A Dissertation on

ASSOCIATION OF hs CRP IN METABOLIC SYNDROME PATIENTS

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CERTIFICATE BY THE INSTITUTION

This is to certify that **Dr. RAGAVENDRA. C,** Post - Graduate Student (May 2013 TO April 2016) in the Department of General Medicine STANLEY MEDICAL COLLEGE, Chennai- 600 001, has done this dissertation on "**ASSOCIATION OF hs CRP IN METABOLIC SYNDROME PATIENTS"** under my guidance and supervision in partial fulfillment of the regulations laid down by the Tamilnadu Dr. M. G. R. Medical University, Chennai, for M.D. (General Medicine), Degree Examination to be held in April 2016.

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I, **Dr. RAGAVENDRA.C,** declare that I carried out this work on "**ASSOCIATION OF hs CRP IN METABOLIC SYNDROME PATIENTS**" at the out patient department and Medical wards of Government Stanley Hospital . I also declare that this bonafide work or a part of this work was not submitted by me or any other for any award, degree, or diploma to any other university, board either in India or abroad.

This is submitted to The Tamilnadu DR. M. G. R. Medical University, Chennai in partial fulfilment of the rules and regulation for the M. D. Degree examination in General Medicine.

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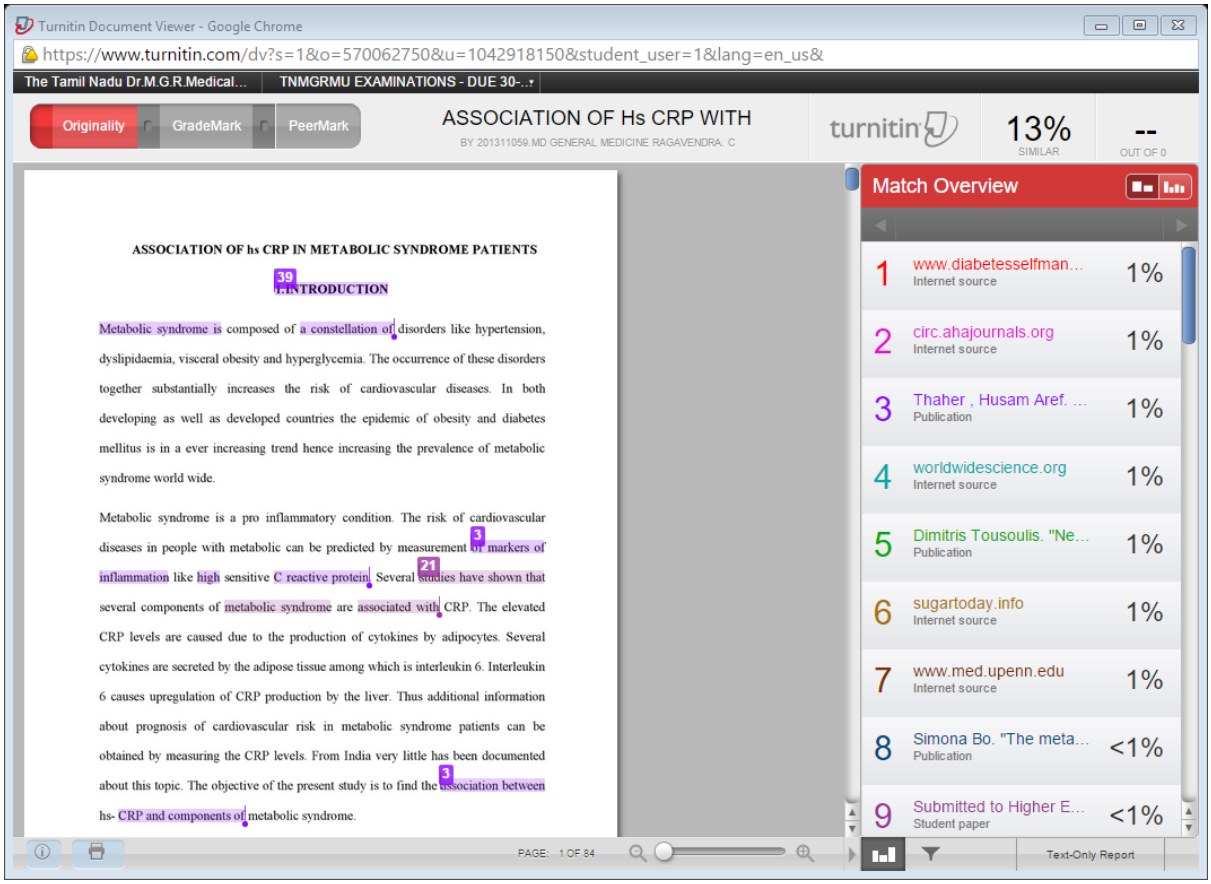
PLAGIARISM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ASSOCIATION OF hs CRP IN METABOLIC SYNDROME PATIENTS
1.INTRODUCTION
Metabolic syndrome is composed of a constellation of disorders like hypertension, dyslipidaemia, visceral obesity and hyperglycemia. The occurrence of these disorders together substantially increases the risk of cardiovascular diseases. In both developing as well as developed countries the epidemic of obesity and diabetes mellitus is in a ever increasing trend hence increasing the prevalence of metabolic syndrome world wide.
Metabolic syndrome is a pro inflammatory condition. The risk of cardiovascular diseases in people with metabolic can be predicted by measurement of markers of inflammation like high sensitive C reactive protein. Several studies have shown that several components of metabolic syndrome are associated with CRP. The elevated CRP levels are caused due to the production of cytokines by adipocytes. Several cytokines are secreted by the adipose tissue among which is interleukin 6. Interleukin 6 causes upregulation of CRP production by the liver. Thus additional information about prognosis of cardiovascular risk in metabolic syndrome patients can be obtained by measuring the CRP levels. From India very little has been documented about this topic. The objective of the present study is to find the association between hs- CRP and components of metabolic syndrome.
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ASSOCIATION

OF hs CRP

IN

METABOLIC SYNDROME

PATIENTS

CONTENTS

ABBREVIATIONS

Hs CRP	:	Highly sensitive C reactive protein
HDL	:	High density lipoprotein
VLDL	:	Very low density lipoprotein
LDL	:	Low density lipoprotein
IFT	:	Impaired fasting glucose
IGT	:	Impaired glucose tolerance
IL	:	Interleukin
TNF	:	Tumour necrosis factor
OSA	:	Obstructive sleep apnoea
NASH	:	Non alcoholic steatohepatitis
DM	:	Diabetes mellitus
CVD	:	Cardiovascular disease
FSH	:	Follicle stimulating hormone
ACS	:	Acute coronary syndrome
NSTEMI	:	Non ST segment elevation myocardial infarction
NAFLD	:	Non alcoholic fatty liver disease
ADA	:	American Diabetes Association
CPAP	:	Continuous positive airway pressure

1. INTRODUCTION

Metabolic syndrome is composed of a constellation of disorders like hypertension, dyslipidaemia, visceral obesity and hyperglycemia. The occurrence of these disorders together substantially increases the risk of cardiovascular diseases. In both developing as well as developed countries the epidemic of obesity and diabetes mellitus is in a ever increasing trend hence increasing the prevalence of metabolic syndrome world wide.[4]

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2. REVIEW OF LITERATURE

METABOLIC SYNDROME

Metabolic syndrome which is also known as syndrome x or insulin resistance syndrome is constituted by a series of metabolic abnormalities which result in enhanced risk to diabetes, cardiovascular and cerebrovascular diseases. It was the World Health Organisation which first formulated the original criteria for metabolic syndrome in the year 1988. However since then the criteria has undergone continuous evolution because of growing analysis, research and clinical evidence by variety of professional organisations and conferences. The important features that make up the metabolic syndrome consists of diabetes mellitus, central obesity, hypertension, hypertriglyceridemia, low high density lipoprotein-HDL[1]

The metabolic syndrome is defined by the Current ATP III criteria as the presence of any **three** of the following five characteristics

- Abdominal obesity, defined as circumference of waist in men greater than 102 cm and in women greater than 88 cm
- Serum triglycerides greater than150 mg/dL or on treatment with drugs for elevated triglycerides
- Serum HDL cholesterol lesser than 40 mg/dL in men and lesser than 50 mg/dL in women or on treatment with drugs for low HDL-C
- Blood pressure greater than130/85 mmHg or on treatment with drugs for elevated BP

- Fasting plasma glucose (FPG) greater than 100 mg/dL or on treatment with drugs for elevated blood glucose[1]

Epidemiology

The prevalence of metabolic syndrome around the world in general increased with age. More than about 40 % of middle aged people are affected with metabolic syndrome in developed countries. With increased growth and development, there is a rising rates of obesity even among developing countries which would increase the prevalence to alarming proportions even in developing countries. Moreover with increasing prevalence of obesity even among children metabolic syndrome might occur in a younger age in the future[6]

RISK FACTORS

Overweight/Obesity

Even though the term metabolic syndrome came into description only in the early part of twentieth century, the epidemic of obesity around the world has been a important force far earlier than the recent recognition of metabolic syndrome. The most important feature of this syndrome is Central Adiposity. This shows that there is a strong association between increasing obesity and waist circumference with development of metabolic syndrome. The major risk factor for development of metabolic syndrome is increased body weight. In NHANES III, 5 % of the people who had normal weight had metabolic syndrome, 22 % of the people who had

overweight had metabolic syndrome, and 60 % of the people who were obese had metabolic syndrome.

In Framingham Heart Study cohort , it was found that with an increase in weight of more than 2.25 kg or more in people who were above 16 years it was found out that there was a increased chance of 21 to 45 % of developing metabolic syndrome. If we use a large waist circumference alone as a criteria it identifies about 46 % of the people who will eventually end up having metabolic syndrome within 5 years time.

With increasing standard of living in our country , there is a alarming increase in the proportion of people who are becoming obese and this leads to even higher chance of metabolic syndrome in future. This shows the importance of increasing the physical activity among people and take measures actively to reduce obesity in order to reduce the prevalence of metabolic syndrome and its complications.[1]

Sedentary Lifestyle

People who have prolonged physical inactivity are more prone to cardiovascular diseases and the mortality that arises from it. Several components which constitute the metabolic syndrome are associated with sedentary lifestyle. Sedentary life style increases adipose tissue in our body particularly the central adipose tissue, reduces the levels of HDL cholesterol and increases the level of triglycerides. It is also associated with increased blood pressure and elevated levels of blood glucose in those with genetic predisposition. A study revealed that in those people who did sedentary work like watching television or computer for more than 4

hours daily have twice the risk of developing metabolic syndrome than those who spent less than one hour in these sedentary activities.[27]

Aging

As the age increases the prevalence of metabolic syndrome increases in most of the population around the world. A study conduction in united states revealed that about more than 44 % of the population over 50 years are affected with metabolic syndrome there. Moreover it was found out that the prevalence of metabolic syndrome was more in females than in males.[42]

Diabetes Mellitus

Diabetes mellitus is a chronic disease due to derangement in glucose metabolism in our body. A array of dysfuncitons constitute diabetes mellitus type 2. These include elevated glucose levels which occurs due to a combination of inadequate insulin secretion, increased resistance to the action of insulin, and excessive glucagon secretion.[32] Most patients are asymptomatic in the beginning. The classical symptoms of diabetes mellitus is polydipsia, polyuria, polyphagia and weight loss. Other associated symptoms include blurring of vision, increased tendency of infection. The ADA criteria for diagnosis of diabetes include fasting plasma glucose value of greater than 126 mg/l, a 2 hour plasma glucose level following meals of more than 200mg/l, a random plasma glucose value of greater than 200mg/ml. The microvascular complication of diabetes include neuropathy, nephropathy and retinopathy. The macrovascular complications of diabetes is due to the atherosclerosis

of large vessels which can lead to myocardial infarctions, stroke and peripheral vascular diseases.

Screening for complication of diabetes include fundus examination, foot examination, urine for microalbuminuria and proteinuria and measurement of serum creatinine and lipid profile.

International diabetes foundation as well as NCEP have diabetes mellitus as part of their definition for metabolic syndrome. Studies have shown that metabolic syndrome is present in about three fourth of patients with impaired glucose tolerance and type 2 diabetes. A higher risk of cardiovascular risk is present in metabolic syndrome patients when compared to those having diabetes or IGT alone without having metabolic syndrome.[6]

Coronary Heart Disease

In those patients who have coronary heart disease the approximate prevalence of metabolic syndrome is 50 %. In those patients who have premature coronary heart disease the prevalence is about 37 %. And this prevalence has been found to be more in women and this prevalence has been found to increase with age. This prevalence can be reduced by incorporating changes in the lifestyle of people like advising them to take proper food with nutritive value, increase in the duration of physical activity undertaken in a day, taking steps to reduce weight and in some exceptional cases taking drugs. Thus with the help of these steps and appropriate cardiac rehabilitation

the occurrence of metabolic syndrome and cardiac morbidity and mortality associated with it can be reduced.[1]

Lipodystrophy

Metabolic syndrome is associated with several lipodystrophic disorders which include both genetic and acquired. The genetic conditions include Berardinelli-Seip congenital lipodystrophy and Dunnigan familial partial lipodystrophy. The acquired conditions include HIV related lipodystrophy.[27] Lipodystrophy leads to severe insulin resistance which in turn leads to several components of metabolic syndrome

Family history

When one of the parent has metabolic syndrome the likelihood of offspring also developing metabolic syndrome is increased.

Other factors —

Women who have attained their menopause, who smoke, who belong to low household income, who take in high quantities of carbohydrates , who do not consume alcohol and those people who consume large quantities of soft drinks are found to be associated with increased risk of developing metabolic syndrome in several studies.[12] People who take atypical antipsychotic medications especially clozapine are associated with significantly higher risk of developing metabolic syndrome.[16] A strong independent predictor for developing metabolic syndrome in both men and women is poor cardiorespiratory fitness.[34] Genetic factors account for as much as 50 percent of variation in the traits of metabolic syndrome in offspring.[35]

PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME

The expanded mass of adipose tissue releases free fatty acids in large quantities into the blood stream. These free fatty acids are transported to the liver were they are processed and are used to produce increased quantities of triglycerides and glucose and increased secretion of VLDL- very low density lipoproteins. This is associated with derangements in lipid with reduction in the good cholesterol which is HDL with increase in bad cholesterol which is LDL.

