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DISSERTATION

A STUDY OF
CAROTID INTIMA-MEDIA THICKNESS,
LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND
PROTEINURIA IN PATIENTS WITH METABOLIC SYNDROME

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CERTIFICATE

This is to certify that this Dissertation entitled, **"A STUDY OF CAROTID INTIMA-MEDIA THICKNESS, LEFT VENTRICULAR DIASTOLIC DYSFUNCTION AND PROTEINURIA IN PATIENTS WITH METABOLIC SYNDROME"** is the bonafide record work done by **Dr. P. Ashok Kumar**, submitted as partial fulfillment for the requirements of M.D. Degree Examinations Branch I, General Medicine, September 2006.

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INTRODUCTION

Mortality and morbidity due to either a cardiovascular or a cerebro-vascular event is not always just an occurrence by chance, but a predetermined insult that might have built up over several years if not decades. Such a build up of a disease is perpetuated by several components, as described by risk factors, some conventional, some non-conventional; some modifiable, some not.

The metabolic syndrome is a conglomeration of some of such risk factors and which when present over a period of time predispose to disease processes in various body systems. The risk factors as the name suggests have a genetic and metabolic background and thus the disease is not uniform in various ethnic groups. However, the presence of these factors under the term `The Metabolic Syndrome` places the patient under a significant cardiovascular and cerebro-vascular disease risk among other processes. This study is aimed to evaluate the metabolic syndrome in its various aspects and the events associated with it namely the carotid intima media thickness, left ventricular diastolic dysfunction and proteinuria.

AIMS OF THE STUDY

1. To evaluate the factors defining the metabolic syndrome in patients attending the medical out-patient department for non-specific symptoms and who were found to have impaired glucose tolerance or a high blood pressure or are obese.

2. To evaluate such patients identified to have the metabolic syndrome for Carotid Intima-media thickness Left ventricular diastolic dysfunction and Proteinuria.

3. To evaluate the above mentioned factors in metabolic syndrome.

4. To study about the co-morbid factors in metabolic syndrome and their influence in the outcome of events studied.

REVIEW OF LITERATURE

Metabolic syndrome is the term used to describe a constellation of metabolic derangements that include insulin resistance, hypertension, dyslipidemia, central or visceral obesity, type 2 diabetes mellitus or IGT/IFG, and accelerated cardiovascular disease.

Metabolic syndrome is very common.

The centers for disease control and prevention estimates that 20% of the US adults have metabolic syndrome. Indian studies report a prevalence that varies between 12.8% and 25.8% [12.]

THE SYNDROME X, THE INSULIN RESISTANCE SYNDROME & THE METABOLIC SYNDROME:

Sensitivity to insulin-mediated glucose disposal varies widely in the population at large[3]. When insulin resistant individuals cannot maintain the degree of hyperinsulinemia needed to overcome the insulin resistance, type 2 diabetes develops [4,5]. Most individuals are able to sustain the level of compensatory hyperinsulinemia needed to maintain a normal or near normal glucose tolerance, however. Unfortunately, this philanthropic effort on the part of the pancreatic beta cell is a mixed blessing. Although the compensatory hyperinsulinemia prevents the development of frank hyperglycemia, insulin-resistant/hyperinsulinemic individuals are greatly at risk of having some degree of glucose intolerance, a high plasma triglyceride and low high-density lipoprotein (HDL-C) concentration and hypertension.[6]. Earlier, in 1988, it was proposed that individuals who displayed this cluster of abnormalities associated with insulin-resistance, compensatory hyperinsulinemia were at significantly

high risk of cardiovascular disease (CVD). Because the importance of insulin resistance and associated abnormalities as CVD risk factors was not widely appreciated at that time, the cluster of related abnormalities was assumed under the rubric of **SYNDROME X.**

Since the introduction of the concept of Syndrome X, a relatively enormous amount of new information has evolved relevant to the role of insulin resistance in human diseases. This resulted in two somewhat disparate approaches to thinking about the clinical implications of insulin resistance and its consequences.

One view represents an effort to acknowledge that the abnormalities related to insulin resistance have broadened considerably and the adverse clinical outcomes extend beyond type 2 diabetes and CVD. Because CVD is recognized as just one of the multiple clinical syndromes associated with insulin resistance, It seems appropriate to replace the term with one more aptly deals with this new information. In this context, the **insulin resistance syndrome (IRS)** seems to be a logical choice to provide a pathophysiologic construct with which to view the different clinical syndromes that occur more commonly in insulin resistant individuals. On a somewhat parallel tract, during this period when the list of abnormalities associated with insulin resistance was rapidly expanding, the cardiology community has formally acknowledged the importance of this defect in insulin action as CVD risk with th-e report of the Adult treatment panel III of the national cholesterol education program [6]. The ATP III recognized the importance of CVD risk factors of what they referred to as a “constellation of lipid and non-lipid risk factors of metabolic origin,” designated this cluster as the **METABOLIC SYNDROME**, and stated this syndrome is closely related to insulin resistance. The goal of the metabolic syndrome is to provide the tools believed necessary to identify presumably insulin resistant individuals at

increased risk of cardiovascular disease (CVD). In marked contrast to the notion of the IRS, its focus is not to provide a physiologic construct with which to put into a cause and affect perspective all of the clinical syndromes that are more likely to occur in insulin resistant individuals. Instead, it should be considered a diagnostic tool and its value evaluated in light of the clinical use of making a diagnosis of the metabolic syndrome by satisfying three of the five criteria listed below. The variables listed in the box seem to have been selected because they seem to cluster together and occur more commonly in insulin resistant individuals.

DEFINITIONS:

Definitions of the metabolic syndrome that also include a measure of central obesity have been developed between 1999 and 2001 by the World health organization (**WHO consultation 1999**), the European group for the study of insulin resistance (**EGIR; Balkau and Charles, 1999**) and the national cholesterol education program (NCEP) expert panel on detection, evaluation and treatment of high blood cholesterol in adults (abbreviated to Adult treatment panel, **ATP-III**).

The ATP-III criteria also recognized the association between the above factors of the metabolic syndrome and pro-inflammatory and pro-thrombotic states as reflected by increased C-reactive protein and plasma plasminogen activator inhibitor levels, respectively, but these are not required for the definition of the syndrome.

The **five** criteria selected by the **ATP III** to identify individuals with metabolic syndrome are given below,

ATP III criteria for diagnosing the metabolic syndrome.

1.Abdominal obesity

Men: waist circumference > 40 inches

Women: waist circumference >35 inches

2. Fasting glucose > 110

3. Blood pressure > 130/85 mm Hg.

4. Triglycerides > 150 mg/dl

5. HDL-C Men: < 40 mg/dl

Women: < 50 mg/dl

The metabolic syndrome is present when three or more of the five criteria are met.

The other criteria include the WHO criteria and the European group for the study of insulin resistance. According to the WHO criteria, demonstration of glucose intolerance and microalbuminuria are required for the diagnosis of the metabolic syndrome.

The WHO and EGIR criteria are described in the table given below,

	WHO Criteria	EGIR Criteria
Central obesity	WHR>0.9-men > 0.85-women BMI>30kg/sq. M	Waist > 94cm-men > 80cm-women
Blood pressure (mmHg)	>140/90	>140/90 or treated (mmHg) for HT
Dyslipidemia	TGL> 150mg/dl HDL< 0.9 male <1.0-female	TGL >175 HDL < 1.0 or
Dysglycemia	FPG> 110 and or 2 h post-challenge non-diabetic. Glucose>140 on diabetics	FPG >110 but non-diabetic
Insulin resistance	Glucose uptake during hyperinsulinemic euglycemic clamp in lowest quartile for population	-
Other factors	Microalbuminuria	-

Because of the effectiveness and the practicality of the ATP III criteria, it is taken as the reference criteria in this study.

It is well reported in various studies that the upper limit of the Waist circumference has to be tailor- made for each ethnic group. [53]

Hence, in our study, the ***Modified ATP III criteria,*** with Waist circumference of more than or equal to 90cm in male, and 85 cm for female has been taken [2, 53, 73,74.]

Pathogenesis of the metabolic syndrome:

Resistance to the action of **insulin** is a central feature of the metabolic syndrome. Liver, skeletal muscle and adipose tissue are considered the major insulin-responsive tissues but the vasculature also can be considered as an insulin-responsive organ. In the metabolic syndrome insulin resistance is linked predominantly to a cluster of disorders involving triglyceride and glucose metabolism, increased blood pressure and vascular inflammation. Although to date there is no central unifying mechanism that explains all of the features of the syndrome, it is most likely that certain of the features occur as secondary consequences of a primary abnormality (or several primary abnormalities). Given that insulin resistance is fundamental to a diagnosis of the syndrome, an understanding of the cause and consequences of insulin resistance is crucial to an understanding of the pathogenesis of the metabolic syndrome.

Low levels of physical activity and relatively high dietary calorie intake adversely affect the metabolic profile by decreasing free fatty acid (FFA) and glucose oxidation in skeletal and cardiac muscle, which potentially contribute to

body fat accumulation and resistance to the biological actions of insulin. Because many **cytokines**, such as tumor necrosis factor (TNF)-alpha, interleukin (lL-6 and IL-1), are secreted by adipose tissue, increasing levels of obesity are often associated with increased concentrations of these proinflammatory cytokines. Chronic low-grade inflammation is undoubtedly a component of the metabolic syndrome but the mechanisms linking insulin resistance and inflammation are uncertain (Nesto, 2004). Proinflammatory cytokines such as TNF-alpha may mediate a link between inflammation and some of the metabolic abnormalities occurring with the metabolic syndrome. For example, TNF-alpha decreases insulin-induced suppression of hepatic glucose production, increases fatty acid and cholesterol synthesis, increases hepatic very-low-density lipoprotein (VLDL) production and increases adipocyte lipolysis. Increased lipolysis causes increased concentrations of non-esterified fatty acids (NEF As), which also provide a stimulus and a substrate for hepatic triglyceride synthesis, to increase further VLDL assembly and secretion. Thus if there is increased lipolysis, such as also occurs in patients with obesity or lipodystrophy, an increased supply of NEFAs to the liver has adverse consequences for lipoprotein metabolism. Increased plasma NEFA concentrations also potentially may interfere with glucose metabolism by reducing glucose uptake and oxidation. Consequently, increased NEFA

concentrations and increased TNF-alpha probably contribute to the classical dyslipidaemia associated with the metabolic syndrome and diabetes, namely increased fasting plasma triglyceride concentrations, decreased HDL-cholesterol and increased LDL-cholesterol concentrations, as well as potentially contributing to increased plasma glucose.

Within the vasculature the metabolic syndrome is also associated with an increase in cellular reactivity. For example, there is evidence of endothelial cell, platelet and monocyte activation, such that these cell types are often in a reactive state. Activation of these key cells predisposes an individual to a pro-coagulant and pro-inflammatory vascular phenotype that probably precedes development of atheromatous plaques. Not only does a developing plaque induce changes within other cell types in the vasculature but dysfunctional activated cell types, such as endothelial, monocyte and platelets, will induce changes in the metabolism of other tissues. Thus it is difficult to distinguish precise causes from subsequent consequences, not least because the metabolic syndrome comprises a dynamic process of evolving vascular and metabolic disease. Cross-sectional studies of plaque biology only study molecular changes within the plaque and the surrounding vasculature at a given instant in time. Understanding the molecular pathogenesis of plaque evolution and healing requires monitoring of the whole process, which is not currently possible.

The **immune response** is undoubtedly involved in the developing atheromatous plaque, but whether a primary disorder of the immune response causes the predisposition to vascular inflammation in the metabolic syndrome is not clear. Within the plaque, helper T cells are predominantly THI cells, secreting generally pro-inflammatory cytokines. However, with marked hyperlipidaemia, in some animal models of atheroma and in atherosclerotic aneurysmal disease a shift to TH2 cells, or those secreting predominantly anti-inflammatory cytokines, has been noted. Whether this finding represents part of the causal pathway, is a consequence of the inflammatory disease process or represents a physiological healing response is uncertain.

