"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"

Submitted By

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In partial fulfillment of the Requirements for the degree of

MD

in

General Medicine

Under the guidance of

DR.M.S.BIRADAR **MD**

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2011

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I hereby declare that this dissertation entitled **"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"** is a bonafide and genuine research work carried out by me under the guidance of **DR.M.S.BIRADAR** M.D. Professor and HOD Of Medicine.

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LIST OF ABBREVATIONS USED

ACE	Angiotensin converting enzyme.
AMP	Adenosine mono phosphate.
ARB	Angiotensin receptor blocker.
BMI	Body- mass index.
BP	Blood pressure
CAD	Coronary artery disease.
CRP	C-reactive protein.
CVD	Cardiovascular disease.
CVE	Cardiovascular events.
DBP	Diastolic blood pressure.
DM	Diabetes mellitus.
EGIR	European group for the study of insulin resistance
FBS	Fasting plasma sugar.
HDL-C	High- density lipoprotein.
HSD	Hydroxy-steroid dehydrogenase.
HT	Hypertension.
IL	Interleukin.
IRS	Insulin resistance syndrome.
LCPUFA	Long chain polyunsaturated fatty acids.
LDL	Low- density lipoprotein.
METS	Metabolic syndrome.
AMI	Acute Myocardial infarction.
NCEP-ATP	National cholesterol education programme-adult treatment panel.
SBP	Systolic blood pressure.
SK	Streptokinase.
TGs	Triglycerides.
TNF	Tumour necrosis factor.
VLDL	Very low- density lipoprotein.
WC	Waist carcumference.

ABSTRACT

BACKGROUND: Metabolic syndrome is a specific clustering of cardiovascular risk factors, which increases the mortality and morbidity. Hence, we aimed to know the incidence of METS in acute myocardial infarction, assess its various components and its impact on hospital outcomes in acute MI.

MATERIALS and METHODS: A total of 197 MI cases admitted to ICCU of Shri..B.M.Patil Medical College Hospital and Reasearch Centre,Bijapur from November 2009 to March 2011 were included in the study. Cases were categorized according to the NCEP ATP III METS criteria (presence of ≥ 3 of the following: hyperglycemia >110 mg/dl, triglycerides >150mg/dl; HDL-C < 40 mg/dl for males, < 50mg/dl for females; blood pressure ≥ 130/85mg/dl; waist circumference >102 cm in men or >88 cm in women).

RESULTS: Among the 197 cases, 96 (48.7%) fulfilled the criteria for METS and were more likely to be men. Low HDL-C (90.63%) was the most prevalent component followed by hyperglycemia (89.58%) ,HT (61.46%) ,TG's(54.17%) and high WC (44.79%). In hospital complications were higher in METS patients compared to those without and associated with four fold increased risk of complications including heart failure (36.46%) and death (26.04%).

CONCLUSION: The incidence of METS was high in MI patients, associated with worse in hospital outcome and with a higher risk of development of heart failure. Among metabolic syndrome components ,hyperglycemia was the main corelate for the risk of development of heart failure and death during acute MI.

KEY WORDS: Metabolic syndrome, Myocardial infarction.

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INTRODUCTION

Multifaceted etiology of cardiovascular diseases (CVD), especially coronary heart disease, has been recognized for a long time.[1]

The Metabolic syndrome(METS) is a specific clustering of cardiovascular risk factors in the same person (abdominal obesity, atherogenic dyslipidemia, elevated blood pressure(BP), insulin resistance(IR), a prothrombotic state and a proinflammatory state).[2]

A recent review of insulin resistance syndrome revealed a rapid escalation of this syndrome among Indians and the prevalence of predominant component of METS varies from region to region.[9]

Studies have revealed the pathophysiology of this syndrome, with close to a six fold increase in cardiovascular mortality in those possessing this disorders.[4]. Different proposed definitions would appear to result in different predictions of risk, and risk appears to differ according to which components of the proposed definitions are present.[6]

The increased risk of morbidity and mortality associated with the METS makes it essential that there is a clear understanding of the dimensions of this syndrome for the allocation of health care and research resources and for other purposes.[7]

These traditional risk factors all together account for approximately half of the risk of a first myocardial infarction, especially in the Asian Indian population. As a result, both incident and prevalent CVD will likely to continue to increase in the next decades with significant socio-economic consequences.[8]

However, very few studies have reported on the prevalence of IRS as a whole in the native Indian population based on epidemiological studies. This is particularly

relevant as India has the maximum number of diabetes patients in any given country in the world.[12]

Early intervention of this METS with intensive life style changes in the form of diet, exercise and pharmacotherapy can prevent the future development of CVD like myocardial infarction. Hence, this study is undertaken to identify and assess the predominant component of METS in high risk group patients with myocardial infarction and to study the prognosis of myocardial infarction in patients with METS during hospital stay.

AIMS AND OBJECTIVES

1. To study the incidence rate and impact of metabolic syndrome on hospital outcomes in AMI , in particular death and heart failure.
2. To assess the relative influence of each of the five components of NCEP ATP III definition of METS on the risk of heart failure and death

REVIEW OF LITERATURE

The concept of METS has existed for at least 80 years. This constellation of metabolic disturbances, all risk factors for CVD, was first described in the 1920s by Kylin, a Swedish physician, as the clustering of hypertension, hyperglycemia, and gout.[14]

Abnormalities of glucose metabolism and diabetes were added to this risk factor conglomerate later. IR in diabetes was reported by Himsworth in 1939 in a series of Goulstonian lecturer to the Royal College of Physicians in London.[15]

Later in 1947, Vague drew attention to upper body adiposity (android or male-type obesity) as the obesity phenotype that was commonly associated with metabolic abnormalities associated with type 2 diabetes and CVD.[16]

The Reaven Banting lecture from the year 1988 introduced the concept of syndrome X as a fundamental factor in the pathogenesis and clinical course of what are often referred to as the diseases of western civilization – type 2 diabetes, hypertension(HT), and atherosclerotic CVD – received much attention.[17]

Reaven's syndrome X originally consisted of resistance to insulin stimulated glucose uptake, hyperinsulinemia, hyperglycemia, an increased concentration of very-low-density lipoprotein triglycerides, a decreased concentration of high-density lipoprotein cholesterol (HDL-C), and high BP.[17]

Reaven did not offer specific criteria for having syndrome X, and he did not include obesity or visceral obesity as a criterion. Later, others, including leading

organizations and associations working in primary and secondary prevention of CVD, added measures of visceral obesity and offered specific criteria to define this syndrome.[18]

The causes of the METS remain obscure. Reaven proposed that IR was the most important abnormality, while Lemieux proposed that visceral obesity and hyperglyceridemic waist was important.[17,19,20]

Despite the ongoing arguments among various groups, the ultimate importance of this condition is that it helps to identify individuals at high risk of CVD.[19]

Table.1 Various terminologies used to describe the METS[21]
Athero-thrombogenic syndrome
Beer-belly syndrome
Cardiovascular syndrome
Chronic cardiovascular risk factor clustering syndrome
Deadly quartet
DysMETS
IR syndrome
Metabolic cardiovascular syndrome
METS
Multiple syndrome
Multiple METS
PluriMETS
Reaven's syndrome
Syndrome X
New world syndrome

DEFINITION AND CONSTITUENTS OF METABOLIC SYNDROME

The contemporary definition of METS "refers to a cluster of metabolic abnormalities related to a state of IR which is often associated with a high-risk overweight/obesity phenotype. The major characteristics of METS include IR, abdominal obesity, elevated BP, and lipid abnormalities [i.e., elevated levels of triglycerides (TGs) and low levels of HDL-C]. METS is associated with a proinflammatory / prothrombotic state that may include elevated levels of C-reactive protein(CRP), endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, increased levels of plasminogen activator inhibitor 1, elevated uric acid levels, microalbuminuria, and a shift toward small, dense particles of low-density lipoprotein (LDL-C) cholesterol"[8].

Several groups have attempted to develop diagnostic criteria for diagnosis of METS.

The World Health Organisation[23](WHO) proposal was designed as a first attempt to define the syndrome in 1999 includes Diabetes or impaired fasting glycemia or impaired glucose tolerance or IR (under hyperinsulinemic and euglycemic conditions, glucose uptake in lowest 25%) plus two or more of the following:

1. Obesity: body mass index >30 kg/m^2 or waist: hip ratio >0.9 (male) or >0.85 (female).
2. Dyslipidemia: TGs ≥ 1.7 mmol/L or HDL-C <0.9 (male) or <1.0 (female) mmol/L.
3. Hypertension: BP ≥ 140/90 mmHg.
4. Microalbuminuria: albumin excretion ≥ 20 µg/min.

The European group for the study (EGIR)[24] of IR also defined the METS in 1999 includes – IR (defined as hyperinsulinemia, top 25% of fasting insulin values among the non-diabetic population) plus two or more of the following:

1. Central obesity: waist circumference ≥ 94 cm (male) or ≥ 80 cm (female).
2. Dyslipidemia: TGs >2.0 mmol/L or HDL-C <1.0 mmol/L.
3. Hypertension: BP ≥140/90 mmHg and/or medication.
4. Fasting plasma glucose >6.1 mmol/L.

The National cholesterol Education Program(NCEP) Expert Panel on detection, evaluation and treatment of high blood cholesterol in adults – otherwise known as the Adult Treatment Panel III (ATP III) definition of METS presented in 2001[21] includes –

Three or more of the following :

1. Central obesity : waist circumference > 102 cm(male) or > 88 cm (female).
2. Hypertriglyceridemia : TGs ≥ 1.7 mmol/L
3. HDL cholesterol : <1.0 mmol/L (male) or <1.3 mmol/L (female)
4. Hypertension: BP ≥130 /85 mmHg or medication.
5. Fasting plasma glucose ≥ 6.1 mmol/L.

In retrospect, it is apparent that the WHO definition more suited as a research tool whereas the NCEP: ATP III definition was more useful for clinical practice[22].

The criteria for defining METS in adult Asian Indians needs revision. Inclusion of modified cutoffs of waist circumference (>90 cm for men, > 80 cm women) and BMI (>23 kg/m^2) and in the NCEP ATP III definition requires further validation.[26]

Yet another attempt at definition came from the American Association of Endocrinology and American Association of clinical endocrinologist.[27]

There were problems associated with all these definitions in terms of applicability, uniformity and positive predictive value. A major problem was applicability to different ethnic groups, especially among East Asians and South Asians.[22]

The International Diabetes Federation (IDF)[28] has recently revised the guidelines to remedy the ethnic group based disparities in the original classification.

According to the new IDF, for a person to be defined as having the METS, they must have: Central obesity (defined as waist circumference ≥ 94 cm for European men and ≥ 80 cm for European women, with ethnicity specific values for other groups).

In addition, any 2 of the following 4 factors :

- Raised TGs level: ≥150 mg/dl (1.7 mmol/L), or specific treatment for this lipid abnormality.

- Reduced HDL – cholesterol: <40 mg/dl (1.03 mmol/L) in men and <50 mg/dl (1.29 mmol/L) in women, or specific treatment for these lipid abnormalities.

- Raised Blood pressure: systolic BP ≥130 or diastolic BP ≥85 mmHg, or treatment of previously diagnosed HT.

- Raised fasting plasma glucose: fasting plasma glucose ≥100 mg/dl (5.6 mmol/L), or previously diagnosed type 2 diabetes.

If above 5.6 mmol/L or 100mg/dl, an OGTT is strongly recommended, but is not necessary to define the presence of the syndrome.

There is a need for standardized definition of METS. Furthermore, a definition tailored for children and adolescents is essential.

Prospective long-term studies are needed to validate the prognostic power of these definitions. As new information becomes available, the definition of METS might be further modified.[29]

METS is estimated to affect more than one in five adults, and its prevalence is growing in the adults and pediatric population.[64]

PREVALENCE OF METS:

Comparisons of published prevalence of different population are difficult despite attempts to reach agreement on the definition of the METS[13].

Despite differences in the design of these studies and other variables, certain inferences can be made. For example, even for studies involving participants in the same age groups, there is wide variation in the prevalence in both sexes. In those studies that include people 20-25 years and older, the prevalence varies in urban

population from 8% (India) to 24% (USA) in men, and from 7% (France) to 43% (Iran) in women. There is also an ethnic difference in the prevalence of METS[30].

A very consistent finding is that the prevalence of METS is highly age – dependent, in USA (National health and Nutrition examination surgery [NHANES III]) prevalence of METS increased from 7% in participants aged 20-29 years to 44% and 42% for those aged 60-69 years and at least 70 years respectively.[30]

Data from 12-19 years age group is the NHANES III study, with NCEP: ATP III criteria modified for adolescents, reported that the prevalence of the METS in adolescents was 4.2%.[36]

Of particular interest are the two Indian studies, which differed in their definition of obesity; one study used obesity criteria that were suitable for Indians, while the others used the standard ATP III definition of obesity. Both studies used population-based samples writing the same age range but reported prevalence of 13% in Jaipur and 41% in Chennai.[32,33]

Interestingly, a third Indian study[10] also from Chennai, reported a METS prevalence of 11.2% (using EGIR criteria), which was much closer to the prevalence reported for Jaipur than the other Chennai study. Therefore, even within the same ethnic population group it appears that there can be significant differences in the prevalence of both the individual factors that constitute the METS and the METS itself.[13]

The prevalence of METS was found to be elevated in women who abstained from alcohol. Slight and moderate alcohol consumption has been found to be

associated with low coronary heart disease risk possibly through beneficial alterations in HDL cholesterol and BP.[35]

High prevalence of obesity and IR in urban Indian population is well known. A study from Chennai report 18.7% prevalence of IRS in upper socio-economic strata in south India, while it was 6.5% in the low socio-economic strata.[36]

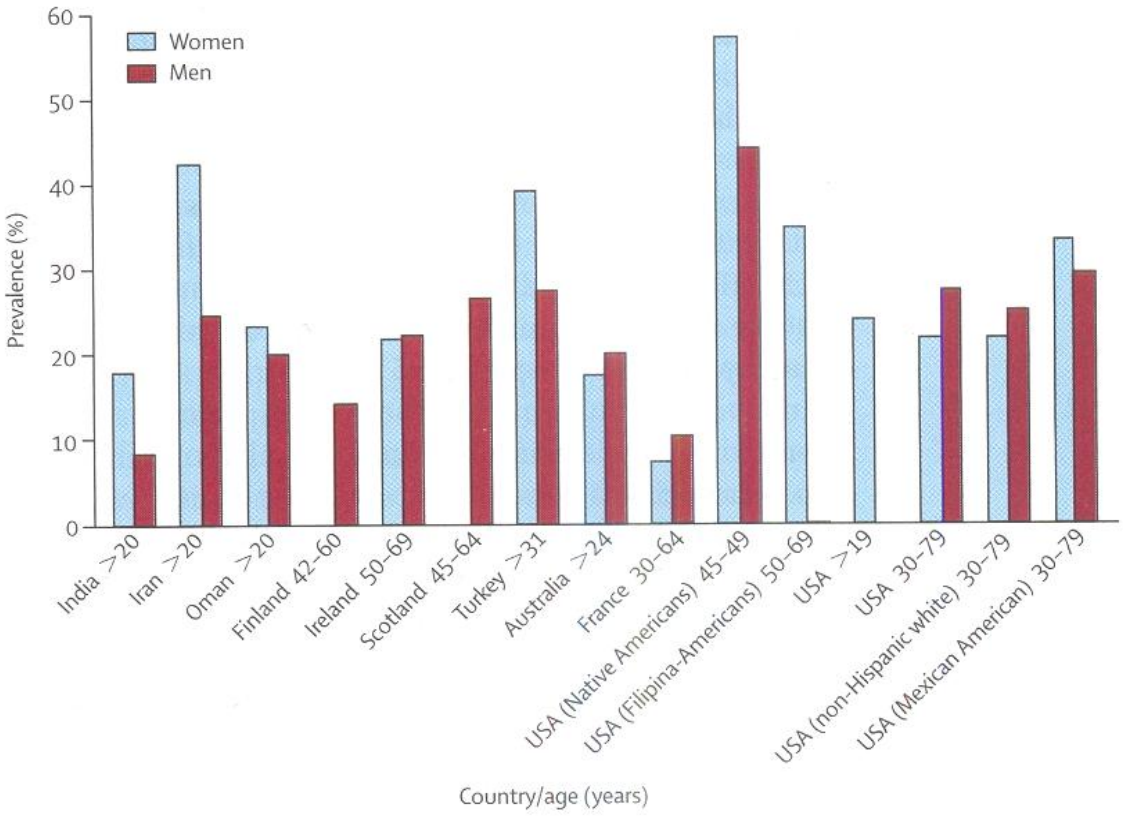


Fig.1: prevalence of the metabolic syndrome from ATP III definition.[13]

