Review Article and Clinical Experience:
THE MetS: ONE OF THE MAJOR THREAT TO HUMAN HEALTH

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ABSTRACT

The metabolic syndrome represents a cluster of risk factors in which CVD has been generally accepted as the primary clinical outcome. When T2DM become clinically manifest, CVD risk rises sharply. Beyond CVD and T2DM, patients with the MetS are likely susceptible to other conditions, notably as mentioned below. Different criteria have been proposed by the WHO (1998) and by the ATP-III (2001) for the diagnosis of the MetS. The author summarized 10 components of the MetS called the "Widened MetS", such as: 1. Visceral Obesity, 2. Insulin Resistance, 3. Atherogenic Dyslipidemia, 4. Raised Blood Pressure, 5. Proinflammatory State, 6. Prothrombotic State, 7. Vascular Abnormalities, 8. Hyperuricemia, 9. Adrenal Incidentaloma, 10. Fatty Acid Deposition in the liver (NASH). Obesity, especially visceral obesity, plays as a key component in contributing to the clustering of such risk factors. The MetS: the Iceberg Concept emphasizes that cardiovascular burden has been recognized as the tip of an iceberg in which the immersed part is the preceding clustering of the metabolic abnormalities. Patients with the MetS are at increased risk for CHD. Almost 50% of the population-attributable risk for diabetes could be explained by the presence of ATP-III metabolic syndrome (the MetS as a predictor of diabetes). Regardless of diagnostic criteria used, lifestyle modifications, with emphasis on weight reduction, contributes first-line intervention for individuals with the MetS. In addition, treatments specifically targeting insulin resistance and metabolic risk factors should be considered for patients with the MetS. The WHO-1998 and the ATP III – 2001 criteria have recently proposed a formal definition of the MetS. The latter identified 6 components (no. 1-6) of the "Widened MetS" that related to CVD. The MetS is a predictor of T2DM and CVD, and the latter can be viewed as its primary clinical outcome. Lifestyle modifications contribute first-line therapy for the MetS. Drug treatment targeting obesity, insulin resistance, and risk factors (atherogenic dyslipidemia, blood pressure reduction, etc) should be initiated. The MetS is one of the major threats to human health. To date, the MetS represents a major worldwide public health problem that should be early detected, prevented, and appropriately managed to minimize the prevalence of its CVD outcome.

Keywords: *Metabolic syndrome (MetS), WHO-1998, ATP III-2001, Widened MetS, Type 2 Diabetes Mellitus, lifestyle modifications*

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INTRODUCTION

In 1998, the WHO proposed the term "Metabolic Syndrome" (MetS) to define the clustering of diseases and risk factors accompanying T2DM, formerly known as "Syndrome-X" (Reaven 1988), "Deadly Quartet" (Kaplan 1989): upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension, or "Insulin Resistance Syndrome" (DeFronzo et al. 1991). Recently (2001), the Third Report of the National Cholesterol Education Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Adult Treatment Panel III (ATP III 2001) provided a working definition of MetS, based on combination of categorical risk factors, easily applicable to the general population. ATP III (2001) identified CVD as the primary clinical outcome of the MetS. Most people with this syndrome have insulin resistance, which confers increased risk for T2DM. When diabetes becomes clinically apparent, CVD risk rises sharply.

ATP-III (2001) identified 6 components of the MetS that relate to CVD:

1. Abdominal obesity
2. Atherogenic dyslipidemia
3. Raised blood pressure
4. Insulin resistance ± glucose intolerance
5. Proinflammatory state
6. Prothrombotic state

The AHA/NHLBI/ADA conference (2004) confirmed CVD as a major clinical outcome of MetS and identified 6 major components of the syndrome as mentioned above. Clinical recognition of the MetS is generally based on finding several well recognized signs in clinical practice (Grundy et al. 2004): abdominal obesity, elevated triglycerides, reduced HDL cholesterol, raised blood pressure, and elevated plasma glucose.

