Obesity and Insulin Resistance: Molecular Basis for Clinical Appraisal

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ABSTRACT

Many persons have a constellation of major risk factors, life-habit risk factors, and emerging risk factors that constitute a condition called the Metabolic Syndrome. Eight components characteristic of the Metabolic Syndrome are: 1. insulin resistance (with or without glucose intolerance), 2. hyperinsulinemia, 3. abdominal obesity, 4. raised blood pressure, 5. atherogenic dyslipidemia (↑ Triglyceride, ↑ Postprandial lipemia, ↓ Small dense LDL or Type B pattern), 6. procoagulant state *(↑ Fibrinogen, ↑ PAI-1), 7. hyperuricemia, 8. endothelial dysfunction (↑ Albumin excretion rate, etc).*

Among the single etiologic factors being considered are: 1. a genetic defect in one or more components of the insulin action cascade leading to insulin resistance, 2. malnutrition during fetal development, and 3. abdominal obesity. It is possible that these three factors could be in some way interrelated.

Several mechanisms implicated in the development of insulin resistance in obesity can be shortly postulated below.

TNF-α oversecreted by the enlarged fat cells impairs insulin action by inhibiting insulin receptor signaling, possibly by increasing IRS-1 serine phosphorylation GLUT-4 expression and translocation to the cell surface will be impaired by TNF-α.

Leptin released from visceral adipocytes may inhibit insulin action in the liver by impairing insulin receptor signaling, leading to reduced down-regulation of PEPCK, the rate-limiting enzyme in gluconeogenesis. Glucose-stimulated insulin released from pancreatic β-cell is also impaired by leptin through STAT-3 production stimulated by leptin via leptin receptor on the surface membrane of β-cell, and then STAT-3 stimulates the opening of K^+_{ATP}-channels, and consequently insulin release will be inhibited.

Resistin, as well as TNF-α and leptin released by adipocytes, decrease insulin sensitivity and to be suggested to inhibit adipogenesis; insulin administration rapidly increases resistin levels to normal in adipose tissue.

Potential therapeutic beneficial effects of metformin for obesity and insulin resistance may be selectively categorized into 3 groups.

In carbohydrate metabolism, metformin prevents pancreatic β-cell from gluco-and lipotoxicity, increases insulin receptor binding, and increases insulin receptor tyrosine kinase (IRTK) activity.

Metformin increases oral glucose-induced GLP-1 amide levels in obese non-diabetic subjects; metformin is able to inhibit GLP-1 degradation induced by dipeptidyl-peptidase IV. GLP-1 is a gastrointestinal hormone, which stimulates insulin secretion and promotes satiety, and hence GLP-1 and dipeptyl-peptidase IV-inhibitor can be proposed as therapeutic goals for the treatment of patients with Type 2-DM (T2DM) and obesity.

In lipid metabolism, metformin may improve lipid profile.

Several vasoprotective effects also belong to Metformin, f.e. ↓ Hyperinsulinemia, ↓ Fibrinogen, ↓ PAI-1, ↓ Factor XIIIa which functions to stabilize fibrin, ↓ Platelet aggregation, ↓ Capillary permeability, ↓ SMC-Fibroblast activity, and ↓ Carbonyl stress (pathway to AGE formation).

***Conclusion:** Obesity and insulin resistance are two major components of the metabolic syndrome, which predispose individuals to the development of T2DM and coronary heart disease. TNF-α and leptin, which are oversecreted by enlarged fat cells, play pivotal roles in the molecular defects of insulin action in obesity-linked insulin resistance. Pleiotropic properties (vasoprotective effects) of metformin beyond carbohydrate and lipid effects may contribute to the beneficial therapeutic tools for obesity-linked insulin resistance.*

***Key words:** Obesity, Insulin Resistance, Metabolic Syndrome*

INTRODUCTION

The dramatic increase in the prevalence of obesity among children and adults has been attributed to increased dietary intake of high energy, high-fat foods and reduced physical activity (Andersen 2000). Excess of visceral adipose tissue accumulation in the presence or absence of obesity, is associated with insulin resistance, hyperinsulinemia, glucose intolerance. These metabolic

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abnormalities become predictive of an increased risk of Type 2-DM (T2DM).

Furthermore, it was reported that excess visceral adipose tissue accumulation is associate with a potentially atherogenic dyslipidemia which includes hypertryglyceridemia, elevated apo B levels, an increased proportion of small dense LDL particles, and low HDL concentrations.

