"A CROSS SECTIONAL STUDY TO KNOW THE PREVALENCE OF INSULIN RESISTANCE AMONG HYPERTENSIVE PATIENTS ATTENDING KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM"

REG NO. BG0108009

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 GENERAL MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

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ENDORSEMENT BY HOD, PRINCIPAL

This is to certify that the dissertation entitled **"A CROSS SECTIONAL STUDY TO KNOW THE PREVALENCE OF INSULIN RESISTANCE AMONG HYPERTENSIVE PATIENTS ATTENDING KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM"** is a bonafide research work done by **THE CANDIDATE REG NO. BG0108009** in the Department of General Medicine, Jawaharlal Nehru Medical College, Nehru Nagar, Belgaum – 590 010.

Dr. V. A. KOTHIWALE MD, Ph.D
Professor and Head,
Department of General Medicine,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

Dr. V. D. Patil MD,DCH
Principal,
J. N. Medical College,
Nehru Nagar, Belgaum – 10

Date:
Place: Belgaum

LIST OF ABBREVIATIONS USED

ACE	-	Angiotensin convertase enzyme
ADP	-	Adenosine diphosphate
AkT	-	Protein kinase B
ALLHAT	-	Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMP	-	Adenosine monophosphate
AMP kinase	-	Adenonine monophosphate kinase
ANG II	-	Angiotensin II
Apo B	-	Apolipoprotein B
ARB	-	Angiotensin receptor blocker
AT1R	-	Angiotensin I receptor
ATP III	-	Adult Treatment Panel
BB	-	Beta blocker
BMI	-	Body mass index
BP	-	Blood pressure
CAD	-	Coronary artery disease
CCB	-	Calcium channel blocker
CHARM	-	Candensartan in Heart Failure; Assessment of Reduction in Mortality and Morbidity
CHD	-	Coronary heart disease
CKD	-	Chronic kidney disease
CMS	-	Cardiometabolic syndrome
COPD	-	Chronic obstructive pulmonary disease
CRP	-	C-reactive protein

CVA	-	Cerebrovascular accidents
CVD	-	Cardiovascular disease
d	-	Deci
DM	-	Diabetes mellitus
eNOS	-	Endothelial nitric oxide synthase
ET	-	Endothelin
FBS	-	Fasting blood sugar
FFA	-	Free fatty acid
GH	-	Growth hormone
GLP1	-	Glucagon like peptide
GLUT	-	Glucose transporter
HDL	-	High density lipoprotein
HIV	-	Human immunodeficiency virus
HOMA IR	-	Homoeostasis model assessment of insulin resistance
HTN	-	Hypertension
IAPP	-	Islet amyloid polypeptide
IFG	-	Impaired fasting glucose
IGF	-	Insulin like growth factor
IGT	-	Impaired glucose tolerance
IHD	-	Ischaemic heart disease
IL	-	Interleukin
IR	-	Insulin resistance
IRS	-	Insulin receptor substrate
Kcal	-	Kilo Calories
Kg	-	Kilogram

KiR	-	Inwardly rectifying potassium channel protein
L	-	Litre
lb	-	Pound
LDL	-	Low density lipoprotein
LPL	-	Lipoprotein lipase
m	-	Meter
MAPK	-	Mitogen activated protein kinase
MEIA	-	Microparticle enzyme immune assay
mg	-	Milligram
mM	-	Milli mole
mmol	-	Milli mole
MR	-	Mineralo corticoid receptor
Na+	-	Sodium
NADPH	-	Nicotine adenine diphospho hydrogenase
NCEP ATP III	-	National Cholesterol Education Programme, Adult Treatment Panel
ng	-	Nano gram
NHANES	-	National Health & Nutrition Examination Survey
NO	-	Nitric oxide
PAI	-	Plasminogen activator inhibitor
PCOS	-	Polycystic ovarian syndrome
PGH	-	Placental growth hormone
Pl3K	-	Phosphotidyl inositol 3 kinase
PPAR	-	Peroxisome proliferator activated receptor
PPBS	-	Post prandial blood sugar

PVD	-	Peripheral vascular disease
QUICKI	-	Quantitative insulin sensitivity check index
RAAS	-	Renin angiotensin aldosterone system
ROS	-	Reactive oxygen species
Ser	-	Serine
SMC	-	Smooth muscle cell
SNS	-	Sympathetic nervous system
TG	-	Triglycerides
TNF	-	Tumor necrosis factor
TPA	-	Tissue plasminogen activator
TZD	-	Thiazolidinediones
U.S.	-	United States
VEGF	-	Vascular endothelial growth factor
VLDL	-	Very low density lipoprotein
WHR	-	Waist hip ratio
WOSCOPS	-	The West of Scotland Coronary Prevention Study

ABSTRACT

Background and objectives

It is estimated that at least 50% of hypertensive patients are insulin resistant, and insulin resistance (IR) is the fundamental abnormality in the pathogenesis of the cardiometabolic syndrome. The present study was undertaken, to know the prevalence of IR in hypertensive individuals.

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 on non diabetic hypertensive patients during the period from January 2009 to December 2009. A total of 65 hypertensive patients were studied. Investigations like FBS and PPBS, lipid profile and ECG were done. Fasting insulin levels were measured by MEIA method and insulin resistance was calculated by homeostasis model for assessment of IR. Insulin resistance was defined as HOMA IR more than 3.8.

Results

In this study males (76.92%) outnumbered females. Majority (50.77%) of the patients, were in the age group of 51 to 60 years and 47.69% had three to six years duration of hypertension. Majority (70.77%) of the patients were on ACE inhibitors or ARBs. The prevalence of IR in this study was 41.54% (HOMA IR > 3.8). Majority (74.08%) of the patients with IR were aged more than 51 years. In patients on ACE inhibitors or ARBs, IR was less (51.85%) as compared to beta blockers (66.67%). In patients with IR, history of CVA was seen in 18.52% and

IHD was noted in 48.15%. Among patients with IR, history of smoking and alcohol consumption was seen in 48.15% and 11.11% respectively. Linear relation between IR and BMI was apparent till the value of 29.9 Kg/m^2 but not beyond. Abnormal WHR was noted in 19 (70.37%) patients with HOMA IR more than 3.8.

Interpretation and conclusion

The prevalence of insulin resistance in hypertensive non diabetic patients was 41.54%. Insulin resistance increased with advancing age, duration of hypertension and obesity.

Keywords

Hypertension; Insulin resistance; Homeostosis model assessment for IR; Obesity;

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INTRODUCTION

Hypertension (HTN) is the most common cardiovascular disease (CVD), affecting approximately 20 percent of the adult population. It is considered both as a disease condition 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 HTN. It is estimated that the global prevalence of HTN will increase to 1.56 billion by 2025.[1]

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.[2]

Various factors implicated in the genesis of Essential HTN 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 factor.[3]

It is estimated that at least 50% of hypertensive patients are insulin resistant, and insulin resistance (IR) is the fundamental abnormality in the pathogenesis of the cardiometabolic syndrome (CMS). Despite major advances in the understanding of the pathogenesis and treatment of HTN and other components of the CMS, these entities continue to contribute to major morbidity and mortality from CVD and chronic kidney disease (CKD).[4]

Asians and Asian Indians have relative increases in visceral fat versus subcutaneous fat with concomitant increase in waist circumference which explains the greater prevalence of IR syndrome in these populations and confers a high risk of diabetes and CVD in them.[3]

Metabolic syndrome is common in the urban Indian population and IR is one of the major components, in the cluster of abnormalities. In view of important pathogenic role of IR in causation of diabetes mellitus (DM) and CVD in Indians, identification of IR by simple measurements, would facilitate selection of high risk individuals for primary prevention of these interrelated diseases.[5,6,7]

Moreover, both IR and HTN are implicated in the pathophysiology of CKD and CVD. Studies in humans demonstrate that improving IR, with insulin sensitizers has a positive effect on blood pressure control.[4]

In view of the above, the present study was undertaken, to know the prevalence of IR in hypertensive individuals.

OBJECTIVES

The objective of the present study was to know the prevalence of insulin resistance among hypertensive individuals.

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.[8]

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.[9]

Data from a meta analytical review examining fasting insulin levels in euglycemic individuals demonstrates a significant correlation with systolic and diastolic blood pressure.[10]

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.[11]

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.[12]

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.[13]

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.[14]

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.[15]

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.

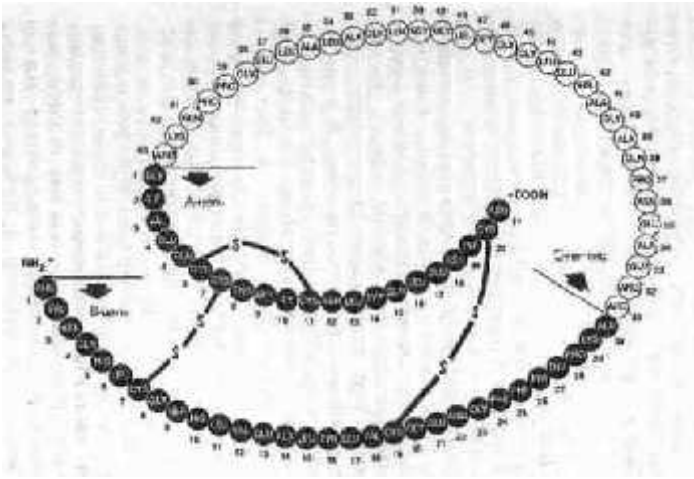


Figure 1. Molecular structure of insulin

Biosynthesis[3,16]

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.

Secretion[3,17]

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.

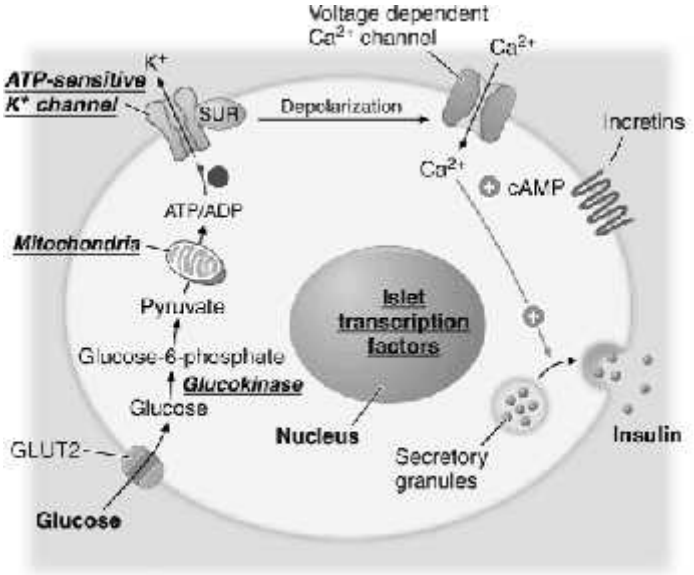


Figure 2. Secretion of insulin[3]

Signaling[16,17]

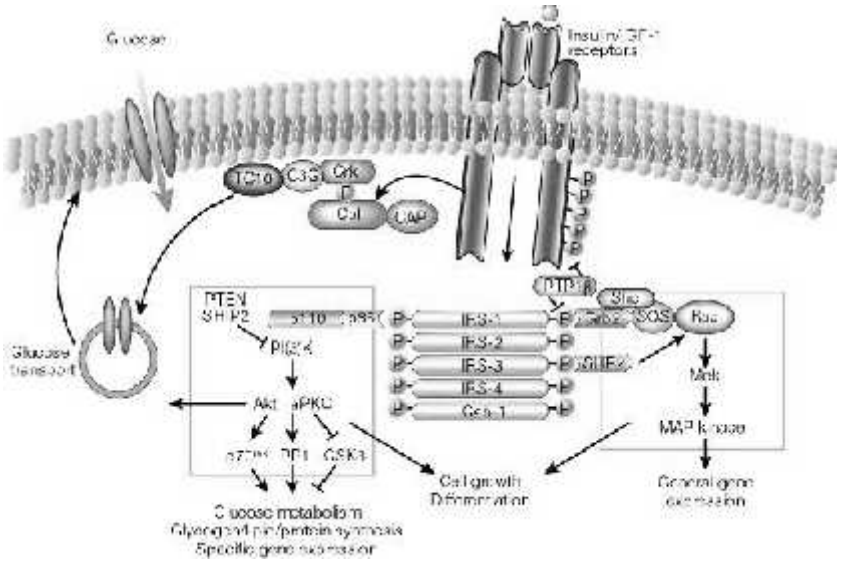


Figure 3. Insulin signalling[16,17]

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).

Effects

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

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

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

Liver

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

Causes[17,18]

Abnormal β-cell secretory product

- Abnormal insulin molecule
- Incomplete conversion of proinsulin to insulin

Circulating insulin antagonists

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

Target tissue defects

- Insulin receptor defects
- Post – receptor defects

Abnormal β-cell secretory product

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.

Circulatory insulin antagonists

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)[19,20] 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.

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.

Glycogen synthesis

Glycogen synthase, the rate-limiting enzyme for glycogen synthesis is another site for a cellular defect causing IR and decreased enzyme activity has been consistently observed in muscle biopsy samples of DM subjects

Other factors

Intramuscular triglyceride (TG)[21,22]

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

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[23]

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.

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.

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.

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.

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.

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 CMS. In this context, patients with HTN have higher fasting and postprandial insulin levels, independent of body mass index or body fat distribution.[4]

Several pathophysiologic factors are involved in the relationship between HTN and the other components of the CMS, 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.[4]

Renal sodium handling[4]

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.

Sympathetic nervous system activation[4]

Clinical studies have shown that individuals with CMS have increased SNS activity, and this increased activity is correlated with insulin resistance. A number of mechanisms are involved in the activation of the SNS in the CMS. 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.

Renin angiotensin aldosterone system also interacts, in a positive feedback fashion, with the SNS. 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 SNS and the RAAS act in a positive feedback regulatory mechanism in the setting of HTN and the CMS.

