DISSERTATION ON INSULIN RESISTANCE IN NON DIABETIC PATIENTS WITH CORONARY ARTERY DISEASE

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CERTIFICATE

This is to certify that the dissertation entitled "**INSULIN RESISTANCE IN NON DIABETIC PATIENTS WITH CORONARY ARTERY DISEASE"** is the bonafide original work of Dr**. M. Santni,** post graduate student, Department of General Medicine, Kilpauk Medical College, Chennai under my guidance in partial fulfillment of the requirements for MD (General Medicine) branch I of the Tamil Nadu Dr. M.G.R Medical university. The period of postgraduate study and training was from May 2007 to March 2010.

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INTRODUCTION

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INTRODUCTION

Cardiovascular disease accounts for approximately 12 million deaths annually & is the commonest cause of death globally. Previously considered a disease of the affluent, the past three decades have seen considerable decline in the incidence and prevalence of atherosclerotic coronary disease in the industrialized western world; whereas at the same time this problem is assuming epidemic proportions in the developing world.

Asian Indians, whether living in their own country or elsewhere, have higher rate of coronary artery disease than any other ethnic groups studied (1-3). Not only CAD is more prevalent, it is more severe and occurs at a younger age in Asian Indians. (3) Even within India, the prevalence of CAD is not homogeneous and is two fold higher in southern parts. The higher prevalence of CAD in Asian Indians is accompanied by paradoxically, a lower prevalence of conventional risk factors such as hypertension, diabetes mellitus, hyperlipidemia and cigarette smoking (4,5). This suggests the prevalence of other risk factors.

Hyperinsulinemia and Insulin resistance have been associated with obesity, Type 2 diabetes mellitus, hypertension, hyperlipidemia and CAD, however the link between endogenous hyperinsulinemia and CAD in non-diabetic adults is at best weak with conflicting results, perhaps suggesting ethnic differences.

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Recent physiological studies have shown that many characteristics of insulin resistance syndrome are more prevalent in Asian Indians compared to Caucasians (13,14,15). Impaired glucose tolerance, elevated fasting plasma glucose and insulin clamp and other techniques, have all been observed in Asian Indian populations (16,17,18,19). In addition to decreased insulin sensitivity, Asian Indians have lipid abnormalities, including increased triglycerides, low HDL and increased LDL, all may contribute to CAD. The present study was designed to examine the relationship between Insulin sensitivity and coronary artery disease in non diabetic patients.

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AIM OF THE STUDY

AIM OF STUDY

To evaluate the association of plasma insulin and insulin resistance (IR) measured by Homeostasis Model Assessment (HOMA-IR) with coronary artery disease (CAD) in non diabetic subjects.

To estimate whether insulin resistance alone without diabetes is an independent risk factor for Coronary artery disease.

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REVIEW OF LITERATURE

REVIEW OF LITERATURE

INSULIN ACTIONS:

Insulin has unique properties as a hormone when compared to other hormones. Insulin is an anabolic hormone, apart from glucose homeostasis, induces protein synthesis, lipogenesis and regulation of various genes. Insulin also has anti inflammatory and anti apoptotic actions & protects endothelial functions

Insulin regulates diverse physiological processes in mammals, including membrane transport, intermediary metabolism and cell growth and differentiation. The most conspicuous metabolic effects of insulin are associated with skeletal muscle, cardiac muscle, adipose tissue and liver either having stimulatory or inhibitory effect. A surprising feature is that to date the only signalling component known to be unique to insulin action is the insulin Receptor (IR) itself, which is widely expressed in mammalian cells, although levels vary greatly between cell types. Thus normal insulin action influences wide range of tissues and insulin resistance can adversely affect diverse tissue functions, though not all to same extent.

THE INSULIN RECEPTOR FAMILY

The insulin receptor is a large, hetero tetrameric, transmembrane glycoprotein containing two types of subunits designated alpha

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(Mr.140.kDa) and beta (95 k Da), linked by disulphide bonds in a beta - alpha - alpha- beta configuration (7). The IR binds insulin with high affinity and specificity and transmits a signal to the cytosol via its intrinsic tyrosine – specific protein kinase activity (8) This phosphorylates a number of intracellular substrates, most especiall y the so-called insulin receptor substrates (IRS), which recruit and activate an array of signalling proteins containing Src homology – 2 (SH2) domains. (9). Two signals have been shown to play major role in insulin action, namely those transmitted by enzyme phospho-inositide 3 kinase (PI 3-kinase), which generates ptd Ins (3,4,5) tris-phosphate at the cytosolic face of membrane and the guanine nucleotide exchange factor Grb2/sos which activates the small G-protein Ras. These act as switch mechanism to change the "currency" of signalling from tyrosine phosphorylation to serine / threonine phosphorylation of target proteins. However these signals and the downstream signalling cascade involving protein kinase B and mitogen – activated protein kinases (MAPKs) have been implicated in the specific actions of Insulin.

Metabolic and antiapoptotic effects of insulin are mediated by signalling pathway involving IRS proteins, (PI-3k), protein kinase B and mToR (Mamalian target of Rapamycin). In contrast, non metabolic,

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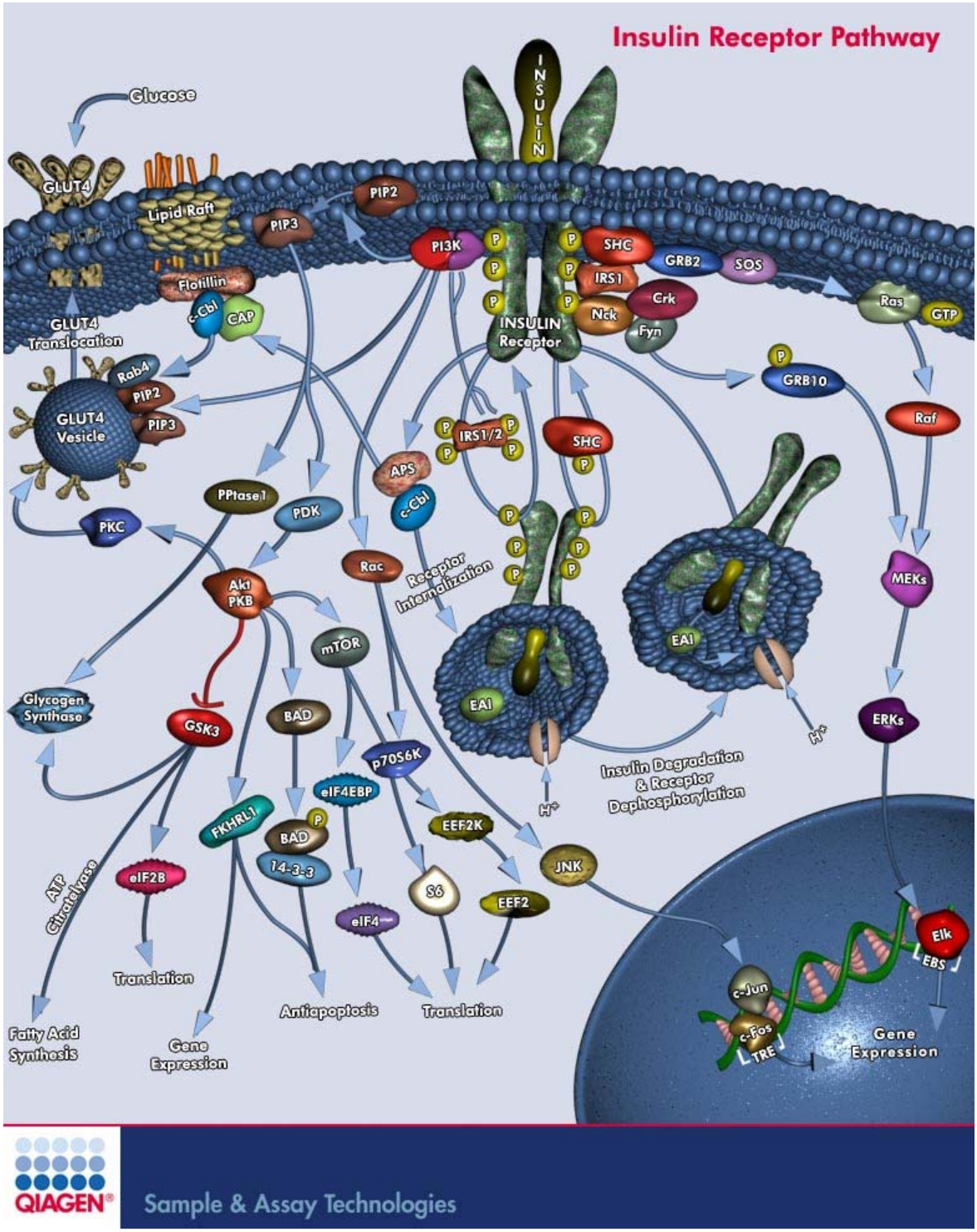
Insulin Receptor Pathway
INSULIN
Glucose
GLUT4
Lipid Raft
PIP2
PIP3
PI3K
SHC
GRB2
SOS
IRS1
Crk
Nck
Fyn
Flotillin
c-Cbl
CAP
GLUT4 Translocation
INSULIN Receptor
Ras
GTP
GRB10
Raf
Rab4
PIP2
PIP3
GLUT4 Vesicle
IRS1/2
SHC
APS
c-Cbl
PPtase1
PDK
PKC
Rac
Receptor Internalization
MEKs
Akt PKB
mTOR
EAI
EAI
Glycogen Synthase
GSK3
BAD
p70S6K
ERKs
Insulin Degradation & Receptor Dephosphorylation
H+
H+
eIF4EBP
FKHRL1
BAD
14-3-3
EEF2K
JNK
ATP Citratelyase
eIF2B
S6
EEF2
eIF4
Translation
Antiapoptosis
Translation
Fatty Acid Synthesis
Gene Expression
Elk
EBS
c-Jun
c-Fos
TRE
Gene Expression
QIAGEN
Sample & Assay Technologies

proliferative and mitogenic effects are mediated largely via activation of Ras, Raf and mitogen activated protein kinase Erk -1, Erk-2.

There is accumulating evidence that obesity associated insulin resistance reflects inhibitory influences on this pathway at the level of insulin receptor substrates (IRS). Insulin resistance syndromes described in adults are either type A IR due to defect in insulin signalling pathways or type B IR due to auto antibodies directed at insulin receptors.

