

EFFECT OF METFORMIN AND VALSARTAN TOWARD HOMA-IR IN METABOLIC SYNDROME PATIENT WITH NON-ALCOHOLIC FATTY LIVER DISEASE (NAFLD)

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ABSTRACT

Background: Insulin sensitizer drugs such as metformin has suggested giving in metabolic syndrome patient and NAFLD, which both pathogeneses were insulin resistance. Angiotensin II receptor blocker (ARB), anti-hypertension drugs, has the similar properties to improve regulation of Proliferator-Activated Receptor Gama (PPAR γ). This aim of the study is to prove the improvement of insulin resistance which examined by HOMA-IR method on metabolic syndrome patient with NAFLD after receiving metformin and valsartan medication.

Method: This study was conducted to the patient in Endocrinology Clinic Sardjito General Hospital aged 35-36 years who meet diagnostic criteria for metabolic syndrome based on the IDF in 2006 and NAFLD. Convenience sampling method is done for 11 months (May 2012 – March 2013) and was expected sample size 35. HOMA-IR examination made before and after administration of metformin and valsartan for 12 weeks. Cut off value for HOMA –IR on pathological metabolic syndrome and NAFLD was ≥ 2 . Medical and Health Research Ethics Committee (MHREC) Faculty of Medicine Universitas Gadjah Mada approved this study protocol.

Result: Subject of study retrieved 15 (43%), six males (40%) and nine females (60%) aged 43-63 years old. Median HOMA-IR baseline was 2.8 (0.6-14.5) and at the end of therapy was 3.8 (1.72-14.1). Eleven (74%) have increased HOMA-IR value and four (26%) experience declined but none of them reach the value below ². In general clinical improvement occurs in the form of AST and ALT reduction but not statistically significant.

Conclusion: This study does not prove that administration of metformin and valsartan in-patient with metabolic syndrome with NAFLD would improve insulin resistance assessed by the HOMA-IR method.

Keywords: Metformin, valsartan, metabolic syndrome, NAFLD, HOMA-IR

ABSTRAK

Latar belakang: Obat insulin sensitizer semacam metformin disarankan untuk diberikan kepada pasien sindrom metabolik dan NAFLD, yang keduanya adalah patogenesis dengan resistensi insulin. Angiotensin II receptor blocker (ARB), obat anti hipertensi, memiliki ciri untuk memperbaiki regulasi dari Proliferator-Activated Receptor Gama (PPAR γ).

Tujuan: Tujuan dari penelitian ini adalah untuk membuktikan penyempurnaan resistensi insulin yang di uji menggunakan metode HOMA-IR pada pasien sindrom metabolik dengan NAFLD setelah menerima pengobatan metformin dan valsartan.

Metode: Penelitian ini dilakukan pada pasien di klinik endokrinologi rumah sakit dr. Sardjito yang berumur 35-36 tahun serta memenuhi kriteria diagnostik untuk sindrom metabolik berdasar

IDF 2016 dan NAFLD. Metode sampling dilakukan selama 11 bulan (Mei 2012-Maret 2013) dan diharapkan ukuran sampel 35. Uji HOMA-IR sebelum dan sesudah pemberian metformin dan valsartan untuk 12 minggu. Pemotongan nilai untuk HOMA-IR patologi sindrom metabolik dan NAFLD ≥ 2 . Komisi Etik Medis dan Kesehatan (MHREC) Fakultas Kedokteran Universitas Gadjah Mada telah menyetujui penelitian ini.

Hasil: Subjek penelitian diambil sebanyak 15 (43%), enam laki-laki (40%) dan sembilan perempuan (60%) berusia 43-63 tahun. Garis dasar Median HOMA-IR adalah 2,8 (0,6-14,5) dan pada akhir terapi adalah 3,8 (1,72-14,1). Sebelas (74%) telah meningkatkan vaton HOMA-IR dan empat (26%) pengalaman dalam bentuk pengurangan AST dan ALT namun tidak signifikan secara statistik.

Kesimpulan: NAFLD akan memperbaiki resistensi insulin yang dinilai dengan metode HOMA-IR.

