Link Between Metabolic Syndrome And Diabetes Mellitus: A Pathophysiological Implication

Merlit James, Treesa P Varghese, Anjaly Vijayan, Pooleriveetil Padikkal Anagha, Muhas C, Mohsina Hyder

Abstract: Metabolic syndrome (Met S), an escalating problem in modern society, may be defined as a group of risk factors that consists of hypertension, dyslipidemia, hyperglycemia, and central obesity. It can be probably due to lifestyle changes and physical inactivity in an individual. In order to analyze metabolic syndrome on the basis of its components, multiple organizations gave various definitions. Type II Diabetes Mellitus (Type II DM) patients with Metabolic syndrome generally have increasing chances of micro and macrovascular complications. Convincing evidence suggests that obesity and insulin resistance can be classified as underlying pathological conditions of Met S. Early diagnosis could aid in employing primary intervention which includes increasing physical activity and diet modification. This is followed by secondary intervention that consists of drug therapy in order to treat the individual components. This study reviewed that the management of Mets reduces premature mortality to a large extent and this can also be effective in controlling various risk elements.

Keywords: Metabolic Syndrome, Diabetes Mellitus, Insulin Resistance, Central Obesity

1. INTRODUCTION

Metabolic Syndrome (MetS) is a widespread and rapidly rising physical health and clinical confrontation of the people faced by the world due to urbanization, overconsumption of energy supplements, rising obesity, and a sedentary way of living [1]. Metabolic Syndrome is defined as a group of terms include hypertension, dyslipidemia, glucose intolerance, and central obesity. It is also referred to as ‘insulin resistance syndrome’, ‘syndrome X’, ‘hypertriglyceridemic waist’, or ‘the deadly quartet’[2]. Metabolic syndrome is a cluster of medical conditions that increase the risk of developing DM by fivefold. Various criteria can be used for diagnosis of MetS and the World Health Organization (1998) diabetes group made it first effort in trying to provide a definition of the Met S. This was followed by the definition of the European Group for the study of Insulin Resistance (EGIR) who contradicted the above definition with a modified one in 1999[3]. This was subsequently accompanied by a variety of definitions given by different organizations such as the National Cholesterol Education Program Adult Treatment Panel III (NCEP/ATP III) and the American Association of Clinical Endocrinologists (AACE) in 2003. This plethora of definitions suggested an immediate need for a new definition that combined all the subsisting views. In 2005 International Diabetes Federation (IDF) came up with an advanced definition of the MetS [4]. The metabolic syndromes are interdependent with the discrepancy in hereditary factors, physical activity, nutritional pattern, gender, and increasing age makes one susceptible to metabolic syndrome and its aftereffects. [5]

2. DEFINITIONS OF METABOLIC SYNDROME

Many expert organizations like World Health Organization (WHO), The National Cholesterol Education Program - Third Adult Treatment Panel (NCEP ATP III), The European Group for the Study of Insulin Resistance (EGIR) and International Diabetes Federation (IDF) tried their hand in generating a unifying definition based on main components of MetS such as obesity, insulin resistance, dyslipidemia and hypertension [6]. The most used definitions for studies and health care programs are given in table 1. Definitions that are slightly different from each other. Organizations like EGIR and AACE are not so commonly used [7].

2.1 NEED OF MET S ASSESSMENT IN DM

Around 425 million adults in the world were detected with diabetes in accordance with various surveys made in 2017 and by 2045 this statistic expected to escalate up to 629 million. Throughout the world, type II DM is more prevalent among individuals of all in the age group of 40-59 years and India is considered to be 6” in terms of having the most number of diabetic patients [8,9]. Type II diabetes is deliberated to be a MetS related disease and inflammatory disease [10]. The development of hypertension, dyslipidemia, and obesity are more profound among diabetic patients [11]. Studies have proved that there is an interrelation between increased glucose level and incidence of microangiopathy which includes diabetic nephropathy, retinopathy, and neuropathy. It is speculated that MetS with or without diabetes, is an indicator of coronary heart disease and premature mortality. It also possesses a potential threat for chronic microvascular complications in diabetic patients, especially individuals diagnosed with type II DM. [12]. The precise mechanism of metabolic syndrome is yet to be resolved but it can be concluded that this is a multifactorial condition that arises due to obesity which could be placed as the causative factor [13]. The two risk factors: Obesity and insulin resistance are highly interconnected and considered as the principal defects underlying the pathophysiology of metabolic syndrome. Hence, it is strenuous to predict which of these plays a crucial role in the pathogenesis and progression of MetS [14].
### 3. PATHOPHYSIOLOGY OF Met S

The precise mechanism of metabolic syndrome is yet to be resolved but it can be concluded that this is a multifactorial condition that arises due to obesity which could be placed as the causative factor [13]. The two risk factors: Obesity and Insulin resistance are highly interconnected and considered as the principal defects underlying the pathophysiology of metabolic syndrome. Hence, it is strenuous to predict which of these plays a crucial role in the pathogenesis and progression of Met S [14].

