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한국인 제2형 당뇨병환자의 초기 치료로 로지글리타존과 메트포르민 효과

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The Effect of Rosiglitazone and Metformin Therapy, as an Initial Therapy, in Patients with Type 2 Diabetes Mellitus

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Abstract

Background: Type 2 diabetes is usually preceded by a long and clinically silent period of increasing insulin resistance. The purpose of this study is to demonstrate that rosiglitazone and metformin fixed-dose combination therapy (RSG/MET) will safely and effectively control glycemia as a first line of oral therapy, better than rosiglitazone (RSG) or metformin (MET) monotherapy in Korean type 2 diabetes patients.

Methods: This study was a 32-week, multicenter, randomized, double-blind study. Twenty-seven type 2 diabetes patients (males 14; females 13) were included and randomly divided into the rosiglitazone, metformin group, or rosiglitazone /metformin combination groups. The primary objective of this study was to determine the change in HbA1c from baseline (week 0) to week 32. The secondary end-points were to determine changes in fasting plasma glucose (FPG) and homeostasis model assessment insulin resistance (HOMA-IR), from baseline to week 32. Other cardiovascular risk markers were also assessed.

Results: At week 32, there were significant reductions in HbA1c and FPG, in all three treatment groups. There was no statistical difference in HbA1c among the three groups, but the decrease in FPG in the RSG/MET group was statistically significant compared to the MET group ($P < 0.05$). RSG/MET significantly reduced HOMA-IR at week 32 compared to baseline, but there was no difference among the three groups. RSG/MET significantly decreased high-sensitive C-reactive protein (hs-CRP) value at week 32, compared to baseline. There were increases in adiponectin from baseline to week 32 in the RSG and RSG/MET groups, and the increase in the RSG/MET group was statistically significant compared to that of the MET group ($P < 0.05$). At week 32, there was a significant decrease in plasminogen activator inhibitor-1 (PAI-1) in all three treatment groups, but no statistically significant difference among them. The RSG/MET group significantly decreased in terms of urinary albumin-creatinine ratio at week 32, compared to baseline.

Conclusions: In this study, rosiglitazone and metformin combination therapy was effective in glycemic control as an initial therapy, and it improved cardiovascular risk markers in Korean type 2 diabetes patients. **(KOREAN DIABETES J 32:445-452, 2008)**

Key Words: Metformin, Rosiglitazone, Type 2 diabetes

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Introduction

The attainment and maintenance of near normal glycemia reduces the risk of long-term complications of diabetes[1,2], but the progressive nature of type 2 diabetes makes it difficult to maintain target levels of glycated hemoglobin (HbA1C) with traditional oral hypoglycemic agents[3]. It generally necessitates the escalation of drug doses and the use of combination therapies or insulin[4].

Type 2 diabetes is usually preceded by a long and clinically silent period of increasing insulin resistance[5], and insulin resistance underlies the pathogenesis of hyperglycemia and cardiovascular disease in most people with type 2 diabetes mellitus[6]. Therefore, a therapeutic strategy that addresses both hyperglycemia and the insulin resistance is logical. Among the oral hypoglycemic agents, metformin and thiazolidinediones (TZDs), counter insulin resistance[7]. Because these agents act by different cellular mechanisms, they can be used in combination, to gain additive benefits that improve glycemic control and to reduce a range of cardiovascular risk factors. Hence, thiazolidinedione and metformin in a fixed-dose combination, might offer a therapeutic advantage in controlling of glycemia and insulin resistance in type 2 diabetes.

The purpose of this study was to demonstrate that rosiglitazone/metformin fixed-dose combination tablets (RSG/MET) safely and effectively control glycemia as a first-line oral therapy, better than rosiglitazone or metformin monotherapy in Korean type 2 diabetes patients.

Patients and Methods

1. Study Population

A total of 27 male and female subjects with a diagnosis of type 2 diabetes according to World Heath Organization criteria were enrolled. The subjects had either been treated with diet and/or exercise alone, or had refrained from taking more than 15 days of oral hypoglycemic agents or insulin in the 12 weeks prior to the study. Each subject had a HbA1c > 7.5% and ≤ 11% and a fasting plasma glucose (FPG) ≤ 15 mmol/L (270 mg/dL) at screening. The following patients were excluded: patients with anemia (defined by hemoglobin concentration < 11.0 g/dL for males and < 10.0 g/dL for females); clinically significant renal or hepatic disease (i.e., serum creatinine ≥ 1.5 mg/dL for males and ≥ 1.4 mg/dL for females); and ALT, AST, total bilirubin, or alkaline phosphatase values > 2.5 times the upper limit of normal reference range) were excluded. Also excluded were those with unstable angina, coronary insufficiency, any congestive heart failure requiring pharmacological treatment, or systolic blood pressure > 170 mmHg or diastolic blood pressure > 100 mmHg while receiving antihypertensive treatment.

