RINGKASAN

INTERVENSI JANGKA PENDEK DENGAN METFORMIN
PADA PREDIABETES NON OBES
Statu perspektif pencegahan primer perkembangan
ke diabetes dan aterosklerosis
(Penelitian Eksperimental)

Diabetes Mellitus tipe-2 (DM tipe-2) merupakan penyakit yang heterogen, dengan dua ciri utama yang menentukan yaitu adanya resistensi insulin dan defek sel β pankreas, telah disepakati oleh para ahli bahwa resistensi insulin merupakan kelainan yang mendahului (awal) dibanding munculnya defek sel β pankreas atau penurunan sekresi insulin pada penderita DM tipe-2.

Fakta yang berkembang menunjukkan, bahwa pada kadar glukosa darah di atas normal tetapi masih di bawah nilai ambang untuk diagnosis DM tipe-2, seperti pada individu dengan gangguan homeostasis glukosa yaitu pada individu dengan glukosa darah puasa terganggu (GDPT) atau individu dengan toleransi glukosa terganggu (TGT), sekarang ini disebut sebagai prediabetes. Individu dengan TGT ditandai adanya resistensi insulin yang masih tinggi dan adanya abnormalitas respon terhadap beban glukosa, dengan kadar glukosa 2 jam pasca beban 75 gram glukosa sekitar 140-199 mg/dl dan kadar glukosa puasa yang normal. Sedangkan individu dengan GDPT ditandai dengan kadar glukosa puasa plasma sebesar 100-125 mg/dl, akibat adanya resistensi insulin yang masih tinggi, dengan jumlah insulin yang tidak cukup untuk mengkompensasi adanya peningkatan resistensi insulin hepatik dengan akibat terjadinya peningkatan glukoneogenesis dan asam lemak bebas dalam hati. Baik GDPT maupun TGT didapatkan resistensi insulin yang masih tinggi, dengan segala manifestasinya. Tahap prediabetes merupakan tahap yang sangat penting, karena dapat teridentifikasi sejumlah besar subyek (± 50 %), dan dalam kurun waktu sekitar sepuluh tahun akan berkembang menjadi DM tipe-2, oleh karenanya perlu intervensi untuk memperlambat atau mencegah perkembangannnya menjadi DM tipe-2.

Pada periode prediabetes juga telah didapatkan peningkatan risiko percepatan timbulnya aterosklerosis, yang selanjutnya terjadi penyakit kardiovaskuler dan kematian dini akibat komplikasi penyakit kardiovaskuler aterosklerotik Namun sampai sekarang belum jelas secara menyeluruh diketahui, mengenai mekanisme terjadinya peningkatan risiko penyakit kardiovaskuler pada individu dengan pre-diabetes.

Atas dasar latar belakang tersebut diatas, dilakukan suatu penelitian prospektif yang bersifat *experimental study* yang dirancang dengan *pretest-posttest control group design*, dengan tujuan membuktikan bahwa pengendalian resistensi insulin dengan intervensi jangka pendek metformin pada subyek dengan prediabetes non obes dapat menurunkan risiko berkembangnya menjadi DM tipe-2, dan menurunkan risiko timbulnya aterosklerosis.

Dari 114 calon subyek penelitian dengan riwayat keluarga DM (+), setelah menjalani TTGO maupun pemeriksaan fisik (termasuk BB, TB, BMI, lingkar pinggang,