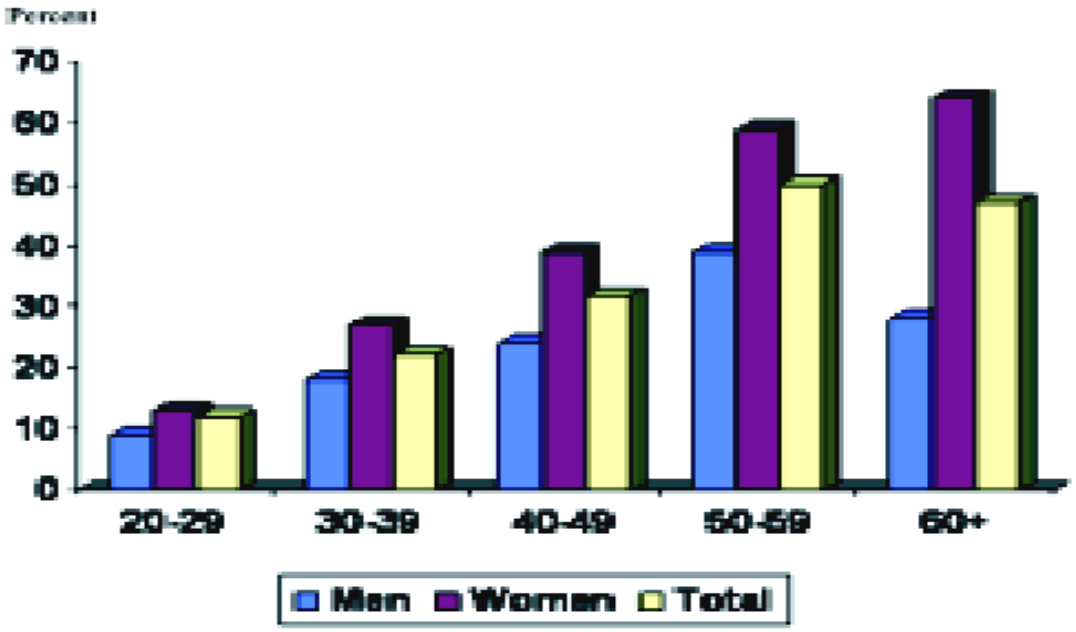


Fig.2: Age-specific prevalence rates of metabolic syndrome (Jaipur Heart Watch-2)[39]

Higher prevalence of METS in women as compared with men is seen in urban south Indian population.[32]

Approximately 20-25 percent of urban souths Asians have evidence of the METS. Furthermore, IR was reported, to be present in nearly 30 percent of children and adolescents in India, more so in girls.[37]

According to a recent study on south Indians, the prevalence of the METS (%) was estimated to be 23.2, 18.3 and 25.8 according to WHO, ATP III and IDF definitions respectively.[38]

High prevalence of cardiovascular risk factors and the METS (~12%) have been shown by our group in intra-country rural-to-urban migrant population belonging to low socio-economic stratum residing in urban shins. Further, certain

communities in India (eg. Punjabi, Bhatia community) have inordinately high tendency to develop obesity, type 2 diabetes mellitus, and METS.[37]

The METS was present in 31.6% of Indian urban population, prevalence was 22.9% in men and 39.9% in women, the age-adjusted prevalence was 24.9%, 18.4% in men and 30.9% in women there was a significant age-related increase in its prevalence.[39]

CARDIOMETABOLIC RISK: is defined as a cluster of modifiable risk factors and markers that identify individuals at increased risk for CVD (myocardial infarction, stroke, peripheral artery disease) and Type 2 diabetes mellitus.

- Cardiometabolic risk factors[25] :
- Elevated BP
- Abdominal adiposity
- Low HDL-C
- Elevated TGs
- Elevated blood glucose
- Smoking
- Elevated LDL-C
- Inflammatory markers
- IR

The risk of cardiovascular events conferred by the presence of the METS was greater than the risk associated with any of the individual components, emphasizing the predictive value of this clinical entity in terms of cardiovascular complications.[42]

Renin-angiotensin system is known to be present in human adipose tissue, thereby offering a potential link between obesity and HT, as well as the prothrombotic properties of CVD[43].

In asymptomatic middle-aged adults, METS also is associated with accelerated atherosclerosis.[5]

INTERHEART study found that nine potentially independent risk factors, such as smoking, history of HT and diabetes, alcohol consumption, psychosocial factors, waist/hip ratio, dietary habits, physical activity and apolipoproteins, were all related to myocardial infarction.[44]

Applying the ATP III criteria to 10537 NHANES III participants resulted in a significant association between the METS with prevalent myocardial infarction and stroke.[45]

In patients who had myocardial infarction with in previous 3 months, 30% of patients had METS.[47]

It is not known if the METS has a greater association with women versus men, but the presence of coronary disease in middle-aged women is highly associated with METS.[48]

People with the METS have atleast a 2 fold increase in the risk of CVD events, and a much poorer prognosis following the event. The METS more strongly predicts congestive heart failure and CVD mortality than its individual components.[55]

The presence of METS is a strong marker indicating the likelihood of CAD, while the strongest association of CAD were found with obesity and microalbuminuria. This seems more strongly significant than traditional risk factors like elevated LDL-C, HT, and TGs.[75]

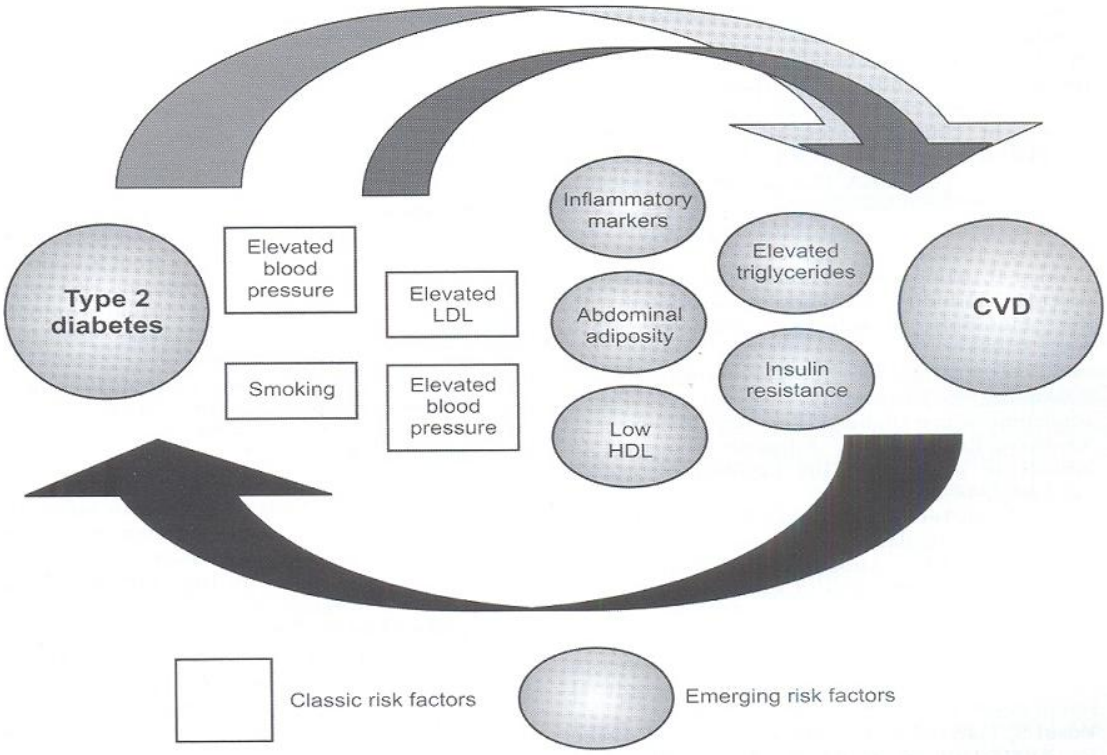


Fig.3: Risk factors Cardiometabolic syndrome[8]

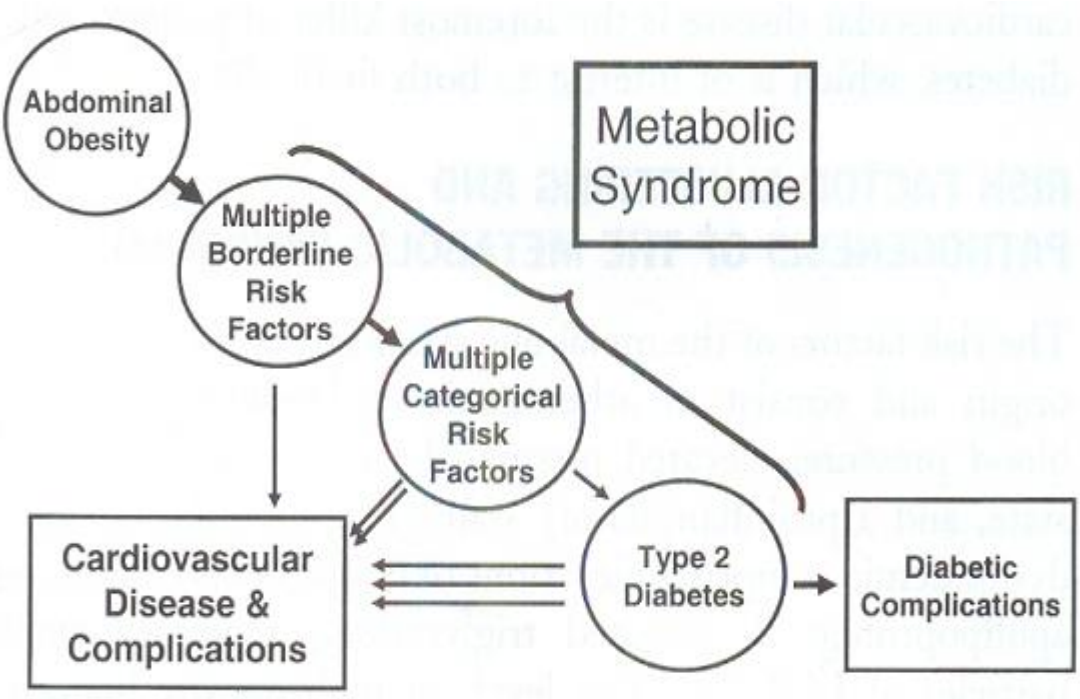


Fig.4: Progression and outcome of metabolic syndrome

MECHANISMS UNDERLYING THE METABOLIC SYNDROME

INSULIN RESISTANCE:

The most accepted and unifying hypothesis to describe the pathophysiology of the METS is IR. IR has traditionally been defined with a glucocentric view i.e., when a defect in insulin action results in fasting hyperinsulinemia to maintain euglycemia. Yet, even before fasting hyperinsulinemia develops, postprandial hyperinsulinemia exists.[22]

Lilloja has showed that IR is a familial trait in nondiabetic pima Indians and has trimodal distribution suggesting an autosomal codominant mode of inheritance.[49]

A major contributor to the development of IR is an overabundance of circulating fatty acids. Plasma albumin born free fatty acids are derived mainly from adipose tissue TGs stores released through the action of the cyclic AMP – dependent enzyme hormone sensitive lipase and also derived through the lipolysis of TGs – rich lipoproteins in tissues by the action of lipoprotein lipase.[50]

Upon reaching insulin sensitive tissues, excessive fatty acids create IR by the added substrate availability and by modifying downstream signaling.

Thus, when IR develops, the increased amount of lipolysis of stored triacylglycerol molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis.[22]

The gold standard for investigation of IR is hyperinsulinemic euglycemic insulin clamp technique; its application in an epidemiological or clinical setting is impractical,

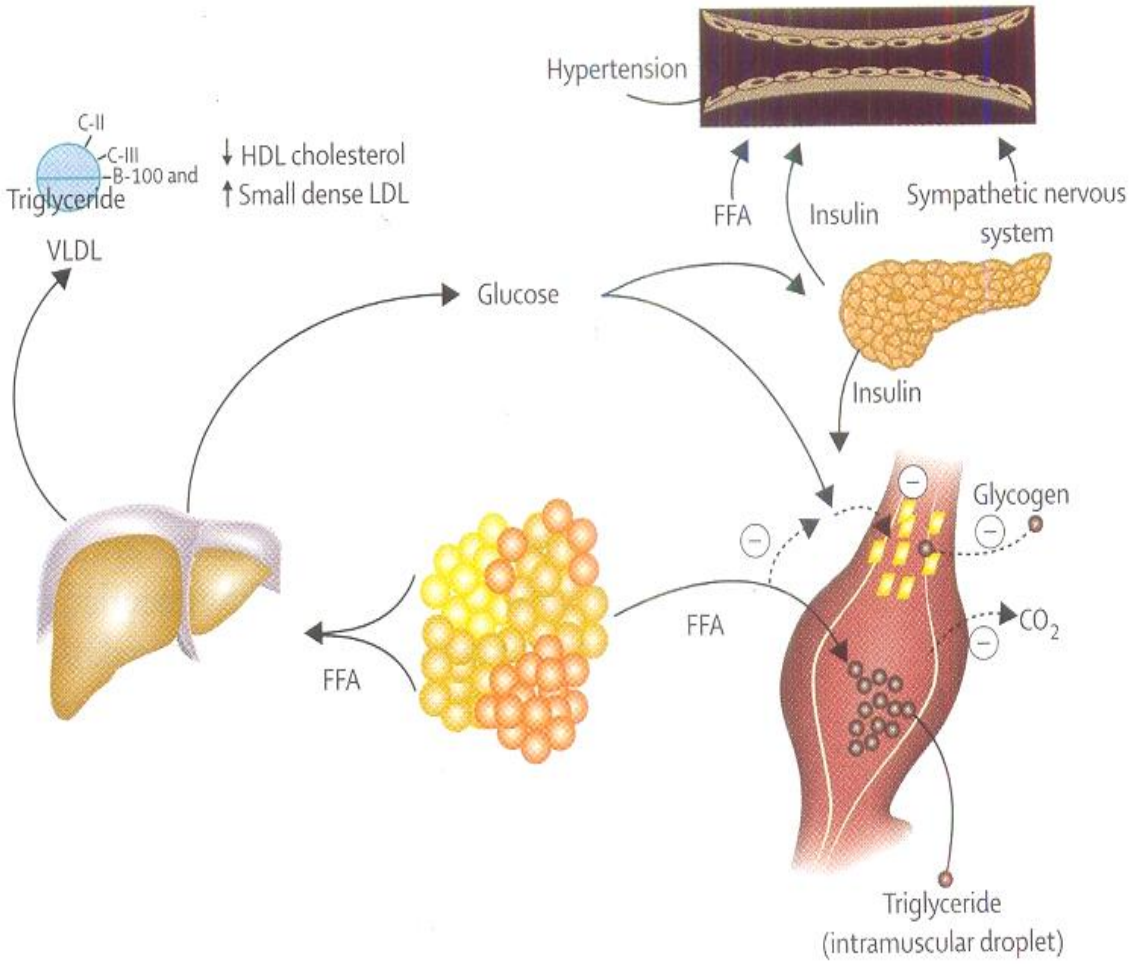


Fig. 5: Pathophysiology of metabolic syndrome (IR)[22]

Free fatty acids (FFA) are released in abundance from an expanded adipose tissue mass. In the liver, FFA produces an increased production of glucose, TGs and secretion of VLDL. Associated lipid/lipoprotein abnormalities include reductions in HDL-C and increased density of LDL. FFA also reduces insulin sensitivity in muscle by inhibiting insulin mediated glucose uptake. Associated defects include a reduction in glucose partitioning to glycogen and increased lipid accumulation in TGs. Increases in circulating glucose and to some extent FFA increased pancreatic insulin secretion resulting in hyperinsulinemia. Hyperinsulinemia may result in enhanced sodium reabsorption and increased sympathetic nervous system activity and contribute to the hypertension as might increase levels of circulating FFA.