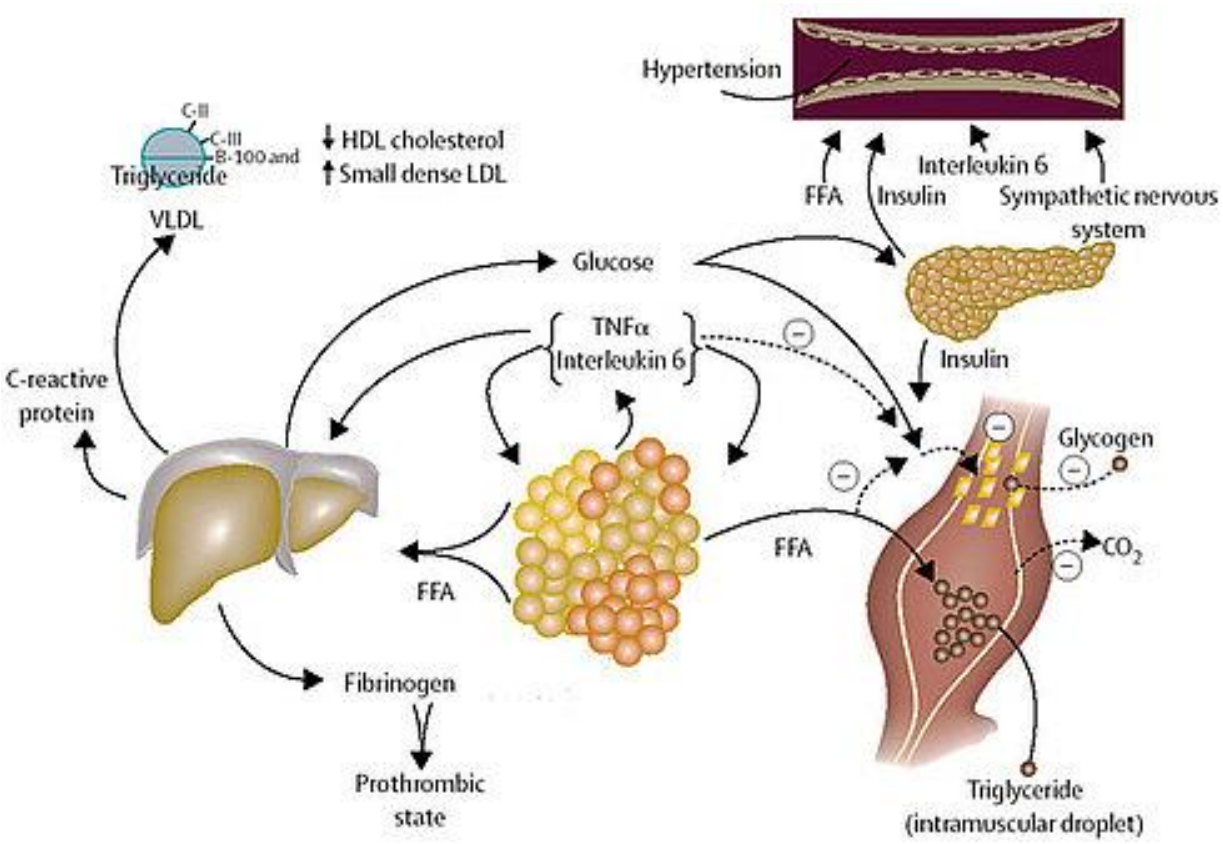
Free fatty acids inhibit the insulin mediated glucose uptake in the muscles reducing the sensitivity of insulin in the muscles. There is also associated increase in the accumulation of lipid in the triglycerides with reduced partitioning of glucose to glycogen. Hyperinsulinemia occurs as a result of increased stimulation of the pancreas by the elevated circulating levels of glucose and free fatty acids resulting in increased insulin secretion. This hyperinsulinemia leads to increased sodium absorption. This increased sodium leads to increased activation of the sympathetic nervous system. Both these contribute to development of hypertension.

There is a proinflammatory state which superimposes and also contributes to the insulin resistance produced by increased free fatty acids. The adipocytes and monocyte derived macrophages secrete increased quantities of tumour necrosis factor and interleukin 6. These inflammatory cytokines increase the insulin resistance and result in increased lipolysis of the triglycerides in the adipose tissue converting them into free fatty acids and thus releasing them in increased quantities into circulation.

These cytokines also increase the glucose production in the liver, enhance the liver production of VLDL and increase the resistance to insulin in the muscles. Cytokines and free fatty acids result in a prothrombotic state by enhancing the fibrinogen production by the liver and enhancing the production of plasminogen activator inhibitor by the adipocytes.

There is increased levels of C- reactive protein due to elevated circulating levels of the inflammatory cytokines which stimulate the liver to produce CRP. Metabolic syndrome is also associated with reduced insulin sensitizing cytokine adiponectin and decreased release of anti inflammatory cytokines.[1]

PATHOPHYSIOLOGY OF THE METABOLIC SYNDROME



DIABETES MELLITUS

Insulin Resistance

Insulin resistance is the widely accepted hypothesis to describe the patho physiology involved in metabolic syndrome.[43] This is due to a incompletely understood dysfunction in the action of insulin. When a person develops insulin resistance there is first postprandial hyperinsulinemia then there is fasting hyperinsulinemia and finally there is hypergylcemia.

Overabundance of free fatty acids in circulation is a important contributor to the development of insulin resistance in our body. The lipolytic enzyme lipase is responsible for the majority of plasma free fatty acids which are bound to albumin.[25] The lipase enzyme acts on the adipose tissue triglyceride stores releasing the free fatty acids. Lipoprotein lipase enzyme causes lipolysis of triglyceride rich lipoproteins releasing fatty acids in blood. Insulin causes both stimulation of lipoprotein lipase as well as antilipolysis in the adipose tissue.[8] The most sensitive pathway in the action of insulin is the inhibition of lipolysis in the adipose tissue. So when resistance to the action of insulin occurs there is increased lipolysis of adipose tissue releasing free fatty acid in bloodstream which further decreases the antilipolytic effect of insulin. This increased fatty acids enhance the availability of substrate and modifies downstream signalling creating insulin resistance. The elevated fatty acids inhibit the insulin mediated glucose uptake and cause triglycerides to accumulate in both cardiac and skeletal muscle. This is associated with accumulation of triglycerides and increased production of glucose in liver. A unifying theory for both predisposition for

metabolic syndrome as well as for aging is provided by oxidative stress hypothesis. Studies showed that there is a defect in oxidative phosphorylation in mitochondria in insulin resistant obese individuals, in elderly, in type 2 diabetic patients and their offsprings. This defect leads to lipid accumulation in the muscle associated with insulin resistance. This defective insulin action causes reduced uptake and metabolism of glucose in the tissues which are sensitive to insulin like adipose tissue and muscles. It also causes decreased suppression of production of glucose by the liver and kidney. Studies conducted in rodents, nonhuman primates and in humans support the relationship between impaired glucose tolerance/impaired fasting glucose and insulin resistance.[52] In order to maintain euglycemia the body modifies the level and rate of insulin secretion and clearance to compensate for the defect in the action of insulin. However ultimately when this compensatory mechanism fails which occurs mainly because of decreased insulin secretion there is progression from IFG/IGT to frank diabetes. [1]

Increased Waist Circumference

One of the important component of the diagnostic criteria which is frequently applied to diagnose patients with metabolic syndrome is waist circumference. But just by measuring the waist circumference we cannot reliably distinguish between increase in visceral fat and subcutaneous adipose tissue. CT or MRI scan is required in order to make this distinction. When there is increase in adipose tissue present in the viscera, the free fatty acids that are derived from adipose tissue are directed to the liver. However when there is increase in subcutaneous fat in the abdomen, the products of

lipolysis are released into the systemic circulation and these avoid the more direct effects on the liver metabolism.[47] In Asians and in Asian Indians the relative increase in visceral fat when compared to subcutaneous fat along with increase in waist circumference when compared with African American men inn whom subcutaneous fat predominates is responsible for the increased incidence of metabolic syndrome among Asian and Asian Indians.[8] Hence visceral fat can be used as a marker for but not source of increased levels of post prandial free fatty acids in obese peoples.[11]

Dyslipidemia

The influx of free fatty acids into the liver causes increased production of apo B containing triglyceride rich very low density lipoproteins.[16] This is done by a complex mechanism but however we can use HYPERTRIGLYCERIDEMIA as an excellent marker for insulin resistant conditions.

The second major derangement in lipid profile in people with metabolic syndrome is reduction in the levels of HDL cholesterol. The changes which occur in the metabolism and composition of HDL is responsible for this reduction. Reduction in the levels of cholesteryl ester in the lipoprotein core along with reduction in cholesteryl ester transfer protein mediated alterations in triglyceride in the presence of hypertriglyceridemia is responsible for decreasing the cholesterol amount in HDL making the particle small and dense.[8]

This changes in composition of lipoproteins also result in increased rate of clearance of HDL from the circulation.[24] The relationship between insulin resistance

and changes in HDL are probably indirect and these occur in coherent with changes in metabolism of triglyceride rich lipoprotein.[1]

In addition to these changes there is modification in the composition of low density lipoproteins too. Small dense LDLs almost always predominate in the blood when fasting serum triglycerides are more than 180 mg/dl. These small dense LDLs are found out to be highly atherogenic. These causes toxic damages to the endothelium of blood vessel and these pass through the basement membrane of the endothelium and adhere to the glycosaminoglycans. These also get easily oxidised and they are bound selectively to scavenger receptors in the monocyte derived macrophages. There is increased cholesterol content in both VLDL1 and VLDL2 subfractions in people with hypertriglyceridemia and elevated levels of small dense LDL particles. The atherogenic risk in patients with metabolic syndrome might be contributed by these relatively cholesterol rich VLDL particles.[1]

Glucose Intolerance

There is impaired suppression of the production of glucose in the liver and in the kidney due to defective action in insulin. The defects in insulin action also leads to decreased uptake of glucose and reduction in metabolism of glucose in the adipose tissues and muscles which are the insulin sensitive tissues. In order to compensate for the defects in the action of insulin either insulin clearance or the rate of secretion of insulin has to be modified if the euglycemic levels are to be sustained.[24] Eventually there is failure of this compensatory mechanism which mostly results from reduction in insulin secretion leading to progression of IGT/IFG to frank diabetes.[1]

Hypertension

There is a well established relationship between hypertension and insulin resistance. Under normal physiologic conditions paradoxically insulin acts like a vasodilator with reabosoption of sodium in the kidney as its secondary effect. But when there is resistance to insulin there is loss of the vasodilatory action of insulin. However the action of insulin on the kidney causing sodium reabsorption is preserved. The activity of the sympathetic nervous system is also increased by insulin , an action which inspite of the presence of insulin resistance is preserved. There is impairment in the pathway in phosphatidylinositol 3 kinase signalling in insulin resistance. This leads to imbalance between the endothelin 1 secretion and nitric oxide production in the endothelium. Inspite of all this insulin resistance leads to only moderate increase in the prevalence of hypertension in metabolic syndrome.[1]

Proinflammatory Cytokines

There is overproduction of proinflammatory cytokines by the expanded mass of adipose tissue. The proinflammatory cytokines include interleukin IL-1, IL-18, IL-6, CRP- c reactive protein, restin and tumour necrosis factor(TNF)[39]. The primary source of these pro inflammatory cytokines both in the systemic circulation as well as locally is the macrophages derived from adipose tissue. However it is unclear as to how much the paracrine and endocrine effects of these cytokines lead to insulin resistance.[1]

Adiponectin

Adipocytes produce an anti inflammatory cytokine exclusively called adiponectin. This adiponectin increases the sensitivity of insulin and it inhibits the inflammatory process in several steps. Adiponectin inhibits the gluconeogenic enzymes and thus reduces the rate of production of glucose in the liver.[8] Adiponectin enhances the transport of glucose in the muscles and increases the oxidation of fatty acids partly because of activation of adenosine monophosphate kinase. In metabolic syndrome this adiponectin is reduced. This increases the inflammation associated with metabolic syndrome[1].

ASSOCIATED DISEASES

Cardiovascular Disease

The patients who have metabolic syndrome have a increased relative risk of about two to three fold for developing new onset cardiovascular diseases. According to Framingham offspring study which is a 8 year follow up study the attributable risk for metabolic syndrome to develop in men is about 34% and in women is about 18 %. This study also showed the increased risk of developing ischemic stroke in patients who had both metabolic syndrome and diabetes than diabetes alone especially among females. There is increased risk of peripheral vascular diseases also among metabolic syndrome patients.[1]

Type 2 Diabetes

The overall risk of developing diabetes is increased three to five fold among metabolic syndrome patients. The Framingham offspring study showed that the risk of developing diabetes in metabolic syndrome patients during its 8 year follow up period was 62 percent in men and about 47 percent in women.[1]

Other Associated Conditions

Metabolic syndrome is associated with other metabolic alterations which accompanies insulin resistance in addition to specific features associated with it. These include increase in CRP, uric acid, prothrombotic factors like fibrinogen and plasminogen activator inhibitor 1, asymmetric dimethylarginine, homocysteine, proinflammatory cytokines, obstructive sleep apnea (OSA), microalbuminuria, in

apoB and apoC-III, white blood cell count, nonalcoholic fatty liver disease (NAFLD) and/or nonalcoholic steatohepatitis (NASH), polycystic ovarian disease (PCOS) and serum viscosity[8]

Nonalcoholic Fatty Liver Disease

Both inflammation and triglyceride accumulation coexist in non-alcoholic fatty liver diseased. Studies show that 2-3% of the population in western countries and in united states suffer from non alcoholic fatty liver disease. Non alcoholic fatty liver disease has increasingly now become a very common cause of end stage liver cirrhosis and carcinoma of liver due to ever increasing prevalence of obesity and metabolic syndrome increases all over the world including developing nations like india.[45]

Hyperuricemia

Defective insulin action on absorption of uric acid by the renal tubules leads to hyperuricemia. [1]

Endothelial dysfunction

Increase in asymmetric dimethylarginine which is a endogenous inhibitor of the enzyme nitric oxide synthase leads to damage and dysfunction of endothelium.[8]

Microalbuminuria

Altered endothelial pathophysiology in persons with insulin resistant state cause microalbuminuria.

Polycystic Ovary Syndrome

In persons with metabolic syndrome there is high association of 40 -50 % for developing polycystic ovary syndrome. Studies show that there is two to four fold likelihood of developing PCOS in women with metabolic syndrome than in normal women.[1]

Obstructive Sleep Apnea

The factors which are commonly associated with obstructive sleep apnea include increased circulating cytokines, IGT, insulin resistance, obesity and hypertension. These are the same conditions which are associated with metabolic syndrome and so its not surprising to find a high association between metabolic syndrome and OSA. Studies have shown that when we compare insulin resistance bio markers between weight matched controls and people with OSA, insulin resistance is more severe in patients with OSA. It has been shown that CPAP-continuous positive airway pressure as treatment improves the sensitivity to insulin in metabolic syndrome patients.[1]

DIAGNOSIS

Metabolic syndrome is diagnosed by a criteria given by several organisation using bedside tools and using lab investigation. All patients with OSA and PCOS should be evaluated for history if they have metabolic syndrome. Family history will help us estimating the risk of developing DM and CVD. Measurement of waist circumference and blood pressure will provide essential information for diagnosis.[1]

Laboratory Tests

Glucose and fasting lipids are necessary to diagnose if metabolic syndrome are present. The measurement of extra biomarkers has to be individualized. These include high sensitivity CRP, uric acid, fibrinogen, liver function test, urinary microalbuminuria and apoB .If OSA is suspected then the patient must be subjected to sleep study. If symptoms of PCOS are present based on clinical features and anovulation then testosterone, FSH and luteinizing hormone should be measured.[1]

THERAPY

The recommendations of ATPIII in 2001 for patients having metabolic syndrome include two major therapeutic goals. Studies from National Institutes of Health, The Endocrine Society and American Heart Association have reinforced these goals. These include

- The underlying cause of metabolic syndrome which is physical inactivity and obesity have should be treated first by increasing physical activity and intensifying steps to manage overweight.[1]
- The cardiovascular risk factors should be treated if these risk factors persist despite of making lifestyle modifications[11]

Lifestyle

The major driving force behind metabolic syndrome is obesity. Thus the primary approach to treat this disorder is reduction of weight. When there is reduction in weight there is improvement in sensitivity to insulin and is accompanied by favourable changes in several metabolic syndrome components. For reduction in weight the general recommendations include a combination of restriction of calorie intake, taking appropriate balanced nutritional diet, avoiding junk food, increasing physical activity and modification of behaviour. Caloric restriction is the most important component for weight reduction. However for maintenance of the reduced weight the most important component is physical activity. Some studies show that when exercise is combined with caloric restriction there is increased loss of visceral

depot of fat. Long lasting behavioural changes are necessary to prevent regaining of weight in people who have successfully reduced their weight.[1]

Diet

The following specific diet approaches have been recommended:

- The Mediterranean diet- it consist of a diet high in vegetables, fruits, whole grains, nuts and olive oil with a low fat. Studies showed that subjects who were in this Mediterranean group had higher weight loss, improved lipid profiles, lower blood pressure, decreased resistance to insulin, less endothelial dysfunction and reduced levels of markers of inflammation.[50]
- The DASH diet- it consist of a diet with limited daily sodium intake of 2400 mg. this diet emphasised a higher diary intake of when compared to Mediterranean diet. This diet gave importance to healthy food choices resulting in improvements in lipid profile, reduction in diastolic blood pressure and fasting blood glucose even after causing reduction in weight.[9]

The glycemic status and lipid abnormalities can be improved by taking foods with low glycemic index, by consuming increased amount of fruits and vegetables, by replacing refined grains with whole grains, stopping consumption of high glycemic beverages and taking high fiber foods.[52]

It is important to emphasize when we prescribe a weight loss diet that it takes long time to achieve a expanded fat mass. Hence we need not quickly do the corrections. When the carbohydrate rich diets are restricted there is initial rapid loss of

weight. But however the amount of weight loss after one year remain unchanged. So adherence to the diet is very important. In diets which contain high amounts of saturated fat with reduced carbohydrates there is a increased risk of developing cardiovascular diseases. Hence a good quality diet must be encompass vegetables, fruits, whole grains, fish, lean poultry and the person should be encouraged to take such a diet to provide maximum overall health benefit.[1]

Physical Activity

When physical activity is recommended for metabolic syndrome patients it is important to make sure that the increased activity does not cause risk.[21] Cardiovascular evaluation must be done for high risk patients before they are started on an exercise program. A gradual level of increase in physical activity should be encouraged since it would reduce the injury risk and enhance adherence. A 60 to 90 min or daily physical activity is required to achieve modest weight loss. If an obese person is not able to achieve this level of physical activity, at least a 30 min moderate level of physical activity daily will result in tremendous benefit to them. Formal exercise such as jogging, swimming and tennis alone do not define physical activity. Routine house hold activities like walking, house cleaning , gardening etc.. which require moderate physical activity can be included.[1]

Obesity

However for a few patients life style interventions alone will not suffice. The two major classes for weight loss reducing drugs include appetite suppressants and

absorption inhibitors. US FDA approved appetite suppressants include sibutramine and phentermine. Orlistat reduces the incidence in type 2 DM and inhibits fat absorption by 30 %.