INSULIN RESISTANCE:

Insulin Resistance is defined as an inability of a known quantity of exogenous or endogenous insulin to increase glucose uptake & utilization in an individual as such as it does in a normal person. Both insulin resistance and decreased insulin secretion are genetically programmed. This program is modified by a variety of environmental factors especially diet and activity (11).

It was in 1988, at the Banting lecture of the American Diabetes Association Annual meeting, that "Dr Gerald Reaven" first proposed the concept that insulin resistance and compensatory hyperinsulinemia were the cornerstones of a plurimetabolic syndrome that included hyper triglyceridemia, reduced plasma HDL cholesterol levels, essential hypertension and some degree of glucose intolerance (12).

`

The concept was first referred to as “syndrome X”, implied that the Insulin Resistance syndrome might be associated with significant elevation in the risk of cardiovascular disease. It was also suggested that a significant proportion of non-diabetic individuals in the general population perhaps as many as 2.5 percent, might display some features of the syndrome. Both IR and decreased insulin secretion are genetically programmed which is modified by a number of environmental factors especially diet & activity(16).

INSULIN RESISTANCE AND HYPERTENSION

The direct association between hyperinsulinemia, insulin resistance and essential hypertension that could not be attributed to confounding obesity was most convincingly demonstrated by Ferrannini and colleagues in 1987 (20). A number of epidemiological studies have also been demonstrated on the association between insulin levels and blood pressure (21).

It is unlikely that hyperinsulinemia directly causes hypertension and the relationship between insulin resistance and vascular dysfunction is not direct and simple. Patients with insulinoma do not tend to have hypertension (22). Nevertheless prospective studies have shown that individuals with

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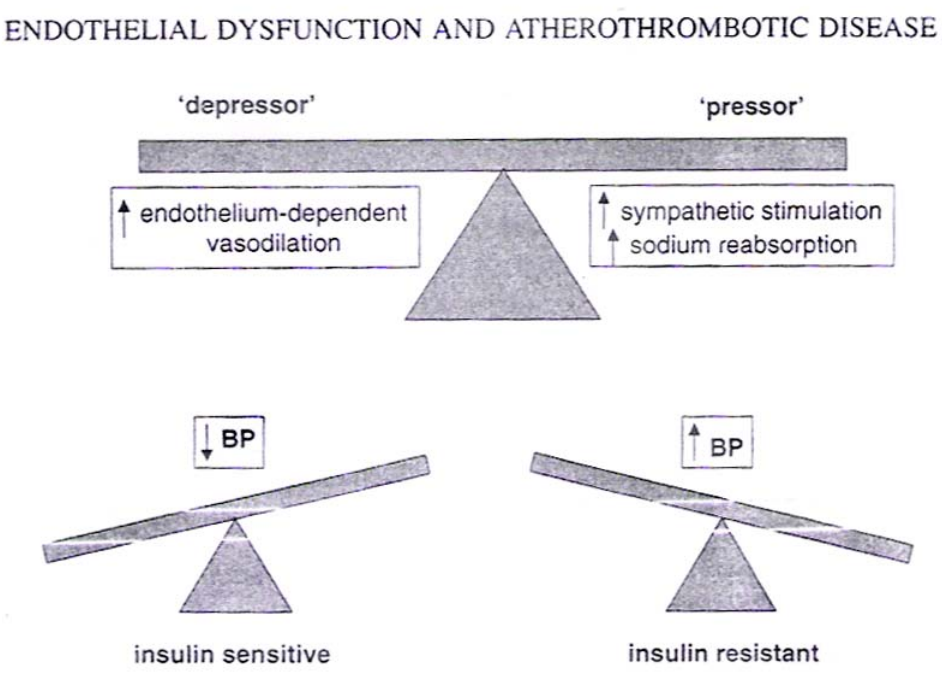
hyperinsulinemia have a risk of developing both hypertension and coronary events (23).

Insulin Resistance is absent in secondary hypertension patients, but present in normotensive offsprings of essential hypertensive patients(24) suggesting that it may precede the development of high blood pressure.



The relation between IR and hypertension relates to several different mechanisms. First it is important to note that insulin is a vasodilator, that is mediated by nitric oxide release from endothelial cells, when given intravenously to people of normal weight (25) with secondary effects on sodium absorption in the kidney (26). Evidence indicate that sodium

reabsorption is increased in white people but not in Africans or Asians. (27). In the setting of Insulin Resistance, the vasodilator effect of insulin can be lost (28), but renal effect is preserved (29). Because nitric oxide accounts for all of insulin induced vasodilation, it is likely that hypertension is result of partial nitric oxide deficiency or resistance (30).

Insulin also increases the activity of sympathetic nervous system (31) an effect that might also be preserved in the setting of insulin resistance (32) due to hyperinsulinemia. In pathophysiological states such as obesity, the balance may be disrupted by enhanced sympathetic activation in response to hyperinsulinemia together with "blunting" of insulin mediated vasodilatation (Vascular insulin resistance).

Insulin Resistance and Dyslipidemia

Insulin Resistance is associated with many lipid abnormalities, including increased triglycerides, low high density lipoprotein (HDL) cholesterol and increased lipoprotein (a), all of which may contribute to excess coronary artery disease (33,34).

In general, with increases in free fatty acid flux to the liver, increased production of apo B containing triglyceride rich VLDL occurs (35). The effect of insulin on this process is complex. In the setting of insulin

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resistance, increased flux of free fatty acid to the liver increases hepatic triglyceride synthesis but under physiological conditions, insulin inhibits VLDL secretion in systemic circulation (36). This response in part is an effect of insulin on the degradation of apo B. Yet insulin is also lipogenic, increasing transcription of many genes related to triglyceride biosynthesis.

Additionally, Insulin Resistance could also reduce the concentration of lipoprotein lipase in peripheral tissues (ie in adipose tissue more than muscle). This alteration in lipoprotein lipase, however contributes less to hypertriglyceridemia than does overproduction of VLDL. Nevertheless hypertriglyceridemia is an excellent reflection of insulin resistance condition.

In the presence of hypertriglyceridemia, a decrease in the cholesterol content of HDL results from decreases in cholesteryl ester content of the lipoprotein core, with variable increase in triglyceride, making the particle small and dense, a function in part of cholesteryl ester transfer protein (38). This change in lipoprotein composition also results in an increased clearance of HDL from circulation (39). The relation of these changes in HDL to insulin resistance is probably indirect, arising in concert with changes in triglyceride rich lipoprotein metabolism.

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In addition to HDL, the composition of LDL is also modified in similar way. In fact, with fasting serum triglycerides >2mmol/L, almost all patients have a predominance of small dense LDL (40). This change in LDL composition is attributable to relative depletion of unesterified and esterified cholesterol and phospholipids, with either no change or an increase in LDL Triglyceride (41).

Small dense LDL is more atherogenic than buoyant LDL because

(i) it is more toxic to the endothelium,

(ii) it is more able to transit through the endothelial basement membrane,

(iii) it adheres well to glycosaminoglycans,

(iv) it has increased susceptibility to oxidation,

(v) it is more selectively bound to scavenger receptors in macrophages (42).

Hypertriglyceridemia is a major determinant of the distribution of LDL particles. The higher the fasting triglyceride level, the greater the preponderance of small dense LDL in total LDL concentration (43).

Insulin Resistance and Obesity

Recent studies of body fat distribution have shown that insulin resistance is associated with central obesity and visceral fat (13,14)

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importantly. The increase in central obesity often is not apparent from measurement of body mass index (BMI), which may be in the normal range as defined by standard weight tables and other readily available criteria (44,45).

International Association for the study of obesity and the international obesity task force defined central obesity as waist circumference > 8ocm for women and >90cm for men (46).

A distinction between a large waist due to increase in subcutaneous adipose tissue versus visceral fat is debated. This distinction can be made with computed tomography or MRI (47).

With increases in intra-abdominal or visceral adipose tissue, a higher rate of flux of adipose tissue derived free fatty acids to liver through splanchinc circulation would be expected, whereas increases in abdominal subcutaneous fat would release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism (ie glucose production, lipid synthesis, and secretion of prothrombotic proteins such as fibrinogen and plasminogen activator inhibitor - 1 (48)).

Despite these potential differences in mechanisms related to excessive abdominal adipose tissue distribution, the clinical diagnosis of metabolic

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syndrome does not distinguish between increases in subcutaneous and visceral fat.

Yet perhaps by a mechanism related to free fatty acid flux and metabolism, the relative predominance of visceral rather than increase in adipose tissue with increasing waist circumference in Asians and Asian Indians (49) renders the relative prevalence of the syndrome higher than in African American men in whom subcutaneous fat predominate (50).

However, there is evidence that the elevated post prandial free fatty acid release in upper body obese women originates from the non-splanchnic upper body fat, and not from the visceral depot (51). These results suggest that visceral fat might be a marker for, but not the source of excess post prandial free fatty acid in obesity.

The effect of insulin to reduce circulating Non Esterified fatty acid (NEFA) concentrations is an important part of coordination of metabolic processes that occurs after a meal. At that time, glucose becomes the major oxidative fuel for skeletal muscle and it is appropriate that "substrate competition" from fatty acids is minimized.

Also, plasma NEFAs are potent stimulus for hepatic gluconeogenesis and glucose output and again this stimulus is not appropriate in the

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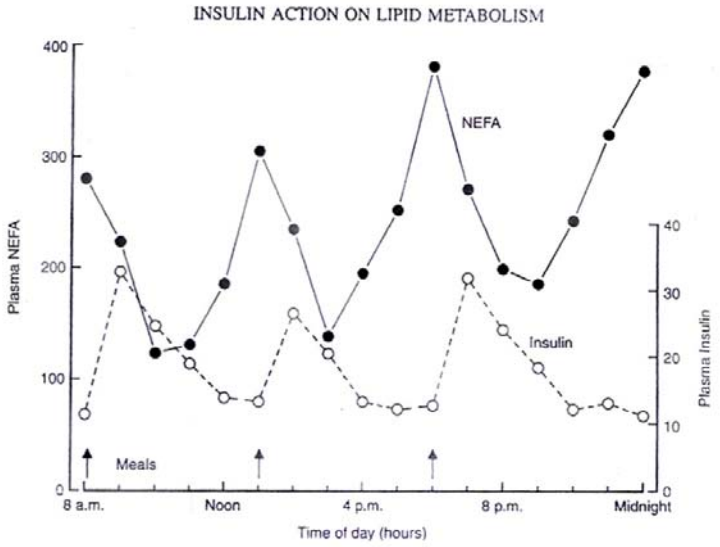
postprandial period when hepatic glucose output needs to be suppressed to maintain glucose homeostasis

The plasma NEFA concentrations display a marked diurnal variation, the reverse of insulin concentration, with troughs after meals and peaks before the next meal.