Adiponectin is a recently described molecule that may be important in the pathogenesis of the metabolic syndrome. Adiponectin is exclusively secreted by adipocytes (Fain et al, 2004) and has high affinity for adiponectin receptors expressed in two other insulin-sensitive tissues, namely skeletal muscle and the liver (Yamauchi et al, 2003). It has been shown that adiponectin concentrations are decreased in insulin resistance with either obesity or lipodystrophy. Interestingly, and relevant to the pathogenesis of the metabolic syndrome, treatment with adiponectin increases insulin action and ameliorates features of the metabolic syndrome (Chandran et al, 2003; Diez and Iglesias, 2003; Kinlaw and Marsh, 2004). In transgenic mice in which the adiponectin gene was

'knocked out', adiponectin deficiency caused diet-induced glucose intolerance, insulin resistance and increased NEFA concentrations (Kubota et al, 2002; Maeda et al, 2002). Increased expression of the adiponectin gene also has been shown to increase insulin sensitivity, improve glucose tolerance and decrease NEFA concentrations (Combs et al, 2004). Thus, these results suggest a beneficial effect of increased adiponectin concentrations to decrease insulin resistance and ameliorate features of the metabolic syndrome. Adiponectin may not only have a direct beneficial effect on insulin sensitivity, fat and glucose metabolism but may also confer benefit within the vasculature, mediated through its ability to increase the phosphorylation and activation of AMPK/malonyl-CoA signaling, and to decrease the inflammatory pathway via reduction of nuclear factor (NF)-KB activity (Chandran et al, 2003; Diez and Iglesias, 2003; Goldstein and Scalia, 2004). Specifically in endothelial cells adiponectin signaling acts to suppress inflammatory changes by blocking inhibitory NF-KB phosphorylation and NF-KB activation. The NF-KB/Rel family of proteins are inducible transcription factors that play a central role in regulating the expression of a wide variety of genes associated with cell proliferation, inflammation and cell survival (Ghosh and Karin, 2002; Li and Verma, 2002). Thus, the net effect of increased adiponectin signalling is increased fatty acid oxidation, increased glucose utilization, reduced

endogenous glucose production and decreased inflammation (Chandran et al., 2003; Diez and Iglesias, 2003).

Insulin resistance also may lead directly to **impaired endothelial function**. Endothelial cells respond to insulin, and insulin resistance is associated with impaired endothelium-dependent vasodilatation in response to acetylcholine. Furthermore, it has been shown that hyperinsulinaemia can increase the expression of the adhesion molecule ICAM-l, increasing macrophage attachment to the endothelium (Nesto, 2004). Healthy endothelium should not normally facilitate binding of leucocytes. Activated endothelial cells express adhesion molecules that bind various classes of leucocytes. In particular, vascular cell adhesion molecule-l (VCAM-1) binds those classes of leucocytes found in atheromatous plaques, namely the monocyte and the T lymphocyte. The mechanism of VCAM-l induction probably depends on inflammation instigated by modified lipoprotein particles accumulating in the arterial intima in response to the hyperlipidaemia that may be relevant to the metabolic syndrome. Constituents of modified lipoprotein particles, among them certain oxidized phospholipids and short-chain aldehydes arising from lipoprotein oxidation, can induce transcriptional activation of the VCAM-J gene mediated in part .by NF-KB (Collins and Cybulsky, 2001), and pro-inflammatory cytokines such as IL-l or TNF-a which are increased with the metabolic

syndrome, induce VCAM-l expression by this pathway. Thus, pro-inflammatory cytokines may link altered endothelial function to the dyslipidaemia of the metabolic syndrome.

There are many similarities between Cushing's disease (or syndrome) and the metabolic syndrome. These similarities have suggested to investigators that some component of the **cortisol** production or signalling pathway may be involved in the pathogenesis of the metabolic syndrome. However, the mechanism by which glucocorticoid hormone action contributes to the metabolic syndrome has not been fully elucidated, Many of the properties of glucocorticoid hormones are antagonistic to the actions of insulin, with important consequences for carbohydrate and lipid metabolism, suggesting a key role for abnormal glucocorticoid action in the metabolic syndrome. A recent review on this topic discusses the actions of glucocorticoids in the metabolic syndrome in more detail (Wang, 2005). Glucocorticoid hormones also have a permissive effect to enhance actions of other insulin counter-regulatory hormones such as adrenaline and glucagon. For example, glucocorticoid hormones enhance the sensitivity of adipocytes to adrenaline to increase lipolysis and to skeletal muscle to release lactate. Glucocorticoid hormones acutely activate lipolysis in adipose tissue. Lipolytic activity and consequently plasma FFA levels are reduced in adrenalectomized animals and

return to normal within 2 h after glucocorticoid administration. This permissive effect may be mediated by altered sensitivity to other lipolytic hormones, such as catecholamines and growth hormone, but the molecular mechanisms responsible are uncertain. Several authors have suggested that a neuroendocrine disturbance involving the hypothalamic-pituitary axis (HPA) may play an important part in the causation of the metabolic syndrome (Pasquali er al, 1993; Bjorntorp, 1995). Case-control and cross-sectional studies show that elevated plasma cortisol concentrations in morning samples are associated with high blood pressure, glucose intolerance, insulin resistance and hyperlipidaemia (Filipovsky et al, 1996; Stolk et al, 1996; Phillips et al., 1998). In contrast, other studies, particularly of centrally obese subjects, show a flattening of 24-hr cortisol secretion with reduced morning cortisol concentrations (Marin et at., 1992; Hautanen and Adlercreutz, 1993; Pasquali et al, 1993; Rosmond, Dallman and Bjorntorp, 1998). Thus it is unlikely that altered activity of the HPA alone underlies the etiology of the metabolic syndrome.

Recent evidence has suggested that altered cellular glucocorticoid hormone action may mediate features of the metabolic syndrome. Genetic polymorphisms of the glucocorticoid receptor (GR) have been described that alter glucocorticoid hormone action and are associated with features of the metabolic syndrome (Weaver, Hitman and Kopelman, 1992). However, recent

studies suggest that the relative contribution of GR genotype to blood pressure is small (Kenyon et al., 1998). This has led to suggestions that tissue-specific molecular determinants of glucocorticoid hormone action may underlie the causative role of modest alterations in glucocorticoid hormone action in the pathogenesis of the metabolic syndrome (Buemann et al, 1997; Panarelli et al, 1998). Altered patterns of GR expression in skeletal muscle are associated with the metabolic syndrome. In a cross-sectional study to investigate relationships between glucocorticoid hormone action and insulin sensitivity hyperinsulinaemic euglycaemic clamps and skeletal muscle biopsies were taken in 14 men (Whorwood et al., 2002). In muscle cell cultures established from these subjects it was showed that GR mRNA levels are positively correlated with the degree of insulin resistance. These data suggest a strong link between tissue sensitivity to glucocorticoid hormone and both resistance to insulin-mediated glucose uptake in skeletal muscle and obesity. The net effect of increased tissue glucocorticoid activity may contribute to the pathogenesis of the metabolic syndrome but more evidence is needed. In physiological states, plasma glucocorticoid hormones circulate as plasma protein-hormone complexes with a corticosteroid-binding globulin. Free hormone diffuses into the cell and binds intracellular GR. After binding of hormone to cytosolic GR, there follows translocation of the complex to the nucleus. Ligand-bound GR

interacts with a number of transcript factors, including API, and through interactions between these GR-transcription factor complexes and complex glucocorticoid response elements it brings about regulation of gene expression. Whether any component of this process affects or is altered by the metabolic syndrome is uncertain.

By comparison there has been considerable recent interest in the role of II f3hydroxysteroid dehydrogenase (11f3-HSD) in the pathogenesis of the metabolic syndrome, as discussed in a recent review by Seckl and Walker (2004). Dynamic regulation of intracellular cortisol levels is mediated predominantly by the activity of the II f3-HSD enzymes, which can be regarded as pre-receptor signalling mechanisms regulating glucocorticoid hormone action through the conversion of hormonally active cortisol to inactive cortisone, or vice versa. Clinical and experimental animal studies have revealed the expression of at least two kinetically distinct 11f3-HSD isoforms, which have been characterized (White, Mune and Agarwal, 1997; NarayFejes-Toth, Colombowala and Fejes-Toth, 1998). Type I llf3-HSD (1lf3-HSD-l) encodes relatively low-affinity NADP/NADPH-dependent II-dehydrogenase (cortisol to cortisone) and oxo-reductase (cortisone to cortisol) activity (Km for cortisol = 1 J,JM, Km for cortisone = 0.3 ~M). In contrast, type 2 1113-HSO (1113HSO-2) encodes high-affinity NAO-dependent ll-dehydrogenase activity. The kinetic

characteristics of these isoforms, together with their distinct tissue-specific distribution, suggest distinct physiological roles (Whorwood, Ricketts, and Stewart 1994; Whorwood et al., 1995).

Recent evidence has also suggested a role for cortisol metabolism in the possible pathogenesis of programming of the metabolic syndrome. Fetal overexposure to increased concentrations of glucocorticoids may influence subsequent development of the metabolic syndrome in adulthood. Glucocorticoids slow fetal growth and may alter the size of the placenta, depending on the dose and timing of exposure (Langley-Evans. 1997). These prenatal effects appear to persist after birth, e.g. if a moderate dose of dexamethasone (a synthetic glucocorticoid that readily passes through the placenta) is given to a pregnant rat it results in fetal growth retardation (average reduction by approximately 14 per cent), without affecting the gestation time or the viability of the fetus. A rise in systolic blood pressure in the adult offspring has been observed months after this exogenous glucocorticoid exposure (Benediktsson et al., 1993). Glucocorticoids have important effects on the maturation of tissues involved in blood pressure control. For example, development of catecholamine receptor expression is affected, and glucocorticoids influence second messenger systems in renal and vascular tissue. Glucocorticoids also may affect blood pressure by inducing growth

factors such as IGF or, alternatively, via indirect effects on carbohydrate and fat homeostasis (Seckl, 1994). In sheep, fetal blood pressure is increased when glucocorticoids are infused into the mother. The glucocorticoids affect the blood pressure directly by potentiating vasoconstrictor effects on the vasculature and also by regulating the synthesis of catecholarnines, nitric oxide and angiotensinogen, as well as having actions on the central nervous system (Tangalakis et al, 1992). Fetal cortisol levels are raised' in intra-uterine growth retardation (Goland et al., 1993) and normally the fetus is protected from high maternal levels of physiological glucocorticoids (5-10 times higher concentration than in the fetus) by the placental enzyme 111beta-HSO-2, which catalyses conversion of active cortisol to inactive cortisone. The efficiency of the placental barrier to maternal glucocorticoids varies considerably (Edwards et al., 1993) and prenatal glucocorticoid exposure affects maturation of organs, an effect that may persist throughout life (Goland et al., 1993). In rats, the lowest placental 111beta-HSO-2 activity, and therefore presumably the highest fetal exposure to maternal glucocorticoids, is associated with low-birth weight fetuses, presumably as a result of cortisol retarding growth. It is these fetuses that develop the highest blood pressure, blood glucose and glucocorticoid levels in adulthood (Benediktsson et al., 1993). Treatment of pregnant rats with an 111beta-HSO-2 inhibitor, carbenoxolone, also reduces birth weight (by up to 20

per cent) and raises blood pressure in the adult offspring (mean increase of 7-9 mmHg) (Walker et al, 1998). However the effect of fetal exposure to increased cortisol levels may differ depending upon the timing of exposure during gestation because the intracellular GR is expressed in most fetal tissues from mid-gestation.

CLINICAL CONSEQUENCES OF THE METABOLIC SYNDROME:

The association of the Metabolic Syndrome with Cardiovascular events is well known and is the dogma of this study. In addition to the increased risk of cardiovascular disease, patients with the metabolic syndrome are also predisposed to the following clinical syndromes- type 2 diabetes, peripheral arterial disease, gall stones, asthma, essential hypertension, PCOD,

non- alcoholic fatty liver disease, certain forms of cancer and sleep apnea. [53.]