For patients who have a body mass index of greater than 40 kg/m^2 or greater than 35 kg/m^2 with co morbidities bariatric surgery is an option. There is dramatic reduction in weight and improvement in features of metabolic syndrome following bariatric surgery.[35]

LDL Cholesterol

LDL cholesterol should be reduced to <100 mg/dl for patients with metabolic syndrome and diabetes. The 10 year risk of cardiovascular diseases in in patients with metabolic syndrome without diabetes according to the Framingham risk score exceeds greater 20 %. In these subjects the LDL target is less than 100 mg/dl. For those in whom the Framingham risk score is less than 20 % the targeted LDL cholesterol goal is < 130 mg/dl.[26]

Lipid control

The diet should be restricted in trans fats, saturated fats and cholesterol. Pharmacologic intervention is needed if the level of LDL cholesterol remains above the goal. HMG CoA reductase inhibitors- Statins are the first choice of drugs which lower the LDL cholesterol by 20 to 60 %. However whenever we double the dose of statins there is only additional 6% lowering of LDL cholesterol. Myopathy and elevation in hepatic transaminases are rare side effects with statin therapy. The second

choice of drug is ezetimibe which is a cholesterol absorption inhibitor. Colestipol and cholestyramine which are bile acid sequestrants are more effective than ezetimibe however these increase the levels of triglycerides and hence should be used in caution with metabolic syndrome patients. When the fasting triglycerides are more than 200 mg/dl bile sequestrants should not be administered. The side effects are bloating, constipation, difficult palatability, belching and anal irritation. Nicotinic acid increases the level of HDL however the LDL lowering capabilities is only modest. When both LDL cholesterol and triglycerides are elevated fibrates are the best choice of drugs to lower LDL cholesterol. Fenofibrate is a better drug and more effective than gemfibrozil in this group.[1]

Triglycerides

The focus of NCEP ATP III has been more on non HDL cholesterol rather than triglycerides. However the recommended value of fasting triglyceride level is less than 150 mg/dl. The response of fasting triglycerides is directly related to the amount of loss of weight achieved. In order to lower the level of fasting triglycerides a weight reduction of greater than 10% is required

The drug of choice to reduce the level of fasting triglyceride level is fibrates like gemfibrozil and febofibrate. These typically reduce the levels by 35- 50%. However when these drugs are administered with other drugs metabolised by the 3A4 cytochrome P450 system including some statins then the chances of developing myopathy is greatly increased. Fenofibrate is a more preferred drug when compared to statins in these settings. Even though several clinical trials have been conducted there

is no clear cut evidence to support the CVD risk lowering effect by using fibrates to reduce the triglyceride level.[1]

Statins, high doses of omega 3 fatty acids and nicotinic acid are other drugs which lower triglyceride level. When statin is used, the more potent ones like simvastatin, rosuvastatin and atorvastatin should be given in moderate doses while the less potent ones like lovastatin, fluvastatin and pravastatin should be given in high doses. Nicotinic acid has a dose related and less effect than fibrates on fasting triglyceride levels. Omega 3 fatty acid preparations contain high doses of eicosapentaenoic acid and docosahexaenoic acid.[38] These lower the fasting triglyceride levels by 40%.

HDL Cholesterol

Reduction of weight increases the level of HDL. There are only a very few lipid modifying compounds which are capable of increasing HDL cholesterol values. Nicotinic acid is the only drug which is currently available which has a predictable HDL cholesterol raising properties. There is dose related response and it can cause about 30 % increase in HDL values above baseline. The drugs which have a modest action on HDL levels are statins, fibrates and bile acid sequestants. Omega 3 fatty acids and ezetimibe have no effect on HDL cholesterol levels. However there is only limited evidence at present that raising HDL cholesterol independent of lowering LDL cholesterol has a reducing effect on cardiovascular diseases in patients with metabolic syndrome.[1]

Blood Pressure

A well established relationship is the one between blood pressure and all cause mortality rate.[11] In those patients who have metabolic syndrome without diabetes mellitus angiotensin converting enzyme or angiotensin II receptor blocker should be the first choice to reduce hypertension since they reduce the incidence of type II DM among metabolic syndrome.[14] The diet for these patients must have low sodium, high quantities of fruits and vegetables and low dairy fat products. Good blood pressure control can be maintained by home monitoring of blood pressure.[1]

Impaired Fasting Glucose

Prevention of type 2 diabetes

Studies have shown that by doing lifestyle modifications we can substantially reduce the risk of developing type two diabetes mellitus and the chances of developing cardiovascular diseases. In diabetes prevention program about 3234 obese subjects with impaired glucose tolerance or impaired fasting glucose were put into three groups. One group with intensive lifestyle changes through exercise and low fat diet, second group with metformin with information about exercise and diet and third group on placebo with information on exercise and diet. After three years of follow up it was found out that less number of patients in the intensive lifestyle group developed diabetes.[9]

Oral hypoglycemic agents

Within the oral hupoglycemic agents which are used to treat type 2 diabetes mellitus it was found out that metformin and thiazolidinediones like rosiglitazone and pioglitazone enhance the sensitivity to insulin in part and hence have better glucose tolerance.[12] The development of diabetes in patients with impaired glucose tolerance can be delayed or prevented by using metformin. According to Diabetes Prevention Program trial the group of people on metformin were associated with 31% reduction in risk of developing diabetes when compared to those on placebo. But it was found out that metformin was inferior to lifestyle modification in preventing diabetes. Both intensive lifestyle intervention and metformin therapy are good in preventing the occurrence of metabolic syndrome in those who doesn't have the syndrome in baseline.

Diabetes related end points can also be reduced by the use of metformin. According to the United Kingdom Prospective Diabetes Study (UKPDS) [51]it has been found out that metformin reduces all the diabetes related end point such as angina, myocardial infarction, stroke, heart failure, renal failure, retinopathy, monocular blindness, cataract, hypo or hyperglycemia and sudden death. [14]

The current recommendations for people suffering from impaired glucose tolerance and impaired fasting glucose is to reduce the weight loss to about 5 to 10 % of the base line and take a diet with low levels of trans fats, saturated fats, simple sugars, cholesterol, increased intake of fruits, vegetables, whole grains and do moderate intense physical activity for atleast 30 minutes per day. We need not

routinely give drugs to prevent diabetes. However in certain patients with IGT and IFG we can consider giving metformin.

In those patients who have both type 2 diabetes mellitus and metabolic syndrome aggressive glycemic control will result in reducing the levels of triglycerides and increasing HDL levels. The transition from IFG to frank type 2 diabetes can be reduced by undergoing lifestyle intervention like dietary fat reduction, weight reduction and increased physical activity. Metformin was also found to retard the progression to diabetes however the action is less efficient than what is seen with lifestyle modification.[1]

Insulin Resistance

Biguanides and thiazolidinediones are the drugs which increase the sensitivity to insulin. The prevalence of metabolic syndrome can be reduced by using these drugs because insulin resistance is the major pathophysiologic mechanism for development of metabolic syndrome. Both these drugs suppress the endogenous glucose production and increase the action of insulin in the liver. Insulin mediated uptake of glucose in the adipose tissue and the muscle is improved by thiazolidinediones.[25] These drugs decrease the levels of small dense LDL and reduce the inflammatory markers. Both patients with PCOS and NAFLD are found to benefit from these drugs[1].

CRP- C REACTIVE PROTIEN

An important component of our immune system is CRP. About approximately 70 years ago CRP was first discovered by scientist when they were exploring the human inflammatory response. It has been only recently uncovered about the role of CRP in heart diseases.

CRP is being made in everyone but the level varies from person to person depending upon a wide range of factors including lifestyle habits and genetics. It has been found that on a average the CRP levels are higher in those individuals who are over weight, who fail to exercise, who smoke , who have high blood pressure that those who are athletic thin individuals. It has been found that about half of the variation in CRP levels have been inherited and are due to genetic reasons. However this is not a surprising fact since the fundamental role of CRP is inflammation and inflammation is a very important proves in healing of wounds, in protecting us against virus and bacteria and it is a component of various processes which are critical for survival.

It has been found out by studies that too much inflammation in detrimental in few circumstances especially in the blood vessels which are responsible for carrying nutrients and oxygen to all the tissues in our body. Several research shows us that atherosclerosis which is a process that leads to accumulation of cholesterol in the arteries are due to inflammation of the blood vessels just like how arthritis is a inflammatory disorder of the joints and bones.

It has been found out that among those individuals who have a future high risk of developing heart diseases there has been found to be elevation of markers of inflammatory process in our blood. Inflammation plays a very huge role in all the steps of heart diseases. Inflammation is found to be involved in early initiation of atherosclerotic plaques in the vessel walls. Inflammation is also responsible for the acute rupturing of the plaques that causes heart attacks and in sudden death as well. CRP serves as a easy and very stable biomarker to measure inflammation.

It has been demonstrated in about a dozen major studies that in apparently healthy individuals baseline CRP values serve as a predictor for future risk of developing stroke, peripheral arterial disease, myocardial infarction and sudden cardiac death. Several studies also reveal that the recurrence of coronary events among patients who already suffer from heart diseases is predicted by CRP levels and the CRP is also tightly connected with the prognosis of patients during the acute phase of heart attack. However the most important current use of CRP is in the field of primary prevention. It is used to detect high risk among those people who don't still yet know they have a problem.[53]

HIGH SENSITIVE CRP

There is two to three times higher risk in individuals who have high CRP levels than those who have low levels. It is important to do high sensitive CRP if it is used to assess the risk of cardiovascular diseases. Its important because older test for CRP don't have the ability to measure levels in the range which detects cardiovascular risk. Older CRP test monitor only severe inflammatory conditions. Hs CRP is just a simple

inexpensive blood test. When blood cholesterol levels are checked, Hs CRP levels can be checked along with it to assess the overall risk .[53]

C reactive protein is a blood marker for inflammation. It has a role in several chronic diseases such as diabetes, heart disease and stroke. Several scientific studies have shown that C reactive protein is not only a risk factor for stroke and heart diseases but when the levels of C reactive protein are reduced then the persons risk for heart diseases is substantially lowered.[54] Inflammation is thought to augument the deposition of fat and other materials in the lining of blood vessels and promote the build up of atherosclerotic plaques. Inflammation favours especially the built up of vulnerable plaques which are highly prone to break up and disseminate as clots which can block the vessels causing stroke and heart attack.[3]

Physicians health study revealed that over a 8 to 10 years follow up the men who had heart attacks and strokes had a higher level of CRP than those who didn't have them. Those who had the highest CRP levels had two times more risk of stroke and three times more risk of myocardial infarction than those with lowest levels. According to a study report in DIABETES CARE journal in 2004 men with diabetes with highest quartile of CRP levels had nearly thrice cardiovascular events like heart attack , angioplasty, bypass surgery and stroke) than those with lowest quartile.[54]

The concept of CRP underwent a drastic change following the publication of two landmark studies in the January 6, 2005 issue of the of *The New England Journal of Medicine*. The studies are those published by Paul M. Ridker, MD, and colleagues at Brigham and Women's Hospital and Harvard Medical School in Boston. These

studies studied the effect of high doses of statin drugs which decrease the levels of both cholesterol and CRP in patients who had severe heart ailment. It was found out that Lower the levels of CRP the lesser the heart attacks and deaths in subjects irrespective of their LDL cholesterol levels. Studies conducted at the Cleveland clinic in Ohio by Steven E Nissen MD and colleagues showed that people who take high dose statin therapy had slower progression to atherosclerosis when compared to those taking moderate doses. They also found out that those with lower CRP levels had slower progression irrespective of their cholesterol levels. It was found out that lowering CRP levels was as important as lowering cholesterol values in prevention of heart diseases.[54]

In development of diabetes too inflammation plays a important role. According to the cardiovascular health study it was found out that those people who had high level of CRP were twice as likely to develop diabetes than those who had low values. Thus many researchers postulate that inflammation might be the same underlying pathology for both diabetes and atherosclerosis explaining the reason why diabetes are more prone to develop atherosclerosis , heart attacks and stroke.[54]

According to the American Heart Association and the Centers for Disease Control and Prevention current guidelines, CRP testing is recommended for those with intermediate risk of heart attack- that is those people who have a 10 to 20 % risk of developing heart attack in the next 10 years.[30] The risk factors for heart diseases are being order than 55 years for female, being older than 45 years for male, overweight ,

having high blood pressure, smoking, having low HDL levels and high LDL levels, family history of diabetes , stroke and heart attacks.[54]

For those people who have elevated levels of CRP the steps to prevent heart diseases include losing weight, diet control, exercise, stopping smoking all of which lower the level of CRP. Statins which are usually used to lower the levels of cholesterol has been found to lower the CRP values. Moreover CRP levels tend to increase with increasing glycosylated haemoglobin levels. Hence CRP levels can be reduced if blood glucose levels are kept under control.

Interpreting CRP results

It is desirable to have CRP levels less than 1 mg/L and this reflects low overall risk of cardiovascular diseases. Those who have levels between 1 and 3 mg/L have moderate risk. And elevated risk of cardiovascular diseases has been found in patients who have CRP values in excess of 3 mg/L. [53]

Who have to be tested for CRP?

According to the American Heart Association and The Centers for Disease Control and Prevention, evaluation of CRP should be considered as a part of prediction of vascular risk in individuals especially those who have intermediate risk.[34] To avoid unnecessary blood draws and to increase the risk of clinical practice many physicians add CRP testing to standard cholesterol evaluation. American heart association and CDC also endorse the evaluation of CRP in those who have history of heart attack and those who were have been admitted with acute coronary syndromes in hospital.[3]

People in their mid-30s should be subjected to CRP evaluation. It was found out that CRP levels in your teens and 20s is predictive of CRP levels in the later part of ones life. The risk over next 30 to 40 years is predicted by elevated CRP levels. This gives us ample time to advocate for changes in lifestyle , diet , exercise and if needed to initiate pharmacological interventions to prevent first ever attack of stroke and heart attack. [53]

DIABETES AND CRP

Type 2 diabetes is a prothrombotic, pro atherosclerotic and pro inflammatory condition with high association for cardiovascular morbidity. CRP serves as a bio marker for low grade of inflammation in type 2 diabetes patients. The likelihood of developing cardiovascular events are elevated with increase in CRP levels in both diabetic and non diabetic populations. In healthy individuals the elevated level of CRP serves as a marker for developing diabetes. There is also evidence that CRP might be a active participant in atherogenesis besides its rode as a marker for cardiovascular diseases. [49]

Human atherosclerotic plaques express CRP. The vascular cells and monocytes and macrophages are the source of CRP in the vessel wall. Within the atherosclerotic plaques activation of the main cell types causes release of CRP within the lesion contributing to the development and progression of atherosclerosis. Recent studies reveal that CRP production by the monocytes, macrophages, endothelial cells and smooth muscles are triggered by several metabolic and inflammatory factors associated with diabetes like adipokines, high glucose levels, free fatty acids and modified lipoproteins. Studies suggest that diabetic atherosclerotic plaques might have

higher levels of CRP concentration when compared to non diabetic ones. This might lead to accelerated development of vascular disease in type 2 diabetes patients.

