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## Review Article

# Metabolic syndrome- Rapidly spreading non infectious Neo-epidemic

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### Abstract

Metabolic syndrome, a combination of various cardiovascular risk factors, is one of the fast increasing non communicable diseases. It has been considered to be mainly a disorder affecting cardiovascular system. Unfortunately, the subtle, but important clinical features of this syndrome due to involvement of other systems go unrecognized, leading to lot of morbidity for the patient. Hence, we conducted review to highlight the evidence about various complications due to this syndrome. We searched more than thousand relevant articles from Cochrane, pubmed, embase, medline databases. We have found that metabolic syndrome can affect virtually every organ systems in the body. But the silver lining is, most of them can be prevented by appropriate patient education, life style changes and other non pharmacologic intevention itself. Proper control of the components of metabolic syndrome with the drugs is also important in unresponsive cases. Increasing physical activity, weight reduction, dietary alteration are the key to prevent complications related to this preventable, treatable and curable disease.

**Keywords:** metabolic syndrome, dyslipidemia, insulin resistance

## 1. Introduction

Metabolic syndrome (MetS) is also known as metabolic syndrome X, cardiometabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome (named for Gerald Reaven), and CHAOS (in Australia).[1] It is a combination of elevated blood pressure, blood sugar levels and dyslipidemia. Very often, it is unrecognized by the clinicians leading to the progression of complications related to this disease.

It has been defined by various organizations differently. Various definitions are given by different organizations and are as follows:

**Table 1: Definition of metabolic syndrome**

| Organizations | Main Criteria | Additional Criteria (any Two) | | | | |
|---|---|---|---|---|---|---|
| | | Raised Triglycerides | Reduced Hdl Cholesterol | Blood Pressure (BP) | Fasting Plasma Glucose (FPG) | Other Criteria |
| International Diabetes Federation (2006)[2] | Central Obesity (waist circumference with ethinicity specific values) | >150mg/dL (1.7mmol/L) or specific treatment for this lipid abnormality | <40mg/dL (1.03mmol/L) in males, < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality | systolic BP > 130 or diastolic BP >85 mm Hg or treatment of previously diagnosed hypertension | >100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes | - |

| | | | | | | |
|---|---|---|---|---|---|---|
| World Health Organization (1999)[3] | Central obesity: WHR>0.9 (males) & 0.85 (females), BMI>30kg/m2 | ≥ 1.695 mmol/L | ≤ 0.9 mmol/L (male), ≤ 1.0 mmol/L (female) | Blood pressure: ≥ 140/90 mmHg | - | Microalbuminuria : albumin excretion ratio ≥ 20 µg/min or albumin:creatinine ratio ≥ 30 mg/g |
| European Group For The Study Of Insulin Resistance (1999)[4] | insulin resistance defined as the top 25% of the fasting insulin values among nondiabetic individuals | ≥ 2.0 mmol/L | < 1.0 mmol/L (or treated dyslipidemia) | ≥ 140/90 mmHg or antihypertensive medication | ≥ 6.1 mmol/L | waist circumference ≥ 94 cm (male), ≥ 80 cm (female) |
| US National Cholesterol Education Program – Adult Treatment Panel – III (2001)[5] | - | TG ≥ 1.7 mmol/L (150 mg/dl) | < 40 mg/dL (male), < 50 mg/dL (female) | ≥ 130/85 mmHg (or treated for hypertension) | ≥ 6.1 mmol/L (110 mg/dl) | waist circumference ≥ 102 cm or 40 inches (male), ≥ 88 cm or 36 inches(female) |
| American Heart Association/Updated NCEP (2004)[6,7] | - | ≥150 mg/dL (1.7 mmol/L) | <40 mg/dL (1.03 mmol/L) in males, <50 mg/dL (1.29 mmol/L) in females, | ≥130/85 mmHg or use of medication for hypertension | >100 mg/dL (5.6 mmol/L) or use of medication for hyperglycemia | waist circumference ≥ 40 inches (102 cm) in males, ≥35 inches (88 cm) in females |

6 components of metabolic syndrome identified by Adult Treatment Panel – III (ATP-III) in relation to cardiovascular diseases are:[8]

Abdominal obesity, Raised BP, Proinflammatory state, Prothrombotic state, Atherogenic dyslipidemia, Insulin resistance ± glucose intolerance. Other factors are: physical inactivity, atherogenic diet, cigarette smoking, hypertension, elevated LDL cholesterol, low HDL cholesterol, family history of premature coronary heart disease (CHD) and aging.

## 2. Epidemiology:

The prevalence of metabolic syndrome is increasing throughout the world[10]. The prevalence of metabolic syndrome is high in western countries than with developing countries.[11,12] As per NHANES 2003-2006 [13] (National health and examination survey) 34% of population meet the criteria for metabolic syndrome. As per ATP III 2001 guidelines, 27% meet criteria for metabolic syndrome and as per ATP III revised guidelines 32.3% meet the criteria.[14] It has been observed that there is 5% increase in the metabolic syndrome in last 15 years.

