"STUDY OF VASCULAR COMPLICATIONS IN OBESE, NON DIABETIC, HYPERTENSIVE INDIVIDUALS AND ITS CORRELATION WITH FASTING INSULIN LEVELS"

By

Dr. KIRAN.B.J

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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Under the guidance of

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Dr. KIRAN B J

ABSTRACT

STUDY OF VASCULAR COMPLICATIONS IN OBESE, NON DIABETIC, HYPERTENSIVE INDIVIDUALS AND ITS CORRELATION WITH FASTING INSULIN LEVELS

Background:

Various factors implicated in the genesis of hypertension include genetics, age, sex, an abnormal lipoprotein profile, smoking, glucose intolerance and obesity etc..

High prevalence of hyperlipidemia among hypertensive population and its relation with coronary artery disease, is well documented. Insulin plays an important role in lipid metabolism. Insulin resistance has a key role to play in the pathogenesis of many disorders including obesity, diabetes mellitus and hypertension. Excessive Insulin levels result in insulin resistance, increased sympathetic activity, high VLDL and endothelial cell proliferation predisposing to atherogenesis.

As active intervention in individuals with increased fasting insulin levels may prevent the overt development of diabetes and its complications in future, which made us to take up this study to find the vascular complications in obese, non diabetic, hypertensive individuals and its correlation with fasting insulin levels.

Objectives:

1. Study of vascular complications in obese, non diabetic, hypertensive individuals and its correlation with fasting insulin levels.
2. Micro vascular complications of hypertension for example retinopathy and nephropathy.
3. Macro vascular complications of hypertension such as stroke and myocardial infarction.

Materials and Methods:

30 Patients who are diagnosed to have hypertension stage-1 according to Joint National Committee (JNC) -7 with obesity (BMI≥25kg/m^2) and non diabetic were selected for our study.

Age and sex matched 30 clinically healthy individuals who are non obese, non hypertensive and non diabetic were included as controls.

Blood is drawn for serum insulin levels after overnight fasting of 8 to 10 hours, insulin assays will be done by chemiluminescence method after considering its limitations.

BMI will be calculated by Quetelet index = weight in kg / height in m^2

Results:

Maximum numbers of subjects were seen in age group 51- 60 yrs. Mean age of Distribution is 55.08 in cases and 57.93 in controls. In that 16 (53.3%) were male and 14 (46.7%) were female.

Out of 30 patients, hyperinsulinemia were seen in 8 patients (27.6%) with a strongly significant P value of <0.001, remaining 17 (56.7%) had normal insulin levels, and 5 (16.7%) were hypoinsulinemic. The mean insulin level in cases and controls was 21.64 and 11.38 respectively.

In the cases, 22 (73.3%) had vascular complications with a strongly significant p value < 0.001. Out of 30 cases, 19 (63.3%) had microvascular and 13 (43.3%) had macrovascular complications. Both microvascular and macrovascular complications were significantly more in cases when compared to controls with P value of < 0.001 (strongly significant).

Total cholesterol and triglycerides was significantly high in cases with increased fasting insulin levels. (P value <0.001which was strongly significant).

CONCLUSION:

The results of the present study suggests that obese, non diabetic, hypertensive individuals will have hyperinsulinemia. Incidence of both microvascular and macrovascular complications was more in obese, hypertensive individuals even though they were non diabetic. And hyperinsulinemia in these obese, hypertensive, non diabetic individuals was associated with significant dyslipidemia. And incidence of vascular complications will be more in obese, hypertensives as the duration of hypertension and age increases.

Key Words: Fasting insulin levels, microvascular and macrovascular complications, dyslipidemia.

LIST OF ABBREVATIONS:

• AGT	Angiotensinogen
• AT1 R	Angiotensin type 1 receptor
• ATP-III	Adult treatment panel
• ACE inhibitor	Angiotensin converting enzyme inhibitor
• ARB	Angiotensin receptor blockers.
• BMI	Body mass index.
• CCB	Calcium channel blockers.
• CAD	Coronary artery disease
• CVA	Cerebrovascular accident
• CVD	Cardiovascular disease
• CRP	C-reactive protein
• CMS	Cardiometabolic syndrome
• DM	Diabetes mellitus
• ECG	Electrocardiogram
• ECHO	Echocardiography
• eNOS	endothelial Nitric oxide synthase
• ET-1	Endothelin-1
• FFA	Free fatty acid
• GH	Growth hormone
• GLUT-4	Glucose transporter-4
• HDL	High-density lipoprotein
• HOMA-IR	Homeostasis model assessment-Insulin resistance

- HTN — Hypertension
- IAPP — Islet amyloid polypeptide
- IFG — Impaired fasting glucose
- IGF-I — Insulin-like growth factor I
- IGT — Impaired glucose tolerance
- IRS — Insulin receptor substrate
- IR — Insulin resistance
- JNC VII — Joint National Committee VII
- LDL — Low-density lipoprotein
- LPL — Lipoprotien lipase
- LV — Left ventricle
- MAPK — Mitogen activated protein kinase
- NCEP — National cholesterol education program
- NO — Nitric oxide
- PAD — Peripheral arterial disease
- RAAS — Renin angiotensin aldosterone system
- ROS — Reactive oxygen species
- SNS — Symphathetic nervous system
- TNF- α — Tumor necrosis factor alpha
- TG — Triglyceride
- VEGF — Vascular endothelial growth factor
- VLDL — Very low-density lipoprotein
- WHO — World Health Organization

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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. It is estimated that the global prevalence of hypertension will increase to 1.56 billion by 2015.[1]

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

High prevalence of hyperlipidemia among hypertensive population and its relation with coronary artery disease is well documented.[4] Insulin plays an important role in lipid metabolism.[5] Insulin resistance has a key role to play in the pathogenesis of many disorders including obesity, diabetes mellitus and hypertension.[6,7] Insulin resistance leads to elevated insulin levels, increased sympathetic activity, high VLDL and endothelial cell proliferation predisposing to atherogenesis.

Asians and Asian Indians have relative increase in visceral fat versus subcutaneous fat with concominant increase in waist circumference which explains the

greater prevalence of insulin resistance (IR) syndrome in these populations and confers a high risk of diabetes and CVD in them.[3]

Prospective studies have shown fasting insulin levels to be a surrogate marker of insulin resistance and a predictor of coronary artery disease (CAD).[8] IR has also been shown to be associated with most of the cardiovascular risk factors viz., dyslipidemia, hypertension, obesity, abdominal obesity and glucose intolerance, and a combination of these abnormalities could lead to CAD.[9]

There has been increasing number of evidences connecting insulin resistance to future cardiovascular events in hypertensives suggesting that insulin resistance is the basis for the so called metabolic syndrome irrespective of diabetes status.[10]

As active intervention in individuals with increased fasting insulin levels may prevent the overt development of diabetes and its complications in future, which made us to take up this study to find the vascular complications in obese, non diabetic, hypertensive individuals and its correlation with fasting insulin levels.

OBJECTIVES

1. Study of vascular complications in obese non diabetic, hypertensive individuals and its correlation with fasting insulin levels.
2. Micro vascular complications of hypertentension such as retinopathy and nephropathy.
3. Macrovascular complications of hypertension such as stroke and myocardial infarction.

REVIEW OF LITERATURE:

Epidemiological evidence support a link between hyperinsulinemia and blood pressure and it has been shown that blood pressure is independently related to plasma insulin levels.[11] Patients with untreated hypertension have been shown to be resistant to insulin stimulated glucose uptake. They are also hyperinsulinemic and hypertriglyceridemic when compared with control groups with normal blood pressure.[7]

There is increasing incidence and prevalence of hypertension along with obesity and other constituents of the **"**deadly quartet**"** 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.

Prevalance of diabetes mellitus was significantly more frequent among obese patients with coronary heart disease as compared to non obese patients with coronary heart disease.[12]Body weight and prevalence of obesity and its complications are rising so rapidly in many countries of the world,that WHO has recognized that there is 'Global epidemic of obesity'.[13-14]

Insulin resistance describes an impaired biological response to insulin.[15-18] In the early states of insulin resistance there is a compensatory increase in insulin concentrations. Although hyperinsulinemia may compensate for resistance to some biological actions of insulin, it may result in over expression of actions in tissues that retain normal or minimally impaired sensitivity to insulin. In addition, high

concentrations of insulin can act through receptors for insulin-like growth factor I (IGF-I).[19-22]

A study done by Paulo Brambilla et al to evaluate the interrelationships of adiponectin, blood pressure, obesity, body fat distribution, puberty and insulin resistance in a selected group of children, concluded that, in childhood, the levels of adiponectin are inversely related to hypertension. This relationship is partly independent of obesity, fat distribution and insulin resistance. Low values of adiponectin in both obese and normal weight children are associated with a higher probability of hypertension.[23]

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.[24]

Grandi, A. M., et al concluded that genetic predisposition to hypertension is associated with a reduced insulin sensitivity and affects the response of the myocardium to increased insulin levels, inducing a greater impairment of diastolic function. Insulin sensitivity and genetic predisposition to hypertension seem to have no influence on LV mass.[25]

A study done by Sujatha R et al showed that, among the hypertensive patients, obese hypertensive patients exhibited significantly increased insulin resistance and altered adipocytokine profile compared to the non-obese control subjects. Among the adipocytokine, serum leptin levels were significantly increased in hypertensive patients and were also associated with IR and hypertension. Thus, findings suggest that leptin may be playing an important role in the development of hypertension in study population.[26]

Framingham study showed that the degree of obesity is proportional to the rate of development of cardiovascular diseases and there is dramatic increase of sudden cardiac death, among those patients who are 20% overweight as compared to those with normal weight.[27]

Obesity is associated with an increase in circulating inflammatory markers, including C-reactive protein and cytokines. The increase in inflammatory markers is associated with insulin resistance[28.29] and is an important predictor of atherosclerotic events.

The association between visceral obesity and metabolic syndrome is well known, but the pathophysiological mechanisms that explain this link are not completely understood. Metabolic syndrome is a complex of clinical features, the most important of which is an increased visceral fat depot.

Obesity results in a proinflammatory state starting in the metabolic cells (adipocyte, hepatocyte, or myocyte) and also recruiting immune cells with the consequent release of inflammatory cytokines (TNF-α, IL-6, adiponectin, etc.).

