STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION

Submitted By

DR. SANDEEP.H.M

Dissertation submitted to

BLDE UNIVERSITY, BIJAPUR , KARNATAKA

In partial fulfillment of the

Requirements for the degree of

MD

in

General Medicine

Under the guidance of

DR. BADIGER. SHARANABASAWAPPA MD

PROFESSOR,

DEPARTMENT OF MEDICINE

B.L.D.E.U 's SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR.

2011

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION"** is a bonafide and genuine research work carried out by me under the guidance of **DR.BADIGER SHARANABASAWAPPA** Professor of Medicine.

Date:

Place: Bijapur. **DR. SANDEEP.H.M**

B. L. D. E. U 'S

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTRE, BIJAPUR.

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION"** is a bonafide research work done by **Dr.SANDEEP.H.M** in partial fulfillment of the requirement for the degree of MD in General Medicine.

DR.BADIGER. SHARANABASAWAPPA MD
Professor of Medicine
BLDEU's Shri. B. M. Patil Medical College,
Hospital, and Research Centre, Bijapur

Date:
Place: Bijapur.

B. L. D. E. U 'S

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTRE, BIJAPUR.

ENDORSEMENT BY THE HOD

This is to certify that the dissertation entitled **"STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION"** is a bonafide research work done by **DR. SANDEEP.H.M** under the guidance of **DR.BADIGER SHARANABASAWAPPA** Professor of Medicine.

DR.M.S.BIRADAR $_{MD}$

Professor and Head,
Department of Medicine.
B.L.D.E.U's Shri. B. M. Patil
Medical College, Hospital
and Research Centre, Bijapur

Date:
Place: Bijapur.

B. L. D. E. U 'S

SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL &

RESEARCH CENTRE, BIJAPUR.

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the dissertation entitled **"STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION"** is a bonafide research work done by **DR.SANDEEP.H.M** under the guidance of **DR.BADIGER SHARANABASAWAPPA** Professor of Medicine.

DR. R. C. BIDRI MD

Principal

B.L.D.E.U's Shri. B. M. Patil

Medical College, Hospital

and Research Centre, Bijapur

Date :

Place : Bijapur

COPYRIGHT

Declaration by the candidate

I hereby declare that the BLDE University, Bijapur shall have the rights to preserve use and disseminate this dissertation/ thesis in print or electronic format for academic/research purpose.

Date:

Place: Bijapur **DR. SANDEEP.H.M**

ACKNOWLEDGEMENT

On completion of this contribution of scientific document it gives me deep pleasure to acknowledge the guidance provided by my distinguished mentors.

With privilege and respect I like to express my gratitude and indebtedness to my guide Dr.Badiger.Sharanabasawappa M.D, *Professor of Medicine and unit V chief, Shri.B.M. Patil Medical College, Bijapur for his constant inspiration, extensive encouragement and support, which he rendered in pursuit of my post-graduate studies and in preparing this dissertation.*

I express my sincere gratitude to Dr.M.S.Biradar M.D *, Professor and Head, Department of Medicine for his advise ,valuable suggestions, encouragement and support.*

I am forever grateful to prof Dr.M .S.Mulimani, Prof Dr.S. S. Devarmani, Prof Dr.L.S.Patil, Prof Dr.R.M.Honnutagi, Dr.R.B.Jakareddy Assoc Prof, Dr A P Ambali Assoc Prof , Dr V G Warad Assoc prof , Dr P G Mantur Assoc prof, Dr S M Biradar Asst prof, Dr G S Mahishale Asst prof, Dr Javeed Patel Asst prof , Dr S B Bhagwati Assoc Prof , Dr. S.G.Balaganur Asst Prof, Dr Sanjay Patil Asst Prof, Dr.Shankargouda Patil (senior resident) & Dr Nitin Agarwal (senior resident) for their valuable help and guidance during my study.

I am extremely thankful to Dr.R.C.Bidri, Principal & Dr.M.H.Patil, Medical Superintendent of B.L.D.E.U's Shri B.M.Patil Medical College Hospital and Research Centre, Bijapur for permitting me to utilize resources in completion of my work.

I would like to express my gratitude to the statistician Mrs.Wali, who helped me in my dissertation work .

My thanks to all the Library Staff, Medicine Dept Staff and Hospital Staff for their co-operation in my study.

I am thankful to my seniors Dr Asna, Dr Utkarsha, Dr Jagdeesha, Dr Tanmay, Dr Amit ,Dr Murali,Dr Surendra,Dr Mujawar,Dr Ravi, Dr Sandeep and my batchmates Dr Chandrakanth, Dr Sachin, Dr Abhishek, Dr Aveg, Dr Prashanth (orthopaedic Postgraduate) for their suggestions and advice.

I am deeply indebted to my parents Mrs.Vijayalakshmi, Dr.H.L.Mahendra and my brother Sagar whose constant encouragement, patience and support helped me to complete this dissertation.

I convey my heartfelt gratitude to my wife Dr Deepti, without whose co-operation this study would be incomplete.

My special thanks to Mr. Kalyan Kumar and Asif of 'Preeti net zone' Bijapur for computerizing my dissertation work in a right format. I sincerely appreciate his skills and recommend him for my junior colleagues.

At last but not the least, I convey my heartfelt gratitude to all my patients & Department of Biocemistry, without whose co-operation this study would be incomplete.

Date: **DR. SANDEEP.H.M.**

Place: Bijapur

LIST OF ABBREVIATIONS

ACE	–	Angiotensin converting enzyme
ACS	–	Acute coronary syndrome
ADA	–	American Diabetic Association
ARB	–	Angiotension receptor blocker
BP	–	Blood pressure
BMI	–	Body mass index
CKD	–	Chronic kidney disease
CVD	–	Cardio vascular diseases
ECG	–	Electrocardiogram
ET-1	–	Endothelin 1
ELISA	–	Enzyme linked immuno sorbent assay
GFR	–	Glomerular filtration rate
HDL	–	High density lipoprotein
HTN	–	Hypertension
JNC	–	Joint National Committee
LVH	--	Left ventricular hypertrophy
LDL	–	Low density lipoprotein
MA	–	Microalbuminuria
NIDDM	–	Non insulin dependent diabetes mellitus
OR	–	Odd s ratio

RIA	–	Radio immuno assay
TER_{alb}	–	Transcapillary albumin leak
TOD	–	Target organ damage
UAE	–	Urinary albumin excretion

ABSTRACT

BACKGROUND :

Essential hypertension usually clusters with other cardiovascular risk factors such as age ,overweight, diabetes, insulin resistance and dyslipidemia. Subtle target organ damage such as left ventricular hypertrophy, microalbuminuria ,acute coronary syndrome, stroke and cognitive dysfunction takes place early in course of hypertension. Though the prevalence of hypertension ishigh in India, the relationship between MA and target organ damage in hypertension is not well studied. We aim at detecting MA in essential HTN & its relation to severity of HTN, duration of HTN, body mass index, age & TOD such as HTN retinopathy & ACS.

MATERIALS AND METHODS:

The present study was done in 100 patients of essential hypertension non diabetics admitted to B.L.D.E.U's Shri B.M.Patil Medical College, Bijapur, from October 2008 to July 2010. The patients underwent detailed history and clinical examination. Early morning 5 ml of urine sample was collected & MA was estimated by immunoturbidometry method. The relationship of MA with the duration & severity of HTN, BMI, age, sex and TOD's like hypertensive retinopathy, ACS was assessed by univariate analysis.

OBSERVATION & RESULTS:

The prevalence of MA in this study was found to be 63 % . In that 42% were male & 21% were female.We found out a significant association between MA & the duration

of hypertension (p = 0.036) & (OR =0.438) . Longer the duration of hypertension, more possibility of microalbumin in urine . Also there was a significant association between severity of hypertension & MA (p=0.045) &(OR=0.093). MA was positive in 50 (79.4%) patients out of 63 ,whose blood pressure was >160/100 mm Hg . We also found out a significant association between MA & the grades of hypertensive retinopathy (p =0.011) (highly significant). And we also found out a significant association between microalbuminuria & acute coronary syndrome (p = 0.041) (OR =2.805). Gender & BMI did not pose high risk for MA in this study.

CONCLUSION:

The prevalence of MA in essential hypertension is high in this part of the community & MA will increase the risk of developing target organ damage. Early screening of patients with essential hypertension for MA and aggressive management of positive cases might reduce the burden of chronic kidney diseases and cardiovascular diseases in the community.

CONTENTS

LIST OF TABLES

LIST OF GRAPHS

LIST OF FIGURES

NEED FOR THE STUDY

Hypertension is the commonest cause of cardiovascular disorder affecting over one billion individuals worldwide. Essential (primary) hypertension continues to be the commonest cause of hypertension.

Essential hypertension usually clusters with other cardiovascular risk factors such as age, overweight, diabetes, insulin resistance and dyslipidemia. Subtle target organ damage such as left ventricular hypertrophy, microalbuminuria and cognitive dysfunction takes place early in course of hypertension. Hypertensive nephropathy is a common cause of chronic kidney disease, in which chronic renal ischemia as a result of small and large vessel renovascular disease can be left under recognized. Progressive nephrosclerosis from vasculo-endothelial disease is the renal correlate of same process, that leads to coronary artery diseases and cerebrovascular diseases.

The concept of hypertension existed since centuries from the time Sir William Harvey successfully measured arterial blood pressure[1].This has posed several challenging problems to the medical profession. Sir Henry Platt (1948) first enunciated the idea of secondary hypertension since then pendulum has swung the other way to look for a cause of hypertension especially for a curable cause[2]. Advances in technique of modern surgery has been successfully able to alleviate the cause of hypertension in few of those lucky hypertensives who have curable cause.

This idea has made modern practicing clinician to look for a secondary cause of hypertension especially in a young individual and rule out. But, in essential hypertension urine examination is the most neglected examination in this modern era. A rethinking has propped up as to whether the whole battery of tests which are extensive, time consuming, expensive and laborious are necessary in investigating a hypertensive patient.

INTRODUCTION

Historical perspectives

The effect of hypertension on various systems of the body has been known from prehistoric times. Laennac (1819) noted the existence of left ventricular hypertrophy[3]. Blood pressure was measured for the first time by Stephen Hales in 1773[4].Hales also described the importance of blood volume in blood pressure regulation. The contribution of peripheral arterioles in maintaining blood pressure described as "tone" was first described by Lower in 1669 and subsequently by Senac in 1783[4]. Such eminent investigators such as Claude Bernard, Charles E. Edouard, Charles Brown-Séquard and Augustus Waller observed the role of vasomotor nerves in the regulation of blood pressure. William Dayliss advanced this concept in a monograph published in 1923. Cannon and Rosenblueth developed the concept of humoral control of blood pressure and investigated pharmacologic effects of epinephrine[4].

The studies made by the Richard Bright (1827) opened new vista in the study of hypertension[5]. He described 3 varieties of cases:

- Oedema associated with albuminuria
- Degenerative glomerulonephritis
- Chronic glomerulonephritis with secondary constriction of the kidney.

He observed the changes of hypertension on the cardiovascular system in patients with chronic renal disease. George Johnson in 1868 postulated that the cause of LVH in Bright disease was the presence of muscular hypertrophy in the smaller arteries throughout the body[4].

William Senhouse Kirke's (1822–1864) main interest was in cardiology and vascular disease, and he gave the first account of embolism from vegetations in infective endocarditis in 1852[5]. Three years later, he published a study of apoplexy in Bright's disease in which he pointed clearly to the role of raised intra-arterial tension in the causation of arterial disease, a point that had eluded Bright, Johnson, and other contemporaries.We place his contributions within the setting of the development during the 19th century of understanding of the relationship between the kidney, vascular disease, and high blood pressure.

Adoption, twin, and family studies document a significant heritable component to blood pressure levels and hypertension. Family studies controlling for a common environment indicate that blood pressure heritabilities are in the range of 15–35%. In twin studies[7], heritability estimates of blood pressure are = 60% for males and 30–40% for females. High blood pressure before age 55 occurs 3.8 times more frequently among persons with a positive family history of hypertension. Although specific genetic etiologies have been identified for relatively rare causes of hypertension, this has not been the case for the large majority of hypertensive patients. For most individuals, it is likely that hypertension represents a polygenic disorder in which a single gene or combination of genes act in concert with environmental exposures to contribute only a modest effect on blood pressure.

Hypertension is the third leading killer disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide. The prevalence of hypertension is known to increase with age[8]. Over 50% of individuals aged 60 to 69 and over 75% of those aged 70 years and older are affected. Observations involving more than 1 million individuals have shown that death from both CVD and stroke increases progressively and linearly from BP levels

of as low as 115mm Hg systolic and 75mm Hg diastolic upwards[8]. The increased risk are present in all age groups ranging from 40 to 89 years old. For every increment of 20 mm Hg systolic or 10 mm Hg diastolic there was a doubling of mortality from both ischemic heart disease and stroke.

Evidence also warrants greater attention to the importance of systolic blood pressure as a major risk factor for cardiovascular diseases[8]. The rise in systolic BP continues throughout life, in contrast to diastolic BP, which rises until approximately 50 years age, tends to level off over the next decade and may remain same or fall later in life. Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, cardiovascular mortality, and stroke and heart failure events.

The prevalence of hypertension has been increasing in developing countries and community surveys have documented that it is more prevalent among the Indians between the third and sixth decades of their life. Hypertension is a major modifiable risk factor for cardiovascular disease, which accounts for 57% and 24% of all deaths due to stroke and coronary heart disease respectively. Oxidative stress, which results from either overproduction of free radicals or depletion of antioxidant reserve, has been implicated in the development of cardiovascular disorders including hypertension[9,10].

Previous studies have assessed oxidative stress by-products like protein carbonyls and antioxidant activities in elderly hypertensive subjects and indicated an altered oxidant-antioxidant balance in them. This hypothesis has been supported by several experimental studies, which documented an increased oxidative stress in animal models like renovascular hypertension and obesity related hypertension and its subsequent reduction on treatment with antioxidants.

It has been reported that at young age the prevalence of hypertension is higher among males compared to females. This can be attributed to the fact that females are more protected from oxidative stress through estrogen. Oxidative stress has been implicated in the pathogenesis of various cardiovascular disorders including hypertension. Oxidative stress stimulates vascular smooth muscle proliferation and reduces nitricoxide bioavailability, causing endothelial dysfunction, which plays a crucial role in the pathogenesis of hypertension by reducing endothelium dependent vasodilatation[9,10].

In contrast with the huge number of experimental studies, clinical studies supporting the involvement of oxidative stress in the pathogenesis of essential hypertension are lacking.

Significant increase in erythrocyte glutathione peroxidase levels and reduction in catalase levels has been told in oxidative stress[10,11]. The primary catalytic cellular defense that protects cells and tissues against lipid peroxidation is the glutathione peroxidase enzyme. It has been observed that glutathione peroxidase can be rapidly induced in some conditions when cells or organisms are exposed to oxidative stress. The increased glutathione peroxidase activity in red blood cells of the test subjects may be interpreted as a compensatory mechanism due to the increased oxidative stress.

The levels of glutathione peroxidase may be related to the stages of hypertension[9,10]. There are no reports which point out whether oxidative stress sets in first or hypertension. The decrease in catalase activity may be attributed to its inactivation as a result of continuous exposure to hydroperoxides and hydrogen peroxide. This decrease can also be due to a downregulation of its expression. The depletion of glutathione and the accumulation of free radicals could induce the

enhanced expression of glutathione peroxidise. This decrease in catalase and an increase in glutathione peroxidase explain the negative correlation found between them. Because it has been shown that glutathione peroxidase is more potent on a molar basis than catalase and other antioxidant enzymes to protect cells from oxidative stress, it can be hypothesized that body tends to combat stress by over expressing glutathione peroxidase gene as the first line of defense in essential hypertension[9,10]. As the severity of hypertension advances into stage II and above, even the defences of glutathione peroxidase may deteriorate because of the increased production of free radicals.

One concept postulates that more albumin leaks through exaggeratedly permeant glomeruli that reflect the systemic damaging impact of subclinical atherogenesis, a process characterized by a diffuse involvement of the entire vascular system. This hypothesis, which was originally formulated to account for the higher cardiovascular morbidity rate in diabetic patients, may also apply to essential hypertensive patients[10]. Microalbuminuria (increased urinary albumin excretion that is not detected by the usual dipstick methods for macroproteinuria) predicts cardiovascular events in essential hypertensive patients. A possible reason for this behavior is that albumin leaks through exaggeratedly permeant glomeruli exposed to the damaging impact of subclinical atherogenesis. Blood pressure, particularly systolic and cardiac mass were higher in microalbuminuric patients in whom albuminuria correlated with both cardiovascular variables and indicated the influence of the hemodynamic load on urinary albumin levels[11]. Thus, TER_{alb}, a parameter influenced by the permeability surface area product for macromolecules and the filtration power across the vascular wall, is altered in essential hypertensives. However, this abnormality is dissociated from the amount of albuminuria, which is contrary to the

hypothesis that a higher albumin excretion reflects a greater degree of systemic microvascular damage in essential hypertension[11].

The studies of microalbuminuric patients have shown that if high BP is transmitted to renal glomeruli, it might increase the glomerular ultrafiltration of albumin[11]. Hypertension may increase capillary pressure and acute elevation in systemic perfusion pressure may accelerate hyperfiltration, transcapillary macromolecular transport and might damage each of several different pathways, such as diffusion through endothelial cell membranes, passage via intercellular junctions, transendothelial channels of organs and tissues with highly different permeability, and the surface area products. In conclusion, systemic capillary permeability is altered in essential hypertension[11].

Microalbuminuria, defined as a urine albumin/creatinine ratio above the upper decile (1.07 mg/mmol), was the strongest predictor of ischemic heart disease . Microalbuminuria confers a 4-fold increased risk of ischemic heart disease among hypertensive or borderline hypertensive subjects[12]. Urinary albumin excretion should be measured regularly in a hypertension clinic, and a vigorous control of blood pressure and of other atherosclerotic risk factors is recommended in hypertensive patients with microalbuminuria. Also a study has showed that arterial hypertension or borderline hypertension with microalbuminuria confers an increased risk of subsequent ischemic heart disease in hypertensives that is 4 times than in hypertensives or borderline hypertensives with normoalbuminuria, irrespective of the later use of antihypertensive therapy[12]. Furthermore, the predictive effect of microalbuminuria seems to be independent of and stronger than the effect of the

conventional atherosclerotic risk factors, such as smoking, dyslipidemia, obesity, high blood pressure, male gender, and advanced age.

Persistent MA is the earliest indicator of chronic kidney disease in patients with diabetes mellitus and hypertension. Patients with MA have high risk for TOD resulting in stroke, retinopathy and adverse cardiovascular events[13]. Though the prevalence of hypertension is high in India, the relationship between MA and TOD in hypertension is not well studied. A total of 100 hypertensives without diabetes mellitus and/or other conditions causing MA were studied in this study.

The patients with longer duration of hypertension, older age, higher BMI and adverse lipid profile are more prone to develop MA. Regular treatment of hypertension tends to reduce the development of MA. Higher grades of hypertensive retinopathy are associated with higher chance of development of MA. High prevalence of MA is seen in hypertensives presenting with stroke. Early screening of hypertensives for MA and prompt treatment of positive cases might reduce the disease burden related to severe CKD and cardiovascular events in the community[13].

Hypertension is associated with functional and morphological alterations of the endothelium, which disturbs delicate balance of endothelium derived factors resulting in endothelial dysfunction. The endothelial dysfunction could then facilitate the maintenance of elevated peripheral resistance, which would favor the occurrence of atherosclerosis. Endothelin-1 is a potent vasoconstrictor. Since ET-1 plays a role in the regulation of vascular tone, it has been hypothesized that increased production or release of ET-1 or both may contribute to the pathogenesis of hypertension[14]. Local vascular generation of ET-1 may contribute to elevated peripheral resistance in hypertension.

Elevated levels of vasoconstrictors in untreated essential hypertension subjects as compared to controls confirmed the presence of endothelial dysfunction,even in mild cases of hypertension. Early detection of endothelial dysfunction may be a useful measure to guide therapy before the damaging effects of hypertension manifests.

Increased urinary albumin excretion is associated with a worse pattern of cardiovascular risk factors and is a marker of concomitant cardiovascular damage in essential hypertension. Microalbuminuria can therefore be regarded as a useful, relatively inexpensive, integrated marker to help identify patients at higher cardiovascular risk for whom more aggressive preventive strategies and/or additional treatment measures may be advisable. Patients with retinal vascular changes were more often men and on the average older and with a longer duration of hypertension and a lower glomerular filtration rate as indicated by creatinine clearance[15]. Furthermore, microalbuminuria was associated with the presence of target organ damage {eg, electrocardiographic (ECG) abnormalities and retinal vascular changes}. Age and the presence of microalbuminuria acts as independent risk factors for the development of ECG abnormalities and retinal vascular changes[15].

