A COMPARITIVE STUDY OF MICROALBUMINURIA BETWEEN PREHYPERTENSIVE AND NORMOTENSIVE INDIVIDUALS

Dissertation submitted to

THE TAMILNADU DR.MGR MEDICAL UNIVERSITY

CHENNAI- TAMILNADU

In partial fulfillment for the Degree of

DOCTOR OF MEDICINE

BRANCH I –M.D.,(General Medicine)

APRIL-2015

DEPARTMENT OF MEDICINE

TIRUNELVELI MEDICAL COLLEGE

TIRUNELVELI- 627011,TAMIL NADU

CERTIFICATE

This is to certify that the Dissertation entitled " **A COMPARITIVE STUDY OF MICROALBUMINURIA BETWEEN PREHYPERTENSIVE AND NORMOTENSIVE INDIVIDUALS"** submitted by **Dr.B.ARUN KUMAR** to The Tamilnadu Dr. M.G.R. Medical University, Chennai, in partial fulfillment of the requirement for M.D.(Branch-I) General Medicine Examination to be held on April 2015 is a bonafide work carried out by him under my guidance and supervision. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

Prof.Dr.VAIRAMUTHURAJU,MD.,
Professor and HOD,
Department of Medicine
Tirunelveli Medical College,
Tirunelveli – 627011.

The Dean,
Tirunelveli Medical College,
Tirunelveli – 627 011.

TIRUNELVELI MEDICAL COLLEGE

INSTITUTIONAL RESEARCH ETHICS COMMITTEE
TIRUNELVELI, STATE OF TAMILNADU, SOUTH INDIA PIN 627011
91-462-2572733-EXT; 91-462-2572944; 91-462-2579785; 91-462-2572611-16
online@tvmc.ac.in, tirec@tvmc.ac.in; www.tvmc.ac.in

CERTIFICATE OF REGISTRATION & APPROVAL OF THE TIREC REF NO: 351/GM/2013/29.03.13

PROTOCOL TITLE: A Comparitive Study of Micro-Albuminuria between Prehypertensive & Normotensive Individuals

NAME OF PRINCIPAL INVESTIGATOR: Dr.B.Arun Kumar

DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate Resident

DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

Dear Dr. Dr.B.Arun Kumar, *the Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on* 29.03.2013.

THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED

1.	TIREC Application Form	☑
2.	Study Protocol	☑
3.	Department Research Committee Approval	☑
4.	Patient Information Document and Consent Form in English and Vernacular Language	☑
5.	Investigator's Brochure	☑
6.	Proposed Methods for Patient Accrual Proposed	☑
7.	Curriculum Vitae of the Principal Investigator	☑
8.	Insurance /Compensation Policy	☐
9.	Investigator's Agreement with Sponsor	☐
10.	Investigator's Undertaking	☑
11.	DCGI/DGFT approval	☐
12.	Clinical Trial Agreement (CTA)	☐
13.	Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA)	☑
14.	Clinical Trials Registry-India (CTRI) Registration	☐

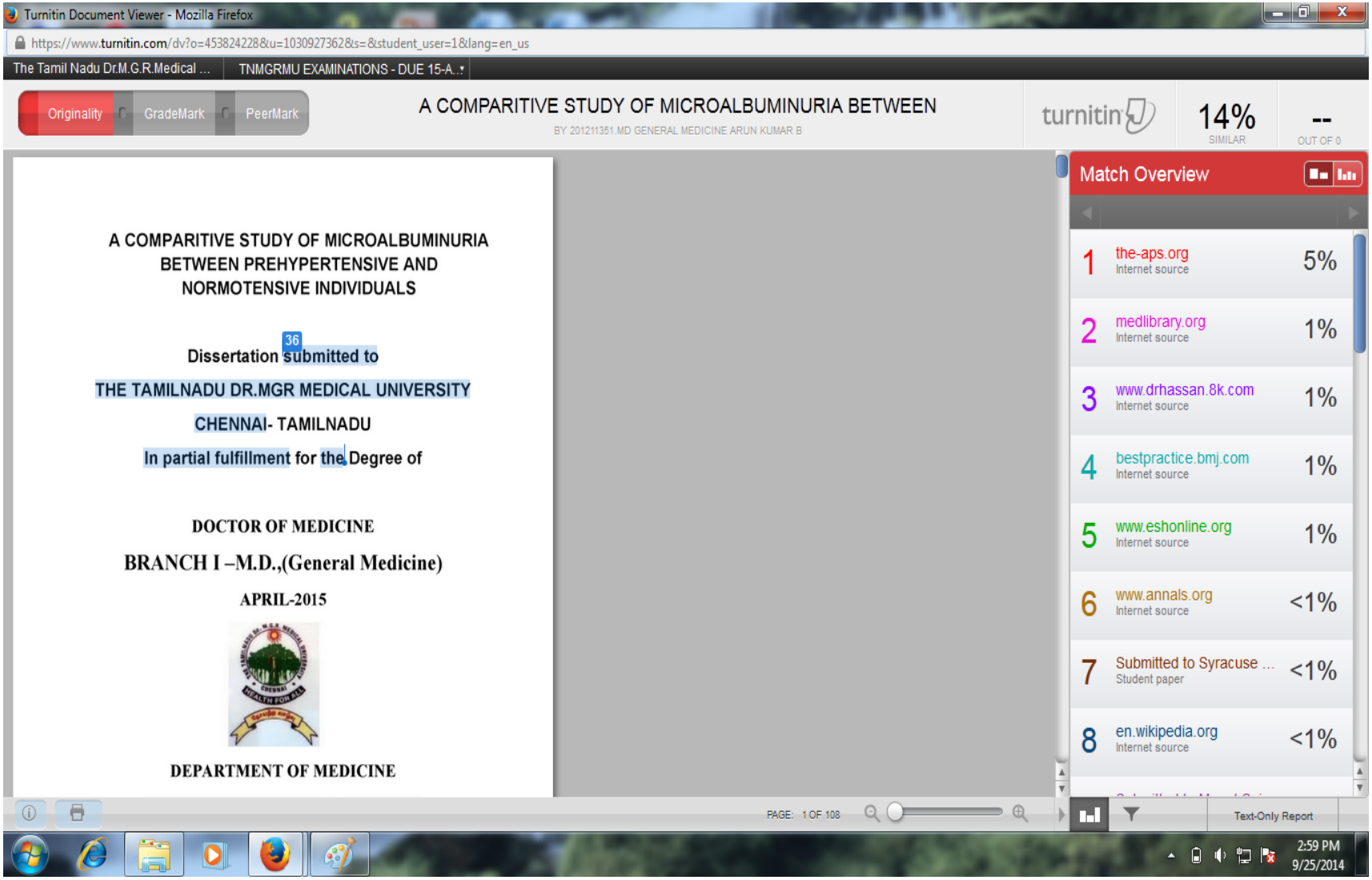
THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
   c. If the amendments require a change in the consent form, the copy of revised Consent Form should be submitted to Ethics Committee for approval. If the amendment demands a re-look at the toxicity or side effects to patients, the same should be documented.
   d. If there are any amendments in the trial design, these must be incorporated in the protocol, and other study documents. These revised documents should be submitted for approval of the IEC, only then can they be implemented.
   e. Approval for amendment changes must be obtained prior to implementation of changes.
   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

STANDS APPROVED UNDER SEAL

Dr.K.Shantaraman MD
Registrar, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India

Dr.V.Ramasubramanian MD DM
Member Secretary, TIREC
Tirunelveli Medical College, Tirunelveli – 627011
State of Tamilnadu, South India


Turnitin Document Viewer - Mozilla Firefox
https://www.turnitin.com/dv?o=453824228&u=1030927362&s=&student_user=1&lang=en_us
The Tamil Nadu Dr.M.G.R.Medical ...
TNMGRMU EXAMINATIONS - DUE 15-A...
Originality
GradeMark
PeerMark
A COMPARITIVE STUDY OF MICROALBUMINURIA BETWEEN
BY 201211351.MD GENERAL MEDICINE ARUN KUMAR B
turnitin
14%
SIMILAR
--
OUT OF 0
A COMPARITIVE STUDY OF MICROALBUMINURIA BETWEEN PREHYPERTENSIVE AND NORMOTENSIVE INDIVIDUALS
Dissertation submitted to
THE TAMILNADU DR.MGR MEDICAL UNIVERSITY
CHENNAI- TAMILNADU
In partial fulfillment for the Degree of
DOCTOR OF MEDICINE
BRANCH I –M.D.,(General Medicine)
APRIL-2015
DEPARTMENT OF MEDICINE
Match Overview
1 the-aps.org Internet source 5%
2 medlibrary.org Internet source 1%
3 www.drhassan.8k.com Internet source 1%
4 bestpractice.bmj.com Internet source 1%
5 www.eshonline.org Internet source 1%
6 www.annals.org Internet source <1%
7 Submitted to Syracuse ... Student paper <1%
8 en.wikipedia.org Internet source <1%
PAGE: 1 OF 108
Text-Only Report
2:59 PM
9/25/2014

[4]

DECLARATION

I**, Dr.B.ARUN KUMAR**, solemnly declare that I carried out this work on **"A COMPARITIVE STUDY OF MICROALBUMINURIA BETWEEN PREHYPERTENSIVE AND NORMOTENSIVE INDIVIDUALS"** at Department of General Medicine, Tirunelveli Medical College and Hospital during the period of August 2013 to August 2014.

This is submitted to the Tamilnadu Dr.M.G.R. Medical University, Chennai, in partial fulfillment of the rules and regulations for the MD Degree Branch I (General Medicine) Examination.

It was not submitted to the award of any degree/diploma to any University either in part or in full previously.

Place: TIRUNELVELI

Date:

DR.B.ARUN KUMAR,

POST GRADUATE,

M.D. GENERAL MEDICINE

TIRUNELVELI MEDICAL COLLEGE HOSPITAL

ACKNOWLEDGEMENT

At the outset I wish to thank our Dean Dr. THULASIRAM M.S, for permitting me to carry out this study in our hospital.

I express my sincere thanks to our Professor and H.O.D and my Unit Chief, DR.VAIRAMUTHURAJU M.D for his support and encouragement throughout the study.

I would like to thank Prof .DR.RAMASUBRAMANIAM M.D.,D.M.,HOD, Department of Nephrology for his valuable suggestions.

I would also like to thank Prof .DR.RAVICHANDRAN EDWIN M.D.,D.M., HOD, Department of Cardiology for his support in carrying out my study.

I am thankful to my assistant professors DR.RAVI, DR.RENUGA and DR. MOHAMMED RAFI for their constant support.

I also thank the Departments of Microbiology and Biochemistry for the laboratory support to this study.

No words of gratitude will be enough to thank my parents for their unconditional support and encouragement at each step in my way.

Last but not the least , I sincerely thank all the individuals who cooperated with me by participating in the study.

CONTENTS

A COMPARITIVE STUDY OF MICROALBUMINURIA BETWEEN PREHYPERTENSIVE AND NORMOTENSIVE INDIVIVIDUALS

ABSTRACT

BACKGROUND:

The aim of the study is to look for the presence of microalbuminuria in two groups namely a prehypertensive group (BP 120-139/80-89mmHg) and a normotensive group (BP <120/80mmHg) and to find out is there a significant difference in presence of microalbuminuria in both groups. Also to look for the other end organ damage such as diastolic dysfunction and fundus changes and to find out is there a significant difference in both the groups.

METHODS:

The study participants who were selected from ward patient's attenders were divided into two groups based on their blood pressure measurement. A brief history was recorded. Urine albumin creatinine ratio for microalbuminuria, fundus examination for retinopathy and echocardiogram to detect diastolic dysfunction was done in all participants. Other relevant investigations were done.

RESULTS:

The distribution of microalbuminuria in two groups are 2% and 28% in normotensive and prehypertensive group respectively (‘p’ value is<0.001) which is statistically significant. The distribution of diastolic dysfunction is 32% in prehypertensive group while none had diastolic dysfunction in normotensive group (‘p’ value is 0.004) which is statistically significant. 60% of those participants with microalbuminuria had associated diastolic dysfunction also.

CONCLUSION:

End organ damage starts to occur even at a prehypertension stage of blood pressure. So screening for high BP should start early and if detected to be prehypertensive, life style modification should be strongly recommended.

KEY WORDS: Prehypertension, Normotension, Microalbuminuria, Diastolic Dysfunction, Hypertension, End Organ Damage.

INTRODUCTION

Prehypertension is a blood pressure reading where the patient's BP is more than normal but not up to the level which is considered as hypertension. Prehypertension is a warning sign that the patient may develop hypertension in his near future. According to American Heart Association, around 59 million people are having prehypertension in United States.

The NHANES(The National Health And Nutrition Examination Survey) which is a part of National Center for Health Statistics (NCHS), located within CDC (Center for Disease Control and Prevention) was conducted in the year 1999 and 2000. The data obtained from this survey showed that around 31 percent of people in United States had prehypertension[1]. The prevalence was 39 percent among men and 23 percent among women[2].

NHANES(1999-2000) also found that almost 29% of the adult non institutionalized U.S. population, which is an estimated 58.5 million individuals, had hypertension , with systolic BP of >=140 mm Hg and diastolic BP of >=90 mm Hg. The prevalence has increased by 3.7% compared with the previous NHANES data from 1988 to 1991. NHANES

(2011-2012) had found that the prevalence of hypertension was 29.1 percent which is almost similar to that in 1999-2000.

Based on classification proposed by JNC 7, prehypertension is termed as a person's BP falling within the range of systolic blood pressure (120-139 mmHg) and diastolic blood pressure (80-89) . The person is said to be hypertensive if his BP falls in the range of systolic BP (>= 140 mmHg) and diastolic BP (>=90mmHg)[4]

Table 2. Joint National Committee On Prevention, Detection, Evaluation, And Treatment Of High Blood Pressure (JNC 7).

Normal	< 120/80
Prehypertension	120-139/80-89
Hypertension	≥ 140/90
Stage 1	140-159/90-99
Stage 2	≥ 160/100

Prehypertensive individuals are usually asymptomatic. They don't come to the clinicians unless they are symptomatic either due to end organ damage or symptoms due to elevated blood pressure or coming to clinicians due to some other problems. But the prehypertensive individuals are always at risk of progression to overt hypertension if left undetected.

Hence screening and identification of prehypertensive individuals becomes utmost important.

The prevalence of prehypertension in India has been found to be 32%. The study was done on a urban population in central India. Another study showed that the prevalence of prehypertension was around 36 percent in Chennai and 44 percent in Delhi[24].

RISK FACTORS AND ASSOCIATION OF PREHYPERTENSION:

- Many studies have found that prehypertension is more common in males than in females[60] and in some studies it has shown that its prevalence is more common than hypertension itself.
- Prehypertension is more prevalent in diabetics than non diabetics. When both coexist together, the cardiovascular risks is considerably higher.
- The prevalence of metabolic syndrome is more in prehypertensives than in normotensives[59].
- The prehypertensives tend to have higher levels of low density lipoprotein, triglycerides and lower levels of high density lipoproteins when compared to normotensive individuals.[58]
- The waist circumference and body mass index are considerably higher in prehypertensives than normotensives

- Prehypertensives has higher levels of C-reactive protein[62], tumour necrosis[factor- alpha[63], homocysteine leves and white cell count when compared to normotensives
- Prehypertensives also have higher levels of uric acid and ferritin when compared to normotensive individuals.

PROGRESSION TO HYPERTENSION:

In Framingham Heart Study, the rate of progression of prehypertension to hypertension was studied. It was found that the rate of progression was 19% over a period of 4 years[61]. One more related study, showed that the progression was 40% over a period of 2 years. The rate of rise depends on the age and BP of that individual.

Those with BP in the range of 130-139/85-89mmHg, has a progression rate of 43% over a period of 4 years when compared to those in the lower BP range that is BP of 120-129/80-84mmHg who has a progression rate of 20% over a period of 4 years. In accordance with the age, those in the age group of 65 years and above progresses from prehypertension to hypertension at a rate of 42% when compared to lower age group whose progression rate was 27%[61].

CARDIOVASCULAR RISK AND PREHYPERTENSION:

Since there is higher prevalence of C-reactive protein, homocysteine, uric acid and other inflammatory markers in the prehypertensive group the risk of acquiring a cardiovascular problem is more common in the prehypertensive individuals than the normotensive individuals. The Jichi Medical School Cohort Study Of Japan found that prehypertensive individuals are at a 45% higher risk of having a cardiovascular event over a period of 10 years when compared to normotensive individuals[64].

TARGET ORGAN DAMAGE AND PREHYPERTENSION:

In a study done in Sungkyunkwan University School of Medicine in Korea, the presence of microalbuminuria was done in prehypertensive individuals. The prehypertensive individuals are divided into two groups as BP in the range of 130-139/85-89mmHg and BP of 120-129/80-84mmHg. The study showed that presence of microalbuminuria is significantly higher in the higher BP group individuals[66]. In another chinese study the presence of microalbuminuria was found to be higher in prehypertensive group than in normotensive group. In the same study the levels of serum uric acid was found to be higher in prehypertensive people than the normotensive

people[65]. Also the cardiovascular risk is higher in the group with microalbuminuria.

In a study published in pubmed which was done in Turkey, the diastolic dysfunction was assessed in prehypertensive individuals. The diastolic dysfunction was assessed using various parameters. The result was diastolic dysfunction was higher in prehypertensives than normotensives[67].

In another study done in another institution in Turkey published in pubmed, apart from diastolic dysfunction, the degree of aortic stiffness is also measured using ultrasonography. It was found that both are comparatively higher in prehypertensive individuals and also C – reactive protein was measured in these individuals which showed a higher levels of C- reactive protein in those with end organ damage[68].

In a study done in a School Of Medicine in Greece which was published in the Journal of American Heart Association, they compared the common carotid artery intima media thickness and left ventricular mass in 25 prehypertensive individuals and 25 normotensive individuals. It was done to test subclinical atherosclerosis and target organ damage in heart. The study concluded as prehypertensive individuals had a higher intima media

thickness and left ventricular mass when compared to normotensive individuals.

In all these studies, the ultimate result is that subclinical target organ damage is more common in prehypertensive individuals than normotensive individuals. Also those with target organ damage have a faster progression to overt hypertension. Hence the prehypertensive individuals are the risky individuals who are not addressed often and usually less considered when compared to overtly hypertensive individuals. So screening prehypertensive individuals also becomes important and lifestyle modifications should be initiated even at that level of BP.

AIM OF THE STUDY

PRIMARY OBJECTIVES:

To look for the presence of microalbuminuria in the both the groups (prehypertensive group and normotensive group) and to find out is there a significant difference in presence of microalbuminuria in both groups.

SECONDARY OBJECTIVES:

- To look for the presence of target organ damage in both groups such as fundus changes and diastolic dysfunction.
- To look for association of prehypertension with factors like age, sex, smoking, alcohol consumption.
- To look for association of microalbuminuria with various factors like age, sex, smoking, alcohol consumption in both groups.
- To look for association of fundus changes and diastolic dysfunction with factors like age, sex, smoking and alcohol consumption in both groups.
- To look for association of microalbuminuria with fundus changes and diastolic dysfunction in both groups.

REVIEW OF LITERATURE

The arterial blood pressure is a measure of the potential energy of arterial wall or lateral force per unit area of vascular wall. It is usually expressed in units of dynes per cm^2. But clinically the measurements of arterial pressure are usually made by mercury manometer. It is expressed in mmHg.

1 mmHg = 1.332 dynes/cm^2 i.e. 120/80 mmHg = 160/106.5 dynes/cm^2

COMPONENTS OF BLOOD PRESSURE:

1. Systolic Blood Pressure: It is the amount of maximum pressure exerted during systole. It indicates the amount of work done by the heart or force with which the heart is working. It also indicates the degree of pressure that the arterial walls have to withstand
2. Diastolic Blood Pressure: It is the minimum pressure that is exerted during diastole of cardiac cycle. It measures the total peripheral resistance. It also indicates the constant load against which the heart has to work
3. Pulse pressure: It is the obtained when the diastolic blood pressure is subtracted from the systolic blood pressure. It indicates the volume of the pulse during each cardiac cycle

4. Mean blood pressure: It indicates the average blood pressure that is present throughout the cardiac cycle.

   Mean blood pressure = diastolic blood pressure + 1/3 pulse pressure

   The blood flow to each organ depends on the mean arterial blood pressure. Normal mean arterial pressure is 95- 100 mmHg

5. Proportional pulse pressure: It is obtained when the pulse pressure is divided by the systolic blood pressure and is measured in percentage.

   Proportional pulse pressure = pulse pressure /systolic blood pressure * 100%

   If it is < 25% then it identifies 90% of patients with systolic failure and a cardiac index of < 2.2 L/min/m^2 (normal cardiac index – 2.6 to 4.2L/min/$m^{2)}$

DETERMINANTS OF ARTERIAL BLOOD PRESSURE:

- Arterial BP is the product of cardiac output (CO) and peripheral resistance(PR) so, BP = CO * PR.
- Cardiac output is calculated by multiplying heart rate (HR) and stroke volume (SV)
- CO = HR* SV
- If the increase in CO is due to increase in SV, then it is the systolic blood pressure which increases.
- If the increase in CO is due to increase in HR, then it is the diastolic blood pressure which increases.

- If the increase in CO is due to both increase of CO and HR, both the systolic and diastolic blood pressure increases.
- The peripheral resistance is determined mainly by the arterioles and it depends on four factors,
    1. Elasticity of the vessel wall
    2. Velocity of the blood flow
    3. Viscosity of the blood
    4. Total blood volume in the arterial system

HISTORY:

Stephen Hales was the first person to measure blood pressure. In 1733 he first recorded it on a horse. He inserted a long tube vertically upwards into an artery and observed the raise in pressure as the blood column was forced up the tube by the movement of the blood in the artery[3]. The first sphygmomanometer was invented in 1881 by Samuel Siegfried Karl Ritter Von Basch[5]. It had a rubber bulb that was filled with water which restricted the blood flow in the artery. The bulb was connected to a mercury column that translated the pressure into millimeters of mercury.

In 1896 further improvement was done by Scipione Riva- Rocci. He first introduced the cuff that would be applied around the limb for

compressing the artery. He was the one who designed the prototype for the present day instrument[6]. Until 1905, BP was measured using palpatory method only after which it was Nikolai Korotkoff[7], a Russian surgeon who introduced the Korotkoff sounds which includes five phases, the appearance and disappearance of the sounds corresponding to the systolic and diastolic blood pressure respectively. This method was known as auscultatory method of recording BP.

Currently the various methods available for the measurement of BP includes

1. Sphygmomanometric measurement : palpatory and auscultatory method
2. Doppler ultrasound method
3. Oscillometric method
4. Self measurement (home BP recording)
5. Ambulatory BP monitoring

PROPER TECHNIQUE FOR BP RECORDING:

The width of the cuff should be 40% of the limb circumference and the length of the cuff should be 80% of the limb circumference[4]. The ratio between width and length of the cuff should be 1:2. The standard cuff size available and we are commonly using size is a width of 5 inch and a length of 10 inch.

If this standard cuff is applied to a larger arm as in obese individual or a normal adult thigh, the BP is overestimated and if the same cuff is applied to a smaller arm the BP is underestimated.

In patients with arteriosclerosis, the systolic BP can be overestimated as high as 30mmHg. The cuff width should be 1.5 inch in infants and small children, 3 inch in older children and 8 inch in obese individuals.

Before recording the patient should avoid caffeine, exercise and smoking at least 30 minutes before measurement. The patient should be seated quietly and comfortably for at least 5 minutes in a chair. His/hers arm should be supported at the heart level and feet on the floor. Cuff should be applied over the artery at the level of heart and the lower edge of cuff should be at least 1 inch above the antecubital fossa.

BP recording to be done both by palpatory and auscultatory method and the cuff should be deflated rapidly. A complete one minute should elapse before recording the BP in the same limb. If the cuff is elevated before that it may artificially elevate the diastolic BP. Ideally BP recording should be done in both upper limb and at least one lower limb.

PHYSIOLOGY OF BLOOD PRESSURE:

There are five physiological mechanisms which is responsible for maintaining blood pressure within normal range.

1. Response of the autonomic nervous system
2. Capillary fluid shift mechanism
3. Role by kidney and fluid balance mechanism
4. Hormonal actions
5. Local regulatory factors

a) AUTONOMIC NERVOUS SYSTEM:

A drop in blood pressure which may be secondary to decreased cardiac output will be sensed by the baroreceptors located in carotid sinus and aortic arch[11]. This sends signals to the vasomotor center located in brain so that efferent signals are sent that lead to sympathetic nervous system activation that in turn leads to adrenaline and noradrenaline release.

The response to this stimulus is achieved through alpha and beta receptors

- Alpha receptor stimulation leads to adequate perfusion in essential territories like cerebral and coronary vascular beds. But it may lead to hypoperfusion of less essential vascular bed because of increased vascular resistance and afterload can lead to decreased cardiac output

- Beta receptor stimulation leads to stimulation of adenylyl cyclase which increases the levels of cyclic AMP. This lead on to positive chronotropic, inotropic and lusiotropic effect that results in increase in heart rate, increase in force of contraction and improved diastolic relaxation respectively. It also stimulates the release of renin from juxta glomerular apparatus (JGA).

b) CAPILLARY FLUID SHIFT MECHANISM:

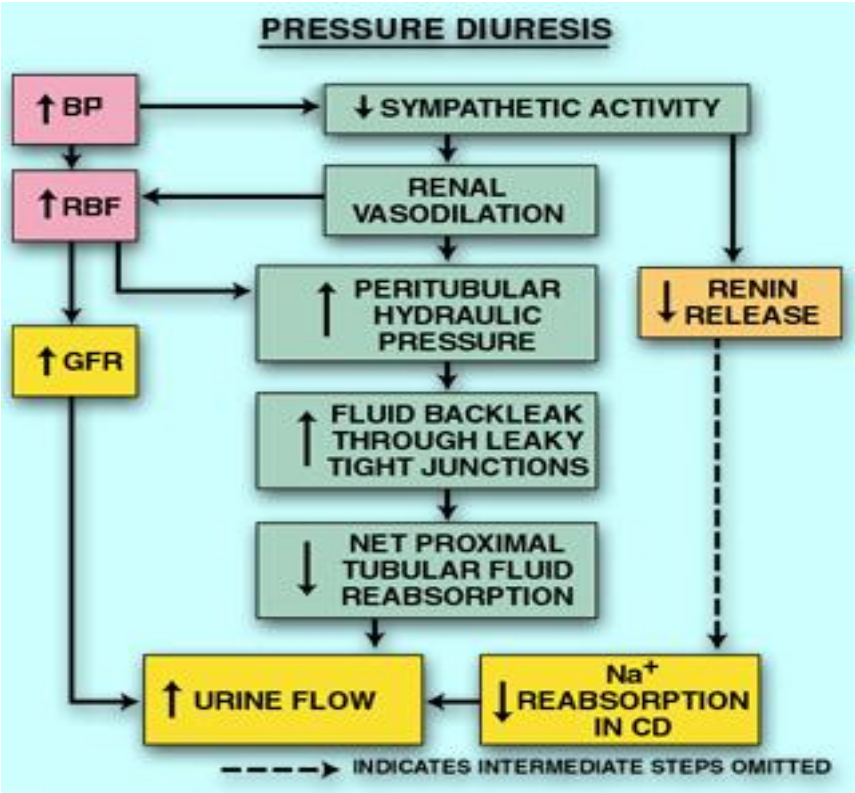
According to Starling Hypothesis, there is a fluid exchange happening at capillary level that is determined by hydrostatic and oncotic pressure. Higher hydrostatic pressure in blood and decreased oncotic pressure in interstitium shifts the fluid out of intravascular compartment. Lower hydrostatic pressure and increased oncotic pressure in interstitium shifts the fluid into intravascular compartment. In hypotensive states , the interstitial fluid enters into intravascular compartment leading fluid expansion in vessel and thus increased BP.

c) KIDNEY AND FLUID BALANCE MECHANISM:

In addition to the RAAS system, blood pressure is regulated by:

- Pressure Diuresis: As the blood pressure increases, the flow through the kidneys also increases and this increases glomerular filtration rate and hence urine output and decreased fluid volume.

