INSULIN RESISTANCE AND SIGNIFICANCE OF POSTPRANDIAL LIPID PROFILE IN NORMOGLYCEMIC CORONARY ARTERY DISEASE PATIENTS

DISSERTATION SUBMITTED IN FULFILLMENT OF THE
REGULATIONS FOR THE AWARD OF
M.D.GENERAL MEDICINE

DEPARTMENT OF GENERAL MEDICINE

PSG INSTITUTE OF MEDICAL SCIENCES AND RESEARCH

THE TAMIL NADU DR M.G.R MEDICAL UNIVERSITY

CHENNAI, TAMIL NADU

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CERTIFICATE

This is to certify that the thesis entitled "**INSULIN RESISTANCE AND SIGNIFICANCE OF POSTPRANDIAL LIPID PROFILE IN NORMOGLYCEMIC CORONARY ARTERY DISEASE PATIENTS"** is a bonafide work of **DR.MOOKAMBIKA .R.V** done under my guidance and supervision in the department of General Medicine, PSG Institute Of Medical Sciences And Research, Coimbatore for fulfilment of the regulations of Tamilnadu Dr MGR Medical University for the award of M.D in General Medicine.

Dr.K.Jayachandran, M.D

Guide & HOD

General Medicine

PRINCIPAL

DECLARATION

I hereby declare that this dissertation entitled "**INSULIN RESISTANCE AND SIGNIFICANCE OF POSTPRANDIAL LIPID PROFILE IN NORMOGLYCEMIC CORONARY ARTERY DISEASE PATIENTS"** was prepared by me under the direct guidance and supervision of Professor Dr.K.Jayachandran MD and Dr.G.Rajendiran DM Cardiology, PSG Institute of Medical Sciences And Research, Coimbatore.

This dissertation is submitted to Tamilnadu Dr MGR Medical University in fulfilment of the regulations for the award of M.D in General Medicine. This dissertation has not been submitted for the award of any degree or diploma.

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INTRODUCTION

Coronary artery disease (CAD) is a continuum of a pathological process, in which the coronary arteries gradually thicken, harden and atherosclerotic plaques develop which further occludes the blood flow. This leads to clinical manifestations such as angina and acute coronary events resulting from disruption of plaques, such as acute coronary syndromes, myocardial infarction and death.

The prevalence of CAD is rising rapidly in urban India. Lifestyle changes and aggressive control of risk factors are urgently needed to reverse this trend. Asian Indians have considerably higher prevalence of premature coronary artery disease (CAD) and standardized mortality rates for CAD compared with Europeans .Within the Indian subcontinent, a dramatic increase in the prevalence of CAD has been predicted in the next 20 years due to rapid changes in demography and lifestyle consequent to economic development

There are various risk factors of CAD which have been extensively studied, out of which **Type-2 diabetes** is an important etiopathogenic factor of accelerated CAD. **Insulin resistance** plays an important role in the pathogenesis of the development of type- 2 diabetes. Elevated insulin levels and insulin resistance may be evident several years prior to the diagnosis of type-2 diabetes. There are evidences supporting association of Insulin and CAD which indirectly reflects glucose intolerance, hypertension and dyslipidemia . However, the results from several studies are conflicting. Despite the clear relationship between type-2 diabetes and CAD, **the association of insulin resistance and CAD is more obscure in people without diabetes**.

It is well established that dysfunctional endothelium contributes to development and progression of atherosclerosis. Consequently, **early detection and treatment of endothelial dysfunction may be an attractive strategy for preventing CAD.** Unfortunately, established validated methods for assessment of endothelial dysfunction for chronic heart disease risk prediction in the clinical setting are not

currently available. Current techniques to assess endothelial function are invasive, expensive, or suffer from lack of high sensitivity, specificity, reproducibility, or clinically defined cut-off values. **Therefore, at this time, targeting established and modifiable risk factors for endothelial dysfunction and insulin resistance is the best primary strategy to prevent these conditions.**

Hypercholesterolemia and hypertriglyceridemia are considered the independent risk factors but most of the earlier studies in this area have considered only the fasting lipid profiles and lipoproteins. Recently it has been proposed that **postprandial lipoproteins may be better indicators of deranged lipoprotein metabolism and hence of atherosclerosis and CHD**.Postprandial hypertriglyceridemia (PHTG) and delayed triglyceride (TG) rich lipoprotein clearance have been found to impair endothelial function significantly either directly or by increasing superoxide anions.
It has also been reported that magnitude and duration of postprandial lipidaemia is positively related to the pathogenesis and progression of CHD. **There is comparatively more transfer of cholesterol and cholesterol esters from HDL to LDL in postprandial state leading to their low levels and this along with higher triglycerides and VLDL levels are better indicators of coronary heart disease**

Thus the present study aims to investigate the association of insulin resistance in normoglycemic patients with CAD, and to evaluate the role of postprandial lipid profile as an indicator of the efficiency of lipoprotein metabolism and its relationship with development of CHD. The age and gender matched non diabetic, non CAD controls underwent same series of investigations. Those with insulin resistance and dyslipidemia were identified and appropriate counseling for lifestyle modifications and preventive measures and treatment were given and were followed up.

OBJECTIVES

- **To find the association between insulin resistance and Coronary artery disease**

and

- **To evaluate the role of postprandial lipid profile and its relationship with development of CHD.**

- **Evaluation of apolipoproteins (A and B) on the same group.**

Of those normoglycemic Acute CAD patients admitted in ICCU/CCU of PSGIMS &R, Peelamedu, Coimbatore,Tamil Nadu

- **To give relevant health education on life style modification and preventive measures regarding insulin resistance and dyslipidemias for controls with abnormal results.**

REVIEW OF LITERATURE

Ischemic heart disease (IHD) is a condition in which there is an inadequate supply of blood and oxygen to a portion of the myocardium and it typically occurs when there is an imbalance between myocardial oxygen supply and demand. The most common cause of myocardial ischemia is atherosclerotic disease of an epicardial coronary artery (or arteries) sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery.

IHD causes more deaths and disability and incurs greater economic costs than any other illness in the developed world. **Obesity, insulin resistance, and type 2 diabetes mellitus are increasing and are powerful risk factors for IHD**. With urbanization in the developing world, the prevalence of risk factors for IHD is increasing rapidly in these regions such that a majority of the global burden of IHD is now occurring in low-income and middle-income countries. Population subgroups that appear to be particularly affected are men in South Asian countries, especially India.

My study Aims at

- Assessing Insulin resistance in patients with coronary artery disease

- Investigating on an upcoming investigations which have only a few reviews and journal- published so far- postprandial dyslipidemia – observing for any abnormalities pertaining to patients with CAD

- Estimation of apolipoprotein A and B on same patients.

Insulin resistance and cardiovascular disease

HISTORY:

Insulin resistance can be seen as a molecular and genetic mystery involving defective insulin signaling and glucose transport into cells. Insulin resistance represents a major underlying abnormality driving cardiovascular disease, the major cause of morbidity and mortality in much of the world.

The history starts with Margaret Albrink who was probably the first investigator to identify a cluster of factors, including obesity and hypertriglyceridemia, that was associated with increased risk for coronary artery disease (CAD) (1). The groundbreaking development of the insulin radioimmunoassay by **Berson and Yalow,** and the subsequent observation that many diabetics were actually hyperinsulinemic, enabled Albrink and others, including **Reaven and Farquhar** and their colleagues (2), to begin to define the insulin resistance syndrome and its links to both hypertriglyceridemia and CAD.

The next decades brought several prospective cohort studies in which hyperinsulinemia was often associated with CAD, at first in univariate and more recently in multivariate analyses. These efforts culminated recently in the demonstration by investigators in the Insulin Resistance Atherosclerosis Study (IRAS) of a link between a direct measure of insulin resistance itself and atherosclerosis (3). In addition, the 1970s brought a new understanding of protective roles of HDL (4). Together with the characterization of small dense LDLs in the 1980s, this advance led to the identification of a typical dyslipidemic pattern that is a central component of the insulin resistance syndrome. Another important addition to the complex was the observation by **Welborn and colleagues in the mid-1960s** that hypertension was commonly associated with hyperinsulinemia (5). Finally, the realization that individuals with insulin resistance both were hypercoagulable and had impaired fibrinolysis (6) added a pathologic basis for an increase in acute CAD events to the well accepted association of the insulin resistance syndrome with risk factors for atherosclerosis.

As the components of the syndrome have increased the scientific interest , opportunities to investigate the links between insulin resistance and cardiovascular disease, have multiplied.

PATHOPHYSIOLOGY:

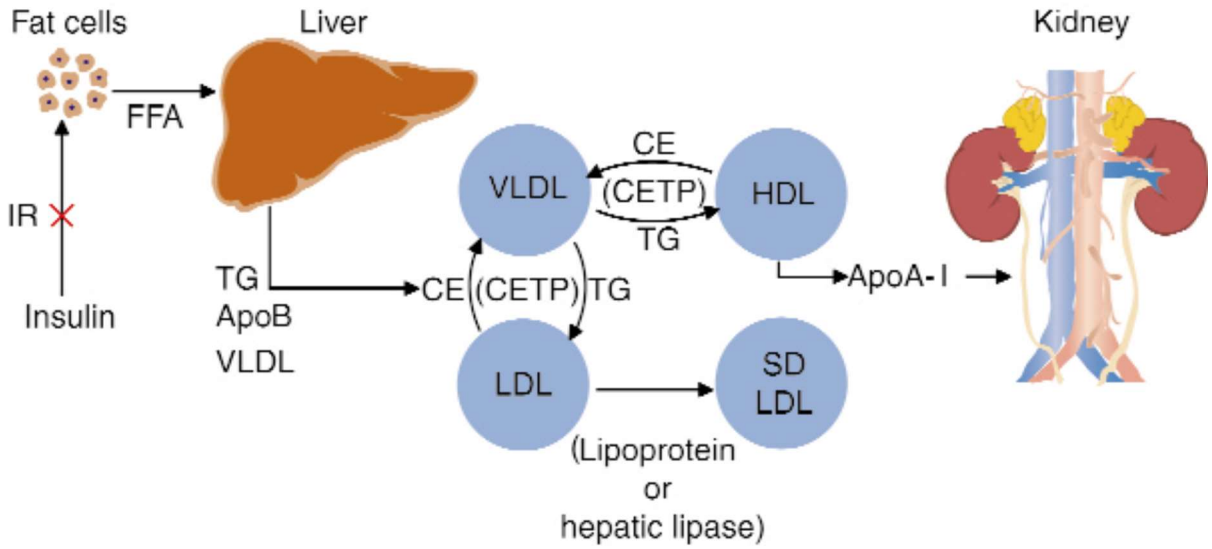
In brief insulin resistance is not simply a problem of deficient glucose uptake in response to insulin, but a multifaceted syndrome that increases significantly the risk for cardiovascular disease.

The links between insulin resistance and the associated dyslipidemia, hypercoagulability, and atherosclerosis are numerous and complex. This complexity derives both from the almost certain multiple causes of the insulin resistance syndrome and from the interaction of genes predisposing to insulin resistance with other genes that have their own, independent impact on lipid metabolism, blood pressure regulation, coagulation, and artery wall biology.

Dysregulation of fatty acid metabolism plays a central role in the development of this phenotype. Thus, the association between insulin resistance and dyslipidemia is clearly initiated by increased FFA release from, or defective uptake of FFAs into, adipocytes. Recent studies linking fatty acids to endothelial dysfunction, together with the clear role of VLDL in the stimulation of PAI- 1, further support the view that dysregulation of fatty acid metabolism sits close to the center of the pathophysiology of the insulin resistance syndrome, at least as it relates to risk for cardiovascular disease.

The more detailed illustration is given below.

Insulin resistance and dyslipidemia



A simplified model relating insulin resistance to dyslipidemia and cardiovascular disease.

- Insulin resistance at the adipocyte results in increased release of fatty acids into the circulation. A similar accumulation of fatty acids could arise from defects in fatty acid transporters or intracellular binding proteins.
- Increased FFA flux to the liver stimulates the assembly and secretion of VLDL resulting in hypertriglyceridemia.
- In addition, VLDL stimulates the exchange of cholesteryl esters from both HDL and LDL for VLDL TG.
- ApoA-I can dissociate from TG-enriched HDL. This free apoA-I is cleared rapidly from plasma, in part by excretion through the kidney, thus reducing the availability of HDL for reverse cholesterol transport.
- TG-enriched LDL can undergo lipolysis and become smaller and more dense.
- Low levels of HDL and the presence of small dense LDL are each independent risk factors for Cardiovascular disease.

