SERUM LEPTIN LEVEL AND ITS ASSOCIATION WITH BLOOD PRESSURE, BODY MASS INDEX, WAIST HIP RATIO AND WAIST HEIGHT RATIO

Dissertation submitted to

THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY

CHENNAI – 600032

In partial fulfilment of the requirement for the degree of

Doctor of Medicine in Physiology (Branch V)

M.D. (PHYSIOLOGY)

APRIL 2015

DEPARTMENT OF PHYSIOLOGY

COIMBATORE MEDICAL COLLEGE

COIMBATORE – 14.

CERTIFICATE

This dissertation entitled **"SERUM LEPTIN LEVEL AND ITS ASSOCIATION WITH BLOOD PRESSURE, BODY MASS INDEX, WAIST HIP RATIO AND WAIST HEIGHT RATIO"** is submitted to The Tamil Nadu Dr. M.G.R Medical University, Chennai, in partial fulfilment of regulations for the award of M.D. Degree in Physiology in the examinations to be held during April 2015.

This dissertation is a record of fresh work done by the candidate **Dr. G.MALARVIZHI ,** during the course of the study (2012-2015).

This work was carried out by the candidate herself under my supervision.

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I, **Dr. G. MALARVIZHI** solemnly declare that the dissertation entitled **"SERUM LEPTIN LEVEL AND ITS ASSOCIATION WITH BLOOD PRESSURE, BODY MASS INDEX, WAIST HIP RATIO AND WAIST HEIGHT RATIO"** was done by me at Coimbatore Medical College, during the period from August 2013 to March 2014 under the guidance and supervision of **Dr. R.Shanmughavadivu M.D** Professor, Department of Physiology, Coimbatore Medical College, Coimbatore.

This dissertation is submitted to The Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of the requirement for the award of M.D. Degree (Branch - V) in Physiology. I have not submitted this dissertation on any previous occasion to any University for the award of any degree.

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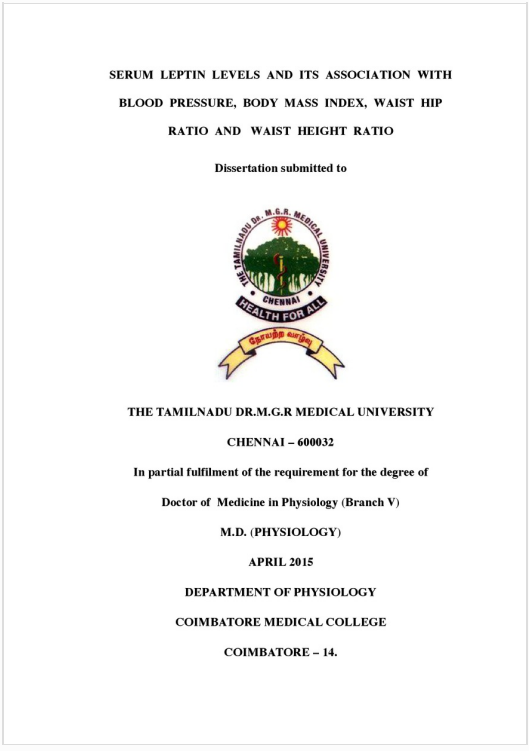

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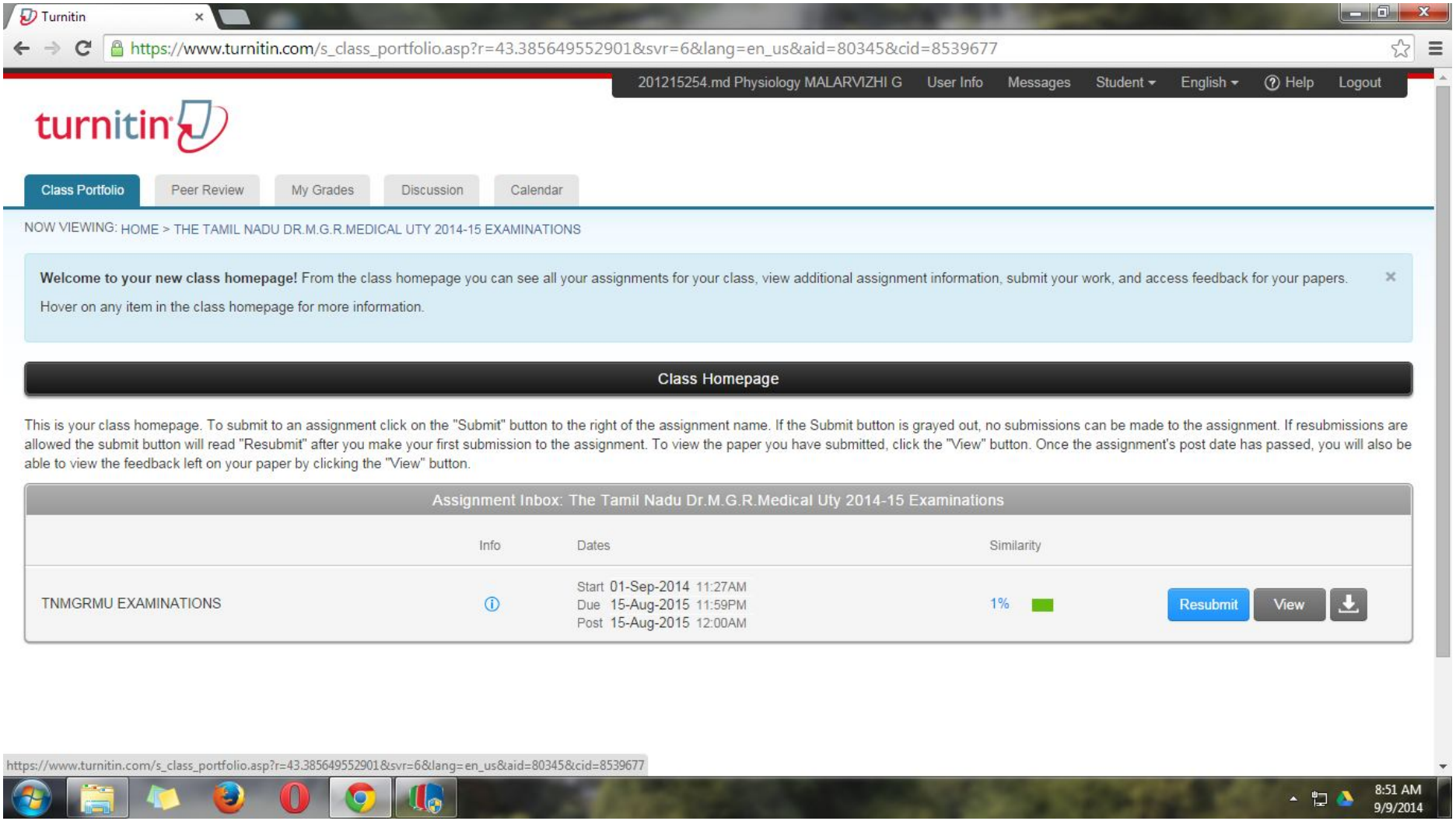
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SERUM LEPTIN LEVEL AND ITS ASSOCIATION WITH BLOOD PRESSURE, BODY MASS INDEX, WAIST HIP RATIO AND WAIST HEIGHT RATIO

CONTENTS

ABBREVIATIONS USED IN THE STUDY

- BMI — BODY MASS INDEX
- DALY — DAILY ADJUSTED LIFE YEAR
- KDa MW — KILO DALDON MOLECULAR WEIGHT
- BP — BLOOD PRESSURE
- KPa — KILO PASCAL
- GFR — GLOMERULAR FILTRATION RATE
- BUN — BLOOD UREA NITROGEN
- NaCl — SODIUM CHLORIDE
- WHO — WORLD HEALTH ORGANISATION
- DEXA — DUAL ENERGY X - RAY ABSORPTIOMETRY
- ABPM — AMBULATORY BLOOD PRESSURE MONITORING
- WHR — WAIST HIP RATIO
- WHtR — WAIST HEIGHT RATIO
- WHHR — WAIST HIP HEIGHT RATIO
- UCP — UNCOUPLING PROTEIN
- PET — POSITRON EMISSION TOMOGRAPHY
- SREBP — STEROL REGULATORY ELEMENT BINDING PROTEIN

- JAK – STAT JANUS KINUS – SIGNAL TRANSDUCER AND ACTIVATOR OF TRANSCRIPTION
- POMC PRO OPIO MELANOCORTIN
- NP Y NEUROPEPTIDE Y
- AgRP AGOUTI – RELATED PROTEIN
- MSH MELANOCYTE STIMULATING HORMONE
- AMPK ADENOSINE MONOPHOSPHATE KINASE
- ATP ADENOSINE TRIPHOSPHATE
- fMRI FUNCTIONAL MAGNETIC RESONANCE IMAGING
- CNS CENTRAL NERVOUS SYSTEM
- HIV HUMAN IMMUNO DEFICIENCY VIRUS
- NO NITRIC OXIDE
- CSF CEREBROSPINAL FLUID
- SOCS SUPPRESSORS OF CYTOKINE SIGNALLING
- PTP PROTEIN TYROSINE PHOSPHATASE
- SBP SYSTOLIC BLOOD PRESSURE
- DBP DIASTOLIC BLOOD PRESSURE
- AMI ACUTE MYOCARDIAL INFARCTION
- JNC JOINT NATIONAL COMMITTEE
- HDL HIGH DENSITY LIPOPROTEIN

SERUM LEPTIN LEVEL AND ITS ASSOCIATION WITH BLOOD PRESSURE, BODY MASS INDEX, WAIST HIP RATIO AND WAIST HEIGHT RATIO

Abstract:

Background: Leptin is a product of Ob gene secreted from adipose tissue. It is a key neuroendocrine hormone regulating food intake, metabolism, and fat accumulation, and it may also affect blood pressure and contribute to hypertension through sympathetic activation in the vasculature or at the renal level. Hyperleptinemia also seen in obesity, which is a major comorbid condition of hypertension. **Aim** : To study the relationship between serum leptin level and Blood pressure in association with Age, Gender, Body mass index, Waist hip ratio and Waist height ratio. **Materials and methods:** Study group : 48 hypertensive patients (26 males, 22 females) in the age group of 35-75 years. Control group include 42 normotensive persons (22 males, 20 females) in the same age group. After recording the history, clinical examination and blood pressure, weight (in Kg), height (in cms) waist circumference (in cms) and hip circumference (in cms) were measured. BMI, waist hip ratio and waist height ratio were calculated. Blood sample was collected under strict aseptic precaution after overnight fasting and then centrifuged to collect the serum. Serum leptin level was estimated by using KAP 2281 Human leptin ELISA kit. The values were statistically analyzed by chi square tests and student 't' test. **Result :** In the present study, serum leptin level was significantly increased with the p value of < 0.0001 in hypertensive patients (8.15 ± 2.68) when compared to normotensive persons (1.74 ± 1.04). And also it was found that serum leptin level positively correlated with systolic blood pressure ($P < 0.0268$**)**, age **(**$P< 0.0001$), BMI ($P <0.0467$), waist hip ratio ($P<0.0001$) and waist height ratio ($P <0.0001$). **Conclusion:** From this study it was concluded that, there is a strong positive correlation between serum leptin level and high blood pressure, age, body mass index, waist hip ratio and waist height ratio.

Key words: leptin, blood pressure, body mass index, waist hip ratio, waist height ratio.

INTRODUCTION

“Healthy citizens are the greatest asset any country can have” - A popular Quote by Winston Churchill explains the importance of health. But health is not merely an absence of disease. Nowadays we live in a rapidly changing environment and the human health is constantly challenged by factors like Demographic aging, Urbanization, and Globalization of unhealthy lifestyles. They contribute to sharp rise in prevalence of chronic diseases like hypertension, diabetes mellitus, cardiovascular diseases, cancer etc. These pathologies constitute a heavy social and economic burden because they directly contribute to the loss of DALY (Disability adjusted life years) for citizens and represent considerable healthcare expenditure for society. With longer life expectancy we need to improve our quality of life also.

Hypertension, one among the chronic diseases also called a silent killer has more impact on acute social and economic effects on population. Affecting 1 billion people worldwide, Hypertension remains the most common, readily identifiable, treatable and preventable risk factor for Heart disease and stroke. Currently high blood pressure causes about 54% of stroke, 47% of Ischemic

Heart Disease worldwide[1]. There is continuous relationship between blood pressure and its complications from values as low as 115/75 mm Hg. The relationship is steeper for stroke than for Coronary artery disease. The mortality doubles with every 20/10 mm Hg rise in blood pressure[2].

Thus high blood pressure remains the number one attributable risk factor for death throughout the world[3]. Its global burden is rising and projected to affect 1.5 billion people - 1/3 of world's population by the year 2025. Nearly half of this burden is with hypertensives and half lies in prehypertensives[1].

So hypertension becomes one of the world's greatest public health problems. Inherent variability in blood pressure and asymptomatic nature of the disease can delay diagnosis and treatment[4]. So it demands to establish simple and better diagnostic tools to detect the condition well before the rise in blood pressure.

The etiology of hypertension is multifactorial. The most important predictors are behavioural determinants like dietary consumption of calories and salt, stress, lack of physical activity[4]. Among them, obesity gains more importance because of changing lifestyle and

sedentary habits. It has become a growing epidemic, the world is facing today.

Not to be surprised that most of the health problems are related to our ever expanding waistlines. The reasons for the increased morbidity and mortality due to excess body weight are high blood pressure, dyslipidemia, glucose intolerance, and development of metabolic syndrome[5].

The INTERSALT study involving more than 10000 men and women reported that a 10 kg increase in weight was associated with a 3 mmHg rise in systolic blood pressure and 2.3 mmHg rise in diastolic blood pressure[6]. In obese individuals the development of complication is highly correlated with intra abdominal fat (visceral) than with peripheral (subcutaneous) fat[6]. So the BMI, most widely used indicator of weight status could not be a much useful one anymore[7].

In recent years many cross sectional and prospective studies have shown that the most precise indices like Waist hip ratio and Waist height ratio are needed to be focused more than BMI. In one such study of systemic review and meta analysis of data on more than 300,000 individuals from diverse populations across the world,

it has been proven that measures of abdominal obesity provide superior tools for discriminating obesity related cardiometabolic risk compared with BMI[8].

After the discovery of leptin, a neuroendocrine hormone, the concept of obesity has completely changed. Leptin is a peptide hormone of 16 KDa MW, having 167 aminoacids[9]. It is a product of Ob gene secreted by adipose tissue[10]. Its main function is regulation of food intake, metabolism, fat accumulation by acting on its receptors in hypothalamus. It also influences autonomic, cardiovascular, renal and endocrine functions[11].

Leptin, the name was derived from a Greek word called leptos meaning thin[12]. Since it acts as an appetite suppressant and prevents excessive weight gain, its deficiency leads to hyperphagia and obesity[13]. So it plays a key role in regulating energy intake and expenditure, including appetite and hunger, metabolism and behaviour.

In contradictory to this, obesity is associated with elevated plasma leptin levels. Here the elevated leptin levels are not sufficient to prevent dysregulation of energy balance, suggesting that obese people are leptin resistant. The mechanisms of leptin resistance is

still not known. This resistance is only to the energy regulating action of leptin in the hypothalamus. So it is called selective resistance[10] which means the other peripheral actions of leptin are preserved.

The peripheral actions of leptin include widespread activation of sympathetic nervous system, sodium retention by kidneys and activation of Renin angiotensin system. All these actions of leptin contribute to the development of hypertension[14]. So hyperleptinemia causes hypertension resulting in increased cardiovascular complications in normal weight as well as obese individuals.

Anoop Shankar and Jie xiao in their study observed a positive association between plasma leptin levels and hypertension was observed and this association existed both in normal weight and overweight / obese individuals[15].

In a cross sectional study done by Costas thomopoulos and his colleagues, they have found that increased plasma leptin is independent of confounders, including body size and metabolic parameters[14]. In another study also, done by Kawaljit Kaur Khokhar and colleagues, both normal weight and obese, hypertensive

Pre menopausal women showed significantly higher leptin levels than their normotensive counterparts[16].

So the pathophysiological role of leptin in the development of hypertension might be implicated on the adverse hemodynamic regulation beyond the centrally, obesity - mediated mechanisms of leptin resistance[14]. Thus it affects the blood pressure and contributes to the development of hypertension by not only acting on energy expenditure but also through sympathetic activation in the vasculature and at the renal level.

So this study mainly concentrates on association between Serum leptin levels and blood pressure and also its association with BMI, Waist hip ratio and Waist height ratio.

AIMS & OBJECTIVES

AIM :

To study the relationship between serum leptin level and Blood pressure in association with Age, Gender, Body mass index, Waist hip ratio and Waist height ratio.

OBJECTIVES :

1. To compare Serum leptin level and Blood pressure.
2. To correlate Serum leptin level and Blood pressure with Age, Gender, Body mass index, Waist hip ratio and Waist height ratio.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

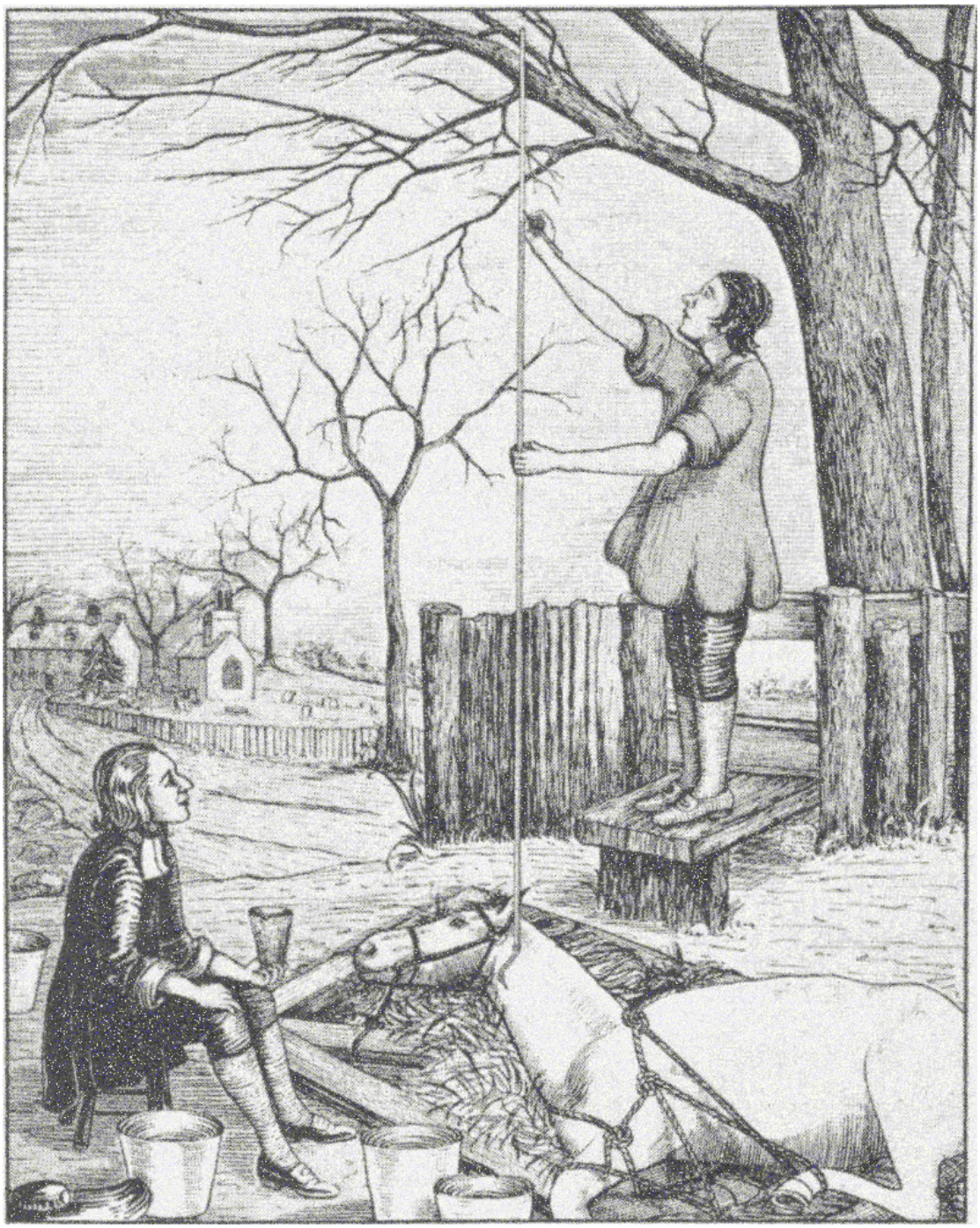
Blood pressure is defined as the force exerted by the blood against any unit area of the vessel wall. It is usually measured in millimetres of mercury (mm Hg)[17]. Blood pressure unless otherwise specified, refers to the systemic arterial pressure.

This pressure is not constant throughout the cardiac cycle, the highest pressure achieved during systole is systolic pressure and is about 120 mm Hg , while the lowest pressure occurs in diastole is diastolic pressure which is about 80 mm Hg.

Blood pressure is conventionally written as systolic pressure over diastolic pressure 120/80 mm Hg. One millimetre of mercury equals 0.133 KPa, so in SI units this value is 16.0 / 9.3 KPa[18].

The mean pressure is the average pressure throughout the cardiac cycle. Because the duration of diastole is longer than systole, it is not the simple average but is calculated as the diastolic pressure + 1/3 of pulse pressure. The difference between systolic and diastolic blood pressure is called pulse pressure and is about 40 mm Hg[18].

HISTORY



Measurement of blood pressure:

The first blood pressure measurement was done by Rev. Stephen Hales, an English clergy man in 1733 in the femoral artery of a horse. He introduced a brass cannula into the animal's artery and it was connected to a long glass tube by the trachea of a goose[19].

In 1828, Poiseuille devised the mercury manometer when he was a medical student. Since the density of mercury is 13.6 times that of water it is used to reduce the length of the glass tube[20].