Microalbuminuric hypertensive subjects were characterized by higher age and systolic BP, and a male predominance, as compared to normoalbuminuric hypertensive subjects[16]. It is concluded that slightly elevated albumin excretion in the urine is not only a pressure dependent functional phenomenon in the glomerular vessel walls, but associated with permanent atherosclerotic abnormalities in the entire vascular system.

Prevalence of microalbuminuria and retinopathy were quite high in a cohort study of elderly hypertensives. A cross sectional study from a teaching hospital in south India studied retinal changes of any grade probably have moderate accuracy in

predicting microalbuminuria and accuracy of retinal changes in predicting microalbuminuria among elderly hypertensive patients[17]. Hence it guides us to initiate work up for TOD, especially in a resource poor setting in patients with essential hypertension.

Microalbuminuria is the strongest independent determinant of ischemic heart disease among subjects with arterial hypertension. On this basis, urinary albumin excretion should be measured regularly in a hypertension clinic. Although intervention studies of the effect of lowering urinary albumin excretion on cardiovascular morbidity are missing, a vigorous control of blood pressure and other modifiable atherosclerotic risk factors in microalbuminuric hypertensives is advisable[18,19] .

MA is associated with a higher prevalence of diabetic complications, metabolic and non-metabolic risk factors, target organ damage as well as adverse cardiovascular diseases in both diabetic and non-diabetic people with essential hypertension. The choice between an ACE inhibitor or ARB in patients with microalbuminuria is uncertain because both appear to be renoprotective. Association of MA with left ventricular hypertrophy may be related to a higher blood pressure load. The expression of atherosclerotic disease in the carotid artery that is manifested as an increase in intimal-media thickness was also noted in both non-diabetic and diabetic individuals with MA[20,21].

This vascular remodeling may be related to endothelial dysfunction, the role of which in atherogenesis was well described and discussed previously. Vascular retinal changes and coronary artery disease are also more common with hypertensive patients with MA than with normoalbuminuria patients [20,21,102]. Interestingly, the incidence of hypertensive retinopathy is lower if MA is reversed with treatment. MA is also

associated with a higher proportion of people developing macroalbuminuria[21] which is an indication of renal disease progression.

DEFINITION OF HYPERTENSION

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

Classification of Blood Pressure

Based on the seventh report of the Joint National Committee[22](JNC) on prevention, detection, evaluation and treatment of high blood pressure (JNC VII report) BP is classified into the following stages –

Normal

Systolic BP < 120 mm Hg

Diastolic BP < 80 mm Hg

Prehypertension

Systolic = 120-139 mm Hg

Diastolic = 80-89 mm Hg

Stage 1 hypertension

Systolic = 140-159 mm Hg

Diastolic = 90-99 mm Hg

Stage 2 hypertension

Systolic ≥ 160 mm Hg

Diastolic ≥ 100 mm Hg

In contrast with the classification provided in the JNC VI report, a new category designated prehypertension has been added and stages 2 and 3 have been combined in JNC VII report. Patients with prehypertension are at increased risk for progression to hypertension .Those in the 130/80 to 139/89 mm Hg BP range are at twice the risk to develop hypertension as those with lower values.

Frequency

Internationally -

Overall, approximately 20% [3,8] of the world's adults are estimated to have hypertension. The 20% prevalence is for hypertension defined as blood pressure in excess of 140/90 mmHg. The prevalence dramatically increases in patients older than 60 years. The prevalence of hypertension in young adults is about 5% , in the age group between 50 & 55 years it is about 10-20%[1,2,8] and in the age group between 55-60, the prevalence is about 20-30%.

The highest incidence of hypertension will be between the group 60-65yrs in which the prevalence of hypertension is about 30-40%[2,8].

Incidence of hypertension in India

3.80% to 15.63% in men and 2% to 15.38% in women in the urban areas and from 1.57% to 6.93% in men and 2.38% to 8.81% in women in rural areas[7] are found to be hypertensive in India.

According to the sex incidence both the sexes are equally affected, but few books mention that males are affected more up to the age of 50yrs,and females are affected more after age of 50 yrs.

Genetic Considerations

Although specific genetic variants have been identified in rare Mendelian forms of hypertension, these variants are not applicable to the vast majority (>98%) of patients with essential hypertension[23]. Blood pressure levels reflect the contributions of many susceptibility genes interacting with each other and with the environment. Essential hypertension is a polygenic disorder, and different patients may carry different subsets of genes that lead to elevated blood pressure and to different phenotypes associated with hypertension. Eg: Obesity, dyslipidemia, insulin resistance.

Current evidence suggests that genes encoding components of the renin-angiotensin-aldosterone system, and angiotensinogen and angiotensin converting enzyme polymorphisms, may be related to hypertension and to blood pressure sensitivity to dietary sodiumchloride. The alpha-adducin gene is also thought to be associated with increased renal tubular absorption of sodium, and variants of this gene may also be associated with hypertension and salt sensitivity of blood pressure.

Other genes possibly related to hypertension include genes encoding the AT_1 receptor, aldosterone synthase, and the $Beta_2$-adrenoreceptor. Preliminary evidence suggests that there may also be genetic determinants of target organ damage attributed to hypertension[23]. Family studies indicate significant heritability of left ventricular mass, and there is considerable individual variation in the responses of the heart to hypertension. Family studies and variations in candidate genes associated with renal damage suggest that genetic factors may also contribute to hypertensive nephropathy[23].

PROTEIN HANDLING IN NORMAL KIDNEY

Normal barriers to protein filtration begins in the glomerulus. The normal glomerular endothelial cells forms a barrier and holds back cells and other particles. They are penetrated by large pores of 100nm called fenestrae that can be easily traversed by proteins. The glomerular basement traps most large proteins (>100Kda), while the foot process of epithelial cells (podocytes) cover the urinary side of the glomerular basement membrane and produce a series of narrow channels (slit diaphragm) to allow passage of small solutes and water. These slit diaphragm bridges the slits between the foot process of the glomerular basement membrane[24]. The visceral epithelial cells are covered with negatively charged heparan sulfate proteoglycans[25]. This negative charge and size selectivity of glomerular basement membrane impedes the passage of anion molecules such as albumin, globulin and large molecular weight protein across the glomerular wall. The smaller proteins that are filtered across the glomerular basement membrane are largely reabsorbed at the proximal tubule and only small amount are excreted.

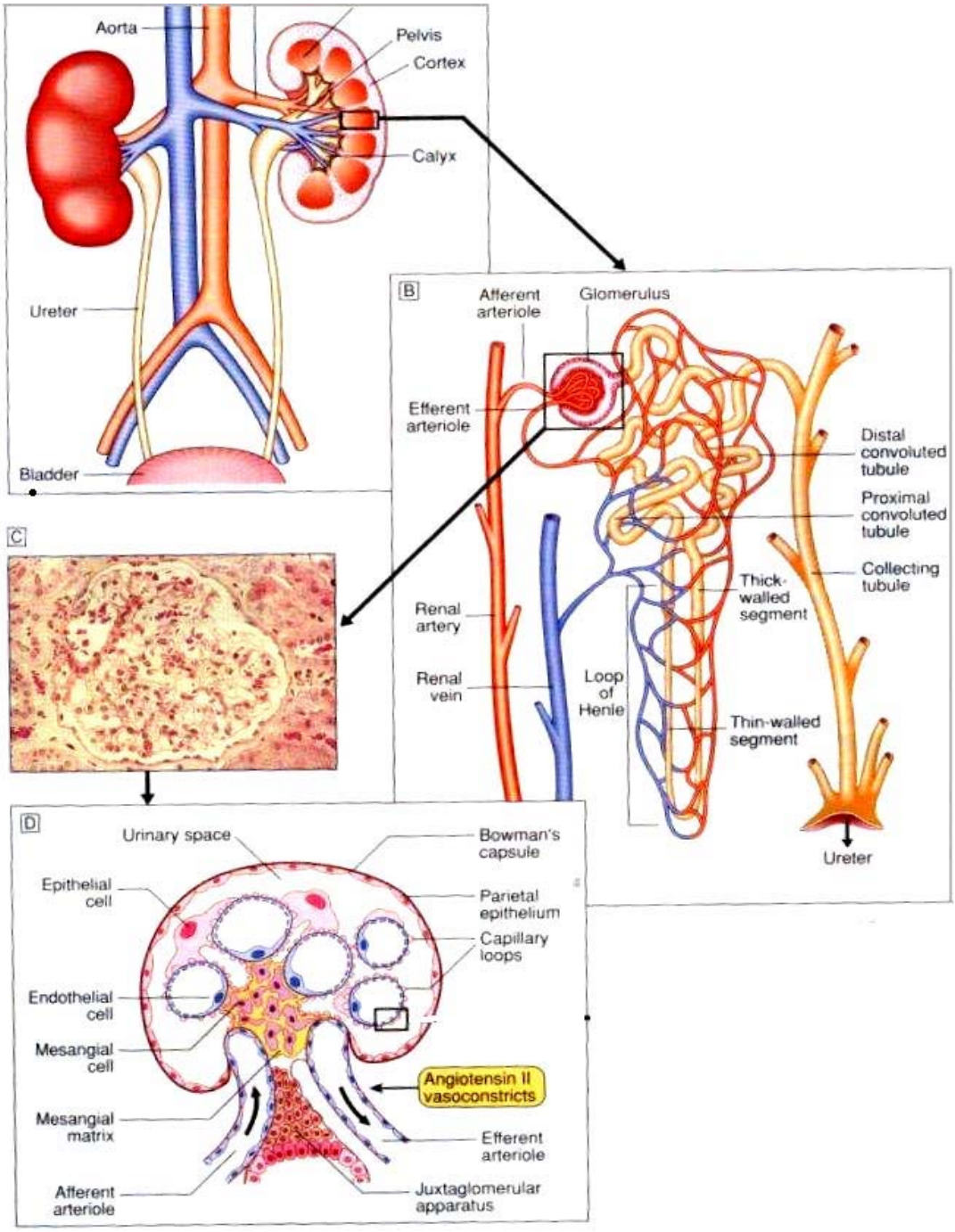


Fig.1 FUNCTIONAL ANATOMY OF KIDNEY

A: Anatomical relations of kidney **B: Single nephron**

C: Histology of normal glomerulus **D: Cross section of glomerulus**

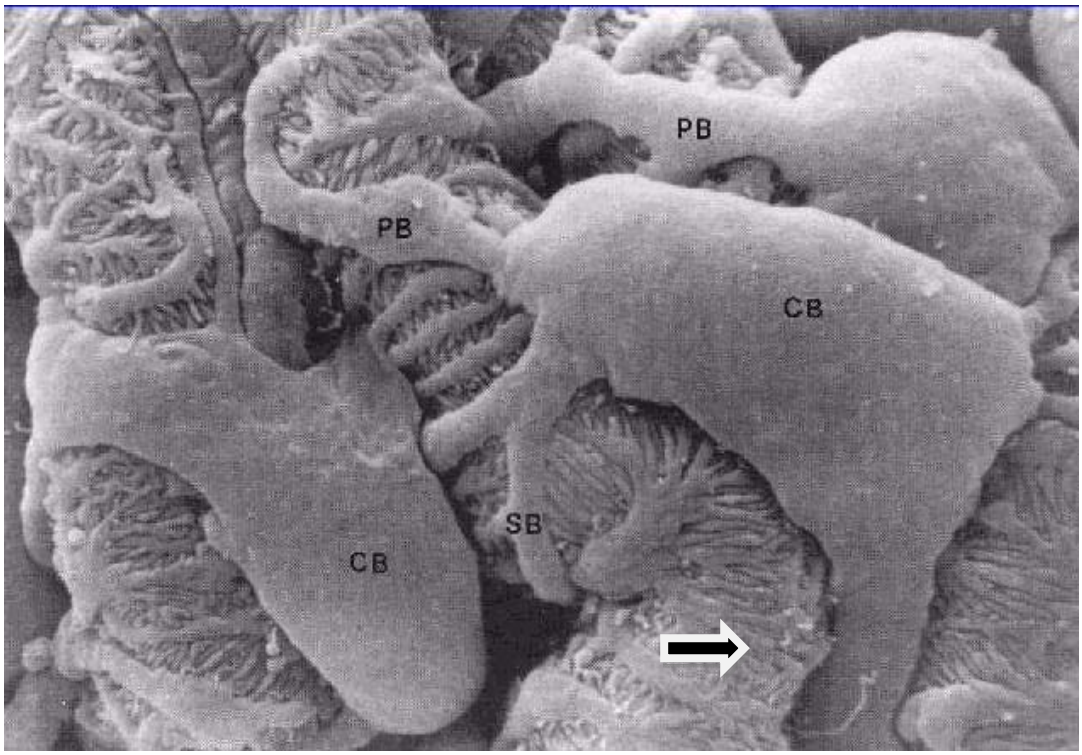


Fig.2. ELECTRON MICROSCOPY OF GLOMERULAR BASEMENT MEMBRANE

CB = capillary bed (tufts), Arrow = podocytes with fenestration slits

PATHOPHYSIOLOGICAL CLASSIFICATION OF PROTEINURIA

A) BENIGN

1. Postural Orthostatic proteinuria
2. Functional
3. Transient
4. Intermittent

B) PATHOLOGICAL

1. Glomerular
2. Tubular
3. Overflow
4. Secretory

A) BENIGN PROTEINURIA

This is a transient proteinuria that occurs with normal renal function, bland urinary sediment, normal blood pressure and without any significant edema.24 hour urine albumin is usually less than 1 gram. They do not indicate any significant renal disease and disappears on repeated testing.

1) Postural /Orthostatic Proteinuria

This is seen in 3 to 5% of adolescents, especially in young males. It is characterized by increased protein excretion in the upright position and normal protein excretion during recumbency[26]. It is diagnosed by split urine protein excretion examination. In orthostatic proteinuria, the day time specimen typically has an increased concentration of protein, with night time specimen having a normal concentration usually less than 50 mg over eight hours[27]. In true glomerular disease there is reduced protein excretion in the supine position but it will not return to normal as with orthostatic proteinuria. Springberg found that long term prognosis of orthostatic proteinuria is benign in virtually all cases over many decades[28] . Data on renal biopsies on orthostatic proteinuria are confusing. Some showed minor glomerular changes[29]. Posture affects urinary protein excretion, probably via an increase in glomerular capillary hydrostatic pressure and for change in permeability of the glomerular capillary walls[31]. An alternate explanation is entrapment of renal veins[31,32]

2) **Functional Proteinuria**

It is a benign proteinuria due to changes in glomerular ultra filtration pressure and/or membrane permeability. It is seen in fever, exercise, cardiac failure, emotional stress and acute illness. It is usually less than 0.5 gm/day but may be as

heavy as 5.0 gm/day (following marathon running). It disappears with the resolution of causative disorder[33].

Kallmeyer et al found that recent exercise can induce several gram of protein per litre of urine, sometimes together with haematuria and even casts so called jogger's nephritis[34]. Post exercise proteinuria is about 15 to 20 times the resting range of proteinuria and require about 4 hours to regain resting value in the recovery period[35]. Poortmans et al found that proteinuria was influenced mostly by the intensity of exercise rather than its duration[36].

3) Idiopathic Proteinuria

This is seen in young healthy adults. This dipstick positive proteinuria disappears spontaneously by next clinical visit.

4) Intermittent Proteinuria

This benign proteinuria is found in half of their different urine samples in absence of other renal or systemic abnormalities.

B) PATHOLOGICAL PROTEINURIA

This is persistent proteinuria that is detected on multiple ambulatory clinical visits. This is seen in both recumbent and upright position and usually signals a structural renal disease.

1) Glomerular Proteinuria

It is the most common cause of proteinuria in clinical practice. It is characterized by a disproportionate amount of albumin in urine[37]. Due to preservation of selectivity and large concentration of albumin in blood glomerular proteinuria is 85 to 90 % albumin, accompanied by pre-albumin, transferrin and

relatively low molecular weight proteins since it contains mostly albumin. They are readily detected by stick or turbidometric methods. Glomerular proteinuria ranges from few hundred mg per 24 hours to 100 gms per 24 hours. McConnell et al on evaluation of proteinuria found that urinary excretion of more than 2 gm per 24 hours is usually a result of glomerular disease[38]. In glomerular proteinuria there is increased glomerular capillary permeability to high molecular weight anionic plasma proteins. How the glomerular barrier is damaged so that it leaks more than normal remains unclear [39] . This may be due to :

-Loss of fixed anionic charge (Congenital nephrotic syndrome, minimal change nephropathy)

- Detachment of epithelial podocytes from basement membrane[40].
- Immune aggregates.
- Increase in glomerular capillary pressure.

The filtered protein, that reach the tubules overwhelm the limited capacity of tubular reabsorption and cause these proteins to appear in urine. Glomerular disease is classified as primary when the pathology is confined to the kidney and secondary when it is a part of multi system disorder.

Glomerular proteinuria is of two types:

a) Selective Proteinuria

b) Nonselective Proteinuria

In selective proteinuria the clearance ratio of immunoglobulin to albumin or transferrin is less than 0.10(<10%).In nonselective proteinuria the clearance ratio of immunoglobulin to albumin or transferrin is more than 0.50(>50%).

GLOMERULAR PROTEINURIA -CAUSES

Primary Glomerulonephropathy :

- Minimal change disease
- Focal segmental glomerulonephritis
- Idiopathic membranous glomerulonephritis
- Membranoproliferative glomerulonephritis
- IgA nephropathy

Secondary Glomerulonephropathy :

- Diabetes mellitus
- Amylodosis
- Collagen vascular disease (Eg-Lupus nephritis)
- Infections
- HIV
- Hepatitis B and C infection
- Post streptococcal
- Syphilis
- Malaria
- Infective Endocarditis
- Drugs
- NSAIDS
- Penicillamine
- Lithium
- Heroin
- Heavy metals
- Gastrointestinal and lung cancers
- Lymphoma

2) TUBULAR PROTEINURIA

Proteinuria results from the damage of proximal tubule so that normally reabsorbed protein, principally of low molecular weight pass into the urine .This usually occurs as part of the fanconi syndrome of proximal tubular dysfunction. Tubular proteinuria usually does not exceed 2gm per day [41,42]. Beta 2-microglobulin is one of the many micro globulin which make up tubular proteinuria. Normal level of Beta 2-microglobulin in urine is less than 0.4 mcg/L. It can be assessed by RIA or ELISA. The urinary albumin and Beta 2-microglobulin ratio of 10 to 1 suggests the presence of Beta 2-microglobulin. Further measurement of Beta 2 lysozyme may help in distinguishing type of urinary tract infection besides diagnosis of heavy metal poisoning[43,44].Urinary protein electrophoresis and/or immuno electrophoresis may aid in distinguishing tubular and glomerular proteinuria.

TUBULAR PROTEINURIA – CAUSES

-Hypertensive nephrosclerosis

-Tubulo intestinal diseases

-Fanconi syndrome

-Heavy metals

-Uric acid nephropathy

-Acute hypersensitivity

-Interstitial nephritis

-Sickle cell disease

-Drugs (NSAID, antibiotics)

3) OVERFLOW PROTEINURIA

It is due to filtration by normal glomerulus of an abnormally large amount of low molecular weight proteins, which exceeds the capacity of the normal tubules for reabsorption. It is characterized by the presence of abnormal peak or spike on urinary electrophoresis. Most often, this is a result of the immunoglobulin over production that occurs in multiple myeloma. The resultant light change immunoglobulin fragments (bence jones proteins) produce a monoclonal spike in the urine electrophresis.[45,46]

OVERFLOW PROTEINURIA – CAUSES

-Multiple myeloma

-Myoglobinuria

-Rhabdomyolysis

-Lymphoproliferative disorders

4) SECRETORY PROTEINURIA

It occurs due to secretion of proteins into the urine after glomerular filtration. About 20 to 30 mg/24 hours of non plasma protein is contributed by renal tubules and lower urinary tract**.** Mostly they are formed by Tamm-Horsfall proteins[28]. Some secretary IgA is added by lower urinary track including the urethral glands together with trace quantity of protein of prostatic or seminal vesicular organ [47,48]. Tamm-Horsfall protein is secreted by the ascending thick limb and early distal convoluted tubule into the tubular fluid. It is an easily polymerized glycoprotein . They form the major constituent of renal tubular casts[49], along with albumin and traces of many plasma proteins, including immunoglobulins[50]. In myeloma, casts contain paraproteins polymerized with Tamm-Horsfall protein, and may show a micro fibrillar structure that will stain positive with congo red, even though no amyloid is present in renal tissue.

