"STUDY OF SERUM TESTOSTERONE LEVELS IN MALE HYPERTENSIVES- A ONE YEAR HOSPITAL BASED STUDY"

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ENDORSEMENT

This is to certify that the dissertation entitled "**STUDY OF SERUM TESTOSTERONE LEVELS IN MALE HYPERTENSIVES- A ONE YEAR HOSPITAL BASED STUDY"** is a bonafide research work done by **REG NO .BG0115012.**

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LIST OF ABBREVIATIONS USED

%	-	Percentage
ACEI	-	Angiotensin Converting Enzyme Inhibitor
AHA	-	American heart association
AMH	-	Anti Mullerian Hormone
AR	-	Androgen Receptor
ARB	-	Angiotensin Receptor Blocker
BP	-	Blood Pressure
CAD	-	Coronary Artery Disease
CAG	-	Cytosine-Adenine-Guanine
CCB	-	Calcium channel blocker
CDC	-	Centers for Disease Control
CHD	-	Coronary heart disease
CHF	-	Congestive Heart Failure
CI	-	Confidence interval
CINAHL	-	Cumulative Index to Nursing and Allied Health Literature
CKD	-	Chronic Kidney Disease
cm	-	Centimeter
CNS	-	Central nervous system
CRP	-	C reactive protein
CV	-	Cardiovascular
CVA	-	Cerebrovascular Accident
CVD	-	Cardiovascular disease
DBP	-	Diastolic Blood Pressure
DHT	-	Dihydrotestosterone

DSD	-	Disorder of Sexual Development
E/A	-	"E" (for early), "A" (for atrial)
ESRD	-	End stage renal disease
FSH	-	Follicle Stimulating Hormone
GFR	-	Glomerular Filteration Rate
GnRH	-	Gonadotrophin Releasing Hormone
HCG	-	Placental Choriongonadotropin
HDL	-	High Density Lipoprotein
HF	-	Heart Failure
HPA	-	Hypothalamic-Pituitary Axis
HR	-	Hazard Ratio
HTN	-	Hypertension
IHD	-	Ischemic Heart Disease
IL	-	Interleukin
INL3	-	Insulin-Like Peptide 3
JNC	-	Joint National Committee
LDL	-	Low Density Lipoprotein
LH	-	Luteinising Hormone
LVH	-	Left Ventricular Hypertrophy
MeSH	-	Medical Subject Headings
MI	-	Myocardial Infarction
Mm	-	Millimeter
MmHg	-	Millimeters of Mercury
MRI	-	Magnetic Resonance Imaging
ng	-	Nanogram

ng/dl	-	Nanogram per Deciliter
ng/dL	-	Nanograms Per Deciliter
NHLBI's	-	The National Heart, Lung, and Blood Institute (NHLBI)
NO	-	Nitric oxide
RCTs	-	Randomized control trials
SBP	-	Systolic Blood Pressure
SPS3	-	Secondary Prevention of Small Subcortical Strokes (SPS3)
SRY	-	Sex Determining Region of the Y chromosome
TNF	-	Tumor Necrosis Factor
WHO	-	World Health Organization
Yrs	-	Years

ABSTRACT

BACKGROUND & OBJECTIVES

Hypertension has reached epidemic proportions worldwide and is responsible for one half of the global health burden. Hypertension is an independent modifiable risk factor for major cardiovascular and cerebrovascular adverse events like ischemic heart disease and stroke which are the leading causes of mortality accounting for 14.6 million deaths worldwide.

Testosterone is the predominant male sex hormone and low serum testosterone levels are usually associated with decreased libido, erectile dysfunction, and decreased muscle mass, however it is also known to be associated with conditions like hypertension, diabetes mellitus, obesity, dyslipidaemia. Testosterone is known to augment vasodilatation and adequate levels may prevent the development or attenuate the progression of hypertension and its related complications.

METHODOLOGY

A one year hospital based observational study was conducted among 100 adult male patients of age > 18 years, who visited the medicine department of a tertiary care hospital in North Karnataka.. Study participants were either known cases of hypertension or newly diagnosed hypertensives according to JNC 8 guidelines. With their consent blood samples were drawn with all aseptic precautions & the levels of serum testosterone were estimated using Centaur XP analyser by chemiluminescent immunoassay technique and its association with

hypertension and its complications were studied. Categorical outcomes are summarized by rates, ratios & chi square test.

RESULTS:

In our study of 100 hypertensive male patients, age of the patients ranged from 25-69 years. Maximum number of cases i.e. 51 (51%) were in the age group of 51-60 years. 79% of the patients had low for age testosterone levels. 65 out of 78 (83.33%) patients with SBP >140mmHg & 44 of 48 (91.66%) patients with DBP >90mmHg had low for age serum testosterone levels which was statistically significant with p value of 0.045 & 0.003 respectively. We also observed that out of the 67 patients with duration of HTN > 10 years 58 (86.56%) patients had low for age testosterone levels which was statistically significant with p=0.001. Out of total 100 patients ,47 (47%) patients had cerebrovascular complications & 45 (95.74%) of them had low for age testosterone levels. 34 (34%) patients had cardiovascular complications & all 34 (100%) of them had low for age testosterone levels. This was statistically significant with p=<0.001. Out of 100, 34 patients consumed alcohol and among them 26 patients(76.47%) had low for age testosterone levels which was statistically significant with p=<0.01. Low for age testosterone levels was associated with level of physical activity.47(85.45%) out of 55 patients with sedentary work, 27 out of 38 (71.05%) patients with moderate work & 5 out of 7 (71.42%) patients with heavy work had low for age testosterone levels which was statistically significant with p=0.001. 61% of the patients also had microvascular complications of HTN in the form of hypertensive retinopathy. Among them 56 (91%) patients had low for age testosterone levels which was statistically significant with p value<0.001. Hence

low for age testosterone levels can predict both micro & macrovascular complications of HTN. 65(86.66%) among the 79 hypertensive males with low for age testosterone levels had normal lipid profile.

CONCLUSION

In our study, maximum number of cases were in the age group of 51-60 years. 79% of the patients had low for age serum testosterone levels. Low for age testosterone levels was observed in majority of patients with SBP >140mmHg , DBP >90mmHg. Low for age serum testosterone levels showed significant association with longer duration of HTN, cerebrovascular & cardiovascular complications of HTN, hypertensive retinopathy, alcohol consumption & sedentary lifestyle. Lifestyle modifications like increase in physical activity ,decrease in alcohol consumption can improve the testosterone levels. Early estimation of serum testosterone levels can predict both micro & macrovascular complications of HTN. But this observation needs to be confirmed in a larger cohort study.

Keywords: Testosterone, Hypertension, Males

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INTRODUCTION

Hypertension is an important global health challenge [1–3]. It is an independent risk factor for major cardiovascular and cerebrovascular adverse events including acute coronary syndrome, stroke[4], which are the leading causes of death worldwide accounting for 14.6 million, or 1 in 4, deaths.[5]

Irrespective of regional variations in the prevalence of coronary heart disease, the burden of coronary disease in men is approximately three times that of women.[6] Furthermore, men develop coronary disease approximately 10 years ahead of women. Multiple logistic regression analyses have shown that these differences are not explained by simple differences in coronary risk factor profiles.[7] The relationship between male gender and the prevalence of coronary heart disease suggests a role for sex hormones in the etiology of cardiovascular disease.

Historically, much attention has been paid to the cardio protective effects of female sex hormones in women. In women, physiological levels of estrogen appear protective against atherosclerosis, whereas conditions associated with estrogen deficiency such as early menopause or bilateral oopherectomy are associated with an increased burden of coronary disease.[8-10]

Testosterone is a steroid hormone synthesized, by the testicular Leydig cells under the control of the gonadotrophins, chiefly, luteinizing hormone. Multiple cross-sectional studies have demonstrated a fall in androgen levels with advancing age.[11–20]

Testosterone is the predominant male sex hormone and low serum testosterone levels are usually associated with decreased libido, erectile dysfunction, and

decreased muscle mass. However it is also known to be associated with conditions like hypertension, diabetes mellitus, obesity, dyslipidemia[4] .

Testosterone levels are inversely associated with both systolic and diastolic blood pressure[21.]Testosterone is known to augment vasodilatation and adequate levels may prevent the development or attenuate the progression of hypertension and its related complications.[22]

Exogenous testosterone therapy is associated with an improvement in cardiac risk factors[23]. The above mentioned data suggest that testosterone replacement therapy may be potentially cardioprotective in patients[24], especially those with hypertension.

Contrary to the concept that higher testosterone levels account for the increased burden of coronary disease in men than women, there is an increasing body of literature indicating that men with coronary artery disease (CAD) have significantly lower testosterone levels than men without CAD. Multiple cross-sectional studies comparing men with and without CAD have demonstrated a significant association of lower levels of both total and bioavailable testosterone in men with CAD than in controls with normal coronary arteries.[25]

Testosterone deficiency is associated with a higher risk of major adverse cardiovascular and cerebrovascular events including mortality in hypertensive males without clinical atherosclerosis[26]. Jones TH, et al[23] studied that testosterone is known to augment vasodilatation and accurate levels may prevent the development of hypertension and its related complications. Ohlsson C et al found that, men in the higher quartile of serum testosterone levels have around a 30% lower risk of

cardiovascular events over five years compared to men in lower three quartile[27]. At present no much studies are done and hence the present study was undertaken to find the association of serum testosterone levels with hypertension and its related complications.

AIMS & OBJECTIVES

1. To study the serum testosterone levels in male hypertensive's.
2. To study the association of serum testosterone levels with major cerebrovascular & cardiovascular complications of hypertension.

REVIEW OF LITERATURE

HISTORICAL PERSPECTIVES OF HYPERTENSION

HYPERTENSION IN THE 1940s

The House staff officers of 1940s recollect that every third or fourth medical bed was occupied by sick, middle-aged patients with some complication of hypertension like heart failure, stroke, accelerated hypertension, or renal failure.[28] The natural history of untreated hypertension is illustrated by the case of President Franklin Delano Roosevelt, who had a BP reading of 162/98 mm Hg in 1937 at the age of 54 but, consistent with medical knowledge and opinion at that time, was not on treatment for BP reduction from his personal physician, Admiral Ross McIntire—an ear, nose, and throat specialist by training.[29,30]

By 1940, Roosevelt's BP had increased to 180/88 mm Hg, and in 1941, a BP reading of 188/105 mm Hg was recorded.[31] In March 1944, cardiologist Howard G. Bruenn, a naval medical officer, examined Roosevelt. The president had pulmonary edema and an enlarged heart on chest x-ray, electrocardiographic signs of left ventricular hypertrophy, and proteinuria on urinalysis.[29] That year, Kempner had reported the BP-lowering effects of a strict, low-salt rice diet consisting of rice boiled in distilled water and fruit juices[32] so, in addition to reducing Roosevelt's alcohol and cigarette use and limiting his workday to 4 hours to allow for bedrest, Bruenn initiated digitalis therapy and tried a low-salt diet, which showed some improvement in heart failure symptoms.

While there were some BP-lowering medications available, all of them had potential severe side effects. Also surgical procedures such as sympathectomy were being performed for severe hypertension, which was not considered in the president's case. BPs of 180–230/110–140 mm Hg were recorded in 1944, and 62-year-old Roosevelt suffered a series of CV accidents[29]. Roosevelt represents a textbook case of untreated hypertension progressing to target organ failure and death from stroke. In the 1940s, elevated BP treatment was not considered appropriate unless malignant or accelerated hypertension was present.

As noted, futile and potentially harmful drug therapy or extensive surgery with a high rate of morbidity were the only treatment options; this approach may have seemed reasonable at that time only in severe cases. In the late 1940s, Dr. Charles Friedberg in his textbook Diseases of the Heart wrote, "In a patient with mild benign hypertension— [defined as a] blood pressure <200/<100 mm Hg, there is no indication for use of hypotensive drugs. Continued observation is desirable and conservative treatment consisting of reassurance, mild sedatives, and weight reduction is indicated[33"].

IN THE 1948 TEXTBOOK CARDIOLOGY,

Evans noted that: the blood pressure is [well thought-out to be] raised when the systolic pressure is 180 or more than 180, and/or the diastolic pressure is 110 or over, on three consecutive readings, and in the presence of clinical, radiological and cardiographic evidence of cardiovascular hypertrophy[34].

HYPERTENSION IN THE 1950s

In 1950, Dr. Tinsley R. Harrison[35] published the first edition of his Principles of Internal Medicine, which continued to advocate that the treatment of hypertension "should be based on symptoms of coronary difficulties and those with chest pain or other overt signs of disease should have their hypertension treated; others should not be treated." Academicians of the early 1950s continued to believe that hypertension was not a disease until it caused symptoms.

In a 1955 paper, Dr. George A. Perera[36] of Columbia University noted that in a study of 300 patients with hypertension diagnosed at an average age of about 40 years, most of these patients did not experience significant organ changes for many years when compared with normotensives and did not die until their mid-50s. Perera commented that hypertension was relatively benign and that "one is forced to conclude that … hypertension lasts longer than generally supposed" but also that the label of hypertension might be applied too readily; for example, it should not be applied "to patients of advanced years with blood pressures of 160/80 mm Hg to 200/110 mm Hg."[37]

HYPERTENSION IN THE 1960s TO THE 1990s

In the 1960s, the Framingham Heart Study[38], a longitudinal study begun in 1949, reported a strong correlation between elevated BP and heart attacks, congestive heart failure, stroke, and kidney damage. Based on epidemiologic and treatment data, the "National High Blood Pressure Education Program was started in 1972, with the goal of enlightening health care professionals and the public on the dangers of hypertension and the lifesaving benefits of treatment".[39, 40]

The early 1960s also witnessed the significant next step that was pharmacologic discoveries in the management of hypertension. Propranolol was the first β blocker introduced into clinical practice, followed later by agents with increased cardio selectivity. The mechanism by which β blockers reduce BP continues to be debated. These agents reduce heart rate, cardiac output, and renin levels, but also have an effect on baroreceptor setting and a direct action on the central nervous system.[41] The β-blocker class is heterogeneous, with the most recently discovered agents having vasodilatory effects, either through α-blockade or by stimulation of the L-arginine/nitric oxide (NO) pathway.[42] Since impaired NO bioavailability and endothelial dysfunction are associated with arterial stiffness, there is some rationale for the hypothesis that vasodilating β blockers may have a greater effect than earlier agents such as atenolol on reducing central aortic pressure.

The next milestone in the story of hypertension treatment occurred in 1977, with the publication of the first report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC).[43] The Committee, was appointed by the National Heart, Lung, and Blood Institute and composed of representatives from most of the major medical organizations.

The first JNC report suggested that if BP was ≥160/95 mm Hg, it should be rechecked in 1 month in all persons.[40] In people 50 years and younger with BPs of 140/90 mm Hg to 160/95 mm Hg, BP should be checked every 2 to 3 months, while people older than 50 years with a BP level in this range should be checked within 6 to 9 months. No specific action was necessary unless the diastolic BP was ≥105 mm Hg.[40] The emphasis in JNC I was on treating the diastolic pressure; there were no recommendations for the staging of hypertension based on systolic pressure.

Since 1977, with the availability of more data from large clinical trials, the recommendations of the JNC reports have become increasingly aggressive and specific, with emphasis shifting more to the treatment of systolic pressures, especially in people older than 55–60 years. One of the highlights of the most recent report, JNC 7, was the introduction of the term prehypertension to stress lifestyle changes and regular monitoring in individuals with BPs previously considered normal or high-normal, i.e., 120–129/80–89 mm Hg.

Lifestyle interventions should be initial treatment in these individuals, but pharmacotherapy may be considered.[44,45] It is interesting to note that at the time of JNC I, there were fewer than 30 drugs available for the management of hypertension; at the time of JNC 7 in 2003, there were more than 100.[40] The availability of excellent, effective, and relatively safe medications—such as calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers in addition to diuretics and β blockers—has made it possible to reduce BP to goal levels in more than 50% of patients. Two or more agents are usually necessary. Lowering BP with one or a combination of medications has been shown to reduce CV events.

HYPERTENSION IN THE 21ST CENTURY

The newer modalities in the management of hypertension represents a major success story in preventive medicine.[46] Almost every large clinical trial has shown that the lower the BP, the better the outcome, regardless of how it is achieved.[47] But there are still challenges how to achieve goal of BP <140/90 mmHg

Epidemiology of hypertension

Hypertension is the third most common disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide[48]. The prevalence of hypertension is known to amplify with age. Over 50% of individuals aged 60 to 69 and over 75% of those aged 70 years and older are affected. Recent Framingham Heart Study reported that lifetime risk of developing HTN is approximately 90% for men and women who are normotensive at 55-65 years old and survived to the age of 80-85 years[49]

Studies have shown that BP is an independent risk factor for CVD. This relationship is independent consistent and continuous. Observations showed that death from both CVD and stroke increases progressively and linearly from BP levels of as low as 115mm systolic and 75 mm diastolic upwards in studies involving more than 1 million individuals. The increased risks are present in all age groups ranging from 40 to 89 years old. For every increment of 20 mm hg systolic or 10mm diastolic there was a doubling of mortality from both ischemic heart disease and stroke[50].

Evidence also warrants greater attention to the importance of SBP as a major risk factor for CVD. The SBP continues to rise throughout life, in contrast to DBP, which rises until approximately 50 years age, tends to level off over the next decade, and may remain same or fall later in life. Clinical trials have demonstrated that control of isolated systolic hypertension reduces total mortality, CV mortality, and stroke and HF events[51,52].

In 2009 about 9000 patients in Denmark suffered a myocardial infarction (MI) and 12,200 patients had a stroke.[53] Although the incidences of MI and stroke have

shown decreasing tendencies from 2000 to 2009 in Denmark, it is noteworthy that the prevalences of both are increasing and estimated to increase from year 2000 to 2020 by approximately 25% for patients surviving an MI and by 50% for patients living with a prior stroke.[53]

The increase in patients surviving MI or stroke may be due to better treatment regimes. However, the increasing prevalence of hypertension, MI and stroke are likely to challenge the health care system in a future perspective. More patients will attend their general practitioner for treatment and control of high BP, and if BP is untreated/uncontrolled it may lead to more patients being hospitalised with either first or second time CVD events which in turn will challenge both the primary and secondary health care system.

Patients with hypertension are primarily treated in general practice.[54-56] In Denmark 27% of the patients with chronic diseases contact the general practioners and are detected with HTN and for 15% of all known cases of HTN contact the general practiconer.[54,55]

It is therefore the most frequent reason for consultations with general practitioners (GPs).[54,55]

Classification of Hypertension:

Patients with arterial hypertension and no identifiable cause are said to have primary, essential, or idiopathic hypertension. Individuals in whom a specific structural organ or gene defect is responsible for hypertension are defined as having a secondary form of hypertension[57].

Classification of Arterial Hypertension:

Systolic hypertension with wide pulse pressure

1. Decreased compliance of aorta (arteriosclerosis)
2. Increased stroke volume
3. Aortic regurgitation
4. Thyrotoxicosis
5. Hyperkinetic Heart Syndrome
6. Fever
7. Arteriovenous fistula
8. Patent Ductus Arteriosus

Systolic And Diastolic Hypertension

(Increased peripheral vascular resistance)

I. RENAL

a) Chronic Pyelonephritis
b) Acute and chronic glomerulonephritis
c) Polycystic renal disease
d) Renovascular stenosis or renal infarction
e) Most other severe renal disease(arteriolar nephrosclerosis, diabetic nephropathy, etc.)
f) Renin-producing tumors

II. ENDOCRINE

a) Oral Contraceptives

b) Adrenocortical Hyperfunction

1. Cushings disease and syndrome

2. Primary hyperaldosteronism

3. Congenital or hereditary adrenogential syndromes.

A. Pheochromocytoma

B. Myxedema

C. Acromegaly

III. Neurogenic

a) Psychogenic

b) Diencephalic syndrome

c) Familial Dysautonomia (Riley-Day)

d) Polyneuritis (acute porphyria, lead poisoning) E. Increased intracranial pressure (acute)

e) Spinal cord section (acute)

IV. Miscellaneous

a) Coarctation of aorta

b) Increased intravascular volume (excessive transfusion, polycythemia Vera)

c) Polyarteritis Nodosa

d) Hypercalcemia

e) Medications e.g. Glucocorticoids, cyclosporine

V. Unknown etiology

a) Essential hypertension (>90% of all cases of hypertension)

b) Toxemia of pregnancy

c) Acute intermittent porphyria

Genetic Considerations

Essential hypertension is almost certainly a polygenic disorder, involving multiple genes, each having small effects on blood pressure[58].