In 1847, German physician Carl Ludwig invented the kymograph and obtained the graphic tracings of blood pressure[20]. In 1896, Sciopine Riva- Rocci devised the modern sphygmomanometer to measure the human blood pressure[19].

In 1905, Russian physician Nikolai Koratkoff found that blood jetting through the partly occluded vessel causes turbulence in the vessel, this sets up the vibrations heard through the stethoscope and the sounds are called Koratkoff sounds. He described that appearance and disappearance of the sound indicate systolic and diastolic pressure[17].

Blood pressure can be measured either directly or indirectly. In direct method, blood pressure is measured by introducing a wide bore needle into an artery and connecting it to transducers and oscilloscope for recording the pressure. But this is rarely done nowadays.

Clinically indirect method is used for the sake of convenience. The principle behind this indirect method is, balancing air pressure against the blood pressure in brachial artery and then estimating the air pressure by means of a mercury or aneroid manometer or a digital blood pressure recording device[21].

There are three methods:

1. Palpatory method
2. Auscultatory method
3. Oscillatory method

In palpatory method the patient should be in comfortable, relaxed, sitting posture. The sphygmomanometer is placed at the heart level and the cuff is wrapped around the upper arm about 3-4 inches above the elbow and fixed in position by a Velcro attachment. Then the radial pulse is felt and the cuff is inflated with the help of the pump. Systolic pressure is indicated by the disappearance of

the pulse. The diastolic pressure cannot be measured by this method. This method is usually done before auscultatory method to get an idea about systolic pressure.

In auscultatory method, the diaphragm of the stethoscope is placed over the region of the brachial artery at the elbow. The cuff is inflated 20 – 30mm of Hg above the level of the systolic pressure which is obtained by the palpatory method. The pressure is now slowly reduced. As the mercury is falling, a clear tapping sound is heard which indicates systolic pressure. Then the sound becomes murmurish followed by a clear loud sound and then muffles and finally disappears. The disappearance indicates the diastolic pressure.

In oscillometric method, when the cuff is inflated, the appearance of the oscillations indicate systolic blood pressure, the disappearance of oscillations indicate diastolic pressure[22].

Physiological variations of blood pressure[21]:

Systolic pressure is liable to variation due to excitement, emotion, exertion etc. Hence, when it is first checked in the doctors clinic it may be little higher than the patient's usual pressure. This high systolic blood pressure observed in some tense patients is called white coat hypertension. The diastolic blood pressure is more stable

and doesn't vary much and is considered to be clinically more significant one.

1. Age :

Systolic pressure (mm Hg)	age
40	Immediately after birth
70	1 month
90	4 – 5 years
110- 120	adult
140 - 150	Mid 50
160	After 70 years

2. Sex : In females before menopause 3 – 5 mm lesser than males due to estrogen. After menopause increase in systolic blood pressure is more in women.
3. In emotional excitement, anger, fear, worry systolic pressure is increased due to impulses from higher centres and release of adrenalin.
4. Posture : Blood pressure is higher in standing position than in sitting posture and is lowest in supine posture.

5. Gravity: With the heart as the reference point, the blood pressure values increase towards the feet but decrease towards the head. For every one cm, the rise or fall is by 0.77 mm Hg.
6. Digestion: There is slight rise in systolic pressure (5-8 mm Hg) after a meal lasting for about an hour.
7. Sleep: Pressure is reduced by about 10- 20 mm Hg during sleep.
8. Exercise: Systolic blood pressure increases up to 180 mm Hg due to increase in stroke volume. In mild and moderate exercises there is no change in diastolic blood pressure whereas in severe exercise it actually falls because of vasodilatation.
9. Diurnal variation : Fluctuations in blood pressure occurs due to circadian rhythm. Pressure is highest in afternoon.
10. Surface area : Blood pressure is directly proportional to the surface area. So blood pressure is more in obese people.
11. Respiration: Blood pressure falls during inspiration and raises during expiration.

Factors affecting blood pressure[23]:

Arterial blood pressure is maintained by five important factors.

1. Cardiac output
2. Peripheral resistance
3. Elasticity of the arterial wall
4. Blood volume
5. Volume of the vascular space

Simply blood pressure = Cardiac output x Peripheral resistance

As cardiac output is the product of stroke volume and heart rate, the factors which affect these two will affect the cardiac output. The stroke volume is affected by preload, afterload and myocardial contractility. Heart rate is mainly affected by autonomic influences.

Blood pressure is directly proportional to peripheral resistance. The resistance mainly depends upon the diameter of the blood vessel, viscosity of the blood and velocity of the blood flow. Peripheral resistance mainly influences the diastolic pressure more than systolic pressure.

Elasticity of arterial wall is responsible for the origin and maintenance of diastolic pressure. The elastic recoiling property of the arterioles is responsible for the conversion of intermittent blood flow into an continuous one.

Increase in blood volume raises both systolic and diastolic pressure, whereas a reduction in blood volume decreases the blood pressure. Vasodilatation causes reduced blood pressure and vasoconstriction causes elevated blood pressure.

Regulation of blood pressure [23] :

Blood pressure is not controlled by a single mechanism but regulated by numerous interrelated mechanisms. They can be broadly divided into three categories. They are short term, intermediate and long term regulation.

A. Short term regulation:

a. Neural : Regulates blood pressure within seconds or minutes. Autonomic nervous system plays an important role in short term regulation.

Baroreceptor reflex : Whenever there is an increase in blood pressure, baroreceptors present in carotid sinus and aortic arch are stimulated, send their impulses via sinus nerve to nucleus tractus

solitarious. This in turn inhibits the vasomotor centre and stimulates cardio inhibitory centre. Vagal tone increases, sympathetic tone decreases. This leads to vasodilation, decreased cardiac output, decreased heart rate and thereby decrease in blood pressure.

This baroreceptor mechanism is highly adaptable. Working range of blood pressure for this mechanism is 60-160 mm Hg. In hypertension, this mechanism is reset at a higher level to maintain pressure at elevated levels.

b. Chemoreceptor reflex: Chemoreceptors present in carotid body and aortic body will respond to hypoxia, hypercapnia and acidosis. When blood pressure falls below 60 mm Hg, chemoreceptors are stimulated, impulses reach the vasomotor centre via the respiratory centre resulting in an increase in heart rate and blood pressure.

c. Cushing's reflex: Fall in blood pressure below 40 mm Hg results in ischemia of central nervous system. This stimulates the vasomotor centre directly resulting in rise in blood pressure. So the blood flow is restored and ischemia is relieved. This powerful short lived response is also called "last ditch effort."

B. Intermediate term regulation:

a. Stress relaxation: Whenever vascular smooth muscle is stretched for prolonged period as a result of increased blood pressure it goes for relaxation and causes reduction in blood pressure. Reverse changes takes place when blood pressure falls. It is known as reverse stress relaxation.

b. Capillary fluid shift mechanism: Increase in blood pressure causes more fluid filtration through the capillary wall into the interstitial space.

c. Tissue fluid shift mechanism : Reduction in blood volume results in fall in blood pressure. In that situation, fluid enters from tissue space into capillary to raise the blood volume and blood pressure.

C. Long term regulation:

1. Hormonal mechanism [24] :

a. Catecholamines: Nor epinephrine is a potent vasoconstrictor, so it causes increase in both systolic as well as diastolic blood pressure. Epinephrine : it mainly acts on heart. Net effect is rise in systolic blood pressure. There is no change in diastolic blood

pressure. Both these hormones influence blood pressure in physiological as well as stressful conditions.

b. Glucocorticoids : Through the permissive action, they sensitise the vascular smooth muscle to the action of catecholamines. They retain sodium, chloride and water by stimulating their reabsorption from distal nephron.

c. Mineralocorticoids: Aldosterone retains sodium, chloride and water by stimulating their reabsorption from kidney thereby increasing the blood volume and blood pressure.

d. Thyroid hormones: They regulate blood pressure by acting on the metabolism and also by potentiating the action of catecholamines.

e. Angiotensin II: It is a potent vasoconstrictor that increases the blood pressure.

f. Vasopressin : By increasing the volume of blood, it increases the blood pressure. It is also a powerful vasoconstrictor.

g. Serotonin, Endothelin: Both are vasoconstrictors thereby increase the blood pressure.

h. Histamine, Endothelium derived relaxing factor: Both are vasodilators cause fall in blood pressure.

i. Atrial natriuretic peptide: Acts on proximal convoluted tubule and prevents absorption of sodium and water thereby reduces blood volume and blood pressure.

Kidney plays an important role in long term control of blood pressure by pressure natriuresis and pressure diuresis. It exerts its effect through Renin – Angiotensin – Aldosterone axis.

Thus blood pressure is effectively controlled by many factors. Any derangement in these mechanisms will result in sustained elevation of blood pressure which is called hypertension.

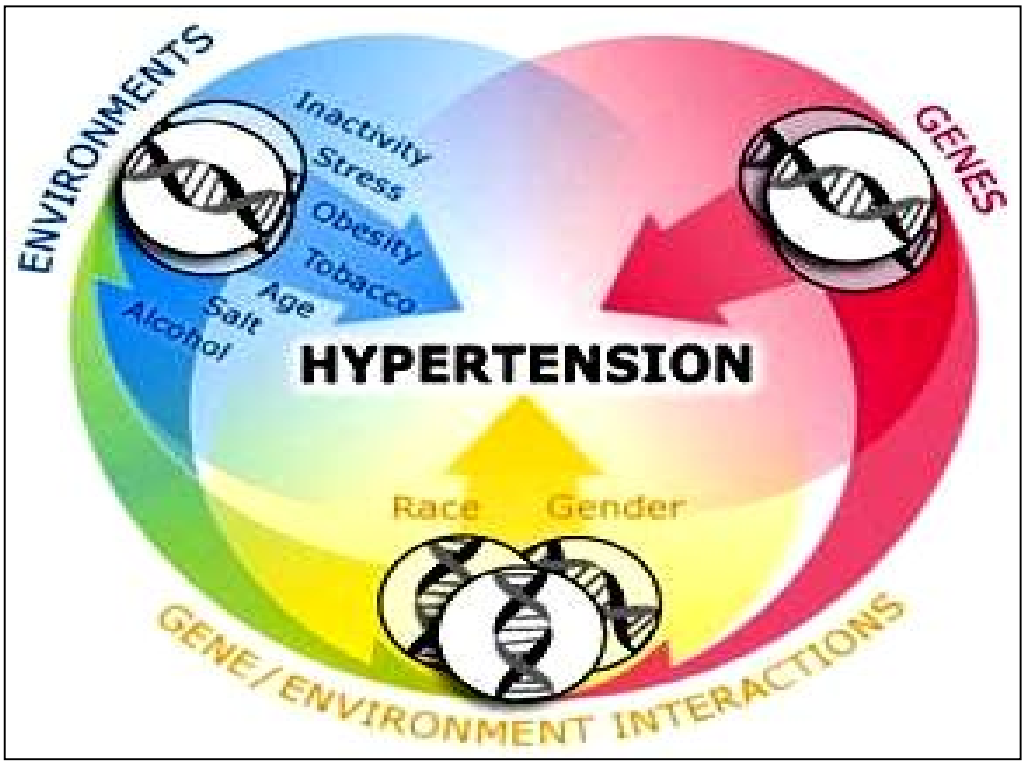
Hypertension is classified into 2 types,

1. Primary or essential hypertension: In which the cause for increase in blood pressure is not known. It constitutes about 90-95% 0f patients.

2. Secondary hypertension: In this type the increase in blood pressure is caused by diseases of kidney, endocrine or some other organs. It comprises 5-10 % of cases[25].

According to the clinical course, both essential and secondary hypertension may be benign or malignant. Benign hypertension is moderate elevation of blood pressure and the rise is slow over years. Malignant hypertension is marked and sudden increase of

ETIOLOGY OF HYPERTENSION



blood pressure to 200/140 mm Hg or more in a known hypertensive patient or in a previously normotensive individual[26].

Etiological factors:

Essential hypertension: (90 %)[26]

1. Genetic factors including Mendelian forms of hypertension

2. Racial and environmental factors: A number of environmental factors have been implicated in development of hypertension including salt intake, obesity, skilled occupation, higher living standards and individuals under high stress.

3. Risk factors modifying the course:

1. Age : Younger the age, lower the life expectancy.

2. Sex: Females with hypertension appear to do better than males.

3. Atherosclerosis: Factors associated with this, like cigarette smoking, elevated serum cholesterol, glucose intolerance, obesity and excess alcohol intake will influence hypertension.

Secondary hypertension: (10 %)[1]

1. Renal - Renovascular and Renal parenchymal disease.

2. Endocrinal – Adrenocortical hyperfunction including primary Aldosteronism, Cushing syndrome, Pheochromocytoma, Hyperparathyroidism, Hypothyroidism, Acromegaly.

3. Oral contraceptive pills and other medications.
4. Coarctation of aorta
5. Neurogenic causes
6. Obstructive sleep apnoea syndrome
7. Hypertension during pregnancy

Pathogenetic mechanisms behind the development of hypertension are explained by many theories. They suggest that increase in blood volume and Cardiac output, high plasma level of Catecholamines producing vasoconstriction, altered responsiveness to renin release and decreased adrenal response to Angiotensin II.

Risks influencing prognosis in patients with hypertension include systolic and diastolic blood pressure levels, age of the patient and associated comorbid conditions like diabetes mellitus, abdominal obesity, dyslipidemia, metabolic syndrome, smoking and alcohol.

Patients having chronic hypertension are more prone to develop target organ damage. Left ventricular hypertrophy, carotid wall thickening or plaque, reduced GFR, microalbuminuria, ankle brachial blood pressure index < 0.9 will be present subclinically in these patients.

Established target organ damages include[27],

Cerebrovascular accidents – stroke, cerebral haemorrhage, transient ischemic attacks.

Heart disease: Myocardial infarction, angina, congestive cardiac failure.

Renal disease: Chronic kidney disease

Peripheral arterial disease, hypertensive retinopathy, papilloedema.

The proposed mechanisms involved in the development of target organ damage are endothelial cell dysfunction and vascular remodelling. By decreasing lumen diameter in the peripheral vasculature, inward eutrophic remodelling increases systemic vascular resistance, the hemodynamic hallmark of diastolic hypertension.

Neural mechanisms are also involved. In young adults, primary hypertension is consistently associated with increased heart rate, cardiac output, plasma and urinary norepinephrine levels, regional norepinephrine spillover, peripheral postganglionic sympathetic nerve firing, α adrenergic receptor mediated vasoconstrictor tone in peripheral vasculature[28].

Initial evaluation of patients with hypertension[1]:

1. Measurement of blood pressure
2. Assessment of target organ damage
3. Detection of identifiable cause for secondary hypertension

Measurement of blood pressure includes home and ambulatory monitoring (ABPM). It provides automated measurements of blood pressure during a 24 hour period while patients are engaged in their usual activities and sleep. It helps to rule out white coat hypertension and masked hypertension. In masked hypertension, pressure recorded in the hospital is normal whereas blood pressure recorded during daily activities is increased because of job / home stress, tobacco use or other adrenergic stimulation that dissipates when they come to hospital.

Laboratory investigations include repeat measurements of renal function that is serum urea, creatinine, microalbuminuria, blood urea nitrogen (BUN), serum electrolytes, fasting glucose, and lipid profile, electrocardiogram have to be done immediately after diagnosis and after introducing a new antihypertensive agent and then annually[29].

Obesity related hypertension deserves special mention here. With weight gain, reflex sympathetic activation may be an important compensation to burn the fat but at the expense of sympathetic over activity in target tissue that produces hypertension[29].

Hypertensive patients with metabolic syndrome with or without diabetes mellitus have near maximal rates of sympathetic firing. The precise stimulus include leptin, other adipokines and angiotensin II[29]. So prevention and treatment of obesity are important for reducing blood pressure and cardiovascular disease risk.

Health – promoting lifestyle modifications are recommended for individuals with pre-hypertension and as an adjunct to drug therapy in hypertensive individuals. Dietary modifications that effectively lower blood pressure are weight loss, reduced NaCl intake, increased potassium intake, Diet rich in fruits, vegetables, and low– fat dairy products with reduced content of saturated and total fat, moderate alcohol consumption and an overall healthy dietary pattern and regular aerobic activity like brisk walking for 30 min / day[29].

OBESITY

Nutrition is an essential interaction of an organism with the environment. Nutrients apart from providing energy for survival, signal the organism in diverse ways and this in turn affects their use and storage[30].

Nutrition underpins health and affects susceptibility to disease. Both malnutrition and obesity put an organism at risk. The factors that determine nutritional status of an individual are the genetic background, the environment, the phase of life cycle, the levels of physical activity and the presence of disease[30].

Anything that leads to a continuous imbalance between food intake and energy consumption will lead to obesity (positive energy balance)[31]. Obesity represents a major medical problem in most of the developed and developing countries.

Worldwide, at least 2.8 million people die each year as a result of being overweight or obese, and an estimated 35.8 million (2.3%) of global DALYs (Disability adjusted life year) are caused by overweight or obesity. In high income countries women's obesity prevalence was similar to that of men. In low and lower middle

OBESITY RISKS

income countries, obesity among women was approximately double that among men[32].

Obesity is defined as a state of excess adipose tissue mass and is best viewed as a syndrome or group of diseases rather than as a single disease entity[33]. The importance of this state is that, its prevalence is increasing worldwide and it is associated with serious morbidity. However the pathogenesis of obesity in vast majority of humans is unknown and remains unexplained.

Obese people are more likely to develop a number of diseases including hypertension, diabetes mellitus, gall stones, cancer, non alcoholic fatty liver disease, obstructive sleep apnoea, osteoarthritis knee, and metabolic abnormalities[33,34].

Endocrine consequences of obesity are insulin resistance, diabetes mellitus, hypothyroidism, gonadal dysfunction, decreased pituitary hormone secretion (particularly growth hormone)[33]. It is not a single disorder but a common manifestation of wide variety of disorders that affect energy balance in some way. Their life span is significantly shortened.

Uncorrected obesity often leads to cardiac hypertrophy, reduced diastolic compliance, ventricular dysfunction, increased blood pressure, arteriosclerosis and other vascular complications[35]. In addition to that, it dramatically enhances the chances of cluster of metabolic diseases such as insulin resistance, hyperinsulinemia, diabetes mellitus, hyperlipidemia, hyperuricemia and low plasma high density lipoprotein cholesterol, collectively known as the metabolic syndrome[36].

Factors influencing obesity:

Environmental and genetic factors play a key role in obesity. Cultural factors relating to both availability and composition of the diet, changes in the level of physical activity both will have important impact on weight gain. In industrial societies, obesity is most common among poor women whereas in underdeveloped countries, wealthier women are more often obese[34].

The prevalence is high among women and children[34]. In children, obesity correlates to some degree with time spent on watching television. Obesity is promoted by high fat diets combined with diets rich in rapidly absorbed simple carbohydrates.

Sleep deprivation leads to increased obesity. Recent advances says that changes in gut microbiome with capacity to alter energy balance and a possible role for obesigenic viral infections continues to receive sporadic attention[34].

Initially the criteria used for assessing obesity is defined on purely statistical grounds as a weight that is 20% or more above the average weight per height[33]. Over the past decade, calculation of BMI has evolved as a more standard measurement used to correlate weight with morbidity and mortality.

BMI is the most important and widely used tool in the world for indicating fat levels in the human body[37], and it is officially recognised by the World Health Organisation. BMI is calculated by determining weight in kilogram and dividing it by the height in meters squared[38]. At a similar BMI, women have more body fat than men. According to this measurement body weight has been divided into four classes.

Classification of BMI:[34]

BODY MASS INDEX	CLASSES
<19	Underweight
19 - 25	Normal
26 - 30	Over weight / pre obese
>30	Obese
>40	Extreme obesity

A BMI of < 19 is considered underweight and carries a modestly increased risk of morbidity and mortality. Overweight category statistically carries a slightly increased risk of co morbidities such as diabetes mellitus and cardiovascular disease compared with the risk in normal weight individuals.

The obese category is further subdivided into class I (BMI 30 to 39) class II (BMI 40 to 49), class III (BMI >50). They carry respective risks of co morbidities that are moderate, severe and very severe respectively[33].

At present 60 % of male population and 50 % of female population have a BMI of more than 25 which is having increased risk of morbidity and mortality[33]. BMI is used as a most common

predictor, because it is the simplest measurement to calculate in the clinic.

A second approach defining the obese state involves quantification of adipose tissue, either directly or indirectly. This include measuring skin fold thickness, waist circumference, waist to hip ratio. Values are obtained for a reference group. Obesity is defined as levels of adiposity exceeding the reference group[33].

Accumulation of adipose tissue in different depots has distinct consequences. Thus many of the complications of obesity like hypertension, insulin resistance , diabetes mellitus and hyperlipidemia are linked to the amount of intra abdominal fat rather than to lower body fat (buttocks, leg) or subcutaneous fat[33].

However, while BMI is an indicator of total fat levels, it provides no indication of how fat is distributed in the body. The manner in which fat is distributed in the body is important, as it has been found that fat which is stored in and around internal organs (such as the liver, kidneys, pancreas and heart) tends to be significantly more harmful than fat which is stored peripherally, particularly in the form of subcutaneous (under the skin) fat.

The mechanism behind this is, because of the fact that intra abdominal adipocytes are lipolytically more active than those from other depots[34]. This activity can have harmful effects such as induced insulin resistance, impaired vascular function and inflammation. Release of free fatty acids into the portal circulation has adverse metabolic actions, especially on the liver.

Abdominal fat, typically evident on physical examination can be estimated by determining the waist to hip ratio, skin fold thickness, recently waist to height ratio , densitometry (underwater weighing), computerised tomography, magnetic resonance imaging and electrical impedance[33,34].

Waist circumference:

Waist circumference measurement is one of the easiest way of determining the abdominal adiposity. To measure the waist circumference the most consistently used site was World Health Organization (WHO) definition of halfway between the lower rib margin and the iliac crest[39].

