



## Review Article

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### METABOLIC SYNDROME: A RISING EPIDEMIC: COMPREHENSIVE REVIEW

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#### ABSTRACT

Metabolic syndrome also known as Insulin resistance syndrome is defined as a cluster of several cardiovascular and non-insulin dependent diabetes mellitus risk factors including insulin resistance, obesity, dyslipidemia and hypertension. Contributing factors for the features of metabolic syndrome can be hereditary or environmental. Thus it is a multifactorial condition with an alarming rate of prevalence having effect upon health and quality of life of patients. This review aims to focus on prevalence, pathophysiology, biochemical changes and possible therapies in the management of metabolic syndrome. Lifestyle modifications with specific recommendations on diet and exercise remains the initial intervention of choice for metabolic syndrome followed by surgical therapies but which face severe drawbacks. Being a collection of various conditions, allopathic management of metabolic syndrome involves combinational treatment than individual therapy of each condition.

**Keywords:** Obesity, Insulin Resistance Syndrome, Diabetes, Epidemic, Dyslipidemia

#### INTRODUCTION

The Metabolic syndrome (MS) characterized by central obesity, dyslipidemia, abnormal glucose tolerance and hypertension is a widely prevalent and multi-factorial disorder. Although obesity and insulin resistance are not one and similar with metabolic syndrome, they are essential features in this derangement of adipocyte physiology and carbohydrate metabolism. Now it is a well-known fact that MS forecasts the development of type 2 diabetes mellitus and cardiovascular diseases (CVD).<sup>1</sup>

#### Background

MS was primarily described as a cluster of hypertension, hyperglycemia and gout as the syndrome in 1923 by Kylin. Twenty years later, Vague described that upper body adiposity was regularly linked with the metabolic anomalies seen with diabetes and cardiovascular disorders.<sup>2</sup> In 1981, Hanefeld and Leonhardt were first to use the phrase "Metabolic Syndrome" to describe the occurrence of hyperlipoproteinemia, hyperglycemia, hypertension, gout and obesity in combination with an augmented incidence of cardiovascular disease, fatty liver and cholelithiasis. In 1985, Modan and his associates proposed a syndrome of insulin resistance or hyperinsulinaemia as a shared pathophysiological feature for obesity, hypertension and glucose intolerance, which could possibly explain their common association. Reaven was first to use the term 'Syndrome X', firmly establishing the clinical importance of this syndrome, excluding obesity.<sup>3</sup> In 1993, it was retitled as 'The Deadly Quartet' by Kaplan and then the term 'The Insulin Resistance Syndrome' was coined by unknown.<sup>4</sup> Currently, the 'Metabolic syndrome' remains the most apt and globally acknowledged description of this cluster of metabolically related cardiovascular risk factors.

#### Definition

Developing a unifying definition for MS globally was an uphill task for expert groups like World Health Organization (WHO), The European Group for the Study of Insulin Resistance (EGIR), The National Cholesterol Education Program - Third Adult Treatment Panel (NCEP ATP III) and International Diabetes Federation (IDF) but these groups had accomplished the task considering obesity, insulin resistance, dyslipidaemia and hypertension as main components of MS.

#### IDF Definition<sup>5</sup>

The WHO, EGIR and NCEP ATP III definitions offer divergent clinical measures to identify MS, hence in clinical practice there is a necessity of simple definition/diagnostic tool. This will help in easy identification of patients at augmented risk of developing type 2 diabetes and/or CVD.

IDF conducted an expert workshop in May 2015 with the motive of developing a new, unifying, universal working definition of MS from existing definitions. According to the IDF, for an individual to be identified as having the MS, they must have central obesity plus any two of four additional factors. The factors are:

- Central Obesity: Waist circumference – ethnicity specific\*
- Fasting plasma glucose:  $\geq 5.6$  mmol/l (100 mg/dl) or formerly diagnosed Type II diabetes.
- Blood pressure:  $\geq 130/80$  mmHg or treatment of earlier diagnosed hypertension.
- Elevated Triglycerides:  $\geq 1.7$  mmol/l (150 mg/dl) or specific treatment for this lipid aberration
- HDL-cholesterol:  $< 1.03$  mmol/l (40mg/dl) in males,  $< 1.29$  mmol/l (50mg/dl) in females or specific treatment for this lipid abnormality

\*If body mass index (BMI) is  $> 30 \text{ kg/m}^2$  then central obesity can be expected, and waist circumference need not to be measured.