Natural history of Untreated Hypertension:

Both the rising SBP and falling DBP levels logically are associated with an increased risk for atherosclerotic vascular diseases. The resultant widening pulse pressures have been widely reported to be the best prognostic indicator of cardiovascular risk. However, an analysis of data from one million adults in 61 prospective studies found that, for predicting mortality from both stroke and coronary disease, the SBP is slightly more informative than DBP and that pulse pressure is much less informative[59].

MECHANISM OF HYPERTENSION

No single or specific cause is known for most cases of hypertension, and the condition is referred to as primary in preference to essential. Since persistent hypertension can develop only in response to an increase in cardiac output or a rise in peripheral resistance, defects may be present in one or more of the multiple factors that affect these two forces as shown in the figure below. The interplay of various derangements in factors affecting cardiac output and peripheral resistance may precipitate the disease, and these abnormalities may differ in both type and degree in different patients.

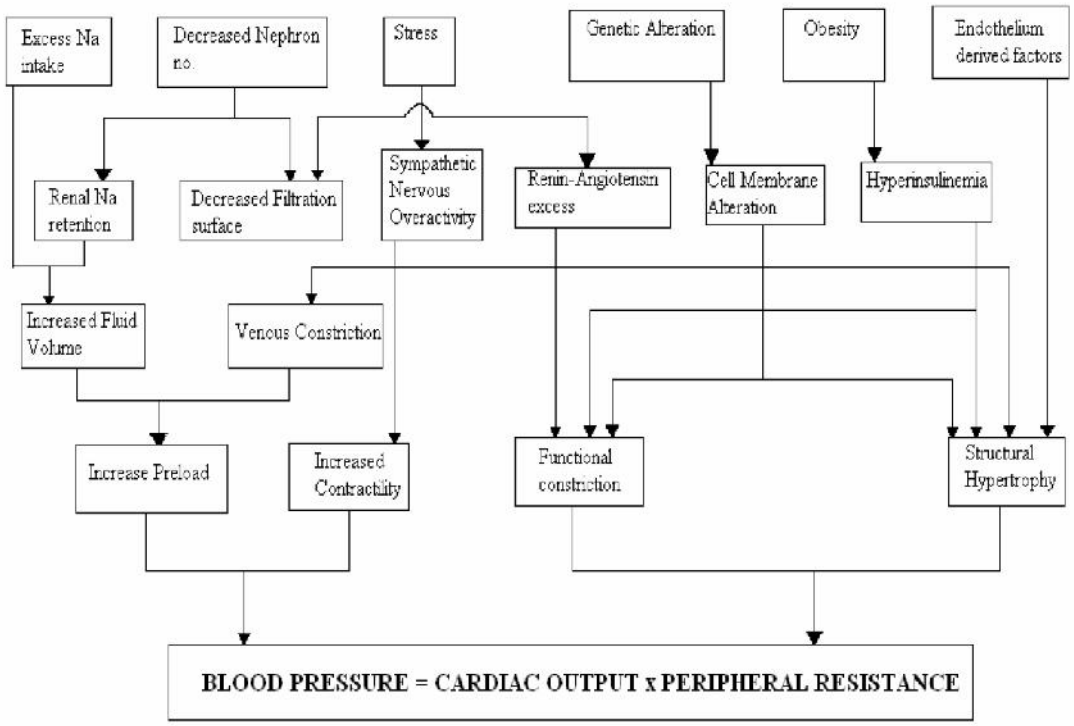


Figure 1- Some of the factors involved in the control of blood pressure[60]

Symptoms and Signs

Uncomplicated hypertension is almost always asymptomatic, so that patient may be unaware of the consequent progressive cardiovascular damage for as long as 10 to 20 years.

Symptoms often attributed to hypertension- Headache, tinnitus, dizziness and fainting – may be observed just as commonly in the normotensive population.

Many symptoms attributable to the elevated BP are psychogenic in origin, often reflecting hyperventilation induced by anxiety over the diagnosis of a life long, insidious disease that threatens well being and survival[61].

When symptoms do bring the patient to the Physician, they fall into three categories. They are related to:

1. The elevated pressure itself
2. The hypertensive vascular disease and
3. The underlying disease, in the case of secondary hypertension .

Though popularly considered a symptom of elevated arterial pressure, headache is characteristic of only severe hypertension: most commonly such headaches are localized to the occipital region and are present when the patient awakens in the morning but subsides spontaneously after several hours. Other complaints that may be related to elevated blood pressure include dizziness, palpitations, easy fatigability, and impotence. Complaints referable to vascular disease include epistaxis, hematuria, blurring of vision owing to retinal changes, episodes of weakness or dizziness due to transient cerebral ischemia, angina pectoris, and dyspnea due to cardiac failure. Pain due to dissection of aorta or to a leaking aneurysm is a rare presenting symptom.

Examples of symptoms related to the underlying disease in secondary hypertension are polyuria, polydipsia, and muscle weakness secondary to hypokalemia in patients with primary aldosteronism or weight gain, and emotional lability in patients with Cushing's syndrome. Patients with pheochromocytoma may present with episodic headaches, palpitations, diaphoresis, and postural dizziness[62].

Association of Hypertension with other conditions:

1. **Obesity**

Hypertension is more common among obese individuals and adds to their increased risk of IHD especially if it is abdominal or visceral in location as a part of the metabolic syndrome. In the Framingham Study the incidence of hypertension was increased 46 % in men and 75 % in female who are overweight defined as a body mass index of 25.0 to 29.9 compared to normal weight persons[63].

2. **Physical Activity**

Physical fitness can help prevent hypertension and persons who are already hypertensive can lower their BP by means of regular aerobic exercise. The relationship may involve a restoration of age related declines in endothelium dependent vasodilation[64].

3. **Alcohol Intake**

Alcohol in large amounts (more than 2 portions a day and even more so when drunk in binges), alcohol increases BP and arterial stiffness. The pressor effect of larger amounts of alcohol primarily reflects an increase in cardiac output and heart rate, possibly a consequence of increased sympathetic nerve activity. Alcohol also alters cell membrane and allows more calcium to enter perhaps by inhibition of sodium transport.

4. **Smoking**

Cigarette smoking raise blood pressure, probably through the nicotine-induced release of nor-epinephrine from adrenergic nerve endings. Smoking also

causes an acute and marked reduction in radical artery compliance, independent of the risk of the increase in blood pressure.

5. Hyperuricemia

Hyperuricemia is present in 25 – 50 % of individuals with untreated primary hypertension, about 5 times the frequency found in normotensive persons. Hyperuricemia reflects decreased renal blood flow presumably a reflection of nephrosclerosis[65].

6. Sleep Apnea

Snoring and sleep are often associated with hypertension, which may in turn be induced by increased sympathetic activity and endothelin release in response to hypoxemia during apnea. Relief of sleep apnea may alleviate hypertension[66].

7. Hematological Findings:

Higher haematocrits are found in hypertensive persons and associated with abnormal left ventricular filling on echocardiography[67].

8. Hypercholesterolemia:

Hypercholesterolemia frequently coexists with hypertension atleast in part because it impairs endothelium dependent vasodilatation. Lipid lowering therapy restores the bioavailability of nitric oxide, reduces arterial stiffness and lowers BP[68].

Complications of Hypertension

Hypertension if left untreated, about 50 % of hypertensive patients die of Coronary Heart Disease or Congestive Failure, about 33 % of Stroke, and 10 to 15 %

of renal failure. Those with rapidly accelerating hypertension die more frequently of renal failure, as do those who are diabetic once proteinuria or other evidence of nephropathy develops.

Effect of Hypertension on the Eye

Vascular changes in the fundus reflect both hypertensive retinopathy and arteriosclerotic retinopathy.

The hypertensive retinal changes are graded by the Keith – Wegner – Baker classification as[69]

Grade 1: Mild to Moderate narrowing or sclerosis of the arterioles.

Grade 2 Moderate to marked narrowing of the arterioles. Local and or generalized narrowing of arterioles. Exaggeration of light reflex.

Grade 3 Retinal arteriolar narrowing and focal constriction, retinal edema, Cotton wool patches, haemorrhage.

Grade 4 Grade 3 + Papilledema

Effects on the heart

Hypertension leads to increased tension on the left ventricular myocardium that is manifested as stiffness and hypertrophy, which accelerates the development of atherosclerosis within the coronary vessels.

Abnormalities in Left Ventricular Function- the earliest functional changes in hypertension are in left ventricular diastolic dysfunction, with lower E/A ratio and longer isovolemic relaxation time[70].

Left Ventricular Hypertrophy- Hypertrophy as a response to the increased afterload associated with elevated systemic vascular resistance can be viewed. Variety of dysfunctions accompany LVH, including lower coronary vasodilatory capacity, depressed left ventricular wall mechanics, and abnormal left ventricular diastolic filling pattern[71].

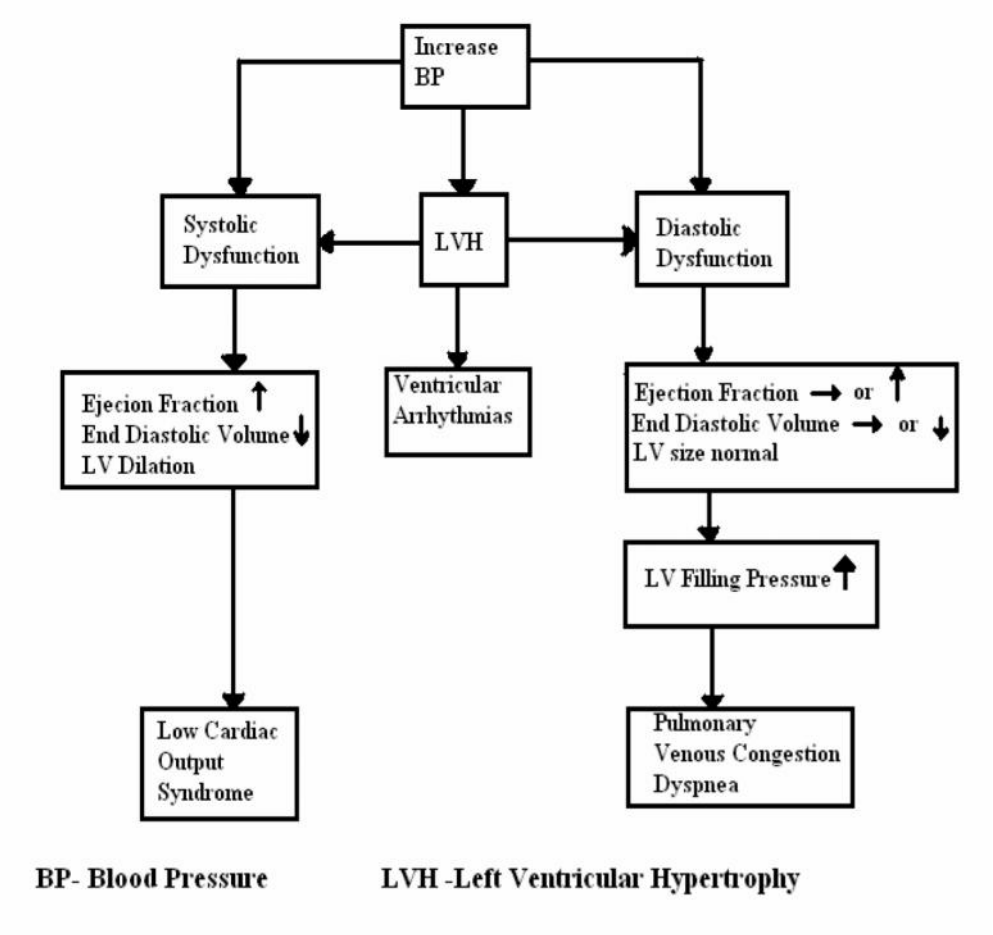


Figure 2 : Consequences of systolic and diastolic dysfunction related to hypertension[72]

Congestive Heart Failure- The various alterations of systolic and diastolic function seen with LVH can progress into congestive heart failure. A 20mm hg increment in systolic blood pressure conferred a 56% increased risk of CHF in the Framingham cohort.

When haemodynamically challenged by stress, persons with hypertension are unable to increase their end diastolic volume, because of decreased left ventricular relaxation and compliance. Consequently, a cascade begins, in which left ventricular end diastolic blood pressure rises, left atrial pressure increases and pulmonary edema develops[73].

Coronary Heart Disease- Hypertension is a major risk factor for myocardial infarction and ischemia. Acute rise in blood pressure may follow the onset of ischemic pain; the blood pressure often falls immediately after the infarct if pump function is impaired. Once an MI occurs, the prognosis is affected by both the pre-existing and the subsequent blood pressure[74].

The prevalence of silent MI is significantly increased in hypertensive subjects, and they have a greater risk for mortality after an initial MI.

Effect on the Kidneys

Renal dysfunction too subtle to be recognized may be responsible for the development of most cases of primary hypertension. Increased renal retention of salt and water may be a mechanism initiating primary hypertension.

Structural damage and functional derangements reflecting intraglomerular hypertension often reflected by microalbuminuria can be found in most hypertensive

person. Microalbuminuria in hypertensive patients has been correlated with left ventricular hypertrophy and carotid artery thickness.

As hypertension induced nephrosclerosis proceeds, the plasma creatinine levels begin to rise, and eventually renal insufficiency may develop[75].

Effect on the Central Nervous System:

Hypertension, particularly systolic is a major risk factor for both ischemic stroke and intracerebral hemorrhage. Cerebral white matter lesions are a common finding by brain MRI seen in 40% of asymptomatic, middle aged hypertensive patients.

Brain hypertrophy is more common past the age of 67 years in hypertensive than in normotensive subjects.

Blood pressure usually rises further during the acute phases of a stroke and caution is advised in lowering blood pressure during this crucial period[76].

Hypertension during Pregnancy

In about 12% of first pregnancies in previously normotensive women, hypertension appears after 20 weeks (gestational hypertension) and in about half this will progress to preeclampsia when complicated by proteinuria, edema, or hematological or hepatic abnormalities, which in turn, increase the risk of progress to eclampsia, defined by the occurrence of convulsions. Women with hypertension predating pregnancy have an even higher incidence of preeclampsia and a greater likelihood of early delivery of small-for-gestational age babies.

Preeclampsia is of unknown cause but occurs frequently in primigravid women and in pregnancies involving, either men or women who were the product of a pregnancy complicated by preeclampsia, supporting a genetic role[77].

Hypertensive Urgency and Emergency

Definition

Hypertensive emergency (crisis) is characterized by a severe elevation in blood pressure (> 180/120 mm Hg) complicated by evidence of impending or progressive target organ dysfunction.[78] Examples of target organ dysfunction include coronary ischemia, disordered cerebral function, cerebrovascular events, pulmonary edema, and renal failure. Hypertensive urgency, on the other hand, is a severe elevation in blood pressure without progressive target organ dysfunction[78]. Notably these definitions do not specify absolute blood pressure levels as hypertensive urgency or emergency may occur with a modest increase in blood pressure in previously normotensive persons (eg, during pregnancy or with acute cocaine intoxication).

The Eighth Joint National Committee report (JNC 8) was released in 2013 and is now serving as a guideline to therapy for patients with hypertension. An expert panel developed JNC 8, and primary literature was used to form nine recommendations regarding the treatment of hypertension as well as blood pressure goals for various patient populations. *The JNC 8 guidelines differed from the previous JNCs by establishing fixed definitions on trials included, a grading system for the evidence, and a systematic method to review the data included.*[79]

THE EVIDENCE REVIEW

The evidence review focused on adults aged 18 years & above with hypertension and studies were included with the following pre specified subgroups: like : diabetes, coronary artery disease, peripheral artery disease, heart failure, previous stroke, chronic kidney disease (CKD), proteinuria, older adults, men and women, racial and ethnic groups, and smokers. Studies with sample sizes smaller than 100 were excluded, as were studies with a follow-up period of less than 1 year, because small studies of brief duration are unlikely to yield enough health-related outcome information to permit interpretation of treatment effects. Only those studies were included in the evidence review which reported the effects of the studied interventions on any of these important health outcomes:

- Overall mortality, cardiovascular disease (CVD)–related mortality, CKD-related mortality
- Myocardial infarction, heart failure, hospitalization for heart failure, stroke
- Coronary revascularization (includes coronary artery bypass surgery, coronary angioplasty and coronary stent placement), other revascularization (includes carotid, renal, and lower extremity revascularization)
- End-stage renal disease (ESRD) (i.e., kidney failure resulting in dialysis or transplantation), doubling of creatinine level, halving of glomerular filtration rate (GFR).

The panel limited its evidence review to RCTs because they are less likely to have bias than other study designs and RCTs represent the gold standard study design for determining efficacy and effectiveness[80]. The studies in the evidence review were from original publications of eligible RCTs. These studies were used to create evidence tables and summary tables that were used by the panel for their deliberations. Because the panel conducted its own systematic review using original studies, systematic reviews and meta-analyses of RCTs conducted and published by other groups were not included in the formal evidence review.

Initial search dates for the literature review were January 1, 1966, through December 31, 2009.. To ensure that no major relevant studies published after December 31, 2009, were excluded from consideration, 2 independent searches of PubMed and CINAHL between December 2009 and August 2013 were conducted. MeSH terms as the original search. Three panel members reviewed the results. The panel limited the inclusion criteria of this second search to the following. (1) The study was a major study in hypertension (eg, ACCORD-BP, SPS3; however, SPS3 did not meet strict inclusion criteria because it included no hypertensive participants. (2) The study had at least 2000 participants. (3) The study was multicentered. (4) The study met all the other inclusion/exclusion criteria. The relatively high threshold of 2000 participants was used because of the markedly lower event rates observed in recent RCTs such as ACCORD, suggesting that larger study populations are needed to obtain interpretable results.

Additionally, all panel members were asked to identify newly published studies for consideration if they met the above criteria. No additional clinical trials met the previously described inclusion criteria. Studies selected were rated for quality

using NHLBI's standardized quality rating tool and were only included if rated as good or fair.

An external methodology team performed the literature review, summarized data from selected papers into evidence tables, and provided a summary of the evidence. From this evidence review, the panel crafted evidence statements and voted on agreement or disagreement with each statement. For approved evidence statements, the panel then voted on the quality of the evidence . Once all evidence statements for each critical question were identified, the panel reviewed the evidence statements to craft the clinical recommendations, voting on each recommendation and on the strength of the recommendation. For evidence statements and recommendations, a record of the vote count (for, against, or recusal) was made without attribution. The panel attempted to achieve 100% consensus whenever possible, but a two-thirds majority was considered acceptable, with the exception of recommendations based on expert opinion, which required a 75% majority agreement to approve.

RESULTS (RECOMMENDATIONS)

"This evidence-based hypertension guideline focuses on the panel's 3 highest-ranked questions related to high BP management identified through a modified Delphi technique".[83] Nine recommendations are made reflecting these questions. These questions address thresholds and goals for pharmacologic treatment of hypertension and whether particular antihypertensive drugs or drug classes improve important health outcomes compared with other drug classes.

1. "In adults with hypertension, does initiating antihypertensive pharmacologic therapy at specific BP thresholds improve health outcomes?

2. In adults with hypertension, does treatment with antihypertensive pharmacologic therapy to a specified BP goal lead to improvements in health outcomes?

3. In adults with hypertension, do various antihypertensive drugs or drug classes differ in comparative benefits and harms on specific health outcomes?