In addition, research shows that other components not routinely measured commonly aggregate with the major components: elevated apo-B, small LDL particles, insulin resistance and hyperinsulinemia, IGT, elevated CRP, and variation in coagulation factors (e.g., PAI-1, and fibrinogen). Cumulatively, Tjokroprawiro (2003, 2004) summarized 10 components of the MetS called the "Widened MetS" that can be seen in FIGURE 1. WHO (1998) and ATP-III (2001) proposals for the definition of the MetS are comparatively summarized by Tjokroprawiro (2004) as seen in Table 1. Based on such a short description, it can be concluded that the MetS may become one of the major threat to human health. Subsequently, the MetS will definitively pose a big public health problem worldwide and this syndrome may present one of the major causes of CVD, responsible for a great number of premature deaths throughout the world.

The aim of these manuscript and presentation is to transfer to readers and audiences the recent knowledge of the MetS and its widening that contains 10 components in which the first 6 components of them are responsible for the primary clinical outcome as cardiovascular events.

CLINICAL DIAGNOSIS OF THE METS: ATP-III (2001) VS WHO (1998)

Clinical identification of the MetS based on ATP-III (2001) and WHO (1998) criteria are shown and summarized in Table 1.

TABLE 1 - Clinical Identification
Metabolic Syndrome, Insulin Resistance Syndrome
(Summarized : Tjokroprawiro 2004)

National Cholesterol Education Program Adult Treatment Panel III Metabolic Syndrome (NCEP-ATP III, 2001)	Modified WHO (1998)
At least (3) of the Following (cm, mg/dl, mmHg) : (diabetes is not excluded) (1) Abdominal Obesity (Waist Circumference) Men* : > 102 ; Women** : > 88 Predisposition Pts : *94, **80 INA : Men > 90; Women > 80 (2) Serum Triglyceride ≥ 150 (3) Serum HDL-Cholesterol Men : < 40 ; Women : < 50 (4) Blood Pressure ≥ 130 / ≥ 85 (5) Fasting Glucose ≥ 110	**Hyperinsulinemia and or** **Fasting Plasma Glucose ≥ 110 mg/dl*)** **and/or** **2 h Post Glucose Load > 140 mg/dl** **plus** At least (2) of the Following : (1) **Abdominal Obesity :** BMI > 30 kg/m^2 WHR > 0.90 for men, > 0.85 for women (2) **Dyslipidemia :** Serum Triglyceride > 150 mg/dl or HDL-Cholesterol < 35 mg/dl (3) **Hypertension :** Blood Pressure ≥ 140/90 mmHg or on Hypertensive Medication

***) New Criterion for FPG : < 100 mg/dl (ADA – 2004)**

Criteria of ATP-III (2001) are shown in the left side of TABLE-1. When 3 of 5 of the listed characteristic are present, a diagnosis of the MetS can be made ATP-III (2001) identified CHD / CVD as the primary clinical outcome of the MetS. Abdominal obesity, diagnosed by increased waist circumference, is the first criterion listed; hence, the priority given to abdominal obesity as a key player in the MetS. Insulin resistance is not required for diagnosis; however, most individuals meeting ATP-III criteria will be insulin resistant. In addition, the presence of T2DM does not exclude a diagnosis of the MetS. In contrast to WHO criteria, ATP-III criteria can not be used in the retrospective study if waist circumference is not available in the medical record of the patients. Body weight and body height are routinely measured, thus, body mass index

(BMI) as listed in the WHO criteria can be calculated; therefore, the WHO criteria can be used for either retrospective or prospective studies.

The guideline group of WHO also recognized CVD as the primary outcome of the MetS, however insulin resistance is required as a component for diagnosis. The criteria diagnosis of insulin resistance is shown in right part of TABLE-1. However, the new criteria for impaired fasting glucose level have been lowered to 100-125 mg/dl (*ADA-2004*) instead of 110-125 mg/dl by old criteria (*ADA-2003*).

In addition to insulin resistance, 2 other risk factors are sufficient for diagnosis of the MetS. A higher blood pressure was required than in ATP-III, BMI (or increased WHR) was used instead of waist circumference, and microalbuminuria was listed as one criterion. Like ATP-III, the presence of T2DM does not exclude a diagnosis of the MetS. A potential disadvantage of the WHO criteria is that special testing of glucose status beyond routine clinical assessment may be necessary to diagnosis the MetS.