WHO has set a higher waist circumference than IDF. Hence, less number of people meet the criteria reflecting lower prevalence of metabolic syndrome. There has been significant rise in metabolic syndrome among developing countries like India.[15]

For example :

**Table 2: Epiemiology of MetS in India**

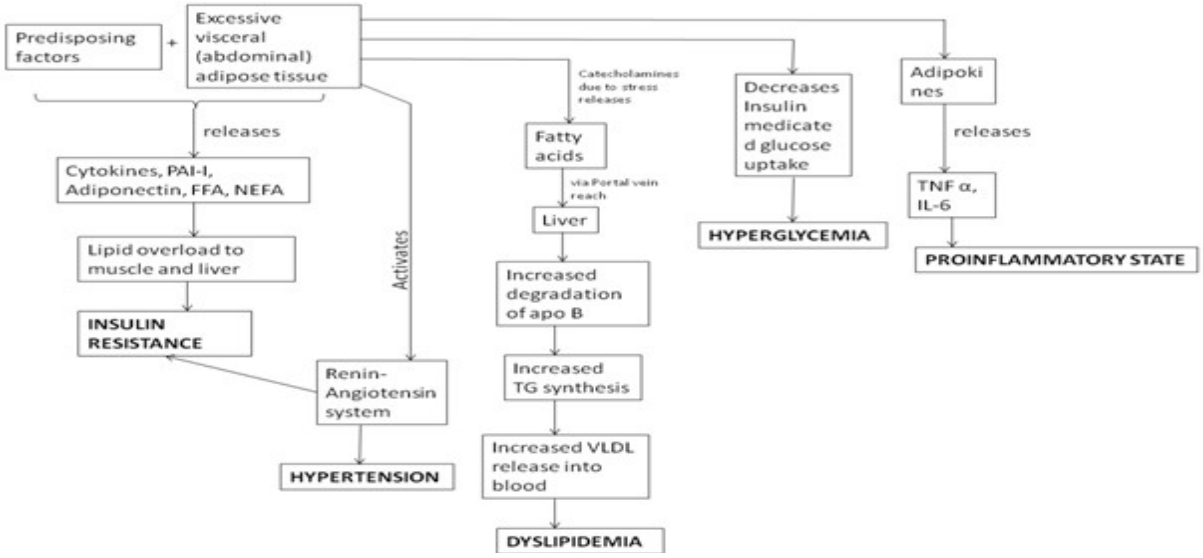
| Studies | Region | Age group | BMI | Waist circumference in cm OR cut-offs for BMI | Prevalence of obesity (%) males | Prevalence of obesity (%) females |
|---|---|---|---|---|---|---|
| Dhurandhar and Kulkarni, 1992[16] | Western India (urban) | >15 y | BMI ≥ 30 | 48 | 7.8 | - |
| Deepa *et al*. 2007[17] | South India (urban) | >20 | BMI ≥ 25 | 43.2 | 47.4 | - |
| Park *et al*. 200618 | Korea | 20–80 | | WC ≥ 90 (M), ≥85 (F) | 19.4 | 22.5 |

The factors responsible for high prevalence of obesity in developing countries are higher life expectancy, changes in life style, changes in diet, physical inactivity etc. There has been no proper criteria for identifying metabolic syndrome in children and adolescents.

**2.1 Risk factors:** Abdominal obesity, Atherogenic Dyslipidemia, Blood Pressure, Insulin Resistance, Proinflammatory state, Prothrombotic state are the main risk factors. The three main contributing factors of metabolic syndrome are – Obesity and adipose tissue disorders, Insulin resistance. Multiple independent factors like Aging, Hormones, Molecules of vascular, immunologic and hepatic origin also have significant role.

**2.2 Pathogenesis:** Many investigators claim that excess visceral fat is more strongly associated with insulin resistance than any other adipose tissue compartment.[19–26] A pattern of abdominal (or upper-body) obesity correlates more strongly with insulin resistance and the metabolic syndrome than does lower-body obesity.[27] The mechanism by which obesity initiates complications of metabolic syndrome is shown in the figure below.

**Fig 1: Pathogenesis of components of Metabolic syndrome**.




**2.3 Insulin resistance:** Next to obesity insulin resistance has an important role in causation of metabolic syndrome. The mechanism by which it initiates atherosclerosis is shown below.