Then, evidence has accumulated to prove that insulin resistance-dyslipidemic syndrome (IR-DS) of visceral obesity is also associated with alterations in haemostatic variables which contribute to increasing the risk of atherothrombotic events in these patients (Reaven 2001).

In obesity, the enlarged fat cells oversecrete TNF-α and leptin in local circulation. The mediators are implicated as candidate mediators of obesity-associated insulin resistance. Both TNF-α and leptin have been shown to have autocrine effects and impair peripheral insulin action also in adipocytes.

Resistin, as well as TNF-α and leptin, released by adipocytes, acts in peripheral tissue to decrease the sensitivity of insulin action.

Taken together, several factors or mediators have been postulated to be responsible for the development of peripheral resistance in obesity.

Based on the results of several studies, metformin may have potential therapeutic benefit for patients with the metabolic syndrome as already described above, since this drug has pleiotropic properties (vasoprotective effects) beyond anti hyperglycemic and lipid modifying actions.

The aim of this short paper is to describe shortly about the metabolic syndrome (esp. Obesity and insulin resistance) and the promising roles of metformin in the management of this syndrome based on molecular basis.

OBESITY-LINKED INSULIN RESISTANCE

The Metabolic syndrome-X is a cluster of metabolic components and cardiovascular risk factors which can be summarized by the author (2002) as follows (Lebovits 2001, Reaven 2001):

1. Insulin resistance
   (with or without Glucose intolerance)
2. Hyperinsulinemia
   (if no defect of pancreatic insulin secretion)
3. Abdominal (Visceral) obesity
4. Raised blood pressure
5. Atherogenic dyslipidemia
   (↑ TG, ↑ PP Lipemia, ↓ HDL-C, ↑ Small dense LDL)
6. Procoagulant state (↑ Fibrinogen, ↑ PAI-1, ↑ Factor VII)
7. Hyperuricemia
8. Endothelial dysfunction (↑ AER, etc)

Insulin resistance develops in both the liver and the peripheral tissues (fat and muscle) in Obesity-linked diabetes.

Several mechanisms postulated to be implicated in the development of insulin resistance in obesity have been summarized by Reaven (2001).

The enlarged fat cell oversecretes TNF-α and leptin in the local circulation.

TNF-α impairs Insulin action by inhibiting insulin receptor signaling, possibly by increasing IRS-1 serine phosphorylation (TNF-α impairs insulin receptor tyrosin kinase = IRTK). TNF-α also impairs GLUT-4 expression.

Leptin released from visceral adipocytes may inhibit insulin action in the liver by impairing insulin receptor signaling, leading to reduced down-regulation of PEPCK, the rate limiting enzyme in gluconeogenesis.

Both TNF-α and leptin have been shown to have autocrine effects and to impair insulin action also in adipocytes.

Resistin, as well as TNF-α and leptin, acts in peripheral tissues to influence sensitivity to insulin and other cellular and metabolic process involved in the use and partitioning of substances (Steppan et al 2001).

Based on clinical experiences since 1997, Tjokroprawiro (2001) has hypothesized the link between insulin resistance–obesity–and T2DM, and termed as clinical classification of insulin resistance-linked obesity and T2DM (Figure 1).

The Classification of insulin resistance–linked obesity and T2DM can be classified into 4 grades; this classification has been already hypothesized by the author since 1997 and to be revised this year (Tjokroprawiro 2002).

Grade-I: Normo Insulinemia with Insulin Resistance

In clinical practice, the Homeostasis Model Assessment (HOMA), has been suggested as method to assess insulin resistance (HOMA-IR) and β-cell secretion (HOMA-b) from the fasting glucose and insulin concentration (Mathews et al 1985). However, this method has not been extensively evaluated, particularly in different ethnic groups (Figure 2).

Patients with Grade-I still have normal insulin blood level whereas insulin resistance may be detected by euglycemic clamp or HOMA-1R; Grade-I usually happens in patients with BMI $\geq$30 kg/m^2 or Visceral obesity.