Studies have suggested that the development of macrovascular complications in diabetes is significantly increased with poor glycemic control. And studies have indicated that CRP is a important risk factor for cardiovascular diseases and with increasing value of HbA_{1c} levels the CRP levels too increase. This shows that a association is present between systemic inflammation and glycemic control in people with established type 2 diabetes mellitus.[49]

Studies have shown that CRP levels have been found to be higher in frank diabetes and impaired glucose tolerance. And moreover elevated CRP levels have been found to be a risk factor for developing diabetes in the later part of life. Studies conducted by Festa et al have showed that there is a link between insulin resistance and CRP. Hyperglycemia promotes Oxidative stress on the endothelium which enhances inflammation. This mechanism has been supported by several studies which document an association between hyperglycemia and inflammation in diabetic patients.[20]

CRP AND CHOLESTEROL

Cardiovascular risk is predicted by both cholesterol and CRP. However cholesterol cannot be used to predict the level of CRP and vice versa. Studies which were conducted predicting cardiovascular risk using both CRP and LDL cholesterol demonstrated that the risk was highest among those who had elevated levels of both CRP and LDL cholesterol. The risk was intermediate for those who had either one

elevated when compared to those who had both CRP and LDL low. This study showed that without CRP evaluation and relying only on cholesterol many people in the intermediate risk category with CRP alone positive will be missed for primary prevention.[3]

LDL is a critical risk factor for heart diseases and lowering LDL cholesterol is important in prevention of cardiovascular diseases. However more than LDL , CRP serves as a overall strong predictor for cardiovascular diseases and stroke. A decision to test for CRP in many ways is similar to test for cholesterol. Knowledge that levels of CRP are high should motivate one to be on diet, to do exercise , to lose weight and to stop smoking. All these changes in lifestyle lower CRP levels and in turn lower the risk of one getting heart diseases.[53]

Role in hypertension

According to the WOMEN'S HEALTH STUDY of over 20000 female health professionals in united states, who had no history of hypertension and had a base line blood pressure of less than 140/90 mm of hg were evaluated for the possible predictive value of CRP for the development of hypertension. Baseline CRP values were measured and the patients were followed up for a period of 7.8 years. It was found that about 11.5 percent of people developed hypertension. It was found out that with progressive increase in CRP values the risk of hypertension increased.[31]

This study suggested that in the pathogenesis of hypertension, inflammation has a role. This might be related in part because of the association of metabolic syndrome and CRP. It is also postulated that CRP causes reduction of synthesis of nitric oxide in the endothelial cells causing a increase in the resistance in the vessels.[36]

Role in central obesity

Inflammation in many overweight patients is because of central obesity or the tendency to put weight around the stomach. The fat cells or adipocytes produce messenger proteins which stimulates the production of CRP.[53] This inflammation also leads to increased risk of diabetes. Thus central obesity predisposes to development of diabetes. Individuals with CRP value of greater than 3 mg/L have four to six times higher risk of developing diabetes.[29]

Role in metabolic syndrome

People with metabolic syndrome are predisposed to develop heart diseases and diabetes. The main pathogenesis of metabolic syndrome is insulin resistance. CRP levels tend to increase with increase in number of components of metabolic syndrome. CRP levels tends to predict the risk of non diabetic metabolic syndrome patients developing diabetes. It also predicts the risk of developing coronary heart diseases in people with metabolic syndrome. CRP has now increasingly become a part of the process of defining metabolic syndrome.[3]

Role in stable coronary disease

CRP has been found to be associated with atherosclerosis and increased levels of CRP reflect the increased risk of rupture of vulnerable plaques. CRP is associated with increased risk of developing future cardiac events in those who have stable angina. Most studies demonstrate a strong relationship between baseline CRP values and risk of future coronary events.[38] In PEACE trial about 3771 patients were evaluated. Patients with hs CRP were measured at baseline and followed up for a

mean period of 4.8 years for myocardial infarction, stroke or cardiovascular death. It was found out that a significantly higher risk of cardiovascular disease was present in those who had a higher baseline CRP values, who were not on statin therapy compared to those who had a low value of CRP.[5]

In addition CRP values might predict the progression of coronary disease. A study was conducted in about 124 patients with stable chronic angina awaiting elective PCI and it was found out that elevated CRP was a independent predictor for progression of rapid coronary stenosis.[3]

Role in plaque rupture and ACS

Plaque rupture followed by thrombus formation is the major primary pathophysiologic event in acute coronary syndrome. In ACS there is elevation of acute phase reactants such as CRP, IL- 6 which shows that there is chronic inflammation in the coronary arterial wall. These elevated levels of acute phase reactants are markers for underlying inflammation in the vessels and increased responsiveness of the inflammation even to very small stimuli.[10] It was found that patients who had pre infarction unstable angina had higher levels of CRP and IL 6 than those with unheralded myocardial infarction. It has been found out that there is association between elevated serum CRP level and plaque vulnerability and activity of coronary disease. Studies show that in patients with NSTEMI serum CRP levels were co related with a number of complex stenosis in vessels in angiography.[8]

Prognosis after non-ST elevation ACS

If the patients who have NSTEMI have elevated levels of CRP concentration at the time of admission and prior to discharge then they have a worse short and long term prognosis. Over 7000 NSTEMI patients were studied in the GUSTO IV ACS trial. It was found out that the patients in the fourth quartile of CRP had increased 30 day mortality from 2 to 6.3 % when compared to those who had CRP in the first quartile. It was also found out that troponin T and CRP had complementary and independent prognostic significance. More over this study confirmed that when measured immediately after ACS CRP had a stronger predictor of mortality when compared to other factors.[10]

According to the PROVE IT- TIMI 22 trial which studied 4162 patients who were stabilized after ACS and followed up for a mean period of 24 months it was found out that those people who had hs CRP greater than 2 mg/L had nearly a two fold higher risk of developing new or increased worsening of heart failure.[13] A smaller TIMI 11A tril showed the predictive value of CRP and the interaction between CRP and troponin T. For those patients with ACS who undergo early revascularization it was found out that serum CRP was a independent predictor of short and long term mortality.[10]

Prognosis after acute MI

After acute myocardial infarction the elevation of CRP levels indicate the extent of myocardial injury. Thus if CRP values are to be used for long term assessment of cardiovascular risk then the measurements have to be delayed by atleast

4 to 6 weeks to permit resolution of acute phase reactants. According to the THROMBO trial in which serum CRP values were assessed in 1045 patients two months after MI the patients in the highest quartile of CRP had increased rate of coronary events.[10]

Predictor of recurrent ischemia after CABG

For patients who have underwent CABG for stable or unstable angina , it was found out those in those who had a elevated pre operative serum CRP > 3 mg/L had a significantly higher risk of new ischemic events.[17]

Predictor of adverse events after PCI

In a study of 121 patients who underwent angioplasty it was found out that those people who had a high pre procedural value of serum CRP concentration had a higher risk of both in hospital as well as intraprocedural complications and higher chance of restenosis at one year. Elevated levels of CRP before elective or urgent coronary stenting, have been associated with worse outcome because the stenting procedure itself can elicit an inflammatory response. A elevated preprocedural value is associated with 2.5 fold increased rate of myocardial infarction or death at 30 days following procedure, four fold increase in mortality at 20 months in those who undergo revascularisation, a five fold increase at the end of 3 years in unstable angina, myocardial infarction or death. It also leads to marked increased in progression of untreated lesions to significant stenosis.[28]

Predictor in heart failure

In patients who had heart failure, the values of CRP were elevated when compared to a general population. The likelihood of death progressively increased in those with elevated CRP levels.

Predictor of sudden death

According to a nested case control study by the PHYSICIANS HEALTH STUDY whish was a 17 year follow up study it was found out that people who had baseline CRP values in the highest quartile had the highest risk of sudden cardiac death.[27]

Predictor in cerebrovascular disease

It has been found that CRP has been an independent marker for the progression of early carotid atherosclerotic disease and is associated with increased risk of ischemic stroke and is associated with poor prognosis following stroke. An elevated levels of CRP in patients with a ischemic stroke within the first 12 to 24 hours is associated with unfavourable outcomes.[30]

Predictor of cardiac allograft survival

In those people who have had heart transplants, the leading cause of death or retransplantion is transplant coronary artery disease in those who survive more than 6 months. Increased levels of has been found to be a marker of transplant vasculopathy and failure of allograft.[32]

Role in Atrial Fibrillation

The high incidence of AF following cardiac surgery suggest that an inflammatory process might play a role in the pathogenesis of atrial fibrillation. Elevated levels of CRP has been found in people with recent atrial arrhythmias, who fail cardioversion, who are likely to have recurrent AF and in person who are prone to develop new onset AF after cardioversion.[33]

METHODS TO LOWER CRP LEVELS

The best way to lower CRP levels is to undergo lifestyle modifications. These include exercise, smoking cessation, blood pressure control and diet. Thus the most important role of measuring CRP levels is to identify people with high risk even with low cholesterol levels and to motivate them towards heart healthy inteventions.

EFFECT OF THERAPY

Undertaking certain modifications in diet and taking a number of drugs to treat cardiovascular diseases can reduce serum CRP levels.

STATINS

Effect on CRP

In patients with hyperlipidemia, multiple statins decrease the serum CRP levels significantly. This effect is found to be independent of the decrease in serum LDL cholesterol levels. The mechanism by which statins reduce the levels of CRP is partly

by reducing the expression of IL-6 and tumour necrosis factor alpha by the monocytes and by direct suppression of transcription of CRP gene.[3]

Statin therapy causes reduction of CRP levels both when used for primary prevention and for reduction of serum CRP after an ACS. As early as 14 days after starting statin therapy serum CRP levels tend to fall. In review of literature of about thirteen controlled trials it was found out that serum CRP levels are reduced from 13 to 50 percent with statin therapy as compared to placebo therapy. And according to five studies comparing different statins it was found out that there was no advantage of one statin over another in reducing the CRP levels. According to the phase Z of the A to Z trial, a modestly greater reduction in CRP levels was found with intensive statin therapy.[22]

REDUCTION IN CORONARY RISK

Several studies have co related that elevated CRP levels is associated with increased cardiovascular risk. Stains because of their anti-inflammatory action are postulated to reduce the risk of cardiovascular events. Several studies have been conducted to support this concept.[43]

In studies conducted in patients undergoing PCI it was found out that satin therapy benefit was seen in those who had higher quartile of CRP levels. According to the AFCAPS/ TEXCAPS trial of primary prevention it was found out that CRP levels are reduced by almost 15 percent by using lovastatin. Reduction in coronary events on using statin was found not only in those with deranged lipid parameters but also who had normal LDL- HDL ratio with elevated CRP levels.

According to phase Z of A to Z trial it was shown that lower level of hs CRP at end of thirty days and at the end of four months after a acute coronary syndrome were associated with increased long term survival and those patients who received aggressive statin therapy were found to have more likelihood of achieving lower hs CRP levels.[18]

A higher two year mortality was found in patients who at the end of 30 days had a hs CRP levels of greater than 3 mg/L when compared to those who had a hs CRP levels less than 1 mg/L. It was found out that patients who were given intensive statin therapy were more likelihood of achieving lower values less than 1 mg/L at the end of 30 days and four months.[22]

According to PROVE IT- TIMI 22 trail in which about 4162 patients with ACS were randomly assigned to either 80 mg/day of atorvastatin or 40 mg/kg of pravastatin. It was found out that at the end of thirty days significant reductions was achieved in levels of CRP in both groups. And a linear relationship was found to exist between the levels of CRP levels attained after statin therapy the risk of developing recurrent myocardial infarction or coronary deaths.

According to REVERSAL trial in which about 502 patients were studied, intravascular ultrasonography was used to monitor the progression of atherosclerosis in patients with angiographic coronary disease. It was found out those the patients in the group who received stains had a significantly slower progression of atherosclerosis and maximum regression was seen in those who had the greatest fall in the levels of CRP.[18]

According to JUPITER trial, patients with LDL value less than 130 mg/dl and CRP level higher than 2 mg/L were assigned into two groups, once which received rosuvastatin 20 mg daily and other which received placebo. It was found out that the treated group had better clinical outcomes.[46]

Antiplatelet agents

Aspirin

According to Physician's Health study it was found out that the cardiovascular risk reduction in those taking aspirin is maximum among those who belong to the high quartile of serum CRP group. This observation suggests that the cardiovascular risk reducing benefit of aspirin is due to its anti inflammatory action as well as the its antiplatelet action.

According to a study conducted in patients with stable angina who were put into two groups one receiving aspirin and other receiving placebo it was found out that after six weeks aspirin therapy lowered the levels of elevated CRP and other proinflammatory cytokines.[37]

GP IIb/IIIa inhibitors

After acute percutaneous coronary intervention it was found out that Abciximab reduces the risk of an acute ischemic event. The anti inflammatory action might contribute to this effect. According to a study conducted with 160 patients it was found out that abciximab decreased the transient increase in serum CRP , TNF alpha and IL-6 induced by angioplasty.[40]

Thiazolidinediones

Reduction in serum CRP concentrations in patients with or without type 2 diabetes is achieved with both pioglitazone and rosiglitazone. This effect is independent of the glycemic control. In PIOSTAT trial about 125 patients who are non diabetic with elevated CRP and cardiovascular diseases were assigned to three groups. One group were assigned to pioglitazone with placebo, second group were assigned to simvastatin with placebo and third group were assigned to a combination of pioglitazone and simvastatin . it was found out that significant reduction in CRP levels are found with pioglitazone and simvastatin as monotherapy and combination therapy had additive effect.[44]

Dietary modification

Studies have shown that certain dietary modifications are found to lower serum CRP levels. It was found out that the diet rich in viscous fibre, plant sterols, soy protein and nuts with low levels of calorie and fat restriction were found to reduce serum CRP levels. And addition of statin to the diet has been found to drastically decrease the levels of serum CRP.[48]

3. AIMS AND OBJECTIVES OF STUDY

1. To test association between hs CRP and various individual components of metabolic syndrome

2. To test the association between hs CRP and metabolic syndrome

4. MATERIALS AND METHOD

Place of study

Stanley Medical College and Hospital, Chennai

Department of General Medicine, OPD, Medical wards

Study population

50 consecutive patients of metabolic syndrome

Study design-

Prospective and observational Study

ETHICAL COMMITTEE APPROVAL

Ethical committee approval was obtained for the study

OPERATIONAL DEFINITIONS

Case definition:

1)**Metabolic syndrome-** was defined the presence of at least 3 of the following criteria:

The cut-off point of waist circumference is ≥90 cm in men and ≥80 cm in women according to the recommendation by the World Health Organization (WHO) guidelines for South Asians[41]

- Triglycerides ≥150 mg/dL or treatment for hypertriglyceridemia.
- HDL-C < 40 mg/dL in men or <50 mg/mL in women or treatment for low HDL-C.
- Blood pressure ≥130/85 mmHg or treatment for hypertension
- Fasting glucose ≥100 mg/dL or treatment for hyperglycemia[15]

2) **High sensitivity CRP (hs.CRP)** levels were measured by enzyme-linked immunosorbent assay, and defined as high when >3 mg/L.[23]

PATIENT SELECTION

Inclusion criteria

1) metabolic syndrome diagnosed patients according to the NCEP ATP 111 criteria considering abdominal obesity as per World Health Organization (WHO) guidelines for South Asians

2) Age –more than 20 years[2]

Exclusion criteria

1) Patients takings statins, asprin, thiazolidinediones,
2) Patients with acute infections
3) Patients with chronic inflammatory conditions like inflammatory bowel disease, osteoarthritis, rheumatoid arthritis, gout, bronchial asthma and chronic hepatits
4) Patients with acute myocardial infarction , cerebral infarction
5) Patients with chronic kidney disease[2]

Methodology

Patients aged above 20 years presenting to the Medicine out-patient service and those admitted to the medical wards at Stanley medical college hospital Chennai were included in the present study. The data were recorded from each subject with an in-person interview by administering a specific questionnaire. The components of metabolic syndrome were defined according to the modified National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria considering abdominal obesity as per World Health Organization (WHO) guidelines for South Asians. Waist circumference was measured using a non-elastic measuring tape at the highest level of iliac crest with the patient standing with feet 1 foot apart. Systolic and diastolic blood pressure was measured by sphygmomanometer. Individuals reporting a history of hypertension and current antihypertensive medication use were defined as having hypertension regardless of the blood pressure values measured at the time of evaluation. Diabetes mellitus was diagnosed as per the American Diabetic Association (ADA) diagnostic criteria and/or concomitant anti-diabetic treatment, regardless of the measured glucose values.[4]

In all the patients, a peripheral venous blood sample was to be drawn in the morning after 8 - 10 hours of fasting, to measure venous plasma glucose, serum total cholesterol, serum high density lipoprotein (HDL) cholesterol, and serum triglyceride levels. Serum glucose was to be measured by the glucose oxidase method; plasma triglycerides, total cholesterol and HDL-cholesterol were to be measured by enzymatic colorimetric assay using autoanalyser.[19] Serum hs-CRP levels were to be determined by immune-turbidometric assay using with dedicated reagents . We used

CRP cut-off values of 3.0 mg/l, as recommended by the Centers for Disease Control and the American Heart Association. The study period is from January 2015 to may 2015.[2]

HUMAN SUBJECT PROTECTION:

The full protocol along with draft questionnaire and Informed consent will be kept in Institutional ethical Committee and approval will be obtained.