A study done by Faloia Emanuela et al to know the inflammation as a link between obesity and metabolic syndrome hypothesized that the obesity-induced inflammatory process may lead to complications such as hypertension, atherosclerosis, dyslipidemia, insulin resistance, and diabetes mellitus which characterize metabolic syndrome.[30]

A study done by T. Ambrosova et al found that, waist circumference and BMI in insulin resistant patients were statistically higher than in hypertensives without IR . Plasma insulin levels in patients with IR was threefold as compared with patients without. And also on comparing TNF-a levels revealed, significant elevation of TNF-a in insulin resistance group as compared with normal insulin metabolism.[31]

Abnormalities of glucose, insulin, and lipoprotein metabolism are common in-patients with hypertension. These changes can also be discerned in normotensive first-degree relatives of hypertensive patients. These metabolic abnormalities may play a part in both the pathogenesis and the complications of hypertension in many patients.

Insulin resistance involves glucose but not lipid or potassium metabolism, is located in peripheral tissues but not the liver, is limited to non oxidative pathways of intracellular glucose disposal, and is directly correlated with the severity of hypertension.[11]

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.[32]

Data from a meta analytical review examining fasting insulin levels in euglycemic individuals demonstrates a significant correlation with systolic and diastolic blood pressure.[33]

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.[34]

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.[35]

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.[36]

Huang GZ et al done a study to see the effects of telmisartan on insulin resistance and visceral fat distribution in Chinese hypertensive patients with obesity. At the end of the study, they found that, the systolic and diastolic blood pressure decreased significantly in both study groups. However, the levels of HOMA-IR, serum adiponectin, and TNF-alpha only improved in the telmisartan group. Similarly, the visceral fat area was reduced in the telmisartan group, while the subcutaneous fat area did not change in either group.[37]

HYPERTENSIVE VASCULAR DISEASE:

Hypertension is an independent predisposing factor for heart failure, coronary artery disease, stroke, renal disease, and peripheral arterial disease (PAD).

HEART:

Heart disease is the most common cause of death in hypertensive patients. Hypertensive heart disease is the result of structural and functional adaptations leading to left ventricular hypertrophy, CHF, abnormalities of blood flow due to atherosclerotic coronary artery disease and microvascular disease, and cardiac arrhythmias.

Both genetic and hemodynamic factors contribute to left ventricular hypertrophy. Clinically, left ventricular hypertrophy can be diagnosed by electrocardiography, although echocardiography provides a more sensitive measure of left ventricular wall thickness.

Individuals with left ventricular hypertrophy are at increased risk for CHD, stroke, CHF, and sudden death. Aggressive control of hypertension can regress or reverse left ventricular hypertrophy and reduce the risk of cardiovascular disease. It is not clear whether different classes of antihypertensive agents have an added impact on reducing left ventricular mass, independent of their blood pressure–lowering effect.

CHF may be related to systolic dysfunction, diastolic dysfunction, or a combination of the two. Abnormalities of diastolic function that range from asymptomatic heart disease to overt heart failure are common in hypertensive patients. Patients with diastolic heart failure have a preserved ejection fraction, which is a measure of systolic function. Approximately one-third of patients with CHF have normal systolic function but abnormal diastolic function. Diastolic dysfunction is an early consequence of hypertension-related heart disease and is exacerbated by left ventricular hypertrophy and ischemia. Cardiac catheterization provides the most accurate assessment of diastolic function. Alternatively, diastolic function can be evaluated by several noninvasive methods, including echocardiography and radionuclide angiography.

BRAIN:

Stroke is the second most frequent cause of death in the world; it accounts for 5 million deaths each year, with an additional 15 million persons having nonfatal strokes. Elevated blood pressure is the strongest risk factor for stroke. Approximately 85% of strokes are due to infarction, and the remainder are due to either intracerebral or subarachnoid hemorrhage. The incidence of stroke rises progressively with increasing blood pressure levels, particularly systolic blood pressure in individuals >65 years.

Treatment of hypertension convincingly decreases the incidence of both ischemic and hemorrhagic strokes.

Hypertension also is associated with impaired cognition in an aging population, and longitudinal studies support an association between midlife hypertension and late-life cognitive decline. Hypertension-related cognitive impairment and dementia may be a consequence of a single infarct due to occlusion of a "strategic" larger vessel or multiple lacunar infarcts due to occlusive small vessel disease resulting in subcortical white matter ischemia. Several clinical trials suggest that antihypertensive therapy has a beneficial effect on cognitive function, although this remains an active area of investigation.

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

KIDNEY:

The kidney is both a target and a cause of hypertension. Primary renal disease is the most common etiology of secondary hypertension. Mechanisms of kidney-related hypertension include a diminished capacity to excrete sodium, excessive renin secretion in relation to volume status, and sympathetic nervous system overactivity. Conversely,

hypertension is a risk factor for renal injury and end-stage renal disease. The increased risk associated with high blood pressure is graded, continuous, and present throughout the distribution of blood pressure above optimal pressure. Renal risk appears to be more closely related to systolic than to diastolic blood pressure, and black men are at greater risk than white men for developing ESRD at every level of blood pressure. Proteinuria is a reliable marker of the severity of chronic kidney disease and is a predictor of its progression. Patients with high urine protein excretion (>3 g/24 h) have a more rapid rate of progression than do those with lower protein excretion rates.

Atherosclerotic, hypertension-related vascular lesions in the kidney primarily affect preglomerular arterioles, resulting in ischemic changes in the glomeruli and postglomerular structures. Glomerular injury also may be a consequence of direct damage to the glomerular capillaries due to glomerular hyperperfusion. Studies of hypertension-related renal damage, primarily in experimental animals, suggest that loss of autoregulation of renal blood flow at the afferent arteriole results in transmission of elevated pressures to an unprotected glomerulus with ensuing hyperfiltration, hypertrophy, and eventual focal segmental glomerular sclerosis. With progressive renal injury there is a loss of autoregulation of renal blood flow and glomerular filtration rate, resulting in a lower blood pressure threshold for renal damage and a steeper slope between blood pressure and renal damage. The result may be a vicious cycle of renal damage and nephron loss leading to more severe hypertension, glomerular hyperfiltration, and further renal damage. Glomerular pathology progresses to glomerulosclerosis, and eventually the renal tubules may also become ischemic and gradually atrophic. The renal lesion associated with malignant hypertension consists of fibrinoid necrosis of the afferent arterioles, sometimes extending into the glomerulus, and may result in focal necrosis of the glomerular tuft.

Clinically, macroalbuminuria (a random urine albumin/creatinine ratio >300 mg/g) or microalbuminuria (a random urine albumin/creatinine ratio 30–300 mg/g) are early markers of renal injury. These are also risk factors for renal disease progression and cardiovascular disease.

PERIPHERAL ARTERIES:

In addition to contributing to the pathogenesis of hypertension, blood vessels may be a target organ for atherosclerotic disease secondary to long-standing elevated blood pressure. Hypertensive patients with arterial disease of the lower extremities are at increased risk for future cardiovascular disease. Although patients with stenotic lesions of the lower extremities may be asymptomatic, intermittent claudication is the classic symptom of PAD. This is characterized by aching pain in the calves or buttocks while walking that is relieved by rest. The ankle-brachial index is a useful approach for evaluating PAD and is defined as the ratio of noninvasively assessed ankle to brachial (arm) systolic blood pressure. An ankle-brachial index <0.90 is considered diagnostic of PAD and is associated with >50% stenosis in at least one major lower limb vessel. Several studies suggest that an ankle-brachial index <0.80 is associated with elevated blood pressure, particularly systolic blood pressure.

INSULINS:

HISTORY OF INSULINS:[38]

- Langerhans identified the islets in 1860's but did not understand their function.
- Von Mering and Minkowski, who demonstrated in 1889 that pancreatectomy, produced diabetes.
- Banting and Best proved the association of islets and diabetes in 1921
- Insulin was the first protein proved to have hormonal action; the first protein crystallized (Abel 1926).
- It was the first protein sequenced (Sanger ET al, 1955), the first protein synthesized by chemical techniques. du et al ; katsoyarris; 1964).
- It is the first protein synthesized as a large precursor molecule, and the first protein prepared for commercial use by recombinant DNA technology.

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.

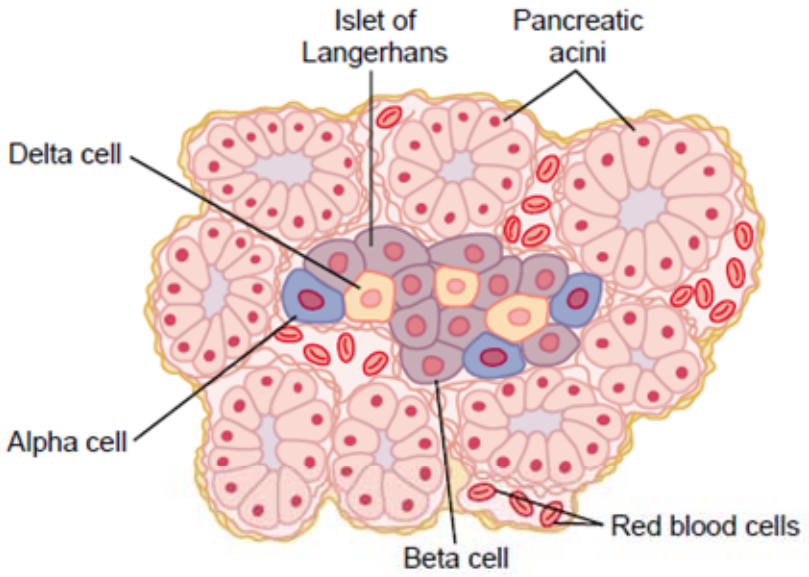


Figure-1: Physiologic anatomy of an islet of Langerhans in the pancreas.