Kata kunci: Metformin, valsartan, sindrom metabolik, NAFLD, HOMA-IR

Introduction

Metabolic syndrome is a clustering of health problems that are increasing the risk of cardiovascular disease. One clinical condition is also closely linked to the metabolic syndrome is Non-Alcoholic Fatty Liver Disease (NAFLD). Some researchers put NAFLD as a component of metabolic syndrome, other researchers think that NAFLD is a manifestation of the metabolic syndrome in the liver.^{1,2} According to pathophysiologic considerations, the association of clinical and laboratory examination concluded that the central role of insulin resistance in the pathogenesis of the metabolic syndrome and NAFLD.³

This understanding is a major reason utilization of insulin sensitizer drugs such as metformin and a thiazolidinedione for the therapy. Norberto et al, in a systematic review article, concludes insulin sensitizer therapy on NAFLD would improve insulin resistance and function liver.⁴ Caldwell et al. (2006) in his review states that the provision of a thiazolidinedione in NAFLD shown to reduce liver fat and reduced evidence of cellular injury liver.⁵

Patients with the chronic liver disease often occur activation of the

renin-angiotensin system (RAS), so that the therapy of hypertension in metabolic syndrome components with NAFLD have drugs known as angiotensin II receptor blockers (ARBs) and angiotensin-converting enzyme inhibitor (ACEI). Another advantage of these drugs is their ant fibrotic characteristics by reducing the liver stellate cell proliferation and improvement of insulin resistance was assessed by Homeostasis Model Assessment-Insulin resistance (HOMA-IR).^{6,7} The validity of this study is limited because of the number of subjects of the study. This study aims to demonstrate that administration of metformin and valsartan in patients with NAFLD metabolic syndrome will improve insulin resistance were examined with the HOMA-IR method.

Materials and Methods

This study uses a before-after design and uses convenience sampling, conducted at the Polyclinic Internal Medicine Endocrinology division of Sardjito General Hospital from May 2012 to March 2013. Patients were in accordance with the criteria for diagnosis of metabolic syndrome (IDF 2006) and NAFLD based on non-

invasive examination. Include as a subject until the deadline of the study. The sample size expected to be calculate from the formula of two groups of numerical data.⁸ Based on the calculation, required sample size is 35 subjects.

Patients who met the inclusion and exclusion criteria were given an explanation of the purpose, benefits and the course of the study and signed informed consent. Then recorded the patient characteristics such as age, gender, medical history, weight, height, blood pressure, body mass index, waist and hip circumference, long-suffering from diabetes (if diabetes mellitus) and acquired the last therapy. Do washout of metformin and valsartan at least 2 weeks, and fasting blood samples to obtain the initial value of HOMA IR.

Patients were given metformin and valsartan therapy treatment for 12 weeks. Metformin was started at a dose of 500 mg and increased gradually until the maximum dose of 2g/day. Valsartan started at a dose of 1 x 80 mg, the dose increased when the target blood pressure has not been reached.

Patients control and equipped with drugs every 4 weeks. The incidence of drug side effects noted. After the completion of the treatment blood samples to assess HOMA-IR end. Patients were asked to record the diet consumed, then do calorie counting. Dietary conducted by nutritionist suitable diet according to the guidelines PERKENI 2011. Patients were asked to record the diet for at least 3 days in 4 weeks.

Result

After 11 months only got 15 subjects who meet the inclusion and exclusion criteria. This amount meets 43% of the samples are expected. All subjects followed the procedure until the study is completed. The research subjects consisted of male subjects as many as six people (40%) and women were nine people (60%) aged between 43-63 years with an average of 56.26 ± 5.35 years. The basic characteristics of 15 patients with Metabolic Syndrome with NAFLD before the therapy can be seen in Table 1, and after treatment in Table 2.

Table 6 base characteristic 15 metabolic syndrome patients with NAFLD before therapy

Variable	Mean \pm SD	Median	Min/Max	Normality test (p)	
				Kolmogorov-Smirnov ⁴	Shapiro-Wilk
Systolic pressure, mmHg	123.33 \pm 8.16	120	110:140	.008	.049
Diastolic pressure, mmHg	78.00 \pm 5.60	80	70:90	.000	.001
Body Mass Index (BMI)	28.23 \pm 3.03	27.78	24.56:33.78	.122	.131
AST	23.20 \pm 7.19	24	15:43	.155	.026
ALT	24.73 \pm 11.70	20	8:46	.148	.345
GGT	34.00 \pm 18.30	31	12:77.0	.200*	.033
Homa-IR	3.77 \pm 3.98	2.8	60:14.50	.003	.001
LP, cm (male)	94.66 \pm 8.35	96.5	83:105	.200	.756
LP, cm (female)	99.00 \pm 8.29	97	89:110	.200	.199