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lingkar panggul) dan laboratorium serta bersedia menanda tangani surat persetujuan untuk ikut serta dalam penelitian, didapatkan 25 subyek penelitian non obes (48 % atau 12 subyek wanita dan 52 % atau 13 subyek pria), umur 35 – 60 tahun, yang memenuhi persayaratan sebagai subyek penelitian. Sebelum penelitian dilaksanakan, selama 1 minggu diberikan program edukasi menganai pola diet dan latihan jasmani yang diharuskan dijalankan selama (12 minggu) masa penelitian. Dilakukan pemilihan secara acak subyek mana yang akan masuk dalam kelompok perlakuan atau kelompok plasebo, didapatkan 13 subyek penelitian non obes dalam kelompok perlakuan (mendapat metformin 2 x 500 mg perhari), dan 12 subyek penelitan non obes dalam kelompok plasebo (mendapat plasebo 2 x 500 mg plasebo perhari). Pada awal penelitian (awal minggu 1) dan akhir penelitian (akhir minggu ke-12) dilakukan pemeriksaan laboratorium yang meliputi GDP, GD2j pasca beban 75 gram glukosa, A1C, insulin puasa, insulin 2j pasca beban 75 gram glukosa, hsCRP, PAI-1, VCAM-1, fibrinogen, kolesterol total, LDL-kol, HDL-kol, dan trigliserida. Juga dilakukan pemeriksaan GDP, GD 2j pasca beban 75 gram glukosa dan fisik pada awal minggu ke-5 dan ke-9.

Hasil penelitian setelah 12 minggu, didapatkan uji beda dua rerata selisih pengukuran post dan pre perlakuan untuk sampel plasebo dan sampel perlakuan didapat : penurunan secara signifikan kadar insulin puasa (p=0,003); peningkatan kadar insulin 2 j pasca beban yang tidak sinifikan (p= 0,051); peningkatan yang tidak signifikan ISI (p=0,259); penurunan kadar glukosa darah puasa yang signifikan (p=0,004); peningkatan kadar glukosa darah 2j pasca beban yang tidak signifikan (p=0,395); penurunan kadar A1C yang signifikan (p=0,001); penurunan kadar kolesterol total yang tidak signifikan (p=0.552); peningkatan kadar HDL-kol yang tidak signifikan (p=0,073); penurunan kadar LDL-kol yang tidak signifikan (p=0,373); penurunan kadar trigliserida yang tidak signifikan (p=0,307); penurunan kadar hsCRP yang signifikan (p=0.001); penurunan kadar PAI-1 secara signifikan (p= 0,015); penurunan kadar VCAM-1 yang tidak signifikan (p=0,061), penurunan kadar fibrinogen yang signifikan (p=0,001).

Pengujian perubahan proporsi prediksi risiko terjadinya penyakit jantung koroner, dengan intervensi metformin dapat menurunkan proporsi prediksi risiko terjadinya penyakit jantung koroner. Pengujian secara serempak menggunakan multivariate test, menghasilkan probabilitas signifikansi sebesar 0.009, yang berarti secara bersama-sama seluruh variabel dipengaruhi adanya intervensi metformin. Pengujian secara individual menggunakan uji variance dengan hasil masing-masing pengaruh intervensi metformin, berpengaruh secara signifikan pada AIC (p=0.001) AIC (p=0.001), glukosa darah puasa (p=0.008), insulin puasa (p=0.004), insulin 2 j.pb (p=0.004), hsCRP (p=0.001), PAI-1 (p= 0.019) dan fibrinogen (p=0.001) ; berpengaruh tidak signifikan pada glukosa darah 2j.pb (p=0.560), VCAM-1 (p=0.113), total kolesterol (p=0.787), HDL kolesterol (p=0.064), LDL kolesterol (p=0.573) dan trigliserida (p=0.341).

Kesimpulan : bahwa intervensi jangka pendek dengan metformin pada subyek prediabetes non obes, dapat menurunkan risiko berkembangnya menjadi DM tipe-2, dan juga dapat menurunkan faktor risiko penyakit kardiovaskuler, namun dalam penelitian ini pengendalian resistensi insulin tidak dipengaruhi secara signifikan.

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SUMMARY

SHORT TERM METFORMIN INTERVENTION IN NON OBESE SUBJECTS WITH PREDIABETES
A perspective of primary prevention for the development to diabetes and atherosclerosis
(Experimental Study)

Type 2 Diabetes Mellitus is a heteregenous disease with two main definitive diagnostic entities namely insulin resistance and B pancreatic cells defect. It has been agreed by many specialists that the insulin resistance has been found as the earliest sign prior the B pancreatic cell defects or the decrease of insulin secretion.