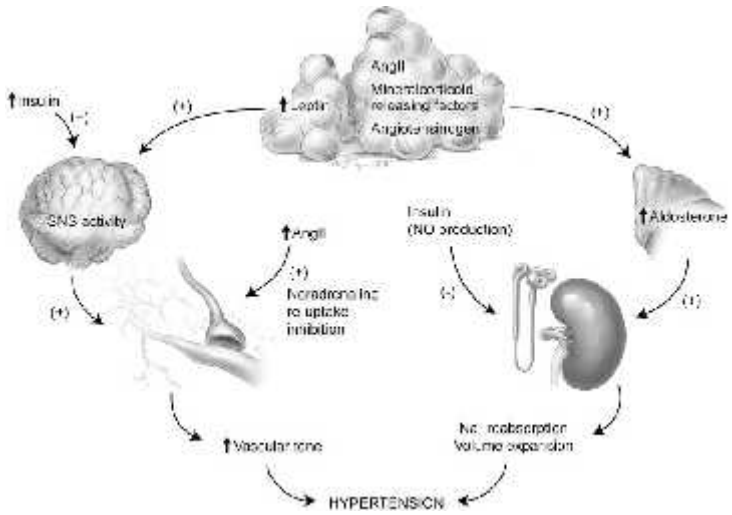


Figure 4. Co-ordinated influence of obesity, IR, activation of RAAS and SNS in pathophysiology of HTN[4]

Renin angiotensin aldosterone system[4]

The interaction between the RAAS and the SNS is at least partially responsible for the development of HTN in states of insulin resistance, such as the CMS. Often in the CMS 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.

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.

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.

Role of oxidative stress[4]

Binding of insulin to its receptor triggers signaling through the PI3K/protein kinase B (Akt) 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.

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 (Akt) pathway signaling is impaired with consequent decreased

production of NO, the MAPK pathway is stimulated by hyperinsulinemia resulting in elevated ET-1 production.

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, CMS, and CVD.

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 (Ser) kinases, including Janus kinase. Activation of these Ser kinases promotes Ser 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.

Impaired Endothelium-Dependent Vasorelaxation[15]

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.

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.

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.

Atherosclerosis[15]

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.

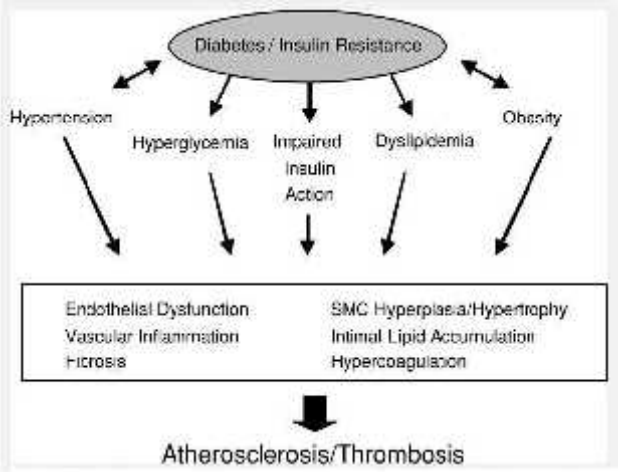


Figure 5. Pathogenesis of atherosclerosis in IR[15]

Complications

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

Impaired glucose tolerance (IGT)[24]

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.

Type 2 diabetes mellitus[17,25]

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.

Hypertension[26]

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.

Dyslipidemia[27,28,29]

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.

Hyperuricemia[30,31]

IR causes impaired renal excretion of uric acid and increases the serum uric acid levels leading to hyperuricemia.

Coronary artery disease[27,28,32,33]

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.

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.

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.

Others[27,34]

IR has also been associated with nonalcoholic steatohepatitis, high procoagulant tendency, high levels of proinflammatory cytokines

Metabolic syndrome / syndrome X[3]

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

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

Epidemiology

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[3]

NCEP: ATPIH 2001[3]

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[3]

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.

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

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.

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.

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.

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.

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.

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.

Mechanism

The most accepted and unifying hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, caused by an incompletely understood defect in insulin action. 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.

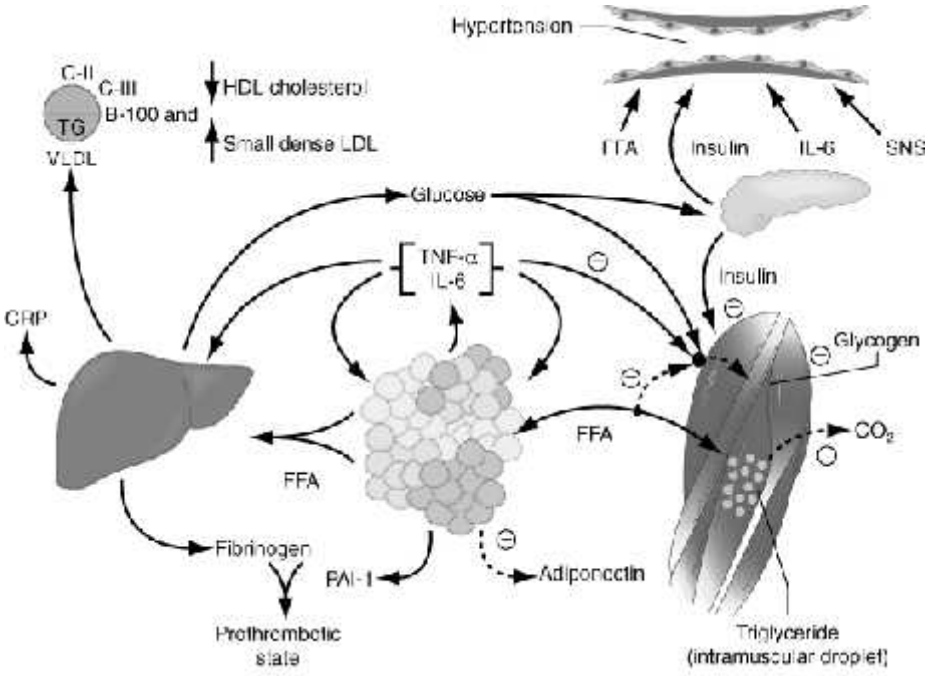


Figure 6. Pathogenesis of metabolic syndrome[3]

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[3]

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.

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.

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.

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.

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.

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.

Insulin assay[35]

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.

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

Assessment of IR

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.

Hyperinsulinemic euglycemic glucose clamp technique[36]

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 plausibleunderlying mechanisms

Minimal model analysis of a frequently sampled iv glucose tolerance test (FSIVGTT)[37]

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.

Homeostasis model assessment (HOMA)[38,39]

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,

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

Quantitative Insulin Sensitivity Check Index (QUICKI)[40]

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).

Fasting Glucose to Insulin ratio[41]

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).

Bennett index[42]

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).

Fasting insulin[43]

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

Few other indices derived from oral glucose tolerance test are also used to quantitate IR.[43]

Other factors in IR

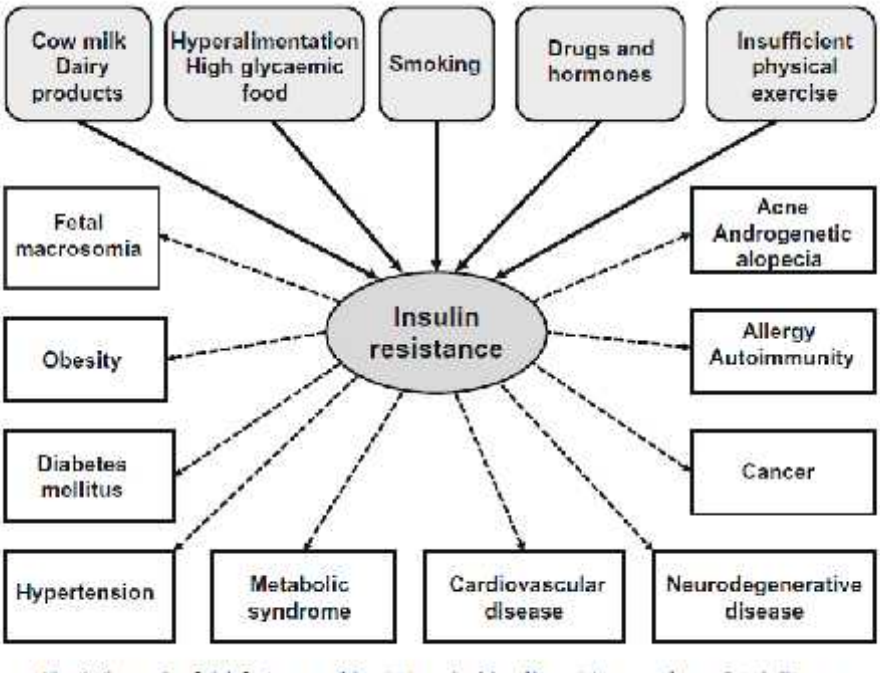


Figure 7. Risk factor resulting in impaired insulin resistant and associated diseases

Pregnancy and IR

Insulin resistance and normal pregnancy

Insulin resistance and resultant hyperinsulinemia are characteristic of normal pregnancy and are maximal in the third trimester. This is probably mediated by several hormonal changes, including elevations in levels of human placental lactogen, progesterone, cortisol, and estradiol. In normal pregnancy insulin resistance develops and assists in the provision of substrates for energy for the baby. This insulin resistance leads to higher levels of glucose and free fatty acids; this effect is counterbalanced, however, by increased secretion of maternal insulin. [44,45]

Hyperinsulinaemia and IR start to develop in the second half of pregnancy, when the maternal GH-axis shifts from pituitary-derived GH toward a predominance of placental GH (PGH).

IR of normal pregnancy is a critical physiologic adaptation to limit maternal glucose uptake to ensure that an adequate supply of glucose is shunted to the growing fetus. The growing fetus requires 80% of his energy source as glucose. Normal pregnancy is characterized by an approximate 50% decrease in insulin-mediated glucose disposal in humans and a 200 to 250% increase in insulin secretion to maintain euglycaemia in the mothers. Placental hormones, especially PGH, reprogram mother's physiology to become insulin resistant.

Features of the insulin resistance syndrome associated with preeclampsia

1. Hypertension
2. Hyperinsulinemia
3. Glucose intolerance
4. Obesity
5. Lipid abnormalities
    a. Elevated triglycerides
    b. Low HDL
    c. Increased dense LDL
6. Increased leptin
7. Increased TNF
8. Increased TPA and PAI-1
9. Elevated testosterone

10. Reduced SHBG

Polycystic ovarian syndrome and IR[15]

The association between a disorder of carbohydrate metabolism and androgen excess was first described in 1921 by Archard and Thiers and was called the "diabetes of bearded women." Since then, the association between PCOS and IR or impaired glucose tolerance has been well recognized.[146]

Studies of well-characterized causes of hyperinsulinemia and androgen excess have illuminated various mechanisms of IR. Factors such as a decrease in insulin binding related to autoantibodies to insulin receptors, postreceptor defects, and a decrease in insulin receptor sites in target tissues are all involved in IR.[289] These rare syndromes, however, are found in an extremely small portion of women with anovulation, androgen excess, and IR, leaving the majority of PCOS patients without any demonstrable abnormalities in the number or quality of receptors or antibody formation. The exact nature of IR in the great majority of women with PCOS is not well understood.

Insulin resistance is associated with the abnormal responses of the ovarian follicle to FSH, which leads to anovulation and androgen secretion. This results in noncyclic formation of estrogen from androgens in peripheral tissues. Estradiol together with increased androgen gives rise to abnormal gonadotropin secretion. This creates an anovulatory state favoring continuous formation of LH, steroid precursors, androgen and estrogen.

Under feeding and overfeeding in the early perinatal period and insulin resistance later in life[46]

Epidemiologic studies in humans have revealed links between perinatal food deprivation and adult incidence of obesity, type 2 diabetes, alterations of the hypothalamic–pituitary–adrenal axis, arterial hypertension and cardiovascular diseases.

Animal studies in mice have demonstrated that underfeeding of mice during the early postnatal period (first two weeks of life) led to alterations in the somatotropic axis which persisted throughout adulthood and caused hypertension and reduced glucose tolerance later in life due to insufficient insulin secretion.

Animal studies in mice have also demonstrated that overfeeding of mice during the first two weeks of life resulted in alterations of the somatotropic axis and induced IR and increased GH and IGF-1 in adulthood at the age of three months. Postnatal overfed mice exhibited hyperinulinaemia and persistent IR throughout adulthood.

These animal experiments allow the conclusion that early perinatal under-nutrition or over-feeding modify the plasticity of growth through developmental changes of the GH–IGF-1-axis in alterations of the somatotropic axis and induce IR and increase GH and IGF-1 in adulthood.

Milk-induced insulin resistance[46]

Milk is a complex, bioactive substance honed by evolution to promote growth and development of the infant mammal. Cow milk and dairy products are

widely consumed by children and adults well after the age of weaning. It is important to note that cow milk contains active IGF-1 (4 to 50 ng/ml) and IGF-2 (40 to 50 ng/ml). Intriguingly, bovine and human IGF-1 share the same amino acid sequences. Therefore, bovine IGF-1 can bind to the human IGF1R. . High milk consumption in humans is associated with a 10–20% increase in circulating IGF-1 levels among adults and a 20 to 30% increase among children. Moreover, milk-consumption elevated the ratio of IGF-1/IGFBP-3 indicating an increased bioavailability of IGF-1. There is good evidence that milk consumption shifts the human intrinsic GH–IGF-1 axis to unusual high levels.

Consumption of milk and dairy during early pregnancy may increase maternal serum IGF-1 levels, which could over-stimulate placental growth resulting in elevated placental glucose flux to the fetus.

Milk-induced hyperinsulinaemia may further increase the physiologic IR of pregnancy, thereby elevating the pool of maternal glucose for the fetus which may also induce IR in the fetus.

Cow milk consumption of the mother during pregnancy and infant feeding with cow milk-based formula may result in inadequate programming of the insulin/IGF-1 axis during fetal and postnatal life.