The American College of Endocrinology (*ACE)* in 2003 proposed a third set of clinical criteria for the Insulin Resistance Syndrome. By such criteria, when a person develops diabetes, the term Insulin Resistance Syndrome no longer applies.

THE "WIDENED METABOLIC SYNDROME": THE "WIDENED METS"

ATP-III (2001) identified 6 components of the MetS that related to CVD:

1. Abdominal obesity
2. Atherogenic dyslipidemia
3. Raised blood pressure
4. Insulin resistance ± glucose intolerance
5. Proinflammatory state
6. Prothrombotic state.

Beyond these components, individuals with the MetS are susceptible to other conditions, notably:

7. Vascular abnormalities (endothelial dysfunction, ACR ≥ 30 mg/g)
8. Hyperuricemia
9. Adrenal incidentaloma (increased cortisol secretion)
10. Fatty acid deposition (fatty liver).

Tjokroprawiro (2003, 2004) summarized such 10 components which can be found in the MetS, and termed the "Widened Metabolic Syndrome" or the "Widened MetS" as shown in Figure 1.

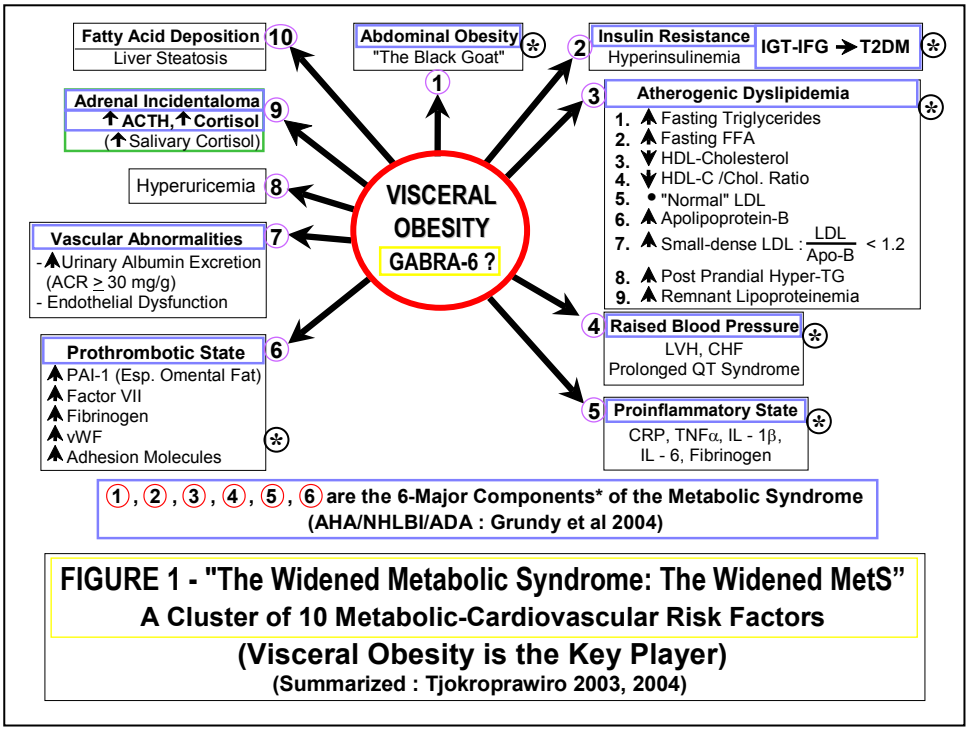

FIGURE 1 - "The Widened Metabolic Syndrome: The Widened MetS"
A Cluster of 10 Metabolic-Cardiovascular Risk Factors
(Visceral Obesity is the Key Player)
(Summarized : Tjokroprawiro 2003, 2004)

The GABRA6 gene is located on chromosome 5q31.1-q35. Rosmond et al. (2002) addressed the hypothesis that the 1519T>C variant of the GABRA6 gene may influence obesity and obesity-related phenotypes as well as circulating hormones, including salivary cortisol. Cortisol is involved in the regulation of the adipose tissue differentiation, function, and distribution, and in excess causes visceral obesity. Allelic variants in the $GABA_A\alpha 6$ receptor subunit gene (GABRA6) is associated with abdominal obesity and cortisol secretion (Rosmond et al. 2002).