**Fig 2: Pathogenesis of atherocsclerosis**

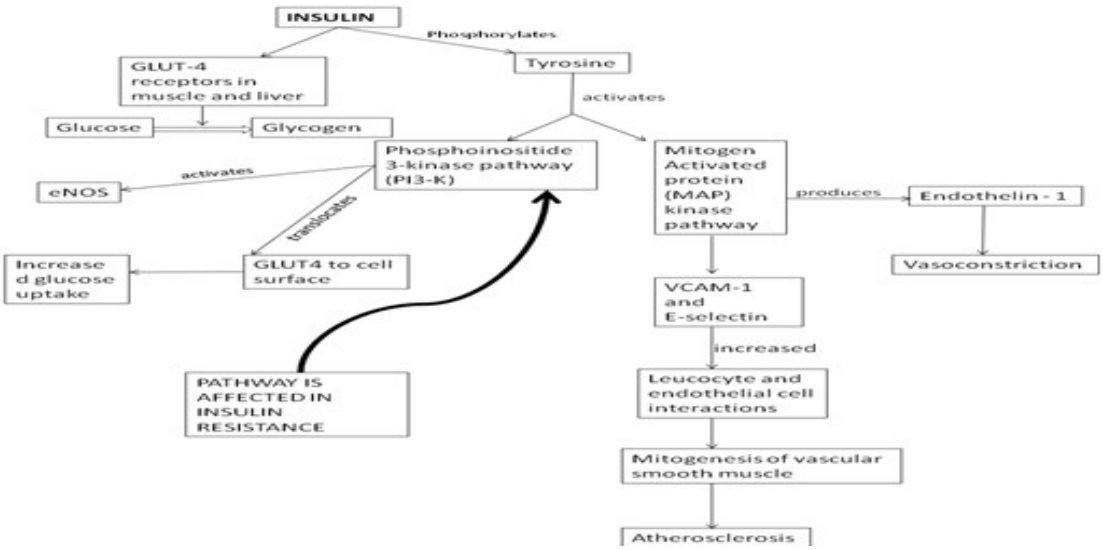
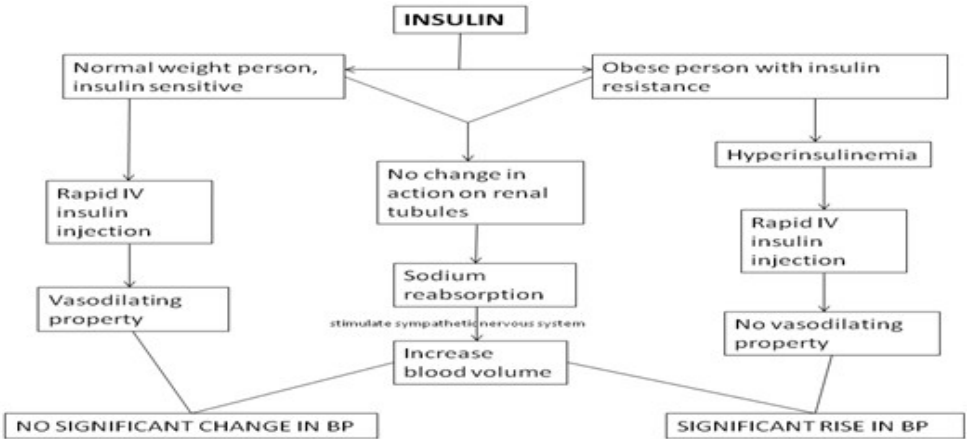


**Fig 3: Pathogenesis of hypertension in obese subjects**




**2.4 Atherogenic Dyslipdemia**

Decreased levels of HDL cholesterol, increased levels of triglycerides, increased small dense LDL are key features.

**Fig 4: Pathogenesis of atherogenic dyslipidemia**

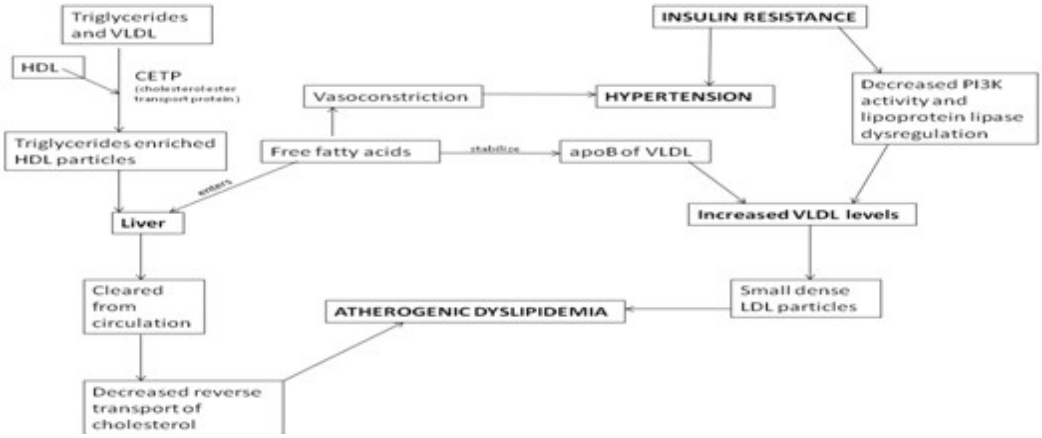
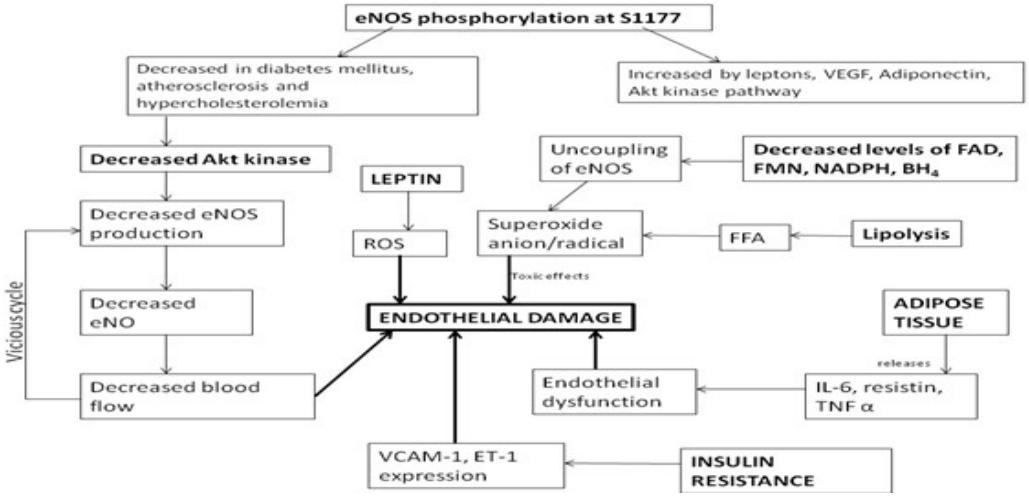