The following recommendations are based on the systematic evidence review described above. Recommendations 1 through 5 address questions 1 and 2 concerning thresholds and goals for BP treatment. Question 3 concerning selection of antihypertensive drugs is addressed by Recommendations 6, 7, and 8

JNC 8

Recommendations for Management of Hypertension

Recommendation 1

In the general population aged ≥60 years, initiate pharmacologic treatment to lower blood pressure (BP) at systolic blood pressure (SBP) ≥150 mm Hg or diastolic blood pressure (DBP) ≥90 mm Hg and treat to a goal SBP <150 mm Hg and goal DBP <90 mm Hg. (Strong Recommendation – Grade A)

Corollary Recommendation

In the general population aged ≥60 years, if pharmacologic treatment for high BP results in lower achieved SBP (eg, <140 mm Hg) and treatment is well tolerated

and without adverse effects on health or quality of life, treatment does not need to be adjusted. (Expert Opinion – Grade E)

Recommendation 2

In the general population <60 years, initiate pharmacologic treatment to lower BP at DBP ≥90 mm Hg and treat to a goal DBP <90 mm Hg. (For ages 30-59 years, Strong Recommendation – Grade A; For ages 18-29 years, Expert Opinion – Grade E)

Recommendation 3

In the general population <60 years, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg and treat to a goal SBP <140 mm Hg. (Expert Opinion – Grade E)

Recommendation 4

In the population aged ≥18 years with chronic kidney disease (CKD), initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

Recommendation 5

In the population aged ≥18 years with diabetes, initiate pharmacologic treatment to lower BP at SBP ≥140 mm Hg or DBP ≥90 mm Hg and treat to a goal SBP <140 mm Hg and goal DBP <90 mm Hg. (Expert Opinion – Grade E)

Recommendation 6

In the general nonblack population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic, calcium channel blocker (CCB), angiotensin-converting enzyme inhibitor (ACEI), or angiotensin receptor blocker (ARB). (Moderate Recommendation – Grade B)

Recommendation 7

In the general black population, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or CCB. (For general black population: Moderate Recommendation – Grade B; for black patients with diabetes: Weak Recommendation – Grade C)

Recommendation 8

In the population aged ≥18 years with CKD, initial (or add-on) antihypertensive treatment should include an ACEI or ARB to improve kidney outcomes. This applies to all CKD patients with hypertension regardless of race or diabetes status. (Moderate Recommendation – Grade B)

Recommendation 9

The main objective of hypertension treatment is to attain and maintain goal BP. If goal BP is not reached within a month of treatment, increase the dose of the initial drug or add a second drug from one of the classes in recommendation 6 (thiazide-type diuretic, CCB, ACEI, or ARB). The clinician should continue to assess BP and adjust the treatment regimen until goal BP is reached. If goal BP cannot be reached with 2 drugs, add and titrate a third drug from the list provided. Do not use an

ACEI and an ARB together in the same patient. If goal BP cannot be reached using only the drugs in recommendation 6 because of a contraindication or the need to use more than 3 drugs to reach goal BP ,other classes of antihypertensive drugs can be used. Referral to a hypertension specialist may be indicated for patients in whom goal BP cannot be attained using the above strategy or for the management of complicated patients for whom additional clinical consultation is needed. (Expert Opinion – Grade E)

In this guideline the recommendations based on RCT evidence differ from recommendations in other currently used guidelines & is supported by expert consensus. For example, JNC 7 and other guidelines recommended treatment to lower BP goals in patients with diabetes and CKD based on observational studies.[84] Recently, several guideline documents such as those from the American Diabetes Association have raised the systolic BP goals to values that are similar to those recommended in this evidence-based guideline.[85-90] Other guidelines such as those of the European Society of Hypertension/European Society of Cardiology also recommend a systolic BP goal of lower than 150 mm Hg, but it is not clear at what age, cutoff in the general population this goal specifically applies.[85] This changing landscape is understandable given the lack of clear RCT evidence in many clinical situations".

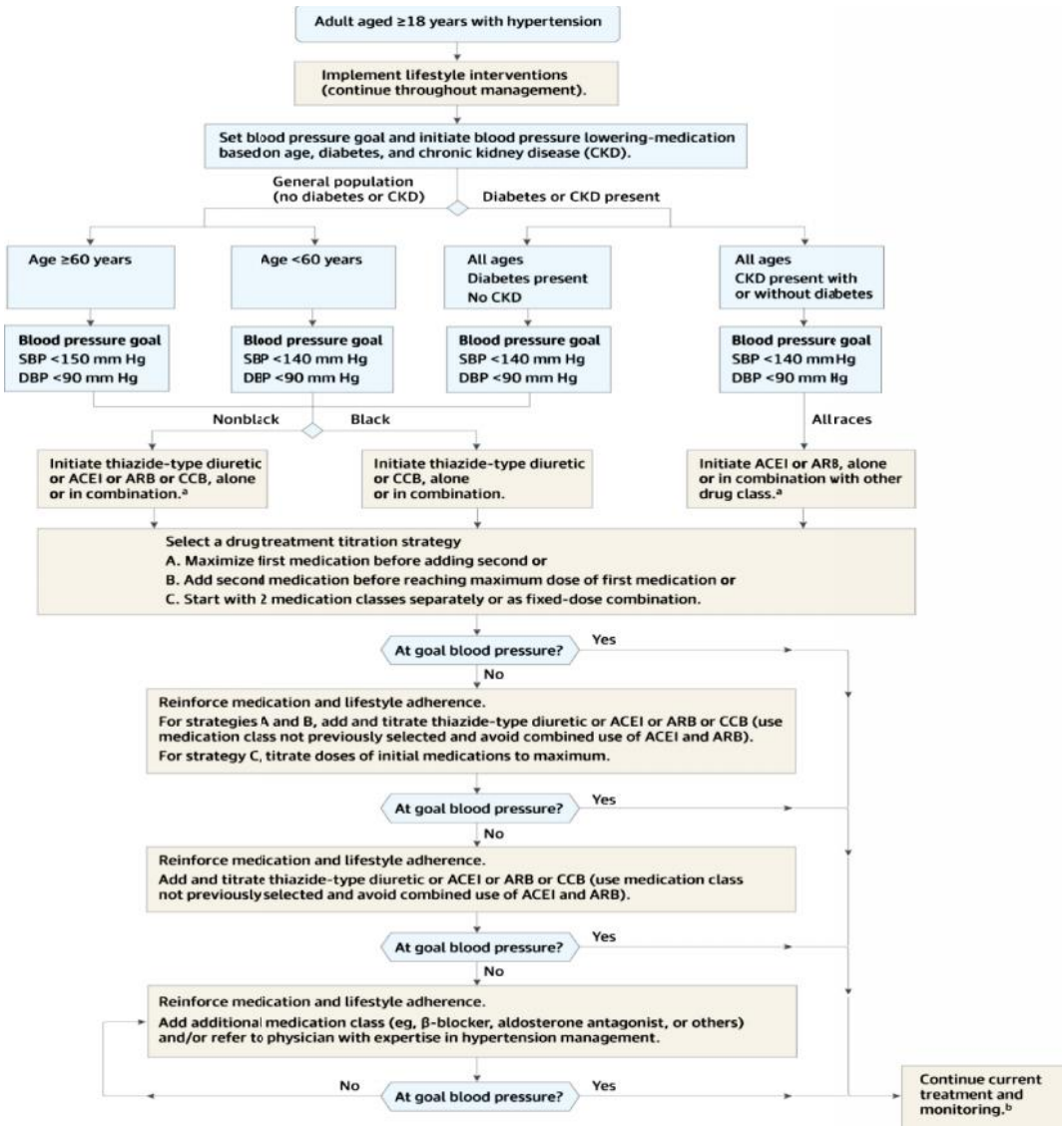


Figure 3- JNC 8 Guidelines

- ***BP goal in all patients with hypertension should be 140/80 except: very elderly → < 150***
- ***Significant proteinuria → <130/80***
- ***In addition to good BP control prompt BP control should be the goal***
- ***One drug at bed time can be considered in patients with hypertension especially in non dippers***
- ***ACE inhibitors and ARB combination is not useful***

TESTOSTERONE

Testosterone is the predominant male sex hormone.

Role of testosterone for male reproductive health

Testis and the adrenal glands produce androgens, which play a pivotal role in male reproductive and sexual function. Androgens are crucial for the development of male reproductive organs, such as the epididymis, vas deferens, seminal vesicle, prostate and penis[91]. Androgens are also needed for puberty, male fertility, male sexual function, muscle formation, body composition, bone mineralisation, fat metabolism, and cognitive functions[92].

Physiology

Male sexual development starts between the 7th and 12th week of gestation. Foetal testis develops from the undifferentiated gonads through expression of multiple genes located on the short arm of the Y chromosome, including the sex-determining region of the Y chromosome (SRY gene complex) and the SOX genes on chromosome 17[93].

The fetal testis produces three hormones: testosterone, insulin-like peptide 3(INSL3) and anti-Mullerian hormone (AMH). Testosterone is needed for the stabilisation of the Wolffian ducts, resulting in formation of the epididymis, vas deferens and seminal vesicle.[94]

AMH activity results in regression of the Mullerian ducts (Figure 1). INSL3 and AMH regulate testicular descent. Under the influence of intratesticular

testosterone, the number of gonocytes per tubule increases threefold during the fetal period[95]

In addition, testosterone is needed for development of the prostate, penis and scrotum. However, in these organs testosterone is converted into the more potent metabolite 5a-dihydrotestosterone (DHT) by the enzyme 5a-reductase. Testosterone and DHT are required for penile growth, both activating the androgen receptor [96].

Intratesticular testosterone is needed to maintain the spermatogenic process and to inhibit germ cell apoptosis [97].The seminiferous tubules of the testes are exposed to concentrations of testosterone 25-100 times greater than circulating levels. Suppression of gonadotrophins (e.g. through excessive testosterone abuse) results in a reduced number of spermatozoa in the ejaculate and hypospermatogenesis[98]. Complete inhibition of intratesticular testosterone results in full cessation of meiosis up to the level of round spermatids [97, 98]

Testosterone does not appear to act directly on the germ cells, but functions through the Sertoli cells by expression of the androgen receptor (AR) and influencing the seminiferous tubular microenvironment [99].

Testosterone can also be metabolised into oestradiol by aromatase, present in fat tissue, the prostate, the testes and bone. Oestradiol is essential for bone mineralisation, also in men [100].

Testosterone production is controlled in the foetus by placental choriongonadotropin (hCG) and after birth by luteinising hormone (LH) from the pituitary gland. Immediately after birth, serum testosterone levels reach adult concentrations over several months (mini puberty). Thereafter and until puberty,

testosterone levels are low, thus preventing male virilisation. Puberty starts with the production of gonadotrophins, initiated by gonadotrophin releasing hormone (GnRH) secretion from the hypothalamus and resulting in testosterone production, male sexual characteristics and spermatogenesis [101].

The androgen receptor (AR)

Testosterone exerts its action through the AR, located in the cytoplasm and nucleus of target cells. During the fetal period, testosterone increases the number of ARs by increasing the number of cells with the AR, but also by increasing the number of ARs in each individual cell[102].

The AR gene is located on the X chromosome (Xq 11-12) defects and mutations in the AR gene can result in male sexual maldevelopment, which may cause testicular feminisation or low virilisation (i.e. disorder of sexual development [DSD]).

Milder mutations in the AR gene may cause mild forms of androgen resistance and male infertility[103].In exon 1 of the gene, the transactivation domain consists of a trinucleotide tract (cytosine-adenine-guanine [CAG-repeats]) of variable length. Androgen sensitivity may be influenced by the length of the CAG repeats in exon 1 of the AR gene [103].

The AR CAG repeat length is inversely correlated with serum total and bioavailable testosterone and oestradiol in men. Shorter repeats have been associated with an increased risk for prostate disease, and longer repeats with reduced androgen action in several tissues[104]. CAG repeat number may influence androgenic phenotypical effects, even in case of normal testosterone levels.[104]

Conclusion

Testosterone is essential for normal male development.

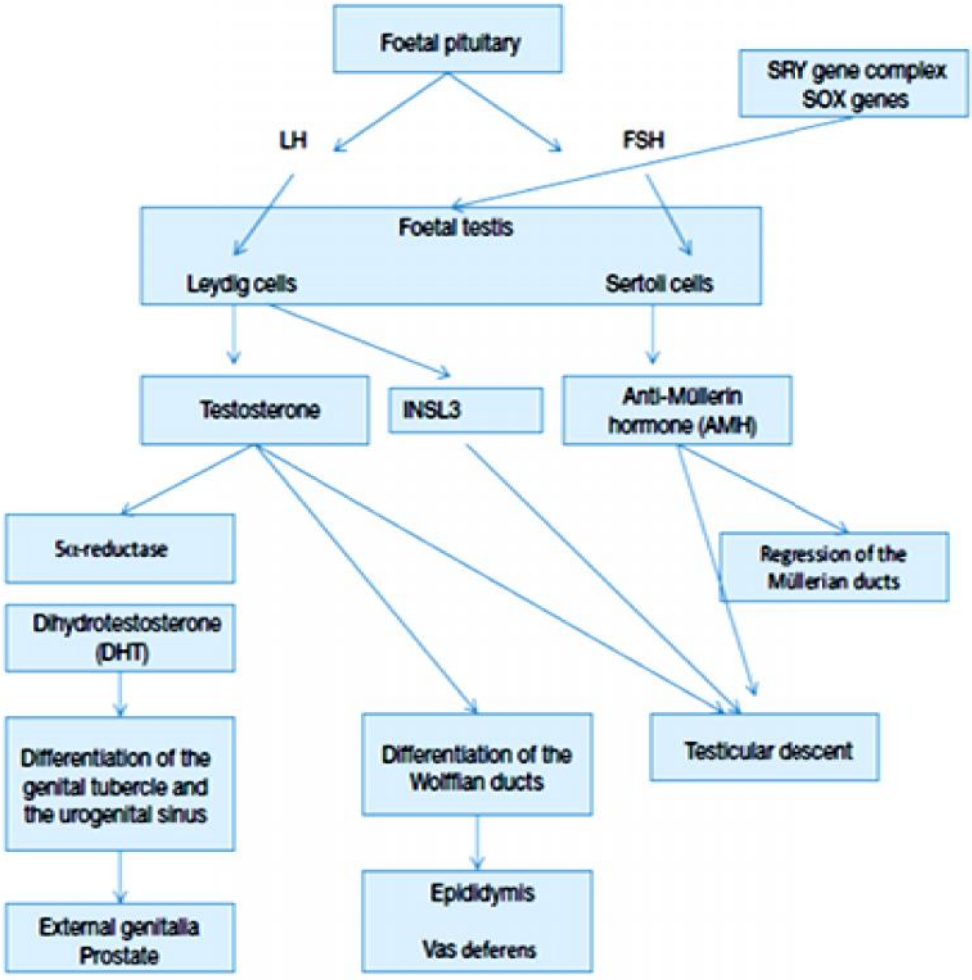
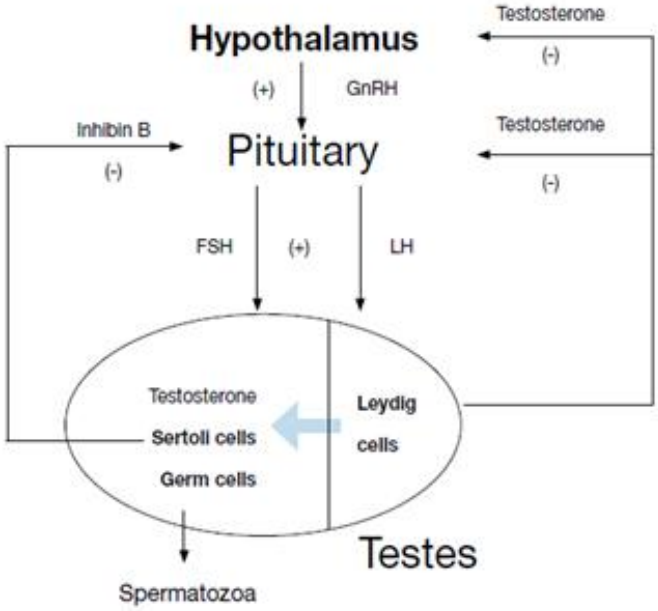


Figure 4: Development of the male reproductive system[105]

FSH = follicle-stimulating hormone; LH = luteinising hormone; SRY = sex determining region of the Y chromosome; INSL3= insulin-like peptide 3.

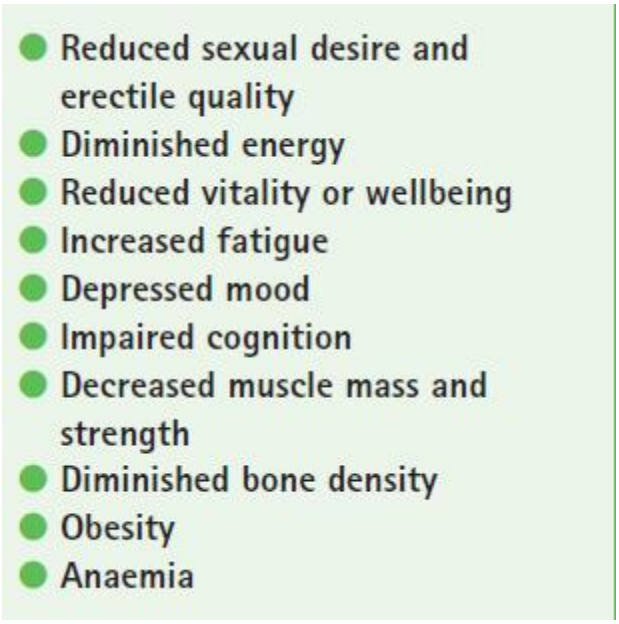


FSH = follicle-stimulating hormone; GnRH = Gonadotrophin-releasing hormone; LH = luteinising hormone

Figure 5: The Hypothalamic Pituitary Testes Axis

The HPA axis plays an important role in regulating many homeostatic systems in the body, including the metabolic system, cardiovascular system, immune system, reproductive system and central nervous system. The HPA axis integrates physical and psychosocial influences in order to allow an organism to adapt effectively to its environment, use resources, and optimize survival[106].

SYMPTOMS AND SIGNS OF LOW TESTOSTERONE



A history of erectile dysfunction, decreased libido, and fatigue may be seen in patients with low testosterone. However, one must realize that these symptoms—as well as others reported by men with low testosterone, such as depression, difficulty concentrating, irritability, and insomnia—are nonspecific and may be related to other medical conditions.[107]

Likewise, physical findings such as muscle weakness, reduced body hair, and altered fat distribution (abdominal obesity) are seen in men with low testosterone, but also in those with a number of other medical conditions.

Additional features suggest specific disorders, e.g., anosmia in Kallmann syndrome; eunuchoid body habitus, gynecomastia, and small testes in Klinefelter syndrome[108].

Men with low testosterone may have low bone mineral density or anaemia, or both.

Careful examination of the breasts for gynecomastia and the testes for size, consistency, and masses (testicular tumours) helps in formulating a differential diagnosis and in appropriately directing subsequent laboratory evaluation and diagnostic imaging[109]

TESTOSTERONE AND INFLAMMATORY STATE

Pro-inflammatory cytokines such as TNFα, IL-1 and IL-6 are involved in atherogenesis. By contrast, IL-10 and adiponectin are atheroprotective.

Testosterone exerts an immunosuppressive effect on the immune system. Inflammation, infection and trauma reduce testosterone levels as a result of the suppressive action of inflammatory cytokines on the hypothalamic-pituitary-testis axis. Testosterone also directly inhibits cytokine production from lymphocytes.

Administration of testosterone to hypogonadal men with coronary heart disease reduced serum TNFα and IL-1β, but not IL6 levels and raised levels of IL-10. In testosterone deficient men suffering from diabetes type 2[110], baseline testosterone levels inversely correlate with IL-6 and CRP levels. This is also the case in non-diabetic men.

In the study of diabetic men, testosterone replacement had no effect on TNFα, IL-6 or CRP levels. Testosterone did reduce serum leptin and adiponectin levels. This effect may potentially be mediated via reduction in adipose tissue. Similar effects of testosterone replacement in these men have been shown in non-diabetic hypogonadal men.

Testosterone therapy suppressed serum TNFα and IL-1β and increased the anti-atherogenic cytokine interleukin-10 [111] in a study of hypogonadal men of whom the majority had coronary heart disease.

Adiponectin is atheroprotective and the drop in the level of this cytokine is opposite to the effects of testosterone on other components of the atherogenic cytokine profile[111].

PHYSIOLOGY AND DECLINE WITH AGE

Testosterone is a steroid hormone predominantly synthesized by the testicular Leydig cells under the control of the gonadotrophins, chiefly, luteinizing hormone. Testosterone secretion demonstrates both diurnal and circannual secretion, peaking in the early morning and in the autumn. Once synthesized, it circulates bound to serum proteins with approximately 68% tightly bound to sex hormone binding globulin and 30% bound more loosely to albumin. Only about 2% circulates freely and it is this free portion along with the albumin bound portion that make up the biologically available (bioavailable) testosterone.[11-20]Testosterone is metabolized by 5-a reductase to dihydrotestosterone or by aromatase, in adipose tissue, to estrogens. Men with increased abdominal fat, therefore, metabolize more testosterone to estrogen, resulting in gynecomastia and a reduction in secondary sexual characteristics. Multiple cross-sectional studies have demonstrated a fall in androgen levels with advancing age.[11-20] However, unlike women; men do not experience the well characterized, sudden and rapid decline in sex hormone levels and cessation of reproductive capability as they age. In men, the decline in sex hormone levels is much more variable appearing to spare some men, fall unknowingly in some, and result in frank and symptomatic hypogonadism in others.