INFORMED CONSENT:

Consent form will be written in both English and Tamil and consent will be obtained from the participant, confidentiality will be maintained.

5. RESULTS AND DISCUSSIONS

Data Analysis

The patients were divided into two groups - hs-CRP negative Group and hs-CRP positive Group. Descriptive statistics was done for all data and were reported in terms of mean values and percentages. Suitable statistical tests of comparison were done. Continuous variables were analysed with the unpaired t test. Categorical variables were analysed with Fisher Exact Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS version 16 and Microsoft Excel 2007.

Sample Size Calculation

Sample size was determined based on the study “Highly sensitive C-reactive protein in metabolic syndrome” authored by Sudha Vidyasagar et al. and published in JIACM 2013; 14(3-4): 230-4. In this study the On univariate analysis, hs-CRP was found to be significantly increased in patients with diabetes mellitus (86%)($p < 0.021$)

The confidence level is estimated at 95% with a z value of 1.96 and the confidence interval or margin of error is estimated at +/-10. Assuming p = 86% and q= 14%.

$n=p \times q \times [z/e]^2$

$n= 86 \times 14 \times [1.96/12]^2$

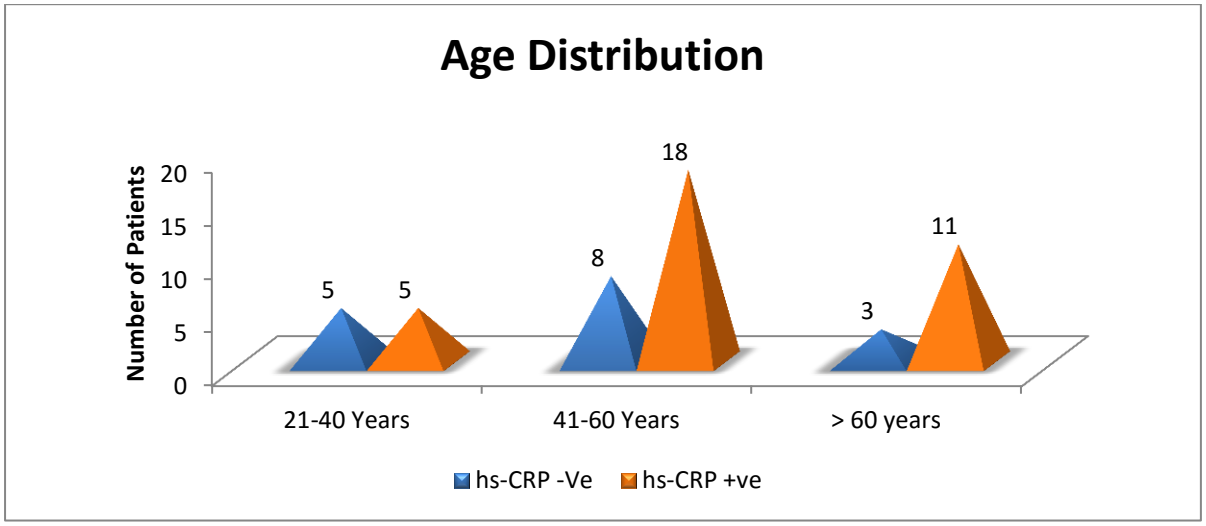
n= 46.25

Therefore 46 is the minimum sample size required for the study.

In our study we have taken 50 as the sample size

- n=14 in hs-CRP negative Group
- n=36 in hs-CRP positive Group

Age



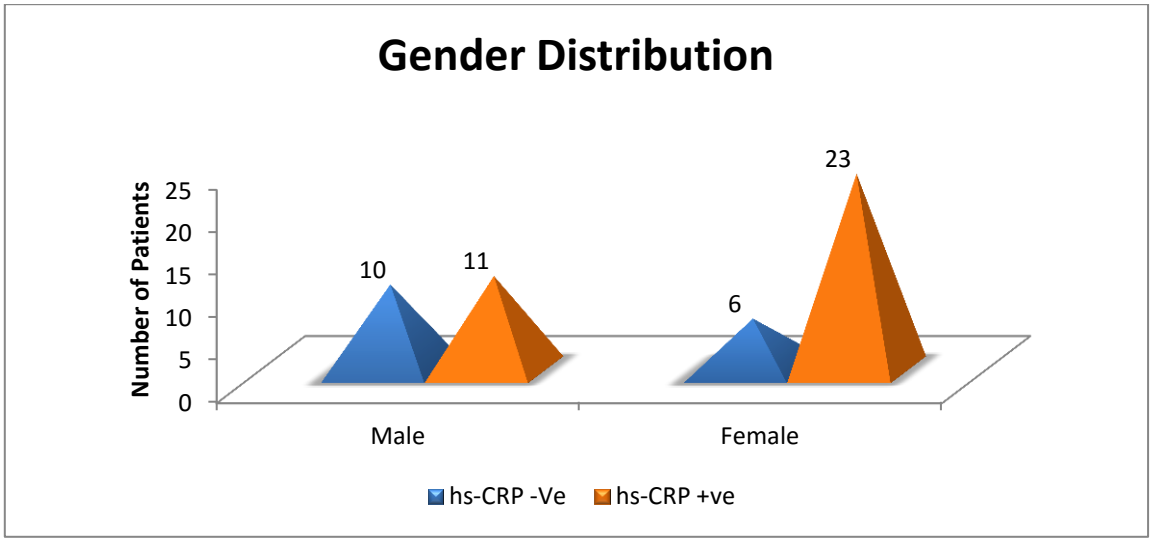
Age Distribution	hs-CRP -Ve	%	hs-CRP +ve	%
21-40 Years	5	31.25	5	14.71
41-60 Years	8	50.00	18	52.94
> 60 years	3	18.75	11	32.35
Total	16	100	34	100

Age Distribution	hs-CRP -Ve	hs-CRP +ve
N	16	34
Mean	46.63	55.35
SD	11.41	14.23
P value **Unpaired t Test**		0.1258

DISCUSSION

Majority of the hs-CRP -Ve Group patients belonged to the 41-60 Years age class interval (n=8, 50.00%) with a mean age of 46.63 years. In the hs-CRP +Ve group patients, majority belonged to the 41-60 years age class interval (n=18, 52.94%) with a mean age of 55.35 years. The association between the study groups and age distribution is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.

Gender

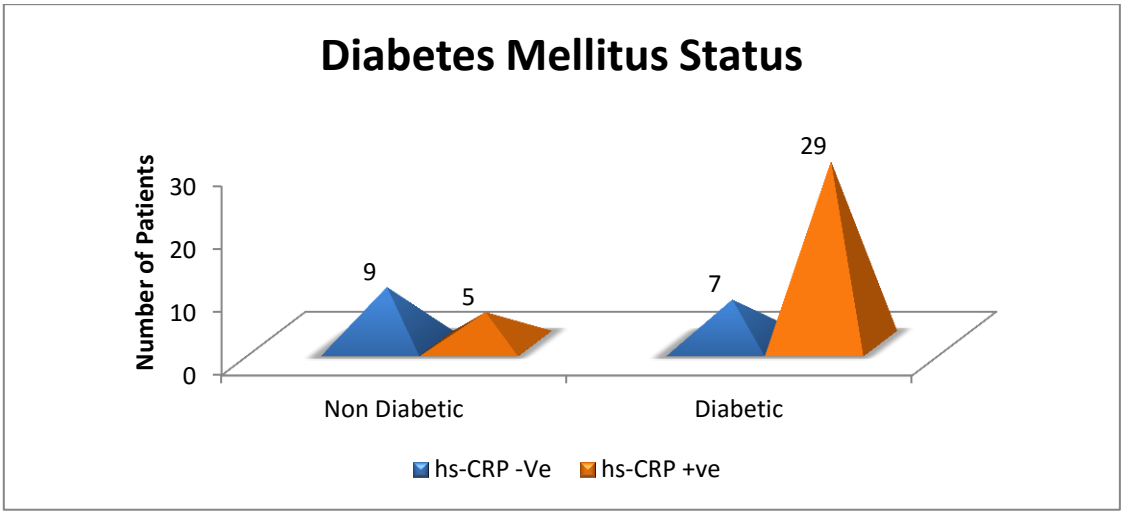


Gender Distribution	hs-CRP -Ve	%	hs-CRP +ve	%
Male	10	62.50	11	32.35
Female	6	37.50	23	67.65
Total	16	100	34	100
P value **Fishers Exact Test**			0.1439	

DISCUSSION

Majority of the hs-CRP -Ve Group Group patients belonged to the male gender group (n=10, 62.50%). In the hs-CRP +Ve group patients, majority belonged to the female gender group (n=23, 67.65%). The association between the study groups and gender distribution is considered to be not statistically significant since $p > 0.05$ as per Fishers Exact test.

Diabetes Mellitus Status

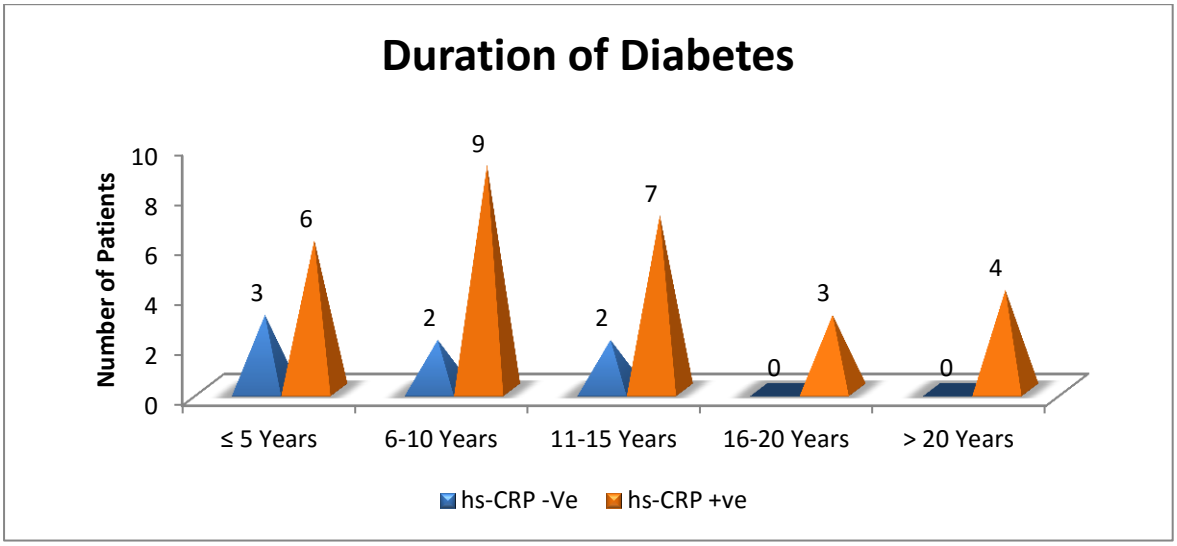


Diabetes Mellitus Status	hs-CRP -Ve	%	hs-CRP +ve	%
Non Diabetic	9	56.25	5	14.71
Diabetic	7	43.75	29	85.29
Total	16	100	34	100
P value **Fishers Exact Test**			0.0023*	

DISCUSSION

There is a true difference among study groups study groups in relation to diabetes mellitus status and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. In simple terms, Most of the hs-CRP -Ve Group patients are non diabetics (n=9, 56.25%). In the hs-CRP +Ve Group patients, majority were diabetics (n=29, 85.29%). This diabetes mellitus status distribution among the study groups expressed a p-value of 0.0001. The incidence of diabetes mellitus was meaningfully less in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 41.54 percentage points. This significant difference of 1.95 times increase in incidence of diabetes mellitus in hs-CRP +Ve Group compared to hs-CRP -Ve Group is true and has not occurred by chance. In this study we can safely conclude that hs-CRP positivity results in significantly increased incidence of diabetes mellitus compared to hs-CRP negativity in metabolic syndrome patients.

Duration of Diabetes



Duration of Diabetes	hs-CRP -Ve	%	hs-CRP +ve	%
≤ 5 Years	3	42.86	6	20.69
6-10 Years	2	28.57	9	31.03
11-15 Years	2	28.57	7	24.14
16-20 Years	0	0.00	3	10.34
> 20 Years	0	0.00	4	13.79
Total	7	100	29	100

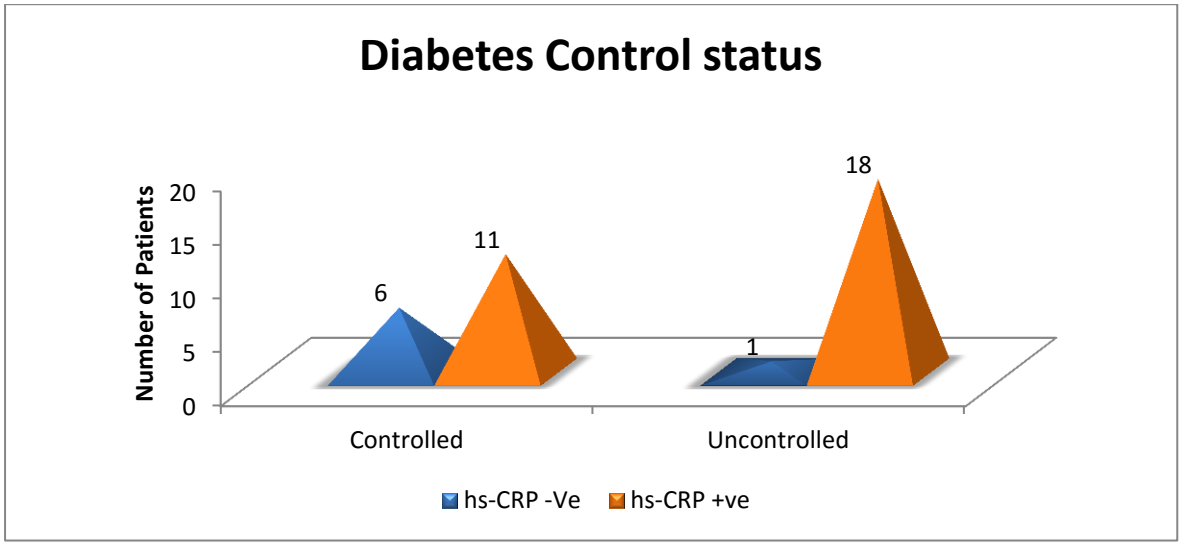
Duration of Diabetes	hs-CRP -Ve	hs-CRP +ve
N	7	29
Mean	7.00	10.86
SD	4.28	6.27
P value **Unpaired t Test**		0.0446*

DISCUSSION

There is a true difference among study groups study groups in relation to duration of diabetes mellitus and this difference is considered to be statistically significant since $p < 0.05$ as per unpaired t test. In simple terms, Most of the hs-CRP -Ve Group patients belonged to the ≤ 5 Years duration of diabetes class interval (n=9, 56.25%) with a mean duration of 7 years. In the hs-CRP +Ve Group patients, majority belonged to the 6-10 Years duration of diabetes class interval (n=9, 31.03%) with a mean duration of 10.86 years.