**Fig 5: Pathogenesis of Endothelial Dysfunction**




It is the final and common pathway for the development of Cardio-Vascular Diseases.

**2.5 Genetic:** Both the acquired and the genetic factors play an important role. MetS is polygenic disease. The incidence is influenced by non modifiable factors like heredity, age and race; Modifiable risk factors like physical activity, diet, other co-morbidities, drugs also play very significant role in occurrence of this syndrome.

McCathy and coworkers studied 207 SNPs in 110 candidate genes among coronary artery disease patients, a population enriched for metabolic abnormalities.[28] The number of abnormalities was determined in 214 male and 91 female patients and the association with each polymorphism was evaluated. Polymorphisms in 8 genes were associated metabolic syndrome in the whole population: LDLR, GBE1, IL1R1, TGFB1, IL6, COL5A2, SELE and LIPC. Variants in 7 additional genes showed significant gene interaction by gender. Separate analysis in men and women revealed strong association with a silent polymorphism in the gene encoding LDLR related protein associated protein 1(LRPAP1) among females but not males; Several other genes showed association only in females; Only 1 gene PRCP, was significantly associated in men alone.

Study by Qing Song *et al*. in Atlanta in 507 white nuclear families demonstrated a strong link between chromosome band 3q27 and 6 traits. The chromosome locus of 16p13 pter was also implicated in the MetS. This same broad region of chromosome 2 has been implicated by at least 14 other studies for phenotypes related to MetS. Relatives of patients with type 2 diabetes are insulin resistant, compared with 20% of people without a family history of diabetes.[29,30,31] The heritability of blood pressure is about 40–50%, and hypertension is associated with insulin resistance.[32] The heritability of HDL cholesterol is stronger than the heritability of triglycerides;[34] the triglyceride levels are also dependent on the duration of fasting and blood glucose levels.

**2.6 Stress:** Chronic stress among patients with genetic predisposition leads to release of excessive cortisol which results in excessive visceral fat accumulation, decreased growth hormone and hypogonadism.[35,36] Sleep apnea in some patients which causes release of more of stress hormones like IL-6, cortisol, noradrenaline, TNFα [37] increases the risk.

**2.7 MicroRNAs (miRNAs):** Play a role in many processes like adipocyte differentiation, metabolic integration, regulation of cellular gene expression by post transcriptional or translational level, suppression of protein coding genes, cleaving target mRNAs etc.[38] Antagomirs (cholesterol conjugated antisense oligonucleotides) target silent miRNAs by locking hepatic miR-122 blockade[39] which has been tested in phase I clinical trial. In future we may have miRNAs as new markers for metabolic syndrome.

Metabolic syndrome, by the mechanisms described above, is an important risk factor in causation of various diseases affecting different organ systems.

**2.8 Cardiovascular And Cerebrovascular Diseases:** MetS is a very strong risk factor for ischemic macrovascular diseases, The following studies illustrate the association between cardiovascular, cerebrovascular diseases with MetS.

**Table 3: Cerebrovascular, cardiovascular diseases and Metabolic syndrome**

| S No | Name of The Study | Type of Study | Conclusion |
|---|---|---|---|
| 1 | Junttila *et al*.[40] | Cohort study | Patients with type 2 diabetes are at higher risk for SCD after MI than are non diabetic patients. The incidence of sudden cardiac death in post-MI type 2 diabetic patients with left ventricular ejection fraction >35% is equal to that of non diabetic patients with left ventricular ejection fraction <35%. |
| 2 | Suarez *et al*.[41] | Retrospective study | Sudden cardiac death was correlated with atherosclerotic heart disease and nephropathy, and to a lesser degree with diabetes autonomic neuropathy and HDL cholesterol. |
| 3 | Jacqueline *et al* [42] | Cohort study | The MetS, however defined, is associated with an approximate 2-fold increased risk of incident cardiovascular morbidity and mortality in a European population. |
| 4 | Kurl.*et al*.[43] | Cohort study | The risk of any stroke is increased in men with metabolic syndrome, in the absence of stroke, diabetes and cardiovascular disease at baseline. |
| 5 | Hiroyasu *et al*.[44] | Prospective study | The MetS is a major determinant of ischemic cardiovascular disease among middle-aged Japanese men and women, in particular among smokers. |
| 6 | Jouven *et al*.[45] | Cohort study | Circulating NEFA concentration is an independent risk factor for sudden death in middle-aged men. Some form of primary prevention could be envisaged in subjects at high risk of sudden death. |