The relative risk of Diabetes Mellitus is at least threefold higher among people with the metabolic syndrome than among those without the syndrome. Relative risks of the metabolic syndrome are highest for coronary artery disease mortality in various studies. Based on the data from the Framingham Offspring Study of 3323 men and women (mean age 52) with an 8 year follow-up it has been estimated that the metabolic syndrome (as defined by the ATP III criteria)

contributed almost half of the population-attributable risk for Diabetes and approximately a quarter of all incident cardiovascular disease. [71, 72]

Evaluation of the Adult treatment panel III diagnostic criteria [53]:

WAIST CIRCUMFRENCE: the inclusion of a measure of excess adiposity as one of the ATPIII criteria for identifying individuals with the metabolic syndrome is interesting because, as distinguished from other criteria, it is not a consequence of insulin resistance. Instead, obesity seems to be a life style variable that, along with physical inactivity, has an adverse effect on insulin mediated glucose disposal [7,8,9] which increases chances that the abnormalities and clinical syndromes associated with insulin resistance/compensatory hyperinsulinemia will develop. Although waist circumference may be more closely related to insulin resistance and its consequences than generalized obesity as estimated by body mass index, its superiority as a clinical tool can be questioned. The evidence that the waist circumference is more sensitive than body mass index as an approach to identify insulin resistant individuals at increased risk of developing CVD comes from the results presented by the European group for the study of insulin resistance[10]. These investigators evaluated the relationship between insulin mediated glucose disposal as measured by the euglycemic clamp technique and obesity in more than 1100 volunteers without diabetes. They reported that the magnitude of correlation between insulin resistance and obesity did not increase when the ratio of waist to hip was substituted for body mass index as the marker for obesity.

The following paragraph contains the directions for measuring waist circumference according to the national health and nutritional survey protocol[11]

`The subject stands and the examiner at the right palpates the upper bone to locate the iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal is drawn, and then crossed with a vertical mark on the mid-axillary line. The measuring tape is placed in a horizontal plane in the abdomen at the level of the marked point. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at normal minimal inspiration'.

To use waist circumference as one of the criteria, the upper limit of normal would have to be almost tailor-made for each ethnic group [53]. In this study WC more than or equal to 90 for males and 85 for females was used instead of 102 and 88 respectively as per the ATPIII criteria [2, 53, 73, 74]. These were derived using the mean +1 SD of the value for the non-diabetic, non-obese healthy people in tamilnadu (chennai) [12].

FASTING PLASMA GLUCOSE CONCENTRATION:

The American diabetic association has proposed the term `impaired fasting glucose` be used to describe individuals with a fasting plasma glucose concentration of 110 to 126 mg/dl (13) and that they may be prediabetic. Because a value of more than 126 is indicates diabetes and unequivocally increases the risk of CVD, it seems likely that the selection of ATPIII is to detect people with insulin resistance from the new ADA diagnostic criteria.

The results of the **DECODE study** group[14, 15] showed that post glucose challenge plasma concentration were superior to fasting values in predicting the CVD risk.of the 490 people, 25% of the individuals in the normal glycemic range were insulin resistant. These findings indicate that the presence of

impaired fasting glucose occurs too frequently to be useful in the diagnosis of the metabolic syndrome.

BLOOD PRESSURE:

The relationship between insulin resistance, blood pressure and risk of CVD is significant because though no more than 50% of patients with essential hypertension are insulin resistant that this is the subset of patients at risk of CVD.

Those patients with ECG evidence of ischemia and hypertensive are more glucose intolerant and hyperinsulinemic than those who are not. Dyslipidemia was observed in a significantly increased number in these patients than in normotensives.

The **Copenhagen Male Study** [16] and **Jeppenson et al** [17] showed the development of CVD in individuals with a high triglyceride and low HDL-C concentration was independent of the differences in baseline systolic or diastolic blood pressure. In contrast, the higher the systolic or diastolic blood pressure was at the beginning of the study, the greater the incidence of CVD in individuals without the dyslipidemic changes associated with insulin resistance.

DYSLIPIDEMIA:

The dyslipidemic components of the metabolic syndrome are probably the features linked most closely with insulin resistance and the risk of CVD. The ability of a low HDL-C to predict risk of CVD is well known for years. The role of increased triglycerides as an independent risk factor is well documented in recent studies [18,19]. Evidence from the **Helsinki Heart Study and the Veterans Affairs HDL Intervention Trial (VA-HIT) study** [20] demonstrates that the use

of Gemfibrozil, an agent that lowers plasma triglycerides and raises HDL-C concentrations, significantly decreases risk of CVD [2021]. VA-HIT also postulates that those who had the highest plasma insulin concentrations at baseline and were presumably the most insulin resistant benefited the most from gemfibrozil treatment.

An overview of **PROTEINURIA**:

Microalbumiuria has emerged in the last decade as a recognized independent cardiovascular risk factor in addition to being a predictor of diabetic kidney disease [22,23]. It has been associated with essential hypertension [24,25]; elevate triglycerides, total cholesterol and reduced HDL cholesterol, endothelial dysfunction [26,27,28], all features of the metabolic syndrome [29,30.]

The significance of microalbuminuria was first described in 1982 by Viberti et al., who showed a 24 fold increased risk of development of clinical proteinuria in Type 1 diabetic patients [31]. The finding was later extended to be associated with Type 2 diabetes mellitus also [32 33 34]. Similar observations in non-diabetic individuals have also been reported in population studies [35-40]. Thus proteinuria is an independent cardiovascular risk factor, the pathophysiology of which may be related to insulin resistance or hyperinsulinemia. It is probable that insulin resistance and proteinuria are both manifestations of a central mechanism yet to be identified which causes the clustering of metabolic and hemodynamic derangements in cardiovascular disease. In essential hypertension or diabetes, insulin resistance can be found in the absence of proteinuria but the reverse is uncommon. Therefore, the presence of proteinuria in these patients should serve as a warning signal for the metabolic syndrome.

CAROTID INTIMA MEDIA THICKNESS:

Carotid sonographic imaging is valuable in the determination of the presence and extent of disease. Visual inspection of longitudinal gray-scale images of the layers of normal carotid wall demonstrates two nearly parallel echogenic lines, separated by a hypoechoic to anechoic region. The first echo, bordering the vessel lumen, represents the lumen-intima interface; the second echo is caused by the media adventitia interface. The media is the anechoic/hypoechoic zone between the echogenic lines. The distance between these lines represents the combined thickness of the intima and media (I-M complex). The free wall of the Common carotid artery is measured. Normal thickening is usually less than 0.8mm. An increase in carotid IMT may represent the earliest changes of atherosclerotic disease. IMT increases with age. Numerous articles support the relationship between IMT and increased risk of myocardial infarction and stroke in asymptomatic populations [41,42,43.] A recent reference suggests that IMT may be superior to the coronary artery calcification score for identifying patients at high risk for these cardiovascular events [44]. Assessment of carotid IMT has been advocated as a means of assessing effectiveness of medical interventions to reduce the progression of IMT or even reverse carotid wall thickening.

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION:

Left ventricular diastolic dysfunction is recognized as an important contributing factor in the pathophysiology of many common cardiovascular diseases. Diastolic dysfunction may be present prior to, or concomitant with, systolic dysfunction. Although treatments are often aimed at improving the left ventricular contractile performance, they may conflict with appropriate therapy

for diastolic abnormalities. Recently, attention has been increasingly directed towards the diagnosis, evaluation, and treatment of diastolic dysfunction.

LVDD in METABOLIC SYNDROME:

Abnormalities of left ventricular filling have been reported in asymptomatic, otherwise healthy obese persons who have some degree of insulin resistance [45,46]. Prolongation of isovolumetric relaxation time is a common finding in obese individuals. These findings may be noted in the absence of systolic dysfunction and are consistent with diastolic dysfunction. It is possible that impaired relaxation, compliance or both occur in the metabolic syndrome. Weight reduction and control of other factors is associated with improvement in left ventricular diastolic filling and isovolumetric relaxation [47,48].

Echocardiography findings include, decreased peak early filling velocity, increased peak atrial filling velocity, reduced peak early to atrial filling velocity ratio, increased atrial contribution to filling and reduced deceleration rate of early filling [49].

The use of pulsed Doppler echocardiography to describe events of left ventricular filling is based on the assumption that transmitral blood flow velocities are representative of volumetric flow. The typical pulsed wave Doppler transmitral spectral pattern is shown below in figure A.

The two phases of forward flow in early diastole and late diastole can be readily identified by their triangular shape and are separated by a brief period of diastasis. The early phase, or E wave represents flow during the rapid filling phase, while the second peak, or A wave, represents transmitral flow occurring

as a result of atrial contraction. The E and A waves are two well defined peaks and usually display a linear upstroke and down slope that can be measured as acceleration and deceleration respectively, in centimeters per second. Other conventional measures include the peak E and A velocities, as well as the integrated areas within each phase, Ei and Ai. Occasionally a separate distinct and positive inflow wave is seen immediately after the E wave; this wave has been designated the L wave. A normal peak E wave velocity is in the range of 70 to 100 cm per second, with a peak A wave velocity 40 to 70 cm per second resulting in an E/A ratio of 1.0 to 1.5. The normal deceleration time (DT) for the E wave is 160 to 220 msec. Normal values vary within echo laboratories. Therefore, normative data should be established for each laboratory using standard examination and measurement techniques so that individual subjects can be evaluated against control subjects.

ABNORMAL TRANSMITRAL FLOW PATTERNS:

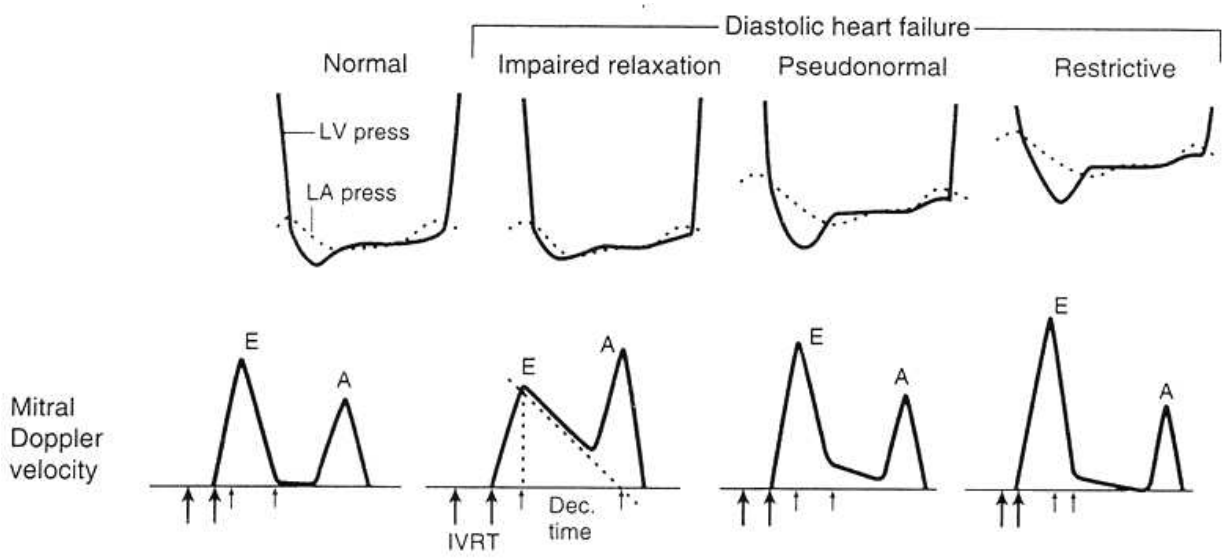
Although the ranges for normal values are wide and Doppler parameters are affected by a variety of hemodynamic and physiologic factors, patients with a proven diastolic dysfunction have been shown to demonstrate characteristic abnormalities in the spectral flow profile. Three distinct clinical patterns of abnormal transmitral flow have been described.