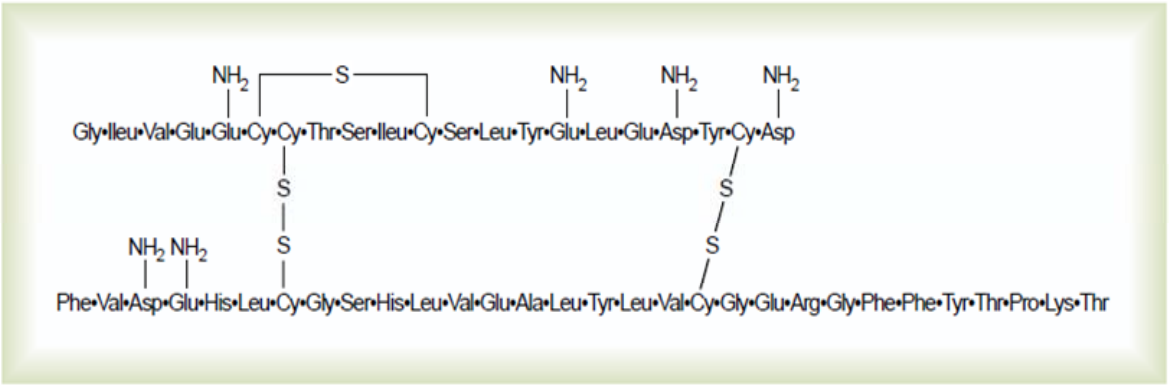


Figure-2: Human insulin molecule

BIOSYNTHESIS:

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.[3.39]

SECRETION:

Glucose is the key regulator of insulin secretion by the pancreatic beta cell, although amino acids, ketones, various nutrients, gastrointestinal peptides, and neurotransmitters also influence insulin secretion. Glucose levels more than 3.9 mmol/L (70 mg/dL) stimulate insulin synthesis, primarily by enhancing protein translation and processing. Glucose stimulation of insulin secretion begins with its transport into the beta cell by the glucose transporter 2 (GLUT2). Glucose phosphorylation by glucokinase is the rate-limiting step that controls glucose-regulated insulin secretion. Further metabolism of glucose-6-phosphate via glycolysis generates adenosine triphosphate (ATP), which inhibits the activity of an ATP-sensitive potassium channel. This channel consists of two separate proteins: one is the binding site for certain oral hypoglycemics (for example, sulfonylureas, meglitinides); the other is an inwardly rectifying potassium channel protein (Kir). Inhibition of this potassium channel induces

beta cell membrane depolarization, which opens voltage-dependent calcium channels (leading to an influx of calcium), and stimulates insulin secretion. Insulin secretory profiles reveal a pulsatile pattern of hormone release, with small secretory bursts occurring about every 10 minutes, superimposed upon greater amplitude oscillations of about 80 to 150 minutes. Incretins are released from neuroendocrine cells of the gastrointestinal tract following food ingestion and amplify glucose-stimulated insulin secretion and suppress glucagon secretion. Glucagon-like peptide 1 (GLP-1), the most potent incretin, is released from L cells in the small intestine and stimulates insulin secretion only when the blood glucose is above the fasting level.[3,40]

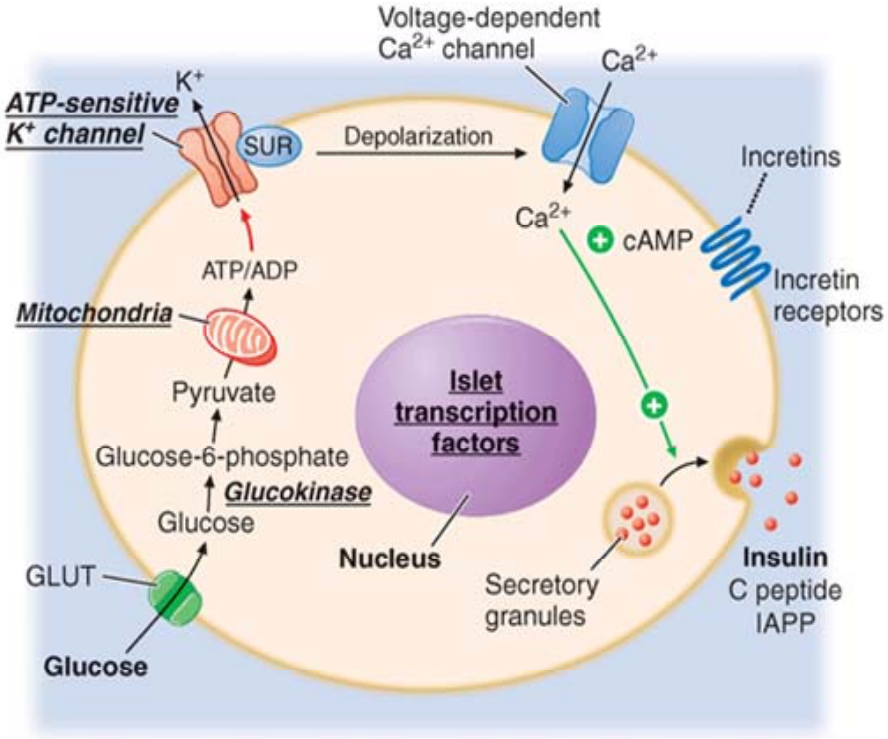


Figure-3: Secretion of insulin

SIGNALING

Once insulin is secreted into the portal venous system, approximately 50% is removed and degraded by the liver. Unextracted insulin enters the systemic circulation where it binds to receptors in target sites. 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 (IRS). IRS 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 (PI-3-kinase) pathway stimulates translocation of a facilitative glucose transporter (e.g., GLUT4) to the cell surface, an event that is crucial for glucose uptake by skeletal muscle and fat. Activation of other insulin receptor signaling pathways induces glycogen synthesis, protein synthesis, lipogenesis, and regulation of various genes in insulin-responsive cells.

Glucose homeostasis reflects a balance between hepatic glucose production and peripheral glucose uptake and utilization. Insulin is the most important regulator of this metabolic equilibrium, but neural input, metabolic signals, and other hormones (e.g., glucagon) result in integrated control of glucose supply and utilization . In the fasting state, low insulin levels increase glucose production by promoting hepatic gluconeogenesis and glycogenolysis and reduce glucose uptake in insulin-sensitive tissues (skeletal muscle and fat), thereby promoting mobilization of stored precursors such as amino acids and free fatty acids (lipolysis). Glucagon, secreted by pancreatic alpha cells when blood glucose or insulin levels are low, stimulates glycogenolysis and gluconeogenesis by the liver and renal medulla. Postprandially, the glucose load elicits a rise in insulin and fall in glucagon, leading to a reversal of these processes. Insulin, an

anabolic hormone, promotes the storage of carbohydrate and fat and protein synthesis. The major portion of postprandial glucose is utilized by skeletal muscle, an effect of insulin-stimulated glucose uptake. Other tissues, most notably the brain, utilize glucose in an insulin-independent fashion.[3]

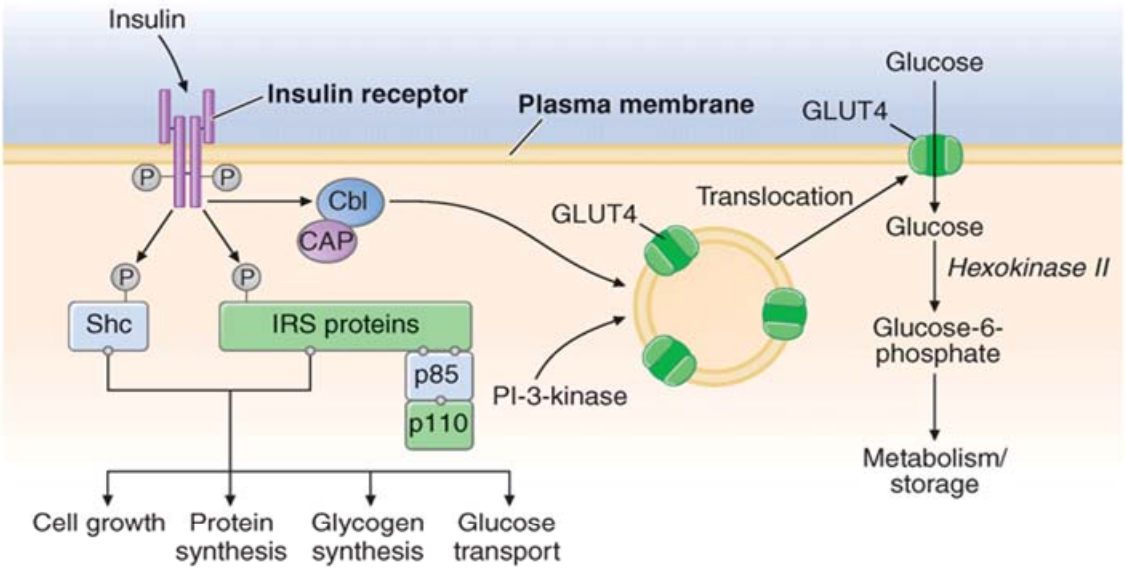


Figure-4: Insulin signaling

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:

1. Increased glucose entry
2. Increased fatty acid synthesis
3. Increased glycerol phosphate synthesis
4. Increased triglyceride deposition
5. Activation of lipoprotein lipase
6. Inhibition of hormone sensitive lipase
7. Increased potassium uptake

MUSCLE:

1. Increased glucose entry
2. Increased glycogen synthesis
3. Increased aminoacid uptake
4. Increased protein synthesis
5. Decreased protein catabolism
6. Decreased released of gluconeogenic aminoacids
7. Increased ketone uptake
8. Increased potassium uptake

LIVER:

1. Decreased ketogenesis
2. Increased protein synthesis
3. Increased lipid synthesis
4. Decreased glucose output due to decreased gluconeogenesis, increased glycogen synthesis, and increased glycolysis

CAUSES OF INSULIN RESISTANCE:[40,41]

ABNORMAL B -CELL SECRETORY PRODUCT:

1. Abnormal insulin molecule
2. Incomplete conversion of proinsulin to insulin

CIRCULATING INSULIN ANTAGONISTS:

1. Elevated levels of counter regulatory hormones for example, growth hormone (GH), cortisol, glucagons or catecholamines.
2. Anti-insulin antibodies
3. Anti-insulin receptor antibodies

TARGET TISSUE DEFECTS:

1. Insulin receptor defects
2. Post -receptor defects

ABNORMAL B -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 counter regulatory hormones are not an important contributory factor to peripheral insulin resistance.

NON HORMONAL ANTAGONISTS:

Free fatty acids (FFA)[42,43] : 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):[44,45]

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:

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.

INSULIN RESISTANCE IN OBESITY:[46]

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 intraabdominal 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 cardiometabolic syndrome (CMS). In this context, patients with HTN have higher fasting and postprandial insulin levels, independent of body mass index or body fat distribution.[51]

Several pathophysiologic factors are involved in the relationship between HTN and the other components of the CMS, including inappropriate activation of the renin 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.