A milk-induced increase of maternal and fetal IR might change intrinsic hormonal growth axis in the mother and her fetus and induce epigenetic changes persisting throughout life.

Insulin resistance in adolescence and young adults[46]

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.

Oral contraceptives[46]

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.

Androgens[46]

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.

Smoking[46]

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.

Alcohol[47]

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.

Drug-induced insulin resistance[46]

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.

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.

Cancer[46]

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.

Neurodegenerative diseases[46]

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.

Chronic obstructive pulmonary disease (COPD)[48]

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.

Therapetic aspects of insulin resistance[49]

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

Non Pharmacological

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.

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.

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

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.

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.

ANTIHYPERTENSIVES AND THEIR EFFECT ON INSULIN RESISTANCE[50]

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.

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).

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

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.

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.

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.

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.

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.

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.

Mechanisms

Thiazide Diuretics

Thiazide diuretics appear to worsen glycemic control in a dose-dependent fashion by reducing insulin secretion and peripheral insulin sensitivity. Development of hypokalemia (and perhaps hypomagnesemia) appears to be important because the use of potassium supplementation to prevent hypokalemia reduces the occurrence of thiazide-induced glucose intolerance. Nevertheless, deterioration in glucose metabolism occurs even with minimal reductions in serum potassium levels. Since ACE inhibitors and ARBs appear to counteract some of the adverse effects associated with the use of thiazide diuretics, including potassium wasting and aldosterone secretion, early combined therapy has been recom- mended. Although combination therapy likely leads to better blood pressure control, head-to-head randomized controlled trials are lacking in determining the metabolic outcomes of such combinations.

β-Blockers

Therapy with β-blockers has been shown to inhibit pancreatic insulin secretion and peripheral glucose utilization. Weight gain, decreased skeletal muscle blood flow, and unopposed stimulation of β-2-receptor–mediated

glycogenolysis are also potential mechanisms by which β-blockers might exert adverse effects.

Third-generation β-blockers, such as carvedilol and nebivolol, that possess vasodilator actions. The proposed mechanisms as nitric oxide release, antioxidant effects, and calcium ion blockade. Basic and clinical studies suggest that these drugs may improve insulin sensitivity or are at least metabolically neutral in patients with impaired glucose tolerance.

In Carvedilol-Metoprolol Comparison in Hypertensives trial, the comparison of carvedilol to metoprolol in the presence of reninangiotensin system blockade on glycemic control showed that carvedilol was superior in improving insulin sensitivity, preserving hemoglobin A1c levels, and preventing the progression to microalbuminuria, despite similar blood pressure responses in patients with diabetes mellitus and hypertension. Therefore, third-generation β-blockers may become the preferred antiadrenergic blood pressure drugs in patients with insulin resistance.

Calcium Channel Blockers

Calcium channel blockers have been shown to reduce insulin resistance or new-onset diabetes among patients with metabolic syndrome, seeming to be intermediate in effectiveness between ACE inhibitors and ARBs (which reduce the incidence of diabetes mellitus) and are superior to thiazide diuretics and β-blockers (which increase it). Both dihydropyridine and long-acting non dihydropyridine, calcium antagonists have shown metabolic benefits, with effects on insulin sensitivity and insulin secretion. These agents may improve insulin

sensitivity by exerting vasodilatory action in insulin-sensitive tissues without stimulating sympathetic nervous activity, by preventing the inhibition of glucose transporters and glycogen synthase by calcium, or through antioxidant effects.

Centrally Acting Agents

Centrally acting antihypertensive agents are not widely used because of a relatively high incidence of adverse effects. Most central adverse effects appear to be through the α2-receptor. The α2-agonists appear to have minimal effects on lipid profiles but may inhibit pancreatic β-cell insulin secretion, thereby impairing glucose metabolism.

Imidazoline receptor agonists such as moxonidine are selective for the I1-imidazoline receptor in the sympathetic vasomotor centers with little effect at the central α2-receptor. Therefore, the adverse effect profile is favorable compared with other centrally acting agents. Moxonidine has been shown to diminish sympathetic activity, and it reduces arterial pressure by lowering systemic vascular resistance without affecting heart rate and cardiac output.

Drugs such as moxonidine may exert favourable metabolic effects, including improved insulin sensitivity. Animal studies have suggested that this may be due to decreased vasoconstriction in insulin-sensitive tissues such as skeletal muscle and improved insulin signaling, which leads to increased glucose uptake.

α-1 Blockers

α-Adrenergic blockers have also been shown to have beneficial metabolic effects. Selective α1-blockers, such as prazosin, terazosin, and doxazosin, are the only class of antihypertensive agents that appear to have the combined effect of improving insulin sensitivity, raising high-density lipoprotein cholesterol levels, and lowering low-density lipoprotein cholesterol levels. α1-blockers are generally not considered for firstline therapy in essential hypertension, even in patients with diabetes or metabolic syndrome because of high incidence of their adverse effects.

Angiotension convertase enzyme inhibitors / Angiotensin receptor blockers

Insulin sensitivity

Patients with essential hypertension frequently have impaired glucose tolerance due to increased insulin resistance. ACE inhibitors and ARBs may influence skeletal muscle toward a greater percentage of type I fibers, which are more sensitive for insulin mediated glucose uptake and may improve insulin sensitivity.

ARBs like telmisartan may interact with the nuclear hormone receptor peroxisome proliferator-activated receptor γ independent of angiotensin II receptors. This interaction may represent a potential mechanism by which ARBs improve insulin sensitivity, since peroxisome proliferator activated receptor γ is the cellular target for the insulinsensitizing thiazolidinedione drugs.

Vascular effects

Increased skeletal muscle blood flow and resulting improvements in insulin delivery may be important mechanisms by which attenuation of the renin-angiotensin system improves glucose uptake and metabolism in insulin-sensitive tissues.

One potential mechanism would be via the inhibiting effects of ACE inhibitors on kininase II, thereby increasing bradykinin and the subsequent enhancement of nitric oxide production. Other potential mechanisms of renin-angiotensin system blockade are improved vascular sensitivity to insulin and improved endothelial function.

Moreover, both ACE inhibitors and ARBs increase skeletal muscle blood flow by diminishing the vasoconstricting effects of angiotensin II, particularly at the level of the small arteriole. Thus, ACE inhibitors and ARBs likely improve insulin-mediated glucose disposal in hypertensive and insulin-resistant conditions by augmenting blood flow to insulin-sensitive tissues and by having direct effects on skeletal muscle glucose uptake capacity.

Signalling pathways

Insulin-dependent skeletal muscle glucose transport involves the binding of circulating insulin to the plasma membrane (sarcolemma) receptor, which results in the activation of a cascade of phosphorylation steps. Ultimately, the pathway leads to the translocation of the insulin-sensitive glucose transporter (GLUT4) to the sarcolemma, facilitating glucose uptake into the cell.

Angiotensin II interferes with insulin signalling in skeletal muscle. Skeletal muscle glucose uptake is diminished in transgenic hypertensive rats that overproduce tissue angiotensin II. Angiotensin II might inhibit insulin signaling pathways by generatig of reactive oxygen species or alterations in production of nitric oxide through the activation of membrane-bound NADPH oxidase. This cascade of events causing insulin resistance is prevented by ARBs, thus improving insulin sensitivity.

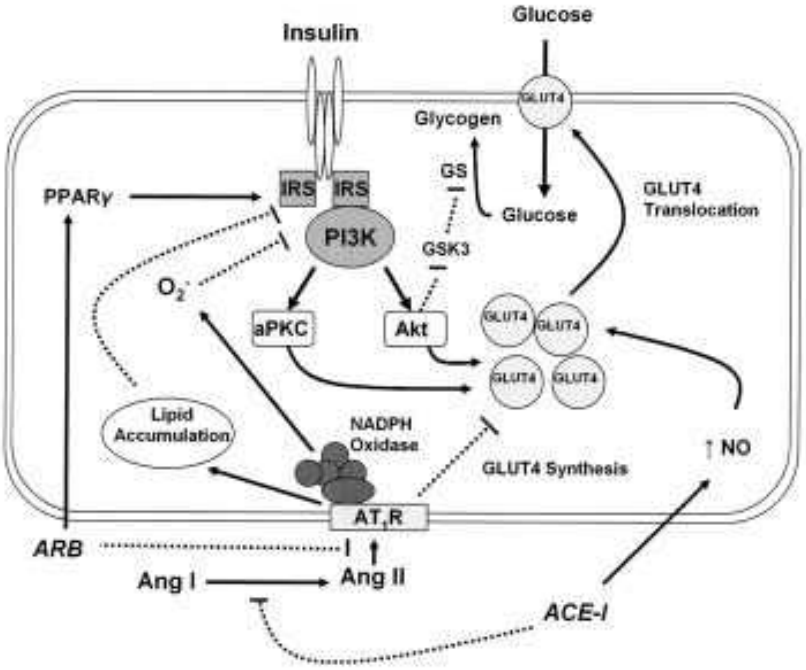


Figure 8. Mechanisms by which the renin-angiotensin system affects insulin sensitivity and glucose transport in skeletal muscle tissue and action of ACE inhibitors /ARB at various levels.[50]

Lipoprotein lipase[50]

High Lipoprotein lipase activity is known to increase insulin sensitivity in transgenic rabbits. Lipoprotein lipase is levels are reduced in hypertensives

during aging and in people with low physical activity, all the conditions which are associated with HTN and IR. Interestingly, the ARB losartan has been shown to reverse the diminished lipoprotein lipase activity observed in adipose tissues from hypertensive rats.

Islet cell protection[50]

The risk of diabetes developing in patients with hypertension may depend on the preservation of β-cells and insulinsecreting capacity in the pancreas. Evidence suggests that the pancreas has a local renin-angiotensin system. Moreover, angiotensin II was shown to suppress insulin secretion in perfused pancreas preparations but not in in vitro systems.

Thus, it has been proposed that the reninangiotensin system affects pancreatic function primarily by altering islet perfusion. Animal studies have shown that angiotensin II causes vasoconstriction in the endocrine pancreas, whereas ACE inhibition and angiotensin II receptor blockade preferentially increase islet blood flow. ACE inhibition in patients with hypertension resulted in improved first-phase insulin secretion in response to oral or intravenous glucose.

Statins in insulin resistance[51]

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.

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 and Akt, resulting in the translocation of glucose transporters to cell membrane and enhanced glucose uptake. This cascade is inhibited by circulating cytokines (TNF alfa 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.

METHODOLOGY

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on non diabetic hypertensive patients during the period from January 2009 to December 2009.

Study design

One year cross-sectional study.

Study period

The present study was conducted during period of January 2009 to December 2009.

Method of collection of data

Source of Data

Hypertensive patients, attending outpatient department or admitted in the wards of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum.

Sample size

A total of 65 hypertensive patients were studied.

Sampling procedure

The sample size was calculated based on following formula.

$4 X p X q / d^2$

Where p = prevalence (50)[3,52]

q = 100 – p

d = standard error (15)

Based on the above formula the sample size was calculated as 45. However consecutive 65 patients fulfilling the study criteria were selected.

Selection criteria

Inclusion Criteria

- All cases of essential hypertension aged 18 to 65 years with BP of more than or equal to 140/90 mm Hg who are newly detected.
- All cases of essential HTN on treatment.

Exclusion Criteria

- Type 1 DM.
- Cases of Type 2 DM.
- Insulinomas.
- Secondary HTN.

Procedure

The study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum. During the study period, all patients presenting with and fulfilling the inclusion criterion were included in this study after obtaining informed written consent (Annexure–I).

Detailed relevant history was taken and clinical examination was done according to predesigned and pretested proforma (Annexure-II). 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.[53]

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

The WHR was calculated as;

$$\text{WHR} = \frac{\text{Waist circumference (Cms)}}{\text{Maximum hip circumference (Cms)}}$$

Waist hip ratio of less than 0.9 in males and 0.85 in females was considered as normal.[54]

The blood pressure recording was done in all the patients. Patients on antihypertensive treatment were categorized as optimal controlled (less than 140/90 mm Hg) and uncontrolled (more than 140/90 mm Hg).

Investigations like fasting blood sugar, post prandial blood sugar, lipid profile and electrocardiogram (ECG) were done.

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;

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

Subjects also underwent other investigations like fasting lipid profile.

Homa IR

Patients were considered as insulin resistant if HOMA IR was more than 3.8.[55,56]

Statistical methods

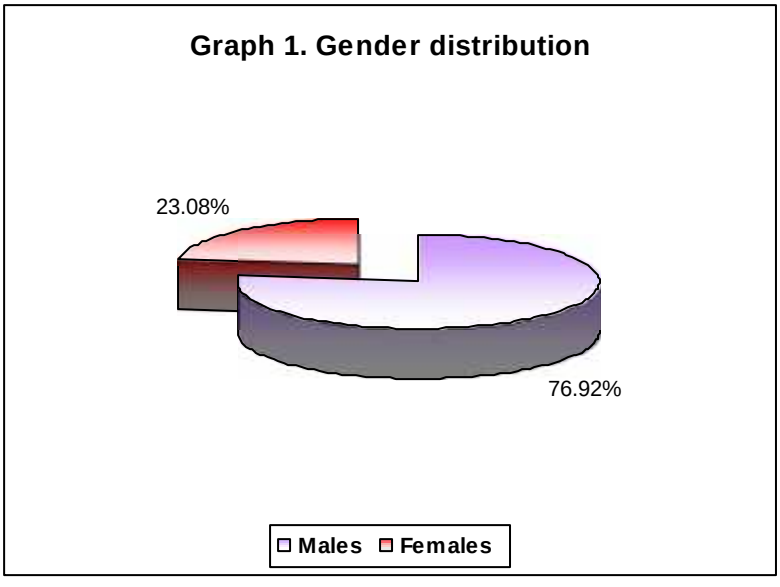
The data obtained was tabulated and analyzed using rates, ratios and percentages. Correlation was done using chi-square test. A ‘p’ value of less than 0.05 was considered as significant.