#### 3.1 INSULIN RESISTANCE (IR)

The beta cells of the islet of Langerhans secretes polypeptide hormone insulin and acts on tissues of the skeletal muscle, adipocytes, and liver which has glycoprotein receptors [15]. Different mechanisms that develop insulin resistance and metabolic syndrome are put forward by various clinical studies. These mechanisms involve a variety of conditions like inherited defects in proteins associated with the insulin action cascade, rising levels of free fatty acid (FFA), visceral adiposity levels, and chronic inflammation [16, 17]. An increase in FFA secretion from fat cells and/ or decline in FFA intake by fat cells is brought about by IR in adipose tissue, irrespective of its molecular or environmental principles [18]. Insulin-dependent glucose uptake is usually inhibited by free fatty acids in the skeletal muscle while in the liver, FFA brings about an escalated outcome in the production of triglycerides, glucose, and apo B–containing triglyceride-rich very-low-density lipoproteins. During lipolysis, the action of cyclic adenosine monophosphate releases free fatty acids that are generally present in triglyceride stores of adipose tissue [19]. Throughout the periods of fasting, this process is set in motion by catecholamines but usually, this activity is suppressed by insulin which involves a proposed process of decreasing cAMP activity following meals [20].

### Table No.1 Diagnostic criteria suggested by various agencies for clinical diagnosis of Metabolic syndrome

<table>
<thead>
<tr>
<th>CLINICAL FEATURES</th>
<th>WHO</th>
<th>NCEPATPIII</th>
<th>IDF</th>
<th>EGIR</th>
<th>AACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSULIN RESISTANCE</td>
<td>Presence of insulin resistance or glucose along with any two or more of the following:</td>
<td>None presence of any three or more of the following features:</td>
<td>None</td>
<td>Plasma insulin (&gt;75th percentile) and any 2 of the following:</td>
<td>IG or IGT plus any of the following:</td>
</tr>
<tr>
<td>WAIST CIRCUMFERENCE</td>
<td>Waist/hip ratio: men&gt;0.90 women&gt;0.85 or BMI&gt;30 kg/m2</td>
<td>Waist: men &gt;102 cm women&gt;88 cm</td>
<td>WC (population specific) For south Asians Waist &gt;90 cm (men) or &gt;80 cm (women) plus two or more of the following:</td>
<td>WC ≥94 cm in men or ≥80 cm in women</td>
<td>BMI &gt;25 kg/m2</td>
</tr>
<tr>
<td>HDL LEVEL</td>
<td>HDL cholesterol: men&lt;1.0 mmol/L (40 mg/dl) women &lt;1.3 mmol/L (50 mg/dl) or specific drug treatment for HDL-C</td>
<td>HDL cholesterol &lt;1.0 mmol/L (40 mg/dl) for men, &lt;1.3 mmol/L (50 mg/dl) for women or drug treatment for lipid abnormality</td>
<td>HDL-C &lt;39 mg/dl</td>
<td>HDL-C &lt;40 mg/dl in men or &lt;50 mg/dl in women</td>
<td></td>
</tr>
<tr>
<td>TG LEVEL</td>
<td>Triglycerides &gt;1.7 mmol/L (150 mg/dl)</td>
<td>Blood triglycerides &gt;1.7 mmol/L (150 mg/dl) or specific treatment for elevated triglycerides</td>
<td>Blood triglycerides &gt;1.7 mmol/L (150 mg/dl) or drug treatment for elevated triglycerides</td>
<td>TG level &gt;150 mg/dl and specific drug treatment</td>
<td>TG &gt;150 mg/dl and specific treatment</td>
</tr>
<tr>
<td>BLOOD PRESSURE</td>
<td>≥140/90 mmHg</td>
<td>Blood pressure : &gt;130/85 mmHg or treatment for hypertension</td>
<td>Blood pressure : &gt;130/85 mmHg or drug treatment for hypertension</td>
<td>BP&gt;140/90 mm Hg or on hypertension</td>
<td>BP≥130/85 mm Hg</td>
</tr>
<tr>
<td>GLUCOSE</td>
<td>IGT, IFG, or T2DM</td>
<td>Blood glucose greater than 100 mg/dl (5.6 mmol/L) or drug treatment for elevated blood glucose</td>
<td>Blood glucose greater than 5.6 mmol/L (100 mg/dl) or diagnosed type II DM</td>
<td>IGT or IFG (but not diabetes)</td>
<td>IGT or IFG (but not diabetes)</td>
</tr>
<tr>
<td>OTHERS</td>
<td>Microalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td>Other features of insulin resistance</td>
</tr>
</tbody>
</table>

**LINK BETWEEN METABOLIC SYNDROME AND DIABETES MELLITUS**
The rate of lipolysis will increase when the effects of insulin are diminished during insulin resistance and this results in the rise in fatty acid production. Thus leading to a negative

- **INSULIN RESISTANCE**
  - Hyperglycemia
  - Glucose level
  - Insulin dependent glucose

- **METABOLIC SYNDROME**
  - Lipolysis & Glucose impairment
  - Inhibit the antilipolytic property of insulin
  - Production of glucose, TG, APO-β (TG rich VLDL)