- IR, insulin resistance; CE, cholesteryl ester; SD, small dense**. (** ***The Journal of Clinical Investigation | August 2000 | Volume 106)***

Insulin resistance at the level of the fat cell is shown as the initiating insult, leading to increased intracellular hydrolysis of triglycerides (TGs) and release of fattyacids into the circulation. It seems that insulin resistance in adipose tissue results from the interaction of multiple defective or less than optimally function in genes with an environment that leads to increased pressure on the fat cell to store energy (Kahn and Flier, this Perspective series, ref. 7). This interaction results in a fat cell that cannot meet the demands placed upon it. Whatever the molecular or environmental basis for insulin resistance in adipose tissue, *the result is that FFA uptake by fat cells is decreased and/or FFA release from fat cells is increased, confronting the liver with increased availability of energy.*

Indeed, the *hypertriglyceridemia of insulin resistance can be viewed as a Ping-Pong match between the hepatocytes and fat cells, where VLDLs and FFAs are the Ping-Pong balls carrying energy back and forth between the liver and the adipose tissue*.Both the absence of fat and the abundance of fat are associated with increased fatty acid flux to the liver and subsequent increased secretion of VLDL. Candidate genes that could underlie the increased flow of fatty acids include regulators of fatty acid uptake and storage by adipocytes, such as those for hormone-sensitive lipase (HSL) (9), lipoprotein lipase (LPL) (10), and complement component C3a (whose proteolytic product is the acylation-stimulating protein [ASP] [ref. 11]), as well as for various fatty acid transporters and binding proteins.

Thus the inability of insulin-resistant fat cells to store TG is very likely the initial step in the development of the dyslipidemia characteristic of insulin resistance. Importantly, this link between the fat cell and hepatic production of VLDL does not seem to be necessarily linked, in mouse models, to insulin resistance at the level of muscle. No candidate genes have been linked unequivocally to either the dyslipidemia or the insulin resistance in humans. Indeed, although the CD36 gene appears to be an important candidate, the data from the CD36 knock-out mice indicate that any CD36 defect would have to be specific to adipose tissue to cause both hypertriglyceridemia and insulin resistance.

Cardiovascular disease and the dyslipidemia of insulin resistance.

The available in vitro and in vivo data suggest that, as long as adequate insulin is available to prevent excessive lipid oxidation, FFA-driven lipid synthesis is the major determinant of VLDL TG secretion. Hyperinsulinemia probably is a marker of insulin resistance, rather than a major, direct contributor to the process. The basis for the rise in FFA flux in insulin resistance is probably oligogenic in nature, but whatever its ultimate cause, the rest of the dyslipidemic phenotype associated with insulin resistance follows once VLDL secretion increases. Hypertriglyceridemia, leading to low HDL cholesterol and increased small dense LDL particles, is due mainly to the actions of cholesteryl ester transfer protein (CETP) (12).

In plasma, collisions between VLDL and HDL, in the presence of CETP, stimulate the transfer of VLDL TG to HDL in exchange for HDL cholesteryl esters. The resulting TG-enriched HDL becomes a good substrate for hepatic lipase (and possibly LPL), and the TG is hydrolyzed. This, in turn, generates a smaller HDL that must shed some of its surface, including apoA-I. ApoA-I is a small protein that can be filtered by the kidney and then degraded by renal tubular cells (13). In a similar fashion, intravascular collisions between VLDL and LDL allow for CETP-mediated exchange of VLDL TG for LDL cholesteryl esters. The succeeding hydrolysis of LDL TG generates small dense LDL particles.

Since both normoglycemic insulin-resistant individuals and patients with type 2 diabetes mellitus do not have higher LDL cholesterol levels than the general population, how does the resulting dyslipidemia increase the risk of insulin-resistant individuals to cardiovascular disease?

- Multiple aspects of their lipid profiles are atherogenic.

- First, not only are there increased levels of VLDL particles, which can enter the vessel wall and accumulate in atherosclerotic plaques (14,15), but these VLDL are, by virtue of receiving CETP-transferred cholesteryl esters, able to deliver more cholesterol per particle to the vessel wall.Increased VLDL secretion can contribute to postprandial hyperlipidemia by providing competition for chylomicron clearance pathways; postprandial hyperlipidemia is independently associated with CAD (16).

- Second, reduced HDL cholesterol and apoA-I levels mean that there are fewer HDL particles engaged in cholesterol efflux from peripheral tissues, which is the first step in reverse cholesterol transport. Fewer HDL particles also mean that HDL cannot fulfill

several proposed direct antiatherogenic actions at the vessel wall, including the role of HDL as an antioxidant.

- Krieger and colleagues recently identified scavenger receptor B1 (SRB1) (17), which appears to mediate the selective delivery of HDL cholesteryl esters to the liver (delivery of core lipid by the HDL particle without endocytosis and degradation of the whole particle), targeting that cholesterol for excretion via the biliary pathway.

- CETP-mediated transfer of HDL cholesteryl esters to VLDL not only may enrich an atherogenic lipoprotein with cholesterol but also can divert that cholesterol from the specific reverse cholesterol transport pathway. Theoretically, the reduced HDL cholesterol characteristic of insulin resistance could be the result of increased SRB1 expression; this is unlikely, however, because such an increase would likely reduce the risk of atherosclerosis (18).

- Finally, small dense LDL, first identified by Sniderman and colleagues (19) and then studied in depth by Krauss and Austin and their colleagues (20), may be more atherogenic than an equal number of larger more cholesteryl ester–rich LDL, because small dense LDL may be more liable to oxidation or may more readily penetrate and stick to the ECM of the artery wall.

Insulin resistance and clotting

Numerous epidemiologic and clinical studies have provided evidence of the importance of several factors integral to clotting and fibrinolysis, including fibrinogen, factor VII, and plasminogen activator inhibitor 1 (PAI-1), for the risk of developing cardiovascular disease. It has also been demonstrated that these factors are increased in individuals with insulin resistance.

The basis for increased levels of fibrinogen in the insulin resistance syndrome is not clear, but it may be related to obesity. Factor VII activity has been shown to increase during postprandial hyperlipidemia (21), suggesting a risk for acute CAD events after consumption of a high-fat meal.

PAI-1 was shown by Hamsten et al. (22) to be a marker for risk of premature CAD, and the link between elevated PAI- 1 and insulin resistance has been studied extensively in tissue culture models. Both hepatic cells and endothelial cells respond to increased levels of insulin by synthesizing and secreting more PAI-1. Incubation of endothelial cells with VLDL also increases PAI-1 synthesis and secretion; a putative VLDL response element, recently identified in the gene for PAI-1, may be responsible for this induction (23).

Insulin resistance and the artery wall

There is increasing evidence that insulin resistance may be directly atherogenic. The results of IRAS suggest a direct relationship between insulin resistance, as measured by the frequently sampled intravenous glucose tolerance test and carotid artery intima/media thickness, even after adjusting for several associated risk factors (3). Although those results could simply indicate that there are other risk factors for atherosclerosis that were not measured in IRAS, they can also be taken to indicate direct effects of impaired insulin action at the level of endothelial or vascular smooth muscle cells.

Finally, as described above, insulin signaling pathways in smooth muscle cells may be differentially affected in the insulin resistance syndrome so that Hyperinsulinemia, resulting from insulin resistance in muscle, fat, and liver, may stimulate proatherogenic pathways in vascular smooth muscle cells. The potential role

of PPARg receptors in those cells offers new targets for affecting atherogenesis directly in insulin-resistant patients.

Identifying insulin resistance

Besides using guidelines such as ATP III or World Health Organization criteria for identifying patients with the metabolic syndrome, there are other surrogate markers of insulin resistance that can be employed in clinical practice.

1. **Triglyceride level greater than 130 mg/dL, triglyceride- to-HDL ratio greater than 3, and serum insulin level greater than 15 mU/mL** can be used to assess insulin resistance (24).

   In the ***primary care setting***, Reaven and colleagues suggest that the most practical approach to identify patients with insulin resistance is using either the serum triglyceride level or the triglyceride-to-HDL ratio.

2. **Homeostatic model assessment (HOMA) of insulin resistance**

   HOMA IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5

   This equation is the ratio of the insulin sensitivity of the patient in question to the insulin sensitivity of a normal individual (with a normal fasting serum insulin of 5 mU/mL, a normal fasting serum glucose of 4.5 mmol/L, with the product of these two values equaling 22.5, the normalizing factor) (25,26)

   Therefore, a ***HOMA greater than 1 represents an insulin resistant state***.

3. **Hyperinsulinemic - euglycemic clamp:**

   Measure the mean glucose rate required to maintain a euglycemic state with a constant insulin infusion.

   Thus, a ***greater glucose requirement indicates greater insulin sensitivity***.

4. **Steady state plasma glucose (SSPG):**

It is the glucose level measured in the setting of a fixed infusion of both insulin and glucose.

The lower the glucose level measured, the greater the degree of insulin sensitivity

Hyperinsulinemic - euglycemic clamp and Steady state plasma glucose (SSPG) are used for research purpouses

Therapeutic interventions

Therapeutic interventions targeting endothelial dysfunction and insulin resistance (Acquired and genetic factors) influence metabolic, vascular, and inflammatory homeostasis that involve multiple cellular and physiologic mechanisms that contribute, to development of insulin resistance and endothelial dysfunction.

But there are no validated screening tools for assessing endothelial dysfunction in the clinical setting. Therefore, ***clinical assessment of conventional risk factors and a comprehensive management approach is needed to effectively treat or prevent endothelial dysfunction and insulin resistance.***

Interventions aimed at improving either insulin resistance or endothelial dysfunction that raise plasma adiponectin levels, block renin angiotensin and endothelin systems, lower oxidative stress, and attenuate inflammation are predicted to have simultaneous beneficial effects on both metabolic and cardiovascular function.

Dietary and lifestyle modifications

Diet, weight loss, and physical exercise decrease insulin resistance and improve endothelial dysfunction (27,31-59)

Therapeutic intervention	Mode of benefit	
Diet	• Increases eNOS expression in human skeletal muscle [102]. • Improves NO-dependent vasodilation • Reduces circulating ET-1 levels, • Increases adiponectin levels in insulin resistant individuals	Calorie restriction alone (25% less than baseline energy requirements)
Mediterranean-style diet	• reduces serum concentrations of inflammatory markers • decreases insulin resistance • improves endothelialfunction	
Physical exercise	• Same as above • Enhanced insulin signaling • Accentuated enos activity and expression • Reduced oxidative and inflammatory stress • Enhanced NO availability • Restoration of balance between vasoconstrictor and vasodilator actions	

.

Pharmacologic interventions:

Routinely used pharmacotherapies, such as

- ✓ insulin sensitizers
- ✓ hypolipidemic agents
- ✓ angiotensin II antagonists

improve endothelial dysfunction in insulin-resistant individuals (31,58-74) These studies suggest that a combinatorial therapeutic strategy may be more effective in ameliorating endothelial dysfunction frequently observed in insulin-resistant states.

Latest in medicine:

- ✓ ***Pramlintide*** is an analogue of the glucose-lowering peptide amylin, which is produced by pancreatic cells. In combination with insulin, pramlintide slows gastric emptying and suppresses the release of glucagons. Glucagon-like peptide-1 (GLP-1), which is produced by the small intestine, inhibits gastric emptying, resulting in a slowed rate of glucose absorption; it also stimulates insulin secretion by pancreatic β-cells and suppresses inappropriately elevated glucagon secretion.(75)

- ✓ **GLP-1 mimetics: Exenatide** is a GLP-1 mimetic that lowers blood glucose levels and reduces body weight.

- ✓ ***Sitagliptin,*** an inhibitor of the enzyme dipeptidyl peptidase-4, acts by increasing the activity of GLP-1 and gastric inhibitory polypeptide.(76)

- ✓ Under trial:
  - **Cholesteryl ester transfer protein (CETP) inhibitors (eg, torcetrapib)**
    - increase HDL-C and apolipoprotein-A1 concentrations. (77)
    - Torcetrapib production was halted due to its adverse events, the therapeutic approach of reducing CVD risk by increasing HDL-C concentrations has been established, and the US Food and Drug Administration is now working closely with companies that are currently developing CETP inhibitors.

  - **Endocannabinoid** receptor system in the regulation of body weight and other metabolic processes that may influence CVD risk.

    - Endocannabinoids are endogenous substances that activate a family of CNS receptors that are important in the regulation of appetite, food intake, and lipid metabolism.

    - In animal studies, activation of endocannabinoid receptors within the hypothalamus was shown to stimulate feeding, whereas agents that block endocannabinoid receptors were shown to increase satiety and decrease food intake .(78,79)

- The efficacy and safety of **the Cannabinoid1 antagonist rimonabant*** for the treatment of obesity was recently examined in several 1- and 2-year, Phase III clinical trials:
    - Rimonabant significantly reduced body weight and waist circumference. It also improved several measures of lipid and glucose metabolism, including TG, HDL-C, and small dense LDL particle levels, the level of C-reactive protein (an inflammatory marker), and insulin sensitivity.(80,81)
- Rimonabant is not yet approved in the United States pending submission of a new drug application with the US Food and Drug Administration and review of safety data

POST PRANDIAL DYSLIPIDEMIA & ITS SIGNIFICANCE

***Postprandial dyslipidemia is now being recognized as a marker of insulin resistance syndrome and its related lipid abnormalities*.**

Traditionally, we are all used to conduct fasting lipid profile estimations since the TG levels are markedly affected by meals and it takes 8-10 hours of fasting state for a steady state to be reached. Total cholesterol levels are not affected by fasting or postprandial states and can be conducted at random. However, since LDL levels are derived from mathematical calculations dependent on TG levels total lipid profile is only done in fasting state, although some labs do direct LDL estimation now.

