“STUDY OF INSULIN RESISTANCE AND INFLAMMATION IN RELATION TO VARIOUS DEGREES OF BLOOD PRESSURES IN ADULTS - A ONE YEAR CROSS SECTIONAL STUDY”

REG NO. BG0110001

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

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ENDORSEMENT

This is to certify that the dissertation entitled **"STUDY OF INSULIN RESISTANCE AND INFLAMMATION IN RELATION TO VARIOUS DEGREES OF BLOOD PRESSURES IN ADULTS - A ONE YEAR CROSS SECTIONAL STUDY"** is a bonafide research work done by **THE CANDIDATE REG NO. BG0110001.**

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LIST OF ABBREVIATIONS USED

ACE	- Angiotensin converting enzyme
AGT	- Angiotensinogen
ALLHAT	- Antihypertensive lipid lowering treatment to avoid heart attack
AMP	- Adenosine monophosphate
ANG	- Angiotensin
ANOVA	- Analysis of variance
ARB	- Angiotensin receptor blocker
ATP	- Adenosine triphosphate
BMI	- Body mass index
CAD	- Coronary artery disease
CCB	- Calcium channel blocker
CHARM	- Candesartan in Heart Failure: Assessment of reduction in mortality and morbidity
CKD	- Chronic kidney disease
CMS	- Cardiometabolic syndrome
COPD	- Chronic obstructive pulmonary disease
CRP	- C reactive protein
CVD	- Cardiovascular disease
CVD	- Cardiovascular disease
DBP	- Diastolic blood pressure
DM	- Diabetes mellitus
ELISA	- Enzyme linked immunosorbent assay
ET	- Endothelin
FBS	- Fasting blood sugar

FFA - Free fatty acid

GH - Growth hormone

GH - Growth hormone

GLP - Glucagon like peptide

GLUT - Glucose transporter

HDL - High density lipoprotein

HIV - Human immunodeficiency virus

HOMA - Homeostasis model assessment

hs-CRP - Highly sensitive C reactive protein

HTN - Hypertension

IDF - International diabetes federation

IGF - Insulin like growth factor

IGT - Impaired glucose tolerance

IL-6 - Interleukin 6

IR - Insulin resistance

IRS - Insulin receptor substrate

JNC - Joint National Committee

LDL - Low density lipoprotein

LPL - Lipoprotein lipase

MAPK - Mitogen activated protein kinase

NCEP ATP III - National Cholesterol Educational Programme Adult Treatment Panel

NHANES - National health and nutritional examination survey

NO - Nitric oxide

NOS - Nitrate oxide synthase

PCOS	- Polycystic ovarian syndrome
PI3K	- Phosphatidyl inosotol 3 kinase
PPAR	- Peroxisome proliferators activated receptor
PPBS	- Post prandial blood sugar
QUICKI	- Quantitative insulin check index
RAAS	- Renin angiotensin aldosterone system
ROS	- Reactive oxygen species
SBP	- Systolic blood pressure
SMC	- Smooth muscular cells
SNS	- Sympathetic nervous system
TG	- Triglyceride
TNF	- Tumor necrosis factor
TZD	- Thiazolidinediones
VEGF	- Vascular endothelial growth factor
VLDL	- Very low density lipoprotein
WOSCOPS	- West of Scotland Coronary Prevention Study

ABSTRACT

Background and objectives

There has been increasing number of evidences connecting insulin resistance to future cardiovascular events in hypertensives suggesting that insulin resistance is the basis for the so called metabolic syndrome irrespective of diabetic status. The present study was aimed to assess the insulin resistance and inflammation in relation to various degrees of blood pressures in non diabetic adults and to evaluate insulin resistance as a marker of inflammation.

Methodology

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011 on a total of 180 patients divided into three groups of 60 each namely, normotensives, prehypertensives and hypertensives.

Results

In this study male preponderance was seen in all three study groups (76.67% in normotensives, 73.33% in prehypertensives and 75% in Hypertensives). Among normotensives equal distribution of age was observed whereas, among prehypertensives 61.67% and among hypertensives 63.33% had age from 46 to 60 years. The mean age among normotensives, prehypertensives and hypertensives was 48.40±15.38, 53.03±10.86 and 50.76±8.05 years respectively. Highest HOMA index among hypertensives (4.59±1.87) compared to prehypertensives (2.91±1.27) and normotensives (2.17±0.66).

Conclusion and interpretation

Waist circumference and total cholesterol showed significant positive correlation with HOMA index in all the three groups that is, normotensives, prehypertensive and hypertensives whereas, serum LDL and TG positively correlated with HOMA in all three groups but correlation was statistically significant in prehypertensives only. Serum HDL showed negative correlation with HOMA index in all three groups but statistically significant only in prehypertensive population.

hs-CRP showed statistically significant positive correlation with HOMA index in all three groups that is normotensives, prehypertensive and hypertensive.

Keywords

Hypertension; Highly sensitive C-reactive protein; Homoeostasis Model Assessment; Inflammation; Insulin resistance; Prehypertension;

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Chapter 1

Introduction

INTRODUCTION

Hypertension is a medical condition in which the arterial blood pressure is raised. Persistent hypertension is a source of a plethora of medical complications including stroke, renal failure, myocardial infarction and other end organ damages. Hypertension has been classified in three stages namely Prehypertension, Stage 1 and Stage 2 according to JNC 7.[1]

Hypertension is becoming an important public health problem worldwide. A recent report on the global burden of hypertension indicates that nearly one billion adults (more than a quarter of the world's population) had hypertension in 2000, and this is predicted to increase to 1.56 billion by 2025.[2]

Subjects with hypertension are known to have a two-fold higher risk of developing coronary artery disease (CAD), four times higher risk of congestive heart failure and seven times higher risk of cerebrovascular disease and stroke compared to normotensive subjects.[3]

Hypertension has been identified as one of the leading risk factors for mortality, and is ranked third as a cause of disability adjusted life-years.[4] Existing data suggests that the prevalence of hypertension has remained stable or has decreased in economically developed countries during the past decade, while it has increased in developing countries.[2]

Insulin resistance (IR) has recently been found to be a common feature of essential hypertension. It is a condition characterized by decreased response of target tissues to insulin.[5]

IR develops first when tissues are unable to respond to normal circulating concentrations of insulin. This reduced sensitivity in body tissues to the action of insulin consequently limits glucose disposal in muscle and fat. In response, to maintain glucose homeostasis, β cells in the pancreas secrete more insulin, which eventually results in pancreatic β cell exhaustion, decompensation, and eventual failure.[5]

Prospective studies have shown fasting insulin levels to be a surrogate marker of insulin resistance and a predictor of Coronary Artery Disease (CAD).[6] IR has also been shown to be associated with most of the cardiovascular risk factors viz., dyslipidemia, hypertension, obesity, abdominal obesity and glucose intolerance, and a combination of these abnormalities could lead to CAD.[7]

Insulin resistance clusters with many other metabolic abnormalities, and this is known as the insulin resistance syndrome or metabolic syndrome [MS].[8] It is considered by many scientists to be the main link between diabetes and cardiovascular disease [CAD], even in the absence of glucose intolerance and indeed IR is a strong predictor of coronary artery disease.[9]

Alarming trends have been reported in the prevalence of CAD worldwide.[10] More recently, it is recognized that the major contribution to CAD is from developing countries.[11] This has been confirmed by the Global Burden of Disease study, which predicts an increasing burden of CAD among the developing countries in the next decade.[10]

A recent analysis[12] has also projected that the greatest impact of the global epidemic of CAD will fall in developing countries. While the decline in

CAD mortality has been demonstrated among some developed countries, the reverse trend appears to be seen in developing countries particularly in India. Indeed, India seems to be particularly badly affected with nearly a 100% increase in the prevalence rates of CAD predicted between 1985 and 2015.[13]

Asian Indians are known to have very high rates of premature coronary artery disease (CAD) and diabetes.[14] This is attributed to the so-called "Asian Indian Phenotype" characterized by relatively lower prevalence rates of obesity but larger waist measurements indicating abdominal obesity and increased insulin resistance.[15]

There has been increasing number of evidences connecting insulin resistance to future cardiovascular events in hypertensives suggesting that insulin resistance is the basis for the so called metabolic syndrome irrespective of diabetes status.[16]

Since the initial report of disproportionately high plasma insulin concentrations in response to glucose ingestion in patients with essential hypertension,[17] numerous population-based and cohort studies[18-23] have reported cross-sectional and longitudinal associations between measures of arterial blood pressure (systolic, diastolic, or mean) and plasma insulin level (fasting or postglucose). Covariance of blood pressure and plasma insulin has also been shown in normotensive, nondiabetic subjects within the physiological domain of the two variables.[24] These observations have raised the possibility that insulin like salt intake, alcohol consumption, obesity, and aging may be a determinant of

blood pressure variability and may possibly contribute to the pathogenesis of essential hypertension.[25]

Association of various degrees of blood pressure with the rising titers of subclinical inflammatory markers as HsCRP has been well observed and documented.[26]

On the other hand, some investigators[27-28] have challenged the significance of the association between blood pressure and plasma insulin on the grounds that (1) it is often weak; (2) it depends on the characteristics of the study population (population-based survey versus hospital sample, ethnicity, inclusion criteria with respect to blood pressure, and glucose tolerance); and (3) it is strongly confounded by age and obesity.

Despite increasing evidence relating insulin resistance and cardiovascular risk, the association between insulin resistance and hypertension still remains controversial. Also there is lack of clinical evidence relating high blood pressure with IR and its importance in Indian context has not been well documented.

Hence the present study was undertaken to assess the insulin resistance and inflammation in relation to various degrees of blood pressures in adults and to evaluate IR as a marker of inflammation.

Chapter 2

Objectives

OBJECTIVES

The objectives of the present study were;

1. To study the insulin resistance and inflammation in relation to various degrees of blood pressures in adults.

2. To evaluate Insulin resistance as a marker of inflammation.

Chapter 3

Review of Literature

REVIEW OF LITERATURE

There is increasing incidence and prevalence of hypertension along with obesity and other constituents of the **"**deadly quartret**"** which has contributed to increase in mortality and morbidity globally. It has affected the population in the prime of their life leading to greater economic and social burden. Early identification and aggressive corrective measures is an absolute necessity.

It is now established that hyperinsulinemia due to insulin resistance is the biochemical hallmark of metabolic abnormalities encountered in this population.

Although it is commonly encountered in patients with impaired glucose tolerance and Diabetes mellitus, growing literature suggests it is also encountered in non-diabetic individuals. Hyperinsulinemia has been incriminated in the genesis of hypertension and obesity.

A study conducted in Chennai urban population of south India concluded that fasting insulin levels were high in hypertensives and prevalence of hypertension increased with increased quartiles of fasting insulin levels.[29]

Another study conducted in Pakistan from 2004-2006, concludes that hypertensive individuals have higher insulin resistance than subjects without hypertension and vigorous search has to be made to detect insulin resistance and to demonstrate other components and metabolic syndrome.[30]

Data from a meta analytical review examining fasting insulin levels in euglycemic individuals demonstrates a significant correlation with systolic and diastolic blood pressure.[31]

One of the studies conducted in Kuwait in 2001 for prevalence of metabolic syndrome in hypertensive patients, concludes that the prevalence of metabolic syndrome is high in hypertensives.[32]

A comparative study of non obese hypertensive patients with normotensives was conducted in the city of Dares Salaam in Africa, showed that basal insulin levels tended to be higher in hypertensive subjects. The basal insulin resistance was twice high compared to normotensives. Their insulin sensitivity was low. This study also raised the causal relation between insulin resistance and hypertension.[33]

Another study conducted at PM Research Centre, Lahore for fasting insulin levels in non diabetic, non obese hypertensives demonstrated higher fasting insulin levels in them compared to normotensives.[34]

INSULIN RESISTANCE (IR)

Definition

Insulin Resistance has been defined as a metabolic state in which a normal concentration of insulin produces a less than normal biological response.

It has originally been stated by Berson and Yalow as, a state (of a cell, tissue, system or body) in which greater than normal amounts of insulin are required to elicit a quantitatively normal response.[35]

Insulin secreted from the beta cells of the pancreas travels through the circulation to the target tissue, and binding to its receptor in target tissue brings

about its metabolic and mitogenic effects. Hence events at any one of these loci can influence the ultimate action of the hormone.[36]

Insulin

Insulin was discovered in 1921 by Banting and Best who demonstrated the hypoglycemic action of an extract of pancreas prepared after the degeneration of the exocrine part by ligation of pancreatic duct. It was first obtained in pure crystalline form in 1926 and the chemical structure was fully worked out in 1956 by Sanger.

Insulin is an important hormone that is secreted from the islets of Langerhans in the pancreas. The human pancreas contains one to two millions islets and they make up about two percent of volume of the pancreas. There are at least four distinct types of cells in the islets named A, B, D and F cells. A, B, and D cells are also called α, β, and δ cells.

The β cells are the most common, accounting for 60 to 75% of the cells in the islets, and are generally located in the center of each islet. It is these β cells that synthesize and secrete insulin.

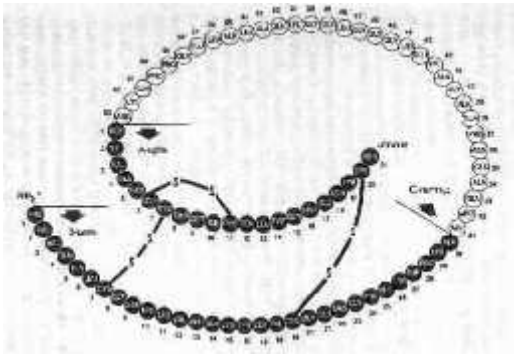


Figure 1. Molecular structure of insulin

Biosynthesis

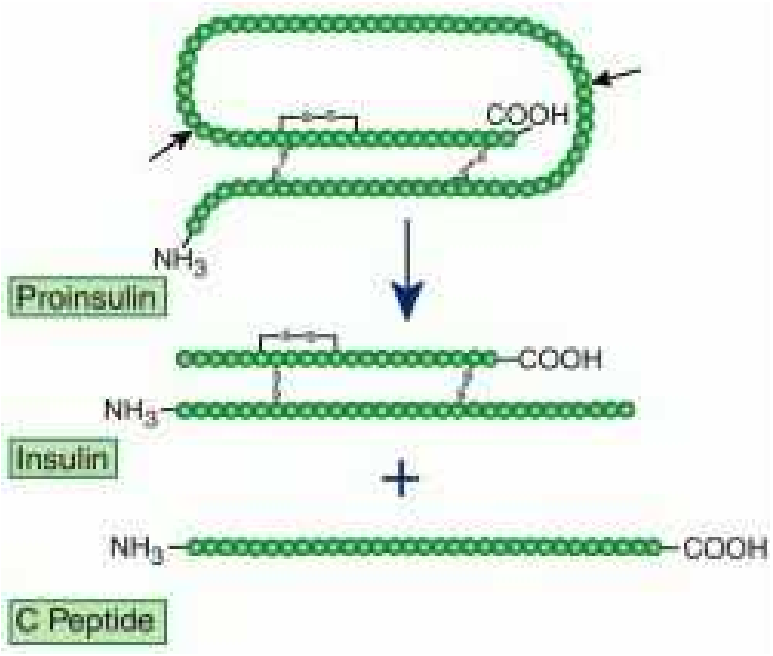


Figure 2. Biosynthesis of insulin

Insulin is produced in the beta cells of the pancreatic islets. It is initially synthesized as a single-chain 86-amino-acid precursor polypeptide, preproinsulin. Subsequent proteolytic processing removes the aminoterminal signal peptide, giving rise to proinsulin. Proinsulin is structurally related to insulin-like growth factors I and II, which bind weakly to the insulin receptor. Cleavage of an internal 31-residue fragment from proinsulin generates the C peptide and the A (21 amino acids) and B (30 amino acids) chains of insulin, which are connected by disulfide bonds. The mature insulin molecule and C peptide are stored together and cosecreted from secretory granules in the beta cells. Pancreatic beta cells cosecrete islet amyloid polypeptide (IAPP) or amylin, a 37-amino-acid peptide, along with insulin.[37,38]

Secretion

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion. Glucose levels more than 3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by the glucose transporter 2 (GLUT2). Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates adenosine triphosphate (ATP), which inhibits the activity of an ATP-sensitive potassium channel. This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemics (for example, sulfonylureas, meglitinides); the other is an inwardly rectifying potassium channel protein (Kir). Inhibition of this potassium channel induces beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium), and stimulates insulin secretion. Insulin secretory profiles reveal a pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 minutes, superimposed upon greater amplitude oscillations of about 80 to 150 minutes Incretins are released from neuroendocrine cells of the gastrointestinal tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion. Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in the small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level.[37,39]

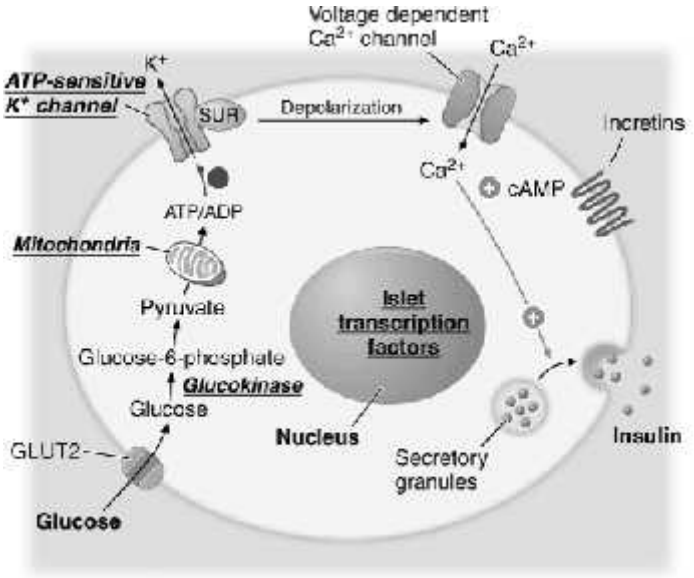


Figure 3. Secretion of insulin[37]

Signaling

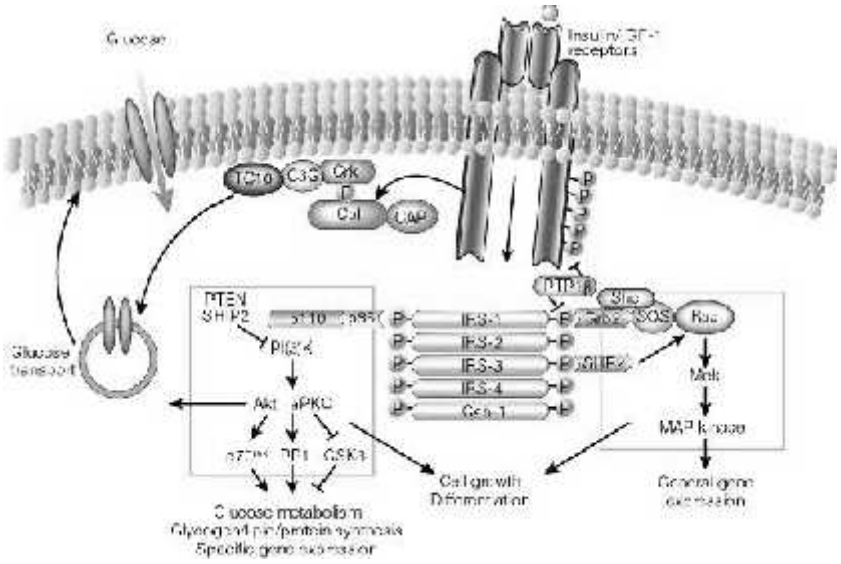


Figure 4. Insulin signalling[38,39]

It is initiated through the binding of insulin and activation of cell-surface receptor which initiates a cascade of phosphorylation and dephosphorylation events, second messenger generation, and protein to protein interactions that

result in the diverse metabolic events in nearly every tissue. Insulin receptors are found on many different cells in the body, including cells in which insulin does not increase glucose uptake. The insulin receptor is a tetramer made up of two α and two β glycoprotein subunits. These subunits are bound to each other by disulfide bonds. The α subunits bind insulin and are extracellular, whereas the β subunits span the membrane, the intracellular portions of the β subunits have tyrosine kinase activity. Insulin binding to its receptor stimulates intrinsic tyrosine kinase activity, leading to receptor autophosphorylation and the recruitment of intracellular signaling molecules, such as insulin receptor substrates. These and other adaptor proteins initiate a complex cascade of phosphorylation and dephosphorylation reactions, resulting in the widespread metabolic and mitogenic effects of insulin. (As an example, activation of the phosphatidylinositol-3'kinase (PI3K) pathway stimulates translocation of glucose transporter like GLUT-4, to the cell surface).[38,39]

Physiological effects of insulin

Insulin is an anabolic hormone that in overall causes cell growth. Its effects in various tissues differs and the main effects are given below

1. Adipose tissue

- Increased glucose entry
- Increased fatty acid synthesis
- Increased glycerol phosphate synthesis
- Increased triglyceride deposition
- Activation of lipoprotein lipase

- Inhibition of hormone sensitive lipase
- Increased potassium uptake

2. Muscle

- Increased glucose entry
- Increased glycogen synthesis
- Increased aminoacid uptake
- Increased protein synthesis
- Decreased protein catabolism
- Decreased released of gluconeogenic aminoacids
- Increased ketone uptake
- Increased potassium uptake

3. Liver

- Decreased ketogenesis
- Increased protein synthesis
- Increased lipid synthesis
- Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis

CAUSES OF INSULIN RESISTANCE

1. Abnormal β-cell secretory product

- Abnormal insulin molecule
- Incomplete conversion of proinsulin to insulin

Several patients secrete a structurally abnormal, biologically defective insulin molecule due to a mutation in the structural gene for insulin. Patients with familial hyperproinsulinemia, demonstrate incomplete conversion of proinsulin to insulin. These syndromes do not represent insulin resistant states in the most common usage of this term, as the hormone is abnormal and the patients are resistant only to their endogenous insulin and not to exogenous insulin.[39,40]

2. Circulating insulin antagonists

- Elevated levels of counterregulatory hormones for example, growth hormone (GH), cortisol, glucagons or catecholamines
- Anti-insulin antibodies
- Anti-insulin receptor antibodies

These antagonists are grouped into hormonal and nonhormonal antagonists.

Hormonal antagonists:

Includes all of the known counter regulatory hormones such as cortisol, GH, glucagon and catecholamines. However, in obesity or type 2 DM, excessive levels of these counteregulatory hormones are not an important contributory factor to peripheral insulin resistance.

Non hormonal antagonists:

Free fatty acids (FFA)[41,42] elevated circulating levels of free fatty acids impair peripheral glucose utilization. The proposed mechanism underlying this

effect is that fatty acids are taken up by cells and oxidized intracellularly. As a result of the elevated cellular rates of fatty acid oxidation, glycolysis and glucose uptake are inhibited, leading to antagonism of insulin action.

Anti-insulin antibodies:

Anti-insulin antibodies develop in patients treated chronically with exogenous insulin. By binding and trapping insulin within the plasma compartment, these antibodies can alter the usual time and course of insulin action. However, only in unusual cases do such antibodies actually cause a true insulin-resistant state. Few patients spontaneously develop anti-insulin antibodies, but these do not cause IR.

Insulin-receptor antibodies:

This condition is rare and is associated with acanthosis nigricans, severe insulin resistance and diabetes mellitus. The circulatory antibody binds to the insulin receptor in vivo, leading to the insulin-resistant state.

3. Target tissue defects

Impaired access of insulin to target cells

It has been shown that insulin's in vivo effects to stimulate glucose disposal are well correlated with the appearance of insulin in the interstitial fluid and that there are substantial delays in the transcytosis of insulin from the plasma compartment to the sites of action. This raises the possibility that either the rate or the amount of insulin transferring from the plasma to the interstitial compartment could be abnormal in Type 2 DM or obesity, contributing to the

insulin-resistant state. Conceivably, impaired transcapillary passage could contribute to the defects in in-vivo insulin action kinetics which have been described in obesity and Type 2 DM. Another physical factor that may relate to insulin resistance is capillary density. It has been shown that an inverse relationship exists between skeletal muscle capillary density and in vivo insulin-mediated glucose disposal. Taken together, defects in any of the above physical and mechanical factors, although possibly contributory, cannot explain the major component of IR.

Cellular defects in insulin action:

The available evidence points to a target tissue defect in insulin action as the major cause of the insulin resistance. As has already been described, it is the binding of insulin to its receptor and subsequent signaling through a cascade of events that brings about the effects of this hormone, hence abnormalities anywhere along this sequence can lead to insulin resistance.

Decreased cellular insulin receptors:

This is described in a variety of pathophysiological situations, most common being obesity and Type 2 DM. However, this potential relationship between insulin receptors and insulin action is not straightforward because cells poses ‘spare receptors’. For example, in isolated adipocytes, maximal insulin stimulation of glucose transport occurs when only 10% of the adipocyte insulin receptors are occupied. Thus 90% of the normal complement of receptors are ‘spare’. And studies have shown the predominant lesion to be post-binding defect rather than insulin binding to receptors.

Insulin receptor function

It has been shown that receptors isolated from insulin-resistant Type 2 DM patients have severely compromised autophosphorylation/kinase activity. But receptors isolated from insulin resistant, obese, nondiabetic subjects have normal kinase activity.