The recommended limits of waist circumference set by the World Health Organisation for both males and females, also specifies the corresponding risk categories for metabolic disease:

Metabolic Risk Category	**Males: Waist Circumference**	**Females: Waist Circumference**
Normal	≤ 94 cm	≤ 80 cm
Increased Risk	>94 cm	>80 cm
Greatly Increased Risk	> 102 cm	> 88 cm

From this table it is clear that men should strive to maintain a waist circumference of 94 cm or less, and for women the corresponding goal is 80 cm[40].

Even though waist circumference is a reliable indicator of cardiometabolic risk in defined populations, it has been found that a healthy waist circumference in one ethnic group can differ from that in another. For example, Asians have a higher metabolic risk than Europeans at any given waist circumference, due to the fact that Asians tend to carry more truncal fat than Europeans for any given BMI[41]. This is the main disadvantage of measuring waist circumference alone as a screening tool.

Waist to Hip Ratio:

A rough index of the relative amounts of visceral and abdominal fat is the waist to hip ratio. This is calculated by dividing the waist circumference by the hip circumference. Hip circumference is taken as the largest standing horizontal circumference of the buttocks[42]. Waist hip ratio is commonly abbreviated as WHR. Ratio > 0.72 is considered abnormal. It is accurately quantified by dual energy X –ray absorptiometry (DEXA) scanning or computed tomography[33].

Points to be noted while measuring the waist and hip circumference:

- A flexible but not a stretchable tape should be used.
- It has to be measured directly on the skin, not over the clothing.
- It has to be ensured that the tape is horizontal and correctly placed.
- The person whose measurement is taken should stand straight.
- The tape should be held lightly so as not to compress the skin.
- The person should relax his / her muscles, breath out fully while the circumference is being measured.

- A record of the serial measurements can be kept to track the progress over time.
- For measurements taken over a period of time, it should be done at the same time of the day.

Body fat distribution can alternatively be described as pear shaped (low WHR) and apple shaped (higher WHR)[33]. 'Apple' shaped people store fat centrally (around the waist), while 'pear' shaped people store fat peripherally (around the hips and buttocks). These shapes become more obvious and pronounced in the overweight and obese categories of BMI.

An apple shaped person of the same gender, age and ethnicity as a pear shaped person, and with the same BMI, will tend to have a much greater risk of developing cardiometabolic diseases such as diabetes, dyslipidaemia, hypertension, coronary heart disease and stroke[43].

The relative risk of morbidities associated with obesity is lower when the WHR is < 0.8 and it is more when the WHR is > 1[34,44]. Hence, the metabolic syndrome, which is a clustering of obesity and other cardiovascular risk factors is more likely to be associated with visceral obesity[33].

Waist to hip ratio is the best predictor and it is noteworthy that increased WHR is associated with increased incidence of cardiovascular morbidity in women even at the relatively low BMI of 25[33]. Visceral obesity is associated with increased occurrence of hypertension and an atherogenic lipid profile both of which contribute to the development of cardiovascular disease.

It is known that the waist-to-hip ratio can predict mortality, as BMI, but the taller we are, the longer we live. So by adding this to the waist-to-hip ratio, “people who are taller, their waist-hip ratio can be bigger, because the height is reducing their risk."

Waist to height ratio:

Another measure of distribution of body fat is waist to height ratio. The waist to height ratio of a person is defined as the person's waist circumference, divided by the person's height. The normal waist to height ratio should be ≤ 0.5[44]. So it is clear that men and women should strive to keep their waist circumference to no more than half their height. The most consistently used abbreviation for this waist to height ratio is WHtR[39].

A systemic review and meta analysis done by M. Ashwell et al had revealed that waist height ratio was a better predictor than waist circumference for diabetes, dyslipidemia, hypertension, and cardiovascular disease risk in both genders in populations of various nationalities and ethnic groups. They had analyzed data of more than 300,000 individuals from diverse populations across the world and suggested that measures of abdominal obesity provide superior tools for discriminating obesity related cardiometabolic risk compared with BMI. Moreover, waist height ratio has better discriminatory power than waist circumference[8].

A systemic review of 78 cross sectional and prospective studies exploring waist height ratio waist hip ratio or body mass index as predictors of diabetes and cardiovascular disease published between 1950 and 2008. This review employed specificity and sensitivity comparisons, indicated that waist to height ratio could be a useful screening tool, with a weighted mean boundary value of 0.5. This supports the simple public health message " keep your waist circumference to less than half your height[39]".

There is an another new indicator introduced recently, waist-to-hip-to-height ratio (WHR divided by height). It is abbreviated as WHHR. This is also one of the best predictor for cardiovascular morbidity and mortality. It needs to be tested in more diverse population.

Rather than BMI alone, if it is added along with waist hip ratio, waist height ratio and waist hip height ratio, then the risk – prediction tool would become more accurate[37,39,44].

These indicators like waist circumference, waist hip ratio and waist height ratio, collectively known as waist metrics, they describe the extent of central fat distribution, and for this reason they are a valuable complement to BMI. However, they are not a substitute for BMI. While these waist metrics take fat distribution into account and BMI does not, BMI takes total fat into account while waist metrics do not[6,33]. So, when used together, these measures tend to provide a more reliable indicator of cardiometabolic risk than either measure used alone.

Therapy for obesity[6]:

Assessment of overweight / obese patients should include:

1. H/o weight gain and maximum body weight
2. Consideration of medications that contribute to weight gain, such as corticosteroids, thiazolidinediones, antipsychotic agents.
3. Previous approaches to weight reduction
4. Patterns of food intake, including binge eating
5. Physical activity levels

On examination,

1. Measurement of weight, height, waist circumference.
2. Calculation of BMI, waist to hip ratio, waist to height ratio.
3. Evaluation of blood pressure, glycemia, cholesterolemia, liver and cardiovascular function
4. Associated signs and symptoms to rule out genetic deficiencies should be performed.

The treatment options for weight loss are:

1. Lifestyle modification
    a. Diet
    b. Exercise
    c. Behavioural modification

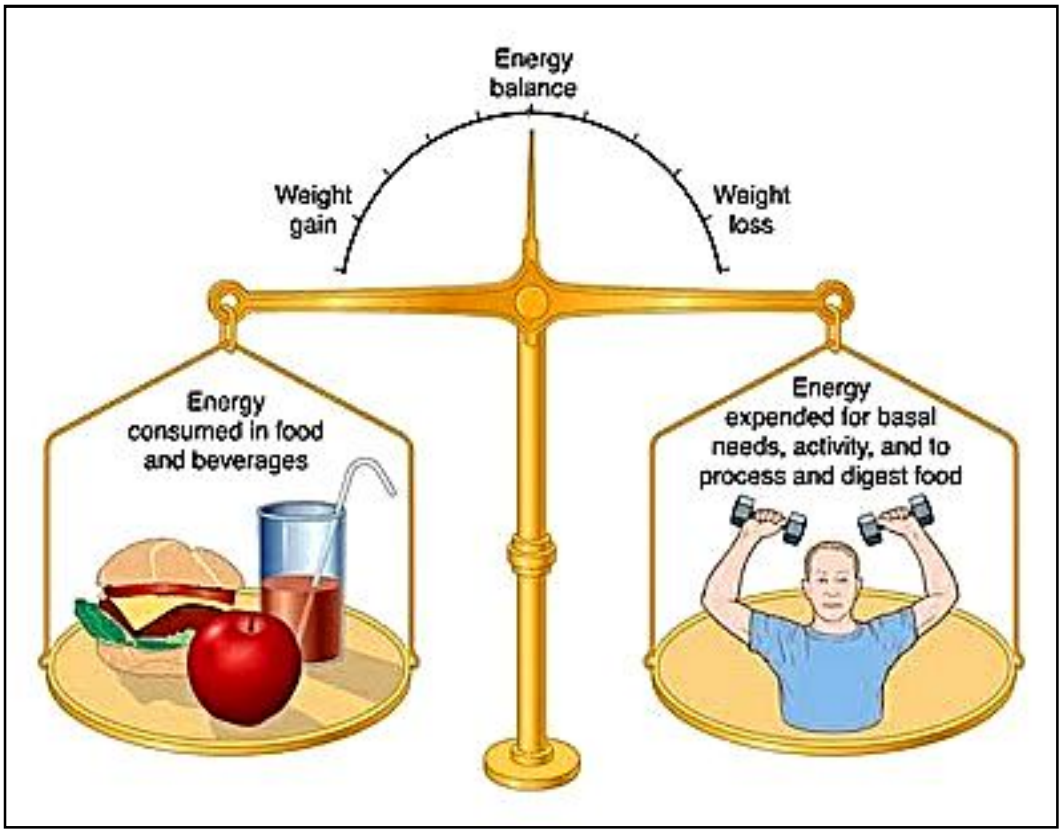
2. Pharmacotherapy

3. Bariatric surgery

The discovery of leptin held great promise as a direct therapy for obesity. Although leptin effectively reduces body weight in rodents, high pharmacologic doses elicit only moderate weight loss in obese humans. This is because selective resistance to its weight reducing action in obese people. However a 24 week proof of concept clinical study has demonstrated that the combination of leptin and pramlintide (which is an amylin analogue drug used in treatment of type 2 Diabetes mellitus) produced significantly greater weight loss compared to leptin, pramlintide alone[6].

The advertisements for miracle weight loss programs raise false hopes because the total energy of the body will only decrease if it does work on the external environment or transfers heat or waste materials to the environment. Whatever maybe the cause for the obesity, behaviour modification to decrease the food intake and moderate exercise to increase caloric expenditure represent the effective management[45].

ENERGY BALANCE



We, human beings eat food intermittently, most often three times a day. For survival, continuous supply of energy is required. So the ability to store excess energy is essential. This is done by our fat cells which reside within widely distributed adipose tissue depots.

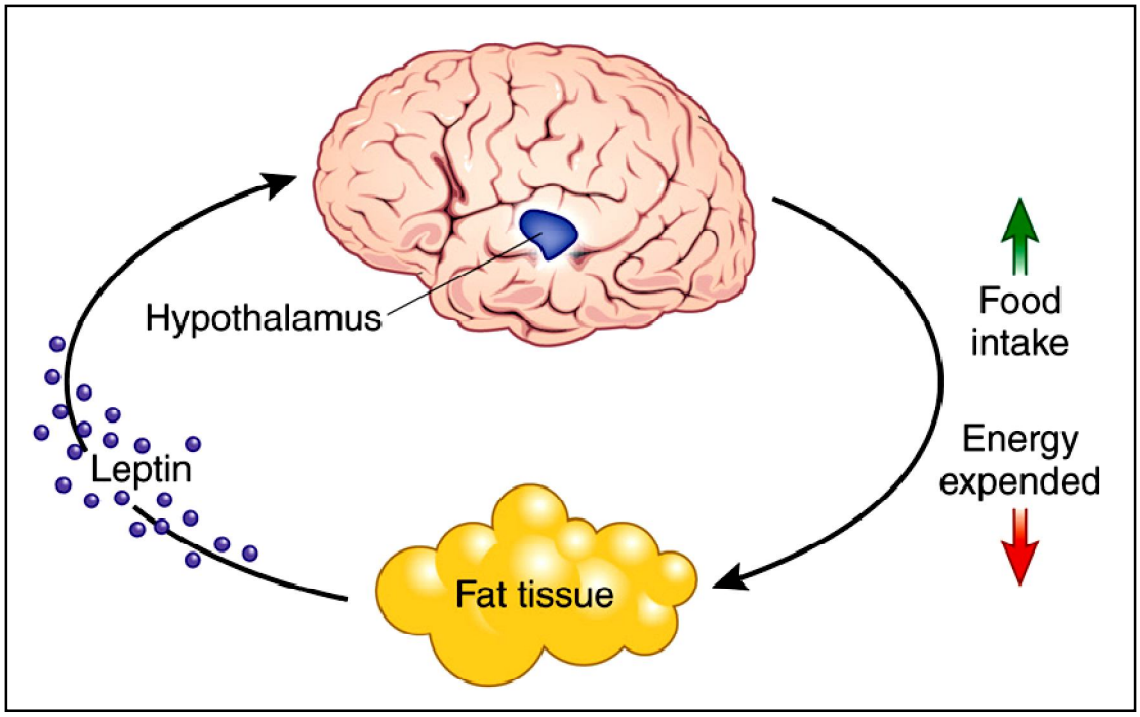
The fat cells are adapted to store excess energy efficiently as triglycerides and release stored energy as free fatty acids whenever needed. This is necessary for humans to survive in starvation that is why this physiological system is well orchestrated through endocrine and neural pathways.

Physiologic regulation of energy balance:

The effector arms of energy intake and expenditure are regulated by both endocrine and neural components that regulates the body weight. The system is very complex even a small imbalance between energy intake and expenditure will result in large changes in body weight. For example a 0.3 % positive balance over 30 years would result in a 9 kg weight gain[34].

This regulation cannot be done easily by calorie counting in relation to physical activity. If there is any alteration in the stable weight of an individual by forced overfeeding or food deprivation, the physiological changes include, increase in appetite and fall in

ENERGY EXPENDITURE



energy expenditure with weight loss and reverse occurs with overfeeding.

The compensatory mechanism frequently fails, permitting obesity to develop when food is abundant and physical activity is limited. These adaptive responses are regulated mainly by the adipose tissue derived hormone leptin[34]. It predominantly acts in hypothalamus to reduce appetite and increase energy expenditure. Thus it acts as a neuroendocrine hormone.

Hypothalamus in brain is the important centre in regulation of food intake which is influenced by many factors. Signals acting on this hypothalamic centre include neural afferents, hormones and metabolites. Among them vagal inputs are important one, they bring information from viscera, such as gut distension. Hormonal signals include insulin, leptin, cortisol and gut peptides like peptide YY, ghrelin and cholecystokinin.

Metabolites, including glucose, can influence appetite, as seen by the effect of hypoglycaemia to induce hunger. All these hormonal, metabolic, and neural signals act on hypothalamus to influence the expression and release of peptides like Neuropeptide Y, Agouti related protein, α melanocyte stimulating hormone and melanin

concentrating hormone integrated with catecholaminergic, seratonergic, endocannabinoid and opioid signalling pathways[34].

Psychological and cultural factors also play a role in the final expression of appetite. Apart from the rare genetic syndromes involving leptin, its receptors and the melanocortin system, specific defects in this complex appetite control network that influence common cases of obesity are not well defined.

The components of Energy expenditure are[34]:

1. Resting or basal metabolic rate
2. Energy cost of metabolizing and storing food
3. Thermic effect of exercise
4. Adaptive thermogenesis

In daily energy expenditure, basal metabolic rate accounts for 70%. Physical activity contributes 5-10%[34]. Thus a significant component of daily energy consumption is fixed. Any alteration in this physiological system like nutritional abundance and sedentary life style influenced by genetic endowment results in excess adipose tissue energy storage and produces adverse health consequences.

It has been long understood that increased energy intake without increase in energy expenditure is associated with obesity. This is characterised by increased adiposity in terms of both the number of adipocytes and their fat content. There are 2 forms of adipose tissue, brown adipose tissue and white adipose tissue.

Brown adipose tissue plays an important role in thermogenesis[46]. It expends stored energy as heat. In brown adipose tissue, hydrogen ion gradient in the oxidative respiratory chain, is dissipated by a mitochondrial uncoupling protein (UCP -1) and the energy is released as heat[34]. Thus brown adipose tissue takes part in adaptive thermogenesis and plays an important role in energy metabolism in mammals.

Leptin increases the metabolic activity of brown adipose tissue via activating the sympathetic nervous system. Identification of functional brown adipose tissue in many adults using PET imaging has increased interest in the implications of the tissue for pathogenesis and therapy of obesity[34].

In contrast to brown adipose tissue, white adipose tissue is used to store energy in the form of lipids. This is useful for cushioning, for example in orbits surrounding the eyeballs. It also acts as a

classic endocrine organ that releases numerous molecules in a regulated fashion. The tissue is composed of several cell types. The triglyceride storing cell is called adipocyte[46].

Adipocyte differentiation is promoted by a transcription factor called sterol regulatory element binding protein 1c (SREBP – 1c). An increase in food consumption leads to activation of SREBP – 1c and causes conversion of preadipocytes into small adipocytes. This also upregulate enzymes within the adipocyte to allow storage of excess fat[46].

Adipose tissue produces paracrine and endocrine hormones including energy balance regulating hormone leptin, adiponectin, resistin (collectively called as adipokines), cytokines such as tumour necrosis factor, interleukin 6, a component of the blood pressure regulating system angiotensinogen, acylation stimulating protein, growth factors, compliment factors such as factor D, prothrombotic agents such as plasminogen activator inhibitor[46-48]. These factors, and others not yet identified, play a role in the physiology of lipid homeostasis, insulin sensitivity, blood pressure control, coagulation, vascular health and are likely to contribute to obesity – related pathologies.

Ob Gene Knocked Out Mice **Normal Mice**

The main molecule among them to carry information about the fat stores is leptin. In addition to white adipose tissue, leptin is also produced by brown adipose tissue, placenta, ovaries, skeletal muscle, stomach, mammary epithelial cells, bone marrow, pituitary and liver[43,49-51]. This is responsible for the considerable variation in leptin concentrations among persons with the same BMI.

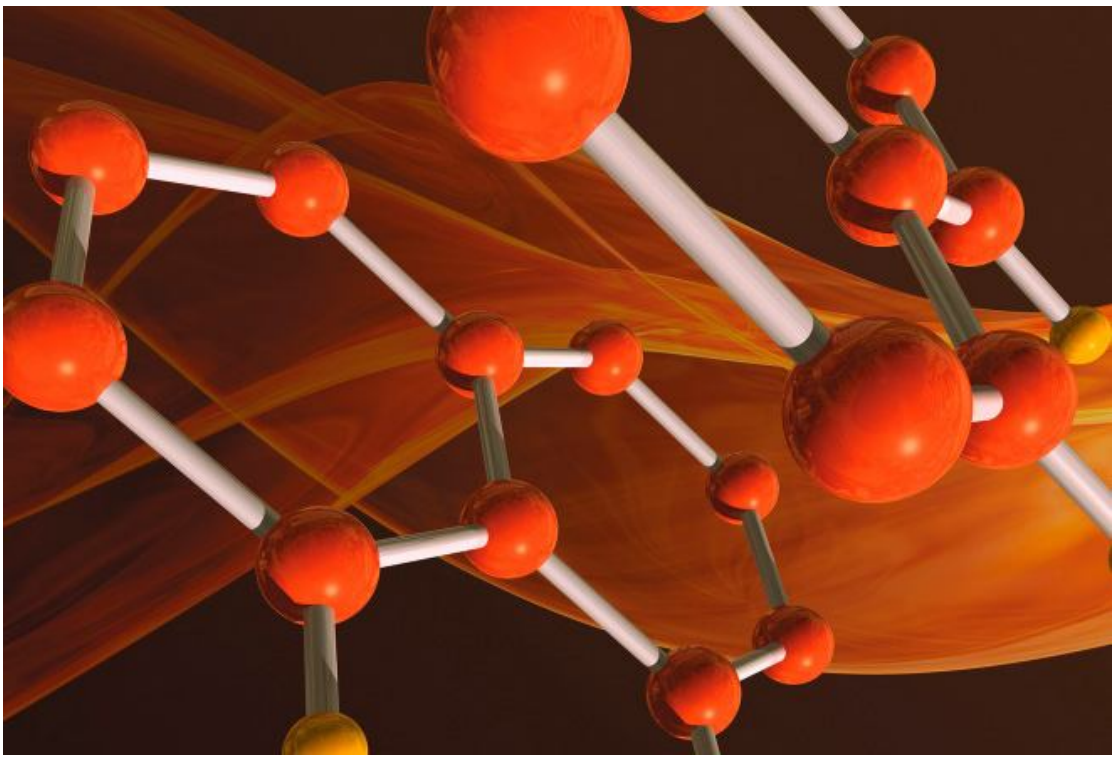
History[52]:

The original notion of homeostatic regulation of energy balance dates back to Lavoisier and Laplace. The role of brain was determined later from clinical observations and was confirmed by stereotaxic lesions of different regions of brain.

Hypothalamic feedback loop in regulating body energy stores was postulated later with many theories. One such theory was glucostatic theory in which blood glucose was said to be the sensed signal for the feedback loop, proposed by Jean Mayer. Then Kennedy postulated the lipostatic theory which is having a fat metabolism factor.