- Pressure Natriuresis: Increased renal perfusion pressure result in increased sodium excretion. If more sodium is excreted less water is reabsorbed and hence the extracellular fluid volume decreases thereby decreasing BP[12].



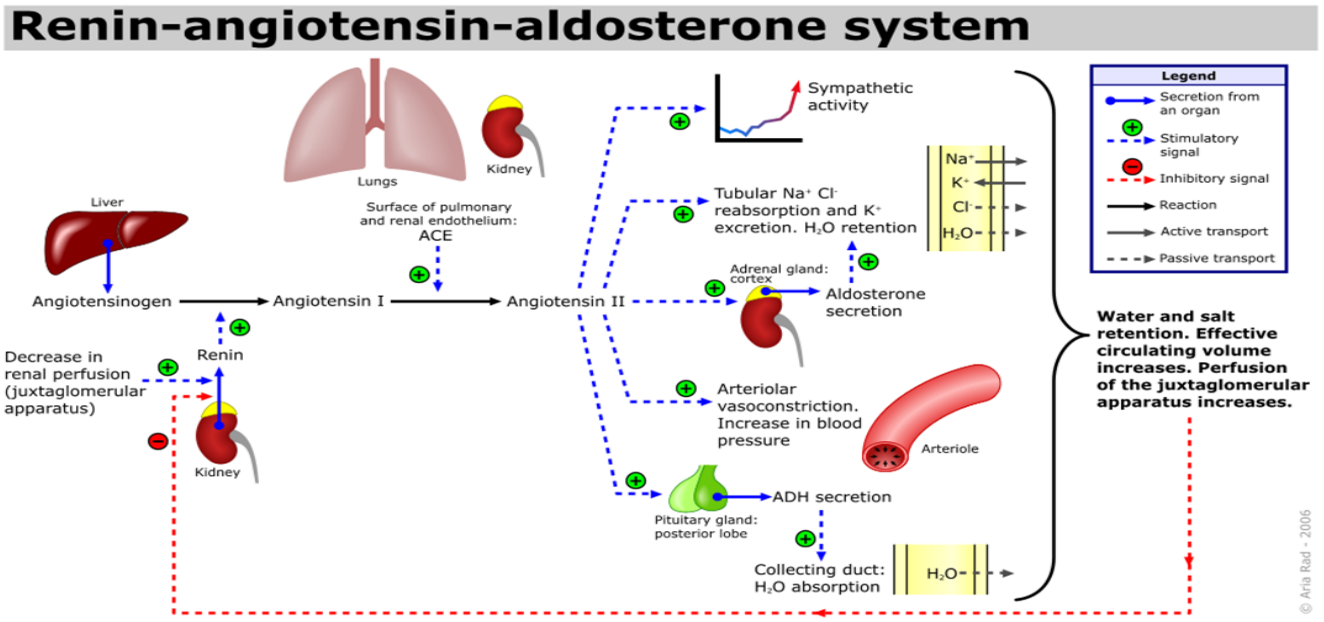
d) HORMONAL ACTIONS:

JGA maintains BP through Renin -Angiotensin -Aldosterone System (RAAS). Renin is released by Juxta Glomerular cells through various stimuli which include:

1) Baroreceptors located in afferent arteriole stimulated by drop in renal blood flow.

2) Decreased delivery of sodium chloride to distal tubule which is sensed by the macula densa, a chemoreceptor like action
3) Beta receptor mediated release of renin by the release of adrenaline as sensed by the carotid sinus and aortic arch baroreceptors.

Renin is aspartyl protease which is synthesized as an inactive precursor, prorenin. Most of the renin in circulation is synthesized by the juxta glomerular cell located in the afferent arteriole. Prorenin is secreted directly into the circulation or it may be activated inside the secretory cells and released as active renin[13]. Plasma contains two to five times more amount of prorenin than renin but there is no evidence that prorenin has physiological activity.



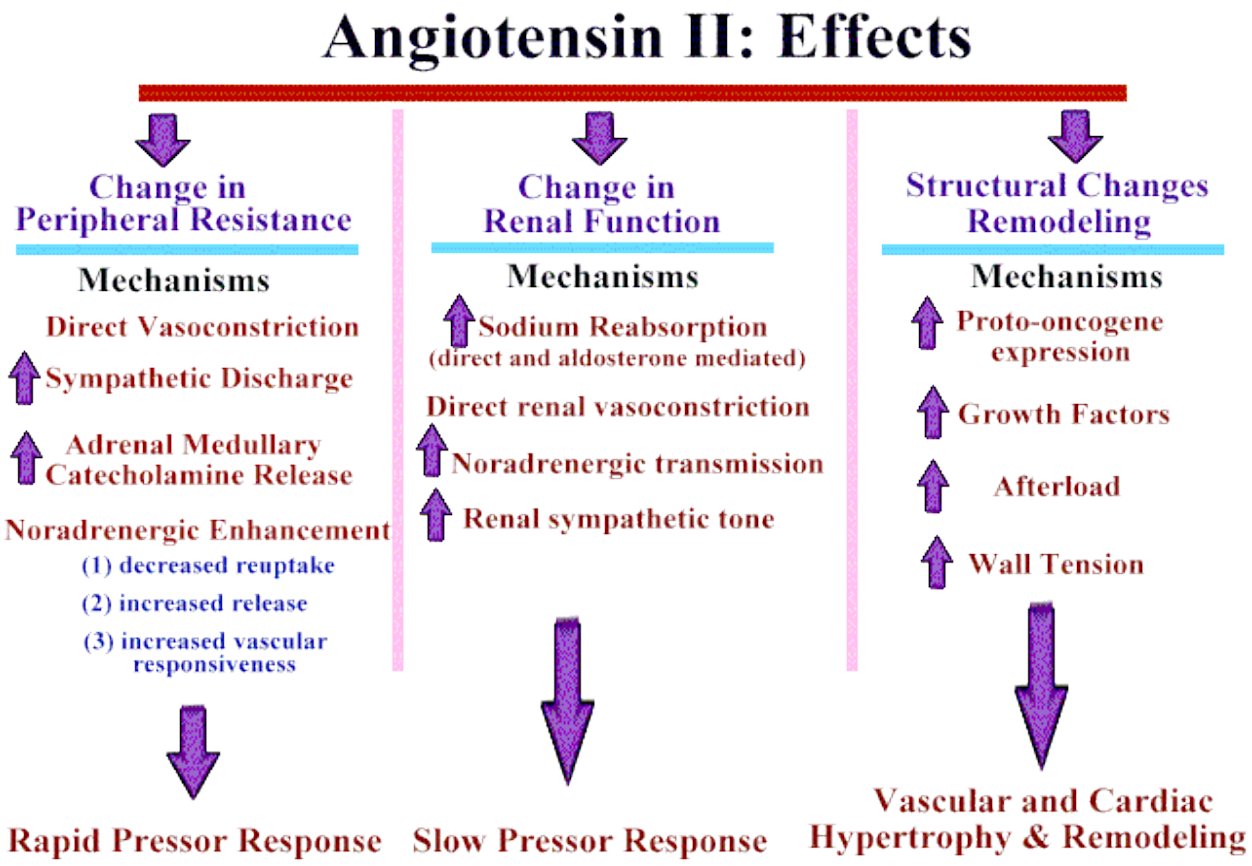
Renin breaks down Angiotensinogen which is produced by the liver to Angiotensin I which is further converted to Angiotensin II by the Angiotensin Converting Enzyme (ACE). This action occurs at lungs. Angiotensinogen is an alpha 2 globulin and it is a member of serpin family. Its levels are increased by plasma corticosteroid, thyroid hormone and estrogens. It has 453 amino acids and the first 12 amino acids are required for its activity.

ACE is secreted by endothelial cells in the vessel wall in lungs and kidneys. ACE apart from breaking Angiotensin I it also degrades bradykinin[14][15]. ACE has two isoenzymes. One form is the one secreted in the lung and kidneys and the other is the one present in brain. This brain ACE prevents the formation of toxic form of beta amyloid. Hence any ACE inhibitors used which crosses blood brain barrier may lead to progression of dementia.

Angiotensin II has half life of 30 seconds in blood and 15 to 30 minutes in tissues. It has the following actions:

- It is a potent vasoconstrictor present in the body, so it directly increases the mean arterial pressure
- Increases the reabsorption of sodium chloride in proximal convoluted tubule

- Increases the sensitivity of tubuloglomerular feedback
- Stimulates the release of anti diuretic hormone (ADH) from pituitary
- Has a prothrombotic effect through stimulation of adhesion and aggregation of platelets
- Increases the synthesis and secretion of aldosterone through direct stimulation of zona glomerulosa of adrenal cortex.
- Aldosterone increases sodium and water reabsorption and promotes potassium secretion



e) LOCAL REGULATORY FACTORS:

1. Endothelin: A 21 amino acid peptide produced by endothelium result in vasoconstriction[16]. So they are secreted by endothelium they are called endothelins. There are three isoforms of endothelin like ET-1, ET-2, ET-3. It bounds to four types of endothelin receptors like $ET_{A,}$ $ET_{B1,}$ ET_{B2} and ET_C[17].
2. Prostaglandins/prostacyclins: They are the group of hormone like compounds that are produced from fatty acids. They are not endocrine hormones but have an autocrine and paracrine action. They are two pathways in the synthesis of these compounds which depends on the enzyme with which they are produced. They are cyclooxygenase and lipoxygenase pathway. They include PGE_2, PGF_2, PGI_2, PGD_2, TXA_2, LTA_4, LTB_4, LTC_4, LTD_4, LTE_4. Of these compounds it is PGE_2 and PGI_2 (prostacyclin) are the ones which cause vasodilation.
3. Nitric oxide: It is vasodilator which is synthesized in the endothelium of the vessel wall. It is produced endogenously (within the body) from L-arginine, NADPH and O2 by nitric oxide synthase enzymes. The endothelium (inner lining) of blood vessels make use of nitric oxide and send signals to the surrounding smooth muscle to relax which will produce vasodilation and increased perfusion to that corresponding regions. It has a halflife period lasting for few seconds. But it can diffuse freely across membranes. All

these factors leads to its paracrine (between adjacent cells) and autocrine (within a single cell) actions[18].

Nitrate-rich vegetables, like spinach, arugula and beetroot…, have been found out to elevate cardioprotective levels of nitric oxide. It was also found to decrease the BP pre-hypertensive persons[19]. It maintains vessel homeostasis by inhibiting vascular smooth muscle contraction and growth. It also inhibits both platelet aggregation and adhesion of the leucocytes to the endothelium. Persons with atherosclerosis, diabetes mellitus or hypertension are found to have impaired NO pathway[20]. Also high salt intake tend to decrease nitric oxide synthesis[21]. Drugs like minoxidil used in hair growth, sildenafil citrate used in pulmonary hypertension and erectile dysfunction and nitroglycerine in angina all act through nitric oxide pathway.

HYPERTENSION:

EPIDEMIOLOGY:

Hypertension arising as the major cause of burden of diseases in the world[22]. Around 76 lakh deaths and 9.2 crores disability-adjusted life years worldwide were caused due to increased blood pressure as per 2001. If a person has hypertension, the major risk of him having cardiovascular diseases like coronary artery disease or congestive heart failure or ischemic

and hemorrhagic stroke (CVA) or renal failure or peripheral vascular disease is doubled. Though antihypertensive therapy reduces some risks of cardiovascular and renal disease still a huge segment of hypertensives are either left untreated or inadequately managed.

BP levels and prevalence of hypertension may vary among countries. In industrialized and well developed population the blood pressure may rise steadily for the first two decades of life. During adulthood period, average systolic blood pressure is higher for men than women, but among old, there is steeper rise for women. As a result, among individuals more than 60 years old, systolic blood pressure is higher for women than for men. Among adults, diastolic blood pressure increases progressively up to 55 years, after which it decreases, leading to a wide pulse pressure beyond 60years. The probability for an adult or elderly to develop hypertension in his or her lifetime is around 90%.

Recent evidences are suggesting that the prevalence of hypertension in India is increasing, due to increasing obesity. In African American decent, hypertension may appear earlier and might generally be more severe, and results in high rates of morbidity and mortality from its complications than in whites.

The prevalence of hypertension was estimated to be around 40.8% in urban and 17.9% in the rural Indian population in the year 2013. Gupta et al reported the highest prevalence of hypertension (48.2%) in a recent multi-centric study, conducted in the urban population of India[23]

GENETIC CONSIDERATIONS:

Although there are specific genetic variants, these usually won't be applicable to more than 98% of patients having essential hypertension. For most people, hypertension is a polygenic disorder where a combination of genes acts in association with environmental factors to make a contribution to blood pressure.

Several strategies are used to identify specific hypertension-related genes. Animal models often aid a powerful approach to evaluate the genetic loci and other related genes in association with hypertension. In these studies, different alleles of specific candidate genes are compared in hypertensives and normotensive control subjects.

Current evidences suggest that genes that encode for RAAS, angiotensinogen and angiotensin-converting enzyme (ACE) polymorphisms, would relate to hypertension. Another gene that is thought to be associated with hypertension is the alpha-adducin gene and is thought to increase the

renal tubular absorption of sodium. Other genes possibly associated with hypertension may include genes coding for AT_1 receptor, aldosterone synthase enzyme and $beta_2$ adrenoreceptor..

Some evidences also suggest that there may be genetic determinants available to predict target organ damage due to hypertension. Those evidences indicate a significant heritability of left ventricular mass and also any variation in genes associated with renal damage which suggests that some genetic factor also may play a role in hypertensive nephropathy. Some genetic variants have also been linked to CHD and stroke.

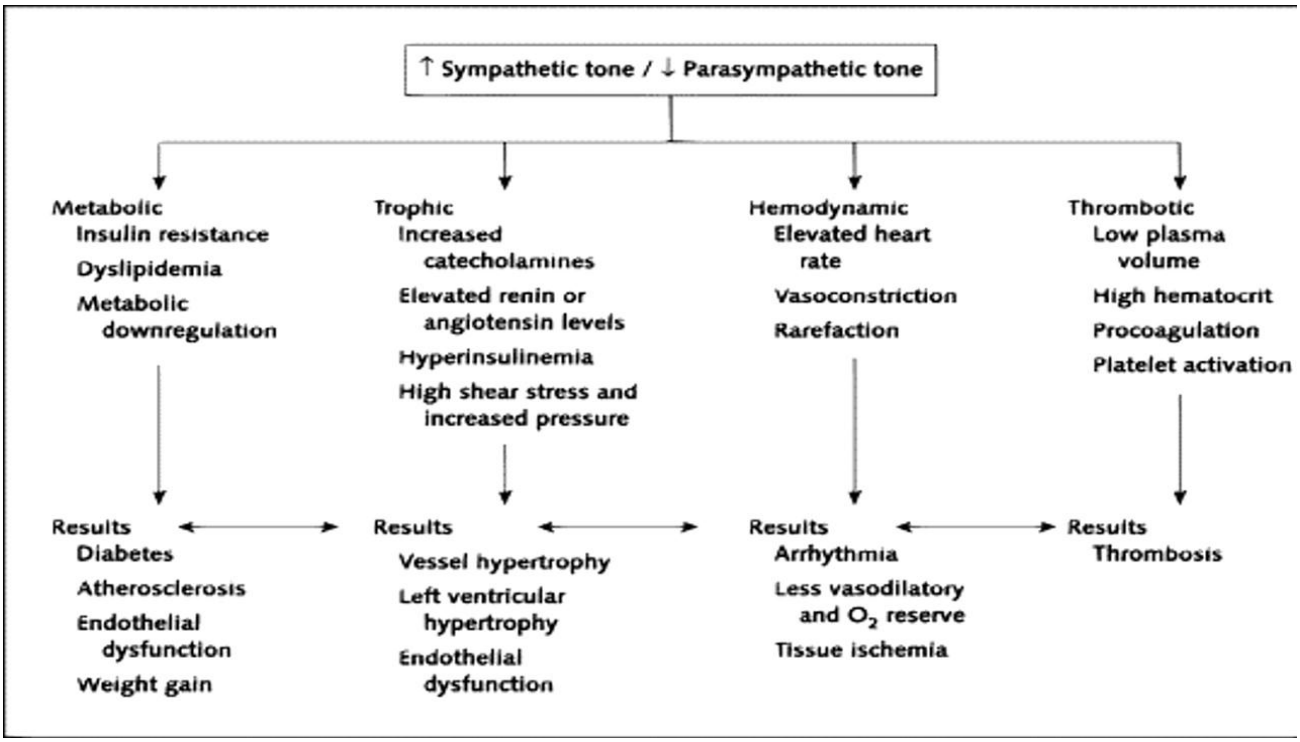
In the future, it would be possible that DNA analysis will assess and identifies the individual risk for hypertension and target organ damage and will also identify those who respond to specific classes of antihypertensive agents.

PATHOGENESIS OF HYPERTENSION:

Multiple factors contribute to the pathogenesis of hypertension apart from genetic and environmental considerations. Those include multiple system involvement, multiple hormonal involvement and multiple local vasoregulatory factors.

a) AUTONOMIC NERVOUS SYSTEM:

Increased sympathetic activity increases blood pressure and it leads to the development and maintenance of high BP through stimulation of multiple systems like heart, blood vessels and kidneys. The net result is the increased cardiac output, increased peripheral vascular resistance and finally fluid retention[25]. There is an autonomic imbalance which is like high sympathetic tone with decreased parasympathetic tone. This is associated with metabolic, hemodynamic and trophic abnormalities that may finally result in increase in cardiovascular morbidity and mortality rates[26].



The mechanism that leads to high sympathetic activity in hypertension is complex due to changes in baroreceptor and chemoreceptors actions at both peripheral and central areas. Arterial baroreceptors are reset to a higher level in hypertensive patients and this is known as pressure resetting. There is also central resetting of aortic baroreflex in hypertensive patients. This pressure resetting seems to be mediated by angiotensin II through its central action[27]. Angiotensin II simply amplifies the response to sympathetic stimulation in periphery by presynaptic release of norepinephrine[28].

Additional mediators suppressing baroreceptor activity and contributing to sympathetic overactivity in hypertension include reactive O2 species and endothelin[29][30]. Recently, it is also found that there is evidence of increased chemoreflex function, that are leading to enhanced sympathetic activation which occur due to hypoxia[31]. Clinically it can be made out by exaggerated increase in sympathetic activity which sustains even in the awake state and this also seems to be a contributory factor to hypertension in patients suffering with obstructive sleep apnea syndrome.

Sympathetic stimulation over a long period of time induces vascular remodeling and hypertrophy of the left ventricle, presumably by both direct and indirect actions of norepinephrine on alpha and beta receptors, as well as

stimulate release of various trophic factors that includes fibroblast growth factors, transforming growth factor and insulin-like growth factor 1[26]. Clinical studies show positive correlations between left ventricular mass, circulating norepinephrine levels and reduced radial artery compliance (an index of vascular hypertrophy). Thus, sympathetic overactivity mechanisms contribute to target organ damage and hence pathogenesis of hypertension[32].

b) VASCULAR REACTIVITY:

The vasoconstriction effect of infused norepinephrine is much higher in hypertensive patients than the normotensive controls. This vasoconstrictor response to norepinephrine is also higher in normotensive siblings of hypertensive parents compared to controls who don't have a family history of hypertension. All these effects suggest that the hypersensitivity may have a genetic origin rather than just a consequence of high blood pressure.

Exposure to stress always provokes sympathetic overactivity, and if someone is continuously under stress, then the stress-induced vasoconstriction may lead to vascular hypertrophy, and hence there is an incremental response to peripheral resistance and blood pressure [33]. This could partly explain why people of lower socioeconomic status have greater

incidence of hypertension, since they lead a day to day stressful life. When there is an associated family history of hypertension, then there is an augmented vasoconstrictor response and sympathetic response to lab stressors, like cold pressor testing and mental stress that may ultimately predispose them to hypertension. This is true in young Indians as well. Hence there is increased incidence of hypertension in patients with exaggerated stress responses.

c) VASCULAR REMODELLING:

In hypertension there is always an increase in peripheral vascular resistance due to the alterations in structure, function and mechanical properties of small arteries. High blood pressure and associated target organ damage is due to the remodeling of these vessels[34]. It is determined at the precapillary level that includes arterioles and small arteries. Increased resistance in hypertensive patients can be subjected to rarefaction (decreased number of parallel-connected vessels) and narrowed lumen of resistance vessels. Examination of specimens from gluteal skin biopsy of patients with untreated essential hypertension has uniformly revealed reduced lumen areas due to thickening of vessel wall and increased tunica media–lumen ratios.

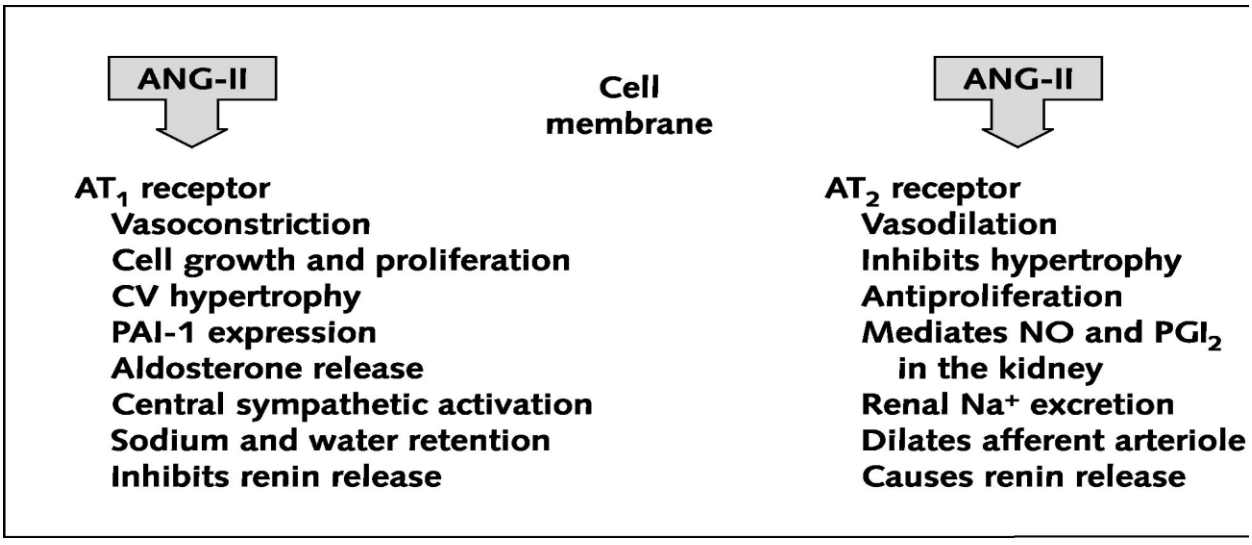
d) ARTERIAL STIFFNESS:

As age advances there is reduced elasticity (increased stiffness) of the large conduit arteries, hence both systolic blood pressure and pulse pressure increases. Arteriosclerosis as a result of collagen deposition and smooth muscle cell hypertrophy occurs in these arteries. There is thinning, fragmenting, and fracture of elastin fibers in the tunica media[37]. Other factors that contribute to a decrease in the central arterial compliance include estrogen deficiency, hyperhomocysteinemia, diabetes, high dietary salt intake and tobacco usage, by damaging the vascular endothelium.

Progressive arterial stiffness increases pulse wave velocity that contributes to the wide pulse pressure that is commonly seen in elderly hypertensive patients. Younger personalities may have lower pulse wave velocity. Therefore we can jump into an conclusion that pulse pressure can be used as a single better predictor of cardiovascular disease risk rather than either systolic blood pressure or diastolic blood pressure per se.

e) RENIN ANGIOTENSIN ALDOSTERONE SYSTEM:

Blood pressure is increased by angiotensin II by various mechanisms as described earlier in blood pressure regulation. Angiotensin II induced cardiac and vascular cell hypertrophy and hyperplasia occurs by directly activating the angiotensin II type 1 (AT1) receptor and by indirectly stimulating the release of various growth factors and cytokines. AT1 receptor activation stimulates various tyrosine kinases, which in turn phosphorylates the tyrosine residue that occurs in several protein degradation, leading to vasoconstriction, cell growth proliferation[38]. AT2 receptor activation stimulates a phosphatase which inactivates a mitogen-activated protein kinase, which is a key enzyme in transducing signals from the AT1 receptor. Hence the action of AT1 receptor is exactly opposite to AT2 receptor.

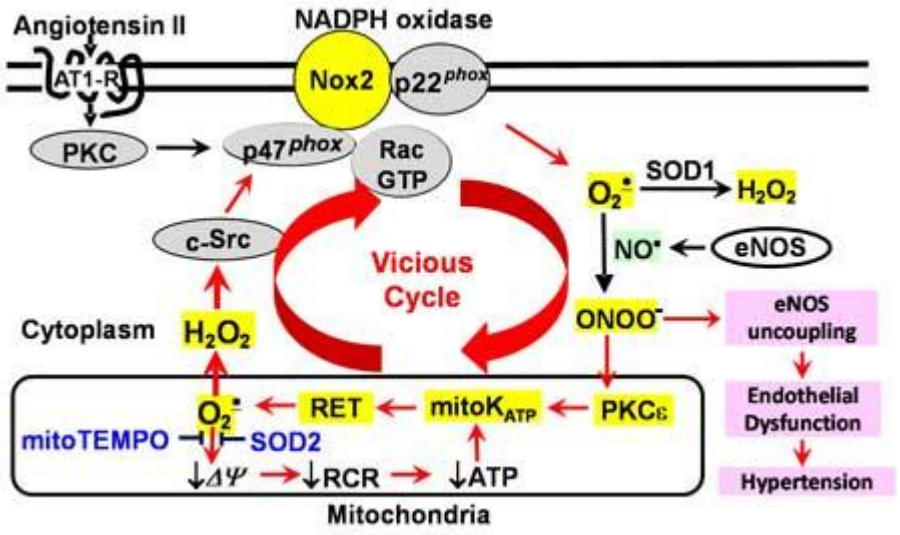


f) ANGIOTENSIN II AND OXIDATIVE STRESS:

Stimulating the oxidant production by angiotensin II is an alternative mechanism by which it increases cardiovascular risk. Hypertension because of increased angiotensin II is also found to be due to vascular p22phox messenger RNA (mRNA) up regulation, which is a component of the oxidative enzyme nicotinamide adenine dinucleotide phosphate [NADPH] oxidase[39]. The angiotensin II receptor– dependent NADPH oxidase activation is associated with enhanced oxidant superoxide anion formation. Superoxide instantly reacts with NO and forms the oxidant peroxynitrite (ONOO)[40]. Due to reduction in NO bioactivity it may provide another mechanism to explain the enhanced vasoconstrictor response to angiotensin II in hypertension.