The first pattern consists of a prolonged IVRT (isovolumetric relaxation time) and deceleration time (DT) with a reduced peak E and an increased peak A velocity. These findings have been associated with normal early diastolic filling ventricular relaxation.

The second transmitral flow pattern has been termed *restrictive*, characterized by a short IVRT and a reduced deceleration time, along with increased E wave and diminished A wave velocities. Thus the filling is shifted predominantly to the rapid filling phase in early diastole and is thought to be due to a high crossover pressure at the time of mitral valve opening in the presence of a relatively non-distensible left ventricle.

A third pattern has been termed pseudonormal or normalized, characterized by normal velocities but results from counterbalancing influences of both abnormal relaxation and restrictive forces. The deceleration time is either normal or shortened.[50] [51,52].

Figure A:



E: Early diastolic filling, A: Atrial filling,

IVRT: Iso volumetric relaxation time, Dec.Time: Deceleration time.

MATERIALS AND METHODS

Study design and methods:

Study population:

67 patients aged between 30 and 65 years satisfied the diagnostic criteria for the metabolic syndrome among the patients evaluated at the medical OPD for non-specific symptoms and who were initially found to have either one or a combination of the three following,

1. Impaired fasting glucose (more then equal to 110mg/dl)
2. High blood pressure (more than or equal to 130/85mmHg)
3. Obese individuals (waist circumference > 90cm in male

   > 85 cm in female**)

The study was conducted between January 2005 and December 2005.

The study group included 36 females and 31 males.

CONTROLS

60 apparently healthy individuals who were age and sex matched and who did not have any of the criteria for metabolic syndrome were taken as controls for the evaluation of B mode Carotid Intima media thickness and diastolic dysfunction and 24 hour protein estimation.

INCLUSION CRITERIA:

1. Patients who do not have overt symptoms of diabetes mellitus (like polyuria, polydipsia, polyphagia, weight loss, easy fatigability etc.,)

2. Patients who do not have overt symptoms of hypertension (headache, giddiness, angina, dyspnea, palpitations, leg swelling)

3. Patients who satisfied three or more of the following five criteria,

A. Waist circumference:	Male: 90 cms or more **
	Female: 85 cms or more **
B. Fasting blood glucose:	110 mg/dl or more
C. Blood pressure:	130/85 mmHg or more
D. Triglycerides:	150 mg/dl or more
E. HDL-C:	< 40 mg/dl in males
	< 50 mg/dl in females

****** It is well reported in various studies that the upper limit of the Waist circumference has to be tailor- made for each ethnic group. [53]
(Ramachandran et al, 2003; Kim et al., 2002)
Hence, in our study, the ***Modified ATP III criteria,*** with Waist circumference of more than or equal to 90cm in male, and 85 cm for female has been taken [2, 53, 73,74.]

EXCLUSION CRITERIA:

1. Patients who carried a diagnosis of Diabetes mellitus earlier and on anti-diabetic medications.

2. Known Diabetic patients on non-pharmacological measures for blood sugar control.

3. Known hypertensives on drug therapy.

4. Known hypertensives on Life style modification protocols for blood pressure control.

5. Known cases of hypercholestrolemia.

6. Patients who have suffered a cardiovascular or cerebro-vascular event earlier (as defined by angina, unstable angina, MI, TIA, stroke etc.,)

7. Patients who are known to have other end organ damage.

8. Patients who had serious diseases like valvular heart disease, congenital heart disease, nephritic syndrome, nephritis, and renal failure.

METHODS

A brief history and clinical examination was done before subjecting the patients for investigations.

Patients who satisfied the diagnostic criteria for the metabolic syndrome were subjected to further studies that included,

Blood urea, serum creatinine, serum electrolytes, urinalysis, and electrocardiography.

Optic fundus was examined in all patients. Patients who showed any evidence of end-organ damage were excluded.

Further studies on patients after applying the exclusion criteria include,

24-hour urine protein estimation,

Carotid intima-media thickness by B mode Ultrasonography,

Left ventricular diastolic dysfunction - Echocardiogram wise.

24-hour urine protein estimation: [54]

Proteinuria was estimated from a 24-hour collection of urine sample. ‘‘Patients are instructed to empty the bladder at the beginning of the collection period, discard the urine, and note the time. Then, to collect all urine passed (including overnight) during the subsequent 24 hours. Exactly 24 hours after the commencement of collection, empty the bladder. Urine thus voided is to be collected.

The 24-hour urine sample thus collected is submitted for quantitative estimation of protein. ’’

Carotid intima-media thickness:

Carotid intima-media thickness (IMT) was measured in all the patients by B-Mode Ultrasonography (7.5MHz probe). Three pre-defined sites (distal common carotid, carotid bifurcation and proximal internal carotid) on each side were selected for IMT and the mean derived. Two observers independently did the B-Mode examination at different times of the same day at the pre-defined sites. Inter-observer error in the evaluation of mean IMT was 6%.

ECHOCARDIOGRAPHY:

Echocardiogram was done with an *ALOKA* Echocardiogram machine.

Subjects were examined in the left lateral decubitus position using standard parasternal short axis and apical views. All the recordings and measurements were done by the same observer according to the recommendations of the American society of echocardiography and were always performed at the mid-day to avoid the influence on the left- ventricular diastolic function. Left-ventricular diastolic dysfunction (LVDD) was evaluated using well-

standardized diagnostic criteria and all Doppler measurements were assessed at the end of expiration.

From the trans-mitral recordings, the following measurements were carried out. Peak `E` velocity in centimeters per second (peak early trans-mitral filling velocity during early diastole), peak `A` velocity in centimeters per second (peak trans-mitral filling velocity during late diastole) and deceleration time in milliseconds (time elapsed between peak E velocity crosses the zero baseline. IVRT, (iso-volumetric relaxation time) defined as time elapsed between closing of aortic valve and opening of mitral valve.

The definitions published by the *Canadian consensus* on diastolic dysfunction by echocardiography were used to classify diastolic function as follows,

Normal,

Impaired relaxation,

Pseudo-normal and

Restrictive pattern.

No subject had echocardiographically detectable regional wall motion abnormalities and each subject had normal ejection fractions. All cardiac valves were examined for significant valvular disease. Two patients had trivial mitral regurgitation.

Serum total cholesterol and triglycerides and HDL were analyzed enzymatic ally (fasting sample). Serum LDL cholesterol was calculated with Friedewald`s formula.

LDL cholesterol = Total cholesterol – HDL cholesterol- TGL/5.

STUDY LIMITATIONS:

Patients selected for the study were more in the age group of 40 to 60 years as it is well known that increased Carotid intima- media thickness and LV Diastolic dysfunction can occur in aged individuals irrespective of the presence of the Metabolic Syndrome. This selection bias may show an apparently low prevalence of the Metabolic Syndrome in the elderly.

Measurement of the Carotid intima-media thickness is not without observer variation. Though measures have been taken to reduce this by doing the same with two different observers at different times of a day, and evaluating the inter-observer error, minor variations are still bound to occur.

Though all patients were subjected to urine protein estimation, the ideal marker of cardiovascular risk estimation is microalbuminuria rather than proteinuria. Proteinuria may occur in a humpty number of other conditions. This limitation was seriously considered and hence to rule out renal causes of proteinuria, all patients underwent urinalysis, blood urea, serum creatinine

and electrolyte. However, chances of patients having very subtle renal dysfunction and normal lab values of such parameters are always there. Studies have been conducted using proteinuria instead of microalbuminuria for similar cardiovascular risk estimations. Based on such studies, we have used proteinuria instead of microalbuminuria, as the latter is not readily available in all centers. [70]. Also, proteinuria is routinely preceded by microalbuminuria.

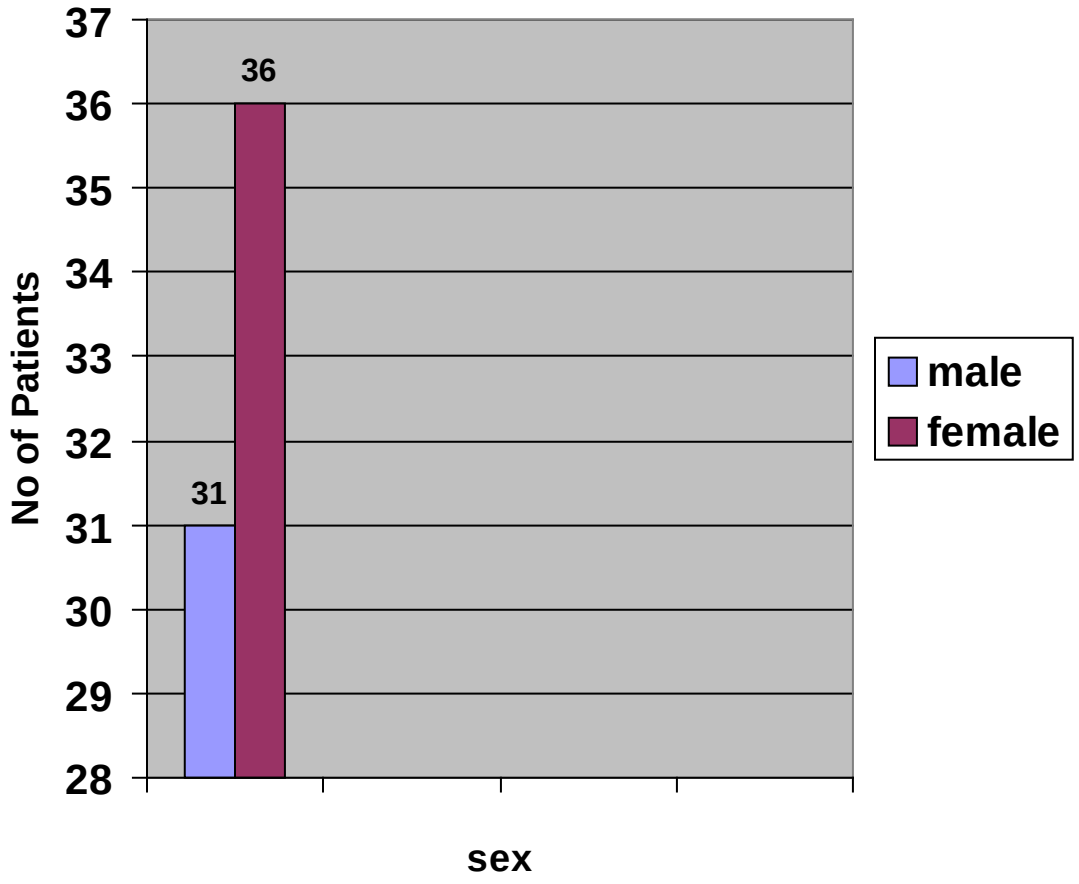
Hence the estimation of proteinuria may be an underestimate of microalbuminuria and hence the cardiovascular risk. [31]

OBSERVATIONS AND RESULTS

The study population consists of 67 patients with 36 females and 31 males.