RESULTS

The present study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on non-diabetic, hypertensive patients during the period from January, 2009 to December 2009. A total of 65 hypertensive patients were studied. The data obtained was tabulated and analysed as below.

Table 1. Gender distribution

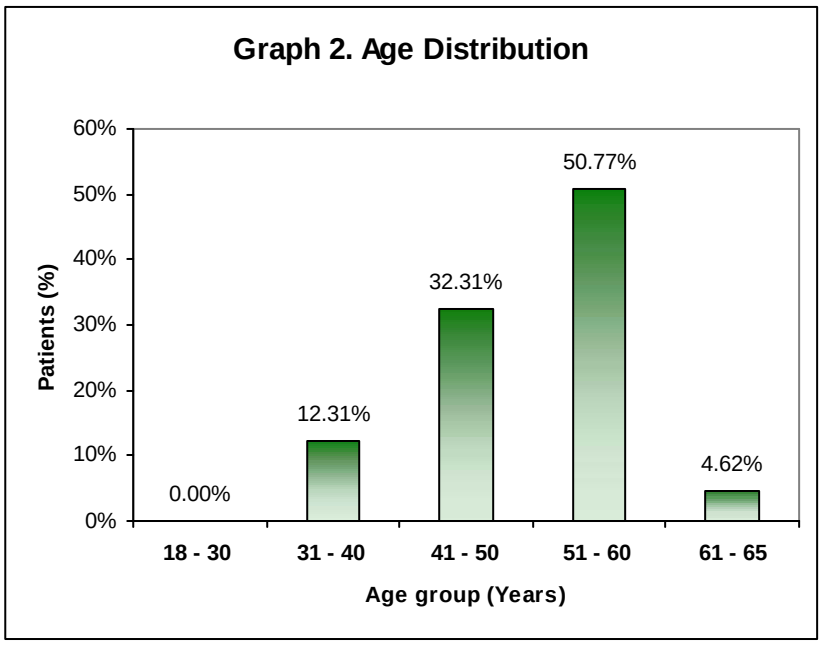
Gender	Patients	
	Number	Percentage
Male	50	76.92
Female	15	23.08
Total	**65**	**100.00**



In this study males (76.92%) outnumbered females (23.08%). The male to female ratio was 3.33:1.

Table 2. Age distribution

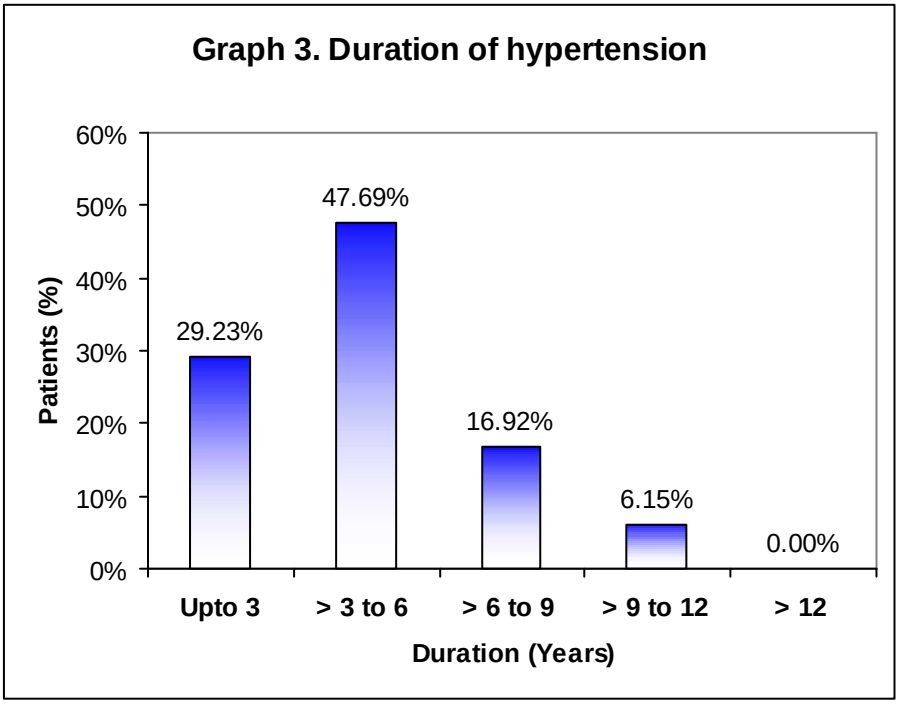
Age (Years)	Patients	
	Number	**Percentage**
18 to 30	0	0.00
31 to 40	8	12.31
41 to 50	21	32.31
51 to 60	33	50.77
61 to 65	3	4.62
Total	**65**	100.00



In this study, majority (50.77%) of the patients, were in the age group of 51 to 60 years, followed by 41 to 50 years (32.31%), 31 to 40 years (12.31%) and 61 to 65 years (4.62%). None of the patients were in the age group of 18 to 30 years.

Table 3. Duration of hypertension

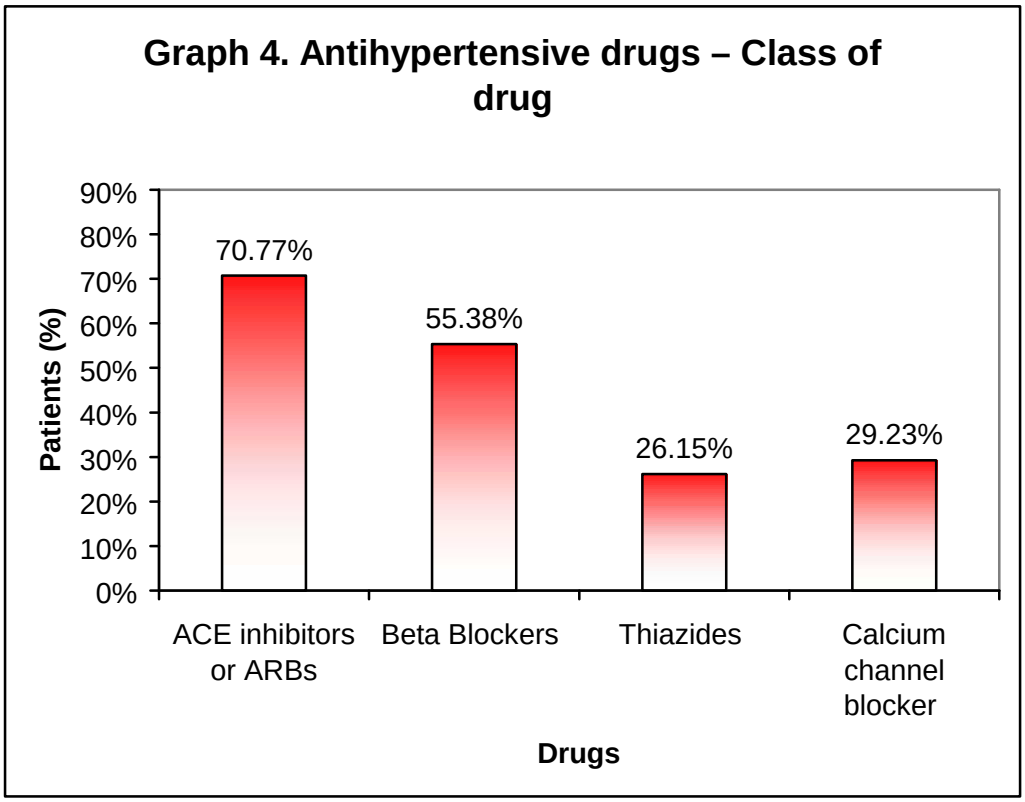
Duration (Years)	Patients	
	Number	Percentage
Upto 3	19	29.23
>3 to 6	31	47.69
>6 to 9	11	16.92
>9 to 12	4	6.15
More than 12	0	0.00
Total	**65**	100.00



In the present study, majority (47.69%) of the patients had duration of hypertension between three to six years followed by less than three years (29.23%), six to nine years (16.92%) and nine to twelve years (6.15%). None of the patients had duration of more than 12 years.

Table 4. Antihypertensive drugs – Class of drug

Drugs	Patients	
	Number	**Percentage**
ACEs inhibitors or ARBs	46	70.77
Beta blockers	36	55.38
Thiazides	17	26.15
Calcium channel blockers	19	29.23



In this study majority (70.77%) of the patients were on ACE inhibitors or ARBs. The other patients were on beta blockers (55.38%), thiazides (26.15%) and calcium channel blocker (29.23%).

Table 5. History of complications

Complications	Patients	
	Number	Percentage
CVA	6	9.23
PVD	1	1.54
IHD	22	33.85

The above table shows history of complications among patients with hypertension. Ischaemic heart disease was noted in 33.85% of patients whereas cerebrovascular accidents were present in 9.23% patients and peripheral vascular disease was present in one patient (1.54%).

Table 6. Other drugs

Other drugs	Patients	
	Number	Percentage
Aspirin	24	36.92
Atorvastatin	23	35.38
Clopidogrel	23	35.38
Isosorboide mononitrate	20	30.77

In this study 36.92% of the patients were on aspirin, 35.38% each were on atorvastatin and clopidogrel and 30.77% were on isosorbide mononitrate.

Table 7. Family history

Family history	Patients	
	Number	Percentage
Hypertension	40	61.54
Diabetes mellitus	25	38.46
Ischaemic heart disease	5	7.69

Family history of hypertension, diabetes and IHD was noted in 61.54%, 38.46% and 7.69% patients respectively.

Table 8. Personal history

Personal history	Patients	
	Number	Percentage
Smoking	32	49.23
Alcohol	5	7.69
Sedentary	42	64.61
Non sedentary	23	35.39

History of smoking was noted in maximum number of patients (32, 49.23%) followed by alcohol in 7.69% of patients.

Table 9. Control of hypertension

Hypertension	Patients	
	Number	Percentage
Controlled	38	60.31
Uncontrolled	25	39.69

In the present study, out of 63 patients on treatment, 38 (60.31%) had optimal control of hypertension and 25 (39.69%) were inadequately controlled.

Table 10. Body mass index

Body mass index (Kg/m^2)	Patients	
	Number	Percentage
Underweight (< 18.5)	*0*	*0.00*
Normal range (18.5 to 22.9)	*7*	*10.77*
Overweight (>23)	*58*	*89.23*
At Risk (23 to 24.9)	16	24.62
Obese I (25 to 29.9)	32	49.23
Obese II (> 30)	10	15.38

In this study, majority of the patients were overweight (89.23%). Among them 24.62% were at risk, 49.23% were in obesity grade I and 15.38% were in obesity grade II. **(**Classification of overweight and obesity by BMI in adult Asians)

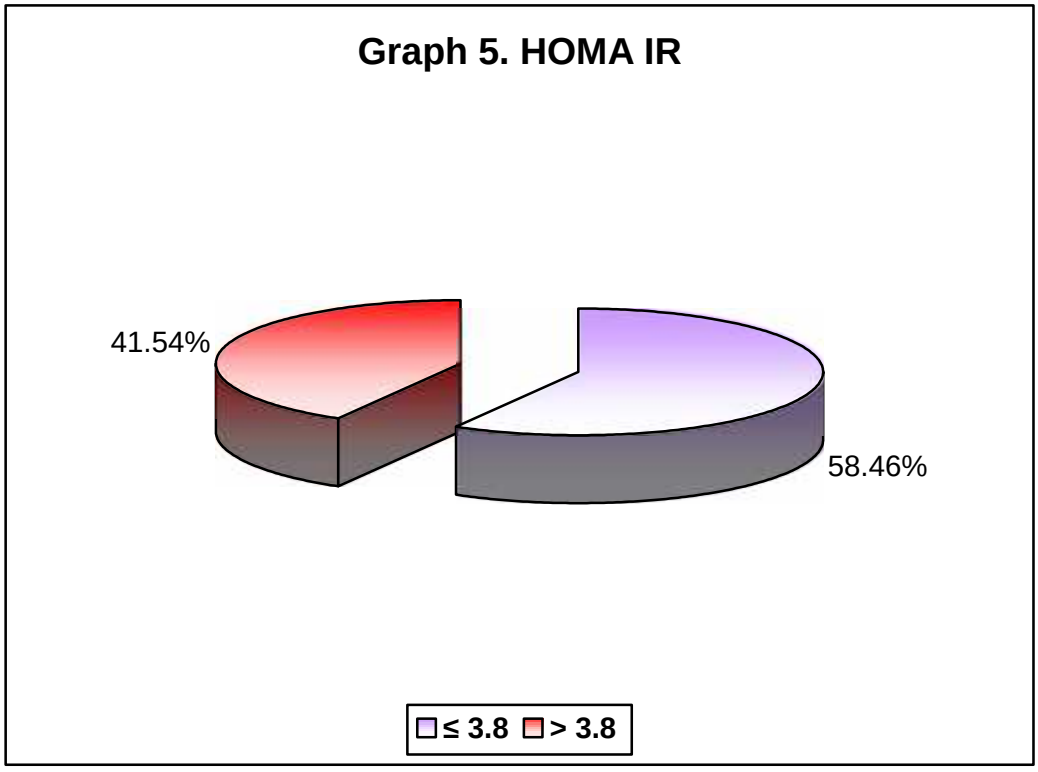
Table 11. Waist hip ratio

Waist hip ratio	Patients	
	Number	**Percentage**
Abnormal (Males >0.9; Female >0.85)	42	64.62
Normal (Males <0.9; Female <0.85)	23	35.38

In the present study, 64.62% patients had abnormal waist hip ratio (Males >0.9; Female >0.85).

Table 12. HOMA IR

HOMA IR	Patients	
	Number	**Percentage**
≤ 3.8	38	58.46
> 3.8	27	41.54



In the present study, HOMA IR was more than 3.8 in 41.54% of the patients and in 58.46% patients it was less than or equal to 3.8.