Randle's hypothesis

The glucose fatty acid hypothesis proposed by Randle et al in 1963 attempted to delineate the relationship between increased non - esterified fatty Acids (NEFAs) and insulin resistance. Randle and co-workers conducted a series of invitro experiments in rat cardiac muscle that suggested substrate competition between NEFAs and glucose as an energy

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source for muscle. These studies observed a relative increase in the rate of fat oxidation compared with carbohydrate metabolism in response to increase in NEFAs. In addition, studies revealed a reduction in insulin stimulated glucose uptake and utilization by the cardiac muscle.

The mechanism by which NEFAs bring about insulin resistance may be explained by recent studies that reveal NEFAs, induce different isoforms of protein kinase C. These isoforms can interfere with the intracellular signalling pathway of insulin and ultimately block glucose transport activity.

Insulin resistance and increased NEFA supply to liver are associated with increased prevalence of Non – alcoholic steatohepatitis (NASH), which contributes to liver fibrosis and cirrhosis in a proportion of patients.

Insulin Resistance and Atherosclerosis

The risk of coronary artery disease is greatly increased in the type 2 diabetes. In a study examining the seven year incidence of myocardial infarction, Haffner et al (54) reported that the 10 year risk of a non-diabetic subject without previous MI was 3.5 percent, if a subject had previously had an MI, the risk of a further event was 18.8 percent. In contrast in diabetic subjects without previous MI, the risk was comparable to that of a non diabetic post MI subject (20.2 percent), while the risk of second MI in a

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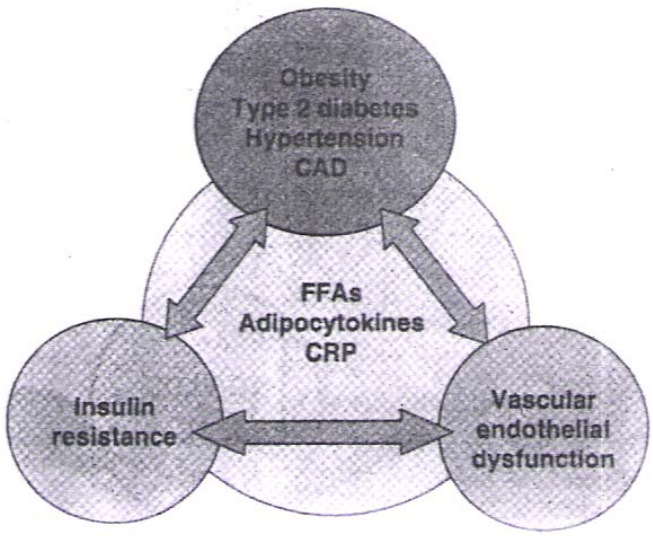
diabetic subject was 45 percent. Thus, diabetes that is characterised by insulin resistance and hyperinsulinemia is associated with an accelerated risk of atherosclerosis.



However, in patients without overt type 2 DM, the independent association between insulin resistance and atherosclerosis risk has been less easy to demonstrate. Nevertheless, there are now several good epidemiological studies that suggest that insulin resistance is an independent risk factor for cardiovascular disease. For example, surrogate measures of insulin resistance are associated with carotid artery intima-media thickness, a measure of atherosclerosis (55,56).

As yet there are no prospective data on the predictive role of insulin resistance on cardiovascular event rate, although the European group for the

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study of insulin resistance (EGIR) is currently conducting a large multicenter study to address the issue.

Adipokines and Insulin Resistance

The adipose tissue is now regarded as a major endocrine organ and a variety of factors released by adipose cells potentially mediate insulin resistance (57). Evidence suggest that one or more of these adipokines could impair insulin signalling and cause insulin resistance early in pre diabetics. (58) These factors include tumour necrosis factor TNF α, leptin, lnterleukin 6 (IL-6) and recently resistin and adiponectin: HSL : hormone sensitive lipase, IL-6: interleukin - 6, LPL: lipoprotein lipase, NEFA non esterified fatly acids, PAI-1, Plasminogen activator Inhibitor -1; SR: soluble receptor, TNF α tumour necrosis factor – alpha, VLDL -TG : very low density lipoprotein - triglyceride. However the precise role of these factors and the molecular mechanisms whereby they generate insulin resistance have remained elusive (59). Recently adiponectin has gained significance as a mediator of insulin sensitivity. Many studies reported lower levels of adiponectin in insulin resistant states and plasma adiponectin is inversely associated with overall and central fat distribution.

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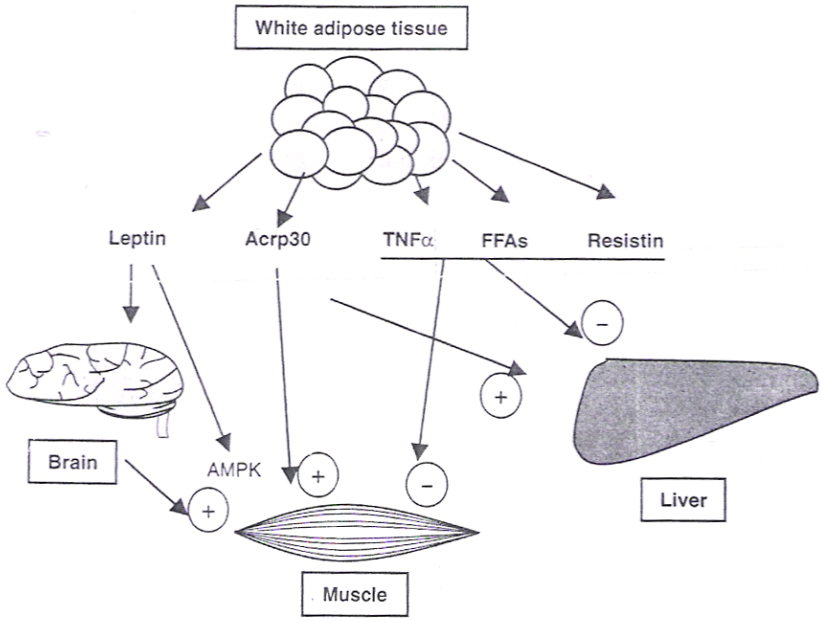

Figure 5.2 Adipose tissue (AT) as an endocrine organ

Dietary Factors in Insulin Resistance

Obesity is strongly linked to impaired insulin sensitivity, but acute changes in total energy intake influence insulin independently of changes in body weight or fat mass. (59).

A high intake of saturated fat reduces insulin sensitivity, but that of mono unsaturated and poly unsaturated fat are neutral or beneficial at least in the setting of moderate total fat intake

The effect of carbohydrate are less clear. However, unrefined carbohydrate with a low glycemic index, whole grain and high fibre foods

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appear to have beneficial effects on insulin sensitivity compared with more refined carbohydrates.

There may also be an influence of specific micronutrients such as magnesium, chromium and vitamin E, however , the evidence is limited

Exercise and Physical Activity

Physical activity has a positive effect on risk factors and diseases, in obese population. Though the exact mechanism is not known, exercise has many benefits for health and CAD risk factors, and reduces cardiovascular morbidity and mortality.

Exercise has a favorable action on modifying blood lipids, particularly HDL cholesterol in overweight individuals. Other studies have shown beneficial effect on blood pressure. Exercise has been shown to increase insulin sensitivity, GLUT-4 concentration and glucose disposal (66). Regular physical exercise improves endothelial function, by increasing vasculature shear stress and by increased production of nitric oxide. (67).

In overweight and insulin resistant subjects, exercise has been shown to reduce the non traditional cardiovascular risk factor homocysteine. It is known that regular exercise , even in overweight individuals leads to an improvement in fibrinolytic system. (69).

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However little is gained unless long term changes are established and this is known to be difficult to acheive in the majority of individuals. The compliance is generally poor.

Measurement of Insulin Resistance

The concept of insulin resistance is relatively easy to understand, but determining precisely who is insulin resistant is more complicated (70).

A World Health Organization consensus group recently concluded that the insulin sensitivity index (SI) of the lowest 25 percent of a general population can be considered insulin resistant (71). The European group for the study of insulin resistance took a more restricted view, defining insulin resistance as the SI of the lowest 10 percent of a non-obese, non-diabetic, normotensive Caucasian population. Richard Legro and his associates also used the SI of the lowest 10 percent of an obese, non PCOS population to define insulin resistance (72).

Hyperinsulinemic Euglycemic Clamp

The gold standard for evaluating insulin sensitivity, this clamp technique requires a steady intravenous infusion of insulin to be administered in one arm. The serum glucose level is “clamped” at a normal fasting concentration by administering a variable intravenous glucose

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infusion ((73) in the other arm. Numerous blood samplings are taken to monitor serum glucose so that a steady “fasting” level can be maintained. (In theory the intravenous infusion should completely suppress hepatic glucose production and not interfere with the test’s ability to determine how sensitive target tissues are to the hormone).

The degree of insulin resistance should be inversely proportional to the glucose uptake by target tissues during the procedure. In other words, the less glucose that is taken up by tissues during the procedure, the more insulin resistant the patient is.

The hyperinsulinemic - euglycemic clamp technique is most scientifically sound technique for measuring insulin sensitivity and it is against this standard that all other tests are usually compared Because this and similar “clamp” techniques are expensive, time consuming, and labour intensive, they are not very practical in an office setting.

To overcome these obstacles, alternative tests have been developed, including the frequently sampled intravenous glucose tolerance test (FSIVGTT), insulin tolerance test (ITT), insulin sensitivity test (IST), and continuous infusion of glucose with model assessment (CIGMA). Unfortunately all of these methods require intravenous access and multiple venipunctures, making them relatively impractical for office assessment.

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The oral glucose tolerance test (OGTT) does not require intravenous access but does involve several venipunctures and 2 to 4 hours of patient and technician time. Each of these tests have been shown to correlate reasonably well with dynamic clamp techniques.