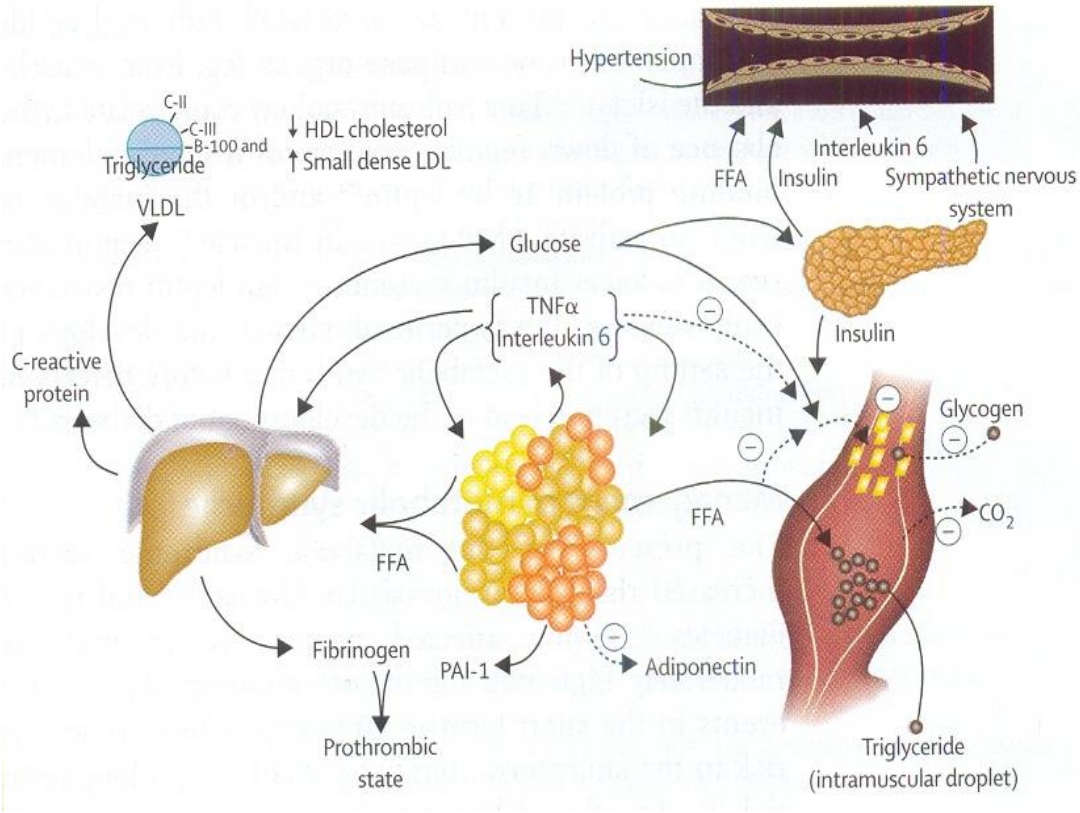


Fig. 5: Pathophysiology of metabolic syndrome (IR)[22]

Superimposed and contributory to the insulin resistance produced by excess FFA is the paracrine and endocrine effect of the proinflammatory state, produced by a variety of cells in adipose tissue including adipocytes and monocyte-derived macrophages, the enhanced secretion of IL-6 and TNF-α among others results in more IR and lipolysis of adipose tissue TG stores to circulating FFA. IL-6 and other cytokines also are increased in the circulation and may enhance hepatic glucose production, the production of VLDL by the liver and IR in muscle. Cytokines and FFA also increase the production of fibrinogen and plasminogen activator inhibitor-1 (PAI-1) by the liver that complements the overproduction of PAI-1 by adipose tissue. This results in a prothrombotic state. Reductions in the production of the anti-inflammatory and insulin sensitizing cytokine adiponectin are also associated with the METS and may contribute to the pathophysiology of the syndrome.

Although the homeostasis model assessment (HOMA) model could be used as an alternative method.[52,53]

Table.2 Clinical syndromes associated with insulin resistance
Type 2 diabetes
Cardiovascular disease
Essential hypertension
Polycystic ovary syndrome
Nonalcoholic fatty liver disease
Certain forms of cancer
Sleep apnea

It has been recognized that IR / hyperinsulinemia and the underlying consequent related to defects in insulin metabolism are associated with the presence of cardiovascular risk factors such as Hypertriglyceridemia, low HDL – cholesterol, HT, abdominal obesity, impaired fibrinolytic system capacity even in the absence of diabetes.[8]

Table. 3 Associations of insulin resistance with other risk factors in South Asians[37]

Factors with evidence of positive association	Factors with weak/no evidence of association	Poorly investigated factors
1. Excess body fat	1. C-reactive protein	1. Non-alcoholic fatty liver disease
2. Abdominal obesity	2. Intramyocellular triglycerides	2. Endothelial dysfunction
3. High truncal subcutaneous fat	3. Leptin	
4. Low birth weight		
5. High levels of procoagulant factors		

Earlier studies both on migrant Indians and on native Indians have shown high prevalence rates of the components of IRS namely hyperinsulinemia, IR and diabetes.[10]

In fact, the components of IRS particularly hyperinsulinemia have been shown to have a contributing role for coronary events in Asian Indians.[11]

There are several unique features of the METS in women. An IR state associated with both polycystic ovarian syndrome and increased abdominal fat may contribute to the development of the METS and increase cardiovascular risk when present. Menopause heralds a decline in circulating estrogen levels, which may increase cardiovascular risk through effects on adiposity, lipid metabolism, and prothrombotic state.[54]

A recent study in India has shown the importance of IR as a risk factor for carotid artery intima/media thickness, an indirect marker of atherosclerosis.[57]

The Ala 54 Thr polymorphism in the fatty acid binding protein-2(FABP2) gene as well as T-455C and C-482T polymorphisms in apolipoprotein C-III (APOC3) gene promoter polymorphisms were associated with the METS in south Asians.[65]

OBESITY AND INCREASED WAIST CIRCUMFERENCE:

For several definitions of the METS waist circumference is included.[23-25]

Mechanistically, a distinction between a large waist due to increase in subcutaneous adipose tissue versus visceral fat is debated. This distinction can be made with computed tomography or magnetic resonance imaging.[58]

With increases in intra-abdominal or visceral adipose tissue, a higher rate of flux of adipose tissue derived free fatty acids to liver through the splanchnic circulation would be expected, whereas increases in abdominal subcutaneous fat would release lipolysis products into the systemic circulation and avoid more direct effects on hepatic metabolism.[59]

Abdominal obesity is considered to be more highly associated with metabolic risk factors than overall (subcutaneous) obesity.[60]

The visceral fat is recognized as a source of inflammatory cytokines such as Tumour necrosis factor-alpha (TNF-α) and Interleukin-6 (IL-6) that have been associated with both IR and increased risk of cardiovascular events.[8]

The relative predominance of visceral rather than subcutaneous adipose tissue with increasing waist circumference in Asians and Asian Indians renders the relative prevalence of the syndrome higher than in African – American men in whom subcutaneous fat predominates.[22]

However, there is evidence that the elevated postprandial free fatty acid release in upper body obese women originates from the non-splanchnic upper body fat, and not from the visceral depot. These results suggest that visceral fat might be a marker for, but not the source of, excess postprandial free fatty acids in obesity.[22]

Obesity is necessary but not sufficient to produce the METS. There must be other factors, including genetic and aging factors.[61]

In the setting of partial or complete lipoatrophy, IR and the METS typically co-exist. Evidence from these less common disorders does support a genetic basis of the syndrome including single gene defects in peroxisome – proliferator activated

receptor –T, lamin A/c, 1-acylglycerol-3-phosphate, 0-acyltransferase, seipin, the β-2 adrenergic receptor, and adiponectin.[22]

It appears that excess truncal subcutaneous adipose tissue is an important determinant of IR in Asian Indians.[26]

Introduction of waist circumference rather than the body mass index has been the major conceptual leap, recognizing the greater role of abdominal rather than overall obesity as the most prevalent cause of the METS in our phenotypical, sedentary population.[56]

Because of the tropical climate, the calorie requirement for maintaining body temperature is comparatively less among Indians, which enhances the visceral obesity. In addition, parents in India stuff their children with adult portions of the food items, which terms out to be counter productive leading to more beta cell loss.[71]

Probably obesity is the link between METS and IR. The best reason to consider diagnosis of METS is to identify obese people who are most likely to be benefited from aggressive efforts.[76]

Body composition of south Asians is conducive to development of the METS; south Asians have high percentage of body fat, abdominal obesity, IR, hyperinsulinemia and low muscle mass. In particular, abdominal obesity is common in south Asians, and evident even in non-obese people.[37]

The emerging typical Asian Indian urban/migrant has phenotype of higher percentage of body at a lower value of BMI, waist hip ratio at a relatively low waist circumference and less lean body mass as compared to ethnic groups[64] .

The incidence of abdominal obesity and IR is common in Indians but it is not clear why they should occur frequently in them.[66]

DYSLIPIDAEMIA:

In the setting of IR, increased flux of free fatty acids to the liver increasing the hepatic TGs synthesis; however, under physiological conditions, insulin inhibits rather than increases the secretion of VLDL into the systemic circulation.[62]

Additionally, IR could also reduce the concentrations of lipoprotein lipase in peripheral tissues (i.e., in adipose tissue more than muscle). This alteration in lipoprotein lipase, however seems to contribute less to the hypertriglyceridemia than does the overproduction of VLDL. Nevertheless, hypertriglyceridemia is an excellent reflection of the insulin resistant condition and is one of the important criteria for diagnosis of the METS.[22]

The other major lipoprotein disturbance in the METS is a reduction in HDL cholesterol. In the presence hypertriglyceridemia, a decrease in the cholesterol content of HDL results from decreases in the cholesteryl ester content of the lipoprotein core with variable increases in TGs making the particle small and dense, a function in part of cholesteryl ester transfer protein.[63]

This change in lipoprotein composition also results in an increased clearance of HDL from the circulation.

In addition to HDL, the composition of LDL is also modified in a similar way. These small dense LDL might be more atherogenic than buoyant LDL.[22]

GLUCOSE INTOLERANCE:

The relation between impaired fasting glucose or impaired glucose tolerance and IR is well supported by human, non-human primate, and rodent studies. To compensate for defects is in insulin action, insulin secretion and/or clearance must be modified to sustain euglycemia. If this compensation fails, defects in insulin secretion predominate.

IR in pancreatic islet B-cells implies that signals that generate glucose – dependent insulin secretion have been adversely modified, and fatty acids are prime candidates. Although free fatty acids can stimulate insulin secretion, increasing and prolonged exposure to excessive concentration results in falls in insulin secretion. The mechanism for this alteration has been attributed to lipotoxicity through several potential different mechanisms.[22,67]

METS is a major stress to beta cells of the islets of pancreas, which tries to cope up with the metabolic challenge by hypertrophy, hyperplasia or apoptosis.[72]

Insulin also can feedback on its own secretion. When the insulin receptor is deleted in skeletal muscle, hyperglycemia does not result; however, Beta-cell specific knockout of the insulin receptor produces progressive glucose intolerance and diabetes. In people with genetic predispositions to development of diabetes, the presumed stress of the insulin resistant environment on beta-cell function causes glucose and ultimately higher risk of diabetes.[22]

HYPERTENSION:

The relation between IR and HT is well established, and relates to several different mechanisms.[22]

In the setting of IR, the vasodilatory effect of insulin can be lost, but the renal effect on sodium reabsorption preserved. Fatty acids themselves can mediate relative vasoconstriction. Insulin also increases the activity of the sympathetic nervous system, an effect that might also be preserved in the setting of IR. However, when assessed by concentrations of fasting insulin, HOMA or HOMA IR index, IR contributes only modestly to the increased prevalence of HT in the METS. The IR in patients with HT is due to low adiponectin levels.[66,68-70]

In hypertensive subjects, the METS amplifies cardiovascular risk associated with high BP, independent of the effect of several traditional cardiovascular risk factors.[79]

These have been two enduring hypothesis, the first considers that sympathetic system under activity is present in obesity and through consequential failed stimulation of thermogenesis provides a metabolic basis for the obesity and second consider that in obesity, sympathetic nervous system over-activation occurs with chronic overeating where it facilitates energy balance and weight stabilization, but at the cost of adverse consequences attributable to chronic sympathetic stimulation, in particular, elevation in BP.[80]

OTHER MANIFESTATIONS:

IR is accompanied by many other alterations that are not included in the diagnostic criteria for the METS.

PROINFLAMMATORY CYTOKINES:

The increases in proinflammatory cytokines including IL-6, resistin, TNF-α and CRP reflect overproduction by the expanded adipose tissue mass.[22]

There is increasing evidence that IR in the liver, muscle and adipose tissue is not only associated with the abundance of proinflammatory cytokines (and relative deficiency of the anti-inflammatory cytokine adiponectin), but is a direct result of this burden. It remains unclear, however, how much of the IR related to the adipose tissue content of macrophages is paracrine versus endocrine.[22]

The concentrations of CRP were higher in healthy Indian Asians than in European white people and were related to greater central obesity and IR in Indian Asians.[22]

It was observed that higher adiposity indicates higher CRP levels in children and adults. A strong relation between elevated CRP levels and cardiovascular risk factors, fibrinogen, and HDL cholesterol has been noted, suggesting a role for inflammation throughout life in the development of atherosclerosis and cardiovascular disease.

The CRP levels greater than 3.0 mg/L was significantly associated with increased incidence of myocardial infarction, stroke, coronary revascularization or cardiovascular deaths. This prospective data suggest that measurement of CRP adds clinically important prognostic information to the METS.

