

Review Article and Clinical Experience

**METABOLIC SYNDROME VS INSULIN RESISTANCE SYNDROME
(A CLUSTER OF COMPONENTS AND STRATEGIES FOR TREATMENT)**

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ABSTRACT

Metabolic Syndrome = MS (in which abdominal Obesity is the culprit of the MS) is defined by NCEP-ATP III in 2001, whereas Dysmetabolic Syndrome = DMS and Insulin Resistance Syndrome = IRS are recommended terms by AACE (in 2002) and ACE (in 2002), respectively. Both AACE and ACE stated that insulin resistance plays central role in the syndrome. All these terms of the syndrome are originally and firstly coined by Reaven as Syndrome-X in 1988, and then Metabolic Syndrome-X in 1999. Either MS or DMS or IRS has become major issues because of its impact on the risks of Type 2 DM (T2DM) development and cardiovascular diseases. The criteria of MS, IRS (including its risk factors), and the clusters of components belong to MS and IRS, are listed in this paper. Rational strategies for the treatment of MS and IRS are focused on obesity and insulin resistance, respectively, and can be summarized as follows: A. Improving insulin sensitivity and lifestyle (weight loss 5-10%, aerobic exercise $\pm$ 30-40 min, 4 times/week). B. Pharmacological Interventions directed to the targets for (mmHg, ml/dl): Blood Pressure < 130/85, and 130/80 in diabetic patients, Fasting Plasma Glucose (FPG) < 110 or 2 Hour Post-75 Glucose Challenge < 140, Triglyceride (TG) < 150, and HDL-Cholesterol > 40 for men, and > 50 for women. Clinical evidence-based data supported, that Metformin (UKPDS Outcomes), Sibutramine (STORM Landmark Trial), and Orlistat (XENDOS Study), to date, are the promising drugs for the treatment of MS/IRS. However, the drugs specifically to improve the insulin sensitivity are hoped to treat this Syndrome. Conclusions: Syndrome-X, Metabolic Syndrome-X, MS, DMS, or IRS, all have become major issues because of their roles in the development of either T2DM or Cardiovascular Diseases. The cluster of components of this Syndrome and its risk factors should be well recognized. Improving insulin sensitivity, losing body weight, aerobic exercise, and pharmacologic interventions (Metformin, Sibutramin, Orlistat) are rational strategies for the treatment of MS/IRS.

Keywords: *metabolic syndrome, dysmetabolic syndrome, insulin resistance syndrome, type 2 diabetes mellitus, cardiovascular diseases,*

Abbreviations: NCEP-ATP III = The National Cholesterol Education Program – Adult Treatment Panel III, AACE = The American Association of Clinical Endocrinologists, ACE = The American College of Endocrinology, UKPDS = United Kingdom Prospective Diabetes Study, STORM = Sibutramine Trial in Obesity Reduction, and Maintenance, XENDOS = XENical in the prevention of Diabetes in Obese Subjects.

**METABOLIC SYNDROME AND INSULIN
RESISTANCE SYNDROME:
A DIFFERENCE?**

Metabolic Syndrome = MS (NCEP-ATP III, 2002) or
Dysmetabolic Syndrome = DMS (AACE – ICD-9 Code

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227.7, 2002) or Insulin Resistance Syndrome = IRS (ACE, 2002) which was originally coined by Reaven as to Syndrome-X in 1988 and then Metabolic Syndrome-X in 1999, leads to a cluster of abnormalities with many clinical consequences. The components of such a Syndrome are cumulatively summarized by the author into 10 groups (listed below), in which Visceral Obesity plays a role as the central problem. Now, however, Obesity and Diabetes Mellitus (DM) are assessed as strong risk factors and serious clinical consequence in IRS (also f.e = CVD, PCOS, NASH, etc), respectively.

The 10 findings of MS summarized by Tjokroprawiro (2002-2003) are:

1. Visceral Obesity (“The Black Goat”)
2. Insulin Resistance (Hyperinsulinemia)
3. IFG, IGT, DM
4. Atherogenic Dyslipidemia (Increased Triglycerides, Decreased HDL-Cholesterol, Increased Apolipoprotein-B, Increased Small Dense LDL)
5. Hypertension (LVH, CHF)

6. Prothrombotic State (Increased PAI-1 [Esp. Omental Fat], Increased Factor VII, Increased Fibrinogen, Increased vWF, Increased Adhesion Molecules)
7. Vascular Abnormalities (Increased Urinary Albumin Excretion, Endothelial Dysfunction)
8. Inflammatory Markers (CRP, TNF α , IL-1 β , IL-6)
9. Hyperuricemia
10. Increased ACTH, Increased Cortisol (Increased Salivary Cortisol)

However, ACE Statement (2002) outlined that the relationship between Obesity and the IRS differs in two respects.