Non Dynamic Measurements of Insulin Sensitivity

These tests, which include fasting insulin alone, are the HOMA test (homeostasis assessment model) (78 and 79) and the QUICKI (Quantitative Insulin Sensitivity Check Index). These tests are simple to perform, being based on fasting insulin and glucose measurements alone.

HOMA has been widely employed in clinical research to assess insulin sensitivity. Rather than using fasting insulin or a G/I ratio, the product of the fasting values of glucose (GO) expressed as mg/dl and insulin (IO) expressed as mcU/ml is divided by a constant.

$$\frac{IO \times GO}{405}$$

The constant 405 should be replaced by 22.5 if glucose is expressed in S.I. Units. Unlike IO and the G/I ratio, the HOMA calculation compensates for fasting hyperglycemia. The HOMA value correlates well with clamp techniques and has been frequently used to assess changes in insulin

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sensitivity after treatment. HOMA has also been used to study insulin resistance among PCOS patients of differing ethnic origins.

Like HOMA, QUICKI can be applied to normoglycemic and hyperglycemic patients. It is derived by calculating the inverse of the sum of logarithmically expressed values of fasting glucose and insulin:

$$\frac{1}{\{\log (IO) + \log (GO)\}}$$

Both HOMA and QUICKI values increase in the insulin – resistant patients.

Ischemic Heart Disease

Ischemic heart disease is defined as myocardial impairment due to imbalance between coronary blood flow and myocardial requirement. The commonest cause of IHD is atherosclerotic coronary artery disease

Spectrum of myocardial ischemia.

Traditionally, ischemic heart disease has been divided into several seperate syndromes such as stable effort angina, unstable angina, non – Q wave MI and Q wave MI. The recent understanding of the conversion of a stable atherosclerotic lesion to a plaque rupture with thrombosis has

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provoked a unifying hypothesis for the aetiology of acute coronary syndrome.

Nomenclature of myocardial ischemia

Old	Present
Asymptomatic	Asymptomatic
Stable effort angina	Stable effort angina
Unstable angina	Acute coronary syndrome, unstable angina without necrosis
Non Q wave MI	Non ST elevation MI (evidence of myocardial necrosis)
Q wave MI	ST elevation MI
Sudden death	Sudden death
Silent ischemia	Ischemic cardiomyopathy

The concept of myocardial ischemia as a spectrum provides framework for understanding the pathogenesis, clinical features and outcome of patients

Pathophysiology

Atherosclerotic obstruction of the coronary arteries leads to a spectrum of clinical syndromes varying between effort or stable angina to acute coronary syndrome (ACS) where an atheromatous plaque becomes vulnerable to rupture and produces sudden, complete or partial occlusion of the coronary artery. A complete occlusion leads to ST elevation myocardial

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infarction (STEMI) whereas partial occlusion leads to non – ST elevation myocardial infarction (NSTEMI)

Site & size of MI

Left anterior descending (LAD)	- Antroseptal MI
Left circumflex artery	- Anterolateral MI
Right coronary artery	- Inferoposterior wall MI with or without RVMI

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MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted at the out patient department of cardiology at Government Royapettah Hospital.

Selection of Cases

A total of fifty patients with coronary artery disease were chosen from the outpatient department of cardiology.

Fifty healthy controls matched for age and glycemia were chosen from the master health check up at Government Royapettah hospital.

Women chosen for the study were in the post menopausal age group or in follicular phase of their menstrual cycle to decrease the potential influence of gonadal steroids on insulin action.

Inclusion criteria

Coronary artery disease in the study was defined as:

1) Documented myocardial infarction, substantiated by Q waves in electrocardiogram (ECG) and / or regional wall motion abnormality on echocardiogram,
2) Angina supported by (i) ST depression or T wave inversion and/or (ii) coronary angiographic evidence of >70% stenosis of one or more vessels.

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A control was defined as an induvidual without a history of angina and with a normal ECG

Exclusion criteria

(i) Diabetes Mellitus, which was diagnosed according to American diabetes association (80)

(ii) Patients with fasting plasma glucose over 110 mg/dl.

(iii) Acute heart failure

(iv) Hepatic dysfunction

(v) Serum creatinine>1.4 mg/dl

(vi) Patients receiving hormone replacement therapy

(vii) Patients on antidiabetic agents or steroid therapy

(viii) Patients who had an acute coronary event in the past 6 weeks.

A detailed history and physical examination was carried out in each patient including measurement of blood pressure, height and weight. All the candidates were screened for blood chemistry abnormalities.

Anthropometric measurements

Height and weight were measured by standard procedures. Body mass index was calculated by using the formula

$$\text{BMI} = \frac{\text{Weight in kg}}{(\text{Height in m})^2}$$

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The waist to hip circumference ratio (WHR) was measured using a flexible tape. The waist circumference was measured in the horizontal plane above the iliac crest. The hip circumference was measured at the maximum circumference at the level of the femoral trochanters.

Biochemical Analysis

In our patients, samples were collected from venous blood after overnight fasting and blood chemistry was performed. Fasting blood sugar was measured by enzymatic oxidase method. The concentrations of serum lipids including total cholesterol, triglyceride, HDL cholesterol &LDL - cholesterol were measured. LDL cholesterol was calculated using Fridewald formula. Insulin was estimated by ELISA assay.

Insulin resistance was calculated by the homeostasis model assessment of insulin resistance (HOMA-IR), proposed by Mattews et al., whose formula was (78).

$$\text{HOMA -IR} = \frac{\text{Fasting glucose (mgldl) x fasting insulin (µU/ml)}}{405}$$

Fasting insulin and HOMA –IR were used as surrogate markers of insulin resistance in our study.

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STATISTICAL ANALYSIS

STATISTICAL ANALYSIS

Data were expressed as mean ± SD or geometric mean (95% confidence interval). The case and control group were analyzed using unpaired t tests. The categorical variables were analyzed using x^2 or Fisher exact test. The association between insulin resistance and all other parameters were first analyzed by univariate analysis. Multivariate analysis to evaluate associations of CAD was performed by using multivariate logistic regression tests. A p value <0.05 was considered statistically significant.

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OBSERVATIONS AND ANALYSIS

OBSERVATIONS AND ANALYSIS

Clinical characteristics of the study subject and baseline laboratory results are given in Tables l and 2.

Group = Control Group

Table -1

Descriptive statistics

	N	Mean	Std. Deviation
AGE	50	51.1800	5.95798
BMI	50	27.4908	3.124834
WHR	50	.7390	.08229
SBP	50	125.1600	15.05956
DBP	50	79.0000	6.46813
HDL	50	41.6600	3.05467
LDL	50	97.5200	12.09021
TGL	50	143.9400	23.70861
TC	50	189.4800	30.79109
FBS	50	91.7800	8.62907
SI	50	11.4140	2.49399
HOMA-IR	50	2.6974	.55524
Valid N (listwsie)	50		

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Group = Case Group

Table – 2

DESCRIPTIVE STATISTICS

	N	Mean	Std. Deviation
AGE	50	51.600	6.91641
BMI	50	24.4288	3.03031
WHR	50	.8452	.09943
SBP	50	126.0000	13.09307
DBP	50	78.6000	5.34907
HDL	50	32.2800	3.72548
LDL	50	100.5600	20.26272
TGL	50	174.8600	27.86557
TC	50	204.3400	41.26352
FBS	50	100.5600	6.07827
SI	50	21.6040	6.23892
HOMA-IR	50	5.3952	1.75469
Valid N(listwsie)	50		

`

In the studied subjects age wise distribution of patients were as follows

Table - 3

Frequency table

Age	Cases	Control
40-50	24	21
50-60	20	26
>60	6	3

COMPARISON OF AGE: T TEST

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std. Error Mean
AGE	Case Group	50	51.6000	6.91641	.97813
	Control Group	50	51.1800	5.95798	.84259

p value : 0.746

p-Value of 0.746 indicates the difference in age across case and Control groups is not significant. In other words both Case and Control groups have subjects with similar age group.

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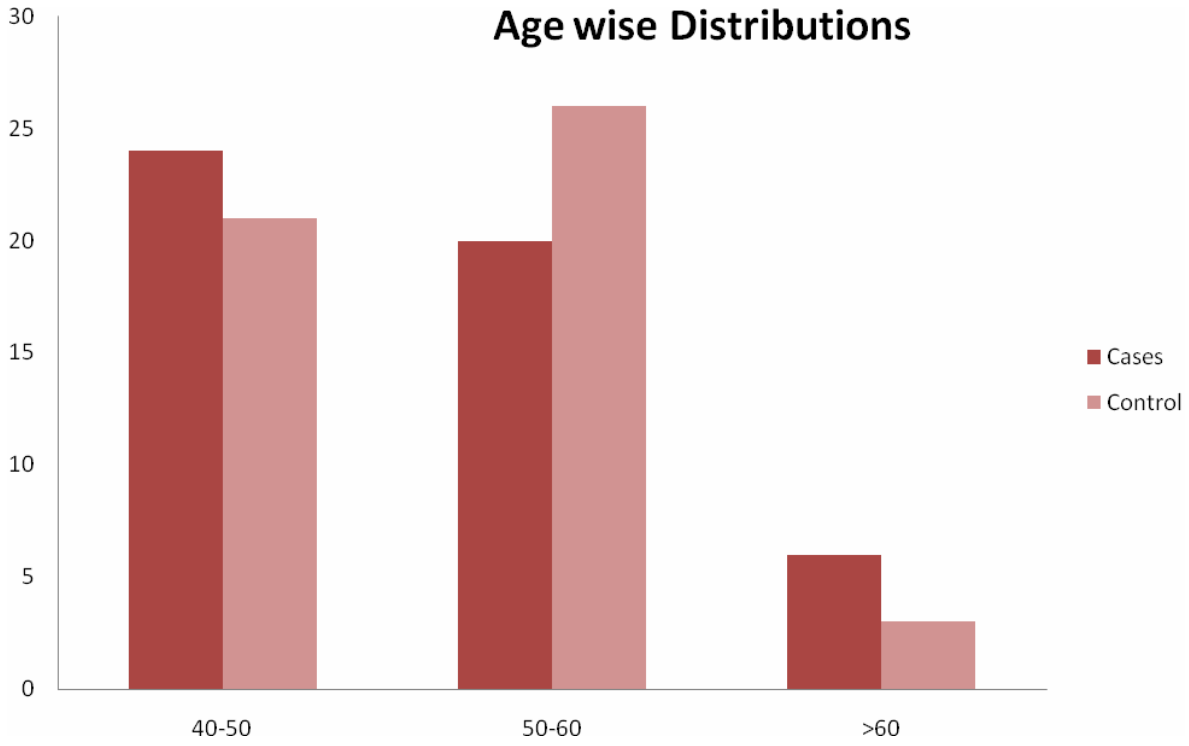
Age wise Distributions
30
25
20
15
10
5
0
40-50
50-60
>60
Cases
Control

`

Comparison of BMI (T test)

Table - 5

Group Statistics

Group		N	Mean	Std. Deviation	Std. Error Mean
BMI	Case Group	50	24.4288	3.03031	.42855
	Control Group	50	27.4908	3.124834	4.41918

p. Value : 0.494

p-Value of 0.494 indicates the difference in BMI across Case and Control groups is not significant (i.e.,) the BMI of subjects in Case and Control groups is the same.