#### **Guide for measuring waist circumference**

Waist circumference measurement is carried out in a horizontal plane, midway between the inferior margin of the ribs and the superior border of the iliac crest.

#### **Prevalence**

IDF (2005) guidelines, also known as modified ATP III guidelines had played a vital role in bringing uniformity in the definition of MS globally and standardizing it. Epidemiological studies have been carried out based on IDF guidelines only. MS prevalence depends upon age, ethnic background and gender and it increases progressively from 20 to 50 years and stabilizes thereafter. Grounded on prevalence studies carried out throughout the world, involving population samples aging from 20 to 25 and high, the prevalence of MS varies from 46% (India) to 7% (France) in women and 8% (India) to 24% (United States) in men.<sup>6</sup>

In India, one prevalence study was carried out in Chennai using standard IDF definition of obesity and another in Jaipur using obesity criteria fit for Indians and included sample population of same age.<sup>7,8</sup> Studies revealed prevalence of 13% in Jaipur, 41% in Chennai and further larger variations were noted for the presence of fasting plasma glucose (5% vs. 27%), hypertension (39% vs. 55%) and triglycerides (30% vs. 46%), each of which reported having used the same cut off points. Another study carried out in Chennai, using EGIR criteria reported a MS prevalence of 11.2%, which was much close to the prevalence rate reported for Jaipur than the other Chennai study.<sup>9</sup> Thus it seems that there can be significant variances in the prevalence of both the individual factors that constitute the MS and the MS itself even within the same ethnic population group.

Connection between a higher mortality rate due to cardiovascular disease and low socio-economic status had been reported by many studies. Illiteracy links cardiovascular disease with risk factors such as diabetes mellitus, hypertension, impaired glucose tolerance, physical inactivity, smoking and overweight.<sup>4,10,11</sup> The prevalence of MS was found to be higher in women consuming alcohol.<sup>12</sup>

#### **Pathophysiology of metabolic syndrome**

Obesity and Insulin resistance are treated as the core defects underlying the pathophysiology of metabolic syndrome. These two risk factors are highly interconnected; therefore, it is difficult to predict which plays a key role in pathogenesis and progression of MS. In addition, MS pathophysiology is more complicated by causative factors such as age, ethnicity/race, diet, physical inactivity, dysregulation of adipose tissue-derived cytokines, genetics, inflammation, imbalances in hormone levels and drugs. Hence, it is unrealistic to assume that MS is caused by a single underlying defect. Instead, it is a combination of numerous risk factors, principally driven by insulin resistance and obesity, which gives rise to the development of this cluster of metabolic health disorders.<sup>13</sup>

#### **Insulin Resistance (IR)**

Insulin is the most effective anabolic hormone synthesized in the body, exerting a plethora of effects on protein and lipid metabolism, amino acid and iron transport, cell cycle proliferation, cell differentiation and nitric oxide synthesis.<sup>14</sup>

Insulin resistance is a physiologic state of the body where the target tissues (e.g., muscle, liver, fat) fail to respond to the regular actions of insulin leading to compensatory hyperinsulinaemia. The high percentage of persons with MS also have insulin resistance. Insulin resistance and/or associated hyperinsulinaemia are thought to be the direct cause of other MS risk factors.<sup>15</sup> Hyperinsulinaemia may compensate for insulin resistance by maintaining normoglycemia in some tissues and on the other hand may also cause over expression of insulin action in some sensitive tissues. This varied effects of insulin on tissues leads to clinical expression of MS.<sup>16</sup>

The physiological actions of insulin are thought to be mediated by binding of insulin to insulin receptors. After binding, the action advances in two pathways as follows:

Phosphorylation of the insulin receptor substrate (IRS) 1 & 2 followed by activation of phosphatidylinositol (PI) 3-kinase is the most studied pathway that appears to be absolutely necessary for mediating metabolic and mitogenic effects of insulin. In vascular endothelial cells, under normal conditions insulin is anti-atherogenic and stimulates the production of a potent vasodilator, nitric oxide (NO) and reduces the expression of adhesion molecules thereby shielding endothelial cells from excessive interaction with circulating monocytes. But in insulin resistant state, the PI 3-kinase pathway is impaired and no longer insulin acts as an anti-atherogenic agent. Where the second pathway involves the phosphorylation of the SHC and activation of Ras, Raf, MEK and mitogen activated protein (MAP) kinases (ERK1 and 2). This pathway contributes exclusively to the mitogenic and nuclear effects of insulin and does not involve the metabolic actions of insulin. This pathway is unaffected in insulin resistance, instead it is more powerfully activated by compensatory hyperinsulinaemia leading to augmented activity of growth promoting agents. Excessive stimulation of this pathway may be the source of proatherogenic mechanism of insulin.<sup>14</sup>