This duration of diabetes mellitus distribution among the study groups expressed a p-value of 0.0446. The duration of diabetes mellitus was meaningfully less in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 4.29 years. This significant difference of 1.65 times increase in incidence of diabetes mellitus in hs-CRP +Ve Group compared to hs-CRP -Ve Group is true and has not occurred by chance. In this study we can safely conclude that hs-CRP positivity is significantly increased in metabolic syndrome patients with longer duration of diabetes mellitus compared to hs-CRP negativity which occurs more in metabolic syndrome patients with lesser duration of diabetes mellitus.

Diabetes Control Status

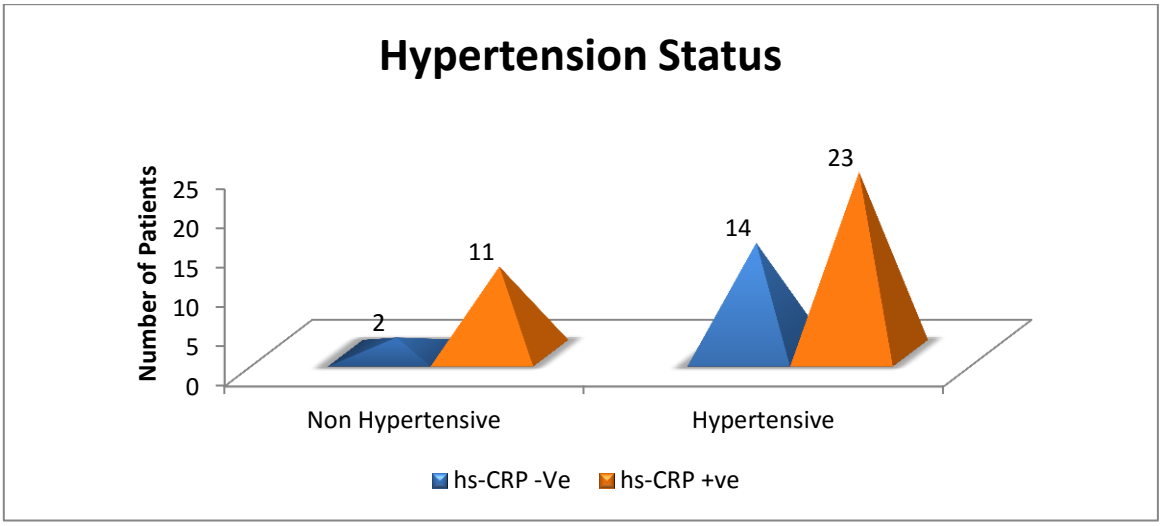


Diabetes Control Status	hs-CRP -Ve	%	hs-CRP +ve	%
Controlled	6	85.71	11	37.93
Uncontrolled	1	14.29	18	62.07
Total	7	100	29	100
P value **Fishers Exact Test**			0.0365*	

DISCUSSION

There is a true difference among study groups study groups in relation to diabetes mellitus control status and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. In simple terms, Most of the hs-CRP -Ve Group patients who are diabetics, are under strict blood glucose control (n=6, 85.71%). In the hs-CRP +Ve Group patients who are diabetics, majority are not under strict blood glucose control (n=18, 62.07%). This control of blood sugar in diabetics among the study groups is expressed with a p-value of 0.0365. The incidence of strict blood glucose control among diabetics was meaningfully more in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 47.78 percentage points. This significant difference of 2.26 times increase in incidence of diabetes mellitus in hs-CRP -Ve Group compared to hs-CRP +Ve Group is true and has not occurred by chance. In this study we can safely conclude that strict blood glucose control among diabetics in metabolic syndrome patients results in hs-CRP negativity and poor blood glucose control among diabetics in metabolic syndrome patients results in hs-CRP positivity.

Hypertension Status

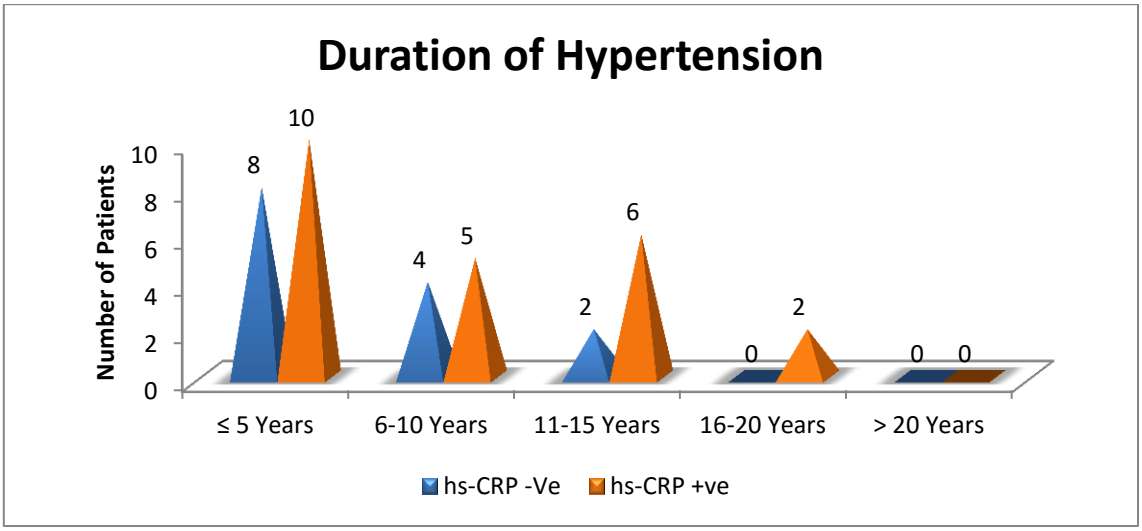


Hypertension Status	hs-CRP -Ve	%	hs-CRP +ve	%
Non Hypertensive	2	12.50	11	32.35
Hypertensive	14	87.50	23	67.65
Total	16	100	34	100
P value **Fishers Exact Test**			0.1792	

DISCUSSION

Majority of the hs-CRP -Ve Group Group patients were hypertensives (n=14, 87.50%). In the hs-CRP +Ve group patients, majority were hypertensives (n=23, 67.65%). The association between the study groups and hypertension status is considered to be not statistically significant since $p > 0.05$ as per Fishers Exact test.

Duration of Hypertension



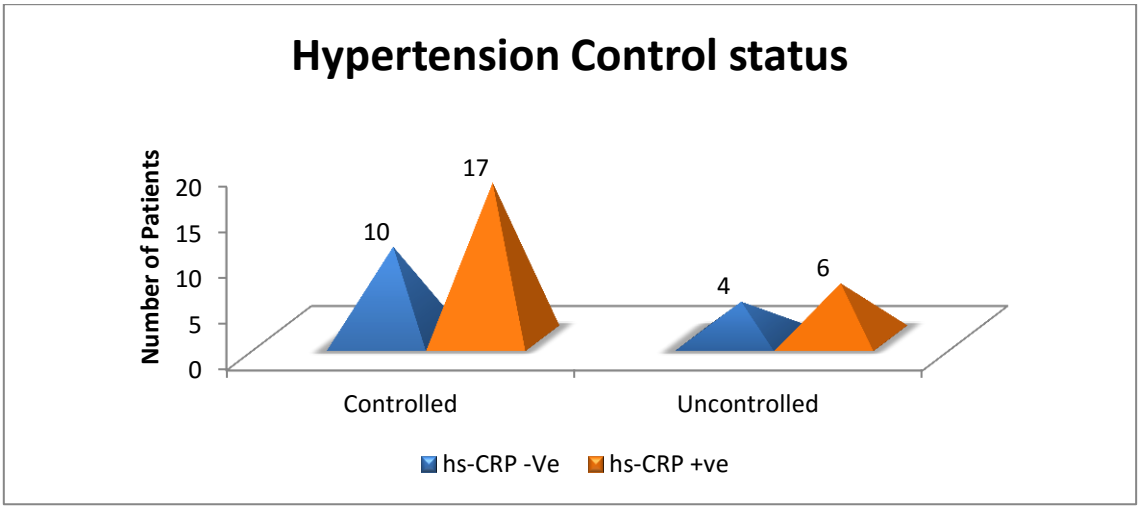
Duration of Hypertension	hs-CRP -Ve	%	hs-CRP +ve	%
≤ 5 Years	8	57.14	10	43.48
6-10 Years	4	28.57	5	21.74
11-15 Years	2	14.29	6	26.09
16-20 Years	0	0.00	2	8.70
> 20 Years	0	0.00	0	0.00
Total	14	100	23	100

Duration of Hypertension	hs-CRP -Ve	hs-CRP +ve
N	14	23
Mean	6.36	8.09
SD	3.86	5.12
P value **Unpaired t Test**		0.2518

DISCUSSION

Majority of the hs-CRP -Ve Group patients belonged to the ≤ 5 Years duration of hypertension class interval (n=8, 57.14%) with a mean duration of 6.36 years. In the hs-CRP +Ve group patients, majority belonged to the ≤ 5 Years duration of hypertension class interval (n=10, 43.48%) with a mean duration of 8.09 years. The association between the study groups and duration of hypertension is considered to be not statistically significant since $p > 0.05$ as per 2 tail unpaired t test.

Hypertension Control status

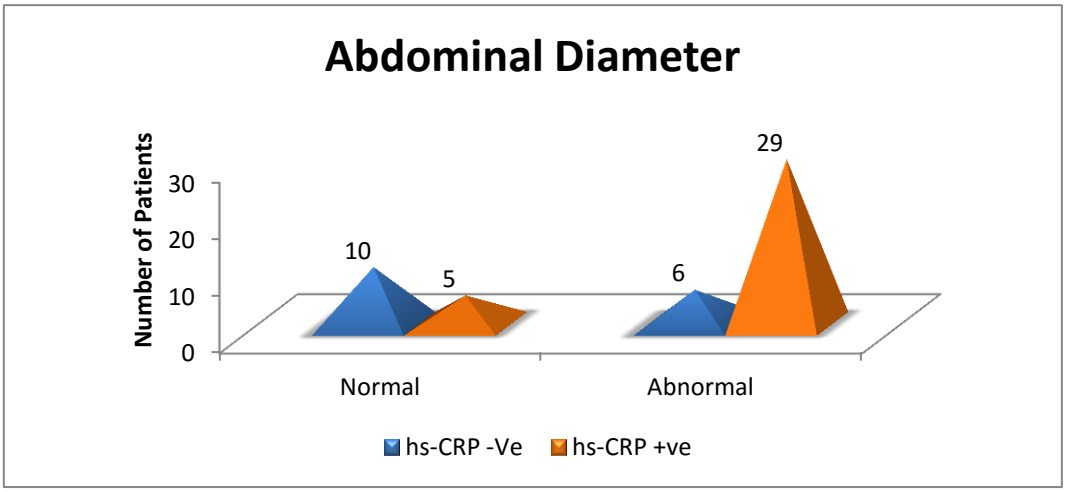


Hypertension Control status	hs-CRP -Ve	%	hs-CRP +ve	%
Controlled	10	71.43	17	73.91
Uncontrolled	4	28.57	6	26.09
Total	14	100	23	100
P value Fishers Exact Test			0.2883	

DISCUSSION

Majority of the hs-CRP -Ve Group hypertensive patients were under strict control (n=10, 71.43%). In the hs-CRP +Ve group hypertensive patients, majority were under strict control (n=17, 73.91%). The association between the study groups and hypertension control status is considered to be not statistically significant since p > 0.05 as per Fishers Exact test.

Abdominal Diameter

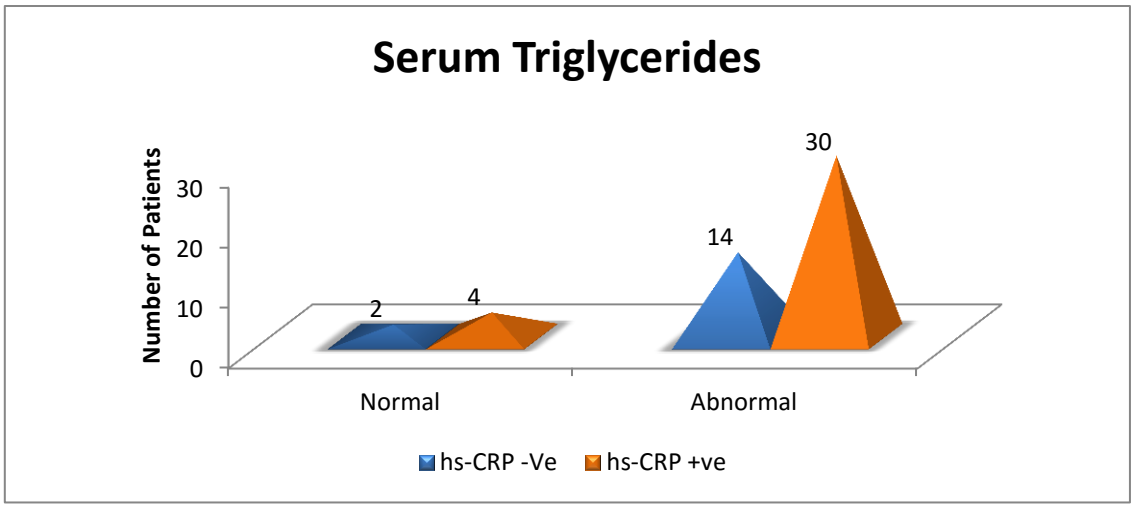


Abdominal Diameter	hs-CRP -Ve	%	hs-CRP +ve	%
Normal	10	62.50	5	14.71
Abnormal	6	37.50	29	85.29
Total	16	100	34	100
P value **Fishers Exact Test**			0.0019*	

DISCUSSION

There is a true difference among study groups study groups in relation to abdominal diameter status and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. In simple terms, Most of the hs-CRP -Ve Group patients had normal abdominal diameter (n=10, 62.50%). In the hs-CRP +Ve Group patients, majority had abnormal abdominal diameter (n=29, 85.29%). This abnormality in abdominal diameter among the study groups is expressed with a p-value of 0.0019. The incidence of abnormal abdominal diameter was meaningfully less in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 47.79 percentage points. This significant difference of 2.27 times increase in incidence of abnormal abdominal diameter in hs-CRP +Ve Group compared to hs-CRP -Ve Group is true and has not occurred by chance. In this study we can safely conclude that abnormal abdominal diameter in metabolic syndrome patients results in higher hs-CRP positivity and normal abdominal diameter in metabolic syndrome patients results in higher hs-CRP negativity.

Serum Triglycerides

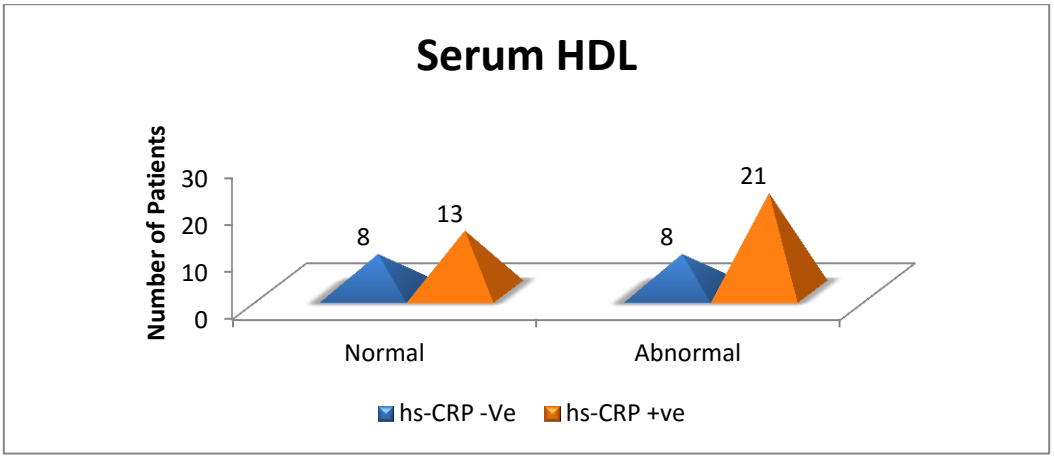


Serum Triglycerides	hs-CRP -Ve	%	hs-CRP +ve	%
Normal	2	12.50	4	11.76
Abnormal	14	87.50	30	88.24
Total	16	100	34	100
P value **Fishers Exact Test**			>0.9999	

DISCUSSION

Majority of the hs-CRP -Ve Group patients had abnormal triglyceride levels (n=14, 87.50%). In the hs-CRP +Ve group patients, majority had abnormal triglyceride levels (n=30, 88.24%). The association between the study groups and serum triglyceride levels is considered to be not statistically significant since $p > 0.05$ as per Fishers Exact test.