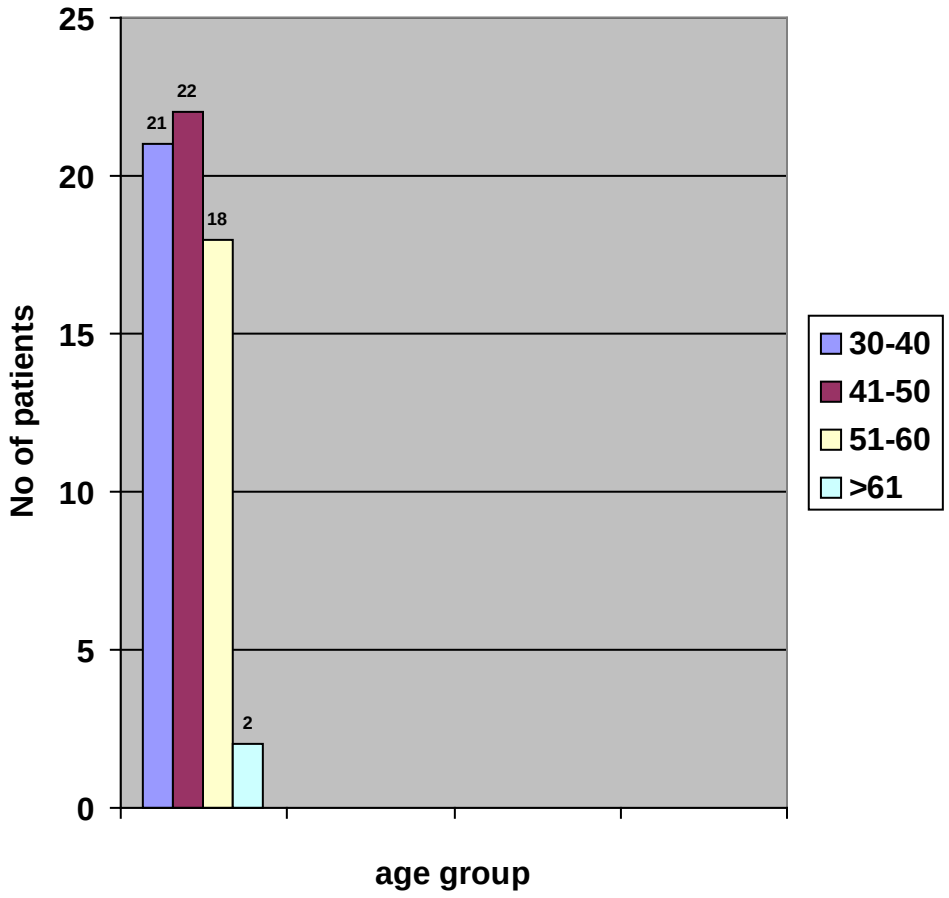
All patients studied belong to places in and around Tanjavur district,

Tamil Nadu.



AGE:

The **age** of the study group was between 30 and 65. Twenty-one patients were between 30 and 40 years of age. Twenty-two patients were between 41 and 50 years of age. Eighteen patients were between 51 and 60 years of age and two patients were above 61 years of age.



SOCIO-ECONOMIC GROUP:

The study population was categorized into low, medium and high **socioeconomic groups** according to the monthly income. Patients with a monthly income of less than 3000 Rs per month were categorized under low, those between 3000 and 7000 medium, and those > 7000 as high socio-economic class respectively. 19 patients (28.35%) of the patients fell under the low socio-economic group. All the remaining 48 (71.64%) fell under the medium group.

RISK FACTORS:

Conventional risk factors for atherosclerosis were sought in the general history taking of the patient and it was found that 34 patients (50.74%) had one or more of these factors like smoking, excess alcohol intake, sedentary life style habits etc.

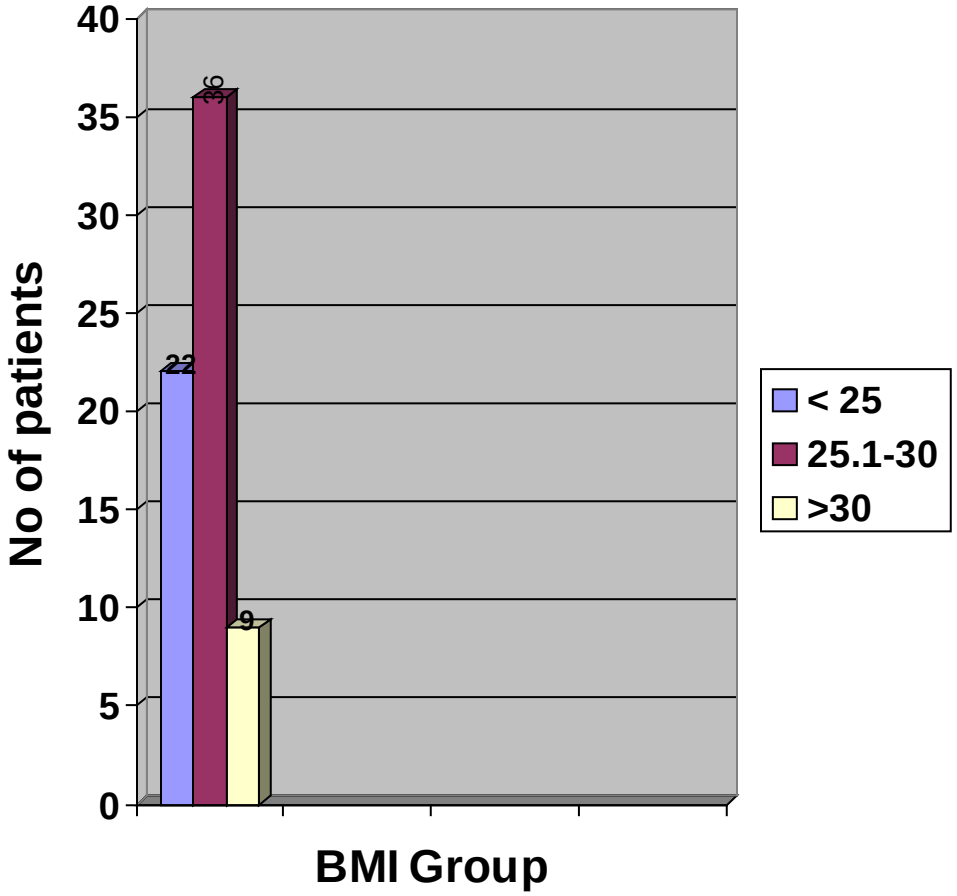
BODY MASS INDEX:

Anthropometrical analysis of patients revealed that 22 patients (32.83%) had a BMI of less than 25; 36 patients (53.73%) had a BMI between 25.1 and 30; 9 patients (13.43%) patients had a BMI of >30. Comparing the BMI with waist circumference the following observations were made,

The Mean WC of patients in the normal BMI group was 87.68

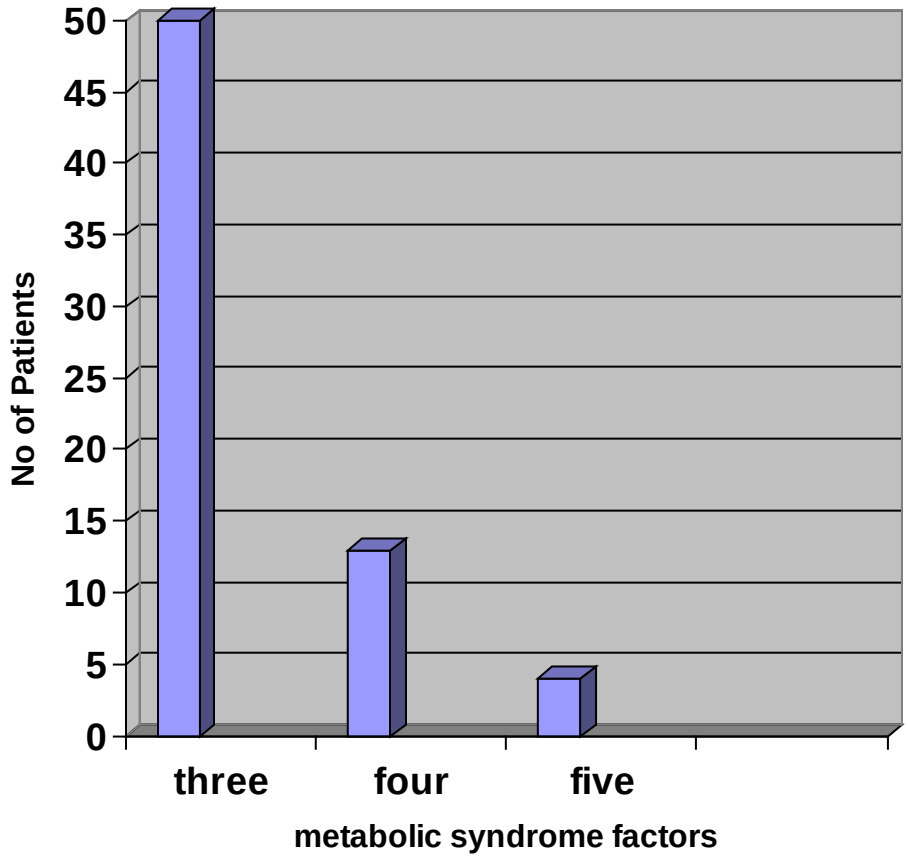
The Mean WC in the overweight group was 92.30

The Mean WC in the obese group was 100.66.



METABOLIC SYNDROME:

Applying the ATP III criteria for the diagnosis of the metabolic syndrome, of the 67 patients, 50 patients (74.62%) had three out of the five variables for the diagnosis; 13 patients (19.40%) had four out of the five variables and 4 patients (5.97%) had all the five variables for the diagnosis of the metabolic syndrome.



Patients who showed gross ECG abnormalities like Ischemia, injury, infarction, left ventricular hypertrophy and conduction disturbances were excluded. However three patients who showed non-specific ST-T wave changes were included in the study. Two patients who showed trivial mitral regurgitation were also included, however, one patient showed a mild mitral regurgitation was excluded.

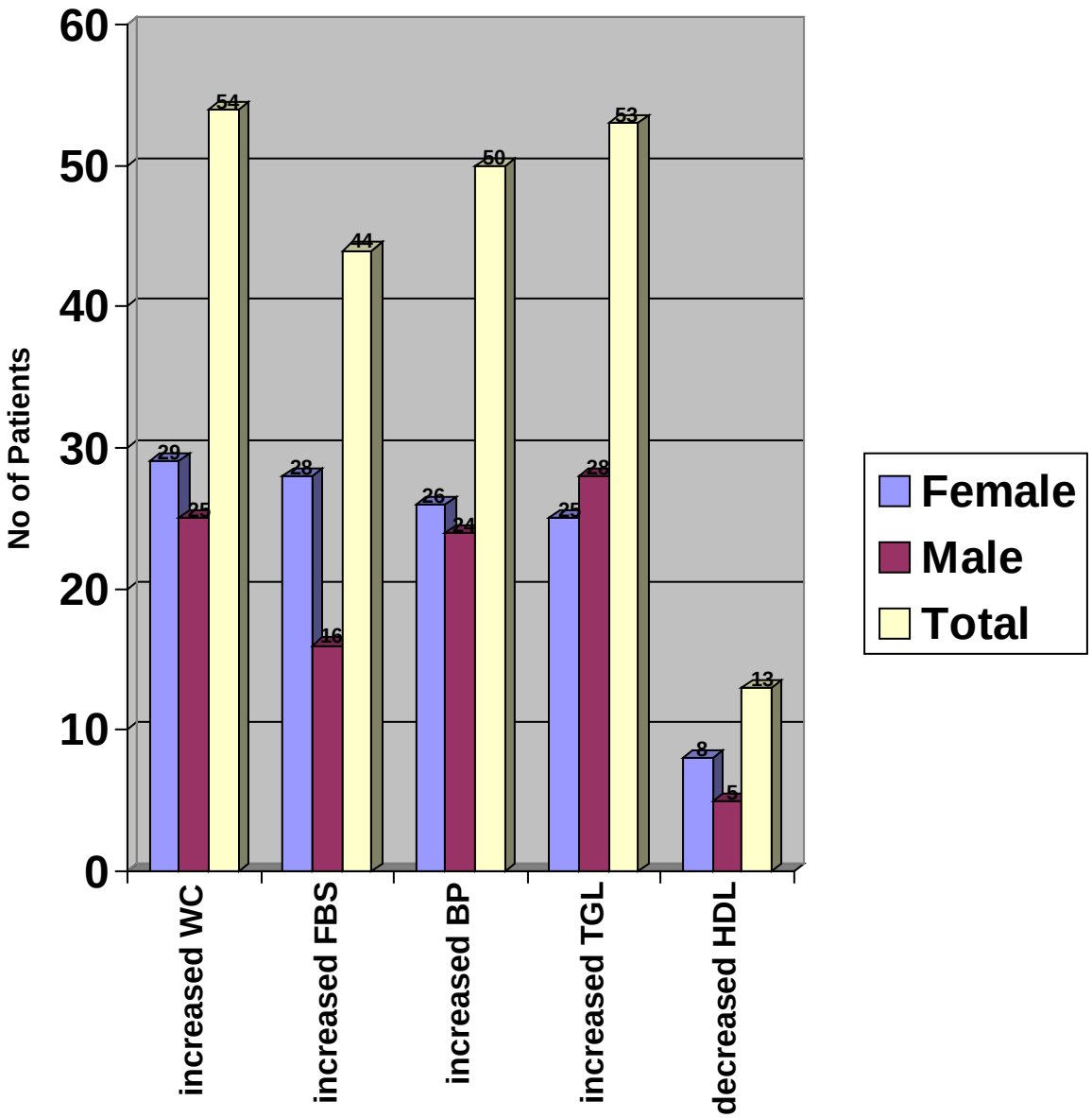
Fifty-four patients (80%) had an increased waist circumference. 29 were females and the remaining 25 were males. The mean waist circumference in the female and male population was 92.79 and 96.2 respectively.