1. Obesity is not a consequence of Insulin Resistance/Hyperinsulinemia, but a physiological variable that decreases Insulin-Mediated Glucose Disposal (IMGD). Not all insulin resistant persons are overweight or obese, and not all overweight or obese persons are insulin resistant. The descriptions of the IRS often include Obesity, usually Visceral Obesity, as one of the features of the Syndrome, rather than as a lifestyle factor that, because of its adverse effects on IMGD, increases the risk of the IRS.
2. It is proposed that Body Mass Index (BMI), rather than Waist Circumference (WC), be used to identify individuals at increased risk to have the IRS. One of several reasons of this statement is that height and weight are simple and routine measurements that are easily quantified, in contrast to estimates of WC, which are neither routinely performed nor is its quantification as well standardized. For these reasons, it has been suggested that BMI be used as the marker to identify persons that should be evaluated for the IRS. However, it would not be a great deal to lose, if WC was used instead of BMI as a tool to identify individuals at increased risk to have the IRS. Hence, ACE Position Statement on the IRS outlined the 7-components of the IRS which will be mentioned below.

The 7-Groups of Components of the Insulin Resistance Syndrome are (ACE 2002):

1. Some degree of glucose intolerance
 - a. Impaired fasting glucose
 - b. Impaired glucose tolerance
2. Abnormal uric acid metabolism
 - a. Plasma uric acid concentration
 - b. Renal uric acid clearance
3. Dyslipidemia
 - a. Triglycerides
 - b. HDL-C
 - c. LDL-particle diameter (small, dense LDL-particles)

- d. Postprandial accumulation of TG-rich lipoproteins
4. Hemodynamic changes
 - a. Sympathetic nervous system activity
 - b. Renal sodium retention
 - c. Blood pressure (~ 50% of patients with hypertension are insulin resistant)
5. Prothrombotic factors
 - a. Plasminogen Activator Inhibitor-1
 - b. Fibrinogen
6. Markers of inflammation
 - a. C-reactive protein, WBC, etc.
7. Endothelial dysfunction
 - a. Mononuclear cell adhesion
 - b. Plasma concentration of cellular adhesion molecules
 - c. Plasma concentration of asymmetric dimethylarginine
 - d. Endothelial dependent vasodilatation

The criteria of MS (NCEP-ATP III, 2002) are, at least 3 of the following (in cm, mg/dl, or mmHg):

1. Abdominal Obesity (WC for men > 102, and for women > 88)
2. Serum Triglyceride (TG) = 150
3. HDL -Cholesterol, men < 40, women < 50
4. Fasting Plasma Glucose (FPG) = 110
5. Blood Pressure (BP) = 130 / 85.

In difference, for epidemiological purposes, however, ACE (2002) concluded that 2 or more of the 4 mentioned abnormalities in persons with risk factors (outlined below) constituted the IRS (in mg/dl or mmHg):

1. FPG 110 – 125, or 120 min. Post-75g Glucose Challenge 140-200 (the latter is more focused to replace FPG)
2. TG > 150
3. HDL-Chol., men < 40, women < 50, and
4. BP > 130/85.

The 7 risk factors of IRS are (ACE 2002):

1. Age > 40 years
2. BMI > 25.0 (or WC > 40 inches in men, > 35 inches in women)
3. Sedentary Lifestyle
4. Diagnosis of CVD, Hypertension PCOS, NASH, or Acanthosis Nigricans
5. Family History of T2DM, Hypertension, or CVD
6. History of GDM or IGT
7. Non-Caucasian Ethnicity (e.g Native American, Asian American, African American, Latino / Hispanic American, Pacific Islander).

Based on the pathogenesis of IRS that Insulin Resistance plays as the central role in this Syndrome, ACE emphasized additional points:

1. Not all overweight or obese people are insulin resistant, or have manifestations of the IRS, and weight loss does not lead to significant increase in insulin sensitivity in these people
2. There is no evidence that obese, insulin resistant people have any more difficulty in losing weight in response to energy-restricted diet than do equally overweight persons who are not insulin resistant.