DEGREE OF PROTEINURIA AND CAUSES [51]

(According to daily protein excretion)

Causes -

0.15 – 2.0 gm

Mild glomerulopathies

Tubular proteinuria

Overflow proteinuria

2.0 –3.5 gm

Usually glomerular

>3.5 gm

Always glomerular

HYPERTENSION NEPHROPATHY

Numerous trials in cardiovascular medicine have focused attention on the clinical significance of the rate of UAE as an early and powerful predictor of systemic vascular diseases. Both systemic and renal endothelial beds are subject to oxidant stress, inflammation, and hemodynamic injury, a measurable response (elevated UAE) is detectable in the renal microcirculation years before the emergence of systemic disease and/or adverse events in other vascular beds. The strong correlation between UAE and cardiovascular risk, and the parallel improvements noted in both with pharmacologic therapy, support the emerging concept of the renal circulation as an early detection site for endothelial injury and an integrated marker of cardiovascular risk[52].

The atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect the preglomerular arterioles, resulting in ischemic changes in the

glomeruli and postglomerular structures. Glomerular injury may also be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft[53].

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio > 300 mg/l) or microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/l) are early markers of renal injury. These are also risk factors for renal disease progression and for cardiovascular disease.

Arteriolar nephrosclerosis is seen in patients who are hypertensive (BP > 150/90 mmHg) for an extended period of time but whose hypertension has not progressed to a malignant form . Such patients, usually in the older age group, are often discovered to be hypertensive on routine physical examination or as a result of nonspecific symptomatology (e.g., headaches, weakness, palpitations).

The characteristic pathology is in the afferent arterioles, which have thickened walls due to deposition of homogeneous eosinophilic material (hyaline arteriolosclerosis), narrowing of vascular lumina results, with consequent ischemic injury to glomeruli and tubules. Physical examination may reveal changes in retinal vessels (arteriolar narrowing and/or flame shaped haemorrhages), cardiac muscle hypertrophy and possibly signs of congestive heart failure[52]. Renal disease may manifest as a mild to moderate elevation of serum creatinine concentration, microalbuminuria or proteinuria.

HYPERTENSIVE NEPHROSCLEROSIS

Uncontrolled systemic hypertension causes permanent damage to the kidneys in about 6% of patients with elevated blood pressure. As many as 27% of patients with end-stage kidney disease have hypertension as a primary cause[54]. Although there is not a clear correlation between the extent or duration of hypertension and the risk of end-organ damage, hypertensive nephrosclerosis is fivefold more frequent in African Americans than Caucasians.

Associated risk factors for progression to end-stage kidney disease include age, sex, race, smoking, hypercholesterolemia, duration of hypertension, low birth weight, and pre-existing renal injury. Kidney biopsies in patients with hypertension, microhematuria, and moderate proteinuria demonstrate arteriolosclerosis, chronic nephrosclerosis, and interstitial fibrosis in the absence of immune deposits. Today, based on a careful history, physical examination, urinalysis, and some serologic testing, the diagnosis of chronic nephrosclerosis is usually inferred without a biopsy. Treating hypertension is the best way to avoid progressive renal failure; most guidelines recommend lowering blood pressure to <130/80 mmHg if there is preexisting diabetes or kidney disease. In the presence of kidney disease, most patients begin therapy with two drugs, classically a thiazide diuretic and an ACE inhibitor; many will require three drugs. There is strong evidence in African Americans with hypertensive nephrosclerosis that therapy initiated with an ACE inhibitor can slow the rate of decline in renal function independent of systemic blood pressure[54]. Patients with lower levels of hypertension are usually started on a thiazide diuretic or an ACE inhibitor alone. Malignant acceleration of hypertension can complicate the course of chronic nephrosclerosis, particularly in the setting of

scleroderma or cocaine use. The hemodynamic stress of malignant hypertension causes fibrinoid necrosis of small blood vessels, thrombotic microangiography, a nephritic urinalysis, and acute renal failure. In the setting of renal failure, chest pain, or papilledema, the condition is treated as a hypertensive emergency[54]. Slightly lowering the blood pressure often produces an immediate reduction in glomerular filtration rate that improves, as the vascular injury attenuates and autoregulation of blood vessel tone is restored.

In contrast to the systemic endothelial bed in which early atherosclerotic injury is undetectable, the high volume of fluid filtered across the glomerular endothelium (140–180 litres/day) markedly amplifies the functional consequence (increased albumin filtration) of early endothelial (and podocyte) injury in the glomerulus. The emergence of microalbuminuria thus unmasks systemic endothelial injury likely occurring simultaneously in other vascular beds, progressing silently to overt disease years later[54].

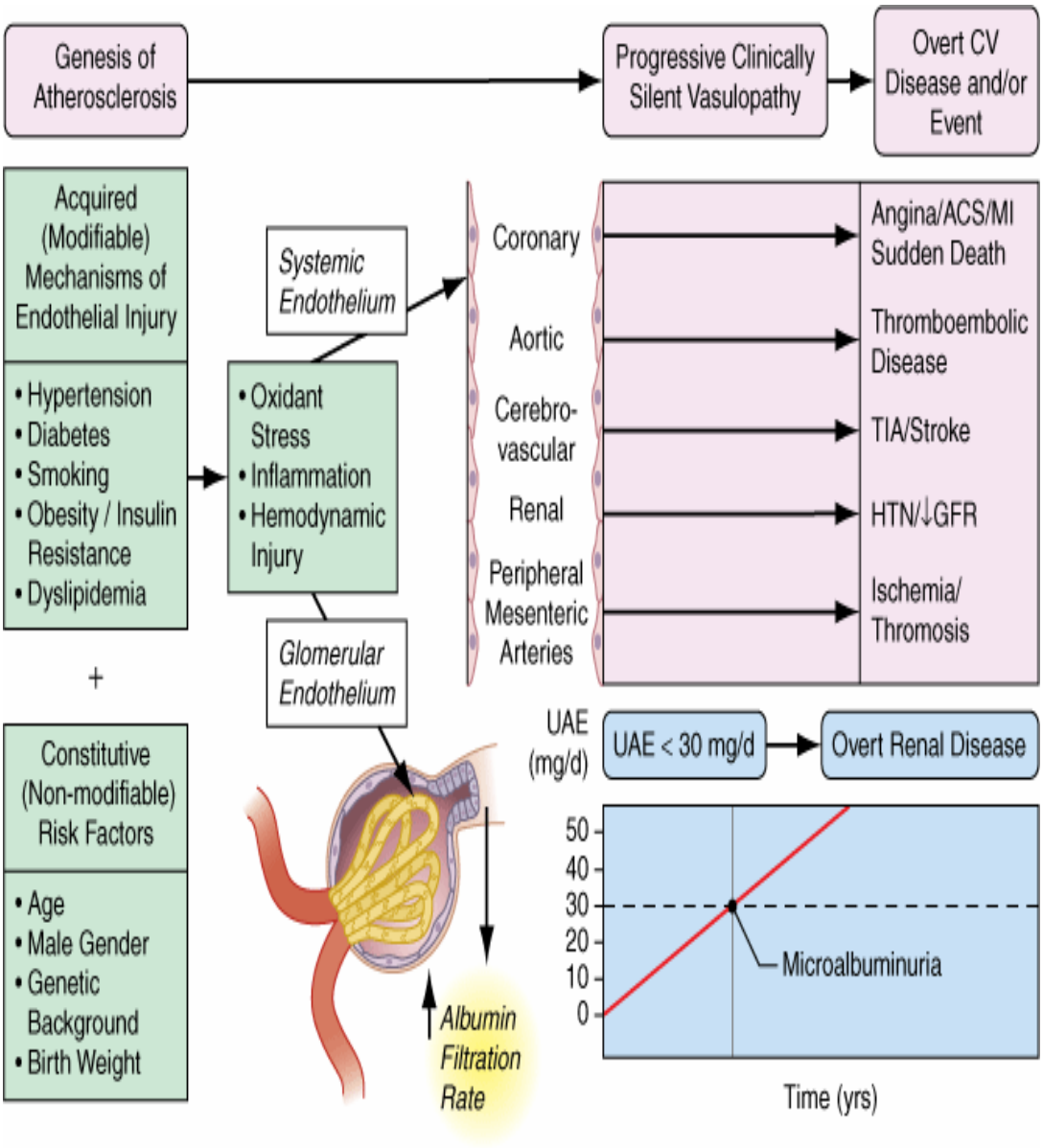


Fig 3.1. RISK FACTORS & PATHOPHYSIOLOGY OF MICROALBUMINURIA

CV= cardiovascular; ACS = acute coronary syndrome; MI= myocardial infarction; TIA= transient ischemic attack; HTN= hypertension; GFR= glomerular filtration rate; UAE= urinary albumin excretion.

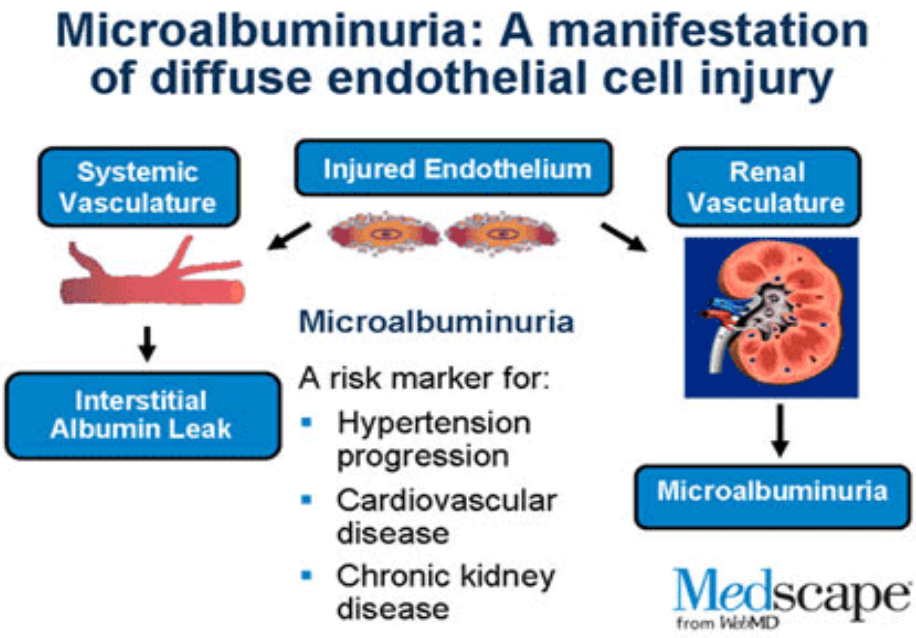


Fig.3.2. PATHOPHYSIOLOGY OF MICROALBUMINURIA

Currently, the pathophysiological mechanisms leading to the development of microalbuminuria are not fully understood. This may be the result of altered intrarenal hemodynamics and may represent as in insulin-dependent diabetes mellitus, an early feature of renal impairment, or it may be simply a marker of capillary leakiness at the glomerular level and thus reflect generalized atherosclerotic vascular damage. The latter hypothesis is supported by several epidemiological studies that show an association between microalbuminuria and increased morbidity and mortality, especially that caused by cardiovascular disease independently of other risk factors. Recently, interest in the study of microalbuminuria has grown because it may represent a useful and relatively inexpensive clinical tool for the identification of hypertensive patients at higher risk for cardiovascular damage.

AIMS AND OBJECTIVES

To detect prevalence of microalbuminuria in essential hypertension & its relation to severity of hypertension, duration of hypertension, body mass index, age & target organ damage such as hypertension retinopathy & acute coronary syndrome.

REVIEW OF LITERATURE

Microalbuminuria

Microalbuminuria or dipstick negative albuminuria is conventionally defined as urinary albumin excretion between 30-300 mg/24 hour for timed 24 hours urine collections and between 20-200 mg/L for untimed samples[55.] High normal albuminuria is defined as morning urinary albumin concentration upto 30 mg/l. Low-normal albuminuria is morning urinary albumin concentration of less than 10 mg/l.

Normoalbuminuria = < 30 mcg/min .

Microalbuminuria (Incipient nephropathy) = 30 – 300 mcg/min .

Macroalbuminuria (Clinical nephropathy/ Overt nephropathy) > 300 mcg/min .

Mechanism of microalbuminuria

The intimate relationship between low-level albumin excretion and vascular permeability makes urinary albumin excretion highly sensitive to the presence of any inflammatory processes. Pathophysiological processes associated with microalbuminuria :

Local process

1. Increased intraglomerular capillary pressure
2. Increased shunting of albumin through glomerular membrane pores

Systemic process

1. Activation of inflammatory mediators
2. Increased transcapillary escape rate of albumin
3. Vascular endothelial dysfunction

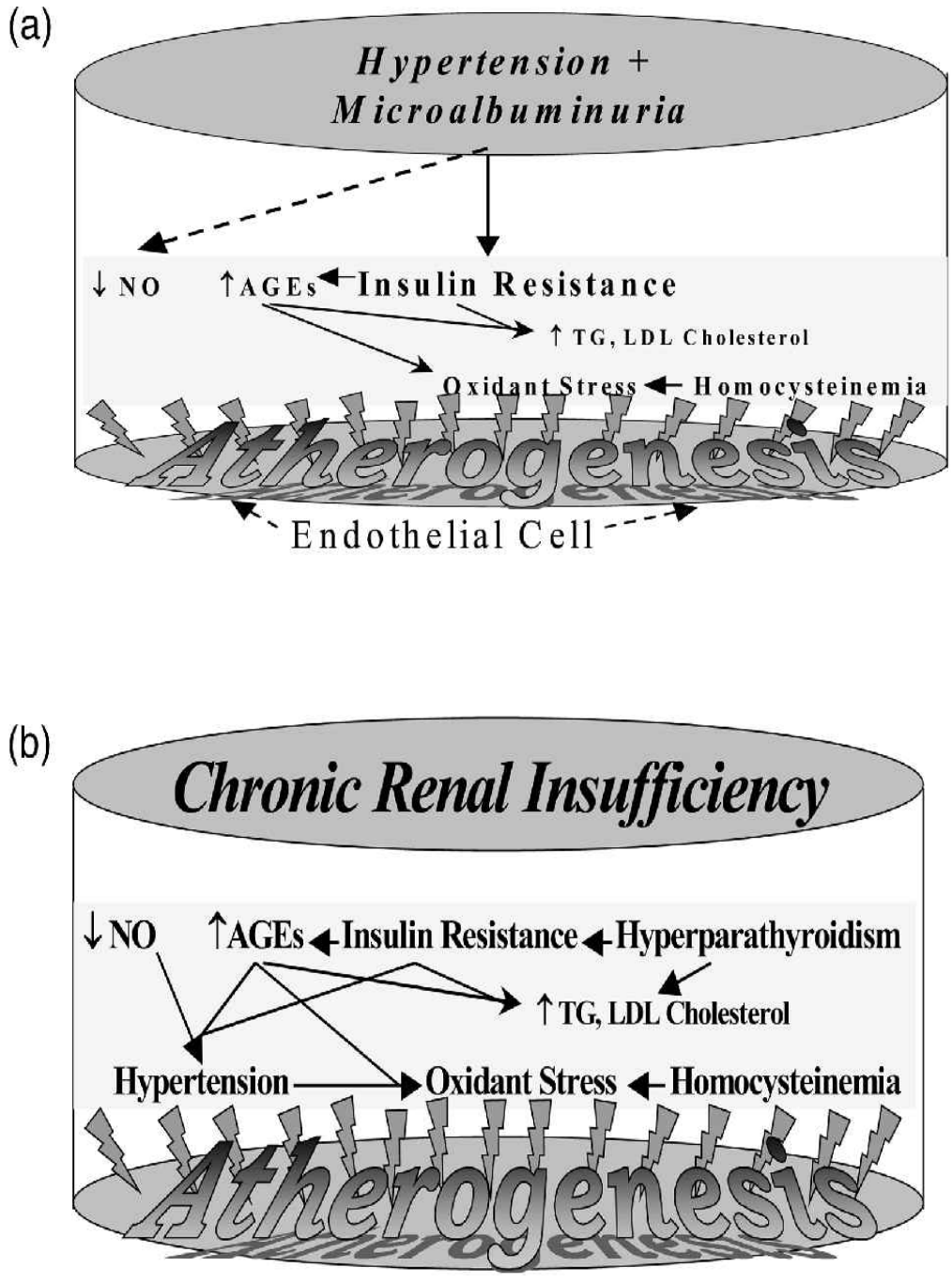


FIG.4. HTN LEADING TO KIDNEY DISEASE & ATHEROSCLEROSIS

(AGE = glycated end products)

The kidney is ideally placed to amplify any small changes in the systemic vascular permeability. The glomeruli receive 25% of the cardiac output. Of the 70 kg of albumin that pass through the kidneys every 24 hours, less than 0.01% reaches the glomerular ultra filtrate (i.e less than 7g/24 hour) and hence enters the renal tubules.

Almost all the filtered albumin is absorbed by the proximal tubule via a high affinity, low capacity endocytotic mechanism, with only 10-30 mg/24 hr appearing in the urine. Assuming that 7 gm of albumin is filtered every 24 hour, 1% increase in systemic vascular permeability in response to an inflammatory stimulus would result in an additional 70 mg of albumin passing into the filtrate. Since tubular mechanisms for albumin reabsorption are near saturation, urinary albumin excretion would increase from a maximum of 30 to approximately 100 mg/24 hour[56] Glomerular permeability to albumin is dependent on endothelial charge selectivity as well as size selectivity. The negative charge conferred on the glomerular memrane by its consistent glycoprotein plays a role in restricting the permeability of anionic proteins. Loss of glomerular charge selectivity has been found in both diabetic and non-diabetic population with microalbuminuria[57].Other possible mechanisms of microalbuminuria include the following :

1. Systemic transvascular albumin leakage: TERalb is defined as the fraction of the intravascular mass of albumin going through the vascular bed per unit time. The transcapillary escape rate of albumin is an overall measure of macromolecular permeability of the vascular bed in vivo. As microalbuminuria reflects systemic transvascular leakiness for albumin, which may also allow for a higher degree of lipid insudation into the large vessel wall, this may link microalbuminuria to atherogenesis.[58]

2. Role of sialic acid: Sialic acid has been reported to affect several haematological factors, transvascular permeability and accumulation of lipid in the arterial wall. Studies showed that in subjects without diabetes mellitus, an elevated serum concentration of sialic acid is predictive of atherosclerotic vascular disease in presence of concomitant elevation of urinary albumin excretion.[58]

3. Impaired arterial dilatory capacity: Slightly elevated urinary albumin excretion is associated with impaired conduit arterial dilatory capacity in clinically healthy subjects, and this impairment may be explained by a reduced dilatory response to nitric oxide of both endogenous and exogenous origin. Impaired arterial dilatory capacity may contribute to the increased cardiovascular risk in subjects with elevated urinary albumin excretion.[59]

4. Elevated Von Willebrand Factor concentrations and other prothrombotic factors: Studies showed that prothrombotic factors like fibrinogen and factor VII C, von willebrand factor antigen are elevated in patients with type 1 diabetes complicated by microalbuminuria, so also in hypertensive patients. These were considered a potential markers of endothelial dysfunction.[60,61]

5. Hyperinsulinaemia: In vitro insulin has been shown to cause smooth muscle cell proliferation. It stimulates LDL binding to smooth muscle cells, fibroblasts and monocytes and stimulate cholesterol synthesis in monocytes[62] Hyperinsulinaemia and microalbuminuria are components of metabolic syndrome and are associated with a highly abnormal cardiovascular risk factor pattern.

6. Hyperhomocysteinaemia: The enhanced risk of cardiovascular and cerebrovascular disease with microalbuminuria may also be due in part to an association with hyperhomocysteinemia, a risk factor for atherosclerosis.[63]

SIGNIFICANCE OF MICROALBUMINURIA

Microalbuminuria signifies abnormal vascular permeability and its presence may be considered as kidney's notice for markedly enhanced cardiovascular risk[64] The importance of microalbuminuria was first appreciated in the early 1980s when two landmark studies in London and Denmark independently reported that it was predictive of development of overt diabetic nephropathy and progressive renal failure[65,66].Since then, various studies have established the significance of microalbuminuria in several conditions :

1. Several studies have shown that microalbuminuria in diabetic patients predicts diabetic nephropathy as well as increased cardiovascular and overall mortality[67.] Persistent microalbuminuria in these patients also correlates with the presence of hypertension, obesity and dyslipidemia[68] .American Diabetes Association has adopted cut off values for diagnosis of diabetic nephropathy[69] .In 1998, ADA included positive microalbuminuria as the risk factor for coronary artery disease in diabetic subjects[70 .]

2. Studies have shown that the prevalence of microalbuminuria is enhanced in hypertensive subjects, in particular in those with blood pressure characteristics that are associated with enhanced cardiovascular risk, such as salt sensitivity and an abnormal diurnal blood pressure rhythm.Microalbuminuria possibly identifies at an early stage, hypertensive patients with an enhanced risk of developing the well-known renal and cardio vascular hypertensive complications[71] .

3.Studies have documented the relationship between the presence of microalbuminuria and other atherosclerotic risk factors such as hypertension, dyslipidaemia and smoking in the general population. Studies have revealed the

significance of microalbuminuria as predictor of increased mortality in elderly persons[72].