Glucose transport system

A large decrease in insulin-stimulated glucose transport has been shown in Type 2 DM patients. Three possible mechanisms exist for this decrease in insulin-stimulated glucose transport. First, could be a decrease in the ability of insulin to signal recruitment, or translocation, of GLUT4 to the cell surface. Second, recruitment could be normal, but there could be a marked decrease in the intrinsic activity of GLUT4. third, there could be a deficiency of GLUT4 proteins. From various studies, general consensus is that no deficiency of GLUT4 proteins exists and marked decrease in the intrinsic activity of GLUT4 contributing to the disease is exceedingly uncommon. Hence it is the first mechanism i.e. a decrease in the ability of insulin to signal recruitment, or translocation, of GLUT4 to the cell surface that contributes much to IR.

Trans membrane signaling:

A variety of post-receptor signaling systems and mediators link the insulin receptor to glucose transport stimulation. Most thoroughly studied of these is pp185 also called insulin receptor substrate 1 (IRS1). In type 2 DM subjects striking decrease in phosphorylated IRS 1 content has been observed. As

IRS 1 proves to be a key downstream signaling molecule of the insulin receptor, this abnormality could represent an important aspect of IR.

Other factors influencing insulin resistance

- *Intramuscular triglyceride (TG):* It has been found that insulin-stimulated glucose uptake is inversely related to the amount of intramuscular TG. The mechanism for accumulation of TG in the skeletal muscle of obese and insulin-resistant individuals is probably related to the mismatching of FFA uptake and oxidation.[43,44]

- *Hyperinsulinemia:* Hyperinsulinemia per se has been proposed to cause IR. Elevated concentrations of insulin can cause IR by down-regulating insulin receptors and desensitizing post receptor pathways. Suppression of insulin secretion in obese, insulin-resistant people results in increased insulin sensitivity.

- *Tumor Necrosis Factor (TNF):* Although the basis for the changes in the expression and activity of key molecules involved in the insulin signaling pathway is, in general, unknown, a TNF-α mediated mechanism for the decreased activity in the initial steps of the insulin signaling cascade has been proposed.

- *Glucotoxicity, Glucosamine:* Hyperglycemia itself can cause IR. Evidence suggests that the hexosamine pathway underlies the defect in glucose utilization associated with hyperglycemia. Hexosamines, such as glucosamine, induce IR in fat cells and in skeletal muscle.

- *Human immunodeficiency virus infection (HIV):* A syndrome with many of the clinical and metabolic features of IR is increasingly being recognized in patients with HIV infection. An unusual form of lipodystrophy is observed in certain of these patients in whom there is significant fat redistribution from the extremities and face to the torso with accumulation of intraabdominal and intrascapular fat. Studies have associated this syndrome with previous or current treatment with antiretroviral protease inhibitors or nucleoside reverse transcriptase inhibitors.

Insulin Resistance in Obesity

IR in obesity is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle and by impaired suppression of hepatic glucose output. These functional defects may result, in part, from impaired insulin signaling in all three target tissues and, in adipocytes, also from down regulation of the major insulin-responsive glucose transporter, GLUT4. In both muscle and adipocytes, insulin binding to its receptor, receptor phosphorylation and tyrosine kinase activity, and phosphorylation of Insulin Receptor Substrates are reduced.[45]

The signaling defects in obesity may be due to the increased expression and activity of several protein tyrosine phosphatases, which dephosphorylate and thus terminate signaling propagated through tyrosyl phosphorylation events. In morbid obesity, the expression of various insulin signaling molecules is reduced in skeletal muscle. In obesity, a major factor contributing to the impaired insulin-

stimulated glucose transport in adipocytes is the down regulation of GLUT4. However, in skeletal muscle of obese, GLUT4 expression is normal and defective glucose transport appears to be due to impaired translocation, docking, or fusion of GLUT4- containing vesicles with the plasma membrane.[45]

Adipocytes express and secrete numerous peptide hormones and cytokines. This raises many possibilities for additional links between adipose function or mass and IR, independent of the adipocyte's role in energy storage and release. Of various peptides and cytokines, Leptin and TNF-α are widely studied which have been shown to increase and decrease insulin sensitivity respectively.[45]

Increased adipose energy storage in obesity results in increased FFA flux to other tissues and increased TG storage in these tissues, which promote IR and other adverse effects, referred to by some as 'lipotoxicity'. Studies have shown that the TG content of muscle correlates directly with IR, and the fatty acid composition of muscle phospholipids influence insulin sensitivity.[45]

Though increase in body fat content confers IR, central obesity is much more strongly linked to IR and is explained by the hypothesis that intra-abdominal adipocytes are more lipolytically active. This would increase intraportal FFA levels and flux, which might inhibit insulin clearance and promote IR. Alternate hypothesis suggests that the array of factors secreted by intra-abdominal adipocytes may be particularly harmful to systemic insulin sensitivity.[45]

MECHANISM OF HYPERTENSION BY INSULIN RESISTANCE

It is estimated that at least 50% of hypertensive patients are insulin resistant, and insulin resistance is one fundamental abnormality in the pathogenesis of the cardiometabolic syndrome. In this context, patients with HTN have higher fasting and postprandial insulin levels, independent of body mass index or body fat distribution.[46]

Several pathophysiologic factors are involved in the relationship between HTN and the other components of the cardiometabolic syndrome, including inappropriate activation of the rennin angiotensin aldosterone system (RAAS), oxidative stress, and inflammation. Other factors include impaired insulin-mediated vasodilatation, enhanced sympathetic nervous system (SNS) activation, and abnormal sodium handling by the kidney.[46]

1. Renal sodium handling

Several abnormalities in renal handling of sodium have been demonstrated in both HTN and the CMS. insulin enhances sodium reabsorption in the diluting segment of the distal nephron, in part, through increased expression of sodium transporters, such as the epithelial sodium channel, with consequent decrease in sodium excretion. This effect could potentially contribute to the genesis of hypertension under hyperinsulinemic conditions secondary to selective insulin resistance of nonrenal tissues. In opposition to this hypothesis, using a murine model of selective knockout of the insulin receptor in the renal tubule epithelial cells, it was reported that the absence of insulin action results in impaired natriuresis and increased blood pressure, findings that were correlated

with reduced renal nitric oxide (NO) production. This novel evidence can explain how decreased NO production would lead to renal vasoconstriction and increased sodium reabsorption with resultant HTN in conditions of insulin resistance.[46]

2. Sympathetic nervous system activation

Clinical studies have shown that individuals with cardiometabolic syndrome have increased sympathetic nervous system activity, and this increased activity is correlated with insulin resistance. A number of mechanisms are involved in the activation of the sympathetic nervous system in the cardiometabolic syndrome. In states of IR, compensatory hyperinsulinemia can cause enhanced sympathetic output in humans through ventromedial hypothalamus mechanisms. Additionally leptin, which is elevated in obesity, increases sympathetic nerve activation.[46]

Renin angiotensin aldosterone system also interacts, in a positive feedback fashion, with the sympathetic nervous system. Injection of angiotensin II (Ang II) in the brain of experimental models causes increased sympathetic output. Additionally, the activation of the RAAS facilitates sympathetic ganglia transmission and inhibits the reuptake of noradrenaline in the nerve terminals. Thus, enhancement of the sympathetic nervous system and the RAAS act in a positive feedback regulatory mechanism in the setting of HTN and the cardiometabolic syndrome.[46]

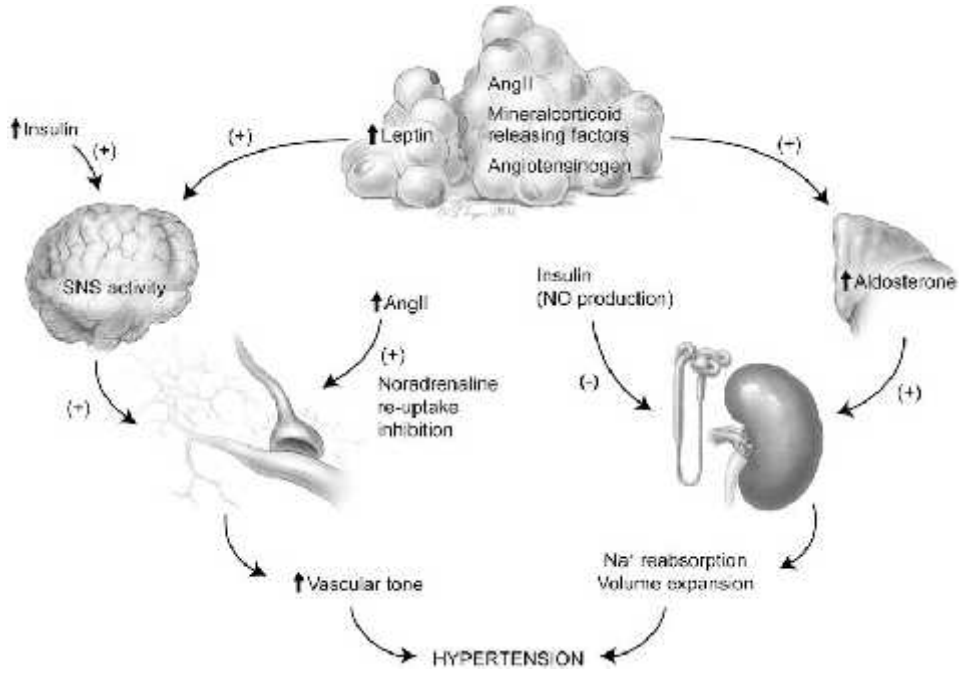


Figure 5. Co-ordinated influence of obesity, IR, activation of RAAS and sympathetic nervous system in pathophysiology of HTN[46]

3. Renin angiotensin aldosterone system

The interaction between the RAAS and the sympathetic nervous system is at least partially responsible for the development of HTN in states of insulin resistance, such as the cardiometabolic syndrome. Often in the cardiometabolic syndrome there is an increase in visceral adipose tissue and the increased inflammation and oxidative stress in this tissue leads to increased production of components of the adipose renin angiotensin system. Angiotensinogen (AGT) and Ang II produced in adipose tissue have local affects to enhance adipocyte tissue growth and expansion, and systemic effects on blood pressure regulation.[46]

Angiotensin II exerts many of its detrimental effects through its interaction with the angiotensin II type 1 receptor (AT1R). AT1R activation in

the zona glomerulosa of the adrenal cortex stimulates the production of mineralocorticoids. Furthermore, the activation of AT1R, in nonadrenal tissues, results in a myriad of intracellular events including production of reactive oxygen species (ROS), which contribute to reduced insulin metabolic signaling, and proliferative and inflammatory responses. These AT1R-mediated signals can cause impaired vascular insulin metabolic signaling and endothelial dysfunction, with secondary increases in blood pressure.[46]

Aldosterone is also increased in conditions of increased adiposity and insulin resistance. Adipose tissue is capable of secreting potent mineralocorticoid-releasing factors. Aldosterone increases blood pressure both by its classic actions, mainly sodium retention and plasma volume expansion, and through nongenomic mineralocorticoid receptor mediated actions.[46]

4. Role of oxidative stress

Binding of insulin to its receptor triggers signaling through the PI3K/protein kinase B cascade, which results in glucose transporter-4 (GLUT4) translocation to the plasma membrane and facilitated glucose uptake. In addition, Akt phosphorylates and activates endothelial nitric oxide synthase (eNOS) resulting in nitric oxide (NO) production and vasodilatation. Therefore, insulin resistance states exhibit impaired insulin-mediated vasodilatation.[46]

On the other hand, data from experimental animal models have shown that insulin can stimulate vasoconstriction through production of endothelin 1 (ET-1), a process that requires intact mitogen-activated protein kinase (MAPK) signaling. It has been proposed that in insulin-resistant states while the PI3K/

protein kinase B pathway signaling is impaired with consequent decreased production of NO, the MAPK pathway is stimulated by hyperinsulinemia resulting in elevated ET-1 production.[46]

The main tissues involved in the pathophysiology of insulin resistance are skeletal muscle and adipose tissue. However, decreased insulin metabolic signaling in vascular tissue can also contribute to endothelial dysfunction, HTN, and atherosclerosis. Increased oxidative stress and resulting impairment in insulin metabolic signaling may play a key role in the pathogenesis of HTN, cardiometabolic syndrome, and CVD.[46]

In vitro and in vivo studies have demonstrated an association between increased ROS production and insulin resistance. Prolonged exposure of adipose cells to oxidative stress results in decreased insulin-stimulated glucose transport, lipogenesis, and activity of glycogen synthase, consistent with impaired insulin action.

Adipocytes obtained from high-fat diet-induced insulin resistance display increased production of ROS and stimulation of the protein kinase C delta, a serine/threonine kinase implicated in impaired cellular insulin metabolic signaling.

This, in turn, results in blunted insulin-stimulated glucose uptake and severely decreased expression/activation of GLUT4 and facilitated glucose transport.

Oxidative stress is strongly associated with increased adiposity and impaired insulin sensitivity in humans, suggesting a role for ROS in the generation of obesity-related insulin resistance. Conversely, it has been demonstrated in humans that insulin resistance is associated with reduced endogenous intracellular antioxidant mechanisms.

The mechanisms implicated in oxidative stress-mediated insulin resistance remain to be fully elucidated, but several experimental studies support a role for activation of redox-sensitive serine kinases, including Janus kinase. Activation of these serine kinases promotes serine phosphorylation of substrates, including the insulin receptor and the docking proteins insulin receptor substrate-1 (IRS) or 2. This increased Serphosphorylation of IRS-1 results in decreased engagement of IRS-1 with PI3K and impaired downstream insulin metabolic signaling.

5. Impaired Endothelium-Dependent Vasorelaxation

Impaired endothelium-dependent relaxation also occurs in insulin-resistant patients in the absence of overt type 2 diabetes. Endothelial dysfunction reflects the combined adverse effects of metabolic and hormonal abnormalities associated with insulin resistance, such as an increase in free fatty acids and reduced insulin action.[36]

Some reports have shown that vasodilator response to NO donors is also impaired in IR, suggesting that in certain situations impaired endothelium-dependent vasorelaxation may be superimposed on impaired endothelium-independent relaxation.[36]

Multiple mechanisms have been proposed to explain the decreased eNOS activity in IR. Reduced eNOS expression has been described in adipose microvessels isolated from obese insulin-resistant Zucker rats and coronary microvessels from alloxan-induced diabetic dogs, suggesting that reduced protein levels of eNOS may contribute to lower NO production. In addition, the elevation of circulating levels of asymmetric dimethylarginine, an endogenous NOS inhibitor, and a deficiency in tetrahydrobiopterin, a cofactor for eNOS, have also been implicated in contributing to reduced NO generation in IR.[36]

6. Atherosclerosis

Vasoactive hormones, cytokines, and growth factors, including Ang II, TNF-α, and vascular endothelial growth factor (VEGF) amplify and in part mediate the adverse vascular effects of these metabolic abnormalities. These metabolic and hormonal imbalances can induce endothelium dysfunction, vascular inflammation, SMC growth, intimal lipid accumulation, fibrosis, and hypercoagulability, leading to atherosclerosis and thrombosis.[36]

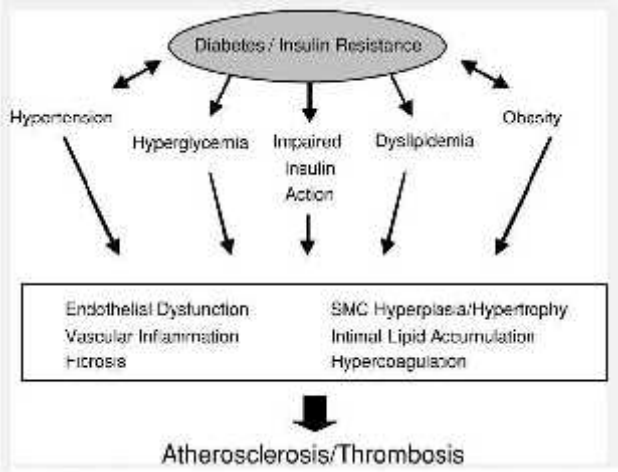


Figure 6. Pathogenesis of atherosclerosis in IR[36]

COMPLICATIONS OF INSULIN RESISTANCE

IR is considered to be central in the pathogenesis of many of the metabolic disorders. The disorders that are commonly associated with IR are as follows

1. Impaired glucose tolerance (IGT)

Most IGT subjects are insulin resistant and the number of persons progressing from IGT to frank Type 2 DM ranges up to 60% and so IGT is considered to be a pre-diabetic state, and the contribution of IR to this state is significant.[47]

2. Type 2 diabetes mellitus

IR is a consistent finding in patients with type 2 DM and resistance is present, years before the onset of diabetes. Prospective studies have shown that IR predicts the onset of diabetes. IR is associated with the progression to IGT and type to diabetes.[39,48]

3. Hypertension

There is a strong association between IR and hypertension. IR is a characteristic feature of primary hypertension which is independent of obesity. It has even been postulated that hyperinsulinemia is a causative factor for the development of HTN.[49]

4. Dyslipidemia

IR is commonly associated with hypertriglyceridemia and low levels of high density lipoprotein (HDL) cholesterol. Although the low density lipoprotein levels have not been shown to be consistently elevated, they are shown to be qualitatively different in being small and dense, and being more atherogenic.[50-52]

5. Hyperuricemia

IR causes impaired renal excretion of uric acid and increases the serum uric acid levels leading to hyperuricemia.[53,54]

6. Coronary artery disease

Clustering of the risk factors leading on to coronary artery disease (metabolic syndrome) is seen in insulin resistant subjects. Apart from increasing the risk factors for CHD, hyperinsulinemia has been shown to be an independent risk factor for ischemic heart disease. Reaven in 19884 proposed the concept of syndrome X, wherein various metabolic disorders occur in the same individual. The disorders include resistance to insulin-stimulated glucose uptake, hyperglycemia, hyperinsulinemia, an increased plasma concentration of very low density lipoprotein (VLDL), TG, a decreased HDL cholesterol, and HTN.[50,51,55,56]

The common feature of the syndrome is Insulin Resistance. All five of the consequences of IR have been shown to increase the risk of CAD. Insulin is a major risk factor for the development of CAD and that the effect is independent of blood pressure and plasma lipid levels. The major effects of insulin on arterial tissues are proliferation of smooth muscle cells, enhanced cholesterol synthesis

and low density lipoprotein (LDL) receptor activity, increased formation and decreased regression of lipid plaques, stimulation of connective tissue synthesis and stimulation of growth factors. The atherosclerotic plaque is characterized by excessive amounts of lipid and collagen, foam macrophages, and proliferated smooth muscle cells, all of which are affected by the plasma insulin concentration.[50,51,55,56]

Whether the abnormalities in blood pressure regulation, plasma lipid profile, and/or susceptibility to atherogenesis observed in obese, diabetic, elderly, and hypertensive individuals are related to the IR per se or to the compensatory increase in plasma insulin concentration is a difficult issue to address, as the two conditions usually go hand in hand5. However as it is the IR that leads to hyperinsuinemia, the basic defect is the IR that predisposes the individual for CAD.[50,51,55,56]

METABOLIC SYNDROME / SYNDROME X

The metabolic syndrome (syndrome X, insulin resistance syndrome) consists of a constellation of metabolic abnormalities that confer increased risk of CVD and DM.[37]

The major features of the metabolic syndrome include central obesity, hypertriglyceridemia, low HDL cholesterol, hyperglycemia, and hypertension.

Epidemiology of metabolic syndrome

Prevalence of the metabolic syndrome varies across the globe, in part reflecting the age and ethnicity of the populations studied and the diagnostic criteria applied. In general, the prevalence of metabolic syndrome increases with age. The highest recorded prevalence worldwide is in Native Americans, with nearly 60% of women ages 45 to 49 and 45% of men ages 45–49 meeting National Cholesterol Education Program, Adult Treatment Panel III (NCEP:ATPIII) criteria.

NCEP: ATP III 2001 and IDF criteria for the metabolic syndrome[37]

NCEP: ATPIII 2001[37]

Three or more of the following:

- Central obesity: Waist circumference >102 cm (M), > 88 cm (F)
- Hypertriglyceridemia: Triglycerides ≥ 150 mg/dL or specific medication
- Low HDL cholesterol: < 40 mg/dL and < 50 mg/dL, respectively, or specific medication.
- Hypertension: Blood pressure ≥ 130 mm systolic or ≥ 85 mm diastolic or specific medication.
- Fasting plasma glucose ≥ 100 mg/dL or specific medication or previously diagnosed type 2 diabetes.

IDF criteria for central adiposity

Waist circumference

Men	Women	Ethnicity
< 94 Cms	> 80 Cms	Europid, Sub-Saharan African, Eastern and Middle Eastern
> 90 Cms	> 80 Cms	South Asian, Chinese, and ethnic South & Central American
> 85 Cms	> 90 Cm	Japanese

- Fasting triglycerides >150 mg/dL or specific medication
- HDL cholesterol <40 mg/dL and <50 mg/dL for men and women, respectively, or specific medication
- Blood pressure >130 systolic or >85 mm diastolic or previous diagnosis or specific medication
- Fasting plasma glucose 1O0 mg/dL or previously diagnosed type 2 diabetes

In this analysis, the following thresholds for waist circumference were used: White men, ≥ 94 cm; African-American men, ≥ 94 cm; Mexican-American men, ≥ 90 cm; white women, ≥ 80 cm; African-American women, ≥ 80 cm; Mexican-American women, ≥ 80 cm. For participants whose designation was "other race including multiracial," thresholds that were once based on Europid cut points (≥ 94 cm for men and ≥ 80 cm for women) and once based on South Asian cut points (≥ 90 cm for men and ≥ 80 cm for women) were used. For participants who were considered "other Hispanic," the IDF thresholds for ethnic South and Central Americans were used.[37]

Based on data from the National Health and Nutrition Examination Survey (NHANES) III, the age-adjusted prevalence of the metabolic syndrome in the United States is 34% for men and 35% for women. Greater industrialization worldwide is associated with rising rates of obesity, which is anticipated to dramatically increase prevalence of the metabolic syndrome, especially as the population ages.

Risk Factors of metabolic syndrome

1. Overweight/Obesity

Central adiposity is a key feature of the syndrome, reflecting the fact that the syndrome's prevalence is driven by the strong relationship between waist circumference and increasing adiposity.

2. Sedentary Lifestyle

Many components of the metabolic syndrome are associated with a sedentary lifestyle, including increased adipose tissue (predominantly central); reduced HDL cholesterol; and a trend toward increased triglycerides, blood pressure, and glucose in the genetically susceptible.

3. Aging

The metabolic syndrome affects 44% of the United States population older than age 50. A greater percentage of women older than age 50 have the syndrome than men. The age dependency of the syndrome's prevalence is seen in most populations around the world.

4. Diabetes Mellitus

It is estimated that the large majority (~75%) of patients with type 2 diabetes or IGT have the metabolic syndrome. The presence of the metabolic syndrome in these populations relates to a higher prevalence of CVD compared to patients with type 2 diabetes or IGT without the syndrome.

5. Coronary Heart Disease

The approximate prevalence of the metabolic syndrome in patients with CHD is 50%, with a prevalence of 37% in patients in patients with premature coronary artery disease (more than or equal to age 45), particularly in women.

6. Lipodystrophy

Both genetic (for example, Berardinelli-Seip congenital lipodystrophy, Dunnigan familial partial lipodystrophy) and acquired (for example, HIV-related lipodystrophy in patients treated with highly active antiretroviral therapy) forms of lipodystrophy may give rise to severe insulin resistance and many of the metabolic syndrome's components.

Role of insulin resistance in pathophysiology of metabolic syndrome

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, caused by defect in insulin action which is incompletely understood. The onset of insulin resistance is heralded by postprandial hyperinsulinemia, followed by fasting hyperinsulinemia and ultimately, hyperglycemia.

An early major contributor to the development of insulin resistance is an overabundance of circulating fatty acids. Plasma albumin-bound FFAs are derived predominantly from adipose tissue triglyceride stores released by hormone-sensitive lipase. Fatty acids are also derived through the lipolysis of TG rich lipoproteins in tissues by lipoprotein lipase (LPL). Insulin mediates both antilipolysis and the stimulation of LPL in adipose tissue. Of note, the inhibition

of lipolysis in adipose tissue is the most sensitive pathway of insulin action. Thus, when insulin resistance develops, increased lipolysis produces more fatty acids, which further decrease the antilipolytic effect of insulin.

Excessive fatty acids enhance substrate availability and create insulin resistance by modifying downstream signaling. Fatty acids impair insulin-mediated glucose uptake and accumulate as TG in both skeletal and cardiac muscle, whereas increased glucose production and TG accumulation are seen in liver. The oxidative stress hypothesis provides unifying theory for aging and the predisposition to the metabolic syndrome. There is defective mitochondrial oxidative phosphorylation, leading to the accumulation of TG and related lipid molecules in muscle. The accumulation of lipids in muscle is associated with IR.