All guidelines for classification, detection and management of dyslipidemias recommend fasting lipid profiles for a uniform pattern and we do need to stick to this for all routine purposes.1 However, disturbances in postprandial lipemia have been observed in subjects with Type 2 Diabetes Mellitus (DM) and in those with visceral obesity or features of metabolic syndrome/ Insulin resistance. We need to be conscious and aware of the relevance of this phenomenon of postprandial dyslipidemia.(82,83) , and hence the current study design

In 1979 Zilversmit first proposed that triglyceride-rich liproproteins (TRL) seen in postprandial dyslipidemias play an independent role in atherosclerosis.(87) Since then many studies have shown the role of postprandial lipoprotein particles in the development of CHD. In fact some studies have shown that postprandial hyperlipidemia may be a better discriminant of the presence of CHD than fasting TG Levels.(88) There is no large epidemiological study available showing that postprandial hyperlipidemia is an independent risk factor for CHD. However, it has been shown that postprandial hypertriglyceridemia was more closely correlated to carotid intima-media thickness than fasting TG levels.(89,90)

Proposed Mechanism of Postprandial dyslipidemia in concern to atherosclerosis:

TG rich lipoproteins in PP state act adversely on vascular endothelium through increasing superoxide anion radicals or by direct impairment of vascular endothelium by decreasing coronary bioactivity.(85,86,91-93)

In another study, it was found that atherosclerosis was associated with PP TG levels independently of fasting TG suggesting that lipoprotein characteristics specific to PP state are atherogenic.(94)

Roche et al have shown that magnitude and duration of PP lipemia is positively related to the pathogenesis and progression of CHD.

An elevated lipemic response precipitates a number of adverse metabolic events by activating the coagulation factor VII and plasminogen activator inhibitor.(95,96)

Postprandial state modulates both metabolism and composition of apo B-100 containing lipoprotein particles and it is probable that the intravascular cholesterol redistribution due to postprandial lipidaemia modifies plasma lipoproteins such that there is an increased generation of potentially atherogenic TG rich lipoproteins and small dense LDL.(96)

Delayed lipid clearance from body might reveal a state of fat intolerance linked to an elevated risk of CHD that is under genetic control and cannot be detected by simple measurement of fasting lipids.

In fed state, with the influx of TG rich lipoproteins from the intestines and subsequent lipolysis of triglycerides, there is transfer of cholesterol esters from HDL and LDL to these particles through the action of CETP (Cholesterol ester transfer protein). This results in a decrease in LDL-C and HDLC in the fed state as compared with the fasting state .

Decreased HDL-C in patients indicate decreased rate of reverse cholesterol transport and therefore accumulation of TG rich lipoproteins leading to increased risk of atherosclerosis and CHD in patient group.

Thus, higher TG and VLDL-C and lower HDL-C levels are better indicators of CHD than the classical risk factors like total cholesterol and LDL-C supporting the hypothesis that postprandial lipoprotein metabolism and their catabolic rate play a crucial role in the development and progression of atherosclerosis

Implications:

It essentially implies disproportionate rise in postprandial triglyceride levels. This is akin to impaired glucose tolerance and is metabolically related to insulin resistance and thus clinically related to visceral obesity. Other features of obesity related dyslipidemia including low HDL levels and increased small dense LDL particles are accompaniments of postprandial dyslipidemia and are already well recognized risk factors for CHD.

There are no standard guidelines regarding levels which define postprandial dyslipidemia. In some large studies a postprandial triglyceride (TG) concentration of more than 220 mg% has been taken as abnormal. Postprandial dyslipidemia has been proposed as an independent marker and risk factor for CHD.

In fact a study from Japan shows that it correlated more closely to carotid intimal media thickness than fasting TG levels. It essentially implies inability of body metabolism in presence of insulin resistance to handle postprandial lipid load.

CHD is associated with a 76% increase in risk for women and 32% for men for every 1 mmol/l increase in triglyceride levels. The increased risk of CHD remains significantly elevated for both sexes even when adjusted for HDL concentration.(6)

Measurement Of fasting lipids vs postprandial. Does it matter? Is one better than the other?

BASICS:

Lipids (cholesterol and triglycerides) are oils and not soluble in aqueous solutions like plasma. Thus, lipids are transported inside of protein wrapped vehicles called lipoproteins. The proteins wrapping and making soluble the lipids are called apolipoproteins, of which there are many. No human has free cholesterol or TGs in their plasma.

Thus when we look at lipid profile, we are looking at lipid not lipoprotein concentrations:

- ie values of the cholesterol content inside various lipoproteins per deciliter of blood (LDL-C, VLDL-C, HDL-C) or TG (which is the TG content in all of the lipoproteins in a deciliter of blood).
- Total cholesterol (TC) is the sum of: HDL-C + LDL-C + IDL-C + VLDL-C + Lp(a)-C + chylomicron-C + remnant-C
- The atherogenic cholesterol (that capable of arterial wall macrophage ingestion) is that carried in the above particles that have apoB on their surface. That would be all of the above except HDL particles (an apolipoprotein A-I particle). Collectively all of the apoB particles are termed betalipoproteins.

- *NCEP guidelines suggest identifying beta-lipoproteins by using the surrogate non-HDL-C level*

  Non-HDL-C calculation:

  Non-HDL-C = TC minus HDL-C

  Non-HDL-C = LDL-C + IDL-C + VLDL-C + Lp(a)-C + chylomicron-C + remnant-C

  Non-HDL-C = beta-lipoprotein cholesterol

  Non-HDL-C is a superior surrogate for apolipoprotein B levels than LDL-C

The beta-lipoprotein particles other than LDL are just as atherogenic as LDL if present in increased quantities and if their diameter is < 70 nm. Such particles enter the artery wall, just like LDL particles.

NCEP states remnant lipoproteins (smaller VLDLs and chylomicrons and IDLs) convey atherogenicity substantially beyond that predicted by LDL-C.. Since remnants are mostly TG-rich postprandial particles, they are easy to miss if lipid profiles are done fasting and would be missed less often if postprandial profile was done.
A normal TG value is 170-200 mg/dL postprandially. Anyone with more than 200 md/dl is pathologic either genetic and/or more likely insulin resistance.

TRIGLYCERIDE/HDLC INDEX

Triglycerides and triglyceride–high-density lipoprotein (HDL) ratio are good surrogate markers for identifying insulin resistance in overweight patients, according to the results of a cross-sectional study published in the Nov. 18 issue of the Annals of Internal Medicine. Since triglycerides and HDL are independent predictors of cardiovascular risk (97), their ratio could be used as a simple cardiovascular risk marker Based on receiver-operating characteristic curve analysis, the optimal cut-points were 1.47 mmol/L (130 mg/dL) for triglyceride, 1.8 in SI units (3.0 in traditional units) for the triglyceride–HDL cholesterol ratio, and 109 pmol/L for insulin. These cut-points achieved a sensitivity of 67%, 57%, and 68%, and specificity of 64%, 71%, and 85%, respectively. The ability of these markers to identify insulin-resistance was similar to that of the criteria proposed by the Adult Treatment Panel III to diagnose the metabolic syndrome, which had a sensitivity of 52% and specificity of 85%

Some surrogate indexes have attempted to help in the recognition of insulin resistance in patients with overweight or glucose abnormalities. The Spanish MESYAS (98)(Metabolic Syndrome in Active Subjects) group has studied the correlation between TG/HDL ratio and the presence of Metabolic Syndrome in 18,778 active workers (77.6% men; mean age 42.2 ± 10.7 years) enrolled in 3 insurance companies in Spain from their annual health examinations. Prevalences of MS were 18.8% in men and 6.1% in women. Mean value of the TG/HDL ratio was 2.50 ± 2.2 and increased in parallel to the number of MS components present. Subjects with MS had a ratio that was 2 times higher compared with those without (5.10 vs 2.03, $p < 0.001$). Receiver operating

characteristic curves showed that values >2.75 in men and >1.65 in women of the TG/HDL ratio were highly predictive to the diagnosis of MS with 80% sensitivity and 78% specificity(99).

Another more recent study of this group has aimed to correlate the TG/HDL ratio with the incidence of a first coronary event (myocardial infarction, unstable angina or subclinical myocardial ischemia detected through electrocardiogram abnormalities) in male workers according to body mass index (BMI) in a case-control study design (208 cases and 2080 controls, mean age 49.9 years). TG/HDL ratio was significantly higher in cases compared to controls, and a significant increasing prevalence of cases and mean TG/HDL in each category of BMI was present. Multivariable analysis demonstrated that TG/HDL increased by 50% the risk of a first coronary event (OR: 1.47; 95% CI 1.26-1.71), meanwhile LDL-C values obtained more moderate increased-risk (OR: 1.01; 95% CI 1.005-1.012); metabolic syndrome (OR: 1.76; 95% CI 0.94-3.30) and hypertension (OR: 1.50; 95% CI 0.81-2.79) did not reach statistical significance. TG/HDL ratio was associated to first coronary event in all categories of BMI(98)

A number of studies have shown that the ratio TG/HDL has a good correlation with the generally accepted methods to define insulin sensitivity, with the possible exception of African Americans(100). Some drugs (thiazolidindiones, angiotensin and aldosterone antagonists, moxonidine) (98)have demonstrated favourable effects on IR, although we do not have enough data to confirm if TG/HDL also change in the good direction.(98)

MATERIALS AND METHODS

Fifty patients of CAD admitted to ICCU/CCU of PSGIMS & R were studied. The cases of this present study were 50 non diabetic CAD patients and controls were selected based on age and sex matched non diabetic and non CAD patients who has to undergo similar set of investigations as cases.

Defining criteria for Coronary artery disease:

WHO criteria-2000

A cardiac troponin rise accompanied by either typical symptoms, pathological Q waves, ST elevation or depression or coronary intervention are diagnostic of MI.

Defining criteria for Diabetes Mellitus:

WHO criteria:

1) Symptoms of diabetes mellitus plus a random glucose concentration >200 (11.1mmol/l). The classic symptoms of diabetes mellitus include polyuria, polydipsia and unexplained weight loss

OR

2) Fasting blood glucose >126 mg/dl (7.0mmol/l). Fasting is defined as no caloric intake for at least 8 hours

OR

3) 2 hour post prandial glucose > 200mg/dl (11.1 mmol/l). Among diabetics, the above criteria were **considered to exclude** the patients for the study.

Inclusion criteria for case selection:

1) Acute coronary event
2) Non diabetics

Exclusion criteria for case selection:

1) Diabetics on insulin/ Oral hypoglycemic agents
2) Severe cardiac failure (classes 3–4)
3) Renal,hepatic, and other systemic diseases
4) Morbid obesity
5) History of malignancy
6) Previous h/o dyslipidemia

The selected patients were studied in detail with history and physical examination

History:

- Patient's characteristics age, sex
- All details regarding the presenting complaints were noted.
- History regarding type II DM, SHT, and other comorbid conditions were noted.
- The family history regarding diabetes and CAD was taken.
- Personal history regarding smoking, alcohol consumption, bowel and bladder habits and drug intake were noted.

A complete clinical examination was carried out in each patient with particular reference to ischemic heart ,dyslipidemia,systemic hypertension.

Height and weight were measured in all cases and body mass index (BMI) was calculated by weight in kg / height in m2

Hypertension was said to be present when there was a history of hypertension or the systolic blood pressure was recorded greater than 160mm of hg and/or diastolic pressure greater than 90 mm of hg on 3 consecutive occasions.

Ischemic heart disease was recorded to be present in the presence of suggestive history of angina or myocardial infarction with electrocardiographic evidence with elevated cardiac troponins.

Peripheral vascular disease was considered to be present with history of amputations and /or absent of one or more peripheral pulses and /or presence of gangrenous foot.

Peripheral markers of dyslipidemia was also considered

T*he following investigations were done in all the patients.*

- Complete blood picture
- Urine analysis
- Renal function tests
- Fasting Blood sugar and Postprandial blood sugar
- Glycosylated hemoglobin
- Fasting and post pransial lipid profile
- Apolipoprotein a and b
- Fasting insulin levels
- Chest x-ray
- Electrocardiogram
- Echocardiogram
- Coronary Angiography

Estimation of Insulin resistance by HOMA score:

The homeostasis model assessment insulin resistance index (HOMA IR) evaluates insulin resistance via calculation from fasting insulin and glucose concentrations.

HOMA IR = fasting insulin (mU/L) × fasting glucose (mmol/L)/22.5

SPECIMEN COLLECTION:

At the time of admission:

CBC, Urine analysis, RFT, CXR, ECG, RBS, LFT, Troponin T 6hours following the onset of symptom

Second day of admission:

Fasting:

Blood glucose, lipid profile and insulin, Apolipoprotein A and B

Post prandial: (2 Hours/Breakfast)

Lipid profile, blood glucose

ECG

During hospital stay:

ECHO

Coronary angiogram if indicated

Blood Sample	***Method***
Glucose	*Hexokinase / Integra 400*
Cholesterol	*Enzymatic/ Integra 400*
Triglyceride	*Enzymatic/ Integra 400*
HDL	*Direct / Integra 400*
LDL	*Direct / Integra 400*
Apo A	*Immunometric / Integra 400*
Apo B	*Immunometric / Integra 400*
Insulin	*CLIA / ELECSYS 2010*

Statistical methods[75, 76]

- ***Chi-square and Fisher Exact test :***

To find the significance of proportion of incidence of insulin between various levels of study parameters namely BMI, Age, abnormal lipid profile and complications etc.