Rational Strategies for the treatment of IRS, thus are focused on 2 main effects (ACE) 2002):

- A. Improving Insulin Sensitivity (McLaughlin et al 2002)
 - i. Lifestyle (weight loss 5-10 %, aerobic exercise $\pm$ 30-40 min, 4 times / week)
 - ii. Pharmacological Treatments, f.e Glitazone Compounds (no data in non-DM with IRS), Metformin (many evidences with significant clinical benefits), Sibutramine and Orlistat (both attenuate the manifestations of the IRS)
- B. Treating the Manifestations of IRS
 - i. Lifestyle: Medical Nutritional Therapy = MNT, Regular Exercise (Tuomilehto et al 2001). MNT: to minimize the intake of saturated fat (SAFA), would be to replace with unsaturated fat (PUFA, MUFA), rather than

with carbohydrate (Cbh), emphasizing to maintain Cbh plus MUFA which constitute approximately 70% of the total calories per day.

- ii. Pharmacological Interventions. This treatment is directed to the targets (mmHg, ml/dl) for H, D, and L: Hypertension (H): < 130/85, and < 130/80 for Diabetic patients, Diabetes Mellitus (D) – FPG < 110 or 2 hour Post-75 Glucose Challenge < 140, and Lipids (L) – TG < 150, and HDL-Cholesterol > 40 for men, and > 50 for women.

Before ending this paper, three subtopics of summarized clinical results of 3 drugs for MS or IRS will be shortly described:

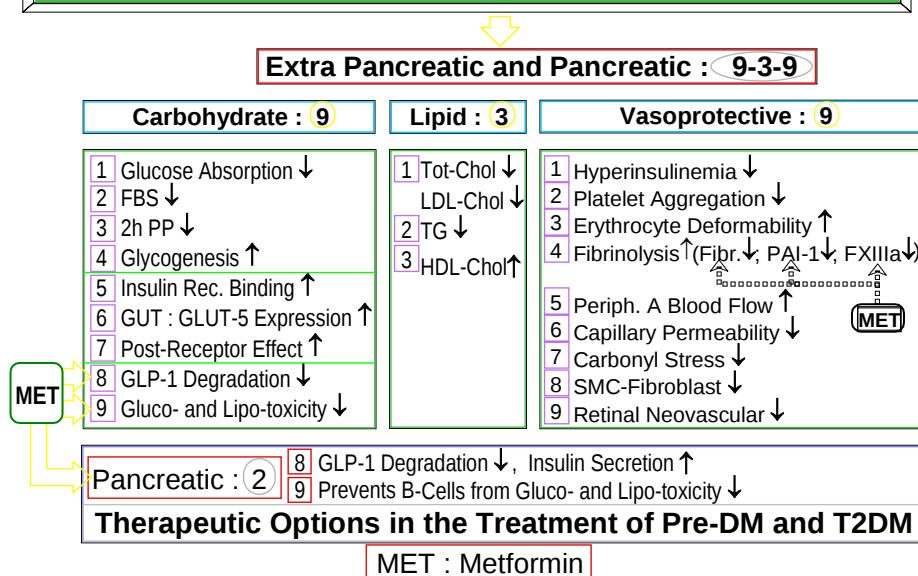
1. The 21 Clinical and Pleiotropic Effects of Metformin
2. The Results of Prominent Trial of Sibutramine
3. The Results of Large Trial of Orlistat.

1. The 21 Clinical and Pleiotropic Effects of Metformin

As seen in TABLE 1, since the years: from 1994 through 2003, Tjokropawiro (2002,2003) has summarized 21 Clinical and Pleiotropic Effects of Metformin which can be categorized into 3 groups: 9 for Carbohydrates, 3 for Lipids, and 9 for Vasoprotective Properties.

TABLE 1-Metformin with 21 Clinical and Pleiotropic Properties

(Summarized : Tjokropawiro 1994, 1997, 1999, 2002, 2003)



In 1998, UKPDS reported the outcome of intensive glycemic therapy (Metformin, Sulphonylurea / Insulin).

It can be seen that Metformin therapy showed many significant clinical benefits (TABLE 2).