Comparison of WHR (T test)

Table 6

Group Statistics

Group		N	Mean	Std. Deviation	Std.Error Mean
WHR	Case Group	50	.8152	0.09943	.01406
	Control Group	50	.7390	0.8229	.01164

p-Value <0.01

p- Value less than 0.01 indicates the difference in WHR across Case and Control groups is highly significant (Significant at 1%). The group statistics table shows Case group is associated with higher waist to hip ratio than control group inspite of having normal BMI, indicating a tendency towards central obesity.

`

Comparison of SBP (T test)

Table – 7

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std. Error Mean
SBP	Case Group	50	126.0000	13.09307	1.85164
	Control Group	50	125.1600	15.05956	2.12974

p-Value: 0.767

p-Value of 0.767 indicates the difference in SBP across Case and Control group is not significant.

Comparison of DBP (T test)

Table – 8

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std. Error Mean
DBP	Case Group	50	78.600	5.34904	.75647
	Control Group	50	79.0000	6.46813	.9473

p - Value : 0.737

p- Value of 0.737 indicates the difference in DBP across Case and Control groups is not significant.

`

Comparison of HDL (T test)

Table – 9

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std. Error Mean
HDL	Case Group	50	32.2800	3.72548	.52686
	Control Group	50	41.660	3.05467	.43200

p value : <0.01

p-Value less than 0.01 indicates the difference in HDL across Case and Control groups is highly significant (Significant at 1%). The Group statistics table shows Case group is associated with lower HDL than control group.

Comparison of LDL (T test)

Table – 10

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std. Error Mean
LDL	Case Group	50	100.5600	20.26272	2.86558
	Control Group	50	97.5200	12.09021	1.70981

p - Value : 0.365

p-Value of 0.365 indicates the difference in LDL across Case and Control groups is not significant.

`

Comparison of TGL (T test)

Table -11

Group		N	Mean	Std. Deviation	Std.Error Mean
TGL	Case Group	50	174.8600	27.86557	3.94079
	Control Group	50	143.9400	23.70861	3.35290

p - Value <0.01

p-Value less than 0.01 indicates the difference in TGL across Case and Control groups is highly significant (Significant at 1%). The Group statistics table shows Case group is associated with higher TGL than control group.

Comparison of TC (T test)

Table – 12

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std. Error Mean
TC	Case Group	50	204.3400	41.26352	5.83554
	Control Group	50	189.4800	30.79109	4.35452

p -Value : 0.044

p-Value less than 0.044 indicates the difference in TC across Case and Control groups is significant (Significant at 5%). The Group statistics table shows Case group is associated with higher TC than controls.

`

Comparison of FBS (T test)

Table - 13

Group		N	Mean	Std. Deviation	Std.Error Mean
FBS	Case Group	50	100.5600	6.07827	.85960
	Control Group	50	91.7800	8.62907	1.22033

P value <0.01

P-Value less than 0.01 indicates the difference in FBS across Case and Control groups is highly significant (Significant at 1%); The Group statistics table shows Case group is associated with higher FBS than control group though it was lower than in diabetics.

Comparison of SI (T test)

Table – 14

GROUP STATISTICS

Group		N	Mean	Std. Deviation	Std.Error Mean
SI	Case Group	50	21.6040	6.23892	.88232
	Control Group	50	11.4140	2.49399	.35270

p -Value :<0.01

p-Value less than 0.01 indicates the difference in SI across Case and Control groups is highly significant (Significant at 1%). The Group statistics table shows Case group is associated with higher SI than control group.

`

Comparison of HOMA – IR (T test)

Table - 15

Group	N	Mean	Std. Deviation	Std.Error Mean
HOMA-IR Case Group	50	5.3952	1.75469	.24815
Control Group	50	2.6974	.55524	0.7852

p value : <0.01

p-Value less than 0.01 indicates the difference in HOMA-IR across Case and Control groups is highly significant (Significant at 1%). The Group statistics table shows Case group is associated with higher HOMA-IR than control group.

`

Categorical Variables Analysed By Chi Square Test

Table - 16

		Group		Total
		Control Group	Case Group	
Gender	Female Count	18	20	38
	Expected count	19.0	19.0	38.0
	Male Count	32	30	62
	Expected count	31.0	31.0	62.0
Total	Count	50	50	100
	Expected Count	50.0	50.30	100.0

Table - 17

	Value	dt	Asymp. Sig (2 sided)	Exact sig (2sdides)	Extract sig (1sides)
Pearson chi-square	.170	1	.680		
Continuity correction	.042	1	.837		
Likelihood Ratio	.170	1	.680		
Fihser's exact test				.837	.418
Linear- by – Linear association	.168	1	.682		
N of valid cases	100				

Based on Pearson Chi-Square test, p-Value of 0.680 indicates the difference in gender across case and control groups is statistically not Significant

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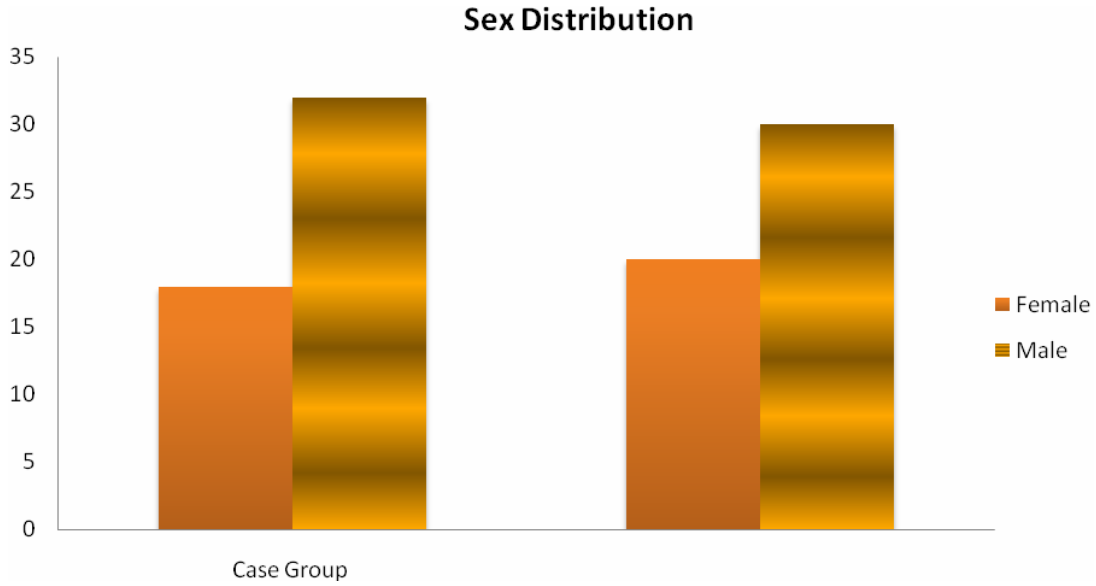
Sex Distribution
35
30
25
20
15
10
5
0
Case Group
Female
Male

`

Table - 18

		Group		Total
		Control Group	Case Group	
FAM-HIST	Negative Count	38	28	66
	Expected Count	33.0	33.0	66.0
	Positive Count	12	22	34
	Expected Count	17.0	17.0	34.0
Total	Count	50	50	100
	Expected Count	50.0	50.0	100.0

Table - 19

	Value	Dt.	Asymp. Sig (2 sided)	Exact sig (2sdides)	Extract sig (1sides)
Pearson chi-square	4.456	1	.035		
Continuity correction	3.610	1	.057		
Likelihood Ratio	4.506	1	.034		
Fihser's exact test				.057	.028
Linear- by – Linear association	4.412	1	.036		
N of valid cases	100				

Based on Pearson Chi-Square test, p-Value of 0.035 indicates the difference in distribution of Family History across Case and control groups is statistically significant (at 5%), from the chart of distribution we can conclude that the case group has higher cases of positive family history than controls.