A major contributor for the progress of IR is surplus of circulating free fatty acids (FFA) released from an expanded adipose tissue. FFA increases insulin resistance by impeding insulin-mediated glucose uptake and additionally augmented levels of circulating glucose leads to hyperinsulinaemia by increasing pancreatic insulin secretion. Further FFA increases the hepatic production of glucose, triglycerides, and secretion of very low density lipoproteins (VLDL) causing reduced transformation of glucose to glycogen leading to increased conversion of glucose to triglycerides (TG). Anti-lipolytic effect of insulin on adipose tissue is hindered due to IR further causing increased lipolysis of stored triglycerides leading to surplus of FFA in circulation.<sup>17</sup>

#### **Obesity**

Even though IR is considered to be the most important pathological process in MS, obesity was found to be most important driving force behind the increased prevalence in MS.<sup>18</sup>

Recent reports suggested that central adiposity precedes the development of the other components of MS and the best way to prevent MS at that point could be weight reduction.<sup>19</sup> Furthermore, Carr et al. evaluated the differential effects/ roles of insulin resistance and central body fat in determining MS, based on the ATP III criteria using 218 healthy men and women with a wide age range.<sup>20</sup> Adipose tissue, which was once considered to be a storage depot for triglycerides, is now recognized as a complex and active endocrine tissue that secretes many factors that regulate vascular and metabolic biology. These factors, collectively called adipokines, include adiponectin, tumor

necrosis factor- $\alpha$  (TNF-  $\alpha$ ), leptin, resistin, angiotensinogen, interleukin-6, plasminogen activator inhibitor-1 (PAI-1) and C-reactive protein (CRP). Dysregulation of these adipokines may also result in the pathogenesis of MS.<sup>21</sup> There are significant differences in the several adipose tissue depots, with visceral adipose tissue being associated with numerous medical morbidities, as well as MS. Secretions from the visceral adipose depots directly enter into portal system, and have direct access to the liver with relatively greater effect on hepatic metabolic function.<sup>22</sup>

### Glucose Intolerance

The defects in insulin action in glucose metabolism consist of inability of the hormone to suppress hepatic and renal glucose production and in mediating glucose uptake and metabolism in insulin sensitive tissues such as adipose and muscular tissue. The relationship between impaired glucose tolerance or impaired fasting glucose and insulin resistance is well explored in rodent, primate and human studies. To compensate the defects in insulin action, insulin secretion and/or clearance must be modified to sustain euglycaemia and if this compensation fails, defect in insulin secretion predominates.<sup>23</sup>

Insulin resistance in pancreatic  $\beta$  islet cells infers the signals that generate glucose-dependent insulin release have been adversely modified and fatty acids are principal candidates. Although FFA can stimulate insulin secretion, increased and prolonged exposure of  $\beta$  islet cells to excessive concentrations FFA results in fall in insulin secretion. The mechanism for this variation has been ascribed to lipotoxicity through several potential diverse mechanisms resulting in  $\beta$ -cell dysfunction. People who are genetically predisposed to diabetes, the presumed stress of the insulin resistant environment on  $\beta$ -cell physiology causes glucose intolerance and ultimately higher risk of diabetes.<sup>24</sup>

### Hypertension

During Insulin resistance, the cellular mechanisms of vascular smooth muscle contraction are found to be altered. Normally, insulin inhibits voltage operated calcium ion channels and activates calcium ( $\text{Ca}^{++}$ ) - ATPase's resulting in the reduction of intracellular calcium ion concentration. This decrease in cytosolic calcium ion concentration leads relaxation of vascular smooth muscle decreasing vascular resistance. In the environment of IR, this vasodilatory effect of insulin is lost due to loss of insulin sensitivity in vascular smooth muscles whereas the sodium re-absorption is preserved.<sup>25</sup> The origin of hypertension in MS is multifactorial and it comprises all the elements of the syndrome, including insulin resistance, obesity and dyslipidemia. Even though obesity is an important factor the other elements of the syndrome also play a role in crafting and facilitating the changes that ultimately result in hypertension.<sup>26</sup>

Epidemiological evidence state excess body weight is the main cause of essential hypertension. Increased renal sodium retention in obesity has been assumed to be associated with increased sympathetic and renin-angiotensin system (RAS) activity as well as hyperinsulinaemia and insulin resistance. This results in increased cardiac output and the arteries respond with vasoconstriction resulting in hypertension.<sup>27</sup>

### Biochemical changes during metabolic syndrome <sup>28,29</sup>

In MS, apart from hyperglycemia, IR and dyslipidemia many other physiological changes occur in the body, that are not included as a part of the diagnostic criteria for the MS, which are listed in table 1.