Forty- four patients (65%) had a fasting blood sugar of more than or equal to 110 mg/dl. 28 were females and 16 were males. The mean fasting blood sugar for females and males were 116mg/dl and 138mg/dl respectively.

Fifty- three (79%) patients had an elevated triglyceride level of more than or equal to 150 mg/dl. 28 were males and 25 were females. The mean triglyceride levels were 189.85mg/dl and 187.44 for males and females respectively.

Only thirteen patients had a HDL cholesterol level below normal. (Less than 40mg/dl, for males and less than 50mg/dl, for females). Of these 8 were females with a mean HDL-C value of 40.5mg/dl and five were males with a mean of 30.8mg/dl.

Fifty patients (74%) had an elevated Blood pressure, 26 were females and 24 were males. The mean BP in the female population was 148/94 mmHg and in the males, 150/92 mmHg.



EVENTS:

Proteinuria:

Thirty nine patients (58.20%) had proteinuria defined by excretion of more than 150mg per day in a timed collection of urine. Of these, 22 were females

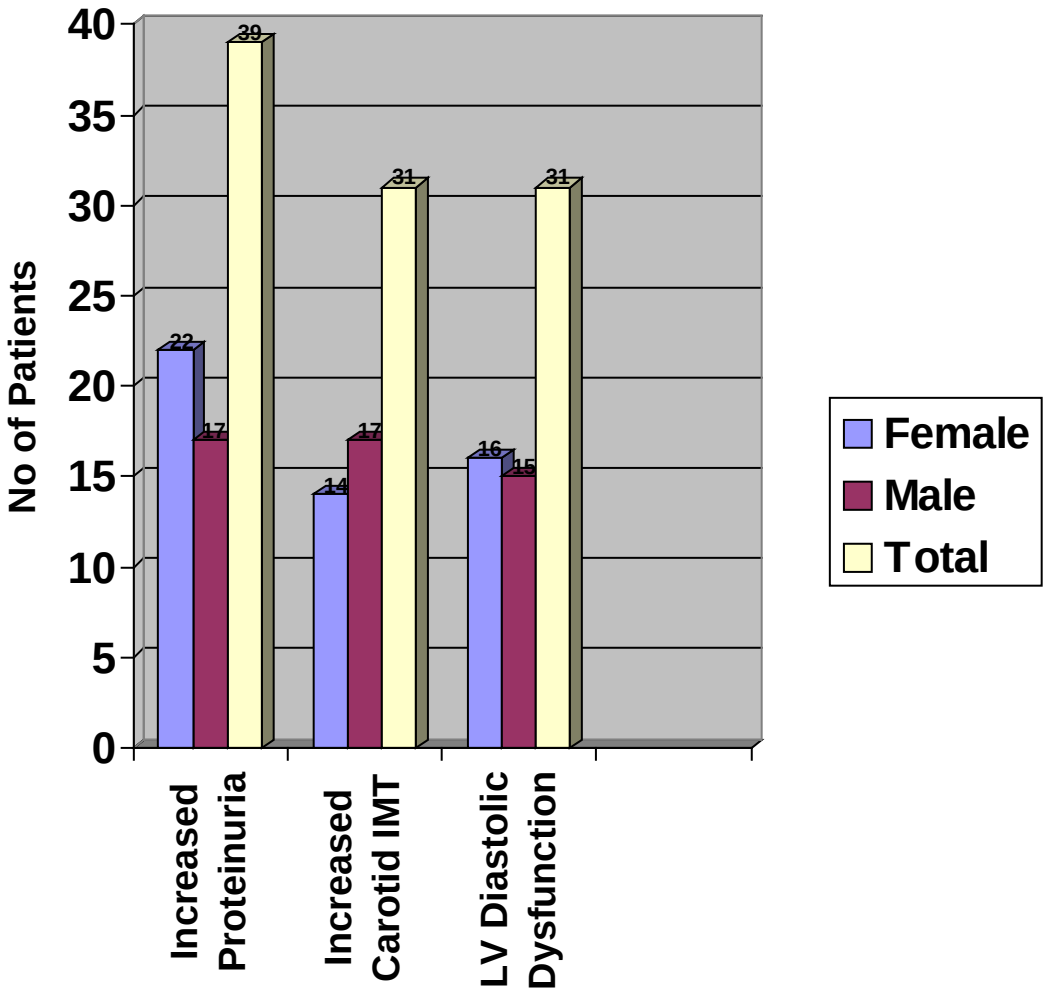
and the mean level of proteinuria was 578mg per day and 17 were males with a mean of 558.89mg/day.

Carotid Intima Media Thickness:

Thirty-one patients (46.26%) had a carotid intima media thickness of greater than or equal to 0.8mm. 14 were females with a mean of 0.821mm and 17 were males with a mean value of 0.835mm.

Left ventricular Diastolic dysfunction:

Impaired relaxation was the only diastolic dysfunction noted in subjects. No patient showed a restrictive or pseudonormal pattern. Of the 31 subjects who were found to have diastolic dysfunction, 16 were females and 15 were male.



CONTROLS:

Control group included 60 individuals in whom none of the criteria was positive for the metabolic syndrome. Such age matched and sex matched individuals were selected for 24 hour protein estimation, carotid intima media thickening and LV diastolic dysfunction study.

It was observed that proteinuria was present in six out of the sixty individuals.

Increased Carotid IMT was observed in eight out of the sixty individuals.

Impaired relaxation was observed in six out of the sixty individuals.

STATISTICAL ANALYSIS OF DATA:

Within the group, (cases) statistical Analysis of the individual factors with the individual events revealed the following results, Applying the *Chi square test*, there was a statistically significant difference between the means of the proteinuria group and the blood sugar values at 5% level. Similarly, there was a statistically significant difference between the means of Waist circumference and the LV diastolic dysfunction at 5% level. The events that occurred in rest of the factor analysis showed that even though there is an absolute increase in the incidence of events with the factors subgroups, the association was not statistically significant.

The comparison of the study group with the control group revealed the following results,

Applying the *Chi square test*, it was found that,

The presence of the metabolic syndrome and the increase in the Carotid intima media thickness are highly associated at 5% significance level. ($p < 0.05$) and the occurrence is not mere increase in the number of cases.

The presence of the metabolic syndrome and the occurrence of LV diastolic dysfunction are highly associated at 5% significant level. ($p < 0.05$) and the association is not mere increase in the apparent number of cases.

Also, the metabolic syndrome and increased protein excretion in urine are highly associated at 5% level of significance. ($p < 0.05$).

	CASES	CONTROLS	P value
CAROTID INTIMA MEDIA THICKNESS	39	6	<0.05
LV DIASTOLIC DYSFUNCTION	31	8	<0.05
PROTEINURIA	31	6	<0.05

DISCUSSION

SEX:

The metabolic syndrome is observed in more number of females than males. This correlates with the earlier studies, both native and foreign. According to *Gupta et al., 2003* 7.9% of males and 17.5% of females in western India suffer from the metabolic syndrome. *A. Ramachandran et al., 2003* reports an increase in the metabolic syndrome in women in studies conducted in south India. *Jaber et al., 2004* reports 23% and 28% respectively in Arab Americans. Our results correlate with these studies with more females suffering from the metabolic syndrome.

AGE:

The incidence of the metabolic syndrome increases with age. *Villegas et al., 2003* reports an increasing prevalence of metabolic syndrome with increasing age from 20.7% in < 50 group to 24.3% in >60-year group. Similar results were shown by studies by Indian researchers. *A. Ramachandran et al.*, reports increasing trend with age. However, in our study it is noticed that more number of people in the 41 to 50 years age group had metabolic syndrome than the >50 group. Probably this has occurred as a result of patient selection bias in order to include younger individuals as the incidence of LV diastolic dysfunction and Carotid IMT

increases with age and this study aims to evaluate these parameters in young individuals with metabolic syndrome.

SOCIO-ECONOMIC STATUS:

A significant increase in the number of cases of metabolic syndrome in the medium socio-economic class was noted as compared to the low socio-economic class. This correlates with both Indian and foreign observations and relates to the increasing prevalence of obesity in this group. More than half of the study group had a body mass index in the overweight range, i.e., between 25 and 30. This shows that the metabolic syndrome is more prevalent in the overweight group. The increased occurrence of the Metabolic syndrome in the obese individuals in well known. *NHANES III study* showed that the prevalence of the metabolic syndrome increased from up to 3% in <20 BMI group to 22.5% in the 25to 27 BMI group. Other studies that reported similar observations include the St. *Onge, Janssen and Heymsfield, et al., 2004 Weiss et al., 2004 and Cook et al., 2003.*

RISK FACTORS:

Conventional risk factors have a bearing in patient's long-term morbidity and mortality. Common risk factors observed include history of smoking, excessive alcohol consumption, sedentary life style etc. almost 50% of the

patients were observed to have at least one of these factors. *Whitehall II study* on White European civil servants found that risk factor modification by increasing leisure time activity was associated with a reduced incidence of the metabolic syndrome. *Laaksonen et al., 2002* and *rennie et al., 2003* report similar results in geographically separated areas. *Farrell, Cheng and Blair et al., 2004* report an increase in incidence of metabolic syndrome in smokers compared to non-smokers.

Thus a conclusion prevails in the form of life style modifications for reducing the risk of metabolic syndrome.

Factor analysis of the metabolic syndrome showed that the percentage of hypertriglyceridemia (79%), low HDL-C and hypertension (74%) were higher when compared to the *Mexican study, Phase II San Antonio Heart study* and the earlier *Indian studies*. This shows that there is an increased incidence of dyslipidemias and hypertension in this study compared to the other studies. This may be explained by the diet habits of the people in this part of the state or by some other factors to be evaluated further.