Contrasting with the female menopause, the male 'andropause' often results in rather non-specific symptoms, including reduced libido, fatigue, weakness, depression, dry skin and poor concentration, symptoms which are often regarded simply as a natural part of the aging process. Clinical signs can include fine-wrinkled dry skin, low hairline, gynecomastia and muscle wasting. Due to the non-specific nature of the symptoms, hypogonadism often remains undiagnosed and thus untreated in many cases. In others, it is diagnosed but remains untreated due to a perceived concern regarding adverse iatrogenic effects on the prostate and heart.

Harman et al.[20] investigated the nature and potential etiological factors involved in the change in sex hormone levels with age in the Baltimore Longitudinal Study of Aging. They found that in 890 generally healthy men, both total and free testosterone decreased at a constant rate from the third to ninth decade. Total testosterone fell at a rate of 0.11 nmol l^{-1} $year^{-1}$, but the fall in free testosterone was more impressive and due, at least in part, to the significant rise of sex hormone binding globulin with age. These observations were independent of obesity, comorbid illnesses, medication, smoking and alcohol consumption.

TESTOSTERONE AND CORONARY RISK FACTORS

It was previously believed that the higher prevalence of coronary disease in men may be explained by differences in risk factor profiles between genders. It is widely regarded that men display behaviors which are considered, cardiologically, more risky with increased levels of smoking and with diets richer in saturated fats.[7] However, multiple logistic regression analysis has shown that differences in behavioral profiles do not account for the excess burden of coronary disease in men.[7,

[112] The development and progression of coronary atherosclerosis is heavily influenced by the interaction of multiple risk factors.

The lipid profile in men is naturally more pro-atherogenic than in women, a difference that in the past has been attributed to higher circulating testosterone levels. However, it is low, not normal, nor high, testosterone levels that have been found to be associated with adverse lipid profiles. Testosterone levels are found to correlate positively with the cardio-protective high-density lipoprotein (HDL) cholesterol and negatively with atherogenic low-density lipoprotein (LDL) cholesterol and triglycerides.[113-117] some studies have demonstrated that testosterone causes a fall in the cardio-protective HDL cholesterol.[118] However, any observed decline in HDL cholesterol is generally smaller and less pronounced than the positive effects on the other lipid fractions. Hypotestosteronaemia is associated with raised pro-inflammatory cytokines (tumor-necrosis factor-a, interleukin 6 and reduced anti-inflammatory cytokines (interleukin 10)[119] which are, in turn associated with pro-atherosclerotic and inflammatory states. Additionally, low testosterone is associated with raised fibrinogen and hypercoagulable states, [120-122] theoretically, promoting atherosclerosis and atherosclerotic plaque instability and thus acute coronary syndromes. The metabolic syndrome is a well-recognized risk factor for atherosclerosis and coronary morbidity and mortality. All of the components of the syndrome—hypertension, dyslipidaemia, insulin resistance, type II diabetes and hyperglycemia—are independently associated with Hypotestosteronaemia and frank hypogonadism. Moreover, there is a negative correlation between the number of components of the metabolic syndrome and the absolute serum testosterone level with a 10-fold increase in the relative risk of frank hypogonadism, if all four of the components of the metabolic syndrome are present.[123] In an analysis of data from the

Massachusetts Male Aging Study, it was found that, over a 15-year period, in non obese men, low testosterone at baseline led to a two- to fourfold increased risk of developing metabolic syndrome. The authors concluded that low testosterone may act as an early warning sign for the development of the metabolic syndrome, and provide an opportunity for early (primary) intervention.

TESTOSTERONE LEVELS IN MEN WITH CORONARY HEART DISEASE

Contrary to the belief that higher testosterone levels account for the higher burden of coronary disease in men than women, there is an increasing body of literature indicating that men with coronary artery disease (CAD) have significantly lower testosterone levels than men without CAD. Cross-sectional studies comparing men with and without CAD have repeatedly demonstrated significantly lower levels of both total and bioavailable testosterone in men with CAD than in controls with normal coronary arteries.[25] However, there is heterogeneity in the consistency of these findings, especially in earlier reports.[124] Explanations for the apparent inconsistency of earlier reports include variability in study design, in the assays applied, in the measures of testosterone quoted and in the definitions of 'hypogonadism' and 'cardiovascular disease' used. Some authors performed retrospective analyses from frozen samples as the original intention was not to study testosterone at all, and these studies took no account of the instability in testosterone level when frozen samples are stored over many years. Some studies measured total testosterone level, others used free or bioavailable testosterone or used calculated free-androgen index. There are different opinions and criteria regarding what 'hypogonadism' actually is in terms of assay, cut-off and whether the criteria should include associated symptoms. More modern studies have been more consistent in design and definition, especially when

the primary hypothesis was related to the question of the link between testosterone blood level and CAD. Despite some heterogeneity, the majority of studies that investigated androgen levels in men with coronary disease showed that testosterone levels were significantly lower in men with coronary disease than in matched controls.

Do levels of total and free testosterone truly reflect androgenisation? Testosterone circulates partly bound to albumin (weakly) and partly bound to sex hormone binding globulin (strongly) and only a small fraction is free. The albumin-bound and free portions are biologically available to the tissues. It could be argued that bioavailable testosterone quantification would provide a more accurate measurement. It is possible to measure bioavailable testosterone by the method of Tremblay and Dube, [125] but the assay is labor-intensive and time consuming and, as such, is mainly restricted to the research laboratory. It is believed by some that this fraction accurately reflects the true serum androgen level. Bioavailable testosterone assays have been utilized in several studies of men with coronary artery disease and more consistently demonstrate decline with age. One study of over 900 men found that both total and bioavailable testosterone were significantly lower in men with coronary artery disease than in those without.[126] The magnitude of the difference in testosterone levels between men with coronary artery disease and those without is clinically significant. The same study demonstrated a prevalence of hypogonadism of 24% in men with coronary artery disease, by strict criteria, which is approximately three times higher than the expected background rate. One question which remains unanswered is whether low testosterone levels accelerate the development of CAD or whether they are simply a consequence of chronic illness?

CAUSE OR A CONSEQUENCE

Coronary artery disease is a chronic illness and patients with CAD often have other associated chronic illnesses such as hypertension, diabetes and hypercholesterolaemia. Maybe this is the cause of the lower testosterone levels? Regression analysis has demonstrated that even when the effects of such comorbid conditions are controlled the relationship between CAD and lower testosterone levels remains.[7, 112] Furthermore, if hypogonadism was a consequence of CAD, it might be expected that patients with more severe CAD might have lower testosterone levels than those with milder disease. This hypothesis has not been proven. The prevalence of hypogonadism in men with asymptomatic coronary plaque is similar to the prevalence in men with symptomatic CAD and both groups have lower levels of testosterone than men with normal coronary arteries, favoring a causative role more than a symptomatic consequence (Morris PD, 2001. unpublished data).

Studies in male animals have shown accelerated atherosclerosis after castration—an effect that is abrogated by androgen replacement therapy.[126,127] Risk factors for coronary disease such as diabetes are also associated with lower testosterone levels. Individuals affected by hypogonadal hypogonadism such as men with Klinefelter syndrome are known to have increased levels of insulin resistance, dyslipidaemia and central obesity[129]—all the constituents of the metabolic syndrome, which carries a strong association with coronary disease and morbidity, testosterone supplementation in these men improves their risk factor profile with improvements in glycemic control, adiposity and lipid profiles.[128]. Aside from coronary disease, Klinefelter patients have been shown to have higher rates of congenital heart disease, mitral valve prolapse, reduced left ventricular function and more procoagualable

states.[130-132] Furthermore, accelerated coronary artery disease has been demonstrated in patients treated with testosterone-suppressive therapy. In a study of over seventy thousand men (73 196) treated with androgen suppressive therapy for prostate cancer, there was

44% increase in the risk of developing diabetes and16% increase in the risk of cardiovascular death or myocardial infarction, effects which were evident as early as1–4months.[133] Similar conclusions were drawn in a study of men treated by orchidectomy, where, over a 10 year period, there was a twofold increase of cardiovascular mortality.[134] Androgen suppressive therapy has also been linked with increased central blood pressure, insulin resistance, and hyperglycaemia.[135-138] However, one must be careful to consider the difference in androgen levels between the moderate Hypotestosteronaemia associated with aging and the more extreme low testosterone levels associated with androgen suppressive therapy used in prostate cancer treatment. A recently published meta-analysis of 19 prospective studies40 investigated some of the previously found heterogeneity in the results and design of studies in this area. Although the analysis failed to confirm that low testosterone increases the risk of cardiovascular disease in middle aged men, it did find a significant inverse association between testosterone and coronary disease in men older than70 years. Whether low testosterone levels are cause or consequence of coronary disease remains unknown. There appears to be evidence supporting both sides of this controversy. It is of course possible that it plays a causative role and is also a consequence of illness and frailty. A great deal of research work will be needed to carefully untangle all the possible mechanisms underlying this relationship. Further work will undoubtedly expand our knowledge regarding the underlying mechanisms and relationships between low testosterone and coronary disease and this will be of

great interest. If low testosterone is found to be a significant etiological factor in the development of acceleration of coronary disease then, given the high prevalence of hypogonadism in this population, it would be beneficial considering screening for testosterone levels in men with coronary disease.

VASO-ACTIVE PROPERTIES OF TESTOSTERONE

Although some people have suggested that the reported positive effects of androgens in cardiovascular disease may simply reflect non-specific effects on skeletal muscle function and mood, it has been demonstrated that testosterone does have direct vasoactive effects. It is known that testosterone levels inversely correlate with penile artery smooth muscle compliance with men with lower testosterone levels more likely to suffer erectile dysfunction.[139] In animal models, testosterone causes vasodilatation of isolated coronary, femoral and pulmonary arteries in a dose-dependent fashion.[140-143] Interestingly, these effects are not mediated by the endothelium(unlike estrogen)nor via the nuclear androgen receptor. In these models, testosterone appeared to act directly on the vascular smooth muscle, having an antagonistic action on calcium channels similar in effect to that of the antianginal drug nifedipine.[144] In vitro studies of isolated male arteries have demonstrated similar vasodilatory actions. In vivo studies have also demonstrated a vasodilatory action for testosterone. One study showed that acute intracoronary administration of testosterone, at physiological concentrations, induces coronary artery dilatation and increases coronary blood flow in men with established coronary artery disease.[145] Other studies of acute intravenous testosterone therapy have demonstrated increased cardiac output mediated by a reduction in the systemic vascular resistance and increased ischemic threshold in men with CAD.[146,147] Clinical trials have

demonstrated that chronic and physiological dose testosterone supplementation significantly improves anginal symptoms and the time to electrocardiographic ischemia on exercise treadmill testing,[148-151] an effect which is proposed to be mediated by testosterone's vasodilatory action.

TESTOSTERONE LEVELS AND MORTALITY

The aforementioned decline in testosterone in some men has previously been regarded by some simply as part of the natural physiology of ageing. However, five recent studies have demonstrated that lower baseline testosterone levels are a significant predictive marker for mortality even after controlling for the effects of comorbid conditions. In 2004, Shores ET al.[152] reported that Hypotestosteronaemia was a marker for mortality in a group of 44 geriatric inpatients within a 6month period. In a following study, the same group performed a computerized analysis of the Veteran's Affair's clinical database.[153] they looked at 850 men over a 4- to 8-year period controlling for comorbid conditions which would affect mortality, e.g. concurrent cancer. They found that men with low testosterone levels had an 88% (20.1% vs. 34.9%, P,0.001) relative increase in all-cause mortality risk when compared with those with normal testosterone levels at baseline. In 2007, the In CHIANTI study demonstrated that an age associated fall in bioavailable testosterone was associated with increased risk of death.[154] In a 6-year follow-up study of 410 men aged over 65 years, they found that this effect was made more pronounced and more statistically significant when low testosterone was associated with similar decline in insulin-like growth factor and dehydroepiandrosterone sulphate. In contrast to men with all three hormones above the lowest quartiles, men with one, two or three hormones in the lowest quartiles were increasingly at more risk of death. In 2008,

Laughlin ET al.[155] studied an older group (mean age of 71 years) of 794 men over a period of up to 20 years. They found a significant fall in bioavailable testosterone but not total testosterone with age. The risk of death was greater for men in the lowest baseline quartile of both total and bioavailable testosterone compared with those in the highest quartile. Afteradjustingforage, adiposityandlifestylechoices,therisk of death was 44% greater between the lowest and highest quartiles for total testosterone (hazard ratio (HR): 1.44; 95% confidence interval (CI): 1.12–1.84) and 50%higher between the lowest and highest quartiles for bioavailable testosterone (HR:1.50;95%CI:1.15–1.96).In the largest study to date investigating the effects of endogenous testosterone levels and mortality, the European Prospective Investigation into Cancer Norfolk study[156] prospectively investigated all-cause and cardiovascular mortality in 11 606 healthy men between the ages 40 and 79 years at baseline. Over a 6- to 10-year follow-up period, they observed a statistically significant association between baseline serum testosterone level and all-cause (HR: 0.75; 95% CI: 0.55–1.00), cardiovascular (HR: 0.62; 95% CI: 0.45–0.84) and cancer related (HR: 0.59; 95% CI: 0.42–0.85) deaths (P, 0.001) for each association after controlling for co morbid conditions and behaviors. They found that every one standard deviation increase in baseline testosterone was associated with a, 14% risk reduction in mortality over the study period. Recently published study by Malkin et al[126] is more relevant than the current article in which, 930 men with angiographically proven CAD were prospectively followed up over a 7 year period. They observed a baseline prevalence of hypogonadism in this group (by a strict criteria) to be 24%. In this androgen deficient group, the mortality was 21% versusonly 12% in the eugonadal group (P50.002). Low testosterone therefore, appears to be a marker for mortality. However, a similar ‘cause or consequence’ argument arises. Does low testosterone

have a causative role in promoting worsening cardiovascular health or does it simply mark out a population of less healthy men, or both?

TESTOSTERONE AND HEART FAILURE

Coronary heart disease is the biggest underlying cause of heart failure in the Western world. However, the specific relationship between testosterone and heart failure has not been studied to the same degree as that of testosterone and coronary disease. Heart failure is characterized by a catabolic state with activation of inflammatory cytokines, vasodilator in capacity and maladaptive neuro hormonal activation. As described above, testosterone exerts an effect which opposes all of these adaptations. Serum testosterone levels have been shown to correlate positively with cardiac output in men with heart failure and in one study acute, intravenous administration of testosterone acutely increased cardiac output.[147] The effects of chronic testosterone supplementation have also been studied. In a small randomized placebo controlled clinical trial, Pugh et al.[157] demonstrated improvements in exercise capacity and in symptom scores after 12 weeks of testosterone therapy in men with heart failure. Similar results were found in larger placebo-controlled randomized controlled trials with improvements in exercise capacity, symptom scores, VO2 max, maximal strength, insulin resistance and a reduction in electrocardiographic Q-T dispersion.[158-160] Although these early studies are positive, more evaluation is needed to elucidate the mechanisms of action of testosterone in heart failure and on the long-term effects of supplementation.

TESTOSTERONE THERAPY IN CARDIOVASCULAR DISEASE

Evidence regarding the cardiovascular effects of testosterone therapy can be broadly divided into two groups: the effects on cardiovascular risk factors, such as lipid profiles, blood pressure, etc., which exert an indirect effect on coronary artery disease and the direct clinical effects of testosterone therapy on the heart itself. Testosterone supplementation in men with type II diabetes has been shown to reduce total and LDL cholesterol and lipoprotein a, even in men already established on statin therapy.[161,162] In studies of elderly and hypogonadal men, testosterone therapy has been associated with improved lipid profiles with reductions in total and LDL cholesterol.[163-165] Hypotestosteronaemia is associated with hypertension and arterial stiffening. There have been several trials of testosterone replacement therapy in eugonadal, hypogonadal and obese men which have observed impressive reductions in both systolic and diastolic blood pressure over periods as short as 6months and for as long as10years.[166-168] Similar beneficial effects of chronic testosterone therapy were demonstrated in reducing body mass index in a study of testosterone therapy over a 12-month period.[151] Testosterone therapy induces increased insulin sensitivity and improved glycemic control in type II diabetic men.[161] Studies of testosterone therapy have also observed beneficial modifications in pro- and anti-inflammatory cytokine profiles.[119] Rosano et al.[25] investigated the acute effects of intravenous testosterone therapy in a group of men about to perform exercise, treadmill testing. When compared to baseline and a placebo, time to ischemia was significantly prolonged after intravenous testosterone. English et al.[149] demonstrated similar effects, but in the context of chronic testosterone therapy. In men with angiographically- proven coronary disease, 12 weeks of transdermal testosterone therapy significantly increased time to ischemia at exercise testing. The anti-ischemic

effect was greatest in those men with the lowest baseline testosterone levels. Malkin et al.[150] advanced this hypothesis by performing a similar, blinded, placebo-controlled and crossover study of testosterone therapy in men with angina, but only recruited men with significant hypogonadism. At treadmill testing, the increase in time to ischemia was even greater (74 s). In addition, there were significant improvements in symptom scores and beneficial changes in lipid profiles and reductions in the proinflammatory cytokine tumor-necrosis factor-a. In a further study by the same group, the anti-ischemic effects of testosterone therapy were demonstrated up to the end of the study period at1 year.[151] In a recent review paper by Saad et al.,[169] the beneficial effects of testosterone therapy on cardiovascular risk factors including on body composition, lipids profile, glycemic control and blood pressure were described. They found that the beneficial effects of testosterone therapy started to become apparent after 3 months of therapy onwards. However, continuing benefit was observed with therapy up to 9 months in the case of improvements in blood pressure, 12 months in the case of improved glycemic control and up to 2 years in the case of improved lipid profiles. Despite historical concerns over testosterone therapy in aging males, there is now a large and rapidly increasing body of evidence suggesting that testosterone replenishment in men with cardiovascular disease is safe and effective. However, the effect of testosterone replacement therapy on mortality and patient outcome will need to be subject to large, prospective and randomized controlled trials. This surely will be the next big step in this interesting area. With millions of men affected by CAD worldwide, and a prevalence of hypogonadism estimated at approximately one-quarter in this population, the rewards for successfully replacing testosterone in affected males are potentially very large indeed.

CONCERNS OVER TESTOSTERONE THERAPY IN MEN

Historically, there have been two main concerns regarding testosterone therapy in middle aged and older men. The first was the concern that it might promote coronary heart disease and acute coronary syndromes. The second was that testosterone supplementation might promote prostate cancer. Hopefully, the current article has dealt with the former concern and has brought reassurance regarding physiological levels of testosterone and the male heart. In one recent interventional study of frail hypogonadal men, supra physiological dosages of testosterone replacement therapy was used in an attempt to improve muscle strength.[170] The study showed that pharmacological doses of testosterone significantly increased muscle strength, but the trial was stopped early because of an excess of cardiovascular side effects. The authors reported that 23 patients taking testosterone had cardiovascular complications compared with five in the placebo group and on this basis stopped the trial. Critical review of this paper shows that in fact there were only six hard end points in the treatment group compared with one in the placebo group. About half the group had a history of cardiovascular disease and the rest had significant cardiovascular risk factors. Our view is that this study showed that men with hypogonadism should be treated only with physiological doses of testosterone for true replacement therapy. The literature showed that testosterone replacement should be managed in the same way as thyroid hormone replacement. Replacement dosages should aim to maintain normal physiological levels. If the Basaria trial had been done in hypothyroid patients with high cardiovascular risk and replacement had aimed at supra-physiological levels, the same (or worse) results would have been seen.

The second concern is likely to be fuelled by the knowledge that prostate cancer can be successfully treated by androgen suppressive therapy. However, over the last decade, epidemiological and clinical investigations have failed to demonstrate any association between underlying testosterone levels and the risk of developing prostate cancer. Similarly, no studies cancer.[171-174] In the study by English et al., [149] where men with proven angina were given transdermal testosterone, prostate-specific antigen levels were monitored over the study period and did not change significantly. In men with prostate cancer, testosterone therapy is clearly contra-indicated and lower levels of testosterone are beneficial. However, to our knowledge, there is no evidence supporting a causative role of testosterone supplementation on the levels in the physiological normal range, with the risk of developing prostate cancer. In fact, in view of the data concerning low testosterone and increased mortality, it has even been suggested that testosterone suppressive therapy could be withheld from elderly men with T1 to T2 localized prostate cancer due to reduced survival.[175] Any future trials looking at the effects of chronic testosterone therapy in patients with coronary disease should monitor the effects on prostate specific antigen and look for any deleterious effects on the prostate gland.