RENAL SODIUM HANDLING:[47]

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:[47]

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 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.

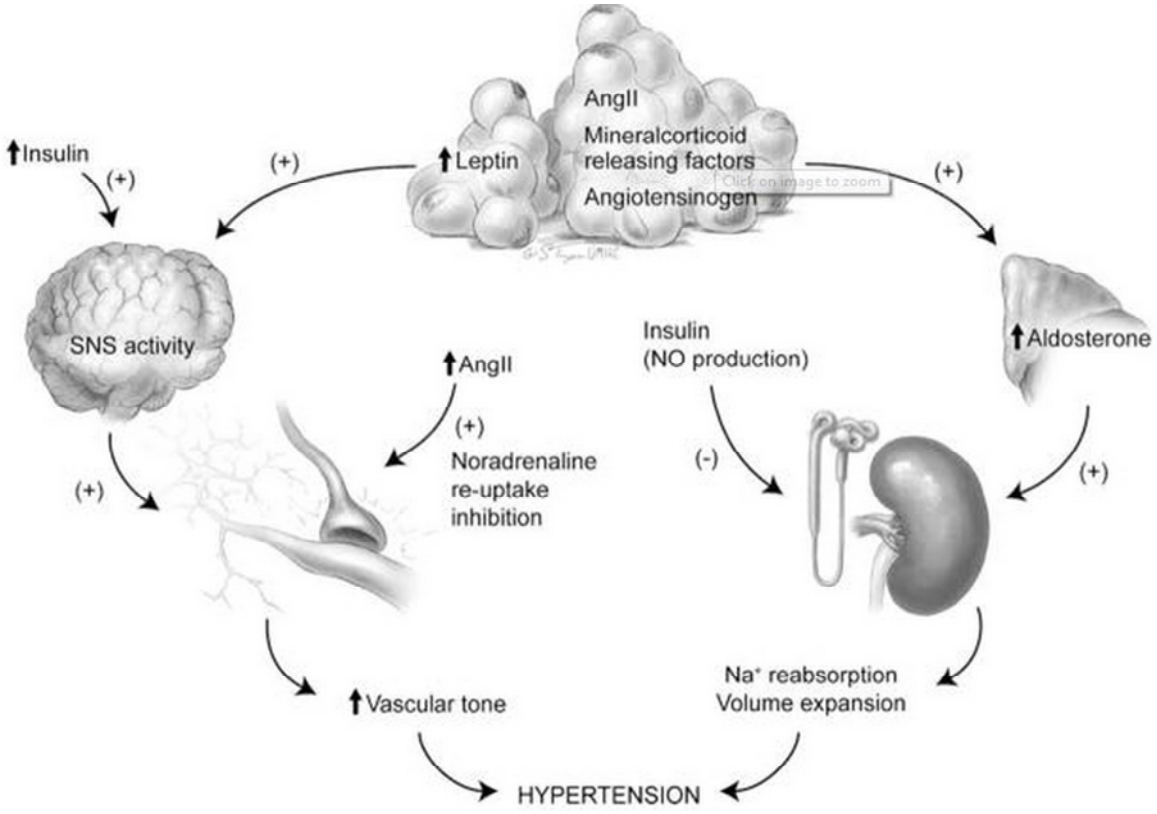


Figure 5: Co-ordinated influence of obesity, IR, activation of RAAS and SNS in pathophysiology of HTN[47]

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM[47]:

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:[47]

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 Ser phosphorylation of IRS-1 results in decreased engagement of IRS-1 with PI3K and impaired downstream insulin metabolic signaling.

IMPAIRED ENDOTHELIUM-DEPENDENT VASORELAXATION:[48]

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:[48]

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,intimal lipid accumulation, fibrosis, and hypercoagulability, leading to atherosclerosis and thrombosis.

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):[49]

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:[40,50]

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:[51]

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:[52-54]

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:[55,56]

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

CORONARY ARTERY DISEASE:[52,53,57,58]

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 1988 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 hand. However as it is the IR that leads to hyperinsuinemia, the basic defect is the IR that predisposes the individual for CAD.

OTHERS:[52,59]

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

METABOLIC SYNDROME:

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: ATP III 2001:

Three or more of the following:

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

IDF CRITERIA FOR CENTRAL ADIPOSITY:

Waist circumference:

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

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.

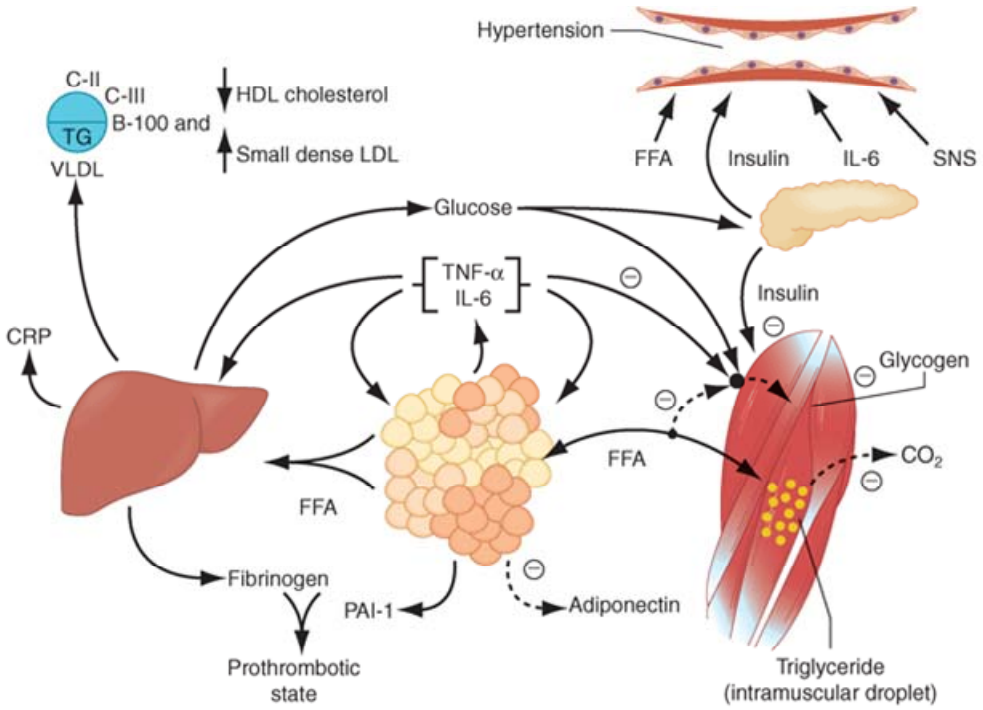


Figure-6: Pathogenesis of metabolic syndrome[3]

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.

A study done by Justo Sierra et al on US non diabetic subjects concluded that apoB/apoAI ratio is significantly associated with insulin resistance in non-diabetic subjects, independently of the traditional risk factors, metabolic syndrome components, and inflammatory risk factors. Important clinical risk information provided by apoB/apoAI ratio should be recognized and implemented in future clinical guidelines.[60]

ANTIHYPERTENSIVES AND THEIR EFFECT ON INSULIN RESISTANCE:[61]

It also is becoming increasingly clear that antihypertensive medications have disparate effects on insulin sensitivity in patients with essential hypertension. Both diuretics and beta 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 □-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 beta -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.

STATINS IN INSULIN RESISTANCE:[62]

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 signaling 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.

MATERIAL AND METHODS:

SOURCE OF DATA:

- 30 Patients who are diagnosed to have hypertension stage-1 according to Joint National Committee (JNC)-7 with obesity (BMI>25kg/m^2) and non diabetic will be selected for our study.
- Age and sex matched 30 clinically healthy individuals who are non obese, non-hypertensive and non-diabetic will be included as controls.

METHOD OF COLLECTION OF DATA:

- Blood is drawn for serum insulin levels after overnight fasting of 8 to 10 hours, insulin assays will be done by chemiluminescence method after considering its limitations.
- BMI will be calculated by Quetelet index - weight in kg/height in m^2

INCLUSION CRITERIA:

- Patients aged more than 18 years who are diagnosed to have hypertension stage-1 according to JNC- 7. Obesity index with BMI>25kg/m^2 will be included for our study.

EXCLUSION CRITERIA:

Patients with history of or clinically proven

- Diabetes mellitus and impaired glucose tolerance
- Alcoholics
- Smokers

- Familial hypercholesterolemia will be excluded from our study as these factors are known to alter the insulin levels.

A detailed enquiry of name, age, sex and address of the patients were taken. History of present illness and past history of any illness and treatment history of hypertension was noted. Family history of hypertension and diabetes was noted.

Each patient is subjected to detailed general physical examination and vital signs are noted. Each patient is subjected to detailed systemic examination; including respiratory system, cardiovascular system, GIT system and central nervous system.

The following investigations were done:

1. ECG
2. Insulin assays in serum sample.
3. Urine routine
4. Fundoscopy
5. CT brain, 2D echo and carotid doppler was done depending on the need.

STUDY DESIGN :

It is a case control study.

STUDY PERIOD:

From January- 2012 to February 2013.

STATISTICAL METHODS :

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max)

and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance.

Analysis of variance (ANOVA) has been used to find the significance of study parameters between three or more groups of patients , Student t test (two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups Inter group analysis) on metric parameters. Chi-square/ Fisher Exact test has been used to find the significance of study parameters on categorical scale between two or more groups.