Table 13. Family history of diabetes in insulin resistant individuals

Family history	Patients (n=27)	
	Number	Percentage
Present	22	81.49
Absent	05	18.51

In this study family history of diabetes was present in 81.49% of patients with insulin resistance.

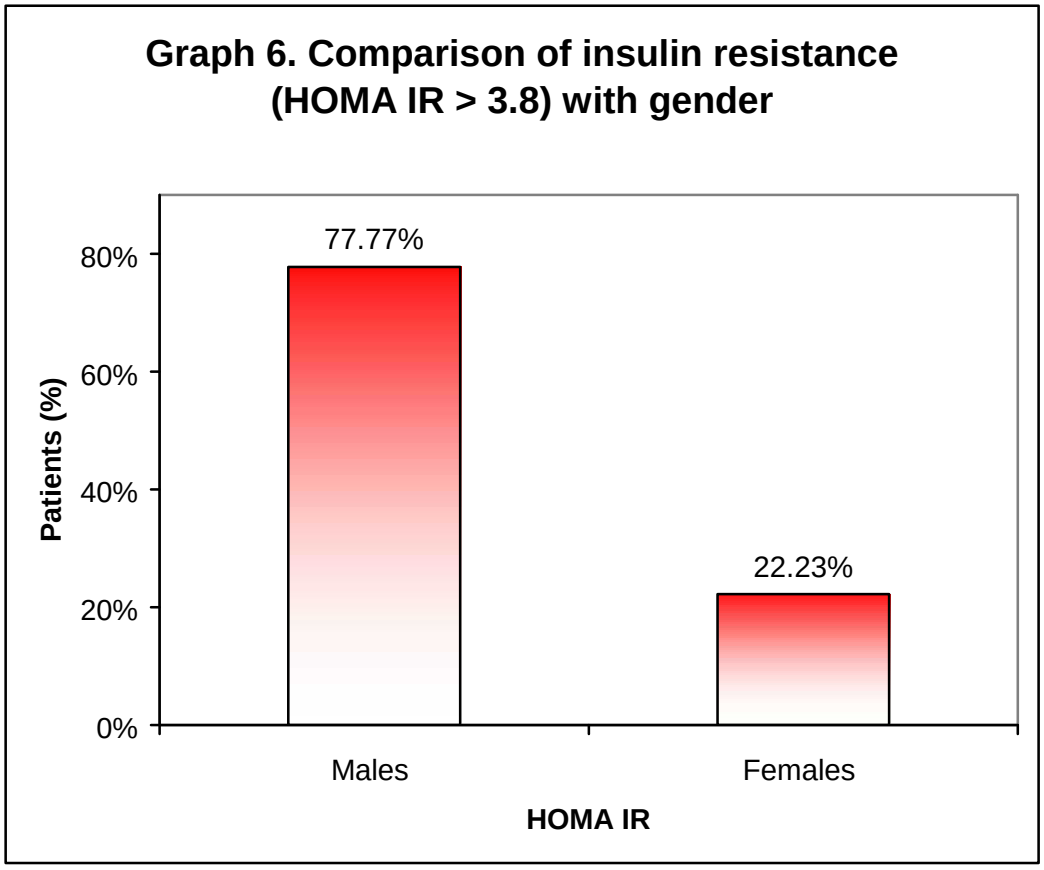
Table 14. Control of hypertension among insulin resistant individuals

Hypertension	Patients (n=27)	
	Number	Percentage
Controlled	9	33.33
Uncontrolled	18	66.67

Among the insulin resistant patients on antihypertensive treatment, 33.33% had optimal control of hypertension whereas 66.67% had uncontrolled hypertension.

Table 15. Comparison of insulin resistance (HOMA IR > 3.8) with gender

Gender	Patients	
	Number	Percentage
Male	21	77.77
Female	6	22.23



In this study, the HOMA IR was more than 3.8 in 77.77% of males and 22.23% of females.

Table 16. Fasting insulin level

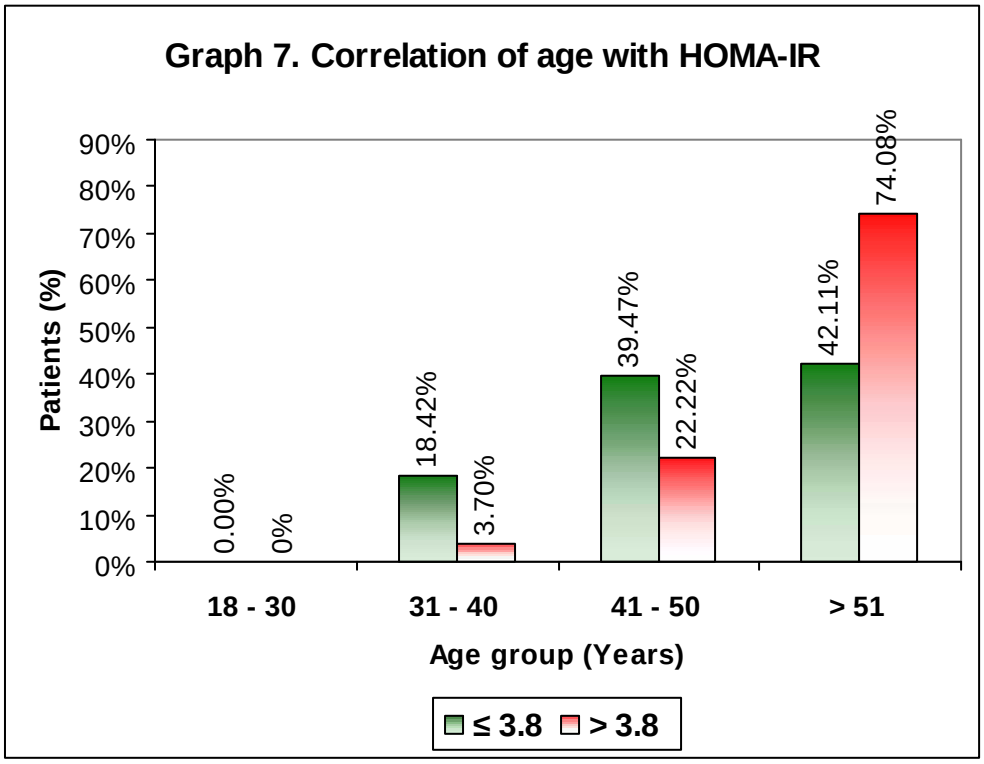
Fasting insulin level (IU)	Patients	
	Number	**Percentage**
0 to 10	19	29.23
11 to 20	19	29.23
21 to 30	18	27.69
31 to 40	7	10.77
More than 40	2	3.08

This table shows distribution of fasting insulin levels among the study population. 37 patients had insulin levels between 11 to 30 while, seven (10.77%) patients revealed insulin levels more than 31, suggesting Insulin Resistance.

Table 17. Correlation of age with HOMA-IR

Age group	≤ 3.8 (n=38)		> 3.8 (n=27)	
	Number	**Percentage**	**Number**	**Percentage**
18 to 30	0	0.00	0	0.00
31 to 40	7	18.42	1	3.70
41 to 50	15	39.47	6	22.22
> 51	16	42.11	20	74.08

x^2=7.145 DF=2 p=0.028



In the present study, majority (74.08%) of the patients with insulin resistance were aged more than 51 years suggesting that insulin resistance is more in elderly individuals. These findings were statistically significant (p=0.028).

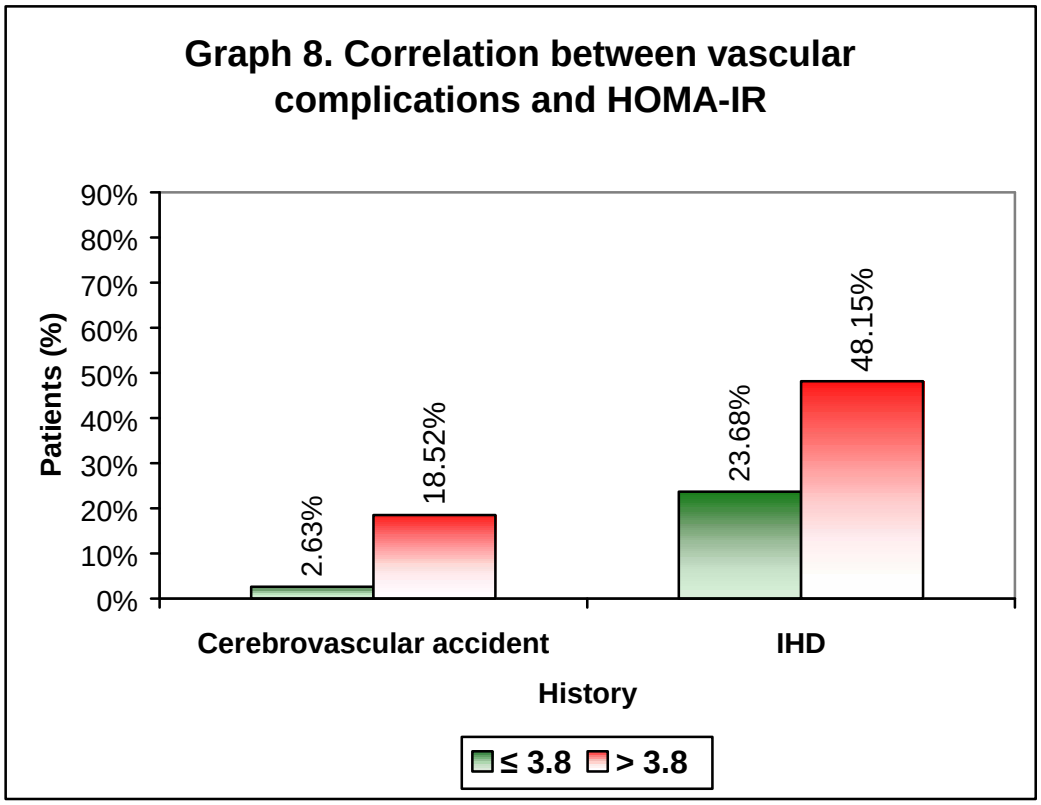
Table 18. Correlation of class of drug with HOMA-IR

Class of Drugs	≤ 3.8 (n=38)		> 3.8 (n=27)	
	Number	**Percentage**	**Number**	**Percentage**
ACE inhibitors / ARBs	28	73.68	14	51.85
Beta blockers	18	47.37	18	66.67
Thiazides	11	28.94	6	22.22
Calcium channel blockers	10	26.31	9	33.33
x^2=0.266	DF=1		p=0.606	

In patients on ACE inhibitors or ARBs, insulin resistance was less (51.85%) as compared to beta blockers (66.67%). However, 22.22% patients on thiazides and 33.33% of patients on calcium channel blocker were insulin resistant and this difference was statistically not significant (p=0.606).

Table 19. Correlation between vascular complications and HOMA-IR

Complications	≤ 3.8 (n=38)		> 3.8 (n=27)		Z	P
	No	%	No	%		
Cerebrovascular accident	1	2.63	5	18.52	2.18	0.029
IHD	9	23.68	13	48.15	2.06	0.039



Among the patients with insulin resistance, history of CVA was seen in 18.52% and IHD was noted in 48.15%. These findings suggest that cardiovascular and cerebrovascular complications among patients with insulin resistance was more. This was statistically significant (p=0.029, 0.039 for Cerebrovascular accident and IHD respectively).

Table 20. Correlation between substance abuse and HOMA-IR

Personal history	≤ 3.8 (n=38)		> 3.8 (n=27)		Z	P
	No	%	No	%		
Smoking	13	34.21	13	48.15	1.13	0.258
Alcohol	2	5.26	3	11.11	0.87	0.384

In the present study, among patients with insulin resistance, history of smoking and alcohol consumption was seen in 48.15% and 11.11% respectively. However these findings were statistically not significant.

Table 21. Correlation between lifestyle and HOMA-IR

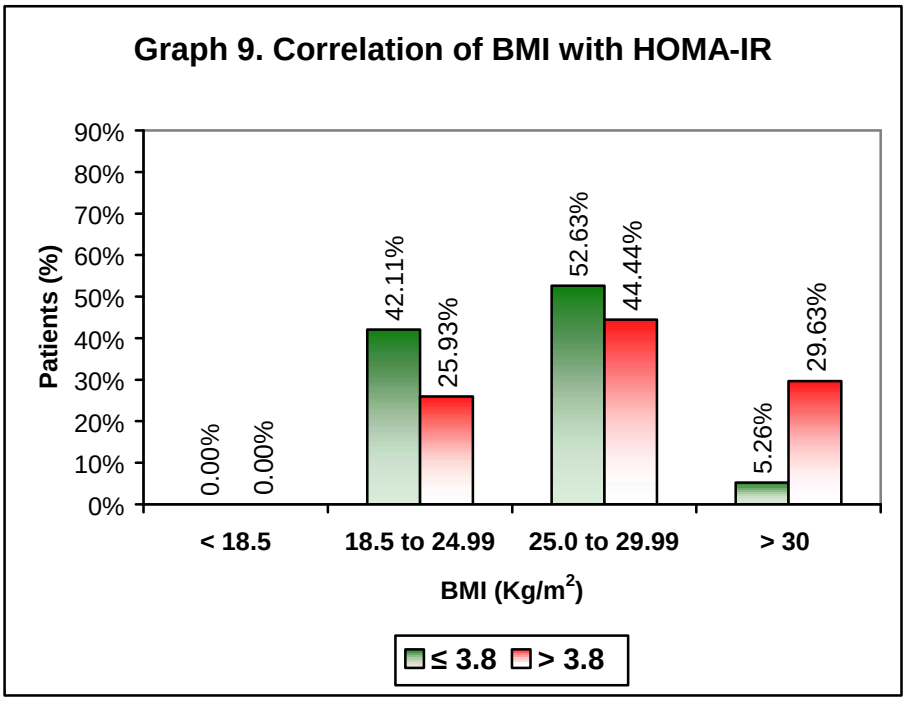
Lifestyle	≤ 3.8 (n=38)		> 3.8 (n=27)	
	No	%	No	%
Sedentary	27	71.05	15	55.56
Non Sedentary	11	28.95	12	44.44
x^2=1.650	DF=1		p=0.198	

Sedentary lifestyle was predominantly noted among patients with insulin resistance, however, it was statistically not significantly.