The measurement of CRP, TNF-α, IL-6, IL-4, IL-10, endothelial nitric oxide and adiponectin could be used as markers to predict, prevent and prognosticate the development of METS.[66]

Table.4 changes associated with insulin resistance	
Life style	Cigarette smoking Sedentary behavior
Lipoproteins	Increased Apo B Decreased apoA-1 Small dense LDL and HDL Increased apo C–III
Prothrombotic	Increased fibrinogen Increased PAI-1 Increased viscosity
Inflammatory markers	Increased White Blood Cell Count Increased Il-6 Increased TNF-α Increased Resistin Increased CRP Decreased Adiponectin
Vascular	Microalbuminuria Increased Asymmetric dimethylarginine
Others	Increased Uric acid Increased Homocysteine Non-alcoholic steatohepatitis Polycystic ovarian syndrome Obstructive sleep apnoea

Table.5 The metabolic syndrome: evidence for a pro-inflammatory state
Increased Highly sensitive-CRP levels
Increased Adiponectin
Increased Pro-inflammatory cytokines (IL-6 and TNF-alpha)
Increased Serum amyloid A
Increased Leptin
Increased IL-10 levels

Higher CRP levels are associated with an increased risk of METS, and this association was independent of lifestyle factors, education level, family history of chronic disease and BMI.[81]

LOW GRADE SYSTEMIC INFLAMMATION IN INDIANS[66]:

Indians as a race may have a higher risk to develop various features and METS, what are these genetic factor(s) has never been elucidated, one suggestion that has been made is the thrifty gene hypothesis.[74] It was postulated the existence of metabolically thrifty genes that permit efficient utilization of food leading to fat deposition and weight gain at times of food abundance making the gene-bearer better able to survive during times of famine. Examples of thrifty genes include insulin and leptin.

In addition to genetic component, type 2 diabetes mellitus and METS also involves environment and lifestyle risk factors in the form of high caloric intake and low exercise.[66]

Increased expression of perilipins in the mesenteric/omental adipose cells leads to IR and increased production of pro-inflammatory eicosanoids due to the activation of phospholipase A2. This ushers in low-grade systemic inflammation seen in METS.[78]

Indians are genetically programmed to have increased expression of perilipins and 11β-hydroxysteroid dehydrogenase type-1(11β-HSD-1) (especially in the mesenteric /omental adipose cells) that predisposes them to develop abdominal obesity and METS. This genetic predisposition coupled with lack of adequate exercise and consumption of energy rich diets renders then highly susceptible to develop all the features of METS. This explains how the interaction between genetic predisposition in the form of constitutionally increased expression of perilipins and 11β-HSD-1 interact with environmental factors (in the form of lack of exercise and consumption of energy rich diets) could lead to an explosion in the incidence of METS as is seen in the Indian subcontinent at present.[78]

PERINATAL ORIGIN OF METS IN INDIANS[66]:

Low birth weight has been associated with high prevalence of METS in later life. Indian babies are small[114], with low birth weights. METS was 10 times greater in those who were 2.95 kg or less at birth compared with those whose birth weight was more than 4.31 kg. This suggests that early nutrition has a bearing on the development of METS in later life.

It is possible that factor(s) that influence fetal growth and development; modulate TNF-α, IL-6, IL-4, and IL-10 production; actions of insulin, and IGFs; and suppress 11β-HSD-1 activity might have role in the pathobiology of METS. Long chain polyunsaturated fatty acids (LCPUFA): eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), and arachidonic acid (AA) are endogenous molecules/factors that have an important role in the pathophysiology of METS in Indians.

It is suggested that METS occurs in Indians due to perinatal deficiency of EPA, DHA and AA.

EPA, DHA, and AA supplementation after the onset of METS is not highly beneficial, and suggests that supplementation of LCPUFAs to pregnant women, infants, children, and adolescent is necessary to prevent METS in later life.

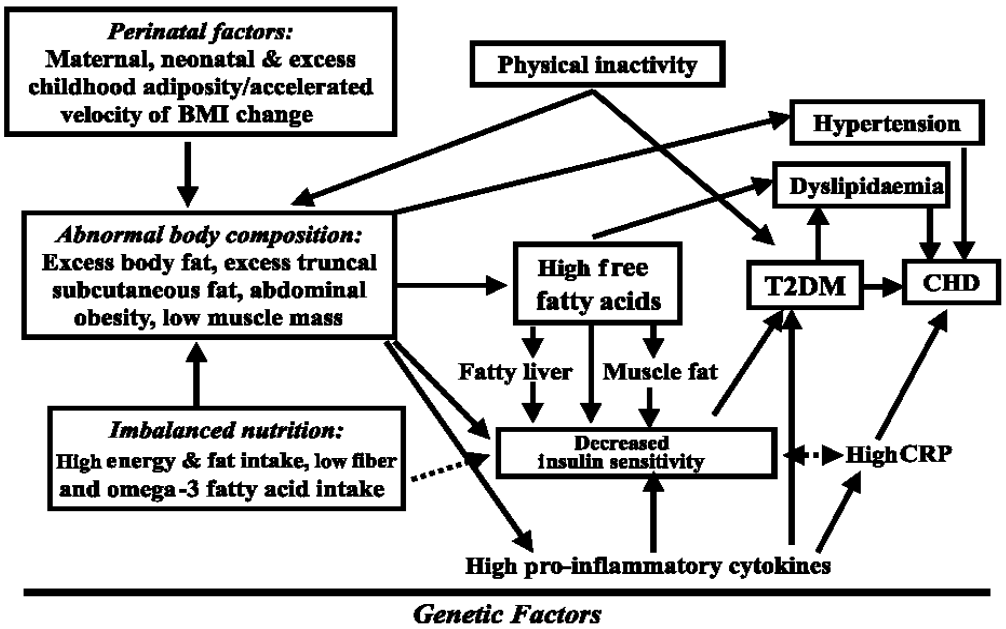


Fig. 6 : Complex interactions of genetic, perinatal, nutritional and other acquired factors in development of insulin resistance, type 2 diabetes and coronary heart disease in South Asians. T2DM, type 2 diabetes mellitus; CRP, C-reactive protein; CHD, coronary heart disease; dotted lines represent weak relationship.[37]

ADIPONECTIN (ACRP 30)[22]

Adiponectin is an anti-inflammatory cytokine that is produced exclusively by adipocytes. Adiponectin both enhances insulin sensitivity and inhibits many steps in the inflammatory process. In the liver, it inhibits both the expression of hepatic gluconeoogenetic enzymes and the rate of endogenous glucose production. In muscle, it increases glucose transport and enhances fatty acid oxidation, effects that are partly due to the activation of Adenosine Mono Phosphokinase. (AMP-kinase)

Some reports link low concentration of adiponectin to myocardial infarction and to the progression of subclinical coronary heart disease.

An alternative concept suggested by Unger to explain the METS is Leptin resistance. In general, conditions in which leptin deficiency or resistance are present are associated with triglyceride accumulation in non-adipose organs (liver, muscle and the islets). This pathophysiology could relate to the absence of down regulation of sternal response element binding protein 1c by leptin and/or the inability of leptin to activate AMP-kinase in muscle. Leptin also seems to lower insulin resection, but leptin resistance could relate to the hyperinsulinemia that develops in the setting of the METS before defects in insulin resection lead to the development of diabetes.[77]

Plasma adiponectin levels are decreased in obese and type 2 diabetic subjects. An inverse association has been described between plasma adiponectin level and IR.[73]

MANAGEMENT OF METABOLIC SYNDROME

The therapeutic goals for and clinical recommendations for management of METS have been defined (Table-6).[19]

LIFE STYLE MODIFICATION:

Non-pharmacologic lifestyle management is important for obesity control. Many studies demonstrate that obese subjects can lose up to 0.5kg/week by restricting calories to less than 500-1000 kcal below daily requirements. Although exercise in addition to

Calorie intake only marginally increases the success of calorie intake program but is associated with many long-term benefits. Use of principles of behavior changes is important. Achievement of target weight loss to decrease BMI to less than 23 (Asians) or 25 (Caucasians) through lifestyle modifications will reduce most of the constituent risk factors as well as the METS. Several studies results support use of multiple lifestyle modifications for individuals with the METS.[19,22]

Weight reduction and diet intervention:

The available current evidence suggests that the first step in management of patients with METS should be focused on weight loss and increased physical activity. A realistic goal for weight reduction should be 7% to 10% over 6 to 12 months. This results in decrease in body weight as well as the IR.[19]

The current dietary recommendations include a balanced low energy diet containing fruits, vegetables, whole grains, fish and lean meats while minimizing fats, salt, simple sugars, and highly processed foods.[83] The general dietary recommendations include low intake of saturated fats, trans fats and cholesterol, and diets with low glycemic index.

Table.6 Therapeutic goals and clinical recommendations for the management of metabolic syndrome[19]

Target	Goal	Recommendations
Abdominal obesity	10% weight loss in first year and continued weight loss thereafter.	Diet control and increased physical activity.
Physical inactivity	Regular moderate physical activity.	30-60 minutes of exercise daily.
Atherogenic diets	Reduced intake to saturated fats, trans fats and cholesterol	Total fats 25-35% of total calories, saturated fats <7% of calories.
Smoking	Complete cessation.	Complete cessation
High LDL cholesterol	LDL cholesterol <100mg/dl in moderate risk patients and <70mg /dl in high-risk patients.	Lifestyle changes and cholesterol lowering drugs to achieve targets.
Low HDL cholesterol	Insufficient data.	Lifestyle changes and HDL-raising drugs (nicotinic acid, CETP inhibitors) to achieve targets.
High blood pressure	Blood pressure <135/<85 mmHg. In diabetes and chronic kidney disease <130/80 mmHg.	Lifestyle therapy and antihypertensive drugs to achieve targets.
Elevated glucose	Reduction and maintenance of fasting glucose <90mg/dl. HBA1C<7.0% for diabetics.	Lifestyle therapy and hypoglycemic drugs if required.
Prothrombotic state	Reduction of prothrombotic state	Low-dose aspirin in all high and moderate risk patients. Consider clopidogrel if aspirin not tolerated.
Proinflammatory state	Reduction of proinflammatory state	No specific therapies. Aspirin and/or statins are being evaluated.

Individuals with the metabolic syndrome need to be categorized according to absolute 10-year risk. Individuals with overt coronary heart disease, stroke or diabetes are in the high risk category and should be treated accordingly. For other individuals the Framingham risk scoring is advised. This assessment triages subjects into high risk (10 year risk >20%), moderately high risk (10 year risk 10-20%), and moderate risk (10 year risk <10%).[84]

Table.7 Therapeutic approaches for metabolic syndrome[19]	
Multi-level lifestyle approaches	Dietary therapy Physical activity enhancement Weight reduction
Obesity-specific therapy	Drugs for weight control Sibutramine Orlistat Cannabinoid receptor blockers Rimonabant Surgical approaches Liposuction Bariatric surgery
Individual risk factor targeted pharmacotherapy	Blood pressure control ACE inhibitors Angiotensin receptor blockers Calcium channel blockers Beta blockers Alpha blockers LDL cholesterol reduction Statins Statin-ezetimibe and others Triglyceride reduction Fibrates Statins Statin-fibrate combinations Omega-3 fatty acids, fish oils HDL cholesterol enhancement Niacin Torcetrapib Insulin sensitizers Metformin Thiazolidinediones Antithrombotic and anti-inflammatory Aspirin, Clopidogrel Statins Hyperglycemia management
Polypharmacy approach	Polypill-like combinations.

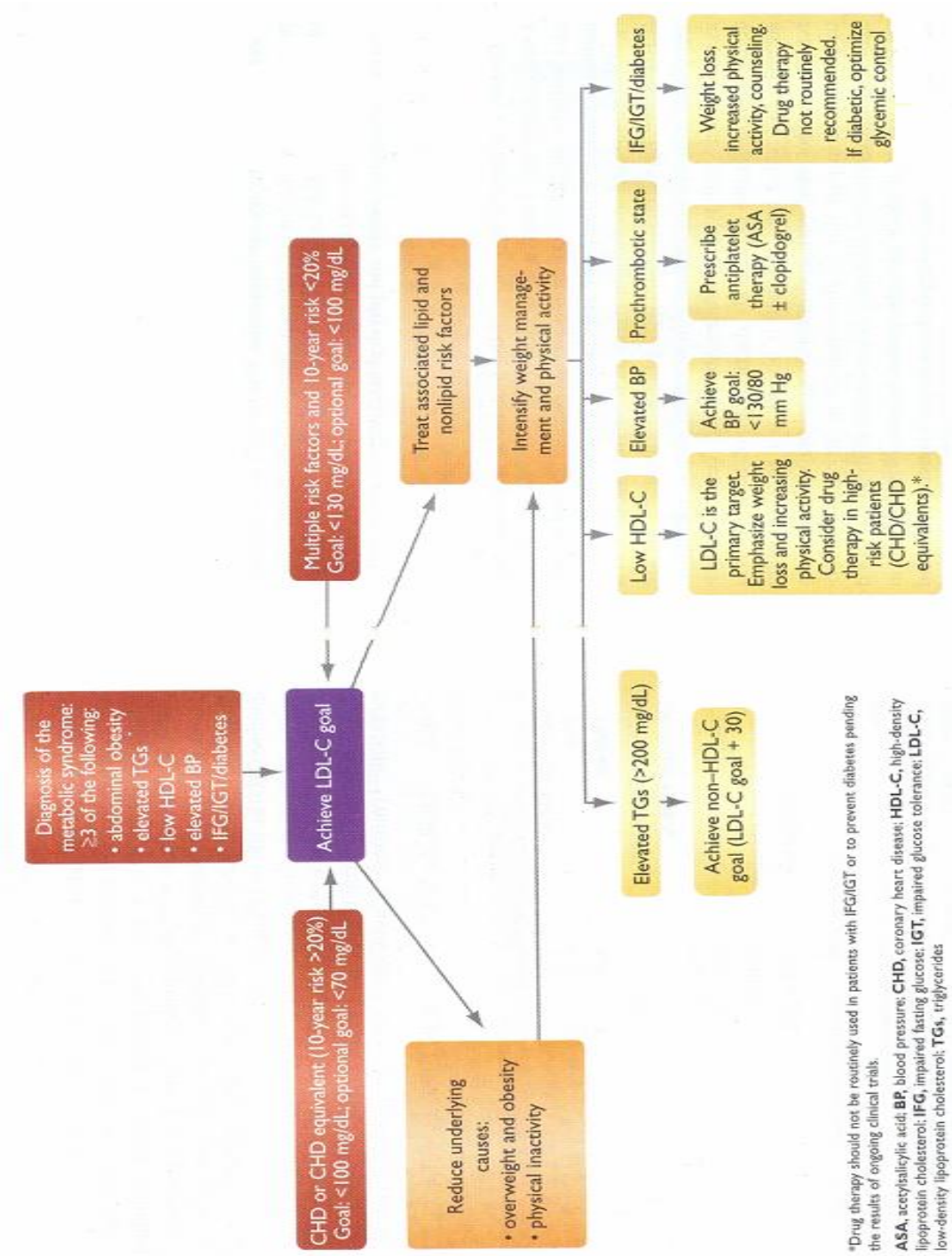


Fig.7: Therapeutic approach to the metabolic syndrome.

To avoid worsening of atherogenic dyslipidemia some investigators favor fat intakes in the range of 30-35% and most prefer fat intakes of 25-30% to avoid weight gain.[84]

Thus, it is clear that weight loss rather than the diet type is more important in ameliorating the risk factors of the METS.[19]

Physical activity:

Physical activity is associated with successful weight reduction and these therapeutic lifestyle changes can reduce by half the progression to new-onset diabetes in patients with METS. It also reduces overall cardiovascular risk. Physical activity recommendation should include practical, regular, and moderated regimens of exercise, with a daily minimum of 30 to 60 minutes. More exercise adds more benefit. Regular exercise also improves endothelial function and vascular health. An equal balance between aerobic exercise and strength training is advised.[19]

Yoga interventions:

Important issues in lifestyle management include behavior modification through counseling and adherence promoting techniques. Use of traditional Indian systems such as yoga and transcendental meditation can be important adjunct to lifestyle changes and promote compliance.