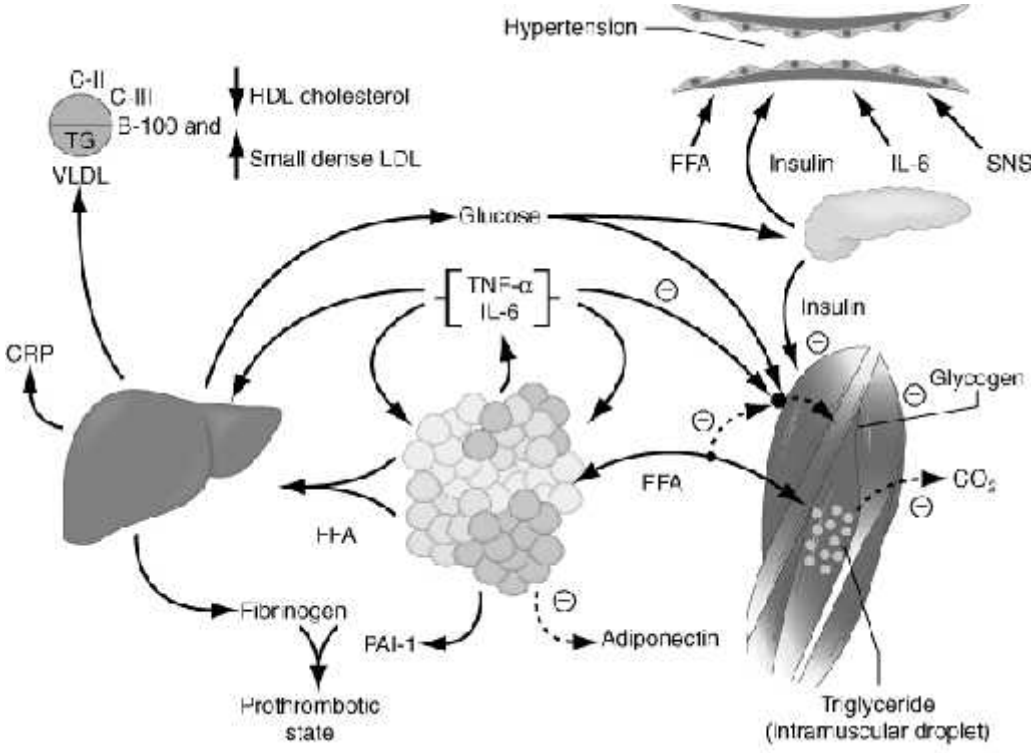


Figure 7. Pathogenesis of metabolic syndrome[37]

With increases in visceral adipose tissue, adipose tissue-derived FFAs are directed to the liver. On the other hand, increases in abdominal subcutaneous fat release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism. Relative increases in visceral versus subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians may explain the greater prevalence of the syndrome in these populations compared to African-American men in whom subcutaneous fat predominates. Dyslipidemia in general causes FFA flux to the liver is associated with increased production of apo B containing, TG rich VLDLs.

The other major lipoprotein disturbance in the metabolic syndrome is a reduction in HDL cholesterol. This reduction is a due to changes in HDL composition and metabolism. In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL is a consequence of reduced cholesteryl ester content of the lipoprotein core in combination with cholesteryl ester transfer protein–mediated alterations in triglyceride making the particle small and dense. This change in lipoprotein composition also results in an increased clearance of HDL from the circulation.

In addition to HDL, LDLs are also modified in composition. With fasting serum triglycerides more than 2.0 mmol (~180 mg/dL), there is almost always a predominance of small dense LDLs. Small dense LDLs are thought to be more atherogenic. They may be toxic to the endothelium, and they are able to transit through the endothelial basement membrane and adhere to glycosaminoglycans. They also have increased susceptibility to oxidation and are selectively bound to scavenger receptors on monocyte-derived macrophages. Subjects with increased

small dense LDL particles and hypertriglyceridemia also have increased cholesterol content of both VLDL1 and VLDL2 subfractions. This relatively cholesterol-rich VLDL particle may also contribute to the atherogenic risk in patients with metabolic syndrome.

Glucose Intolerance defects in insulin action leads to impaired suppression of glucose production by the liver and kidney and reduced glucose uptake and metabolism in insulin-sensitive tissues, that is, muscle and adipose tissue. To compensate for defects in insulin action, insulin secretion and/or clearance must be modified to sustain euglycemia. Ultimately, this compensatory mechanism fails, usually because of defects in insulin secretion, resulting in progress from IFG and/or IGT to DM.

Relationship of hypertension between insulin resistance and hypertension is well established. Paradoxically, under normal physiologic conditions, insulin is a vasodilator with secondary effects on sodium reabsorption in the kidney. However, in the setting of IR, the vasodilatory effect of insulin is lost, but the renal effect on sodium reabsorption is preserved. Insulin also increases the activity of the sympathetic nervous system, an effect that may also be preserved in the setting of the IR.

Increase in proinflammatory cytokines, including interleukin (IL) 1, IL-6, IL-18, resistin, tumor necrosis factor (TNF α), and C-reactive protein (CRP), reflect overproduction by the expanded adipose tissue mass. Adipose tissue-derived macrophages may be the primary source of pro-inflammatory cytokines locally and in the systemic circulation which may cause insulin resistance.

Adiponectin is an anti-inflammatory cytokine produced exclusively by adipocytes. Adiponectin enhances insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, adiponectin inhibits the expression of gluconeogenic enzymes and the rate of glucose production. In muscle, adiponectin increases glucose transport and enhances fatty acid oxidation, partially due to activation of adenosine monophosphate kinase (AMP). Adiponectin is reduced in the metabolic syndrome.

Treatment of metabolic syndrome

1. Lifestyle

Obesity is the driving force behind the metabolic syndrome. Thus, weight reduction is the primary approach to the disorder. With weight reduction, the improvement in insulin sensitivity is often accompanied by favorable modifications in many components of the metabolic syndrome. In general, recommendations for weight loss include a combination of caloric restriction, increased physical activity, and behavior modification. For weight reduction, caloric restriction is the most important component, whereas increases in physical activity are important for maintenance of weight loss. Some evidence suggests that the addition of exercise to caloric restriction may promote relatively greater weight loss from the visceral depot. The tendency for weight regain after successful weight reduction underscores the need for long-lasting behavioral changes.[37]

2. Diet

Before prescribing a weight-loss diet, it is important to emphasize that it takes a long time for a patient to achieve an expanded fat mass; thus, the correction need not occur quickly. On the basis of ~3500 kcal equal to one lb of fat, ~500 kcal restriction daily equates to a weight reduction of 1 lb per week. Diets restricted in carbohydrate typically provide a rapid initial weight loss. However, after one year, the amount of weight reduction is usually unchanged. Thus, adherence to the diet is more important than which diet is chosen. Moreover, there is concern about diets enriched in saturated fat, particularly for patients at risk for CVD. Therefore, a high quality of the diet that is, enriched in fruits, vegetables, whole grains, lean poultry, and fish should be encouraged to provide the maximum overall health benefit.[37]

3. Physical Activity

For the inactive participant, gradual increases in physical activity should be encouraged to enhance adherence and to avoid injury. Although increases in physical activity can lead to modest weight reduction, 60 to 90 minute of daily activity is required to achieve this goal. Even if an overweight or obese adult is unable to achieve this level of activity, they still derive a significant health benefit from at least 30 min of moderate intensity daily activity.[37]

4. Impaired Fasting Glucose

In patients with the metabolic syndrome and type 2 diabetes, aggressive glycemic control may favorably modify fasting TG and/or HDL cholesterol. In

those patients with IFG without a diagnosis of diabetes, a lifestyle intervention that includes weight reduction, dietary fat restriction, and increased physical activity has been shown to reduce the incidence of type 2 diabetes. Metformin has also been shown to reduce the incidence of diabetes, although the effect was less than that seen with lifestyle intervention.

5. Insulin Resistance

Several drug classes [biguanides, thiazolidinediones (TZDs)] increase insulin sensitivity. If insulin resistance is the primary pathophysiologic mechanism for the metabolic syndrome, then representative drugs in these classes should reduce its prevalence. Both metformin and TZDs enhance insulin action in the liver and suppress endogenous glucose production. TZDs, but not metformin, also improve insulin-mediated glucose uptake in muscle and adipose tissue. In general, the beneficial effects of TZDs appear superior to those of metformin.

6. Bariatric surgery

Bariatric surgery is an option for patients with the metabolic syndrome who have a body mass index (BMI) of more than 40 kg/m^2 or >35 kg/m^2 with comorbidities. Gastric bypass results in a dramatic weight reduction and improvement in the features of metabolic syndrome. At present, however, a survival benefit has yet to be realized.

ASSESSMENT OF INSULIN RESISTANCE

Insulin assay

There are various assays for the measurement of the insulin. They can be divided into bioassays and immunoassays. Bioassays for insulin have the advantage of measuring biologically active rather than immunoreactive moieties, but the techniques are lengthy, relatively imprecise, and insensitive and are also affected by insulin agonists (for example, insulin-like growth factors) and antagonists (for example, Counter regulatory hormones). Various animal systems have been used for the bioassay of insulin. Bioassays can either be In vivo assays or In vitro assays (using different tissues), and the effect of insulin or the competition between radiolabelled and unlabelled hormone for specific receptor is assessed. In immunoassays, the antigen (like insulin) is measured using its specific reaction with an antibody. It can be of different types based on the label used to follow the reaction. The different labels used are radioisotope, enzyme, flurophor and luminescence. In immunoassays, a variable amount of unlabelled antigen (either unknown samples, or known standards) is incubated with constant amounts of labeled antigen and antibody. After reaction, the antibody bound and the free antigen fractions are separated, and the amount of labeled antigen (radiation from radioisotopes in radioimmunoassay) is measured. The percentage of labeled antigen bound to antibody is inversely proportional to the amount of unlabelled antigen present in the sample.[57]

The measurement of peripheral insulin concentration by radioimmunoassay is the most widely used method for quantifying beta cell functions in vivo.

Calculation of insulin resistance

From the time Himsworth demonstrated that large number of people with diabetes were 'insulin insensitive', there have been efforts to quantitate the insulin action. Various methods have been described to assess the IR, which have been studied and validated.

1. Hyperinsulinemic euglycemic glucose clamp technique

It is considered as the "gold standard" for quantifying insulin sensitivity in vivo because it directly measures the effects of insulin to promote glucose utilization under steady state conditions. In this technique the plasma insulin concentration is acutely raised and maintained at that level by a prime-continuous infusion of insulin. The plasma glucose concentration is held constant at basal levels by a variable glucose infusion using the negative feedback principle. Under these steady-state conditions of euglycemia, the glucose infusion rate equals glucose uptake by all the tissues in the body and is therefore a measure of tissue sensitivity to insulin. The concept of a causal relationship between alcohol consumption and insulin sensitivity would be supported by the knowledge of plausible underlying mechanisms.[58]

2. Minimal model analysis of a frequently sampled iv glucose tolerance test (FSIVGTT)

It is also considered to be a standard method for the measurement of IR. Here after overnight fast of 12 hours, subjects baseline values of glucose and insulin are noted and the same are repeatedly noted at frequent intervals after an iv glucose load. The sensitivity is assessed by using minimal model analysis.[59]

3. Homeostasis model assessment (HOMA)

Proposed in 1985, it has become one of the most widely used index of IR. In this only the fasting glucose and fasting Insulin values are needed and hence is more convenient. A high HOMA score denotes IR. This model has been validated by many studies and is also extensively used. It is given by the formula,[60,61]

$$\text{HOMA IR} = \frac{\text{Fasting serum insulin (}\mu\text{U/ml) X Fasting plasma glucose (mmol/L)}}{22.5}$$

4. Quantitative Insulin Sensitivity Check Index (QUICKI)

This is also determined using a fasting blood sample and has been validated. It is given by the formula, $QUICKI = 1/[\log (I_0) + \log (G_0)]$, where I_0 is the fasting insulin (μU/ml), and G_0 is the fasting glucose (mg/dL).[62]

5. Fasting Glucose to Insulin ratio

It has also been shown to be a useful measure for Insulin sensitivity. It is given by the formula G_0/I_0 where I_0 is the fasting insulin (μU/ml) and G_0 is the fasting glucose (mg/dL).[63]

6. Bennett index

Recognized as a measure of IR, it is given by the formula $1/ \ln(G_0) \times \ln(I_0)$, where, I_0 is the fasting insulin (μU/ml), and G_0 is the fasting glucose (mg/dL).[64]

7. Fasting insulin

Fasting insulin and inverse of fasting insulin are also used as a measure of IR.[65]

Few other indices derived from oral glucose tolerance test are also used to quantitate IR.[65]

Other factors in IR

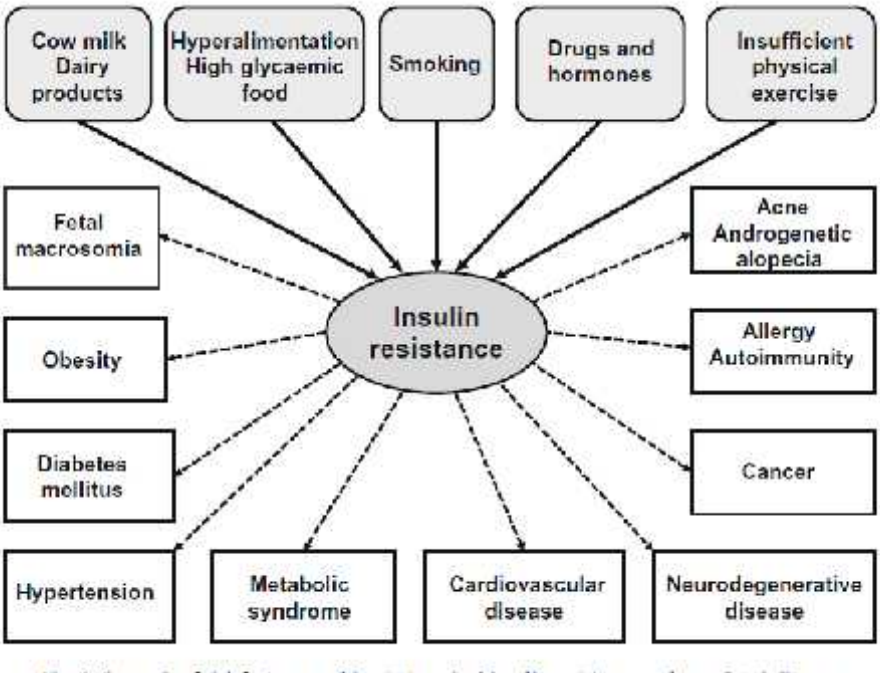


Figure 8. Risk factor resulting in impaired insulin resistant and associated diseases

Other causes of insulin resistance

1. Insulin resistance in adolescence and young adults

Puberty, the final growth period, is mediated by partial IR. The increased secretion of pituitary GH increases hepatic secretion of IGF-1, the mediator of growth. From GH replacement therapies, it is known that GH increases IR. Physiologic IR is regarded as the driving force for the final growth spurt.[66]

2. Oral contraceptives

Oral contraceptives can cause deterioration in glucose tolerance and hyperinsulinaemia. A significant deterioration of IR by etonogestrel has been

observed in women with PCOS which is associated with IR. A present study confirms that desogestrel, even when associated with low ethinylestradiol decreases insulin sensitivity, whereas ethinylestradiol in combination with chlormadinone acetate does not deteriorate insulin sensitivity.[66]

3. Androgens

Another factor increasing IR becomes effective in boys and young men who start abuse of androgens to increase muscularity and physical appearance. There is increasing evidence linking the excess of androgen and the development of IR. Shorter androgen receptor CAG repeat length polymorphism has been correlated with androgenetic alopecia, hirsutism and acne. Shortest CAG repeat length was found in men with androgenetic alopecia and acne, and women with hirsutism compared to normal controls in men and women. Early androgenetic alopecia has been identified as a marker of IR. Androgenetic alopecia and persistent acne in adulthood should be regarded as important clinical markers of individuals with increased androgen receptor signal transduction associated with lower insulin sensitivity. These individuals will be most susceptible to exogeneous androgens, and all other factors increasing IR.[66]

4. Smoking

Smoking promotes IR, hyperinsulinaemia, dyslipidaemia with evidence of epithelial dysfunction as compared with non-smokers. Recent epidemiologic data have suggested that cardiovascular disease in smokers is primarily seen in those individuals who are insulin-resistant. It is argued that IR is the major mechanistic link between cigarette smoking and cardiovascular disease. Acute smoking has

been shown to increase ghrelin levels. It has been recognized that ghrelin is a physiologic ligand of GH secretagogue receptor and induces GH release from the pituitary thus causing IR.[66]

5. Alcohol

Evidence from cross-sectional studies suggests an association between alcohol intake and improvement in insulin sensitivity. Moderate consumption of alcohol is known to reduce the risk of cardiovascular diseases. The underlying mechanisms have not been clarified, although the beneficial effects on lipid metabolism and other effects are well known. Alcohol may also improve insulin sensitivity and thereby have beneficial effects on several associated risk factors. Relationship between alcohol consumption and insulin sensitivity has a U-form, consumption. Alcohol consumption in lower to moderate range improves insulin sensitivity where as, at chronic higher doses causes insulin resistance.[67]

6. Drug-induced insulin resistance

Of special concern for long-term implications for increased risk of adverse outcomes are thiazide diuretics, niacin, and beta-adrenergic blockers, whereas angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have beneficial metabolic effects on glucose homeostasis.[66]

Thiazide diuretics, beta-adrenergic blockers, especially non-selective and higher-dose selective agents, have been implicated in altering glucose homeostasis, primarily through inhibition of pancreatic insulin secretion and promoting IR. Chronic systemic exposure to glucocorticoids is associated with

central adiposity, dyslipidaemia, skeletal muscle wasting, IR, glucose intolerance and overt diabetes. Glucocorticoid-induced protein catabolism has been linked to IR, and glucocorticoid-induced dyslipidaemia reduces insulin sensitivity.[66]

7. Cancer

Metabolic syndrome, diabetes mellitus, and obesity are associated with increased cancer incidence. Hyperinsulinaemia and increased serum levels of IGF-1 have been associated with increased risk of cancer. IGF-1 and insulin act through the tyrosine kinase growth factor signalling cascade enhancing tumour cell proliferation, but inhibit apoptosis. The intrauterine environment, that is, pathologically increased insulin, IGF-1 and impaired IR, might contribute to the predisposition of women for breast cancer in adulthood.[66]

8. Neurodegenerative diseases

The major risk factor for the development of neurodegenerative disease is aging. . The insulin–IGF-1 pathway is the major candidate to link aging, proteotoxicity and late-onset neurodegenerative disease. Recent insights implicate the interconnection of IGF1R signalling, regulation of lifespan, neurotrophin signaling and loss of neurogenic capacity and development of Alzheimer's disease. Recent evidence underlines the relationship between dementia and metabolic disorders such as diabetes, obesity, hypertension, and dyslipidaemia. Insulin may interfere with Ab degradation via its regulation of the metalloprotease insulin degrading enzyme. Thus recent evidence points to IR as a convergent mechanism that may underlie co-morbid metabolic disorders like diabetes, Alzheimer's disease and vascular dementia.[66]

9. Chronic obstructive pulmonary disease (COPD)

The risk of developing type 2 diabetes is increased in patients with COPD, even in those with mild disease. Recent evidence suggests that elevated levels of pro-inflammatory molecules present in COPD, such as CRP, IL-6 and TNF-α, may contribute to an altered metabolic state and insulin resistance. Tumor necrosis factor α is a key inflammatory mediator in the process of muscle wasting, promotes cachexia by reducing peripheral insulin action. Muscle loss and decreased fat oxidative capacity lead to further muscle loss and fat gain which, in turn, elevate TNF-α levels and so escalate IR and muscle loss.[68]

THERAPEUTIC ASPECTS OF INSULIN RESISTANCE

Of the non-pharmacologic therapy, the most effective measures to improve insulin sensitivity are weight loss and exercise.[69]

Non Pharmacological

1. Dietary and lifestyle modifications

Diet, weight loss, and physical exercise decrease insulin resistance and improve endothelial dysfunction. Calorie restriction alone (25% less than baseline energy requirements) or a combination of calorie restriction and physical exercise for 6 months increases eNOS expression in human skeletal muscle. Calorie restriction and exercise also improves NO-dependent vasodilation, reduces circulating ET-1 levels, and increases adiponectin levels in insulin resistant individuals.

A Mediterranean-style diet significantly reduces serum concentrations of inflammatory markers, decreases insulin resistance, and improves endothelial function in patients with metabolic syndrome when compared with match subjects on a control diet. Likewise, a two year lifestyle intervention consisting of weight loss, physical exercise, and a Mediterranean-style diet decrease BMI and inflammatory markers while increasing adiponectin levels in a cohort of obese women.

2. Weight loss

Weight loss is a highly effective treatment which besides attenuating the IR, also reduces the other co-morbidities. Weight loss can reduce hepatic glucose production, IR, fasting hyperinsulinemia, improve glycemic control and lipid profile and reduce blood pressure. One possible mechanism for improvements in insulin sensitivity through weight loss may be effects on the pattern of muscle fatty acid metabolism and the accumulation of lipid within muscle.

3. Exercise

It is clearly effective in increasing insulin sensitivity. Both acute exercise and exercise training increase glucose utilization and improve IR. Acute exercise leads to a increase in glucose transport and to translocation of intracellular GLUT 4 glucose transporters to the cell surface. Exercise training enhances insulin sensitivity by up-regulation of glucose transporter number, changes in capillary density, and increases in the number of red, glycolytic (type IIa) fibres.

Pharmacological treatment

1. Metformin

It is the only biguanide available for clinical use. Although metformin has a small ffect as a peripheral insulin sensitizer, it primarily works by reducing hepatic gluconeogenesis and hepatic glycogenolysis, and by enhancing insulin-stimulated glucose uptake and glycogenesis by skeletal muscle. It has become the first line pharmacological treatment for type 2 diabetes in overweight individuals. Beneficial effects for metformin in patients with IR but without type 2 diabetes have also been show. Metformin treatment lower plasma insulin levels and corrects many of the non-traditional cardiovascular risk factors associated with the insulin resistance syndrome.

2. Thiazolidinediones

These are novel compounds causing increased insulin sensitivity in insulin-resistance. The actions of the thiazolidinediones are mediated through binding and activation of the peroxisome proliferators activated receptor (PPAR) γ, a nuclear receptor. Binding of thiazolidinediones to PPARγ causes a conformational change, and allows activation of regulatory sequences of DNA, which in turn controls expression of specific genes. Thus, increased expression of insulin-sensitive genes, through the activation of PPARγ is perceived as the main mechanism by which thiazolidinediones reduce IR. Pioglitazone and Rosiglitazone are the two drugs belonging to this class which are now used to treat IR.

3. Antihypertensives

It also is becoming increasingly clear that antihypertensive medications have disparate effects on insulin sensitivity in patients with essential hypertension. Both diuretics and β-blockers are reported to accelerate the appearance of new-onset type 2 diabetes mellitus in patients with hypertension. The greater incidence of diabetes in reports comparing diuretics and β-blockers with angiotensin-converting enzyme (ACE) inhibitors may reflect in part the beneficial effects of ACE inhibitors on glucose metabolism. Compared with calcium channel blockers (CCBs), which are generally considered metabolically neutral, diuretics and β-blockers are associated with new-onset diabetes mellitus. Evidence is accumulating that overcoming insulin resistance with antihypertensive agents that interrupt the RAAS may prevent or delay the emergence of type 2 DM in patients with essential HTN.[70]

The Captopril Prevention Project was the first controlled clinical trial to show that an ACE inhibitor reduces the development of diabetes in patients with hypertension. This trial was designed to compare the effect of ACE inhibition with conventional antihypertensive therapy (β-blocker, diuretic, or both) on cardiovascular morbidity and mortality. The number of patients with newly diagnosed diabetes was 14% lower in the captopril group than in the group receiving conventional therapy. These data were confirmed in the Heart Outcomes Prevention Evaluation trial in which a fixed dose of ramipril or placebo was added to whatever other therapy was prescribed for patients at high risk of cardiovascular events (including β-blockers, CCBs, and diuretics).[70]

During the 4.5 year trial, 35% fewer patients in the ramipril group than in the placebo (control) group developed diabetes (3.6% of the 4645 patients in the ramipril group vs 5.4% of the 4652 patients in the placebo group.[70]

It has been suggested that, by blocking both kininase II and ACE, ACE inhibitors may increase not only nitric oxide production but also bradykinin, thus improving blood flow to skeletal muscle, properties that should improve insulin-mediated glucose uptake.[70]

Several clinical trials demonstrate that ARBs also have beneficial effects on glucose metabolism that likely are independent of bradykinin-mediated mechanisms. The Losartan Intervention for Endpoint Reduction in Hypertension study showed that losartan reduced the relative risk of developing type 2 diabetes mellitus by 25% compared with the β-blocker atenolol. However, since the study did not include a placebo control group, it is likely that the reduction in incident diabetes reflects the net result of both increased insulin sensitivity in the losartan group and increased insulin resistance in the atenolol group.[70]

Similar findings relative to placebo were reported in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) studies. In CHARM-Overall, candesartan (32 mg/d) reduced the relative risk of developing diabetes by 22% compared with placebo.[70]

After 1 year, candesartan had reduced the relative rate of incident diabetes by 88% compared with hydrochlorothiazide in patients with newly diagnosed hypertension in the Antihypertensive Treatment and Lipid Profile in a North of Sweden Efficacy Evaluation study. The Valsartan Antihypertensive Long-term

Use Evaluation trial demonstrated the advantage of an ARB, valsartan, over a CCB, amlodipine, in reducing the relative risk of new-onset diabetes by 23% in patients with hypertension 50 years or older at high risk of cardiac events who were treated for a mean of 4.2 years.[70]

Because amlodipine is considered neutral in its effects on insulin sensitivity and was substantially better than a thiazide diuretic in this regard in the ALLHAT study.[70]

The possibility that an ARB can prevent transition from impaired glucose tolerance, which is common in patients with essential hypertension, to type 2 diabetes mellitus is being explored in the Nateglinide and Valsartan on Impaired Glucose Tolerance Outcomes Research study.[70]

4. Statins

A retrospective analysis of the WOSCOPS examining the development of new diabetes mellitus revealed that pravastatin therapy reduced the risk of developing diabetes by 30%. This prevention in the onset of diabetes was associated with significant reduction in triglyceride levels, but upon further analyses the reduction in triglycerides did not account for the effect of statins on the development of diabetes.[71]

Recent advances in understanding the cellular actions of statins may explain mechanisms that mediate the statin effect on insulin sensitivity. Statins affect substrate delivery to insulin-sensitive tissues or modulate insulin activated signalling cascades that mediate glucose uptake. Insulin increases skeletal muscle

perfusion and substrate delivery by enhancing eNOS activity. Statins also increase eNOS expression, which may result in increased capillary recruitment and glucose disposal. Insulin activates a series of kinase cascades that involve PI3K, resulting in the translocation of glucose transporters to cell membrane and enhanced glucose uptake. This cascade is inhibited by circulating cytokines (TNF α and IL-6). Statins, like insulin, activate PI3K and Akt, which may play a role in glucose uptake. Statins, in addition to decreasing cytokine levels, also inhibit the cellular cascades such as Rho-kinase that inactivate the insulin receptor and signaling. Nitric oxide is a potential intermediary, because it has been shown to stimulate skeletal muscle glucose uptake. Further studies (in vivo and in vitro) are needed to better understand the favorable effect of statin on glucose metabolism and insulin sensitivity.