| | | | |
|---|---|---|---|
| 7 | Jianjun *et al*.[46] | Prospective study | The MetS defined by the 6 criteria except for the American College of Endocrinology definition predicts stroke in elderly subjects. However, impaired glucose tolerance alone is as strong a predictor of stroke as is the metabolic syndrome defined by the World Health Organization, NCEP and updated NCEP criteria. |
| 8 | Haralampos *et al*.[47] | Case control study | MetS is associated with an increased risk for acute ischemic/nonembolic stroke in elderly subjects with significant contributions from its individual components. In the presence of metabolic syndrome, HDL cholesterol loses its protective role against ischemic stroke. |
| 9 | Boden *et al*.[48] | Prospective study | The MetS is an important risk factor for ischemic stroke, with differential effects by sex and race/ethnicity. |
| 10 | Protopsaltis *et al*.[49] | Longitudinal study | MetS per se at baseline or combinations of its components does not predict the development of ischemic stroke in type 2 diabetic patients. Waist circumference represents an independent prognostic factor and could be used as a clinical tool for stroke prevention in this population. |

Sudden cardiac death describes the unexpected natural death from a cardiac cause within a short time period, generally ≤1 hour from the onset of symptoms, in a person without any prior condition that would appear fatal.[50,51] It is well known that the risk factors for sudden death and non sudden death caused by myocardial infarction are type-2 diabetes, circulating free fatty acid levels and waist circumference.[52-54] Dyslipidemia and elevated blood pressure are also risk factors in the causation of sudden cardiac death which complete the pentad of MetS.[55] Its presence also strongly correlates with early atherosclerosis (greater carotid artery wall thickness and lower endothelial flow-mediated vasodilation) and is associated with increased morbidity and predicts the risk of future adverse cardiac events.[56, 57]

**2.9 Gastrointestinal Manifestations:** Non Alcoholic Fatty Liver Disease (NAFLD) and Non Alcoholic Steatohepatitis (NASH) constitute a spectrum of liver disease commonly associated with components of the MetS. Here are a few studies relating the same:

**Table 4: Gastro-intestinal diseases and Metabolic syndrome**

| | | |
|---|---|---|
| Lu *et al* [58] | Meta analysis and review | NAFLD is a potent predictor of Cardiovascular disease and MetS. |
| Rodríguez-Hernández *et al*[59] | Review | The chronic inflammatory state in obesity plays a crucial role in the manifestations of MetS. |
| Wu *et al*[60] | Retrospective study | Fatty pancreas is also a manifestation of MetS |
| Zelber-Sagi *et al*[61] | Prospective cohort study | NAFLD is a strong indicator of pre diabetes mellitus. |
| Park *et al*[62] | population-based prospective cohort study | Heavy alcohol intake and MetS had a supraadditive deleterious effect on Liver function. |
| Rosmorduc[63] | Review | Cirrhosis as a complication of NAFLD and NASH may lead to increased HCC risk. |
| Holterman *et al*[64] | Prospective study | Adolescents who were severly obese had greater liver damage, systemic inflammation and signs suggesting NAFLD and rapid disease progression. |
| Schild *et al*[65] | Prospective study | The diagnosis of MetS is strongly associated with the presence of NAFLD. |
| Stacy *et al*.[66] | Prospective study | Aminotransferase levels are strongly correlated with cardiometabolic risk factors, visceral fat and insulin resistance. |

NAFLD is the most common chronic liver disease in the western world and its incidence is increasing in developing countries particularly due to the epidemic of obesity and diabetes in industrialising countries.[67] Its prevalence is about one third of the population in the West and it is associated with other cardiometabolic risk factors like type 2 Diabetes Mellitus and central obesity.[68] The pathologic spectrum includes simple fatty liver and non specific inflammation (having a relatively good prognosis) to NASH, cirrhosis and Hepatocellular carcinoma[67,63] The exact role of NAFLD in the

pathogenesis of MetS remains to be defined: whether the disease is a manifestation of the syndrome or has an active role in its natural history. HDL-C levels are reduced with increase in TG's, cholesterol and hyperglycaemia.[69,70] The two hit hypothesis proposed by Day and James [71] says that the first hit is likely to be an imbalance in triglyceride formation and turnover with insulin playing a crucial role. The second hit is likely to originate from adipocytokines and ROS that initiate inflammation, stellate cell activation and fibrosis. Inflammation and fibrosis in the liver are indicators of the presence and severity of the MetS.[72] The possible roles of adipose tissue[73] itself, adiponectin,[74] resistin,[75] FFA,[76] TNF-alpha,[77] Leptin,[78] have been elucidated by various studies. Fatty pancreas has also emerged as another manifestation of MetS.[60] Intake of excess carbohydrate, especially fructose is known to be a risk factor for the development of NAFLD.[79] Other incriminating factors that may have a synergistic role include excessive alcohol intake and cigarette smoking.[62] Moderate alcohol consumption seems to reduce the risk of NAFLD.[80]