Other vasculotoxic responses in relation to angiotensin II are due to the activation of NADPH oxidase that may include low-density lipoprotein oxidation and increased mRNA expression for monocyte chemoattractant protein-1 and vascular cell adhesion molecule-1[41]. It is clear that ACE inhibitors and ARBs block the activation of NADPH oxidase and hence limit oxidative reactions in the vasculature. These findings reveal that the ACE inhibitors and ARBs not only lower blood pressure but also has clinically

important vasoprotective effects. Important randomized clinical trials have also supported this hypothesis.



g) ENDOTHELIAL DYSFUNCTION:

Nitric oxide is known to be a potent vasodilator, also inhibits platelet adhesion and aggregation, and suppresses migration and even proliferation of vascular smooth-muscle cells. Normal endothelial cells produce nitic oxide in response to various stimuli, which includes blood pressure changes, shear stress, and pulsatile stretch. It has an important role in the regulation of blood pressure, and thus indirectly both thrombosis and atherosclerosis[42].

Healthy persons are continuously exposed to NO-dependent vasodilator tone, but this mechanism is diminished in hypertensive persons.

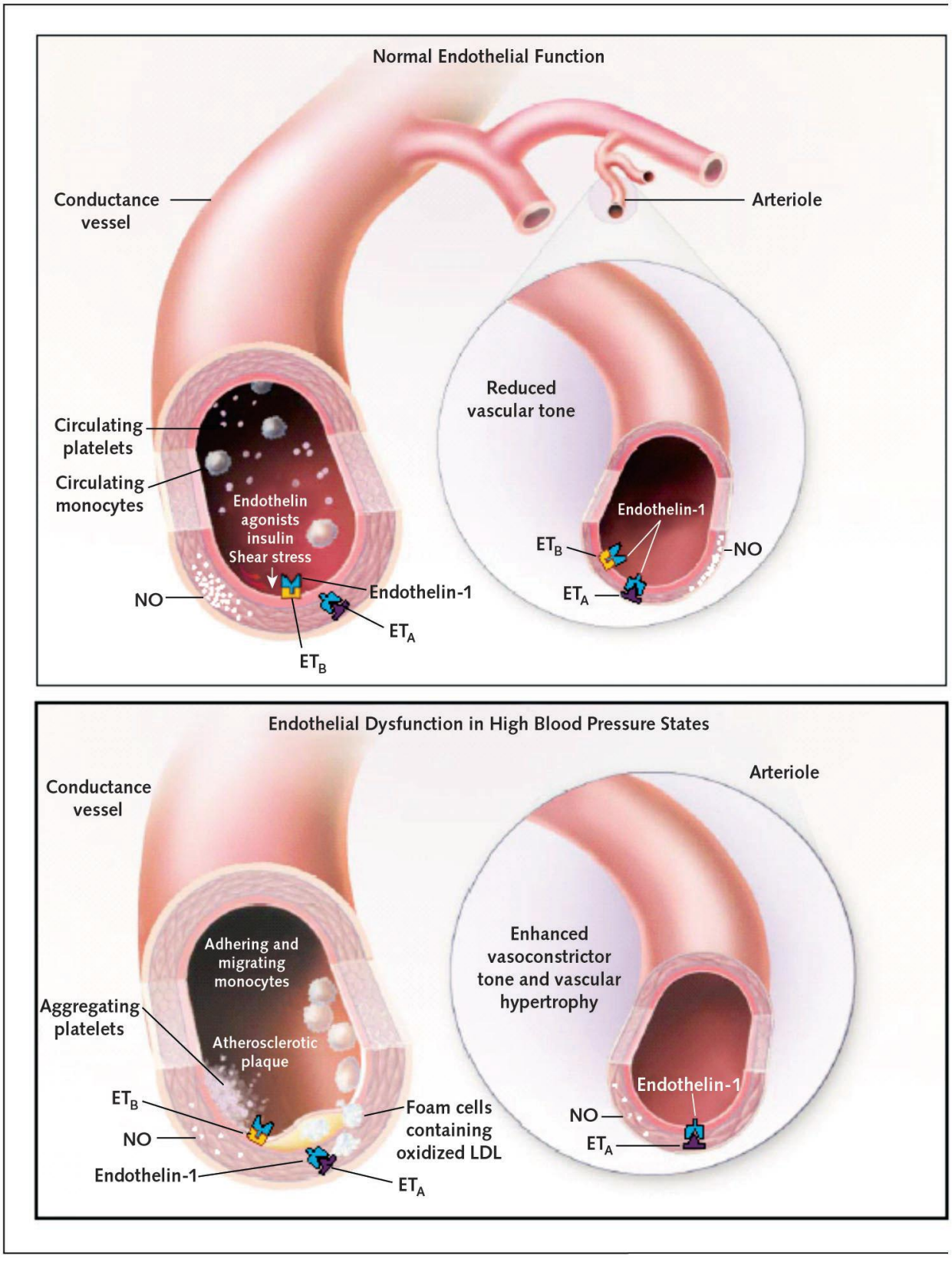
Some observations reveal that in vivo superoxide dismutase (an intracellular enzyme reducing superoxide to hydrogen peroxide) delivery reduces blood pressure and even restores NO bioactivity. These evidences reveal that oxidant stress also contributes to the inactivation of NO in hypertensives and also lead to the development of endothelial dysfunction[43]. It is suggested that angiotensin II increases oxidant superoxide formation at minimal concentrations that bring minimal blood pressure changes[44]. Hence it is proposed that both increased oxidant stress and also endothelial dysfunction predisposes to hypertension.

Though this concept is subject to debate, it is clear that antihypertensive drugs that inhibit the renin–angiotensin– aldosterone system, including ACE inhibitors, ARBs, and mineralocorticoid receptor antagonists, are effective in reversing endothelial dysfunction. This action at least partly accounts for their cardioprotective effect.

h) ENDOTHELIN:

The antagonists to endothelin receptor reduce the blood pressure and also peripheral vascular resistance in both normotensives and mild to moderate hypertensives . This strongly interprets that endothelin plays a major role in the pathogenesis of hypertension[45].

The following illustrated figure shows both large conductance vessels (*left*), like epicardial coronary arteries, and resistance arterioles (*right*). It is well noted that in normal conductance arteries (*top*), there is free circulation of platelets and monocytes, and low-density lipoprotein oxidation is prevented by a preponderance of nitric oxide (*NO*) formation. There is a constant release of nitric oxide at the level of the small arterioles, hence reduced vascular tone is maintained. Nitric oxide is known to be a potent vasodilator, also inhibits platelet adhesion and aggregation, and suppresses migration and even proliferation of vascular smooth-muscle cells. It is produced endogenously (within the body) from L- arginine , NADPH and O2 by nitric oxide synthase enzymes.


Normal Endothelial Function
Conductance vessel
Arteriole
Circulating platelets
Circulating monocytes
Endothelin agonists insulin Shear stress
NO
Endothelin-1
ET_A
ET_B
Reduced vascular tone
Endothelin-1
ET_B
NO
ET_A
Endothelial Dysfunction in High Blood Pressure States
Conductance vessel
Arteriole
Adhering and migrating monocytes
Aggregating platelets
Atherosclerotic plaque
ET_B
NO
Endothelin-1
Foam cells containing oxidized LDL
ET_A
Enhanced vasoconstrictor tone and vascular hypertrophy
Endothelin-1
NO
ET_A

Normally endothelin - 1 doesn't induce vasoconstriction or there will be only minimal vasoconstriction through type A endothelin receptors (ET_A) stimulation found on smooth-muscle cells and also contributes to basal release of nitric oxide by stimulating type B endothelin receptors (ET_B) located on endothelial cells. In the microvasculature (*bottom*) of hypertensives, decreased nitric oxide activity and increased ET_A-mediated vasoconstrictor activity of endothelin-1 result in increased vascular tone and hypertrophy of tunica media, consequently resulting in increase in the systemic vascular resistance.

A similar imbalance at the level of conductance arteries, leads to a proatherosclerotic picture like low-density lipoprotein oxidation, followed by the migration of monocytes, and then formation of foam cells. These activities culminates in the development of atherosclerotic plaques. If the plaque ruptures which is associated with enhanced platelet aggregation and impaired fibrinolysis, terminate in acute intravascular thrombosis, which explains why there is increased risk for cardiovascular problems in patients with hypertension[46].

HYPERTENSION INDUCED TARGET ORGAN DAMAGE:

HYPERTENSION AND HEART:

1. LEFT VENTRICLE HYPERTROPHY(LVH):

LVH can be identified by electrocardiography in only 5% to 10% of patients with hypertension but by echocardiography it goes upto 30% and it increases to 90% in patientss with severe hypertension[47]. More LVH is seen with abuse, diabetes, and hypercholesterolemia[48]. On the other hand, cardiac hypertrophy in response to excess load is nonpathologic in three circumstances such as maturation in infancy and childhood pregnancy, and high-level exercise.

The chronic adaptation of the left ventricle to increased cardiac load is myocardial hypertrophy. Increased wall stress signals mRNA transcription to increase muscular proteins[48]. Pure BP overload leads to an increase in left ventricle wall thickness without concomitant increase in cavity volume, i.e., concentric hypertrophy. The LVH pattern can be modified by increased pulse-wave velocity, increased arterial stiffness and blood viscosity.

2. SYSTOLIC DYSFUNCTION:

Hypertension can lead on to both systolic and diastolic dysfunction leading on to symptoms of congestive cardiac failure. Most of the time in cardiac failure, both co-exist together. It is characterized by a dilated heart and reduced ejection fraction in Echocardiogram.

3. DIASTOLIC DYSFUNCTION:

Diastolic dysfunction is more common in isolated hypertensive patients. Also around 1/3 of patients with congestive heart failure have diastolic dysfunction but their systolic function remains absolutely normal. Diastolic dysfunction is one of the earliest consequences of hypertension-related heart disease and is aggravated by left ventricular hypertrophy and also ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function of the heart. It can also be evaluated by echocardiography and radionuclide angiography which are noninvasive.

Some of the important causes of diastolic dysfunction include hypertension, diabetes, aortic stenosis, constrictive pericarditis and restrictive cardiomyopathy. Diastole is the period of cardiac cycle during which both ventricles receive blood from their respective atrium by relaxation of ventricles.

Diastolic failure occurs when the ventricle can't be filled properly because its wall becomes thick or rigid so that it is difficult for it to relax normally. This situation occurs in a concentric hypertrophy. But in systolic heart failure there is usually an eccentric hypertrophy[49].

Diastolic failure is diagnosed by an elevated diastolic pressure in the left ventricle, but end diastolic volume will be normal. Histologically there is increased interstitial collagen deposition and infiltration of the myocardium. These leads to a decrease in distensibility and elasticity(ability to stretch) of the affected myocardium. As a result, cardiac output becomes diminished. When the left ventricular diastolic pressure is elevated, the pressure in atrium will also increase which is reflected in elevated pulmonary venous pressure which may lead on to pulmonary edema.

The prognosis of diastolic dysfunction patients is better when compared to those with systolic dysfunction. Diastolic dysfunction is not synonymous with diastolic heart failure. Diastolic dysfunction can occur even in asymptomatic individuals and usually diagnosed during screening for some other cardiac problem. So diastolic dysfunction describes an abnormal mechanical property of ventricle whereas diastolic heart failure represents a clinical syndrome

Characteristics of Patients with Systolic or Diastolic Heart Failure

Characteristics	Systolic Heart Failure	Diastolic Heart Failure
Age	All ages, typically 50-70 years	Frequently elderly
Sex	More often male	Frequently female
Left ventricular ejection fraction	Depressed, approximately 40% or lower	Preserved or normal, approximately 40% or higher
Left ventricular cavity size	Usually dilated	Usually normal, often with concentric left ventricular hypertrophy
Left ventricular hypertrophy on electrocardiography	Sometimes present	Usually present
Chest radiography	Congestion and cardiomegaly	Congestion with or without cardiomegaly
Gallop rhythm present	Third heart sound	Fourth heart sound

4. CORONARY ARTERY DISEASE:

Hypertension is mostly the largest risk factor for coronary artery disease. The development of myocardial ischemia or infarction reflects an imbalance between myocardial oxygen supply and oxygen demand. Hypertension increases the risk by reducing the supply and increasing the demand.

Hypertensives suffer more silent ischemia and painless MI than do normotensives, perhaps because they have a lower sensitivity to pain[51]. And preexisting hypertension may not be recognized in patients who are seen immediately after an MI. Initially there may be an sudden increase in BP due

to the ischemia related pain, but the BP often falls immediately if pump function is impaired leading to cardiac failure[50].

Once an MI occurs, the prognosis or long term survival depends on blood pressure taken before and after the existing illness. In a study done by Kenchiah et al, the 28-day case fatality rate among 635 men who had an acute MI was 24.5% in those with a prior systolic BP <140 mm Hg, 35.6% with a prior systolic BP of 140- 159 mm Hg, and 48.2% with a prior systolic BP of >=160 mm Hg.

On the other hand, an increase in post-MI mortality has been noted among those whose BP fell significantly, presumably a reflection of poor pump function. If the BP of these subjects remained elevated, the prognosis was even worse, likely representing a severe load on a damaged myocardium, so that care must be taken with patients who have either lower or higher BP after an infarction.

5. ATRIAL FIBRILLATION:

In a 16-year follow-up of 2,482 previously untreated hypertensives, 61 developed atrial fibrillation, a rate of 0.46 per 100 person years (Verdecchia et al., 2003b)[52]. The likelihood increased with increasing age, blood pressure levels, thickness of left ventricle, and diameter of the left

atrium. The risk of developing atrial fibrillation was reduced by over 60% in hypertensives treated down to a level below 120/80 (Young-Xu et al., 2004)[53].

6. AORTIC STENOSIS:

Among 193 patients with symptomatic aortic stenosis, hypertension was present in 32%, and the additional workload was likely responsible for symptoms developing with larger valve areas and lower stroke work loss (Antonini-Canterin et al., 2003)[54]. The presence of aortic stenosis serves as an independent risk for cardiovascular disease in hypertensives (Olsen et al., 2005)[55].

HYPERTENSION AND BLOOD VESSEL:

The vascular lesion caused by hypertension can be described as follows.

- Fibrinoid necrosis as seen with acute rise of BP.
- Hyperplastic or proliferative arteriolar sclerosis.
- Hyaline arteriolar sclerosis, with thickening and hyalinization of the intima and media.
- Miliary aneurysms in small cerebral penetration arterioles, usually at their first branching, which represent post stenotic dilations beyond areas of

intimal thickening and which, when they rupture, cause the cerebral hemorrhages so typical of hypertension.

- Atherosclerotic plaques where thrombi form and which likely are responsible for the ischemia and infarction of heart, brain, kidney, and other organs that occur more frequently among hypertensives.
- Medial damage in the wall of the aorta may lead to the formation of large plaques with eventual aneurysmal dilation and rupture, as well as aortic dissections.

HYPERTENSION AND BRAIN:

Stroke is the second most common cause of death in the world. It causes 5 million deaths per year. High blood pressure is the one of the strongest risk factor for stroke. Around 85% of strokes are due to infarction, and the remaining are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years.

Hypertension also is associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Hypertension-related cognitive

impairment and dementia may be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function.

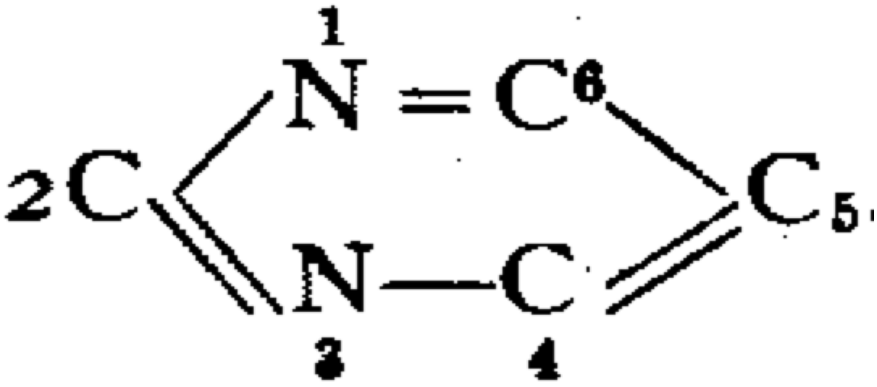
Cerebral blood flow remains unchanged over a wide range of arterial pressures (mean arterial pressure of 50–150 mmHg) through a process termed *autoregulation* of blood flow. In patients with the clinical syndrome of malignant hypertension, encephalopathy is related to failure of autoregulation of cerebral blood flow at the upper pressure limit, resulting in vasodilation and hyperperfusion. Signs and symptoms of hypertensive encephalopathy may include severe headache, nausea and vomiting (often of a projectile nature), focal neurologic signs, and alterations in mental status.

Untreated, hypertensive encephalopathy may progress to stupor, coma, seizures, and death within hours. Differential diagnoses for hypertensive encephalopathy includes cerebral ischemia, hemorrhagic or thrombotic stroke, seizure disorder, mass lesions, pseudotumor cerebri, delirium tremens, meningitis, acute intermittent porphyria, traumatic or chemical injury to the brain, and uremic encephalopathy.

HYPERTENSION AND KIDNEY:

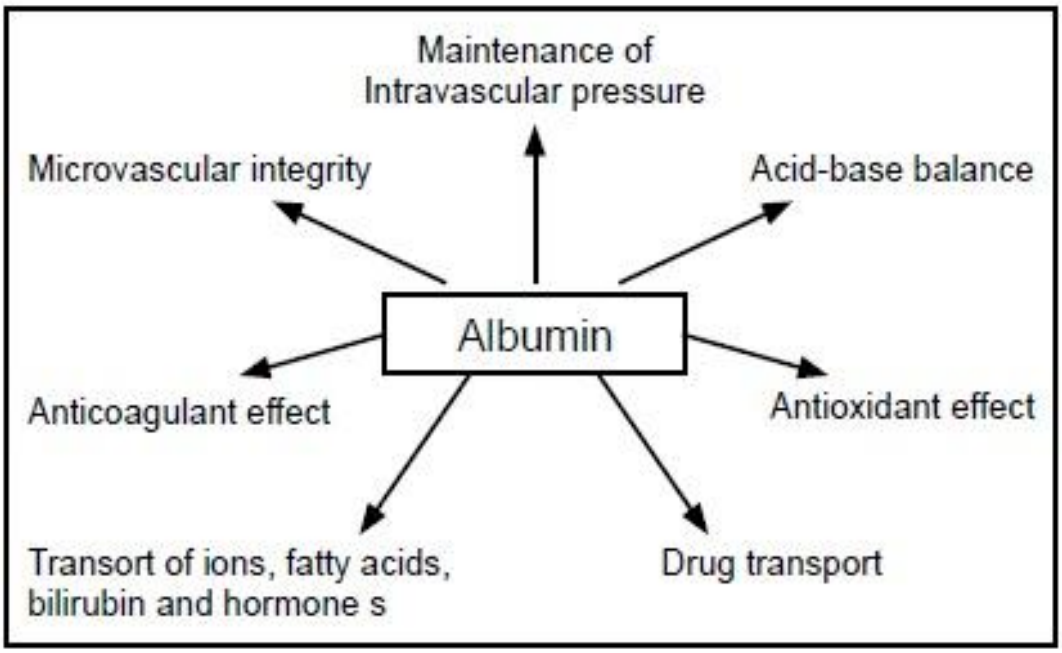
ALBUMIN

The most abundant human protein available in blood is human albumin. Its main source of production is from the liver and constitutes more than one half of total blood protein[56]. T1/2= 20 days approximately. It is supposed to have a molecular mass of about 66.5kDa. The gene coding for albumin is found in chromosome 4. Any mutation in this gene may lead to formation of abnormal proteins. Preproalbumin is converted to proalbumin in the endoplasmic reticulum of liver, which is then cleaved to albumin in golgi apparatus and secreted out.



Albumin helps in transportation of various hormones and other substances, buffers pH, maintain oncotic pressure. In healthy persons, albumin is not excreted through kidneys, because of their size and negative

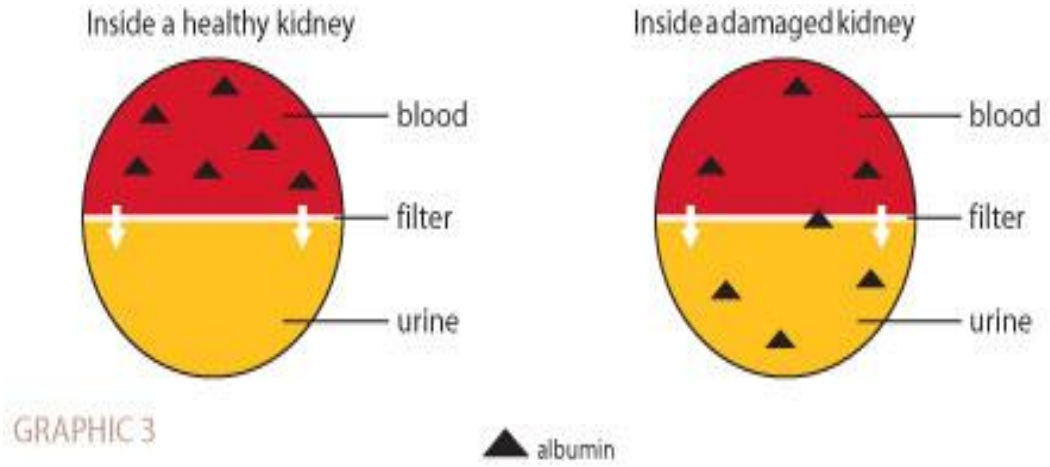
electric charge. So the patient may have nil albumin, microalbuminuria or frank albuminuria in their urine sample.



1. Figure 1 – Physiological effects of exogenous albumin.

Microalbuminuria is the term used when urine albumin is 30-300mg/l. The significance of microalbuminuria is that there is damage in the glomerulus leading to increased permeability of albumin and hence filtered out. It also indicates any evidence of subclinical cardiovascular abnormality, alterations in normal vascular endothelial function and also a prognostic marker in case of diabetes mellitus, systemic hypertension and post infectious glomerulonephritis. Progressive worsening of microalbuminuria

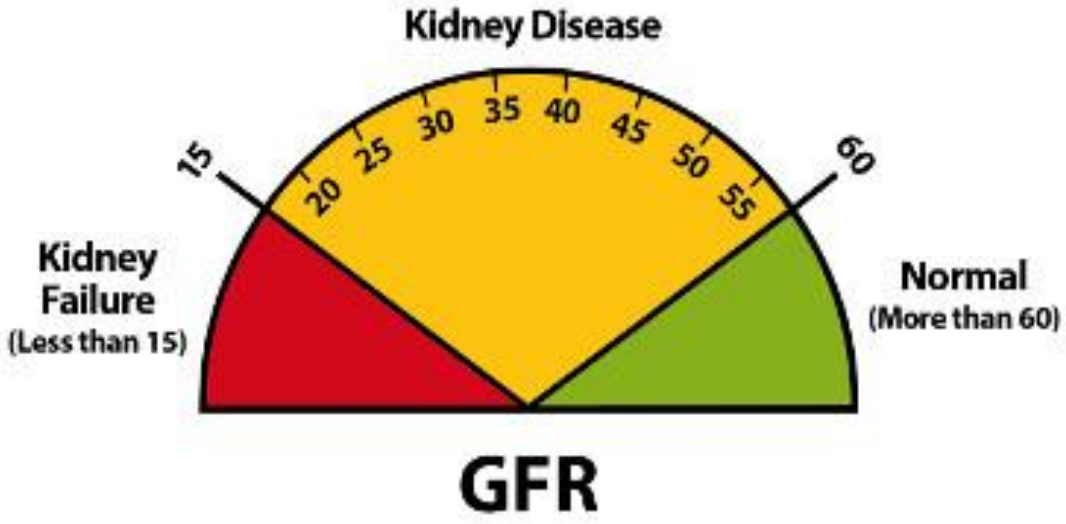
during first 24 hours of admission in a critical care unit may predict increased likelihood of morbidity and mortality.



GRAPHIC 3

Hypertensive Nephropathy:

Also termed as hypertensive nephrosclerosis or hypertensive renal disease refers to a condition causing damage to kidneys due to chronic hypertension.



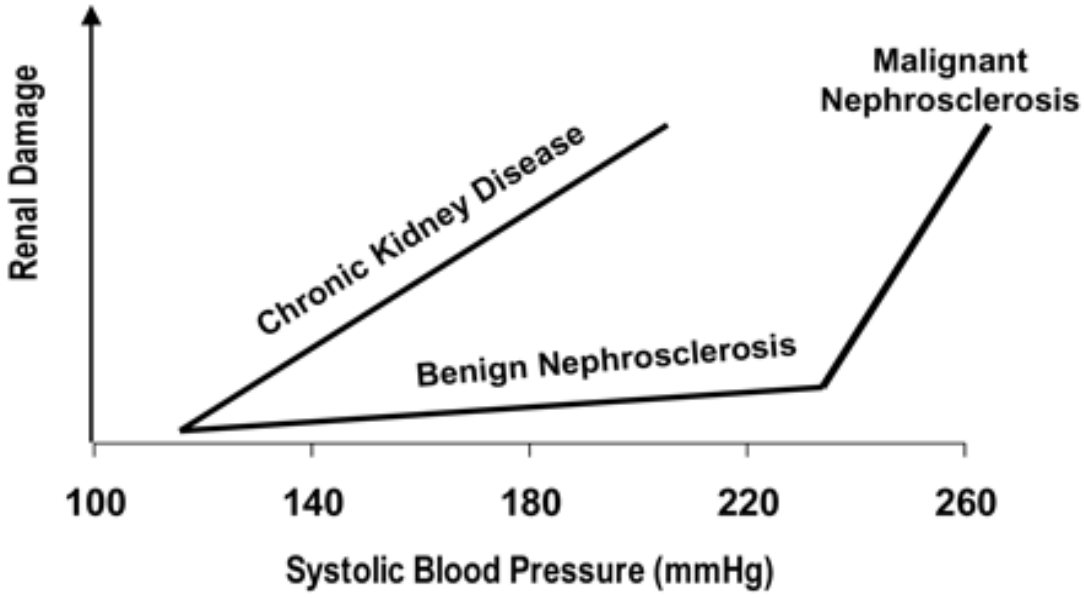
The pathogenesis of hypertensive nephropathy can be separated into 3main categories,

a) The levels of systolic and diastolic BP

b) The degree of transmission of the pressure load to the renal vascular bed

c) Localized susceptibility of tissues to any given degree of barotrauma

Normal auto regulatory mechanisms prevent the episodic or sustained increase in blood pressure from reaching the renal microvasculature. Hence they provide a primary protection against hypertensive renal damage. As long as the BP remains within the autoregulatory range, only a benign nephrosclerosis is observed. If the blood pressure exceeds the threshold, acute disruptive injury (malignant nephrosclerosis) develops despite intact autoregulatory mechanisms. Once vascular injury develops autoregulatory mechanisms can be secondarily compromised and results in amplification of renal damage. Hence acute increase in BP (malignant hypertension) is more dangerous than chronic of the same range of blood pressure because of the time interval to get adapted by autoregulatory mechanisms.