C-REACTIVE PROTEIN

C-reactive protein is a protein found in the blood, the levels of which rise in response to inflammation (an acute-phase protein). Its physiological role is to bind to phosphocholine expressed on the surface of dead or dying cells (and some types of bacteria) in order to activate the complement system via the C1Q complex.[72] CRP is synthesized by the liver[73] in response to factors released by adipocytes.[74] It is a member of the pentraxin family of proteins.

History

CRP was originally discovered by Tillett and Francis in 1930 as a substance in the serum of patients with acute inflammation that reacted with the *C* polysaccharide of pneumococcus.[75] Initially it was thought that CRP might be a pathogenic secretion as it was elevated in people with a variety of illnesses including cancer,however discovery of hepatic synthesis demonstrated that it is a native protein.

Genetics

The *CRP* gene is located on the first chromosome (1q21-q23). CRP is a 224-residue protein with a monomer molar mass of 25106 Da. The protein is an annular pentameric disc in shape and a member of the small pentraxins family.

Function

CRP is a member of the class of acute-phase reactants, as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocytes. CRP binds to phosphocholine on microbes. It is thought to assist in complement binding to foreign and damaged cells and enhances phagocytosis by macrophages, which

express a receptor for CRP. It is also believed to play another important role in innate immunity, as an early defense system against infections.

CRP rises up to 50,000-fold in acute inflammation, such as infection. It rises above normal limits within 6 hours, and peaks at 48 hours. Its half-life is constant, and therefore its level is mainly determined by the rate of production and hence the severity of the precipitating cause.

Diagnostic use

CRP is used mainly as a marker of inflammation. Apart from liver failure, there are few known factors that interfere with CRP production.[73] Measuring and charting CRP values can prove useful in determining disease progress or the effectiveness of treatments. Various analytical methods are available for CRP determination, such as ELISA, immunoturbidimetry, rapid immunodiffusion, and visual agglutination.

A high-sensitivity CRP (hs-CRP) test measures low levels of CRP using laser nephelometry. Normal concentration in healthy human serum is usually below 3 mg/L. Higher levels are found in late pregnant women, inflammation, viral infections, bacterial infections and burns.[76]

Baseline C-reactive protein (CRP) levels add to the predictive value of lipid parameters in determining the risk of first myocardial infarction in

apparently healthy men and women without a history of coronary heart disease. Baseline CRP levels also were found to be predictive of symptomatic peripheral vascular disease in a cohort of healthy men. CRP reflects systemic inflammation, and these results support the hypothesis that chronic inflammation may play a role in the pathogenesis and progression of atherosclerosis.

Chapter 4

Methodology

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Study design

The study design was one year cross sectional study.

Study period and duration

The present one year study was conducted during the period of January 2011 to December 2011.

Place

This study was conducted at Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum a teaching hospital attached to Jawaharlal Nehru Medical College, Belgaum.

Source of Data

Patients attending both OPD and IPD of Department of General Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

A total of 180 patients were selected for the study.

Sampling procedure

The sample size was calculated based on the formula as mentioned below.

$n = 4 X p X q / d^2$

Where p = Prevalence 50%.

q = 100 – p

d = Standard error 7.5

$n = 4 X 50 X 50 / 10^2$

n = 100

Using the above formula sample size was calculated as a total of 180 patients. Further this sample was randomized in 3 subgroups that is;

- Normotensives : 60
- Prehypertensives :60
- Hypertensives : 60

Sampling method

On an average 10 to 12 new hypertensives attend the Medicine OPD of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum everyday making it around 480 patients every year. Prehypertensive patients and Normotensive patients will be pool matched with hypertensives according to their age and will be studied accordingly. According to the above matching in the derived sample size every 8^{th} patient was put in the hypertensive pool and the 1^{st} patient was selected randomly.

Selection criteria

Inclusion Criteria

- Age > 18 years (after ruling out the exclusion criteria)

Exclusion Criteria

- Diabetic patients.
- Pregnant females.
- Patients suffering from any clinical signs of infection.
- Subjects taking drugs known to alter inflammation and insulin resistance namely statins, metformin, smoked tobacco etc.

Ethical clearance

Before the commencement of the study Ethical Clearance was obtained from the Ethical and Research Committee, Jawaharlal Nehru Medical College, Belgaum.

Informed Consent

All the patients fulfilling selection criteria were explained about the purpose of study and a written informed consent was obtained before enrollment (Annexure I).

Method of collection of data

Demographic data such as age, sex, occupation, history regarding hypertension were recorded. A thorough physical examination such as

anthropometry, vitals and systemic examination was conducted. These findings were recorded on a predesigned and pretested proforma (Annexure II).

Study variables

Body mass index

Body mass index was calculated based on formula;

$$\text{Body Mass Index} = \frac{\text{Weight (Kg)}}{\text{Height}^2 \text{ (m)}}$$

Body mass index was classified according to Overweight and obesity by BMI in adult Asians as below.[77]

Classification	BMI (Kg/m^2)	Risk of co-morbidities
Underweight	< 18.5	Low (But increased risk of other clinical problems
Normal range	18.5 to 22.9	Average
Overweight	≥ 23	
At risk	23.0 to 24.9	Increased
Obese I	25.0 to 29.9	Moderate
Obese II	≥ 30.0	Severe

Waist circumference

The waist circumference was measured using a standard measuring tape in Cms. Waist circumference of ≥ 90 cms in males and ≥ 80 cms in females was considered as abnormal.

Blood pressure measurement

During the course of interview, two measurements of blood pressure of each study participant were measured using mercury sphygmomanometer, first by palpatory method followed by auscultatory method as per JNC VII guidelines. Both blood pressure measurements were obtained after the subject had rested for at least five minutes in a seated position. The first blood pressure measurement was recorded after obtaining sociodemographic information from study subject, while second was recorded after clinical examination. All blood pressure measurements were made on left arm of each subject, using a cuff of appropriate size at the level of the heart. The average of two SBP and DBP reading in mm Hg were noted to describe the blood pressure of the participant.[78]

Categorization of subjects by blood pressure levels: The subjects were divided into "Normotensives" or "Hypertensives" on the basis of their blood pressure levels and "prehypertensives" were included as normotenives.

Normotensives: Systolic blood pressure less than 120 mm Hg and Diastolic blood pressure less than 80 mm Hg.

Prehypertensives: Systolic blood pressure (BP) in the range of 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mmHg.

Hypertensives: Systolic blood pressure 140 mm Hg or above Diastolic blood pressure 90 mm Hg or above.

Investigations

Investigations such as haemogram, fasting blood sugar, post prandial blood sugar, lipid profile (total cholesterol, triglycerides, HDL, LDL), hs-CRP, blood glucose and fasting plasma insulin levels were done.

HOMA IR

Fasting blood sample was drawn for measuring plasma insulin levels and insulin levels were measured by microparticle enzyme immune assay (MEIA) method. Insulin resistance was calculated by HOMA;

$$\frac{\text{Fasting Insulin } \mu U/L \text{ X Fasting plasma glucose mmol/L}}{22.5}$$

The HOMA IR index was interpreted as below;[67]

- Normal - < 2.0
- Boderline – 2.0 to 2.2
- Moderate rise – 2.2 to 2.9
- Severe – > 3.0

Statistical analysis

The data obtained was coded and entered into Microsoft Excel Worksheet. The categorical data was expressed as rates, ratios and proportions. The continuous data was expressed as mean ± standard deviation (SD). The comparison of HOMA IR between and within groups was analysed by one way

ANOVA test. Multiple comparisons were done between the groups using Sceffe's test. The Karl pearson's correlation co-efficient was used to correlate HOMA IR levels and lipid profile and obesity. A probability value ('p' value) of less than or equal to 0.05 was considered as statistically significant.

Chapter 5

Results

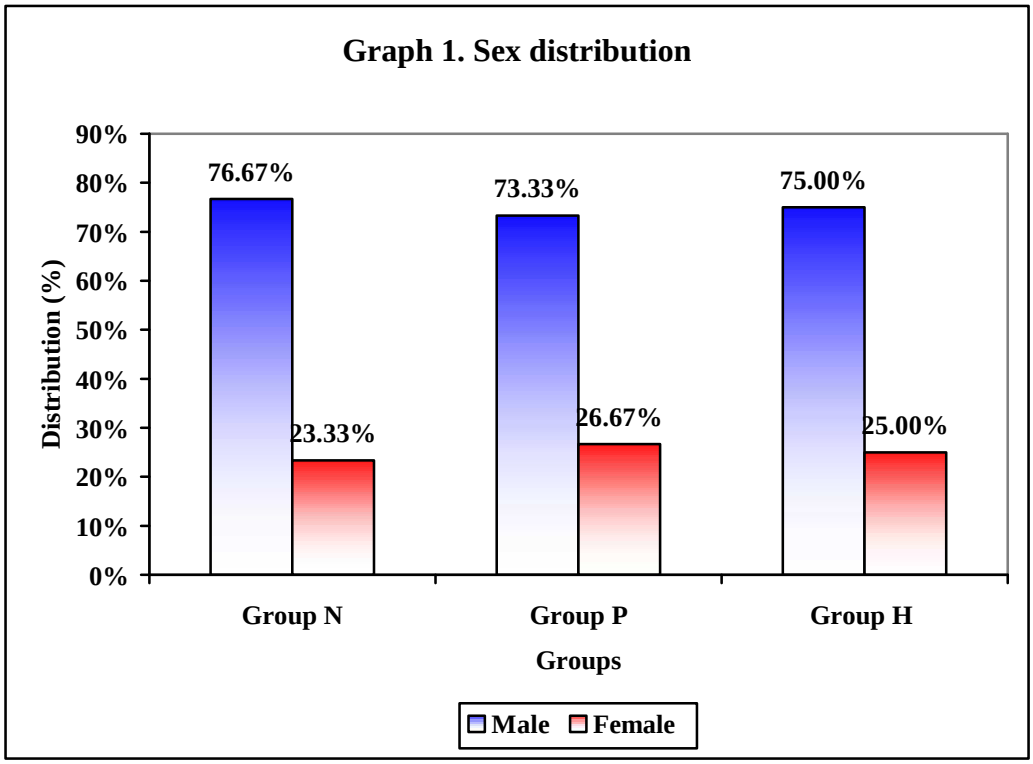
RESULTS

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011 on a total of 180 patients divided into three groups of 60 each namely, normotensives, prehypertensives and hypertensives.

The data obtained was tabulated on Microsoft excel spreadsheet and analysis was done. The final results are tabulated as below.

Table 1. Sex distribution

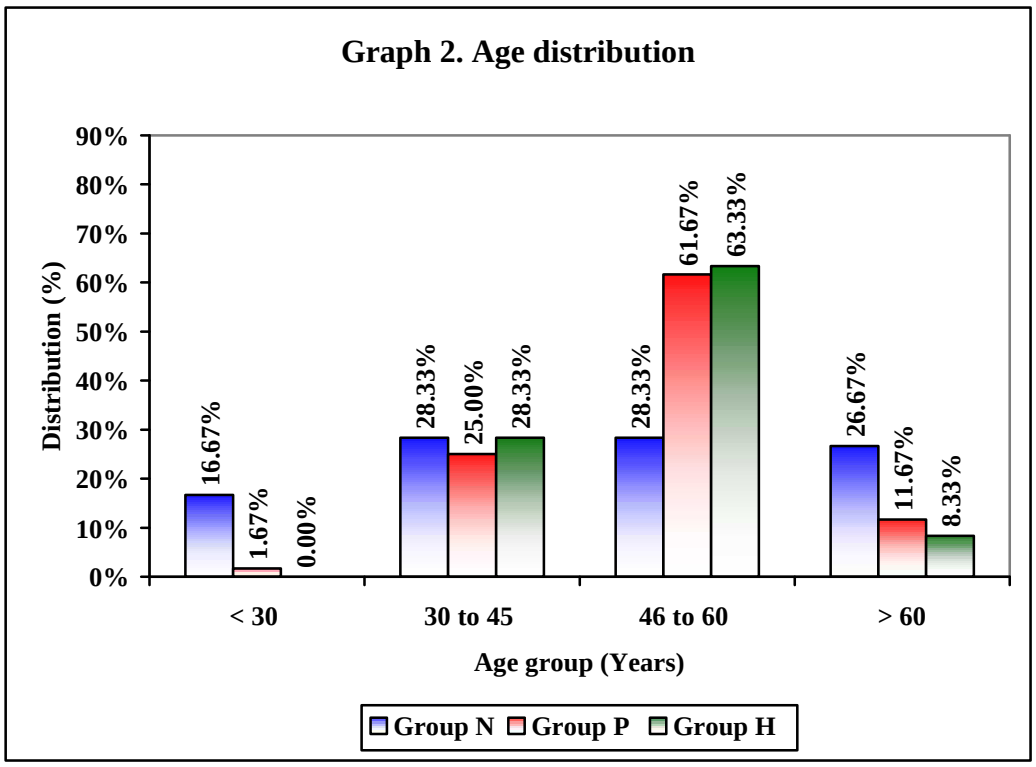
Gender	Group N (n=60)		Group P (n=60)		Group H (n=60)	
	Number	**Percent**	**Number**	**Percent**	**Number**	**Percent**
Male	46	76.67	44	73.33	45	75.00
Female	14	23.33	16	26.67	15	25.00
Total	**60**	**100.00**	**60**	**100.00**	**60**	**100.00**



In this study male preponderance was seen in all three study groups. Group N had 76.67%, Group P had 73.33% and Group H had 75% male subjects.

Table 2. Age distribution

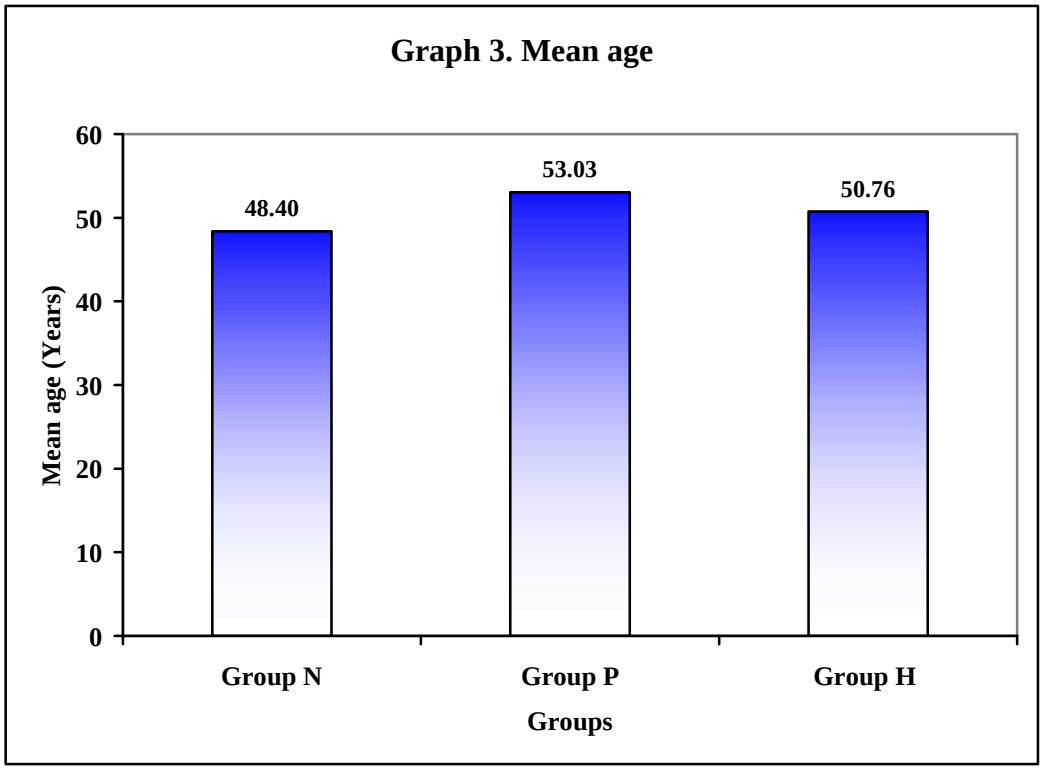
Age group	Group N (n=60)		Group P (n=60)		Group H (n=60)	
(Years)	**Number**	**Percent**	**Number**	**Percent**	**Number**	**Percent**
< 30	10	16.67	1	1.67	0	0.00
30 to 45	17	28.33	15	25.00	17	28.33
46 to 60	17	28.33	37	61.67	38	63.33
> 60	16	26.67	7	11.67	5	8.33
Total	**60**	**100.00**	**60**	**100.00**	**60**	**100.00**



In this study Normotensive group had almost equal distribution of the subjects >30years. Prehypertensive Group had maximum subject strength in 46-60 year bracket (61.67%) and Hypertensives similar to prehypertensives had maximum subject strength in 46-60 year bracket (63.33%)

Table 3. Mean age

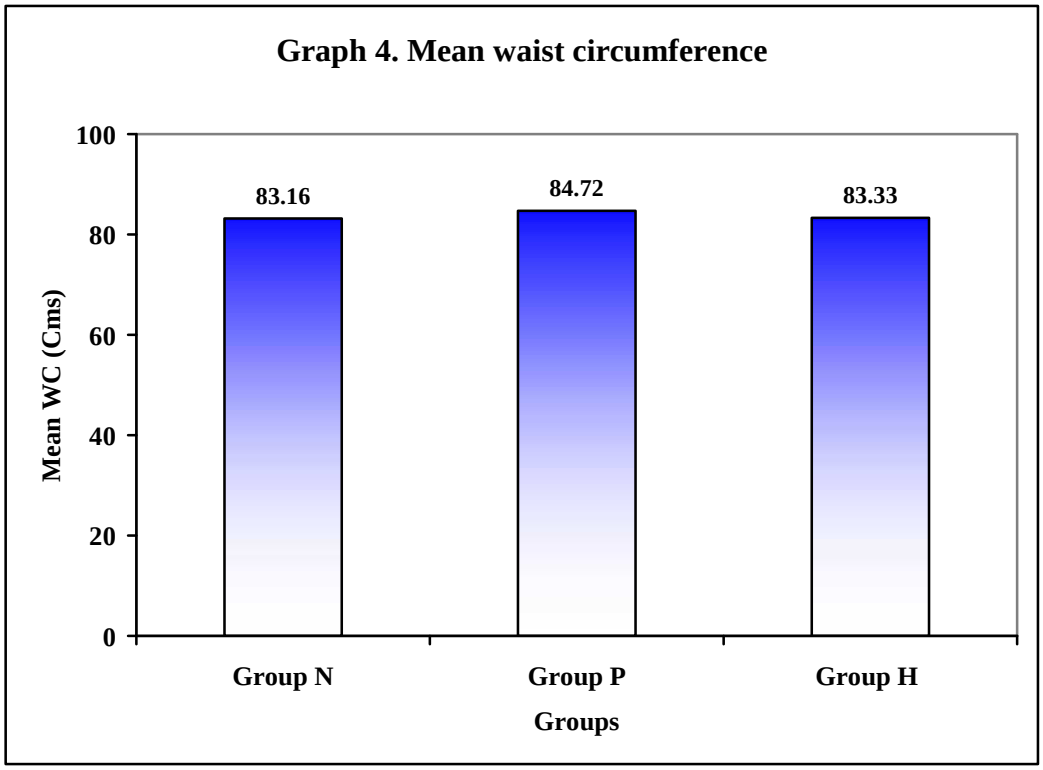
Groups	Distribution (n=180)	
	Mean	**SD**
Group N	48.40	15.38
Group P	53.03	10.86
Group H	50.76	8.05



In this study, mean age in Group N was 48.40 ± 15.38 years, Group P was 53.03 ± 10.86 years and Group H was 50.76±8.05 years

Table 4. Mean waist circumference

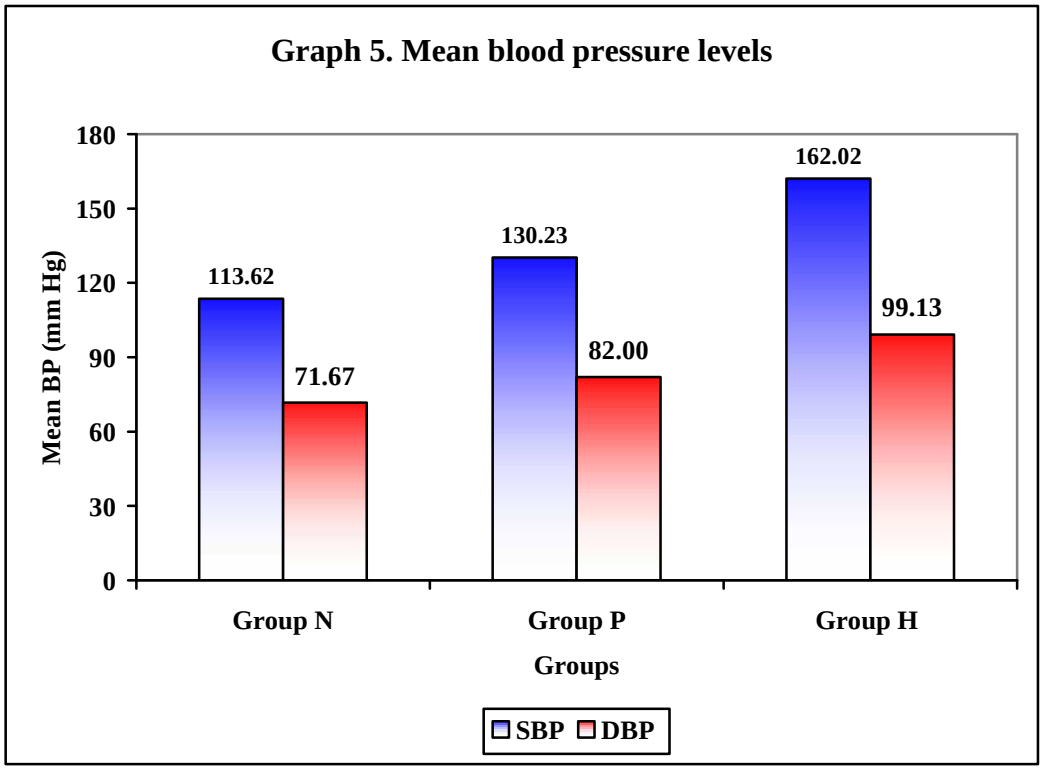
Groups	Mean ± SD	
	Mean	**SD**
Group N	83.16	7.10
Group P	84.72	7.04
Group H	83.33	6.63



In this study the mean waist circumference of the subjects in three groups were 83.16±7.10, 84.72±7.04 and 83.33±6.63 for Group N, P and H respectively.