NAFLD can be diagnosed by liver biopsy, CT, MRI or H-MRS and is defined as steatosis be greater than 5 percent by weight in the absence of excess alcohol consumption (>20g per day).[69] Common Liver markers such as ALT, AST and to a lesser extent GGT can be used to monitor the severity of the disease and serve useful tools in its surveillance and screening among MetS patients.[81,82,83]

With no wide consensus on its management, NAFLD has to be treated with the same measures as one would approach other features of the MetS. These include lifestyle modifications and pharmacological therapies. Increased physical activity[84] and cardio respiratory exercises[85] are known to reduce the risk for NAFLD. Calorie restriction, diet modification[86] and body weight management are also found to help.[87] Pharmacological therapies include metformin to improve insulin sensitivity and lipid lowering drugs such as statins and fibrates. Large scale RCTs are required to further clarify their role in the management of NAFLD.

**2.10 Metabolic Syndrome and Kidney Disease:** Metabolic syndrome has been recently identified as a major risk factor for chronic kidney disease (CKD).[88] There seems to be a steeper decline in kidney function over time in patients with MetS.[89]

Below is a list of renal complications of metabolic syndrome.

**Table 5: Metaboolic syndrome and Kidney diseases**

| Main Author | Type of Study | Conclusion |
|---|---|---|
| Chen *et al* [90] | Cross-sectional study | MetS might be an important factor in the cause of chronic kidney disease. |
| Agarwal *et al* [91] | Prospective cohort study | Additive interaction present between Mets and Chronic kidney disease |
| Hill *et al* [92] | Retrospective cross-sectional study | There is a strong association between obesity and kidney disease in type 1 diabetes and confirmed their association in type 2 diabetes. |
| Johns *et al* [88] | Cross-sectional study | CKD is more common among individuals with the MetS |
| Banerjee *et al* [93] | Cross-sectional study | MetS is common in CKD and renal transplant patients in North India |
| Thomas *et al* [94] | Systematic review and meta-analysis. | MetS and its components are associated with the development of eGFR <60 ml/min per 1.73 $m^2$ and microalbuminuria or overt proteinuria |
| Alexander *et al* [89] | Cross-sectional study | Prevalence of microvascular disease high in patients with MetS |
| Kambham *et al* [95] | Prospective cohort study | Occurrence of nephrotic range of proteinuria in centrally obese individuals. |
| Tanaka *et al* [96] | Cross-sectional study | A strong, positive relationship between MetS and the prevalence of CKD |
| Palaniappan *et al* [97] | Cross-sectional study | Micro-albuminuria is strongly associated with incidence of MetS |

Estimated GFR has been found to be lower among these individuals with MeS.[88] It has been found that triglyceride-rich apolipoprotein B clearly promotes the progression of human renal insufficiency.[98] It is known that high triglyceride levels are a risk factor for developing proteinuria which forms a component of MetS.[99] Both CKD and MetS are independent predictors of Cardiovascular disease (CVD), but their combination furthers the risk of developing CVD.[91]

**2.11 Metabolic Syndrome And Depression:** Metabolic syndrome is known to be associated with depression and there seems to be a rather bidirectional association between them. The table below shows a few important studies conducted in the same direction.

**Table 6: Metabolic syndrome and Depression**

| Main Author | Type of Study | Conclusion |
|---|---|---|
| Pan *et al* [100] | Review & metaanalysis | Bidirectional association between MetS and depression. |
| Malhotra *et al*[101] | Prospective and longitudinal | Bipolar disorder and schizophrenic patients have higher risk of developing MetS |
| James *et al*[102] | Cross-sectional | Assosciation between depression and MetS present in a heterogeneous population |
| Oliver *et al*[103] | Review | Prevalence of MetS in Depressed population was confirmed. |
| Debra *et al*[104] | Cross-sectional study | No association between major depression and MetS |
| Edie *et al*[105] | Prospective cohort | Major depression is a significant predictor of the onset of MetS. |
| Tasnime *et al*[106] | Prospective cohort | MetS associated with Depressive symptoms in middle aged and older adults. |
| Raikkonen *et al*[107] | Prospective cohort | Psychological factors significantly predict the risk of developing MetS. |
| Koponen *et al*[108] | Prospective cohort | MetS is an important risk factor for the development of depression |
| Anne Herva *et al*[109] | Prospective birth cohort | Poor association between MetS and psychological distress in 31year olds |

In particular, depression has been closely linked with low HDL cholesterol levels and large waist circumferences according to several studies[10,106,110] Depression associated with MetS is also said to be more common in females than among males most likely owing to the fact that the risk factors for MetS is more common in females.[103,107]

Certain studies report no association between MetS and depression.[105] A study by Anna *et al* in Northern Finland showed that there was no relationship between MetS and Depression among a young study group of 31year olds.[109] Hence the association between MetS and Depression is more likely to be multifactorial such as with Diabetes,[111] coronary heart disease and hypertension.