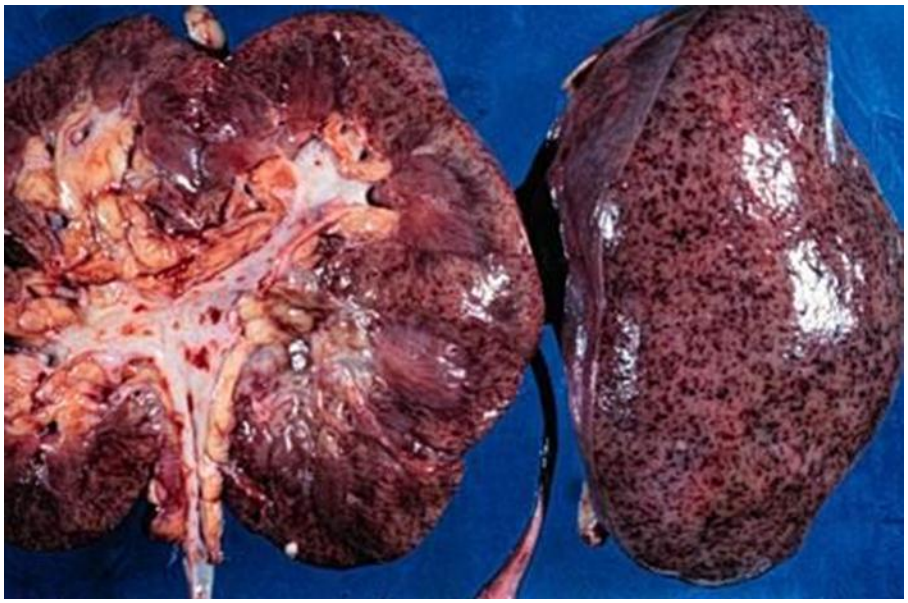


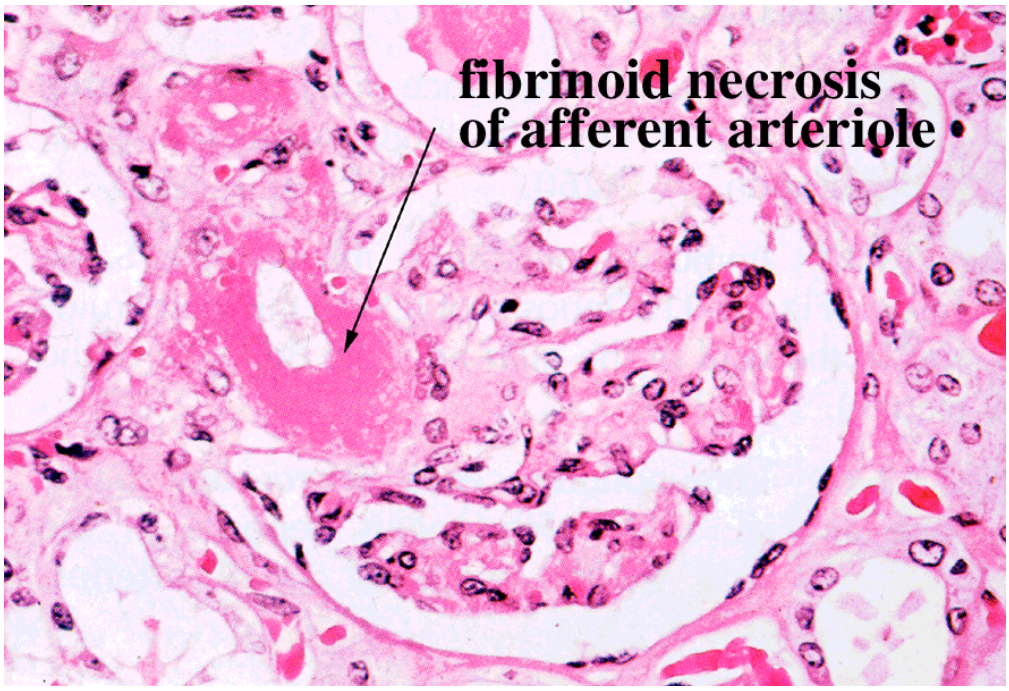
However in the absence of severe hypertension, renal damage can still develop when the elevated systemic pressure is transmitted to the renal microvasculature. Such a situation primarily leads to accelerated glomerulosclerosis. In a vasoconstricted bed, the consequences of impaired autoregulation primarily results in decreased ability to maintain renal blood flow and GFR. When the systemic pressure is reduced in the patients, they may develop ischemic tubulointestitial disease.

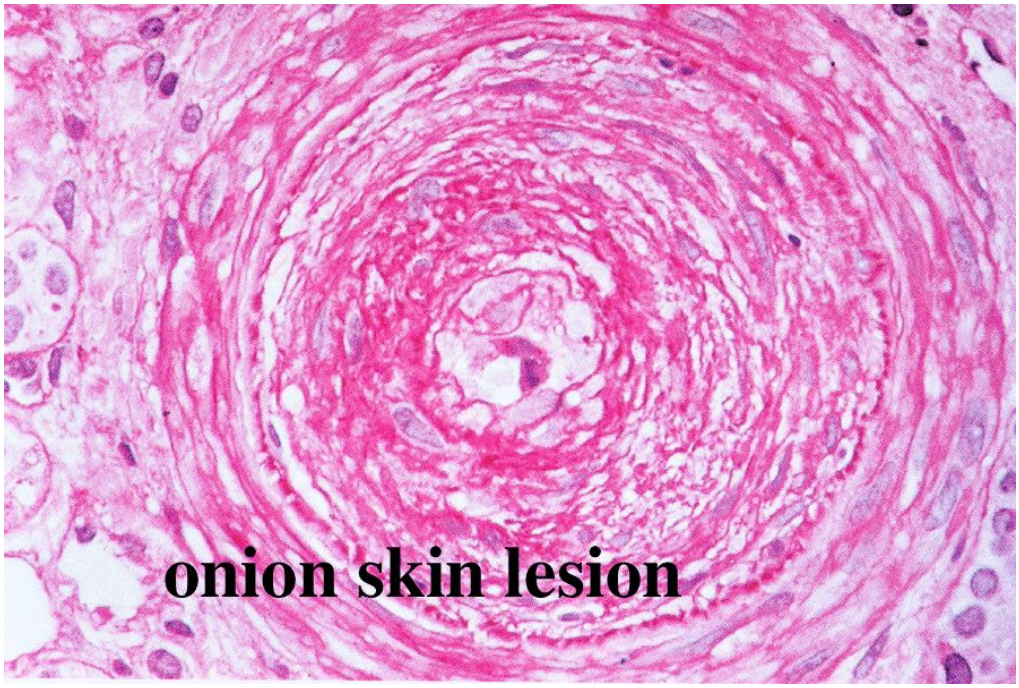
Benign nephrosclerosis: In benign nephrosclerosis, renal arterioles, particularly afferent arterioles, appear sclerosed due to hypertension, which further causes focal ischemia and ultimately leading to moderate decrease in glomerular filtration rate. Grossly, kidneys are shrunken with leathery appearance. The microscopic features reveal hyalinized arterioles with

thickened vessel wall, fibroelastic hyperplasia of the lobular/arcuate arteries, atrophy of the tubules, fibrosis of the interstitial and periglomerular regions which finally culminates to glomerulosclerosis. Vascular changes predominate in the afferent arteriole and particularly these vessels have characteristic absence of internal elastic lamina.

Malignant nephrosclerosis: This refers to irreversible end organ damage of one or more organs. Grossly, the cortical surface of the kidney show pinpoint petechiae, which gives the characteristic flea bitten appearance. Microscopy reveals fibrinoid necrosis of the renal arterioles. The collagen is deposited in concentric layers appearing like onion skinning of arterioles (hyperplastic arteriolitis). There is also myointimal hyperplasia owing to persistently elevated blood pressure. The earliest change is the reduction in the size of the lumen due intimal thickening probably by myxoid connective tissue. Below are figures depicting the gross appearance of kidney in malignant nephrosclerosis with flea bitten appearance and microscopic appearance of fibrinoid necrosis of arterioles and histological appearance of onion skin lesion in hypertension.




fibrinoid necrosis
of afferent arteriole



HYPERTENSION AND EYE:

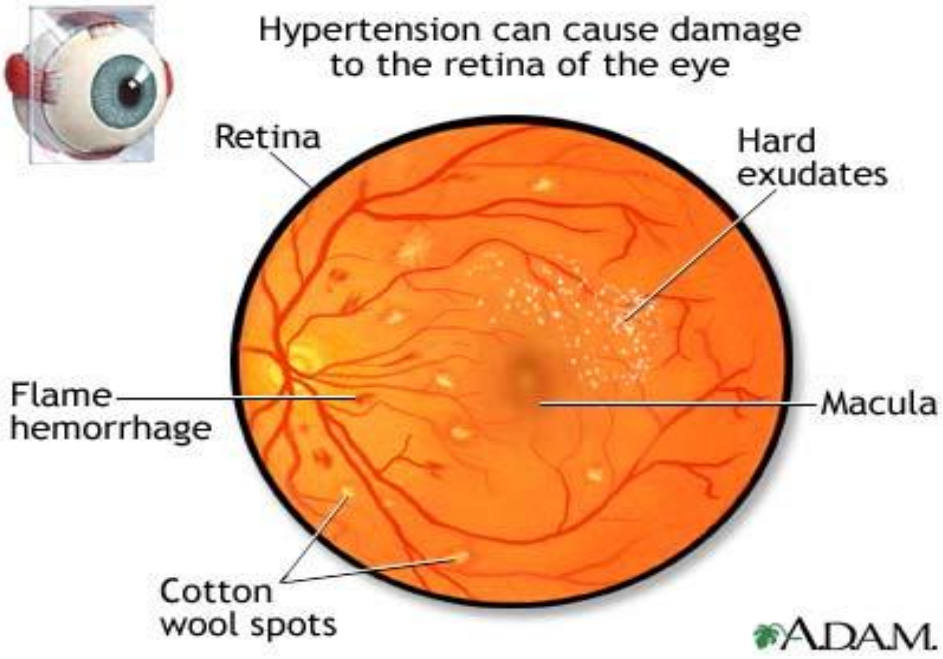
The patients with hypertensive retinopathy are expected suffer from hypertension which may be acute or chronic. However, the disease might be unknown to the patient and examination of the eye may yield us the first clue to his/her relatively asymptomatic disease. The age group most commonly involved may be middle age or elderly. Hypertension is interestingly more common in african-americans rather than the Caucasians. These patients are mostly free of symptoms or sometimes may present with nonspecific symptoms[57].

The fundoscopic picture seen in hypertensive retinopathy includes cotton wool spot and most often with associated flame shaped hemorrhages. Rarely there may be any evidence of retinal or even macular edema. In end stage cases, there may be a macular star (appearance of ring of exudates extending from the disc upto the macula) and associated disc edema. Arteriolosclerosis leading to narrowing of arterioles, venous constriction and banking due to arterio-venous crossing, arteriolar color changes, sclerosis of vessels are often found concurrently[57].

Hypertension may lay down cholesterol into tunica intima of arteries of medium and large size, which further reduces the lumen size of the vessels. In arteriolosclerosis, there may be focal closure of the retinal microvasculature, when this is associated with hypertension it may aggravate formation of micro infarcts and formation of superficial hemorrhages. There may be associated disc edema in extreme cases. The exact mechanism is unclear, increase in intracranial pressure which can be attributed to hypertension is proposed and hence it can be presumed to be a true papilledema[57].

Even if the systemic blood pressure is brought under control, the arteriosclerotic changes occurred in the vasculature of retina persists. But the other retinopathy changes associated with hypertension may resolve in a

certain period of time with adequate control of BP. Within 24-48hours of increase in blood pressure, the patient may begin to develop cotton wool spots which may resolve in two to 10 weeks period with adequate control of blood pressure. Papilledema develop within few hours to days and takes weeks to months to revert back to normal. A macular star developing in a few week time, may take months to disappear after bringing the blood pressure under control[57].



Managing hypertensive retinopathy is as simple as bringing the blood pressure under control as the first step. Whenever a patient presents with blurred vision due to papilledema as a result of hypertension, then the patient can be suspected to have malignant hypertension and should be suspected to be in crisis and intervened as early as possible. The patient immediately

needs a physician opinion, and has to be transported to a hospital with sophisticated emergency setup.

It must be kept in mind, that there are many other conditions causing papilledema. Other probability like an intracranial mass must be kept in mind in such presentations. When a patient presents with extremely elevated blood pressure (e.g. 250/150mmhg) with associated disc edema and a macular star, malignant hypertension is the most likely cause unless proves otherwise.

Chronic hypertension producing retinal changes include the following,

1. Arteriolosclerosis - narrowing of vessels which may be localized/generalized
2. Arteriolar Copper wiring and silver wiring due to arteriolosclerosis
3. Arteriovenous nicking due to arteriolosclerosis occurring in old age
4. Any associated evidence of hemorrhage in the retina
5. Loss of nerve fiber layer
6. Increased vascular tortuosity
7. Remodeling changes due to capillary non perfusion, such as shunt vessels and micro aneurysms.

The first attempt to relate the retinal vascular changes to survival in the hypertensive patient was proposed by 3 personalities namely Keith, Wagner and Barker in the year 1939, who divided hypertensive patients into four groups on the basis of opthalmoscopic characteristics. This grouping correlated directly with the degree of systemic hypertension and inversely with the prognosis for survival.

Grade 1

Mild generalized arteriolar constriction and associated vascular tortuosities.

Grade 2

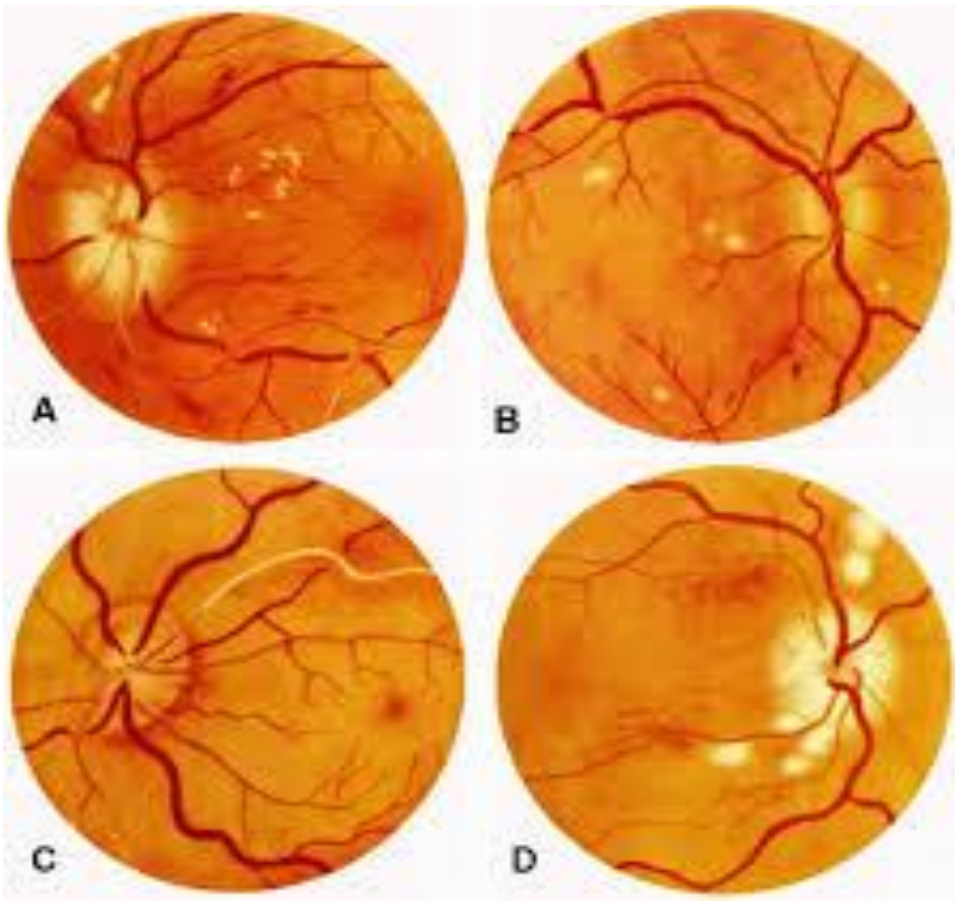
Grade 1 + `arteriovenous nicking` or `arteriovenous nipping`

Grade 3

Grade 2 + associated cotton wool spots and also flame shaped hemorrhage

Grade 4

Grade 3 + swelling of the disc i.e. papilledema



Hypertensive retinopathy can occur in 4 situations. In young patients where simple hypertension is not associated with any sclerosis , there will be generalized constriction of arterioles that may appear to be pale and unduly straight associated with acute angled branching, also flame shaped hemorrhages and cotton wool spots may occur. No evidence of hard exudates.

Hypertension with involutionary sclerosis, as occuring in older patients, the picture of arteriosclerotic retinopathy occurs. There is localized constrictions and dilatations of the vessels with the thickening of the vessel

wall and deposition of hard exudates and sometimes hemorrhages without any edema. Gunn's sign- nipping and perpendicular placement of the veins is a diagnostic finding. Although vascular changes are bilateral, retinopathy remain confined to one eye due to carotid artery insufficiency on that side.

In diffuse hyperplastic sclerosis, there will be proliferative and fibrotic changes mainly affecting the media. Vessels are narrow and tortuous with nicking at the arteriovenous crossing; multiple hemorrhages are present. In early stages, edema and cotton wool patches are seen while in later stages hard exudates are scattered diffusely, but usually forms a macular star. Though blindness doesn't occur in these patients, vision is severely impaired[57].

Hypertensive neuroretinopathy is the fundus change occuring in malignant hypertension. The entire disc is clouded by generalised edema which may be particularly attenuated at the disc, resulting in a marked degree of disc edema with multiple cotton wool patches, profuse hard exudates and prominent macular star. Vision is seriously impaired. With marked disc edema, prognosis is poor unless hypertension is under control.

MATERIALS AND METHODS

STUDY DESIGN:

Comparative study between two groups:

- Prehypertension group:

  It includes individuals belonging to the systolic BP of 120-139mmHg and a diastolic BP of 80-89mmHg.

- Normotension group:

  It includes individuals belonging to the systolic BP of <120mmHg and a diastolic BP of <80mmHg.

SAMPLE:

Totally 100 subjects were selected and they were divided equally so that 50 members will be in each group. All were volunteers and all were mostly attenders of patients admitted to our wards in Tirunelveli Medical College Hospital. Volunteers from patient's attenders were selected because our study is to detect prehypertensive and normotensive individuals and to find out subclinical target organ damage in them. Patients will already be having some disease which itself would cause microalbuminuria and may bias our obtained results.

The age group of individuals enrolled in this study are taken as above 30 years as per Non Communicable Diseases Screening Program. In all district hospitals non communicable diseases screening clinic is established and all patients above 30 years are screened for blood pressure and random blood sugar to detect diabetes and hypertension at early stages. The upper limit of age is kept within 60 years because at this age they develop any one of the risk factors like diabetes, hypertension and cardiovascular diseases. So getting a volunteer with purely prehypertension without any co morbidities becomes difficult at the age of above 60 years.

INCLUSION CRITERIA:

Healthy volunteers, mostly patient's attenders above the age of 30 years and below 60 years without any diseases or co morbidities mentioned in the exclusion criteria. Total sample size is 100, with 50 in each group.

EXCLUSION CRITERIA:

1. History of (H/O) Diabetes
2. H/O Hypertension
3. H/O Intake Of Drugs(aspirin, steroids, amoxicillin or antihypertensives)
4. Pregnancy

5. History suggestive of urinary tract infection

6. H/O Acute/ Chronic Kidney Disease

7. H/O Coronary Artery Disease/Congestive Cardiac Failure

8. H/O Acute Febrile Illness

METHODOLOGY:

Informed consent of the volunteer was obtained first. A pro forma was prepared which includes the individual's name, age, sex, occupation and any specific complaints he was having at that time. These particulars were filled first. He was asked for any previous history of diabetes, hypertension, any drug intake, renal disease, cardiac disease or any acute illness. It was made sure that they do not have any of these diseases.

A routine systemic examination of the individuals was done including cardiovascular, respiratory, abdomen and nervous system. Their pulse rate and BP were measured. The BP was measured using standard BP cuff with the help of mercury sphygmomanometer. Before recording the patient it was made sure that the individual has avoided caffeine, exercise and smoking at least 30 minutes before measurement. The individual should be seated quietly and comfortably for at least 5 minutes in a chair. His/her

arm should be supported at the heart level and feet on the floor. Cuff should be applied over the artery at the level of heart and the lower edge of cuff should be at least 1 inch above the antecubital fossa. The blood pressure was measured in both the upper limb and also one of the lower limbs. Second measurement was done again with a gap of 30 minutes to confirm the previous readings. The average of upper limb BP recordings is noted.

Basic blood investigations like blood sugar, renal function tests and urine for albumin, sugar and deposits and electrocardiogram and chest X ray were performed routinely in all participants.

ASSESSMENT OF END ORGAN DAMAGE:

MICROALBUMINURIA:

The various different methods available by which microalbuminuria can be estimated are:

1. Microalbumin urine test strips: It uses immunochemical strips which are specific for albumin.
2. Radio immunoassay: This technique is highly sensitive and has good accuracy but carries the disadvantage of radioactivity.
3. Radio immune diffusion: This method requires long incubation period and hence is not widely accepted.

4. ELISA: Competitive and sandwich ELISA techniques are employed for quantification of albumin.
5. Immunoturbidometry: Quantifies the amount of albumin based on spectrophotometric analysis and is suitable for analyzing large number of samples at a faster rate.

TRADITIONAL METHOD FOR ALBUMINURIA:

In the laboratory, proteinuria/microalbuminuria has traditionally been detected with the use of multi-reagent urinary dipstick testing.

- It is detected by a colorimetric reaction with the dipstick-impregnated reagent.
- It has limited sensitivity for non-albumin protein and is therefore often falsely negative tubular proteinuria.
- The sensitivity ranges from 83% to 98% with a specificity of 59% to 86%.
- This reaction depends on the concentration of albumin, so the testing of larger volume diluted urine underestimates the degree of albuminuria.
- Similarly, testing highly concentrated urine may overestimate the degree of albuminuria.
- Markedly alkaline pH (>8.0) and administration of iodinated radio contrast agents can also produce false-positive results.

- The result obtained is reported as trace, 1+ up to 4+ which corresponds to urine albumin as designated in below table.

negative	0 mg/dL
trace	15-30 mg/dL
1+	30-100 mg/dL
2+	100-300 mg/dL
3+	300-1000 mg/dL
4+	>1000 mg/dL

OTHER METHODS FOR MICROALBUMINURIA:

A 24 hour urine sample can be obtained and albuminuria estimated is reported as follows:

- <30mg/24 hours – normal
- 30-300mg/24 hours - micro albuminuria
- >300 mg/24 hours – macro albuminuria

The disadvantage of this method is need for a 24 hour collection which is little inconvenient for the patient and the test may give false positive or false negative result depending on the concentration of urine. For example if the urine volume is less, the concentration of albumin may increase so it may overestimate albuminuria. Similarly if a large volume of urine is obtained and it is dilute, it may underestimate albuminuria.

Alternatively, nowadays a spot urine sample is preferred and spot urine albumin creatinine ratio (ACR) is performed. It is more reliable comparing to 24 hour urine sample. An early morning urine sample is preferred. The individual undergoing the test should refrain from doing any heavy exercise at least 24 hours before doing the procedure. The disadvantage of this procedure is that the creatinine values may be affected by the muscle mass of the individual.

In our study we estimated the albumin creatinine ratio for assessing the presence of microalbuminuria. The reagent used were micro protein reagent for detection of albumin and sodium hydroxide/picric acid for the detection of creatinine. Both these reagents were filled in a fully automated analyser. The results are obtained using photometric techniques and fully automated turbidometry.

The results are interpreted as:

- <30mg/g - normal
- 30 – 300mg/g - microalbuminuria
- >300mg/g - macroalbuminuria

Since it is a ratio, the result obtained in mg/g are converted into ratio as <0.3 as normal, 0.3 – 3 as microalbuminuria and >3 as macroalbuminuria

FUNDUS CHANGES:

The retina of all the subjects were visualized with the help of direct ophthalmoscope and looked for any changes for hypertensive retinopathy was present or not. If present it was again confirmed with the help of ophthalmologist opinion. The grading were done according to Keith Wagner grading of hypertensive retinopathy

DIASTOLIC DYSFUNCTION:

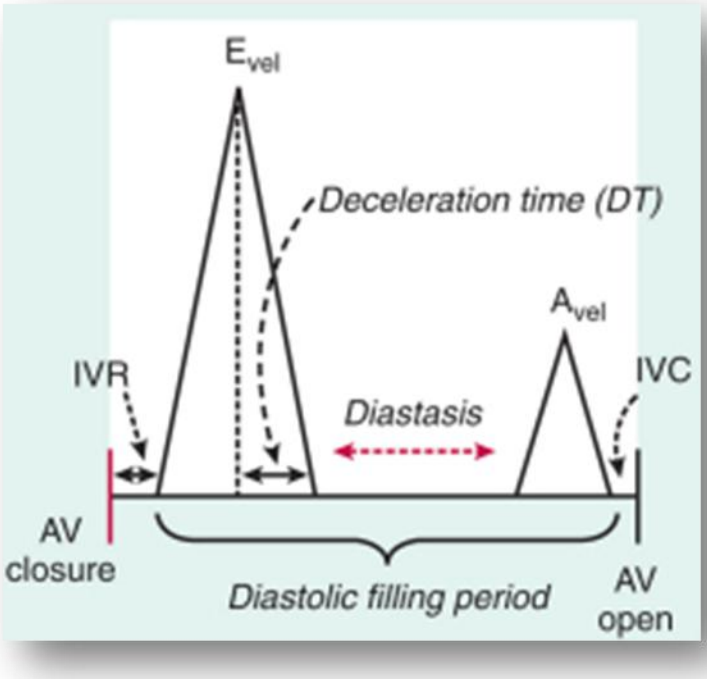
The diastolic period of the heart comprises of four phases mainly:

- Isovolumetric relaxation period - all the valves are closed
- Early filling phase – ventricular filling due to pressure difference between atria and ventricle. Most of the blood enters during this phase
- Diastasis – the pressure difference will become almost equal so very little flow during this period
- Late filling phase or atrial contraction – due to atrial systole the remaining amount of blood enters into ventricle

The diastolic dysfunction was assessed using following parameters:

1. E wave velocity (velocity of flow during early filling phase),
2. A wave velocity (velocity of flow during atrial contraction),

3. E wave deceleration time (EDT)(time interval between the peak of E wave to zero)
4. Isovolumetric relaxation time (IVRT)



Using these parameters the diastolic dysfunction is graded as follows:

1. Grade I: (Abnormal relaxation pattern)
2. Grade II (Pseudo normal pattern)
3. Grade III (Reversible restriction)
4. Grade IV (Irreversible restriction)

GRADE I:

Characterized by a decreased E wave velocity and increased A wave velocity. E/A ratio < 1; Increased IVRT (>100ms); Increased EDT (>240ms)

GRADE II:

The normal left ventricle filling pattern is maintained as the E/A ratio >1. But left ventricle filling pressures are increased. It is identified by measuring a parameter atrial reversal (AR) velocity which is increased >35 cm/s.