The Clustering of risk factors occurred in both males and females in a comparable manner. Earlier studies clearly show that the risk of cardiovascular events increased with the number of factors present within the metabolic syndrome group, Thus, more the clustering was, more were

the events to occur, i.e., carotid Intima Media thickness LV diastolic dysfunction and proteinuria. [55]

CAROTID INTIMA MEDIA THICKENING:

The association of Carotid Intima Media thickness with the metabolic syndrome is found to be **statistically significant** in our study. The analysis of various other studies is as follows,

Compared with young adults without metabolic syndrome, those with metabolic syndrome had greater carotid intima-media thickness on ultrasound, an indicator of sub- clinical atherosclerosis. Carotid intima-media thickness increased with the number of components of the metabolic syndrome present. The burden of sub-clinical atherosclerosis in young adults increases with an increasing burden of components of metabolic syndrome, and increased BP and low HDL-C are especially powerful predictors of increased carotid intima-media thickness.[56]

Among 507 young adults (20 to 38 years old) Using ultrasound, the researchers measured the thickness of the inner layers of the carotid arteries. Carotid intima-media thickness can identify sub- clinical atherosclerosis, that is, hardening and thickening of the arteries before an individual feels

any symptoms. The artery wall thickness is a predictor of cardiovascular risk. The study participants were also classified as having metabolic syndrome if they met the ATP III criteria. This is the first study to demonstrate that metabolic syndrome is associated with increased sub-clinical atherosclerosis in otherwise healthy young adults," **Dr. Stein** said. "Those with the thickest carotid artery walls were two to three times more likely to have metabolic syndrome, independently of age, sex, race and smoking status." [57]

Metabolic Syndrome and the Progression of Carotid Intima-Media Thickness in Elderly Women were found to be statistically significant in several studies. Incident metabolic syndrome is associated with accelerated progression of carotid IMT in elderly women, as shown in a 12-year follow-up study in a population-based sample of 101 women (age range at baseline, 60-70 years). [58]

Early and asymptomatic signs of atherosclerosis could be detected in middle-aged subjects who proved to be hyperinsulinaemic in a screening procedure. The prevention of clinically manifest cardiovascular diseases in these subjects could be of great importance.[59]

The effect of the metabolic syndrome on early atherosclerosis is more prominent in women than in men. [60]

Studies also revealed gender differences for the subcomponents of the metabolic syndrome. [60]

Several studies assess the Intima-media thickness of the carotid arteries in subjects with hyperinsulinaemia (insulin resistance). [61]

One study evaluated the frequency of metabolic syndrome with premature Carotid atherosclerosis in young women with polycystic ovary disease (PCOD). PCOD is one another disease associated with the metabolic syndrome. The study was conducted in 43 young women and IMT was measured and concluded that factors other than hyperandrogenaemia and obesity might be operating as causative factors. [62]

In young adults, Metabolic Syndrome is associated with increased atherosclerotic burden, and therefore, increased cardiovascular risk. These results support the importance of screening and early intervention in this population.[63]

Thus, increased Carotid intima media thickness is a potential marker for early vascular disease in patients and pre-dates the development of cerebro-vascular events. Interventions of various components of the metabolic

syndrome have shown outcome benefits in several studies as discussed above.

LEFT VENTRICULAR DIASTOLIC DYSFUNCTION:

The association of the Left ventricular diastolic dysfunction with the metabolic syndrome is found to be **statistically significant** in our study. The analysis of *various other studies* is as follows,

Several studies have reported various degrees of diastolic dysfunction in asymptomatic obese individuals both with and without diabetes mellitus.[64]

The prevalence of left ventricular diastolic dysfunction in asymptomatic, normotensive patients without significant coronary artery disease is much higher than previously suspected. Tissue Doppler Imaging markedly improved the echocardiographic detection of diastolic dysfunction in asymptomatic patients. [65]

Obesity in young otherwise-healthy women is associated with concentric LV remodeling and decreased systolic and diastolic function. These early abnormalities in LV structure and function may have important implications for explaining the myocardial dysfunction that is associated with increased cardiovascular morbidity and mortality caused by obesity.[66]

Females with metabolic syndrome are more prone for the development of LV Diastolic Dysfunction [67]

The occurrence of diastolic dysfunction was independent of the systolic function and is the first to occur among the two.[68]

Thus, diastolic dysfunction is a significant risk factor for the development of early cardiovascular event especially in female patients with metabolic syndrome. The identification of this is important as this occurs before the systolic dysfunction begins and interventions of various components have shown outcome benefits.

PROTEINURIA:

The association of the proteinuria with the metabolic syndrome is found to be **statistically significant** in our study.

Proteinuria has emerged in the last decade as a recognized independent cardiovascular risk factor in addition to being a predictor of diabetic kidney disease.[22, 23]

It has been associated with essential hypertension, [24, 25] elevate triglycerides, total cholesterol and reduced HDL cholesterol, endothelial dysfunction, [26, 27,] all features of the metabolic syndrome.

The significance of microalbuminuria was first described in 1982 by Viberti et al., who showed a 24 fold increased risk of development of clinical proteinuria in Type 1 diabetic patients [31]. The finding was later extended to be associated with Type 2 diabetes mellitus also. [32, 33, 34]. Similar observations in non-diabetic individuals have also been reported in population studies [35-40]. Thus proteinuria is an independent cardiovascular risk factor, the pathophysiology of which may be related to insulin resistance or hyperinsulinemia. It is probable that insulin resistance and proteinuria are both manifestations of a central mechanism yet to be identified which causes the clustering of metabolic and hemodynamic derangements in cardiovascular disease. In essential hypertension or diabetes, insulin resistance can be found in the absence of proteinuria but the reverse is uncommon. Therefore, the presence of proteinuria in these patients should serve as a warning signal for the metabolic syndrome.

Two other studies postulate a different type of correlation of proteinuria with the metabolic syndrome.

Proteinuria predicted cardiovascular disease mortality independently of the presence of metabolic syndrome in non-diabetic and diabetic Subjects. [70]

Proteinuria predicts Type 2 diabetes, independent of the metabolic syndrome and other known risk markers. [71.]

CONCLUSIONS

The metabolic syndrome, once thought to occur more commonly in affluent societies is now a common disease in people of all socio-economic strata.

In-spite of harboring several factors of the metabolic syndrome, most patients are asymptomatic.

The disease appears to have a slight female preponderance.

Sedentary lifestyle, smoking and excess alcohol are associated with an increase incidence of the metabolic syndrome and studies have shown benefits of life style modifications.

Body mass index, being overweight/obese and the waist circumference are good predictors of cardiovascular risk in patients with the metabolic syndrome. Control of body weight has shown to improve the outcome of cardiovascular events in several studies.

The Carotid Intima media thickness, Left ventricular diastolic dysfunction and Proteinuria all increase with the number of factors of metabolic syndrome present. Several prospective studies have shown an increased cardiovascular mortality and morbidity in such patients.

There is a significant increase in the incidence of Carotid Intima media thickness, diastolic dysfunction and Proteinuria in patients with metabolic syndrome compared to those who do not have metabolic syndrome.

Since several studies have shown that these are easily detectable, early markers of cardiovascular and cerebro-vascular events, identification of such abnormalities should be sought after seriously and treatment options considered in reducing future hi-risk events.

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								MASTER
S.NO	NAME	AGE	SEX	OP No	S-E STATUS	RF	HEIGHT	WEIGHT
							Mts	Kgs
1	Vanaroja	39	F	1703/05	MED	NIL	1.5	65
2	Poongodi	40	F	1967/05	MED	NIL	1.5	47
3	Mustafa	48	M	2029/05	MED	S,A SED	1.77	83
4	Rajeshwari	42	F	2206/05	MED	SED	1.45	61
5	Nachiapilla	65	M	2260/05	MED	S	1.62	70
6	Tamaraisel	40	F	2470/05	LOW	NIL	1.5	53
7	Padma	55	F	2707/05	MED	SED	1.55	65
8	Selvaraj	50	M	2721/05	MED	S,A	1.7	66.5
9	Sarasu	40	F	2868/05	MED	NIL	1.46	62
10	JaitoonBee	52	F	2866/05	MED	NIL	1.61	71
11	Radhakrish	52	M	3046/05	LOW	S A	1.64	65
12	Ganesan	45	M	3067/05	LOW	S A	1.55	54
13	Chandra	39	F	3206/05	LOW	NIL	1.53	50
14	MohdBeev	41	F	3280/05	MED	NIL	1.4	60
15	Uthirapathi	60	M	3281/05	MED	A	1.6	65
16	Muthulaksh	39	F	3485/05	MED	NIL	1.5	59
17	Kalaiselvi	45	F	3478/05	MED	NIL	1.45	50
18	Karupaiyan	56	M	3481/05	MED	A	1.7	61
19	Somasund	55	M	3536/05	MED	S A	1.66	69
20	Ramamoor	53	M	3581/05	LOW	S A	1.73	74
21	MariaJohn	43	F	3602/05	LOW	NIL	1.67	66
22	Sahayama	45	F	3641/05	LOW	NIL	1.43	50
23	Nellavathy	65	F	3721/05	MED	NIL	1.53	65
24	Durairaj	52	M	3892/05	LOW	NIL	1.65	60
25	Mariammal	48	F	3899/05	MED	NIL	1.42	67
26	Saminatha	55	M	3916/05	MED	S A	1.59	61
27	Geetha	48	F	3946/05	MED	SED	1.49	59
28	Gowri	32	F	3977/05	MED	SED	1.75	87
29	Anandavall	60	F	3994/05	MED	NIL	1.5	59
30	SelvarajMu	36	M	3995/05	MED	S A	1.6	82
31	Chandra	43	F	4027/05	MED	NIL	1.4	64
32	Amarjothi	48	F	4039/05	MED	NIL	1.56	58
33	Nallammal	60	F	4132/05	MED	NIL	1.5	60
34	Leelavathy	33	F	4236/05	LOW	NIL	1.56	63
35	Rajam	35	F	4247/05	MED	NIL	1.52	65
36	Vasudevan	41	M	4291/05	MED	A	1.72	94
37	MayaDevi	51	F	4352/05	LOW	NIL	1.59	64
38	Anandaran	56	M	4355/05	LOW	A	1.64	60
39	Panchavar	45	F	4356/05	LOW	NIL	1.6	68
40	Sornam	38	F	4417/05	MED	NIL	1.52	60
41	Andal	56	F	4516/05	MED	NIL	1.56	63
42	Subramani	30	M	4598/05	MED	S A	1.68	88
43	Elavendan	36	M	4601/05	MED	S A	1.62	75
44	Rajarajan	50	M	4701/05	MED	S A	1.63	74
45	Madumadh	36	F	4739/05	LOW	NIL	1.49	59

