METABOLIC SYNDROME

Musbah Made
Clinical Fellow,
Ealing Hospital NHS Trust,
London, UK

ABSTRACT

There are different definitions of the metabolic syndrome that have been recommended by the World Health Organization (WHO), the European Group for Study of Insulin Resistance (EGIR), the National Cholesterol Education Program Expert Panel (NCEP), and the American Association of Clinical Endocrinologists (AACE) separately since 1998. The prevalence of the metabolic syndrome reported from different studies has varied widely, mainly because of differences in the definitions of the syndrome and in the characteristics of the populations studied. There are several studies including a large population-based Italian study, the Framingham Offspring Study, the Botnia Study, the Kuopio Ischemic Heart Disease Study, the National Health and Nutrition Examination Survey II Mortality Study, the San Antonio Heart Study, and the DECODE study have shown that metabolic syndrome is associated with an approximate 2-fold increase in the risk of cardiovascular morbidity and mortality [1].

INTRODUCTION

Kylie in 1920 was the first who described combination of certain metabolic disturbances as hypertension, hyperglycaemia and gout which now known as metabolic syndrome, and after 2 decades Vaque noted the association between upper body obesity and metabolic abnormalities seen with diabetes and cardiovascular disease. During the 1988 Bunting Lecture, Reaven used the term ‘Syndrome X’ and firmly established the clinical importance of this syndrome, although obesity was not included. In 1989, Kaplan renamed it ‘The Deadly Quartet’ and others then coined the term ‘The Insulin Resistance Syndrome’. It is now agreed that the well-established term ‘metabolic syndrome’ remains the most useful and widely accepted description of this cluster of metabolically related cardiovascular risk factors which also predict a high risk of developing diabetes (if not already present) [2].
DEFINITIONS

**WHO DEFINITION [1999]:** It is based on the fact of insulin resistance, being the main culprit of the Deadly syndrome. The insulin resistance was calculated using the insulin clamp, which is not cost effective [3]. The guidelines from the WHO differ from ATP III 2001 and 2005, mainly that it requires the presence of insulin resistance to make the diagnosis of metabolic syndrome.

The **EGIR:** The European Group for study of Insulin Resistance in 1999, came up with a modified definition of metabolic syndrome only for the non diabetic individuals. The definition was based on Insulin resistance only. It used fasting insulin levels to estimate insulin resistance and took into consideration the use of impaired fasting glucose instead of impaired glucose tolerance [4].

The **NCEP ATP 2001** which emphasized only on the cardiovascular risk factors ,was later updated in 2005 [5]. In NCEP ATP 2005, the treatment for low HdL or high triglycerides was with Niacin or fibrates respectively. In Asian patients, the waist =90 cm in men or =80 cm in women [6].

In **AACE 2003 [7]:** The high risk of being insulin resistant was indicated by one of the following:

- Diagnosis of CVD, hypertension, polycystic ovary syndrome, non-alcoholic fatty liver disease or acanthuses Nigerians.
- A family history of Type 2 diabetes, hypertension or CVD.
- History of gestational diabetes or glucose intolerance.
- Non white ethnic group.
- A Sedentary lifestyle.
- The BMI 25 kg/m2 or waist circumference 94 cm for men and 80 cm for women;
- Age being 40 years.

The **IDF 2005:** For South Asian, Chinese and Japanese, waist = 90cm (men) and 80cm (women) while for people of Europid origin it is 94cms for men and 80 cms for women respectively. [8]. The most commonly used definitions are NCEP ATP III 2005 and IDF 2005. Different Criteria of metabolic syndrome were compared to diagnose individuals of different populations at a risk of metabolic syndrome: A population based study when conducted in an urban group in the US, the IDF criteria analysed and rather diagnosed 15 to 20 percent more individuals with the metabolic syndrome than the ATP III criteria did.[6] The relative importance of the different metabolic syndrome definitions for both prognosis and management of
metabolic syndrome, appeared to be same when different studies were conducted [9,10].

**AMERICAN HEART ASSOCIATION/UPDATED NCEP CRITERIA for diagnosis of metabolic syndrome:**

a. elevated waist circumference: male>102cm and female>88cm  
b. elevated TG>150mg/dl  
c. reduced HDL >1.03mmol/l for male and>1.29mmol/l for female.  
d. elevated BP 130/85 or use of medication.  
e. elevated FBG>100mg/dl or use of medication

**NCEP 2001.criteria required at least three of the following:**

a. central obesity, waist circumference >102cm in male and 88cm for female.  
b. dyslipidemia TG>1.7mmol/l/L  
c. dyslipidemia.HDL>40mg/dl in male and >50mg/dl for female  
d. BP >130/85mm/Hg  
e. FBG>6.1mmol/l (110mg/dl)

Last to be mentioned is that high-sensitivity c-reactive protein has been developed and used as marker to predict coronary vascular diseases in metabolic syndrome [11].

**HISTORY OF METABOLIC SYNDROME**

In 1923 Kylin was the first to discover a syndrome which included hypertension, hyperglycemias and hyperuricemia. This was then followed by Vague in 1940, who documented the relation of abdominal obesity, fat distribution to diabetes and other disorders. Then later in the 1965, an abstract article was presented by Avogadro and Crepaldi, highlighted the syndrome which again comprised of hypertension, hyperglycemias and obesity.