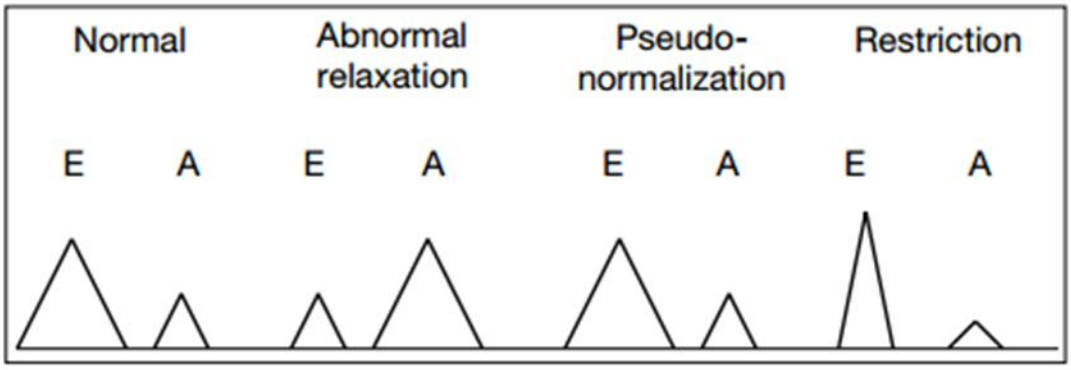
GRADE III:

It is characterized by the following findings. E/A ratio>2.5; decreased EDT (< 150 ms); decreased IVRT (<70 ms); AR >35 cm/s. These findings are reversible with valsalva maneuver.

GRADE IV:

Same as above but are irreversible with valsalva maneuver.

Diagram to illustrate diastolic dysfunction in echocardiography



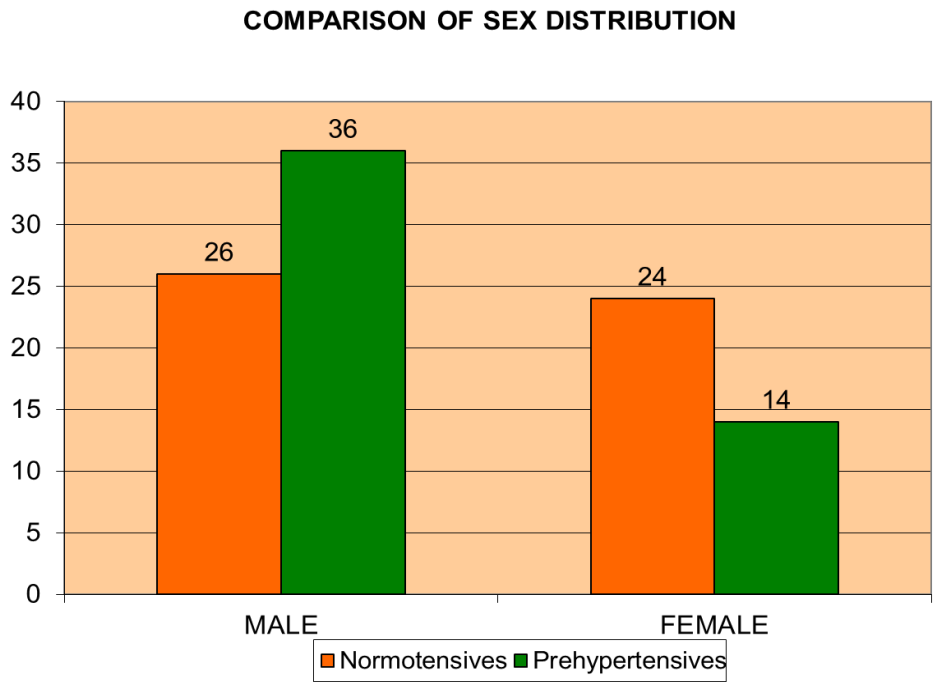
OBSERVATION AND RESULTS

SEX DISTRIBUTION:

Out of the 50 prehypertensive subjects, 36 of them are males and 14 are females. Normotensives has almost equal sex distribution.

TABLE.1

SEX	**Normotensives**	**Prehypertensives**
MALE	26	36
FEMALE	24	14
TOTAL	50	50

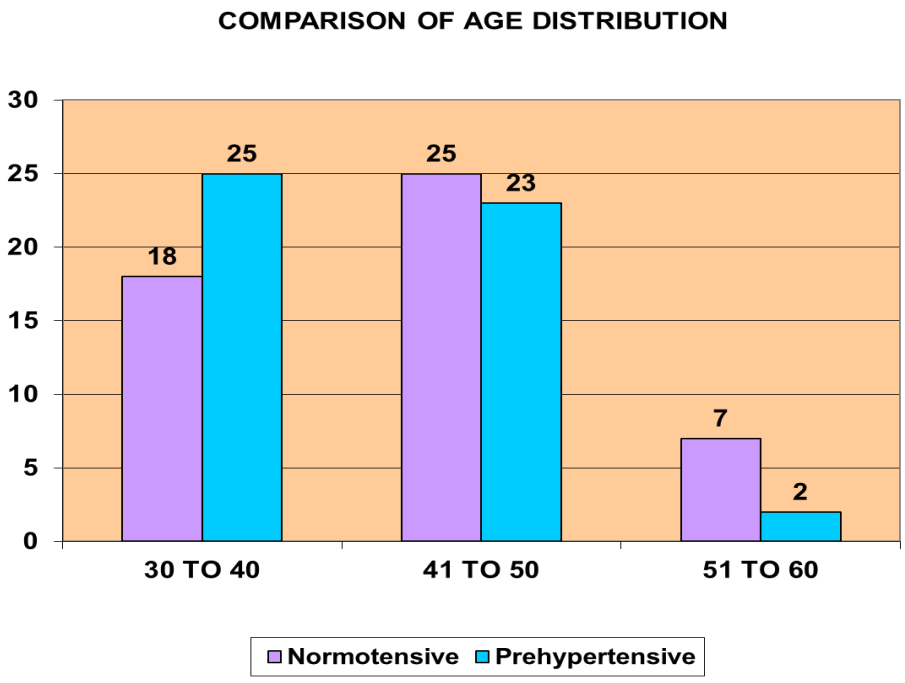


AGE DISTRIBUTION:

Out of 50 prehypertensive individuals, around 48 belong to the age group of 30 to 50 years. Similar percentage is seen in normotensive group.

TABLE.2

AGE	**Normotensives**	**Prehypertensives**
30 TO 40	18	25
41 TO 50	25	23
51 TO 60	7	2
TOTAL	50	50

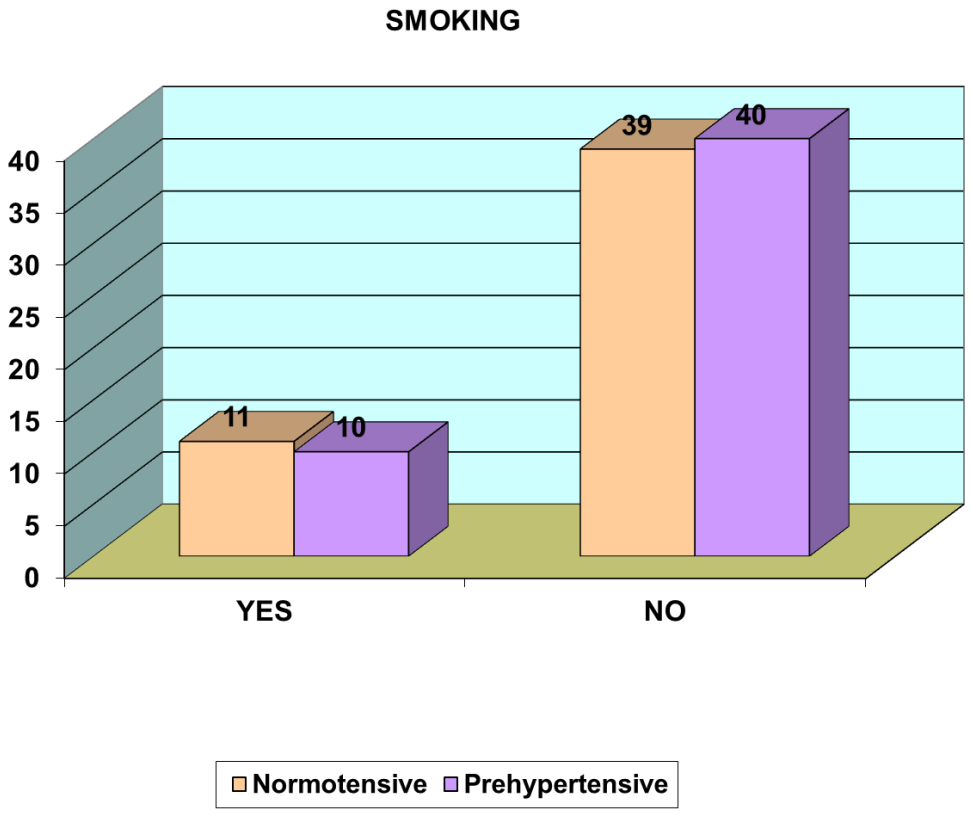


DISTRIBUTION OF SMOKERS IN BOTH GROUPS:

Both the groups have almost equal number of smokers with 11 smokers in normotensive group and 10 smokers in prehypertensive groups.

TABLE.3

SMOKING	Normotensives	Prehypertensives
YES	11	10
NO	39	40
TOTAL	50	50

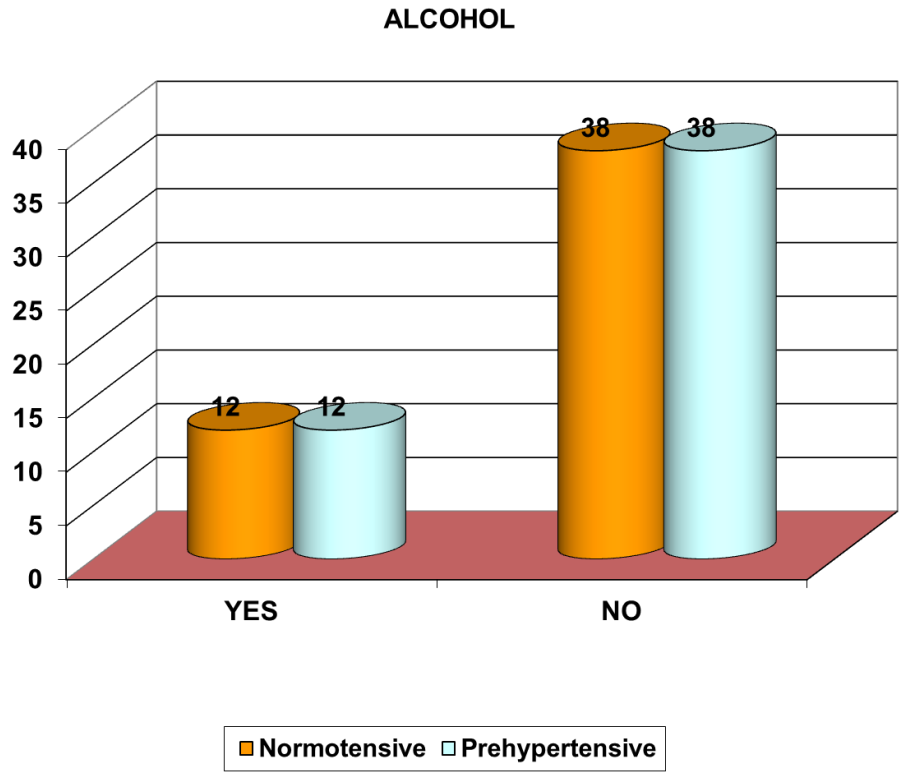


DISTRIBUTION OF ALCOHOL CONSUMERS IN BOTH GROUPS:

As of smokers, the number of persons who consume alcohol is equal in both groups with 12 individuals in both the groups.

TABLE.4

ALCOHOL	Normotensives	Prehypertensives
YES	12	12
NO	38	38
TOTAL	50	50

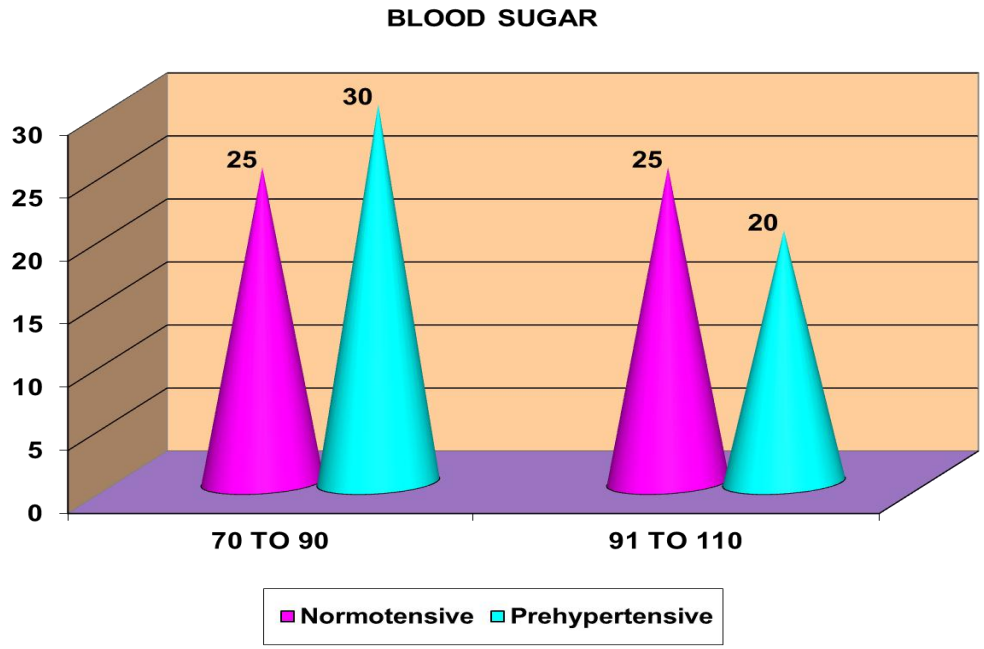


BLOOD SUGAR DISTRIBUTION IN BOTH GROUPS:

All the individuals included in the study are made sure that they are not diabetic and so all of them have blood sugar values less than 110 mg%

TABLE.5

BLOOD SUGAR (mg/dl)	Normotensives	Prehypertensives
70 TO 90	25	30
91 TO 110	25	20
TOTAL	50	50

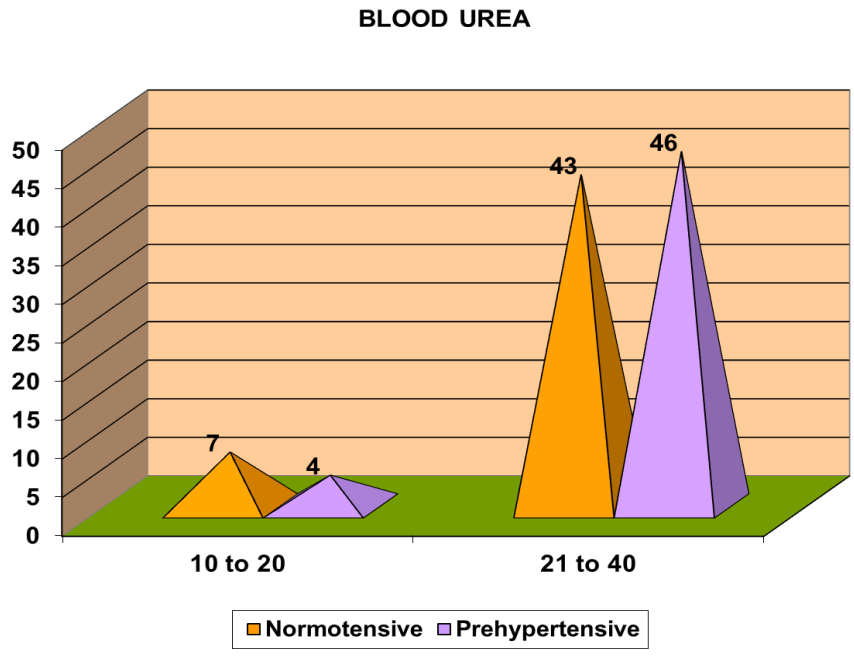


BLOOD UREA DISTRIBUTION IN BOTH GROUPS:

The individuals included in this study are made sure that they don't suffer from any kind of renal diseases. Hence all have blood urea value of less than 40mg%.

TABLE.6

BLOOD UREA (mg/dl)	Normotensives	Prehypertensives
10 to 20	7	4
21 to 40	43	46
TOTAL	50	50

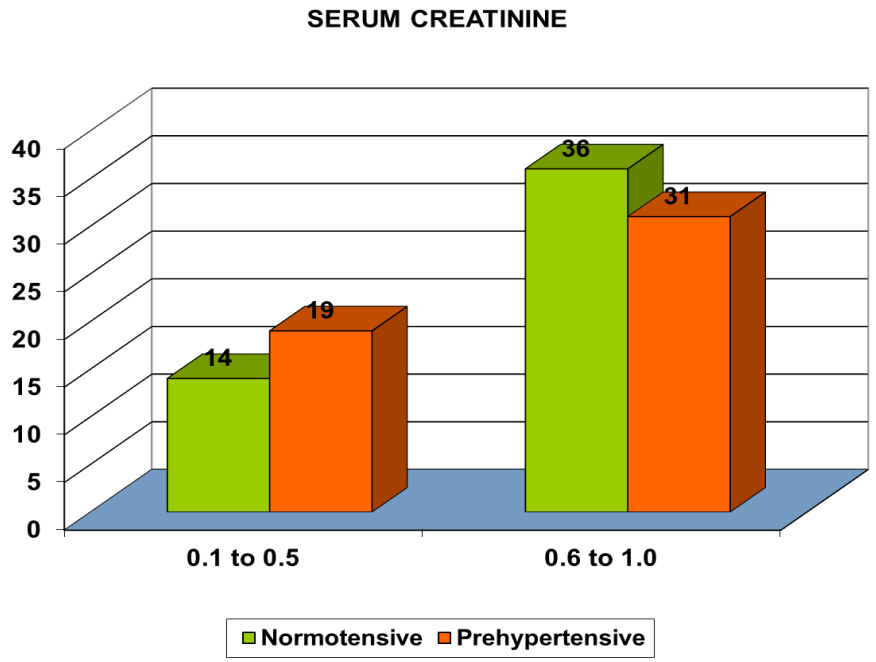


SERUM CREATININE DISTRIBUTION IN BOTH GROUPS:

The individuals included in this study are made sure that they don't suffer from any kind of renal diseases. Hence all of them are having a serum creatinine value less than 1mg%.

TABLE.7

SERUM CREATININE (mg/dl)	Normotensives	Prehypertensives
0.1 to 0.5	14	19
0.6 to 1.0	36	31
TOTAL	50	50

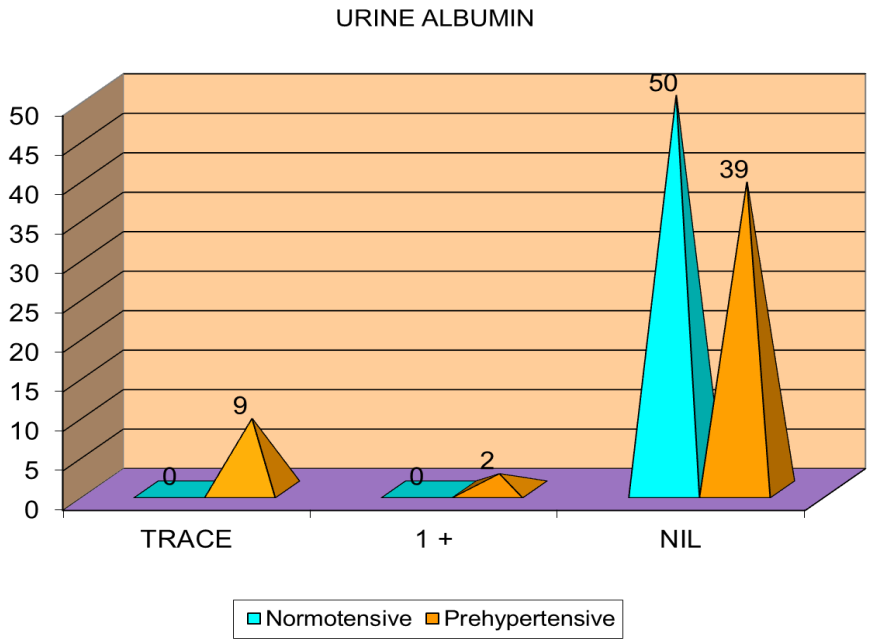


URINE ALBUMIN DISTRIBUTION IN BOTH GROUPS:

In the prehypertensive individuals, 11 has mild excretion of albumin in urine of which 9 has trace albumin and 2 has trace albumin. In normotensive groups none had albumin excretion in urine.

TABLE.8

URINE ALBUMIN	Normotensives	Prehypertensives
TRACE	0	9
1 +	0	2
NIL	50	39
TOTAL	50	50



URINE ALBUMIN/ CREATININE RATIO IN BOTH GROUPS:

A cut off of 0.3 is taken, and those who have a ratio of more than 0.3 are said to have microalbuminuria. Those who have less than 0.3 are designated as normal. In prehypertensive group, 14 members has ratio of more than 0.3. In normotensive group just 1 member is having a ratio of more than 0.3.

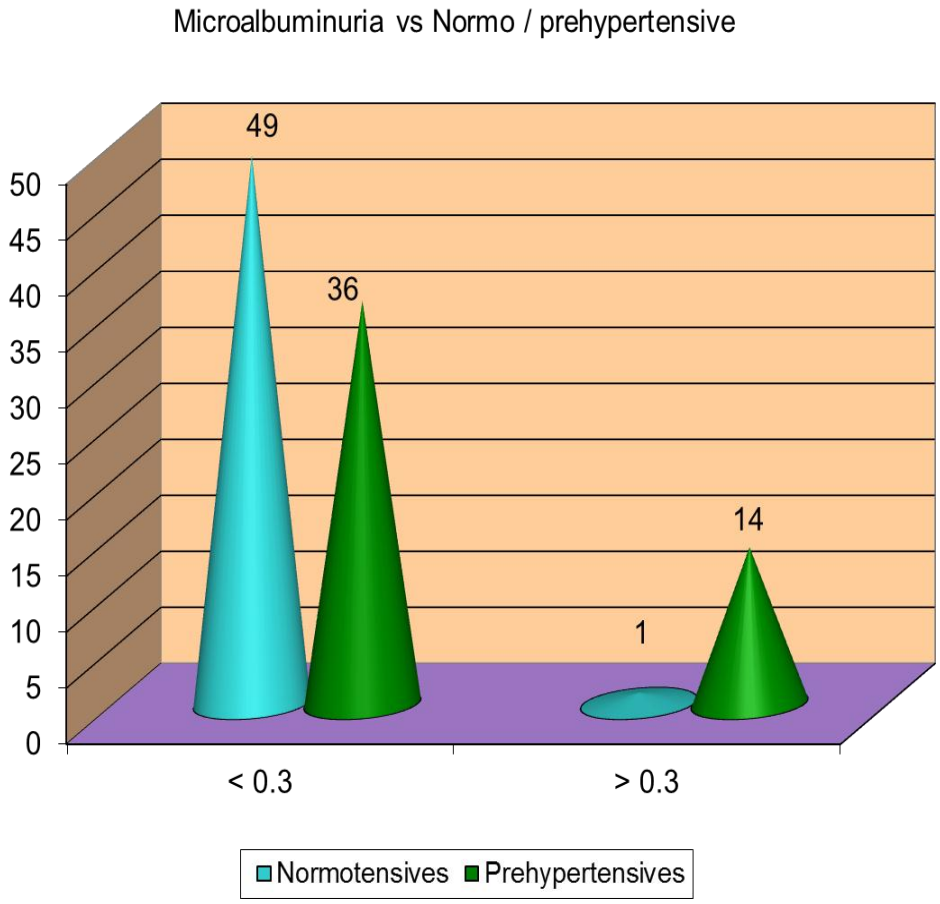
TABLE. 9

URINE ALBUMIN/CREATININE RATIO	**Normotensives**	**Prehypertensives**
< 0.3	49	36
> 0.3	1	14

To find out the significance of microalbuminuria in prehypertensive group, the urine albumin/ creatinine ratio of all the 100 subjects are entered into a master chart. Data analysis was done using software called Epidemiological Information Package.

Using this software, all the range, frequencies, percentage, mean, standard deviation, chi square and p value can be calculated. The tests used are One way ANOVA test and Student's 't' test for data and Kruskul Wallis Chi-square test for consolidated tables.

'p' value is calculated and value of less than 0.05 is considered significant. Here the 'p'value is <0.001 which is highly significant.

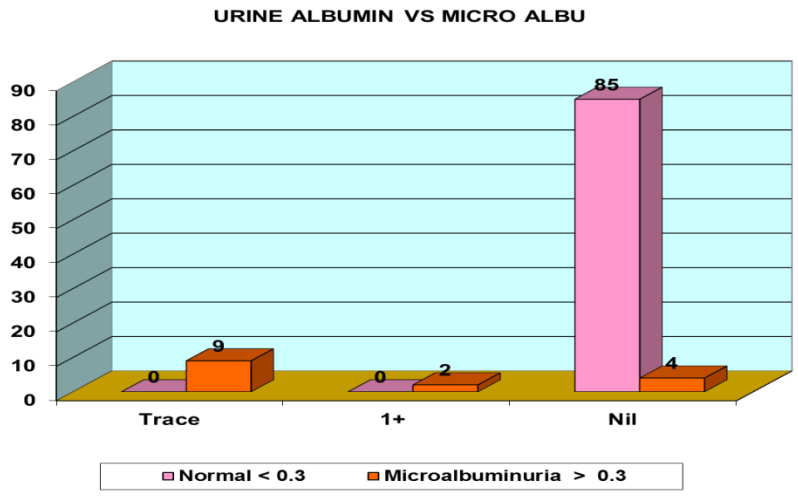


URINE ALBUMIN vs URINE ALBUMIN CREATININE RATIO:

Here albuminuria tested by two different methods are correlated. It can be found that 15 subjects are having microalbuminuria in both the groups using albumin/creatinine ratio. Of these 11 subjects also tested positive for urine albumin through urine dip stick method.

