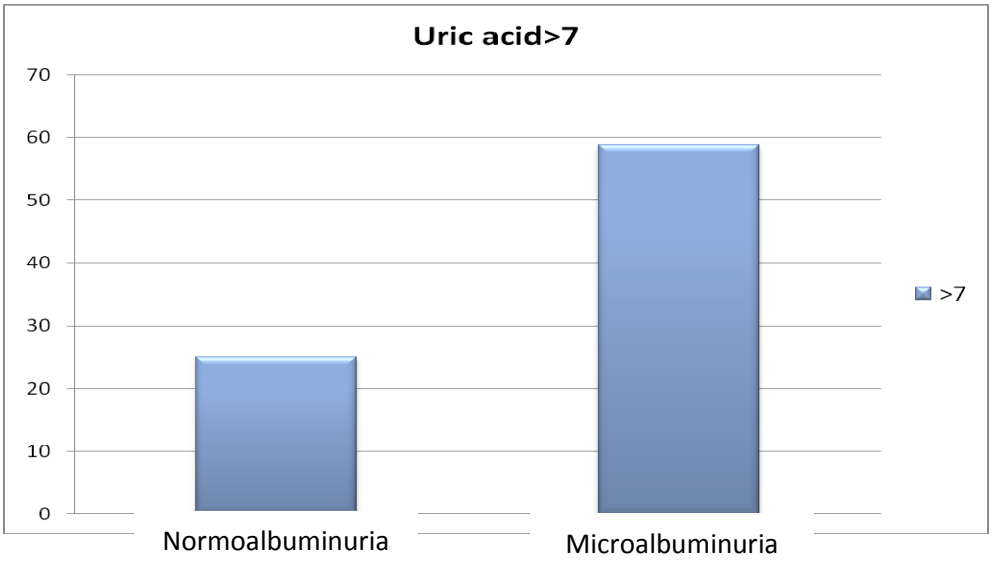
MALES:



BLOOD PRESSURE AND HYPERURICAEMIA-FEMALES:



MICROALBUMINURIA AND URIC ACID-MALES:



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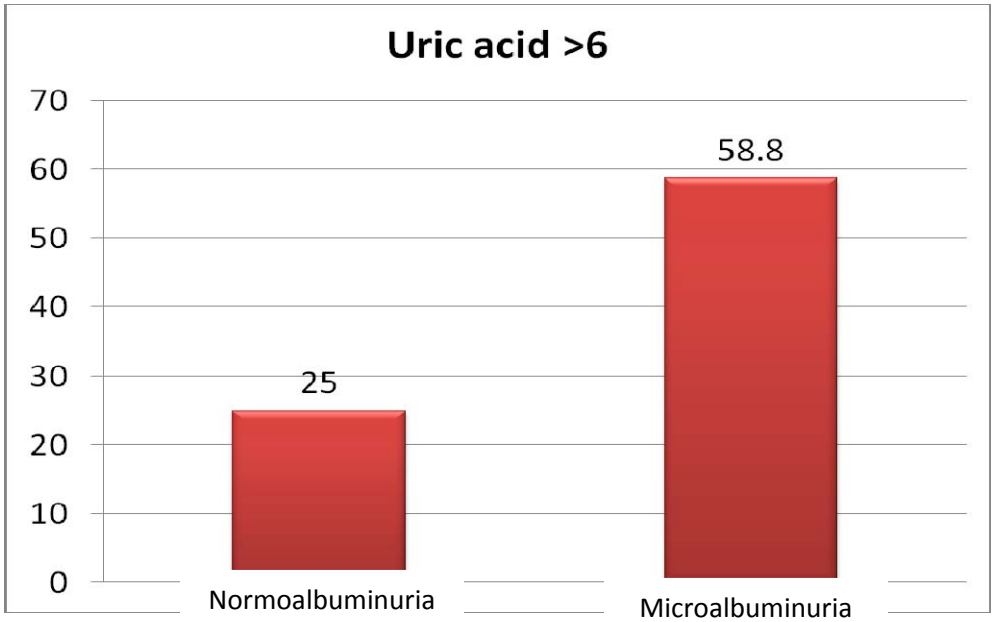

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