The Effect of Telmisartan and Metformin on Insulin Resistance in Metabolic Syndrome Patients with Insulin Therapy

Efek Pemberian Metformin dan Telmisartan terhadap Resistensi Insulin pada Pasien Sindrom Metabolik dengan Terapi Insulin

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ABSTRAK

Latar belakang: *Rekomendasi terapi untuk resistensi insulin adalah metformin dan thiazolidindion. Efek samping udem perifer akibat thiazolidindion terjadi sebanyak 2-5% dan meningkat menjadi 5-15% bila dikombinasi dengan terapi insulin. Telmisartan termasuk angiotensin receptor blocker yang mempunyai efek anti hipertensi sekaligus memperbaiki resistensi insulin. Telmisartan berefek agonis terhadap peroxisome proliferator activated receptor γ dan mempunyai struktur yang sama dengan pioglitazon dari golongan thiazolidindion. Tujuan penelitian ini adalah mengetahui efek pemberian metformin dan telmisartan terhadap resistensi insulin pada pasien sindrom metabolik dengan terapi insulin.*
Metode penelitian: *Penelitian ini menggunakan before-after design. Penelitian dilakukan di poliklinik penyakit dalam sub bagian endokrinologi RSUP Dr. Sardjito Yogyakarta. Subyek penelitian adalah pasien yang memenuhi diagnosis sindroma metabolic berdasar IDF 2005, hipertensi dan mendapat terapi insulin. Subyek diberikan terapi metformin dan telmisartan selama 12 minggu. Subyek diperiksa HOMA IR sebelum dan sesudah terapi. Rata-rata penurunan HOMA IR diuji dengan paired t-test atau tes Wilcoxon. Kemaknaan p <0.05 dianggap signifikan.*
Hasil penelitian: *jumlah sampel penelitian sebanyak 27 subyek. Analisis data dilakukan terhadap 11 subyek. Kadar glukosa darah puasa mengalami penurunan bermakna setelah terapi (p<0.001) namun kadar insulin puasa mengalami kenaikan. HOMA IR mengalami penurunan setelah terapi {p = 0.004 (5.79 –20.26), IK 95%}.*
Kesimpulan: *terdapat penurunan resistensi insulin yang bermakna secara statistic pada pasien sindrom metabolik dengan terapi insulin yang mendapat metformin dan telmisartan.*

Kata kunci: *sindrom metabolik, terapi insulin, metformin, telmisartan, HOMA IR*

ABSTRACT

Background: Recommendations for therapy insulin resistance are metformin and thiazolidindion. Side effects of thiazolidindion due to peripheral edema occurs to 2-5% and increased 5-15% when combined with insulin therapy. Telmisartan, an angiotensin receptor blocker, has anti-hypertensive effects and improve insulin resistance. Telmisartan effect on peroxisome proliferator activated receptor γ agonist and has the same structure of the group thiazolidindion, pioglitazone. The research objective was to determine the effects of telmisartan and metformin on insulin resistance in metabolic syndrome patients with insulin therapy.
Methods: This study used a before-after design. The study was conducted in the internal medicine clinic of the endocrinology department of Dr. Sardjito Hospital Yogyakarta. Subjects were patients who met the diagnosis of

metabolic syndrome based on the IDF 2005, hypertension and received insulin therapy. Subjects given metformin and telmisartan therapy for 12 weeks. Subjects examined HOMA IR before and after treatment. The average decrease in HOMA IR was tested by paired t-test or Wilcoxon test. P value <0.05 was considered significant. **Result**: The total sample were 27 subjects. Data analysis was performed on 11 subjects. Fasting blood glucose before and after treatment was significantly decreased (p<0.001) whereas the fasting insulin levels increased. HOMA IR was significantly decreased after treatment {p = 0.004 (5.79 – 20.26), CI 95%}. **Conclusion**: this study found insulin resistance decreased significantly in patients with the metabolic syndrome of insulin therapy who received metformin and telmisartan.