Amelioration of multiple cardiovascular risk factors has been demonstrated in other studies that have evaluated a similar comprehensive lifestyle modification program including yoga.[86]

Thus, it is clear that a comprehensive approach consisting of weight reduction, regular physical exercise and yoga is crucial in control of the IR state that characterizes the METS.[19]

PHARMACOLOGICAL TREATMENT:

Pharmacological therapy is a critical step in the management of patients with METS when lifestyle modifications fail to achieve the therapeutic goals.

OBESITY MANAGEMENT:

Sibutramine and Orlistat

Currently available weight loss drugs possess limited utility in the management of obesity but may be useful in some patients. Krejs reported that sibutramine-induced weight loss and weight maintenance lead to clinically relevant reductions in risk factors associated with the METS.[88] Treatment with the drug decreases visceral fat, improves lipid levels, decreases glycosylated haemoglobin and decreases uric acid concentrations.

It was concluded that orlistat could effectively manage obesity related co-morbidities, especially IR and atherosclerosis risk. However, the major problem with these currently available anti-obesity drugs is a relatively high rate of adverse side effects leading to poor tolerance and compliance for long-term use.[19]

Cannabinoid$_1$ receptor (CB_1) antagonists

Rimonabant belongs to a new class of drugs, which selectively antagonize cannabinoid type 1 receptors (CB_1). This novel class of drugs has been reported to be

useful in reduction in body weight along with a parallel decrease in waist circumference and amelioration of the metabolic profile.[89,90]

It was also observed that in addition to its effects on weight loss rimonabant had significant weight independent effect on lipid parameters. Rimonabant also reduced fasting insulin levels, glucose and CRP.[19,90]

Rimonabant at a dose of 20 mg also resulted in an increase in plasma adiponectin levels. It was concluded that rimonabant significantly reduces body weight and waist circumference and improves the profile of several metabolic risk factors in high-risk patients who are overweight or obese and have an atherogenic dyslipidemia.[91]

The most frequent adverse events resulting in discontinuation of the drug were depression, anxiety, and nausea [19].

Surgical management of obesity:

Liposuction or bariatric surgeries are being used for severe obesity in many developed countries. In a randomized trial of liposuction, it was reported that despite a significant weight loss there was no influence on lipid profile or other parameters of the METS.[19,92]

However, liposuction did not alter the insulin sensitivity of muscle, liver or adipose tissue and did not alter plasma concentrations of CRP, IL-6 or TNF-α and no change was observed in other coronary risk factors such as lipid levels and BP.[93]

Bariatric surgery techniques using laparoscopic adjustable banding of stomach along with Roux-en-Y and other forms of gastric bypass are now favored for severe

and morbid obesity. It results in weight loss of 25-30% and rapid normalization of glucose handling and BP in patients with diabetes and HT.[22,94] Long-term results are however not available and recent reports of substantial mortality and morbidity of this procedure, especially in the elderly have raised important safety issues for this procedure.

Individual risk factor modification:

A recent American Heart Association and National Heart Lung Blood Institute Scientific statement highlights the importance of control of individual risk factors in METS[84] and suggests a multipronged therapeutic approach. Components of the metabolic control that need control are atherogenic dyslipidemia, elevated BP, elevated fasting glucose, prothrombotic factors, and proinflammatory state.

LIPID MANAGEMENT:

The lipid abnormalities in the METS have been described as atherogenic dyslipidemia. The ATP-III guidelines emphasize that LDL reduction is the primary target in lipid management even in the METS (Fig-7) and low HDL and TGs are secondary targets.[25] LDL cholesterol should be lowered to less than 70 mg/dl in all high risk cases with the METS. This recommendation is supported by the recent TNT-Metabolic syndrome study.[96] The efficacy of statins in reducing LDL cholesterol concentrations is well established. Studies show that statins appear to improve the LDL subfraction profile, possibly by reduction of small dense LDL or by reduction in all LDL subclasses with a shift in LDL particle distribution. In moderate risk subjects the target is <100mg/dl while in high-risk subjects it is <70 mg/dl. The target LDL levels in patients with the METS are difficult to achieve by diet or exercise therapy alone and usually need drug therapy, usually a statin. This class of

drugs also reduces all apolipoprotein B containing lipoproteins and also decreases concentration of CRP.[19,93,97]

Combination therapy for dyslipidemias has been suggested for achieving target LDL and other lipid levels. Ezetimibe is a novel cholesterol lowering agent and studies report when combined with any stain in a dose of 10 mg daily was as effective as the stain monotherapy as the highest dose, e.g., ezetimibe plus 10mg atorvastatin was as effective as 80mg atorvastatin alone. This combination was also more effective that statin alone in reducing TGs and apolipoprotein B (ApoB) and in increasing HDL cholesterol. Statins can also be safely combined with a fibrate, especially fenofibrate, and niacin to achieve target levels of non-HDL cholesterol, TGs and HDL cholesterol[25]

Fibrates:

Fibrates mitigate atherogenic dyslipidemia and are useful in dyslipidemia of the METS. In combination with statins, they are particularly effective for reducing LDL cholesterol as well as TGs. However, the combination therapy carries some increased risk for myopathy. The risk of myopathy is very low when fenofibrate is combined with a statin and the ATP-III has recommended this combination.[19,25]

Fibric acid is a synthetic ligand of the nuclear receptor PPAR-α and promotes oxidation of fatty acids to mediate hypolipidemic action.[98] PPAR-α exerts direct antiatherogenic action on the vessel wall and improves endothelial function. Endothelial dysfunction in the METS is characterized by an impaired insulin stimulated nitric oxide production from the endothelium and decreased blood flow to

skeletal muscle. Fibrates, therefore, may have an action beyond the hypolipidemic action to decrease the incidence of coronary artery disease.

Niacin:

Niacin raises HDL cholesterol levels and reduces non- HDL cholesterol. Patients with impaired fasting glucose, impaired glucose tolerance or diabetes who are treated with nicotinic acid deserve careful monitoring for worsening hyperglycemic. Lower doses of niacin decrease this risk. The combination of a statin with a low dose of niacin is a very attractive option in patients with METS. This combination has been reported to lower LDL cholesterol, ApoB, TGs and lipoprotein (a) and increase HDL cholesterol significantly in an Indian multicentric study.[99]

Dermatological adverse effects flushing, pruritus and rash are common. The studies have shown that low dose niacin is useful in the treatment of mixed dyslipidemia as is present in the METS.[19]

Omega-3 fatty acids:

Fish oils (omega-3 fatty acids) have been studied in trials after myocardial infarction and have been shown to reduce cardiovascular events and death. They are activators of PPAR-α system. Fish oils have been used in patients with diabetes and METS who need additional triglyceride lowering. In METS patients, 3 gm of fish oils have been shown to decrease TGs by 20%, decrease in ApoB production, and decrease in postprandial lipemia and marked reduction in small dense LDL. Extremely high doses should be avoided to prevent increase in LDL cholesterol levels.[19,84]

HDL cholesterol modulation

A number of strategies for increasing HDL cholesterol are under evaluation. These include cholesterol ester transfer protein (CETP) inhibitors (Torcetrapib), increasing ApoA1 (ApoAlMilano), inhibitors of acyl coenzyme A- cholesterol acyltransferase (ACAT), and others.[100]

ELEVATED BLOOD PRESSURE

Lifestyle changes are of prime importance to reduce elevated BP with a goal to reduce it as much as possible, ideally <130/85 mm Hg or even <120/80 mm Hg. Lifestyle therapies include weight control, increased physical activity decreased intake of alcohol, sodium restriction and increased consumption of fresh fruits and vegetables as in the dietary approaches to stop HT (DASH) diet.[101] If HT cannot be adequately controlled by, lifestyle therapies, antihypertensive drug therapies are usually necessary to prevent long term adverse effects.

It is theorized that drugs inhibiting the sympathetic nervous system could be useful but the evidence of efficacy of central imidazoline -receptor binding agents and peripheral beta-adrenergic blocking agents are not convincing. A diabetogenic effect has been unequivocally demonstrated for both thiazide diuretics and beta-blockers and at present, these drugs may not be suitable first line therapy in subjects with METS.[19]

ACE inhibitors

An increasing number of experts support ACE' inhibitors as first line therapy in the METS, especially when type 2 diabetes or renal disease is present. Inhibition of renin-angiotensin system with this class of drugs may lower the risk of diabetes itself as reported in large randomized clinical studies of ACE inhibitors and angiotensin

receptor blockers (ARBs). ACE inhibitors reduced the incidence of diabetes by 14-34% and ARBs reduced the incidence of diabetes by 19-25%. The mechanisms of action of ACE inhibitors or ARBs are not clear and a possible mechanism is improvement in insulin sensitivity and glucose tolerance. Angiotensin II interferes with post receptor ` insulin signaling and blocking of this action enhance insulin sensitivity. This group of drugs also reduces inflammation. In addition, these drugs reduce oxidative stress and improve endothelial function, which would enhance glucose utilization by skeletal muscle due to increased delivery secondary to improved flow.

ARBs may be used when ACE inhibitors are not tolerated and have similar beneficial effects in prevention of diabetes. Clinical considerations such as the presence of coexisting illnesses are important in drugs that blocks rennin-angiotensin system should be one of the initial therapeutic choice.[19]

INSULIN RESISTANCE, FASTING HYPERGLYCEMIA, AND IMPAIRED GLUCOSE TOLERANCE:

Decreasing the raised insulin levels by life style changes and pharmacotherapy can revert many of the abnormalities associated with IR.

Life styles changes:

An attractive option in treatment of the METS might be to begin treatment in individuals with impaired fasting glucose or impaired glucose tolerance before overt hyperglycemia develops. Results of recent studies indicate that targeting these individuals with dysglycemia using aggressive lifestyle interventions or

pharmacotherapy can reduce the incidence of diabetes and might reduce the cardiovascular risk. Influence of life style interventions have been discussed earlier.

Metformin:

Metformin was less effective than lifestyle changes in improving cardiovascular risk factors.[102] More studies are required with metformin in the context of METS.

Acarbose:

Acarbose, an inhibitor of α-glucosidase slows the digestion of carbohydrates in the intestine and reduced postprandial glucose levels. There also a reduces the risk of developing cardiovascular events.[19]

PPAR-α and PPAR-γ agonists:

Thiazolidinedione drugs such as troglitazone, rosiglitazone and pioglitazone enhance insulin sensitivity. Troglitazone has also been shown to be effective in prevention of diabetes but have not been demonstrated to reduce cardiovascular risk. Pioglitazone has been shown to reduce multiple components of METS such as high BP, high blood glucose and TGs in addition to a decrease in urinary albumin/creatinine ratio.[103]

Pioglitazone may be useful in prevention of cardiovascular events in high risk patients with type 2 diabetes although the usefulness of this approach in METS or impaired glucose tolerance subjects is not clear.[84]

Preclinical trials with dual PPAR blockade have shown promising results in ameliorating IR and diabetic hyperglycemia. Cardiovascular risk factor improvements

have to be confirmed in clinical trial setting. Combination therapy of PPAR blockade with other strategies is also being evaluated.[19]

Early insulin therapy:

An interesting hypothesis is of prevention of β-cell fatigue in context of IR. The ORIGIN study is testing glargine insulin in patients with impaired glucose tolerance.[19]

PROTHROMBOTIC AND PROINFLAMMATORY STATE:

For primary prevention, the only long-term approach to counter the thrombotic state is low dose aspirin or other anti-platelet agents. Aspirin is widely recommended in patients with established CVD although its role in prevention of events in diabetes is not well established. In METS patients with a high risk of future cardiovascular events, aspirin in a dose of 75-150 mg/day is an attractive therapeutic option to lower vascular events. It is also important to note that rennin-angiotensin system inhibition also reduces PAI-1 levels and inflammatory cytokines and thus potentially reduces risk of increased thrombotic events in patients with METS.[22,87,106]

Finding of CRP levels >3mg/dl supports the need for lifestyle changes. Weight reduction leads to a decrease in CRP levels and also mitigates other inflammatory factors. No drugs that act exclusively via this mechanism are available for reducing cardiovascular risk. However, several drugs used to treat other metabolic risk factors in the METS have been reported to reduce CRP levels. These drugs group are statins, nicotinic acid, fibrates, ACE inhibitors or ARBs and thiazolidinediones but isolated regular use of these drugs to reduce inflammatory markers has not yet been demonstrated to result in improved clinical outcomes.[19]

POLYPHARMACOLOGICAL APPROACH:

Wald and Law have suggested a polypharmacy concept to prevent cardiovascular disease.[106] A combination "polypill" has been suggested that contains three antihypertensives (thiazide, beta-blocker and ACE inhibitor), a statin, aspirin and folic acid in low doses based on current clinical evidence.

This combination highlights the need for multifactorial interventions in prevention of CVD and underscores the clinical importance of the METS. Such a combination approach has yet to be formally evaluated although a retrospective analysis has reported significant benefits.

Economic issues in such a combination therapy in developing countries should be resolved as polypharmacy can lead to a massive burden.[3]

It was concluded that the combination therapy as suggested by Wald and Law may prove to be effective but may also have side effects and poor adherence, which may be greater or lesser than other preventive approaches. It has also been suggested that randomized trials are needed to evaluate this therapy.

Polypill concept is especially suitable for the management of METS[115]. The issues to be addressed include the evidence – based use of such a combination pill in primary or secondary prevention and cost effectiveness and assessment of its impact on cardiovascular healthful behaviors. Such combinations (2, 3 and 4 drug combos) are already available in India and some other developing countries but issues related to long-term safety and benefits needs to be addressed in properly designed multifactorial randomized clinical trails.[19]

MATERIALS AND METHODS

SOURCE OF DATA:

Acute myocardial infarction patients, who were admitted to ICCU of Shri.B.M. Patil Hospital & Research Centre, Bijapur from November 2009 to March 2011, were taken for the study considering inclusion and exclusion criteria.

SAMPLE SIZE

With prevalence of metabolic syndrome 41%[9] (Type 2 diabetes in South Asians) and allowable error at 25% and at 5% risk, worked out sample size is 92.

Using the statistical formula,

(n=4pq/L2)

P=prevalence rate

Q=1-p

L=allowable error

STATISTICAL ANALYSIS

Descriptive statistics like :

Mean$\pm$SD

Bar chart

Inferentional statistics like :

Chi square test ,

Z statistics are used .

METHOD OF COLLECTION OF DATA:

- The study has been carried out on patients who presented with acute myocardial infarction within 24 hrs
- All subjects were interviewed as per the prepared proforma and then complete clinical examination was done.
- Diagnosis of myocardial infarction based on WHO(2000) criteria.
- Estimation of RBS at admission and FBS on day 4 and 5 of admission .
- Echocardiography was performed on day 3 or 4 to calculate left ventricular ejection fraction(LVEF).
- Follow up of patients was done with reference to course in hospital ; till patient gets discharged or till death
- In hospital treatment and outcome data was collected including death , ventricular arrhythmia , stroke , recurrent myocardial infarction and cardiogenic shock.
- Waist circumference was measured on admission , midway between the last rib and iliac crest.

INCLUSION CRITERIA:

1. Patients with acute myocardial infarction diagnosed based on WHO(2000) criteria. Any two of the following criteria

a) Cardiac chest pain

b) ECG changes

c) Elevated Cardiac Enzymes.

2. Patients more than 18 years of age

3. Any three of the following criteria's (NCEP ATP III guidelines)

- Abdominal Obesity (Waist Circumference)

  Men> 102 cm

  Women > 88 cm

- Triglycerides

  >150 mg / dl

- HDL cholesterol

  Men < 40 mg/dl

  Women< 50 mg/dl

- Blood Pressure

  ≥130 / ≥ 85 mm Hg

- Fasting glucose

  >110 mg/dl

7.4 EXCLUSION CRITERIA:

Patients aged < 18 years

Patients with non Cardiac chest pain

Patients with stable / unstable angina

OBSERVATION AND RESULTS

Table -8 : TOTAL ADMITTED CASES IN ICU OF ACUTE MI

	No of Cases Admitted
Acute MI	**197**
METS with Acute MI	**96**

A total of 197 cases were admitted during the study period from November 2009 - March 2011, out of which 96 (48.7%) has METS.