- ***Student t test :***

To find the significance of mean levels of lab parameters between the presence and absence of insulin resistance.

Statistical software:

The Statistical software namely SPSS 11.0 and Systat 8.0 were used for the analysis of the data

Microsoft word and Excel have been used to generate graphs, tables etc**.**

RESULTS AND ANALYSIS

Study design

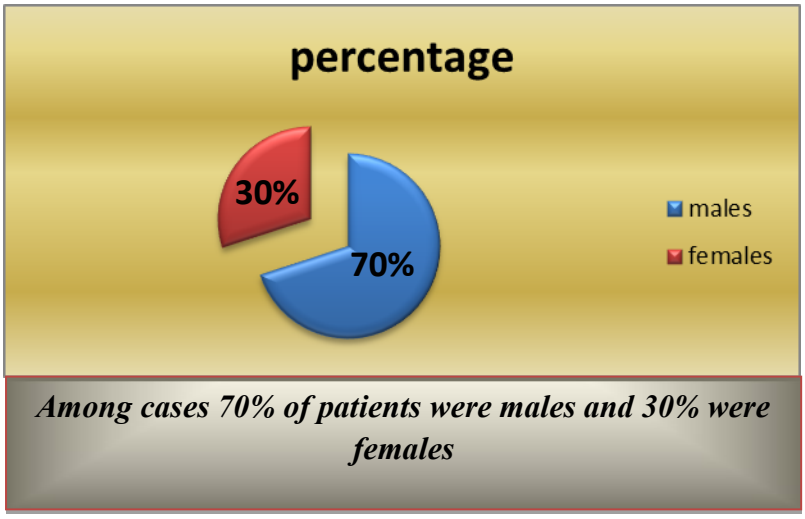
A Case control study consisting of age and sex matched 50 CAD patients(50 non diabetics with and without CAD) were investigated to find out association of insulin resistance by using HOMA score and to find out the significance in abnormalities of postprandial lipid profile in these patients.

DISTRIBUTION OF SIGNIFICANT VARIABLES AMONG CASES AND CONTROLS

Table-1 Sex distribution of cases and controls

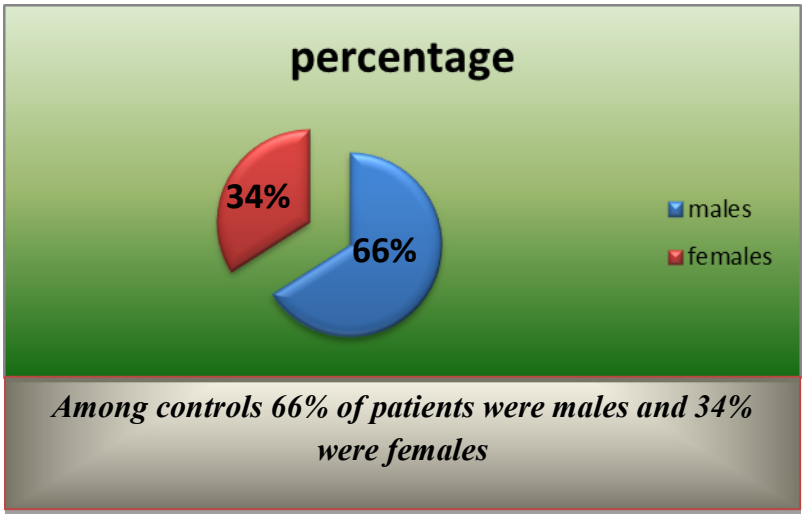
Gender	Cases		Controls	
	No	%	No	%
Male	35	70.0	33	66.0
Female	15	30.0	17	34.0
Total	50	100.0	50	100.0

Figure-1



Among cases 70% of patients were males and 30% were females

Figure-2



Among controls 66% of patients were males and 34% were females

Table-2 RISK FACTORS AMONG CASES AND CONTROLS

RISK FACTORS	Cases		Controls	
	No	%	No	%
ALCOHOL CONSUMPTION	5	**10.0**	9	**18.0**
NIL ADDICTION	21	***42.0***	25	***50.0***
SMOKING	9	**18.0**	5	**10**
SMOKING AND ALCOHOL	15	**30.0**	11	**22.0**
Total	50	100.0	50	100.0

Figure-3

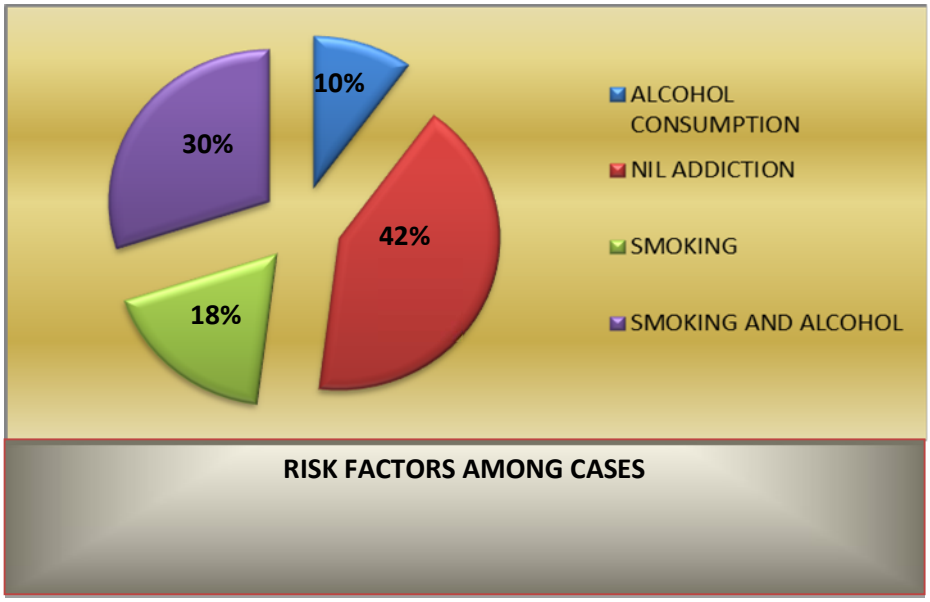


Figure-4

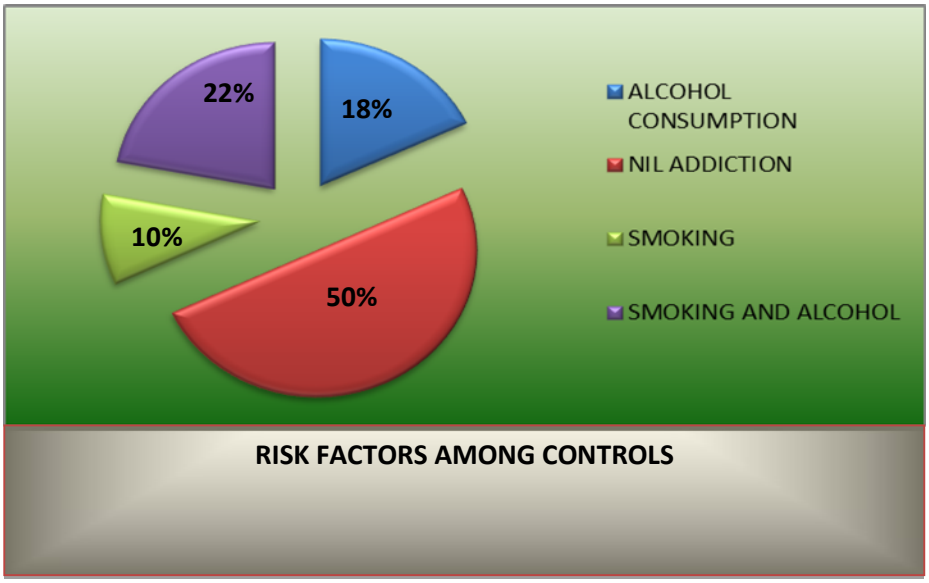
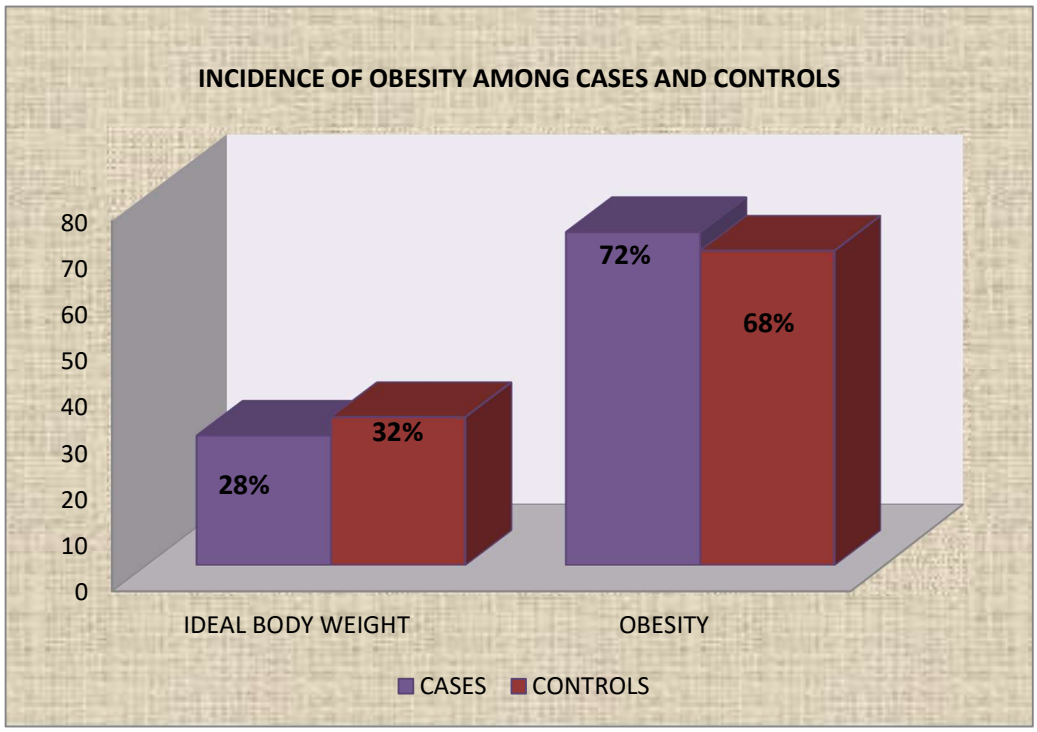


Table-3 INCIDENCE OF OBESITY AMONG CASES AND CONTROLS

BMI	Cases		Controls	
	No	%	No	%
Ideal body weight	14	**28.0**	16	**32.0**
Obesity	36	***72.0***	34	***68.0***
Total patients	50	**100.0**	50	**100.0**

Figure-5



CASES

Table-4 INCIDENCE OF INSULIN RESISTANCE IN CAD PATIENTS

	No	Percent
Normal HOMA SCORE	4	8.0
INSULIN RESISTANCE	**46**	**92.0**
Total	50	100.0

Figure-6

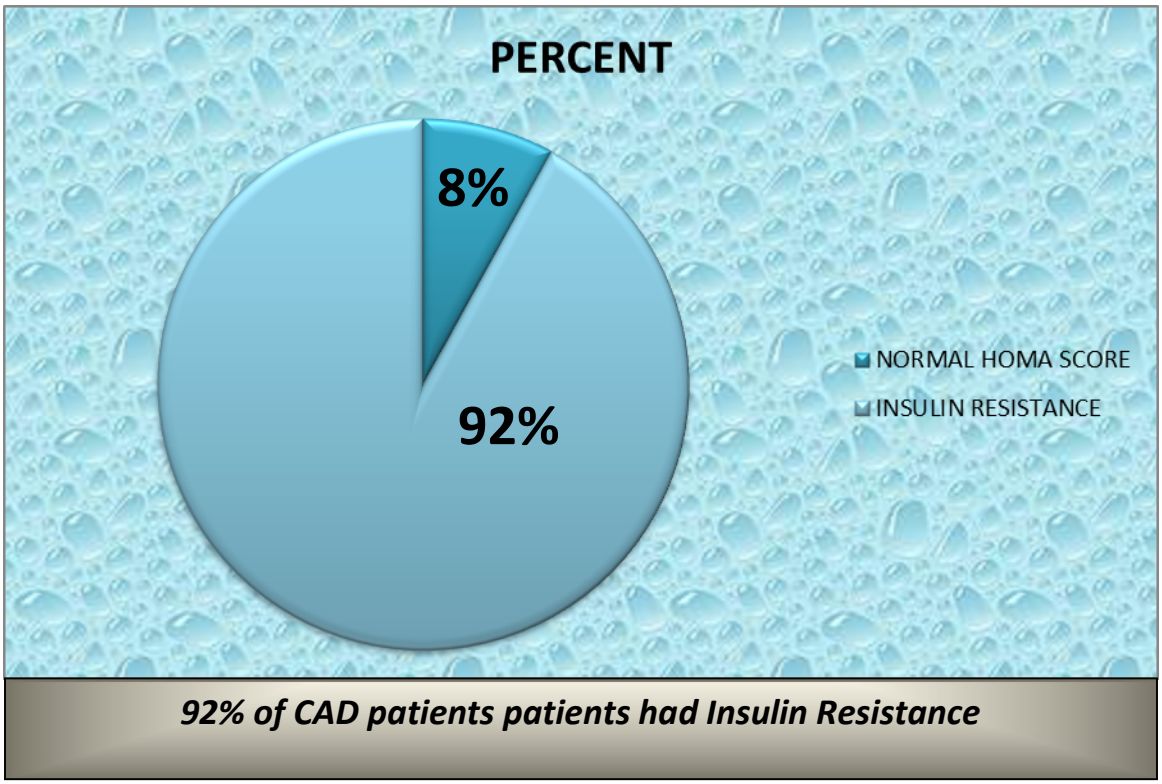


Table-5 INCIDENCE OF ELEVATED APOLIPOPROTEIN B LEVELS

APO B	Cases		Controls	
	No	%	No	%
Normal levels (66 to 133)	8	16.0	46	92.0
Abnormal levels (more than 133)	42	**84.0**	**4**	**8.0**
Total	50	100.0	50	100.0