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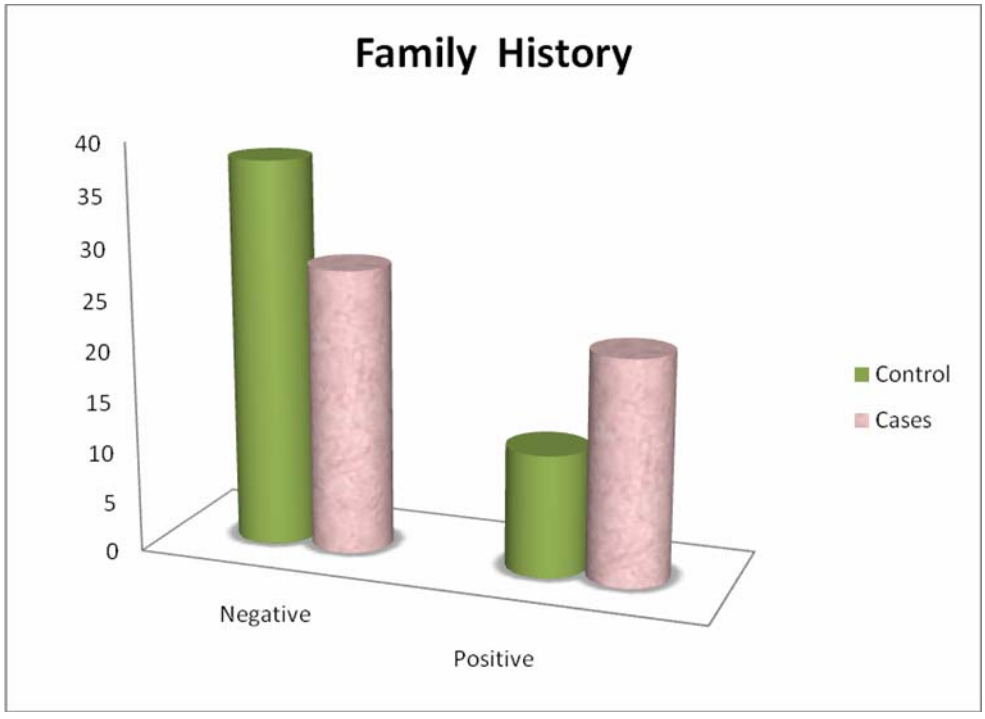
Family History
40
35
30
25
20
15
10
5
0
Negative
Positive
Control
Cases

`

Table - 20

			Group		Total
			Control Group	Case Group	
SMOKING	Negative	Count	36	28	64
		Expected Count	32.0	32.0	64.0
	Positive	Count	14	22	36
		Expected Count	18.0	18.0	36.0
Total		Count	50	50	100
		Expected Count	50.0	50.30	100.0

Table - 21

	Value	dt	Asymp. Sig (2 sided)	Exact sig (2sdides)	Extract sig (1sides)
Pearson chi-square	2.778	1	.096		
Continuity Correction	23127	1	.145		
Likelihood Ratio	2.795	1	.095		
Fisher's Exact Test				.144	.072
Linear- by – Linear association	2.750	1	.097		
N of valid cases	100				

Based on Pearson Chi-Square test, p-Value of 0.096 indicates the difference in smoking across case and control groups is statistically not significant.

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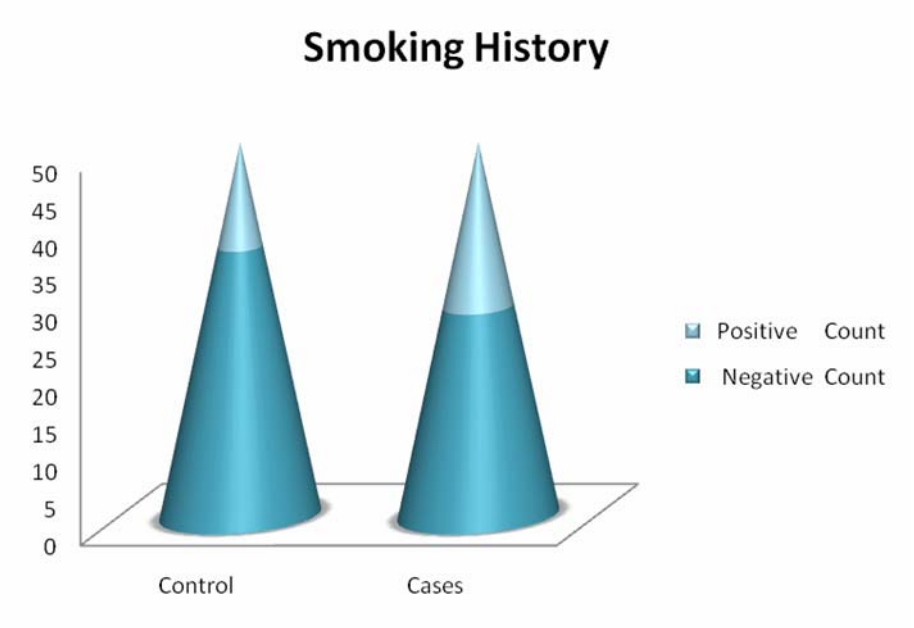
Smoking History
50
45
40
35
30
25
20
15
10
5
0
Control
Cases
Positive Count
Negative Count

`

Table - 22

		Group		Total
		Control Group	Case Group	
ALCOHOL Negative	Count	37	33	70
	Expected Count	35.0	35.0	70.0
Positive	Count	13	17	30
	Expected Count	15.0	15.0	30.0
Total	Count	50	50	100
	Expected Count	50.0	50.30	100.0

Table - 21

	Value	dt	Asymp. Sig (2 sided)	Exact sig (2sdides)	Extract sig (1sides)
Pearson Chi-square	.762[b]	1	.383		
Continuity Correction	.429	1	.513		
Likelihood Ratio	.764	1	.382		
Fisher's exact test				.513	.257
Linear- by - Linear association	.754	1	.385		
N of valid cases	100				

Based on Pearson Chi – Square test, p- Value of 0.383 indicates alcohol consumption do not differ across case and control group.

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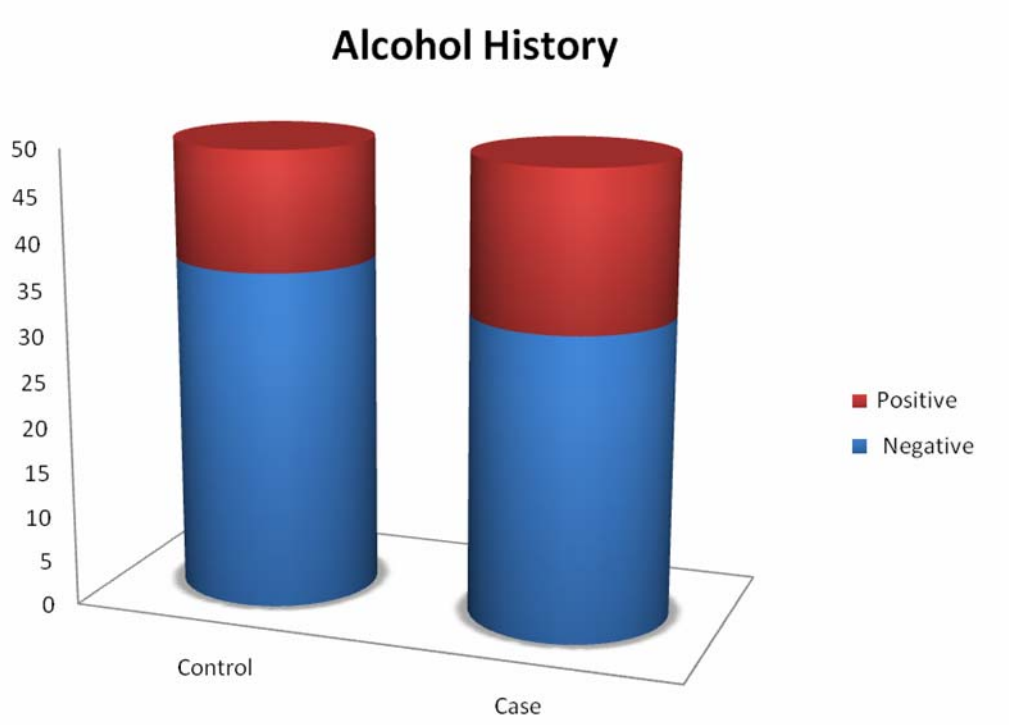
Alcohol History
50
45
40
35
30
25
20
15
10
5
0
Control
Case
Positive
Negative

`

Multivariate Analysis – Multiple Linear Regression

A multiple linear regression analysis was performed to study the association between coronary artery disease case group and HOMA-IR by controlling for all other factors.

Table - 24

COEFFICIENTS

Model		Unstandardized Coefficients		Standardized coefficients	t	Sig.
		B	Std. Error	Beta		
1	constant)	-7.941	1.984		-4.003	.000
	AGE	.032	.018	.111	1.795	.076
	GENDER	-.246	.258	-.064	-.954	.343
	FAM-HIST	-.073	.235	-.018	-.309	.758
	SMOKING	.122	.257	.031	.473	.637
	ALCOHOL	.004	262.	.001	.015	.988
	BMI	.002	.005	.025	406	.686
	WHR	3.077	1.398	0.162	2.201	.030
	SBP	.005	.008	0.37	609	.544
	HDL	-.058	.034	-.180	-1.695	.094
	LDL	.021	.010	.188	2.128	.036
	TGL	.006	.008	.088	.670	.504
	TC	-.005	.005	-.107	-1.070	.287
	FBS	.074	.016	.340	4.511	.000
	GROUP	1.092	.465	.293	2.348	.021

a. Dependent Variable: HOMA -IR

`

Variable named as “Group” is the indicator for coronary artery disease. Coding of Group is given by Group = 1 for case Group and Group = 0 for control group.

Based on the multivariate controlled study, after controlling for all other factors the difference in HOMA-IR between the case and control group is significant. Based on the p-value of 0.021 for Group variable and a positive regression coefficients of 1.092 suggests that we can conclude at 5% level of significance that the Coronary artery disease (case group) is associated with higher HOMA-IR and the case group has on an average 1.092 units of HOMA-IR higher than the control group.

`

DISCUSSION

DISCUSSION

Insulin resistance plays an important role in promoting CAD and the degree of insulin resistance correlates with the severity of CAD. (81). Insulin resistance has been considered to promote atherosclerosis by directly affecting blood vessels. The relationship between insulin resistance and atherosclerosis has been studied from various aspects. Hyperinsulinemia is an only indirect indicator of insulin sensitivity. Several large scale studies have revealed that hyperinsulinemia is closely associated with the mortality due to cardiovascular disease (82).

To date, however, few large scale studies have been conducted to examine the relationship between insulin resistance and coronary heart disease. Recently, IRAS (Insulin Resistance Atherosclerosis study) group has conducted large-scale epidemiological studies, and has reported that insulin resistance rather than insulin concentration is an independent powerful risk factor for coronary heart disease.(83).

There are different theories as to how insulin resistance affects coronary artery disease (84). Insulin resistance is related to the vasomotor dysfunction of the endothelial cells that line the coronary artery (85). It is well known that endothelial function is impaired in patients with coronary artery disease. In our study, we evaluated the effect of impaired glucose

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metabolism and insulin resistance that may play some role in the pathophysiology of CAD. We found increased fasting insulin levels in patients with CAD. Increased insulin resistance may play at least some role in patients with CAD.

Recent evidences indicate that insulin resistance is linked to untraditional CAD risk factors and possibly pro-atherosclerotic inflammatory state. Study conducted by Prof. Sidhartha Das and colleagues in angiographically established patients with CAD revealed the prevalence of IR in 40% and hyperinsulinemia in 50% of subjects having angiographically proven IHD who were normoglycemic.