TABLE -9: AGE GROUPING

Age in years	MI With METS		MI Without METS		Total	
	N = 96	%	N=101	%	N=197	%
20 – 35	2	2.08	6	5.94	8	4.06
36 – 50	27	28.13	39	38.61	66	33.50
51 - 65	46	47.92	37	36.63	83	42.13
66 – 80	18	18.75	18	17.82	36	18.27
> 80	3	3.13	1	0.99	4	2.03

Mean age 55.5 years

Graph 1

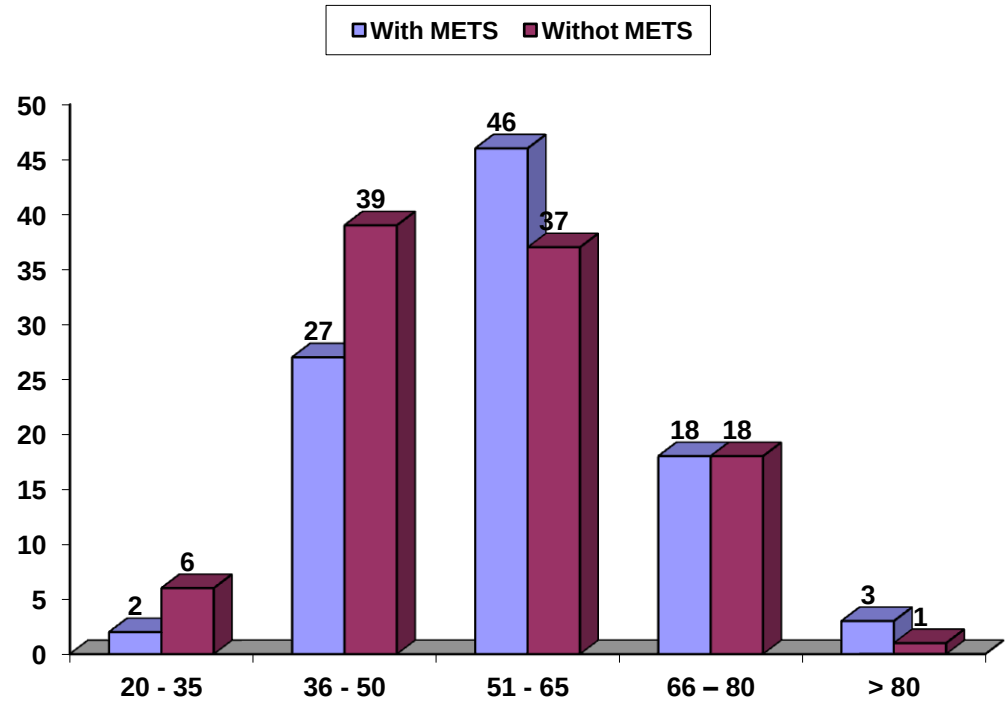


TABLE -10: SEX DISTRIBUTION

Sex	MI With METS		MI Without METS		Total	
	N = 96	%	N=101	%	N=197	%
Males	59	61.46	73	72.28	132	67.01
Females	37	38.54	28	27.72	65	32.99

It was observed that 132 cases among the 197 cases were males . The males predominated in the both the groups with METS and without METS.

Graph 2

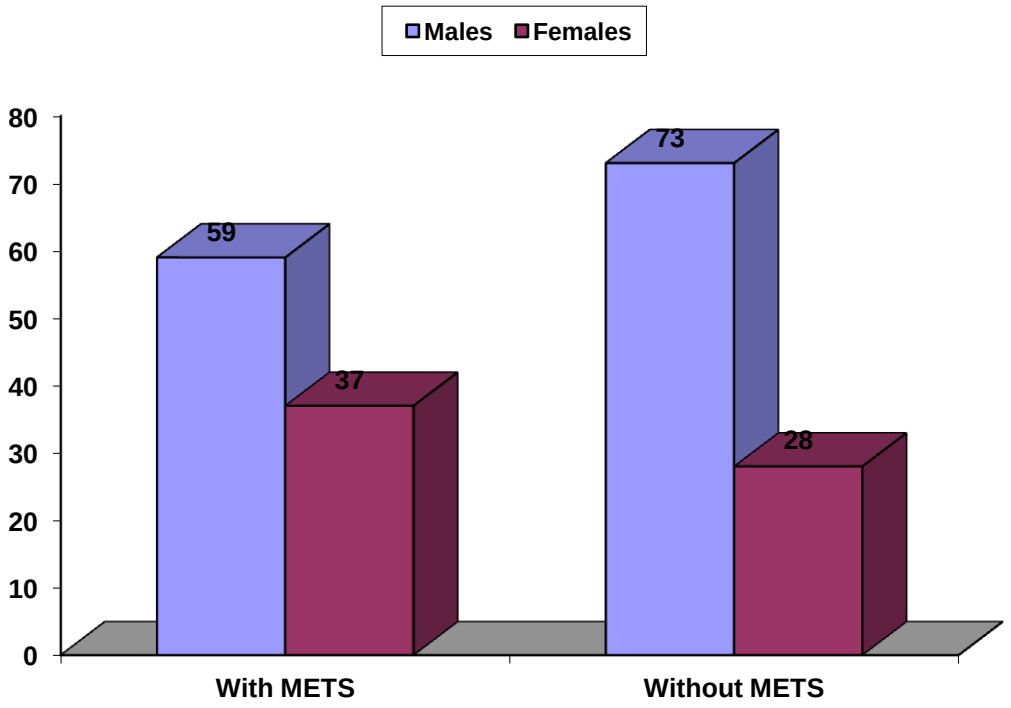


TABLE -11: SYMPTOMATOLOGY AT PRESENTATION

Symptoms	MI With METS		MI Without METS		Total	
	N = 96	%	N=101	%	N=197	%
Chest pain	82	85.42	88	87.13	170	86.29
Sweating	41	42.71	41	40.59	82	41.62
Breathlessness	29	30.21	23	22.77	52	26.40
Cough/sputum	5	5.21	7	6.93	12	6.09
Palpitation	17	17.71	20	19.80	37	18.78
Vomiting	34	35.42	37	36.63	71	36.04
Syncope	6	6.25	4	3.96	10	5.08

The most common mode of presentation in both groups were chest pain followed by sweating . Breathlessness and syncope were more common in METS compared to those without METS.

Graph 3

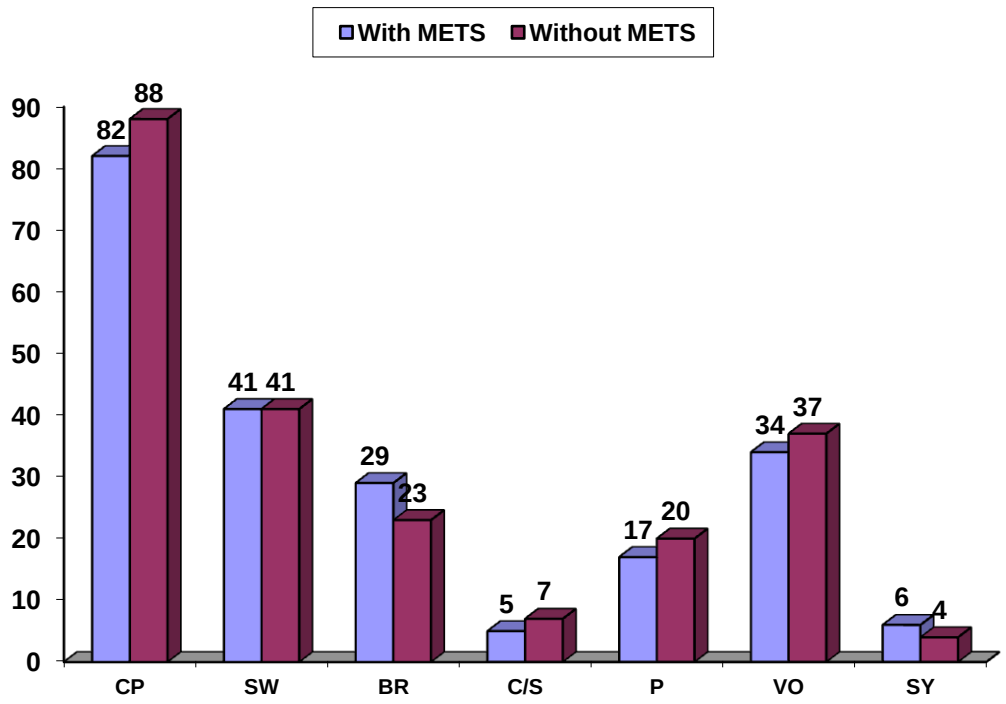


TABLE -12: RISK FACTORS

Risk factors	MI With METS		MI Without METS		Total	
	N = 96	%	N=101	%	N=197	%
Past H/o DM	29	30.21	12	11.88	41	20.81
Past H/o HT	21	21.88	19	18.81	40	20.30
Current smoker	37	38.54	22	21.78	59	29.94
Alcohol	17	17.71	30	29.70	47	23.86
Family H/o CAD	14	14.58	8	7.92	22	11.17

The past h/o DM was more common in METS compared to those without METS

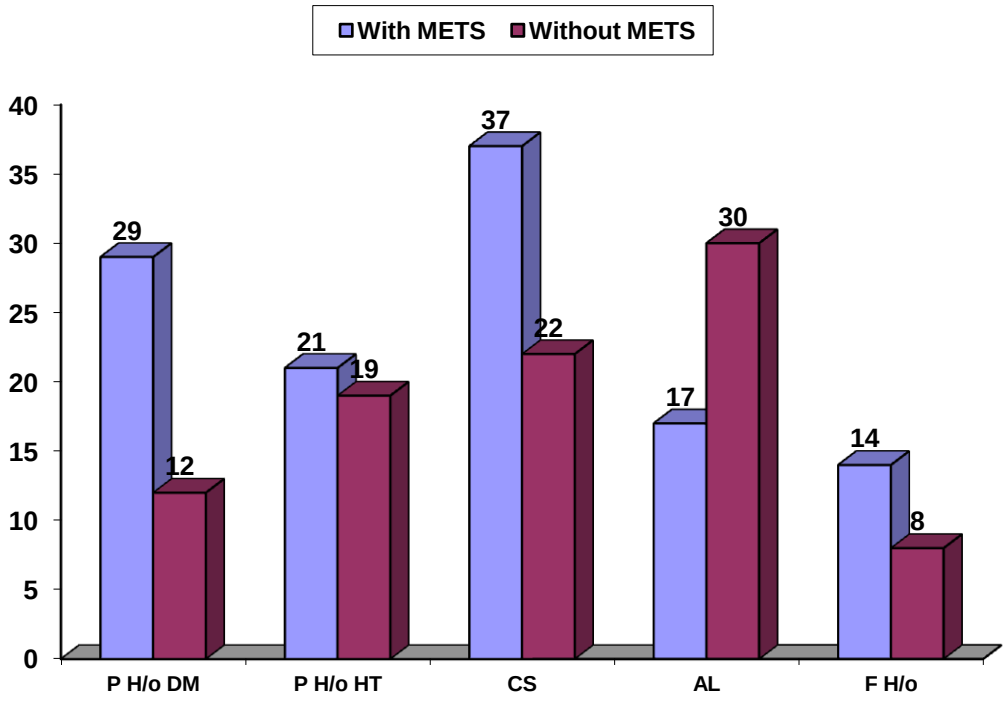


TABLE -13: COMPONENTS OF METS

Components of METS	MI With METS		MI Without METS		Total	
	N = 96	%	N=101	%	N=197	%
DM or FBS >110mg/dl	86	89.58	27	26.73	113	57.36
HT or BP ≥130/85mm Hg	59	61.46	29	28.71	88	44.67
TGS >150mg/dl	52	54.17	19	18.81	71	36.04
HDL <40mg/d(males) <50mg/dl(females)	87	90.63	75	74.26	162	82.23
WC >102cm (males) >88cm(females)	43	44.79	7	6.93	50	25.38

It was observed that , all the components were more common in the METS group compared to those without METS group. Low HDL-C was the major component in both the groups .

Calculated value of Chi square is 26.88 whereas tabled value for 4 degrees of freedom at $p<0.05$ is 13.27. Since calculated value > table value at $p<0.05$ the association is very high between components of METS and status of METS

Graph 5

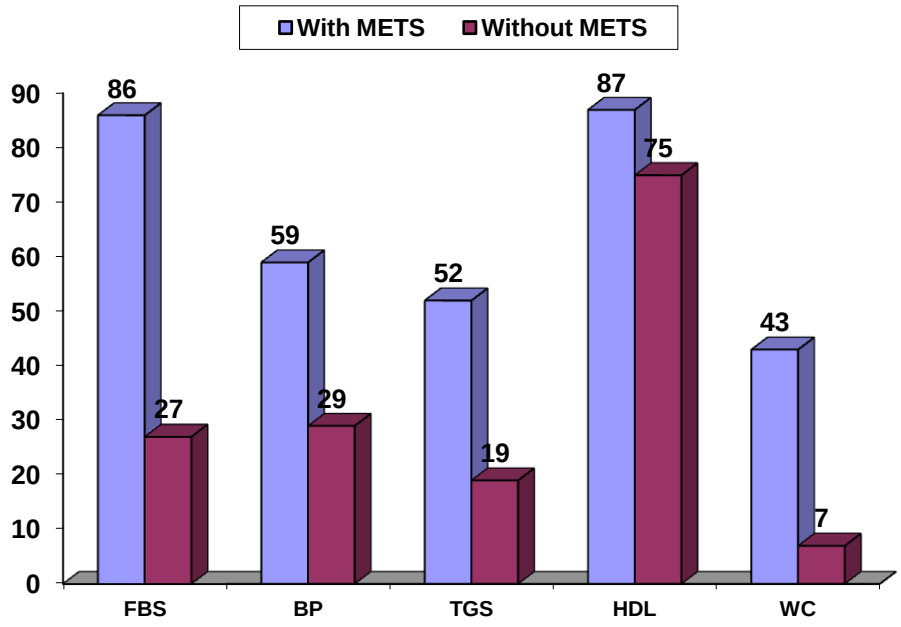


TABLE -14: TEST OF SIGNIFICANCE BETWEEN METS AND WITHOUT METS IN CASE OF VARIOUS PARAMETERS

	MI With METS	MI Without METS	Z-Test	P-value
FBS (mg/dl)	170.64 ± 60.19	117.93 ± 48.98	6.72	0.002
TGS (mg/dl)	153.86 ± 40.97	129.57 ± 35.82	4.42	0.002
HDL (mg/dl)	35.91 ± 5.47	37.24 ± 6.39	1.57	0.118
SBP mm of Hg	143.56 ± 29.59	124.42 ± 29.03	4.58	0.002
DBP mm of Hg	87.43 ± 14.43	78.18 ± 14.34	4.51	0.002
WC mm of Hg	94.46 ± 10.34	86.47 ± 7.27	6.24	0.002

All the components of METS had values greater than those without METS and are statistically significant except for the HDL-C which are same in both the groups.

TABLE 15: OTHER FACTORS

Other factors	MI With METS		MI Without METS		TOTAL	
	N = 96	%	N=101	%	N=197	%
Obesity (BMI > 30kg/$m^{2)}$	35	36.46	8	7.92	43	21.83
STEMI	77	80.21	61	60.40	138	70.05
NSTEMI	19	19.79	40	39.60	59	29.95
HbA1c > 7	50	52.08	8	7.92	58	29.44

The obesity with BMI > 30 Kg /m^2 was present more in METS compared to those without METS. (36.4% V/S 7.90%). HbAlc>7 was present more in METS compared to those without METS.