Keywords : metabolic syndrome, insulin therapy, metformin, telmisartan, HOMA IR

BACKGROUND

Metabolic syndrome is defined as a group of specific clinical conditions including visceral obesity, hyperglycemia, dyslipidemia and high blood pressure. Constituent factors of the metabolic syndrome is a significant risk factor for development of cardiovascular disease and type 2 diabetes mellitus (DM).[1] Insulin resistance and central obesity is thought to be the basis of the underlying pathogenesis of the metabolic syndrome.[2]

Treatment of metabolic syndrome based on the IDF 2005 include lifestyle modification and therapeutic intervention to improve all components of the metabolic syndrome. Recommendations of therapy for insulin resistance component are metformin and thiazolidindion class. Both are proven to prevent the development of pre-diabetes individuals to type 2 diabetes.[2] Thiazolidindion group is limited its use due to side effects of fluid retention, edema and weight gain.[3] Incidence of peripheral edema due to monotherapy with thiazolidindion is 2-5% and increased to 5-15% when combined with insulin therapy.[4]

Hypertension is a common component that accompanies metabolic syndrome. Telmisartan, an angiotensin receptor blockers (ARB) class has the same structure of the group thiazolidindion, pioglitazone. Telmisartan is an agonist of the peroxisome proliferator activated receptor γ (PPAR γ) used for the treatment of type 2 diabetes mellitus.[1]

Hyperinsulinemic euglycemic glucose clamp technique is the gold standard tool to measure insulin sensitivity.[5] HOMA IR is a simple mathematical calculation and is not invasive and have been approved to measure insulin resistance.[5] Research declared HOMA IR value of 3.875 in patients with DM had a sensitivity and specificity of 49.7% and 69.6%, while the limit value of 4.325 at 45.4% and 69%.[6]

Research on the effects of telmisartan in hypertension has been done but has not been performed in patients with metabolic syndrome with insulin therapy. The research objective was to determine the effects of telmisartan on metformin and insulin resistance in metabolic syndrome patients with insulin therapy.

METHODS

The study design was a before-after design. The study was conducted in the internal medicine department of endocrinology Dr. Sardjito Hospital Yogyakarta. The study began in October 2012 until January 2013. Inclusion criteria were all patients in the internal medicine department of endocrinology ≥35-65 years old, met the diagnosis of metabolic syndrome based on the IDF 2005, hypertension, on

insulin therapy, were willing to participate in research, and have a number to call. Diagnosis of metabolic syndrome according to IDF 2005 was abdominal obesity plus any 2 of the following 4 criterias: triglyceride levels ≥150 mg/dL, HDL-C in men <40 mg/dL and women <50 mg/dL, blood pressure ≥130/85 mmHg, fasting blood glucose ≥100 mg/dL.[2] Exclusion criteria were taking drugs that affect glucose tolerance such as diuretics and α or β blockers, steroids, renal dysfunction (serum creatinine >1.5 mg/dL), cardiac disorders (unstable angina pectoris, myocardial infarction, heart failure) and impaired liver function (SGOT and SGPT levels >2 times the upper limit of normal) and pregnancy.

Data recorded patient characteristics including age, gender, medical history, weight, height, body mass index, waist circumference, hip circumference, blood pressure, and fill out the questionnaire Beck Depression Inventory (BDI). Assessment of depression using restriction score >16. Blood samples were taken at baseline, including fasting blood glucose and fasting insulin levels to calculate HOMA IR. The formula to calculate HOMA IR is[7]:

$$\frac{\text{fasting plasma insulin (mU/L) x fasting plasma glucose (mmol/L)}}{22.5}$$

$$\frac{\text{fasting plasma insulin levels (µU/dL) x fasting plasma glucose (mg/dL)}}{405}$$

Patients given metformin and telmisartan treatment for 12 weeks. Metformin dose started 500 mg and gradually increased every week until a maximum dose of 2 grams everyday. Telmisartan 80 mg was given everyday. Monitoring of fasting blood glucose and blood pressure performed every 4 weeks. After treatment is completed, the patients are taken blood tests and calculate HOMA IR. Monitoring the side effects of therapy conducted during the study to complete. Patients received an explanation of the recommended diet and physical activity by nutrition experts explaining according to Perkeni 2011.