TABLE.10

Urine albumin	**Normal**	**Microalbuminuria**
	< 0.3	**> 0.3**
Trace	0	9
1+	0	2
Nil	85	4
TOTAL	85	15

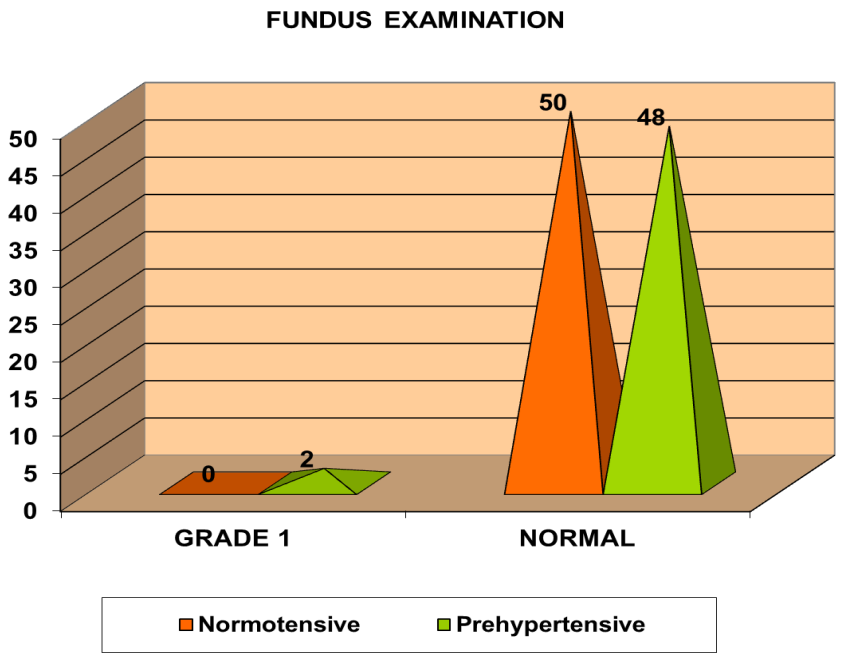


FUNDUS FINDINGS IN BOTH GROUPS:

Out of 100 subjects, only 2 individuals had retinopathic changes related hypertension. Both had just generalized arteriolar constriction which falls under grade 1 hypertensive retinopathy according to Keith Wagner classification of hypertensive retinopathy.

TABLE. 11

FUNDUS - RETINOPATHY GRADING	Normotensives	Prehypertensives
GRADE 1	0	2
NORMAL	50	48
TOTAL	50	50

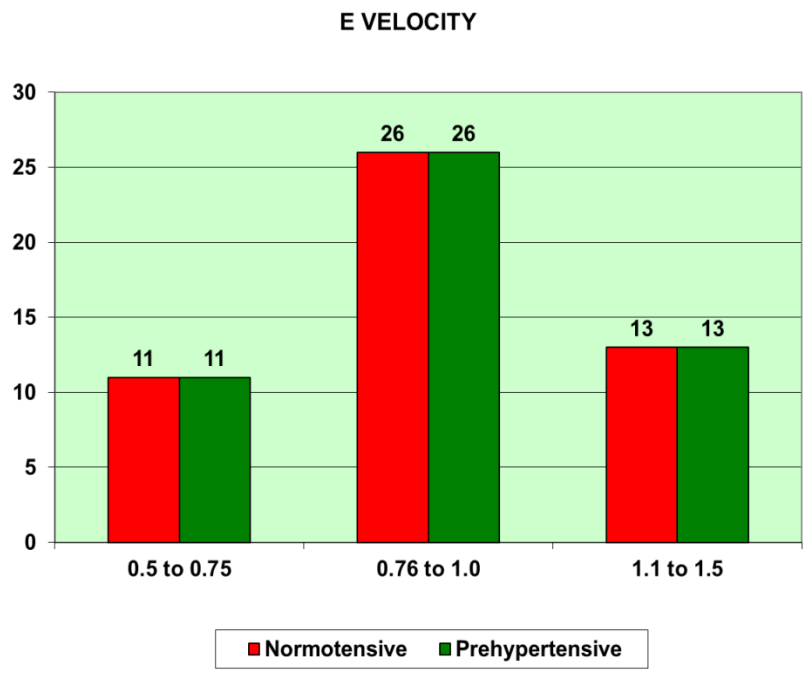


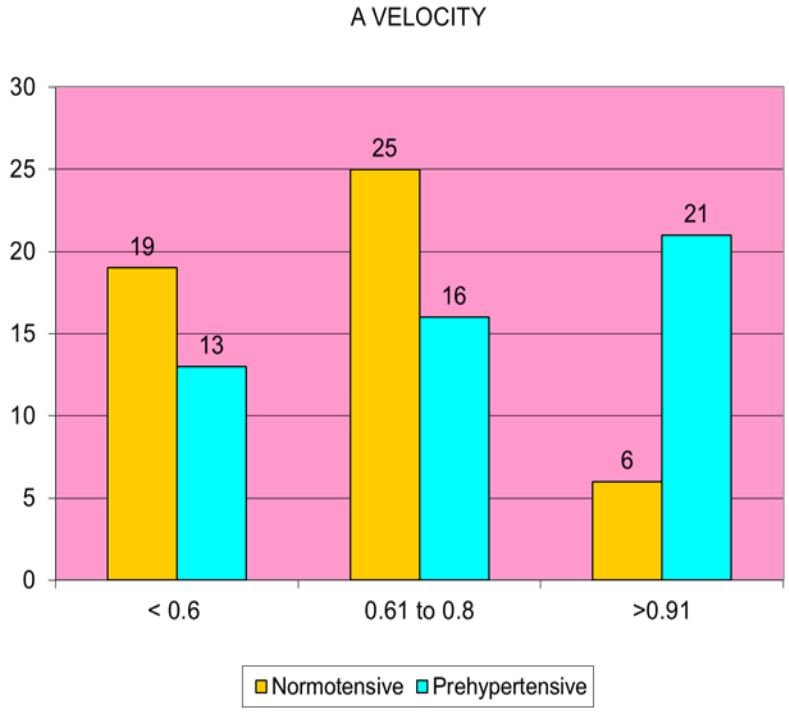
DIASTOLIC DYSFUNCTION IN BOTH GROUPS:

Diastolic dysfunction can be identified using various parameters and it is usually graded from grade I to grade IV. Here we used E velocity which is velocity of blood flow during early diastole and A velocity which is velocity of blood flow during late diastole or atrial systole. Both the velocities are calculated and the ratio between them is made out. Normally the ratio is > 1 but in grade I diastolic dysfunction there is a reversal of this ratio with <1. For calculating other grades, other parameters must be taken into account. Since in our study population all belonged to either normal or grade I diastolic dysfunction, other parameters are not taken into account for data collection, manipulation and for 'p' values.

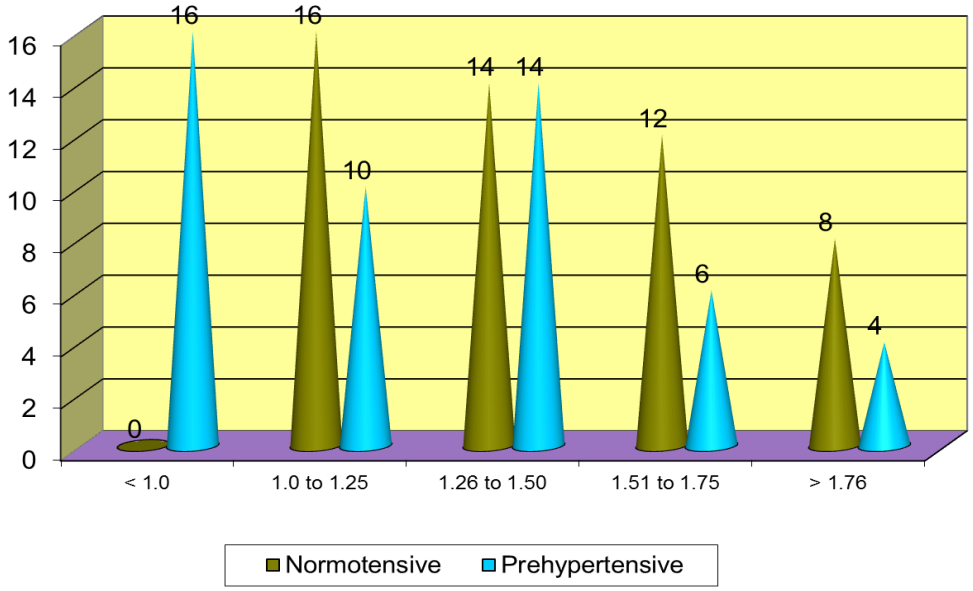
TABLE.12

E/A RATIO	**Normotensives**	**Prehypertensives**
< 1.0	0	16
1.0 to 1.25	16	10
1.26 to 1.50	14	14
1.51 to 1.75	12	6
> 1.76	8	4
TOTAL	50	50

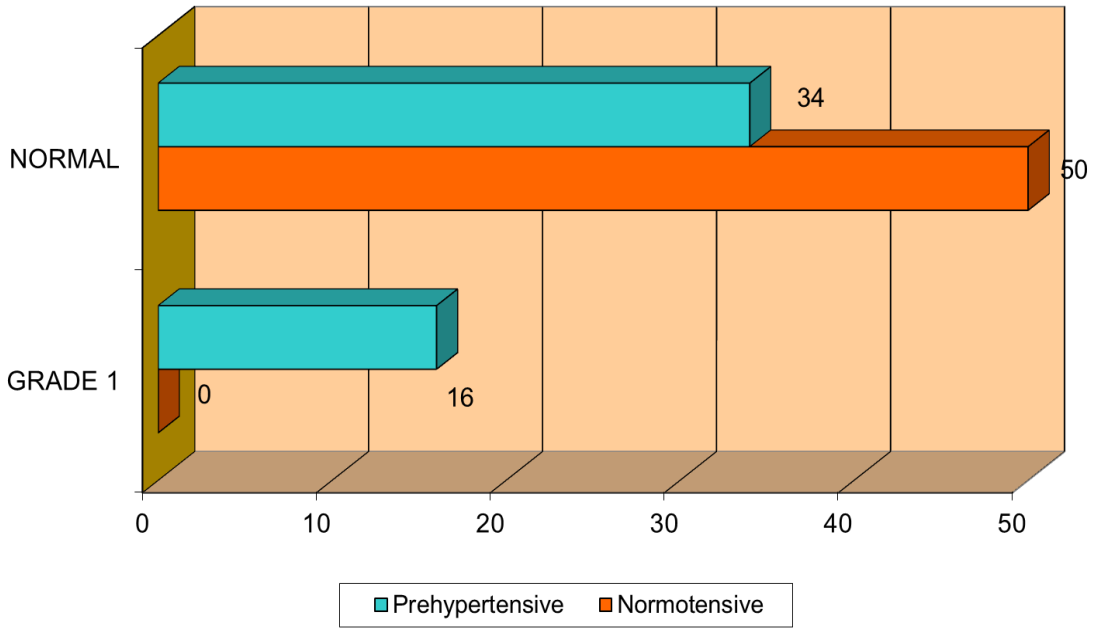

E VELOCITY
30
25
20
15
10
5
0
11
11
26
26
13
13
0.5 to 0.75
0.76 to 1.0
1.1 to 1.5
Normotensive
Prehypertensive


A VELOCITY
30
25
20
15
10
5
0
19
13
25
16
6
21
< 0.6
0.61 to 0.8
>0.91
Normotensive
Prehypertensive

E/A RATIO



GRADE OF DIASTOLIC DYSFUNCTION



To find out whether there is significant difference in presence of diastolic dysfunction between the two groups, the E velocity and V velocity values are entered into a master chart and E/A ratio is calculated which is also entered into the master chart. Data analysis was done using software called Epidemiological Information Package.

Using this software, all the range, frequencies, percentage, mean, standard deviation, chi square and p value can be calculated. The tests used are One way ANOVA test and Student's 't' test for data and Kruskul Wallis Chi-square test for consolidated tables.

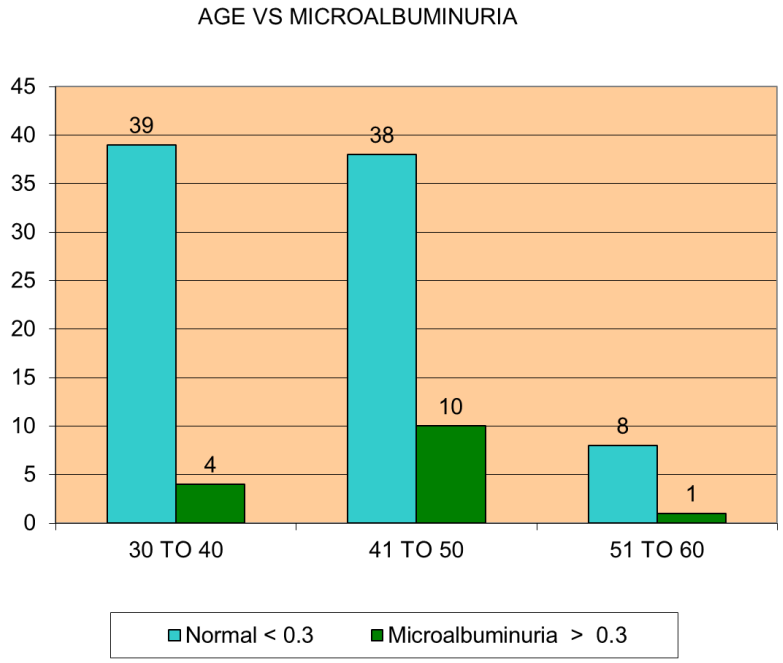
'p' value is calculated and value of less than 0.05 is considered significant. Here the 'p'value is 0.004 which is less than 0.05 and hence it is highly significant.

AGE vs MICROALBUMINURIA:

Out of the 15 individuals who are having microalbuminuria, only 4 belong to the age group of 30 to 40years and 10 individuals belong to the age group of 40 to 50.

TABLE.13

AGE	**Normal**	**Microalbuminuria**
	< 0.3	**> 0.3**
30 TO 40	39	4
41 TO 50	38	10
51 TO 60	8	1
TOTAL	85	15

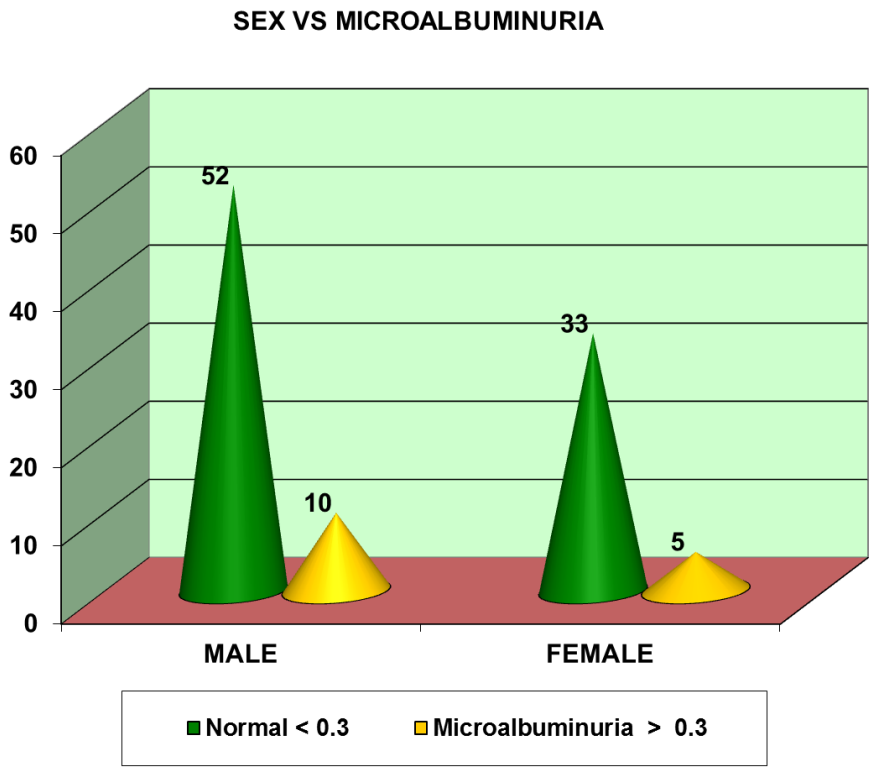


SEX vs MICROALBUMINURIA:

Out of the 15 individuals having microalbuminuria, 10 individuals are males and 5 are females.

TABLE.14

SEX	**Normal**	**Microalbuminuria**
	< 0.3	**> 0.3**
MALE	52	10
FEMALE	33	5
TOTAL	85	15

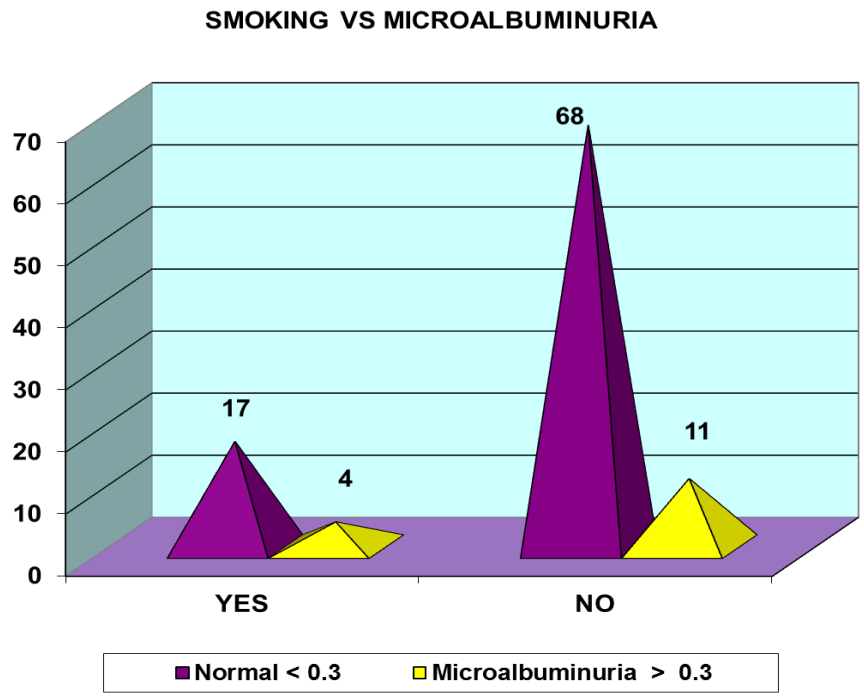


SMOKING vs MICROALBUMINNURIA:

Out of the 15 individuals who are having microalbuminuria, it can be noted that 4 are smokers and 11 are non smokers.

TABLE.15

Smoking	**Normal**	**Microalbuminuria**
	< 0.3	**> 0.3**
YES	17	4
NO	68	11
TOTAL	85	15

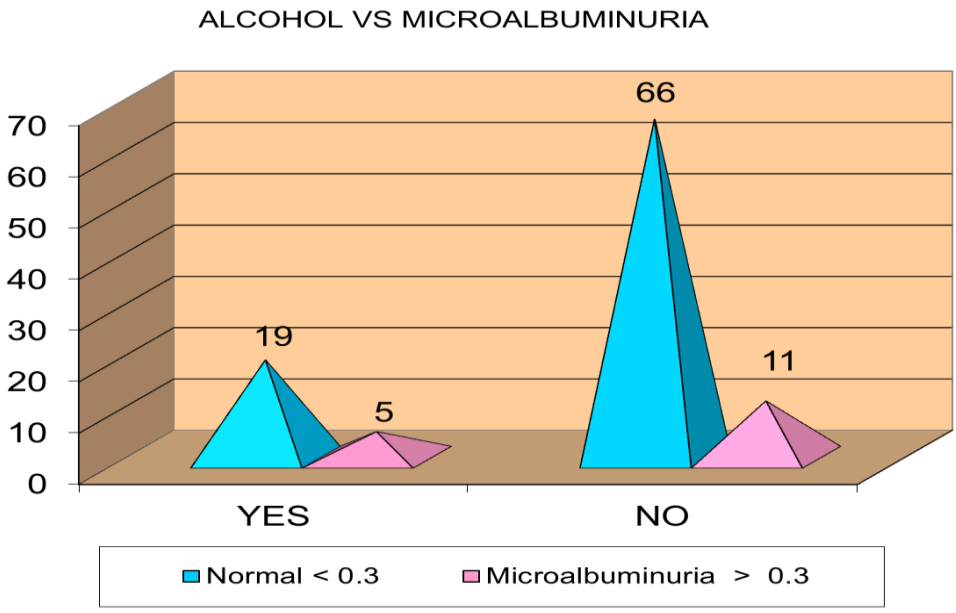


ALCOHOL vs MICROALBUMINURIA:

Out of the 15 individuals who are having microalbuminuria, 4 individuals are the one who consumes alcohol and 11 individuals doesn't consume alcohol.

TABLE.16

Alcohol	**Normal**	**Microalbuminuria**
	< 0.3	**> 0.3**
YES	19	5
NO	66	11
TOTAL	85	15

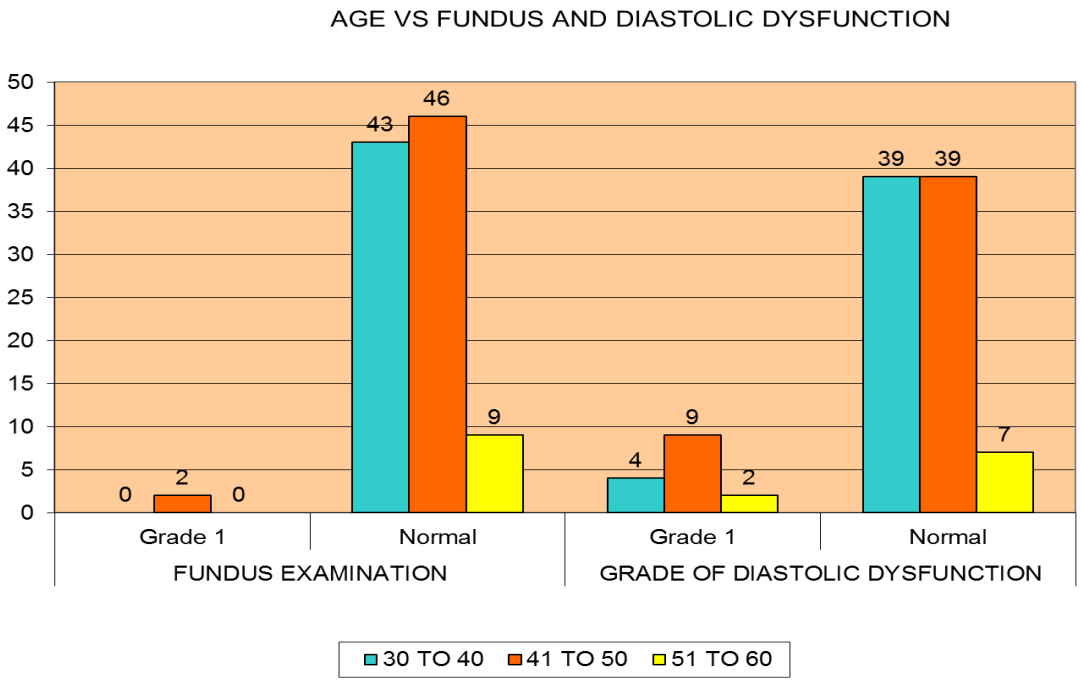


AGE vs FUNDUS/DIASTOLIC DYSFUNCTION:

Both the prehypertensive individuals with grade I hypertensive retinopathy falls in the age group of 41 to 50. Out of 16 individuals with diastolic dysfunction, 10 fall in the age group of 41 to 50.

TABLE.17

	FUNDUS EXAMINATION		GRADE OF DIASTOLIC DYSFUNCTION		TOTAL
AGE	Grade 1	Normal	Grade 1	Normal	
30 TO 40	0	43	4	39	43
41 TO 50	2	46	9	39	48
51 TO 60	0	9	2	7	9
TOTAL	2	98	15	85	100

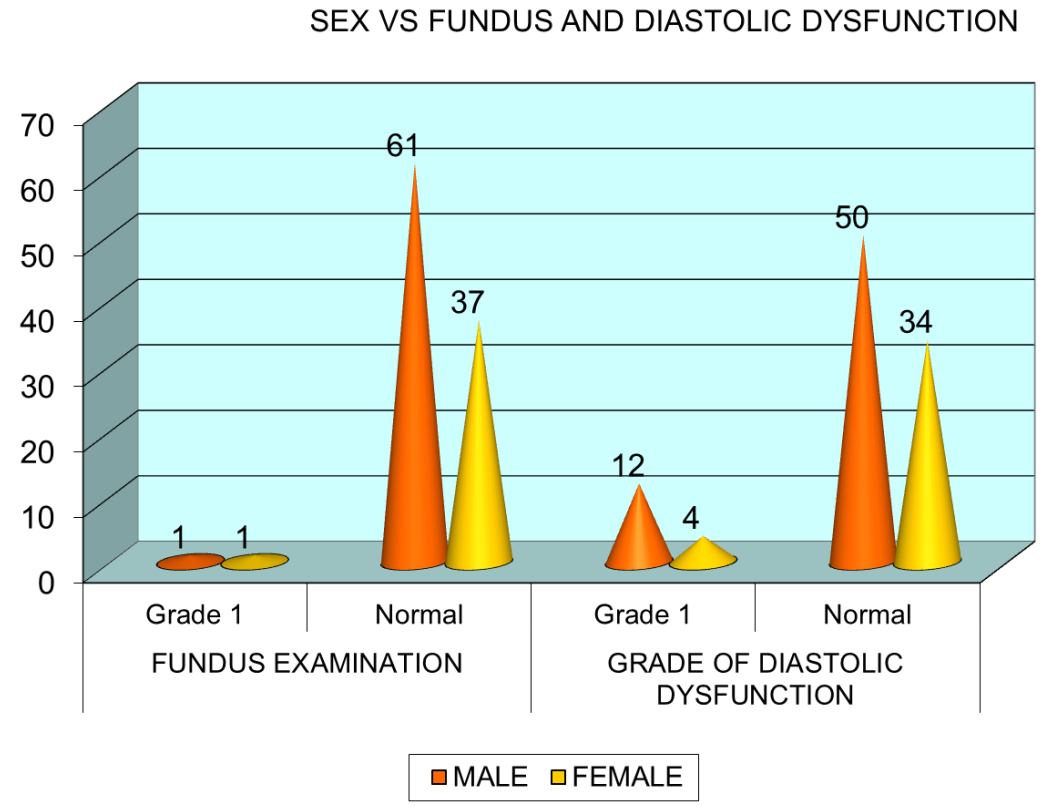


SEX vs FUNDUS/DIASTOLIC DYSFUNCTION:

Out of the 16 subjects with diastolic dysfunction, 12 are males and those with fundus changes fall one in each sex.