Graph 6

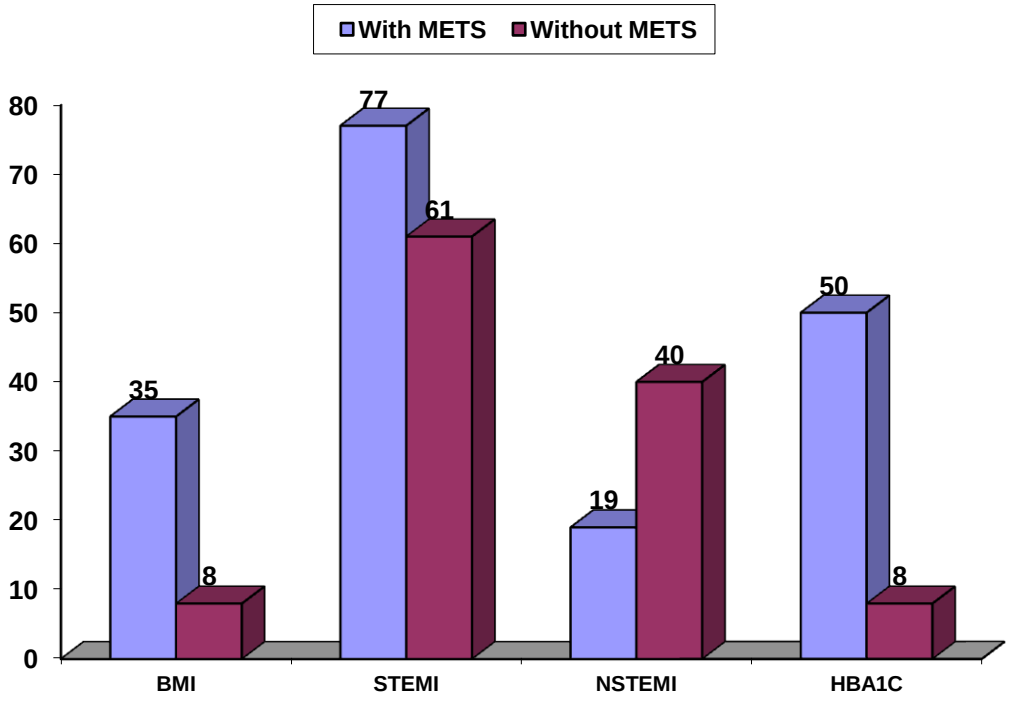


TABLE -16: IN HOSPITAL PROGNOSIS OF MI DURING HOSPITAL STAY

Prognosis In 1 Week of hospital stay	MI With METS		MI Without METS		Total	
	N = 96	%	N=101	%	N=197	%
Heart failure	35	36.46	12	11.88	54	27.41
VT/VF	4	4.17	1	0.99	5	2.54
Impulsive Recovery	37	38.54	86	85.15	123	62.44
Death	25	26.04	4	3.96	29	14.72

All the complications were more common in METS group compared to those without METS groups. Recovery was more common in without METS group compared to those with METS.

Calculated value of Chi square is 49.02 whereas tabled value for 3 digits of freedom and 1% level of significance is 11.345 . Since calculated value > tabled value at p<.0.05: there is association between complications and status of METS

Graph 7

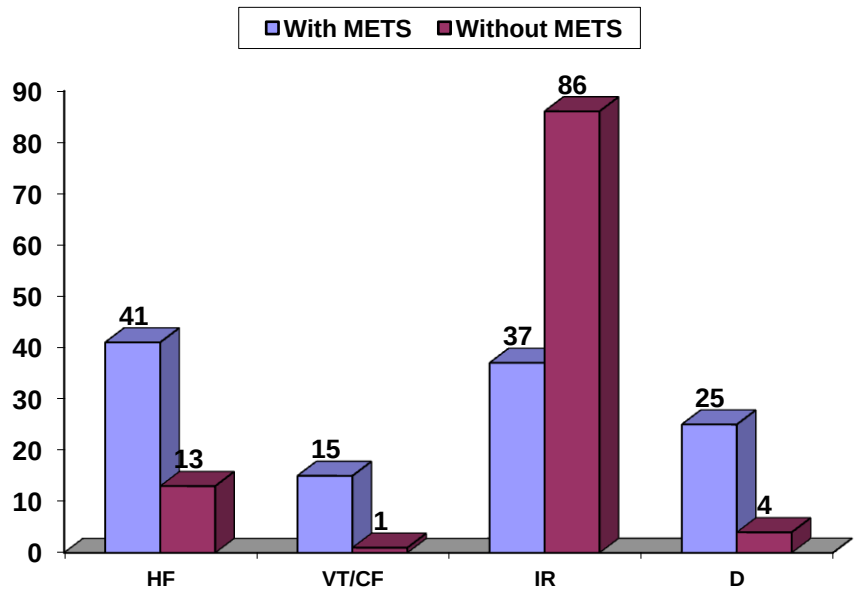


TABLE -17: ASSOCIATION OF COMPONENTS OF METS WITH HEART FAILURE IN AMI

	Heart Failure	
	MI With METS	MI Without METS
FBS (mg/dl) >110	35 (25.17)	6 (25)
TGS (mg/dl) > 150	23 (16.55)	3 (12.50)
HDL (mg/dl)Males<40	20 (14.39)	6 (25)
HDL (mg/dl)females<50	18 (12.95)	3 (12.50)
BP mm of Hg ≥130/85	25 (17.99)	5 (20.83)
WC > 102 cm in Male	3 (2.16)	0 (0)
WC >88 cm in Female	15 (10.79)	1 (4.17)

Hyperglycemia amongst the components of METS has the strongest corelation with the outcome of the heart failure in AMI.

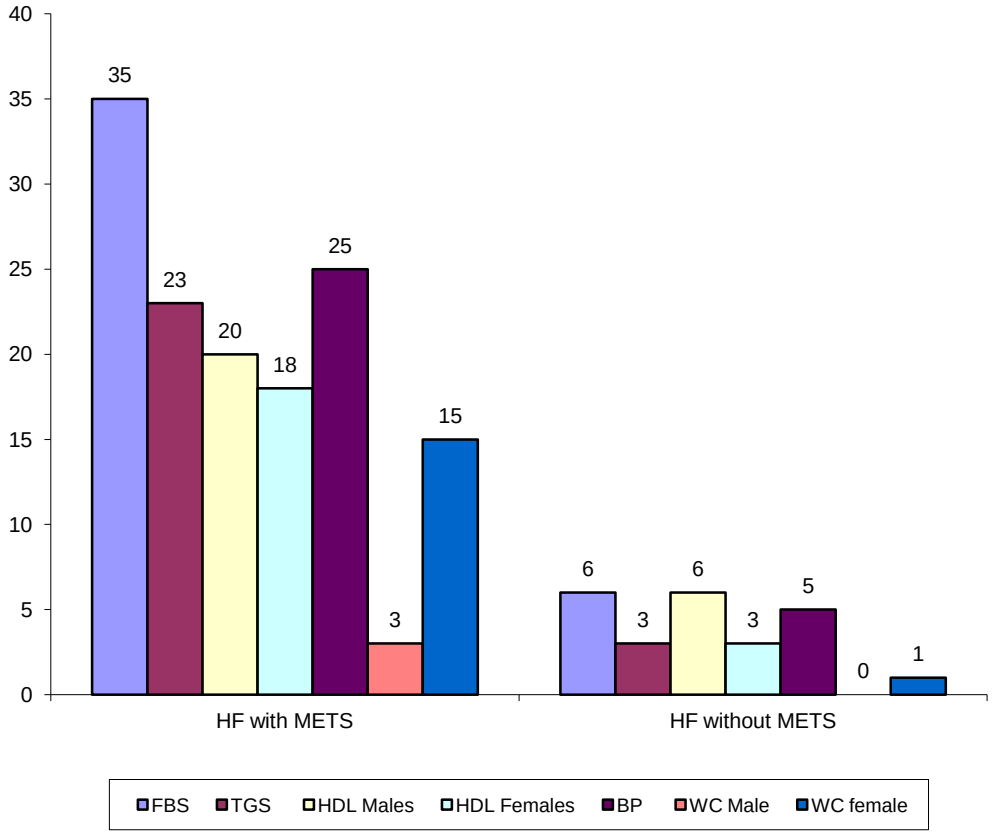
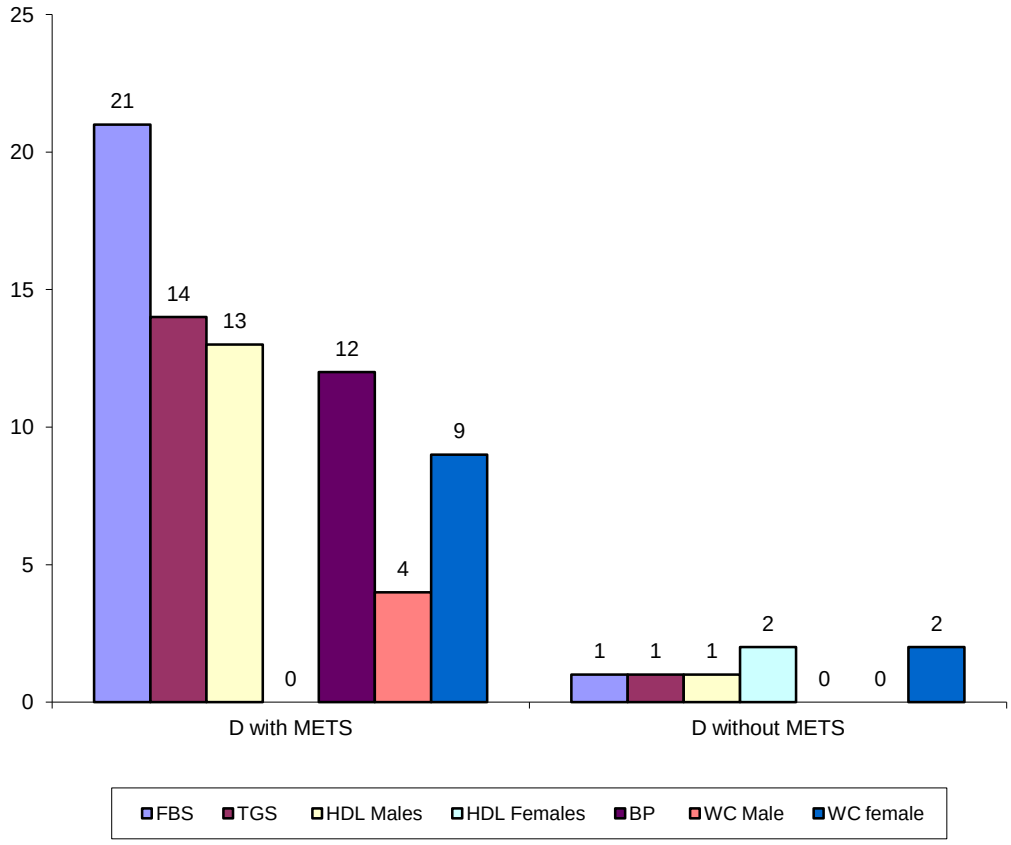


TABLE -18: ASSOCIATION OF COMPONENTS OF METS WITH DEATHS IN AMI

	Deaths	
	MI With METS	MI Without METS
FBS (mg/dl) >110	21 (28.77)	1 (14.29)
TGS (mg/dl) > 150	14 (19.18)	1 (14.29)
HDL (mg/dl)Males<40	13 (17.81)	1 (14.29)
HDL (mg/dl)females<50	0 (0)	2 (28.57)
BP mm of Hg ≥130/85	12 (16.44)	0 (0)
WC > 102 cm in Male	4 (5.48)	0 (0)
WC >88 cm in Female	9 (12.33)	2 (28.57)

Hyperglycemia among the components of METS has strongest association with the outcome of death in patients of AMI.



DISCUSSION

In the present study, which included 197 cases of acute MI, METS was present in 96 cases (48.73%).

TABLE-19: INCIDENCE OF METS

STUDY	% OF METS IN MI
Zeller M[110] et al (2005)	46%
Schwartz G[111] et al (2005)	38%
Levatasi G[47] et al (2005)	29%
Ninomiya[45] et al (2004)	41.5%
Milani R[4] et al (2003)	58%
Present study	48.73%

These findings suggest the METS, as defined by the NCEP ATP III criteria, is very common among patients with acute MI, because almost 1 in 2 patients had METS and that is associated with advanced coronary artery vascular damage.

This high incidence may be related to the vascular damage in METS by oxidative stress, endothelial dysfunction and pro-inflammatory state.[34]

AGE INCIDENCE:

In the present study age incidence was more between the age group 51-65 years (47.9 in METS group and 36.3% in without METS group). There was no difference in mean age of presentation between the two groups. (55 vs. 54 years) .

TABLE -20: AGE OF PEAK INCIDENCE OF METS

Study	Age in years
Zeller M[110] et al (2005)	70 (57-67)
Schwartz G[111] et al (2005)	65 ± 11
Levatasi G[47] et al (2005)	68.2
Ninomiya[45] et al (2004)	58.6 ± 10.3
Milani R[4] et al (2003)	65.7 ± 10.3
Jeppesen et al (2007)	61(41-71)
Present study	55(21-90)

There is early incidence of METS in Acute MI patients in the present study compared to the other studies which can be attributed to rapid nutritional and lifestyle transition in Indians[37].

SEX INCIDENCE:

In the present study the males predominated in both the groups (61.46% in METS group and 72.28% in without METS group).

TABLE -21: SEX INCIDENCE

Study	Males	Females
Zeller M[110] et al (2005)	63%	37%
Schwartz G[111] et al (2005)	55%	45%
Levatasi G[47] et al (2005)	85%	15%
Milani R[4] et al (2003)	64%	32%
Jeppesen et al (2007)	55%	45%
Present study	61.46%	38.54%

Comparison between the two groups indicates that patients with METS were more likely to be a male, which was consistent with the other studies.

SYMPTOMATOLOGY:

There was no difference in the 2 groups in presenting symptoms except that more number of patients with METS had breathlessness and syncope (30.21% and 6.25% as compared to22.77% and 3.96% without METS).

RISK FACTORS:

In the present study past history of diabetes mellitus was more in METS (30.21%) patients compared with no METS(11.88%). However, there was no no difference in hypertension, alcohol consumption and family h/o CAD.

TABLE -22: RISK FACTORS

	Zeller M[110] et al (2005)	Schwartz G[111] et al (2005)	Jeppesen et al(2007)	Present study
Past history of DM	48%	48%	8.1%	30.21%
Past history of HT	79%	-	17.1%	21.88%
Current smoker	23%	25%	44%	28.13%
Family history of CAD	32%	-	-	14.58%

All the risk factors were comparable to other studies but there was wide variation for the past history of HT.

BODY MASS INDEX:

The BMI of $\geq$30kg/m^2 as obesity was present in 36.46% of METS group as compared to 7.92% of without METS group.

TABLE -23: BODY MASS INDEX

Study	BMI kg/m^2
Zeller M[110] et al (2005)	25(23-37)
Schwartz G[111] et al (2005)	46%
Milani R[4] et al (2003)	38%
Present study	36.46%

COMPONENTS OF METS:

All the components were more common in METS group compared to those without METS and were statistically highly significant.