Significant figures

+ Suggestive significance (P value: $0.05<P<0.10$)

* Moderately significant (P value:$0.01<P \leq 0.05$)

** Strongly significant (P value : $P \leq 0.01$)

Statistical software:

The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1 ,Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS AND OBSERVATIONS:

Table 1: Age distribution

Age in years	Cases		Control	
	No	%	No	%
31-40	1	3.3	2	6.7
41-50	7	23.3	6	20.0
51-60	11	36.7	10	33.3
61-70	7	23.3	7	23.3
71-80	2	6.7	4	13.3
81-90	2	6.7	1	3.3
Total	30	100.0	30	100.0
Mean ± SD	59.07±12.55		57.93±12.52	

P=0.727

Graph 1:

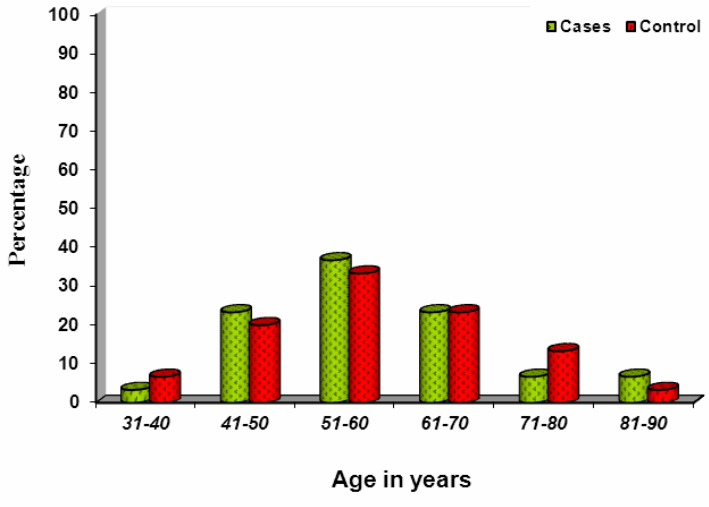


Table 2: Gender distribution

Gender	Cases		Control	
	No	%	No	%
Male	16	53.3	17	56.7
Female	14	46.7	13	43.3
Total	30	100.0	30	100.0

P=0.795

Graph 2:

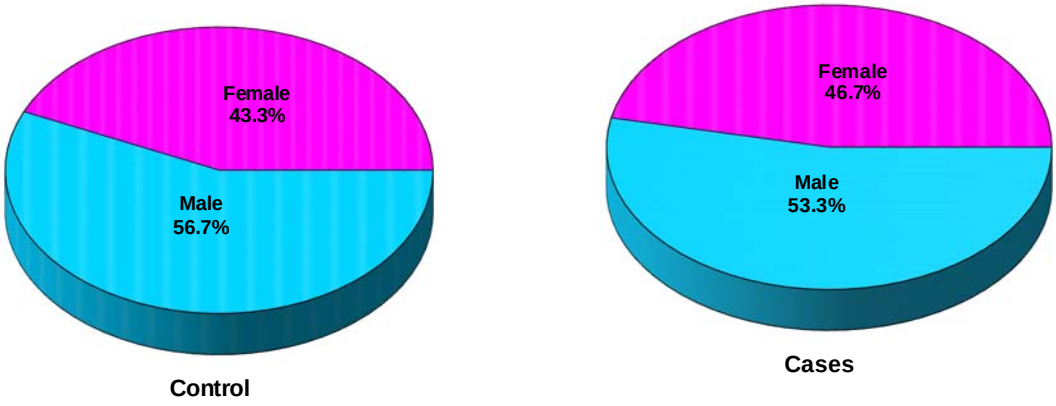


Table 3: Comparison of hypertension in duration (years) with fasting insulin levels in cases.

Hypertension duration	Cases		Serum Insulin
	No	%	
0-5	8	26.7	38.13±13.92
6-10	16	53.3	16.39±7.81
>10	6	20.0	13.67±4.06
Total	30	100.0	21.64±5.77

F=1.555; P=0.229

Graph 3:

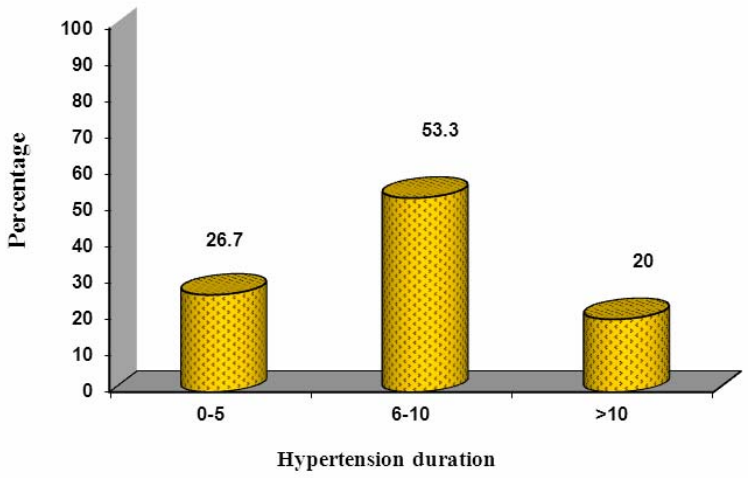


Table 4: Comparison of fasting insulin levels in cases and controls.

Serum Insulin	Cases		Control	
	No	%	No	%
<2.6	5	16.7	0	0.0
2.6-24.9	17	56.7	30	100.0
>24.9	8	26.7	0	0.0
Total	30	100.0	30	100.0
Mean ± SD	21.64±5.77		11.38±0.99	

Elevated Insulin levels in patients with 26.7% is significantly more in cases with P<0.001**

Graph 4:

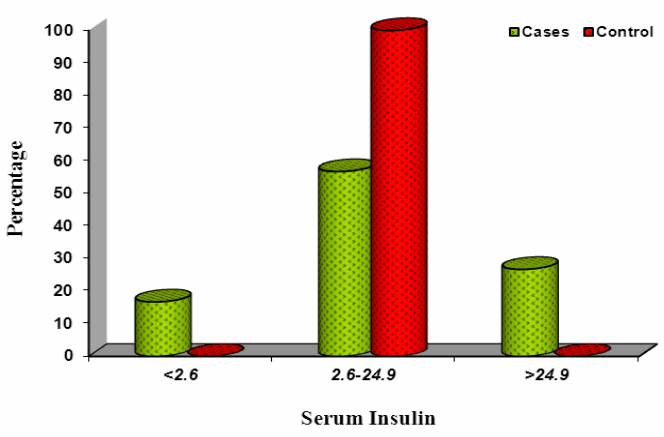


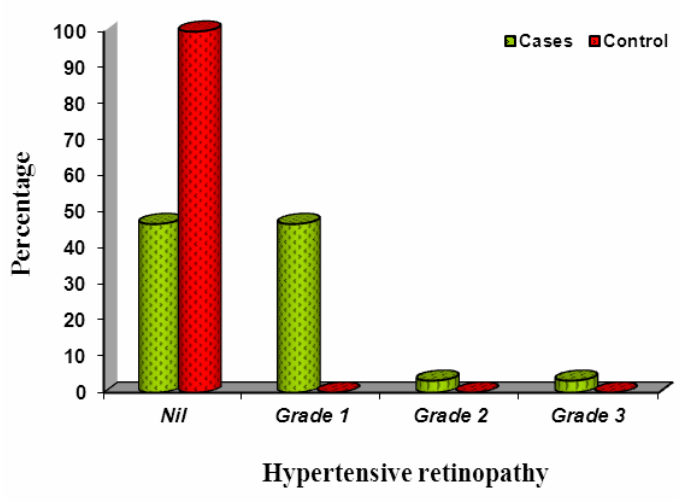
Table 5: Pearson correlation between fasting insulin levels and BMI in cases and controls

Pair	Cases		Control	
	r value	p value	r value	p value
BMI vs Serum Insulin	0.049	0.797	-0.040	0.034

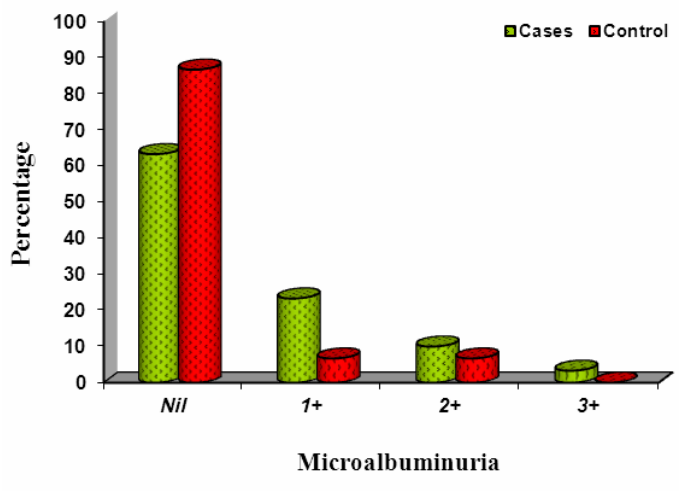
Table 6: Microvascular and macrovascular complications in cases and controls

Complications studied	Cases (n=30)		Control (n=30)	
	No	**%**	**No**	**%**
Hypertensive retinopathy				
• Nil	14	46.7	30	100.0
• Grade 1	14	46.7	0	0.0
• Grade 2	1	3.3	0	0.0
• Grade 3	1	3.3	0	0.0
Microalbuminuria				
• Nil	19	63.3	26	86.7
• 1+	7	23.3	2	6.7
• 2+	3	10.0	2	6.7
• 3+	1	3.3	0	0.0
Unstable angina				
• Negative	27	90.0	30	100.0
• Positive	3	10.0	0	0.0
NSTEMI				
• Negative	26	86.7	30	100.0
• Positive	4	13.3	0	0.0
CVA				
• Negative	25	83.3	30	100.0
• Positive	5	16.7	0	0.0
CKD				
• Negative	29	96.7	30	100.0
• Positive	1	3.3	0	0.0

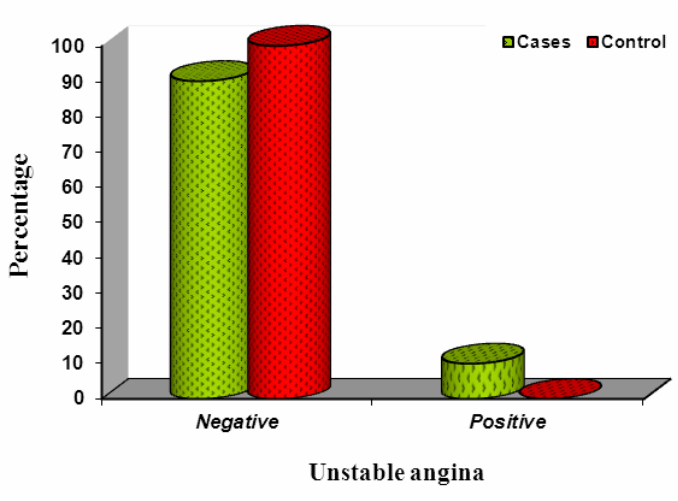
Graph 5:



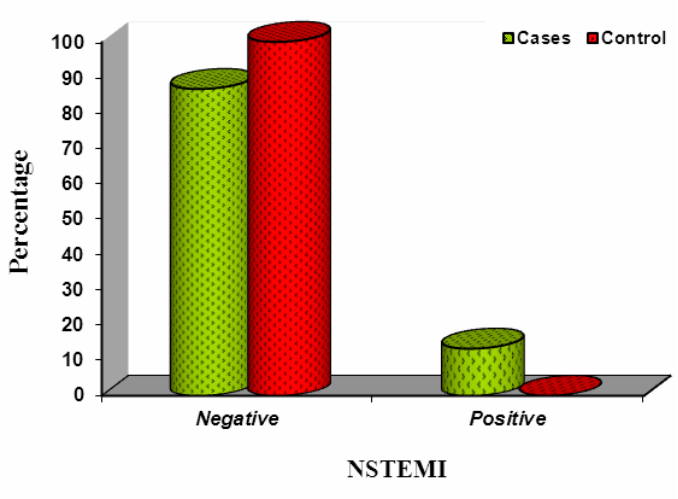
Graph 6:



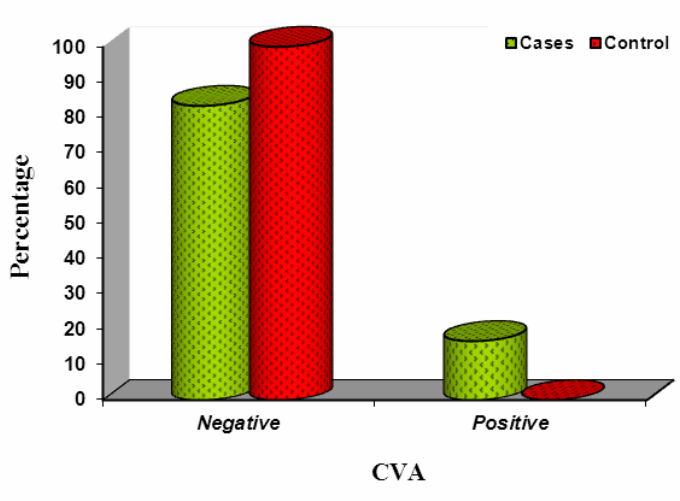
Graph 7:



Graph 8:



Graph 9:



Graph 10:

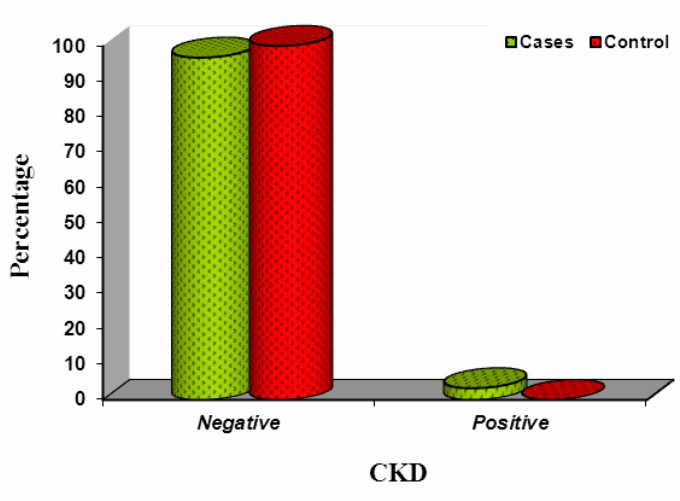


Table 7: Comparison of vascular complications in cases and controls

Vascular complications	Cases (n=30)		Control (n=30)	
	No	%	No	%
No	8	26.7	26	86.7
Yes	22	73.3	4	13.3

Vascular complications are significantly more in cases with P<0.001**

Graph 11:

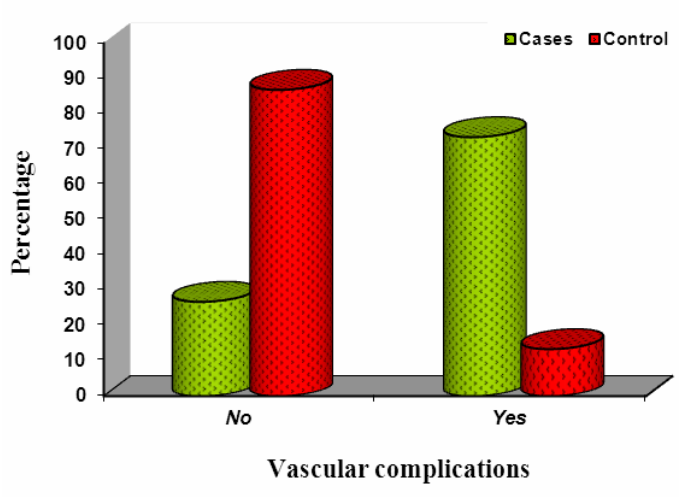


Table 8: Comparison of microvascular and macrovascular complications in cases and controls

Complications studied	Cases (n=30)		Control (n=30)		P value
	No	%	No	%	
Micro-vascular complications	19	63.3	4	13.3	<0.001**
Macro-vascular complications	13	43.3	0	0.0	<0.001**

Vascular complications that is both microvascular and macrovascular are significantly more in cases with P<0.001**

Graph 12:

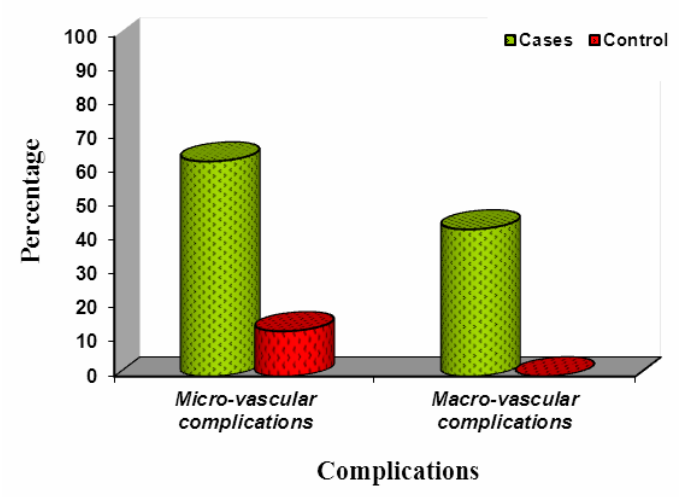
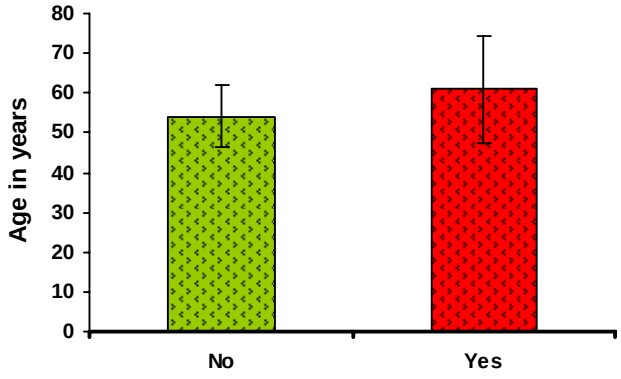


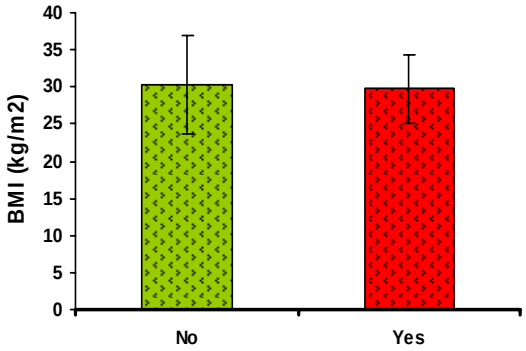
Table 9: Comparison of Clinical variables according to absence and presence of Vascular complications in cases

Variables	Vascular complications		P value
	No	Yes	
Age in years	54.13±7.83	60.86±13.58	0.199
BMI (kg/m2)	30.22±6.63	29.77±4.66	0.835
Duration of HTN	6.4±3.73	8±4.4	0.367

Graph 13:



Graph 14:



Graph 15:

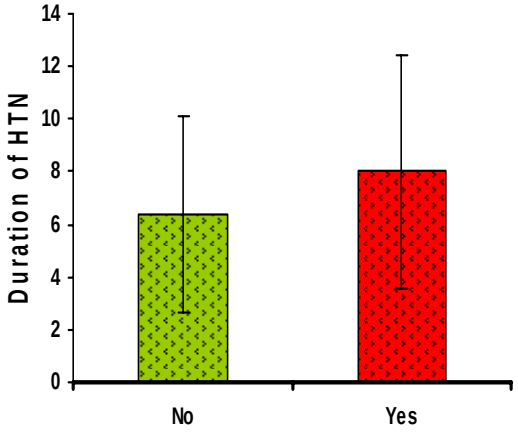


Table 10: Correlation of fasting insulin levels to absence and presence of vascular complications in cases

Serum Insulin levels	Vascular complications	
	No	Yes
<2.6	1(12.5%)	4(18.2%)
2.6-24.9	4(50.0%)	13(59.1%)
>24.9	3(37.5%)	5(22.7%)
Total	8(100.0%)	22(100.0%)

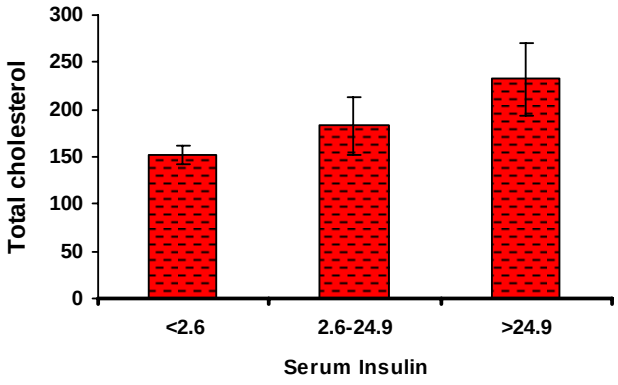
P=0.852

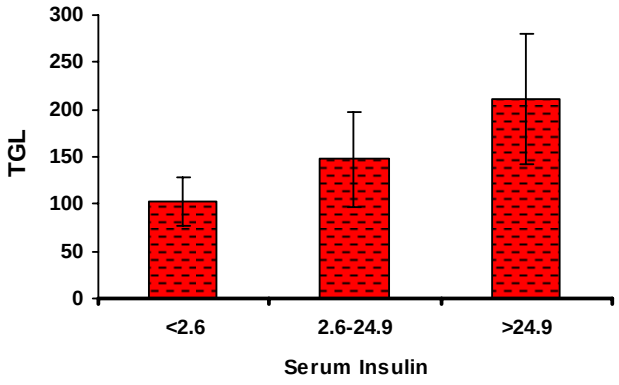
Table 11: Comparison of Lipid profile with fasting insulin levels in cases