Table 7 Base characteristic 15 metabolic syndrome patients with NAFLD before therapy

Variable	Mean ±SD	Median	Min/max	Normality test (p)	
				Kolmogorov-Smirnov ⁴	Shapiro-Wilk
systolic pressure, mmHg	125±11.02	125	.200*	.208	.208
diastolic pressure, mmHg	82.66±7.76	80	.026	.96	.096
Body Mass Index (mmHg)	28.12±2.82	27.08	.146	.075	.075
AST	21.53±8.20	20	.200*	.027	.027
ALT	22.93±11.38	23	.200*	.750	.750
GGT	35.26±20.71	26	.003	.004	.004
Homa-IR	5.03±3.59	3.79	.144	.022	.022
LP, cm (male)	95.41±5.37	96.5	.089	.075	.075
LP, cm (female)	100.66±6.36	101	.200*	.509	.509

Description:

A: Correction Lillie for significance.

*: The lower limit of a significant value

AST: aspartate aminotransferase

ALT: alanine aminotransferase

GGT: Gamma-glutamyltransferase

LP: Waist circumference

From the above explanation that the average value of HOMA-IR before and after therapy, which illustrated by the following graph (Figure 1).

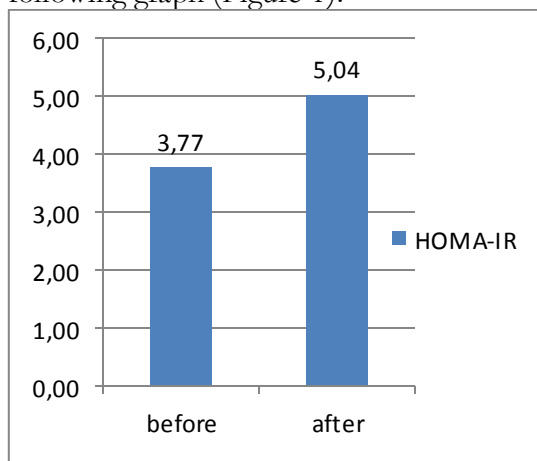


Figure 1. Graph of mean HOMA-IR before and after therapy

Discussion

This study cannot prove that administration of metformin and valsartan in patients with metabolic syndrome with NAFLD would improve insulin resistance assessed by the HOMA-IR method. On average HOMA-IR at the end of the treatment is higher than before treatment (Figure 1). Another parameter test results also showed an increase in value at the end of the treatment, only the value of AST are lower in the examination at the end of the treatment. AST but the decline is not statistically significant. Four of the fifteen (26%) samples showed a decrease in HOMA-IR but no decline that reached a value below two, the cut-off for the pathological condition of insulin resistance.

The results that were largely not in line with the concept of the study according to the researchers this caused mainly due to the samples obtained are not representative of the population to be observe. Both are the weakness of the study.

There are four reasons why the samples were not representative of the population to be observed. First, the number of samples is too little. Second, 43% of the target sample size. Then, the data obtained from the sample is not homogeneous. The last, there are variations in the value of a very wide and the conditions are not naturally form were on insulin treatment.

The sampling method used in this study convenience sampling, to the limit, just acquired 15 research subjects or meet 43% of the large sample desired. This will affect the internal validity of the study because the sample obtained is not representative of the population target.⁸

The number of samples that do not fit this target also has an effect on the distribution of the data obtained; most of the data obtained are not normally distributed. Although there is a statistical method that can analyze the data were not normally distributed, but the results are not as good when using distributed data normal.⁸

Very wide variation value as the initial value of HOMA-IR research lows is 0.6 while the highest value of 14.5 indicates as an heterogeneous data (not homogeneous). Data are not homogeneous either cannot be represented by a set of data.⁸

Sampling sites considered the main cause of acquired samples are less representative of the population to be observed. Research survey in the United States stated that complaints were made with metabolic syndrome come to the doctor is overweight, this complaint theoretically and regulations more easily

found or complaints in health facilities primer.⁹ The results of the survey also revealed that cases of metabolic syndrome are also more many found in urban areas compared to rural areas.