The data were processed using the computer program. Characteristics of the study sample shown descriptively. The average decrease in HOMA IR before and after treatment were tested with paired t-test if the data were normally distributed. The data were not normally distributed will be tested with Wilcoxon test. Significance p <0.05 was considered significant.

RESULTS

This study was followed by 27 subjects to complete the study. Subjects who did not comply with treatment instructions were excluded from data analysis. There were 4 people who can not be calculated because the value of HOMA IR was very low fasting insulin levels <2 µU/dL. So the amount of sample that can be analyzed as many as 11 people. Subjects consisted of 7 men (63.6 %). The subjects had an age range 50-65 years with an average age of 57±4.40 years old. Characteristics of the study subjects were summarized in table 1.

Table 1. Basic Characteristics of the Study Subjects

Variable	N = 11 Mean ± SD	Total (%)
Gender:		
- Women		4 (36.4)
- Men		7 (63.6)
Age :		
- ≤ 60 years old		9 (81.8)
- > 60 years old		2 (18.2)
Body mass index	28.40 ± 3.65	
Waist circumference, cm	96.64 ± 8.20	
Fasting blood glucose, mg/dL	194.91 ± 57.85	
Systolic pressure, mmHg	130.45 ± 12.34	
Diastolic pressure, mmHg	84.55± 5.22	
Stress		1 (9.1)
Smoke		1 (9.1)

Table 2. Comparison of Variables Before and After Treatment

Variable	Before (N=11) Mean ± SD	After (N=11) Mean ± SD	p
Fasting blood glucose, mg/dL	194.91± 57.85	58.27±58.50	< 0.001 *
Insulin darah puasa, μU/dL	27.59± 19.55	32.01± 22.12	0.688 *
HOMA IR	13.99±11.05	12.84± 10.97	0.004 *

* paired t – test

The average of metformin dose was 1478 mg everyday. Telmisartan dose was 80 mg everyday. Subjects using a mixture of short acting insulin injections and the medium as much as 8 subjects (72.7%) and 3 (27.3%) using long acting insulin. Average insulin dose received at the beginning of therapy was 35.82 units per day while at the end of therapy was 29.45 units. At the end of the study was evaluation of patient adherence to recommended dietary food recall way. There were 7 (63.6%) subjects who were adherent to recommended diet.

Results of this study HOMA IR scores decreased after therapy compared to before { p=0.004 (5.79 to 20.26), 95% confidence interval}. HOMA IR improvement after treatment in line with improvements in fasting blood glucose (p <0.001) but not in line with fasting insulin. Fasting insulin levels increased after therapy. Comparison of variables before and after treatment can be seen in table 2.

Dietary variables were analyzed to look for effects on HOMA IR. This study get no association between dietary adherence and decreased HOMA IR (p=0.47). Other confounding variables such as stress and smoking were not analyzed further because the amount was very small.

DISCUSSION

The pathophysiology of the metabolic syndrome are central obesity and insulin resistance. Management of metabolic syndrome include lifestyle modification and pharmacological therapy. Pharmacological therapy on metabolic syndrome is aimed at dealing with the excess adipose tissue, insulin resistance, dyslipidemia, hypertension, prothrombotic and proinflammatory state. Therapy to overcome insulin resistance is metformin and thiazolidindion.[8]

Metformin improved insulin resistance by lowering fasting blood glucose and insulin concentrations. Metformin increases in hepatocytes through suppression of gluconeogenesis and lowers insulin stimulation of gluconeogenesis by glucagon. Metformin increases glucose disposal in non insulin-dependent diabetes mellitus patients who are working in the target muscle. Metformin also increases glucose uptake and oxidation in adipose tissue as lipogenesis. Metformin increases the translocation of GLUT-1 and GLUT-4 . Metformin also lowers the oxidation of fatty acids by 10-20% and will lower blood glucose levels through a glucose-fatty acid cycle.[9]