Subsequently Hervy performed the parabiosis studies and confirmed that blood borne signals coming from the adipose tissue regulates the food intake and body weight. Not too long after Douglas

LEPTIN MOLECULE



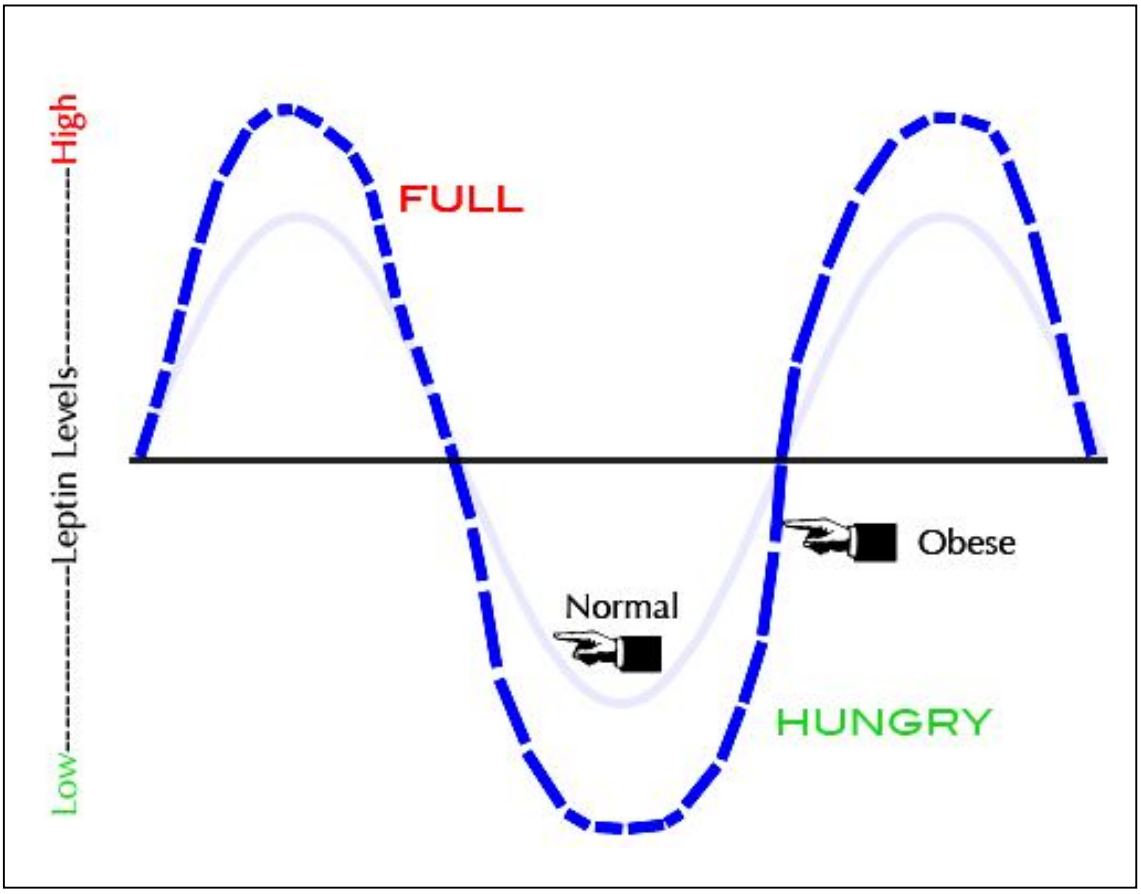
Coleman at the Jackson laboratory performed the seminal parabiosis studies using single gene mice models of obesity and diabetes[12]. Ob/ob gene encoded a hormone whereas db/db gene encoded the receptor for that particular hormone.

He concluded that the hormone was secreted by the adipose tissue, transported by the blood and received by its receptor in the hypothalamus. This laid the foundation for positioning cloning studies of ob and db genes that laid to the publication of the discovery of leptin in 1994[10] by Jeffrey M. Friedman, Rudolph Leibel at the Rockefeller university together with Douglas Coleman. Dr. Friedman won the time magazine, Best of Science in 1994 and the Albert Lasker Basic Medical Research Award in 2010 for his discovery of Leptin.

Structure of leptin:

Leptin is a peptide hormone of 16 KDa MW, having 167 amino acids[10]. The gene responsible for leptin production is ob gene. Leptin belongs to cytokine family of proteins like tumour necrosis factor α , interleukin 6. Nuclear magnetic resonance and crystal structure analysis revealed a four helix bundled structure for leptin

REGULATION OF PLASMA LEPTIN LEVEL



with four antiparallel α helices linked with two long crossover arms and one short loop[35].

Leptin metabolism:

Leptin circulates in bloodstream as a free protein[53]. It shows a diurnal rhythm with minimal values during the day time and a nocturnal rise with maximal values during early sleep to mid sleep[13]. Leptin concentration varies among persons with the same BMI suggesting that leptin production is also regulated by factors other than adipose tissue mass[54].

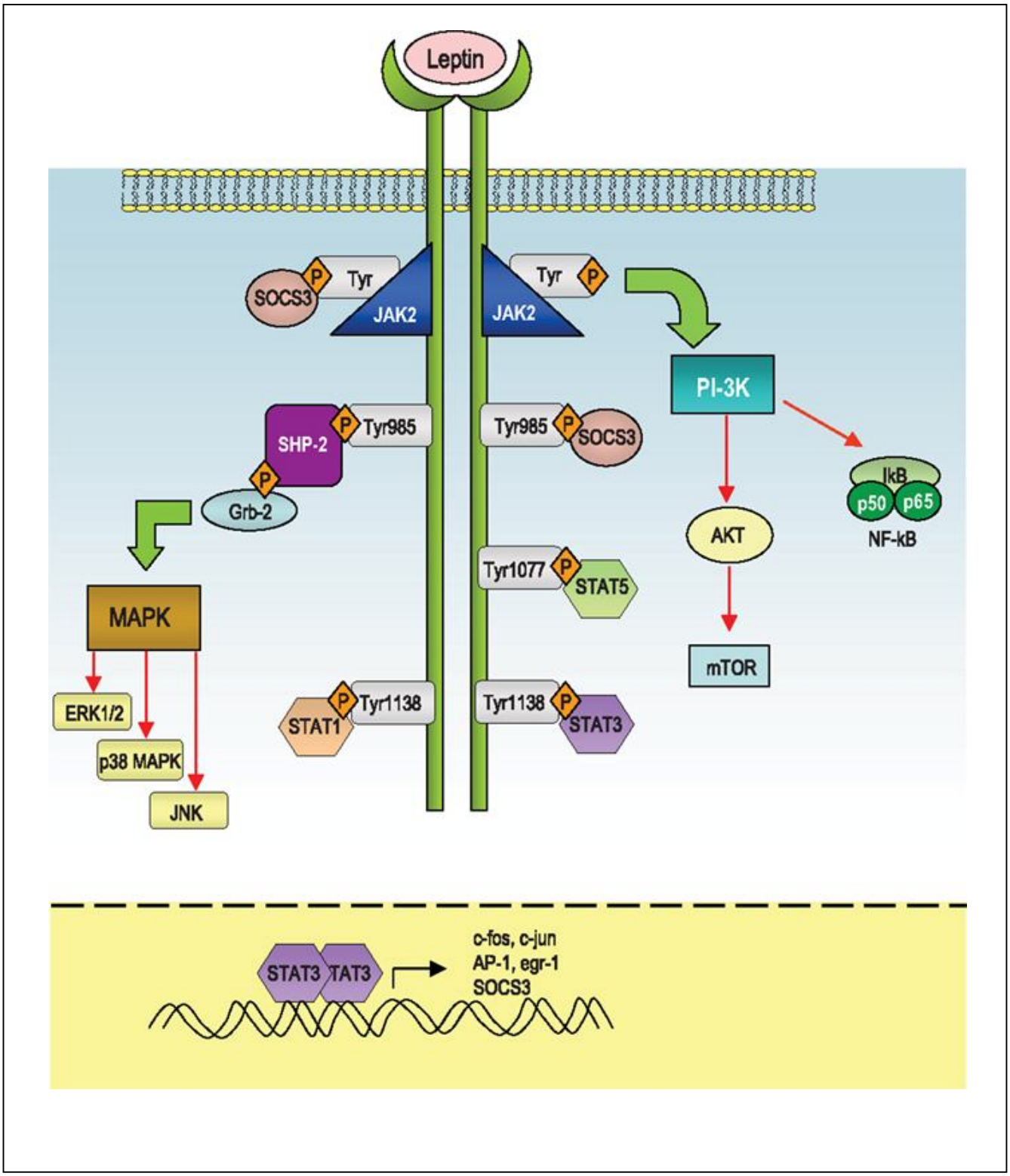
Factors affecting plasma leptin level:

Leptin level mainly depends on the timing of meals. Fasting and eating are associated with decrease and an increase in the plasma leptin levels respectively. It is increased by emotional stress[49]. Leptin level is decreased when testosterone level is increased whereas its level increases along with the increase in estrogen. It is chronically reduced by physical exercise training[54,55].

Mechanism of action:

Leptin signals through six splice variants of membrane receptors known as Ob – Ra to Ob – Rf. It is also named as LepRa to LepRf. Among them most common is long form Ob – Rb. They

MECHANISM OF ACTION OF LEPTIN



belong to cytokine receptor superfamily[10,47]. All of them have an extracellular binding domain and an intracellular tail. These receptors are encoded by a single gene, called LEPR.

Leptin crosses the blood brain barrier through a saturable active transport system and binds with its receptor[13]. Binding of leptin to its membrane receptor results in homodimerization. It activates many intracellular enzyme cascades involve Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways[10]. The STAT proteins then migrates to the nucleus and activates leptin target genes. The long form leptin receptor is required for normal energy homeostasis.

Leptin receptors are highly expressed by several hypothalamic nuclei including arcuate , dorsomedial, ventromedial, ventral premamillary nuclei[10]. The extrahypothalamic sites include Nucleus tractus solitarius, substantia Nigra, ventral tegmental area, para brachial and dorsal raphe nucleus[56].

Leptin signalling is required for normal energy balance. Humans and animals lacking leptin or leptin receptor have severe hyperphagia and obesity. It causes lipid accumulation in many tissues and cellular damage which is called lipotoxicity. Leptin gene

expression is regulated by food intake, insulin, growth hormone, sympathetic system, steroids, thyroid hormone, poly unsaturated fatty acids, retinoic acid and leptin itself[57]. Any homozygous frameshift , nonsense, missense mutations in this leptin gene (LEP) lead on to congenital leptin deficiency.

Patients with congenital leptin deficiency have normal neurobehavioural development and no dysmorphic features. They will have normal birth weight but show rapid weight gain there after resulting in severe obesity. Other features include type 2 diabetes mellitus, abnormalities in sympathetic nerve function, hypothalamic hypothyroidism, hypogonadotropic hypogonadism, delayed onset of puberty, decreased T cell count and function resulting in increased infection in childhood. The condition is diagnosed on the basis of undetectable serum leptin measurement followed by genotyping of LEP gene[52].

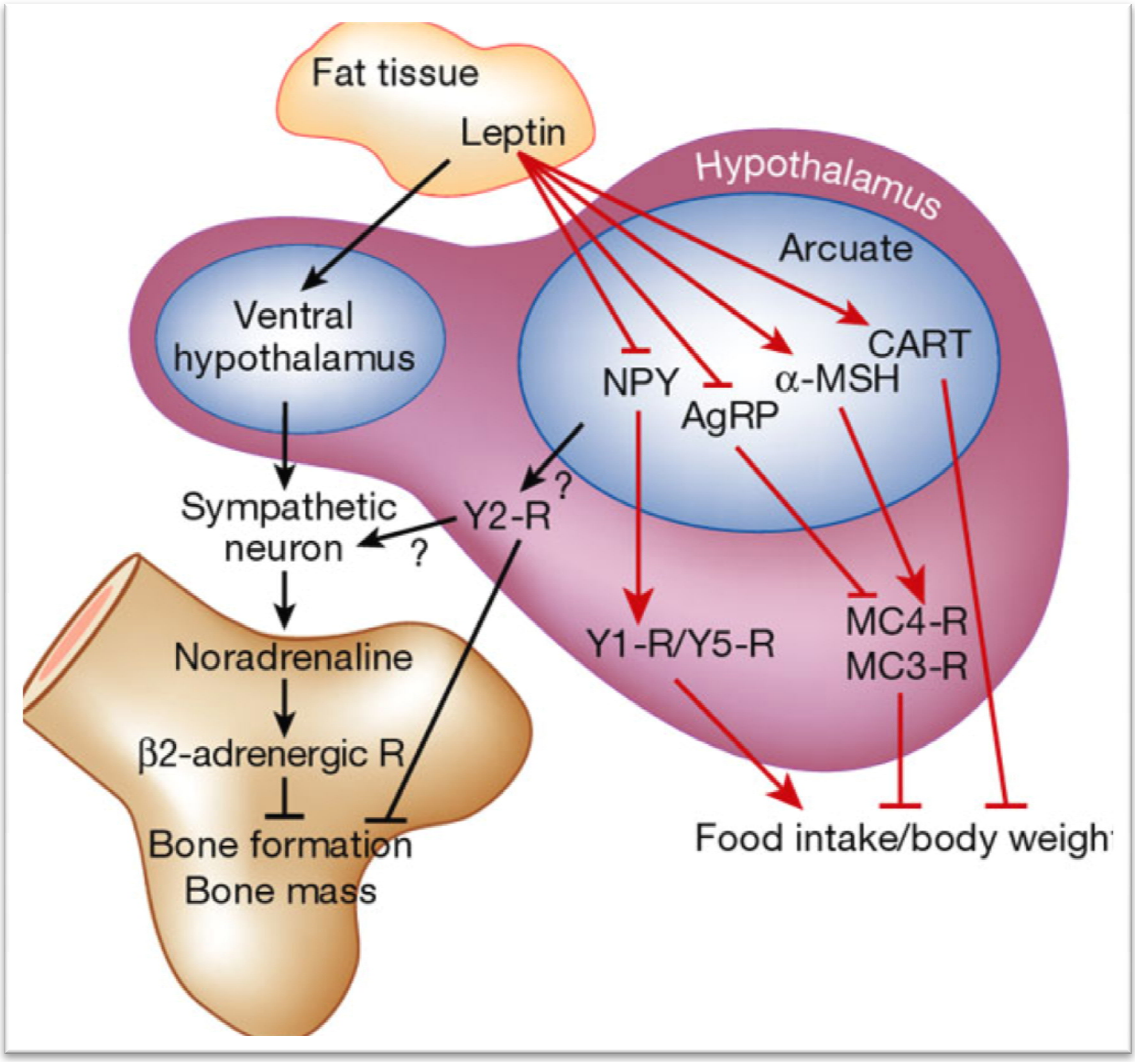
Upto 3% of patients with severe obesity will have loss of functional gene mutation encoding leptin receptor (LEPR). This is measured by an inability of leptin to phosphorylate STAT3 proteins in invitro studies. Clinical phenotype is similar to leptin deficiency. Serum levels are not elevated disproportionately. Only in particular

types in which the mutation affects the transmembrane domain results in truncated extracellular domain that may act as a false binding protein leads to abnormally elevated leptin levels[52].

Patients can be treated with r- Leptin as daily subcutaneous injections[47]. It improves insulin sensitivity and leads to decrease in fasting glucose. Hypertriglyceridemia refractory to traditional lipid lowering agents shows best response to leptin replacement. An analogue of human leptin, Metreleptin is under investigation for the treatment of diabetes, hypertriglyceridemia and rare forms of lipodystrophy with severe metabolic abnormalities.

In children r- leptin therapy reduces food intake and body weight with no effects on energy expenditure and fat oxidation. In adults it affects the food intake as well as energy expenditure. It is observed as weight loss and increase in fat oxidation by more than 3 times in 24 hours[52]. Large and frequent doses are needed because of leptin's low circulating half life, low potency and poor solubility.

LEPTIN ARCUATE PATHWAY



Functions of leptin:

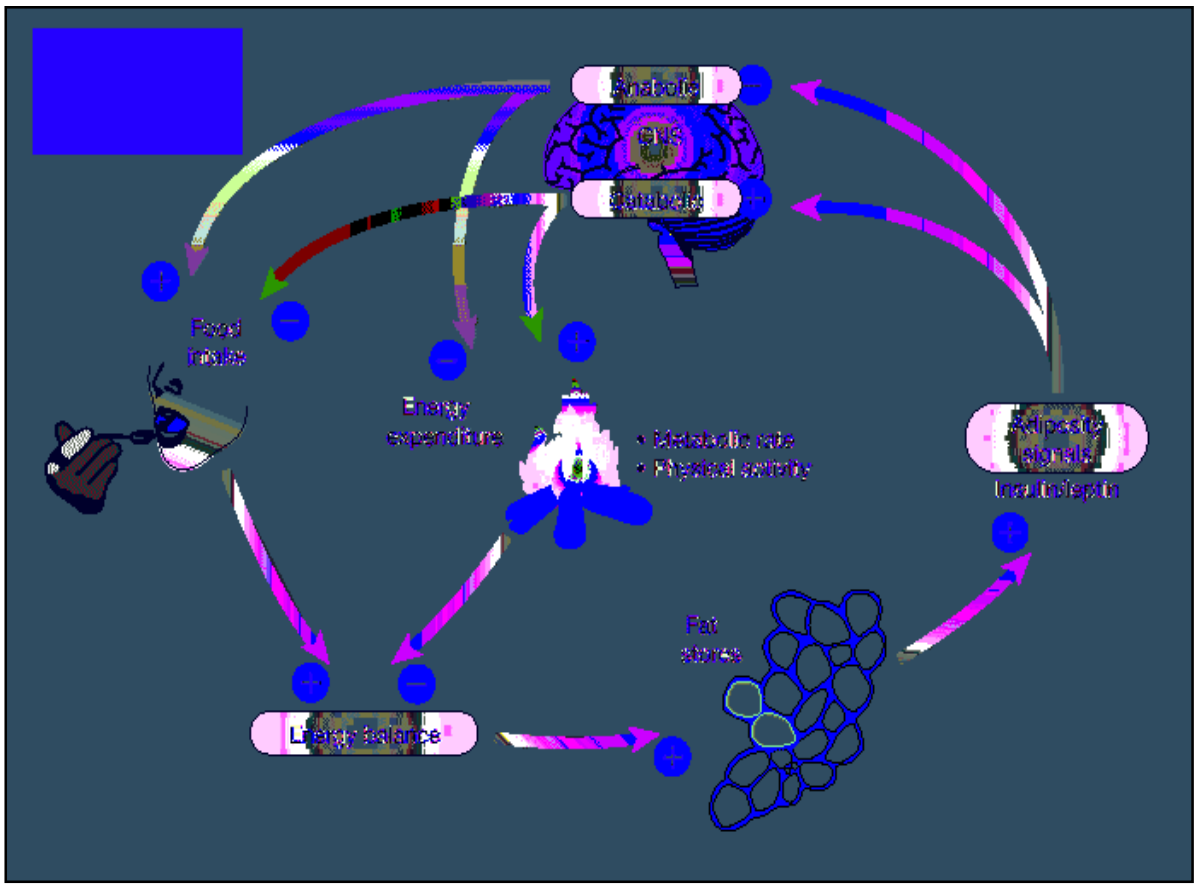
1. Role in enegy expenditure:

It is a potent appetite suppressor and primary regulator of energy expenditure. The critical physiological role of leptin appears to be, signalling caloric deficiency and thus mediate the appropriate metabolic changes rather than signalling caloric excess[49]. It maintains minimum level of energy stores during periods of caloric restriction.

So whenever the energy stores become insufficient, leptin concentrations become very low, commanding the body to seek food and become thrifty. Thus leptin acts as a bidirectional signal that switches physiologic regulation between fed and starved states[56]. Lack of leptin is responsible for multiple neuroendocrine abnormalities caused by starvation.

Leptin controls appetite by acting on hypothalamic arcuate and paraventricular nuclei. A complex network of neuropeptides are involved in signals regulating appetite and hunger in hypothalamus. These include catabolic POMC (pro opio melanocortin), anabolic neuropeptide Y / agouti – related protein (NPY / AgRP). POMC produces a number of peptides, including α MSH (melanocyte

METABOLIC ACTIONS OF LEPTIN



stimulating hormone) to suppress appetite whereas both NPY / AgRP are orexigenic (appetite inducing) peptides[10].

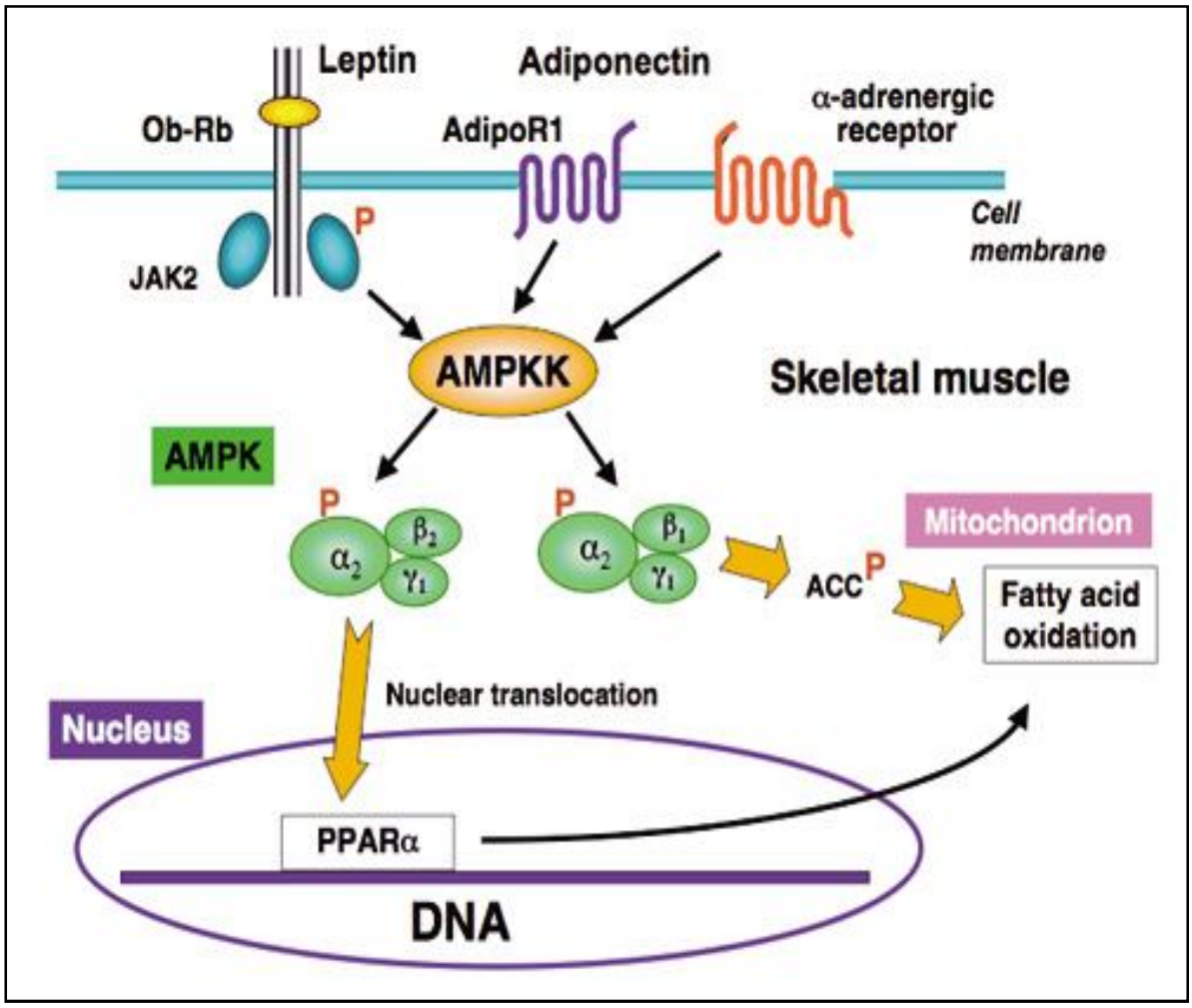
Leptin directly depolarizes POMC neurons thus activating them to suppress appetite. It also inhibits NPY / AgRP neurons by hyperpolarising them[10]. Deletion of leptin receptors selectively in POMC neurons produces obesity. Until now leptin to arcuate pathway represents the best characterised pathway involved in the regulation of body weight[52].