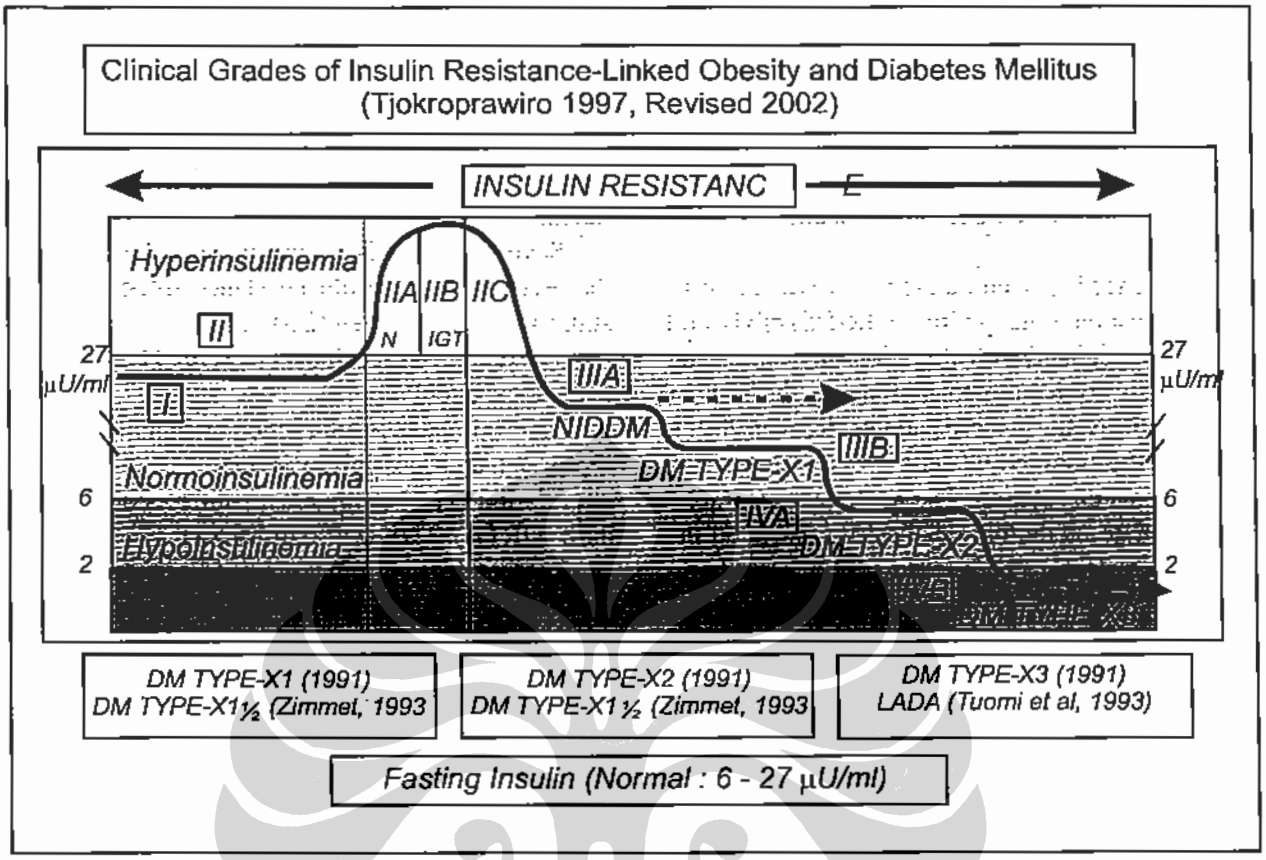

Figure 1. Clinical Grades of Insulin Resistance-Linked Obesity and T2DM

Grade-II: Can be subdivided into Grade-IIA, IIB, and IIC

- Patients with Grade-IIA : Hyperinsulinemia with normal glucose tolerance, usually with BMI ≥30 or visceral obesity
- Grade-IIB : Hyperinsulinemia plus glucose intolerance and BMI ≥30 or visceral obesity
- Grade-IIC : Hyperinsulinemia plus T2DM and BMI ≥30 or visceral obesity

Grade-III: Can be subdivided into Grade-IIIA and Grade-IIIB

- Grade-IIIA : Normoinsulinemia plus T2DM, and BMI is usually less but sometimes still more than 30. Visceral obesity is still present
- Grade-IIIB : Low normoinsulinemia plus Type-X_1 DM. (Type X-DM (TXDM) is T2DM with poor response of β-cell to glucose stimulation, but the fasting C peptide is still ≥0,8 µu/ml)

TX_1DM (firstly coined by the author in 1991) is identical with Type 1½-DM (T1½DM) as firstly termed by Zimmet in 1993.

Grade-IV can be subdivided into Grade-IVA and Grade-IVB

- Grade-IVA : Hyperinsulinemia (fasting insulin <6 µU/ml, normal value: 6–27 µU/ml plus Type X_2-DM T1½DM but fasting C-peptide becomes lower (0-6-0.8 uU/ml)
- Grade IVB : Hyperinsulinemia plus Type X_3-DM (TX_3DM) LADA (as coined by Tuomi in 1993) and fasting C peptide has been less than 0.6 µu/ml.