Table 5. Mean blood pressure levels

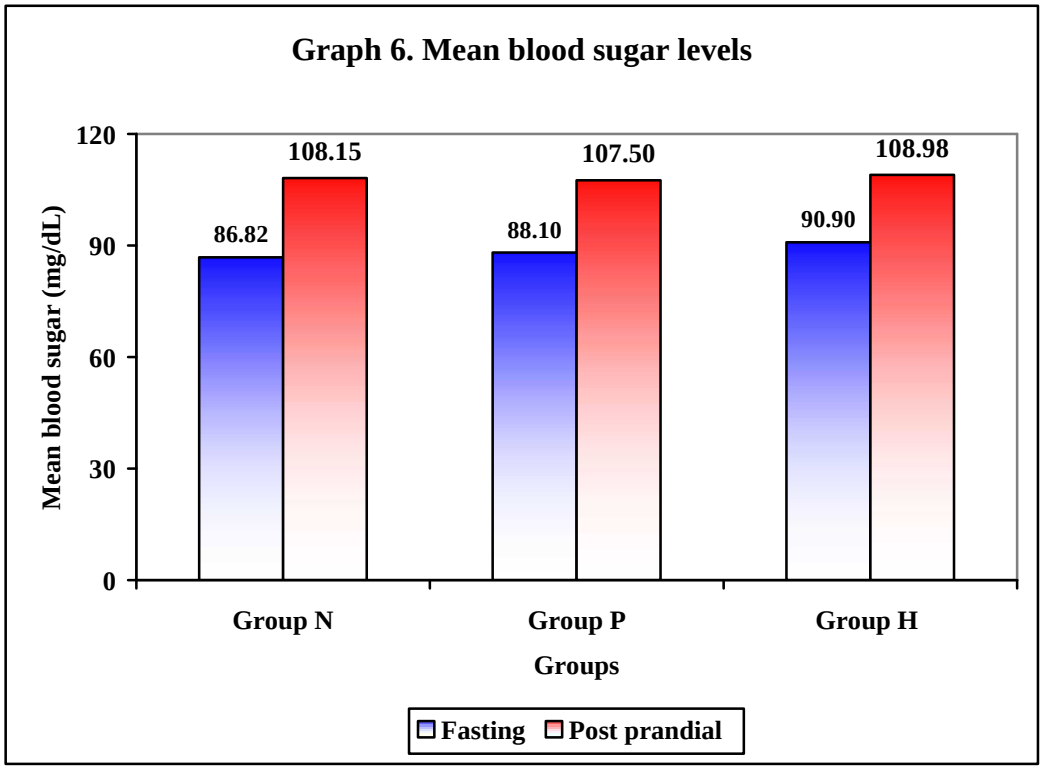
Groups	Systolic BP		Diastolic BP	
	Mean	**SD**	**Mean**	**SD**
Group N	113.62	3.51	71.67	7.86
Group P	130.23	6.42	82.00	6.42
Group H	162.02	13.33	99.13	8.61



In this study, Normotensive group had mean systolic and diastolic blood pressures of 113.62±3.51 mm of Hg and 71.62±7.86 mm of Hg respectively. Prehypertensive group had mean systolic and diastolic blood pressures of 130.23±6.42 mm of Hg and 82±6.42 mm of Hg respectively and hypertensive group had mean systolic and diastolic blood pressures of 162.02±13.33 mm of Hg and 99.13±8.61 mm of Hg respectively.

Table 6. Mean blood sugar levels

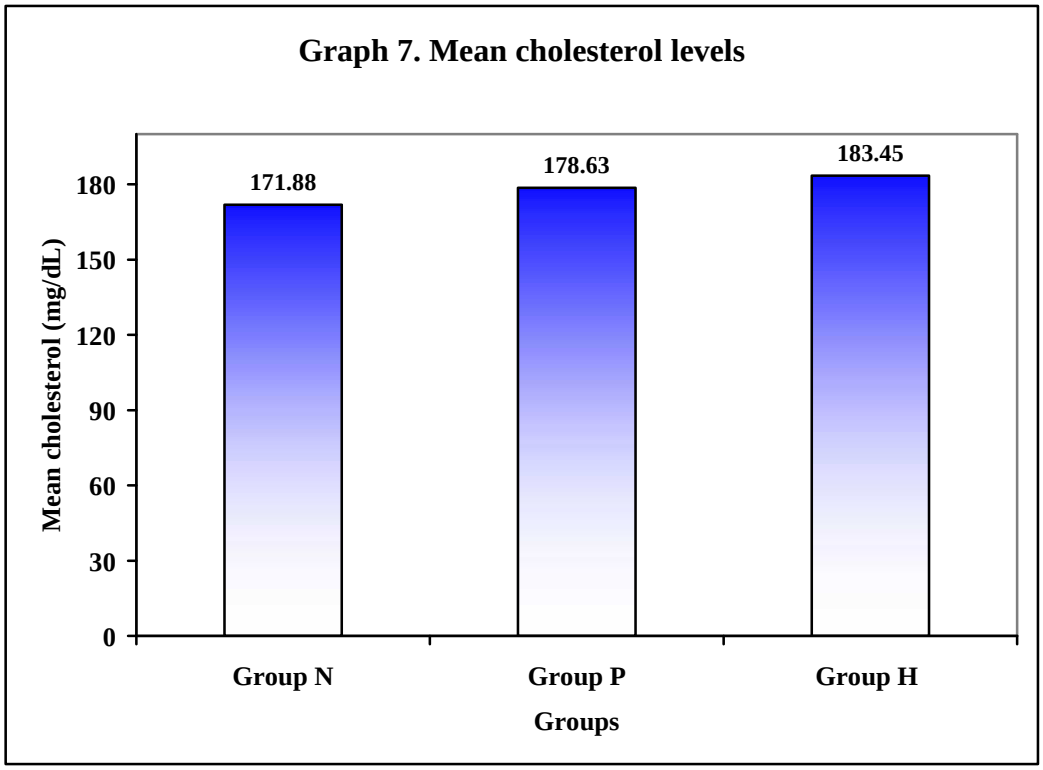
Groups	Fasting		PPBS	
	Mean	**SD**	**Mean**	**SD**
Group N	86.82	11.44	108.15	12.78
Group P	88.10	8.91	107.50	9.07
Group H	90.90	7.04	108.98	6.69



In this study, normotensives had mean FBS and PPBS of 88.82±11.44mg/dl and 108.15±12.78 mg/dl respectively. Prehypertensives had mean FBS and PPBS of 88.10±8.91 mg/dl and 107.50±9.07mg/dl respectively and Hypertensives had mean FBS and PPBS of 90.90±7.04 and 108.98±6.69 mg/dl respectively.

Table 7. Mean cholesterol levels

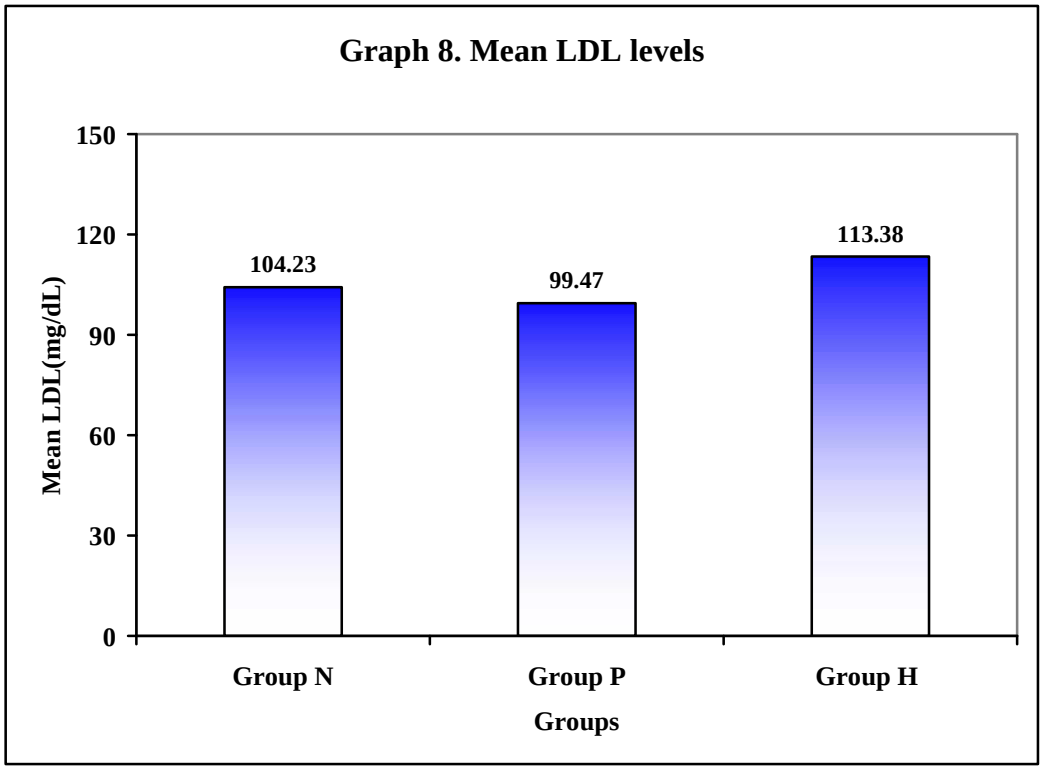
Groups	Mean ± SD	
	Mean	**SD**
Group N	171.88	39.58
Group P	178.63	44.13
Group H	183.45	50.06



In this study Group N, Group P and Group H had a mean Total Cholestrol level of 171.88±39.58, 178.63±44.13 and 183.45±50.06 respectively.

Table 8. Mean LDL levels

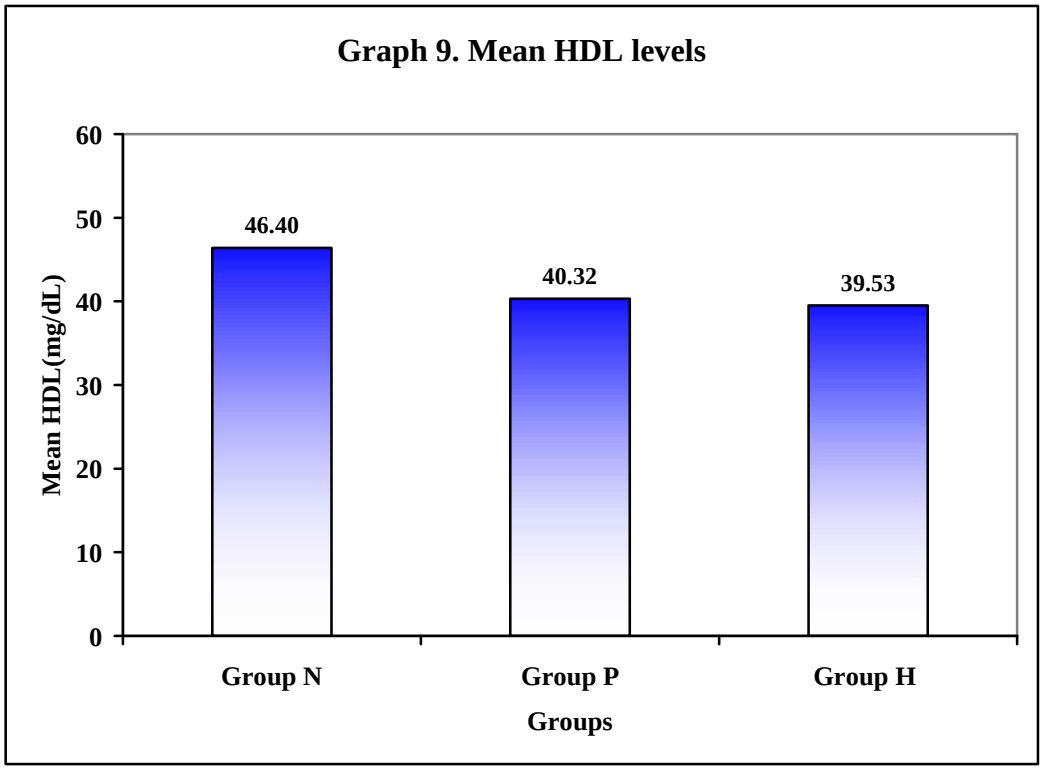
Groups	Mean ± SD	
	Mean	**SD**
Group N	104.23	37.03
Group P	99.47	30.38
Group H	113.38	50.22



In this study Group N, Group P and Group H had a mean LDL level of 104.23±37.03, 99.47±30.38 and 113.38±50.22 respectively.

Table 9. Mean HDL levels

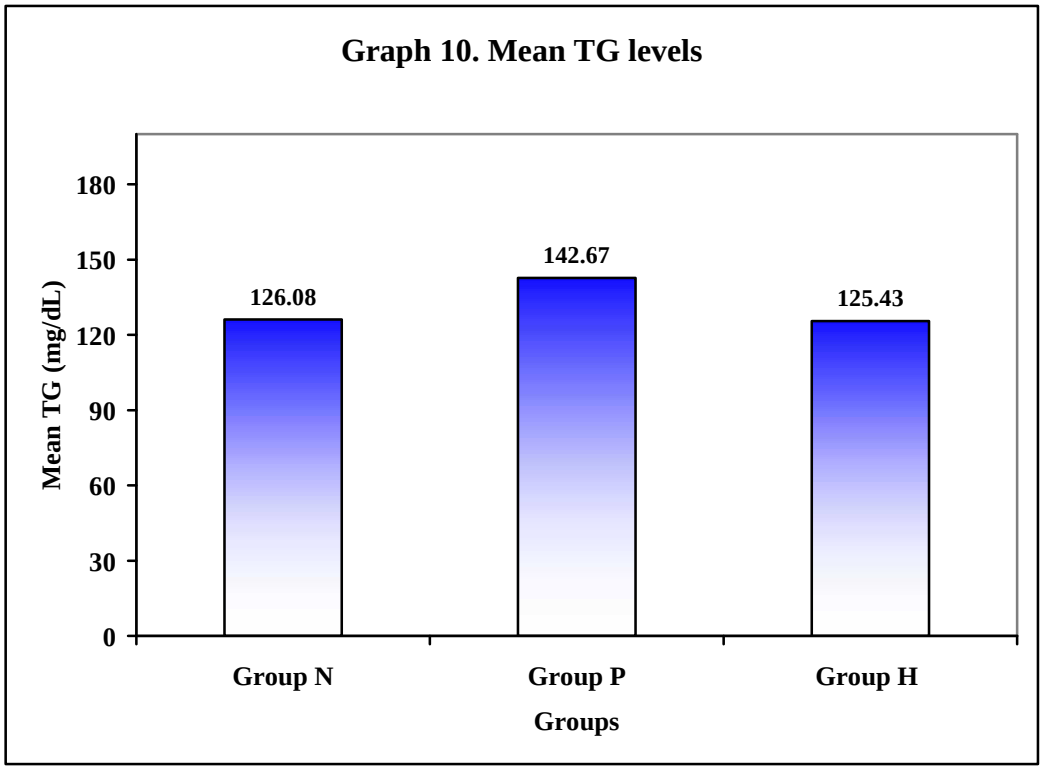
Groups	Mean ± SD	
	Mean	**SD**
Group N	46.40	12.22
Group P	40.32	7.57
Group H	39.53	11.44



In this study Group N, Group P and Group H had a mean HDL level of 46.40±12.22, 40.32±7.57 and 39.53±11.44 respectively.

Table 10. Mean TG levels

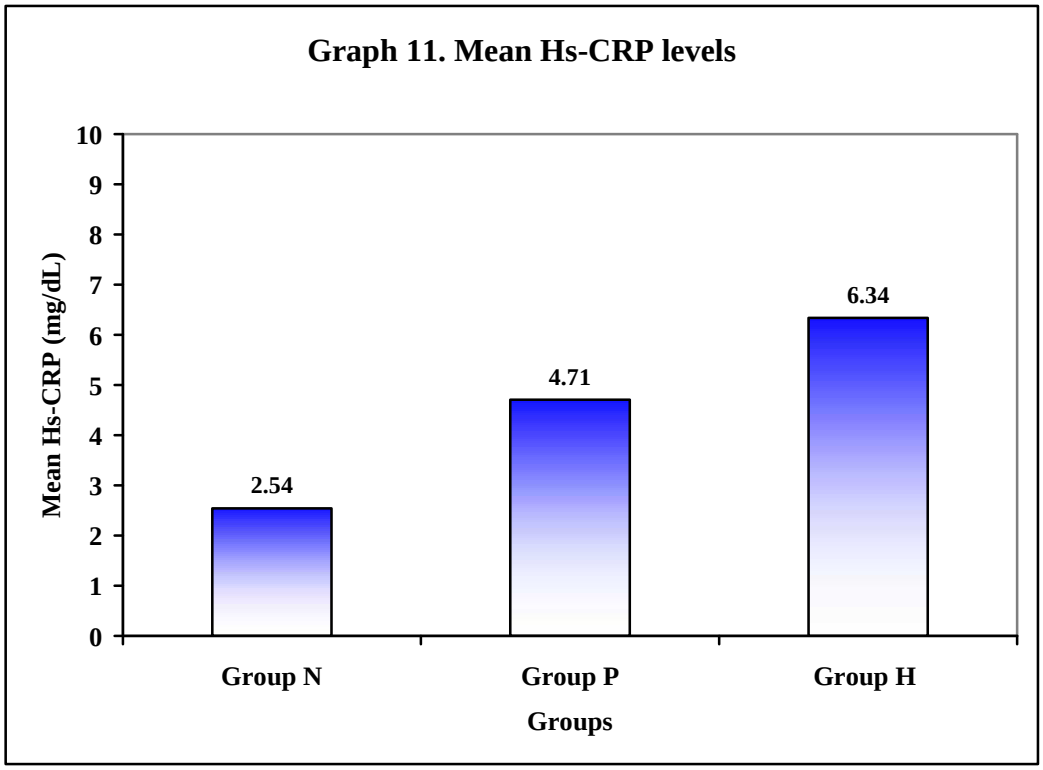
Groups	Mean ± SD	
	Mean	**SD**
Group N	126.08	47.04
Group P	142.67	56.54
Group H	125.43	58.93



In this study Group N, Group P and Group H had a mean TG level of 126.08±47.04, 142.67±56.54 and 125.43±58.93 respectively.

Table 11. Mean Hs-CRP levels

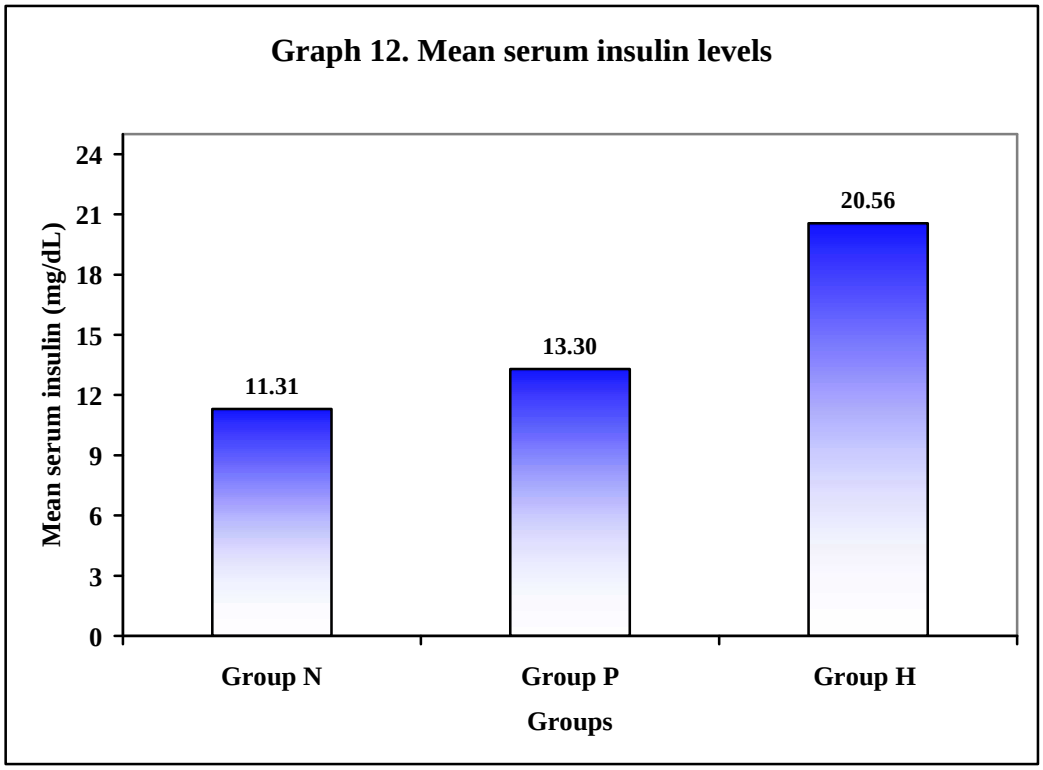
Groups	Mean ± SD	
	Mean	**SD**
Group N	2.54	1.00
Group P	4.71	2.04
Group H	6.34	3.52



In this study Group N, Group P and Group H had a mean hs-CRP level of 2.54±1, 4.71±2.04 and 6.34±3.52 respectively.

Table 12. Mean serum insulin levels

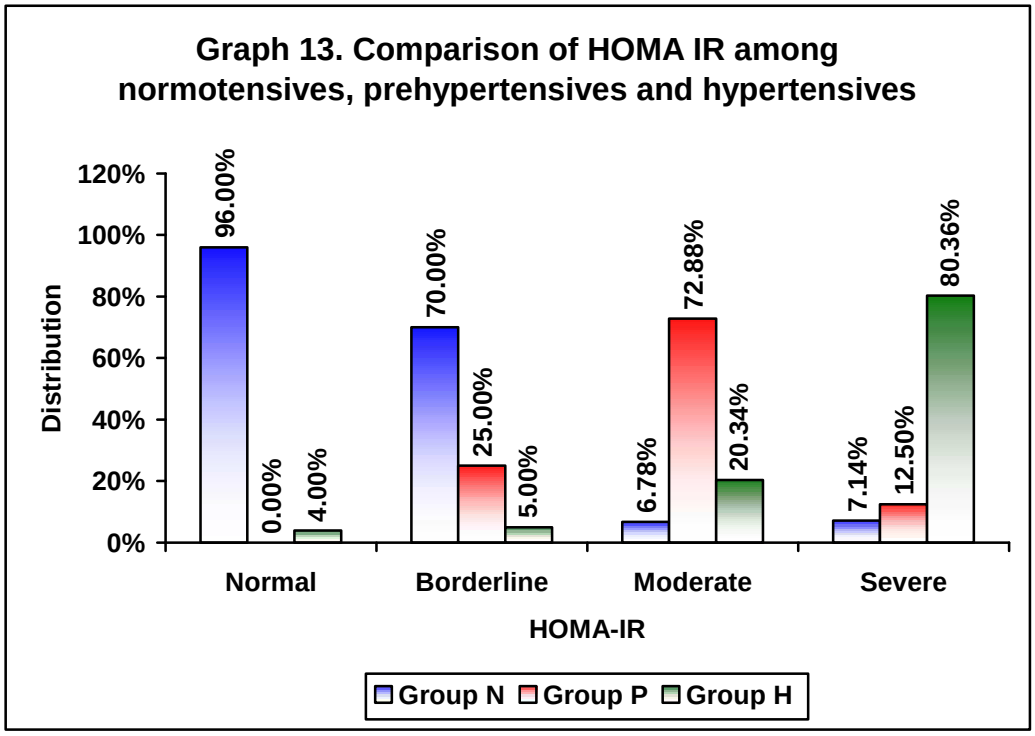
Groups	Mean ± SD	
	Mean	**SD**
Group N	11.31	9.34
Group P	13.30	5.04
Group H	20.56	8.86



In this study highest fasting serum insulin was noted in hypertensive group with 20.56±8.86 while prehypertensives and normotensives had 13.30±5.04 and 11.31±9.34 respectively.

Table 13. Comparison of HOMA IR among normotensives, prehypertensives and hypertensives

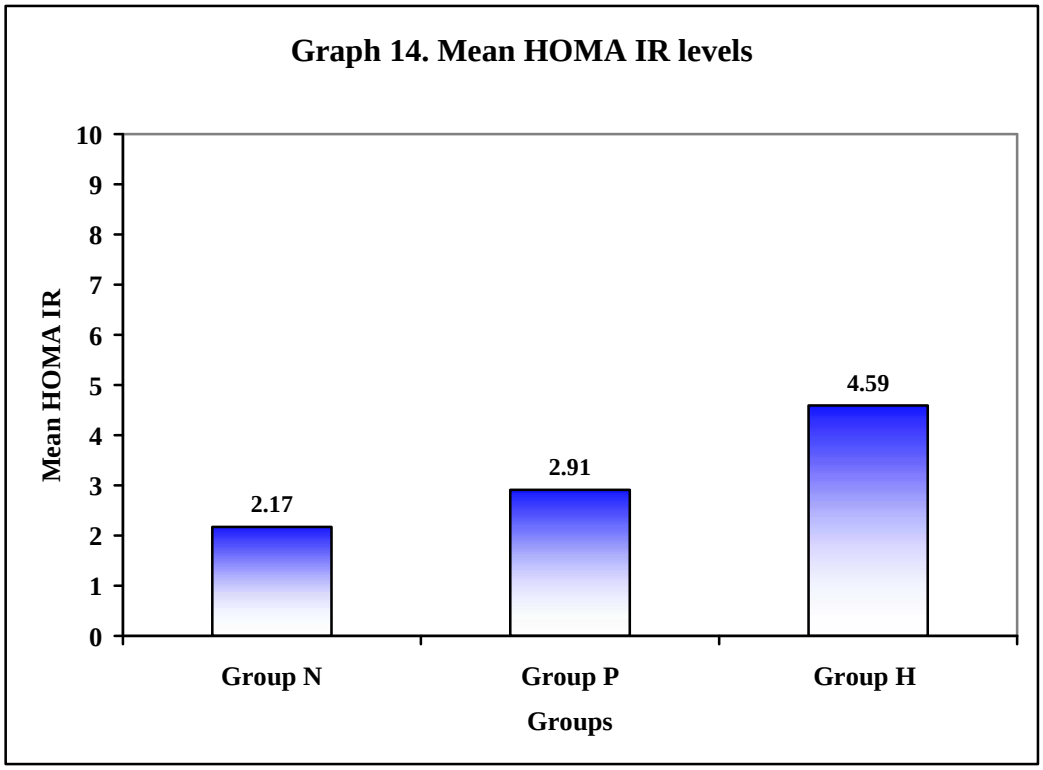
HOMA-IR	Group N		Group P		Group H	
	No.	%	No.	%	No.	%
Normal (<2.0) (n=25)	24	96.00	0	0.00	1	4.00
Borderline (2.0 to 2.2) (n=40)	28	70.00	10	25.00	2	5.00
Moderate (2.2 - 3.0) (n=59)	4	6.78	43	72.88	12	20.34
Severe (>3.0) (n=56)	4	7.14	7	12.50	45	80.36



In this study, 96% of the subjects with normal HOMA index were normotensives, 72.88% of subjects with moderate insulin resistance were prehypertensives and 80.36% of the subjects with severe insulin resistance were hypertensives.