The existing facts show that the prediabetes defined by the findings of blood glucose in above normal level but within the below threshold level for type-2 Diabetes Mellitus, seen in the glucose homeostatic disorder such as found in the individuals with abnormal fasting blood glucose or abnormal glucose tolerance. The findings found in the abnormal glucose tolerance individual e.g. high insulin resistance and abnormal response to the glucose level of 75 gram 2 hr.postloading blood glucose around 140-199 mg/dl with normal level fasting blood glucose. Whereas the findings in the abnormal blood glucose tolerance individuals e.g. fasting blood glucose of 100-125 mg/dl due to the high insulin resistance with insufficient amount of insulin to compensate the increase of hepatic insulin resistance due to the increase of hepatic gluconeogenesis and free fatty acid. Either the abnormal fasting blood glucose or abnormal blood glucose tolerance, in both conditions found high insulin resistance with all of its clinical manifestations. This prediabetes is stated as the very important stage as it is found almost in so many subjects (around 50%) and predictedly the ten years later can proceed into the type 2 Diabetes Mellitus For this reason its is deemly important to do intervention in order to prevent or delay the development into this type 2 Diabetes Mellitus. In this prediabetic stage it is also found accelerated increase of the development of atherosclerosis,which can proceed into the development of cardiovascular disease and early death as the manifestation ˄f its complication. But the full mechanism of this increased cardiovascular complication risk, up to present is still unclear yet.

Based on the above background, our perspective experimental study was implemented with pretest-posttest control group design, is performed to clarify the hypothesis whether insulin resistance can be controlled by short term metformin intervention in non obese subjects with prediabetes (IGT and IFG), and decrease the risk of development to overt diabetes and the risk of development of atherosclerosis.

From 114 study subject candidates with positive history of DM and have followed TTGO, and laboratory tests with the signed agreement for the study, there were only 25 non obese subjects with prediabetes selected, ranging of 35-60 yrs old who met and fulfilled to the criteria conditions (48% /12 females and 52% / 13 males). For one week prior to the study, all the above study subjects had joined the diet regimen education program and should follow physical exercises for the 12 weeks of study period. The above subjects ,then, being randomly selected into two groups, e.g. treatment group and placebo group. Thirteen subjects were defined as the treatment group who have received twice a day 500 mg metformin and twelve subjects as the placebo group who have

received twice a day 500 mg placebo. Early,in the first week of study and at the end of the twelfth week the subjects had the necessary laboratory tests including fasting blood glucose, blood glucose 2 hr post loading, A1C, fasting insulin, insulin 2 hr post loading, hsCRP, PAI-1, VCAM-1, fibrinogen, total cholesterol, cholesterol LDL, cholesterol HDL and triglyceride tests.

After 12 weeks, the results showed in the 2-way test average deficit of post and pretreatment for both groups, significant results for fasting insulin level (p=0,003); insignificant increase of 2 hr post loading insulin level(p=0,051); insignificant increase of ISI level (p=0,259); significant decrease of fasting blood glucose level (p=0,004); insignificant increase of 2 hr post loading blood glucose level (p=0,395), significant decrease of AlC (p=0,001); insignificant decrease of cholesterol total level (p=0,552), insignificant decrease of HDL level (p=0,073), insignificant decrease of LDL level (p=0,373), insignificant decrease of triglycerides level (p=0,307); significant decrease of hsCRP (p=0,001); significant decrease of PAI-1 (p=0,015); insignificant decrease of VCAM-1 (p=0,061) and significant decrease of fibrinogen level (p=0.001) .

The tests for the proportional change in the prediction of coronary heart disease' risk, with metformin intervention showed the proportional decrease risk for the development of the coronary heart disease. The result for examination procedure in concern that yield probability of significant equal to 0.009, meaning by together entire dependent variable : AIC, fasting blood glucose, 2 hr post loading blood glucose, fasting insulin, insulin 2 hr post loading, hsCRP, PAI-1, VCAM-1, fibrinogen, total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride, is influenced the existence of metformin intervention. The individual tests using variance test with their results, after metformin intervention, showed the significant influence to AlC (p=0.001), fasting blood glucose (p=0.008), fasting insulin (p=0.004), insulin 2 hr post load (p=0.004), hsCRP (p=0.001), PAI-1 (p= 0.019) and fibrinogen (p=0.001) ; insignificant influence to blood glucose 2 hr post loading (p=0.560), VCAM-1 (p=0.113), total cholesterol (p=0.787), HDL cholesterol (p=0.064), LDL cholesterol (p=0.573) and triglyceride (p=0.341).