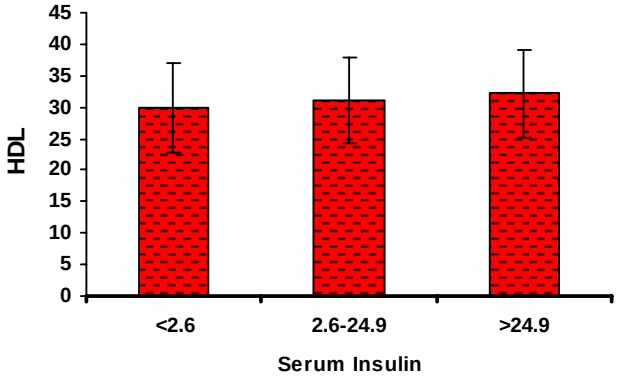
Lipid parameters	Fasting insulin levels			P value
	<2.6	2.6-24.9	>24.9	
Total cholesterol	151.6±10.01	183.18±30.79	232.25±38.74	<0.001**
TGL	103±25.14	147.06±49.54	211.63±69.22	0.003**
HDL	29.8±7.09	31.12±6.87	32.25±6.96	0.824
LDL	115.6±28.4	129.88±21.32	123±25.22	0.468

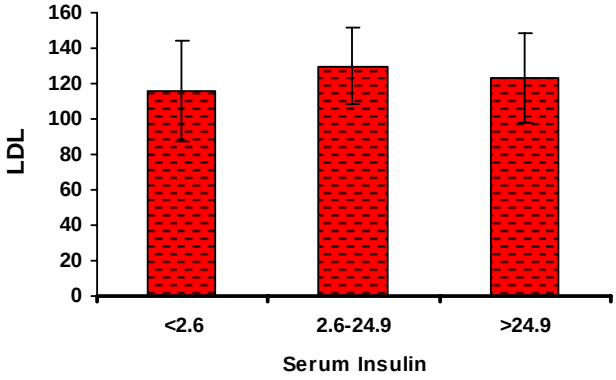
Total cholesterol and triglycerides was significantly high in cases with high fasting insulin levels.

GRAPH 16:


Total cholesterol
300
250
200
150
100
50
0
<2.6
2.6-24.9
>24.9
Serum Insulin


TGL
300
250
200
150
100
50
0
<2.6
2.6-24.9
>24.9
Serum Insulin


HDL
45
40
35
30
25
20
15
10
5
0
<2.6
2.6-24.9
>24.9
Serum Insulin


LDL
160
140
120
100
80
60
40
20
0
<2.6
2.6-24.9
>24.9
Serum Insulin

\

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 at least 50% of hypertensive patients are insulin resistant, and insulin resistance is the fundamental abnormality in the pathogenesis of the cardiometabolic syndrome (CMS).[47]

Hypertension and its complications such as ischemic heart disease, left ventricular hypertrophy, retinopathy, cerebrovasuclar diseases are associated with hyperinsulinemia.

Several studies have concluded such an association that hyperinsulinemia could be an etiological factor for the pathogenesis of hypertension and its complications.

The present study is conducted to know the role of fasting insulin in obese, hypertensive and non diabetic individuals and also its correlation with vascular complications.

In the present study, 30 obese, hypertensive, non diabetic individulas were selected as cases. These cases were selected based on inclusion criteria and exclusion criteria.

Similarly, normal age and sex matched healthy controls were selected and they were also 30 in number.

They underwent detailed clinical history, examination, investigation and insulin estimation by chemiluminescence method. The results were compared and analyzed.

In the present study, out of 30 cases and 30 controls mean age distribution was 59.07 in cases and 57.93 in controls, which is little higher to age distribution seen in other studies like Bhatnagar MK et al[63], Reaven GM et al[64] and Ferrannani et al[65] which was 53.23, 54.2 and 49.54 respectively.

And in both cases and controls, maximum clustering was seen in age distribution of 51-60 years, that is out of 30 cases, there were 11 (36.7%) cases and out of 30 controls there were 10 (33.3%) controls in the age group of 51-60 years.

Out of 30 patients, 16 were male (53.3%) and 14 were female (46.7%) in our study, which was of almost equal ratio. This when compared to studies done by Bhatnagar et al[63] and Reaven GM et al[64], male ratio was more in their studies.

And when vascular complications was studied, there was a slight increase in incidence of vascular complications in cases as the age increased with mean age of 60.86 which when compared to cases without vascular complications mean age was 54.13 (but P value was 0.199 which was not significant).

In the present study, out of 30 cases, there were 8 (26.7%), 16 (53.3%) and 6 (20%) cases with hypertension duration of 0-5 years, 6-10 years and >10 years respectively. And when hypertension duration was compared with the fasting insulin levels, there was increase in the fasting insulin levels with mean value of 38.13 in the hypertension group of 0-5 years, which was not statistically significant.

But there was a slight increase in incidence of vascular complications among cases with more duration of hypertension, that is mean age was 8 years in cases with vascular complications and 6.4 years in cases without vascular complications. (but P value was 0.367 which was not significant).

This findings when compared with other two studies[63,64], 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 not in accordance with the above mentioned studies.

In the present study, out of 30 patients, hyperinsulinemia were seen in 8 patients (27.6%), remaining 17 (56.7%) had normal insulin levels, and 5 (16.7%) were hypoinsulinemic. The mean insulin level in cases and controls was 21.64 and 11.38 respectively. The normal insulin level was 2.6- 24.9 mIU/ml.

Our study showed increased insulin levels in 8 (27.6%) cases when compared to controls which was statistically strongly significant with a p value of <0.001. And mean insulin levels was also high in cases when compared to controls.

Study conducted by M.K Bhatnagar[63], New Delhi, showed 74% of the hypertensive cases showed hyperinsulinemia. The mean insulin level was 45.99.

Reaven et al[64] study showed 41% were hyperinsulinemic, mean insulin was 66.83.

Ferrani et al[11] study, "Insulin resistance and hypertension", > 80% hypertensive cases were found to have hyperinsulinemia.

Harper R.Ennas C.N[65] concluded that > 60% hypertensives 436 studied population was hyperinsulinemic.

In the present study, BMI and vascular complications of cases was correlated with fasting insulin levels, but both P value was not significant.

In the present study, out of 30 cases, 22 (73.3%) had vascular complications and out of 30 controls, 4 (13.3%) had vascular complications.

Vascular complications are significantly high in cases with p value < 0.001 (strongly significant).

And out of 30 cases, 19 (63.3%) had microvascular complications in the form of hypertensive retinopathy and microalbuminuria. 13 (43.3%) cases had macrovascular complications in the form of unstable angina, NSTEMI, CVA and CKD.

Both microvascular and macrovascular complications are significantly more in cases when compared to controls with P value of < 0.001 (strongly significant).

Out of 30 cases, 16 (53.3%) had hypertensive retinopathy. Among them 14 had grade-1 and remaining 2 cases had grade-2 and grade-3 hypertensive retinopathy respectively. And 11 (36.6%) cases had microalbuminuria, among them 7 cases had 1+ , 3 cases had 2+ and 1 case had 3+ microalbuminuria.

Out of 30 cases, 3 cases had unstable angina (10%), 4 cases had NSTEMI (13.3%), 5 cases had CVA (16.7%) and 1 case had CKD (3.3%).

In the present study, vascular complications in cases was compared with BMI, but P value was not significant.

In Jean-Pierre Després study, "Hyperinsulinemia as an Independent Risk Factor for Ischemic Heart Disease" study[66] 2103 men who were 45 to 76 years of age and who did not have ischemic heart disease. A first ischemic event (angina pectoris, acute myocardial infarction, or death from coronary heart disease) occurred in 114 men (case patients). Fasting insulin concentrations at base line were 18 percent higher in the case patients than in the controls (P<0.001).

In the present study, when lipid parameters were compared with fasting insulin levels in cases, total cholesterol and triglycerides was significantly high in cases with increased fasting insulin levels. (P value was significant).

These above findings are in concordance with the other studies such as, MK Bhatnagar study wherein most hypertensives with hyperinsulinemia demonstrated an abnormal lipid profiles, but there was no statistical correlation between absolute values of lipoproteins and insulin.

Haffener et al[67] 1992 studied 1288 patients and observed that subjects with increased fasting insulin concentration at baseline have an increased incidence of hypertriglyceridemia (6.8%) and HDL cholesterol (20.9%). The results were statistically significant.

The kuopio Ishaemic heart disease risk factor study[68] 1990, observed that hyperinsulinemia was associated with increased triglycerides and decreased HDL levels.

In Israeli –Jewish population study[69], majority of hypertensive subjects was found to have hypertriglyceridemia.

CONCLUSION:

1. Obese, non diabetic, hypertensive individuals will have hyperinsulinemia.

2. Incidence of microvascular complications was more in obese, hypertensive, non diabetic individuals.

3. Incidence of macrovascular complications was more in obese, hypertensive, non diabetic individuals.

4. Hyperinsulinemia in obese, hypertensive, nondiabetic individuals will cause dyslipidemia.

5. Incidence of vascular complications will be more in obese, hypertensives as there is increase in age.

6. Incidence of vascular complications will be more in obese, hypertensives as the duration of hypertension increases.

SUMMARY:

This work was aimed to study the vascular complications in obese, non diabetic, hypertensive individuals and its correlation with fasting insulin levels. As active intervention in individuals with increased fasting insulin levels may prevent the overt development of diabetes and its complication in future.

Fasting serum insulin levels were estimated in 30 obese, hypertensive, nondiabetic subjects and 30 matched healthy controls by chemiluminesece method. 26.7% of cases showed hyperinsulinemia.

There was significant increase in the incidence of vascular complications such as hypertensive retinopathy, microalbuminuria, unstable angina, NSTEMI, chronic kidney disease and cerebro vascular accident in cases when compared to controls.

And fasting insulin levels was significantly high in cases when compared to controls.

Among the cases, when fasting insulin levels was compared with lipid profile, there was significant increase in total cholesterol and triglyceride values in cases with increased fasting insulin levels, which was statistically significant.