Table 14. Mean HOMA IR

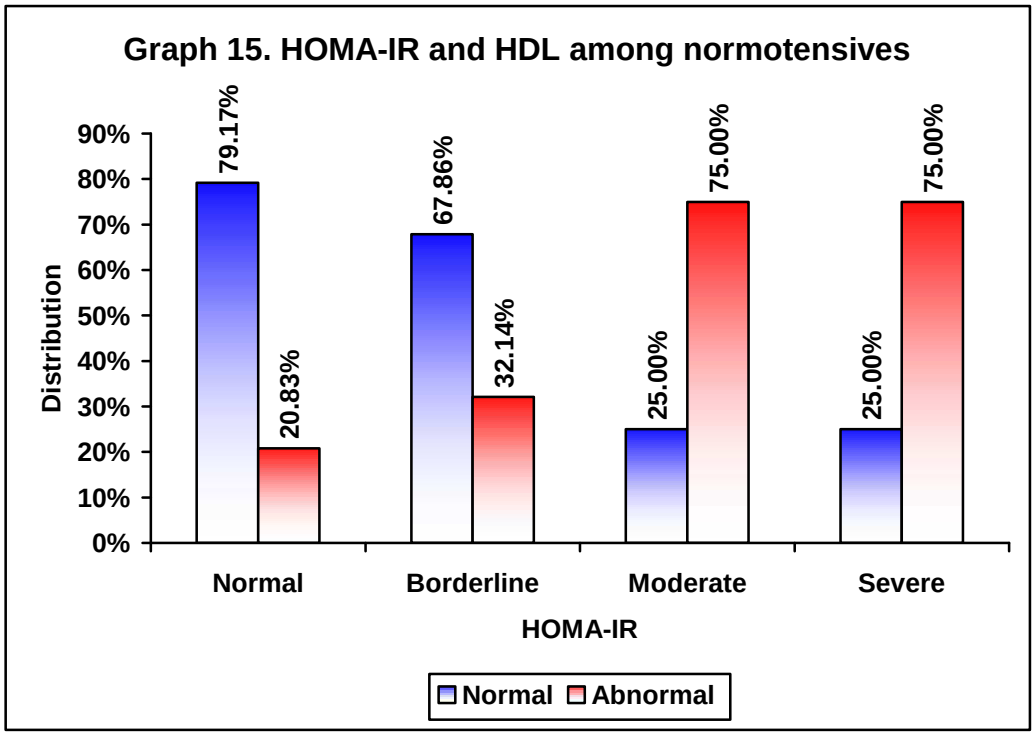
Groups	Mean ± SD	
	Mean	**SD**
Group N	2.17	0.66
Group P	2.91	1.27
Group H	4.59	1.87



In this study, highest HOMA index was noted in Hypertensive group as 4.59±1.87 while prehypertensives and normotensives had HOMA index of 2.91±1.27 and 2.17±0.66 respectively.

Table 15. HOMA-IR and HDL among normotensives

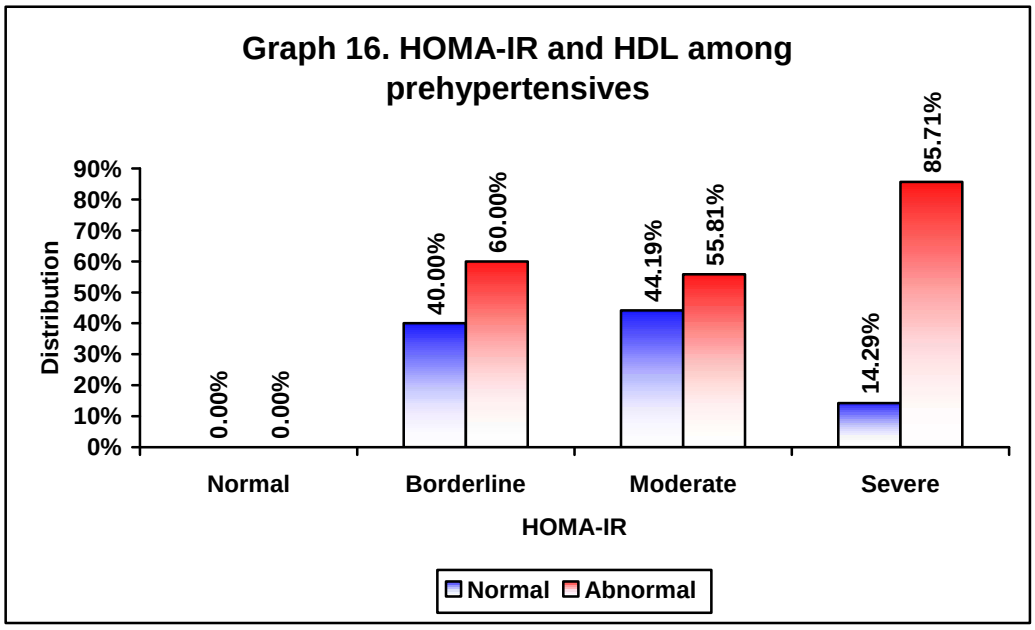
HOMA-IR (n=60)	HDL Levels				Total (n=60)	
	Normal (n=40)		Abnormal (n=20)			
	No.	%	No.	%	No.	%
Normal (<2.0) (n=24)	19	79.17	5	20.83	24	40.00
Borderline (2.0 to 2.2) (n=28)	19	67.86	9	32.14	28	46.67
Moderate (2.2 - 3.0) (n=4)	1	25.00	3	75.00	4	6.67
Severe (>3.0) (n=4)	1	25.00	3	75.00	4	6.67



Majority (52) of normotensives had normal to borderline insulin resistance with most of the subjects having normal HDL levels.

Table 16. HOMA-IR and HDL among prehypertensives

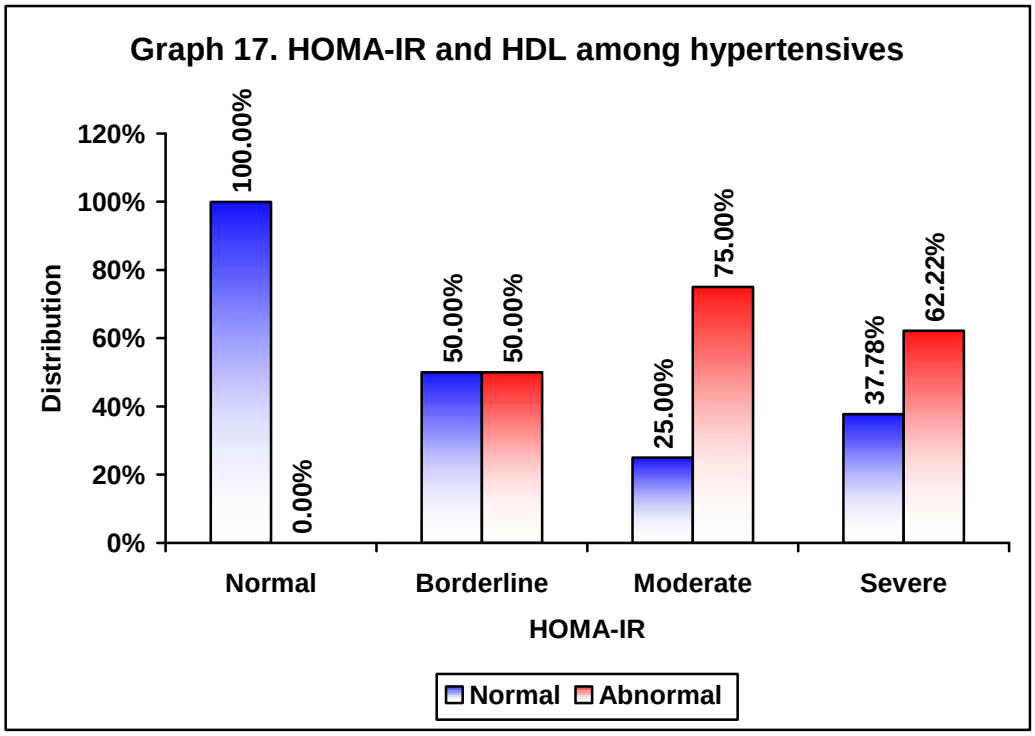
HOMA-IR (n=60)	HDL Levels				Total (n=60)	
	Normal (n=24)		Abnormal (n=36)			
	No.	%	No.	%	No.	%
Normal (<2.0) (n=0)	0	0.00	0	0.00	0	0.00
Borderline (2.0 to 2.2) (n=10)	4	40.00	6	60.00	10	16.67
Moderate (2.2 - 3.0) (n=43)	19	44.19	24	55.81	43	71.67
Severe (>3.0) (n=7)	1	14.29	6	85.71	7	11.67



In prehypertensive group, majority had moderate insulin resistance (43, 71.67%). Of these subjects 55.81% had abnormal HDL levels. 6 out of 7 subjects with severe insulin resistance had abnormal HDL levels. None of the subjects in this group had normal insulin resistance.

Table 17. HOMA-IR and HDL among hypertensives

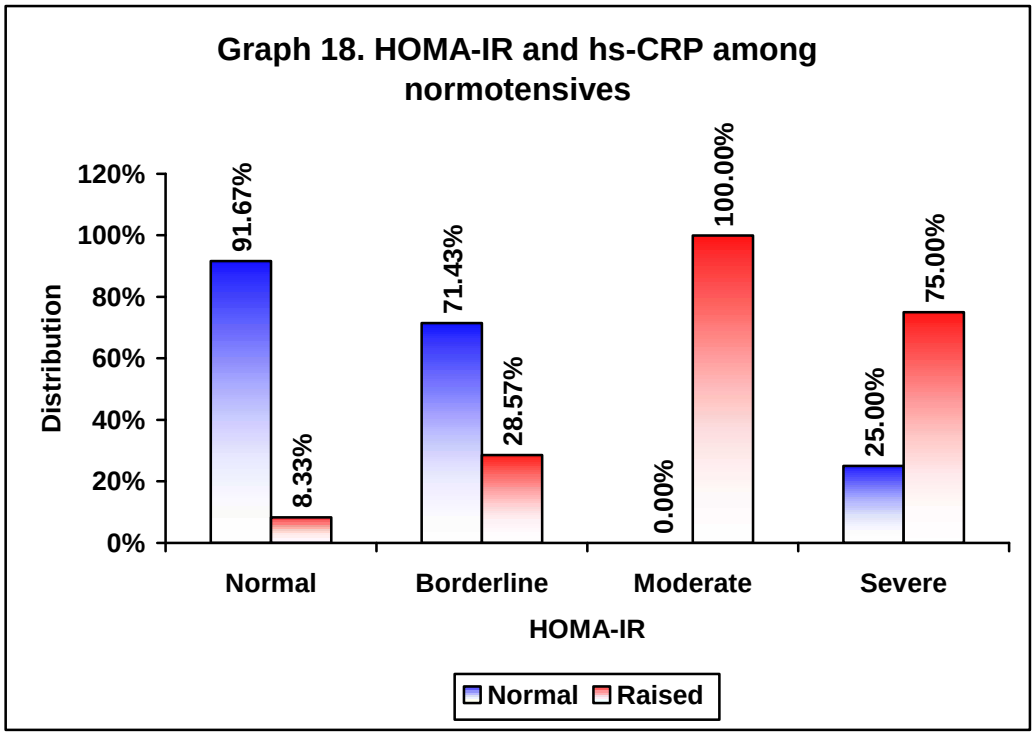
HOMA-IR (n=60)	HDL Levels				Total (n=60)	
	Normal (n=22)		Abnormal (n=38)			
	No.	%	No.	%	No.	%
Normal (<2.0) (n=1)	1	100.00	0	0.00	1	1.67
Borderline (2.0 to 2.2) (n=2)	1	50.00	1	50.00	2	3.33
Moderate (2.2 - 3.0) (n=12)	3	25.00	9	75.00	12	20.00
Severe (>3.0) (n=45)	17	37.78	28	62.22	45	75.00



Majority of subjects in the hypertensive group had severe insulin resistance (45, 75%). Out of these, most of the subjects (62.2%) had abnormal HDL levels.

Table 18. HOMA-IR and hs-CRP among normotensives

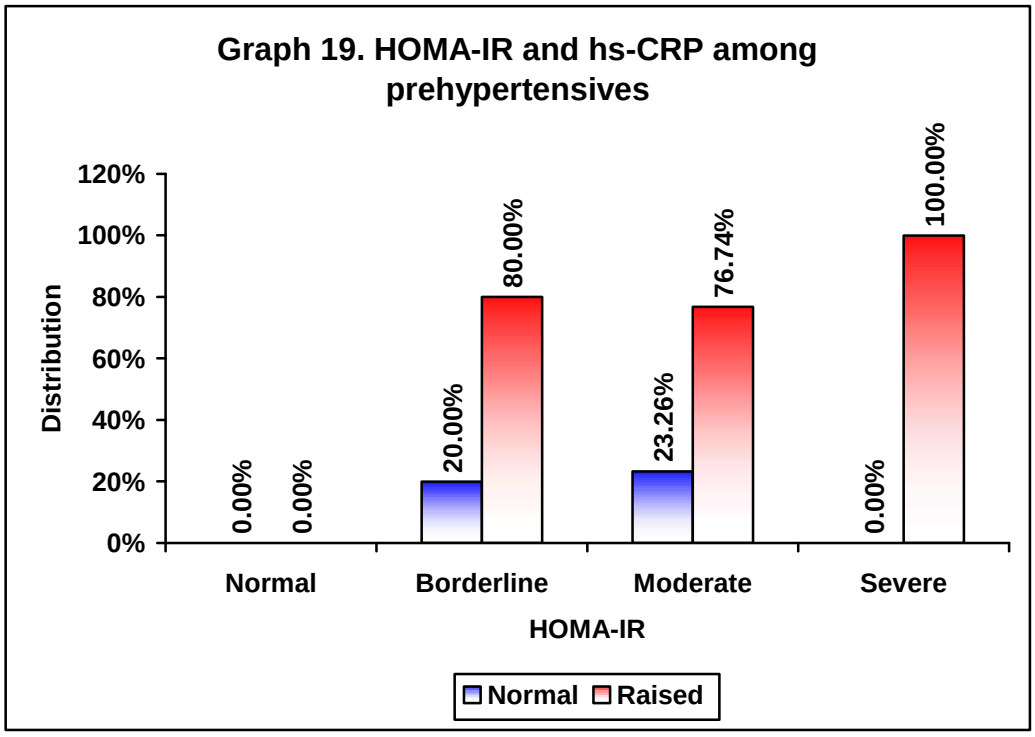
HOMA-IR (n=60)	hs-CRP Levels				Total (n=60)	
	Normal (n=43)		Raised (n=17)			
	No.	%	No.	%	No.	%
Normal (<2.0) (n=24)	22	91.67	2	8.33	24	40.00
Borderline (2.0 to 2.2) (n=28)	20	71.43	8	28.57	28	46.67
Moderate (2.2 - 3.0) (n=4)	0	0.00	4	100.00	4	6.67
Severe (>3.0) (n=4)	1	25.00	3	75.00	4	6.67



52 out of 60 normotensives had normal to borderline insulin resistance. Of these 42 subjects had normal hsCRP levels.

Table 19. HOMA-IR and hs-CRP among prehypertensives

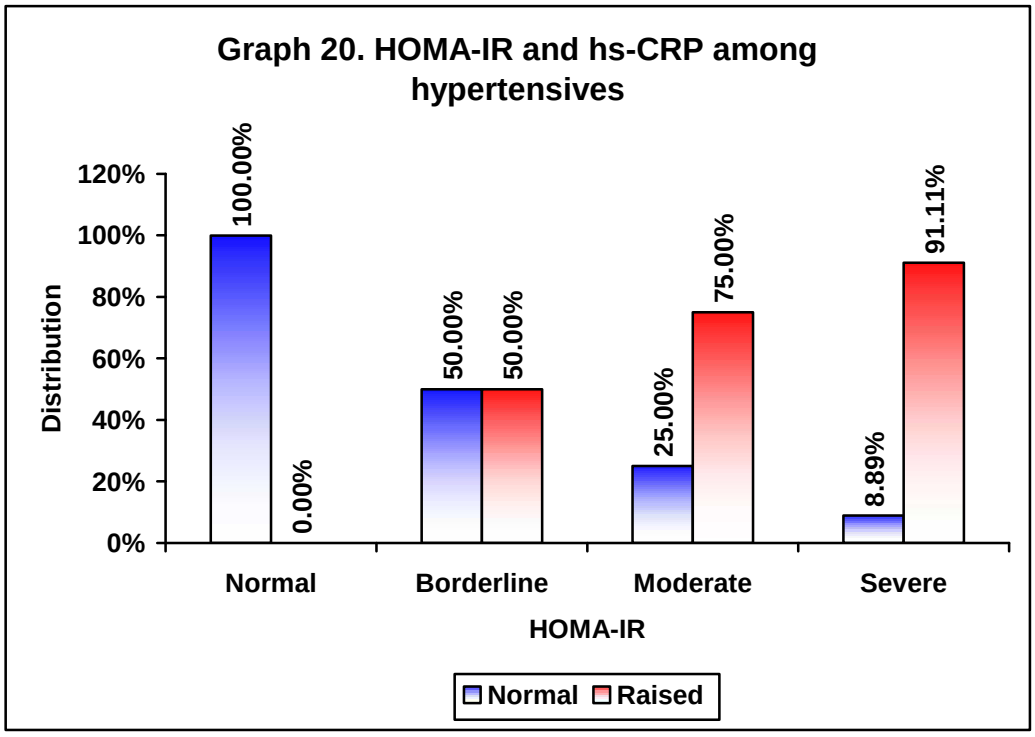
HOMA-IR (n=60)	hs-CRP Levels				Total (n=60)	
	Normal (n=12)		Raised (n=48)			
	No.	%	No.	%	No.	%
Normal (<2.0) (n=0)	0	0.00	0	0.00	0	0.00
Borderline (2.0 to 2.2) (n=10)	2	20.00	8	80.00	10	16.67
Moderate (2.2 - 3.0) (n=43)	10	23.26	33	76.74	43	71.67
Severe (>3.0) (n=7)	0	0.00	7	100.00	7	11.67



Majority of prehypertensives (71.67%) had moderate insulin resistance. Of these, 76.74% subjects had raised hsCRP levels.

Table 20. HOMA-IR and hs-CRP among hypertensives

HOMA-IR (n=60)	hs-CRP Levels				Total (n=60)	
	Normal (n=40)		Raised (n=20)			
	No.	%	No.	%	No.	%
Normal (<2.0) (n=1)	1	100.00	0	0.00	1	1.67
Borderline (2.0 to 2.2) (n=2)	1	50.00	1	50.00	2	3.33
Moderate (2.2 - 3.0) (n=12)	3	25.00	9	75.00	12	20.00
Severe (>3.0) (n=45)	4	8.89	41	91.11	45	75.00



Most of the hypertensives (75%) in this study had severe insulin resistance. Of these 91.11% subjects had raised hsCRP values.

Table 21. One way anova for HOMA INDEX

	Sum of Squares	df	Mean Square	F	p value	Inference
Between Groups	184.807	2	92.403	49.872	<0.001	Highly significant
Within Groups	327.950	177	1.853			
Total	512.757	179				

One way analysis of variance(ANOVA) was performed to determine any significance in HOMA index variation between normotensives, prehypertensives and hypertensives. It shows highly significant variation in the means of HOMA index between all three groups with the p value of $p<0.001$.

Table 22. Multiple Comparisons

Group	Group	Mean difference	P value	Inference
Group N	Group P	0.74350*	0.013	Significant
Group N	Group H	2.42250*	<0.001	Highly Significant
Group P	Group H	1.67900*	<0.001	Highly Significant

Sceffe's test

Scheffe test was done to confirm the results of ANOVA test and to determine the intergroup variation between normotensives, prehypertensives and hypertensive. Intergroup variation for HOMA index between normotensive and prehypertensive, normotensive and hypertensive and prehypertensive and

hypertensive were significant (p=0.013), highly significant (p<0.001) and highly significant (p<0.001) respectively.

Table 23. Karl person's correlation coefficient between HOMA index other variables

Variables	Coefficient	P value	Coefficient	P value	Coefficient	p value
Waist girth (Cms)	0.6439	<0.001	0.5223	<0.001	0.3531	0.0057
Cholesterol(mg/dL)	0.3967	0.0017	0.4752	0.0001	0.3193	0.0129
LDL (mg/dL)	0.2384	0.0666	0.3206	0.0125	0.0971	0.4604
HDL (mg/dL)	-0.0864	0.5114	-0.3783	0.0029	-0.0572	0.6645
TG (mg/dL)	0.2500	0.0541	0.4319	0.0006	0.2199	0.0914
Hs-CRP (mg/dL)	0.4355	0.0005	0.4789	0.0001	0.2646	0.0410

Karl Pearsons Corelation coefficient test was performed in all three groups between their HOMA index and waist circumference, total cholesterol, LDL, HDL, TG and hsCRP. Waist circumference and total cholesterol showed significant positive correlation with HOMA index in all the three groups that is, normotensives, prehypertensive and hypertensives (p<0.050) whereas, serum LDL and TG positively correlated with HOMA in all three groups but correlation was statistically significant in prehypertensives only. (LDL p=0.012, TG-p=0.0006). Serum HDL showed negative correlation with HOMA index in all three groups but was statistically significant only in prehypertensives (p=0.0029).

hsCRP showed statistically significant positive correlation with HOMA index in all three groups that is normotensives, prehypertensive and hypertensive (p<0.050).

Chapter 6

Discussion

DISCUSSION

Hypertension is the most common CVD, affecting approximately 20 percent of the adult population. It is considered both as a disease condition in itself and as one of the major risk factors for heart disease, stroke, and kidney disease. An estimated 600 million people have high blood pressure worldwide. About 15 to 37 percent of the adult population worldwide is afflicted with hypertension. It is estimated that the global prevalence of hypertension is expected to be 1.56 billion by 2025.[79]

The prevalence of HTN in India is 34.7% (Stage I, 20%, and Stage II, 14.7%). In urban India, less than 18% of adults have normal blood pressure (BP) of less than 120/80 mm Hg.[80]

Various factors implicated in the genesis of Essential hypertension include genetic influence, age, sex, salt sensitivity, an adverse lipoprotein profile, smoking, glucose intolerance and obesity. Hyperinsulinemia, of late, has also generated considerable interest as a potential risk factor.[37]

It is estimated that at least 50% of hypertensive patients are insulin resistant, and insulin resistance is the fundamental abnormality in the pathogenesis of the cardiometabolic syndrome.[46]

Despite major advances in the understanding of the pathogenesis and treatment of HTN and other components of the cardiometabolic syndrome, these entities continue to contribute to major morbidity and mortality from CVD and CKD.

Asians and Asian Indians have a relative increase in visceral versus subcutaneous fat with concomitant increase in waist circumference which explains the greater prevalence of insulin resistance syndrome in these populations and confers a higher risk of diabetes and CVD in them.[37] The present study was aimed to assess the prevalence of insulin resistance in hypertensive individuals.

In this study male preponderance was seen in all three study groups. Normotensives had 76.67%, Prehypertensives had 73.33% and Hypertensives had 75% male subjects whereas in a study[81] conducted in Sao Paulo to know the prevalence of insulin resistance, males were 41.9% and females were 50.9%.

In another study[82] in Saudi Arabia 36.4% were males and 63.6% were females. Compared to the above mentioned studies, females were less in number in the present study.

A study[83] conducted on patients undergoing general health check up in Thailand reported that prevalence of insulin resistance (IR) was ~25.1% in men and 21.5% in women. Another study[84] done on Finnish general population, showed slightly higher prevalence of IR in women than in men. However this type of association could not be made in this study due to fewer female patients.