4. Microalbuminuria is detected early in the course of acute myocardial infarction and is considered as an independent predictor of early mortality in this condition. Microalbuminuria has been found to be proportional to the size of the infarct. Gosling et al suggested that early rise in urinary albumin concentration is useful in distinguishing myocardial infarct from angina[73]. Spyridon K et al found that microalbuminuria is a strong independent predictor of 3 year adverse prognosis in patients who has sustained acute myocardial infarction[74].

5. Roine et al demonstrated that microalbuminuria distinguished bacterial meningitis from aseptic meningitis with specificity of 94%[75].

6. Shearman et al found that microalbuminuria peaked 36 hours after admission in patients with acute pancreatitis and that serious complications developed later, only in those with the higher values of microalbuminuria[76].

7. Pallister et al found that microalbuminuria levels 8 hours after admission in trauma victims predicted the development of acute respiratory distress syndrome with a positive predictive value of 85% and a negative predictive value of 95%[77].

8. Microalbuminuria has been found to be associated with wide variety of inflammatory conditions like rheumatoid arthritis, inflammatory bowel disorder, and surgery etc[78,79].

9. Highly significant association between microalbuminuria and carotid artery intima-media thickness has been reported a finding which suggests that microalbuminuria may be a marker for early development of carotid artery atherosclerosis and points to a possible linkage between microalbuminuria and atherothrombotic stroke

mechanism[80].Microalbuminuria is unlikely to be a marker for susceptibility to the development of clinical nephropathy but it is more likely to be a sign of early disease.

Microalbuminuria the fifth pillar of Syndrome X:

Reavon in a seminar article has proposed that insulin resistance/ hyperinsulinemia forms the common denominator between conventional cardiovascular risk factors and the development of atherosclerosis[81].

Thus individual risk factors such as hypertension, obesity, hyperlipidemia and glucose intolerance, which commonly aggregate simply represent the "rainbow colors" of a clinical syndrome characterised by an underlying state of insulin resistance and a devastating cardiovascular outcome in which Reavon referred to collectively as Syndrome X[81]. Interestingly there is now evidence to promote microalbuminuria as a distinct and independent facet of this disorder. Investigating the influence of microalbuminuria and hypertension on insulin resistance in NIDDM patients. Group et al reported that glucose metabolism, as measured during insulin clamp technique was impaired in normotensive NIDDM patients with microalbuminuria compared with normotensive normoalbuminuric patients[81]. The defect in insulin action was shown to correlate with urinary albumin excretion. Furthermore, diabetic subjects with a combination of hypertension and microalbuminuria had a greater reduction in insulin-mediated glucose disposal and widespread disturbances in lipid metabolism. Perhaps the most surprising finding of these studies was the observation that insulin stimulated glucose disposal was remarkably normal in normotensive NIDDM patients who did not have microalbuminuria. A similar conclusion has also been reached by Nosadini and Zambon et al who showed that insulin sensitivity was not compromised in healthy NIDDM patients unless either microalbuminuria or hypertension or both existed[81].

Thus, the association between insulin resistance and microalbuminuria in NIDDM as revealed by the findings of these studies raises the interesting question of whether the two phenomena might in some way be causally related. However, the presence of microalbuminuria in NIDDM has not been marked by a reduction in insulin sensitivity in all of the studies thus far reported. For the present, therefore the mechanism relating insulin resistance/hyperinsulinemia to albuminuria remains largely speculative[82,83]. Finally, two recent reports have shed further insight into the significance of microalbuminuria in NIDDM. Haffner et al in a cross-sectional study and Mykannen et al in a prospective study have reported that microalbuminuria in non-diabetic individuals may precede and even predict the onset of NIDDM[84]. Moreover, microalbuminuric subjects who remained glucose tolerant after 3.5 years of follow-up still demonstrated multiple cardiovascular abnormalities, including elevated blood pressure, high triglycerides concentration, high insulin concentration, and low high density lipoprotein cholesterol concentration i.e. a cardiovascular risk profile akin to that observed in prediabetic individuals. Microalbuminuria may be regarded as a prominent feature of the prediabetic state. The above findings therefore provide probably the most damaging evidence against microalbuminuria as a serious phenomenon in the evolution of NIDDM and atherosclerotic disease [84,85]

Reducing Intraglomerular Hypertension and Proteinuria

Increased intraglomerular filtration pressures and glomerular hypertrophy develop as a response to loss of nephron number from different kidney diseases. This response is maladaptive, as it promotes the ongoing decline of kidney function even if the inciting process has been treated or spontaneously resolved. Control of systemic and glomerular hypertension is at least as important as dietary protein restriction in

slowing the progression of CKD. Therefore, in addition to reduction of cardiovascular disease risk, antihypertensive therapy in patients with CKD also aims to slow the progression of nephron injury by reducing intraglomerular hypertension[86]. Elevated blood pressure increases proteinuria through its transmission to the glomerulus. Conversely, the renoprotective effect of antihypertensive medications is gauged through the consequent reduction of proteinuria. Thus, the more effective a given treatment is in lowering protein excretion the greater the subsequent impact on protection from decline in GFR. This observation is the basis for the treatment guideline establishing 125/75 mmHg as the target blood pressure in proteinuric CKD patients[86].

ACE inhibitors and ARB's inhibit the angiotensin-induced vasoconstriction of the efferent arterioles of the glomerular microcirculation. This inhibition leads to a reduction in both intraglomerular filtration pressure and proteinuria. Several controlled studies have shown that these drugs are effective in slowing the progression of renal failure in patients with both diabetic and non diabetic renal failure. This slowing in progression of CKD is strongly associated with their proteinuria-lowering effect[86].

In the absence of an anti-proteinuric response with either agent alone, combined treatment with both ACE inhibitors and ARB's can be tried. Adverse effects from these agents include cough and angioedema with ACE inhibitors, anaphylaxis and hyperkalemia with either class. A progressive increase in plasma creatinine concentration may suggest the presence of renovascular disease within the large or small arteries. Development of these side effects may mandate the use of second-line antihypertensive agents instead of the ACE inhibitors or ARB's. Among

the calcium channel blockers, diltiazem and verapamil may exhibit superior anti-proteinuric and renoprotective effects compared to the dihydropyridines. At least two different categories of response can be considered: one in which progression is strongly associated with systemic and intraglomerular hypertension and proteinuria (e.g., diabetic nephropathy, glomerular diseases) and in which ACE inhibitors and ARB's are likely to be the first choice and another in which proteinuria is mild or absent initially (e.g., adult polycystic kidneydisease and other tubulointerstitial diseases) and hence the contribution of intraglomerular hypertension less prominent, for which reason other antihypertensive agents can be useful for control of systemic hypertension[86].

Control of Blood Pressure and Proteinuria

Hypertension is found in the majority of type 2 diabetic patients at diagnosis. This finding correlates with the presence of albuminuria and is a strong predictor of cardiovascular events and nephropathy. Microalbuminuria, the finding of albumin in the urine not detectable by the urine dipstick precedes the decline in GFR and heralds renal and cardiovascular complications. Testing for microalbumin is recommended in all diabetic patients & hypertensive patients at least annually. If the patient already has established proteinuria, then testing for microalbumin is not necessary. Antihypertensive treatment reduces albuminuria and diminishes its progression even in normotensive diabetic patients. In addition to treatment of hypertension in general, the use of ACE inhibitors and ARB's in particular is associated with additional renoprotection[86]. These salutary effects are mediated by reducing Intraglomerular pressure and inhibition of angiotensin-driven sclerosing pathways.

TESTS FOR ALBUMINURIA

In 1963, Keen and Chlouveraskis described the first specific RIA for albumin in urine[87]. Since then several methods have been described for measurement of urinary albumin excretion with emphasis on unexpensive, easy to apply, rapid tests which can be used on a large scale population. The various methods used are :

1. Dipstick method.

2. Semi quantitative method.

   - Chemical precipitation (Sulphosalicyclic acid trichloroacetic acid)
   - Immuno precipitation (Micral Test).

3. Photometric method, Immunoturbidimetric assay

4. Nephelometric method.

5. Sensitive Quantitative methods

   - Radio immuno assay.
   - Cellulose acetate, agarose gel electrophoresis.

The procedures of various important methods include the following:

1. **Dipstick method**: Chemically impregnated dipstick contains methyl red and bromophenol blue with buffering salts. The later dissolve on contact with urine and protein in the urine lowers the pH turning it green. It was traditionally known to detect albuminuria >300 mg/L and hence not advocated for screening for microalbuminuria. But, in a study by Alfredo Pegoraro et al, they found that the combination of sulfosalicylic acid testing and chemstrips was as good as and less expensive than micral-test in ruling out microalbuminuria[85].

2. **Chemical precipitation (Sulphosalicylic acid test)**: 5 drops of 20% sulphosalicylic acid is added to 3 ml of urine in one test tube. This test tube is compared with test tube of untreated urine held against a dark background, immediately and turbidity is taken to indicate proteinuria[89].

3. **Immunoprecipitation (Micral test)**: It is based on color shift of monoclonal antibody to human albumin labelled with gold. Here gold labelled optically read Immuno assay detects microalbuminuria. A specimen of the urine sample passes via the wick fleece into the conjugate fleece. Any albumin present in the urine binds itself specifically to the gold labelled antibodies. Excess antibodies are bound by immobilized albumin in the capture matrix. Only antibodies bound to albumin from the urine sample can pass through the capture matrix. These gold-labelled antibodies flow to the detection pad and turn it red. Test is performed on early morning random urine sample by immersing the strip for 5 sec and reading the result at 2 min, visually comparing with color blocks on vial (0 mg/l, 20mg/l, 50 mg/l and 100 mg/l albumin).[89]

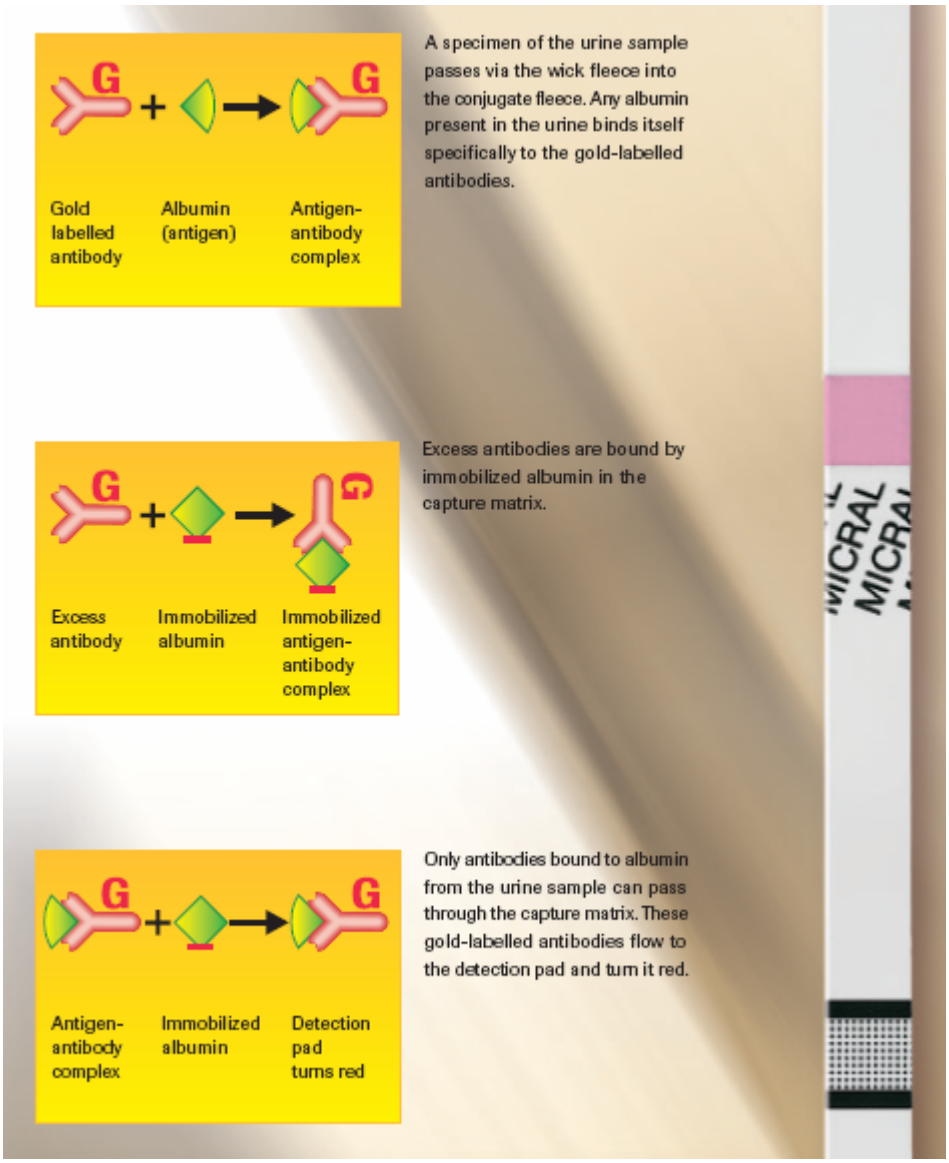


Fig.5 Principle of micral Test

The absorbed urine enters a zone on the test strip containing a conjugate fleece. Albumin in the urine binds itself specifically to gold labeled antibodies. These flow into detection pad, which in the presence of albuminuria turns the white detection to a shade of red.

4. Radioimmuno assay:

It is the "gold standard" for estimation of albuminuria. It is a double antibody technique where albumin in the sample has to compete with the fixed amount of 125

labelled albumin for the binding sites of the specific antibodies. Bound and free albumin is separated by addition of a second antibody immuno absorbent followed by centrifugation and decanting. The radio activity in the pellet is measured with a C-counter, Albumin concentration in the sample is inversely proportional to the radioactivity. The sensitivity for radio immune assay method was 0.3 mg/l.

METHOD OF URINE COLLECTION

For the diagnosis of microalbuminuria, a 24-hour urine collection is the gold standard. Because of the effort involved, it is not the method of choice for screening. The second best is a timed overnight urine collection. Again, because this requires collection of urine over a given time period, this may be acceptable for screening specific patient groups such as patients with diabetes or hypertension, but it is less feasible for population screening. The next best is a first-morning urine sample. This has the advantage over a spot-urine sample because it is always performed at the same time of the day, and it is least influenced by hydration status and physical activity of the patient, reducing the variability that is caused by these factors.In clinical practice however, a spot-urine sample is collected when the patient visits either the general practitioner or the health care office, where the screening takes place.

To express albuminuria, preferably the excretion of albumin per unit of time should be used {UAE per 24 hours or per minute (in case of timed overnight collections)}.For untimed samples, the albumin-to-creatinine ratio is advocated[90].

The albumin-to-creatinine ratio however, introduces the need to use different definitions for an abnormal value for men and women. Moreover, creatinine excretion in the urine depends not only on gender but also on age and race[91,92]**.** This may

explain why urinary albumin concentration from a spot sample performs equally well for the definition of microalbuminuria as albumin-to-creatinine ratio[93].

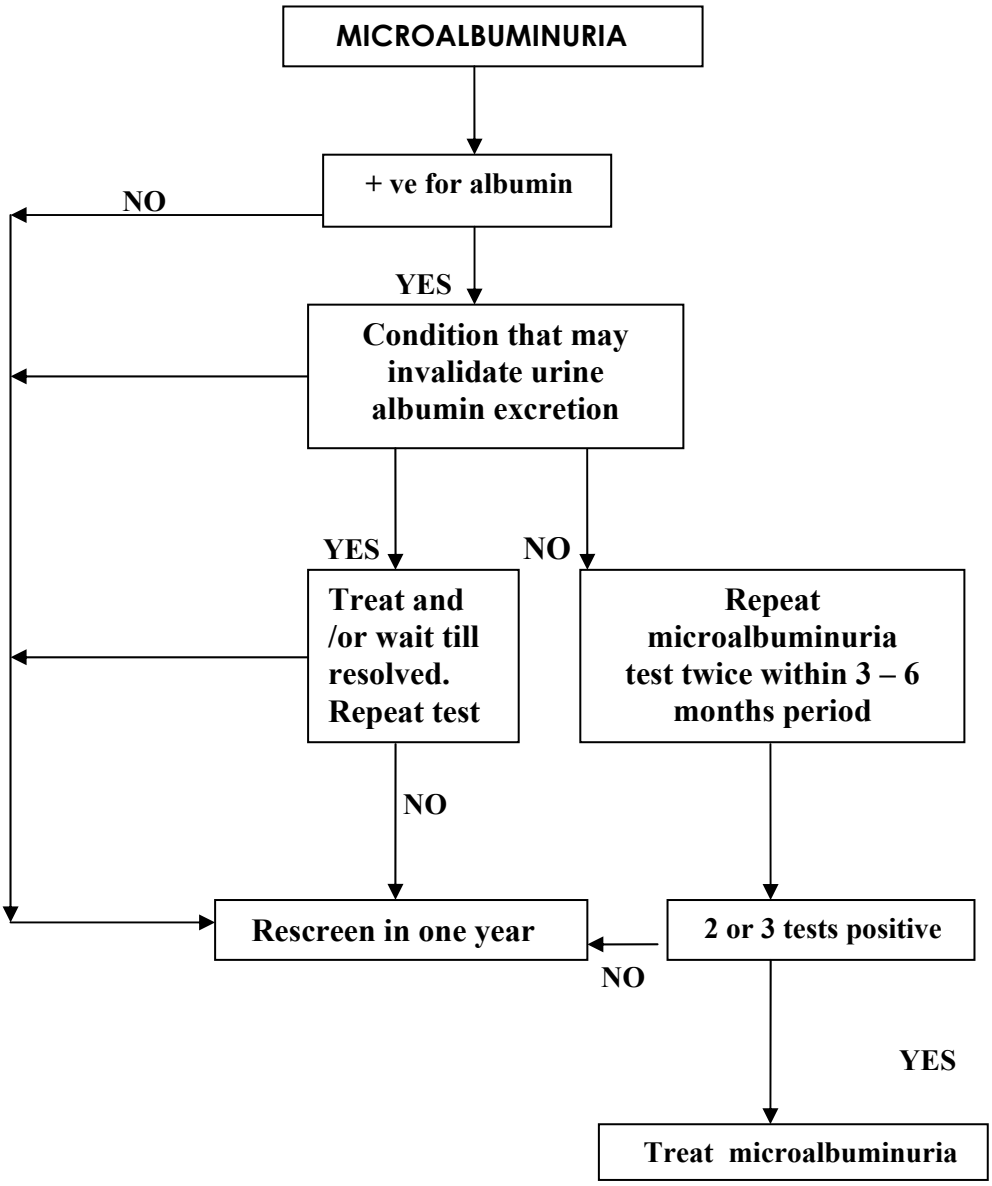
In this study a kit was used to detect microalbumin in urine . First morning mid stream urine sample that was collected in a sterile container was used for determining microalbuminuria. Also it has the advantage over a spot-urine sample because it is always performed at the same time of the day, and it is least influenced by hydration status and physical activity of the patient, reducing the variability that is caused by these factors. By quantitative immunochemical and turbidometric method, the turbidity formed was measured at 340 nm and the levels of microalbumin in urine was detected.

Reference (cut off) values of microalbumin in urine = 0 to 30 mg / litre

Microalbuminuria = 30 to 300 mg / litre

When someone is found to be positive for microalbuminuria, one first should confirm the positive test by repeated testing. It has been argued that two of the three tests need to be positive. Repeated urine for microalbumin, twice to be done in period of 3 to 6 months and after that if 2 or 3 tests become positive, then only microalbuminuria should be treated, as depicted in the fig no.6.

FIG.6. AN ALGORITHM FOR SCREENING OF MICROALBUMINURIA



HYPERTENSIVE RETINOPATHY

Hypertension can affect the retina, choroid and optic nerve of the eye, particularly more severely with stage 2 hypertension. These changes can be appreciated with inspection of the retinal vessels by direct ophthalmoscopy, photography or angiography[94].

Hypertensive retinopathy is most commonly manifested by generalized or focal narrowing of retinal arterioles. Prevalence of microalbuminuria and retinopathy were quite high in a cohort study of elderly hypertensives[94]. A cross sectional study from a teaching hospital in south India studied retinal changes of any grade probably have moderate accuracy in predicting microalbuminuria and accuracy of retinal changes in predicting microalbuminuria among elderly hypertensive patients[94]. Hence it guides us to initiate work up for target organ damage, especially in a resource poor setting in patients with essential hypertension.