THERAPEUTIC INTERVENTION FOR THE METS

ATP-III (2001) recommended that obesity and body fat distribution are the primary target of intervention for the MetS. Insulin resistance would be an attractive target if this component is in the chain of causation of the MetS. Weight loss lowers serum cholesterol and triglycerides, raises HDL cholesterol, lowers blood pressure and glucose, and reduces insulin resistance. Recent data further show that weight reduction can decrease serum level of CRP and PAI-1. Two classes of drug are currently available that reduce insulin resistance, notably metformin and glitazones (TZDs). In spite of promise, at present, metformin and TZDs cannot be recommended for the express purpose of reducing risk for CVD in persons with the MetS. Specific metabolic risk factors should be taken into account as targets of therapy, f.e: hyperglycemia, atherogenic dyslipidemia, elevated blood pressure, prothrombotic and proinflammatory states. Based on clinical experiences and practical point of view, Tjokroprawiro (2003, 2004) summarized strategies for the treatment of the MetS as shown in Table 2.

TABLE 2 - Strategies for Treatment
Metabolic Syndrome (MetS) - Insulin Resistance Syndrome (IRS)
(Summarized : Tjokroprawiro 2003, 2004)

A Weight Reduction Improving Insulin Sensitivity	B Treating Metabolic Risk Factors
1) Healthy Lifestyle Modifications - Weight Loss 5-10% - Aerobic Exercise ± 30-40 minutes, 4 x/week 2) Pharmacological Treatment - Metformin - Glitazones - Sibutramine (R/ Reductil) - Orlistat (R/ Xenical) - Rimonabant (CB_1-Rec. Antagonist)	1) Lifestyle Modifications - MNT = Medical Nutritional Therapy - Regular Exercise 2) Recommended Treatment Goals (mg/dl, mmHg) : B, H, D, L * Reduced BW by ≤ 5-10% (6-12 Months) * BP < 130/85; BP < 130/80 for DM (H) * FPG < 100; 2h-PG < 140 (D) * LDL < 100, TG < 150 (L) * HDL > 40 (♂), HDL > 50 (♀) (L)

Attention: Weight reduction reinforced with increased physical activity should be the first-line therapy for the MetS. Lifestyle modification contributes a pivotal role in weight reduction. Weight loss improves metabolic risk factors, reduces insulin resistance, and decreases serum levels of CRP and PAI-1.

THE ENDOCANNABINOID SYSTEM AND OBESITY

The physiological control of appetite and satiety, in which numerous neurotransmitters and neuropeptides play a role, is extremely complex. The role of the newly discovered endocannabinoid system as a further level of modulation of feeding in animals and in humans is being studied. So far, two principal receptors have been

found to part of the endocannabinoid system (Berry et al. 2002):

1. CB_1, which present mainly in the brain and to a lesser extent in the periphery
2. CB_2, which is located mainly in the immune system

The CB_1 cannaboid receptor antagonist SR141716A blocks the effects on feeding produced by endocannabinoids (endogenous ligands). Three types of endocannabinoids have been identified:

1. anandamide (anachidonoyl ethanolamide)
2. noladine ether
3. arachidonyl glycerol

The endocannabinoid system seems to be involved in the regulation of food intake and body weight. CB_1 receptor antagonist demonstrated reduced body weight and fat mass (due to an increased peripheral lypolysis), and reduced appetite in experimental mice.

The Sanofi-Synthelabo Research Group recently has presented their results of the effects of SR141716 in obese male patients (Le Fur et al. 2001). Obese male patients in a double-blind cross-over study (20 mg s.i.d vs placebo) were treated for 7 days followed by a 28-day washout period. While this drug had no effect on taste, it induced a significant decrease of hunger, caloric intake, and weight. In a separate study, at doses of 5, 10, and 20 mg s.i.d, the drug significantly reduced body weight in obese patients in comparison with placebo. It was also reported that the tolerability of SR141716 was excellent and that the observed decreased in weight did not reach a plateau during a 4-month study. These results point out that SR141716 may become a promising therapeutic drug in obesity and may be useful for persons with the MetS.

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