TABLE. 18

	FUNDUS EXAMINATION		GRADE OF DIASTOLIC DYSFUNCTION		
SEX	**Grade 1**	**Normal**	**Grade 1**	**Normal**	TOTAL
MALE	1	61	12	50	62
FEMALE	1	37	4	34	38
TOTAL	2	98	16	84	100

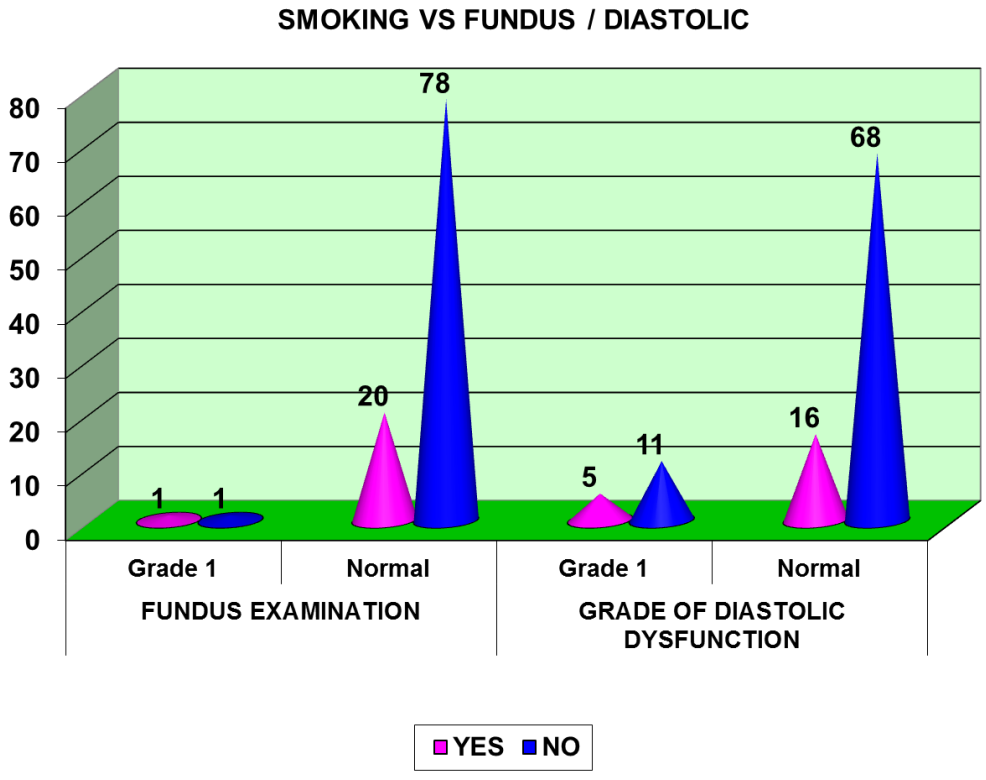


SMOKING vs FUNDUS/DIASTOLIC DYSFUNCTION:

In the individuals with diastolic dysfunction out of 16, 11 are non smokers and 5 are smokers. In those with retinopathy, one is a smoker and other is a non smoker.

TABLE.19

	FUNDUS EXAMINATION		GRADE OF DIASTOLIC DYSFUNCTION		
SMOKING	Grade 1	Normal	Grade 1	Normal	TOTAL
YES	1	20	5	16	21
NO	1	78	11	68	79
TOTAL	2	98	16	84	100

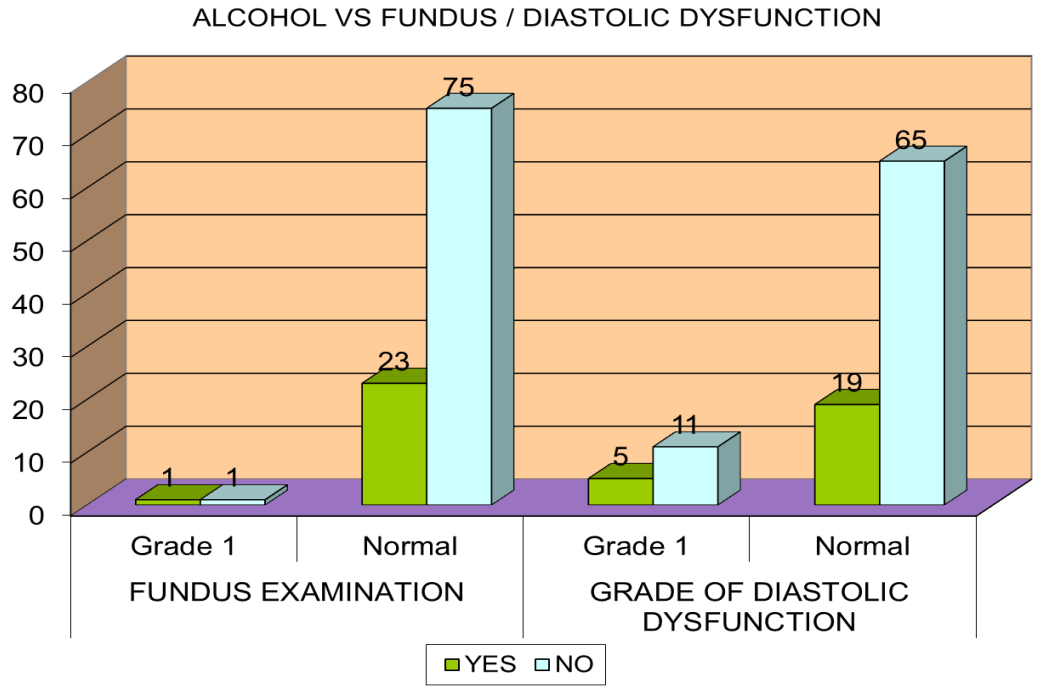


ALCOHOL vs FUNDUS/DIASTOLIC DYSFUNCTION:

The distribution among alcohol consumers is exactly similar to that of smokers. 5 alcohol consumers in individuals with diastolic dysfunction and 1 in subjects with retinopathy.

TABLE.20

	FUNDUS EXAMINATION		GRADE OF DIASTOLIC DYSFUNCTION		
ALCOHOL	**Grade 1**	**Normal**	**Grade 1**	**Normal**	TOTAL
YES	1	23	5	19	24
NO	1	75	11	65	76
TOTAL	2	98	16	84	100

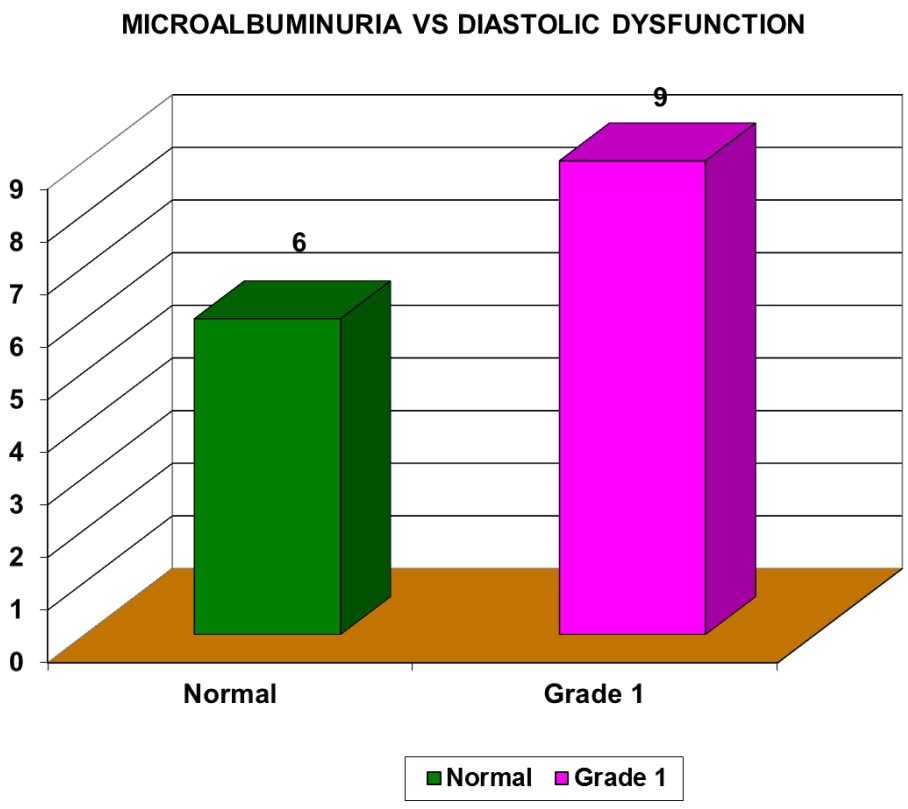


MICROALBUMINURIA vs DIASTOLIC DYSFUNCTION:

Out of the 15 subjects who are having microalbuminuria, 9 subjects are having associated diastolic dysfunction.

TABLE.21

	Diastolic dysfunction	
ACR	Normal	Grade 1
> 0.3	6	9

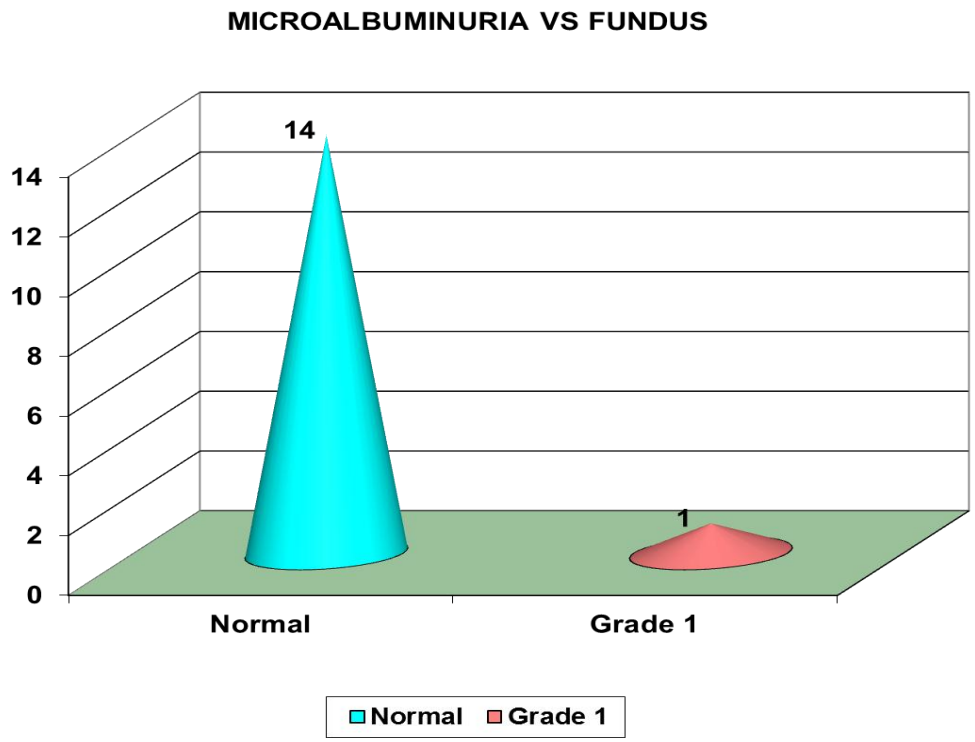


MICROALBUMINURIA vs FUNDUS CHANGES:

Out of 15 subjects with microalbuminuria, only one has associated fundus changes in the form of grade I hypertensive retinopathy.

TABLE.22

	Fundus	
ACR	Normal	Grade 1
> 0.3	14	1



DISCUSSION

SEX DISTRIBUTION:

It can be noted from Table.1 that distribution of males and females is almost equal in the normotensive group whereas in the prehypertensive group, around 68% are males and the remaining 32% constitutes females. According to the survey did by NHANES in the United States, the prevalence of prehypertensives in that population was 39 percent among men and 23 percent among females[2].

AGE DISTRIBUTION:

As per our study (Table.2), around 96% of individuals in prehypertensive group belonged to the age group of 30 to 50 years. After the age of 50 years the incidence of hypertension itself increases. And the end organ damage caused by increased blood pressure also increases along with the age. So detecting prehypertensive individuals at early age becomes important. According to Framingham Heart Study, those in the age group of 65 years and above progresses from prehypertension to hypertension at a rate of 42% when compared to lower age group whose progression rate was 27%[61].

SMOKING AND ALCOHOL CONSUMPTION DISTRIBUTION:

As per our study, around 47% of smokers had prehypertension and 50% of non smokers had prehypertension, (Table 3 and Table 4). In case of alcohol consumption the distribution is exactly 50%.

Alcohol consumption, smoking and hypertension are always associated with each other in causing a cardiovascular event. They act synergistically together. Whether smoking has a long term effect on elevation of BP is a question to rise. After a puff of cigarette smoking there is an acute rise of BP due to increased sympathetic activation. But long term effect of smoking on BP has been studied.

In a health survey done in England[70], it has been found that the light smokers has a significantly lower BP when compared to heavy smokers. But these individuals do not consume alcohol. When alcohol considered along with alcohol BP is more in those with both the habits than with smoking alone.

In another epidemiological survey[71], the blood pressure was found to slightly lower in the smokers when compared to non smokers. This has been attributed to the vasodilatory effect of nicotine present in the cigarette.

BLOOD SUGAR, BLOOD UREA and SERUM CREATININE:

One of the important causes of microalbuminuria apart from hypertension is diabetes and renal disease. Diabetes and renal failure patients can be a confounding factor in our study if included in our study. Hence in our study it is made sure that all of them had a blood sugar values and the blood urea and serum creatinine values within normal range (Table 5, Table 6 and Table 7).

URINE ALBUMIN and URINE ALBUMIN CREATININE RATIO:

In our study, the presence of albumin in urine was tested by both routine dipstick method and by deriving albumin creatinine ratio. According to dipstick method, around 22% of prehypertensive individuals had albumin in urine in which 4% had a 1+ albumin which corresponds to 30 – 100mg/dl of albumin and remaining 18% had a trace albumin which corresponds to 30-100mg/dl.

In the other method of measurement of albumin creatinine ratio, 2% of normotensive individuals had microalbuminuria and 28% of prehypertensive individuals had microalbuminuia. ‘p’ was calculated which was < 0.001 which was highly significant.

In a study done in Korea, the presence of microalbuminuria was studied in prehypertensive individuals. The prehypertensive individuals are divided into two groups as BP in the range of 130-139/85-89mmHG and BP of 120-129/80-84mmHg. The study showed that presence of microalbuminuria is significantly higher in the high BP group individuals[66].

In another similar study the presence of microalbuminuria was found to be higher in prehypertensive group than in normotensive group. In the same study the levels of serum uric acid was found to be higher in prehypertensive people than the normotensive people[65].

RETINOPATHY IN PREHYPERTENSION:

In our study, only 4% of them had changes of grade I hypertensive retinopathy(Table.11). That too they belonged to the prehypertensive group. Though this is statistically insignificant still the presence of arteriolar changes in those individuals needs to be addressed.

In a study done in a Medical University in Italy[72], they noticed incipient signs of hypertensive retinopathy in patients who had a normal BP. They did an ambulatory BP measurement in those individuals and they found that they fall in the prehypertensive BP range. It was termed as Minimal Lesion Hypertensive Retinopathy.

DIASTOLIC DYSFUNCTION IN PREHYPERTENSION:

In our study population, around 32% of them had a grade I diastolic dysfunction according to their recorded E velocity, A velocity and its ratio (Table.12). All belonged to the prehypertensive group. The ‘p’ value is calculated by chi square test and it was 0.004 which was highly significant.

In a study published in pubmed, the diastolic dysfunction was assessed in prehypertensive individuals. The diastolic dysfunction was assessed using various parameters. The result was diastolic dysfunction was higher in prehypertensives than normotensives[67].

AGE AND END ORGAN DAMAGE:

In prehypertensive group those with microalbuminuria, 9% fall in the age group of 30-40 years, 20% in the age group of 40-50 years and 11% in the age group of 50-60 years (Table13). As age advances, the risk of end organ damage increases. In the same group, the distribution of diastolic dysfunction is in the form of 9% in age group of 30-40 years, 18% in age group 40-50 years and 22% in age group 50-60 years(Table 17).

The diastolic dysfunction increases as age progresses as the effect of sustained high BP on end organ occurs faster in older age group population.

SEX AND END ORGAN DAMAGE:

In the prehypertensive group those with microalbuminura, 16% are males and 13% are females (Table 14). In the same group those with diastolic dysfunction, 19% are males and females are 10% (Table 18). So males have more end organ damage than females. The rate of progression of BP is usually higher in males than females up to age of 60 years after which it raises for females. The males have associated risk factors like smoking and alcohol consumption which would have contributed to their higher percentage of end organ damage.

SMOKING AND END ORGAN DAMAGE:

In the prehypertensive group those with microalbuminura, 19% are smokers and 13% are non smokers(Table 15). In those with fundus changes 1 is a smoker and the other is a non smoker(Table19). In those with diastolic dysfunction, 25% are smokers and 13% are non smokers(Table 19).

So smokers have higher percentage of end organ damage when compared to non smokers.

Stephan R. Orth et al, studied the relationship of smoking and kidney. The result obtained was that when smoking present in a hypertensive individual, the risk microalbuminuria is doubled and smoking itself is a risk

factor for microalbuminuria even in a non diabetic and non hypertensive individuals[73].

Stork et al studied the correlation of smoking and diastolic function. The smokers with coronary artery disease had associated diastolic dysfunction. This is because the nicotine in smoke had caused a shift of mitral blood flow from E wave to A wave thus reversing the normal E/A ratio.

ALCOHOL AND END ORGAN DAMAGE:

In our study population, the prehypertensive individuals with microalbuminuria had 20% alcohol consumers and 14% of them don't consume alcohol (Table 16). In those with fundus changes 1 consumes and the other doesn't consume (Table 20). In those with diastolic dysfunction similar to microalbuminuria, 20% of them consume alcohol and 14% of them don't consume alcohol (Table 20).

Alcohol usually worsens the existing microalbuminuria. The toxins and wastes produced by alcohol consumption are not properly filtered by the existing end organ damage which may further cause renal injury. Also alcohol favours dehydration, in a state where protein excretion is increased in urine.

MICROALBUMINURIA AND DIASTOLIC DYSFUNCTION:

Around 60% of those with microalbuminuria had an associated grade I diastolic dysfunction which is significant (Table 21). In several studies it has shown that microalbuminuria is a risk factor for a future vascular event either in the form of coronary heart disease or a stroke either in the background of hypertension, diabetes or a renal disease. And the prognosis is comparatively poor for those individuals.

MICROALBUMINURIA AND RETINOPATHY:

Only 6% percent of those with microalbuminuria had retinopathy changes. The retinopathy usually occurs after long standing hypertension. Since our study is on prehypertension we had only two subjects with retinopathy. But still there is a good association between microalbuminuria and retinopathy in presence of high blood pressure in which several studies has been done.

The relationship between retinopathy and microalbuminuria was studied by Biesenbach in a group of patients with essential hypertension. He found that retinopathy is more in patients with persistant microalbuminuria than in patients whose microalbuminuria has been adequately treated[75].

CONCLUSION

As per our study,

- Prehypertension is more common in males than females
- Most of the individuals with prehypertension belonged to the age group of 30 to 50 years than above 50 years
- Out of prehypertensive individuals, the distribution of smokers and alcohol consumers was almost 50%. So significant correlation between smoking and alcohol consumption with prehypertension could not be made out
- None of the individuals included in the study had diabetes or renal disease as evidenced by normal blood sugar values and normal renal function tests
- Presence of microalbuminuria is more common in prehypertensive individuals than normotensive individuals. It is statistically significant
- Retinopathy is more common in prehypertensive individuals than normotensive individuals though it is statistically insignificant.

- Diastolic dysfunction is more common in the prehypertensive group than normotensive individuals evidenced by statistically significant ‘p’ value.
- The percentage of presence of end organ damage increased as the age progressed.
- Males had a more percentage of end organ damage when compared to females.
- The presence of end organ damage is more common in smokers and alcohol consumers.
- Most of the individuals with microalbuminuria had associated diastolic dysfunction.

So according to our study even at the prehypertensive stage people starts to develop end organ damage. So whether they have to be treated with antihypertensive drugs need to be addressed. According to TROPHY (Trial Of Preventing Hypertension)[76] trial which included 800 prehypertensive subjects were treated with candesartan 16mg for 2 years and placebo. At the end of study there was a significant reduction in incident hypertension in subjects who received candesartan compared with those who receive placebo.

But JNC 7 advises life style modification for prehypertensive individuals[4]. However JNC 8[77] doesn't address the prehypertensive stage. So detailed studies needed regarding drug therapy for prevention of progression of prehypertension to overt hypertension and for prehypertensive individuals with end organ damage.

At the outset of our study, we suggest that all the patients need to be screened for the presence of high blood pressure above the age of 30 years whatever may be their presenting symptom. If detected to be in a prehypertensive stage of blood pressure, advise at least a urine albumin test to look for any microalbuminuria. They needed to be followed up with regular monitoring of BP either every 6 months, 1 year or whatever way it is feasible.

Above all life style modifications should be strongly encouraged for those individuals. It includes:

- DIET - They should be advised DASH (Dietary Approaches To Stop Hypertension) diet. It is rich in fruits and vegetables and low fat or non fat diary. It is rich in potassium and calcium and contains limited amounts of meats and sweets[78] .DASH diet reduces systolic BP by 5.5mmHg and diastolic BP by 3.0mmHg.

- Increased body weight is a risk factor for prehypertension and hence a weight reduction should be strongly recommended for them. Studies found that for 1 kg reduction of weight systolic BP decreases by 1.05mmHg and diastolic BP decreases by 0.92mmHg. It also improves the abnormal left ventricular relaxation[79].
- Limitation of salt intake. It has a definite role in preventing hypertension but it is difficult to maintain in general public and so a strong motivation needed.
- Regular physical activity. They should exercise > 3 times a week at least 30 minutes they should exercise.

BIBLIOGRAPHY

1. http://www.uptodate.com. Prehypertension and Borderline Hypertension, Nov 15, 2007
2. Hsia J, Margolis KL, Eaton CB et al. (February 2007). "Prehypertension and cardiovascular disease risk in the Women's Health Initiative". *Circulation* 115 (7): 855–60. doi:10.1161/CIRCULATIONAHA.106.656850. PMID17309936.
3. Hales S. Statistical Essays: Containing Haema-staticks; or, an Account of some Hydraulick and Hydrostatical Experiments Made on the Blood and Blood Vessels Of Animals. London: Innys W Manby R;1733
4. Chobanian AV, Bakris GL, Black HR et al. (May 2003). "The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report". *JAMA* 289 (19): 2560–72.
5. Booth J. A short history of blood pressure measurement. Proc R Soc Med 1977
6. Riva-Rocci S. Un Sfigmomanometro Nuovo. Gaz Med Torino 1896
7. Korotkoff NS. On methods of studying blood pressure: second presentation. Izv Imper Voen-Med Acad. 1906

8. Pickering T. Recommendations for the use of home and ambulatory blood pressure monitoring. American Society Of Hypertension Ad Hoc Panel. Am J Hypertens 1996;9(1):1-11
9. Kario K, Pickering TG, Umeda Y, et al. Morning surge in blood pressure as a predictor of silent and clinical cerebrovascular disease in elderly hypertensives: a prospective study. Circulation 2003;107:1401-1406.
10. Franklin SS, Gustin W. Wong ND, et al. Hemodynamic patterns of age related changes in blood pressure. The Framingham Heart Study. Circulation 1997;96(1):308-315.
11. Klabunde, RE (2007). "Cardiovascular Physiology Concepts – Arterial Baroreceptor". Retrieved 2008-09-09. Archived version 2009-10-03
12. McDonough AA, Leong PK, Yang LE: Mechanisms of pressure natriuresis: how blood pressure regulates renal sodium transport. *Ann N Y Acad Sci* 2003, 986**:**669-677.
13. Imai, T.; Miyazaki, H.; Hirose, S.; Hori, H.; Hayashi, T.; Kageyama, R.; Ohkubo, H.; Nakanishi, S.; and Murakami, K. (December 1983). "Cloning and sequence analysis of cDNA for human renin precursor". *Proceedings of the National Academy of Sciences U.S.A.* 80 (24): 7405–9. doi:10.1073/pnas.80.24.7405. PMC 389959. PMID 6324167.

14. Zhang R, Xu X, Chen T, Li L, Rao P (May 2000). "An assay for angiotensin-converting enzyme using capillary zone electrophoresis". *Anal. Biochem.* 280 (2): 286–90.
15. Imig JD (March 2004). "ACE Inhibition and Bradykinin-Mediated Renal Vascular Responses: EDHF Involvement". *Hypertension* 43 (3): 533–5.
16. Agapitov AV, Haynes WG (March 2002). "Role of endothelin in cardiovascular disease". *J Renin Angiotensin Aldosterone Syst* 3 (1): 1–15.
17. *Medical physiology a cellular and molecular approach* (2nd ed., International ed. ed.). Philadelphia, PA: Saunders/Elsevier. 2009. p. 480. ISBN 9781437720174.
18. Stryer, Lubert (1995). *Biochemistry, 4th Edition*. W.H. Freeman and Company. p. 732. ISBN 0-7167-2009-4.
19. Ghosh, S. M.; Kapil, V.; Fuentes-Calvo, I.; Bubb, K. J.; Pearl, V.; Milsom, A. B.; Khambata, R.; Maleki-Toyserkani, S.; Yousuf, M.; Benjamin, N.; Webb, A. J.; Caulfield, M. J.; Hobbs, A. J.; Ahluwalia, A. (2013). "Enhanced Vasodilator Activity of Nitrite in Hypertension: Critical Role for Erythrocytic Xanthine Oxidoreductase and Translational Potential". *Hypertension* **61** (5): 1091–102.
20. Dessy, C.; Ferron, O. (2004). "Pathophysiological Roles of Nitric Oxide: In the Heart and the Coronary Vasculature". *Current Medical Chemistry* –

Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry **3** (3): 207–216.

21. Osanai, T; Fujiwara, N; Saitoh, M; Sasaki, S; Tomita, H; Nakamura, M; Osawa, H; Yamabe, H; Okumura, K (2002). "Relationship between salt intake, nitric oxide, and asymmetric dimethylarginine and its relevance to patients with end-stage renal disease".

22. Lawes CMM et al: Global burden of blood pressure-related disease, 2001. Lancet 371:1513, 2008[PMID: 18456100]

23. Gupta R, Pandey RM, Misra A, Agrawal A, Misra P, Dey S, Rao S, Menon VU, Kamalamma N, Vasantha Devi KP. High prevalence and low awareness, treatment and control of hypertension in Asian Indian women. J Hum Hypertens. 2012;26:585-59

24.http://www.japi.org/february_2013_special_issue_hypertension_guidelines/06_epidemiology_of_hypertension.pdf.

25. Mark AL**.** The sympathetic nervous system in hypertension: a potential long term regulator of arterial pressure. J Hypertens Suppl. 1996;14:S159-65. [PMID:9120673]

26. Brook RD, Julius S**.** Autonomic imbalance, hypertension, and cardio vascular risk. Am J Hypertens. 2000;13:112S-122S. [PMID: 10921530]

27. Guo GB, Abboud FM**.** Angiotensin II attenuates baroreflex control of heartrate and sympathetic activity. Am J Physiol. 1984;246:H80-9. [PMID: 6696093]

28. Abboud FM**.** Effects of sodium, angiotensin, and steroids on vascular reactivity in man. Fed Proc. 1974;33:143-9. [PMID: 4359754]

29. Li Z, Mao HZ, Abboud FM, Chapleau MW**.** Oxygen-derived free radicals contribute to baroreceptor dysfunction in atherosclerotic rabbits

30. Chapleau MW, Hajduczok G, Abboud FM**.** Suppression of baroreceptor discharge by endothelin at high carotid sinus pressure. Am J Physiol.

31. Somers VK, Mark AL, Abboud FM**.** Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. Hypertension.

32. Grassi G, Giannattasio C, Failla M, Pesenti A, Peretti G, Marinoni E, et al. Sympathetic modulation of radial artery compliance in congestive heart failure. Hypertension. 1995; 26:348-54. [PMID: 7635545]

33. Light KC**.** Environmental and psychosocial stress in hypertension onset and progression. In: Oparil S, Weber MA, eds. Hypertension: A Companion to Brenner and Rector's The Kidney. Philadelphia: WB Saunders; 2000:59-70.