**2.12 Metabolic Syndrome And Cognitive Dysfunction:** Metabolic syndrome and the chronic inflammatory state associated with it are known to play a role in chronic neurological diseases associated with cognitive decline. These include Alzheimer's and Non Alzheimer's Dementia including vascular dementia.[112] Following studies are apt to illustrate this association:

**Table 7: Metabolic syndrome and cognition**

| | | |
|---|---|---|
| Birdsill *et al*.[113] | Longitudinal Study | Maintaining CBF and minimizing CV Risk factors are important in the management of MetS |
| Yaffe *et al*. [112] | A 5-year prospective observational study | MetS is associated with cognitive impairment in the geriatric population esp. in an inflammatory state. |
| Watts *et al*. [114] | Longitudinal Study | MetS is not associated with the cognitive decline in healthy older adults as compared with those with early AD. |
| Dik *et al*. [115] | Longitudinal Study | Poorer cognitive performance was found in patients with MetS as compared to healthy non MetS controls especially associated with hyperglycaemia and an inflammatory state. |
| Yates *et al*. [116] | Evidence based review | Positive association between MetS and cognitive dysfunction with involvement of multiple domains associated with insulin resistance. |
| Berg *et al*. [117] | Longitudinal study | The association between MetS and cognitive impairment does not seem to be applicable in the oldest old. |
| Yaffe [118] | Review | MetS is a well established risk factor for accelerated cognitive loss especially in patients with an inflammatory state. |
| Yau *et al*. [119] | Cross sectional study | Adolescents with MetS reported lower cognitive function and brain function. |
| Lindenmayer *et al*. [120] | Cross sectional study | Patients with Schizophrenia with added MetS showed significant loss in cognitive function. |
| Raffaitin *et al*. [121] | | Association between high triglycerides, diabetes and vascular dementia and the need for early detection of risk factors in the management. |

The underlying mechanism for MetS induced cognitive loss is poorly understood. Birdsill *et al*.[113] reported that Cerebral Blood Flow(CBF) was lower in MetS patients and associated memory loss. The cognitive impairment was significantly associated with a high inflammatory state as measured by IL-6 and CRP levels[112,122]. Hypertension, DM and other cardiovascular risk factors have been thought to play a role in the pathogenesis of Alzheimer's and Non Alzheimer's dementia.[123] Similar studies have suggested the predominant role of DM in cognitive impairment particularly involving toxic AGE's.[124]

The association between MetS and cognitive impairment was found to be stronger in women[125] The term Metabolic Cognitive Syndrome (MCS) has been applied to this particular association involving cognitive impairment of degenerative or vascular origin.[126]

Management of this particular aspect of MetS requires early screening practises and aggressive management of the parameters involved. Viscogliosi *et al* reported that the Mini Mental Status Examination(MMETSE) scores are related directly to cognitive dysfunction and can function as an adequate screening test [127] The detection and treatment of metabolic risk factors particularly DM and dyslipidaemia is essential to prevent the likelihood of cognitive diseases.[121]

**2.13 Metabolic Syndrome And Polycystic Ovary Syndrome (PCOS):** Polycystic Ovary Syndrome is a very prevalent and common gynaecologic problem in women in the reproductive age group. The Syndrome in addition to its obvious effects on reproductive health and fertility also has significant morbid associations with higher hysterectomy rates, diabetes and hypertension.[128] Its associations with obesity, impaired glucose tolerance and cardiovascular risk are further explored in the following studies:

**Table 8: Metabolic syndrome and Polycystic ovary syndrome**

| | | |
|---|---|---|
| Glueck *et al*. [129] | Cohort study | Metformin and diet modification should reduce risk for DM and atherosclerosis in PCOS patients. |
| Coviello *et al*. [130] | cross-sectional case-control study | PCOS and Hyperandrogenemia is a risk factor for MetS in adolescent girls |
| Silfen *et al*. [131] | Cross sectional study | Variation in the HPA axis in non obese adolescents with PCOS and marked dysregulation of insulin sensitivity in their obese counterparts. There are also differences in the IGF system between nonobese and obese adolescents with PCOS. |
| Dokras *et al*. [132] | Case control study | Women with PCOS have a 11-fold increase in the prevalence of MetS. The risk of MetS is high even at a young age. |
| Ehrmann *et al*. [133] | Multicentre clinical trial | The MetS is prevalent in women with PCOS particularly associated with High BMI and insulin levels. |
| Apridonidze *et al*. [134] | Retrospective chart review | Women with PCOS have an increased incidence of MetS |
| Bozd`ag *et al*. [135] | Review | Metformin and statins are associated with improved dyslipidaemia picture. |
| Faloia *et al*. [136] | Prospective study | Obesity seems to be the link underlying metabolic disturbances leading to increased CV risk in PCOS patients. |
| Glintborg, *et al*. [137] | Cross sectional study | Lower adiponectin levels found in obese PCOS patients associated with higher risk for MetS. |

Adolescents with PCOS exhibited characteristics both clinical and metabolic that were similar to adult women; Dysregulation of insulin levels and insulin resistance was found to more significant in obese girls with PCOS[131] On the contrary Sam, Susan, *et al*. reported that there might be a heritable trait involved as LDL levels are increased in sisters of women affected with PCOS[138].