In acute or advanced hypertension, the retinal vasculature may be injured sufficiently to cause occlusion or leakage. These changes may be manifested as nerve fiber layer infarcts (soft exudates or cotton-wool patches), extravascular edema (hard exudates), intraretinal hemorrhages, and retinal arterial macroaneurysms. Hypertensive choroidopathy is most frequently seen in young patients with acute hypertension, including cases of eclampsia or phaechromocytoma. Findings include elschnig spots (non perfused areas of the choriocapillaris) and siegrist streaks (linear hyperpigmentation over choroidal arteries)[95].Hypertensive optic neuropathy occurring with severe hypertension may present with flame hemorrhages, optic disc edema, venous congestion, and macular exudates.

Hypertensive Retinopathy (Keith, Wagener, Barker – 1939)

Vascular changes in the fundus reflect both hypertensive retinopathy and arteriosclerotic retinopathy. The hypertensive retinal changes are graded by the Keith – Wegner – Baker classification[96] as :

Grade 1 -

Mild to moderate narrowing or sclerosis of the arterioles.

Grade 2 -

Moderate to marked narrowing of the arterioles, local and or generalized narrowing of arterioles, exaggeration of light reflex.

Grade 3 -

Retinal arteriolar narrowing and focal constriction, retinal edema, cotton wool patches, haemorrhage.

Grade 4 -

Grade 1,2,3 + papilledema

Arteriosclerotic changes

- Arteriolar narrowing that is almost always bilateral
  - Grade I - 3/4 normal caliber
  - Grade II - 1/2 normal caliber
  - Grade III - 1/3 normal caliber
  - Grade IV - thread-like or invisible

- Arterio-venous crossing changes ("AV nicking") with venous constriction and banking.
- Arteriolar color changes :
  - Copper wire arterioles are those arterioles in which the central light reflex occupies most of the width of the arteriole.
  - Silver wire arterioles are those arterioles in which the central light reflex occupies all of the width of the arteriole.
- Vessel sclerosis.

- Ischemic changes (e.g."cotton wool spots").
- Hemorrhages, often flame shaped.
- Edema **:** ring of exudates around the retina called a "macular star".
- Papilledema or optic disc edema : in patients with malignant hypertension.
- Visual acuity loss, typically due to macular involvement.

The findings in hypertensive retinopathy all stem from hypertension-induced changes to the retinal microvasculature.Hypertension leads to a laying down of cholesterol into the tunica intima of medium and large arteries. This leads to an overall reduction in the lumen size of these vessels. In arteriolosclerosis, hypertension leads to focal closure of the retinal microvasculature. This gives rise to microinfarcts (cotton wool spots) and superficial hemorrhages. In extreme cases, disc edema develops. The mechanism behind this phenomenon is poorly understood, but it may be related to a hypertension-related increase in intracranial pressure, and hence is considered true papilledema. Arteriolosclerotic changes in the retinal microvasculature persist even with the reduction of systemic blood pressure.

However, hypertensive retinopathy changes resolve over time with the reduction of systemic BP. Cotton wool spots develop in 24 to 48 hours with the elevation of BP, and resolve in 2 to 10 weeks with the lowering of BP. A macular star develops within several weeks of the development of elevated BP and resolves within months to years after the BP is reduced. Papilledema develops within days to weeks of increased BP and resolves within weeks to months following BP lowering.

Management of hypertensive retinopathy involves appropriate treatment of the underlying hypertension. Medical co-management with the primary physician is of paramount importance. However, if a patient presents with papilledema from hypertension, then the patient has malignant hypertension and should be considered to be in medical crisis. This patient needs immediate consult with a primary care physician and, most likely, immediate transport to a hospital emergency room. It must be reiterated, however that there are many causes of papilledema. Other causes of papilledema, such as an intracranial mass lesion, must also be considered in the patient with hypertension. However, in a case where blood pressure is extremely elevated (e.g. 250/150mmHg) and there is disc edema with a macular star, malignant hypertension is the likely cause.

Clinical Pearls

- In order for cotton wool spots to develop from hypertension, autoregulatory mechanisms must first be overcome. For this to happen, the patient must have atleast 110 mmHg diastolic readings.
- Patients who develop papilledema from hypertension have malignant hypertension and typically have BP in the range of 250/150 mmHg

- Hypertensive retinopathy presents with a ‘dry’ retina (few hemorrhages, rare edema, rare exudates, and multiple cotton wool spots) whereas diabetic retinopathy, in comparison presents with a ‘wet’ retina (multiple hemorrhage, multiple exudates , extensive edema, and few cotton wool spots).

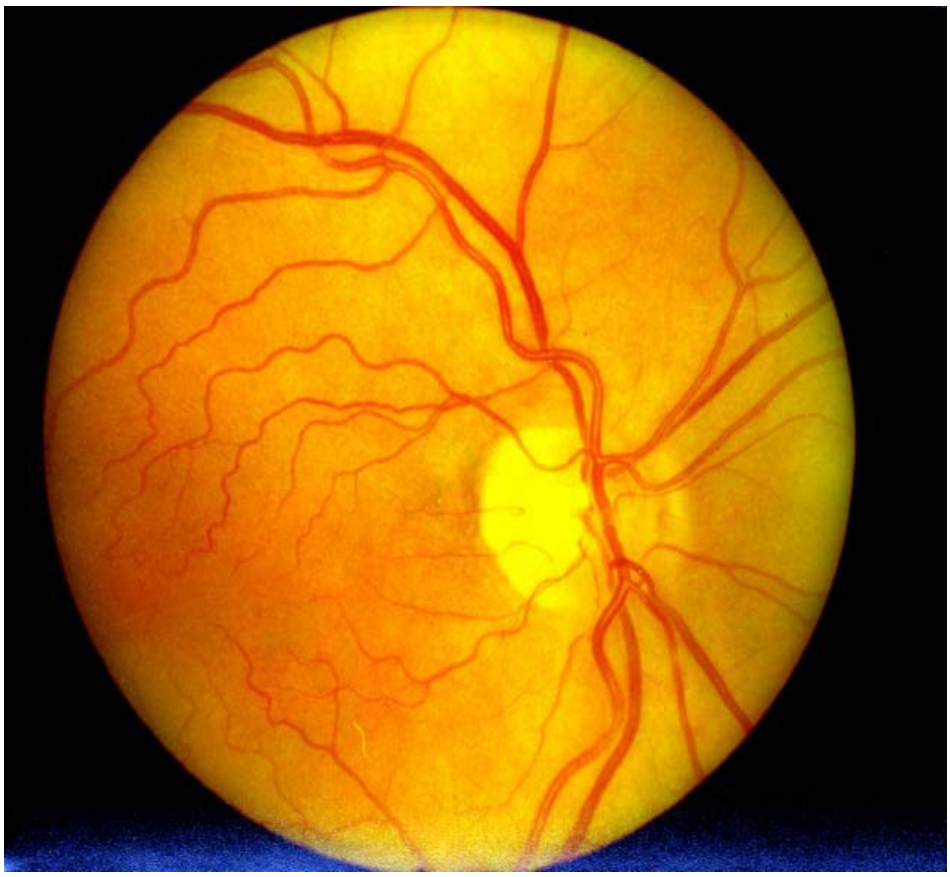


Fig.7. Grade I of hypertensive angiospastic retinopathy : general attenuation and increased tortuousity of arterioles, minimal dilatation of the venules.

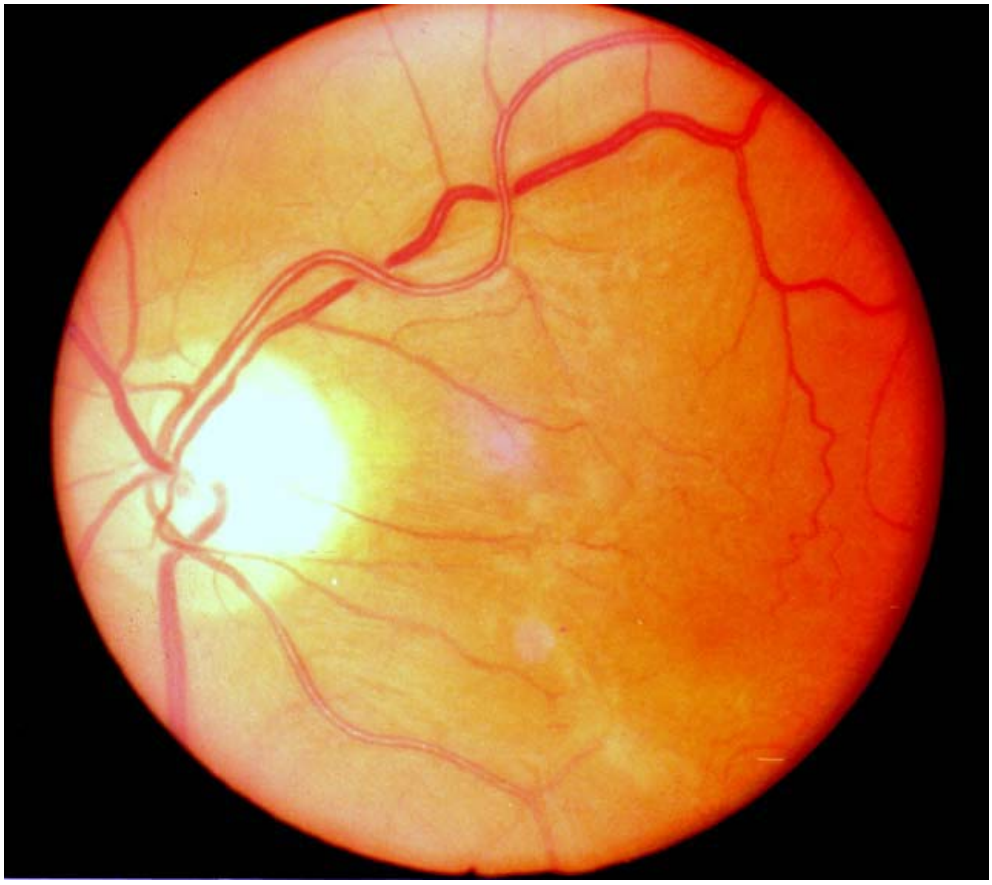


Fig.8. Grade II of hypertensive angiospastic retinopathy: Gunn-salus sign, increased light reflection of the artery, lumen irregularity.

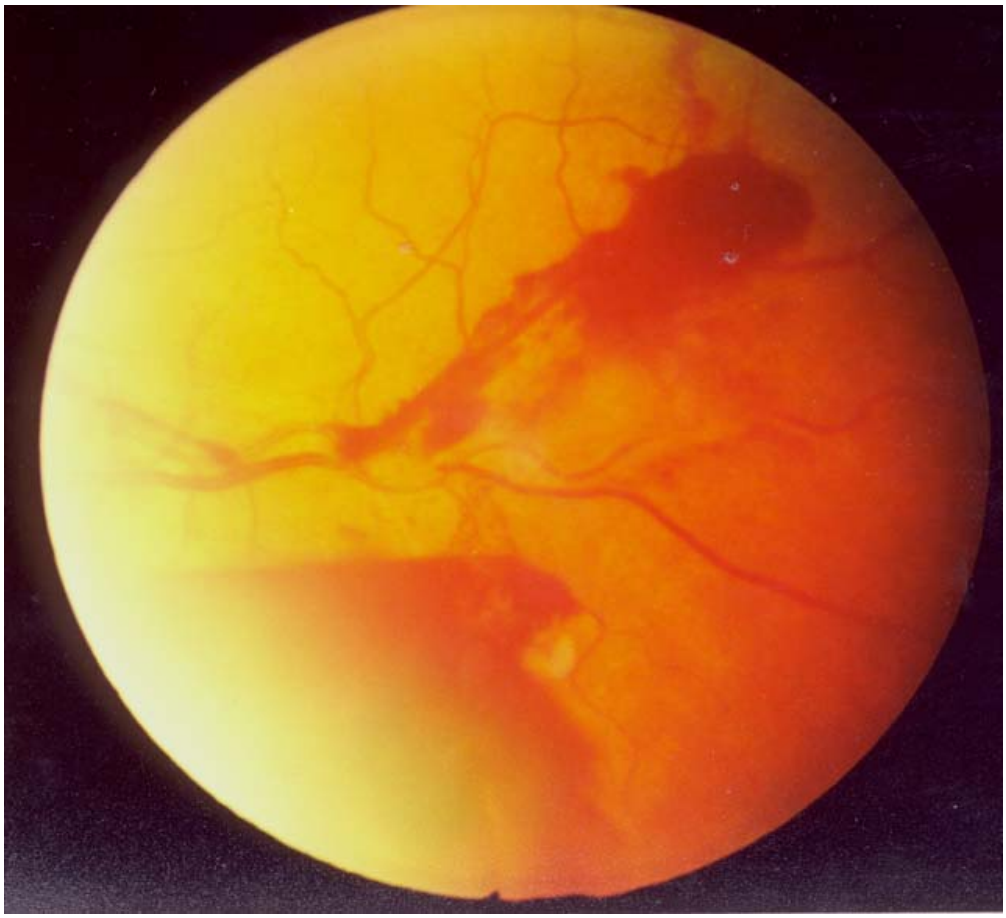


Fig.9. Grade III of hypertensive angiospastic retinopathy : marked attenuation of retinal arterioles is apparent with numerous large retinal haemorrhages.

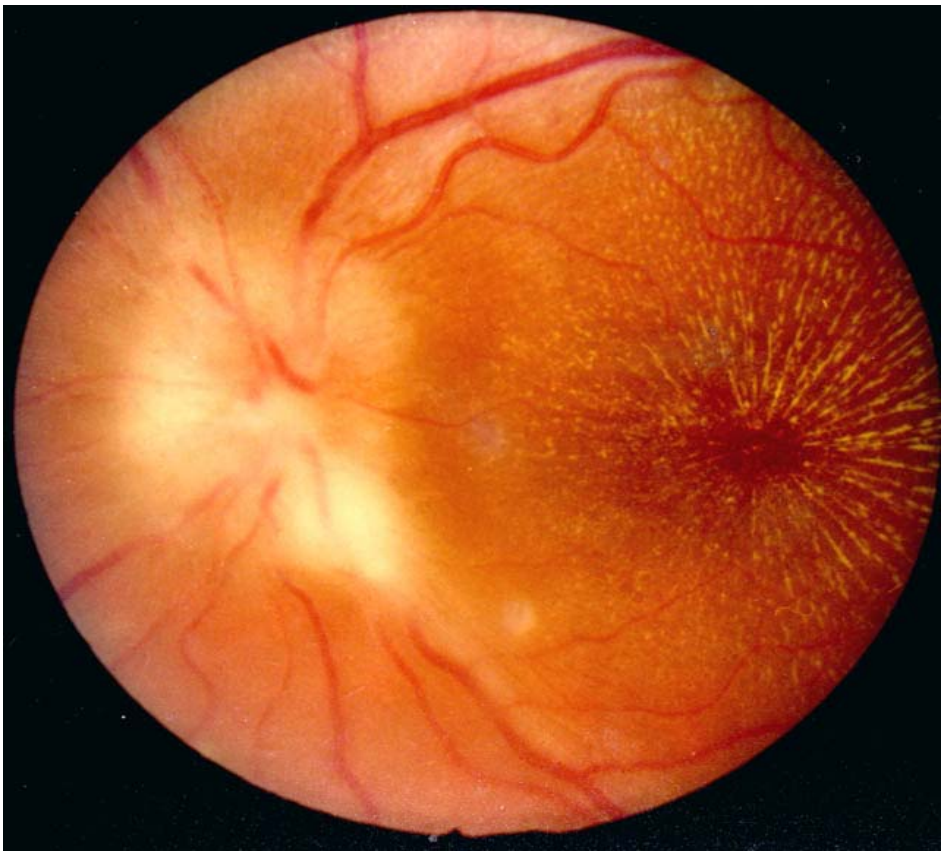


Fig.10. Grade IV of hypertensive angiospastic retinopathy : Grade III retinal changes including marked attenuation of the retinal arterioles, tortuosity, retinal hemorrhages, cotton wool spots, star form sign & additional optic disc oedema.

Hence microalbuminuria has been detected as a good screening test for early presence of microvascular disease in chronic kidney diseases. Those with rapidly accelerating hypertension die more frequently of renal failure, as do those who are diabetic once proteinuria or other evidence of nephropathy develops. Early screening of essential hypertension for microalbuminuria and prompt treatment of positive cases, might reduce the disease burden related to severe chronic kidney diseases and cardio vascular events in the community. Hence there is a need for early detection and treatment of microalbuminuria in patients with essential hypertension. Recognition of microalbuminuria stemmed from diabetes research four decades ago. A renewed interest in microalbuminuria and essential hypertension occurred when several studies pointed out the importance of microalbuminuria as a risk factor for renal and cardiovascular diseases.

Regression of left ventricular hypertrophy and decrease in microalbuminuria independent of blood pressure changes have been shown with the ARB's valsartan and losartan[97].

It is of interest that the presence of microalbuminuria may even precede the onset and manifestation of diabetes and hypertension. Microalbuminuria may be considered one of the earliest manifestations of the insulin resistance syndrome. Indeed, it has been shown that the prevalence of microalbuminuria increases according to the number of components of the metabolic syndrome present. This raises doubt whether we should limit our screening strategies to those with known risk factors or preferably should screen the general population.

TREATMENT OF MICROALBUMINURIA

1. Control of Blood pressure: Systolic BP is one of the most relevant determinants of microalbuminuria. Studies of secondary prevention have shown that blood pressure reduction effectively reduces the albumin excretion rate. Among anti-hypertensives, ACE inhibitors and ARB's seem to be particularly effective[98] **.** The target BP should be < 140/90 mmHg in non-diabetics and < 130/80 mmHg in diabetic patients.

2. Glycemic control: Intensive antidiabetic therapy can significantly reduce the risk of development of microalbuminuria and overt nephropathy in people with diabetes[99] **.**

3. Treatment of Dyslipidemia: Statins modify endothelial dysfunction, inflamatory response, plaque vulnerability and thrombus formation. Their usage is known to slow progression of microalbuminuria and is associated with stabilization of UAE[100].

4. Smoking cessation: Smoking should be strongly discouraged in patients with microalbuminuria not only to retard the progression of microalbuminuria but also to guard against cardiovascular disease.

5. Protein restriction: Animal studies have shown that restriction of dietary proteins intake reduces hyper filtration and intraglomerular pressure hence retarding the progression of microalbuminuria. The general consensus is to prescribe a protein intake of 0.8 g/mg/day in patients with overt nephropathy.

MICROALBUMINURIA: A PRACTICAL PERSPECTIVE

Several pathways may link microalbuminuria and vascular disease. Several factors that cluster with microalbuminuria include insulin resistance, central obesity, low levels of high-density lipoprotein cholesterol, high triglyceride levels, systolic hypertension, lack of nocturnal dip in blood pressure on 24 hour monitoring, salt sensitivity, endothelial dysfunction, hypercoagulability, impaired fibrinolysis and renal dysfunction. This provides enough proof to support the role of microalbuminuria as a predictor or vascular events in high-risk population. Hence, screening for microalbuminuria on a regular basis may help to identify a subgroup of patients who are at high risk for cardiovascular disease and need more intensive therapy and closer follow-up because they could benefit from early intervention and treatment[101].

MATERIALS AND METHODS

AIM OF STUDY – To study MA in essential HTN & its relation to severity of HTN, duration of HTN, BMI, age & TOD such as HTN retinopathy & ACS.

SOURCE OF DATA

100 consecutive patients presenting with essential hypertension and admitted to B.L.D.E.U's Shri. B. M. Patil Medical College Hospital and Research Centre, Bijapur from October 2008 To July 2010.

SAMPLE SIZE

With the prevalence of 27% microalbuminuria in essential hypertension (reference : Saudi Journal of Kidney diseases and transplantation 2008; 19: 411-419) and confidence level of 95% and with 30 % allowable error, using statistical formula -

$$n = \frac{4pq}{L^2}$$

Sample size = 99.5 = 100

STATISTICAL ANALYSIS :

Univariate analysis (chi square test) was used to determine the relationship between MA and other variables, and the results were expressed as p values and odds ratios (OR).Diagramatic & graphical representations were given wherever necessary. Analysis tables were also shown for each variables.

METHOD OF COLLECTION OF DATA

This study was performed in 100 patients presenting with essential hypertension & admitted to B.L.D.E.U's Shri. B.M. Patil Medical College and Research Centre, Bijapur from October 2008 to July 2010.

Five ml of first voided early morning sample of urine was collected and tested for microalbuminuria.

INCLUSION CRITERIA :

Patients admitted to this hospital within the study period, aged 30 to 90 years, with a diagnosis of essential hypertension according to JNC VII criteria –

1. Hypertension.

   Stage 1 **:** systolic = 140 to 159 mm hg and diastolic 90 to 99 mm hg.

   Stage 2 **:** systolic > 160 mm hg and diastolic > 100 mm hg.

2. Past history of essential hypertension.

EXCLUSION CRITERIA :

1. Secondary hypertension.
2. Pregnant women.
3. Diabetes mellitus or newly detected diabetes mellitus.
4. Urinary tract infections.
5. Acute / Chronic renal failure.
6. Macroproteinuria.
7. Patients already on angiotensin converting enzyme inhibitor drugs .