### Management of metabolic syndrome

Lifestyle modification, surgical treatment and allopathic treatment are the approaches available for the management of MS. All patients diagnosed with MS should be encouraged to change their diet and cultivate the habit of daily exercise. Further weight reduction is found to be main stay of the treatment.<sup>30</sup>

### Lifestyle program to combat metabolic syndrome

Loss of weight with lifestyle modification is the vital procedure to manage MS. It is evident from recent research reports that lifestyle intervention produce a marked reduction in the prevalence of MS and a decline of body weight, waist circumference, fasting glucose, triglycerides, and blood pressure.<sup>31</sup>

### Dietary recommendations <sup>31</sup>

- 1200–1600 Kcal/day for overweight men and 1000–1200 Kcal/day for overweight women.
- Low intake of saturated fats, trans fats and cholesterol, and diets with low glycemic index.
- Use of nutritional factors specifically designed for managing MS, including antioxidants, oat beta-glucan, alpha-lipoic acid (ALA), chromium, vanadium, phaseolamin (Phase 2), biotin and vitamins that will reduce blood homocysteine levels.

### Physical exercise recommendations <sup>31</sup>

- Walking and engaging in moderate-to-vigorous exercise for at least 60 minutes (at least 5 days per week)
- Physical exercise is envisioned to produce a calorie deficit of at least 400 K cal/day, favoring weight loss, maintenance of muscle mass and prevention of weight cycling.

### Behavioural modifications <sup>31</sup>

- Behavioural modification, including a change in amount and patterns of food intake.
- Indulging in any behavior incompatible with eating like knitting, writing, exercising, housekeeping and taking a bath etc.,
- Change in lifestyle including smoking cessation, reducing the intake of caffeine, simple sugars and avoidance of substances of abuse.

### Surgical management of Metabolic Syndrome

Liposuction or bariatric surgeries are under use for the management of severe obesity. Liposuction decreases the volume of subcutaneous abdominal adipose tissue. However, liposuction was not found to alter the insulin sensitivity of muscle, adipose tissue or liver and also was not found to alter plasma concentrations of interleukin-6, C-reactive protein (CRP) or Tumor necrosis factor (TNF)-alpha. Further it was found that liposuction had no impact change any other coronary risk factors such as blood pressure or lipid levels.

Obesity is also being managed by bariatric surgery techniques using laparoscopic adjustable banding of stomach along with Roux-en-Y resulting in 25-30% of weight loss with swift recovery in patients with hypertension and diabetes. However long-term results are not available and recent reports of substantial mortality and morbidity of this procedure, especially in the aged have raised significant safety issues for this procedure.<sup>32</sup>

**Therapeutic management of Metabolic Syndrome** <sup>33</sup>

MS, being a cluster of diseases, has no single drug employed in its management. Hence, each condition is treated being treated with specific drugs, which are listed in the table no 2 respectively.

**Combinational management of Metabolic Syndrome**

Pharmacological management of MS generally follows multidrug therapy, which commonly includes a hypoglycemic agent, in

combination with a cholesterol lowering agent and a blood pressure lowering agent. In addition, if needed an anti-platelet agent, vitamins and supplements can be included. This composition can be used clinically whenever required to treat NIDDM and when appropriate, the MS and obesity. The desired dosage for each of these components obviously depends on the pharmaceutical dosage form used. The effective dosage ranges for these compounds are well known. <sup>33</sup>