34. Mulvany MJ, Aalkjaer C**.** Structure and function of small arteries. Physiology Rev. 1990;70:921-61. [PMID: 2217559]

35. Culleton BF, Larson MG, Kannel WB, Levy D**.** Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med.1999;131:7-13. [PMID: 10391820]

36. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, et al. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physio 2002;282:F991-7.

37. O'Rourke MF, Hayward CS, Lehmann ED. Arterial stiffness. In: Oparil S,Weber MA, eds. Hypertension: A Companion to Brenner and Rector's The Kidney. Philadelphia: WB Saunders; 2000:134-51.

38. Mulvany MJ. Small artery remodeling in hypertension. Curr Hypertens Rep.2002;4:49-55. [PMID: 11790292]

39. Fukui T, Ishizaka N, Rajagopalan S, Laursen JB, Capers Q 4th, TaylorWR, et al**.** p22phox mRNA expression and NADPH oxidase activity are increasedin aortas from hypertensive rats. Circ Res. 1997;80:45-51.

40. Rajagopalan S, Kurz S, Mu¨nzel T, Tarpey M, Freeman BA, Griendling KK, et al**.** Angiotensin II-mediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. J Clin Invest. 1996;97:1916-23. [PMID: 8621776]

41. Chen XL, Tummala PE, Olbrych MT, Alexander RW, Medford RM. Angiotensin II induces monocyte chemoattractant protein-1 gene expression

in rat vascular smooth muscle cells. Circ Res. 1998;83:952-9. [PMID: 9797345]

42. Cai H, Harrison DG. Endothelial dysfunction in cardiovascular diseases: the role of oxidant stress. Circ Res. 2000;87:840-4. [PMID: 11073878]

43. Nakazono K, Watanabe N, Matsuno K, Sasaki J, Sato T, Inoue M. Doessuperoxide underlie the pathogenesis of hypertension? Proc Natl Acad Sci U S A.1991;88:10045-8. [PMID: 1658794]

44. Laursen JB, Rajagopalan S, Galis Z, Tarpey M, Freeman BA, HarrisonDG**.** Role of superoxide in angiotensin II-induced but not catecholamine induced hypertension. Circulation. 1997;95:588-93. [PMID: 9024144]

45. Krum H, Viskoper RJ, Lacourciere Y, Budde M, Charlon V. The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. N Engl J Med.1998;338:784-90. [PMID: 9504938]

46. Panza JA. High-normal blood pressure—more “high” than “normal” [Editorial]. N Engl J Med. 2001;345:1337-40. [PMID: 11794154]

47. Schmieder RE, Messerli FH. Hypertension and the heart. J Hum Hypertens 2000;14:597â€“604.

48. de Simone G, Pasanisi F, Contraldo F. Link of nonhemodynamic factors to hemodynamic determinants of left ventricular hypertrophy. Hypertension 2001;38:13â€“18.

49. Eric J. Topol; Robert M. Califf (2007). *Textbook of cardiovascular medicine*. Lippincott Williams & Wilkins. pp. 420–. ISBN 978-0-7817-7012-5. Retrieved 16 November 2010.

50. Flack JM, Neaton J, Grimm R Jr, et al. Blood pressure and mortality among men with prior myocardial infarction. Circulation 1995;92:2437â€“2445.

51. Kannel WB, Dannenberg AL, Abbott RD. Unrecognized myocardial infarction and hypertension. Am Heart J 1985; 109:581â€“585

52. Verdecchia P, Reboldi GP, Gattobigio R, et al. Atrial fibrillation in hypertension: predictors and outcome. Hypertension 2003b;41:218â€“223.

53. Young-Xu Y, Ravid S. Optimal blood pressure control for the prevention of atrial fibrillation [Abstract]. Circulation 2004;110(Suppl 3):III-768.

54. Antonini-Canterin F, Huang G, Cervesato E, et al. Symptomatic aortic stenosis: does systemic hypertension play an additional role? Hypertension 2003;41:1268â€“1272.

55. Olsen MH, Wachtell K, Bella JN, et al. Aortic valve sclerosis relates to cardiovascular events in patients with hypertension (A LIFE substudy). Am J Cardiol 2005;95:132â€“136.

56. Farrugia A (January 2010). "Albumin usage in clinical medicine: tradition or therapeutic?". *Transfus Med Rev* 24 (1)

57. Parson's diseases of the eye. Twentieth edition. Elsevier publication.

58. S. L. Wu, Z. Q. Zhang, S. B. Song, et al., "Prevalence of prehypertension and associated cardiovascular risk: two years follow up results," Chinese Journal of Epidemiology, vol. 38, no. 5, pp. 415–419, 2010.

59. A. Cordero, M. Laclaustra, M. León et al., "Prehypertension is associated with insulin resistance state and not with an initial renal function impairment: a Metabolic Syndrome in Active Subjects in Spain (MESYAS) Registry substudy," American Journal of Hypertension, vol. 19, no. 2, pp. 189–196, 2006.

60. Wang Y, Wang QJ. The prevalence of prehypertension andhypertension among US adults according to the new JointNational Committee guidelines. Arch Intern Med.2004;164(19):2126-34

61. Vasan RS, Larson MG, Leip EP, et al.Assessment of frequencyof progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet.2001;358(9294):1682-6

62. King DE, Egan BM, Mainous AG III, Geesey ME. Elevation ofC-reactive protein in people with prehypertension. *J ClinHypertens.* 2004;6(10):562-8

63. Chrysohoou C, Pitsavos C, Panagiotakos DB, *et al.* Associationbetween prehypertension status and inflammatory markersrelated to atherosclerotic disease: the ATTICA Study. *Am JHypertens*. 2004;17(7):568-7321. Lee JE, Kim YG, Choi YH, *et al.*

64. Y. Ishikawa, J. Ishikawa, S. Ishikawa et al., "Prevalence anddeterminants of prehypertension in a Japanese general population:the Jichi Medical School cohort study," Hypertension Research, vol. 31, no. 7, pp. 1323–1330, 2008.

65. Lee JE, Kim YG, Choi YH, Huh W, Kim DJ, Oh HY. *Serum uricacid is associated with microalbuminuria in prehypertension.Hypertension 2006;47:962-7.*

66. Byung jin kim MD, hyun jong lee et al, Division Of Cardiology, Department Of Internal Medicine, Kangbuk Samsung Hospital , Sungkyunkwan University School Of Medicine.

67. The association of diastolic dysfunction and circadian variation of blood pressure in prehypertension. Atatürk Education and Research Hospital, Department of Cardiology, Ankara, Turkey.

68. Vascular inflammation and aortic stiffness relate to early left ventricular diastolic dysfunction in prehypertension. School of Medicine, Department of Cardiology, Gulhane Military Medical Academy, Etlik-Ankara, Turkey.

69. Impact of Prehypertension on Common Carotid Artery Intima-Media Thickness and Left Ventricular Mass. Efstathios Manios, MD; Georgios Tsivgoulis, MD, FESO; Eleni Koroboki, MD. UNIVERSITY OF ATHENS. GREECE.

70. Paola Primatesta, Emanuela Falaschetti, Sunjai Gupta, Michael G. Marmot, Neil R. Poulter. Association Between Smoking and Blood Pressure. Evidence From the Health Survey for England.

71. Blood pressure in smokers and nonsmokers: epidemiologic findings.Green MS, Jucha E, Luz. Am Heart J. 1986;111(5):932.

72. 'Minimal-change hypertensive retinopathy' and 'arterial pre-hypertension', illustrated via ambulatory blood-pressure monitoring in putatively normotensive subjects. Department of Clinical Sciences, University La Sapienza, Rome, Italy.

73. Smoking and the Kidney. Stephan R. Orth. Division of Nephrology and Hypertension, University Hospital Berne (Inselspital), Berne, Switzerland.

74. T. STORK, M.D., H. EICHSTADT, M.D., M. MOCKEL ,M.D., Changes of Diastolic Function Induced by Cigarette Smoking.

75. Biesenbach G . High prevalence of retinopathy in patients with persistant microalbuminuria. Clin Nephrol. 1994

76. Stevo Julius, MD, DSc (University of Michigan, Ann Arbor) TROPHY: Trial Of Preventing Hypertension

77. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

78. N. M. Karanja, E. Obarzanek, P. H. Lin et al., "Descriptive characteristics of the dietary patterns used in the Dietary Approaches to Stop Hypertension trial," *Journal of the American Dietetic Association*, vol. 99, supplement 8, pp. S19–S27, 1999.

79. G. Cocco and S. Pandolfi, "Physical exercise with weight reduction lowers blood pressure and improves abnormal left ventricular relaxation in pharmacologically treated hypertensive patients," *Journal of Clinical Hypertension*, vol. 13, no. 1, pp. 23–29, 2011.

ANNEXURE – 1

PROFORMA

S. No:

NAME: AGE/SEX:

OCCUPATION:

COMPLAINTS IF ANY:

GENERAL EXAMINATION:

Pulse rate: BP:

SYSTEMIC EXAMINATION:

1. CVS:

2. RS:

3. P/A:

4. CNS:

PAST HISTORY:

1. H/O DIABETES: YES/NO
2. H/O HYPERTENSION: YES/NO
3. H/O KIDNEY DISEASE: YES/NO
4. H/O CAHD/CCF: YES/NO
5. H/O ACUTE FEBRILE ILLNESS: YES/NO
6. H/O DRUG INTAKE: YES/NO
7. H/O TUBERCULOSIS: YES/NO
8. H/O PREGNANCY: YES/NO

PERSONAL HISTORY:

1. H/O SMOKING: YES/NO

2. H/O ALCOHOL INTAKE: YES/NO

3. H/O DRUG ABUSE: YES/NO

INVESTIGATIONS

- BLOOD SUGAR:
- BLOOD UREA:
- SERUM CREATININE:
- URINE ROUTINE:
- ELECTROCARDIOGRAM:
- CHEST X RAY:
- SPOT URINE ALBUMIN CREATININE RATIO:
- ECHOCARDIOGRAM:
- FUNDUS:

ANNEXURE – 2

MASTER CHART

S.NO	NAME	AGE	SEX	SMOKING	ALCOHOL	BLOOD PRESSURE (mmHg)	INVESTIGATIONS						ECHOCARDIOGRAM			
							BLOOD SUGAR (mg/dl)	BLOOD UREA (mg/dl)	SERUM CREATININE (mg/dl)	URINE ALBUMIN	URINE ALBUMIN/CREATININE RATIO	FUNDUS EXAMINATION	E VELOCITY	A VELOCITY	E/A RATIO	GRADE OF DIASTOLIC DYSFUNCTION
1	KRISHNA	31	M	YES	NO	110/70	90	23	0.7	NIL	0.08	NORMAL	1.14	0.54	2.11	NORMAL
2	ASHRAF	39	M	NO	NO	134/88	90	31	0.4	TRACE	0.42	NORMAL	1.07	0.53	2.01887	NORMAL
3	PANDI	54	M	YES	YES	130/86	84	36	0.9	TRACE	0.431	NORMAL	0.64	1.1	0.58182	GRADE 1
4	RAM	46	M	YES	YES	100/68	96	31	0.7	NIL	0.184	NORMAL	0.61	0.54	1.12963	NORMAL
5	ARIVU	49	M	NO	NO	118/74	90	30	0.6	NIL	0.194	NORMAL	0.864	0.54	1.6	NORMAL
6	ARAVAN	42	M	NO	YES	108/70	88	30	0.5	NIL	0.24	NORMAL	0.613	0.41	1.49512	NORMAL
7	KUMARI	51	F	NO	NO	118/70	78	18	0.6	NIL	0.08	NORMAL	0.763	0.546	1.3974	NORMAL
8	RAJATHI	36	F	NO	NO	112/74	91	31	0.8	NIL	0.112	NORMAL	0.861	0.542	1.5885	NORMAL
9	KASI	50	M	NO	YES	116/72	96	34	0.4	NIL	0.342	NORMAL	0.962	0.512	1.878	NORMAL
10	VAIRAM	49	M	YES	YES	130/86	90	31	0.7	NIL	0.24	GRADE 1	1.081	0.725	1.491	NORMAL
11	RATHNABAI	58	F	NO	NO	110/70	86	14	0.8	NIL	0.15	NORMAL	1.17	0.62	1.887	NORMAL
12	SHEELA	46	F	NO	NO	112/76	96	21	0.6	NIL	0.16	NORMAL	0.89	0.56	1.589	NORMAL
13	PUSHPAM	36	F	NO	NO	116/76	90	24	0.7	NIL	0.2	NORMAL	0.84	0.424	1.98	NORMAL
14	LEELAVATHI	38	F	NO	NO	132/88	82	29	0.6	NIL	0.24	NORMAL	0.864	0.563	1.534	NORMAL
15	THANUSHA	39	F	NO	NO	128/86	88	24	0.7	NIL	0.181	NORMAL	0.681	0.452	1.506	NORMAL
16	SRINIVASAN	48	M	NO	YES	110/70	78	28	0.7	NIL	0.25	NORMAL	0.751	0.563	1.33	NORMAL
17	SRIDHAR	33	M	NO	NO	130/88	90	30	0.9	NIL	0.49	NORMAL	0.751	0.44	1.783	NORMAL
18	RAJESWARI	46	F	NO	NO	112/60	91	30	0.7	NIL	0.1	NORMAL	0.8621	0.53	1.626	NORMAL
19	THANGAM	55	F	NO	NO	110/60	99	33	0.6	NIL	0.26	NORMAL	0.864	0.527	1.639	NORMAL
20	GANESH	38	M	NO	NO	132/84	96	30	1	NIL	0.17	NORMAL	0.912	0.67	1.361	NORMAL
21	RAJU	43	M	YES	YES	130/88	96	28	0.7	TRACE	0.51	NORMAL	1.05	0.82	1.28	NORMAL
22	THANGARAJ	56	M	NO	YES	108/70	76	28	0.9	NIL	0.25	NORMAL	0.93	0.85	1.09	NORMAL
23	LEELA	44	F	NO	NO	138/88	94	27	0.7	NIL	0.43	NORMAL	0.85	0.71	1.197	NORMAL
24	HEPCIBA	37	F	NO	NO	112/78	98	20	0.4	NIL	0.15	NORMAL	0.735	0.61	1.204	NORMAL
25	GEETHA	33	F	NO	NO	116/78	101	23	0.6	NIL	0.23	NORMAL	0.86	0.621	1.384	NORMAL
26	ANTHONYRAJ	32	M	NO	NO	130/84	86	18	0.5	NIL	0.26	NORMAL	1.07	0.93	1.15054	NORMAL
27	ALAGAPPAN	37	M	NO	NO	128/88	91	17	0.6	NIL	0.141	NORMAL	0.954	0.84	1.13571	NORMAL
28	KUMAR	42	M	NO	NO	110/60	97	21	0.7	NIL	0.261	NORMAL	0.76	0.62	1.22581	NORMAL
29	SITALAKSHMI	42	M	NO	NO	130/86	95	28	0.4	NIL	0.251	NORMAL	0.94	1.02	0.92157	GRADE 1
30	RAJESH	46	M	NO	NO	114/72	101	27	0.6	NIL	0.172	NORMAL	0.9	0.73	1.23288	NORMAL
31	DEEPAK	40	M	NO	NO	132/88	90	30	0.4	NIL	0.223	NORMAL	0.968	0.62	1.561	NORMAL
32	NARASIMAN	49	M	NO	NO	112/60	104	31	0.4	NIL	0.21	NORMAL	0.762	0.65	1.17	NORMAL
33	SATHASIVAM	54	M	YES	YES	114/70	99	29	0.9	NIL	0.2	NORMAL	1.14	0.84	1.357	NORMAL
34	ALAGURAJ	46	M	YES	YES	128/84	101	20	0.6	TRACE	0.52	NORMAL	0.712	0.89	0.8	GRADE 1
35	RAJENDRAN	50	M	YES	YES	136/80	104	30	0.9	1 +	0.6	NORMAL	0.84	0.91	0.92	GRADE 1
36	ARASAN	42	M	YES	YES	116/76	100	31	0.8	NIL	0.15	NORMAL	0.72	0.63	1.14	NORMAL
37	RADHA	37	F	NO	NO	106/70	96	31	0.6	NIL	0.22	NORMAL	0.84	0.73	1.13	NORMAL
38	RAMESH	40	M	YES	YES	126/84	94	29	0.9	NIL	0.16	NORMAL	0.75	0.61	1.22	NORMAL
39	THANGAMMAL	48	F	NO	NO	108/70	99	17	0.7	NIL	0.27	NORMAL	0.85	0.64	1.32	NORMAL
40	NIRMALA	44	F	NO	NO	112/70	96	31	0.7	NIL	0.22	NORMAL	0.64	0.52	1.23	NORMAL
41	ALAGESAN	44	M	NO	YES	126/86	106	33	0.9	NIL	0.24	NORMAL	0.82	0.76	1.08	NORMAL
42	POORNIMA	40	F	NO	NO	118/74	96	36	0.7	NIL	0.2	NORMAL	0.82	0.71	1.16	NORMAL
43	ABI	40	M	NO	NO	130/80	92	28	0.6	NIL	0.24	NORMAL	0.72	0.53	1.35	NORMAL
44	ABINAYA	41	F	NO	NO	130/88	90	40	0.6	NIL	0.16	NORMAL	1.02	0.62	1.64	NORMAL
45	SEETHA	40	F	NO	NO	110/70	86	26	0.6	NIL	0.14	NORMAL	0.53	0.95	1.79	NORMAL
46	NESAN	40	M	YES	NO	112/76	88	31	0.4	NIL	0.16	NORMAL	1.14	0.83	1.37	NORMAL
47	PETER	48	M	NO	NO	130/80	96	26	0.5	TRACE	0.54	NORMAL	0.63	0.78	0.8	GRADE 1
48	ANBU	48	M	YES	YES	134/86	94	30	0.4	NIL	0.22	NORMAL	0.86	0..64	1.34	NORMAL
49	REKHA	49	F	NO	NO	100/70	84	17	0.4	NIL	0.15	NORMAL	0.67	0.43	1.55	NORMAL
50	NAGESH	46	M	NO	YES	134/86	78	21	0.7	NIL	0.15	NORMAL	0.76	0.49	1.55	NORMAL
51	RATHNAM	52	F	NO	NO	110/70	88	21	0.6	NIL	0.14	NORMAL	1.08	0.73	1.48	NORMAL
52	SAKTHI	48	F	NO	NO	112/70	82	23	0.6	NIL	0.25	NORMAL	1.24	0.86	1.43	NORMAL
53	KRISHNAMOORTHI	42	M	NO	NO	110/70	97	25	0.9	NIL	0.16	NORMAL	0.96	0.67	1.44	NORMAL
54	REENA	41	F	NO	NO	130/88	90	27	0.4	NIL	0.28	NORMAL	0.85	0.93	0.91	GRADE 1`
55	MAKHIL	39	F	NO	NO	128/82	86	24	0.6	NIL	0.17	NORMAL	0.78	0.64	1.21	NORMAL
56	ARASI	40	F	NO	NO	110/60	93	31	0.3	NIL	0.2	NORMAL	0.67	0.45	1.48	NORMAL
57	SHANKAR SIVAM	37	M	NO	NO	126/84	86	24	0.7	NIL	0.09	NORMAL	1.13	0.64	1.76	NORMAL
58	SANTHOSH	41	M	NO	NO	126/80	86	21	0.7	NIL	0.16	NORMAL	1.2	0.78	1.53	NORMAL
59	PREM	39	M	NO	NO	130/88	90	27	0.4	NIL	0.16	NORMAL	0.67	0.56	1.19	NORMAL
60	ABDUL	41	M	NO	NO	102/70	90	29	0.2	NIL	0.16	NORMAL	0.64	0.58	1.1	NORMAL
61	GLADY	41	F	NO	NO	112/70	87	26	0.2	NIL	0.12	NORMAL	1.07	0.68	1.57	NORMAL
62	VEERA	39	M	NO	NO	128/86	90	28	0.6	NIL	0.26	NORMAL	0.86	0.74	1.15	NORMAL
63	GUHAN	33	M	NO	NO	134/86	81	33	0.6	NIL	0.06	NORMAL	0.87	0.92	0.94	GRADE 1
64	HARI	37	M	NO	NO	122/82	90	24	0.3	NIL	0.14	NORMAL	0.82	0.63	1.29	NORMAL
65	BALAN	37	M	NO	NO	130/80	83	27	0.3	NIL	0.12	NORMAL	0.68	0.81	0.83	GRADE 1
66	ALEX	39	M	NO	NO	126/86	79	29	0.4	NIL	0.1	NORMAL	1.09	0.83	1.31	NORMAL
67	ANBU	33	M	NO	NO	110/70	94	26	0.4	NIL	0.07	NORMAL	0.76	0.61	1.24	NORMAL
68	PRABHU	37	M	NO	NO	126/84	96	19	0.2	NIL	0.17	NORMAL	0.68	0.48	1.41	NORMAL
69	RAMAN	42	M	YES	YES	132/82	97	21	0.9	NIL	0.24	NORMAL	1.15	1.24	0.92	GRADE 1
70	RAJAN MOORTHY	40	M	YES	YES	106/70	91	24	0.3	NIL	0.11	NORMAL	1.24	0.64	1.93	NORMAL
71	MURUGAN	47	M	YES	YES	110/70	90	29	0.7	NIL	0.12	NORMAL	0.92	0.45	2.06	NORMAL
72	MOHAN	50	M	NO	NO	132/84	78	24	0.3	TRACE	0.52	NORMAL	1.08	1.13	0.95	GRADE 1
73	MOOKIAH	48	M	NO	NO	118/78	81	17	0.6	NIL	0.12	NORMAL	0.85	0.49	1.73	NORMAL
74	KOMBIAH	42	M	NO	YES	118/78	86	24	0.9	NIL	0.23	NORMAL	0.69	0.45	1.53	NORMAL
75	RAJIAH	45	M	NO	NO	130/86	86	26	0.6	TRACE	0.79	NORMAL	1.08	1.32	0.81	GRADE 1
76	ATHINARAYANAN	31	M	NO	NO	132/88	90	31	0.4	NIL	0.22	NORMAL	0.79	0.56	1.41	NORMAL
77	GUPTA	37	M	NO	NO	110/70	86	34	0.7	NIL	0.15	NORMAL	0.86	0.69	1.24	NORMAL
78	NANDHINI	36	F	NO	NO	138/84	96	24	0.6	TRACE	0.46	NORMAL	0.99	1.17	0.84	GRADE 1
79	NALINI	39	F	NO	NO	132/84	94	27	0.3	NIL	0.41	NORMAL	0.96	1.24	0.77	GRADE 1
80	THANGALEELA	43	F	NO	NO	110/60	86	34	0.6	NIL	0.09	NORMAL	1.42	1.05	1.35	NORMAL
81	THANGAPUSHPAM	43	F	NO	NO	134/88	90	30	0.5	1 +	0.72	NORMAL	0.78	0.94	0.82	GRADE 1
82	SITA	40	F	NO	NO	130/86	88	24	0.6	NIL	0.26	NORMAL	1.13	0.76	1.48	NORMAL
83	MARY	39	F	NO	NO	108/60	92	26	0.6	NIL	0.06	NORMAL	0.76	0.68	1.11	NORMAL
84	PUSPAM	40	F	NO	NO	130/84	90	25	0.7	NIL	0.16	NORMAL	0.82	0.69	1.18	NORMAL
85	BALA	47	M	NO	YES	112/72	94	29	0.7	NIL	0.14	NORMAL	0.87	0.74	1.17	NORMAL
86	VELAYUDHAM	51	M	YES	NO	110/70	90	31	0.6	NIL	0.28	NORMAL	1.25	0.76	1.64	NORMAL
87	DUKE	40	M	NO	NO	128/80	78	36	0.4	NIL	0.22	NORMAL	0.67	0.53	1.26	NORMAL
88	JENISHA	43	F	NO	NO	126/86	86	22	0.3	TRACE	0.42	GRADE 1	0.96	0.87	1.1	NORMAL
89	JEEVITHA	40	F	NO	NO	106/70	81	19	0.7	NIL	0.2	NORMAL	1.07	0.68	1.57	NORMAL
90	DURUVAI	49	F	NO	NO	108/60	73	31	0.4	NIL	0.19	NORMAL	0.87	0.64	1.35	NORMAL
91	RAMKRISHNAN	41	M	NO	YES	130/86	90	24	0.8	NIL	0.2	NORMAL	0.78	0.91	0.85	GRADE 1
92	MANI	50	M	YES	NO	110/70	83	24	0.3	NIL	0.17	NORMAL	1.14	0.67	1.7	NORMAL
93	MABEL	39	F	NO	NO	100/60	89	21	0.6	NIL	0.08	NORMAL	0.68	0.64	1.06	NORMAL
94	BALIAH	51	M	YES	NO	130/88	94	27	0.7	NIL	0.23	NORMAL	0.86	0.93	0.92	GRADE 1
95	KAVUNDAR	40	M	YES	NO	100/70	95	27	0.4	NIL	12	NORMAL	1.2	0.68	1.76	NORMAL
96	ARUMUGAM	45	M	NO	NO	132/86	97	28	0.7	NIL	0.27	NORMAL	0.94	0.68	1.38	NORMAL
97	GEETHA	46	F	NO	NO	128/82	82	23	0.4	NIL	0.16	NORMAL	0.86	0.57	1.5	NORMAL
98	RAHUL	36	M	YES	YES	110/78	96	33	0.6	NIL	0.08	NORMAL	0.98	0.76	1.28	NORMAL
99	NIRANJAN	42	M	YES	YES	122/84	104	36	0.7	NIL	0.16	NORMAL	1.13	0.53	2.13	NORMAL
100	ANUSHA	44	F	NO	NO	132/86	110	26	0.7	NIL	0.22	NORMAL	0.68	0.46	1.47	NORMAL

ANNEXURE 3

KEY TO MASTER CHART:

SEX: Male and Female

SMOKING: Yes or NO

ALCOHOL CONSUMPTION: Yes or No

BLOOD PRESSURE: <120/80mmHg – normotensive individuals

120-139/80-89mmHg – prehypertensive individuals

URINE ALBUMIN: Dipstick method. Reported as follows: Trace , 1+ 2+, 3+ and 4+

URINE ALBUMIN CREATININE RATIO: <0.3 – normal , >0.3- microalbuminuria

FUNDUS EXAMINATION: Normal or Grade I to Grade IV hypertensive retinopathy.

DIASTOLIC DYSFUNCION: E/A ratio > 1 – normal

E/A ratio <1 Grade I diastolic dysfunction

ANNEXURE 4

ABBREVIATIONS

NHANES - The National Health And Nutrition Examination Survey

NCHS - National Center for Health Statistics

CDC - Center for Disease Control and Prevention

BP - Blood Pressure

CO - Cardiac Output

HR - Heart Rate

SV - Stroke Volume

JGA - Juxta Glomerular Apparatus

RAAS - Renin Angiotensin Aldosterone System

ACE - Angiotensin Converting Enzyme

ACR - Albumin Creatinine Ratio

DASH - Dietary Approach to Stop Hypertension

TROPHY - Trial Of Preventing Hypertension