- **CENTRAL OBESITY**
  - Inflammation
  - Overproduction of Adipocytokines
  - Hypoxia
  - Reduced blood supply
  - Adipocyte enlargement

- **TYPE II DM**

**FFA** (free fatty acid), **TG** (triglyceride), **VLDL** (very low density lipoprotein), **DM** (diabetes mellitus)

**SKELETAL**

**LIVER**

**ADIPOSE TISSUE**

Over consumption of nutrients and low physical activity

The rate of lipolysis will increase when the effects of insulin are diminished during insulin resistance and this results in the rise in fatty acid production. Thus leading to a negative

4203
cycle that involves inhibition of the antilipolytic properties of insulin, causing further lipolysis [21, 22]. Impairment in glucose controlled by skeletal muscle and adipose tissue is found during the insulin-resistant state. In most cases, IR individuals are diagnosed with hyperglycemia and associated vascular endothelial damage which is usually contributed by impaired glucose intake [23, 24].

3.2 CENTRAL OBESITY

Body Mass Index (BMI) or Waist Circumference (WC) obesity is an indication of excess body fat. In both men and women, a BMI ≥ 25 kg/m² is referred to as overweight while a BMI ≥ 30 kg/m² indicates obesity. In men WC ≥ 94 shows that the individual is overweight whereas WC ≥ 102 cm obese [25]. In women waist circumferences ≥80 cm and waist circumferences ≥ 88 cm indicates overweight and obesity respectively [26]. During the diagnosis of Met S, central obesity is given the most significant position. The occurrence of obesity has increased and rose up to reach a very dangerous level [27, 28]. Obesity and overweight are correlated with an enlarging threat for hypertension, cardiovascular diseases, Type II DM, certain cancers and numerous disorders [29]. Many risk factors manifested in Met S which include impaired glucose tolerance, Insulin sensitivity, Dyslipidemia, and elevated blood pressure are caused due to abdominal obesity. Obesity is a multi-dimensional crisis present among humans due to the advancement in our way of living. It may be due to the conventional unhealthy way of consumption which includes sugar-sweetened beverage intake, sedentary lifestyle or it may be due to progress in technology and reduced physical activity which may be due to extreme use of electronic devices and modern gadgets [30]. Adipose tissue, a miscellaneous mix of adipocytes, immune cells, stromal preadipocytes, and endothelium, can retaliate at a great rate and vigorous to variations in nutrient surplus through adipocytes hyperplasia and hypertrophy [31]. An obese individual with increasing adipocytes enlargement undergoes hypoxia due to a reduction in blood supply to adipocytes [32]. An overproduction of adipokines, biologically active metabolites which include free fatty acids (FFA), glycerol, proinflammatory mediators (IL-6 and TNFα), C-reactive protein (CRP), and plasminogen activator inhibitor-1 (PAI-1) results in necrosis and macrophage into the adipose tissue of whose underlying factor is hypoxia [33]. Comorbidities associated with obesity can be brought about due to systemic inflammation throughout the body which is in turn caused by inflammation in the local area of adipose tissue [34].

4. MANAGEMENT OF METABOLIC SYNDROME

The timely diagnosis of Met S patients is very significant in terms of treatment and management that could decrease the potential danger of subsequent diseases [35]. Management of Met S involves changing one’s lifestyle which in turn focusing on the modification of underlying risk factors of overweight and obesity, physical inactivity, and an atherogenic diet [36]. Physicians apply various methods in treating each component of Met S. For example, physicians and dieticians may have different opinions about adopting various therapies like drug therapy, lifestyle modification when it comes to treating various problems associated with blood pressure, blood glucose, and triglycerides [37]. Lifestyle modification may have lesser influence than drug therapy but it can prove to be very useful in controlling metabolic risk factors [38]. Patients with Met S are recommended in reducing their weight by limiting calorie intake, behavioral change, physical activity, and anti-obesity medications [39, 40]. This helps in reducing fasting blood glucose, insulin, hemoglobinA1c levels, and contributes to abdominal fat loss and also helps in lowering blood pressure, affects lipid profile (decrease triglyceride and increase high-density lipoprotein levels), and improving insulin resistance [41, 42]. These could be achieved by increasing physical activity and decreasing calorie intake by 500–1000 calories per day [43]. About 30–60 minutes of moderate rate of physical workout coupled along with everyday escalating lifestyle variations could serve as the physical activity component [44, 45]. This could help in the treatment of Met S and limit the escalation of diabetes [46].

5. CONCLUSION

The prevalence of metabolic syndrome is at hike due to unhealthy living style and lack of physical exercise which in turn leads to premature morbidity and mortality. Even though the ultimate pathophysiological mechanism of metabolic syndrome is not yet known, it could be understood that obesity and insulin resistance plays a crucial role in the occurrence of metabolic syndrome. Due to various confusing definitions, metabolic syndrome is underdiagnosed and untreated. Health and quality of life of the population can be safeguarded by preventing the onset of more comorbidity. This can be done through public awareness and health care programs. Maximum compliance to therapeutic regimen will be achieved through the identification of Met S and its factors and thus help the individual to lead a healthy lifestyle.

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