This research data is partial data from a study that designed to do in a referral hospital type A Dr. Sardjito Hospital. The study, entitled The Effect of Metformin and Metformin compared Telmisartan in Lowers Fatty Liver in Obese Diabetic Mellitus and Hypertension.

Unnatural condition is also present in all the samples in the form of all subjects was erect suffering from diabetes and is on insulin therapy into its own weaknesses of this study. Sampling sites at referral hospitals type A return is considered to be the cause of this condition because DM is the most accepted referral cases poly endocrinology.

DM patients included in this study is justified because the criteria for metabolic syndrome used is the IDF (2006).¹⁰ The metabolic syndrome is more precise to mention the concept rather than a diagnosis, many organizations are proposing the criteria for metabolic syndrome. Organizations that adhered to the concept that metabolic syndrome a pre-diabetic condition is certainly not going to enter into a group with diabetes mellitus metabolic syndrome. IDF is a concept that metabolic syndrome is a cluster of health problems that are increasing the risk of disease heart and vascular so the inclusion of people with DM in the criteria for metabolic syndrome.

Use of insulin in all subjects regarded as a weakness of the study, in addition to the calculation of the HOMA-IR based on measurements of blood insulin levels, but also because of the amount of insulin that used by each individual changes.

Wallace et al, on the results of the review actually allow the use of HOMA-IR method for evaluating insulin resistance in individuals who are on insulin therapy but with a record of the patient's condition is stable, which means the dose of insulin that is used does not changes.¹¹ Insulin dosage obtained the subject of this research is still changing but the change of insulin dose is not specifically analyzed.

Owen and Robert proved that cross-react exogenous insulin analog in the measurement of endogenous insulin levels with five tools immunoassay berbeda.¹² Li et al. proposed the use of C-peptide values for the calculation of HOMA-IR. The C-peptide value proportional to the levels of endogenous insulin. C-peptide is a proinsulin.¹³ Modification fragment of the formula: $Homa-IR (CP) = 1.5 + x \text{ fasting glucose fasting levels of C-peptide} / 2800$.

Changes in blood glucose and insulin levels also influenced by diet and physical activity. This variable cannot be completely controlled, study subjects received nutrition education and motivation of physical training of educators before the study and were evaluated every month during a visit to the clinic. At the end of the study to evaluate, the patients' adherence to the diet recommended by the way food recall. Researchers did not make an assessment of the physical activity the subject of research to be biased against the results of this study. Another confounding factor is the use of drugs such compliance is not controlled.

Use of metformin for metabolic syndrome remains controversial, until today this drug has not officially recommended in the metabolic syndrome in the American containment procedures. Unity Internal Medicine Indonesia also not recommends this therapy despite insulin resistance has agreed with an

underlying condition syndrome metabolic.¹⁴

Systematic review of five studies randomized control trial (RCT) about the benefits of metformin in obese patients conducted Park et al. concluded that the short-term metformin therapy was shown to improve insulin resistance in a moderate in the younger age group.¹⁵ From the data, the average age of subjects, of this study included older age group, 56.26 years.

Dosing metformin different as accepted by the subjects of this study cannot explain the results of this study are unfavorable, research Oy et al. proved that there should be improvement of insulin resistance by receiving metformin even low dose (250mg per day).¹⁶

Research Bahadir et al., and Sarac et al. get a result like this research that provision does not fix HOMA IR valsartan in hypertensive patients with the syndrome metabolik.^{17, 18} While research DeRosa et al. showed that valsartan administration for 12 weeks in diabetic patients with the metabolic syndrome can improve blood pressure and levels of HOMA IR.¹⁹

Research Vitale et al. showed that telmisartan given to patients with metabolic syndrome would improve resistance parameter insulin.²⁰

A meta-analysis conducted Takagi and Umamoto that compared the drugs in the ARB class effect of improving insulin resistance conclude that the only proven telmisartan significantly improved resistance insulin.²¹

Conclusion

This study does not prove that administration of metformin and valsartan in patients with metabolic syndrome with NAFLD would improve insulin resistance assessed by HOMA-IR method.

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