The conclusion : short term metformin intervention in non obese subjects with prediabetes (IGT and IFG), result in reduce risk of diabetes and lowered risk factor of cardiovascular disease, however non significant improvement of insulin resistance in this study was obtained.

ABSTRACT

SHORT TERM METFORMIN INTERVENTION
IN NON OBESE SUBJECTS WITH PREDIABETES
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to diabetes and atherosclerosis
(Experimental Study)

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In March 2002 the Department of Health and Human Services as well as the American Diabetes Association have stated referring person impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) as being prediabetics. Delaying treatment place prediabetic persons at great risk of developing of type-2 diabetes mellitus as well as the more devasting events associated with diabetic atherosclerosis and its inherent 2-4 fold increase in atherosclerotic coronary heart which is so costly in terms of morbidity, mortality, quality of life issues, and furthermore causing a huge financial burden to society.

The study is performed to clarify the hypothesis whether insulin resistance can be controlled by short term metformin intervention in non obese subjects with prediabetes (IGT and IFG), and decrease the risk of development to overt diabetes and the risk of development of atherosclerosis.

A perspective experimental study was implemented with a pretest-posttest control group design in 25 non obese subjects, 35-60 yrs old. Those fulfil the criteria were twelve (48%) non obese females and thirteen (52%) non obese males. For one week prior to the study, all the above subjects had joined the diet regimen education program and joined the physical exercises that should be followed during the 12 weeks of study period. The above subjects , then, being randomly selected into two groups, e.g. treatment group and placebo group. Thirteen subjects were defined as the treatment group who have received twice a day 500 mg metformin and twelve subjects as the placebo group who have received twice a day 500 mg placebo. Early, in the first week of study and at the end of the twelfth week the subjects had the necessary laboratory tests including fasting blood glucose, blood glucose 2 hr post loading, A1C, fasting insulin, insulin 2 hr post loading, hsCRP, PAI-1, VCAM-1, fibrinogen, total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride tests. In the first of the fourth and eighth week, the subjects had the fasting blood glucose test and blood glucose 2 hr post loading test.

Homogenity was assessed with Chi Square test for qualitative variable, and t-test for equality of mean for quantitative variable. Normality was tested using Kolmogorov Smirnov analysis. Analysis change of monthly conducted with analysis of statistic ANOVA and of Post-Hoc Test-LSD. Examination simultaneously to entire dependent variable influenced by metformin use tests multivariate, with Pillai's Trace procedure, Wilks' Lambda, Hotelling's Trace and Roy's Largest Root. While examination individually use test of variance.

The result for examination procedure in concern that yield probability of significant equal to 0.009, meaning by together entire dependent variable : A1C, fasting blood glucose, 2 hr post loading blood glucose, fasting insulin, insulin 2 hr post loading,

hsCRP, PAI-1, VCAM-1, fibrinogen, total cholesterol, HDL cholesterol, LDL cholesterol and triglyceride, is influenced the existence of metformin intervention. The individual tests using variance test with their results, after metformin intervention, showed the significant influence to A1C (p=0.001), fasting blood glucose (p=0.008), fasting insulin (p=0.004), insulin 2 hr post load (p=0.004), hsCRP (p=0.001), PAI-1 (p= 0.019) and fibrinogen (p=0.001) ; insignificant influence to blood glucose 2 hr post loading (p=0.560), VCAM-1 (p=0.113), total cholesterol (p=0.787), HDL cholesterol (p=0.064), LDL cholesterol (p=0.573) and triglyceride (p=0.341).

The conclusion : short term metformin intervention in non obese subjects with prediabetes (IGT and IFG), result in reduce risk of diabetes and lowered risk factor of cardiovascular disease, however non significant improvement of insulin resistance in this study was obtained.

Keywords : prediabetes, metformin, insulin resistance, atherosclerosis and type-2 DM.