This patients (TX_3DM) become totally insulin dependent but more resistant to ketoacidosis compared with T1DM.

$$HOMA\text{-}IR = \frac{Fasting\ insulin\ (\mu U/ml) \times fasting\ glucose\ (mmol/l)}{22.5}$$

$$HOMA\text{-}\beta\ cell = \frac{20 \times Fasting\ insulin\ (\mu U/ml)}{Fasting\ glucose\ (mmol/l) - 3.5}$$

Figure 2. Homa – Formula (Mathews et al 1985)

METFORMIN AND POTENTIAL THERAPEUTIC BENEFITS

Several results of recent studies can be shortly summarized below (selected)

1. GLP-1 is a gastrointestinal hormone which stimulates insulin secretion and promotes satiety. GLP-1 and drugs that inhibit its degradation, such as dipeptidyl-peptidase IV-inhibitors, have been proposed as therapeutic tools for T2DM and obesity (Mannucci et al 2000). In this study, metformin is able to inhibit in vitro GLP-1 degradation by human plasma and by dipeptidyl–peptidase IV. GLP-1 is also able to delay gastric emptying process.This action could provide an explanation for the observed anorectic effects of metformin, and may contribute to its hypoglycemic properties (due to GLP-1 effect as *indirect* insulin secretagogue).
2. Ruggiero–Lopez at al 2000 reported that metformin reduced methylglyoxal levels (Carbonyl compound) by formation of a stalk condensation product (Triazepinone). Thus, metformin appeared to act as an extracellular scavenger of methylglyoxal independent of its anti hyperglycemic effect, and could thereby contribute to the prevention of chronic diabetic complications by reduction of carbonyl stress and AGE generation would be inhibited.
3. Patane et al (2000) cultured rat pancreatic islets with either high glucose or FFA concentration, and then for additional 24 hours in the presence or absence of metformin. The results indicated that metformin could reverse both glucose abnormalities and glucose-induced insulin release impairment consequent to islet exposure to either high glucose or FFA. These effects may contribute to the therapeutic benefits of metformin in T2DM patients.
4. Previously, it was demonstrated that metformin increased erythrocyte insulin-stimulated IRTK (Insulin Receptor Tyrosine Kinase) activity of obese patient with normal glucose tolerance, but this increase was associated to a decrease in plasma insulin concentrations.

Nomizo et al (2000) investigated the effect of metformin *in vitro* in the insulin receptor of NIH 3T3 cells.

The Cells were maintained in metformin supplemented with 10% FCS, and the rate grown to influence in 94 mm dishes and starved in a serum free medium supplemented with 1mM glucose for 12 hours.

The results showed that metformin increased insulin–stimulated IRTK, but did not have effect on the endogenous IRTK of receptor from NIH 3T3 cells, after 6 and 12 hours incubation. These metformin properties on IRTK may contribute to a potential therapeutic effect on obese diabetic patients.

Based on the results of all these studies (provided with previous data), Tjokroprawiro (2002) summarized several possible potential therapeutic properties (Pleitropic effects) of metformin which can be classified into 3 groups

I. Carbohydrate Metabolism
   1. Decreased Intestinal Glucose Absorption
   2. Decreased FBP and 2 h Post Medical Blood Glucose
   3. Prevents β-cell from Gluco-or lipotoxicity effect
   4. Increased glycogenesis
   5. Increased insulin receptor binding
   6. Increased GLUT-5 expression in the glut
   7. Increased insulin-receptor tyrosine kinase activity = IRTK
   8. Inhibited GLP-1 degradation and promoted satiety

II. Lipid
   1. Decreased total cholesterol
   2. Decreased LDL-cholesterol
   3. Decreased triglyceride
   4. Increased HDL-cholesterol

III. Vasoprotective Effects

1. Decreased platelet aggregation
2. Improved erythrocyte
3. Decreased PAI-1
4. Decreased factor XIIIa
5. Increased peripheral blood flow
6. Decreased capillary permeability
7. Decreased retinal neovascularisation, and
8. Decreased SMC-fibroblast

CONCLUSION

Evidence has accumulated that the insulin resistance–dyslipidemia syndrome in obesity is also associated with alterations in haemostatic variables which contribute to increasing the risk of atherothrombotic events in these patients. All these components of the metabolic syndrome have been summarized. Pleiotropic properties of metformin beyond blood glucose and lipid lowering (anti hyperglycemic, and hypoglycemic effect via decreased GLP-1 degradation) may contribute several possible potential therapeutic benefits in the treatment of patients with obesity and insulin resistance.

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