A detailed physical examination was performed on all patients, specifically emphasizing on assessment of cardiovascular system and dilated ophthalmic fundus examination.

All base line investigations like haematological, biochemical, electrocardiography, random blood sugar/fasting blood sugar and post prandial blood sugar (if necessary), lipid profile and urine for microalbumin was done.

METHOD OF TEST

ESTIMATION OF MICROALBUMINURIA IN URINE –

Five ml of first voided early morning sample of urine was collected for the study. The patients was asked to avoid exercise or exertion prior to urine collection. In women, urine was collected during the non menstrual phase of their cycles.

A kit was used to detect microalbumin in urine. By quantitative immunochemical and turbidometric method, the turbidity formed was measured at 340 nm and the levels of microalbumin in urine was detected .

Reference (cut off) values of microalbumin in urine = 0 to 30 mg / litre Microalbuminuria = 30 to 300 mg / litre.

OBSERVATION AND RESULTS

100 patients of essential hypertension were included in this study and in them 63 patients were found to be having microalbuminuria as shown in the graph below. The variables which were observed in this study are as follows :

Table no.1. Distribution of MA :

MA-Microalbuminuria

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	<30	37	37.0	37.0	37.0
	>=30	63	63.0	63.0	100.0
	Total	100	100.0	100.0	

Graph no.1

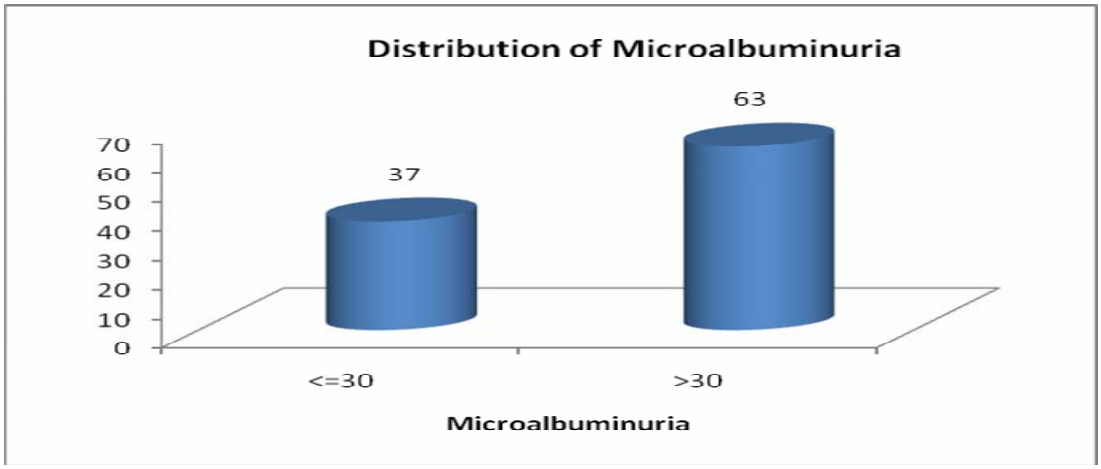
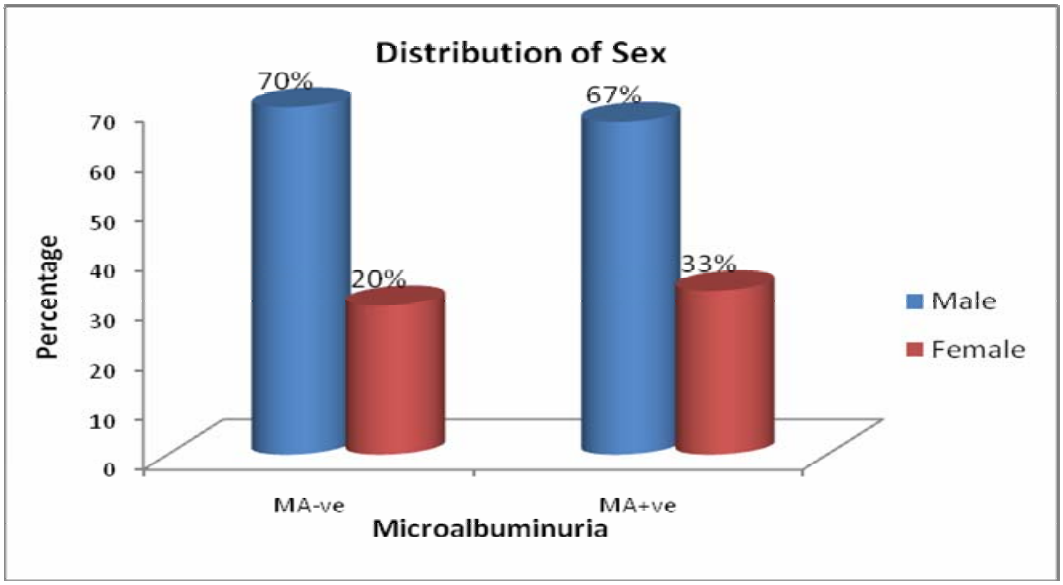


Table no.2. Sex distribution

Sex

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	68	68.0	68.0	68.0
	Female	32	32.0	32.0	100.0
	Total	100	100.0	100.0	

Graph no.2. Sexwise distribution of MA



In this study 67 % males & 33 % females were found to be having MA.

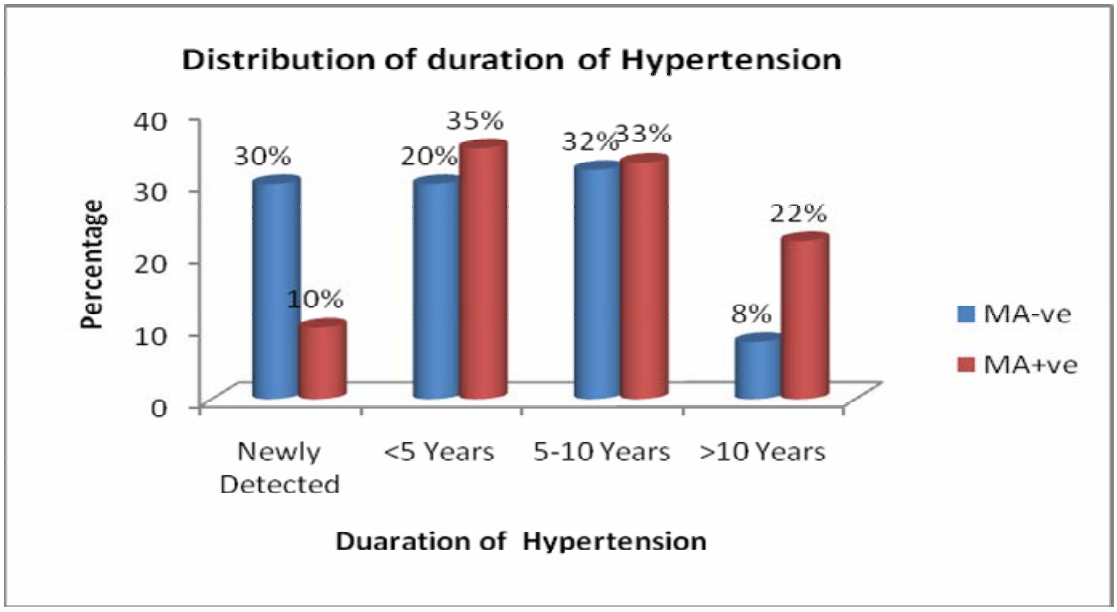
Table no.3. Analysis of MA & duration of HTN

Crosstab

			MA-Microalbuminuria		
			<30	>=30	Total
Period of Hypertension	Newly detected	Count	11	6	17
		% within MA-Microalbuminuria	29.7%	9.5%	17.0%
	Less than 5 years	Count	11	22	33
		% within MA-Microalbuminuria	29.7%	34.9%	33.0%
	5-10 years	Count	12	21	33
		% within MA-Microalbuminuria	32.4%	33.3%	33.0%
	More than 10 years	Count	3	14	17
		% within MA-Microalbuminuria	8.1%	22.2%	17.0%
Total		Count	37	63	100
		% within MA-Microalbuminuria	100.0%	100.0%	100.0%

[Chi-square =8.526 , df=3 , p value = 0.036 (<0.05)]

Graph no.3:



As the duration of HTN increases, MA also increases.

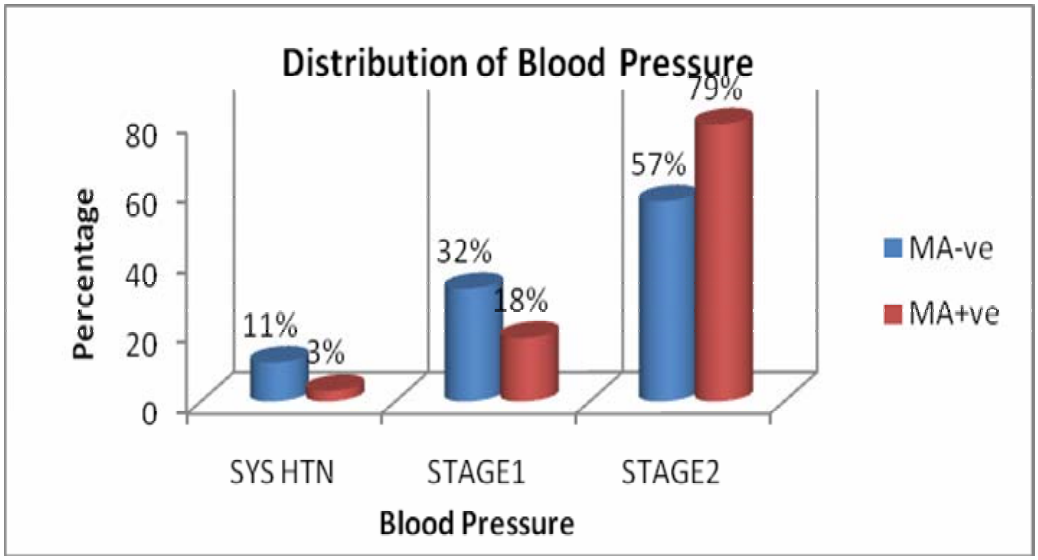
Table no.4 .Analysis of MA & severity of HTN.+

Crosstab

			MA-Microalbuminuria		
			<30	>=30	Total
Blood Pressure Category	140-159/90-99	Count	4	2	6
		% within MA-Microalbuminuria	10.8%	3.2%	6.0%
	>140/<90	Count	12	11	23
		% within MA-Microalbuminuria	32.4%	17.5%	23.0%
	>160/>100	Count	21	50	71
		% within MA-Microalbuminuria	56.8%	79.4%	71.0%
Total		Count	37	63	100
		% within MA-Microalbuminuria	100.0%	100.0%	100.0%

[Chi-square=6.215 , df=2 , p value = 0.045 (< 0.05)]

Graph no.4



In this study 79% of MA positive patients were in the stage 2 HTN.

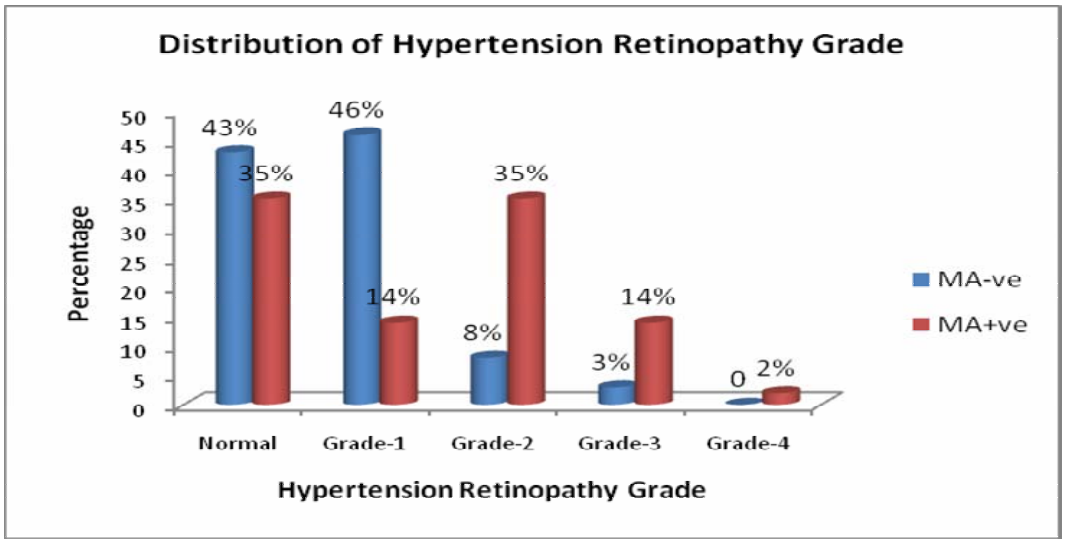
Table no.5. Analysis of MA & grades of HTN retinopathy

Crosstab

			MA-Microalbuminuria		Total
			<30	>=30	
Hypertension retinopathy grade	Normal	Count	16	22	38
		% within MA-Microalbuminuria	43.2%	34.9%	38.0%
	Grade 1	Count	17	9	26
		% within MA-Microalbuminuria	45.9%	14.3%	26.0%
	Grade 2	Count	3	22	25
		% within MA-Microalbuminuria	8.1%	34.9%	25.0%
	Grade 3	Count	1	9	10
		% within MA-Microalbuminuria	2.7%	14.3%	10.0%
	Grade 4	Count	0	1	1
		% within MA-Microalbuminuria	.0%	1.6%	1.0%
Total		Count	37	63	100
		% within MA-Microalbuminuria	100.0%	100.0%	100.0%

[Chi-square=19.829 , df=4 , p value = 0.001 (< 0.05)]

Graph no.5



In this study 35% of MA positive patients had grade 2 & 14 % had grade 3 HTN retinopathy.

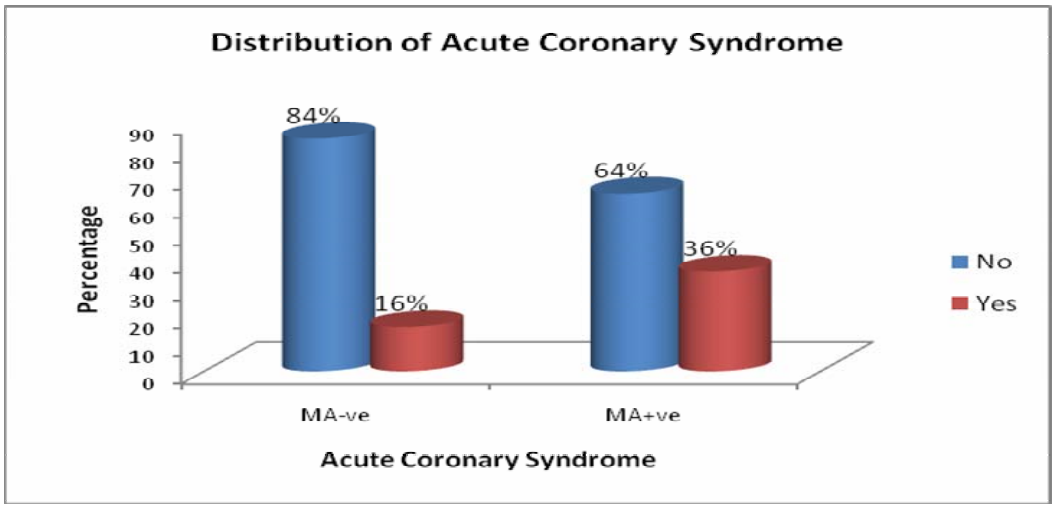
Table no.6. Analysis of MA & ACS

Crosstab

			MA-Microalbuminuria		
			<30	>=30	Total
Acute Coronary Syndrome	No	Count	31	40	71
		% within MA-Microalbuminuria	83.8%	63.5%	71.0%
	Yes	Count	6	23	29
		% within MA-Microalbuminuria	16.2%	36.5%	29.0%
Total		Count	37	63	100
		% within MA-Microalbuminuria	100.0%	100.0%	100.0%

[Chi-square=4.661 , df=1 , p value = 0.031 (< 0.05)]

Graph no.6



In this study 36% of MA positive patients had acute coronary syndrome.

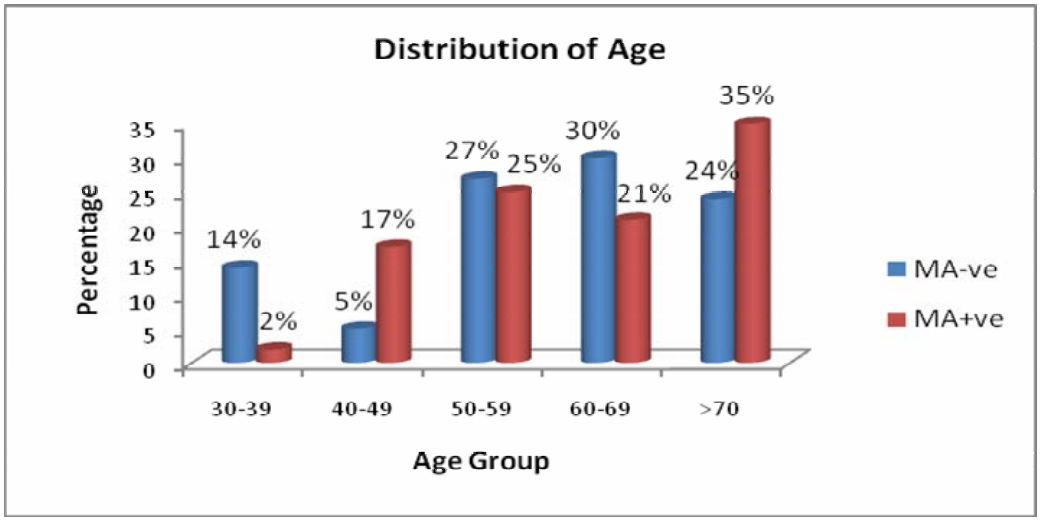
Table no.7. Analysis of MA & age groups

Crosstab

			MA-Microalbuminuria		Total
			<30	>=30	
Age Category	30-39 years	Count	5	1	6
		% within MA-Microalbuminuria	13.5%	1.6%	6.0%
	40-49 years	Count	2	11	13
		% within MA-Microalbuminuria	5.4%	17.5%	13.0%
	50-59 years	Count	10	16	26
		% within MA-Microalbuminuria	27.0%	25.4%	26.0%
	60-69 years	Count	11	13	24
		% within MA-Microalbuminuria	29.7%	20.6%	24.0%
	>70 years	Count	9	22	31
		% within MA-Microalbuminuria	24.3%	34.9%	31.0%
Total		Count	37	63	100
		% within MA-Microalbuminuria	100.0%	100.0%	100.0%

[Chi-square= 9.803 , df=4 , p value = 0.044 (< 0.05)]

Graph no.7



In this study 17% of MA positive patients were in the age group 40-49 yrs, 25% were in the age group 50-59 yrs, 21% were in the age group 60-69 yrs & 35 % were in the age group of >70 yrs.

Table no.8. Analysis of MA & gender.

Crosstab

			MA-Microalbuminuria		
			<30	>=30	Total
Sex	Male	Count	26	42	68
		% within MA-Microalbuminuria	70.3%	66.7%	68.0%
	Female	Count	11	21	32
		% within MA-Microalbuminuria	29.7%	33.3%	32.0%
Total		Count	37	63	100
		% within MA-Microalbuminuria	100.0%	100.0%	100.0%

[Chi-square= 0.139 , df=1 , p value = 0.709 (> 0.05)]

DISCUSSION

MA and vascular dysfunctions are known to occur early in the course of essential hypertension.Hypertensive nephropathy is a common cause of chronic kidney disease , in which chronic renal ischemia as a result of small and large vessel renovascular disease can be left under recognized. Progressive nephrosclerosis from vasculo-endothelial disease is the renal correlate of same process, that leads to coronary artery diseases, cerebrovascular diseases, hypertensive retinopathy,left ventricular dysfunctions etc.

In this study, out of 100 hypertensive patients come 63 patients were found to be having MA (> 30 mg/l) . Hence the prevalence of MA in essential hypertension in our study was found to be 63 %. Hence, our observation on the high prevalence of MA in patients with essential hypertension, must alert the clinicians regarding the high prevalence of subclinical CKD in this part of the community .Out of 68 males, 42(67%) were found to having microalbuminuria & out of 32 females, 21(33%) were found to having microalbuminuria .Though the prevalence of MA was found to be high in males, there was no statistical significant difference in the risk for MA between the two sex groups (p=0.709).We found out that there is a statistically significant difference between MA & the duration of hypertension (p = 0.036) & (OR =0.438) Longer the duration of hypertension, more possibility of microalbumin in urine. Also there was a statistically significant difference between severity of hypertension & MA (p=0.045) & (OR=0.093). MA was positive in 50(79%) patients out of 63, whose blood pressure was found to be >160/100 mmhg. We also found out a statistically significant difference between MA & the grades of hypertensive retinopathy (p =0.001) which is highly significant. Also we found out a

significant association between microalbuminuria & acute coronary syndrome (p = 0.031) & (OR=3.517).