In 1988 a lecture was given by Gerry Reaven, who described the risk factors for diabetes and cardiovascular disease and named it as syndrome X. He also introduced the term and the concept of insulin resistance. In 1989, Kaplan, reframed the syndrome as ‘The Deadly Quartet ‘and was again renamed as ‘The insulin Resistance Syndrome’.

It has been labelled as ‘Syndrome X’ , since ‘X’ is found in both men and women . Hence both genders are at a high risk if they come under the umbrella of the deadly ‘Metabolic Syndrome’. It has been seen that in both genders of the Mexican Americans have high prevalence of metabolic syndrome, but the African American women are at a higher incidence risk than the men.
The major culprit for ‘The Deadly Quartet’ is abdominal obesity. All the elements revolve around this abdominal obesity. The reason behind this culprit the imbalance between food intake and the energy expenditure.

The deadly Quartet is also global burden for all the counties worldwide. India has already been named as the Diabetes Capital of the world and by year 2020 it shall have the highest number of people with cardiovascular disease.

As we all know that prevention is better that cure so individuals who are at a high risk of metabolic syndrome should be targeted and treated in order to decrease long term morbidity [12].

METABOLIC SYNDROME, COMPONENTS AND CLINICAL PRACTICE

Like its name and different definitions MetS has divided its components into different categories with essential components of “obesity, insulin resistance, dyslipidaemia and hypertension”. (1) In WHO (World Health Organisation) insulin resistance is a major contributory factor and to validate this they will need IGT (impaired glucose tolerance) or diabetes to be present among other two for diagnosis. In contrast EGIR (European Group for the study of insulin resistance) will accept IFG (impaired fasting glucose) replacing IGT to get it accepted widely in practice. When it comes to blood pressure WHO and EGIR seems to agree on =140/90mmHg but NCEP ATP III (National Cholesterol Education Program-Third Adult Treatment Panel) has lower there threshold to =130/=85 mmHg and it is also interesting that they have not included insulin resistance in their criteria. (1) WHO has another unique component of micro-albuminuria that has been open to debate about its application in clinical practice? For obesity WHO uses either waist-hip ratio or BMI comparing to waist circumference. Later has been shown to have greater affectivity to assess abdominal adiposity. (1) When it comes to its application in clinical practice AACE (American Association of Clinical Endocrinology Position statement, 2002) has decided not to define MetS instead leave it to the clinician to decide on their verdict [13].

DIAGNOSIS

One of the important factor for diagnosis of metabolic syndrome is obesity, where there is insulin resistance, dyslipidemia, hypertriglyceridemia and type 2 DM. this syndrome associated with cardiovascular risk and hypertension.

The metabolic syndrome is associated also with reduction in the level of testosterone which associated with inflammation in male while in women it is associated with reduce androgen [14].

The diagnosis of metabolic syndrome can be made if 3 of 5 of the ATP III (Adult treatment panel) are present:
- Abdomen obesity-men >102cm  
- Female >88cm  
- Triglyceride’s >150mg/dl  
- HLD cholesterol-men<40mg/dl,Femal<50mg/dl  
- Blood pressure>130/85mmHg  
- Fasting glucose >110mg/dl  
- And in this criteria the CVD consider a primary risk of the metabolic syndrome [15].

**RISK OF CARDIOVASCULAR DISEASE**

According to many studies its show that the presence of metabolic syndrome is associated with increase of total morbidity and mortality [16]. This increase of cardiovascular risk is mainly secondary to increase level of triglyceride and LDL with decrease in the level of HDL.

**MANAGEMENT**

Life style modification is the most important aspect of the management of metabolic syndrome and Preventing of DM and ASCVD. Once a diagnosis of the MetS is made, individuals should receive increased attention with the aim of reducing the risk for CVD and Type 2 diabetes. They should undergo a full cardiovascular risk assessment, which would include smoking status. Primary management for the MetS is healthy lifestyle promotion. This includes:

- Moderate calorie restriction (to achieve a 5–10% loss of body weight in the first year) moderate increases in physical activity.  
- Change dietary composition to reduce saturated fat and total intake, increase fibre and, if appropriate, reduce salt intake.

Whenever possible, a normal BMI and/or normal waist circumference ought to be a long-term target of lifestyle intervention. The results of the Finnish and American prevention of diabetes studies have, however, both shown the marked clinical benefits associated with a small weight loss in terms of preventing (or at least delaying by several years) the conversion to Type 2 diabetes among high-risk individuals with glucose intolerance who were, on average, obese [17,18]. Moreover, observational studies have shown that moderate to vigorous physical activity for 180 min per week reduces the risk of the metabolic syndrome by 50%—with more vigorous exercise only 60 min is needed. In addition, an improvement in all lipid parameters has been observed with increased physical activity. Similar clinical trial data showing the impact of exercise on the development of CVD and diabetes are, however, lacking for people presenting with metabolic syndrome.
In people who are considered to be at high risk for CVD, drug therapies may be required to treat the metabolic syndrome. There is a definite need for a treatment that can modulate the underlying mechanisms of the metabolic syndrome and thereby reduce the impact of all the risk factors and the long-term metabolic and cardiovascular consequences. As these mechanisms are currently unknown, specific pharmacological therapy is not yet available. It is therefore necessary to treat the individual components of the syndrome, including obesity, dyslipidaemia, abnormal glucose tolerance and elevated blood pressure.