Clearly, further research will be needed in:

1. Bringing some standardization and consistency to what measurement of androgenisation should be used and what should define hypogonadism and Hypotestosteronaemia.
2. Elucidating the long term cardiovascular effects of testosterone therapy in men with coronary disease in large, prospective, randomized, placebo controlled trials;

3. Elucidating any additional benefit in hypogonadal men with coronary disease;
4. Clarifying the safety of testosterone therapy in men with coronary disease;
5. Investigating the role of screening for hypogonadism in men with coronary disease.

Various epidemiological, clinical, and experimental studies have indicated that androgens may be important determinants of sex specific differences in arterial blood pressure

At present not many studies are conducted to establish the relation between low serum testosterone and hypertension in adult men with no secondary causes of hypogonadism. Hence there is a need to study the association of serum testosterone levels in males with hypertension.

MATERIALS AND METHODS

Study Design: Observational study

Study Period: One year from January 2016 to December 2016

Sample Size: 100

Sample Size Calculation: using the formula

$n = (z^2 \times p \times q) \div d^2$

Z= z value for α error (1.96)

P=51.6% (prevalence of HTN in males) Chythera R. Rae et al[176]

q =(100-p) =48.4

d=absolute error 10%

Sample Size: $\{(1.96)^2 \times 51.6 \times 48.4\} / (10)^2$= 96

Source of data: This cross sectional study was conducted among all adult male patients of age > 18 years, who visited the medicine department of K.L.E.s Dr Prabhakar Kore hospital and MRC, Belagavi, who were either known cases of hypertension or newly diagnosed hypertensive with a BP ≥ 140/90 mmHg in two consecutive readings taken 5 minutes apart after rest in the same sitting measured in the same arm.

Method of collection of data: (including sampling procedure)

Standard blood pressure measurement techniques were used with an appropriate sized cuff at the level of the right atrium, with the patient rested for 5 minutes, and with the back supported. As a part of the study blood pressure was measured in both arms using the same sphygmomanometer during the same sitting. All known cases and newly diagnosed cases of hypertension with a BP ≥ 140/90 mmHg in two consecutive readings taken 5 minutes apart after rest in the same sitting measured in the same arm were included in the study.

American Heart Association Guidelines for In-Clinic Blood Pressure Measurement

Recommendation	**Comments**
Patient should be seated comfortably, with back supported, legs uncrossed, and upper arm bared.	Diastolic pressure is higher in the seated position, whereas systolic pressure is higher in the supine position.
	An unsupported back may increase diastolic pressure; crossing the legs may increase systolic pressure.
Patient's arm should be supported at heart level.	If the upper arm is below the level of the right atrium, the readings will be too high; if the upper arm is above heart level, the readings will be too low.
	If the arm is unsupported and held up by the patient, pressure will be higher.

Recommendation	**Comments**
Cuff bladder should encircle 80 percent or more of the patient's arm circumference.	An undersized cuff increases errors in measurement.
Mercury column should be deflated at 2 to3 mm per second.	Deflation rates greater than 2 mm per second can cause the systolic pressure to appear lower and the diastolic pressure to appear higher.
The first and last audible sounds should be recorded as systolic and diastolic pressure, respectively. Measurements should be given to the nearest 2 mm Hg.	
Neither the patient nor the person taking the measurement should talk during the procedure.	Talking during the procedure may cause deviations in the measurement.

Information from Pickering TG, et al[177].

Serum testosterone levels was assessed by blood test in all old and newly detected male hypertensive's, using Cantour XP analyser by chemiluminescent immunoassay technique.

NORMAL TESTOSTERONE LEVELS

AGE (in years)	95% RANGE (in ng/dl)
<25	376-1008
25-29	257-1081
30-34	233-1009
35-39	219-975
40-44	201-993
45-49	220-872
50-54	170-918
55-59	204-900
>60	<200

INCLUSION CRITERIA

- Gender : Male
- Newly detected hypertensive.
- Known cases of hypertension

EXCLUSION CRITERIA

- Diabetes mellitus
- Hypogonadism
- Chronic liver failure
- ESRD
- On medication like anti-androgen, ketoconazole
- Radical prostatectomy

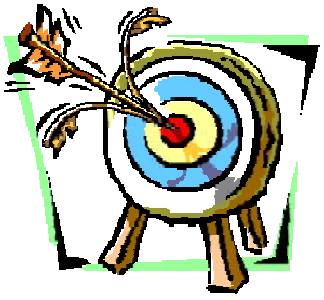
ETHICAL CLEARANCE

Prior to the commencement, the ethical clearance was obtained from Ethics and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

Patients were screened for the eligibility and those fulfilling the selection criteria were briefed about the nature of the study. The patients expressing their willingness to participate in the study were enrolled after obtaining a written informed consent (Annexure I).

Introduction



Objectives

Review of Literature

Methodology

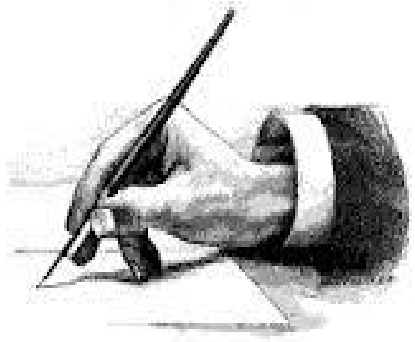
Results

Discussion

Conclusion

Summary

Bibliography



Annexure-I

Annexure-II

Annexure-III

Annexure-IV

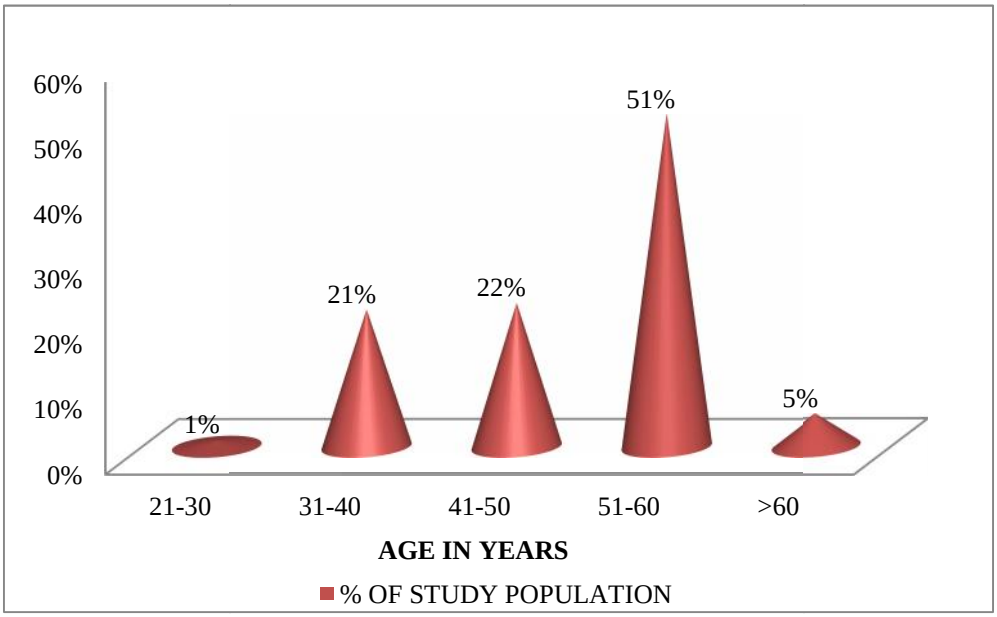
RESULTS

The present one year study titled “Serum Testosterone Levels In Male Hypertensives: A One Year Hospital Based Study” was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi. During the study period from January 2016 to December 2016, a total of 100 Hypertensive adult male patients were studied. The final results are tabulated as below:

TABLE 1: AGE DISTRIBUTION IN THE STUDY POPULATION

AGE (in yrs)	% OF STUDY POPULATION
21-30	1%
31-40	21%
41-50	22%
51-60	51%
>60	5%
TOTAL	100

GRAPH 1: AGE DISTRIBUTION IN THE STUDY POPULATION

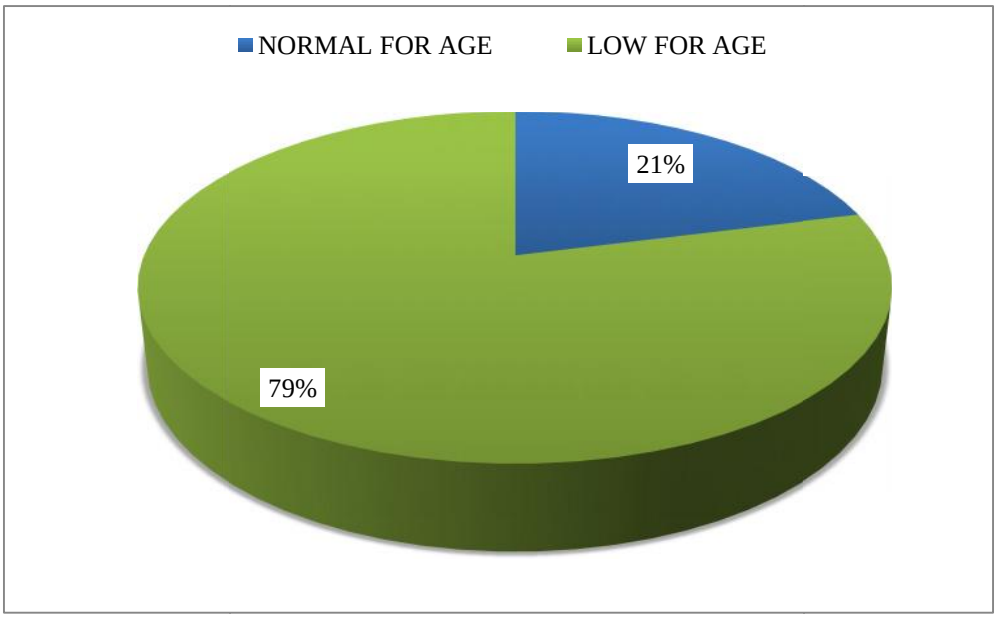


The maximum no of subjects were in the age group of 51-60 years with youngest patient of 25 years and oldest 69 years.

TABLE 2: TESTOSTERONE LEVELS IN STUDY POPULATION (MALE HYPERTENSIVES)

TESTOSTERONE LEVELS	%
NORMAL FOR AGE	21
LOW FOR AGE	79

GRAPH 2: TESTOSTERONE LEVELS IN STUDY POPULATION

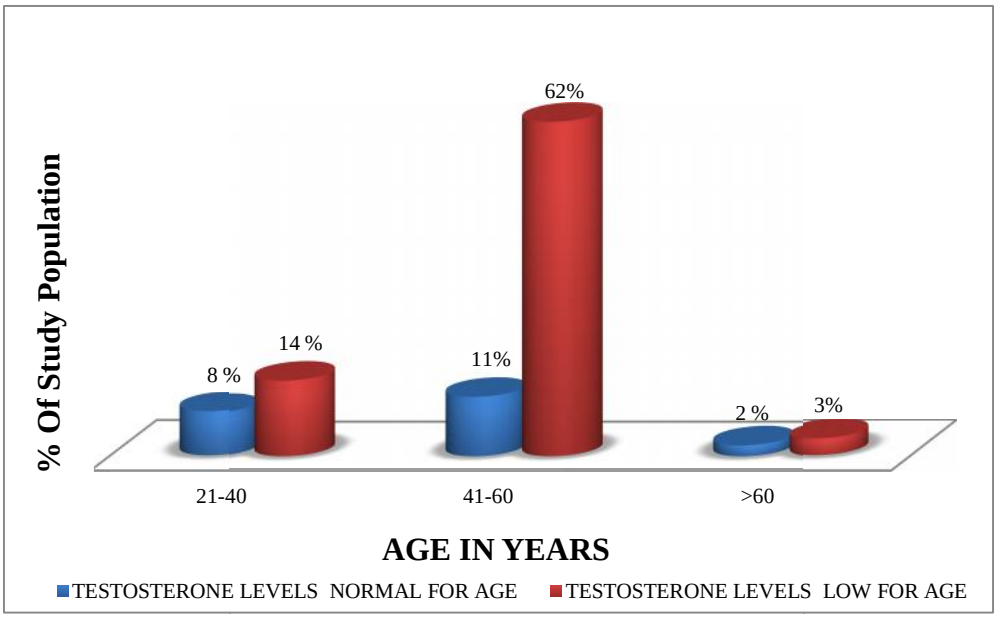


In our study 79% of the male hypertensive subjects had low for age testosterone levels and 21% had normal for age testosterone levels.

TABLE 3: AGE AND TESTOSTERONE LEVELS

AGE (in yrs)	TESTOSTERONE LEVELS NORMAL FOR AGE	TESTOSTERONE LEVELS LOW FOR AGE	Total
21-40	8	14	22%
41-60	11	62	73%
>60	2	3	5%
TOTAL	21	79	100

GRAPH 3: AGE AND TESTOSTERONE LEVELS



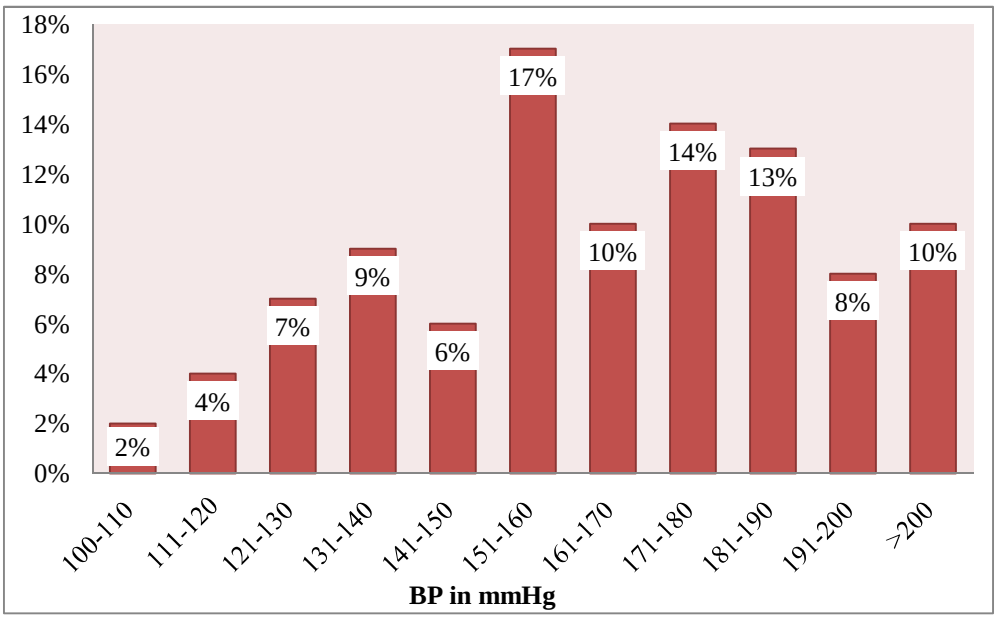
P=0.056 Chi Square 5.766 Not Significant

In our study low for age testosterone levels were observed in all age group of patients with hypertension.

TABLE 4: DISTRIBUTION OF SBP IN STUDY POPULATION

SBP in mmHg	% OF STUDY POPULATION
100-110	2%
111-120	4%
121-130	7%
131-140	9%
141-150	6%
151-160	17%
161-170	10%
171-180	14%
181-190	13%
191-200	8%
>200	10 %

GRAPH 4: DISTRIBUTION OF SBP IN STUDY POPULATION

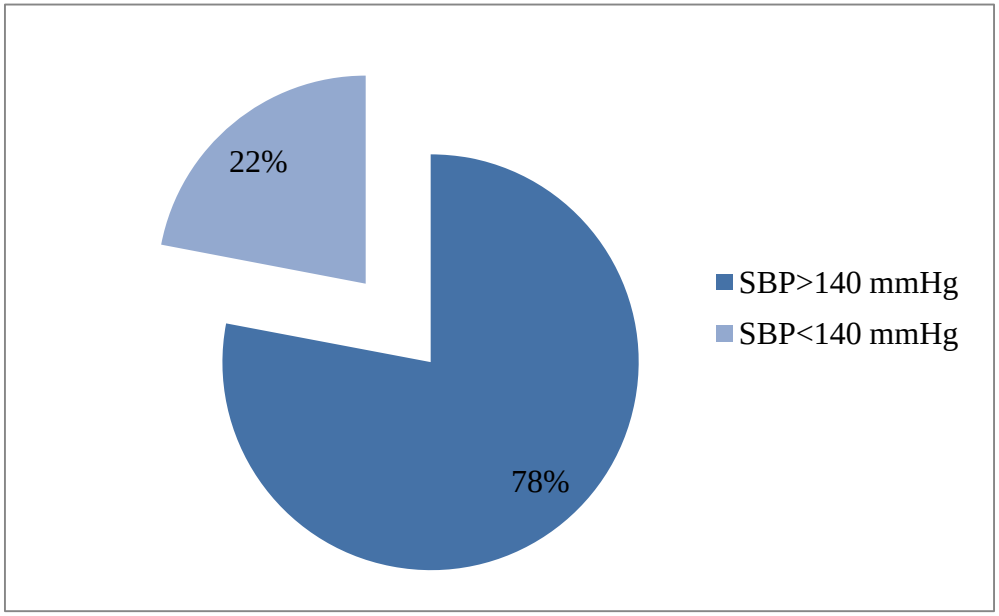


In our study 17% patients had SBP of 151-160 mmHg , followed by 14% 171-180mmHg & 13% 181-190mmHg.