Table 22. Correlation of BMI with HOMA-IR

BMI	≤ 3.8 (n=38)		> 3.8 (n=27)	
	Number	Percentage	Number	Percentage
< 18.5	0	0.00	0	0.00
18.5 - 24.99	16	42.11	7	25.93
25 - 29.99	20	52.63	12	44.44
> 30	2	5.26	8	29.63

x^2 = 7.474 DF = 2 p = 0.024



In the present study, 25.93% patients had BMI between 18.5 to 24.99 kg/m^2, 44.44% had between 25.0 to 29.9 and 29.63% had more than 30 kg/m^2 among patients with insulin resistance. These observations indicating linear relation between insulin resistance and BMI was apparent till the value of 29.9 Kg/m^2 but not beyond. It looses its statistical significant beyond BMI of 29.9% Kg/m^2 (p=0.024).

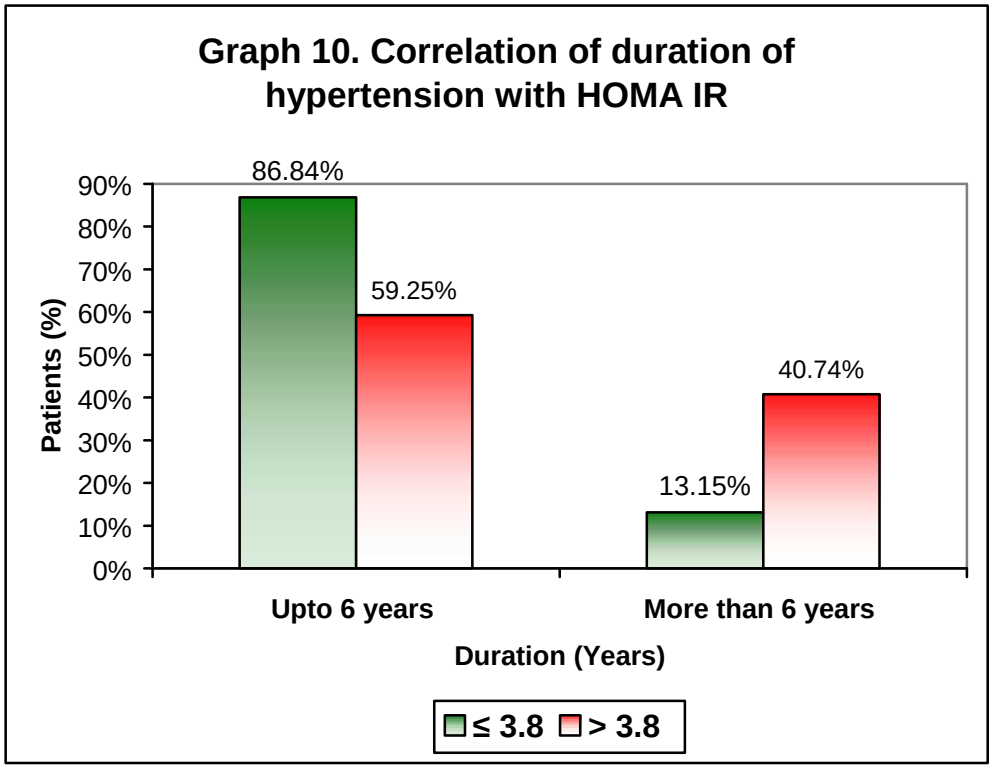
Table 23. Correlation of WHR with HOMA-IR

WHR	≤ 3.8 (n=38)		> 3.8 (n=27)	
	No	**%**	**No**	**%**
Abnormal (Males >0.9; Female >0.85)	23	60.53	19	70.37
Normal (Males <0.9; Female <0.85)	15	39.47	8	29.63
x^2 = 0.669	DF = 1		p = 0.413	

Abnormal WHR was noted in 19 (70.37%) patients with HOMA IR more than 3.8, suggesting positive correlation. It was, however, statistically not significant (p=0.413).

Table 24. Correlation of duration of hypertension with HOMA IR

Duration (Years)	≤ 3.8 (n=38)		> 3.8 (n=27)	
	Number	**Percentage**	**Number**	**Percentage**
Upto 6 years	33	86.84	16	59.25
More than 6 years	5	13.15	11	40.74
$x^2 = 7.474$		DF = 2		p = 0.021



Analysis of patients with hypertension of more than six years revealed that, five (13.15%) patients had HOMA IR less than 3.8, whereas 11 (40.74%) had HOMA IR more than 3.8, suggesting positive correlation between duration of hypertension and insulin resistance. These findings were statistically significant (p=0.021).

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 will increase to 1.56 billion by 2025.[1]

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.[2]

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.[3]

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 CMS.[4]

Despite major advances in the understanding of the pathogenesis and treatment of HTN and other components of the CMS, 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.[3]

This study was aimed at assessment of the prevalence of insulin resistance in hypertensive individuals.

In the present study a total no of 65 patients were enrolled and of which majority (76.29%) were males and 23.08% were females, whereas in a study[52] conducted in Sao Paulo to know the prevalence of insulin resistance, males were 41.9% and females were 50.9%. In another study[55] 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[57] conducted on patients undergoing general health check up in Thailand reported that prevalence of IR was ~25.1% in men and 21.5% in women. Another study[58] done on Finnish general population, showed slightly higher prevalence of IR in women than in men.

NHANES III[3] age adjusted prevalence of insulin resistance syndrome in males is 34% for men and 35% for women. The correlation of gender with HOMA IR in the present study showed that, 77.77% males and 22.22% of females were insulin resistant, however no conclusions could be drawn in view of small number of female patients.

In the present study majority of the patients were in the age group of 51 to 60 (50.77%), similar to other study.[52] In the present study it was observed that the insulin resistance increased with age and it was **statistically significant above the age of 51 years (p=0.028)**, suggesting that IR increases with age.

In a study[59] 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[60] done in India it was concluded that, with increase in age there is increase in IR. The results of the present study were in accordance with the above mentioned studies.

In the present study, majority (47.69%) of the patients had hypertension of less than six years duration. Duration of hypertension revealed positive correlation with insulin resistance. It was observed that, patients with longer duration of hypertension appeared to be insulin resistant, which was **statistically significant for patients with duration of hypertension > 6 years.**

Similar findings were seen in two studies[61,62] where patients with hypertension of more than five years had higher insulin levels compared to other subjects. The above fact may be due to relation between insulin levels and genesis of hypertension. The present study results were in accordance with the above mentioned studies.

In the present study majority (70.77%) of the patients were on ACE inhibitors or ARBs. The other patients were on beta blockers (55.38%), thiazides

(26.15%) and calcium channel blocker (29.23%). A study[52] to assess the prevalence of insulin resistance among hypertensives revealed that, 43% patients were on ACE inhibitors, 16% were on ARBs and 25% were on BB.

In the present study, it was observed that patients on ACE/ARB were more insulin sensitive than patients on BB, though it was statistically not significant.

A study[63] conducted on obese males with IGT demonstrated that, ARBs cause improvement in early phase of insulin secretion and reduction in insulin resistance.

In another study[64] conducted at China it was concluded that, losartan increases insulin sensitivity and glucose homoeostasis in the subjects with type 2 diabetic nephropathy.

In vitro and in vivo studies[65,66] have revealed that telmisartan and irbesartan have the potential to improve insulin sensitivity and beta-cell responsiveness.

A study[67] showed that, treatment with captopril was associated with an improvement of insulin resistance by 18%. In another study[68] in elderly patients, it was shown that, all six different ACE inhibitors improved insulin resistance.

The present study results were in accordance with the above mentioned studies but statistical significance was not obtained probably because of a smaller sample size.

In the present study 36.92% were on atorvastatin. A study[52] conducted in Sao Paulo to assess prevalence of insulin resistance among hypertensives revealed that, 29.36% of the patients were on atorvastatin.

In the present study 33.85% had history of IHD, 9.23% had cerebrovascular accidents and 1.54% had peripheral vascular diseases. The family history of HTN was noted in 61.64% patients, diabetes in 38.46% and IHD in 7.69% patients. Insulin resistance was more frequently noted among patients with ischaemic heart disease and cerebrovascular accidents. This finding was **statistically significant. (p=0.029, p=0.039 respectively).**

A study[29] conduced on male population, in Canada, observed that, high fasting insulin concentrations appeared to be an independent predictor of ischemic heart disease in men.

Clustering of the risk factors leading on to coronary artery disease (metabolic syndrome) is seen in insulin resistant subjects.[33]

A study conducted in Japan[69] showed that, 65.6% of patients with stroke had insulin resistance, prevalence of IR was higher probably because, the study group was older and HOMA IR (>1.73) values defined were lower(42). In our study with respect to cut-off value of more than 1.73 for insulin resistance we found that 78.46% of patients had insulin resistance. Another study[70] showed that, 10% of patients of with stroke were insulin resistant and it was an independent predictor of this clinical event. The present study results were in accordance with the afore mentioned studies.

The history of smoking was present in 49.23% of patients whereas, 7.69% were alcoholics in this study. It was also observed that, 60% of the patients had non sedentary life style and 40% of them were sedentary.

In the present study, among patients with IR, history of smoking and alcohol consumption was seen in 48.15% and 11.11% respectively which was higher compared to the insulin sensitive group. However, these findings were statistically not significant.

A study[71] done in Italy, showed that, chronic cigarette smoking markedly aggravates insulin resistance in patients with NIDDM.

A study[72] done in Sweden, showed that, high alcohol intake was associated with abdominal obesity, which might explain higher insulin resistance and diabetes. The present study results were in accordance with results of above mentioned studies

In the present study, history of sedentary lifestyle among the patients with insulin resistance was 55.56%, which was higher compared to patients who were insulin sensitive, however these findings were statistically not significant.

A study[73] done in Netherlands concluded that time spent sedentary, predicts higher levels of fasting insulin levels independent of amount of time at moderate and vigorous intensity activity levels. This highlights the importance of reducing sedentary time in order to improve metabolic health.

A study[74] conducted at Boston showed physical inactivity was associated with the development of insulin resistance, dyslipedemia, increased blood

pressure and impaired microvascular functions in the study group. The results of the present study were in accordance with the above mentioned studies.

In the present study of 65 patients, the prevalence of insulin resistance (HOMA IR > 3.8) was noted in 27 (41.54%) patients.

In a study[52] conducted at Sao Paulo, it was concluded that, ~50% of patients with essential hypertension are insulin resistant irrespective of antihypertensive treatment. The prevalence of insulin resistance in this study was higher compared to present study because they used insulin mediated glucose uptake method (IMGU) to assess insulin resistance which is more sensitive than HOMA IR.

In another study[75] it was estimated that ~50% of newly diagnosed patients with essential hypertension were hyperinsulinemic, and presumably, insulin resistant. In the above mentioned study,[75] prevalence of IR was higher, probably because they used insulin levels to quantify insulin resistance, and not HOMA IR as in our study.

A study[76] conducted in New Zealand to know insulin resistance on a group representing general population reported a prevalence of 42%. The results of this study were comparable with results of our study (41.25%).

Another study[77] estimated the prevalence of insulin resistance in patients with pharmacologically treated hypertension to be ~20% in nondiabetic subjects. In the present study, the prevalence of insulin resistance was high (41.25%) probably because, majority of patients were obese and insulin resistance is more

in obese individuals.[78] It is also known that, insulin resistance in Indians is more compared to caucasians.[79]

Depending on the populations studied and the methodologies for defining insulin resistance, ~25–50% of non-obese, non-diabetic hypertensives are insulin resistant. The results of the present study were comparable (41.25%) with afore mentioned literature.[3]

In the present study, 60.42% were obese and 35.38% were non obese according to Classification of overweight and obesity by BMI in adult Asians.[53] In the present study it was observed that insulin resistance increased with BMI and it was **statistically significant**. It confers that obese people are more insulin resistant and insulin resistance increases with obesity. However, these observations indicating linear relation between insulin resistance and BMI was apparent till the value of 29.9 Kg/m^2 but not beyond. It looses its statistical significant beyond BMI of 29.9% Kg/m^2 .

In a study[60] done in India it was showed that, insulin resistance increases along with BMI. In another study[80] it was observed that, insulin resistance increases with increase in BMI and insulin resistance is more in obese individuals

The results of the present study were in accordance with the above mentioned studies.

In the present study, WHR was abnormal in 64.62% patients. It was noted that patients who had abnormal WHR were more likely to be insulin resistant though it was statistically not significant in the present study.

A study[81] conducted at Rawalpindi concluded that waist hip ratio is better anthropometric tool to predict underlying insulin resistance. Many other studies[82,83] have also concluded WHR to be a better marker of visceral adiposity and IR.

Several studies[82,83] have demonstrated that, when fat is distributed preferentially in the abdominal area, insulin mediated glucose uptake is reduced, independent of overall degree of adiposity, therefore is conceivable that even in the absence of significant accumulation of total body fat, even a minimal deposition of fat in the abdominal area may induce insulin resistance. Thus abnormal waist hip ratio is a marker of insulin resistance.

Results of the present study were in accordance with the above mentioned studies, but statistical significance was not obtained probably because of a small sample size.

CONCLUSION

1. The prevalence of insulin resistance in hypertensive non diabetic patients was 41.54%, and the prevalence among males and females was 77.77% and 22.22% respectively.

2. Insulin resistance increases with advancing age.

3. Insulin resistance reveals positive correlation with duration of hypertension.

4. Insulin resistance is associated with more frequent vascular complications.

5. Insulin resistance was more among patients who were obese, hence obesity could be a marker of insulin resistance.

6. Insulin resistance was less among patients on ACE inhibitors/ARBs as compared to patients on beta blockers. However, this finding was statistically not significant.