Figure-7

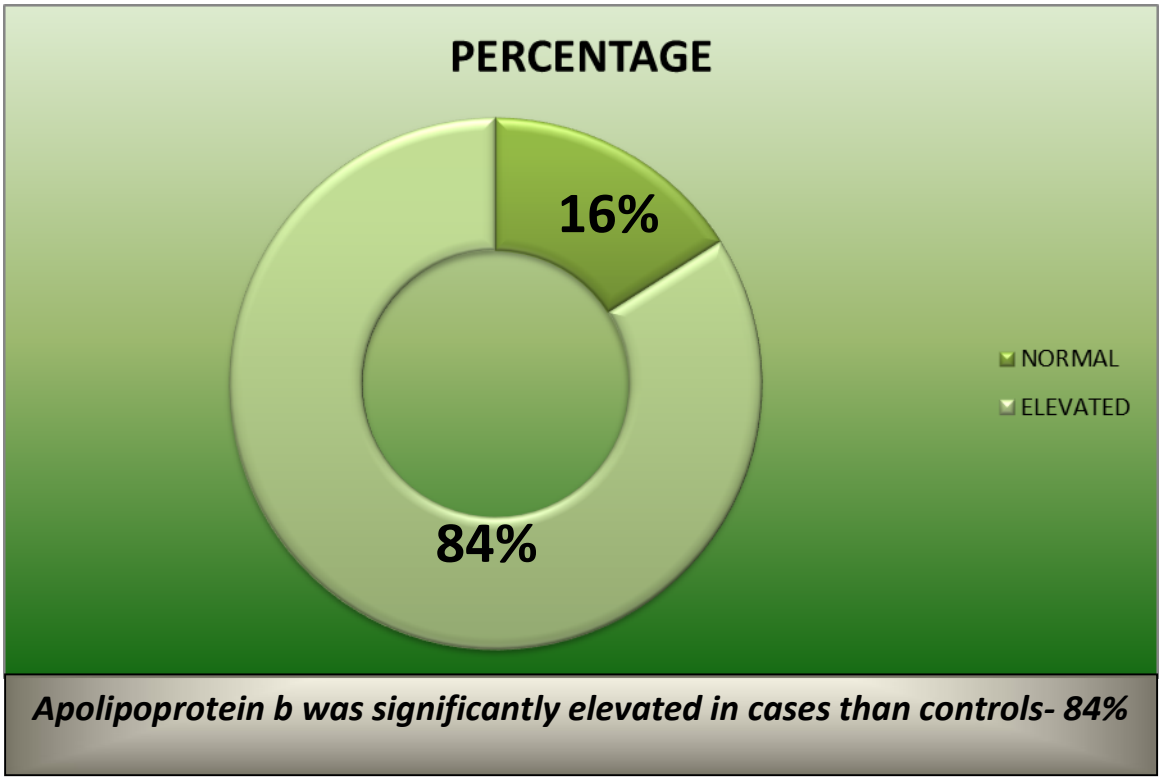
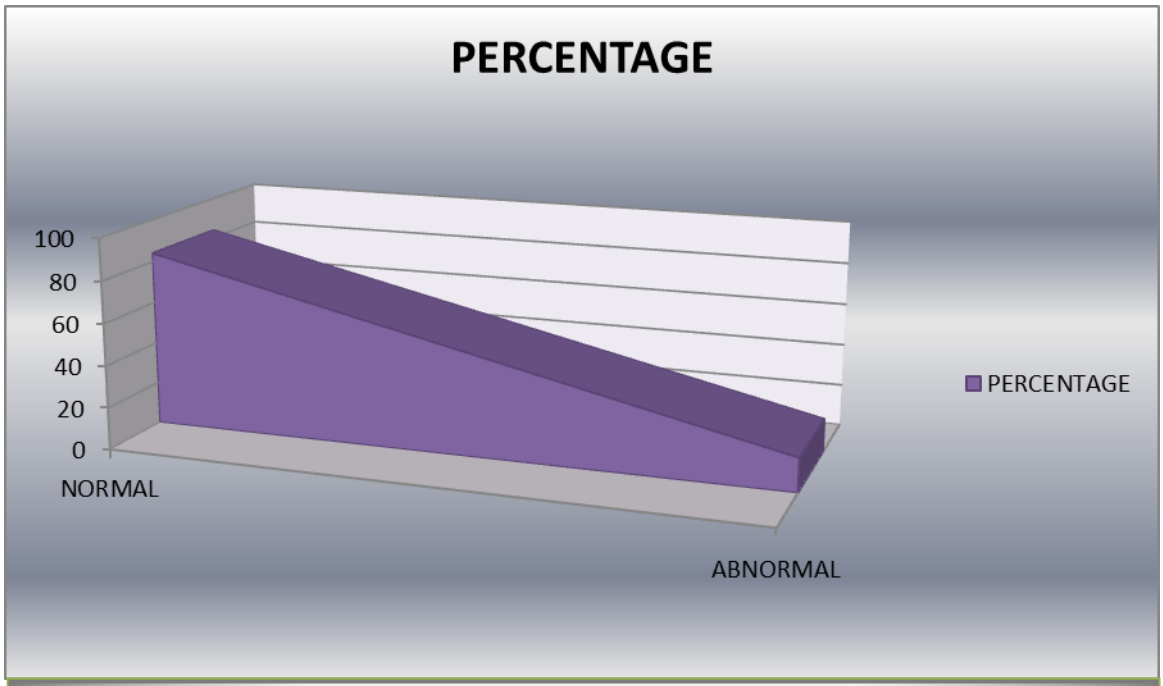


Table 6 APOLIPOPROTEIN A LEVELS IN CAD PATIENTS

APO A	Cases		Controls	
	No	%	No	%
Normal (104 to 202)	42	**84.0**	50	100.0
Abnormal (more than 202)	8	**16.0**	**0**	**0.0**
Total	50	100.0	50	100.0

Figure-8



There was no significant elevation of Apolipoprotein a both in fasting and postprandial state

BLOOD SUGAR AND LIPID PROFILE(FASTING AND POST PRANDIAL) IN PATIENTS OF CORONARY HEART DISEASE

Parameter	Fasting	Postprandial	P value
Blood sugar	91.3 ± 13.3	125.8 ± 14.82	0.000*
Total Cholestrol	293 ± 75.73	293.04 ± 128.39	0.001*
LDL	182 ± 42.18	224.12 ± 62.78	0.000*
HDL	26.96 ± 11.62	27.02 ± 11.65	0.979
triglycerides	**268 ± 124.0**	**344 ± 114.54**	**0.002***

* Significant at 1% level of significance

All patients were normoglycemic.

Serum triglycerides were significantly high in cases than controls in both fasting and postprandial states.

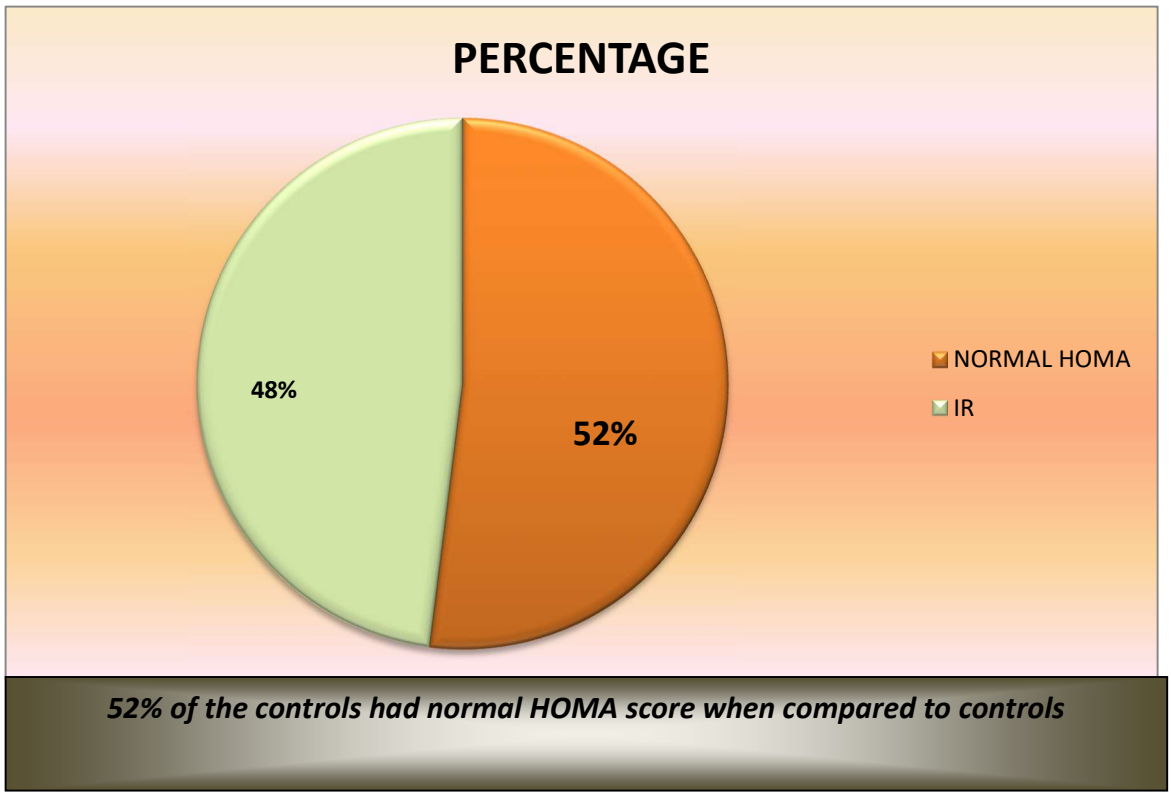
HDL was unchanged both in fasting and postprandial state

LDL cholesterol was found to be mildly increased in patients but not significantly as fasting level