Leptin has satiety inducing effects by suppressing orexigenic signals. It disrupts potential feedback mechanism between body weight changes and plasma ghrelin in lean adult rats[36].

2. Role in metabolism:

Leptin affects metabolism by stimulating fatty acid oxidation and by decreasing lipogenesis. It has an important role in liporegulation of peripheral tissues. It protects peripheral tissues like liver, skeletal muscle, cardiac muscle, β cells from more lipid accumulation by directing excess calories into adipose tissue for storage. This action of leptin contributes to the maintenance of insulin sensitivity in peripheral tissues[46].

AMPK ACTIVATION



Leptin activates AMPK (Adenosine monophosphate kinase) in muscle and liver[10]. As a consequence of AMPK activation, ATP consuming anabolic pathways are inhibited, whereas ATP producing catabolic pathways are activated. Activated mechanisms include glucose transport, β oxidation, glycolysis and mitochondrial biogenesis[52].

3. Circulatory system:

Leptin modulates T cell activity in immune system[58]. It increases the immune response to atherosclerosis in obesity. Exogenous leptin promotes angiogenesis by increasing vascular endothelial growth factor levels. It also increases platelet aggregation. Leptin maintains sufficient energy stores to enhance erythropoiesis, lymphopoiesis and myelopoiesis.

4. Lung surfactant activity:

In fetal lung leptin is secreted from mesenchyme under moderate stretch. Leptin acts on the receptors in alveolar type II epithelium and induces surfactant expression[59].

5. Reproduction:

In mice leptin is required for both male and female fertility. In humans, the effect is minimal. In females the ovulatory cycles are linked to energy balance and if this is highly negative then the cycle stops, the women stops menstruating. Leptin levels outside an ideal range have a negative effect on egg quality and outcome during in vitro fertilization. It also has a role in polycystic ovary syndrome[60]. The mechanism yet to be identified.

Leptin is also produced by placenta. So its level rises during pregnancy and falls after parturition. Leptin is also expressed in fetal membranes and uterine tissue. Uterine contractions are inhibited by leptin. It plays a role in hyperemesis gravidorum.

6. Bone metabolism:

Leptin acts via β2 adrenergic receptors in osteoblasts and inhibits its proliferation. Additionally it favours bone resorption by increasing osteoblastic expression of RANKL. Leptin affects bone metabolism via direct signalling from the brain. It acts to reduce cancellous bone and conversely increases cortical bone[52].

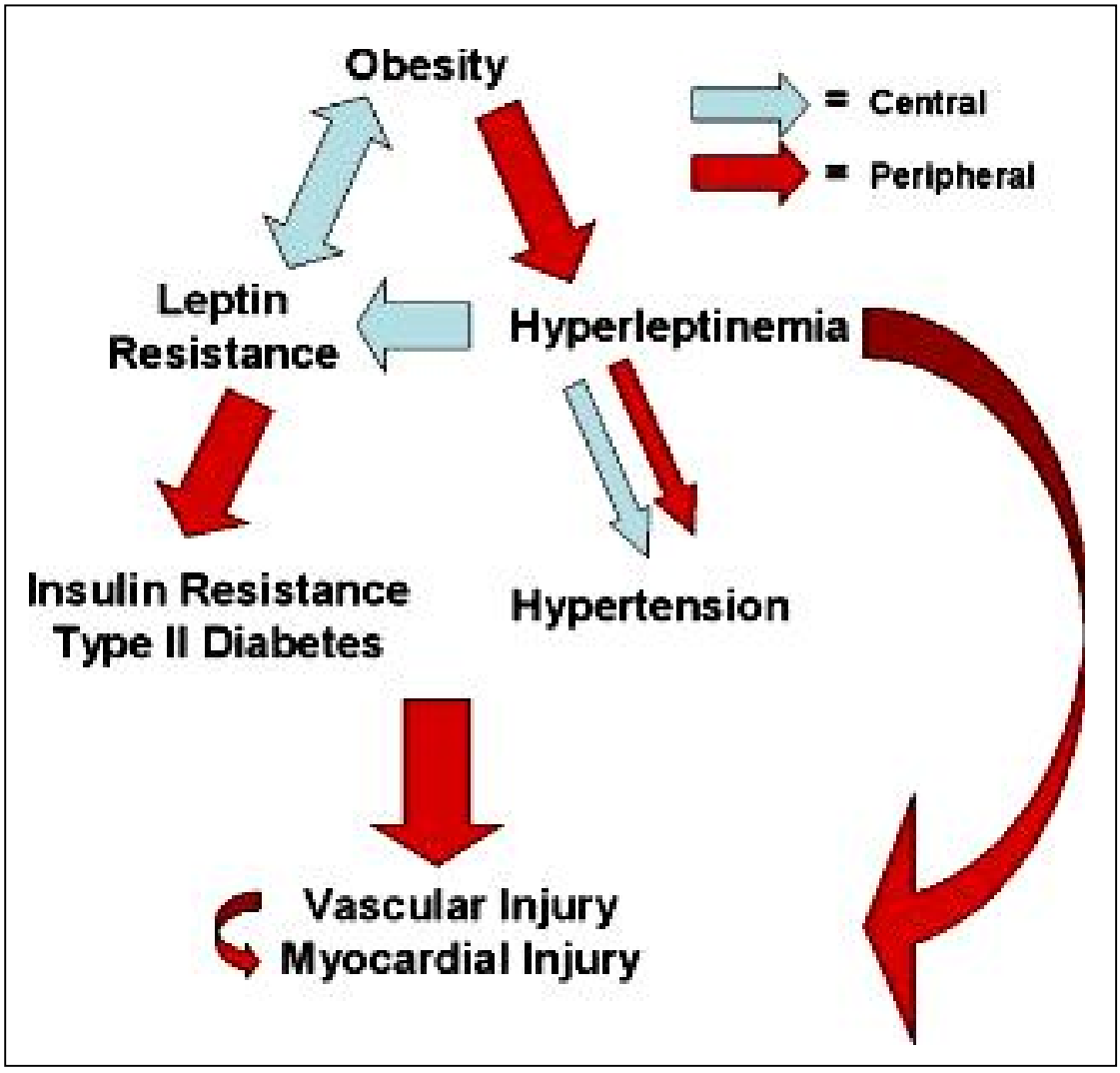
7. Brain:

fMRI studies in humans confirm that leptin mediates its adipostatic effect through hypothalamic and other brain areas that are important in emotional and cognitive control. Fulton and colleagues demonstrated that leptin also affects brain self stimulation suggesting that leptin has the ability to affect CNS circuits classically involved in Reward[56]. Low circulating plasma leptin levels has been associated with anorexia, depression, HIV and the development of Alzheimer's disease.

8. Inflammatory marker:

The structure and function of leptin resembles Interleukin 6 (IL 6) and is a member of cytokine superfamily which will take part in chronic inflammation[12]. It also induces the production of various cytokines, including IL 6[58]. Circulating leptin seems to affect Hypothalamo Pituitary Adrenal axis, suggesting a role for leptin in stress response. Chronically elevated leptin concentrations are associated with increased white blood cell counts, obesity, overeating and inflammation related diseases including hypertension, metabolic syndrome, cardiovascular disease[7].

LEPTIN RESISTANCE



9. Obesity and Lepitn:

In obese individuals there is usually a high circulating concentration of leptin. These people are said to be resistant to the effects of leptin, in much the same way that people with type 2 diabetes are resistant to the effects of insulin. The sustained high concentrations of leptin from the enlarged adipose stores implies leptin desensitization.

Leptin resistance acts as a metabolic disorder that contributes to obesity. This is because the major physiological role of leptin is suggested to be not as a satiety signal to prevent obesity in times of energy excess, but as a starvation signal to maintain adequate fat stores for survival during times of energy deficit. So leptin resistance in overweight individuals is the standard feature of mammalian physiology, which confers a survival advantage.

Leptin and hypertension:

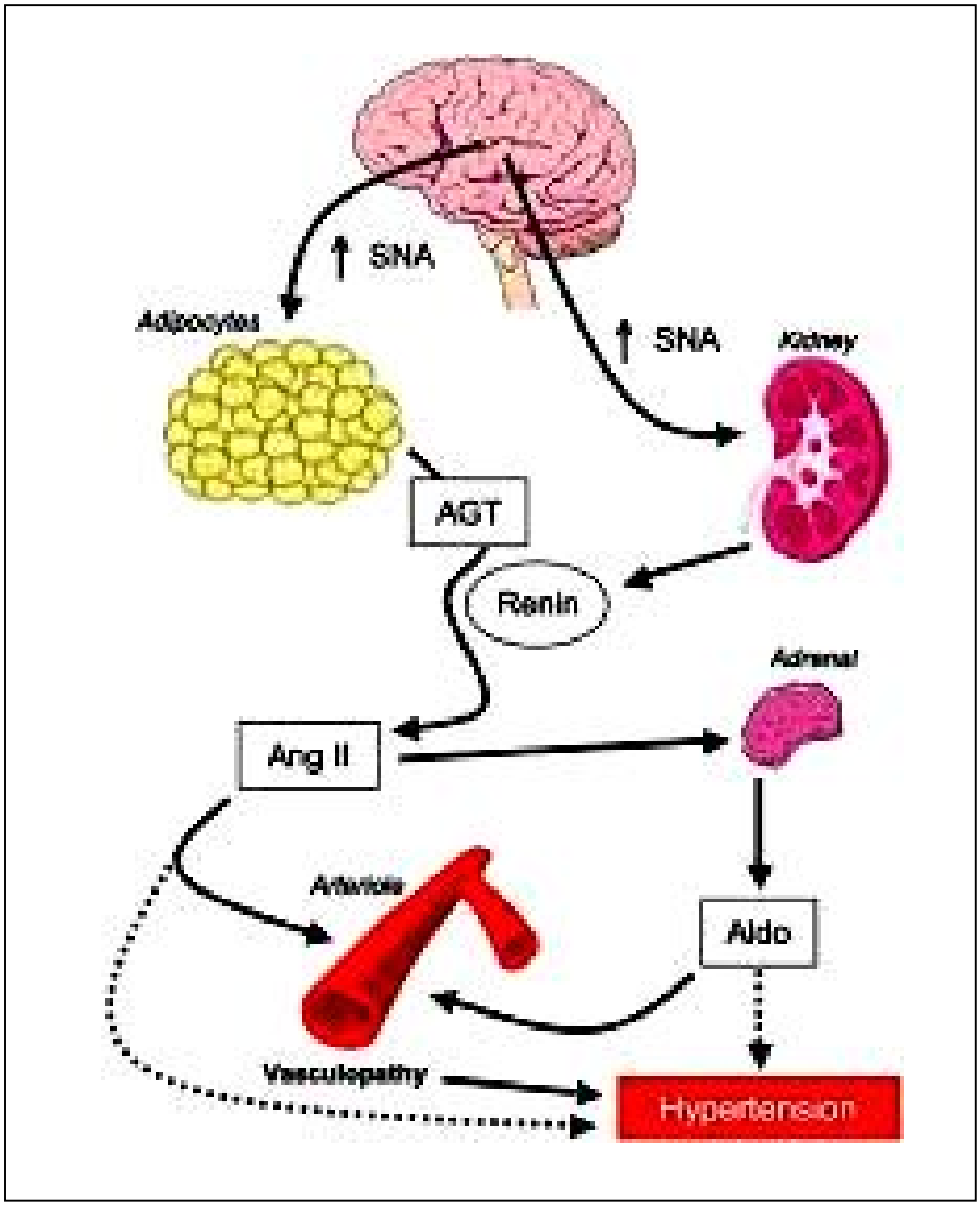
Leptin is a pleotropic hormone with multiple actions that are potentially relevant not only to the control of feeding but also to several systemic and metabolic functions. Several studies have reported that strong correlation exists between high plasma leptin levels and development of hypertension.

Leptin deficient ob / ob mice have lower blood pressure than lean controls despite severe obesity and leptin administration to these mice increases their blood pressure up to the level observed in lean controls[61]. It shows that apart from obesity, other mechanisms also exists via which leptin causes hypertension.

In vivo studies proved that leptin causes widespread sympathoactivation of metabolically active tissues[10]. In concentrations higher than the physiological level it exerts adverse effects on the vasculature by peripheral actions include, stimulation of reactive oxygen species, impaired NO production, renal sodium retention, increased endothelin 1 synthesis, transactivation of epidermal growth factor receptor and inhibition of angiogenesis resulting in blood pressure elevation[14,62].

By interacting with diverse mediators and regulators, leptin stimulates autonomic nervous system activity. Animal studies showed that, transgenic mice with leptin over expression had higher blood pressure as compared with control animals and the hypertension was reversed by sympathetic ganglionic blockade[9]. Immediately after leptin administration sympathetic discharge to brown adipose tissue, kidneys, adrenal glands and hind limbs

LEPTIN IN HYPERTENSION



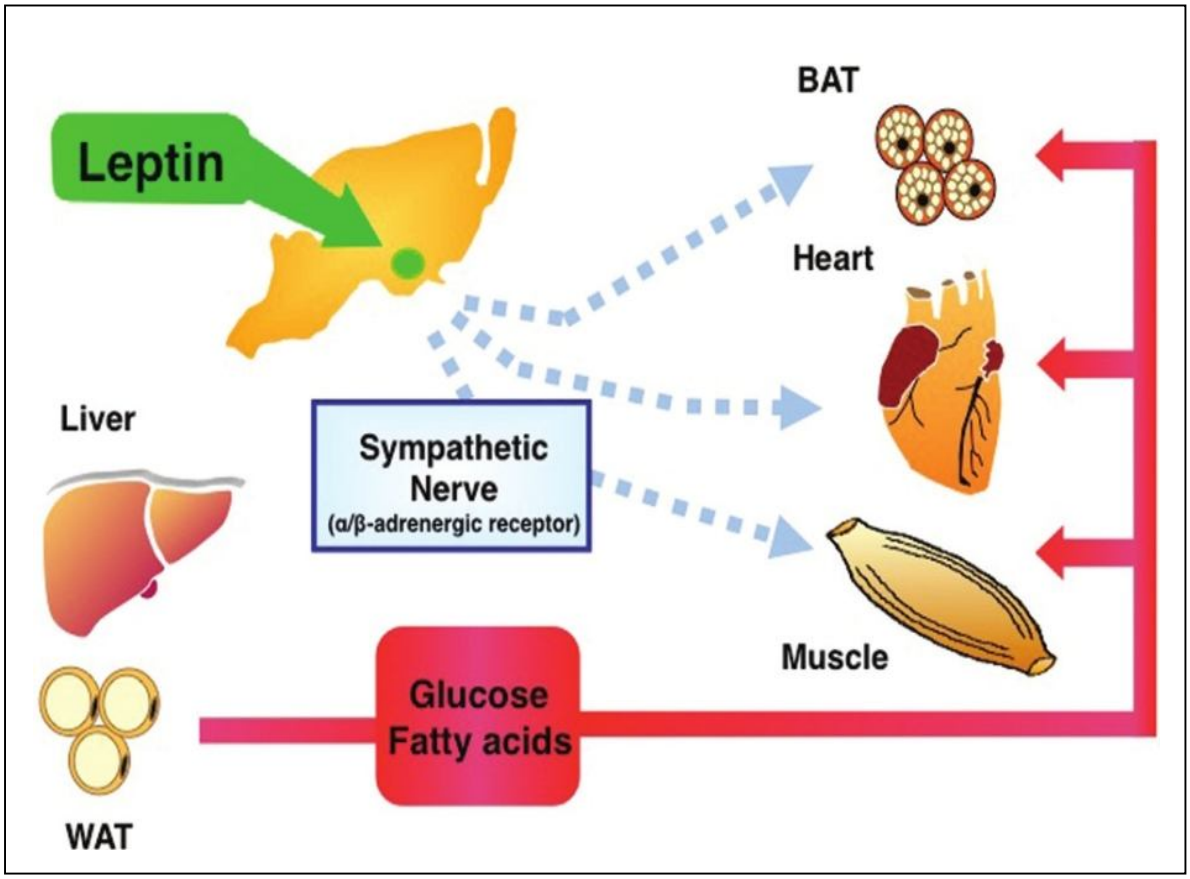
increases in rats whereas chronic administration shifts the pressure natriuresis curve to the right by increasing the renal tubular sodium reabsorption[10,61].

Other possible mechanisms include increased expression of adipose tissue derived hormone Angiotensin II, increased plasma renin activity, higher plasma levels of adrenalin and noradrenalin[50], increased corticotrophin releasing factor from brain.

Obese humans are resistant to anorexic and thermogenic actions of leptin but their sympatho- excitatory and pressor actions of leptin appears to be preserved in these subjects. In animals when compared to normal rats, spontaneously hypertensive rats and obese rats are refractory to natriuretic effects of leptin.

Several mechanisms have been postulated for this selective leptin resistance. Saturation in the transport of leptin in to the central nervous system represents one potential mechanism of leptin resistance in obesity[10]. Studies have shown that decreased CSF concentration of leptin in obese people[13]. Also it involves alteration in intracellular leptin signalling pathways in the hypothalamus.

PERIPHERAL ACTIONS OF LEPTIN



The ability of leptin to stimulate JAK / STAT pathway is impaired by activating the suppressors of the cytokine signalling family (SOCS-3). This SOCS-3 protein acts intracellularly to inhibit STAT phosphorylation induced by the leptin receptor. Protein tyrosine phosphatase 1b (PTP 1b) also inhibits intracellular leptin signalling. Defects in leptin receptor can lead to leptin resistance, but this is rare in humans[10].

Persistent high levels of leptin causes hypertension, insulin resistance[36,48,53] and stimulates vascular smooth muscle cell proliferation[62], accelerates vascular calcification, induces oxidative stress in endothelial cells[53], that contributes to atherogenesis, platelet adhesiveness thereby increasing the cardiovascular risk[50,58].

Studies related to serum leptin and blood pressure:

Freddy Contreras et al in their study, have found out high serum leptin levels in hypertensive subjects. They have concluded that, leptin increases the blood pressure by activating the sympathetic nervous system. Leptin is also involved in the atherogenic process by encouraging platelet aggregation and thrombosis and also inflammatory cytokine production which contributes to insulin resistance and endothelial malfunction[63].

F. Galletti et al in their study, proved that higher plasma leptin levels in normotensive adult male individuals are associated with increased risk of developing hypertension independently of several potential confounders. They have also confirmed that there is a strong association between BMI and plasma leptin concentration[61].

Kawaljit Kaur Khokhar et al in their clinical study, confirmed that both normal and obese hypertensive premenopausal and post menopausal women had significantly higher serum leptin levels than their normotensive counterparts. The results revealed that there was significant influence of systolic blood pressure on serum leptin levels. And also it was significantly higher in both pre menopausal and post menopausal obese women than that of subjects with normal weight[16].

Muayad S Rahma et al found a positive correlation between systolic and diastolic blood pressure and leptin level[64].

Duanduan Ma et al from their National Heart, Lung, and Blood Institute Family Heart Study, had found a significant association between plasma leptin levels and hypertension in women. And also Plasma leptin levels are correlated with SBP and DBP in women. However, after adjusted by BMI, the correlation appreciably

diminished, suggesting that the relationship between plasma leptin levels and blood pressure was mediated by BMI. No significant association was detected in men in their study[65].

In contrast Almeida – pititto et al in their study done on non diabetic Japanese – Brazilian women, have detected that there is no correlation between blood pressure and plasma leptin levels[40].

Keiko Wada et al in their study in Japanese men, showed that there exists a highly significant positive correlation between leptin levels and blood pressure, BMI and age. Leptin was positively related with diastolic blood pressure among the subjects in the normal blood pressure range but not with subjects having hypertension[66].

Studies related to serum leptin level and BMI:

FB Hu et al in their study done in rural Chinese population, have found that there was a significant correlation between leptin concentration and diastolic blood pressure but not the systolic blood pressure. Females had much higher leptin levels than males. Leptin levels in their study strongly correlated with BMI and waist hip ratio[67].

Waleed S. Mohamed et al in their study, found that plasma leptin level showed a significant positive correlation with BMI, waist circumference, systolic blood pressure and diastolic blood pressure in obese individuals and patients with metabolic syndrome[36].

In a cross sectional study done by Costas Thomopoulos et al found that masked hypertension was associated with increased plasma leptin and decreased leptin receptor levels independent of confounders like body size and metabolic parameters. They have also demonstrated that the healthy offspring of hypertensive patients are characterized by hyperleptinemia. So they have suggested that hyperleptinemia may precede and contribute to the development of hypertension rather than secondary to increased blood pressure[14].

Anoop Shankar and Jie Xiao et al observed a positive association between plasma leptin levels and hypertension in both age and sex adjusted model and the multivariable adjusted model. This association was seen both in normal weight and overweight / obese subjects. Their another important finding was, that the average plasma leptin levels were 3 times higher among women compared with men[15].