Serum HDL

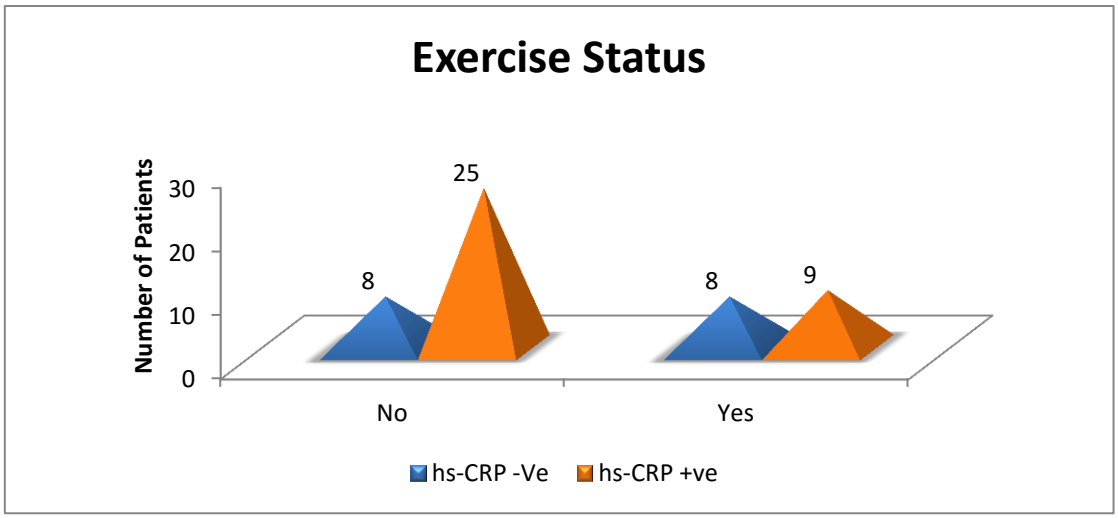


Serum HDL	hs-CRP -Ve	%	hs-CRP +ve	%
Normal	8	50.00	13	38.24
Abnormal	8	50.00	21	61.76
Total	16	100	34	100
P value **Fishers Exact Test**			0.3653	

DISCUSSION

Majority of the hs-CRP -Ve Group patients had abnormal HDL levels (n=8, 50.00%). In the hs-CRP +Ve group patients, majority had abnormal HDL levels (n=21, 61.76%). The association between the study groups and serum HDL levels is considered to be not statistically significant since $p > 0.05$ as per Fishers Exact test.

Exercise Status

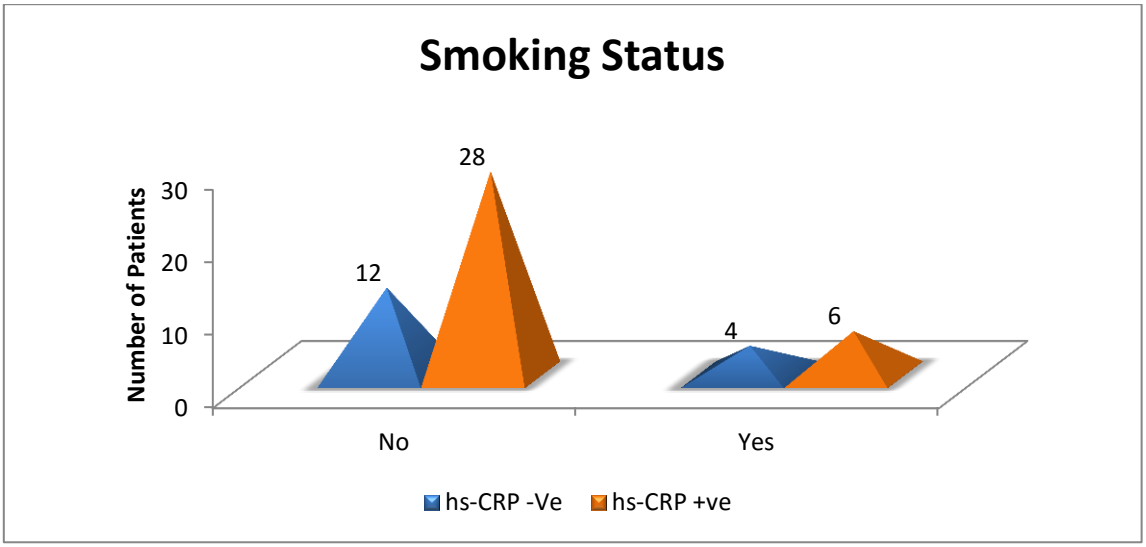


Exercise Status	hs-CRP -Ve	%	hs-CRP +ve	%
No	8	50.00	25	73.53
Yes	8	50.00	9	26.47
Total	16	100	34	100
P value **Fishers Exact Test**			0.0426*	

DISCUSSION

There is a true difference among study groups study groups in relation to exercise status and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. In simple terms, Most of the hs-CRP -Ve Group patients exercised regularly (n=8, 50.00%). In the hs-CRP +Ve Group patients, majority did not exercise regularly (n=25, 73.53%). This abnormality in exercise status among the study groups is expressed with a p-value of 0.0426. The incidence of exercising regularly was meaningfully more in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 23.53 percentage points. This significant difference of 1.89 times increase in incidence of exercising regularly in hs-CRP -Ve Group compared to hs-CRP +Ve Group is true and has not occurred by chance. In this study we can safely conclude that exercising regularly in metabolic syndrome patients results in higher hs-CRP negativity and not exercising regularly in metabolic syndrome patients results in higher hs-CRP positivity.

Smoking Status

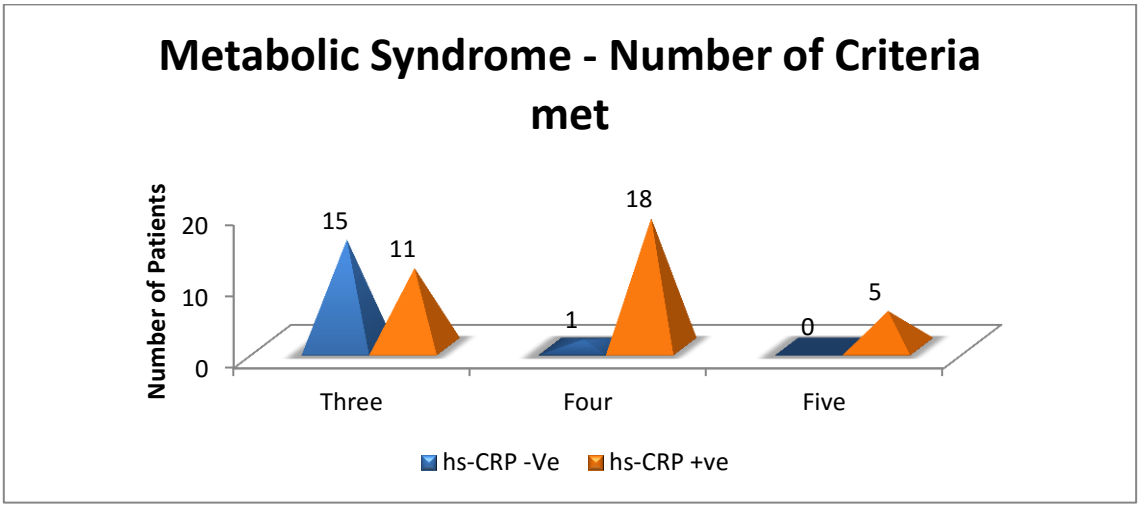


Smoking Status	hs-CRP -Ve	%	hs-CRP +ve	%
No	12	75.00	28	82.35
Yes	4	25.00	6	17.65
Total	16	100	34	100
P value **Fishers Exact Test**			0.7067	

DISCUSSION

Majority of the hs-CRP -Ve Group patients were non smokers (n=12, 75.00%). In the hs-CRP +Ve group patients, majority were non smokers (n=28, 82.35%). The association between the study groups and smoking status is considered to be not statistically significant since $p > 0.05$ as per Fishers Exact test.

Metabolic Syndrome - Number of Criteria Met



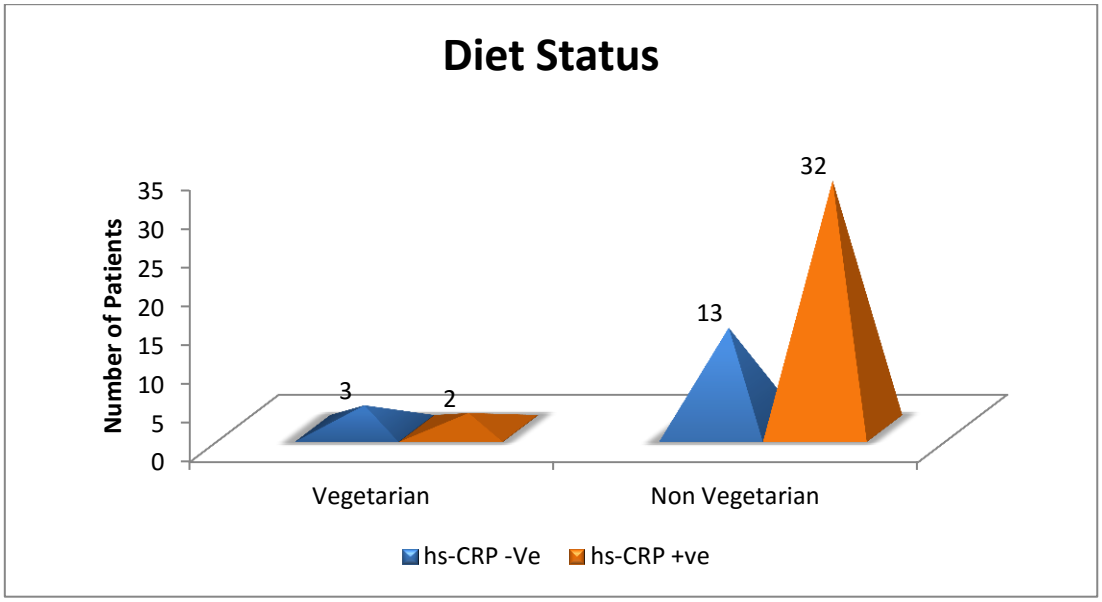
Metabolic Syndrome - Number of Criteria met	hs-CRP -Ve	%	hs-CRP +ve	%
Three	15	93.75	11	32.35
Four	1	6.25	18	52.94
Five	0	0.00	5	14.71
Total	16	100	34	100
P value **Fishers Exact Test**			0.0001	

DISCUSSION

There is a true difference among study groups study groups in relation to number of metabolic syndrome criteria met and this difference is considered to be statistically significant since $p < 0.05$ as per fishers exact test. In simple terms, Most of the hs-CRP -Ve Group patients had three metabolic syndrome criteria met (n=15, 93.75%). In the hs-CRP +Ve Group patients, majority had four metabolic syndrome criteria met did not exercise regularly (n=18, 52.94%). This difference in metabolic syndrome criteria met among the study groups is expressed with a p-value of 0.0001.

Three metabolic syndrome criteria met was meaningfully more in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 61.40 percentage points. Four metabolic syndrome criteria met was meaningfully less in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 46.69 percentage points. Five metabolic syndrome criteria met was meaningfully less in hs-CRP -Ve Group compared to hs-CRP +Ve Group by 14.71 percentage points. This significant difference of 2.90 times increase in incidence of three metabolic syndrome criteria met, 88% decrease in incidence of four metabolic syndrome criteria met in hs-CRP -Ve Group compared to hs-CRP +Ve Group, is true and has not occurred by chance. In this study we can safely conclude that increase in number of metabolic syndrome criteria met in metabolic syndrome patient's results in higher hs-CRP positivity and decrease in number of metabolic syndrome criteria met in metabolic syndrome patient's results in higher hs-CRP negativity.

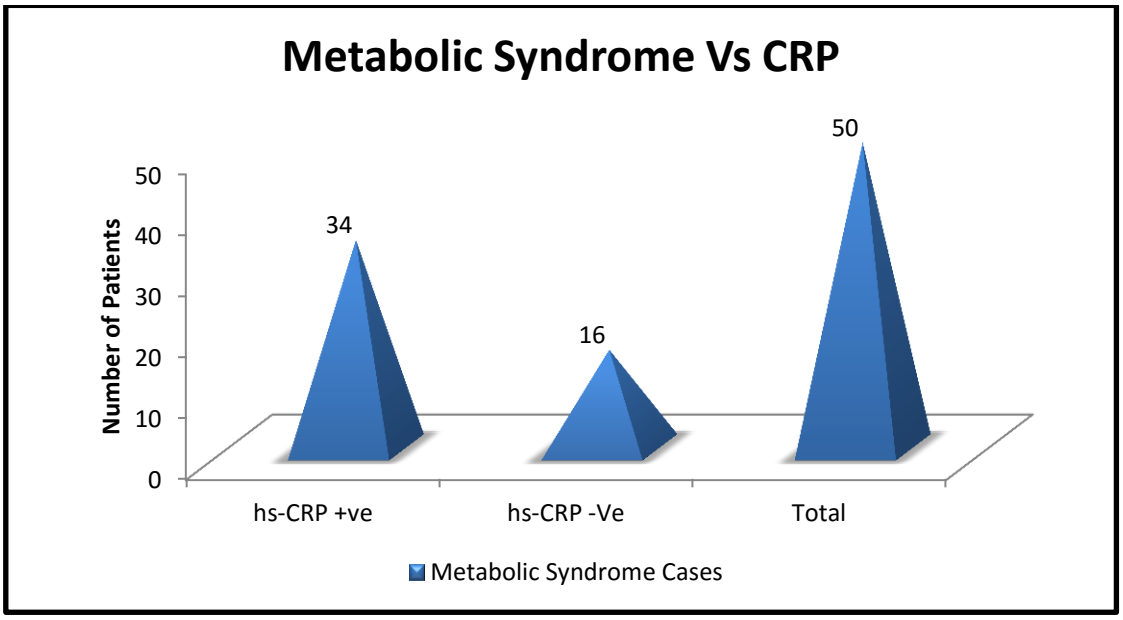
Diet Status



Diet Status	hs-CRP -Ve	%	hs-CRP +ve	%
Vegetarian	3	18.75	2	5.88
Non Vegetarian	13	81.25	32	94.12
Total	16	100	34	100
P value **Fishers Exact Test**			0.3109	

DISCUSSION

Majority of the hs-CRP -Ve Group patients were non vegetarians (n=13, 81.25%). In the hs-CRP +Ve group patients, majority were non vegetarians (n=32, 94.12%). The association between the study groups and diet status is considered to be not statistically significant since $p > 0.05$ as per Fishers Exact test.



Metabolic Syndrome Vs CRP	Metabolic Syndrome Cases	Percentage
hs-CRP +ve	34	68
hs-CRP –Ve	16	32
Total	50	100

About 34 patients had tested positive for Hs CRP in total 50 metabolic syndrome patients. This shows us that there is a 68 % association of CRP with metabolic syndrome

CONCLUSIONS

The following were the conclusion of this study

1. The association between the study groups and age distribution is considered to be not statistically significant.
2. The association between the study groups and gender distribution is considered to be not statistically significant
3. hs-CRP has a positive correlation with increased incidence of diabetes mellitus.
4. hs-CRP has a positive correlation with longer duration of diabetes mellitus.
5. Strict glycemic control among diabetics in metabolic syndrome patients is found to have a negative correlation with hs CRP.
6. Association between the study groups and hypertension status is considered to be not statistically significant
7. Abnormal abdominal diameter in metabolic syndrome patients is found to have a positive correlation with hs CRP.
8. Association between the study groups and serum triglyceride levels is considered to be not statistically significant
9. Association between the study groups and serum HDL levels is considered to be not statistically significant
10. Exercising regularly in metabolic syndrome patients is found to have a negative correlation with hs CRP.
11. Association between the study groups and smoking status is considered to be not statistically significant.