TABLE 2-UKPDS: Outcomes of Intensive Glycemic Therapy-1998

Clinical Endpoints	Metformin Intensive		Sulphonylurea/Insulin Intensive	
	Change in Risk*)	p value	Change in Risk*)	p value
Diabetes-related Deaths	↓ 42%	0.017	↓ 20%	0.19
All Cause Mortality	↓ 36%	0.011	↓ 8%	0.49
Any DM-Related Endpoint	↓ 32%	0.0023	↓ 7%	0.46
Myocardial Infarction	↓ 39%	0.01	↓ 21%	0.11
Stroke	↓ 41%	0.13	↓ 14%	0.60

2. The Results of Prominent Trial of Sibutramine

STORM (Sibutramine Trial in Obesity Reduction, and Maintenance) Trial has proven that Sibutramine is able to achieve weight loss, to maintain weight reduction, and to reduce comorbidities (20.7 % increase in HDL-Cholesterol, and substantial decreases in Triglycerides, VLDL-Cholesterol, C-peptide and Uric Acid). STORM Trial (James et al 2000) involved 605 obese patients (BMI 30-40 kg/m²) for a six month period of weight loss with Sibutramine (10mg/day) and an individualized 600 kcal/day deficit program based on measured resting metabolic rates.

The 467 (77%) patients who achieved 5% weight loss were then randomly assigned to Sibutramine 10 mg/day (n=352) or placebo (n=115) for a further 18 months. Sibutramine was increased to 20mg/day if weight gain recurred. 148 (42%) individuals in the Sibutramine group and 58 (50%) in the placebo group dropped out. Of the 204 Sibutramine treated individuals who completed the trial 89 (43%) maintained 80% or more of their weight loss, compared with 9 (16%) of the 57 individuals in the placebo group. Patients had substantial decreases over the first six months in respect of Triglycerides, VLDL-Cholesterol, C peptide and Uric Acid which were sustained in the treated but not in the placebo group.

Interestingly, HDL-Cholesterol concentrations rose substantially in the second year with overall increases of 20.7% in the Sibutramine group and 11.7% in the

placebo group. Twenty patients (3%) were withdrawn because of elevated blood pressure. The mean increase in blood pressure in the study population was by 0.1 mmHg (SD12.9), diastolic blood pressure by 2.3 mmHg (9.4) and pulse rate by 4.1 beats/min (11.9). The individualized management programme achieved weight loss in 77% of obese patients and sustained weight loss in most patients continuing treatment for two years.

STORM Conclusions:

1. Sibutramine has been proven successfully as a drug to achieve weight loss, and to maintain weight reduction
2. Sibutramin was able to reduce comorbidities (20.7% increase in HDL-Cholesterol, and substantial decreases in: TG, VLDL-Cholesterol, C-peptide, uric acid). This drug can be used for treatment up to 2 years.
3. The Results of Large Trial of Orlistat

XENDOS (XENical in the prevention of Diabetes in Obese Subjects) is a landmark study in weight management with the objectives: to investigate the use of Orlistat plus lifestyle changes compared with lifestyle changes alone for the prevention of T2DM over a period of 4 years. Xendos Study Design: Multi-center, Double-blind, Placebo-controlled, Parallel-group, Randomized, Prospective. Patients were randomized to treatment with Orlistat 120 mg or Placebo three times daily for 4 years in combination with lifestyle changes: 800 kcal/day calorie deficit, moderate daily physical exercise,

lifestyle counseling every 2 weeks for the first 6 months of the study and then monthly. The primary endpoints: progression to T2DM, change in body weight; other efficacy parameters: glycemic parameters, serum lipid levels, waist circumference, and blood pressure. The safety and tolerability are also assessed.

Summarized results of XENDOS Study (O = Orlistat; P = Placebo; BP = Blood Pressure; WC = Waist Circumference) are (Torgerson et al 2004):