Risk factors for CAD in Angiographically proved cases with IHD

Obesity (WHR)	100%
BMI	40%
HTN	60%
TC > 200	20%
LDL > 100	70%
TGL > 150	40%
HDL < 40	60%
Smoking	20%
Insulin resistance (HOMA IR >2.5)	40%

`

Mircoalbuminuria	20%
Hyper insulinemia (>9 μu/ml)	50%

In another study, Yazici et al (86) investigated the relationship between the degree of slow coronary flow (SCF) and serum insulin, glucose and lipid levels. As a result, they found no correlations between corrected TIMI frame count and serum insulin, glucose and lipid levels. However they measured only basal serum insulin, not insulin resistance, without homeostatic models. On the other hand, evaluating insulin resistance by homeostatic modelling is more reliable than the standard method because both fasting glucose and insulin levels are integrated (87).

According to Take zako et al; the profile of insulin resistance based on HOMA – IR model was correlated with severity of coronary atherosclerosis based on Gensini's score (88).

Other studies have reported that the incidence of major adverse cardiac events (MACE) following Percutaneous Coronary Intervention was higher in non –diabetic patients with high concentration of HbA_1C than those with low concentration of HbA_1C although these studies did not evaluate using insulin resistance (89). Here, the concentration of HbA_1C was lower in non-diabetic patients than in diabetic patients although it was high.

`

Some studies have reported that hyperinsulinemia and insulin resistance measured by HOMA are closely associated with restenosis following stenting in non diabetic patients (90, 91). A study from Finland found a significantly increased risk of ischemic loop to loop pdf disease in individuals who had hyperinsulinemia.

The Rancho-Bernardo study found no association between insulin levels and cardiovascular disease in women and an inverse association between post challenge insulin levels and cardiovascular disease in men (higher insulin levels were protective). Likewise, no association was found in the 3 studies that presented data on men and women combined; the study from Finland, the study of Pima Indians, and the Sand Luis valley study. It is possible that some of these differences reflect ethnic or geographic variation between the studies.

Another preliminary study from North India by Rajiv Mahajan & colleagues showed no significant association between fasting insulin and CAD. Similarly there was no significant relationship between HOMA – IR and CAD. However in this study, in addition to excluding diabetes, they excluded hypertension and obesity (BMI>25), as both are also independently associated with hyperinsulinemia. They did not find a significant association between hyperinsulinema and CAD.

`

SUMMARY

SUMMARY

Age and sex distribution between the two groups (cases and controls) were similar.

There was a significant difference in the distribution of family history across cases and control group suggesting a higher prevalence of family history of coronary artery disease in cases.

There was no difference in the prevalence of smoking between the cases and controls group.

Although there was no difference in body mass index (BMI) between the two groups, waist to hip circumference ratio was higher in case group than in control group suggesting higher prevalence of central obesity in cases with coronary artery disease.

Case group had on an average high total cholesterol and triglyceride and lower HDL cholesterol which was statistically significant than control groups. Though LDL was higher in cases it was not statistically significant.

Fasting Blood sugar was significantly higher in cases than in controls although it was lower than in patients with diabetes.

Fasting insulin and Insulin Resistance (HOMA –IR) were significantly higher in cases than in controls.

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Although family history, HDL, TGL, TC, FBS attained significance in univariate analysis, only WHR, LDL cholesterol and fasting blood sugar were significantly correlated with insulin resistance in multivariate analysis.

`

CONCLUSION

CONCLUSION

Thus fasting insulin levels and insulin resistance measured by homeostatic model assessment (HOMA-IR) are higher in patients with coronary artery disease compared to controls.

The mechanism by which insulin resistance provokes cardiovascular disease is mainly associated with the development of metabolic syndrome.

Insulin resistance is significantly associated with cardiovascular disease risk, even in the absence of diabetes, probably insulin resistance alone without diabetes can be considered as a coronary heart disease – risk equivalent in future.

Our study proves that non-diabetic patients with insulin resistance exhibit high concentration of serum triglyceride and low concentration of HDL cholesterol. The present study has shown that the value of HOMA- IR was correlated with levels of triglyceride and inversely correlated with that of HDL cholesterol

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LIMITATIONS OF THE STUDY

LIMITATIONS OF THE STUDY

The limitation of the present study is that it examined only a small number of patients. To date only few studies have been conducted to examine whether insulin resistance is correlated with coronary artery disease. Thus it can be taken as a preliminary study for further large scale studies.

The present study failed to testify the reproducibility since it did not measure the value of HOMA –IR in a repetitive manner. The concentration of serum glucose and insulin can be altered at each different measuring time, although the present study measured them only once. However HOMA-IR index is well reflected in euglycemic hyperinsulinemic clamp test, a standard test and the clinical usefulness has been well established.

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ABBREVIATION

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CAD	-	CORONARY ARTERY DISEASE
BMI	–	BODY MASS INDEX
WHR	–	WAIST HIP RATIO
SBP	–	SYSTOLIC BLOOD PRESSURE
DBP	–	DIASTOLIC BLOOD PRESSURE
HDL	–	HIGH DENSITY LIPOPROTEIN
LDL	–	LOW DENSITY LIPOPROTEIN
TGL	–	TRIGLYCERIDES
TC	–	TOTAL CHOLESTEROL
FBS	–	FASTING BLOOD SUGAR
SI	–	SERUM INSULIN
HOMA–IR	–	HOMEOSTATIC MODEL ASSESSMENT – INSULIN RESISTANCE
IRS	–	INSULIN RECEPTOR SUBSTRATE
IR	–	INSULIN RESISTANCE
VLDL	-	VERY LOW DENSITY LIPOPROTEIN
APO B	–	APOLIPOPROTEIN B
MRI	–	MAGNETIC RESONANCE IMAGING
NEFA	-	NON ESTERIFIED FATTY ACIDS
DM	–	DIABETES MELLITUS

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MI	–	MYOCARDIAL INFARCTION
TNF- ALPHA	–	TUMOUR NECROSIS FACTOR ALPHA
LPL	-	LIPOPROTEIN LIPASE
PAI- 1	-	PLASMINOGEN ACTIVATOR INHIBITOR -1
HSL	-	HORMONE SENSITIVE LIPASE
GLUT -4	-	GLUCOSE TRANSPORTER -4
PCOS	–	POLYCYSTIC OVARIAN SYNDROME
OGTT	–	ORAL GLUCOSE TOLERANCE TEST
QUICKI	–	QUANTITATIVE INSULIN SENSITIVITY CHECK INDEX
G/IRATIO	–	GLUCOSE /INSULIN RATIO
STEMI	–	ST ELEVATION MYOCARDIAL INFARCTION
NSTEMI	–	NON ST ELEVATION MYOCARDIAL INFARCTION
ACS	–	ACUTE CORONARY SYNDROME
RVMI	–	RIGHT VENTRICULAR MYOCARDIAL INFARCITON
ECG	–	ELECTROCARDIOGRAM
IRAS	–	INSULIN RESISTANCE ATHEROSCLEROSIS STUDY
TIMI	-	THROMBOLYSIS IN MYOCARDIAL INFARCTION
MACE	–	MAJOR ADVERSE CARDIAC EVENTS.

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PROFOMA

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PROFOMA

History

Name Age Sex

Occupation op.no

Address

Diabetes : Y/N Hypertension: Y/N

H/o Stable angina:

Smoker :

alcoholic:

Family H/O DM/HT/CAD:

Examination :

Height : Weight:

BMI : WHR:

Pulse : BP :

CVS : RS:

Abd : CNS:

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Investigations

Blood sugar Fasting : PP :

Blood Urea : Serum creatinine

Urine Alb : Sugar : deposits :

Lipid Profile :

TC : TGL : HDL: LDL :

ECG : Echocardiogram:

Fasting insulin: HOMA –IR :

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MASTER CHART

SL.NO	NAME	AGE	SEX	GENDER	FAM HIS	SMOKING	ALCOHOL	BMI	WHR	SBP	DBP	HDL	LDL	TGL	TC	FBS	SI	HOMA IR	GROUP
1	Vincent	51	M	1	1	0	1	28.4	0.91	100	70	37	122	209	244	105	25.4	6.58	1
2	Susainat	58	M	1	1	1	0	24.62	0.88	100	70	29	110	207	220	103	28.4	7.22	1
3	Thangara	64	M	0	1	1	1	29.4	0.92	110	70	31	88	163	147	102	32.4	8.16	1
4	Balarama	65	M	0	1	0	0	23.8	0.82	130	80	34	95	131	158	105	22.9	5.93	1
5	Elumalai	44	M	0	0	0	1	24.6	0.86	140	80	37	95	157	190	106	19.6	5.12	1
6	Mathivan	50	M	0	1	1	0	25.11	0.92	160	90	39	116	199	226	105	23.6	6.11	1
7	Radhakri	47	M	1	0	0	1	27.6	0.84	130	80	33	120	205	246	108	25	6.66	1
8	Akila	44	F	0	0	0	1	28.3	0.93	120	80	27	126	215	266	104	29.5	7.57	1
9	Nasreen	56	F	0	1	0	0	29.6	0.96	130	80	29	104	159	196	109	39.5	10.6	1
10	Akila	42	F	0	1	0	0	21.64	0.76	120	80	27	96	145	186	99	19.8	4.84	1
11	baskar	41	M	1	1	1	0	20.07	0.74	120	80	29	76	123	108	98	17.2	4.16	1
12	Govindan	45	M	1	1	1	1	22.8	0.72	140	70	32	90	152	155	106	22.4	5.86	1
13	Pencilli	65	M	0	0	1	1	26.37	0.9	130	80	35	132	209	264	108	32.9	8.77	1
14	Govindar	56	M	0	0	1	1	29.68	0.92	140	90	31	96	163	189	102	21	5.29	1
15	Padmavathy	55	F	0	0	0	0	21.6	0.76	130	80	37	102	165	176	91	29.5	6.62	1
16	Lakshmi	49	F	0	1	0	0	19.8	0.63	120	80	27	92	153	156	95	18	4.22	1
17	Chinnath	55	M	1	0	1	1	18.6	0.71	130	80	25	90	147	168	94	17.8	4.13	1
18	Selvam	48	M	1	0	0	0	22.5	0.82	120	80	27	92	167	184	98	19.5	4.71	1
19	Vijayala	63	F	0	1	0	0	23.43	0.76	130	70	29	96	165	182	96	14.2	3.36	1
20	Rajendra	52	M	1	1	0	1	28.62	0.92	130	80	33	124	213	258	108	15.8	4.21	1
21	Saravana	48	M	1	1	1	1	21.8	0.68	140	70	35	122	207	268	103	14.6	3.71	1
22	Chinnasa	45	M	1	0	1	1	27.8	0.94	130	80	39	126	209	276	105	14.5	3.75	1
23	Munusamy	46	M	1	0	1	1	22.5	0.68	120	70	35	88	157	161	93	13.8	3.16	1
24	Kuppan	55	M	1	1	0	1	27.5	0.92	150	90	37	86	163	194	102	14	3.52	1
25	Balaji	47	M	1	1	1	0	19.6	0.82	120	70	39	82	153	182	97	14	3.35	1
26	Murali	48	M	1	0	0	0	26.4	0.76	130	80	33	98	167	226	104	17.8	4.57	1
27	Mahohar	44	M	1	1	1	0	24.2	0.74	120	80	31	86	157	186	102	19.8	4.98	1
28	Mani	42	M	1	1	1	0	21.6	0.68	130	80	29	8	147	174	96	14.6	3.46	1
29	Rugavan	40	M	1	0	1	0	22.8	0.86	140	90	27	126	205	252	108	24.8	6.61	1
30	Ganatham	58	M	1	0	0	1	23.6	0.78	130	80	35	122	213	264	109	29.6	7.96	1
31	Jilal	54	M	1	0	0	0	28.6	0.94	140	80	37	120	227	284	107	28.8	7.6	1
32	Daniel	52	M	1	1	1	0	22.5	0.76	120	80	33	96	143	169	94	18.6	4.31	1
33	Arunacha	48	M	1	0	0	0	23.8	0.82	130	80	31	102	163	192	96	17.8	4.21	1