12. Increase in number of metabolic syndrome criteria met in metabolic syndrome patient's is found to have a positive correlation with hs CRP.
13. The association between the study groups and diet status is considered to be not statistically significant.
14. hs CRP was found to be elevated in two thirds (68%) of patients with metabolic syndrome.

SUMMARY

Thus there is positive correlation of hs CRP with diabetes, duration of diabetes, abnormal abdominal diameter and number of metabolic syndrome criteria met.

There is a negative correlation of hs CRP with strict glycemic control and exercise.

Thus there is no statistical significant correlation of hs CRP with age gender, hypertension, serum triglyceride levels, serum HDL level, smoking and diet status.

Thus we can safely conclude that about two third patients with metabolic syndrome have elevated levels of hs CRP.

ANNEXURES

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2. PROFORMA

NAME:

AGE: 1. 25-40yrs 2. 40-60yrs 3. >60 **SEX:** 1.M 2.F

LOCALITY: **CONTACT NO:**

COMPLAINTS :

PAST H/O DIABETES: 1. Yes 2. No If yes specify_____

HYPERTENSION 1. Yes 2. No If yes specify_____

RENAL FAILURE 1. Yes 2. No If yes specify_____

AUTOIMMUNE DISORDER 1. Yes 2. No If yes specify_____

CARDIAC ILLNESS 1. Yes 2. No If yes specify_____

STROKE 1. Yes 2. No If yes specify_____

CONNECTIVE TISSUES DISORDER 1. Yes 2. No If yes specify_____

INFLAMMATORY BOWEL DISEASE 1. Yes 2. No If yes specify_____

OSTEOARTHRITIES , 1. Yes 2. No If yes specify_____

RHEUMATOID ARTHRITIS 1. Yes 2. No If yes specify_____

GOUT 1. Yes 2. No If yes specify_____

BRONCHIAL ASTHMA 1. Yes 2. No If yes specify_____

OTHERS _____

H/O CHRONIC DRUG INTAKE:

H/O OF ANY RECENT FEVER : 1. YES 2 .NO

PERSONAL H/O

FOOD : 1.veg 2.Non veg

SMOKING : 1. Yes 2. No

ALCOHOL INTAKE: 1. Yes 2. No

EXERCISE OF ATLEAST 30 MINS FOR 5 DAYS A WEEK : 1. Yes 2. No

VITALS-

BP: **PR:** **RR:** **TEMPERATURE-**

SYSTEMIC EXAMINATION-

CVS: **RS:** **PA:**

CNS:

INVESTIGATIONS

CBC :

RFT :

FBS :

LIPID PROFILE :

ECG FINDINGS:

hs CRP -

<u>METABOLIC SYNDROME CRITERIA</u>

HYPERTENSION : 1. Yes 2. No BP- Duration-

DIABETES : 1. Yes 2. No FBS- Duration

WAIST CIRCUMFERENCE:

HDL-

TRIGLYCERIDES-

NO OF CRITERIA SATISFIED -

COMMENT:

3. CONSENT FORM

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

A STUDY ASSOCIATION OF hs CRP IN METABOLIC SYNDROME PATIENTS

AT GOVERNMENT STANLEY MEDICAL COLLEGE HOSPITAL, CHENNAI.

Place of study: Govt. Stanley medical college, Chennai

I ……. have been informed about the details of the study in my own language.

I have completely understood the details of the study.

I am aware of the possible risks and benefits, while taking part in the study.

I agree to collect samples of blood/saliva/urine/tissue if study needs.

I understand that I can withdraw from the study at any point of time and even then, I can receive the medical treatment as usual.

I understand that I will not get any money for taking part in the study.

I will not object if the results of this study are getting published in any medical journal, provided my personal identity is not revealed.

I know what I am supposed to do by taking part in this study and I assure that I would extend my full cooperation for this study.

Volunteer:	Witness:
Name and address	Name and address
Signature/thumb impression:	Signature/thumb impression
Date:	Date:

Investigator Signature and date

GOVT. STANLEY MEDICAL COLLEGE, CHENNAI – 600001

INFORMED CONSENT

வளர்சிதை மாற்ற நோய்க்குறி நோயாளிகளுக்கு அதிகபட்ச **CRP** பற்றிய ஒரு ஆய்வு சங்கம்

நான் இந்த ஆராய்ச்சியில் விவரங்களை முற்றிலும் புரிந்து கொண்டேன்.

ஆய்வில் பங்கு எடுத்து போது, சாத்தியமான அபாயங்கள் மற்றும் பயன்களை பற்றி நான் அறிந்துள்ளேன்.

நான் எந்தவொரு வேளையிலும் ஆய்வில் இருந்து திரும்ப முடியும், அதன் பின்னர், நான் வழக்கம் போல் மருத்துவ சிகிச்சை பெற முடியும் என்று புரிந்துகொள்கிறேன்

நான் ஆய்வில் பங்கு எடுத்து பணம் எதையும் பெற முடியாது என்று அறிந்துள்ளேன்.

இந்த ஆய்வின் முடிவுகள் எந்த மெடிக்கல் ஜர்னலில் வெளியிடப்பட இருந்தால் நான் எதிர்க்கவில்லை, என் தனிப்பட்ட அடையாளத்தை வெளிப்படுத்தப்பட்டு இருக்க கூடாது.

நான் இந்த ஆய்வில் பங்கெடுப்பதன் மூலம் நான் என்ன செய்ய போகிறேன் என்று தெரியும்

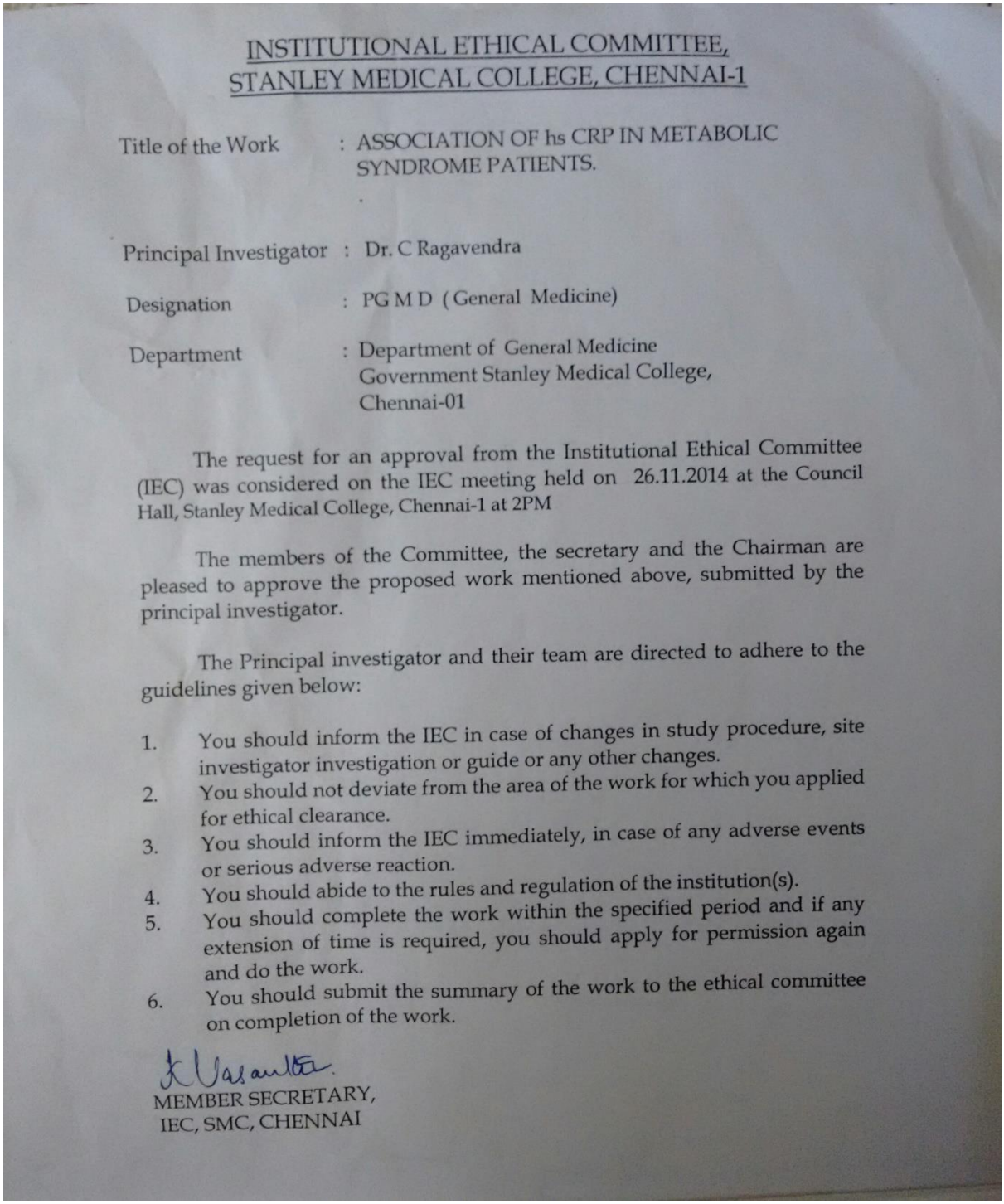
நான் இந்த ஆய்வில் என் முழு ஒத்துழைப்பையும் கொடுப்பேன் என்று உறுதியளிக்கிறேன்.

தன்னார்வளர்	சாட்சி
பெயர் மற்றும் முகவரி	பெயர் மற்றும் முகவரி
கையொப்பம் / விரல் ரேகை:	கையொப்பம் / விரல் ரேகை:

ஆராய்ச்சியாளராக

கையொப்பம் மற்றும் தேதி

4. ETHICAL COMMITTEE APPROVAL LETTER



INSTITUTIONAL ETHICAL COMMITTEE,
STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : ASSOCIATION OF hs CRP IN METABOLIC SYNDROME PATIENTS.

Principal Investigator : Dr. C Ragavendra

Designation : PG M D (General Medicine)

Department : Department of General Medicine
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 26.11.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

5. MASTER CHART

SL NO	AGE	SEX	DIABETIC			HYPERTENSION			AB DIAME	TGL	HDL	EXERICSE	SMOKING	NO OF FACTORS	NV	**hs CRP**
			Y OR N	DURATION	C OR UC	Y OR N	DURATION	C OR UC	Y OR N	Y OR N	Y OR N	Y OR N	Y OR N		Y OR N	**Y OR N**
1	56	F	Y	12	UC	N			Y- 100	Y-274	Y-47	N	N	4	Y	**Y**
2	69	M	Y	15	C	Y	15	C	N	Y-170	N	N	Y	3	Y	**Y**
3	35	M	N			N			Y-98	Y-160	Y-35	Y	N	3	Y	**N**
4	48	F	Y	5	Y	Y	4	U	Y-90	Y-210	Y-44	N	N	5	Y	**Y**
5	41	M	N			Y			Y-96	Y-196	N	Y	N	3	N	**N**
6	27	F	N			N			Y-88	Y-240	Y-31	N	N	3	Y	**Y**
7	55	M	Y	11	U	Y	12	C	Y-94	N	Y-34	N	Y	4	Y	**Y**
8	69	F	Y	18	U	N			Y-109	Y-284	Y-29	Y	N	4	Y	**Y**
9	45	F	Y	2	C	Y	5	C	N	Y-274	N	Y	N	3	Y	**N**
10	52	F	Y	6	U	N			Y-114	Y-198	Y-31	N	N	4	Y	**Y**
11	45	F	N			Y	3	C	Y-95	Y-274	Y-28	Y	N	4	Y	**Y**
12	52	M	N			Y	5	U	Y-99	Y-221	N	Y	N	3	Y	**N**
13	29	F	N			N			Y-119	Y-246	Y- 39	N	N	3	Y	**Y**
14	35	M	N			Y	2	C	Y-99	Y-274	N	Y	N	3	N	**N**
15	45	M	Y	3	C	Y	4	C	N	Y-245	N	Y	Y	3	Y	**N**
16	56	M	Y	7	U	N			Y-101	Y-214	Y-34	N	Y	3	Y	**Y**
17	68	F	Y	12	U	Y	11	U	Y-93	Y- 188	Y-44	N	N	5	Y	**Y**
18	32	M	N			Y	2	C	N	Y-172	Y-36	Y	N	3	Y	**N**
19	45	M	y	5	C	Y	5	U	N	Y-184	N	Y	N	3	N	**Y**
20	54	M	N			Y	8	U	N	Y-199	Y-35	N	Y	3	Y	**N**
21	46	F	Y	7	U	Y	5	C	Y-98	Y-245	N	N	Y	4	Y	**Y**
22	56	M	Y	3	C	Y	3	C	Y-94	Y-178	Y-44	N	N	4	Y	**Y**
23	38	F	Y	4	C	N			Y=119	Y-298	N	N	N	3	Y	**Y**
24	44	F	N			N			Y-110	Y-210	Y-39	N	N	3	Y	**Y**

25	54	F	Y	8	U	Y	3	U	Y-99	Y-343	Y-44	N	N	5	Y	**Y**
26	65	F	Y	15	U	Y	15	C	Y=96	N	N	N	N	3	Y	**Y**
27	62	F	Y	5	C	Y	10	C	Y-110	N	N	N	N	3	Y	**N**
28	47	M	Y	8	U	Y	5	C	Y-94	Y-202	N	Y	N	4	Y	**Y**
29	65	F	Y	21	U	Y	10	C	Y-101	Y-189	N	N	N	4	Y	**Y**
30	40	M	N			Y	5	U	N	Y-175	Y-35	N	N	3	N	**N**
31	58	F	Y	11	U	Y	7	C	Y-91	Y=170	N	N	N	4	Y	**Y**
32	51	M	Y	7	C	Y	4	C	N	Y-198	N	N	Y	3	Y	**N**
33	60	F	Y	16	C	Y	8	U	Y-101	N	N	N	N	3	Y	**Y**
34	63	F	Y	7	C	Y	14	C	N	N	Y-39	N	N	3	Y	**N**
35	54	M	Y	6	U	Y	6	C	Y-94	172	Y-35	Y	N	5	Y	**Y**
36	65	F	Y	14	U	Y	6	C	N	Y-200	N	N	N	3	Y	**N**
37	79	M	Y	24	U	Y	14	C	Y-110	Y-241	N	Y	N	4	Y	**Y**
38	80	M	Y-	22	C	Y	17	C	Y-98	N	Y-35	Y	Y	4	Y	**Y**
39	70	F	Y	16	U	N			Y-90	Y-219	Y-39	N	N	4	Y	**Y**
40	36	F	Y	6	U	N			Y-95	Y-250	Y-35	N	N	4	Y	**Y**
41	54	M	Y	11	C	Y	12	C	N	Y-244	Y-27	Y	Y	4	Y	**N**
42	45	F	N			Y	9	U	Y-91	Y-186	Y-37	N	N	4	N	**Y**
43	82	M	Y	23	C	Y	17	C	N	Y-187	N	Y	Y	3	Y	**Y**
44	49	F	Y	11	U	Y	6	C	Y-101	Y-198	Y-34	N	N	5	Y	**Y**
45	74	F	Y	21	C	Y	16	C	N	Y-166	N	N	N	3	Y	**Y**
46	27	F	N			N			Y-118	Y-177	Y-39	N	N	3	Y	**N**
47	35	M	Y	5	U	Y	5	C	N	Y-167	Y-32	N	N	4	Y	**Y**
48	45	F	N			Y	10	U	N	Y-189	Y-36	N	N	3	Y	**N**
49	57	F	Y	9	C	Y	14	U	Y-95	Y-168	N	N	N	4	Y	**Y**
50	69	F	Y	9	C	N			Y-104	Y-298	Y-35	Y	N	4	Y	**Y**

6. ABBREVIATIONS

M- MALE

F-FEMALE

Y-YES

N-NO

C-CONTROLLED

UC- UNCONTROLLED

NV-NONVEG

AB DIAMETER- ABDOMNIAL DIAMETER

TGL- TRIGLYCERIDES

HDL- HIGH DENSITY LIPOPROTEIN

Hs CRP- high sensitive C reactive protein