Gianvincenzo Barba et al had observed that leptin could have a prohypertensive effect. Plasma leptin levels were significantly and directly associated with blood pressure and BMI. The association still apparent when only normotensive subjects were considered independently of age and BMI. Elevated plasma leptin levels also associated with higher systolic and diastolic blood pressure[68].

Takuya Imatoh et al who performed conditional logistic regression analysis to analyze the association between serum leptin levels and hypertension, found that the subjects in the highest quartile of serum leptin levels had a significantly increased risk of hypertension compared with those in lowest quartile. They have also suggested that increased fasting plasma leptin levels appear to be related to various cardiovascular diseases including stroke and Myocardial infarction. Leptin thus seems to play an important role in development of cardiovascular diseases[69].

Anne E. Sumner et al in their study, established that leptin highly correlates with body fat mass. They also described a significant gender difference in leptin concentration, but there was no significant difference in leptin levels between pre and post menopausal women. They have also observed that there is no

relationship between leptin concentration and age. In conclusion leptin concentration in African Americans is determined by fat mass and gender[70].

Body mass index and waist circumference were strongly positively correlated with leptin concentration in men and women in Paul Zimmet et al cross sectional study. Waist to hip ratio was less strongly correlated with leptin concentration. Concentrations were higher in women than in men, even at the same body mass index or waist circumference[71].

Mikolaj Winnicki et al in their study observed a strong independent association between leptin levels and BMI. A Minocci and his colleagues had observed that leptin concentrations were significantly and directly related to BMI and inversely correlated with waist hip ratio in a single regression model. In multiple regression analysis WHR remained independently associated to leptin concentrations[72].

Rungsunn Tungtrongchitr et al found higher leptin concentration in overweight and obese subjects in Thai when compared with normal subjects. The medians of leptin were significantly higher in overweight and obese males than females[73].

San Antonio heart study which is a population based study, there is a significant gender difference in serum leptin levels after adjustment for BMI. According to them, the possible reason for the gender difference in leptin levels may be the differences in fat depots between men and women. Men have lower levels of overall adiposity but greater visceral adiposity than women[74].

Studies related to gender differences in serum leptin level:

Lonnqvist et al have shown that subcutaneous fat produces more leptin mRNA than visceral fat. This could explain why women have more leptin levels, as they have more subcutaneous fat than visceral fat[13].

In another study done by Constance E Ruhl and James E Everhart , women of all ethnic groups had substantially higher fasting serum leptin concentrations than men. Leptin concentrations were strongly correlated with various anthropometric measures in women and men, both in the univariate analysis and when age and ethnicity were controlled for. This study revealed that, leptin concentrations were associated with both waist and hip circumferences, circumference ratios and with skin fold thicknesses, independent of BMI[75].

Kwang Kon Koh et al had analyzed the results from clinical surveys on leptin interaction with cardiovascular diseases and observed that the plasma leptin is higher in male patients who subsequently develop first ever myocardial infarction than in control subjects. They have concluded that leptin is predictor of myocardial infarction, coronary events and stroke independent of body mass index[47].

S. Soederberg et al in their nested case referent study had observed that high levels of leptin were associated with high BMI, high systolic and diastolic blood pressure. They said that, circulating levels of leptin were found to be significantly associated with established cardiovascular risk factors such as elevated blood pressure and obesity. From their two subsequent studies, they have concluded that plasma leptin strongly predicts first - ever AMI (Acute Myocardial infarction) and also first – ever haemorrhagic stroke [76].

Martins and his colleagues had observed a strong correlation between BMI and serum leptin levels. In their study serum leptin levels in females were three times higher than in males. They have concluded that obesity defined by BMI was the strongest predictor

of high leptin levels and serum leptin could be considered as an additional component of metabolic syndrome and a new cardiovascular risk factor[77].

In their study done in newborn babies, Samsad Jahan and his colleagues found a significant difference in plasma leptin levels between male and female babies. The gender dimorphism in leptin production observed very early in life indicates the genetic difference in leptin production[78].

Hence leptin , which is an important factor in controlling food consumption and energy expenditure may have a role in development of hypertension through its various peripheral actions.

MATERIALS AND METHODOLOGY

Design of the study:

It is a cross sectional type of study.

Place of the study:

The study was conducted in Coimbatore Medical College and Hospital, Coimbatore.

Collaborating Departments:

Department of Medicine and Department of Biochemistry, Coimbatore medical college and Hospital, Coimbatore.

Period of study:

August 2013 to March 2014.

Study subjects:

A total of 90 subjects of age group 35 – 75 years were included in the study. Study group comprised of 48 subjects which include 26 males and 22 females with hypertension. They were selected from the hypertension outpatient department of Coimbatore medical college and hospital, Coimbatore.

Apparently 42 healthy individuals comprising of 22 males and 20 females with normal blood pressure were taken as control group.

Inclusion criteria:

Individuals having essential hypertension in the age group between 35 - 75 years were included in the study and age matched normotensive individuals were included as control group in the study.

Exclusion criteria:

Individuals having Diabetes mellitus and any other medical disorders that predisposes to secondary hypertension like renal problems, endocrine abnormalities, liver diseases, any chronic illnesses and their complications were excluded from the study.

Materials used for the study:

1. Proforma: To obtain detailed history, to record the vital parameters and to measure the anthropometric indices.
2. Portable weighing machine: To record the body weight in kilograms.
3. Stadiometer: To measure the standing height in centimetres.
4. Non elastic inch tape: To measure the waist and hip size in centimetres.
5. Standardized mercury sphygmomanometer: To record the blood pressure.

6. Euro immuno analyzer - To estimate serum leptin levels.

Methodology:

The study was initiated with the approval of institutional ethical committee. The study was carried out after explaining the procedures in detail and getting written informed consent from all the subjects.

The experimental protocol involved are,

1. Recording of a detailed history including family history to rule out Diabetes mellitus and history of Renal, liver diseases to rule out the causes of secondary hypertension.
2. Measurements of anthropometric indices:

   The subjects were asked to stand erect with their arms relaxed by their side and with feet together without shoes. By using a portable standard weighing machine, weight in kilogram was recorded.

   By using a stadiometer , height in centimetres was measured by asking the subject to stand erect without shoes and the vertical height was measured.

   Body mass index was calculated using the Quetelet's index,

   $$BMI = \text{weight (Kg)} / \text{height in meters}^2$$

3. Measurement of Waist circumference:

   Waist circumference was measured using an inch tape at the level of midpoint between the lower rib margin and the iliac crest at the end of normal expiration with the subject in standing position.

4. Measurement of hip circumference:

   Hip circumference was measured at the level of greater trochanter.

5. Measurement of blood pressure:

   First the subjects were asked to sit with arm and back supported and the legs uncrossed in an armed chair for 15 minutes in a quiet room with comfortable room temperature. Then blood pressure was recorded in all subjects using a standard sphygmomanometer having a cuff size of 25 x 12.5 centimetres. The mercury manometer was placed at his / her heart level. Then the blood pressure was recorded first by palpatory method and then by auscultatory method. After 10 minutes again blood pressure was recorded for the same individual by the same 2 methods. Mean value was taken for analysis.

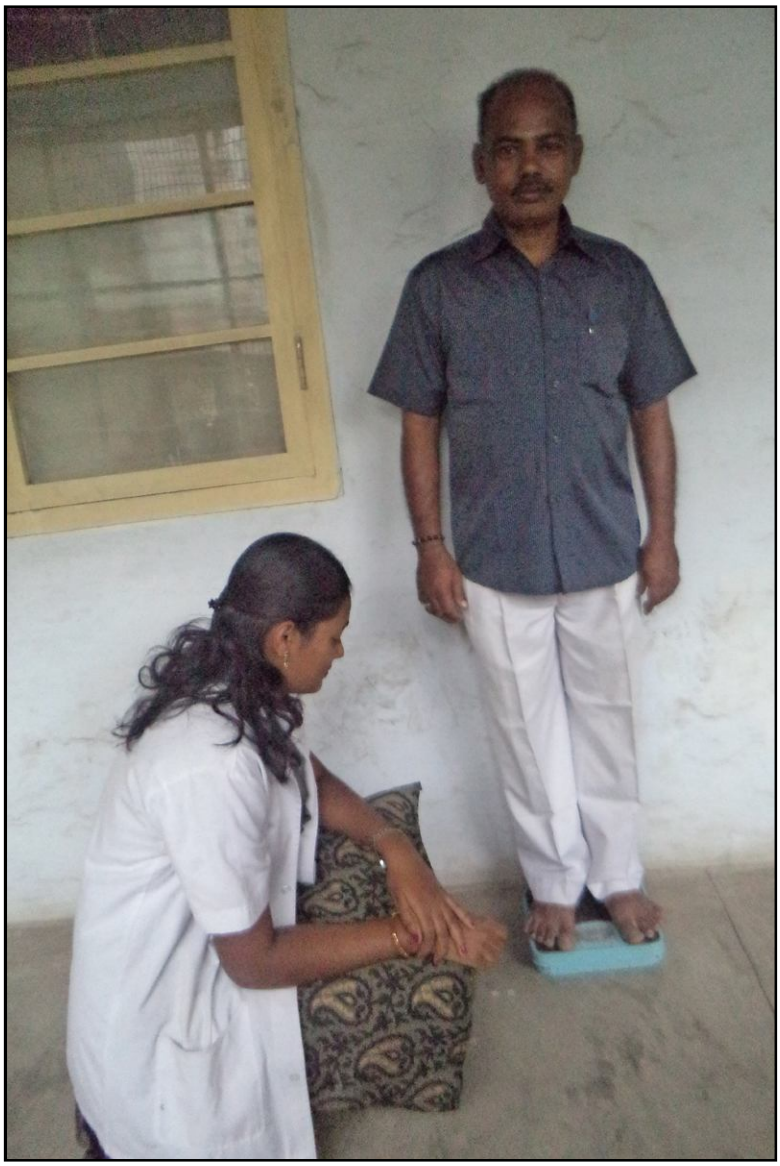
6. Blood investigations:

Blood sample was collected after overnight fasting. Ante cubital vein of the forearm was selected for venous blood collection. The skin over the vein was sterilized with spirit cotton swab. A disposable 5 ml syringe with sterile needle was introduced in to the vein and the required amount of blood was collected. The serum was separated by centrifuging the blood to 3000 rpm for 5 minutes.

The serum was used to estimate leptin level. This was done by Enzyme immuno sorbent assay using KAP 2281 Human leptin ELISA kit (diasource company).

MEASUREMENT OF HEIGHT

MEASUREMENT OF WEIGHT



MEASREMENT OF WAIST CIRCUMFERENCE

MEASUREMENT OF BLOOD PRESSURE

COLLECTION OF BLOOD SAMPLE

ESTIMATION OF LEPTIN BY ELISA

STATISTICAL ANALYSIS

STATISTICAL TOOLS

The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using **Epidemiological Information Package (EPI 2010)** developed by Centre for Disease Control, Atlanta.

Using this software range, frequencies, percentages, means, standard deviations, chi square, ‘t’ and 'p' values were calculated. ‘t’ test was used to test the significance of difference between quantitative variables and Yate’s and Fisher’s chi square tests for qualitative variables. A 'p' value less than 0.05 is taken to denote significant relationship.

RESULTS

RESULTS

Table 1: Age distribution in study group and control group

Groups	**Range in years**	**Mean ± SD**
Study group	36-72	54.4±8.3
Control group	35-72	51.3±9.4

Table 2 : Gender wise distribution between the study group and the control group

Sex	**Study group**		**Control group**	
	No	**%**	**No**	**%**
Male	26	54.2	22	52.4
Female	22	45.8	20	47.6

Age and gender wise distribution is same in both the study and the control group.

Figure : 1 Age distribution in study group and control group

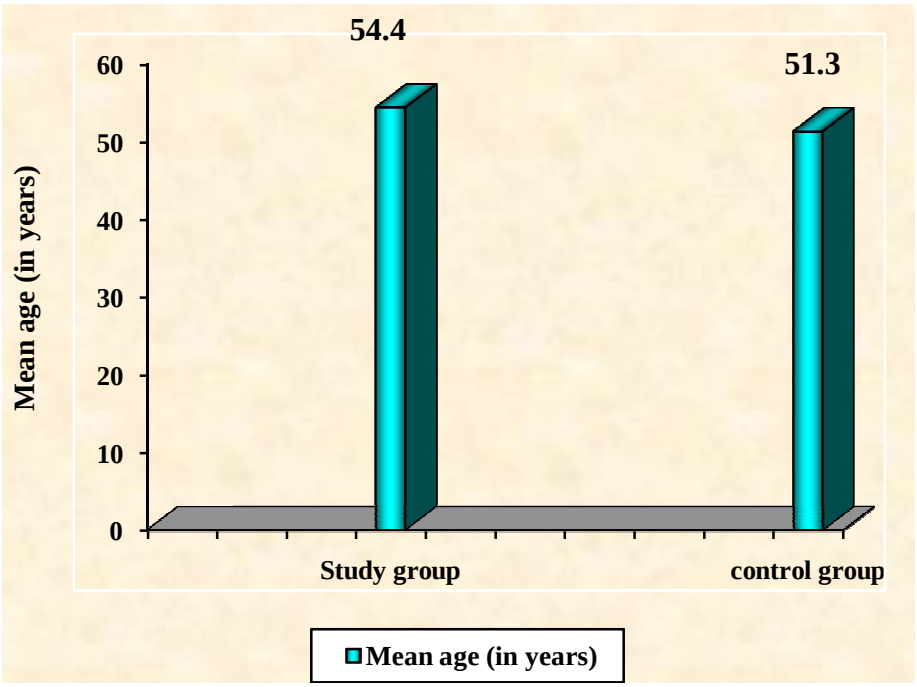


Figure 2 : Gender distribution between study group and control group

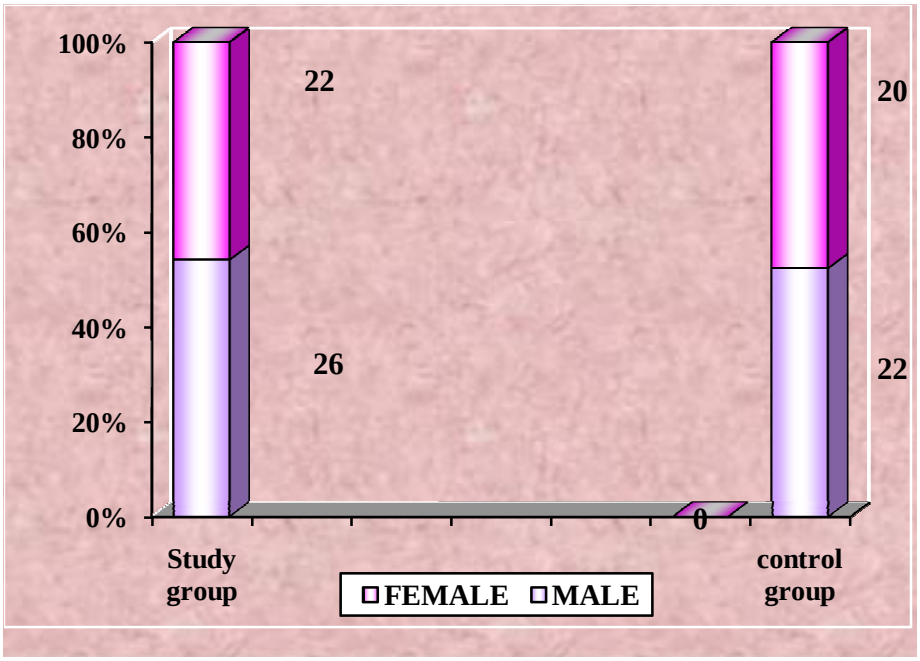


Table 3 : Comparison of Blood pressure between the study group and the control group

Group	Systolic blood pressure	Diastolic blood pressure
	Mean ± SD	**Mean ± SD**
Study group	158.1 ± 23.6	95.9 ± 9.6
Control group	113.3 ± 8.49	73.8 ± 7.0
'p'	**< 0.0001 significant**	**< 0.0001 Significant**

Both the systolic and diastolic blood pressure are high in cases when compared to controls and the difference is statistically significant.

Figure 3 : Comparison of Blood pressure between study group and control group

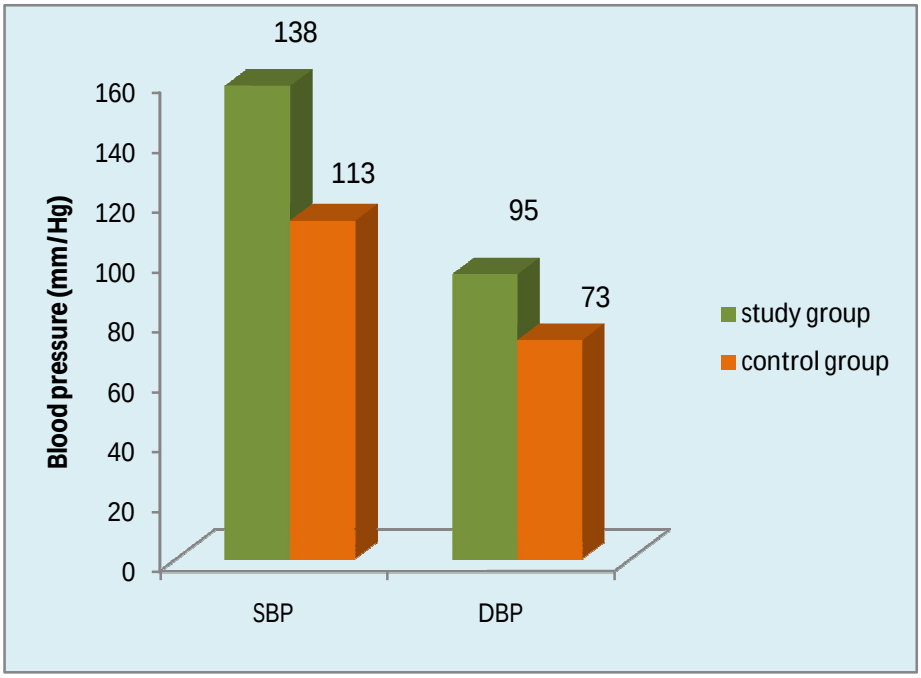


Table 4 : Comparison of serum leptin levels between the study group (hypertensive patients) and the control group (normotensive persons)

Groups	Blood pressure (mm/Hg)	Serum leptin levels (ng/ml)
	Mean ± SD	Mean ± SD
Study group	158.1 ± 23.6 / 95.9 ± 9.6	8.15 ± 2.68
Control group	113.3 ± 8.49 / 73.8 ± 7.0	1.74 ± 1.04

P< 0.0001 significant

Serum leptin levels are increased in the study group when compared to control group and the difference is statistically significant.

Figure 4 : Comparison of serum leptin levels in hypertensive patients (study group) and normotensive persons (control group)

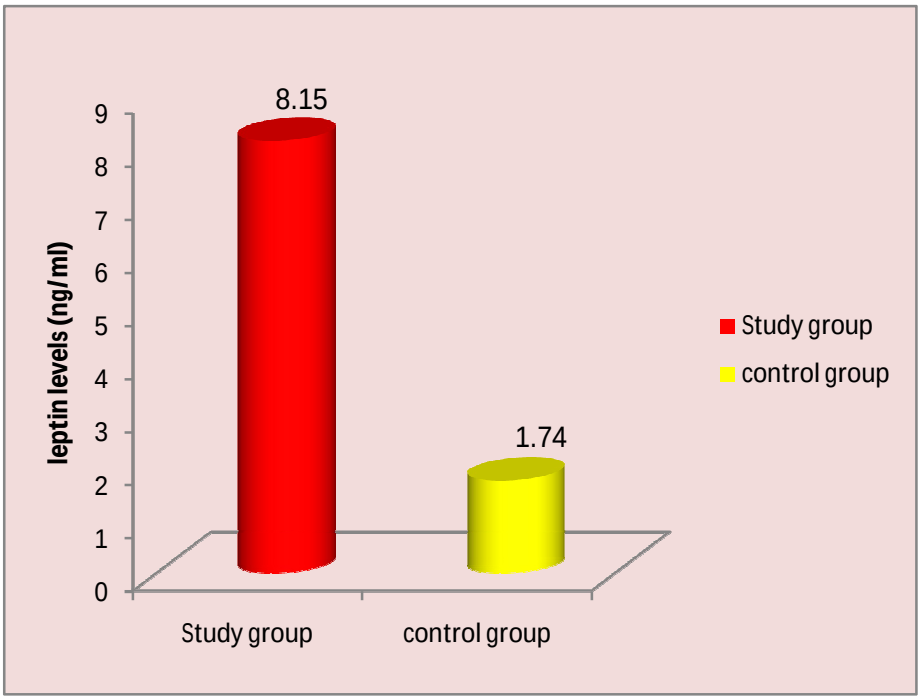


Table : 5 Comparison of systolic blood pressure and serum leptin levels

Groups	Systolic blood pressure (mm/Hg)	Serum leptin levels (ng/ml)
	Mean ± SD	**Mean ± SD**
Study group	161.0 ± 23.9	8.15 ± 2.68*
Control group	138.3 ± 4.1	1.74 ± 1.04

P < 0.0268 Significant

Increase in systolic pressure is associated with an increase in serum leptin levels and the difference is statistically significant.