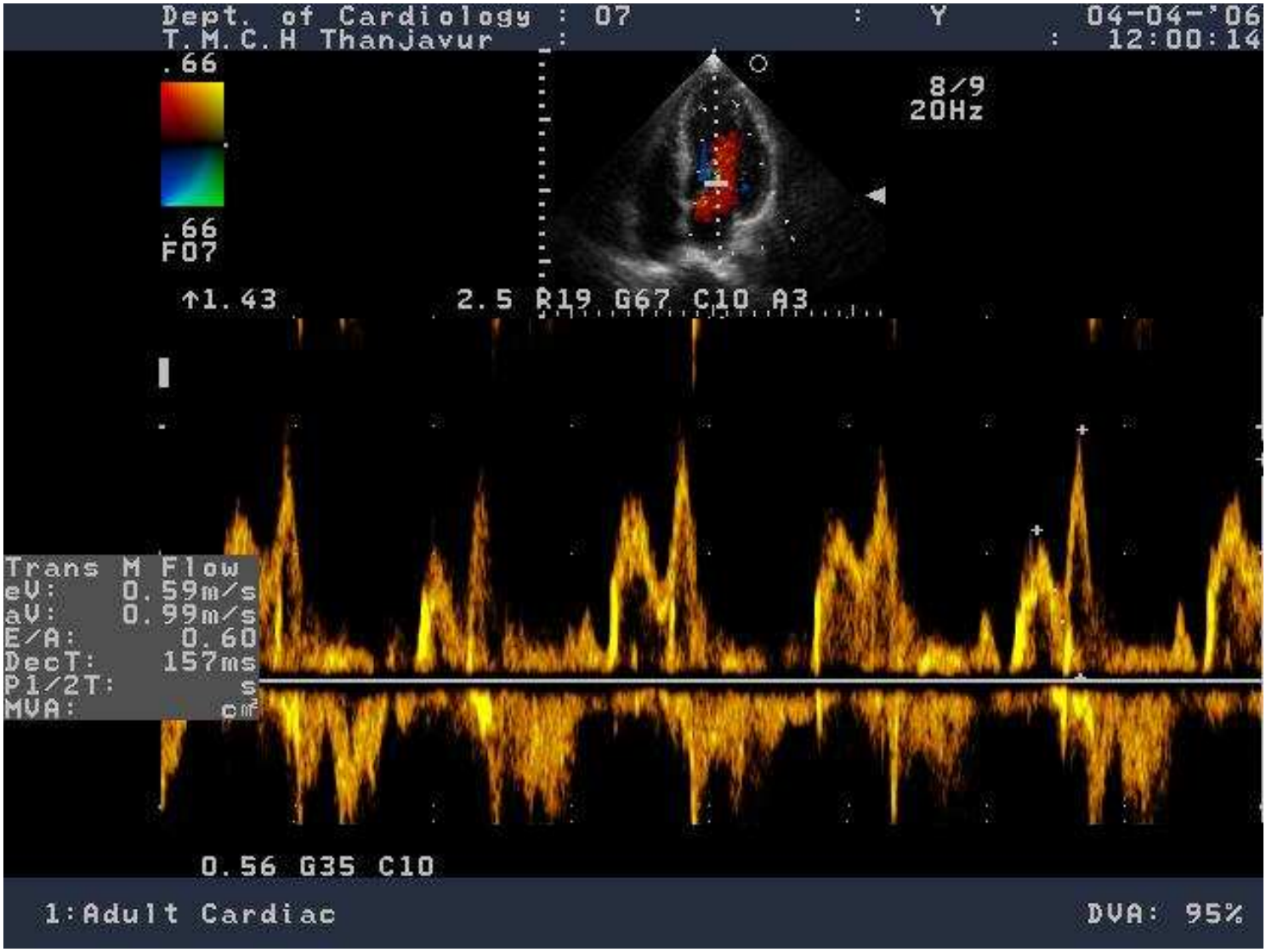
46	Sekar	48	M	4781/05	LOW	S A	1.63	61
47	Sukanya	33	F	4795/05	MED	NIL	1.62	74
48	Rajavel	42	M	4822/05	MED	A	1.64	72
49	Jesima	48	F	4827/05	MED	NIL	1.66	66
50	Rajasekara	55	M	4916/05	MED	S A	1.68	68
51	Sivanandar	48	M	4933/05	LOW	S A	1.75	78
52	Deivendrar	40	M	4934/05	MED	S A	1.6	71
53	Devikala	38	F	4976/05	MED	NIL	1.52	64
54	Vasanthak	45	F	5001/05	MED	NIL	1.53	63
55	Nagarajan	48	M	5013/05	LOW	S A	1.62	60
56	Sridharan	51	M	5032/05	LOW	S A	1.72	69
57	Kalyani	38	F	5136/05	MED	NIL	1.54	62
58	Amirtha	33	F	5207/05	MED	NIL	1.6	66
59	Baskar	43	M	5417/05	MED	NIL	1.58	65
60	Muralidhara	40	M	5475/05	LOW	NIL	1.69	74
61	kirubha	36	M	5491/05	MED	S A	1.75	94
62	sathyanath	57	M	5791/05	LOW	S A SED	1.67	64
63	Mehalai	52	F	5882/05	MED	SED	1.49	63
64	venkatraga	45	M	5889/05	MED	S	1.64	72
65	kannan	38	M	5954/05	MED	S A	1.67	86
66	balakrishna	42	M	5965/05	MED	S	1.72	88
67	rani	38	F	5981/05	MED	NIL	1.58	63

CHART								
BMI	SYMPTOMS		THE METABOLIC SYNDROME					
			WC(cms)	BP(mmHg)	FBSugar(mg/dl)	TGL(mg/dl)	HDL-C(mg/dl)	24 Hr.Ur.Protein
28.8			92	140/94	127	150	60	380
20.8			86	140/90	120	138	55	450
26.5			102	150/90	120	148	45	350
29			88	160/100	115	240	40	200
26.6			96	160/90	110	164	30	380
23.5			77	130/90	123	160	50	nil
27.8			96	140/90	122	126	48	325
23			98	150/90	112	180	30	475
29.1			90	140/90	100	150	50	125
27.4			92	150/100	128	249	50	740
24.25			98	124/80	128	231	48	275
22.5			93	140/86	118	122	56	406
21.6			80	128/80	134	266	45	0
30.6			97	150/100	136	120	60	1380
25.3			97	130/90	142	310	50	1220
26.2			87	130/94	132	204	60	984
23.8			83	130/86	136	166	40	289
21.1			90	136/80	128	188	52	525
25			98	180/100	116	212	86.6	1200
24.7			93	130/80	110	184	50	1200
23.74			92	130/90	111	142	55	391
24.5			83	150/100	125	300	52	138
27.7			92	160/100	102	200	55	170
22			89	138/88	115	168	65	90
33.2			108	170/90	131	145	40	1600
24.2			78	170/100	112	152	50	0
26.5			98	110/80	122	111	27	132
28.4			106	150/110	110	126	65	132
26.2			75	140/90	134	199	50	130
32			100	150/90	102	170	40	84
32.3			95	180/110	89	171	60	1270
23.8			84	130/86	116	154	50	45
26.6			98	160/80	88	150	54	325
25.9			80	120/84	116	150	44	150
28.2			88	140/90	90	160	58	220
31.8			100	154/94	80	172	40	120
25.3			88	140/100	123	140	56	85
22.3			80	134/70	121	176	30	434
26.5			90	148/94	98	156	54	50
25.9			85	134/80	116	200	58	800
25.9			93	144/90	115	148	52	376
31.2			98	142/90	98	140	50	145
28.6			90	150/86	98	178	46	145
27.9			91	148/100	130	220	50	675
26.5			88	132/90	120	194	62	890

23		85	140/90	110	172	60	75
28.2		98	150/100	80	166	65	68
26.8		94	160/90	78	196	50	78
24		90	136/90	116	140	52	325
24.1		88	140/90	94	190	40	470
25.4		98	148/94	110	182	57	375
27.7		91	120/84	122	150	54	135
27.7		88	140/90	98	173	58	0
26.9		102	150/94	130	194	48	650
22.9		90	110/70	120	180	46	50
23.3		94	140/80	122	186	34	325
26.16		90	120/80	128	210	53	75
25.7		88	140/94	92	164	58	50
26.1		91	136/90	84	150	55	115
25.96		95	140/96	90	168	54	80
30.7		109	150/94	100	194	45	54
23		80	132/76	134	211	30	480
28.3		93	162/100	94	160	40	425
26.8		100	164/90	80	226	50	78
30.93		98	150/100	86	204	40	456
30.87		101	164/98	84	202	40	255
25.3		93	144/90	118	148	52	376

EVENTS	
Carotid IMT	ECHO-LVDD
0.8	imp.relaxation
0.82	imp.relaxation
0.76	normal
0.69	imp.relaxation
0.92	imp.relaxation
0.8	normal
0.7	normal
0.84	imp.relaxation
0.6	normal
0.82	normal
0.82	imp.relaxation
0.55	imp.relaxation
0.7	normal
0.76	imp.relaxation
0.67	imp.relaxation
0.7	normal
0.81	normal
0.82	normal
1	imp.relaxation
0.4	normal
0.8	normal
0.6	normal
0.8	imp.relaxation
0.7	normal
0.77	imp.relaxation
0.64	normal
50	imp.relaxation
0.91	imp.relaxation
0.83	imp.relaxation
0.76	normal
0.83	imp.relaxation
0.64	normal
0.78	imp.relaxation
0.84	normal
0.62	normal
0.8	normal
0.68	imp.relaxation
0.81	imp.relaxation
0.66	normal
0.76	normal
0.78	imp.relaxation
0.86	imp.relaxation
0.6	normal
0.8	normal
0.72	normal

0.62	normal
0.8	imp.relaxation
0.8	imp.relaxation
0.75	normal
0.8	normal
0.74	normal
0.62	normal
0.56	normal
0.81	imp.relaxation
0.64	normal
0.8	imp.relaxation
0.66	normal
0.62	normal
0.65	normal
0.7	normal
0.8	imp.relaxation
0.86	imp.relaxation
0.72	normal
0.81	imp.relaxation
0.86	imp.relaxation
0.8	imp.relaxation
0.83	imp.relaxation


Dept. of Cardiology : 07 : Y 04-04-'06
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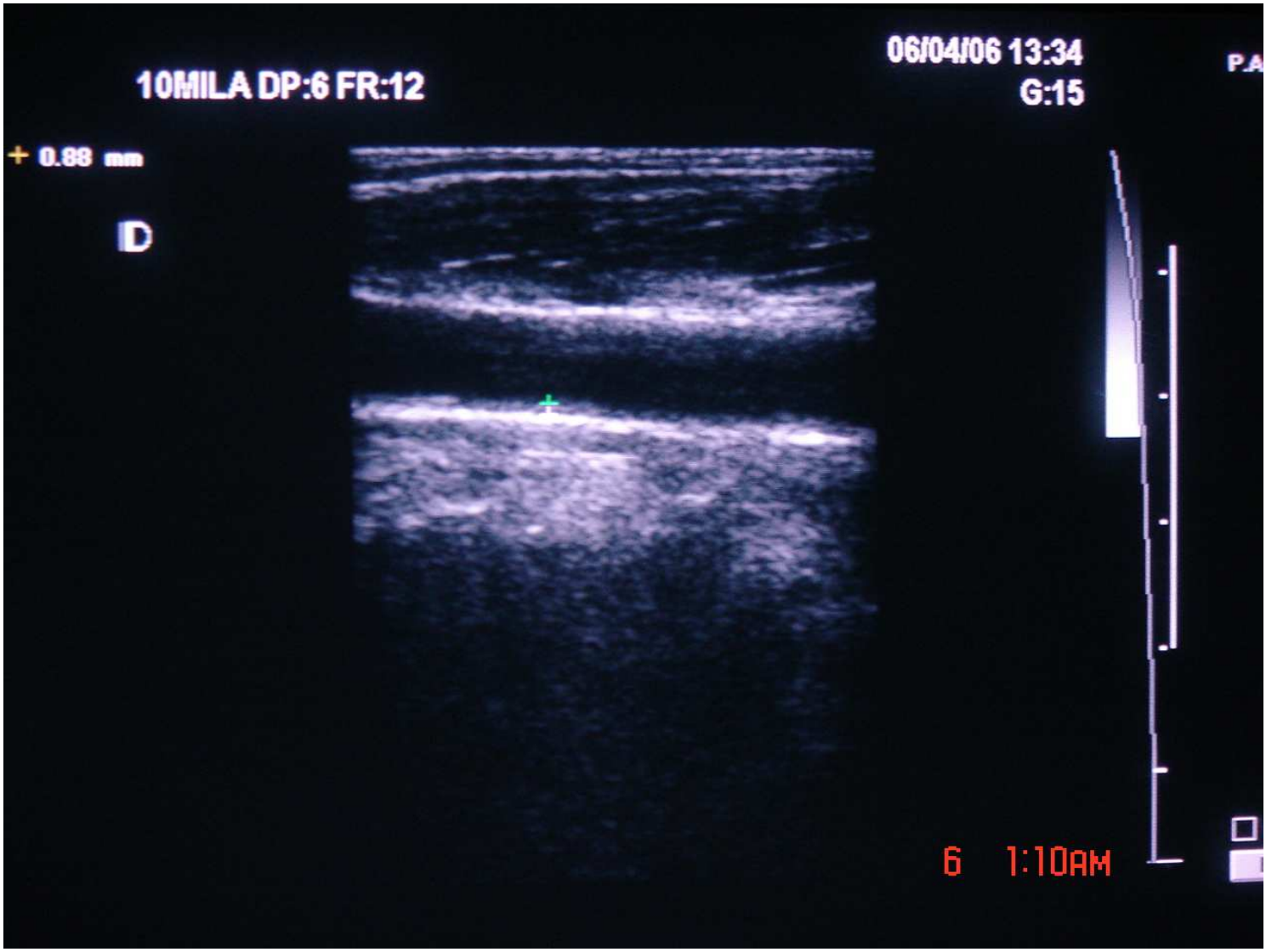
2.5 R19 G67 C10 A3
Trans M Flow
eV: 0.59m/s
aV: 0.99m/s
E/A: 0.60
DecT: 157ms
P1/2T: s
MVA: cm²
0.56 G35 C10
1:Adult Cardiac
DVA: 95%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