**DYSLIPIDEMIA**

Elevated LDL-cholesterol levels in patients with the metabolic syndrome represent a high risk and are one of the primary targets of therapy. Other important therapeutic aims are to lower TG (as well as lowering Apo B and non-HDL-cholesterol) and to raise HDL-cholesterol. Statins will reduce all Apo B-containing lipoproteins and often can achieve the ATP III goals for LDL-cholesterol as well as for non-HDL-cholesterol (Table1). Several clinical studies have confirmed the benefits of statin therapy. Fibrates improve all components of atherogenic dyslipidaemia and appear to reduce the risk for CVD. The Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) showed that raising HDL-cholesterol concentrations using a fibrate in patients with established CHD and both a low HDL-cholesterol and a low LDL-cholesterol level will significantly reduce the incidence of major coronary events [19].

Table 1: Adult Treatment Panel III goals—comparison of low-density lipoprotein (LDL)-cholesterol and non-high-density lipoprotein (HDL)-cholesterol goals for three risk categories [20].

<table>
<thead>
<tr>
<th>Risk category</th>
<th>LDL goal</th>
<th>Non-HDL goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHD and CHD risk equivalent (10-year risk for CHD &gt; 20%)</td>
<td>&lt; 2.6 mmol/l (100 mg/dl)</td>
<td>&lt; 3.3 mmol/l (130 mg/dl)</td>
</tr>
<tr>
<td>Multiple (2+) risk factors and 10-year risk = 20%</td>
<td>&lt; 3.3 mmol/l (130 mg/dl)</td>
<td>&lt; 4.1 mmol/l (160 mg/dl)</td>
</tr>
<tr>
<td>0–1 risk factor</td>
<td>&lt; 4.1 mmol/l (160 mg/dl)</td>
<td>&lt; 4.9 mmol/l (190 mg/dl)</td>
</tr>
</tbody>
</table>

**ELEVATED BLOOD PRESSURE**
All patients with (blood pressure = 140/= 90 mmHg), drug therapies are required according to the USA Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommendations [21]. In patients with established diabetes, antihypertensive drugs should be introduced at an even lower blood pressure (= 130/= 80 mmHg). No particular antihypertensive agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome.

Diuretics and β-blockers in high doses can worsen insulin resistance and atherogenic dyslipidaemia. For thiazide diuretics, doses should be kept relatively low in accordance with current recommendations. β-Blockers are cardioprotective in patients with CHD and are no longer contraindicated in patients with Type 2 diabetes. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs and some clinical trials (but not all) suggest that they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials indicate that most of the risk reduction associated with antihypertensive drugs is the result of blood pressure lowering per se and not due to a particular type of drug.

INSULIN RESISTANCE AND HYPERGLYCAEMIA

Drugs that reduce insulin resistance will delay the onset of Type 2 diabetes and will reduce CVD risk when the metabolic syndrome is present. The Diabetes Prevention Program showed that metformin therapy in patients with IGT will prevent or delay the development of diabetes and recent thiazolidinedione studies have also demonstrated efficacy in delaying or preventing Type 2 diabetes in patients with IGT and insulin resistance [22-24]. Similarly, other studies have shown that both acarbose and orlistat can be used to delay the development of Type 2 diabetes in patients with IGT [25,26].

Further support for the concept of treating insulin resistance is apparent from the UKPDS, which showed that in Type 2 diabetes, treatment with metformin reduced CVD and mortality, whilst treatment with insulin or sulphonylureas did not show such an effect [27,28]. Data do not yet exist to show whether or not any of the currently available thiazolidinediones reduce the risk of CVD in those with the metabolic syndrome, IGT or diabetes. One study has suggested that treating IGT patients with acarbose is associated with a significant reduction in the risk of CVD [29]. The results of various ongoing disease progression and cardiovascular outcome studies using several new drugs, such as thiazolidinediones, are awaited with interest.

The presence of the metabolic syndrome in patients with Type 2 diabetes conveys particularly high risk for CVD. When both are present, appropriate treatment of dyslipidaemia and hypertension is essential in addition to the best possible glycaemic control. The choice of drug therapy, beyond lifestyle
changes, to achieve the recommended glycaemic goal depends on clinical judgement.

CONCLUSION

According to different studies, the incidence of DM & CVD is more in people with metabolic syndrome than the normal people and the intensive lifestyle change are effective & should be encouraged.

REFERENCES

[1] Hu G, Qiao Q, Tuomilehto J,. Diabetes and Genetic Epidemiology Unit, Department of Epidemiology and Health Promotion, National Public Health Institute, Helsinki, Finland. hu.gang@ktl.fi PMID: 18220589.


Cited: 3484