Further study on large sample over a longer duration will provide conclusive evidence of relation between hypertension, insulin resistance and other co-morbidities.

SUMMARY

Hypertension is the most common CVD, affecting approximately 20 percent of the adult population. It is considered both as a disease condition 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. 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 (CMS). Moreover, both IR and HTN are implicated in the pathophysiology of chronic kidney disease (CKD) and CVD. Studies in humans demonstrate that improving insulin resistance, with insulin sensitizers has a positive effect on blood pressure control. Hence the present study was undertaken, to know the prevalence of insulin resistance in hypertensive individuals.

The present one year cross sectional study was conducted in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum on non diabetic hypertensive patients during the period from January 2009 to December 2009. A total of 65 hypertensive patients were studied. Investigations like FBS, PPBS, lipid profile and ECG were done. Fasting insulin levels were measured by MEIA method and insulin resistance was calculated by HOMA IR index. Insulin resistance was defined as HOMA IR more than 3.8.

In this study males (76.92%) outnumbered females. The male to female ratio was 3.33:1. Majority (50.77%) of the patients, were in the age group of 51

to 60 years and 47.69% had duration of hypertension between three to six years. Majority (70.77%) of the patients were on ACE inhibitors or ARBs. The prevalence of insulin resistance in this study was 41.54%. Majority (74.08%) of the patients with insulin resistance were aged more than 51 years. Insulin resistance was less in patients on ACE inhibitors or ARBs as compared to beta blockers (66.67%). Insulin resistance was more frequently noted among patients with IHD (48.15%) and CVA (18.52%). History of smoking and alcohol consumption was seen in 48.15% and 11.11% patients with IR respectively. Linear relation between insulin resistance and BMI was apparent till the value of 29.9 Kg/m^2 but not beyond. Abnormal WHR was noted in 19 (70.37%) patients with HOMA IR more than 3.8.

The prevalence of insulin resistance in hypertensive non diabetic patients was 41.54%, and the prevalence among males and females was 77.77% and 22.22% respectively. Insulin resistance increased with advancing age, duration of hypertension. Insulin resistance was more frequently noted among patients with vascular complications. It was also observed that, insulin resistance was more among patients who were obese and was less among patients on ACE inhibitors/ARBs.

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ANNEXURE I – CONSENT FORM

"A CROSS SECTIONAL STUDY TO KNOW THE PREVALENCE OF INSULIN RESISTANCE AMONG HYPERTENSIVE PATIENTS ATTENDING KLES DR. PRABHAKAR KORE HOSPITAL AND MEDICAL RESEARCH CENTRE, BELGAUM"

Objective and purpose of the study

This research is intended to study hypertension with reference to insulin resistance. The principal investigator of the study is Dr. **** **** under the guidance of Dr. ***** ***** Department of Medicine, J. N. Medical College, Belgaum. 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 my 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 my mind and withdraw from the study. My decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop my 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 my condition.

Privacy and Confidentiality

All information collected about me during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify me in this research record. Information from this study may be published but my 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 I may call Principal and Chairman, J.N.M.C Ethical Committee for Human Research.

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

Study investigator : Dr. ****** *******

Guide : Dr. ****** *******

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 Participant /representative : _____ Signature: _____

Or thumb impression

Name of the Witness _____ Signature:_____

Name of the Investigator: _____ Signature: _____

Date: Place:

ANNEXURE II – PROFOMA

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

Age: Sex:

Date of admission: Date of discharge:

Address:

Presenting complaints

Present History

History suggestive of;

Hypertension :

Duration :

Ischaemic heart disease :

Diabetes Mellitus :

Past History

History of treatment of hypertension

Drug :

Dosage :

Duration :

Family History DM / HTN / IHD / Obesity

No. of siblings

History of Hypertension in siblings

History of diabetes mellitus in siblings

Personal history

Smoking :

Alcohol intake :

Tobacco chewing :

Any other :

Exercise :

Treatment History

Patients on antihypertensive treatment: Yes / No

If Yes,

Drug :

Dosage :

Duration :

General Physical Examination

Built and nourishment:

Pulse :

Peripheral pulses :

Blood pressure :

Supine : 1. 2. 3.

Standing : 1. 2. 3.

Mean of 2nd & 3rd reading:

Anthropometry :

Height (Cms) : Weight(Kg) :

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

Waist hip ratio :

BMI :

Acanthosis Nigricans :

Systemic examination

CVS

Chamber hypertrophy :

S3, S4 :

Murmurs :

RS :

Per abdomen :

CNS :

Investigations

Haemogram

Hb% :

TC :

DC : N - L - M - E - B -

ESR :

Blood Sugar

FBS : PPBS :

Fasting insulin level :

Renal profile :

Blood urea :

Sr. creatinine :

Sr. sodium :

Sr. potassium :

Fasting Lipid profile

Cholesterol :

LDL :

HDL :

TG :

Fundoscopy

Hypertensive retinopathy: Grade:

ECG :

Abdominal USG (If required):

Renal artery Doppler (if required):

MASTER CHART

				History															General Physical Examination										Systemic Exam			Investigations													
				Hypertension	Treatment					Others	Family				Personal Habits					Blood pressure (mm Hg)			Anthropometry						Cardiovascular system			Blood sugar (mg/dL)				Renal profile				Fasting lipid profile					
Serial Number	In patient number	Gender	Age (Years)	Duration (Years)	Class of Drug	Duration (Years)	Cerebrovascular accidents	Peripheral vascular disease	Ischaemic heart disease	Other drugs	Diabetes mellitus	Hypertension	ischaemic heart disease	Obesity	Smoking	Tobacco	Alcohol	Exercise	Pulse (/Min)	Systolic blood pressure	Diastolic blood pressure	Blood pressure control	Height (Cms)	Weight (Kgs)	BMI (Kg/m^2)	Waist Girth (Cms)	Hip Girth (Cms)	Waist hip ratio	Chamber hypertrophy	S3, S4	Murmurs	FBS (mg/dL)	PPBS (mg/dL)	Fasting insulin level (μU/L)	HOMA IR	Blood Urea (mg/dL)	Sr. Creatinine (mg/dL)	Sr. Sodium (meq/L)	Sr. Potassium (meq/L)	Total Cholesterol (mg/dL)	LDL cholesterol (mg/dL)	HDL cholesterol (mg/dL)	Triglycerides (mg/dL)	Fundoscopy	Electrocardiography
1	308412	M	50	4	ARB	4	A	A	A	-	A	A	A	A	A	A	A	A	78	130	80	P	173	74	24.725	86.0	94.0	0.91	A	A	A	90	110	9.9	2.20	24.00	0.80	136	3.9	185	129	30	129	1	N
2	335903	M	50	7	ACE,CCB,BB	7	A	A	A	-	A	P	A	A	p	A	P	A	68	132	86	P	150	64	28.444	96.0	101.0	0.95	A	A	A	76	102	10.2	1.91	30.00	0.90	138	4.0	160	110	38	104	2	AB
3	332712	M	50	4	ACE,BB	4	A	A	A	-	P	P	A	A	A	A	A	A	70	130	80	P	168	68	24.093	84.0	98.0	0.86	A	A	A	94	124	26.0	5.58	32.00	0.80	138	4.2	164	94	38	116	1	AB
4	310841	F	55	8	CCB,BB	8	A	A	P	-	P	P	A	P	A	A	A	P	70	138	82	P	160	58	22.656	67.0	98.0	0.68	A	A	A	84	108	22.4	4.31	22.00	0.80	140	4.3	178	68	34	132	2	AB
5	332674	F	52	2	ACE,BB	2	A	A	A	-	P	A	A	A	A	A	A	A	70	130	70	P	164	68	25.283	85.0	84.0	1.01	A	A	A	96	120	29.0	6.73	30.00	0.90	136	4.1	168	94	38	104	-	N
6	330804	M	59	4	ARB,TZ	4	A	A	A	ASP,CLP,ATR	P	P	A	P	P	A	P	P	80	128	86	P	168	78	27.636	85.0	94.0	0.90	A	A	A	95	122	45.0	10.50	24.00	0.90	140	3.8	214	88	37	168	-	N
7	324194	M	37	3	ARB	3	A	A	A	-	A	P	A	A	P	A	A	A	78	128	84	P	173	74	24.725	86.0	94.0	0.91	A	A	A	88	112	9.9	2.20	16.00	0.80	140	3.8	185	129	30	129	-	N
8	320339	F	59	6	ARB,CCB	6	A	A	A	-	A	P	A	A	A	A	A	A	78	130	90	A	156	62	25.477	89.0	104.0	0.86	A	A	A	88	114	8.9	2.02	30.00	1.10	138	4.0	127	80	38	89	1	AB
9	318472	M	42	2	BB	2	A	A	A	-	A	A	A	A	A	A	A	A	74	124	82	P	174	80	26.424	92.0	78.0	1.18	A	A	A	91	118	6.7	1.52	18.00	0.40	138	4.2	131	76	44	104	-	N
10	318075	M	58	5	ARB,BB,CCB	5	P	A	P	ASP,CLP,ATR	P	P	A	P	A	A	A	P	68	136	90	A	178	84	26.512	90.0	86.0	1.05	A	A	A	98	124	30.2	7.15	18.00	0.80	138	3.8	216	100	45	106	1	AB
11	316700	M	50	8	ACE.BB	8	A	A	P	ASP,CLP,ATR,IMN	P	A	A	A	P	A	A	P	76	136	92	A	180	88	27.16	84.0	82.0	1.02	A	A	A	98	124	22.4	4.31	36.00	1.10	136	3.9	196	102	34	134	1	AB
12	315132	M	45	3	ARB,TZ	3	A	A	A	-	A	P	A	A	A	A	A	A	80	132	84	P	168	68	24.093	86.0	92.0	0.93	A	A	A	91	110	7.6	1.70	26.00	0.80	138	3.9	138	74	34	97	-	N
13	315160	F	52	4	ARB	4	A	A	A	-	P	P	A	A	A	A	A	A	70	128	82	P	168	70	24.802	76.0	84.0	0.90	A	A	A	94	110	29.0	6.73	22.00	0.40	134	4.2	184	90	34	98	-	N
14	310839	M	60	6	ARB,TZ	6	P	A	P	ASP,CLP,ATR,IMN	P	P	A	P	P	A	A	A	74	134	84	P	176	86	27.763	91.0	86.5	1.05	A	A	A	90	124	34.2	8.28	34.00	0.90	140	4.0	168	88	42	180	2	AB
15	309189	M	60	6	ACE,CCB	6	A	A	A	-	P	P	A	A	P	A	A	A	80	140	84	A	162	62	23.624	78.0	89.0	0.88	A	A	A	92	124	40.8	10.07	30.00	0.50	139	4.1	219	148	52	93	1	N
16	336429	M	46	3	ARB	3	A	A	A	-	A	P	A	A	P	A	A	A	64	130	80	P	168	66	23.384	90.0	98.0	0.92	A	A	A	88	124	8.4	1.82	21.00	0.60	140	4.2	174	116	48	81	-	N
17	362837	M	50	8	BB,CCB,	8	A	A	A	-	P	A	A	A	P	A	A	A	78	142	90	A	169	84	29.411	91.0	94.0	0.97	A	A	A	91	124	22.5	5.06	26.00	1.10	140	3.8	184	96	42	60	2	AB
18	341013	M	60	4	CCB	4	A	A	A	-	A	A	A	A	A	A	A	A	74	150	70	A	170	66	22.837	88.0	96.0	0.92	A	A	A	94	120	6.1	1.42	24.00	1.10	140	4.4	180	108	46	90	2	AB
19	363819	M	57	13	ND	-	P	A	A	-	P	P	A	P	P	P	P	P	80	154	92	-	174	91	30.057	90.5	92.0	0.98	A	A	A	88	124	28.4	6.17	28.00	1.10	142	4.1	294	168	38	116	2	AB
20	364072	F	48	3	ACE	3	A	A	A	-	A	P	P	P	A	A	A	A	68	124	80	P	166	72	26.129	96.0	112.0	0.86	A	A	A	72	118	6.8	1.21	18.00	0.60	136	4.4	160	78	46	68	-	N
21	364193	M	55	5	ARB,BB	5	A	A	P	ASP,CLP,ATR,IMN	P	P	A	P	P	A	A	P	78	148	90	A	171	80	27.359	89.0	94.0	0.95	A	A	A	78	130	22.0	4.24	34.00	1.00	140	5.0	188	108	40	102	2	AB
22	364541	M	44	3	BB,CCB,	3	A	A	A	-	A	A	A	A	P	A	P	A	70	132	88	P	174	69	22.79	98.0	89.0	1.10	A	A	A	82	122	6.4	1.30	20.60	1.30	138	4.5	178	106	38	96	-	N
23	364611	M	48	5	ARB,BB,TZ	5	A	A	P	ASP,CLP,ATR,IMN	A	P	P	P	P	A	A	A	74	130	84	P	174	78	25.763	90.0	98.0	0.92	A	A	A	86	118	10.2	2.17	22.00	0.90	139	4.4	188	106	42	101	1	N
24	365529	M	58	5	ARB,BB,TZ	5	A	A	P	ASP,CLP,RSV,IMN	A	A	A	A	P	P	A	A	78	146	79	A	170	76	26.298	98.0	86.5	1.13	A	A	A	84	108	14.8	3.07	22.00	0.90	140	3.8	194	110	34	106	2	AB
25	375190	M	62	8	BB,CCB	8	A	A	P	ASP,IMN	P	A	A	A	A	A	A	A	70	140	80	A	173	94	31.408	104.0	93.0	1.12	A	A	A	79	122	27.0	5.27	32.00	0.90	140	3.9	198	160	39.5	98	2	AB
26	378842	F	55	5	BB,CCB	5	A	A	P	ASP,CLP,RSV,IMN	P	P	A	P	A	A	A	A	72	132	90	A	164	78	29.001	92.0	102.0	0.90	A	A	A	84	124	26.0	5.39	22.00	1.00	138	3.9	216	114	38	112	2	AB
27	374333	F	57	6	ARB,BB	6	P	A	A	ASP,CLP,ATR,IMN	A	P	A	A	A	A	A	A	82	135	83	P	160	70	27.344	92.0	106.0	0.87	A	A	A	80	118	16.4	3.24	14.00	1.00	136	3.9	204	106	42	98	2	AB
28	374303	M	52	5	BB	5	A	A	A	-	A	P	A	A	P	A	A	A	70	133	84	P	169	70	24.509	83.0	93.0	0.89	A	A	A	82	120	16.0	3.24	18.00	0.90	138	4.1	294	166	42	198	2	N
29	374374	M	60	6	ACE,BB,CCB	6	A	A	P	ASP,CLP,RSV,IMN	A	A	A	A	A	A	A	A	80	129	80	P	178	89	28.09	91.5	103.0	0.89	A	A	A	78	124	17.1	3.29	21.00	1.10	140	4.2	192	112	40	92	2	AB
30	374684	M	58	8	ARB,BB,CCB,TZ	8	A	A	P	ASP,CLP,ATR,IMN	A	P	A	A	P	A	A	A	74	138	82	P	170	76	26.298	89.0	96.0	0.93	A	A	A	84	104	13.8	2.86	24.00	1.00	142	4.1	164	106	42	96	2	N
34	374774	F	47	5	BB	5	A	A	A	-	A	P	A	A	A	A	A	A	68	132	80	P	168	71	25.156	87.5	102.0	0.86	A	A	A	74	116	16.0	2.92	20.90	0.80	138	4.1	162	94	39.4	84	-	N
32	345598	M	35	1	ARB	1	A	A	A	-	A	A	A	A	P	A	A	A	80	124	72	P	175	72	23.51	86.0	99.0	0.87	A	A	A	89	110	4.4	0.97	18.00	0.60	138	3.8	148	94	44.4	96	-	N
33	373788	M	41		ARB	1	A	A	A	-	A	A	A	A	A	A	A	A	84	170	100	P	185	80	23.375	86.0	96.0	0.90	A	A	A	80	106	5.1	0.96	20.00	0.80	139	4.1	158	104	38	106	1	AB
34	376074	M	45		ND	-	A	A	A	-	P	P	A	P	P	A	A	A	80	154	94	-	174	78	25.763	91.5	91.0	1.01	A	A	A	88	114	33.6	7.30	31.00	0.90	142	4.0	264	169	34	124	-	N
35	376584	M	50	4	ACE,BB	4	A	A	A	ASP,CLP,ATR,IMN	A	P	A	A	A	A	A	A	68	131	80	P	170	79	27.336	91.5	104.0	0.88	A	A	A	78	120	14.0	2.70	24.00	0.90	136	4.6	168	94	46	80	2	N
36	376464	M	45	4	ARB	4	A	A	A	-	P	P	A	A	A	A	A	A	76	132	90	A	172	89	30.084	91.0	101.0	0.90	A	A	A	78	128	21.0	4.04	20.00	0.80	142	3.4	212	116	39	108	-	N
37	374744	F	47	5	BB	5	A	A	P	-	A	P	A	A	A	A	A	A	68	132	80	P	168	71	25.156	87.5	102.0	0.86	A	A	A	74	116	16.0	2.92	20.90	0.80	138	4.1	162	94	39.4	84	-	N