1. Decreased body weight: (O – 6.9 kg) > (P – 4.1 kg) $p < 0.001$
2. Patients achieving = 5% weight loss: O>P, $p < 0.001$ (Either at Year 1 or at Year 4)
3. Patients achieving = 10% weight loss: O>P, $p < 0.001$ (Either at Year 1 or at Year 4)
4. Cumulative incidence of T2DM: (O 6.2%) > (P 9.0%), $p = 0.0032$, RR = 37%
5. Effect of Orlistat Blood Pressure at Year 1:
 - a. Decreased Systolic BP: (O – 7.3) > (P – 5.2), $p < 0.001$
 - b. Decreased Diastolic BP: (O – 3.6) > (P – 2.6), $p < 0.001$
6. Effect of Orlistat Blood Pressure at Year 4:
 - a. Decreased Systolic BP: (O – 4.9) > (P – 3.4), $p < 0.01$
 - b. Decreased Diastolic BP: (O – 2.6) > (P – 1.9), $p < 0.01$
7. Effect of Orlistat on LDL-Cholesterol:
 - a. Decreased LDL-Chol at Year 1: (O – 11.4) > (P – 1.6), $p < 0.001$
 - b. Decreased LDL-Chol at Year 4: (O – 12.8) > (P – 5.1), $p < 0.001$
8. Effect of Orlistat on Waist Circumference (WC):
 - a. Decreased WC at Year 1: (O – 9.6) > (P – 7.0), $p < 0.01$
 - b. Decreased WC at Year 4: (O – 6.4) > (P – 4.4), $p < 0.001$

XENDOS Conclusions:

1. Orlistat plus lifestyle changes over 4 years resulted in greater weight loss and a significantly reduced incidence of T2DM (37%) compared with intensive lifestyle changes alone
2. Orlistat plus lifestyle resulted in significant and sustained reductions in cardiovascular risk factors such as blood pressure and lipid levels (Reaven et al 2001). The results of Xendos Study confirm the efficacy and safety of long-term Orlistat treatment for up to 4 years.

CONCLUSIONS

Key Words: The Syndrome-X ? The Metabolic Syndrome-X; MS = The Metabolic Syndrome; DMS =

Dysmetabolic Syndrome; IRS = The Insulin Resistance Syndrome; Cluster of Components of MS and IRS; Principles of Strategies for Treatment.

- I. The National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) in 2001 defined MS, whereas the American Association of Clinical Endocrinologists (AACE) in 2002 created DMS, and the American College of Endocrinology (ACE) in 2002 termed IRS. All terms of this Syndrome were firstly coined by Reaven in 1988 as Syndrome-X, and then changed as Metabolic Syndrome-X in 1999. AACE and ACE (AACE / CE) authored by the members of the Task Force appointed by the AACE President, and the Task Force then made its recommendations.
- II. The some characteristic abnormalities of MS and IRS are (mg/dl, mmHg):
 - i. Plasma Glucose: FPG 110 – 125 (NCEP-ATP III). 2 Hour Post-75 Glucose Challenge 140 – 200 (AACE / CE)
 - ii. Triglycerides > 150
 - iii. HDL-Cholesterol: for men: < 40, for women < 50
 - iv. Blood Pressure > 130/85
- III. Ten Components of MS were summarized cumulatively from several publications, whereas 7-groups of components of the IRS and its 7-risk factors were listed subsequently
- IV. While AAACE /ACE have accepted the Lipid and Blood Pressure Guidelines from NCEP-ATP III, they did recommend 6 differences (but only 4 selected differences are presented).
 - i. The IRS is used to describe the cluster of abnormalities produced in insulin resistant / hyperinsulinemic people
 - ii. The IRS is differentiated from Type 2 Diabetes Mellitus (T2DM)
 - iii. BMI, rather than WC, is used as the index of obesity and viewed as a physiological variable that increases insulin resistance, rather than as a criterion for diagnosis of the IRS.
 - iv. FPG is used primarily to identify individuals with T2DM. The 2 Hours after a 75-g Oral Glucose challenge is introduced as a more sensitive measure as risk for the IRS.
- V. Visceral Obesity is the culprit for the MS, whereas Insulin Resistance is assessed as the central problem of the IRS.
- VI. Improving Insulin Sensitivity and Treating the Clinical Manifestations of the MS and the IRS are the main targets of the goals of treatment of the Syndrome. Lifestyle: both Obesity (5-10%

Weight loss) and Aerobic Physical Activity for approximately 30-40 min, 4 times / week are recommended.

- VII. Sibutramine and Orlistat are the promising drugs to attenuate the manifestations of the MS and the IRS.
- VIII. Metformin, with the 21 beneficial effects offers potential clinical profits for the treatment of the MS / the IRS, f.e it has been shown to be effective in the treatment of PCOS, and decreases the progression of T2DM in patients with IGT (Nestler et al 1998). There is evidence that Metformin could lower circulating insulin levels and improve lipid metabolism in patients with characteristics of the MS / the IRS (Hollenbeck et al 1991). The outcome of intensive glycemic therapy with Metformin reported by UKPDS in 1998, has proven significant clinical results.

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