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34	Shanthi	50	F	0	0	0	1	26.2	0.8	140	80	33	104	189	220	98	29.6	7.16	1
35	Kathires	52	M	1	0	1	1	27.6	0.92	140	80	35	120	209	226	104	26.4	6.77	1
36	Yusuf	56	M	1	1	1	0	28.2	0.94	130	80	37	122	213	244	108	32.4	8.64	1
37	Malini	52	F	0	0	0	0	22.4	0.78	120	80	31	96	147	186	102	16.8	4.23	1
38	Madhavan	44	M	1	0	1	0	23.6	0.76	130	80	29	92	145	182	92	14.6	3.31	1
39	Vinodhin	50	F	0	1	0	0	21.6	0.68	120	80	31	86	141	176	96	13.8	3.27	1
40	Srinivas	55	M	1	0	0	0	26.4	0.88	140	80	35	104	183	192	98	21.6	5.22	1
41	Usha	52	F	0	0	0	0	20.6	0.66	110	70	33	86	165	168	88	14.4	3.12	1
42	Chandra	56	F	0	1	0	0	21.2	0.62	100	70	29	82	163	272	92	16.8	3.81	1
43	Durai	57	M	1	0	1	0	22.4	0.72	110	70	31	90	165	178	102	21.4	5.38	1
44	Sakuntha	68	F	0	0	0	0	28.4	0.94	110	80	37	122	209	246	104	26.8	6.88	1
45	Venkates	46	M	1	1	1	0	27.6	0.96	140	80	35	128	217	264	108	24.6	6	1
46	Jayaraj	44	M	1	0	1	0	24.6	0.82	130	80	33	102	205	202	104	24.8	6.36	1
47	Thanagam	52	F	0	0	0	0	22.4	0.78	120	80	29	98	149	186	98	21.4	5.17	1
48	Subraman	53	M	1	0	0	0	23.6	0.8	110	80	31	92	163	182	102	19.6	4.93	1
49	Gajendra	50	M	1	0	0	0	24.8	0.96	120	80	27	94	169	178	88	22.6	4.91	1
50	Dhanalax	66	F	0	0	0	0	20.6	0.68	100	80	29	86	153	168	86	15.5	3.29	1
51	Devaraj	55	M	1	0	0	0	22.6	0.84	130	90	46	92	132	184	109	13.3	3.3	0
52	Ravi	49	M	1	0	1	1	23.4	0.66	100	70	44	126	186	251	102	10.6	2.6	0
53	Kumar	54	M	1	0	1	1	20.8	0.77	130	100	47	70	133	144	103	11.1	2.8	0
54	Yobu	55	M	1	0	1	1	21.2	0.68	140	90	42	84	134	167	96	10.6	2.51	0
55	Rajendra	45	M	1	0	0	0	20.64	0.82	130	90	46	102	136	186	82	10.2	2.06	0
56	Pushpa	55	F	0	0	0	0	21.2	0.71	130	80	48	103	142	196	76	11.5	2.15	0
57	Manjula	56	F	0	1	0	0	22.6	0.58	120	80	42	104	138	168	85	14	2.93	0
58	Latha	54	F	0	0	0	0	21.8	0.66	130	80	38	96	134	188	78	10.8	2.02	0
59	Lalitha	57	F	0	0	0	0	27.6	0.86	120	80	42	115	194	230	95	12	2.8	0
60	Manner	45	M	1	0	1	0	19.2	0.63	130	80	44	84	106	164	102	11.6	2.92	0
61	Viswanat	42	M	1	0	1	1	243.2	0.76	120	80	46	122	146	247	84	11.2	2.32	0
62	Subraman	51	M	1	1	0	0	22.08	0.69	120	70	42	104	136	108	89	10.6	2.33	0
63	Geetha	58	F	0	1	0	0	21.35	0.7	110	70	44	94	108	116	83	10.6	2.61	0
64	Padma	42	F	0	1	0	0	31.62	0.88	120	70	42	126	184	266	99	12.9	2.81	0
65	Muhamed	47	M	1	1	0	0	22.8	0.68	190	80	44	98	125	189	85	11.5	1.99	0
66	Prabu	43	M	1	0	0	0	23.6	0.74	100	70	42	94	128	169	78	9.6	1.96	0
67	Ettiappa	47	M	1	0	0	0	22.4	0.82	100	80	44	92	134	168	104	10.2	3.21	0

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68	Mahima	48	F	0	1	0	0	24.6	0.8	100	70	42	88	142	196	101	12.5	3.21	0
69	Veerarag	56	M	1	0	0	0	24.22	0.72	110	70	39	122	189	246	90	10.2	2.26	0
70	Jayaraj	56	M	1	0	1	1	22.8	0.68	120	70	42	106	196	184	96	11.8	2.79	0
71	Santhosh	55	M	1	0	0	0	20.8	0.72	110	70	40	98	188	208	92	8.2	1.86	0
72	Jahir Hu	40	M	1	0	1	1	22.6	0.67	100	70	36	88	142	196	86	11.5	2.44	0
73	Vijaya	48	F	0	0	0	0	28.6	0.84	108	70	44	122	186	232	91	9.6	2.16	0
74	Chellamm	51	F	0	0	0	0	24.6	0.72	130	80	44	98	136	208	86	10.8	2.25	0
75	Bee Bee	55	F	0	0	0	0	22.6	0.82	140	70	42	84	106	184	82	11.4	2.3	0
76	Parvathy	50	F	0	0	0	0	24.6	0.78	130	80	44	110	164	220	86	10.6	2.25	0
77	Saraswat	62	F	0	0	1	0	20.8	0.8	140	90	46	92	136	196	102	14	3.52	0
78	Vasantha	58	F	0	0	0	0	28.6	0.94	150	90	42	82	132	189	80	10.9	2.15	0
79	Lakshmi	55	F	0	1	0	0	31.1	0.92	130	80	36	78	128	157	88	7.5	1.62	0
80	Thenmozh	54	F	0	0	0	0	22.6	0.68	120	80	42	92	132	185	84	8.3	1.72	0
81	Vijayala	64	F	0	0	0	0	23.43	0.72	130	80	40	90	128	180	96	14.2	3.36	0
82	Selvam	58	M	1	1	1	0	21.8	0.66	120	80	38	88	126	190	109	12.3	3.31	0
83	Frakash	54	M	1	0	0	0	22.6	0.64	120	80	42	96	134	176	98	11.2	2.71	0
84	Vinodh	66	M	1	0	1	1	23.4	0.74	130	80	44	102	142	188	86	12.6	2.67	0
85	Kala	54	F	0	0	0	0	24.8	0.82	120	80	42	108	156	216	96	13.8	3.27	0
86	Vikram	42	M	1	0	0	0	21.6	0.72	130	80	44	104	166	204	104	14.6	3.75	0
87	Sekar	44	M	1	0	1	1	22.8	0.8	140	80	36	94	136	189	88	12.6	2.73	0
88	Sankar	46	M	1	1	0	0	23.6	0.66	130	80	38	96	134	194	92	3.2	2.99	0
89	Gunasaga	44	M	1	0	0	1	24.8	0.92	140	80	40	108	186	226	106	15.8	4.13	0
90	Rajendra	56	M	1	0	1	0	26.5	0.74	130	80	42	96	126	128	92	12.8	2.9	0
91	Kumar	52	M	1	1	0	0	18.5	0.68	120	80	38	94	124	189	88	11.6	2.52	0
92	Ganesh	44	M	1	0	0	1	20.5	0.66	130	80	40	92	134	192	86	10.8	2.29	0
93	Vignesh	52	M	1	0	0	1	21.5	0.71	120	80	37	90	132	184	102	12.5	3.14	0
94	Seetha	46	F	0	1	0	0	22.5	0.72	120	80	38	96	142	168	94	13.5	3.13	0
95	Raju	48	M	1	0	1	1	24.5	0.78	130	80	44	98	186	184	92	14.5	3.29	0
96	Sundaram	49	M	1	0	0	0	22.6	0.64	140	80	42	94	142	194	102	12.2	3.07	0
97	Chandran	51	M	1	1	0	0	20.5	0.71	120	80	36	86	126	178	90	11.8	2.62	0
98	Saravana	46	M	1	0	1	1	18.5	0.66	130	80	40	92	138	194	82	2.3	2.49	0
99	Senthil	52	M	1	0	0	0	20.75	0.68	120	80	42	88	128	174	84	14.2	2.94	0
100	Murugesa	48	M	1	0	0	0	22.75	0.72	130	80	38	98	138	184	88	14.6	3.71	0

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