In the present study, in normotensive group, almost equal distributions of subjects was seen with age >30 yrs. Most of the prehypertensives and hypertensives were aged between 46 to 60 years (61.67% and 63.33% respectively) The mean age in among normotensives, prehypertensives and hypertensives was 48.40±15.38, 53.03± 10.86 and 50.76±8.05 years respectively.

In a study[85] done on Mexican women it was concluded that, an independent relation exists between age and HOMA index supporting the hypothesis that, age per se could be associated with impairment of insulin action.

In a study[86] done in India it was concluded that, with increase in age there is increase in IR.

This correlation between age and HOMA index correlation was not observed in the present study as all three groups had similar mean age.

In this study the mean waist girth among normotensives, prehypertensive and hypertensives was 83.16±7.10, 84.72±7.04 and 83.33±6.63 respectively.

In Olivetti Heart Study[87] performed in Institute of food science and technology, Italy, it was concluded that waist circumference increases with the increase in blood pressure.

In another study[88] conducted in Chile, it was further concluded that waist circumference is directly proportional to blood pressure in young Chilean adults.

However in the present study, all three groups had similar mean waist circumference measurements.

In the present study, among normotensive the mean systolic and diastolic blood pressures were found to be 113.62±3.51 mm Hg and 71.62±7.86 mm Hg respectively. In prehypertensive group, the mean systolic and diastolic blood pressures were raised (130.23±6.42 mm Hg and 82±6.42 mm Hg respectively)

whereas among hypertensives the same were found to be higher (162.02±13.33 mm Hg and 99.13±8.61 mm Hg respectively) compared to other two groups.

These mean values of blood pressure in each group are in concordance with this study methodology of having three groups i.e normotensive, prehypertensive and hypertensive.

In this study, the mean FBS and PPBS of 88.82±11.44 mg/dl and 108.15±12.78 mg/dl was noted among normotensives whereas in prehypertensives the mean FBS and PPBS levels were 88.10±8.91 mg/dl and 107.50±9.07mg/dl respectively and in hypertensives the mean FBS and PPBS levels were found to be 90.90±7.04 and 108.98±6.69 mg/dl respectively.

In this study as per our parameters, only non diabetic patients were included and the above findings of FBS and PPBS are in accordance with our inclusion criteria.

In the present study the mean total cholesterol levels among normotensives, prehypertensives and hypertensives were 171.88±39.58, 178.63±44.13 and 183.45±50.06 respectively.

In this study among the normotensives the mean LDL levels were 104.23±37.03 mg/dl whereas among prehypertensive and hypertensives the same were found to be 99.47±30.38 and 113.38±50.22 respectively.

In the present study decreasing trend of mean HDL levels was noted that is, normotensives had 46.40±12.22 mg/dl, prehypertensives had 40.32±7.57 mg/dl and hypertensives had a mean HDL levels of 39.53±11.44.

In this study the mean triglycerides level among normotensives was 126.08±47.04 and among prehypertensives was 142.67±56.54 mg/dL. The mean triglycerides in hypertensives was found to be 125.43±58.93 mg/dL.

The relationship between the blood pressure and dyslipidemia is well established. There is a known evidence of direct relationship between total cholesterol and blood pressure.

In a study[89] performed in Nigeria, blood pressure was significantly positively correlated with total cholesterol, serum LDL, serum TG and HDL.

In TROMSO study,[90] another population based study conducted in Norway concluded that there exists a strong relationship between the serum total cholesterol, serum LDL and blood pressure. However in TROMSO study there was no significant association between the serum HDL levels and blood pressure. The correlation of the TG levels and blood pressure was also found to be weak.

In a study[91] performed in Shahrekord University of medical sciences, Iran, it was proven that there is a direct significant relationship between the blood pressure and serum LDL, serum cholesterol and triglyceride levels. The same study also postulated that there exists an inverse relationship between the serum HDL levels and the blood pressure.

Another study[92] performed in Pakistan evaluated the relationship between blood pressure and lipid abnormalities in obese and non obese individuals. This study concluded that means of all parameters, except LDL, were higher in females than males; among these BMI and HDL showed significant difference.

There was a significant negative correlation of diastolic blood pressure with HDL in obese subjects; all the other parameters were non-significantly correlated. In the non-obese subjects, there was a significant direct correlation between systolic and diastolic blood pressures and LDL. All other parameters were found non-significantly correlated. The analysis of variance was done in four groups namely, obese non-hypertensives, obese hypertensives, non obese non-hypertensives and non obese hypertensives. BMI, SBP, DBP, LDL-C and total cholesterol had significantly different means in the above four groups, while HDL-C and total triglycerides were statistically non-significant ($p>0.05$) among four groups.

In our study there was a direct relationship between the total cholestrerol and blood pressure while an inverse relationship was found between the serum HDL and blood pressure level which was in concordance with the existing evidence. However the relationship between serum LDL and TG could not be established in our study data.

In this study, 96% of the subjects with normal HOMA index were normotensives, 72.88% of subjects with moderate insulin resistance were prehypertensives and 80.36% of the subjects with severe insulin resistance were hypertensives.

The highest mean fasting serum insulin was noted in hypertensive group with 20.56±8.86 while prehypertensives and normotensives had 13.30±5.04 and 11.31±9.34 respectively.

A highly significant positive correlation was observed between blood pressure and HOMA index ($p<.001$).

In a study done in Europe[25] among normotensive, nondiabetic Europeans, insulin sensitivity and age were significant, mutually independent correlates of blood pressure. An increase in insulin resistance of 10 μmol · min^{-1} · kg^{-1} was associated with ≈2 mm Hg increments in both systolic and diastolic blood pressure levels regardless of adjustment for covariates in the same study.

In another Tanzanian study[33] on non obese Africans, a significant positive association has been demonstrated and confirmed between insulin resistance and essential hypertension, independent of glucose intolerance, and obesity.

In another study[93] conducted in Los Angeles, insulin resistance, but not insulinemia, was positively related to hypertension and blood pressure in subjects without diabetes.

This positive correlation seen between insulin resistance and blood pressure can be postulated due to plethora of mechanisms like increased sodium retention, sympathetic nervous system stimulation, increased oxidative stress and accelerated atherosclerosis in insulin resistant patients. The cause-effect relationship of insulin resistance and blood pressure is not yet established and needs further investigation.

In our study there is a positive correlation between the fasting serum insulin levels and blood pressure which was statistically significant ($p<.0001$)

The Karl Pearsons Correlation coefficient test was performed in all three groups between their HOMA index and waist girth, total cholesterol, LDL, HDL, TG and hsCRP.

Waist girth showed significant positive correlation with HOMA index in all the three groups with HS (p<.0001), HS (p<.0001) and VS (p=.0057) in normotensives, prehypertensives and hypertensives respectively.

In a study[94] done in Pittsburg, USA, it was observed that increasing waist circumference is independently associated with severe insulin resistance in non diabetic white and black patients.

Another Iranian study[95] concluded that waist circumference is directly related to insulin resistance in Iranian women.

Our study results are in concordance with the existing data of positive correlation between waist girth and insulin resistance.

Total cholesterol also showed a statistically positive correlation with HOMA index in all three groups with VS (p=.0017), HS (p=.0001) and S (p=.0129) in normotensivesormotensives, prehypertensives, hypertensives respectively.

Serum LDL and TG positively correlated with HOMA in all three groups but correlation was statistically significant in prehypertensives only (LDL-p=0.0125, TG-p=0.0006). Serum HDL showed negative correlation with HOMA index in all three groups but was statistically significant only in prehypertensives

with a p=0.0029. This could be attributed to smaller sample size of the present study.

In another study[96] done by GM Reavon in Stanford university suggests a profound relationship between insulin resistance and dyslipidemia in non diabetic population. They observed an increase in total cholesterol, serum LDL and triglycerides with an increase in insulin resistance. A negative correlation was observed between HDL and insulin resistance.

In a large population based San Antonio Heart Study[97] conducted in Texas fasting insulin at baseline was found to be correlated positively with 8-year changes in triglyceride levels and negatively with 8-year changes in HDL cholesterol levels ($\rho < 0.05$). Among the non-Hispanic whites, insulin was more strongly correlated with a decline in HDL cholesterol levels in women than in men ($\rho<0.001$). Fasting insulin was also positively correlated with changes in both systolic and diastolic blood pressure in non-Hispanic whites, but not in Mexican Americans, although these correlations were slightly diminished and no longer achieved statistical significance after subjects receiving antihypertensive medications were excluded.

In another study[98] performed in Columbia university shows that insulin resistance and dyslipidemia are strongly correlated with definite evidence of an direct relationship between total cholesterol, LDL, TG and insulin resistance. Whereas an inverse relationship between HDL and insulin resistance was observed.

In another large population based multicentric CARDIA study[99] done in USA, fasting serum insulin was strongly positively correlated with the fasting serum total cholesterol, serum LDL and serum TG while being negatively correlated with the serum HDL levels.

Our study confirms the well established relationship between dyslipidemia and insulin resistance in all the degrees of blood pressure.

Non significance of LDL, TG and HDL in normotensive and hypertensive group can be attributed to smaller sample size.

hs-CRP showed statistically significant positive correlation with HOMA index in all three groups with p values .0005,.0001 and .0410 in normotensives,P and H respectively.

Another study[100] conducted in Harvard University also showed a direct significant relationship between hsCRP and insulin resistance.

Another study[101] done in AIIMS India also concluded that hsCRP and Insulin resistance are significantly directly related in post pubertal non diabetic Asian adults.

In a study[102] conducted in Japan, the levels of hsCRP was found to be significantly positively correlated to the fasting insulin levels and HOMA index.

Our study results are in accordance with the above mentioned studies indicating the direct significant relationship between insulin resistance and hsCRP in normotensives, prehypertensives and hypertensives.

This direct relationship between insulin resistance and inflammation can be due to increase in circulating cytokines secondary to RAAS activation, increased oxidative stress and sympathetic nervous system overactivity in insulin resistant individuals.

Chapter 7

Conclusion

CONCLUSION

The present study showed us:

- Insulin resistance which was measured by HOMA index is directly proportional to the blood pressure irrespective of the diabetic status. The present study showed highest HOMA index among hypertensives (4.59 ± 1.87) compared to prehypertensives (2.91 ± 1.27) and normotensives (2.17 ± 0.66).

- Inflammation which was measured by hs-CRP was significantly positively correlated with HOMA index across all the degrees of blood pressure ($p<0.05$).

- Waist circumference was significantly positively correlated with HOMA index in all the three groups that is, normotensives, prehypertensives and hypertensives.

- Total cholesterol was significantly positively correlated to the HOMA index in all the three study groups i.e. normotensives, prehypertensives and hypertensives whereas serum LDL and TG positively correlated with HOMA in all three groups but this correlation was statistically significant in prehypertensives only. Serum HDL was negatively correlated with HOMA index in all three groups but was statistically significant only in hypertensives.

Chapter 8

Summary

SUMMARY

There has been increasing number of evidences connecting insulin resistance to future cardiovascular events in hypertensives suggesting that insulin resistance is the basis for the so called metabolic syndrome irrespective of diabetic status. The present study was aimed to assess the insulin resistance and inflammation in relation to various degrees of blood pressures in non diabetic adults and to evaluate insulin resistance as a marker of inflammation.

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2011 to December 2011 on a total of 180 patients divided into three groups of 60 each namely, normotensives, prehypertensives and hypertensives.

In this study male preponderance was seen in all three study groups (76.67% in normotensives, 73.33% in prehypertensives and 75% in Hypertensives). Among normotensives equal distribution of age was observed whereas, among prehypertensives 61.67% and among hypertensives 63.33% had age from 46 to 60 years. The mean age among normotensives, prehypertensives and hypertensives was 48.40±15.38, 53.03±10.86 and 50.76±8.05 years respectively.

The present study showed highest HOMA index among hypertensives (4.59±1.87) compared to prehypertensives (2.91±1.27) and normotensives (2.17±0.66).

Waist circumference and total cholesterol showed significant positive correlation with HOMA index in all the three groups that is, normotensives, prehypertensive and hypertensives whereas, serum LDL and TG positively correlated with HOMA in all three groups but correlation was statistically significant in prehypertensives only. Serum HDL showed negative correlation with HOMA index in all three groups but statistically significant only in prehypertensive population.

hs-CRP showed statistically significant positive correlation with HOMA index in all three groups that is normotensives, prehypertensive and hypertensive ($p<0.050$).

Chapter 9

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Annexures

Annexure I

ANNEXURE I – CONSENT FORM

Title of the study: Study of Insulin Resistance and inflammation in relation to various degrees of blood pressures in adults – A one year cross sectional study

Objective and purpose of the study

This research is intended to study the association between insulin resistance and inflammation with various degrees of blood pressures. The principal investigator of the study is Dr. ***** ***** under the guidance of Dr. ***** ******. My co-operation will be of great help to patients with hypertension in future.

Procedure

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

Risk and Benefits

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

Alternatives

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

Privacy and Confidentiality

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

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

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

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about my rights as a participant you may call Principal and Chairman, J.N.M.C Ethical Committee for Human Research phone number ***** ******.

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

Principal investigator	:	Dr. **** *****	Mob No: ***** *****
Guide	:	Dr. ****** *****	Ph. No: *** *******

Consent Statement

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

Name of the Participant : _____

Signature/Thumbprint : _____

Name of the Witness : _____

Signature : _____

Investigator Name : _____

Signature : _____

Annexures

Annexure II

ANNEXURE II – PROFORMA

Patient Name: I.P/O.P number:

Age: Sex:

Date of admission: Date of discharge:

Address:

Presenting complaints

Present History

Past History

Family History DM / HTN / IHD / Obesity

Personal history

Smoking :

Exercise :

Alcohol intake :

Tobacco chewing :

Any other :

Treatment History

General Physical Examination

Built and nourishment:

Pulse :

Peripheral pulses :

Blood pressure : 1. 2. 3.

Mean of 2nd & 3rd reading:

Anthropometry :

Height (Cms) : Weight(Kg) :

Hip girth (Cms) : Waist girth (Cms) :

Waist hip ratio :

BMI :

Systemic examination

CVS :

RS :

Per abdomen :

CNS :

Investigations

Haemogram

Hb% :

TC :

DC : N - M - E -

B -

Blood Sugar

FBS : PPBS :

Lipid profile

Cholesterol :

LDL :

HDL :

TG :

hsCRP :

Serum Insulin :

HOMA Index :

HOMA = insulin (mU/m) x [glucose x 0.8(mg/dl)]

Annexures

Annexure III

ANNEXURE III – KEY TO MASTER CHART

BP	– Blood pressure
Cms	– Centimeters
dL	– Deciliters
F	– Female
HDL	– High density lipoproteins
Kg	– Kilogram
LDL	– Low density Lipoprotein
M	– Male
m	– Metre
mg	– Milligram
mm Hg	– Millimeter of mercury
TG	– Triglycerides

ANNEXURE III - MASTER CHART

Serial Number	In / Out Patient Number	Sex	Age (Years)	Clinical examination findings								Investigations								
										BP (mm Hg)		Blood sugar (mg/dL)		Lipid profile						
				Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m2)	Hip Girth (Cms)	Waist girth (Cms)	Waist hip ratio	Systolic	Diastolic	Fasting	Post prandial	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Hs-CRP	Serum Insulin	HOMA Index
1	493216	F	42	165.0	###	23.0	82.00	73	0.89	140	90	81	107	211	98	48	130	4.3	17.0	3.40
2	183776	M	40	167.0	###	22.0	83.00	70	0.84	160	110	87	109	252	134	36	158	9.3	28.8	6.20
3	482341	F	38	162.0	###	33.0	82.00	90	1.10	150	100	88	111	252	132	46	132	7.8	23.6	7.10
4	483216	F	43	159.0	###	26.0	92.00	85	0.92	140	98	92	119	230	99	40	112	7.8	18.0	4.10
5	456928	M	60	177.0	###	28.0	100.00	90	0.90	160	92	89	116	282	188	27	290	13.2	44.5	9.80
6	483219	M	36	175.0	###	21.0	97.00	84	0.86	164	100	81	116	281	136	25	253	11.4	22.8	4.50
7	457918	M	45	177.0	###	26.0	102.00	90	0.88	170	110	89	99	271	150	37	269	4.4	22.0	4.80
8	483241	M	45	165.0	###	29.0	90.00	90	1.00	168	100	82	101	262	132	40	143	3.4	34.0	6.90
9	1562321	M	50	172.0	###	28.0	96.00	87	0.90	170	100	91	116	250	191	31	211	3.4	36.0	8.10
10	1622132	M	45	170.0	###	27.0	98.00	87	0.89	150	90	92	103	231	192	31	252	6.1	16.7	3.80
11	1612826	F	40	162.0	###	30.0	95.00	87	0.92	152	100	78	111	218	154	34	152	3.8	26.4	5.10
12	1612805	M	48	174.0	###	25.0	99.00	87	0.88	180	120	84	102	232	163	35	218	4.4	19.2	4.00
13	1611556	F	45	165.0	###	27.0	104.00	88	0.84	160	102	91	106	220	136	30	266	2.9	23.1	5.20
14	1611462	M	48	175.0	###	28.0	105.00	99	0.94	190	110	84	105	211	143	45	113	10.6	20.2	4.20
15	1602234	M	52	172.0	###	24.0	94.00	81	0.86	142	96	92	116	214	140	53	105	8.2	22.4	5.10
16	1601916	F	45	163.0	###	26.0	95.00	87	0.92	180	110	91	107	253	140	28	165	7.7	19.5	4.40
17	480233	M	48	172.0	###	27.0	86.00	95	1.10	162	100	86	99	203	120	58	120	3.7	34.0	7.20
18	1597513	M	40	170.0	###	32.0	80.00	95	1.20	172	106	71	99	231	161	58	62	10.1	50.7	8.90
19	467848	M	55	175.0	###	25.0	97.00	85	0.88	180	100	96	114	173	120	17	179	6.9	25.0	5.90
20	468110	M	48	170.0	###	24.0	88.00	79	0.90	190	110	99	118	113	41	29	213	7.7	19.6	4.80
21	1597531	M	40	170.0	###	25.0	100.00	88	0.88	156	96	88	112	133	71	35	139	4.1	23.9	5.20
22	1597489	F	72	162.0	###	24.0	83.00	81	0.98	160	98	87	115	161	80	58	114	6.2	17.2	3.70
23	1596174	F	60	165.0	###	24.0	80.00	72	0.89	152	90	91	113	131	61	31	62	3.2	32.0	7.20
24	1596162	M	46	172.0	###	23.0	94.00	80	0.85	148	100	98	109	199	136	51	59	2.4	14.8	3.60
25	1592129	M	50	175.0	###	24.0	92.00	82	0.89	172	110	96	116	196	101	35	119	6.2	21.9	5.20
26	1590575	F	46	159.0	###	26.0	91.00	84	0.92	160	98	82	99	192	99	39	79	7.9	20.7	4.20
27	1591360	M	46	172.0	###	25.0	93.00	82	0.88	150	100	96	109	172	83	46	92	6.9	13.9	3.30
28	1589031	F	56	162.0	###	24.0	88.00	76	0.86	160	98	97	106	181	99	38	82	12.5	30.0	7.20
29	1590512	M	45	172.0	###	25.0	90.00	81	0.90	154	96	94	101	179	84	39	95	8.2	28.8	6.70
30	439284	M	55	165.0	###	26.0	86.00	79	0.92	170	100	96	108	140	90	42	96	6.2	17.7	4.20
31	1335350	M	48	167.0	###	26.0	90.00	85	0.94	206	120	74	96	160	70	35	128	4.4	24.6	4.50
32	438458	M	56	172.0	###	24.0	88.00	83	0.94	180	90	86	99	135	87	46	62	6.6	33.4	7.10
33	436210	M	50	177.0	###	24.0	90.00	86	0.96	170	110	98	106	171	120	37	69	8.8	38.0	9.20
34	436917	M	48	177.0	###	24.0	100.00	84	0.84	170	90	97	109	152	101	32	112	9.8	27.5	6.60
35	437823	F	56	159.0	###	24.0	75.00	67	0.88	170	110	94	109	154	62	62	128	3.8	14.6	3.40
36	433137	M	50	172.0	###	23.0	92.00	80	0.87	160	90	96	112	129	74	26	143	6.2	22.0	5.20
37	438274	M	60	177.0	###	25.0	94.00	85	0.90	160	100	92	110	140	72	45	118	5.8	21.5	4.90
38	476830	M	50	170.0	###	24.0	84.00	74	0.88	174	100	88	99	105	53	34	92	2.9	16.5	3.60

ANNEXURE III - MASTER CHART

Serial Number	In / Out Patient Number	Sex	Age (Years)	Clinical examination findings								Investigations								
										BP (mm Hg)		Blood sugar (mg/dL)		Lipid profile						
				Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m2)	Hip Girth (Cms)	Waist girth (Cms)	Waist hip ratio	Systolic	Diastolic	Fasting	Post prandial	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Hs-CRP	Serum Insulin	HOMA Index
39	476852	M	60	172.0	###	25.0	99.00	86	0.87	172	96	92	110	180	110	62	40	3.8	15.0	3.40
40	469005	M	60	172.0	###	23.0	82.00	77	0.94	170	100	99	114	176	89	62	124	10.1	20.0	4.89
41	468927	M	58	170.0	###	24.0	90.00	80	0.89	174	100	95	106	105	57	27	105	8.6	18.0	4.20
42	468162	M	48	172.0	###	26.0	99.00	88	0.89	170	90	100	116	162	83	63	80	8.2	16.0	3.90
43	470330	M	40	175.0	###	23.0	97.00	87	0.90	150	110	94	106	136	68	50	92	8.2	15.4	3.60
44	455434	M	45	165.0	###	24.0	100.00	86	0.86	154	100	99	112	193	126	41	132	4.3	17.3	4.20
45	476382	M	50	172.0	###	23.0	97.70	85	0.87	144	96	91	101	144	88	30	130	2.6	15.0	3.40
46	470512	M	50	180.0	###	26.0	95.70	90	0.94	166	92	95	109	120	375	37	39	5.4	10.6	2.50
47	410299	M	46	172.0	###	26.0	87.00	80	0.92	118	84	100	112	128	80	33	74	2	7.6	1.90
48	457938	M	60	175.0	###	22.0	89.00	75	0.84	150	90	89	95	140	93	31	80	3.6	11.8	2.60
49	457775	M	56	162.0	###	21.0	79.00	68	0.86	162	98	96	109	116	62	25	147	6.1	11.8	2.80
50	457783	F	66	162.0	###	23.0	89.00	78	0.88	144	92	90	110	146	101	30	74	5.9	10.8	2.40
51	1667261	M		172.0	###	24.0	95.00	82	0.86	150	80	101	116	179	111	55	63	6.5	10.4	2.60
52	456321	M	60	172.0	###	24.0	98.00	82	0.84	142	98	100	121	130	152	43	131	2.8	8.5	2.10
53	455294	M	M	60.0	###	21.0	86.00	80	0.90	166	98	92	102	112	68	18	130	2.3	14.7	2.90
54	474146	M	56	172.0	###	27.0	95.00	90	0.95	162	106	103	118	230	167	33	150	2.1	11.9	2.90
55	473845	F	56	159.0	###	21.0	85.00	71	0.84	164	110	101	120	119	73	29	84	3.6	11.6	2.90
56	473827	M	48	177.0	###	24.0	98.00	90	0.92	116	72	102	118	279	215	45	94	3.5	6.4	1.60
57	476611	M	60	175.0	###	22.0	91.00	80	0.88	156	102	81	120	131	86	26	97	4.7	10.5	2.10
58	469188	M	56	170.0	###	26.0	95.00	89	0.94	146	94	95	109	271	103	50	56	22.5	11.9	2.80
59	474995	F	46	162.0	###	25.0	102.00	88	0.86	160	92	99	116	185	103	56	56	2	8.1	2.00
60	476559	M	60	167.0	###	24.0	97.00	88	0.90	156	100	86	102	154	94	46	69	10.8	13.0	2.80
61	436876	M	52	177.0	###	31.0	80.00	97	1.40	132	84	97	122	262	132	31	253	10.3	34.0	8.20
62	424766	M	45	175.0	###	28.0	98.00	95	0.97	136	78	99	113	263	133	31	214	7.7	36.0	8.90
63	434766	M	56	170.0	###	29.0	92.00	90	0.98	136	84	99	121	236	144	31	211	8.6	30.0	7.40
64	437917	F	50	167.0	###	27.0	93.40	84	0.92	136	82	94	116	222	123	34	225	5.6	13.0	3.00
65	435983	F	38	162.0	###	25.0	89.00	82	0.92	126	84	94	112	201	98	45	111	8.4	13.3	3.10
66	438248	M	40	177.0	###	28.0	96.00	92	0.96	124	80	88	94	211	125	29	230	4.4	13.8	3.00
67	437210	M	56	170.0	###	26.0	93.00	82	0.88	130	80	84	116	154	61	62	148	3.1	10.6	2.20
68	437619	M	60	172.0	###	24.0	91.00	82	0.90	134	84	80	101	150	79	48	115	7.8	13.1	2.60
69	436918	F	38	159.0	###	28.0	93.00	85	0.91	138	82	91	112	256	127	30	232	2.8	13.3	3.00
70	436823	F	36	162.0	###	27.0	88.00	87	0.99	126	88	70	101	260	120	35	298	3.1	17.3	3.00
71	434137	M	48	177.0	###	24.0	92.00	58	0.92	128	86	83	99	135	87	36	60	9.5	13.6	2.80
72	460747	M	51	172.0	###	27.0	95.00	92	0.98	132	78	88	119	202	136	30	197	7.2	13.8	3.00
73	437701	M	34	170.0	###	21.0	88.00	78	0.88	122	82	72	96	151	82	42	100	2.5	13.5	2.40
74	437619	M	48	175.0	###	26.0	98.00	93	0.95	132	86	85	99	171	102	29	200	4.8	14.2	3.00
75	437157	M	46	180.0	###	22.0	89.00	78	0.87	122	84	88	94	169	106	41	108	3.9	10.5	2.30
76	436927	M	53	174.0	###	25.0	88.00	84	0.95	134	84	88	119	240	180	37	194	8.3	11.9	2.60