Low Adiponectin and ghrelin levels, markers for cardimetabolic risks are found with increased frequency in women with PCOS and MetS and may be due to hyperandrogenemia and insulin resistance,[137] putting them at risk for grave cardiac morbidity.

## 3. Management

Management of these cases include proper screening programmes to identify those at risk and institution of appropriate interventions including lifestyle changes and pharmacological therapy. Dokras, Anuja, *et al*. Reported that

TG/HDL-C ratio is a useful tool and its further role needs to be evaluated[132] Vural, Birol, *et al*. Found that adolescence may be an appropriate time to start interventional strategies as many cardiometabolic risks are present in early adulthood [139] According to some studies[140] all obese women with PCOS should be screened and if the test is negative, it should be repeated every two to three years.

Lifestyle management should be the first line of treatment which includes exercise, diet and behavioural modification; these changes are found to improve the abnormalities, both metabolic and reproductive[141]. Adoption of the wellstudied low sodium DASH eating plan[142] provides heart healthy foods that can be used to promote weight loss, reduce BP in both hypertensive and prehypertensive individuals, and reduce LDL. The benefits of modest lifestyle changes on cardiovascular risk factors are well documented. In the Framingham Heart Study, weight loss of 5 lbs or greater was associated with reductions in cardiovascular risk of about 40 percent.[143] Reduce dietary sodium intake to no more than 100 mmol per day (2.4 g sodium or 6 g sodium chloride).[144, 145] Pharmacological therapies include diet modifying drugs such as orlistat and sibutramine.[141] Insulin sensitising agents such as metformin and statins are found to be particularly efficacious[129, 135] with decrease in total cholesterol, TG's and LDL levels.

**3.1 Coronary Heart Disease risk assessment**

The primary reason for the increased emphasis is being paid for early identification of metabolic syndrome is because of the coronary heart disease risk, which is significantly increased by each of the constituents of the metabolic syndrome. Each of the components of metabolic syndrome increases coronary heart disease risk manifold when adds up with other components. There are several scoring systems which indicate future risk of coronary heart disease in an individual. Framingham risk score, PROCAM score, Vascular age are few of these systeMetS used to convey to a patient future risk of coronary heart disease. Using Framingham risk score, patients can be classified into three risk categories

1. High risk for CHD: 10 year risk > 20% of coronary heart disease-related death or nonfatal MI, and includes patients with a diagnosis of atherosclerotic vascular disease (CAD, cerebrovascular disease or peripheral artery disease), and most patients with chronic kidney disease or established diabetes mellitus.
2. Moderate to high risk for CHD: 10 year risk- 10-20%
3. Lower to moderate risk: 10 year risk- <10%

## 4. Therapeutic Targets

**4.1 Abdominal Obesity:** It is very important to achieve state of negative energy balance in an individual to reduce abdominal adiposity. This should preferably attained by increasing energy expenditure by exercise program as well as reduced energy consumption. Waist circumference should be maintained<40 inches in men <35 inches in women. BMI should be maintained <25kg/$m^2$. Target weight loss in initial year should be around 7% to 10% reduction from baseline total body weight. 500 to 1000 calories should be burnt every day to achieve this. 30 minutes of moderate intensity exercise such as brisk walking is recommended on preferably all days in a week.[146, 147] This should preferably be combined with short (10- to 15-minute) bouts of activity (walking breaks at work, gardening, or household work), jogging, swimming, biking, golfing, team sports, and engaging in resistance training[148]; avoiding sedentary activities for long duration in leisure time (television watching and video games) is also advised.

**4.2 Atherogenic diet** : consumption of saturated fat, *trans* fat, cholesterol should be avoided. saturated fat intake should be restricted to 7% of total calories; dietary cholesterol to 200 mg/dL; total fat 25% to 35% of total calories. Unsaturated fat should constitute most of dietary fat; simple sugars intake should be limited.

**4.3 Goals of therapy**- as per ATP III [9] and its recent update[149]

**LDL**: High risk patients: < 100mg/dl.
Moderately high risk patients: < 130mg/dl.
Moderate risk patients < 130 mg/dl.
Low risk patients < 160 mg/dl.

**Blood pressure:** Reduce BP to at least achieve BP of 140/90 mm Hg (or _130/80 mm Hg if diabetes present).

**Elevated Fasting glucose**: Life style modifications constitute main therapy of elevated fating gliucose. Except for a preliminary trial with acarbose,**[150]** there is evidence till now to document effectiveness of oral hypoglycemic agents in reducing risk for cardiovascular events. And there further, long term safety of drugs like metformin or thiazolidinediones has not been documented.

## 5. Conclusion

- Metabolic syndrome is a rapidly increasing and strong risk factor for diabetes mellitus as well as coronary heart disease.
- It can lead to complications related to virtually all the organ systems.
- Increasing physical activity, weight reduction, dietary alteration are the key to prevent complications related to this preventable, treatable and curable disease.

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