Though high BMI among hypertensives is an important and well-known risk factor for the development of MA, in our study we did not find any statistically significant difference between the MA & BMI (p= 0.745) . 15 patients in our study were bedridden & hence BMI could not be calculated in those individuals.Advancing age was found to be a risk factor for higher prevalence of MA in our study also, as observed in other studies. There was a statistically significant difference between MA & age of the patient (p = 0.044) . The prevalence of MA among hypertensive patients increased steadily with their advancing age as shown in graph.no.7.

When our study parametes were compared to another study done by B Hitha et al the prevalence of MA in essential hypertension was found to be 26.67%, of whom 24 were males and 16 were females[13]. MA was significantly higher in those with longer duration, greater severity of hypertension (p <0.001 in each), also for older age group (p <0.001) and hypertensive retinopathy (OR=9.7) were significantly higher in those with MA. They concluded that the prevalence of MA in essential hypertension is high and patients with MA have high odds for developing TOD like acute coronary syndrome and hypertensive retinopathy.

In another study by Jan Skov Jensen et al, microalbuminuria defined as a urinary albumin/creatinine ratio above the upper decile (1.07 mg/mmol), was the strongest predictor of ischemic heart disease, with an unadjusted relative risk of 4.2 (95% CI 1.5 to 11.9, *P*50.006) and a relative risk of 3.5 (95% CI 1.0 to 12.1, *P*50.05) when adjusted for all other atherosclerotic risk factors, including age and gender[12]. In conclusion, microalbuminuria confers a 4-fold increased risk of ischemic heart disease among hypertensive or borderline hypertensive subjects too. In this study in

patients with MA & hypertension, we found out that OR = 3.517, which tells that the risk of ischaemic heart disease increases in patients with MA & hypertension.

In an another study by GS Sainaniet et al , they found out that hypertension is associated with functional and morphological alterations of the endothelium,which disturbs delicate balance of endothelium-derived factors resulting in endothelial dysfunction[14]. The endothelial dysfunction could then facilitate the maintenance of elevated peripheral resistance,which would favour the occurrence of atherosclerosis. One concept postulates that more albumin leaks through exaggeratedly permeant glomeruli that reflect the systemic damaging impact of subclinical atherogenesis, a process characterized by a diffuse involvement of the entire vascular endothelial system. This hypothesis, which was originally formulated to account for the higher cardiovascular morbidity rate in diabetic patients, may also apply to essential hypertensive patients[10].So it is very important to screen for MA in early stages of essential hypertension, which if treated early can prevent atherosclerotic processes in the entire vascular system.The clinical markers of the generalized endothelial dysfunction becomes manifest in several forms. Microalbuminuria is one such marker, which marks the onset of endothelial dysfunction related to the kidney and whole vascular system.

Yet an other study by Roberto Pontremoli et al found out that the prevalence of microalbuminuria and its relationship with several cardiovascular risk factors and target organ damage were evaluated in a cohort of 787 untreated patients with essential hypertension[15].

The prevalence of microalbuminuria in essential hypertension in this “MAGIC STUDY” was 6.7%. Albuminuric patients were more likely to be men and to be characterized by higher blood pressure, body mass index, and uric acid levels.

Piecewise linear regression analysis demonstrated that uric acid and diastolic blood pressure significantly influence albuminuria and together account for a large part of its variations.K-means cluster analysis performed on the entire cohort of patients confirmed that microalbuminuria is associated with a worse cardiovascular risk profile. Furthermore, microalbuminuria was associated with the presence of target organ damage (eg, electrocardiographic) abnormalities and retinal vascular changes . Age and the presence of microalbuminuria act as independent risk factors for the development of ECG abnormalities and retinal vascular changes. They concluded that increased urinary albumin excretion is associated with a worse cardiovascular risk profile and is a concomitant indicator of early target organ damage, such as hypertensive retinopathy, acute coronary syndrome, atherosclerosis, and stroke also.

Another study by name The PREVEND study , showed that in a multivariate model adjusted for established cardiovascular risk factors, microalbuminuria was independently associated with infarct pattern (7.1%) (OR=1.61), major ischemia (10.6%) (OR=1.43) and minor ischemia (15.1%) (OR=1.32)[106]. When compared with this study, the OR for ACS in MA was found out to be 3.517 which tells that the risk of ACS in MA with hypertension is very high .

Microalbuminuria was detected in 14.8% of those without Diabetes mellitus at baseline in a cohort of heart outcomes prevention evaluation study conducted between 1994 and 1999 [104.] They showed that 20.4% of patients with microalbuminuria had myocardial infarction, stroke or cardiovascular cause of death as compared to 13.8% of those without microalbuminuria .In the PREVEND study, 32.8% of ischemic heart disease patients had microalbuminuria and in the HOPE study cohort mentioned above, 20.4% of patients with a cardiovascular disease had microalbuminuria compared to 23% in our study[106].The present study showed that microalbuminuria can

be used as an additional cardiovascular risk indicator even in non-diabetic patients in essential hypertension.

An other study by G.P.S.Shanta et al on 180 elderly hypertensive patients, documented that microalbuminuria showed a strong association with hypertensive retinopathy ($p<0.0001$)[94]. Logistic regression identified association of icroalbuminuria with duration of essential hypertension ($p=0.001$). Tests for accuracy for hypertensive retinopathy as a predictor of microalbuminuria showed a sensitivity of 72 % & specificity of 82%. They concluded that the prevalence of microalbuminuria & retinopathy was quite high in elderly hypertensive patients & retinal changes of any grade probably have moderate accuracy in predicting microalbuminuria & hence can initiate work up for target organ damage, especially in a resource poor setting.

An another study by Jay P Garg et al, told that agents known to reduce the rise in microalbuminuria or actually reduce the level of microalbuminuria, such as ACE inhibitors, ARBs, HMG-CoA reductase inhibitors, beta blockers, non-dihydropyridine calcium channel blockers and diuretics, have all been shown to reduce cardiovascular mortality and in some cases preserve renal function[19]. This article will present an overview of the data that support the assertion that a reduction in the rise of microalbuminuria is a significant consideration in the selection of agents to treat a given risk factor (cholesterol or blood pressure) to a recommended target goal. Achieving such a goal with agents that also impact microalbuminuria will provide for a more complete cardiovascular risk reduction. They concluded that MA is a early marker of generalised vascular dysfunction and increases the risk for cardiovascular diseases. Hence early screening for MA in patients of essential hypertension and treatment for the same helps in reducing the morbidity and mortality due to TOD.

SUMMARY

This study was conducted at BLDE University's Shri B.M.Patil Medical College Hospital & Research Centre, Bijapur. The present study included 100 inpatients of essential hypertension & non diabetics. In the studied group, 68 % patients were male & 32 % patients were female. The prevalence of MA in essential HTN in this study was found to be 63 %. In that 42% were male & 21% were female. We found a significant association between MA & the duration of hypertension (p = 0.036) & (OR =0.438) .Longer the duration of hypertension, more possibility of microalbumin in urine. Also there was a significant association between severity of hypertension & MA (p=0.045) & (OR=0.093). MA was positive in 50 (79.4%) patients out of 63 , whose blood pressure was >160/100 mm hg. We found out a significant association between MA & the grades of hypertensive retinopathy (p =0.011)(highly significant). We also found out a significant association between microalbuminuria & acute coronary syndrome (p = 0.041) & (OR =2.805). Gender & BMI did not pose high risk for MA in this study. And also as shown above, patients with MA have high odd s for developing TOD such as ACS.

CONCLUSION

1) The prevalence of MA in essential hypertension is high in this part of the community & MA will increase the risk of developing target organ damage.

2) Early screening of patients with essential hypertension for MA and aggressive management of positive cases might reduce the burden of chronic kidney diseases and cardiovascular diseases in the community.

BIBLIOGRAPHY

1. Skalski.J.H , Kuch.J . Polish thread in the history of circulatory physiology. Journal of physiology and pharmacology. 2006 ; 57 : 5- 41.
2. Platt, Sir Harry (1886 - 1986), Plarr's lives of the Fellows Online, Biographical entry. http://livesonline.rcseng.ac.uk/biogs/E000232b.htm .
3. Research Article: Recognition of rheumatic heart disease.Br Heart J. 1977; 39:1045-1050.
4. Albert Dreisbach. W,Sharma.Sat, Claude Kortas, Hypertension .Feb 19, 2010. http://emedicine.medscape.com/article/241381-overview
5. Richard Bright, A vague and obsolete term for disease of the kidneys - Acute or chronic. http://www.whonamedit.com/doctor.cfm/1984.htm
6. Stewart Cameron.J , Elm Bank, Melmerby, Penrith,High blood pressure and the kidney: The forgotten contribution of William Senhouse Kirkes. Kidney International 2000 ; 57 : 724–734.
7. Theodore A, Kotchen, Jane Morley , Clarence.Grim.E ,Varghese, George ,Genetic Determinants of Hypertension , Identification of candidate phenotype. Hypertension..2000 ; 36 : 7.
8. Vickie Andros, Uncontrolled blood pressure in a treated,high-risk managed care population . Am J Manag Care. 2005 ;11: S215 - S219.
9. Anna F, Dominiczak, Delyth Graham,Martin W. McBride, Nick J.R .Brain cardiovascular genomics and oxidative stress .Hypertension. 2005 ; 45 : 636.
10. Antonio Ceriello. Possible role of oxidative stress in the pathogenesis of hypertension, 2008 ; 31: S181-S184

11. Roberto Pedrinelli,Giuseppe Penno,Giulia Dell'Omo,Simona Bandinelli,Davide Giorgi, Vitantonio Di Bello et al . Microalbuminuria and transcapillary albumin leakage in essential hypertension.Hypertension. 1999; 34: 491-495.
12. Jan Skov Jensen, Bo Feldt- Rasmussen, Svend Strandgaard, Marianne Schroll, Knut Borch-Johnsen. Hypertension, microalbuminuria and risk of ischaemic heart disease. Hypertension. 2000 ; 35 : 898-903.
13. Hitha.B, Pappachan.J.M , Balachandran Pillai.H, Sujathan.P , Ramakrishna.C.D, .Microalbuminuria in patients with essential hypertension and its relationship to target organ damage: An Indian Experience. 2008 ; 19 (3): 411.
14. Sainani.G.S, Vibhuti Maru.G. Role of endothelial cell dysfunction in essential hypertension .JAPI. 52 ; 2004 : 966 – 969.
15. Roberto Pontremoli,Antonella Sofia,Maura Ravera.Prevalence and clinical correlates of microalbuminuria in essential hypertension .The MAGIC study .Hypertension. 1997 ; 30 : 1135-1143.
16. Wiinberg.N, Bang L.E, Wachtell.K, Larsen.J , Olsen.M.H, Tuxen.C et al. A population-based study of 1254 hypertensive individuals. Jour of human hypertens. 1997; 11: 727 -732
17. Shanta.GPS , Bhaskar.E, Kumar.A.A, Sundaram.V .Int Urol Nephrol . Nephrology original paper, A cross sectional study from a teaching hospital in south India . 2008 ; 41 (1) : 137-143
18. An Skov Jensen, Bo Feldt Rasmussen, Svend Strandgaard, Marianne Schroll, Knut Borch Johnsen . Arterial hypertension, microalbuminuria, and risk of ischemic heart disease. Hypertension. 2000 ; 35 :898.
19. Jay Garg.P , George Bakris.L . Microalbuminuria : marker of vascular dysfunction, risk factor for cardiovascular disease .Vasc Med . 2002 ; 7 : 35
20. Pontremoli R, Soa A, Ravera M . Prevalence and clinical correlates of microalbuminuria in essential hypertension. The MAGIC study.1997; 30: 1135 – 43 .

21. Biesenbach G, Zazgornik J. High prevalence of hypertensive retinopathy and coronary heart disease in hypertensive patients with persistent microalbuminuria under short intensive antihypertensive therapy. Clin Nephrol. 1994; 41: 211 -218
22. The seventh report of joint national committee on hypertension. http://www.nhlbi.nih.gov/guidelines/hypertension
23. Fauci,Braunwald,Kasper,Hauser,Longo. Harrison's principles of Internal Medicine 17 edition : 2008 ; 2 :1549 – 1550.
24. Flanc RS, Robert MA, Strippoli GF, Chadban SJ, Kerr PG, Atkins RC. Treatment of diffuse proliferative lupus nephritis: A meta – analysis of randomized controlled trials. Am J Kidney Dis.2004; 43: 197-208 .
25. Carroll MF, Temte JL. Proteinuria in adults: A diagnostic approach . American family physician. 2000; 62:1333- 1340.
26. Glassrock RJ. Postural (orthostatic) Proteinuria . N Engl J Med.1980; 18: 395-406.
27. Watt GF, Morris RW, Khank, Polaka.Urinary albumin exerction in health adult subjects: Reference value & some factors affecting their interpretation.Clin Chim Acta.1988; 172: 91-198.
28. Spring Berg , Lt. Col. Peter D , Maj. Leland E Garrett, Nancy F Collins, Roscoe R Robinson. Fixed and reproducible orthostatic proteinuria: Results of a 20 year follow up study : Annals of internal medicine .1982 ; 97: 516-519.
29. Robinson RR. Isolated proteinuria in asymptomatic patients. J of Kidney International . 1980; 18: 395 - 406.
30. Wam LL, Yano S, Hiromurak, Tsukaday, Tomonos, Kawazer. Effects of posture on creatinine clearance and urinary protein exerction in patients with various renal diseases 1995; 3:76 – 79
31. Devarajan P. Mechanism of orthostatic proteinuria: Lessions from a transplant donor. Journal of the American society of Nephrology .1993 ; 4: 36-39

32. Shintaku N, Takahashi Y, Akaishi K, Sano A, Kuroda Y ,Entrapment of the left renal vein in children with orthostatic proteinuria. . Pediatric Nephrology. 1990 ; 4 : 324 - 327.
33. Hotter TH . Proteinuria . Kidney . 1987; 20:13.
34. Kallmeyer G, Miller NM. Urinary changes in ultra-long distance marathon runners. Nephron. 1993; 64: 119-121.
35. Poortmans JR, Rampaer L, Walf JC. Renal protein exerction after exercise in man. Eur J Apply Physiol Occup Physiol. 1989; 48 : 476 - 480.
36. Poortms JR, Labilloy D. The influence of work intensity on post exercise proteinuria. Eur J Appl Physiol Occup Physiol .1988 ; 57 : 260-263.
37. Abuelo JG. Proteinuria : Diagnostic Principles and procedures. Ann Intern Med 1983:98;186-191.
38. McConnell KR, Bia MJ. The Evaluation of proteinuria: An approach for the internist. Res Staff Physician .1994; 41-48 .
39. Savin VJ. Mechanism of proteinuria in non inflammatory glomerular disease. American Journal of Kidney Disease.1993; 21:347-362.
40. Daniels BS. The role of the glomerular epithelial cell in the maintainance of the glomerular filtration barrier – American Journal of Nephrology .1993; 13: 318-323
41. Almeida AF. Clinical Approach to a Patient with Renal Disease . API textbook of medicine 7th edition. Mumbai: The Association of Physician of India : 2003.
42. Turner AN, savill J, Stewart LH, Camming A . Kidney and Genitourinary Disease. Davidson's principles and practice of medicine. 19th edition. London : Churchill Living stone; 2002.
43. Tulkensn PM, Experimental studies on Nephrotoxicity of Aminoglycosides in low doses. Am J Med. 1986; 80 (6 B) : 105-114.
44. Schardijn GHC ,Statius Van Eps LW , Stout Zonnevel .Urinary B_2 microglobulin urinary tract infections, Acta Clin Belg . 1980; 35 :21.

45. Glassrock RJ. Proteinuria. Test book of Nephrology. 3rd edition Baltimore : William Wilkins,1995.

46. Longo DL, Anderson KC, Plasma Cell Disorders. Harrison's Principles of Internal Medicine. 16th edition. New Delhi Mc Graw – Hill Medical Publishing Division;2005

47. Beinenstock J, Tomasi TB. Secretory gamma -A in normal urine. Journal of Clinical Investigation .1968; 47: 1162-1171

48. Rosenman E, Boss JH . Tissue antigens in normal and pathologic urines : A review Kidney International . 1979 ; 16 : 337-344.

49. MC Queen EG. Composition of urinary casts. Lancet .1966 ; 287: 397-398.

50. Rustecki GJ, Goldsmith C, Sehreiner GE .Characterization of proteins in urinary casts. Fluorescent antibody identification of Tamm horsfall protein in matrix and serum protein in granules.New England Journal of Medicines. 1971; 284: 1049-1052.

51. Abuelo JG. Proteinuria : Diagnostic principles and procedures.Ann Intern Med.1983:98; 186-191.

52. Fauci,Braunwald,Kasper,Hauser,Longo. Harrison's principles of Internal Medicine 17 edition : Vascular injuries to kidneys .2008 ; 2 : 1813 – 1814 .

53. Fauci,Braunwald,Kasper,Hauser,Longo. Harrison's principles of Internal Medicine 17 edition : 2008 ; 2 :1551 – 1554.

54. Douglas Cines B, Eleano Pollak S, Clayton Buck A, Joseph Loscalzo, Guy Zimmerman A, Rodger McEver P .Comparative pathophysiology and clinical consequences of atherosclerosis associated endothelial cell injury in vascular disorders .1998 ; 91 (may 15) : 3527-3561.

55. Bernard Rosner (2000), Fundamentals of Bio statistics, 5th Edition, Duxbury.

56. M.Venkataswamy Reddy(2002), Statistics for Mental Health Care Research, NIMHANS publication, INDIA.

57. Chakravarthy B, Taneja V, Sircar S, Kansra U: Microalbuminuria: Association with dyslipidemia in non-insulin dependent diabetes mellitus. JAPI .1997; 45(8) : 608-611.

58. Patel KL, Mhetras SB, Varthakavi PK, Merchant PC, Nihalani KD: "Microalbuminuria in non-insulin dependent diabetes mellitus". JAPI, 1999; 47(5): 596-601

59. Taneja V, Sircar S, Kansra U, Lamba IMS: "Microalbuminuria in normotensive non-insulin dependent diabetic subjects- associations and predictions" J Diab Assoc India . 1997; 37(2): 30-36

60. Jadhav UM, Kadam NN: Association of microalbuminuria with carotid Intima-Media thickness and coronary artery disease - A cross sectional study in Western Indi.JAPI.2002;50:1124-1129.

61. Durrutty P, Diaz J, Zanetti L, De La Varas MA, Garcia de los Rios M: Microalbuminuria, lipid changes and coronary heart disease in non-insulin dependent diabetics. Revista Medica de Chile. 1998; 126(12):1425-33.

62. Bahia L, Gomes MB, Da cruz P Di M., Goncalves: Coronary artery disease, microalbuminuria and lipid profile in patients with non-insulin dependent diabetes mellitus. Arquivos Brasileiros de cardiologia, 1999; 73(1): 11-22

63. American Diabetes Association, Nephropathy in aiabetes (Position statement) Diabetes Care. 2004; 27 (1): 79-83

64. Rush University Hypertension Center. Microalbuminuria: What is it Why is it important? What should be done about it? J Clin Hypertension. 2001; 3(2):99-100.

65. Parving HH .Early detection of patients at risk of developing diabetic nephropathy; a longitudinal study of urinary albumin excretion. Acta Endocrinal (Copenti) 1982; 100: 550-555.

66. Viberti GC, Jeannie Messent W C , Thomas Elliott G , Ronald Hill D , John Jarrett R , Harry Keen. Microalbuminuria as a predictor of clinical nephropathy in Insulin Dependent Diabetes Mellitus. Lancet .1982;1:1430-1432.

67. MogensenCE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity onset diabetes. NEJM 1984; 310: 356-60.

68. Allawi J, Jarrett RJ. Microalbuminuria and cardiovascular risk factors in Type 2 diabetes mellitus. Diabetes Med .1989; 7: 115-118.

69. Jorge L Gross, JL Camargo, MJ De Azevedo. Diabetic Nephropathy: Diagnosis prevention and treatment. Diabetes Care. 2005; 28: 176-188.

70. Consensus development conference on the diagnosis of coronary heart disease in people with Diabetes. Diabetes care 1998; 21: 1551-68.

71. Agarwal B, Berger A, Wolf K .Microalbuminuria screening by reagent strip predicts cardiovascular risk in hypertension. J. Hypertension. 1996; 14(2): 223-228.

72. Dansgaard EM. Microalbuminuria as predictor of increased mortality in elderly people. BMJ 1990; 300: 297-300.

73. Gosling P, Hughes EA, Reynolds TM, Fox JP. Microalbuminuria is an early response following acute myocardial infarction. Eur Heart J .1991; 12: 508-513.