TABLE 5: DISTRIBUTION OF SBP> & < 140MMHG

SBP	NO OF SUBJECTS
SBP>140 mmHg	78
SBP<140 mmHg	22
TOTAL	100

GRAPH 5: DISTRIBUTION OF SBP> & < 140MMHG



78% patients had SBP > 140 mmhg & 22% had SBP <140mmHg

TABLE 6: TESTOSTERONE LEVELS WITH SBP> & < 140MMHG

SBP in mmHg	TESTOSTERONE LEVELS NORMAL FOR AGE	TESTOSTERONE LEVELS LOW FOR AGE	TOTAL
SBP>140 mmHg	13	65	78
SBP<140 mmHg	8	14	22
TOTAL	21	79	100

TABLE 7: % DISTRIBUTION OF TESTOSTERONE LEVELS WITH SBP> & < 140MMHG

SBP in mmHg	TESTOSTERONE LEVELS NORMAL FOR AGE	TESTOSTERONE LEVELS LOW FOR AGE	TOTAL
SBP>140 mmHg	16.66%	83.33%	100
SBP<140 mmHg	36.36%	63.63%	100

83.33% of the hypertensive subjects With SBP >140mmHg had low for Age Testosterone Levels p=0.045

GRAPH 6: % DISTRIBUTION OF TESTOSTERONE LEVELS WITH SBP> & < 140MMHG

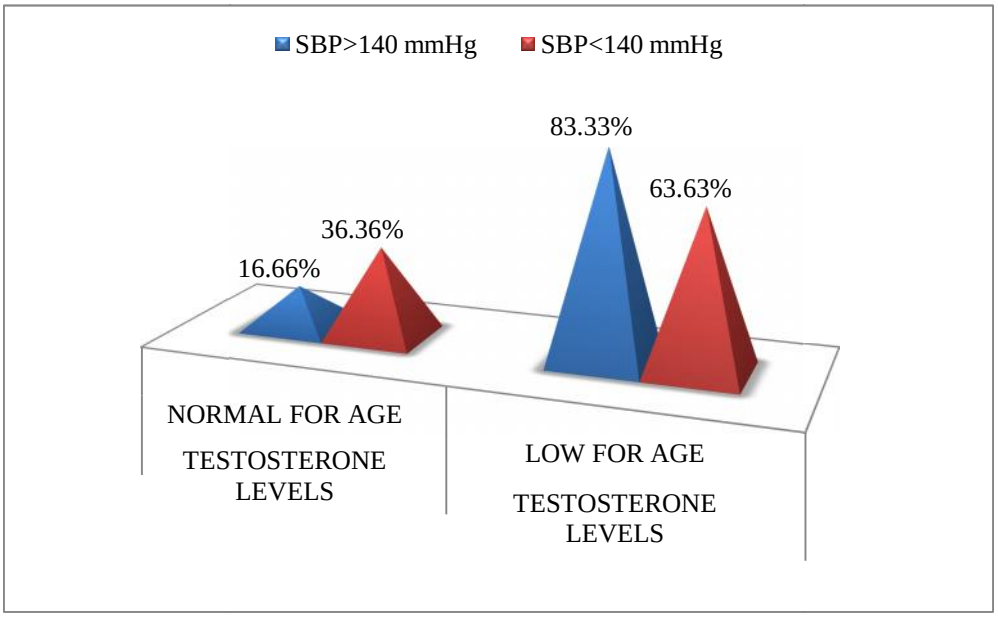
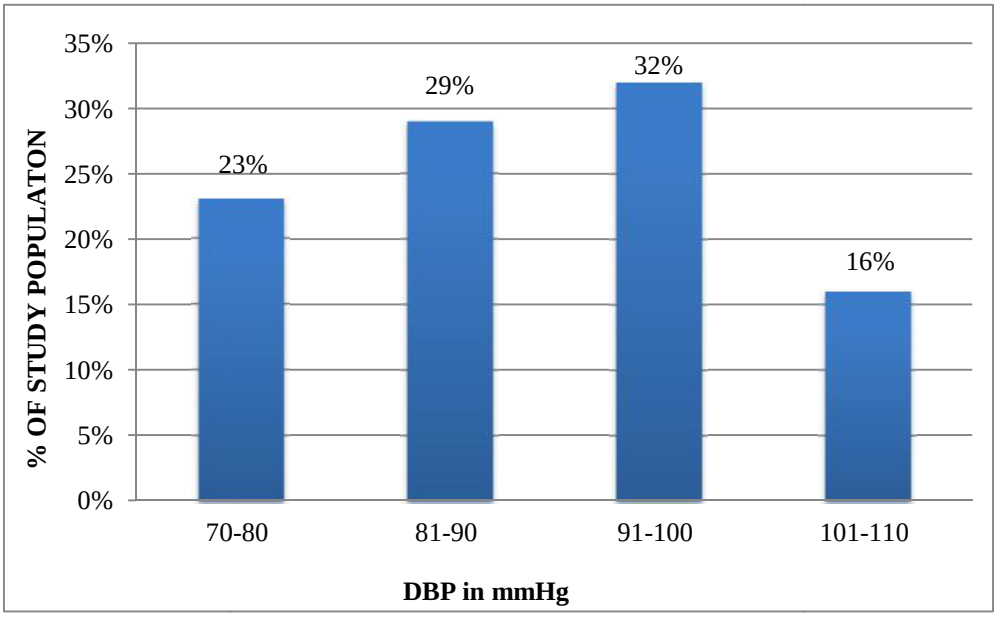


TABLE 8: DISTRIBUTION OF DBP IN STUDY POPULATION

DBP	% OF STUDY POPULATON
70-80	23%
81-90	29%
91-100	32%
101-110	16%
TOTAL	100

GRAPH 7: DISTRIBUTION OF DBP IN STUDY POPULATION



32% patients had DBP 91-100mmHg followed by 29% patients with DBP 81-90 mmHg, 23% 71-80mmHg.

TABLE 9: TESTOSTERONE LEVELS WITH DBP> & < 90MMHG

DBP in mmHg	TESTOSTERONE LEVELS NORMAL FOR AGE	TESTOSTERONE LEVELS LOW FOR AGE	TOTAL
DBP>90 mmHg	4	44	48
DBP<90 mmHg	17	35	52
TOTAL	21	79	100

TABLE 10: % DISTRIBUTION OF TESTOSTERONE LEVELS WITH DBP> & < 90MMHG

DBP in mmHg	TESTOSTERONE LEVELS NORMAL FOR AGE	TESTOSTERONE LEVELS LOW FOR AGE	TOTAL
DBP>90 mmHg	8.33%	91.66%	48
DBP<90 mmHg	32.69%	67.30%	52
TOTAL	21	79	100

91.66% of the hypertensive subjects with DBP >90 mmHg had low for age testosterone levels. p=0.003

GRAPH 8: % DISTRIBUTION OF TESTOSTERONE LEVELS WITH DBP> & < 90MMHG

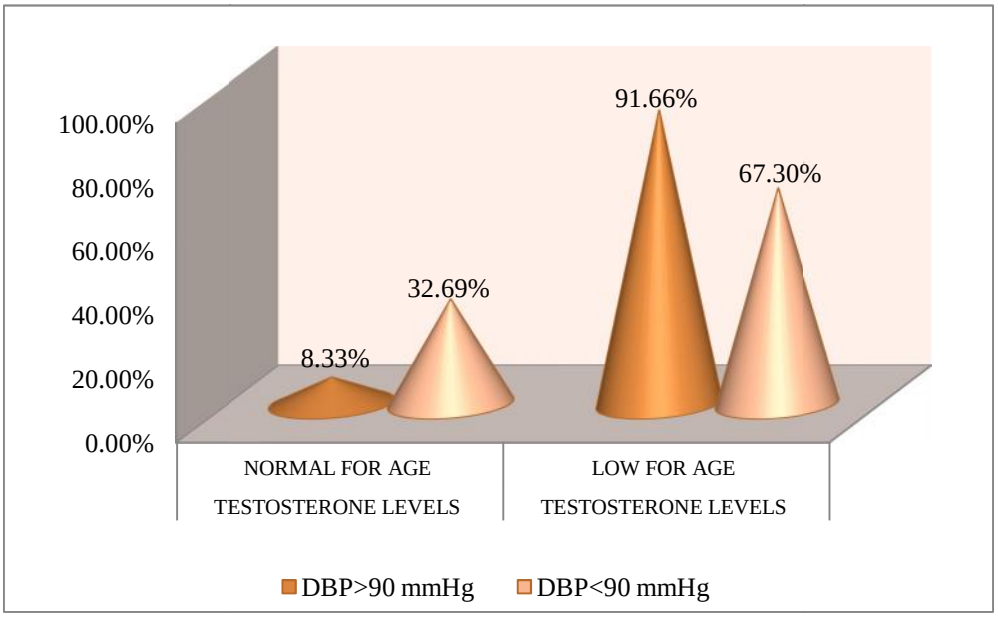


TABLE 11 :DURATION OF HTN IN STUDY POPULATION

DURATION OF HTN	NO OF SUBJECTS
NEW ONSET HYPERTENSION	10
< 10 YEARS	23
10-20 YEARS	28
>20 YEARS	39
TOTAL	100

Maximum No Of Patients 67% Were With A Duration Of Hypertension ≥ 10 Yrs

GRAPH 9 :DURATION OF HTN IN STUDY POPULATION

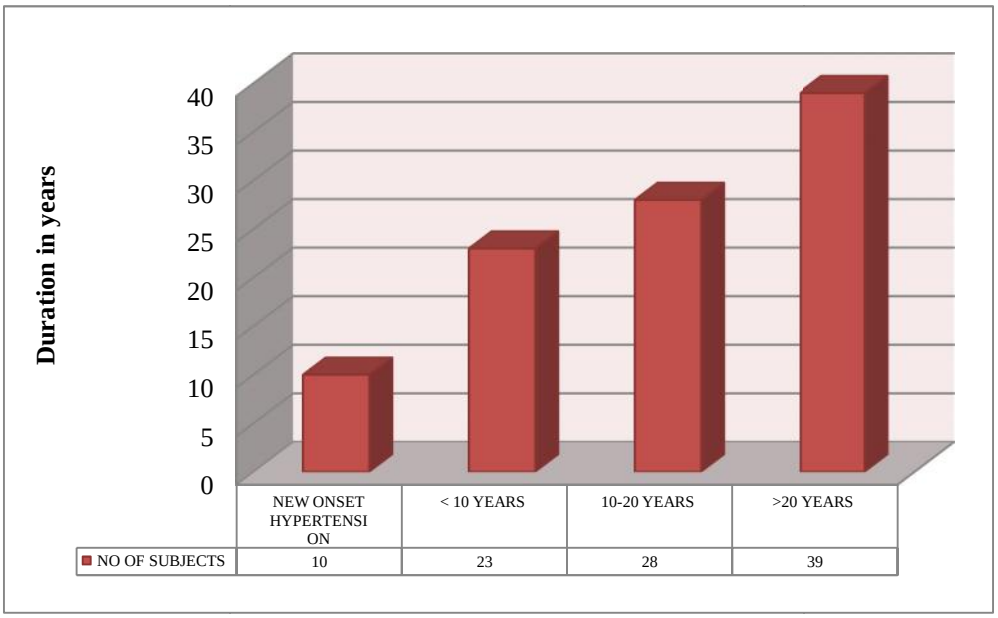
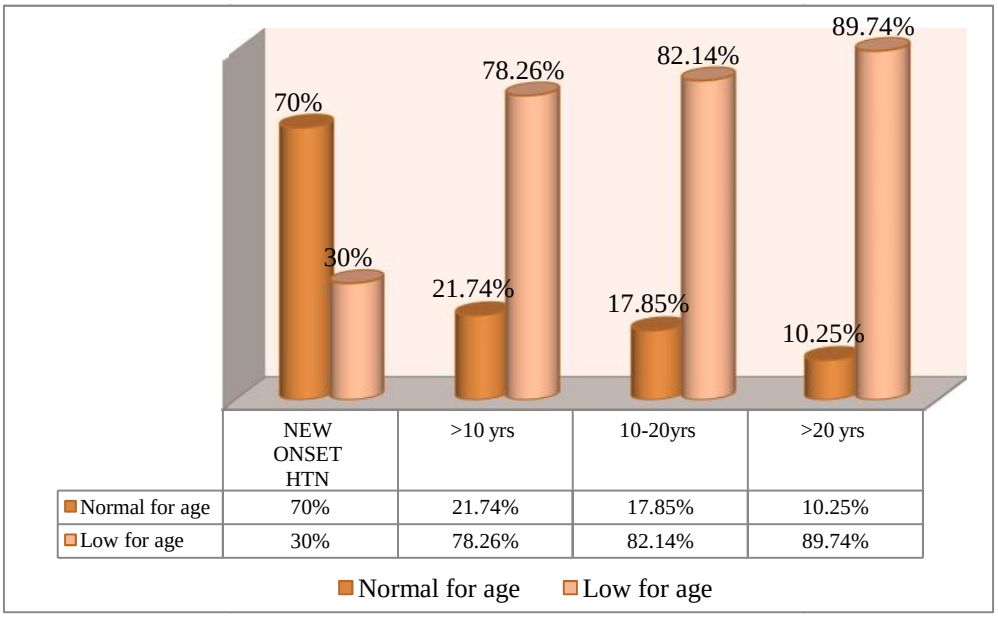


TABLE 12 : DURATION OF HTN WITH TESTOSTERONE LEVELS

TESTOSTERONE LEVELS	NEW ONSET HTN	>10 yrs	10-20yrs	>20 yrs
Normal for age	70%	21.74%	17.85%	10.25%
Low for age	30%	78.26%	82.14%	89.74%

GRAPH 10 : DURATION OF HTN WITH TESTOSTERONE LEVELS



Testosterone levels were found low for age in 89.74% and 82.14 % hypertensives with duration of >20 yrs & 10-20 yrs respectively. Chi sq 17.36, p=0.001

TABLE 13 : HABITS & TESTOSTERONE

Habits	% Of Study Population
Alcohol	12%
Smoking	7%
Tobacco chewing	12%
A+S+T	22%
No Habits	47%
Total	100

TABLE 14 : ONLY ALCOHOL INTAKE & TESTOSTERONE LEVELS

Testosterone levels	Only alcoholic	%
Normal for age	5	41.66%
Low for age testosterone	7	58.33%
Total	12	100

A+T+S & testosterone

TABLE 15: ALCOHOL, SMOKING TOBACCO CHEWING & TESTOSTERONE LEVELS

Testosterone levels	A+S+T	%
Normal for age	3	13.63%
Low for age testosterone	19	86.36%
Total	22	100%

TABLE 16 :ALCOHOL CONSUMPTION & TESTOSTERONE LEVELS

Testosterone levels	Total no of patients with alcohol consumption	%
Normal for age	8	23.52%
Low for age testosterone	26	76.47%
Total	34	100%

76.47% Hypertensives Out Of The Total 34 Patients Who Consumed Alcohol Had Low For Age Testosterone Levels P value <0.01 According To Standard Error Of Proportion

TABLE 17 :LIFESTYLE (PHYSICAL ACTIVITY OF STUDY POPULATION)

Physical activity	% Of Study Population
Sedentary work	55%
Moderate work	38%
Heavy work	7%
Total	100

TABLE 18 : PHYSICAL ACTIVITY & TESTOSTERONE LEVELS

Physical activity	Normal for age testosterone	Low for age testosterone
Sedentary work	14.54%	85.45%
Moderate work	28.94%	71.05%
Heavy work	28.57%	71.42%

85.45% Of The Subjects With Low For Age Testosterone Had A Sendatary Lifestyle P=0.001

GRAPH 11 : PHYSICAL ACTIVITY & TESTOSTERONE LEVELS

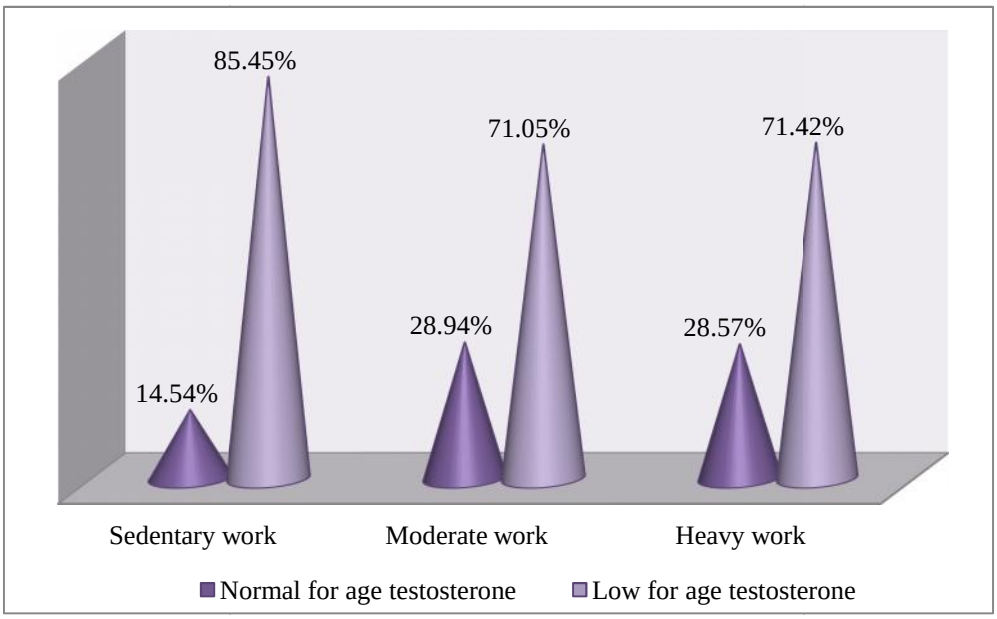
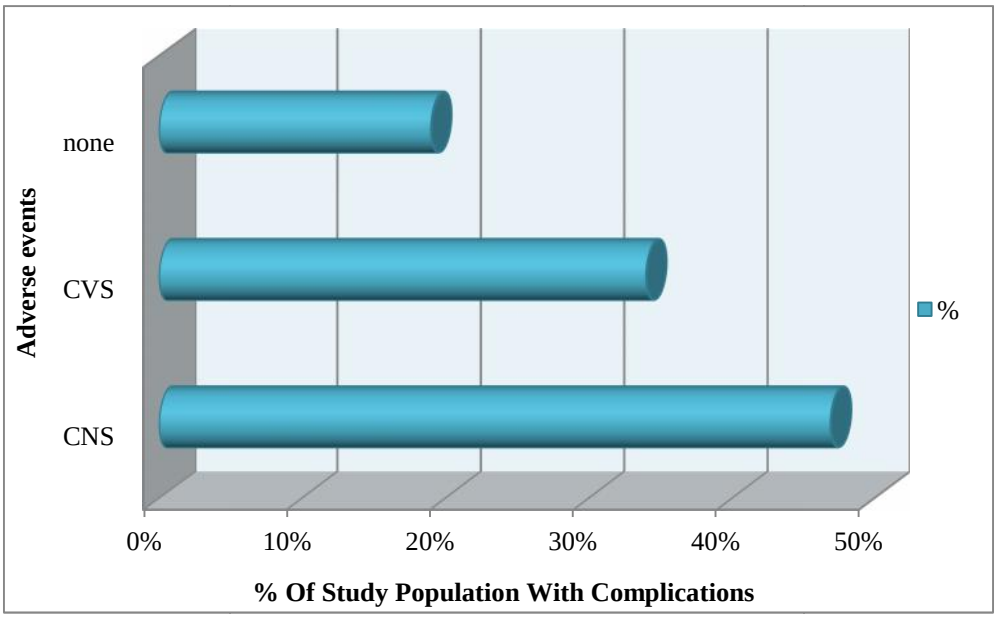


TABLE 19 : COMPLICATONS OF HTN AMONG STUDY POPULATION

ADVERSE EVENTS	%
CNS	47%
CVS	34%
none	19%
Total	100

GRAPH 12 : COMPLICATIONS OF HTN



47% patients had CNS complications and 34% had Cardiovascualr complications.

TABLE 20 : TESTOSTERONE LEVELS WITH ADVERSE EVENTS

Adverse events	Low for age testosterone	Normal for age testosterone	Total
CVS	**34%**	**0%**	**34%**
CNS	**45%**	**02%**	**47%**
NONE	**0%**	**19%**	**19%**
Total	**21%**	**79%**	**100**

45 Of 47 (95.74%) Hypertensives Who Had Cns Adverse Events Had Low For Age Testosterone Levels & 34% (100%) Of All Subjects with Cardiovascular Adverse Events Had Low Levels of Testosterone levels with significant P value of <0.001 Chi Sq =88.45

GRAPH 13 : TESTOSTERONE LEVELS WITH ADVERSE EVENTS

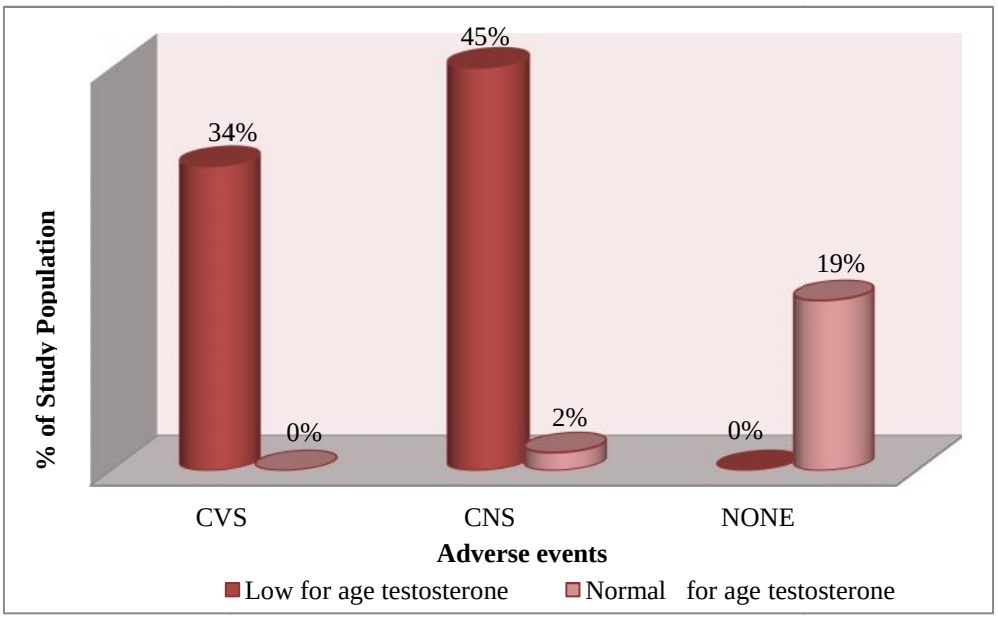


TABLE 21 : CLINICAL FEATURES OF CEREBROVASCULAR COMPLICATIONS

HEMIPARESIS/HEMIPLEGIA	**36%**
ATAXIA	**7%**
SPEECH DISTURBANCES	**2%**
OTHERS	**2%**
TOTAL	**47%**

Hemiplegia Was The Most Common Presentation among the patients with neurodeficits.