ANNEXURE III - MASTER CHART

Serial Number	In / Out Patient Number	Sex	Age (Years)	Clinical examination findings								Investigations								
										BP (mm Hg)		Blood sugar (mg/dL)		Lipid profile						
				Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m2)	Hip Girth (Cms)	Waist girth (Cms)	Waist hip ratio	Systolic	Diastolic	Fasting	Post prandial	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Hs-CRP	Serum Insulin	HOMA Index
77	436319	F	44	165.0	###	23.0	90.00	80	0.88	122	84	78	96	169	106	41	108	4.9	14.0	2.70
78	435169	M	59	175.0	###	24.0	92.00	89	0.97	138	78	76	99	197	132	32	163	4.8	15.9	3.00
79	436287	M	48	172.0	###	24.0	87.00	82	0.94	128	82	98	112	145	85	48	110	4.8	10.3	2.50
80	434593	M	54	170.0	###	23.0	92.00	82	0.89	136	88	94	102	177	92	42	103	3.8	10.3	2.40
81	433920	F	65	159.0	###	22.0	87.00	77	0.88	136	78	89	97	144	70	47	84	3.1	10.4	2.30
82	433875	F	63	162.0	###	25.0	92.00	82	0.89	138	88	81	96	203	133	49	105	5.1	15.0	3.00
83	433777	M	52	172.0	###	26.0	105.00	93	0.88	126	88	87	101	229	163	34	162	4.2	13.0	2.80
84	423777	M	60	170.0	###	21.0	85.00	76	0.89	128	82	95	118	113	92	41	96	3.1	11.9	2.80
85	423777	M	60	172.0	###	23.0	92.00	83	0.90	138	84	95	116	129	93	44	142	3	11.5	2.70
86	433261	M	70	175.0	###	24.0	92.00	85	0.92	128	78	92	109	180	125	37	192	2.3	11.8	2.70
87	433658	M	60	167.0	###	20.0	81.00	72	0.88	132	84	77	96	129	103	44	142	2.1	13.1	2.50
88	420936	F	35	155.0	###	24.0	85.00	74	0.87	126	76	91	105	140	85	37	92	4.3	10.6	2.40
89	420746	M	47	176.0	###	24.0	94.00	83	0.88	138	82	71	93	111	95	37	92	2.5	13.1	2.30
90	420723	F	70	157.0	###	28.0	73.00	80	1.10	145	94	81	109	240	169	40	153	5.2	15.0	3.00
91	420411	F	58	162.0	###	24.0	86.00	78	0.90	138	86	94	118	120	67	38	74	4.9	12.4	2.90
92	420263	M	44	175.0	###	22.0	96.00	86	0.89	128	84	92	116	105	52	28	126	2.6	12.3	2.80
93	419973	M	33	180.0	###	23.0	97.00	88	0.91	128	88	94	112	168	98	52	90	5.9	11.2	2.60
94	419858	F	55	175.0	###	23.0	96.00	85	0.88	136	84	92	112	188	69	43	111	4.1	11.0	2.50
95	419726	M	47	172.0	###	22.5	97.00	85	0.87	136	86	99	109	131	84	48	96	3.8	10.2	2.50
96	419373	M	45	167.0	###	23.0	89.00	80	0.89	128	82	68	92	101	52	40	67	6.6	14.2	2.40
97	419148	M	26	170.0	###	21.0	95.00	80	0.84	136	88	89	96	131	67	52	84	5.4	10.4	2.30
98	418960	M	58	177.0	###	22.0	96.00	83	0.86	132	86	99	111	152	98	42	80	4.8	12.2	3.00
99	418829	M	68	172.0	###	24.0	96.00	85	0.88	126	82	86	92	163	94	39	158	8.2	13.6	2.90
100	418765	M	48	177.0	###	23.0	94.00	85	0.90	134	86	81	112	173	91	44	138	4.2	14.0	2.80
101	417118	M	61	172.0	###	22.0	92.00	83	0.90	128	82	92	111	195	143	42	100	2.8	11.8	2.70
102	417050	F	47	167.0	###	22.0	88.00	72	0.81	138	84	81	102	162	104	42	80	3.1	13.5	2.70
103	416506	M	70	172.0	###	21.0	100.00	82	0.82	124	82	91	107	130	61	48	67	3.2	11.5	2.60
104	416628	M	45	170.0	###	21.0	89.00	78	0.88	138	88	81	98	120	51	58	57	3.6	11.5	2.30
105	416492	M	60	170.0	###	23.0	90.00	83	0.92	132	88	88	106	174	88	43	141	7.2	11.0	2.40
106	1590892	M	42	175.0	###	23.1	90.00	90	1.00	130	90	82	114	181	100	38	213	2.9	13.1	2.65
107	416336	F	61	165.0	###	27.0	86.00	94	1.10	110	84	100	119	230	111	29	214	4.8	9.0	2.10
108	416158	M	70	175.0	###	27.0	82.00	96	1.20	138	88	98	114	244	100	36	201	6.2	9.0	2.20
109	415862	F	58	167.0	###	25.0	106.00	89	0.84	138	84	99	100	211	114	33	214	5.6	9.0	2.20
110	415834	M	60	175.0	###	26.0	95.00	90	0.94	138	86	91	113	184	105	33	191	5.2	9.7	2.20
111	410778	M	72	175.0	###	25.0	95.00	90	0.94	112	84	96	118	160	91	43	156	3.1	9.0	2.10
112	409784	F	74	165.0	###	23.0	93.00	80	0.86	114	82	81	112	132	62	36	135	3.2	10.5	2.10
113	409745	M	67	177.0	###	23.0	92.00	85	0.92	118	78	79	109	132	63	42	185	4.7	10.7	2.10
114	409193	M	70	178.0	###	21.0	94.00	84	0.89	116	88	74	91	171	92	38	96	5.3	11.4	2.10

ANNEXURE III - MASTER CHART

Serial Number	In / Out Patient Number	Sex	Age (Years)	Clinical examination findings								Investigations								
										BP (mm Hg)		Blood sugar (mg/dL)		Lipid profile						
				Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m2)	Hip Girth (Cms)	Waist girth (Cms)	Waist hip ratio	Systolic	Diastolic	Fasting	Post prandial	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Hs-CRP	Serum Insulin	HOMA Index
115	409041	F	65	170.0	###	24.0	107.00	88	0.82	138	90	94	102	167	72	39	111	2.8	9.4	2.20
116	408980	M	60	167.0	###	22.0	82.00	75	0.91	134	96	76	94	160	82	54	96	3.2	11.7	2.20
117	408891	M	44	170.0	###	22.0	92.00	83	0.90	114	90	89	107	150	72	54	123	3.1	9.5	2.10
118	408777	F	45	172.0	###	23.0	103.00	85	0.82	134	92	68	101	140	62	38	121	3.8	13.0	2.20
119	408176	F	70	165.0	###	24.0	100.00	84	0.84	120	78	92	110	171	92	38	113	8.4	9.6	2.20
120	408040	M	32	167.0	###	22.0	83.00	80	0.96	112	86	86	111	171	92	38	143	2.9	9.8	2.10
121	407940	M	31	175.0	###	32.0	80.00	95	1.20	118	66	81	111	222	111	33	217	4.6	21.0	4.20
122	407706	M	70	177.0	###	31.0	85.00	95	1.12	120	70	89	120	232	121	31	217	4.8	17.0	3.80
123	407580	M	53	172.0	###	28.0	84.00	90	1.10	120	60	96	118	245	34	44	203	4.1	15.0	3.60
124	1592067	F	40	162.0	###	27.0	107.00	98	1.09	112	76	90	108	225	163	36	129	4.2	25.7	5.70
125	1591390	M	48	170.0	###	26.0	99.00	90	1.10	118	80	117	118	260	178	39	216	3.8	12.7	3.60
126	1591382	M	46	170.0	###	26.5	96.90	89	1.08	112	68	80	88	153	48	90	76	2.7	15.7	3.10
127	407565	F	63	175.0	###	28.0	101.00	95	0.94	120	60	99	119	245	111	36	174	3.8	13.0	3.10
128	407293	M	60	182.0	###	24.0	92.00	90	0.98	110	56	84	94	201	108	28	174	4.4	14.0	3.00
129	406922	M	71	175.0	###	27.0	94.30	92	0.98	110	60	79	94	217	93	31	172	3.4	12.3	2.40
130	406889	M	58	166.0	###	26.0	89.00	88	0.89	118	66	69	94	227	94	34	152	3.6	14.0	2.50
131	406744	M	65	178.0	###	26.0	100.00	92	0.92	120	64	96	118	207	113	38	168	3.6	9.7	2.30
132	406671	M	40	177.0	###	25.0	97.00	92	0.94	166	70	81	116	218	112	39	162	2.1	14.0	2.80
133	403480	M	60	175.0	###	24.0	98.00	92	0.94	120	70	87	118	171	94	35	212	3.2	14.0	3.00
134	1591845	M	40	175.0	###	23.0	105.00	90	0.85	120	70	109	114	247	177	43	135	2.3	8.5	2.30
135	1590780	F	39	157.0	###	25.5	94.00	85	0.90	111	72	97	149	228	136	76	79	2.1	12.3	2.94
136	405860	M	31	175.0	###	23.0	95.00	90	0.94	108	64	98	119	162	72	45	118	2.9	9.0	2.20
137	405660	M	20	167.0	###	20.0	88.00	78	0.88	112	66	99	111	132	52	45	147	3.2	8.5	2.10
138	405061	M	20	177.0	###	22.0	96.00	90	0.95	106	54	79	101	142	62	45	177	3.2	11.2	2.20
139	404984	M	65	170.0	###	20.0	90.00	80	0.88	116	74	94	119	109	57	39	46	2.8	7.7	1.80
140	404630	M	65	172.0	###	20.0	86.00	80	0.92	118	68	77	94	125	77	40	101	2.9	10.0	1.90
141	404558	M	50	170.0	###	19.0	87.00	82	0.94	114	60	88	116	115	67	40	91	3.7	8.7	1.90
142	404208	F	60	162.0	###	22.0	88.00	78	0.89	114	68	79	97	99	67	38	91	3	8.2	1.60
143	403795	F	38	157.0	###	22.0	81.00	73	0.90	116	78	94	109	203	133	49	105	2.8	9.4	2.20
144	403594	M	42	172.0	###	21.0	90.00	82	0.91	118	70	98	119	193	113	49	84	2.3	78.0	1.90
145	403525	F	58	159.0	###	19.0	89.00	70	0.78	116	76	84	112	106	37	56	64	2	8.6	1.80
146	403134	F	30	159.0	###	20.0	85.20	74	0.88	112	68	88	113	116	54	48	69	2.1	7.3	1.60
147	402658	M	72	175.0	###	23.0	97.00	92	0.92	120	80	81	111	166	59	44	111	2.8	11.0	2.20
148	402822	M	48	172.0	###	24.0	98.00	88	0.89	118	72	98	120	182	94	44	97	1.9	9.0	2.20
149	402687	M	45	165.0	###	22.0	90.00	80	0.88	110	70	69	99	167	69	42	93	1.6	12.3	2.10
150	402607	M	62	182.0	###	24.0	92.00	84	0.92	112	66	96	116	162	91	57	72	1.4	7.5	1.80
151	402498	M	26	165.0	###	24.0	83.00	80	0.96	108	72	63	116	171	104	44	98	2.5	13.5	2.10
152	402359	F	24	154.0	###	22.0	96.00	85	0.89	112	78	69	96	179	112	44	101	2.4	12.3	2.10

ANNEXURE III - MASTER CHART

Serial Number	In / Out Patient Number	Sex	Age (Years)	Clinical examination findings								Investigations								
										BP (mm Hg)		Blood sugar (mg/dL)		Lipid profile						
				Height (Cms)	Weight (Kg)	Body Mass Index (Kg/m2)	Hip Girth (Cms)	Waist girth (Cms)	Waist hip ratio	Systolic	Diastolic	Fasting	Post prandial	Cholesterol (mg/dL)	LDL (mg/dL)	HDL (mg/dL)	TG (mg/dL)	Hs-CRP	Serum Insulin	HOMA Index
153	402318	F	28	167.0	###	24.0	91.00	80	0.88	112	62	95	119	177	95	56	101	2.3	9.3	2.20
154	402327	M	50	162.0	###	24.0	87.00	85	0.98	116	80	81	110	181	101	60	78	2.6	10.0	2.00
155	402248	M	58	175.0	###	23.0	102.00	92	0.90	118	78	89	113	188	105	67	81	1.1	8.6	1.90
156	402115	M	58	182.0	###	21.0	104.00	88	0.84	108	74	93	120	151	94	45	100	1.4	9.1	2.10
157	401999	F	51	159.0	###	20.0	84.00	72	0.84	112	64	69	91	190	107	68	84	2.3	11.7	2.00
158	401939	M	64	180.0	###	19.0	89.00	80	0.90	118	80	75	112	164	57	90	72	2.4	9.3	1.80
159	401614	M	56	177.0	###	23.0	82.00	90	1.10	120	68	78	116	185	104	56	124	3.2	11.4	2.20
160	401442	M	52	172.0	###	22.0	99.00	88	0.88	118	68	99	112	170	102	54	167	1.9	9.0	2.20
161	401274	F	30	157.0	###	20.0	80.00	68	0.82	112	66	81	96	166	130	41	152	1.9	10.5	2.10
162	1592029	F	42	159.0	###	21.0	78.00	78	1.00	116	72	100	110	248	167	47	170	2.6	8.5	2.10
163	401090	M	42	162.0	###	18.0	88.00	70	0.80	116	78	93	111	124	66	58	96	1.1	8.7	2.00
164	400917	M	72	172.0	###	19.0	78.00	70	0.90	118	66	99	118	166	112	42	100	1	7.7	1.90
165	400904	M	34	165.0	###	22.0	80.00	70	0.88	112	66	85	96	109	112	46	97	0.9	8.5	1.80
166	400845	M	42	167.0	###	21.0	77.00	74	0.93	108	80	73	94	170	104	54	67	1.4	11.6	2.10
167	400807	M	42	177.0	###	22.0	92.00	90	0.98	118	78	88	104	132	165	45	143	1.8	10.1	2.20
168	400607	M	40	180.0	###	24.0	91.00	86	0.94	114	68	75	102	192	141	42	131	2	8.6	1.60
169	400605	M	70	165.0	###	23.0	83.00	78	0.94	112	66	68	82	170	118	46	150	2.1	13.2	2.20
170	399905	M	25	170.0	###	24.0	92.00	90	0.98	112	78	96	114	184	112	41	134	2.1	9.2	2.20
171	399899	M	69	172.0	###	23.0	92.00	88	0.92	110	60	68	89	192	129	44	156	1.8	7.7	1.30
172	399408	M	65	165.0	###	22.0	85.00	76	0.88	108	76	82	99	143	170	43	106	1.8	10.3	2.10
173	399311	M	26	170.0	###	21.0	99.00	84	0.84	114	66	94	100	162	110	44	132	1.9	5.7	2.00
174	399293	M	70	167.0	###	19.0	87.00	78	0.89	116	68	103	116	169	110	44	151	1.4	6.8	1.90
175	399272	M	57	177.0	###	20.0	95.00	93	0.98	116	70	88	110	192	170	39	166	1.6	10.1	2.20
176	399254	M	30	175.0	###	18.0	98.00	88	0.90	110	66	82	98	180	155	40	168	2	10.3	2.10
177	399190	M	68	172.0	###	19.0	91.90	82	0.87	106	68	76	102	168	133	44	167	1.6	9.5	1.80
178	1590930	M	40	167.5	###	21.0	96.00	86	0.88	114	70	85	112	179	112	36	155	2.6	7.5	1.50
179	1589134	F	42	154.9	###	22.7	98.75	79	0.80	116	66	88	96	153	71	50	156	2	6.0	1.30
180	1589141	M	46	175.0	###	25.0	112.00	90	0.80	118	70	107	153	244	136	48	296	2.5	8.3	2.20

Normo

Age	BMI	WHR - M	WHR - F	SBP	DBP	FBS	PPBS	Cholesterol (mg/dL)
20	18.0	0.80	0.78	120	78	92	110	99
20	18.0	0.80	0.80	118	66	81	111	106
24	19.0	0.84	0.82	120	70	89	120	109
25	19.0	0.84	0.84	120	60	96	118	109
26	19.0	0.85	0.84	112	76	90	108	115
26	19.0	0.87	0.88	118	80	117	118	116
28	19.0	0.88	0.88	112	68	80	88	124
30	19.0	0.88	0.89	120	60	99	119	125
30	20.0	0.88	0.89	110	56	84	94	132
30	20.0	0.88	0.90	110	60	79	94	132
31	20.0	0.88	0.90	118	66	69	94	142
31	20.0	0.88	0.94	120	64	96	118	143
34	20.0	0.88	1.00	120	70	87	118	151
38	20.0	0.89	1.09	120	70	109	114	153
39	20.0	0.89		111	72	97	149	153
40	21.0	0.89		108	64	98	119	162
40	21.0	0.90		112	66	99	111	162
40	21.0	0.90		106	54	79	101	162
40	21.0	0.90		116	74	94	119	164
42	21.0	0.90		118	68	77	94	166
42	21.0	0.91		120	60	88	116	166
42	22.0	0.92		114	68	79	97	166
42	22.0	0.92		116	78	94	109	167
42	22.0	0.92		118	70	98	119	168
42	22.0	0.92		116	76	84	112	169
45	22.0	0.92		112	68	88	113	170
46	22.0	0.93		120	80	81	111	170
46	22.0	0.94		118	72	98	120	170
48	22.0	0.94		120	70	69	99	171
48	22.0	0.94		112	66	96	116	171
50	22.7	0.94		108	72	63	116	171
50	23.0	0.94		112	78	69	96	177
51	23.0	0.95		112	62	95	119	179
52	23.0	0.96		116	80	81	110	179
53	23.0	0.98		118	78	89	113	180
56	23.0	0.98		108	74	93	120	181
57	23.0	0.98		112	64	69	91	182
58	23.0	0.98		118	80	75	112	184
58	24.0	0.98		120	68	78	116	185
58	24.0	0.98		118	68	99	112	188
58	24.0	1.08		112	66	81	96	190
60	24.0	1.10		116	72	100	110	192
60	24.0	1.10		120	78	93	111	192
60	24.0	1.10		118	66	99	118	192
62	24.0	1.12		120	66	85	96	193
63	24.0	1.20		108	80	73	94	201
64	24.0			118	78	88	104	203
65	24.0			114	68	75	102	207
65	25.0			112	66	68	82	217
65	25.5			112	78	96	114	222

65	26.0
68	26.0
69	26.0
70	26.5
70	27.0
70	27.0
70	28.0
71	28.0
72	31.0
72	32.0

110	60	68	89	225
108	76	82	99	227
114	66	94	100	228
120	68	103	116	232
116	70	88	110	244
110	66	82	98	245
106	68	76	102	245
114	70	85	112	247
116	66	88	96	248
118	70	107	153	260

LDL (mg/dL)	L (mg/dL) ma	TG (mg/dL)	Hs-CRP	Serum Insulin	HOMA Index	Pre BMI
34	28	46	0.9	5.7	1.30	20.0
37	31	64	1	6.0	1.30	21.0
48	31	67	1.1	6.8	1.50	21.0
52	33	69	1.1	7.3	1.60	21.0
54	34	72	1.4	7.5	1.60	21.0
57	35	72	1.4	7.5	1.60	21.0
57	36	76	1.4	7.7	1.80	21.0
59	36	78	1.4	7.7	1.80	22.0
62	36	79	1.6	7.7	1.80	22.0
66	38	81	1.6	8.2	1.80	22.0
67	38	84	1.6	8.3	1.80	22.0
67	38	84	1.8	8.5	1.80	22.0
69	39	91	1.8	8.5	1.90	22.0
71	39	91	1.8	8.5	1.90	22.0
72	39	93	1.9	8.5	1.90	22.0
77	40	96	1.9	8.6	1.90	22.0
91	40	97	1.9	8.6	1.90	22.5
92	40	97	1.9	8.6	1.90	23.0
93	41	98	2	8.7	2.00	23.0
94	41	100	2	8.7	2.00	23.0
94	42	100	2	9.0	2.00	23.0
94	42	101	2	9.0	2.00	23.0
94	42	101	2.1	9.0	2.10	23.0
95	43	101	2.1	9.1	2.10	23.0
101	43	105	2.1	9.2	2.10	23.0
102	44	106	2.1	9.3	2.10	23.0
104	44	111	2.3	9.3	2.10	23.0
104	44	113	2.3	9.4	2.10	23.0
104	44	118	2.3	9.5	2.10	23.0
105	44	124	2.3	9.6	2.10	23.1
107	44	129	2.4	9.7	2.10	24.0
108	44	131	2.4	10.0	2.10	24.0
110	44	132	2.5	10.0	2.20	24.0
110	45	134	2.5	10.1	2.20	24.0
111	45	135	2.6	10.1	2.20	24.0
111	45	143	2.6	10.3	2.20	24.0
112	45	147	2.6	10.3	2.20	24.0
112	45	150	2.7	10.5	2.20	24.0
112	46	151	2.8	11.0	2.20	24.0
112	46	152	2.8	11.2	2.20	24.0
112	47	152	2.8	11.4	2.20	25.0
113	48	155	2.9	11.6	2.20	25.0
113	48	156	2.9	11.7	2.20	25.0
118	49	156	3	12.3	2.20	25.0
121	49	166	3.2	12.3	2.20	25.0
129	50	167	3.2	12.3	2.20	26.0
130	54	167	3.2	12.3	2.30	26.0
133	54	168	3.2	12.7	2.30	26.0
133	56	168	3.4	13.0	2.40	26.0
136	56	170	3.6	13.2	2.50	26.0

136	56	172	3.6	13.5	2.94	27.0
141	57	174	3.7	14.0	3.00	27.0
155	58	174	3.8	14.0	3.00	27.0
163	60	177	3.8	14.0	3.10	27.0
165	67	203	4.1	15.0	3.10	27.0
167	68	212	4.2	15.7	3.60	28.0
170	76	216	4.4	17.0	3.60	28.0
170	90	217	4.6	21.0	3.80	28.0
177	90	217	4.8	25.7	4.20	29.0
178	144	296	8.4	78.0	5.70	31.0

Pre Age	HYP BMI	HYP Age
26	21.0	36
32	21.0	38
33	21.0	40
34	21.0	40
35	22.0	40
36	22.0	40
38	22.0	40
38	23.0	40
40	23.0	45
42	23.0	45
42	23.0	45
43	23.0	45
44	23.0	45
44	24.0	45
44	24.0	45
45	24.0	46
45	24.0	46
45	24.0	46
45	24.0	46
46	24.0	46
47	24.0	48
47	24.0	48
47	24.0	48
48	24.0	48
48	24.0	48
48	24.0	48
48	24.0	48
50	24.0	48
51	24.0	50
52	24.0	50
52	25.0	50
53	25.0	50
54	25.0	50
55	25.0	50
56	25.0	50
56	25.0	52
58	25.0	55
58	25.0	55
58	25.0	56
59	26.0	56
60	26.0	56
60	26.0	56
60	26.0	56
60	26.0	56
60	26.0	56
60	26.0	58
60	26.0	60
61	26.0	60
61	27.0	60
63	27.0	60

65	27.0	60
65	27.0	60
67	28.0	60
68	28.0	60
70	28.0	60
70	28.0	64
70	29.0	66
70	30.0	70
72	32.0	72
74	33.0	M

20	26	36
20	33	38
24	34	40
25	35	40
26	36	40
26	38	40
28	38	40
30	40	40
30	40	42
30	42	43
31	44	45
31	44	45
32	45	45
34	45	45
38	45	45
39	45	45
40	46	45
40	47	46
40	47	46
42	47	46
42	48	46
42	48	48
42	48	48
42	48	48
42	50	48
44	51	48
45	52	48
46	52	48
46	53	50
46	53	50
48	54	50
48	55	50
48	56	50
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51	58	52
52	58	55
57	58	55
58	59	56
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61	60	56
62	60	58
64	60	60
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65	63	60
65	63	60
67	65	60
68	65	60

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M