74. Spyridon Koulouris, Ioannis Lekatsas, Ilias Karabinos, Georgios Ioannidis,Theofanis Katostaras, Athanasios Kranidis et al..Microalbuminuria: A strong predictor of 3-year adverse prognosis in non-diabetic patients with acute myocardial infarction.Am Heart J. 2005 ; 149(5) : 840-845.

75. Roine I. Microalbuminuria: an index of severity in childhood meningitis. Pediatr Infect Dis J .1993;12:584-588.

76. Shearman CP, Gosling P, Walker KJ. Is low-level protein urea a predictor of severity in acute pancreatitis. J Clin Pathol .1989; 42: 1132-1135.

77. Pallister I, Gosling P, Alpar K, Gradley S. Prediction of post-traumatic adult respiratory distress syndrome by albumin excretion rate eight hours after admission. J Trauma. 1997; 42: 1056-61

78. Mahmood N. Microalbuminuria: a disease activity marker of inflammatory bowel disease. Gut 1993; 34: 524

79. Hickey NC. Effect of surgery on the systemic inflammatory response to intermittent claudication. Br J Surg 1990; 77: 1121-1126.

80. Leena Mykkänen, Daniel Zaccaro J, Daniel H. O'Leary, George Howard, David Robbins C, Steven Haffner M. Microalbuminuria and carotid artery intima-media thickness in non-diabetic and NIDDM subjects. The Insulin Resistance Atherosclerosis Study (IRAS). Stroke .1997; 28: 1710 – 1716.

81. Reavon GM, Hoffman BP: A role of insulin in the etiology of and the course of hypertension. Lancet, 1987; 2 : 435-437.

82. Nosadini R, Zambon S, Manzato E, Solini A, Sambataro M, Brocco E et al: Lipoprotein abnormalities in Non insulin dependent diabetes mellitus with impaired insulin sensitivity, hypertension and microalbuminuria .Arteriosclero Thromb. 1994 ; 14(6) : 911-916.

83. Niskanen L, Laakso M: " Insulin resistance is related to albuminuria in patient with type-2 (non-insulin dependent) diabetes mellitus". Metabolism, 1993; 42(2):1541-1545.

84. Haffner SM, Mykannen L, Kuuisto J, Pyorola K, and Laakso M: Microalbuminuria precedes the onset of Non-insulin dependent diabetes mellitus. Diabetes . 1994 ; 43(4) : 552-557.

85. Mykannen L, Kuuisto J, Pyorola K, Laakso M, Haffner SM: Increased risk of NIDDM in elderly hypertensives. J Hypertension . 1994; 12(12): 2425-2452.

86. Fauci,Braunwald,Kasper,Hauser,Longo. Harrison's principles of Internal Medicine 17th edition,Chapter 274, Chronic kidney disease. 2008 ; 2 : 1766 – 1767.

87. Keen H, Chloverakis C. An immunoassay method for urinary albumin at low concentration. Lancet. 1963; 2: 913-914.

88. Arruda, Jose A.L. Simplified screening for Microalbuminuria..Ann Intern Med 1997;127:817-819.

89. Mogensen C E, Viberti GC , Peheim E, Kutter D, Hasslacher C, Hofmann W et al. Multicenter evaluation of the micral-test II test strip, an immunological rapid test for the detection of microalbuminuria..Diabetes care . 1997 ; 20 :1642-1646.

90. Levey AS, Eckardt KU, Tsukumato Y, Levin A, Coresh J,Rossert J, Zeeuw D et al: Definition and classification of chronic kidney disease: A global position statement from Kidney Disease: Improving Global Outcome (KDIGO). Kidney Int .2005 ; 67: 2089–2100.

91. Mattix HJ, Hsu CY, Shaykevich S, Curhan G: Use of the albumin/creatinine ratio to detect microalbuminuria: Implications of sex and race. J Am Soc Nephrol 2002 ; 13: 1034–1039.

92. Verhave JC, Hillege HL, de Zeeuw D, De Jong PE: How to measure the prevalence of microalbuminuria in relation to age and gender. Am J Kidney Dis. 2002 ; 40: 436–437.

93. Gansevoort RT, Verhave JC, Hillege HL, Burgerhof JG, Bakker SJ, de Zeeuw D, De Jong PE; for the PREVEND Study Group: The validity of screening based on spot morning urine samples to detect subjects with microalbuminuria in the general population. Kidney Int Suppl. 2005 ; 94 : S28–S35.

94. Bhaskar E, Shanta GPS, Kumar A,Sundaram V, Accuracy of retinal changes in predicting microalbuminuria among elderly hypertensive patients: A cross-sectional study from a teaching hospital in South India.A cross sectional study from a teaching hospital in south India, 2008. Int Urol Nephrol,Nephrology original paper.

95. Karyn Bourke AB, Milan R. Patel L, Michael Prisant.Images in Hypertension, Hypertensive Choroidopathy.The journal of clinical hypertension. 2007;6(8):471 – 472

96. S Chatterjee, S Chattopadhya, M Hope Ross and Mrs PL Lip Hypertension and the eye: changing perspectives . Journal of Human Hypertension 2002 ; 16 : 667-675.

97. Martin J, Krum H .Role of valsartan and other angiotensin receptor blocking agents in the management of cardiovascular disease. Pharmacological research . 2002 ; 46 : 203 -212.

98. Kristian Wachtell, Hans Ibsen, Michael Olsen H, Knut Borch-Johnsen, Lars Lindholm H, Björn Dahlöf et al. Albuminuria and cardiovascular risk in hypertensive patients with left ventricular hypertrophy. The LIFE STUDY. Ann Intern Med. 2003; 139: 901-906.

99. UK Prospective Diabetes Study (UKPDS) Group intensive blood glucose control with Sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998; 352: 837-853.

100. Smulders YM, Van Eeden AE, Stehouwer CD, Weijers RN, Slaats EH, Silberbusch J. Can reduction in hypertriglyceridemia slows progression of microalbuminuria in patients with NIDDM. Eur J Clin .1997 ; 27(12) : 997-1002.

101. Radrigo Tagle, Monico Acevedo, Donald Vidt G. Microalbuminuria: Is it a valid predictor of cardiovascular risk. Cleveland .Clin J Med.2003;70(3):255-261.

102. Bigazzi R, Bianchi S, Nenci R, Baldari D, Baldari G, Campese VM. Increased thickness of the carotid artery in patients with essential hypertension and microalbuminuria. J Hum Hypertens . 1995; 9: 827 - 833.

103. Diercks GFH, Von Boren AJ, Hillege HL, Janssen WMT, Kors JA, DeJong PE. Microalbuminuria is independently associated with ischemic electrocardiographic abnormalities is a large non-diabetic population. The PREVEND study. Eur Heart J. 2000 ; 21 : 1922-1927.

104. Jensen JS, Feldt-Rasmussen B, Strandgaard S, Schroll M, Borch-Johnson K. Arterial hypertension, microalbuminuria and risk of ischemic heart disease. Hypertension 2000 ; 35 : 898-903

BLDEU's SHRI. B.M.PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE , BIJAPUR

" STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION "

PROFORMA

Name:	IP. No:
Age:	Address
Sex:	Date of Admission:
Occupation:	Date of Discharge:
Religion:	Status at Discharge:
	Unit:

Chief complaints-

Present history-

1. Head ache

Duration

Site

Type

Any diurnal variations

Any aggravating factors

And relieving factors

2. **Palpitations**

    Duration

    Type

    Any aggravating factors

    And relieving factors

3. **Giddiness ;**

    Duration

    Any postural variation

    Any diurnal variation

4. **Blurring of vision :**

5. **Chest pain :**

    Duration

    Site

    Radiation

    Type

    Any aggravating factors

    And relieving factors

6. **Breathlessness**

    Duration

    Grade

    Any aggravating factor

    Any relieving factor

H/o orthopnoea

H/o paroxysmal nocturnal dyspnea

7. Swelling of lower limbs

Duration

Diurnal variation

8. Puffiness of face

Duration

9 .Other symptoms

Past history

History of hypertension

- Duration
- Treatment history

H/o Myocardial infarction / Angina

H/o Diabetes mellitus

H/o Rheumatic heart disease

H/O Swelling/puffiness face

H/O Decreased urine output

H/O Drug intake

- Analgesic
- Oral contraceptives
- Anti hypertensives/ACE inhibitors

Personal history :

Diet/appetite

Sleep

Bladder and bowel habits:

Smoking /Tobacco chewing/Snuff Inhalation

Duration

Number of cigarettes / beedis pack year smoked

Amount of tobacco chewed/ snuff inhaled

Alcohol

Duration

Quantity/Frequency

Type

Family history

History suggestive of Ischemic Heart Disease/ Hypertension/ Diabetes mellitus

GENERAL PHYSICAL EXAMINATION

Pallor:

Icterus:

Cyanosis:

Clubbing:

Pedal edema:

Lymphadenopathy**:**

Body mass index:

Oedema:

CARDIOVASCULAR SYSTEM

Pulse examination –

Arterial Pulse

Rate

Rhythm

Volume

Character

Symmetry

Radio-radial delay

Radio-femoral delay

Pulse deficit

Other Peripheral Pulses	Rt	Lt

Blood Pressure	Rt.	Lt.
Upper Limb		
Lower Limb		

Respiratory rate:

Temperature:

Signs of Congestive Cardiac Failure

Exaggerated hepato-jugular reflex

Raised Jugular Venous pressure

Tender hepatomegaly

Pitting pedal odema

Miscellaneous

Clubbing

Cyanosis

Icterus

Palpable lymph nodes

Systemic examination -

Inspection

- Precordial bulge

- Apical impulse

Other pulsations

Suprasternal pulsation

Supraclavicular pulation

Right and left 2nd intercostals spaces

Parasternal pulsation

Epigastric pulsation

Palpation

Apical impulse

Site

Character

Parasternal palpation

Heave

Diastolic thud (palpable P2)

Thrill

Mitral area

Tricuspid area

Pulmonary area

Aortic area

Percussion

Cardiac border

Left and right 2nd intercostals space

Lower sternum

Upper border of liver

Auscultation

Heart sounds

Mitral area

Tricuspid area

Pulmonary area

Aortic area

Murmurs

Mitral area

Tricuspid area

Pulmonary area

Aortic area

Added sounds

RESPIRATORY SYSTEM

PER ABDOMEN

CENTRAL NERVOUS SYSTEM

PROVISIONAL DIAGNOSIS

INVESTIGATIONS :

HAEMATOLOGY -

Haemoglobin	gm/d1
Total wbc counts	cells/mm ^{3}
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Basophils	%
Monocytes	%
Esr	mm/1hr

BIOCHEMISTRY-

Random blood sugar	
Fasting blood sugar	
Blood Urea	
Serum creatinine	
Urine routine and microscopy	
Lipid profile	

ELECTROCARDIOGRAPHY

CHEST X RAY PA VIEW

CT SCAN BRAIN (if required)

OPTHALMIC FUNDUS EXAMINATION (with dilated pupils)

URINE FOR MICROALBUMIN

B. L. D. E. U's

SHRI. B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR

RESEARCH INFORMED CONSENT FORM

TITLE OF THE PROJECT:

"STUDY OF MICROALBUMINURIA IN ESSENTIAL HYPERTENSION"

GUIDE : DR. BADIGER. SHARANABASAWAPPA.

INVESTIGATOR : DR. SANDEEP. H .M.

PURPOSE OF RESEARCH:

I have been informed that the purpose of this study is to study the microalbuminuria in essential hypertension.

PROCEDURE:

I understand that I will undergo detailed history and clinical examination, laboratory investigations.

RISKS AND DISCOMFORTS:

I understand that there is no risk involved and I may experience mild pain during the above-mentioned procedures.

BENEFITS:

I understand that my participation in this study will help to understand the importance of studying microalbuminuria in essential hypertension & will provide a rationale for early management.

CONFIDENTIALITY:

I understand that the medical information produced by the study will become a part of hospital record & will be subjected to confidentiality and privacy regulations of hospital. If the data is used for publications, the identity of the patient will not be revealed.

REQUEST FOR MORE INFORMATION:

I understand that I may ask for more information about the study at any time.

REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and I may refuse to participate or withdraw for study at any time.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me during the study I will get medical treatment but no further compensations.

(Signature of Guardian) **(Signature of Patient)**

KEY TO MASTER CHART

ACS : Acute coronary syndrome

A : Age in years

BMI : Body mass index

D HTN : Duration of hypertension

FT : First time

F : Female

HTN : Hypertension

HRG : Hypertensive retinopathy grading

HRG 1 : Grade 1 hypertensive retinopathy

HRG 2 : Grade 2 hypertensive retinopathy

HRG 3 : Grade 3 hypertensive retinopathy

HRG 4 : Grade 4 hypertensive retinopathy

IP : In patient number

MA : Microalbuminuria in mg/ltr

M : Male

m : Months

N : Normal

STAGE 1 : BP = 140-159/90-99

STAGE 2 : BP>160/100

SYS : BP>140/<90

S : Serial number

MASTER CHART

SN	IP	A	S	BMI	D HTN	STAGE1	SYS	STAGE2	HRG	ACS
1.	11614	75	M	18.56	10.5YR	-----	150/90	----	3	YES
2.	10601	35	M	----	FT	145/90	-----		3	NO
3.	10745	42	M	22.13	5YR	-----	----	160/100	N	NO
4.	10020	73	M	21.09	3YR	140/98	----	----	1	NO
5.	9837	52	M	25.31	1YR	156/90	----	----	1	NO
6.	6981	60	F	-----	8YR	-----	----	190/100	2	NO
7.	8802	45	M	-----	FT	-----	----	210/120	1	NO
8.	9996	80	M	17.94	12YR	-----	----	160/102	1	NO
9 .	9872	50	F	23.11	1.6YR	-----	-----	170/100	2	NO
10.	3328	59	M	24.22	FT	-----	------	165/100	N	NO
11.	17378	80	F	23.42	5YR	-----	146/90	-----	N	YES
12.	8291	58	M	23.7	FT	-----	------	160/108	N	YES
13.	17065	44	M	21.91	1 YR	-----	178/90		N	NO
14.	10586	87	M	18.3	16YR	-----	180/80	-----	2	YES
15.	11865	65	M	24.72	10YR	-----	-----	188/100	N	NO
16.	7273	70	F	23.67	4YR	-----	212/90		2	NO
17.	11461	40	M	21.91	4YR	-----	------	180/110	3	NO
18.	10135	71	M	16.46	10YR	-----	------	190/100	2	NO
19.	10106	60	F	21.77	8m	-----	170/72	------	2	NO

20.	7974	50	M	22.86	FT	------	------	180/100	1	NO
21.	9665	51	M	20.7	10YR	------	-------	200/110	3	NO
22.	7318	75	F	-----	10YR	------	------	180/100	2	NO
23.	9042	65	F	19.81	11YR	------	172/90		N	NO
24.	17423	71	F	21.2	3YR	------	------	180/102	2	NO
25.	11151	76	F	------	3YR	------	160/86	------	1	NO
26.	9706	62	F	20.6	12YR	------	150/80	------	1	YES
27.	8019	75	M	27.26	10YR	------		168/100	2	YES
28.	10393	60	M	27.98	10YR	------	------	196/102	2	NO
29.	6322	55	F	20.51	5YR	------	------	160/100	2	YES
30.	5924	48	M	19.53	6YR	150/98	------	--------	2	YES
31.	12114	80	M	21.91	7 m	-------	------	200/100	3	YES
32.	12010	70	M	------	6YR	-------	-----	160/102	2	NO
33.	11843	52	M	26.56	5 m	159/90	-----	---------	N	YES
34.	12516	45	F	20.98	2YR	-------	190/90	-------	1	NO
35.	12341	85	F	31.98	5YR	-------	180/90	--------	N	NO
36.	5757	55	F	------	6YR	150/90	-----		2	NO
37.	6447	39	M	28.34	FT	-------	-----	165/100	N	NO
38.	7216	55	M	29.06	5YR	152/99	------	---------	N	NO
39.	16146	53	M	22.53	2YR	-------	------	160/100	2	YES
40.	6276	70	M	21.92	FT	-------	-----	190/102	3	NO

41.	5925	70	F	-----	4YR	-------	-----	240/120	N	NO
42.	11055	61	F	24.8	FT	-------	196/90	----------	1	NO
43.	1187	61	M	20.71	5YR	-------	198/90	----------	1	NO
44.	11040	60	M	23.69	3YR	-------	----	170/100	N	NO
45.	14153	75	F	18.7	15YR	-------	159/88	----------	N	NO
46.	14625	38	M	25.79	4.5YR	-------	-----	160/100	N	NO
47.	14716	60	M	24.88	FT	-------	-----	200/106	1	NO
48.	15067	65	F	23.96	5YR	-------	------	160/106	N	YES
49.	4298	40	M	21.7	FT	-------	------	206/112	2	NO
50.	11859	55	M	24.01	7YR	-------	220/60	----------	3	NO
51.	2657	55	F	23.92	8YR	-------	-------	192/106	N	NO
52.	2781	72	M	21.98	FT	-------	------	160/102	3	YES
53.	3174	55	M	24.91	FT	-------	180/80	-------	1	YES
54.	3557	39	M	24.46	FT	-------	------	210/116	N	YES
55.	3878	48	F	20.87	FT	-------	-------	182/100	N	NO
56.	3948	60	F	21.28	13YR	-------	------	180/100	1	NO
57.	4514	80	M	-----	4YR	-------	-----	220//116	4	NO
58.	1195	55	M	22.03	4YR	-------	-----	194/100	N	NO
59.	14013	50	M	22.48	2.5YR	-------	-----	160/104	N	NO
60.	1242	63	M	-----	15YR	-------	------	210/116	N	NO
61.	10066	55	F	22.65	6YR	-------	------	180/100	1	YES

62.	15791	50	M	-----	6m	-------	------	210/120	2	NO
63.	5224	60	F	22.22	6 m	-------	180/90	------	3	NO
64.	1019	65	M	20.77	7YR	-------	------	160/100	1	YES
65.	1455	80	F	21.89	3YR	------	------	160/110	N	YES
66.	1448	65	F	23.43	11YR	------	-----	180/100	2	NO
67.	1455	80	F	-----	FT	------	-----	160/100	3	YES
68.	1666	60	M	25.32	5.5YR	------	------	170/102	N	NO
69.	1698	**75**	F	20.44	4YR	------	168/86	168/100	1	NO
70.	1780	65	M	21.27	15YR	------	210/90	------	1	NO
71.	1781	70	M	19.48	FT	------	-----	190/100	1	NO
72.	1851	44	M	23.75	5YR	------	-----	160/100	N	NO
73.	2431	74	M	20.71	10YR	------	-----	186/100	N	NO
74.	1923	70	M	22.64	FT	------	-----	168/100	N	NO
75.	10843	50	M	24.52	FT	------	-----	220/130	2	NO
76.	6113	52	M	24.83	FT	------	-----	166/100	N	YES
77.	5927	48	M	21.43	5YR	------	-----	180/110	N	YES
78.	1876	39	F	25.77	4.5YR	------	180/90	---------	1	YES
79.	1629	52	M	22.12	FT	------	-----	200/112	N	NO
80.	2061	50	M	26.74	2m	------	-----	170/100	N	NO
81.	2828	64	M	31.89	3YR	------	-----	160/108	1	NO
82.	9496	38	M	18.98	FT	------	-----	180/100	1	YES

83.	9665	50	M	25	2m	------	------	202/102	1	YES
84.	9587	85	M	25.09	15YR	------	------	160/100	2	YES
85.	7825	43	M	28.7	6YR	------	------	170/100	1	NO
86.	7245	70	M	30.12	1YR	------	------	200/110	2	NO
87.	12516	45	F	23.45	FT	------	------	198/120	N	NO
88.	8096	58	M	21.72	3YR	------	------	170/110	N	YES
89.	6657	67	M	22.02	7YR	------	------	180/100	1	NO
90.	6128	70	M	23.76	6m	------	198/90	-------	1	NO
91.	71848	60	M	20.98	FT	-------	------	172/100	N	NO
92.	5464	65	M	-----	7.5YR	------	------	216/112	2	NO
93.	6453	75	M	24.12	8YR	------	180/88	------	N	YES
94.	5889	55	M	23.48	6YR	------	------	200/102	1	NO
95.	2801	65	F	24.82	4YR	150/98	------	------	N	NO
96.	7166	50	M	20.92	4YR	-------	------	190/108	N	NO
97.	6413	75	F	------	8YR	-------	------	168/110	N	YES
98.	6945	70	M	19.86	9YR	-------	------	188/102	2	YES
99.	10282	60	F	------	12YR	-------	212/90	-----	2	NO
100.	10680	45	M	20.91	6m	-------	------	190/100	N	NO