Table-7 Incidence Of Insulin Resistance among controls

	No	Percent
Normal HOMA	26	52
IR	**24**	**48**
Total	50	100.0

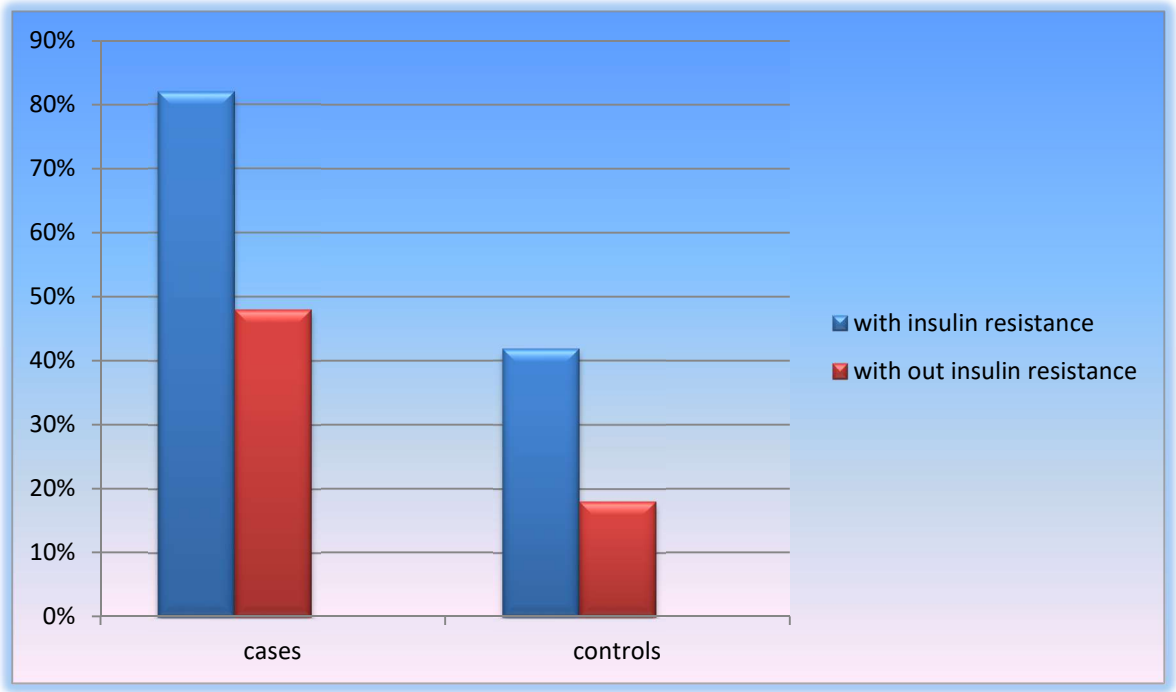
Figure-9



TGL/HDL C INDEX

Among Cases And Controls

Figure-10

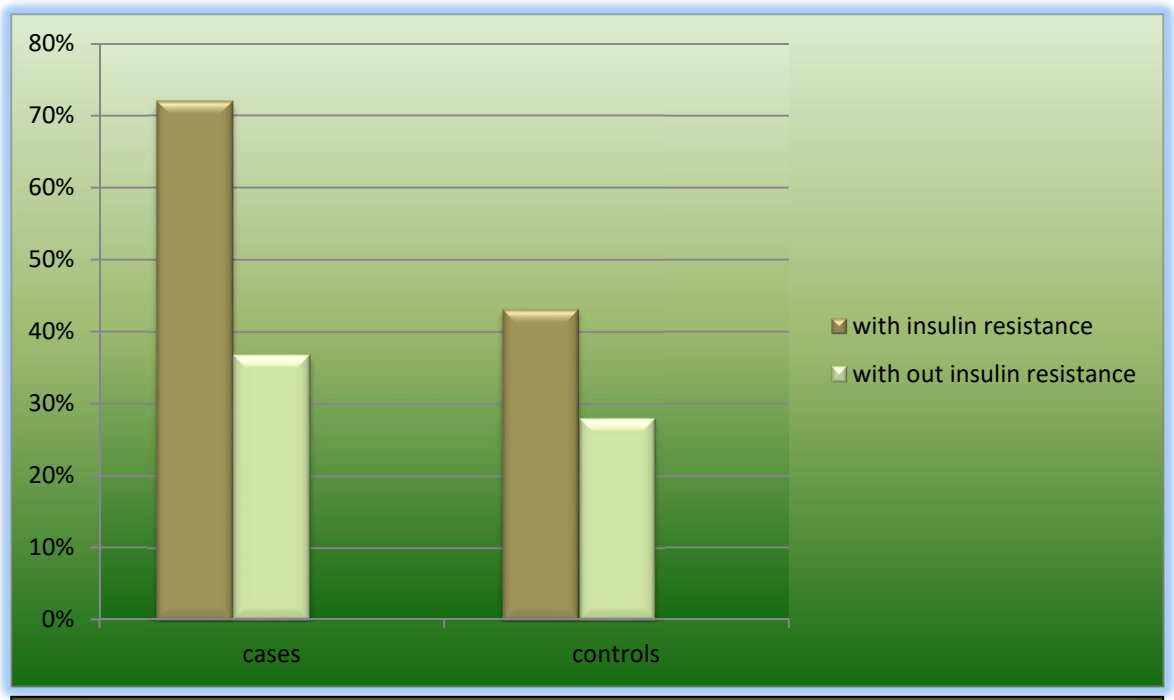


TG/HDL RATIO was found to be > 4 in cases with IR when compared to those with out IR

TC/HDL C INDEX

Among Cases And Controls

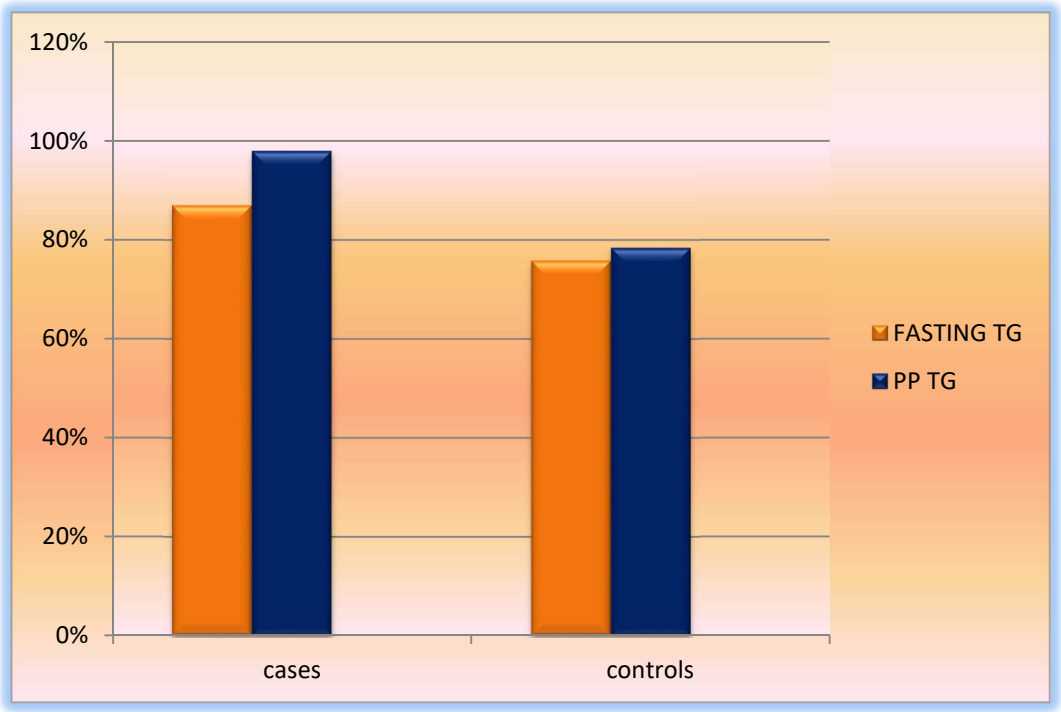
Figure-11



TC/HDL RATIO was found to be > 3.5:1 in high in cases & controls with Insulin resistance (72%,43.2% respectively) when compared to patients with out IR

FASTING Vs POSTPRANDIAL HYPERTRIGLYCERIDEMIA IN CASES AND CONTROLS

Figure-12



Post prandial triglycerides were high when compared to fasting levels among cases when compared to controls

Percentage of postprandial hypertriglyceridemia was much higher in cases when compared to controls.

OBESITY AND INSULIN RESISTANCE IN CASES AND CONTROLS

Table-8 Relationship between Insulin and BMI in CASES Fishers Exact test

	Normal		Obese		Total		P value
	No	%	No	%	No	%	0.041*
Normal	4	40.0	4	10.0	8	16.0	
Abnormal	6	60.0	36	90.0	42	84.0	
Total	10	100.0	40	100.0	50	100.0	

*Significant at 5% level of significance

Figure-13

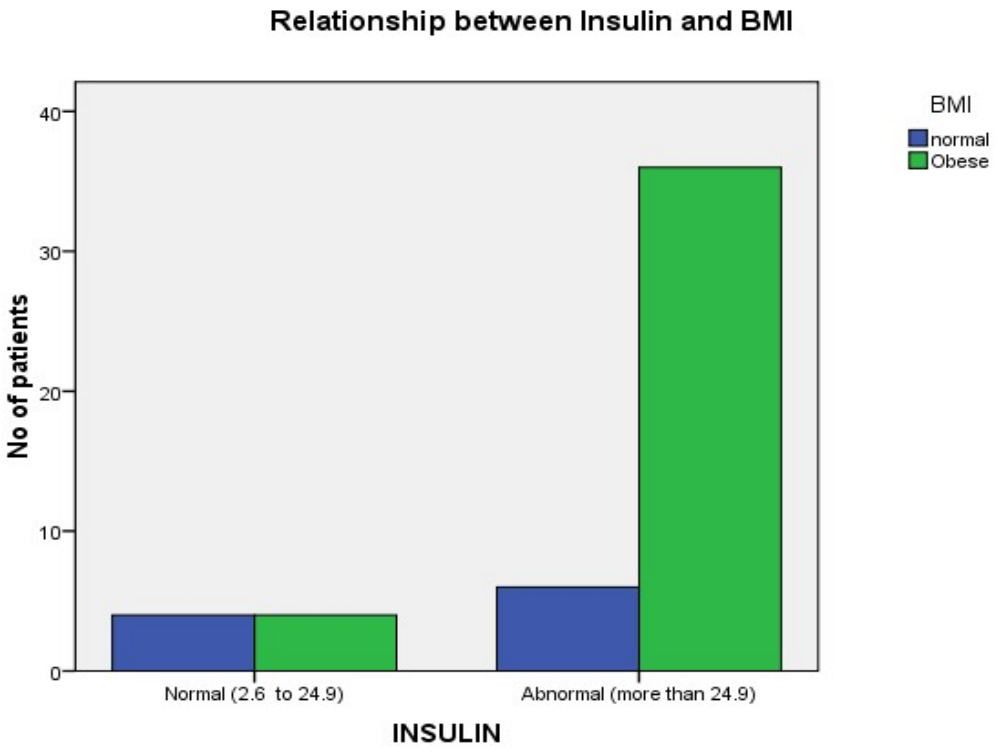
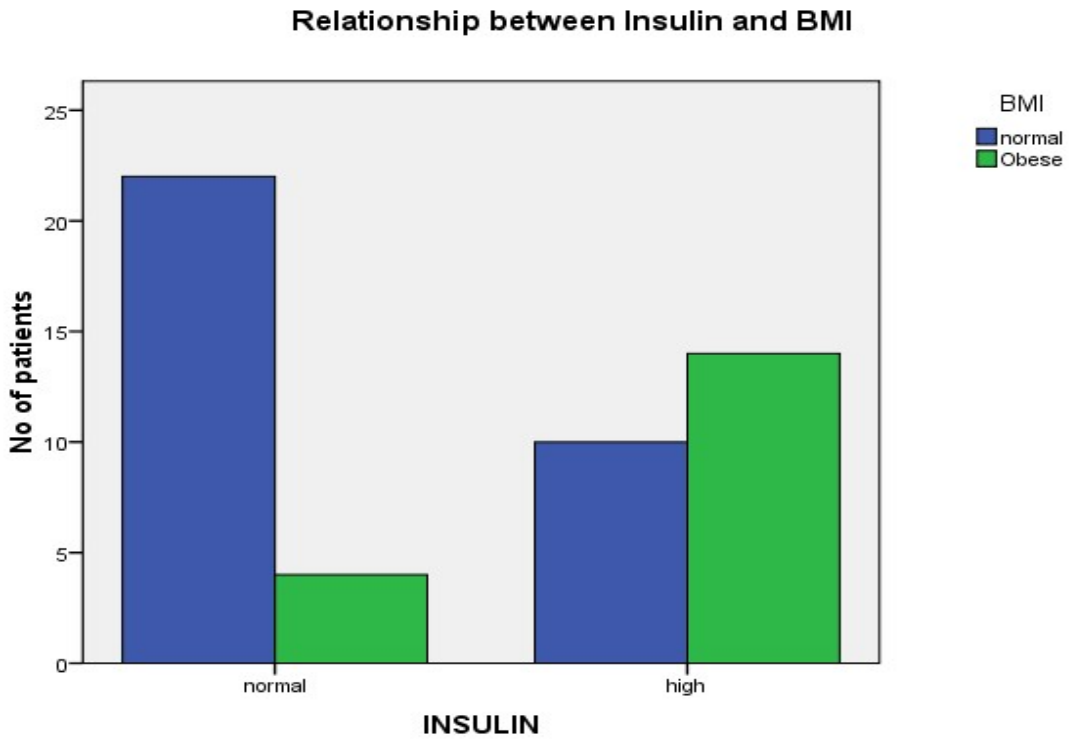


Table-9 Relationship between Insulin and BMI/Fishers exact test- CONTROLS

	Normal		Obese		Total		P value
	No	%	No	%	No	%	0.002*
Normal	22	68.8	4	22.2	26	52.0	
Abnormal	10	31.2	14	77.8	24	48.0	
Total	16	100.0	34	100.0	50	100.0	