TABLE 22 : CNS BRAIN IMAGING

INFARCT	**25%**
HAEMORRHAGE	**20%**
NONE	**2%**
TOTAL	**47%**

Infarction was seen in 25 % patients & haemorrhage in 20 % patients with cerebrovascular complications.

TABLE 23 : SUBTYPES OF CV ADVERSE EVENTS

UNSTABLE ANGINA	**7%**
ACUTE MI	**22%**
OLD MI	**5%**
Total	**34%**

Acute MI Was The Most Common Cvs Adverse Event Seen followed by unstable angina & old MI.

TABLE 24 : 2D ECHO FINDING

EF	
MI WITH REDUCED EF <60%	**15%**
MI WITH NORMAL EF >60%	**12%**
Total	**27%**

15/27 Subjects With MI (Old & Acute) Had Ef<60%

TABLE 25 : FUNDOSCOPY FINDINGS

Normal	39%
Grade 1 retinopathy	**32%**
Grade 2 retinopathy	**25%**
Grade 3 retinopathy	**4%**

61% patients had hypertensive retinopathy

TABLE 26 : TESTOSTERONE LEVELS & FUNDOSCOPY

	FUNDOSCOPY		
TESTOSTERONE	**NORMAL**	**RETINOPATHY**	**TOTAL**
Normal for age	**16**	**05**	**21**
Low for age	**23**	**56**	**79**
TOTAL	**39**	**61**	**100**

91% of the total hypertensive patients with retinopathy had low for age levels of testosterone & 8.19% of hypertensives with retinopathy had normal for age testosterone levels. P=<0.001 chi sq=15.45

GRAPH 14 : TESTOSTERONE LEVELS & FUNDOSCOPY

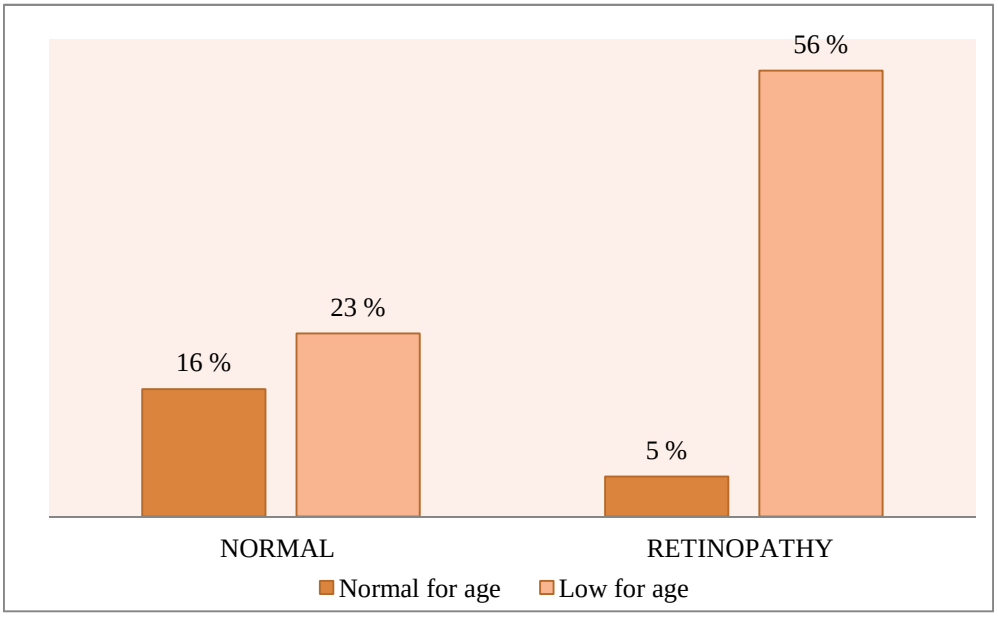


TABLE 27 : LIPID PROFILE OF STUDY POPULATION

NORMAL	**75%**
HYPERTRIGLYCERIDEMIA	**12%**
HYPER CHOLESTROLEMIA	**10%**
BOTH	**03%**
Total	**100**

TABLE 28 : LIPID PROFILE & TESTOSTERONE LEVELS

TESTOSTERONE	HTGS	HCHOL	BOTH	NORMAL	TOTAL
Normal for age	**7**	**4**	**0**	**10**	**21**
Low for age	**5**	**6**	**3**	**65**	**79**
Total	**12**	**10**	**3**	**75**	**100**

86.66% of patients with Normal Lipid Profile Had Low For Age Testosterone Levels.

DISCUSSION

In the present study of 100 patients with Hypertension, serum testosterone levels were estimated.

In our study, age of the patients were in the range of 25 to 69 years, maximum number of cases 51 patients (51%) were in the age group of 51 to 60 years, followed by 41-50 years age group with 22 patients (22%), 31-40 years group with 21 patients (21%) , below 30 years we had 1 patient (1%) and above 60 years 5 patients (5%). Youngest patient was 25 years old and oldest patient was 69 years old.

In our study,79% of the hypertensive males had low for age testosterone levels (less than lower normal limit) and 21% of the hypertensive males had normal testosterone levels for their age. Our observation was comparable to a study done by Shashi k agarwal[4] ,Johan Svartberg, et al[178].

In our study, 22 patients (22%) were in age group of 21-40 years, among the 22 patients 14 patients i,e 63.63% had low for age testosterone levels ,73 patients (73%) were in the age group of 41-60 years and among them 62 patients (84.93%) had low for age testosterone levels. There were 5 (5%) patients in the age group of >60 years, among them 3(60%) had low for age testosterone levels .

In our study, the systolic blood pressures had a wide range from 100 to > 200 mmHg. Majority of the subjects 17(17%) had a SBP of 151-160 mmHg, followed by 171-180 mmHg 14 (14%) & 181-190 mmHg 13 (13%) 8 (8%) subjects had SBP 191-200 mmHg & 10 (10%) of the study group had a SBP of >200mmHg.

A total of 78 (78%) patients had a SBP > 140 mmhg & 22 (22%) had SBP< 140 mmHg . Among the subjects with SBP >140 mmHg, testosterone was found to be low for age in 65(83.33%) & normal for age testosterone in 13 (16.66%) subjects. Out of the 22 subjects with SBP < 140 mmHg 14(63.63%) had low for age testosterone levels & 8 (36.36%) had normal for age testosterone. Thus low for age testosterone levels in patients with SBP > 140mmHg was statistically significant with p value 0.045. This finding was similar to a study done by Johan Svartberg et al[178].

In our study, the diastolic blood pressures had a wide range from 70 to > 110 mmHg. 32(32%) had DBP of 91-100 mmHg, followed by 29 (29%) with DBP 81-90 mmHg, 23 (23%) had DBP 70-80 & 16 (16%) with DBP > 110 mmHg. Among the 48 subjects with DBP> 90 mmHg 44 (91.66%) had low for age testosterone levels & 4 (8.33%) had normal for age testosterone levels. Out of the 52 subjects with DBP <90 mmhg 35 (67.30%) had low for age testosterone levels & 17(32.69%) had normal for age testosterone levels. Thus low for age testosterone levels in patients with DBP > 90mmHg was statistically significant with p value 0.003. This finding was comparable to a study by Johan Svartberg et al[178].

In our study we observed that , there were 39 (39%) subjects with duration of HTN > 20 years, followed by 28 (28%) with duration of HTN between 10-20 years. 23 (23%) had duration of HTN of < 10 years and 10 (10%) were newly detected hypertensives. We observed that majority of the subjects 35 out of 39 (89.74%) with a duration of >20 years had low for age testosterone levels followed by 23 out of 28 (82.14%) subjects with HTN for 10-20 years had low for age testosterone levels,18 out of 23 (78.26%) subjects with duration of HTN of < 10yrs were found to have low

for age testosterone levels & 3 out of 10 (30%) among the newly detected hypertensives had low for age testosterone levels. Hence longer duration of HTN was associated with low for age testosterone levels which was statistically significant with p value 0.001 & Chi square 17.36.

In our study we observed that among the 12 patients who consumed alcohol, testosterone was low for age in 7 patients i,e (58.33%) & 5 out of 12 (41.66%) had normal for age testosterone levels. 22 subjects had additional habits of smoking & tobacco chewing along with alcohol consumption. Among these 22 patients 19 (86.36%) had low for age testosterone levels & 3(13.63%) had normal for age testosterone. It was seen that 34 of the total 100 study subjects consumed alcohol. 26 out of 34 (76.46%) subjects who consumed alcohol had low for age testosterone levels.

This association of alcohol consumption with low for age testosterone levels was statistically significant according to standard error of proportion. with p value <0.01.

In our study we observed 47(85.45%) out of 55 patients with sedentary work, 27 out of 38 (71.05%) patients with moderate work & 5 out of 7 (71.42%) patients with heavy work had low for age testosterone levels. Low for age testosterone levels was associated with level of physical activity which was statistically significant with p=0.001.

In our study we studied the major complications of HTN, 47 patients(47%) had cerebrovascular complications & 45 out of the 47 (95.74%) of them had low for age testosterone levels. 34 patients (34%) had cardiovascular adverse events & all 34

(100%) of these patients had low testosterone levels. This association of low for age testosterone levels with complications of HTN was statistically significant p=<0.001 chi sq =88.45. This finding was similar to a study by Paul D Morris and Kevin S , Channer[179], Rugie et al[24] , Charalambos et al[26].

Brain scan imaging showed that out of 47 stroke patients 25 had infarction & 20 % had haemorrhage. Hemiplegia/hemiparesis followed by ataxia & speech disturbances was the most common presentation in them. One patient presented with recurrent transient ischemic attacks & 1 with seizures.

Among the 34 patients with CV complications, ECG showed 22% had acute MI, & 5% had features of old MI. 15 out the 27 patients with MI had reduced ejection fraction < 60 %, 12 had preserved EF of >60%. only 7 patients had non specific ST-T changes with symptoms suggestive of unstable angina.

In our study, fundoscopy was done in all patients, 61 patients had hypertensive retinopathy, 32 patients had grade 1, 25 patients grade 2 & 4 patients grade 3 retinopathy. Testosterone was found to be low for age in 56 out of 61 (91.80%) patients with retinopathy. This association of hypertensive retinopathy with low for age testosterone levels is statistically significant with p=<0.001

Lipid profile was studied in all the patients. 65 (86.66%) among the 79 hypertensive males with low for age testosterone levels had normal lipid profile. Therefore dyslipidemia & low for age serum testosterone levels did not have any association in our study.

CONCLUSION

Hypertension is responsible for one half of the global health burden . Low serum testosterone levels is known to be associated with hypertension & major cardiovascular and cerebrovascular complications of hypertension in men.

In our study of 100 hypertensive patients,

1. Age of the patients was in the range of 25-69 years, maximum number of cases 51 (51%) were in the age group of 51-60 years.
2. 79% patients had low for age testosterone levels.
3. 65(83.33%) out of 78 patients with SBP >140mmHg & 44 (91.66%) of 48 patients with DBP >90mmHg had low for age serum testosterone levels which was statistically significant with p value of 0.045 & 0.003 respectively.
4. We also observed that out of the 67 patients with duration of HTN > 10 years 58 (86.56%) patients had low for age testosterone levels which was statistically significant with p=0.001.
5. 47 (47%) patients had cerebrovascular complications & 45 (95.74%) of them had low for age testosterone levels. 34 (34%) patients had cardiovascular complications & all 34 (100%) of them had low for age testosterone levels. This was statistically significant with p=<0.001.
6. Out of 100, 34 patients consumed alcohol and among them 26 patients (76.47%) had low for age testosterone levels which was statistically significant with p=<0.01.

7. Low for age testosterone levels was associated with level of physical activity.47(85.45%) out of 55 patients with sedantary work, 27 out of 38 (71.05%) patients with moderate work & 5 out of 7 (71.42%) patients with heavy work had low for age testosterone levels which was statistically significant with p=0.001.
8. 61% of the patients also had microvascular complications of HTN in the form of hypertensive retinopathy . Among them, 56 (91%) patients had low for age testosterone levels which was statistically significant with p value<0.001.
9. Hence low for age testosterone levels can predict both micro & macrovascular complications of HTN.
10. Lipid profile studied among the 79 hypertensive males with low for age testosterone levels showed that 65(86.66%) patients had normal lipid profile.

SUMMARY

The present study of 100 hypertensive male patients was conducted in the Department of Internal Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belagavi during Jan 2016 to December 2016 and their serum testosterone levels were estimated.

In our study, maximum number of cases were in the age group of 51-60 years. 79% of the patients had low for age serum testosterone levels. Low for age testosterone levels was also observed in 83.33% patients with SBP >140mmHg ,91.66% of patients with DBP >90mmHg. Low for age serum testosterone levels correlated well with longer duration of HTN, cerebrovascular, cardiovascular complications of HTN, hypertensive retinopathy, alcohol consumption & sedentary lifestyle. Lifestyle modifications like increase in physical activity ,decrease in alcohol consumption can improve the testosterone levels. Early estimation of serum testosterone levels can predict both micro & macrovascular complications of HTN. But this observation needs to be confirmed in a larger cohort study.

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ANNEXURE I

INFORMED CONSENT

TITLE OF RESEARCH STUDY: "STUDY OF SERUM TESTOSTERONE LEVELS IN MALE HYPERTENSIVES- A ONE YEAR HOSPITAL BASED STUDY"

Introduction and Purpose:

- It is estimated that approximately 20% of the world's adult population suffer from hypertension.
- Hypertension is responsible for one half of the global health burden.
- Nearly 50-60% of the strokes, ischemic heart disease related deaths worldwide are attributed to hypertension.
- HTN and low testosterone levels usually co exist and increase in prevalence with aging, regardless of race & ethnicity.
- Testosterone deficiency has been associated with increase in major cerebrovascular & cardiovascular complications of HTN in men.
- These data suggest that testosterone replacement therapy may be potentially cardioprotective in male patients with hypertension.
- This study was done to study association of the levels of serum testosterone in males with hypertension & its complications.

Procedure:

If you agree to be part of the research study, you will be asked the relevant history and will be subjected to relevant clinical examination and investigations. You will also have to give blood and urine samples for the necessary investigations.

Risk and Benefits:

The only risk and possible discomfort you might get is while taking blood from my arm for the investigations. It may cause swelling, pain, redness, bruising or infection (rarely happens) at the site from where the blood is drawn.

Alternatives:

Taking part in this study is voluntary. You may choose not to take part in this study, or if I decide to take part I can later change my mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study, you will receive the standard treatment for patients with your condition.

Privacy and Confidentiality:

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy:

In the event of injury related to the study, treatment will be made available at KLES Dr. Prabhakar Kore Hospital and Research Centre, Belagavi. There is no compensation or payment for such medical treatment by law.

Financial incentives for participation:

You will not be paid / offered any gifts /incentives for participating in the study.

Queries

In case of the queries during study or in future you may contact following persons,

1. **Dr. GANGA S PILLI,**

   Professor of Pathology & Chairman,

   JNMC Institutional Ethics Committee

   on Human Subjects Research,

   J.N.Medical College, Belgaum.

   Phone number: 09480275601

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not be giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, this entire consent form, and have had all my questions answered.

Name of the Participant: _____Signature / Thumb print _____

Name of the Witness _____ Signature/ Thumb print _____

Investigator Name: _____Signature :_____

Date:

Place

ANNEXURE II – PROFORMA

"STUDY OF SERUM TESTOSTERONE LEVELS IN MALE HYPERTENSIVES: A ONE YEAR HOSPITAL BASED STUDY"

CASE NO:

NAME:

AGE/SEX:

ADDRESS:

OCCUPATION:

COMPLAINTS AT PRESENTATION:

RISK FACTORS

DIAGNOSIS

PHYSICAL EXAMINATION

VITALS : BLOOD PRESSURE=

PULSE=

RESPIRATORY RATE

TEMP=

SYSTEMIC EXAMINATION:

CARDIOVASCULAR SYSTEM:

CENTRAL NERVOUS SYSTEM:

PER ABDOMEN:

RESPIRATORY SYSTEM:

INVESTIGATIONS:

SERUM TESTOSTERONE LEVELS=

ECG

2DECHO

BRAIN SCAN

FUNDOSCOPY

RENAL FUNCTION TESTS

USG ABDOMEN

LIPID PROFILE

DIAGNOSIS:

ANNEXURE-III
KEY TO MASTER CHART

NAME	IP/OP NO	AGE	TESTOSTERONE LEVELS (NG/DL)	SBP IN MMHG	DBP IN MMHG	ADVERSE EVENTS	OCCUPATION	LEVEL OF PHYSICAL AVTIVITY	RISK FACTOORS (A=ALCOHOL, S=SMOKING, T= TOBACCO CHEWING	CVS EXAMINATION	CNS EXAMINATION	ECG	ECHO	BRAIN IMAGING	LIPID PROFILE	FUNDOSCOPY	RENAL PROFILE	USG ABDOMEN-KUB	DURATION OF HTN
Manoj	780841	41	134	200	100	CNS	Business	Sedendtary (s)	A,T ,S	N	E4m1v6,rt dense hemiplegia,global aphasia	BRADYCARDIA	Normal	Subacute infarct left mca-pca watershed areas	NORMAL	Normal	N	N	New onset htn
Sanjay	781694	44	164	170	90	CNS	Army service	Heavy work	A,S,T	N	Conscious,oriented,dysarthria+,left hemiparesis	LVH	Normal	Intraparenchymal haemorrhage rt putamen	N	Grade 1 hypertensive retinopathy	N	N	<10 years
Rupesh	789363	40	165	128	90	CNS	Private business	Sedendtary (s)	A,S,T	N	Drowsy,right brachial hemiparesis	NORMAL	Normal	Intraparenchymal haemorrhage rt frontal and caudate nucleus extending in bilateral lateral ventricles	HYPERTRIGLYCIDEMIA	Normal	N	N	<10 years
Lakappa	781966	55	166	200	100	CNS	Mill worker	Modearte work	A,S,T	N	Right dense hemiplegia with umn facial palsy	NORMAL	Concentric lvh,ef60%	Intracerebral bleed in left putamen	N	Normal	N	N	12
Khadarsab	781859	58	167	190	110	CNS	Daily waged labourer	Modearte work	A,S,T	N	E4m1v6,rt dense hemiplegia,global aphasia	OLD IHD,RBBB	Ihd, hyokinesia withef35%	Left mca infarct	N	Normal	N	N	New onset htn
Mallappa	782600	52	168	180	80	CNS	Farmer	Modearte work	A	N	Right hemiparesis with umn facial palsy	LVH	Concentric lvh,ef60%	Lacunar infarct left mca territory	N	Normal	N	N	11
Sidray	780566	56	169	120	80	CNS	Farmer	Modearte work	A,S,T	N	Vertibrobasilar insufficiency,ataxia,tremors	RBBB	Normal	Normal	N	Grade 1 hypertensive retinopathy	N	N	15
Keshav	782085	52	170	170	100	CNS	Private business	Sedendtary (s)	-	N	Right fasciobrachial palsy	NORMAL	Normal	Left intracerebral bleed in left putamen	HTGS	Normal	N	N	12
Neminath	782640	43	171	150	90	CVS	Lecturer	Sedendtary (s)	-	N	Na	NORMAL	Normal	Not done	N	Normal	N	N	New onset htn
Bhim	782756	35	172	110	70	CVS	Farmer	Modearte work	S	N	Na	OLD AWMI	Good biventricular function with ef 60%	Not done	N	Normal	N	N	16
Mahadev	530229	56	173	130	70	CVS	Clerk	Heavy work	-	N	Na	NORMAL	Normal	Not done	HTGS	Normal	N	N	New onset htn
Mohan	781806	50	174	130	80	CVS	Advocate	Sedendtary (s)	A,S,T	N	Na	SINUS TACHYCARDIA	Tachycardia,hocm,ef 60%	Not done	HTGS	Normal	N	N	17
Bhima	789192	40	175	200	90	CVS	Farmer	Heavy work	-	N	Na	NORMAL	Normal	N	HTGS	Grade 2 hypertensive retinopathy	N	N	<10 years
Satappa	782699	52	176	156	90	CVS	Farmer	Modearte work	-	N	Na	OLD AWMI,RBBB	Ihd,akinesia of anterior wall,lvef; 45%	-	HTGS	Grade 2 hypertensive retinopathy	N	N	16
Pandu	782591	53	177	160	100	CVS	Farmer	Modearte work	A,S,T	N	Na	EVOLVED AWMI	Ihd,akinesia of anterior wall,lvef; 45%	-	HCHOL	Grade 2 hypertensive retinopathy	N	N	<10 years
Yallapa	782438	53	178	170	90	CVS	Mill worker	Heavy work	-	N	Na	NORMAL	Trivial tr with ppg 25mmhg ef 60%	-	N	Grade 2 hypertensive retinopathy	N	N	21
Mehboob	782733	55	179	160	110	CVS	Fruit vendor	Sedendtary (s)	A,S,T	N	Na	IHD; AWMI	Ihd,akinesia of anterior wall,lvef; 45%	-	HCHOL	Grade 2 hypertensive retinopathy	N	N	New onset htn
Sayyad	781040	40	180	160	100	CVS	Private business	Sedendtary (s)	A	N	Na	NORMAL	Dialated cardiomyopthy with global hypokinesia ef 60%	-	HCHOL	Grade 2 hypertensive retinopathy	N	N	<10 years
Shankar	780999	54	181	160	90	CVS	Farmer	Modearte work		N	N	NORMAL	Normal	-	NORMAL	Normal	N	N	11
Paris	780220	56	182	138	90	CVS	Private business	Sedendtary (s)	-	N	N	IWMI	Hypokinesia of inferior wall ef 45%	-	HTGS	Grade 2 hypertensive retinopathy	N	N	14
Dadpeer	4024334	54	183	160	80	CVS	Driver	Heavy work	-	N	N	AWMI	Hypokinesia of anterior wall ef 45%	-	NORMAL	Grade 2 hypertensive retinopathy	N	N	12