TABLE -24: COMPONENTS OF METS

	FBS mg/dl	BP mm of Hg	TGS mg/dl	HDL-C mg/dl	WC in cms
Zeller M[110] et al (2005)	123	-	160	37	106
Schwartz G[111] et al (2005)	-	90%	-	88%	76%
Ninomiya[45] et al (2004)	-	48.2%	43.2%	45%	51%
Present study	89.5%	61.4%	54.1%	90.6%	44.79%

TABLE -25: MEAN VALUES OF COMPONENTS OF METS

Milani R[4] et al (2003)	111± 26	140± 18/76± 13	176± 101	37.7± 11	102 ±12
Present study	170± 60	145 ±29/87± 14	153 ±41	35.9 ±5.4	94.4±10.3

Low HDL-C was the most prevalent individual component in both the groups (90.6% and 74.2%) with mean values lower in the METS group (35.9±5.4 vs. 37.2±6.3).

High FBS was the next major component prevalent in the METS group (89.5%).

The mean FBS was 170± 60 in METS group and 117± 48 in without METS group. Both these values were more than the cutoff value for the inclusion of FBS in the NCEP ATP III criteria for the diagnosis of METS.

WC was the minor component in both the groups but was also found to be statistically significant.

In the present study the METS patients had high FBS (170±60mg/dl) compared to other studies. This may be due to poor control of blood sugar in our study patients and also irregularities in the treatment by the patients.

The HT or BP ≥130/85 was comparable to some studies, and there was also a variation in the incidence of HT in between the studies.

The serum TGS was found to be low in the present study (153.8±40.9mg/dl) compared to the other studies ,though the south Indians have high percentage of body fat and low muscle mass.[37] Additionally insulin resistance also reduces the concentration of lipoprotein lipase in the peripheral tissues.[22]

The predominant component in the present study HDL-C (35.9± 5.4) was found to be same as compared to other studies. This low HDL-C may be due to high TGs which leads to decreased production and also increased clearance of HDL-C from the circulation.[22, 63] Low HDL-C can also be due to high blood sugars as seen in this study

The WC was less in the present study (94.4±10.3) compared to the other studies. This may be related to the adult Asian Indians, along with the other ethnic groups, have different anthropometric characteristics compared to others.

Metabolic abnormalities contributing to cardiovascular risk factors are detectable at a lower WC in Asians comparison with Caucasians, suggesting that NCEP ATP III criteria might have under estimated the prevalence of METS in Asians. Obesity, criteria for the diagnosis of METS need to be revised in Asian Indians and other Asian ethnic groups. Inclusion of modified WC, BMI cutoffs may be considered as defining variables of METS in the future studies on Asian Indians and other Asian ethnic groups.[26] .

The STEMI was present in 80.21% of METS patients in the present study, which is more compared to Zeller[110] et al (67%).

IN HOSPITAL PROGNOSIS OF MI DURING HOSPITAL STAY:

The heart failure (36.4%) is the predominant complication in the present study and is statistically significant. Other complications like VT/VF(4%) and death (26%) were also common and are statistically significant.

TABLE -26: IN HOSPITAL PROGNOSIS OF MI

Complications	Zeller[110] et al	Present study
Heart failure	41.7%	36.4%
Ventricular tachycardia/fibrillation	11.7%	4.17%
Death	10.%	26%

In the acute MI patients presence of METS was associated with about 4 times more chances of complications including death compared to those without METS.

This may be related to the more advanced vascular damage associated with the presence of METS in patients who manifest vascular disease like CAD, which may worsen the prognosis.[113] METS also represent a cluster of several risk factors, each of which may be involved in this poor outcome.

One of the main result of our study is that, the increased risk of development of heart failure and death in patients with METS had strongest association with hyperglycemia (25.17%) among the various components of METS measured several days after the index event which was very high in the present study compared to other studies.

The presence of DM and HT were also associated with diastolic/systolic heart dysfunction, abnormal myocardial substrate metabolism resulting in increased free fatty acid metabolism, and impaired blood flow to the noninfarcted myocardium[113] were the potential factors explaining the higher incidence of heart failure.

Both METS and DM were associated with unfavorable outcomes in terms of morbidity and mortality.[47] A recent study in India has shown the importance of insulin resistance as a risk factor for carotid artery intima/media thickness and indirect marker of atherosclerosis.[57]

People with METS have at least 2-fold increase in cardiovascular events and a much poorer prognosis following the event. The METS more strongly predicts the coronary heart disease and cardiovascular disease mortality than its components.[55]

The increased in hospital death rate observed in the METS may be resulted mainly from the increased incidence of heart failure.[113]

SUMMARY

In the present study, 197 cases of acute myocardial infarction were studied over a period of one year for metabolic syndrome using the NCEP- ATP III criteria and metabolic syndrome was present in 96 cases (48.73%).

- The age of the patients ranged from 21 to 90 years, with a median age of 55 years. Maximum number of cases was in the 51-65 years (47.9%).
- Male cases predominated in both the groups with and without metabolic syndrome (61.4% and 72.2% respectively).
- Chest pain was the most common symptom in both the groups. (85.4% and 87.1%). sweatin(42.7%) and vomiting(35.4%) was more common in metabolic syndrome patients.
- 30.2% and 21.8% of metabolic syndrome patients had past history of diabetes mellitus and hypertension respectively.
- 28.1% of metabolic syndrome cases were smokers at the time of acute myocardial infarction, 17.7% were alcoholic and 14.5% had family history of coronary artery disease.
- The body mass index of $\geq$30 kg/m^2 was present in 36.46% of metabolic syndrome.
- ST-elevation myocardial infarction was present in 80.21% of metabolic syndrome patients
- Among the components of metabolic syndrome low HDL-cholesterol was the most prevalent component in both the groups. (90.6% in metabolic syndrome and 74.2% in without metabolic syndrome cases).
- High fasting blood sugar or diabetes (89.5%) was the next most prevalent component in metabolic syndrome cases followed by hypertension or blood

pressure of ≥130/85 mm of Hg (61.4%) , high serum triglycerides >150mg/dl (54.17%) and high waist circumference (44.79%).

- During stay in hospital prognosis of myocardial infarction (36.4%) of patients had heart failure, (26.04%) had death, (4.17%) had ventricular tachycardia/fibrillation, .
- Development of complications in acute myocardial infarction was around 4 times higher in metabolic syndrome patients compared to without metabolic syndrome cases.
- Recovery was more common in without METS group compared to those with METS group (85.15% v/s 38.54%) .
- Association between individual components of METS and the risk of heart failure and death showed hyperglycemia (25.17% and 28.7%) had the strongest association.

CONCLUSION

The metabolic syndrome is a highly prevalent condition among the patients with acute myocardial infarction and has detrimental impact on outcome Metabolic syndrome is also associated with a higher risk of severe heart failure and death. Among metabolic syndrome components, hyperglycemia was the main corelate for the risk of development of heart failure and death during acute myocardial infarction.

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B.L.D.E.U's

SHRI.B.M.PATIL MEDICAL COLLEGE, HOSPITAL AND RESEARCH CENTRE, BIJAPUR

"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION".

PROFORMA

1) Name: CASE NO:

2) Age: IP NO:

3) Sex: DOA:

4) Religion:

5) Occupation: DOD:

6) Residence:

7) Chief complaints

8) History of presenting illness

9) Past History:

- Diabetes mellitus
- Hypertension
- History of any drug intake

10) Family History

11) General Physical Examination

Pallor: present/absent

Build and nourishment: Poor/Middle /Well

Weight(Kg) :

Height (cm) :

BMI (kg/m^2) :

Waist circumference (cm) :

12) Vitals

PR:

BP:

RR:

Temp:

13) Other Systemic Examination:

- Respiratory System
- Cardiovascular System
- Central Nervous System
- Per Abdomen examination

14) Investigation:

a. Hematology

Hb %	Gm/dl
TC	Cells/mm^3
DC	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Basophils	%
Monocytes	%
ESR	%

b. Urine Examination :

Sugar	
Albumin	
Microscopy	

c. Biochemistry

Serum creatinine	
Random Blood Sugar at admission	
Fasting Blood Sugar day 4	
Fasting Blood Sugar day 5	
Hb A1C	
CPK-MB	
Triglycerides	
HDL cholesterol	

d. 12 LEAD ECG

e. 2D ECHO

FINAL DIAGNOSIS

FOLLOW UP

OUTCOME

CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE AND RESEARCH CENTER, BIJAPUR- 586103

TITLE OF THE PROJECT: **"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"**

PG GUIDE: **Prof & HOD. DR. M.S.BIRADAR**

PG STUDENT: **DR.ARCHANA S KHANAGAVI**

PURPOSE OF RESEARCH:

I have been informed that this is a study of incidence rate and impact of metabolic syndrome in acute myocardial infarction I have also been given a free choice of participation in this study.

PROCEDURE:

I am aware that in addition to routine care received ,I will be asked series of questions by the investigator.I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study.

RISK AND DISCOMFORTS:

I understand there is no risk involved and I will experience some pain and discomfort during my procedures performed.This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

BENEFITS:

I understand that my participation in this study will help the investigator to understand to study the Prevalence and impact of metabolic syndrome in acute myocardial infarction.

CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime. Dr. Archana. S Khanagavi is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

REFUSAL FOR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand

that Dr. Archana. S Khanagavi may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate.

INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. Archana. S. Khanagavi has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr. Archana. S. Khanagavi Date

(Investigator)

KEY TO MASTER CHART

a	Absent
AL	Alcohol Consumption.
BMI	Body Mass Index.
BP	Blood Pressure.
BR	Breathlessness.
c	Crepts
CK_MB	Creatine kinase.
C/S	Cough/Sputum.
CP	Chest pain.
CS	Current Smoker.
CVS	Cardiovascular System.
D	Death
DBP	Diastolic Blood Pressure.
DM	Diabetes Mellitus.
FBS	Fasting Blood Sugar.
FH	Family History.
GPE	General Physical Examination.
HbA1C	Glycated Hemoglobin
HDL	High Density Lipoprotein.
HF	Heart Failure
HT	Hypertension.
LV EF	Ejection fraction(left ventricle)
m	Murmer
NR	Not Recordable
NSTEMI	Non-STEMI
P	Palpitation.
p	Present
RMI	Recurrent Myocardial Infarction
RS	Respiratory System.
S.TR	Serum Triglycerides.
SBP	Systolic Blood Pressure.
SE	Systemic Examination.
STEMI	ST-elevation myocardial infarction
STR	Stroke
SW	Sweating.
SY	Syncope.
TC	Total Cholesterol.
VO	Vomiting.
VT/VF	Ventricular tachycardia/fibrillation
WC	Waist Circumference.

"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"

Submitted By

DR. ARCHANA S KHANAGAVI

Dissertation submitted to

B.L.D.E. UNIVERSITY, BIJAPUR, KARNATAKA.

In partial fulfillment of the Requirements for the degree of

MD

in

General Medicine

Under the guidance of

DR.M.S.BIRADAR **MD**

PROFESSOR AND HOD OF MEDICINE

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, BIJAPUR

2011

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"** is a bonafide and genuine research work carried out by me under the guidance of **DR.M.S.BIRADAR** M.D. Professor and HOD Of Medicine.

Date:

Place: Bijapur.

DR. ARCHANA S KHANAGAVI

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"** is a bonafide research work done by **DR. ARCHANA S KHANAGAVI,** in partial fulfillment of the requirement for the degree of MD in General Medicine.

DR.M.S.BIRADAR **MD**

PROFESSOR AND HOD OF MEDICINE

Date:

Place: Bijapur.

B.L.D.E.U's Shri. B. M. Patil
Medical College, Hospital
and Research Centre, Bijapur

ENDORSEMENT BY THE HOD

This is to certify that the dissertation entitled is **"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"** a bonafide research work done by **DR. ARCHANA S KHANAGAVI** under the guidance of **DR.M.S.BIRADAR** **M.D.** Professor and HOD Of Medicine

Dr.M.S.Biradar **MD**

Professor and Head

Department of Medicine

B.L.D.E.U's Shri. B. M. Patil

Medical College, Hospital

and Research Centre, Bijapur

Date:

Place: Bijapur.

ENDORSEMENT BY THE PRINCIPAL

This is to certify that the dissertation entitled is **"INCIDENCE RATE AND IMPACT OF METABOLIC SYNDROME ON HOSPITAL OUTCOMES IN ACUTE MYOCARDIAL INFARCTION"** a bonafide research work done by **DR. ARCHANA S KHANAGAVI** under the guidance of **DR.M.S.Biradar** **M.D.** Professor and HOD Of Medicine .

Dr. R. C. Bidri **MD**

Principal

B.L.D.E.U's Shri. B. M. Patil Medical College, Hospital and Research Centre, Bijapur

Date :

Place : Bijapur

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DECLARATION BY THE CANDIDATE

I hereby declare that the BLDE University,Bijapur,Karnataka,shall have the rights to preserve, use and disseminate this dissertation / thesis in print or electronic format for academic / research purpose.

Date: **DR. ARCHANA S KHANAGAVI**

Place: Bijapur

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Date:

Place: Bijapur

DR. ARCHANA S KHANAGAVI

LIST OF ABBREVATIONS USED

ACE	Angiotensin converting enzyme.
AMP	Adenosine mono phosphate.
ARB	Angiotensin receptor blocker.
BMI	Body- mass index.
BP	Blood pressure
CAD	Coronary artery disease.
CRP	C-reactive protein.
CVD	Cardiovascular disease.
CVE	Cardiovascular events.
DBP	Diastolic blood pressure.
DM	Diabetes mellitus.
EGIR	European group for the study of insulin resistance
FBS	Fasting plasma sugar.
HDL-C	High- density lipoprotein.
HSD	Hydroxy-steroid dehydrogenase.
HT	Hypertension.
IL	Interleukin.
IRS	Insulin resistance syndrome.
LCPUFA	Long chain polyunsaturated fatty acids.
LDL	Low- density lipoprotein.
METS	Metabolic syndrome.
AMI	Acute Myocardial infarction.
NCEP-ATP	National cholesterol education programme-adult treatment panel.
SBP	Systolic blood pressure.
SK	Streptokinase.
TGs	Triglycerides.
TNF	Tumour necrosis factor.
VLDL	Very low- density lipoprotein.
WC	Waist carcumference.

ABSTRACT

BACKGROUND: Metabolic syndrome is a specific clustering of cardiovascular risk factors, which increases the mortality and morbidity. Hence, we aimed to know the incidence of METS in acute myocardial infarction, assess its various components and its impact on hospital outcomes in acute MI.

MATERIALS and METHODS: A total of 197 MI cases admitted to ICCU of Shri..B.M.Patil Medical College Hospital and Reasearch Centre,Bijapur from November 2009 to March 2011 were included in the study. Cases were categorized according to the NCEP ATP III METS criteria (presence of ≥ 3 of the following: hyperglycemia >110 mg/dl, triglycerides >150mg/dl; HDL-C < 40 mg/dl for males, < 50mg/dl for females; blood pressure ≥ 130/85mg/dl; waist circumference >102 cm in men or >88 cm in women).

RESULTS: Among the 197 cases, 96 (48.7%) fulfilled the criteria for METS and were more likely to be men. Low HDL-C (90.63%) was the most prevalent component followed by hyperglycemia (89.58%) ,HT (61.46%) ,TG's(54.17%) and high WC (44.79%). In hospital complications were higher in METS patients compared to those without and associated with four fold increased risk of complications including heart failure (36.46%) and death (26.04%).

CONCLUSION: The incidence of METS was high in MI patients, associated with worse in hospital outcome and with a higher risk of development of heart failure. Among metabolic syndrome components ,hyperglycemia was the main corelate for the risk of development of heart failure and death during acute MI.

KEY WORDS: Metabolic syndrome, Myocardial infarction.

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