Angiotensin type 1 receptor (AT_1R) blockers used in the treatment of hypertension and cardiovascular disease. The study states AT_1R blockers reduce the risk of type 2 diabetes compared to other antihypertensive. Animal experiments state that ARBs improve insulin resistance by improving the regulation of PPAR γ target gene of GLUT 4.[10] Other studies in mice get PPAR γ activity in skeletal muscle organs through AMPK/SIRT1.[11]

PPAR γ is expressed primarily in adipose tissue. PPAR γ plays a role regulating genes involved in the differentiation of adipose, fatty acid uptake, storage and glucose uptake. PPAR γ stimulates intravascular lipolysis[12], has anti inflammatory effects through the inhibition of TNF-α and IL-6[13], giving the effect of anti-oxidation and anti-proliferation in the cell walls of the blood vessels, reducing the risk of atherosclerosis.[14]

The binding of telmisartan-PPAR γ is different with the binding PPAR γ-rosiglitazone or pioglitazone. Telmisartan binds only partially so as not stimulate PPAR γ in full activity. This activity provides the beneficial effect of providing a safer drug profile in preventing fluid retention, edema and weight gain as was the case with the treatment group thiazolidindion.[3] Telmisartan is an ARB with the highest lipophilic nature so most potent to induce PPAR γ.[10]

HOMA IR is a method developed in 1985 to assess insulin resistance. HOMA IR has accuracy comparable to the gold standard examination with the glucose clamp, but is inferior in terms of accuracy.[6] Results of glucose clamp correlated strongly with levels of fasting insulin and HOMA IR.[15]

In this study, HOMA IR values decreased after therapy. This is consistent with the hypothesis. HOMA IR improvement on this study was supported by improvements in blood glucose levels, but not in line with the increase in fasting insulin levels. Increase in fasting insulin levels can be caused by several factors: genetic and not genetic. Research get fasting insulin levels were positively correlated with body mass index, waist/hip ratio, triglycerides, systolic and diastolic blood pressure and inversely with HDL cholesterol. However, after adjustment for several factors that influence, there is no significant association between genetic factors and not with fasting insulin levels.[16] There is a possibility of an increase in fasting insulin levels in this study does not reflect actual conditions. This subjects are metabolic syndrome patients receiving insulin therapy. Blood insulin were examined to calculate HOMA IR and will increase as affected exogenous insulin administration.[17]

Diabetic patients who use insulin therapy for a period of time will be formed in the circulating insulin antibodies. Proinsulin to insulin injection contained varying amounts can stimulate the formation of antibodies and tie it in circulation. In these patients the endogenous and exogenous insulin and antibodies will bind to obscure the accuracy of measurement of insulin levels with insulin radioimmunoassay method.[18] Research get diabetic patients in insulin therapy increased total fasting insulin in the blood at 2 months and became stable after 5 months. This increase occurred simultaneously with the formation of antibodies.[17]

Decrease in HOMA IR after metformin and telmisartan treatment in this study in line with other studies. Derosa et al. indicate the telmisartan or irbesartan administration for 12 weeks in diabetic patients with metabolic syndrome who received rosiglitazone can improve blood pressure, HOMA IR, HbA1c, adiponectin and resistin.[19] Vitale et al. show the 3 month treatment of telmisartan compared with losartan better in fixing parameters of insulin resistance (HOMA IR, HbA1c and blood pressure) in hypertensive patients with metabolic syndrome.[20] Bahadir et al. get a different result is the provision of telmisartan or losartan did not improve HOMA IR in hypertensive patients with metabolic syndrome. Possible causes HOMA IR did not experience a significant reduction in this study is HOMA IR less than 2.5.[1]

This study has the disadvantage that the number of samples analyzed only 11 subjects. Another weakness of this study is the assessment of patient compliance based solely on interview subjects at the end of the study. Drug compliance is not based on a count of the remaining drug is not taken from the former drug packs. This led medication adherence data become invalid. This study can not control confounding variables such as excessive dieting, low physical activity, stress and smoking so that they can be biased towards research.

CONCLUSION

This study found decreased insulin resistance significantly in patients with the metabolic syndrome of insulin therapy who received metformin and telmisartan.

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