*Significant at 1% level of significance

Figure-14

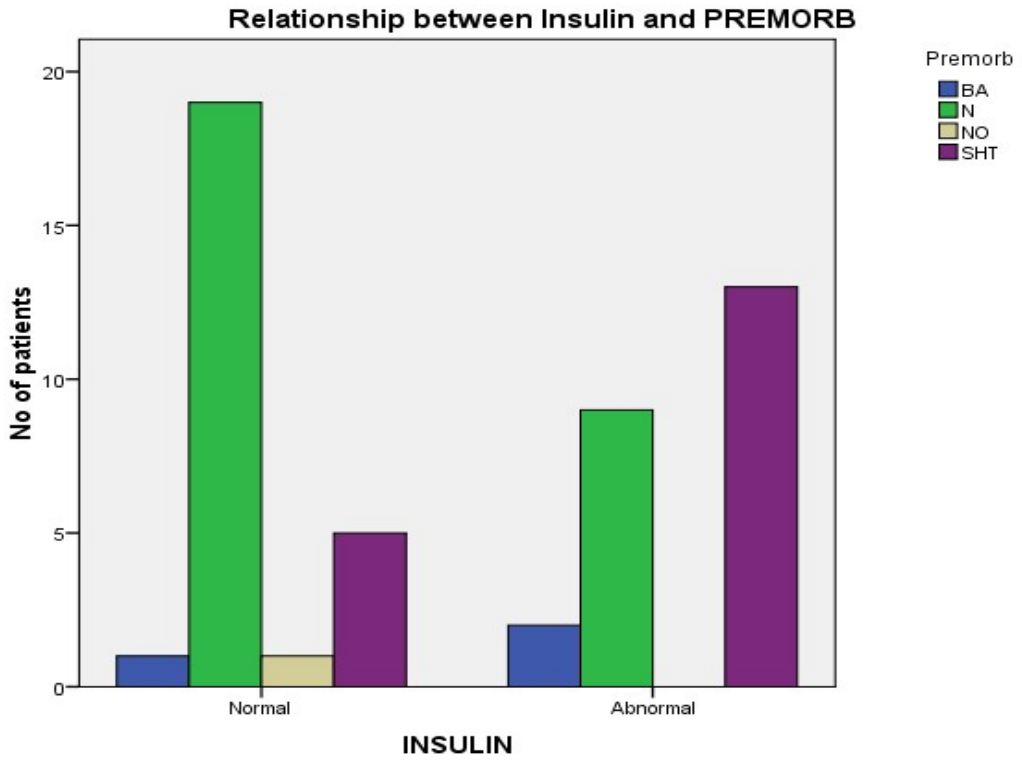


PREMORBIDITIES AND INSULIN RESISTANCE

Table-10 Relationship between Insulin and PREMORB

	BA		N		NO		SHT		Total		P value
	No	%	No	%	No	%	No	%	No	%	0.039*
Normal	1	33.3	19	67.9	1	100.0	5	27.8	26	52.0	
Abnormal	2	66.7	9	32.1	0	0.0	13	72.2	24	48.0	
Total	3	100.0	28	100.0	1	100.0	18	100.0	50	100.0	

Figure-15



FINAL RESULT

Table-11 Final Result

VARIABLES	WITH INSULIN RESISTANCE		WITH OUT INSULIN RESISTANCE	
IN %	CASES (92%)	CONTROLS(48%)	CASES(8%)	CONTROLS(52%)
OBESITY	90%	77.8%	10%	22.2%
HYPERTENSION	72%	72.2%	28%	27.8%
APO A	59.8%	0%	31.2%	0%
APO B	84%	8%	8%	0%
FASTING DYSLIPIDEMIA	78%	37%	22%	63%
FASTING TRIGLYCERIDES (INCREASED)	95.7%	70.8%	4.3%	29.2%
POSTPRANDIAL TRIGLYCERIDES (INCREASED)	97.8%	70.8%	2.2%	35.2%
TG/HDL c INDEX	82%	51.8%	18%	48.2%
TC/HDL c INDEX	72%	43.2%	28%	36.8%
CAD	92%	48%	8%	52%

- ✓ ***Patients with IR showed increased levels of Apolipoprotein B(84%) when compared to patients without IR***
- ✓ ***Patients with IR showed TGL/HDLc value >4 in 82% of the cases with IR ; where as it was only 18% in patients without IR***
- ✓ ***TC/HDLc ratio was found to be >3.5:1 in 72% of the patients with IR and 28% of the cases with normal HOMA score. It still may need follow up.***
- ✓ ***Significant association of Obesity & IR***

DISCUSSION

Coronary artery disease (CAD) is a continuum of a pathological process, in which the coronary arteries gradually thicken, harden and atherosclerotic plaques develop that further occlude blood flow. This leads to clinical manifestations such as angina and acute coronary events resulting from disruption of plaques, such as acute coronary syndromes, myocardial infarction and death

Coronary artery disease is the leading cause of death in India and is also leading cause of death worldwide. It was previously thought to affect primarily in the developed countries. CAD now leads to more death and disability in developing countries such as India. CAD affects people at younger ages in developing countries there by having a greater economic impact on developing countries. Effective screening, evaluation and management strategies for coronary artery disease are well established in developed countries, but these strategies are not fully implemented in India. For this, identifying the risk factor is an important factor to prevent a full blown disease.

An effort has been made to recognize insulin resistance in non-diabetic CAD patients which is a simple and non-invasive practical tool which requires only a single sample assayed for Insulin and glucose and can be calculated by HOMA score as mentioned before.

There was significant insulin resistance(92%) among cases. Controls who were obese also showed significant IR which was 48%.This is similar to a study done by Bertoluci et al from Brazil which showed 82.6% of CAD patients had insulin resistance when compared to the controls/non CAD group. Another American study by David et al showed that IR was responsible (96%) for 46.8%,6.2% and 12.5 % of the annual CHD events I diabetics,non diabetics and total US population respectively. Yet another study by E.Devici et al who compared Insulin resistance among normoglycemic patients with CAD revealed significant association of IR. Metabolic syndrome was similar in both the control and cases and thus HOMA IR values may provide more sensitive information than the Metabolic syndrome definitions about the association of IR and CAD in normoglycemic patients.

Like the above study quoted , there was significant association of obesity and Insulin Resistance in our study which was 84% in the CAD group and 77.8% in the non CAD group.

Among the controls 72.2% of the hypertensive patients had Insulin resistance when compared to cases. Approximately 50% of patients with essential hypertension, both treated and untreated, appear to be insulin resistant based on the study by Nereida et al.

Next aim of our study was to find out the significance of the postprandial lipid profile in patients with CAD. This is a new and emerging study which has only limited references & is not practiced routinely day to day clinical setup.

In this study ***Post prandial triglycerides were high when compared to fasting levels among cases and controls. Percentage of postprandial hypertriglyceridemia was much higher in cases when compared to controls***..A study by Vijay et al done in Haryana showed significant elevation of Serum TG, total cholesterol and VLDL – cholesterol in patients than controls in both fasting and postprandial states ($p<0.001$) and **HDL-cholesterol was found to be decreased significantly in fed state only ($p < 0.05$) and concluded that there is comparatively more transfer of cholesterol and cholesterol esters from HDL to LDL in postprandial state leading to their low levels and this along with higher triglycerides and VLDL levels are better indicators of coronary heart disease.** Were as in our study the Total cholesterol, HDL and LDL were unchanged both in fasting and postprandial state.

Apolipoprotein B was significantly higher in CAD group when compared to controls which is similar to a study by Tobias et al which showed that these proatherogenic lipoproteins were strong predictors of CAD when compared to the non HDL cholesterol. In those controls(4 patients) in whom Apo B was elevated were Insulin Resistant , among them 2 patients were hypertensive and their ECHO and ECG showed features of left ventricular hypertrophy. Other two were obese with out premorbidities and had non specific ST-T changes in ECG with a normal ECHO study.

Apo B, TG/HDLc ratio and Tc/HDL ratio were significantly higher among patients with IR.

SUMMARY

- We studied 100 patients
  - All are non-diabetic patients
  - 50 cases with coronary artery disease
  - 50 controls (age, gender matched) without coronary artery disease
    - To detect the association of insulin resistance/ hyperinsulinemia in CAD
    - To assess the significance of post prandial lipid profile(dyslipidemia) in patients with CAD
    - To find out the relationship of apolipoproteins (a and b) in CAD
- **92% of patients with CAD had Insulin resistance / hyperinsulinemia**
  - **There was strong association between insulin resistance and obesity in both cases and the controls**
  - No significance when correlated with addictions both in cases and controls
- There was a significant **elevation of Apolipoprotein b levels (84%)in CAD** patients than the control and when compared to apolipoprotein a which was only 16%
- ***Postprandial lipid profile:***
  - **Serum triglycerides were significantly high in cases than controls in both fasting and postprandial states.**
  - **Percentage of postprandial hypertriglyceridemia was much higher in cases when compared to controls.**
  - No significant change was observed in HDL, Total cholesterol and LDL in fasting and postprandial state.

- ***Patients with IR showed increased levels of Apolipoprotein B(84%) when compared to patients with out IR***

- ***Patients with IR showed TGL/HDLc value >4 in 82% of the cases with IR ; where as it was only 18% in patients without IR***

- ***TC/HDLc ratio was found to be >3.5:1 in 72% of the patients with IR and 28% of the cases with normal HOMA score. It still may need follow up.***

- The controls with insulin resistance, obesity and dyslipidemia were given advice regarding the lifestyle modification(diet and physical exercise) and appropriate pharmacological intervention (statin/fenofibrates) were given.

Limitations

1. ***Number of study population was less.***
2. ***Following up of teh controls with abnormal results were difficult.***

Suggestions

1. ***Patients belonging to control group need to be followed up.***
2. ***HOMA score can be routinely included as a part of diagnostic profile for assessing the risk factor of CAD in normoglycemic patients.***

CONCLUSIONS

- There is insulin resistance in coronary artery disease / obesity in non diabetic patients
- When insulin resistance in patients with addictions was calculated they had almost similar incidence when taken individually. There may have been some significance if we had included more study population
- Apolipoprotein B levels were significantly raised in CAD patients
- **Serum triglycerides were significantly high in cases than controls in both fasting and postprandial states. Percentage of postprandial hypertriglyceridemia was much higher in cases when compared to controls**
- Fed state did not alter the total cholesterol/ LDL/HDL
- Patients with IR had high TGL/HDLc , TC/HDLc and Apo B values.

Fasting Insulin and Insulin resistance(HOMA SCORE) can be included as one of the panel of investigations to assess the risk factor of CAD among nondiabetic population . Earlier identification of these patients would help to intervene and improve the quality of life. Improving insulin sensitivity would offer substantial benefits by decreasing the morbidity, mortality, and economic burden associated with CAD, respecially in the country like India

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ANNEXURES

PROFORMA

Name:

IP/OP No:

Age: Date of admission:

Sex: Date of discharge:

Religion: Marital status:

Address:

Occupation:

Education:

Income group: High/middle/poor

CHIEF COMPLAINTS:

Chest pain- typical/ atypical angina

Dyspnoea

Palpitation

Syncope

Limb weakness

Other associated symptoms

HISTORY OF PRESENTING ILLNESS

1) **Cardiovascular symptoms:**

Angina/ myocardial infarction/ exertional dyspnea /orthopnea

PND /palpitations/ syncope /sweating/Swelling of feet

2) Cerebrovascular symptoms:

Giddiness /headache/ vomiting/ transient ischemic attacks/Stroke

PAST HISTORY

History of Diabetes mellitus

History of hypertension

History of Angina / Myocardial infarction

History of Transient ischemic attack / stroke

PERSONAL HISTORY

HABITS	YES	NO	STOPPED
Smoking			
Sweets			
Alcohol			
Tobacco			
Appetite /bowel /bladder			

FAMILY HISTORY

(DM/SHT/IHD/CVA/Obesity/Sudden death)

MEMBERS	PRESENT	ABSENTFather
Mother		
Sisters		
Sons		
Daughters		
Spouse		

OBSTETRIC AND GYNECOLOGICAL HISTORY

Menarche/ Menopause

Gravida/Para/ Abortion/History of stillbirths

GENERAL PHYSICAL EXAMINATION

1) BUILT: Well / moderately /poor/ emaciated

2) WEIGHT:

HEIGHT:

BODY MASS INDEX:

3) PULSE:

4) BLOOD PRESSURE:

5)PALLOR/EDEMA/CLUBBING/KOILONYCHIA/CYANOSIS/ICTERUS/LYMPHADENOPATHY

6) JUGULAR VENOUS PULSE

7) PERIPHERAL PULSE

9) EYES:

Normal/ Xanthoma / Arcus / Cataract

10) FUNDUS

SYSTEMIC EXAMINATION (RELAVENT)

1) <u>CARDIOVASCULAR SYSTEM</u>

- INSPECTION
- PALPATION
- PERCUSSION
- AUSCULTATION
- OTHER FINDINGS

<u>2) RESPIRATORY SYSTEM</u>

- INSPECTION
- PALPATION
- PERCUSSION
- AUSCULTATION
- OTHER FINDINGS

<u>3) ABDOMEN</u>

- INSPECTION
- PALPATION
- PERCUSSION

- AUSCULTATION
- OTHER FINDINGS

4) CENTRAL NERVOUS SYSTEM

- HIGHER MENTAL FUNCTIONS
- CRANIAL NERVES
- MOTOR SYSTEM
- NUTRITION
- TONE
- POWER
- CO-ORDINATION
- INVOLUNTARY MOVEMENTS
- SENSORY SYSTEM

  TOUCH / PAIN / TEMPERATURE/VIBRATION /

  POSITION SENSE
- DIABETIC RETINOPATHY: PRESENT/ ABSENT

INVESTIGATIONS

ROUTINE:

1) URINE:

- Sugar
- Microscopy/Albumin

2) BLOOD:

- Fasting blood glucose
- Post prandial blood glucose
- Glycosylated hemoglobin:
- Blood urea:
- Serum creatinine:
- Lipid profile- fasting
  1. Total cholesterol
  2. Triglycerides
  3. HDL
  4. LDL