MASTER CHART

				History															General Physical Examination										Systemic Exam			Investigations													
				Hypertension						Others	Family				Personal					Blood pressure (mm Hg)			Anthropometry						Cardiovascular system			Blood sugar (mg/dL)				Renal profile				Fasting lipid profile					
					Treatment										Habits																														
Serial Number	In patient number	Gender	Age (Years)	Duration (Years)	Class of Drug	Duration (Years)	Cerebrovascular accidents	Peripheral vascular disease	Ischaemic heart disease	Other drugs	Diabetes mellitus	Hypertension	ischaemic heart disease	Obesity	Smoking	Tobacco	Alcohol	Exercise	Pulse (/Min)	Systolic blood pressure	Diastolic blood pressure	Blood pressure control	Height (Cms)	Weight (Kgs)	BMI (Kg/m^2)	Waist Girth (Cms)	Hip Girth (Cms)	Waist hip ratio	Chamber hypertrophy	S3, S4	Murmurs	FBS (mg/dL)	PPBS (mg/dL)	Fasting insulin level (μU/L)	HOMA IR	Blood Urea (mg/dL)	Sr. Creatinine (mg/dL)	Sr. Sodium (meq/L)	Sr. Potassium (meq/L)	Total Cholesterol (mg/dL)	LDL cholesterol (mg/dL)	HDL cholesterol (mg/dL)	Triglycerides (mg/dL)	Fundoscopy	Electrocardiography
38	375162	M	48	5	ARB,BB	5	A	A	P	ASP,CLP,ATR,IMN	P	P	A	P	P	A	P	P	74	136	84	P	179	74	23.095	85.0	98.0	0.87	A	A	A	82	124	22.8	4.62	16.00	0.90	139	4.1	268	124	34	116	-	N
39	375110	F	40	2	ARB	2	A	A	A	-	A	A	A	A	A	A	A	A	78	120	80	P	164	58	21.565	77.0	92.0	0.84	A	A	A	72	118	5.8	1.03	14.00	0.50	140	3.9	168	88	56	74	-	N
40	376358	M	40	3	ARB,TZ	3	A	A	A	-	A	P	A	A	A	A	A	A	74	122	82	P	182	83	25.057	89.0	101.0	0.88	A	A	A	80	116	8.2	1.62	10.60	0.80	139	4.1	148	88	48	74	-	N
41	375687	M	59	10	ARB,BB,TZ	10	A	A	A	ASP,CLP,ATR,IMN	A	A	A	A	A	A	A	A	76	130	90	A	175	84	27.429	91.5	102.5	0.89	A	A	A	85	129	15.8	3.32	20.00	0.90	139	4.1	240	128	38	106	1	AB
42	376084	M	56	6	ARB,BB,TZ	6	A	A	P	ASP,CLP,ATR,IMN	A	A	A	A	P	A	A	P	74	135	84	P	170	84	29.066	95.0	94.0	1.01	A	A	A	80	126	16.4	3.24	24.00	1.00	139	3.8	208	116	40	107	2	N
43	375688	M	58	9	ARB,BB	9	A	A	P	ASP,CLP,ATR,IMN	A	A	A	A	A	P	A	P	76	129	90	A	173	80	26.73	89.0	96.0	0.93	A	A	A	78	124	17.5	3.37	20.00	0.80	141	4.2	188	94	46	100	2	AB
44	375190	M	55	5	ARB,BB	5	A	A	A	-	P	A	A	A	A	A	A	A	82	140	90	A	176	74	23.889	81.5	92.0	0.89	A	A	A	78	126	21.8	4.20	24.00	0.90	141	4.1	240	104	39	116	1	N
45	375361	M	61	10	BB,CCB	10	A	P	P	ASP,CLP,RSV,IMN	P	P	A	A	P	P	A	P	78	151	80	A	175	92	30.041	103.0	101.5	1.01	A	A	A	74	124	30.5	5.57	21.00	1.00	142	4.4	208	116	34	114	2	AB
46	375292	M	56	8	BB,CCB	8	A	A	A	ATR	P	P	A	A	P	A	A	P	78	145	89	A	170	79	27.336	92.5	941.0	0.10	A	A	A	78	128	23.5	4.53	18.00	1.00	144	3.8	238	106	38	117	1	AB
47	376185	M	52	4	ARB	4	A	A	A	-	P	P	A	P	A	A	A	A	70	140	81	A	175	83	27.102	91.5	98.5	0.93	A	A	A	78	124	16.2	3.12	24.00	0.90	136	4.1	158	104	46	81	2	AB
48	376391	F	60	10	ARB,BB,TZ	10	P	A	P	ASP,CLP,ATR,IMN	A	A	A	A	A	A	A	A	76	138	90	A	164	78	29.001	93.0	90.5	1.03	A	A	A	84	136	28.8	5.97	24.00	1.10	143	4.1	264	144	39	124	3	AB
49	376519	M	56	6	ARB,BB,TZ	6	A	A	P	ASP,CLP,ATR,IMN	A	P	P	A	P	A	A	P	78	134	80	P	168	79	27.99	89.0	98.5	0.90	A	A	A	84	122	15.0	3.11	20.00	0.90	142	3.9	210	88	46	104	1	AB
50	376997	M	45	4	CCB	4	A	A	A	-	A	P	A	P	A	A	A	P	88	130	80	P	180	74	22.84	87.0	100.0	0.87	A	A	A	78	110	6.8	1.31	18.00	0.50	138	3.9	146	94	46	106	-	N
51	376522	M	51	5	ARB,BB,TZ	5	A	A	A	-	A	P	A	A	A	A	A	P	68	141	82	A	174	92	30.387	101.5	99.0	1.03	A	A	A	82	118	30.5	6.18	24.00	0.90	141	4.2	204	108	40	116	1	N
52	377059	F	55	5	CCB	5	A	A	A	-	A	A	A	A	A	P	A	P	70	146	80	A	165	60	22.039	81.0	103.0	0.79	A	A	A	80	112	12.0	2.37	16.00	0.90	140	4.1	156	89	39.8	71	1	N
53	377158	M	64	12	ARB,CCB,TZ	12	A	A	A	ATR	A	A	A	A	A	A	A	A	86	141	90	A	175	96	31.347	112.0	105.0	1.07	A	A	A	92	120	36.0	8.18	21.00	0.90	142	3.8	194	148	36	124	2	AB
54	377204	M	60	8	ARB	8	A	A	P	-	A	A	A	A	P	A	A	P	88	152	90	A	170	88	30.45	101.0	99.5	1.02	A	A	A	86	120	24.0	5.10	20.00	1.00	136	4.0	312	198	34	138	2	AB
55	345598	M	36	2	ARB	2	A	A	A	-	A	P	A	A	A	A	A	P	72	126	82	P	178	74	23.356	98.0	112.0	0.88	A	A	A	78	116	4.4	0.85	16.00	0.50	138	3.9	141	78	48	68	-	N
56	364213	M	35	2	ACE,BB	2	A	A	P	ASP,CLP,RSV	P	A	A	A	P	A	A	P	76	135	80	P	169	69	24.159	89.0	96.0	0.93	A	A	A	74	112	5.9	1.08	30.00	0.80	138	4.1	158	98	46	84	-	N
57	374698	M	40	3	ARB,BB,TZ	3	A	A	A	-	A	P	A	A	A	P	A	A	74	116	80	P	175	92	30.041	101.5	99.0	1.03	A	A	A	84	128	28.4	5.89	21.00	0.90	140	3.9	206	108	34	118	-	N
58	376583	M	57	9	ARB,BB,TZ	9	A	A	A	ASP,CLP,ATR	P	A	A	A	A	A	A	P	64	137	82	P	174	90	29.727	100.5	99.0	1.02	A	A	A	80	112	16.5	3.26	24.00	1.10	138	3.8	298	164	36	118	2	AB
59	374651	F	58	9	ACE,BB	9	A	A	P	ASP,CLP,IMN	P	P	A	A	A	A	A	A	76	121	82	P	164	76	28.257	89.0	98.0	0.91	A	A	A	76	124	22.1	4.15	22.00	0.90	139	3.9	194	96	40	104	2	AB
60	337594	M	57	9	ARB,BB	9	P	A	P	ASP,CLP,ATR,IMN	P	P	A	P	P	A	A	P	76	148	86	A	170	69	23.875	83.5	85.0	0.98	A	A	A	90	119	34.0	7.56	21.00	0.90	139	4.2	196	121	34.5	116	2	AB
61	386190	M	51	4	ARB,TZ	4	A	A	A	-	A	A	A	A	A	A	A	P	80	135	82	P	172	78	26.366	92.0	104.0	0.88	A	A	A	80	130	16.0	3.16	18.00	1.00	141	3.9	204	98	40	91	1	AB
62	382146	M	54	4	ARB,CCB,TZ	4	A	A	A	-	A	A	A	P	P	A	A	A	82	150	74	A	174	68	22.46	80.0	92.0	0.87	A	A	A	85	121	14.0	2.94	16.00	0.50	139	3.8	174	108	44	90	1	N
63	384168	M	43	4	ARB	4	A	A	A	-	A	P	A	A	A	A	A	P	84	124	80	P	179	74	23.095	85.0	99.0	0.86	A	A	A	82	106	9.6	1.94	20.00	0.90	139	3.6	168	90	48	74	-	N
64	395143	F	42	3	ARB	3	A	A	A	-	A	P	P	A	A	A	A	P	68	132	70	P	164	82	30.488	89.00	93	0.957	A	A	A	78	102	6.4	1.23	19.00	0.6	141	4.5	179	130	40	106	-	N
65	396264	F	38	2	CCB	2	A	A	A	-	A	P	P	P	A	A	A	A	88	124	82	P	166	86	31.209	94.00	96	0.979	A	A	A	74	108	7.8	1.43	26.00	0.7	139	3.8	188	120	46	102	-	N

KEY TO MASTER CHART

A	-	Absent
AB	-	Abnormal
ACE	-	Angiotensin convertase enzyme inhibitor
ARB	-	Angiotensin receptor blocker
ASP	-	Aspirin
ATR	-	Atorvastatin
BB	-	Beta blockers
CCB	-	Calcium channel blockers
CLP	-	Clopidogrel
Cms	-	Centimeters
d	-	Deci
Exam	-	Examination
F	-	Female
HDL	-	High density lipoprotein
IMN	-	Isosorboid mononitrate
Kgs	-	Kilograms
L	-	Litre
LDL	-	Low density lipoprotein
M	-	Male
m	-	Meter
mg	-	Milligram
Min	-	Minutes

mm Hg	-	Millimeter of mercury
N	-	Normal
ND	-	Newly detected
P	-	Present
Sr	-	Serum
TZ	-	Thiazide