Sanmuk	779919	51	184	190	80	CVS	Farmer	Modearte work	A,S,T	N	N	NORMAL	Bradycardia ef60%	-	NORMAL	Normal	N	N	26
Bapu	780692	50	185	200	110	CVS	Private business	Sedendtary (s)	A,S,T	N	N	NORMAL	Concentric lvh,ef60%	-	HYPERTRIGLYCIDEMIA, HYPERCHOLESTROLEMIA	Grade 2 hypertensive retinopathy	N	N	<10 years
Devraj	782181	56	186	200	110	CNS	Farmer	Modearte work	-	N	N	LVH	Concentric lvh,ef60%	Subacute infarct left parietal region,hypertensive ischemic changes	HTGS	Grade 2 hypertensive retinopathy	N	N	16
Appasab	780959	52	187	140	90	CVS	Farmer	Modearte work	-	N	N	AWMI	Hypokinesia of anterior wall ef 45%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	25
Abdul	780652	58	188	150	96	CVS	Farmer	Modearte work	-	N	N	IWMI	Akinesia of inferior wall ef 45%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	12
Alisab	780959	52	189	160	110	CVS	Fruit vendor	Sedendtary (s)	-	N	N	AWMI	Hypokinesia of anterior wall ef 45%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	<10 years
Abdul	780652	56	190	170	100	CVS	Private business	Sedendtary (s)	-	N	N	IWMI	Akinesia of inferior wall ef 45%	-	HYPERTRIGLYCIDEMIA, HYPERCHOLESTROLEMIA	Grade 2 hypertensive retinopathy	N	N	11
Sidappa	775604	48	191	160	90	CVS	Farmer	Modearte work	-	N	N	EVOLVED AWMI	Hypokinesia of anterior wall ef 60%	-	NORMAL	Normal	N	N	24
Madhu	754867	55	192	180	110	CNS	Private business	Sedendtary (s)	-	N	N	OLD MI	Global hypokinesia of anterior wall ef 35%	Intraparenchymal haemorrhage in rt cerebellar lobe	NORMAL	Grade 2 hypertensive retinopathy	N	N	<10 years
Appasab	754924	54	193	180	90	CVS	Farmer	Modearte work	-	N	N	ACUTE IWMI	Hypokinesia of inferior wall ef 60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	12
Dhakoji	781109	54	194	190	100	CVS	Weaver	Sedentary	-	N	N	ACUTE IWMI	Hypokinesia of inferior wall ef 45%	-	NORMAL	Grade 2 hypertensive retinopathy	N	N	<10 years
Mallapa	3852487	50	195	190	80	CVS	Daily waged labourer	Modearte work	-	N	N	ACUTE LATERAL WALL MI	Hypokinesia of anterolateral wall with ef 60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	26
Mahadev	770783	47	196	220	110	CNS	Milk vendor	Sedentary	-	N	N	NORMAL	Normal	Large subacute infarct left fronto temporo parietal region, perisylvian cortex,internal & external capsule with haemorrhagic transformation	NORMAL	Normal	N	N	16
Ulvesh	774934	35	197	170	110	CNS	Farmer	Modearte work	A,S,T	N	N	NORMAL	Mild pah ef 60%	Subacute infarct in rt pca territory mri angio: b/l posterior communicating artery hypoplastic	NORMAL	Normal	N	N	24
Shiv	778904	58	198	160	80	CNS	Private business	Sedendtary (s)	-	N	N	SINUS BRADYCARDIA	Sinus braddycardia ,normal lv function with ef 60%	-	HTGS	Normal	N	N	21
Venkat	753332	53	199	160	100	CVS	Farmer	Modearte work	-	N	N	AWMI	Hypokinesia of anterior wall ef 35%	-	HYPERTRIGLYCIDEMIA, HYPERCHOLESTROLEMIA	Grade 2 hypertensive retinopathy	N	N	16
Rudrayya	751214	50	200	180	90	CVS	Farmer	Modearte work	-	N	N	ACUTE IWMI	Akinesia of inferior wall ef 35%	Normal	NORMAL	Grade 1 hypertensive retinopathy	N	N	22
Laxman	778616	53	201	190	80	CNS	Lecturer	Sedendtary (s)	-	N	N	LVH	Concentric lvh,ef60% sinus tachycaedia	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	16
Baba	778974	58	202	180	100	CNS	Farmer	Modearte work	-	N	N	NORMAL	Normal	Mri: subacute infarct in rt mca territory	NORMAL	Normal	N	N	<10 years
Balchandra	779019	38	203	180	100	CNS	Lecturer	Sedendtary (s)	-	N	N	NORMAL	Normal	Mri: subacute infarct in rt mca territory	NORMAL	Normal	N	N	11
Sudhir	4161316	40	204	150	90	CNS	Bank manager	Sedendtary (s)	-	N	N	LVH	Concentric lvh,ef60%	-	NORMAL	Normal	N	N	<10 years
Annasab	779163	56	205	180	110	CNS	Farmer	Modearte work	-	N	N	LVH	Concentric lvh,ef60%	-	NORMAL	Grade 2 hypertensive retinopathy	N	N	22
Manohar	770948	48	206	200	100	CNS	Farmer	Modearte work	-	N	N	LVH	Concentric lvh,ef60%	Mri left mca territory infarct	HTGS	Grade 2 hypertensive retinopathy	N	N	12
Nayim	779157	35	207	200	100	CNS	Daily waged labourer	Modearte work	-	N	N	NORMAL	Normal	Ct large parenchymal hemorrhage in rt basal ganglia, corona radiata& medial temporal lobe. Mri : same findings	NORMAL	Normal	N	N	21
Laxman	774216	56	208	190	100	CNS	Farmer	Modearte work	-	N	N	NORMAL	Normal	Mri: subacute infarct in left mca & pca & right mca territory	NORMAL	Grade 2 hypertensive retinopathy	N	N	<10 years
Raja	771741	48	209	190	100	CNS	Daily waged labourer	Modearte work	A,S ,T	N	N	NORMAL	Concentric lvh,ef60%	Old stroke :rt pca infarct	NORMAL	Grade 2 hypertensive retinopathy	N	N	22
Kallangouda	772271	54	210	140	90	CNS	Advocate	Sedendtary (s)	A	N	N	SINUS BRADYCARDIA,TWAVE INVERSION IN 1,AVL,V5,V6	Hypokinesia of anterolateral wall with ef 60%	Small acute infarct in pons	NORMAL	Grade 1 hypertensive retinopathy	N	N	26
Krishna	774608	46	211	220	110	CNS	Farmer	Modearte work	-	N	N	LVH	Normal	Ct intra parenchymal hemorrhage with mass effect & midline shift of 0.7 mm	NORMAL	Grade 2 hypertensive retinopathy	N	N	New onset htn
Pandurang	773989	50	212	180	100	CNS	Clerk	Sedendtary (s)	-	N	N	LVH	Normal	Hypertensive bleed in right putamen and posterior limb of internal capsule	NORMAL	Grade 2 hypertensive retinopathy	N	N	<10 years

Basangouda	771616	58	213	190	110	CNS	Engineer	Sedendtary (s)	-	N	N	NORMAL	Normal	Rt mca territory infarct	HTGS	Grade 3 hypertensive retinopathy	N	N	25
Chidanand 55	775491	53	214	170	100	CNS	Bank manager	Sedendtary (s)	-	N	E2m3v2,drowsy ,eoms restricted	SINUS TACHYCARDIA, LEFT AXIS DEVIATION	Concentric lvh,ef60%	Rt mca territory infarct	NORMAL	Grade 2 hypertensive retinopathy	N	N	<10 years
Pradeep	774498	55	215	160	90	CNS	Lecturer	Sedendtary (s)	-	N	Gcs 15, no lateralising deficits	NORMAL	Concentric lvh,ef60%	Age related cerebral and cerebellar atrophy	NORMAL	Grade 2 hypertensive retinopathy	N	N	11
Prakash	3105337	35	216	200	100	CNS	Private business	Modearte work	-	N	E4m5v4,eoms full, non fluent aphasia ,right dense hemiplegia,rt umn facial palsy	NORMAL	Normal	Left ganglio capsular bleed with midlineshift and mass effect	NORMAL	Normal	N	N	New onset htn
Siddram	3022279	37	217	124	90	CNS	Advocate	Sedendtary (s)	A,S,T	N	Gcs 15, no lateralising deficits, b/l limb and gait ataxia	NORMAL	Normal	Bilateral acute cerebellar infarcts	NORMAL	Normal	N	N	12
Manju	41378191	56	218	220	110	CNS	Tailor	Sedendtary (s)	-	N	Rt dense hemiplegia,rt umn facial palsy	NORMAL	Normal	Left mca infarct	NORMAL	Grade 1 hypertensive retinopathy	N	N	<10 years
Nagappa	774421	40	219	180	110	CNS	Ex-service man	Sedendtary (s)	-	N	Left hemiparesis	NORMAL	Normal	Right cerebellar infarct	NORMAL	Normal	N	N	26
Krishna	774233	52	220	150	100	CNS	Lecturer	Sedendtary (s)	-	N	Right ataxic hemiparesis	ANTERIOR WALL ISCHEMIA	Concentric lvh,ef60%	-	NORMAL	Grade 2 hypertensive retinopathy	N	N	22
Bharat	767473	55	221	140	90	CNS	Farmer	Modearte work	-	N	N	SINUS TACHYCARDIA	Normal	Right intracerebral bleed	NORMAL	Normal	N	N	22
Annasab	77963	56	222	190	110	CNS	Retd. Bank manager	Sedendtary (s)	-	N	Left ataxic hemiparesis	RBBB	Rbbb,trivial tr/ar	-	NORMAL	Grade 2 hypertensive retinopathy	N	N	1
Prakash	765926	53	223	120	70	CVS	Retd. Police service	Sedendtary (s)	-	N	N	ACUTE AWMI	Hypokinesia of anterior wall ef 60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	<10 years
Ravindra	765753	47	224	120	70	CVS	Bank manager	Sedendtary (s)	-	N	N	ACUTE AWMI	Hypokinesia of anterior wall ef 60%	-	NORMAL	Grade 2 hypertensive retinopathy	N	N	12
Sunil	765938	43	225	150	90	CVS	Private business	Sedendtary (s)	-	N	N	NORMAL	Normal	-	NORMAL	Normal	N	N	15
Motichand	766589	65	226	100	70	CVS	Private business	Sedendtary (s)	-	N	N	ACUTE AWMI	Hypokinesia of anterior wall ef 60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	12
Kempegoouda	766365	58	227	220	70	CVS	Advocate	Sedendtary (s)	-	N	N	ACUTE IWMI	Hypokinesia of inferior wall ef 60%	Large intracerebral bleed with midline shift and mass effect	NORMAL	Normal	N	N	24
Nayim	779157	35	228	220	100	CNS	Private business	Sedendtary (s)	S	N	Left dense hemiplegia	NORMAL	Normal	Subacute infarct in left thalamus and cortical sulci of parietooccipital region	NORMAL	Grade 3 hypertensive retinopathy	N	N	<10 years
Tukaram	781006	57	229	130	70	CNS	Police	Heavy work	T	N	Rt fasciobrachial palsy	NORMAL	Normal	Subacute infarct in vertebrobasilar territory	HYPERTRIGLYCERIDEMIA	Grade 1 hypertensive retinopathy	N	N	25
Ganesh	775009	32	230	180	90	CNS	Private business	Sedendtary (s)	S	N	B/l nystagmus, left ptosis, gcs 15,truncal gait ataxia , rt umn facial palsy	SINUS TACHYCARDIA	Normal	Left high parietal venous infarct withleft parietal cortical vein and sagittal sinus thrombosis	NORMAL	Normal	N	N	11
Vadiraj	773818	60	231	170	100	CNS	Driver	Sedendtary (s)	A,S,T	N	Rt hemiparesis	LVH	Concentric lvh,ef60%	Gliosis due to old vascular infarct rt mca territory & hypertensive ischemic changes	NORMAL	Grade 3 hypertensive retinopathy	N	N	21
Jyaneshwar	774116	39	232	190	90	CNS	Sales executive	Sedendtary (s)	S	N	Gcs 15,no lateralsing deficits	NORMAL	Ihd, akinesisa of inferior wall with ef 60%	Subacute infarct left mca-pca watershed areas with haemorrhagic transformation	HYPERCHOLESTEROLEMIA	Normal	N	N	12
Dundappa	771832	45	233	132	80	CNS	Police	Heavy work	A,S,T	N	Rt hemiparesis, rt umn facial palsy, dysarthria	SINUS TACHYCARDIA	Normal	Right mca infarct	NORMAL	Normal	N	N	22
Umesh	775694	52	234	120	70	CNS	Ex-service man	Sedendtary (s)	A,S,T	N	E4m5v1, expressive aphasia	LVH	Concentric lvh,ef60%	Left mca , mca pca territory infarct	NORMAL	Grade 1 hypertensive retinopathy	N	N	16
Madhu	780602	27	235	180	70	CNS	Daily waged labourer	Modearte work	A,S,T	N	Rt dense hemiplegia,rt umn facial palsy,severe expressive aphasia	NORMAL	Normal	Subacute infarct left mca territory	NORMAL	Normal	N	N	24
Nagesh	775165	39	236	180	100	CNS	Private business	Sedendtary (s)	T	N	Dysarthria,left gaze preference,rt hemiparesis, rt umn fascial palsy	NORMAL	Normal	Right periventricular subependymal bleed with intraventricular extension	NORMAL	Normal	N	N	12
Shaik md	768403	64	237	190	110	CNS	Daily waged labourer	Modearte work	A	N	Left hemiparesis, left umn fascial palsy	LEFT AXIS DEVIATION	Normal	Gliosis due to old vascular insult rt mca territory & hypertensive ischemic changes	NORMAL	Grade 1 hypertensive retinopathy	N	N	21
Ganapat	774526	58	238	160	100	CNS	Daily waged labourer	Modearte work	A,S,T	N	E2v2m6, rt hemiparesis	NORMAL	Normal	-	NORMAL	Grade 3 hypertensive retinopathy	N	N	<10 years
Yallapa	766491	48	239	130	80	CVS	Farmer	Modearte work	A	N	N	OLD IWMI	Global hypokinesia of anterior wall ef 60%,trivial mr,grade 1 mr	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	23
Rudrappa	768235	54	240	160	100	CVS	Farmer	Modearte work	A	N	N	EVOLVED IWMI	Akinesia of inferior wall with severe lv dysfunction & ef-60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	27
Venkappa	766894	45	241	210	70	-	Private business	Sedendtary (s)	S	N	N	NORMAL	Normal	-	NORMAL	Normal	N	N	<10 years
Bhimappa	782635	40	242	180	90	CVS	Private business	Sedendtary (s)	A,S,T	N	N	NORMAL	Normal	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	22

Irranna	766366	64	243	160	100	-	Private business	Sedendtary (s)	T	N	N	NORMAL	-	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	<10 years
Ravi desnur	4123302	45	244	140	90	-	Farmer	Modearte work	A	N	N	NORMAL	Normal	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	New onset htn
Jayant	4043568	60	245	122	80	-	Private business	Sedendtary (s)	S	N	N	NORMAL	Normal	-	NORMAL	Normal	N	N	21
Ashok	3456789	44	246	220	84	-	Advocate	Sedendtary (s)	T	N	N	NORMAL	Normal	-	NORMAL	Normal	N	N	22
Deepak	2567389	53	247	160	80	-	Doctor	Sedendtary (s)	A	N	N	NORMAL	-	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	<10 years
Gurulingappa	4252678	52	248	170	100	-	Private business	Sedendtary (s)	T	N	N	NORMAL	-	-	HCHOL	Grade 1 hypertensive retinopathy	N	N	26
Ishwar	4567801	58	249	140	80	-	Farmer	Modearte work	T	N	N	-	-	Normal	HCHOL	Grade 1 hypertensive retinopathy	N	N	24
Gurudas	4234579	54	250	190	100	-	Private business	Sedendtary (s)	A	N	N	LVH	Concentric lvh,ef60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	<10 years
Kumar	4345238	42	251	220	100	-	Saint	Sedendtary (s)	A	N	N	NORMAL	-	-	NORMAL	Normal	N	N	23
Babu	3578908	39	252	210	100	-	Lecturer	Sedendtary (s)	A	N	N	-	-	-	HCHOL	Normal	N	N	<10 years
Basavraj	3456356	56	253	140	90	-	Bank manager	Sedendtary (s)	T	N	N	LVH	Concentric lvh,ef60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	24
Hanamanth	4563378	60	254	140	90	-	Daily waged labourer	Modearte work	A	N	N	NORMAL	Normal	-	HCHOL	Normal	N	N	27
Hanif	4567889	38	255	150	90	-	Private business	Sedendtary (s)	T	N	N	LVH	Concentric lvh,ef60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	New onset htn
Santosh	4567893	40	256	160	90	-	Sales executive	Sedendtary (s)	T	N	N	LVH	Concentric lvh,ef60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	22
Deepak	3876549	53	257	170	100	-	Hotel manager	Sedendtary (s)	A,S,T	N	N	LVH	Normal	Normal	NORMAL	Normal	N	N	21
Virupaxappa	4256781	46	258	208	90	-	Private business	Sedendtary (s)	A,S,T	N	N	NORMAL	Normal	Normal	NORMAL	Normal	N	N	21
Ajit	4533678	59	259	170	100	CVS	Private business	Sedendtary (s)	T	N	N	AWMI	Hypokinesia of anterior wall with ef =60%	-	NORMAL	Grade 1 hypertensive retinopathy	N	N	25
Gajanan	3546478	37	260	190	100	CNS	Daily waged labourer	Modearte work	T	N	Gcs 15, dysartria,rt umn facial palsy with trunkal & gait ataxia	NORMAL	Normal	Subacute infarct in the vertebra basilar territory. B/l cerebellar lobe & vermis infarct diffuse cerebellar edema .	NORMAL	Grade 1 hypertensive retinopathy	N	N	24
Nagappa	2342567	40	261	180	110		Farmer	Modearte work	S	N	N	LVH	Concentric lvh,ef60%	Normal	HCHOL	Grade 1 hypertensive retinopathy	N	N	22
Basavantappa	776477	58	262	160	90	-	Farmer	Moderate work	T	N	N	NORMAL	Concentric lvh,ef60%	-	HCHOL	Grade 1 hypertensive retinopathy	N	N	24

ANNEXURE-IV

KEY TO MASTER CHART

ng	-	Nanogram
ng/dl	-	Nanogram Per Decilitre
mmHg	-	Millimeters Of Mercury
HTN	-	Hypertension
BP	-	Blood Pressure
SBP		Systolic Blood Pressure
DBP	-	Diastolic Blood Pressure
CVA	-	Cerebrovascular Accident
CV	-	Cardiovascular
CVS	-	Cardiovascualr Sysytem
CNS	-	Central Nervous System
ECG	-	Electro Cardiogram
2D ECHO	-	2 Dimensional Echocardiography
CT	-	Computed Tomography
MRI	-	Magnetic Resonance Imaging
IHD	-	Ischemic Heart Disease
EF	-	Ejection Fraction
AWMI	-	Anterior wall myoardial infarction
IWMI	-	Inferior wall myoardial infarction