3) **ELECTROCARDIOGRAM**

4) ECHOCARDIOGRAM

5) CORONARY ANGIOGRAM (selected cases only)

6) ABDOMINAL ULTRASONOGRAPHY(selected cases only)

SPECIFIC FOR THE CURRENT STUDY:

- **Fasting Insulin**
- **Post prandial lipid profile**
- **Apolipoprotein a and b**

DIAGNOSIS

TREATMENT GIVEN:

FOR CONTROLS:

Preventive measures given:

MASTER SHEET

AGE	SEX	FAMILY	ADDICTI(	BMI	'REMORI	FBS	PPBS	INSULIN	FTC	PPTC	FLDL	PLDL	FHDL	PPHDL	FTG	PTG	APO A	APO B
50	M	NO	S/A	Obese	SHT	70	123	**25**	**300**	***305***	170	170	25	25	**265**	**300**	105	**140**
45	M	NO	A/S	obese	SHT	110	100	**29**	**280**	**280**	**180**	**185**	**24**	**24**	**325**	**350**	200	**150**
43	M	YES	S/A	Obese	N	90	140	**56.3**	**263**	**263**	**165**	165	**26**	**26**	**345**	**400**	**204**	**152**
60	M	NO	S/A	Obese	N	91	130	**38.2**	**463**	**463**	**186**	186	**15**	**15**	**265**	**300**	108	66
56	M	YES	S/A	Obese	N	75	125	**35.3**	**400**	**400**	**190**	190	**30**	**30**	**241**	**262**	107	**152**
34	M	NO	S/A	normal	N	80	122	**46.2**	**465**	***466***	**200**	200	**35**	**35**	200	**253**	110	**156**
56	M	NO	N	normal	N	89	100	**42.3**	**425**	**425**	**165**	165	**41**	**41**	**268**	**290**	163	**144**
45	M	NO	N	normal	BA	71	**150**	**28.2**	**400**	**400**	**177**	177	**42**	**42**	**245**	**265**	152	120
34	M	NO	N	Obese	SHT	110	140	**30**	**401**	***402***	**250**	**277**	**45**	**45**	**263**	**301**	145	**175**
23	M	YES	A/S	Obese	SHT	100	132	**30**	**800**	***820***	**300**	300	**48**	**49**	**323**	**350**	149	**145**
56	F	NO	N	Obese	SHT	107	110	2.3	**240**	**240**	**175**	175	**25**	**25**	**500**	**520**	128	**140**
45	M	YES	N	normal	SHT	102	120	5.5	**563**	**563**	**323**	323	56	56	250	251	136	114
76	M	YES	N	Obese	BA	98	130	**40**	**409**	**409**	**293**	**300**	**23**	**23**	**256**	**295**	156	**134**
56	F	YES	N	Obese	NO	80	133	**41**	**432**	**432**	**312**	**320**	**14**	**14**	**236**	236	**290**	**138**
55	M	YES	S	Obese	N	86	123	5.3	**323**	***356***	**295**	295	40	40	**286**	**302**	125	**140**
52	F	YES	N	Obese	N	102	125	**35.6**	**345**	**345**	**312**	312	**12**	**12**	**245**	**250**	156	**146**
70	M	YES	S	Obese	N	104	110	**36.2**	**405**	***450***	**300**	**321**	50	50	**212**	212	185	**149**
34	M	NO	A	Obese	N	100	104	20	**385**	**385**	**300**	300	**15**	**15**	**563**	563	182	**156**
56	M	NO	A	Obese	N	100	140	**30**	**402**	**402**	**304**	304	**36**	**36**	**452**	**503**	145	**157**
45	F	YES	N	Obese	N	101	**150**	**30**	**315**	**315**	**206**	206	**32**	**32**	**256**	**263**	175	**142**
44	F	NO	N	normal	SHT	110	**142**	**30.1**	**300**	**300**	**230**	231	**30**	**30**	**400**	**420**	176	**140**
50	M	NO	S/A	normal	SHT	85	130	**52.1**	**240**	***320***	**160**	160	**25**	**25**	**521**	**532**	165	125
51	M	NO	A	Obese	SHT	86	140	**32.5**	**256**	**256**	**175**	175	**21**	**21**	**410**	**411**	162	114
43	M	YES	S/A	Obese	SHT	70	135	**38.2**	**856**	**856**	**300**	300	**25**	**25**	**300**	**312**	145	100
57	F	NO	N	Obese	N	72	125	24	**256**	**256**	**163**	163	**23**	**23**	**356**	356	145	**145**
60	F	NO	N	Obese	N	76	139	**50**	**245**	***256***	**177**	177	**26**	**26**	**310**	**311**	**210**	**146**
43	F	NO	N	Obese	N	82	140	**51.1**	**296**	**296**	**174**	174	**28**	**28**	**385**	385	**250**	**145**
49	F	YES	N	normal	N	86	120	**28.2**	**275**	**275**	**180**	180	**14**	**14**	**300**	**312**	**212**	**156**
50	M	YES	N	normal	N	81	110	**43.2**	**386**	**386**	**201**	201	**15**	**15**	**320**	**332**	**242**	**140**
54	M	YES	S/A	Obese	N	96	104	**32.3**	**426**	**426**	**362**	362	**14**	**14**	**301**	**303**	156	**135**
47	M	YES	S/A	Obese	SHT	95	96	**31**	**532**	***534***	**397**	**400**	**14**	**14**	**311**	**325**	185	**138**
40	M	NO	S/A	normal	N	90	123	14	**280**	**280**	**160**	160	**23**	**23**	**253**	253	145	**155**
34	M	NO	S	normal	SHT	101	125	**30**	**314**	**314**	**225**	225	**40**	**40**	**320**	**325**	125	**140**
55	F	NO	N	Obese	N	110	140	**35.3**	**356**	**356**	**223**	223	**38**	**38**	**452**	**456**	163	**180**
53	M	NO	S	normal	SHT	108	133	**31.2**	**324**	**324**	**200**	200	**30**	**30**	**201**	**210**	129	**156**

59	F	YES	N	Obese	N	75	135	**49.1**	**385**	**385**	**203**	203	**24**	**26**	**206**	205	124	114
63	M	NO	A	Obese	SHT	86	131	**50**	**240**	***300***	**175**	175	**12**	**12**	**212**	**265**	185	**163**
68	F	YES	N	Obese	N	80	140	15.5	**200**	**200**	**160**	160	**8**	**8**	**212**	**252**	176	**185**
50	F	NO	N	Obese	SHT	100	125	**38.2**	**285**	**285**	**177**	177	**31**	**31**	200	200	146	**140**
37	M	YES	S	Obese	SHT	101	128	**35.3**	**500**	**500**	**253**	253	**35**	**35**	**263**	**300**	183	**133**
46	M	NO	S/A	Obese	SHT	75	110	**46.2**	**421**	**421**	**212**	**215**	**40**	**40**	**256**	**305**	145	**156**
42	M	YES	S/A	normal	SHT	72	113	**38.2**	**245**	***246***	**186**	186	14	14	**300**	**357**	162	125
47	F	NO	N	Obese	N	70	100	**35.2**	**263**	**263**	**174**	174	**25**	**25**	**321**	**356**	149	**145**
36	M	NO	A	Obese	N	85	105	**28**	**262**	**262**	**160**	160	**35**	**35**	**256**	**562**	161	**163**
65	F	NO	N	Obese	N	100	116	**52.1**	**242**	**242**	**188**	188	**40**	**40**	**241**	**256**	**206**	**185**
50	M	YES	S	Obese	N	105	**152**	**32.5**	**323**	**323**	**236**	236	**25**	**25**	**302**	**353**	**100**	**140**
65	M	NO	S	normal	N	110	136	**38.2**	**451**	***460***	**297**	297	23	23	**353**	**402**	105	**145**
39	M	YES	S	Obese	N	110	**152**	**30.5**	**246**	**246**	**195**	195	**15**	**15**	**400**	**427**	110	**142**
44	M	NO	S/A	normal	N	76	128	**24.9**	**363**	**363**	**205**	205	**12**	**12**	**500**	500	166	**148**
56	M	NO	S	Obese	SHT	104	**110**	5.3	**300**	**300**	**175**	**180**	9	9	***800***	*800*	**204**	**150**
AGE	**SEX**	**FAMILY**	**ADDICTION**	**BMI**	***PREMORB***	***FBS***	***PPBS***	***INSULIN***	***FTC***	***PPTC***	***FLDL***	***PLDL***	***FHDL***	***PPHDL***	***FTG***	***PTG***	***APO A***	***APO B***
52	F	NO	N	Obese	SHT	72	133	**high**	**256**	**256**	**165**	**167**	**40**	**40**	**150**	**170**	normal	normal
70	F	YES	N	Obese	SHT	70	123	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
34	M	YES	S/A	Obese	SHT	85	125	**high**	**260**	**266**	**175**	**176**	**30**	**30**	**204**	**210**	normal	normal
56	M	YES	S/A	normal	BA	100	110	**high**	**256**	**256**	**165**	**167**	**40**	**40**	**150**	**170**	normal	normal
45	M	YES	S/A	normal	NO	98	104	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
44	M	YES	S/A	Obese	N	80	140	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
50	M	YES	N	Obese	N	86	**150**	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
51	F	NO	N	Obese	N	102	**142**	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
43	M	NO	N	Obese	N	104	130	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
57	F	YES	N	Obese	N	100	140	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
60	M	NO	S	normal	N	100	135	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
43	F	NO	N	normal	SHT	101	125	**high**	**245**	***249***	**160**	160	**25**	**25**	**201**	**210**	normal	normal
49	F	NO	N	Obese	SHT	110	139	**high**	**257**	**261**	**175**	176	**21**	**21**	**200**	**209**	normal	normal
50	M	YES	N	Obese	SHT	85	140	**high**	**275**	**275**	**180**	180	**14**	**14**	**206**	**211**	normal	normal
54	M	NO	S	normal	SHT	86	120	**high**	**280**	**285**	**165**	169	**30**	**30**	**253**	253	normal	normal
47	M	NO	N	normal	N	70	110	n	**249**	**257**	**161**	165	**40**	**40**	**200**	200	normal	**high**
40	F	NO	N	Obese	N	72	104	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
34	M	YES	A	normal	N	76	140	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
55	F	YES	N	Obese	N	82	132	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
53	M	YES	S	Obese	N	86	**146**	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal

59	M	YES	A	Obese	N	81	120	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
63	M	NO	S/A	Obese	SHT	96	140	**high**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
68	M	NO	A	normal	N	95	120	n	**245**	***246***	**186**	186	40	40	**190**	**200**	normal	**high**
50	M	NO	S/A	Obese	SHT	90	110	**high**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
37	F	NO	N	obese	N	101	104	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
46	F	YES	N	Obese	SHT	105	96	**N**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
42	M	NO	N	Obese	N	110	123	**N**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
47	M	YES	N	Obese	SHT	110	125	**high**	**262**	**262**	**160**	160	**35**	**35**	**256**	**562**	normal	normal
36	F	NO	N	normal	BA	76	140	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
23	M	YES	S/A	normal	N	104	105	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
56	F	NO	N	normal	SHT	91	116	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
45	M	YES	S/A	Obese	SHT	75	**152**	**high**	**247**	***249***	**168**	170	**30**	**30**	**201**	**210**	normal	normal
76	M	NO	S	Obese	SHT	80	136	**high**	**258**	**262**	**176**	177	**21**	**21**	**200**	**209**	normal	normal
56	M	NO	N	Obese	SHT	89	**152**	**high**	**270**	**275**	**180**	187	**40**	**40**	**206**	**211**	normal	normal
55	F	NO	N	normal	N	71	128	n	**280**	**286**	**165**	169	**45**	**45**	**253**	253	normal	**high**
65	F	YES	N	Obese	N	110	**110**	**h**	**250**	**259**	**165**	170	**40**	**40**	**200**	200	normal	normal
50	M	NO	A	Obese	N	100	125	**high**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
65	M	YES	S/A	Obese	N	107	140	**high**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
39	M	NO	S	Obese	N	102	133	**high**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
44	F	NO	S	Obese	N	108	**155**	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
45	F	NO	N	normal	N	75	131	**high**	**263**	**263**	**174**	174	**25**	**25**	**321**	**356**	normal	normal
50	M	NO	S/A	normal	SHT	86	140	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
45	M	YES	N	Obese	SHT	80	125	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
43	M	NO	A	Obese	N	100	**160**	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
60	M	YES	N	normal	N	101	120	**high**	**248**	***254***	**186**	186	43	43	**230**	**245**	normal	normal
56	M	NO	S	OBESE	N	75	130	**high**	**256**	**262**	**174**	180	41	41	**321**	**356**	normal	normal
34	M	NO	S	Obese	N	81	133	**hh**	**272**	**275**	**160**	160	**40**	**40**	**256**	**260**	normal	normal
56	M	NO	S	normal	N	96	123	**h**	**280**	**286**	**160**	160	34	34	**256**	**261**	normal	**high**
45	M	NO	S/A	Obese	BA	95	125	**h**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
34	F	YES	N	Obese	SHT	90	140	**h**	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal
23	M	YES	A	obese	SHT	101	130	n	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	NORMAL	normal	normal

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