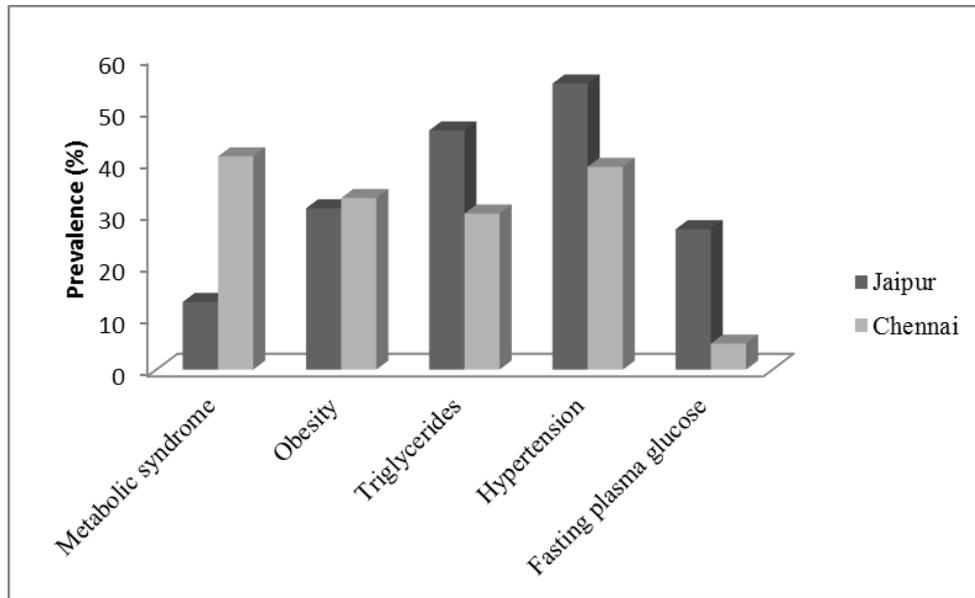


Figure 1: Comparative prevalence of metabolic syndrome between Jaipur and Chennai

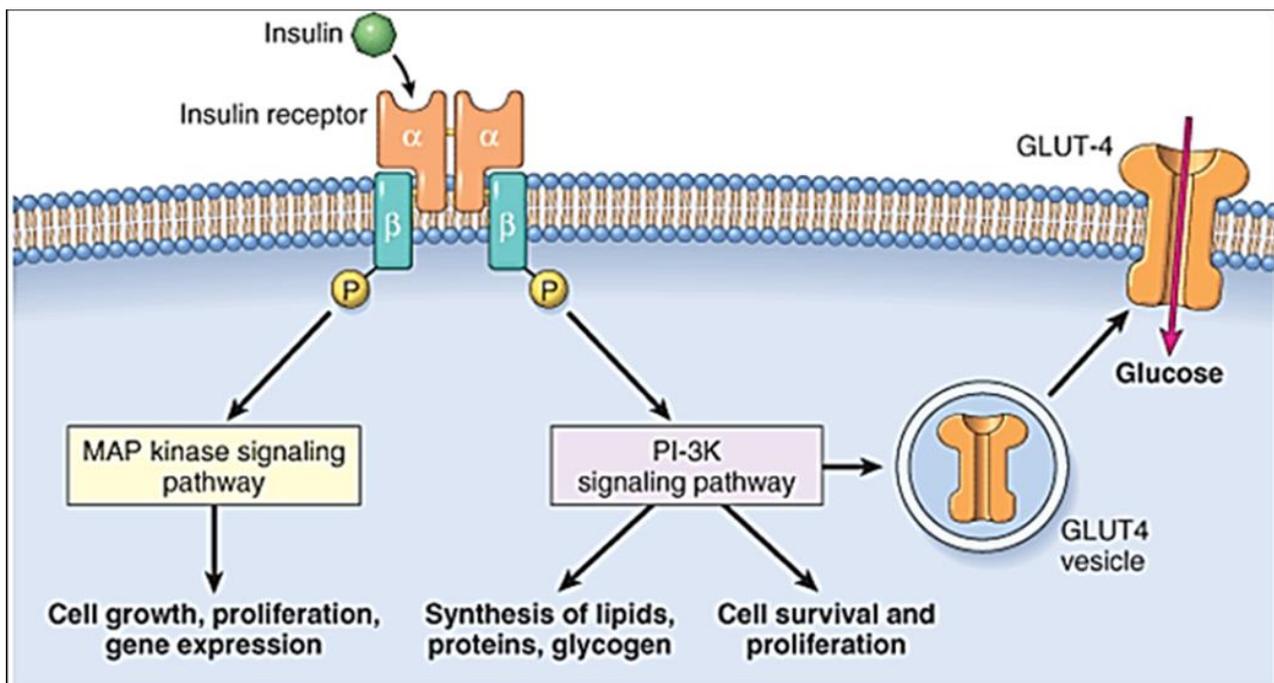


Figure 2: Mechanism of Insulin receptor [17]