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ANNEXURES

PROFORMA:

TITLE OF THE STUDY: STUDY OF VASCULAR COMPLICATIONS IN OBESE, NON DIABETIC, HYPERTENSIVE INDIVIDUALS AND ITS CORRELATION WITH FASTING INSULIN LEVELS.

CASE HISTORY OF THE PATIENTS

Case No:

Name: Mr/Mrs: OP No:

Age: IP No:

Gender: Ward:

Date: Occupation:

Address:

CHIEF COMPLAINTS:

HISTORY OF PRESENTING ILLNESS:

PAST HISTORY:

Hypertension : yes/no if yes , duration:

Diabetes : yes/no if yes , duration:

Others :

FAMILY HISTORY:

Diabetes : yes/no

Hypertension : yes/no

MENSTRUAL HISTORY: Regular/irregular/not applicable/other abnormalities

TREATMENT HISTORY:

GENERAL PHYSICAL EXAMINATION:

Ht: Wt: BMI:

Built: normal / below normal / well built / obese/

Nourishment: well / poor nourished

Oedema: Icterus :

Pallor: Clubbing :

Cyanosis: Lymphadenopathy :

Blood pressure : Pulse rate :

I reading:

II reading:

III reading:

Fundus:

SYSTEMIC EXAMINATION :

CVS :

RS :

CNS :

PER ABDOMEN :

DIAGNOSIS:

INVESTIGATIONS:

BLOOD:

PLASMA FBS: mg/dl

PLASMA PPBS: mg/dl

LIPID PROFILE:

→ SERUM TOTAL CHOLESTEROL: mg/dl

→ SERUM TRIGLYCERIDES: mg/dl

→ SERUM HDL: mg/dl

→ SERUM LDL: mg/dl

HEMOGLOBIN: g/dl

TOTAL COUNT:

PERIPHERAL BLOOD SMEAR:

SERUM FASTING INSULIN LEVELS:

URINE ROUTINE:

Albumin - Sugar–

OTHERS:

ECG:

CT BRAIN:

2D ECHO:

CAROTID DOPPLER:

INFORMED CONSENT

I understand that I remain free to withdraw from this study at any time.

I have read or had read to me and understand the purpose of this study and the confidential nature of the information that will be collected and disclosed during the study.

I have had the opportunity to ask my questions regarding the various aspects of this study and my questions have been answered to my satisfaction.

I, the undersigned agree to participate in this study and authorize the collection and disclosure of my personal information as outlined in this consent form.

---	---
Participant's Name & signature	Date
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Signature of the witness	Date
---	---
Signature of the principal investigator	Date

MASTERCHART- CASES

SL.NO	HOSP. NO	AGE	SEX	HEIGHT	WEIGHT	BMI	FBS	PPBS	HYPERTENSION DURATION	INSULIN	HYPERTENSIVE RETINOPATHY	MICROALBUMINURIA	UNSTABLE ANGINA	NSTEMI	CVA	CKD	TOTAL CHOLESTEROL	TRIGLYCERIDES	HDL	LDL
1	806073	50	F	150	80	35.55	99	114	12	3.21	GRADE-1	1+	-	+	-	-	180	185	40	125
2	927189	41	M	177	101	32.26	86	110	7	16.27	-	-	-	-	-	-	210	245	25	140
3	937238	67	M	170	80	27.68	88	128	10	16.58	GRADE-1	1+	-	-	+	-	160	98	35	135
4	919280	60	M	165	80	29.41	90	118	10	1.75	GRADE-1	1+	-	-	+	-	155	145	30	150
5	720625	65	F	166	75	27.2	94	118	12	15.7	-	-	-	-	-	-	220	160	24	170
6	917915	75	F	168	75	27.27	100	110	8	14.67	-	1+	-	-	+	-	145	90	35	130
7	853844	88	M	145	59	28.09	100	119	6	3.49	-	-	-	-	+	-	230	200	20	180
8	714649	55	M	151	68	29.08	86	128	6	5.09	-	-	-	-	-	-	205	165	41	135
9	862533	62	M	166	90	32.72	90	110	15	31.11	GRADE-1	2+	-	-	-	+	225	170	30	140
10	812519	85	M	168	75	26.59	80	108	12	6.81	-	-	+	-	-	-	170	95	30	120
11	711165	60	F	164	72	26.8	71	89	10	5.78	-	-	-	-	-	-	199	154	38	130
12	812157	60	F	145	82	39.04	75	100	8	1.61	-	1+	+	-	-	-	135	92	29	88
13	869582	50	F	144	58	28.01	90	128	6	11.12	GRADE-1	-	-	-	+	-	170	210	40	95
14	918000	30	M	170	115	39.79	87	118	8 MONTH	31.11	GRADE-1	-	-	-	-	-	270	200	32	108
8	871391	68	M	145	54	25.71	80	110	14	8.8	GRADE-1	-	-	-	-	-	240	200	20	125
16	836535	50	F	168	75	26.59	96	128	9	2.52	GRADE-1	2+	-	-	-	-	150	78	30	110
17	705480	56	M	164	82	30.5	90	118	4	5.86	-	1+	-	-	-	-	160	150	28	120
18	705479	42	M	165	75	27.57	87	110	2	26.44	GRADE-1	-	-	-	-	-	245	326	33	146
19	674040	47	M	170	80	27.68	88	120	4	43.34	-	-	-	-	-	-	282	140	29	118
20	742793	55	M	155	68	28.33	96	128	8	2.13	-	2+	-	-	-	-	160	100	40	140
21	856208	55	M	150	90	40	82	110	10	34.16	GRADE-1	-	-	+	-	-	250	180	20	135
22	811614	68	M	168	70	25.3	90	118	9	3.48	GRADE-2	-	-	+	-	-	190	100	30	125
23	855137	60	F	145	56	26.66	87	82	4	128.2	-	-	-	-	-	-	195	164	42	120
24	853363	64	F	160	69	26.95	92	135	8	128.9	GRADE-1	3+	-	-	-	-	164	312	31	71
25	847812	55	F	140	90	45.91	98	135	2 MONTH	46.92	-	-	-	-	-	-	227	201	41	146
26	854258	80	F	145	54	25.71	88	111	14	16.4	GRADE-3	-	+	-	-	-	190	112	34	140
27	832727	60	M	168	74	26.24	80	120	3 MONTH	11.91	GRADE-1	1+	-	+	-	-	150	78	24	110
28	866937	62	F	154	65	27.42	87	110	NEW	11.27	GRADE-1	-	-	-	-	-	160	108	30	98
29	820029	50	F	55	146	26.19	80	120	8	<0.20	-	-	-	-	-	-	158	100	20	90
30	812570	52	F	160	78	30.46	78	117	10	14.47	GRADE-1	-	-	-	-	-	135	150	35	130

MASTERCHART - CONTROLS

SL.NO	HOSP NO	AGE	SEX	HEIGHT	WEIGHT	BMI	FBS	PPBS	INSULIN	HYPERTENSIVE RETINOPATHY	MICROALBUMINURIA	UNSTABLE ANGINA	NSTEMI	CVA	CKD	TOTAL CHOLESTEROL	TRIGLCERIDES	HDL	LDL
1	712785	53	F	156	50	20.5	80	110	2.95	-	1+	-	-	-	-	173	217	32	97
2	712797	57	M	170	65	22.4	88	128	11.22	-	-	-	-	-	-	221	73	29	172
3	713396	65	M	155	50	20.8	78	104	17.34	-	-	-	-	-	-	157	210	32	83
4	713397	53	M	180	67	20.6	90	110	17.43	-	-	-	-	-	-	242	232	31	90
5	715748	65	F	152	51	22	70	124	13.59	-	-	-	-	-	-	162	367	40	48
6	717951	45	F	172	68	23	94	100	10.65	-	-	-	-	-	-	269	153	36	202
7	719293	75	F	178	68	21.5	80	98	11.82	-	-	-	-	-	-	165	216	33	88
8	722151	68	M	155	53	22	94	89	6.24	-	-	-	-	-	-	220	201	58	121
9	721863	45	F	162	62	23.6	76	98	6.2	-	2+	-	-	-	-	178	511	34	190
10	753967	50	M	149	50	22.2	90	122	15.73	-	-	-	-	-	-	185	526	34	245
11	714649	55	M	165	65	23.8	78	110	5.09	-	-	-	-	-	-	205	165	41	135
12	720625	65	F	167	68	24.4	88	100	15.7	-		-	-	-	-	213	277	39	118
13	751224	85	M	156	48	19.7	80	87	6.77	-	-	-	-	-	-	180	182	38	106
14	674032	63	M	170	60	20.7	80	96	6.2	-	-	-	-	-	-	133	263	32	48
15	711165	60	F	156	57	23.4	71	89	5.78	-	-	-	-	-	-	199	154	38	130
16	715377	62	M	146	46	21.1	57	110	6.1	-	-	-	-	-	-	186	134	33	126
17	715002	75	M	170	70	24.2	76	104	15.82	-	-	-	-	-	-	212	285	39	116
18	713824	32	M	159	60	23.8	70	110	6.38	-	-	-	-	-	-	190	279	42	92
19	674635	43	F	146	45	21.1	78	92	7.5	-	-	-	-	-	-	180	310	40	78
20	676201	68	F	176	70	23.3	75	90	14.37	-	2+	-	-	-	-	164	307	40	62
21	688090	55	F	166	63	22.9	80	89	11.35	-	-	-	-	-	-	192	211	48	101
22	678925	38	F	164	62	23.1	70	110	13.45	-	-	-	-	-	-	211	204	40	130
23	654887	51	M	161	53	20.4	96	114	14.07	-	-	-	-	-	-	209	612	40	230
24	714596	78	M	166	60	21.8	80	88	21.68	-	-	-	-	-	-	141	194	35	67
25	711688	55	M	161	53	20.4	70	89	18.47	-	-	-	-	-	-	180	141	35	116
26	715962	46	M	170	65	22.4	88	108	12.06	-	-	-	-	-	-	202	326	46	94
27	705480	56	M	160	60	23.4	73	86	5.86	-	1+	-	-	-	-	121	170	42	45
28	675160	75	M	149	46	20.7	75	121	5.67	-	-	-	-	-	-	163	263	40	75
29	743901	45	F	159	57	22.6	87	112	11.07	-	-	-	-	-	-	240	307	33	145
30	736843	55	F	174	66	21.8	88	121	24.73	-	-	-	-	-	-	188	280	34	98