Figure 5 : Comparison of systolic blood pressure and serum leptin levels

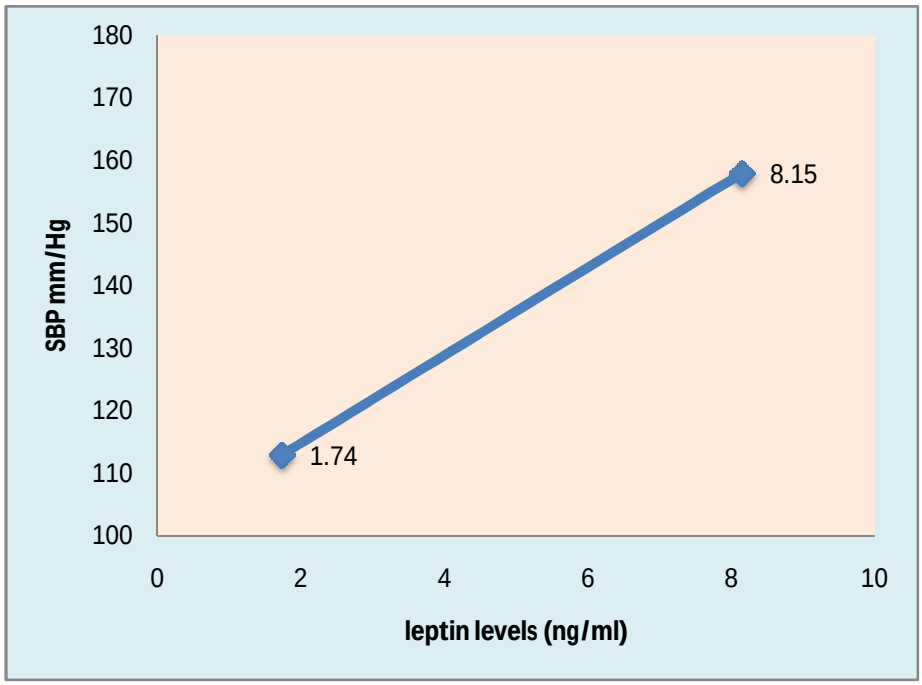


Table : 6 Comparison of Diastolic blood pressure and serum leptin levels

Groups	Diastolic blood pressure (mm/Hg)	Leptin levels (ng/ml)
	Mean ± SD	**Mean ± SD**
Study group	96.6 ± 9.5	8.15 ± 2.68*
Control group	91 ± 8.8	1.74 ± 1.04

P value = 0.1804 Not Significant

Increase in diastolic pressure is associated with an increase in serum leptin levels and the difference is not statistically significant.

Figure 6: Comparison of Diastolic blood pressure and leptin levels

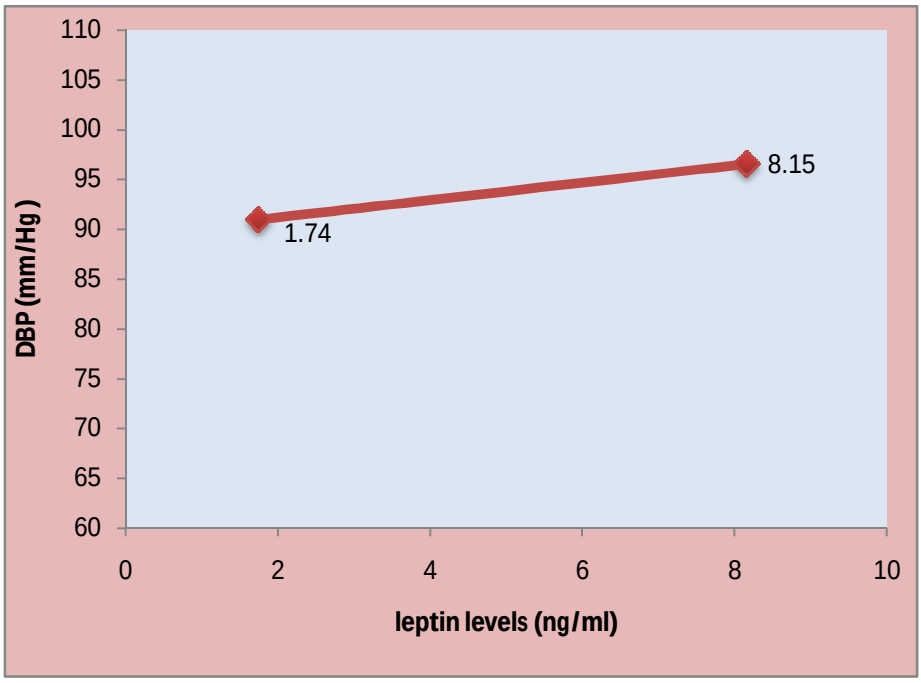


Table : 7 Gender differences in serum leptin levels in the study group

Gender	Number of hypertensive patients	Serum leptin levels (ng/ml)
		Mean ± SD
Males	26	7.81 ± 2.3
Females	22	8.44 ± 2.97

P= 0.4226 not significant

There is no statistically significant gender difference in serum leptin levels in the study group.

Figure 7: Gender differences in serum leptin levels in study group

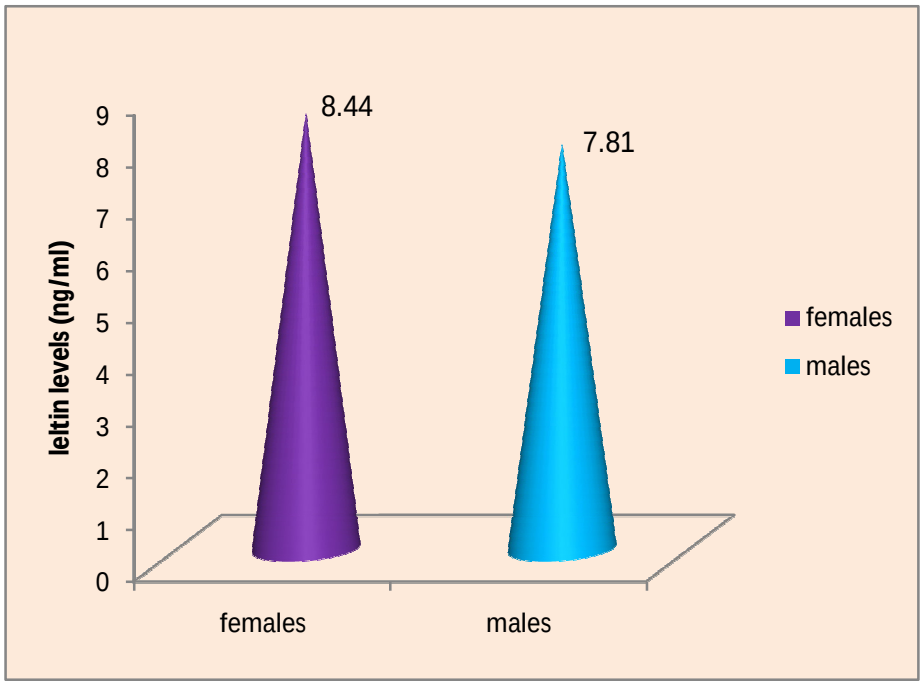


Table : 8 Comparison of age and serum leptin levels in the study group

Groups	Number of hypertensive patients	Serum leptin levels (ng/ml)
		Mean ± SD
Up to 40 years	1	5.5
41- 50 years	16	6.95 ± 1.96
51 – 60 years	23	8.77 ± 2.91
Above 60 years	8	9.11 ± 2.58

P< 0. 0001 significant

There is an increase in serum leptin levels as the age advances and the difference is statistically significant.

Figure 8: Comparison of age and serum leptin levels in study group

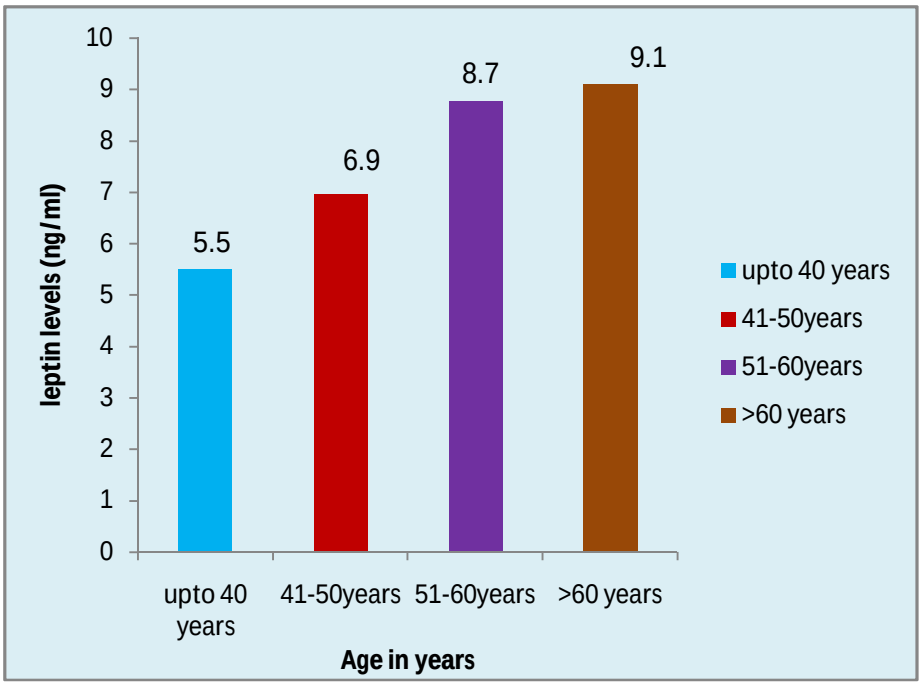


Table :9 Comparison of serum leptin levels and BMI in the study group

Groups according to BMI	Number of hypertensive patients	BMI	Serum leptin levels (ng/ml)
		Mean ± SD	Mean ± SD
Normal BMI (19 – 25)	10	27.16 ± 1.61	5.43 ± 1.59
Overweight (26- 30)	26	29.41± 2.62	6.82 ± 2.52
Obese (>30)	12	31.81 ± 1.43	8.63 ± 2.58

P <0.0467 significant

Increase in BMI is associated with an increase in serum leptin level and the difference is statistically significant.

Figure 9: Comparison of serum leptin levels and BMI in study group

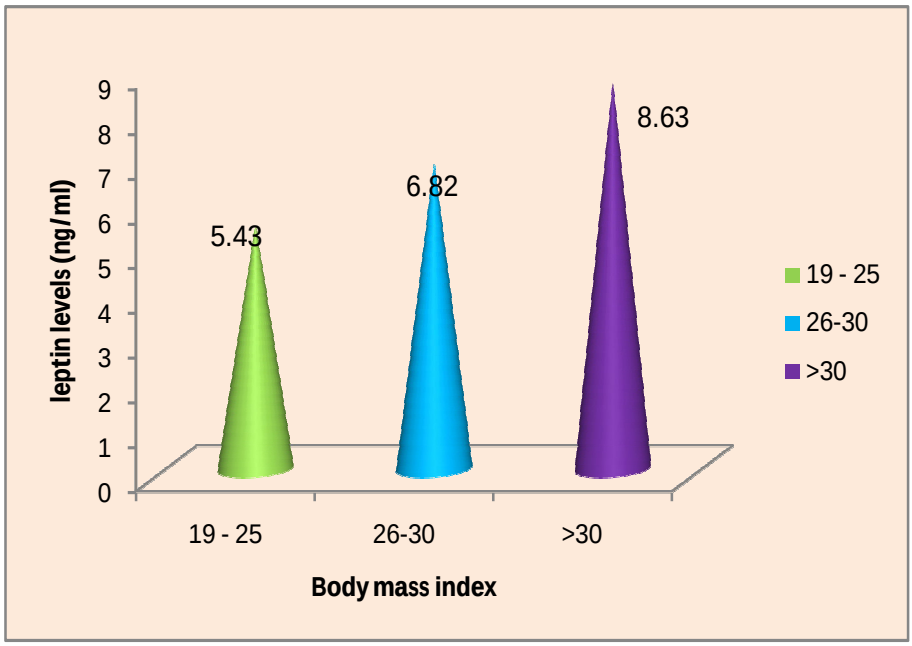


Table : 10 Comparison of Waist/ Hip ratio and serum leptin levels in the study group

Groups according to Waist Hip ratio	Number of hypertensive patients	Waist /Hip ratio	Serum leptin levels (ng/ml)
		Mean ± SD	Mean ± SD
0.85 – 0.90	12	0.88 ± 0.01	6.58 ± 2.20
0.91- 0.95	21	0.93 ± 0.01	7.06 ± 2.29
0.96 – 1.0	15	0.97 ± 0.01	8.33 ± 3.58

P<0.0001 significant

Increase in waist hip ratio is associated with an elevated serum leptin level and this association is statistically significant.

Figure : 10 Comparison of Waist/ Hip ratio and serum leptin levels in study group

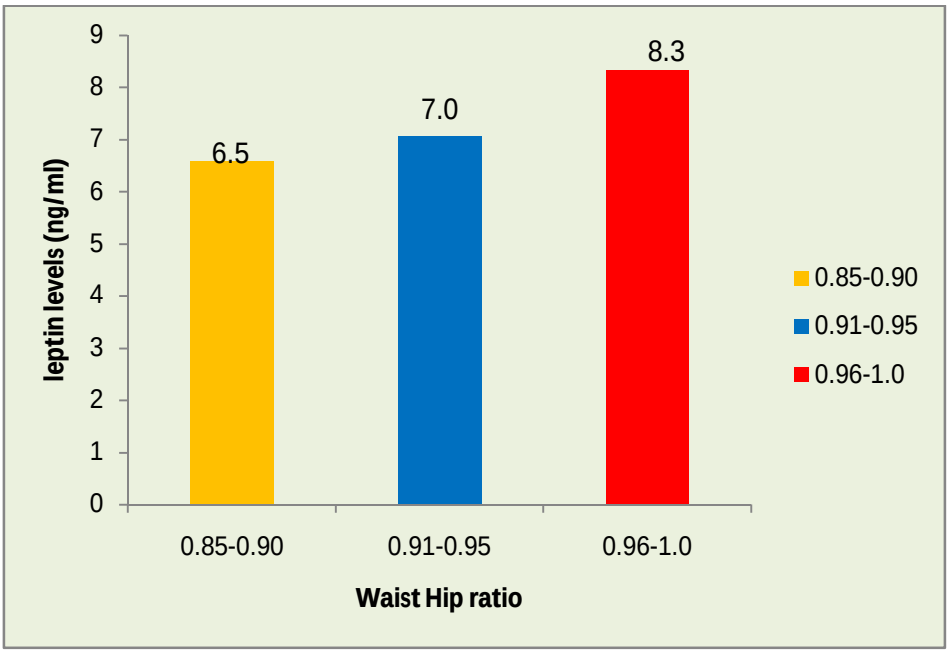


Table :11 Comparison of Waist / Height ratio and serum leptin levels in the study group

Groups according to Waist Height ratio	Number of hypertensive patients	Waist / Height ratio	Serum leptin levels (ng/ml)
		Mean ± SD	Mean ± SD
0.5	22	0.52 ± 0.02	6.33 ± 2.31
>0.5	26	0.63 ± 0.02	8.64 ± 2.79*

P <0.0001 significant

Increase in waist height ratio is associated with elevated serum leptin level and this association is statistically significant.

Figure 11: Comparison of Waist / Height ratio and serum leptin levels

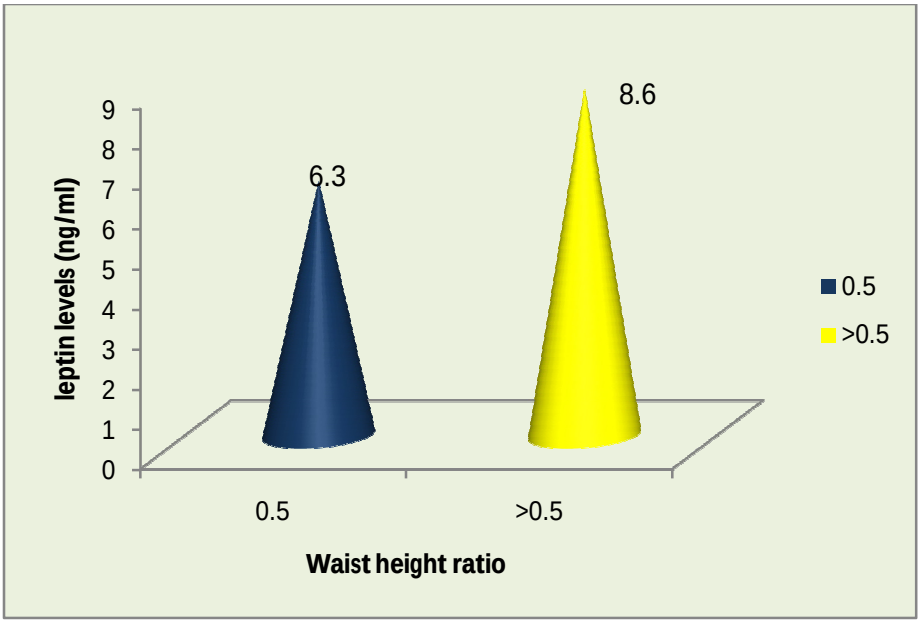


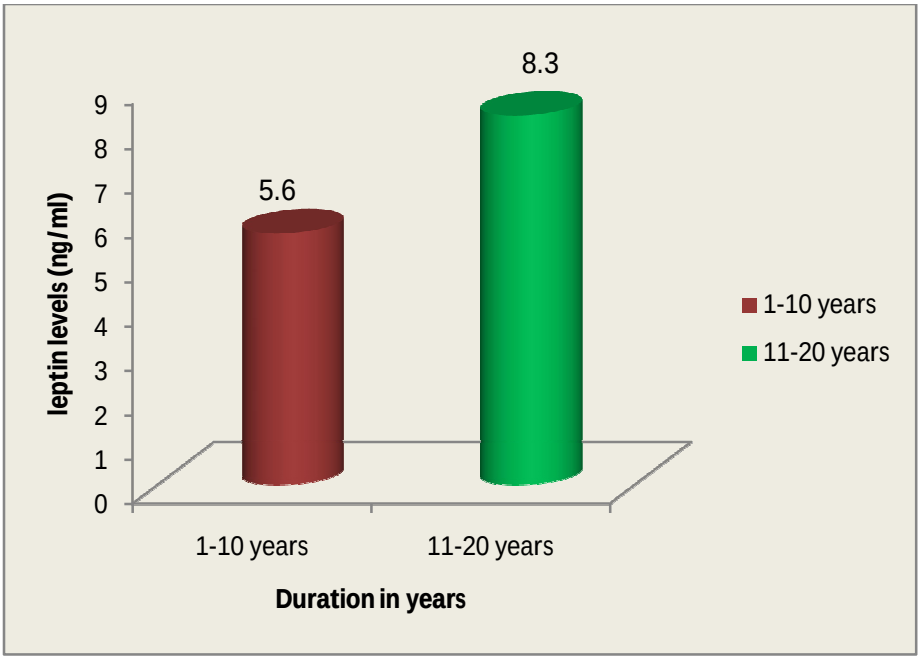
Table 12 : Comparison of duration of hypertension and serum leptin levels in the study group

Duration of hypertension (years)	Number of hypertensive patients	Serum leptin levels (ng/ml)
1-10	28	5.67 ± 2.16
11-20	20	8.33 ± 4.03*

P <0.0329 significant

Patients having long duration of hypertension have increased serum leptin levels when compared to short duration hypertensive patients. This difference is statistically significant.

Figure 12: Comparison of duration of hypertension and serum leptin levels



DISCUSSION

DISCUSSION

This present cross sectional study was done on 48 hypertensive patients in the age group between 35 to 75 years taken as study group and 42 individuals with normal blood pressure in the same age group taken as control group. They were classified as hypertensive and normotensive group according to the JNC 7 criteria. The mean blood pressure for the study group is about 158/ 96 mmHg and the control group is about 114/74 mm Hg.

In this study high serum leptin level is seen in hypertensive patients when compared to the persons with normal blood pressure. And also there is statistically significant correlation between serum leptin level and systolic blood pressure, age, BMI, waist hip ratio and waist height ratio in hypertensive patients. There is some difference in serum leptin levels between males and females, but this difference is not statistically significant.

Similar finding was observed by Anoop Shankar and Jie xiao et al, Costas thomopoulos et al, Kawaljit Kaur Khokhar et al, F. Galletti et al, Freddy Contreras et al, Gianvincenzo Barba et al and Takuya Imatoh et al, Muayad S Rahma et al, Duanduan Ma et al, Keiko Wada et al, FB Hu et al, Waleed S. Mohamed et al,

Anne E. Sumner et al, Mikolaj Winnicki et al, Rungsunn Tungtrongchitr et al, S. Soederberg et al.

In most of the previous studies they have concluded that leptin increases the blood pressure by activating the sympathetic nervous system. Renal sympathetic stimulation mediated by leptin is followed by increased sodium and water retention. Stimulation of renin secretion is also a contributor to the increase in blood pressure.

The mechanism of leptin in rising the blood pressure has been substantiated by animal experiments. An intracerebro ventricular injection of leptin increases the activity of both lumbar and renal sympathetic nerve and reduces arterial blood flow to the skeletal muscle[64].

In another study done in rats, acute systemic leptin administration increases the sympathetic nerve discharge to brown adipose tissue, kidneys, adrenal glands and hind limbs. In the same animal model, hypertension was reversed by administration of α adrenergic or sympathetic ganglionic blockade. Chronic leptin administration shifts the pressure natriuresis curve to the right thereby increases the sympathetic nerve activity and tubular sodium reabsorption[61].

Leptin also correlates positively with systolic and diastolic blood pressure[64,73]. This association between blood pressure and leptin was independent of BMI suggesting that leptin is a physiological mediator of some degree of diastolic blood pressure elevation in obesity[66]. The possible mechanism for strong association between leptin and diastolic blood pressure is that, leptin activates the sympathetic system which leads to an increase in peripheral resistance[66].

The association of leptin and hypertension was independent of traditional factors such as age, sex, smoking and alcohol intake, BMI, Diabetes mellitus and serum cholesterol[47].

F. Galletti et al did an eight year follow up study in 489 untreated normotensive subjects to detect whether serum leptin levels predict the development of hypertension. At the end of follow up period, 264 new cases of hypertension were detected. From this prospective study, they have concluded that, higher plasma leptin levels in normotensive adult male individuals are associated with an increased risk of developing hypertension independently of several potential confounders[61]. So circulating leptin acts as a significant predictor of hypertension development.