**Table 1: Biochemical changes during Metabolic Syndrome**

Biochemical changes	Increased	Decreased
<b>Lipoprotein</b>	Small dense LDL apo B apo C-III	HDL apo A-1
<b>Prothrombotic</b>	Plasminogen activator inhibitor 1 Fibrinogen	
<b>Inflammatory markers</b>	Interleukin 6 White blood cell count Resistin Tumor necrosis factor C-reactive protein	Adiponectin
<b>Vascular</b>	Catecholamines Asymmetric dimethylarginine	NO levels
<b>Hepatic enzymes</b>	Aspartate amino transferase Gamma glutamyl transferase Alkaline phosphate Alanine amino transferase	
<b>Antioxidants</b>	NADPH Lipid peroxidation	Glutathione peroxidase activity Superoxide dismutase activity

**Table 2: Therapeutic management of Metabolic Syndrome**

Therapy	Drugs Used	Adverse Effects
<b>Obesity-specific therapy</b>	<b>Centrally acting drugs</b> Sibutramine (15mg/kg daily for 1 year) <b>Pancreatic lipase inhibitors</b> Orlistat (120mg/kg daily for 2 years) <b>Cannabinoid receptor blockers</b> Rimonabant (20mg/kg daily for one year)	Constipation, anorexia, tachycardia, palpitations, anxiety, sweating. Liquid oily stools, faecal urgency, headache, menstrual irregularities, Anxiety, fatigue, hepatitis. Severe depression and frequent suicidal thoughts.
<b>Blood pressure control</b>	<b>ACE inhibitors</b> Lisinopril and ramipril (20-40mg/day) <b>Angiotensin receptor blockers</b> Losartan, irbesartan, eprosartan (25-100mg/day) <b>Calcium channel blockers</b> Amlodipine, isradipine, nifedipine (5-10mg daily) <b>Beta blockers</b> Carvedilol ( non-selective beta blocker/alpha-1 blocker ,6.25mg twice daily) Nebivolol ( $\beta_1$ receptor blocker,10mg daily)	Cough, angioedema and acute renal failure. Cough angioedema and acute renal failure. Headache, edema and dizziness. Headache, parasthesia and dizziness.
<b>LDL cholesterol reduction</b>	<b>Statins</b> Simvastatin, Pravastatin, Lovastatin and Atorvastatin (20-80mg daily) <b>Statin</b> (20-80mg daily) + <b>Ezetimibe</b> (10mg daily)	Myopathy, hepatotoxicity Myopathy, hepatotoxicity
<b>Triglyceride reduction</b>	<b>Fibrates</b> Clofibrate(2g/day), Fenofibrate (200mgtwice daily), Gemfibrozil (600mg twice daily). <b>Statins</b> Simvastatin, Pravastatin, Lovastatin and Atorvastatin(20-80mg daily) <b>Statin-fibrate combinations</b>	Anemia, myalgia, rashes and impotence. Myopathy, hepatotoxicity and rhabdomyolysis. Myopathy, rhabdomyolysis
<b>HDL cholesterol enhancement</b>	<b>Niacin</b> (2-6 gm/day)	Hepatotoxicity, flushing, dyspepsia and tachyarrhythmias.
<b>Insulin sensitizers</b>	<b>Biguanides</b> Metformin(125mg – 2g daily) <b>Thiazolidinediones</b> Rosiglitazone (2mg-8mg daily) and Pioglitazone (15-45mg daily)	Anorexia, nausea and diarrhoea. Fluid retention, heart failure and weight gain.
<b>Antithrombotic and anti-inflammatory</b>	Aspirin (1-2 mg/kg/d PO ) Clopidogrel(75mg daily)	Gastritis, vertigo and hepatitis Neutropenia, thrombotic thrombocytopenic purpura.

## CONCLUSION

The metabolic syndrome is due to interconnected abnormalities namely obesity, insulin resistance, dyslipidemia, hyperglycemia and hypertension, which ultimately increases the risk of cardiovascular disorders. The pharmacotherapeutical management of MS with multi drug therapy by reducing doses of drugs may be more effective than a single agent with fewer side

effects. In spite of the accessibility of various hypolipidemic agents and hypoglycemic agents, which are generally pooled in the treatment of MS, it is still becoming very tedious to manage MS as they suffer from high incidence of adverse effects. Thus there is still a lacuna of drugs in allopathic system of medicine for effective management of MS with fewer adverse effects, which requires considerable interest in synthesis and evaluation of novel agents against MS.

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