There is some evidence that the antihypertensive medications lower plasma leptin levels. So in all the previous studies done on hypertensive patients taking medications, there is a possibility that the observed association may be an underestimation of true existence. So Anoop Shankar and Jie Xiao et al have also done a supplementary analysis to exclude subjects with antihypertensive medications, even then the association between leptin and hypertension was similar. So they have concluded that plasma leptin levels may serve as a novel adipose tissue derived biomarker for hypertension[15].

The investigation of a large random sample of untreated male participants of the Olivetti heart study shows a graded , statistically significant and clinically relevant association between plasma leptin concentration and blood pressure. It is largely independent of body mass and abdominal adiposity. Elevated levels of plasma leptin in the presence of excess central adiposity reflect a condition called leptin resistance, characterized by the inability of leptin to promote a reduction in body fat accumulation. In that study it was not concluded whether resistance to the physiological effect of leptin

on visceral fat is matched by resistance to other peripheral effects of this hormone.

These results contribute to the understanding of the mechanistic pathways linking overweight and abdominal adiposity to high blood pressure and are relevant to the prevention of the cardiovascular complications of this epidemic metabolic alteration[73].

Leptin and its association with BMI:

In this present study increased serum leptin level is associated with increase in BMI[66], waist hip ratio and waist height ratio. It is similar to the findings of previous studies[36,72]. Leptin concentrations were strongly correlated with various anthropometric measures in women and men, both in the univariate analysis and when age and ethnicity were controlled for. It was revealed that, leptin concentrations were associated with both waist and hip circumferences, circumference ratios and with skin fold thicknesses, independent of BMI[79].

Body mass index and waist circumference were strongly positively correlated with leptin concentration in both men and women[43,77]. Waist hip ratio also strongly correlated with leptin concentration[42]. Concentrations were higher in women than in men, even at the

same body mass index or waist circumference. So it was suggested that blood leptin concentration was regulated by important variables like physical activity, nutritional factors, genotype, fat distribution , insulin and other hormones[71].

Technologies such as bioelectric impedance, hydrodensitometry and dual energy X - ray absorptiometry (DEXA) have shown a strong correlation between leptin and fat mass, weight, percent body fat and BMI[70].

Several studies also found that leptin concentrations were significantly correlated with fat distribution independent of overall obesity. Presence of excessive adipose tissue produces excess hormone leptin. But selective resistance occurs to its weight reducing action[73]. So high level of appetite inducing hormone leptin is seen in obesity. The reason for this is, may be the presence of abnormal leptin protein and leptin receptor protein . This may be because of the mutation in ob gene resulting in malfunctioning of leptin protein. This mutation causes synthesis of a truncated receptor lacking both the transmembrane and the intracellular domain. It blocks binding of leptin to the membrane bound receptor cell in the hypothalamus and led to the hypothesis

of resistance to the action of leptin at the level of hypothalamus causing increased appetite and decreased energy expenditure despite adequate leptin production by adipocytes[73].

More recently it was found that blood brain barrier transportation has a threshold level for serum leptin (about 25 – 30 ng/ml) beyond which increase in serum leptin levels are not translated into proportional increase in cerebrospinal or brain leptin levels.

Sexual dimorphism in serum leptin levels:

In this present study there is a gender difference in serum leptin levels. Females are having high serum leptin levels when compare to males. But the difference is not statistically significant. But many studies have found a statistically significant gender difference in serum leptin levels. Women have more serum leptin levels than men[62,74-75,77]. According to them, the possible reason for the gender difference in leptin levels may be the difference in fat depots between men and women. Men have lower levels of overall adiposity but greater visceral adiposity than women[74]. Females are having more subcutaneous fat than males. Subcutaneous fat produces more leptin mRNA than visceral fat[13,77]. This could

explain why women have more leptin levels, as they have more subcutaneous fat than visceral fat.

So the difference in body fat distribution and the inducing effects of estrogen, progesterone combined with the suppressive effect of androgens on leptin might be the reason for gender difference in serum leptin levels[65]. Leptin regulators such as proopiomelanocortin contain estrogen and testosterone responsive elements.

In one such study, women of all ethnic groups had substantially higher fasting serum leptin concentrations than men. Heightened hypothalamic feedback loop in leptin adiposity regulation in female is the mechanism suggested by them. Samsad Jahan and his colleagues did a study in newborn babies to find out the gender difference in plasma leptin levels. They found a significant difference in leptin levels between male and female babies. So the gender dimorphism in leptin production observed very early in life indicates the genetic difference in leptin production[78].

Another possible explanation for the sexual dimorphism in leptin levels could be differences in the hypothalamus between women and men. Leptin exerts its effect by suppressing hypothalamic neuropeptide Y synthesis thereby decreasing food intake. There are

gender differences in the regional distribution of neuropeptide Y mRNA containing cells in the hypothalamus. However it is not known whether this structural gender difference in hypothalamus is associated with functional differences in leptin signalling and leptin levels[74].

But studies related to serum leptin levels in pre and post menopausal subjects suggested that estradiol concentration is not responsible for the gender difference in serum leptin levels[70,80].

It has been also observed that there is no relationship between leptin concentration and age. Menopausal status, age, Diabetes and body fat distribution do not appear to modulate leptin physiology[74].

Influence of plasma leptin levels in development of cardiovascular complications:

Circulating levels of leptin were found to be significantly associated with established cardiovascular risk factors such as elevated blood pressure and obesity[76]. Increased fasting plasma leptin levels appear to be related to various cardiovascular diseases including stroke and Myocardial infarction[7,50,53,72,81]. Leptin thus seems to play an important role in development of complications of obesity and hypertension.

In one of the previous studies, they had analyzed the results from clinical surveys on leptin interaction with cardiovascular diseases and observed that the plasma leptin is higher in male patients who subsequently develop first ever myocardial infarction than in control subjects. They have concluded that leptin is a predictor of myocardial infarction, coronary events and stroke independent of body mass index[47].

In another study also, they have concluded that plasma leptin strongly predicts first - ever AMI (acute myocardial infarction) and also first – ever haemorrhagic stroke[76] . Thus serum leptin could be considered as an additional component of metabolic syndrome and a new cardiovascular risk factor[48,77].

The following mechanism is proposed to the development of complications: Leptin receptors have also been identified in blood vessels, where they promote angiogenesis[72]. Previous reports have shown that high levels of leptin was associated with insulin resistance and increase in markers of inflammation including high sensitivity CRP levels[58,81].

Farhan Jaleel and Anila Jaleel et al observed a significant positive correlation between leptin and lipid profile except HDL cholesterol in their study[12,43]. These cluster of risk factors like insulin resistance and abnormal lipid profile contribute to the development of metabolic syndrome thereby promoting cardiovascular complications.

In our study we observed a strong positive correlation between serum leptin levels and blood pressure in association with BMI, waist hip ratio, waist height ratio. So high serum leptin level in healthy individuals would indicate future development of hypertension whereas in hypertensives it would indicate increased risk of development of complications. So it is necessary to do an estimation of serum leptin level in all hypertensive patients and persons who are in at risk of developing hypertension.

SUMMARY

SUMMARY

- Serum leptin level is increased in hypertensive patients when compared to normotensive individuals. And also there is positive correlation between serum leptin level and systolic blood pressure in hypertensive patients.

- Increased serum leptin level is associated with increase in Body mass index, Waist hip ratio and Waist height ratio.

- As age advances serum leptin level also increases in hypertensive patients. High serum leptin level is associated with long duration of hypertension.

- There is no gender difference in serum leptin levels in hypertensive patients.

CONCLUSION

CONCLUSION

In developed and developing countries, hypertension has been identified as an expanding health crisis. It is one of the cardinal risk factor for cardiovascular and cerebrovascular complications thereby one of the leading cause of disability and death worldwide. So it has to be detected at the earliest possible stage and treated properly.

Hypertension has a multifactorial etiology, and there are several hypothesis postulated regarding its pathophysiology. One such recent hypothesis is, chronic elevation in serum leptin level leading to the development of hypertension. The mechanism behind this is, leptin causes wide spread activation of the sympathetic nervous system, sodium retention by kidneys, activation of Renin Angiotensin system, stimulation of reactive oxygen species, impaired nitric oxide (NO) production and increased endothelin 1 synthesis thereby resulting in elevation of blood pressure.

Though the central action of leptin is mainly appetite suppression and increase in energy expenditure, high serum leptin levels are seen in obese persons. Since leptin is synthesised from adipose tissue, hyperleptinemia is found in obesity, which is a major

comorbid condition of hypertension. In these patients, selective resistance develops to the central weight reducing actions of leptin whereas peripheral actions like sympathoexcitatory actions of leptin are preserved.

There is a strong positive correlation between serum leptin level and high blood pressure, body mass index, waist hip ratio and Waist height ratio in this present study.

There is also evidence that leptin has a prohypertensive effect, that is increased free leptin level predicts the future development of hypertension. So in high risk individuals like persons with increased BMI, increased waist hip ratio, increased waist height ratio and healthy off springs of hypertensive parents, estimation of serum leptin level may be helpful to predict the risk of developing hypertension in the future.

Leptin seems to play an important role in development of cardiovascular complications. Recent studies report that plasma leptin levels could contribute to various cardiovascular events including stroke and myocardial infarction. Hypertension itself is a risk factor for those complications and leptin acts as an added risk to that.

Hence leptin in hypertension has become a topic of extensive ongoing research and this may contribute to the emerging concept that serum leptin level may serve as a biomarker for hypertension and its complications.

LIMITATION OF THE PRESENT STUDY:

In this present study, sample size is very small. A large sample size and longitudinal study will be of great value to demonstrate the positive association between serum leptin level and blood pressure in our population.

FUTURE SCOPE OF THE STUDY :

The study can be extended as a prospective study to find out the association between high serum leptin level and incidence of hypertension in healthy individuals.

Future studies should emphasize the association between serum leptin levels and complications of hypertension. The possible beneficial role of recombinant leptin administration in the treatment of obesity and prevention of metabolic syndrome and cardiovascular complications can be found out.

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ANNEXURES

CONSENT FORM

Dr.G.Malarvizhi, Post graduate student in the department of physiology, Coimbatore Medical College is studying 'Serum Leptin level and its association with Blood Pressure, Body Mass Index, Waist Hip Ratio and Waist Height Ratio'. The test procedures of the measurement of height, weight, waist and hip circumference, collection of blood specimen, recording of blood pressure with sphygmomanometer were explained to me clearly. I understand that there are no risks involved in the above procedure.

I hereby give my consent to participate in this study. The data obtained herein may be used for research and publication.

Name:

Place:

Sign :

PROFORMA

Name:

Age:

Sex:

Occupation:

Address:

Phone number:

Present history of Hypertension:

H/O Duration :

H/O Drug intake :

H/O any complications:

- Chest pain
- Transient ischemic attacks
- Puffiness of face
- Any visual problems
    - Photopsia
    - Metamorphosis
    - Black spots
    - Floaters

History to rule out Secondary Hypertension:

- H/O Snoring
- H/O Excessive day time sleepiness
- H/O Apnoea

- H/O Nocturnal arousal
- H/O any substance abuse (Amphetamine/Cocaine)
- H/O Drug intake:
    1.Decongestants
    2.Oral contraceptives
    3.NSAIDS
    4.Exogenous thyroid
    5.Hormone replacement therapy
- H/O Weight gain
- H/O Weight loss
- H/O Claudication
- H/O Puffiness of face in early morning
- H/O Decreased urine output
- H/O Bladder incontinence
- H/O Postural Hypotension
- H/O Light headedness

Past history:

H/O Diabetes Mellitus

H/O Any renal diseases

H/O Any liver diseases

H/O Thyroid disorder

Family history:

H/O Systemic hypertension, Diabetes mellitus

Personal history:

H/O Smoking and H/O Alcohol intake.

GENERAL EXAMINATION:

Built:

Height:

Weight: BMI:

Waist circumference : Hip Circumference :

WHR : WHtR :

Peri orbital puffiness, thick dry skin
Pallor, Icterus, Clubbing, Cyanosis
Lymphadenopathy, Pedal edema.

Vital signs :

PR: RR:

BP: Temp:

SYSTEMIC EXAMINATION

INSPECTION

- Shape of the chest
- Apical Impulse
- JVP
- Movement of the chest
- Visible Pulsations
- Engorged veins in the neck , engorged and dilated superficial veins over the precardium.

PALPATION

- Position of trachea
- Apex Beat
- Parasternal Heave
- Thrill

AUSCULTATION:

CVS:

Heart sounds :

Murmur :

RS:

Breath sounds :

Added sounds :

P/A:

Soft :

Tenderness :

Distension:

CNS :

Focal neurological deficit :

INVESTIGATIONS

Fasting serum leptin level :

MASTER CHART

MASTER CHART

Study group : Hypertensive patients; Males

S.No	Sex	age	leptin	SBP	DBP	BMI	hight	weight	waist	hip	WHR	WHtR	Duration
1.	MALE	48	6.2	160	90	27	172	80	89	95	0.96	0.51	7
2.	MALE	36	5.5	140	100	26.95	168	76	94	98	0.95	0.55	2
3.	MALE	49	7.3	186	110	29.53	154	70	99	106	0.93	0.64	6
4.	MALE	68	13.4	210	110	32.82	162	86	102	106	0.96	0.62	10
5.	MALE	59	14.9	180	96	29.49	167	82	101	105	0.96	0.6	12
6.	MALE	45	6.7	148	92	28.47	174	86	96	100	0.96	0.55	5
7.	MALE	50	3.6	140	90	28.48	178	90	96	100	0.96	0.53	7
8.	MALE	43	9.4	170	86	30.17	169	86	103	108	0.95	0.6	3
9.	MALE	49	4.8	130	76	29.77	176	92	101	106	0.95	0.57	7
10.	MALE	48	10.2	160	100	29.41	175	90	96	100.5	0.95	0.54	8
11.	MALE	70	8.4	166	110	32.83	163	87	106	108	0.98	0.65	20
12.	MALE	50	6.6	158	100	32.2	172	95	104	106	0.99	0.6	5
13.	MALE	55	12.5	180	90	32.08	164	86	99	103	0.95	0.6	10
14.	MALE	48	5.3	132	76	29.12	176	90	99.5	104	0.95	0.56	7
15.	MALE	42	8.6	160	80	31.16	152	72	102	104	0.98	0.67	4
16.	MALE	51	11.6	160	100	31.03	179	90	99	105	0.94	0.55	8
17.	MALE	55	10.3	180	110	30.88	161	80	98	102	0.94	0.6	9
18.	MALE	57	6.4	148	92	24.26	165	66	88	93	0.94	0.53	10
19.	MALE	53	5.5	168	96	28.36	168	80	98	102	0.95	0.58	5
20.	MALE	53	5.5	120	92	27.84	154	66	99	104	0.94	0.64	3
21.	MALE	65	7.8	140	90	27.18	176	84	94	98	0.95	0.53	10
22.	MALE	59	9.7	162	96	28.1	175	86	92	97	0.94	0.52	8
23.	MALE	55	11.8	210	110	28.08	171	82	95	100	0.95	0.55	10
24.	MALE	67	12.4	184	100	31.22	162	84	101	104	0.97	0.62	12
25.	MALE	43	7.4	190	90	32.04	153	74	100.5	103	0.97	0.65	4
26.	MALE	57	7.6	130	76	26.08	186	90	92	97	0.94	0.49	7

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; WHR: Waist hip ratio; WHtR: Waist height ratio

Study group : Hypertensive patients; Females

S.No	Sex	age	leptin	SBP	DBP	BMI	hight	weight	waist	hip	WHR	WHtR	duration
1.	FEMALE	69	6.2	160	100	30.18	163	80	90	102	0.88	0.55	12
2.	FEMALE	72	8.4	176	102	28.12	152	65	87	98	0.86	0.57	15
3.	FEMALE	48	5.2	140	100	26.47	165	72	92	100	0.92	0.55	7
4.	FEMALE	46	9.9	180	110	31.96	148	70	102	110	0.92	0.68	6
5.	FEMALE	59	13.4	130	90	27.19	151	62	87	98	0.88	0.57	10
6.	FEMALE	55	8.8	140	90	25.3	158	63	88	99	0.88	0.55	8
7.	FEMALE	65	6.7	160	110	31.7	157	78	97	106	0.91	0.61	5
8.	FEMALE	59	8.9	210	110	37.25	143	76	102	110	0.92	0.71	8
9.	FEMALE	56	7.9	130	100	30.53	162	80	95	102	0.93	0.58	6
10.	FEMALE	60	6.7	140	98	29.68	161	76	90	102	0.88	0.55	10
11.	FEMALE	60	6.8	180	100	32.93	158	82	101	108	0.93	0.63	20
12.	FEMALE	41	5.1	140	90	26.58	159	67	85	96	0.88	0.53	4
13.	FEMALE	56	4.1	140	100	25.66	163	68	86	98	0.87	0.52	7
14.	FEMALE	60	9.8	140	90	28.12	160	72	84	96	0.87	0.52	10
15.	FEMALE	57	12.1	160	110	32.05	153	75	102	110	0.92	0.66	12
16.	FEMALE	58	7.7	140	90	24.05	143	50	82	96	0.85	0.57	10
17.	FEMALE	55	5.7	160	100	27.08	155	65	90	98	0.89	0.58	6
18.	FEMALE	45	6.2	120	80	28.91	158	72	93	102	0.9	0.58	5
19.	FEMALE	55	8.4	140	100	27.92	149	62	87	99	0.88	0.58	8
20.	FEMALE	65	9.6	152	96	26.96	143	55	89	98	0.9	0.62	12
21.	FEMALE	53	5.5	140	90	25.98	170	68	85	95	0.89	0.5	2
22.	FEMALE	43	8.7	200	90	29.19	146	62	91	102	0.89	0.62	2

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; WHR: Waist hip ratio; WHtR: Waist height ratio

Control group : Normotensive males

S.No	Sex	age	leptin	SBP	DBP	BMI	hight	weight	waist	hip	WHR	WHtR
1.	MALE	35	2.2	110	70	26	171	76	92	100	0.92	0.53
2.	MALE	42	0.5	130	78	24.07	180	78	89	98	0.9	0.49
3.	MALE	45	1.3	120	80	24.26	180	84	94	101	0.93	0.52
4.	MALE	52	1.4	118	60	23.16	161	60	90	99	0.9	0.55
5.	MALE	68	3.7	120	80	25.88	176	80	91	97	0.93	0.51
6.	MALE	56	1.4	110	76	23.66	184	80	92	100	0.92	0.5
7.	MALE	72	2.7	112	80	24.05	178	76	88	96	0.91	0.49
8.	MALE	61	0.5	120	70	24.26	184	82	92	98	0.93	0.5
9.	MALE	55	0.4	110	70	22	186	60	86	98	0.87	0.46
10.	MALE	54	0.6	120	80	23.05	172	68	90	101	0.89	0.52
11.	MALE	66	1.4	100	60	24.82	168	70	91	98	0.92	0.54
12.	MALE	44	1.8	110	80	25.55	177	80	98	104	0.94	0.55
13.	MALE	48	1	120	70	25.98	182	86	99	106	0.93	0.54
14.	MALE	54	0.6	120	80	23.52	170	68	91	100	0.91	0.53
15.	MALE	43	0.4	110	70	24.55	183	82	92	98	0.93	0.5
16.	MALE	39	0.8	116	76	25.89	167	72	96	102	0.94	0.57
17.	MALE	58	0.6	110	80	25.16	174	76	98	104	0.94	0.56
18.	MALE	57	2.2	100	80	22.87	175	70	88	98	0.89	0.5
19.	MALE	45	2.5	100	70	24.07	180	78	91	101	0.9	0.5
20.	MALE	43	1.2	110	70	26.75	173	80	100	104	0.96	0.57
21.	MALE	48	0.3	120	82	26.08	186	90	99	103	0.96	0.53
22.	MALE	46	2.6	90	60	25.88	176	80	96	102	0.94	0.54

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; WHR: Waist hip ratio; WHtR: Waist height ratio

Control group : Normotensive females

S.No	Sex	age	leptin	SBP	DBP	BMI	hight	weight	waist	hip	WHR	WHtR
1.	FEMALE	43	0.9	122	78	24.07	146	52	82	92	0.89	0.56
2.	FEMALE	67	1.6	120	80	23.8	152	55	78	90	0.86	0.51
3.	FEMALE	45	1.9	110	68	25.48	161	66	86	96	0.89	0.53
4.	FEMALE	62	1.9	100	60	24.52	163	65	76	88	0.86	0.46
5.	FEMALE	65	1.7	104	78	20.88	158	52	74	84	0.88	0.46
6.	FEMALE	56	1.4	110	70	25.45	166	70	88	92	0.95	0.53
7.	FEMALE	38	2.1	120	80	25.51	156	62	81	94	0.86	0.51
8.	FEMALE	48	3.7	130	76	25.6	157	63	79	91	0.88	0.5
9.	FEMALE	40	1.2	120	78	25.97	152	60	84	96	0.87	0.55
10.	FEMALE	42	0.6	112	76	25.22	149	56	87	99	0.87	0.58
11.	FEMALE	47	1.5	120	70	27.16	163	72	92	102	0.9	0.56
12.	FEMALE	56	3	110	68	26.56	160	68	89	97	0.92	0.55
13.	FEMALE	66	0.3	110	70	24.09	158	60	80	89	0.89	0.5
14.	FEMALE	43	2.5	120	82	27.08	155	65	90	98	0.91	0.58
15.	FEMALE	48	3.2	116	86	27.57	165	75	90	101	0.89	0.54
16.	FEMALE	55	3.6	120	78	26.5	158	66	86	98	0.87	0.54
17.	FEMALE	62	2.7	110	60	22.9	162	60	80	90	0.88	0.49
18.	FEMALE	46	3.6	110	70	25.37	164	68	84	96	0.87	0.51
19.	FEMALE	43	3.2	120	80	26.5	158	66	96	104	0.92	0.6
20.	FEMALE	51	2.3	100	70	26.58	154	63	90	98	0.91	0.58

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index; WHR: Waist hip ratio; WHtR: Waist height ratio