2. Study Design

This study was a 32-week, multicenter, randomized, double-blind study. Subjects were recruited from three centers in Korea and had a two-week screening period. To achieve balance among the three treatment groups, subjects were randomized to one of the three treatment arms: RSG/MET, rosiglitazone, or metformin. Randomization was computer-generated, with central randomization. Each subject received 32 weeks of treatment and attended nine study visits (A1-A9). Dose level 1 of study medication was initiated at week 0 (Visit A1). RSG/MET treatment began with a total daily dose of 2 mg/500 mg (rosiglitazone 2 mg/metformin 500 mg) and was increased up to 8 mg/2,000 mg in increments of 2 mg/500 mg (RSG/MET group). Rosiglitazone treatment began with a total daily dose of 4 mg and was increased to 8 mg (RSG group). Metformin treatment began with a total daily dose of 500 mg and was increased up to 2,000 mg, in 500-mg increments (MET group) (Table 1).

Subjects measured their glucose levels four times daily, in each of the three days prior to each study visit: the results were used to calculate a value for mean daily glucose (MDG). Study medication was increased to the next dose level, unless a tolerability issue existed at the current dose level and the value for calculated MDG was ≤ 6.1 mmol/L (110 mg/dL). The study protocol and informed consent were approved by each center's institutional review board and each patient provided written informed consent.

Table 1. Total daily dose for each dose level by treatment arm

Treatment group	Dose level 1	Dose level 2	Dose level 3	Dose level 4
RSG/MET (Rosiglitazone/Metformin) (n = 11)	2 mg/500 mg	4 mg/1,000 mg	6 mg/1,500 mg	8 mg/2,000 mg
Metformin (n = 8)	500 mg	1,000 mg	1,500 mg	2,000 mg
Rosiglitazone (n = 8)	4 mg	4 mg	8 mg	8 mg

MET, metformin; RSG, rosiglitazone.

3. Study Assessments

Each patient had one screening visit (week -2) and nine study visits (i.e., weeks 0, 4, 8, 12, 16, 20, 24, 28, and 32). The primary object of this study was to determine changes in HbA1c from baseline (week 0) to week 32. The secondary end-points were to determine changes in FPG and Homeostasis model assessment insulin resistance (HOMA-IR) from baseline to week 32. The equation for HOMA-IR was as follows: HOMA-IR = fasting insulin (uU/mL) × fasting glucose (mmol/L) / 22.5[8]. Additional measurements were of changes to cardiovascular risk biomarkers; high sensitive C-reactive protein (hs-CRP); adiponectin; plasminogen activator inhibitor-1 (PAI-1); urinary albumin-creatinine ratio (ACR); lipid parameters (including total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and free fatty acids (FFAs)). Assays were performed at a central laboratory (Quest Diagnostics UK Ltd., Heston, UK), using standard assays. HbA1c levels were determined using high-performance liquid chromatography (HPLC; Bio-Rad Variant, Bio-Rad Laboratories Ltd., UK), and FPG was determined using a hexokinase method (Olympus AU 640/2700/5400, Olympus UK Ltd., UK). Plasma insulin was determined using the AutoELFIA insulin kit (Perkin-Elmer, Inc., Beaconsfield, UK). Total cholesterol, HDL cholesterol and LDL cholesterol were analyzed using cholesterol esterase assays (Olympus AU 640/2700/5400); triglycerides were measured by enzymatic determination of glycerol using Olympus reagents and analyzed using the Olympus AU 640/2700/5400. FFA values were measured by using an enzymatic colorimetric assay (Wako reagent kit, Wako Chemicals GmbH, Germany), while CRP was measured with fixed-time nephelometry using the Behring Nephelometer II (Dade Behring Limited, UK).

4. Data Analysis

All data were expressed as means ± standard deviations (SDs). Statistical analyses were performed using the SPSS 11.0 statistical software program (SPSS Inc., Chicago, IL, USA). Changes from baseline to week 32 in HbA1c, FPG, HOMA-IR, lipid profiles and cardiovascular biomarkers in each group were compared using paired Student's t-tests. Significant differences among the three treatment groups were determined by one-way analysis of variance (ANOVA). Differences among groups with a $P < 0.05$ in a Turkey test were considered statistically significant.

Results

1. Baseline Characteristics

In total, 40 patients had been randomized to receive double-blind medication. Of these patients, 11 patients withdrew because of their own decisions; 27 patients completed 32 weeks of double-blind treatment, and all underwent final-visit procedures. These subjects' baseline characteristics are listed in Table 2. The mean age of the subjects was 51.4 ± 8.99 years, the duration of diabetes was 1.89 ± 2.42 years, and the HbA1c was 8.82 ± 1.09%. There were no significant differences in baseline variables among the groups.

2. Body Weight, Glycemic Control, and Insulin Sensitivity

There was no change in body weight from baseline to week 32, within each of the three treatment groups. At week 32, there were significant reductions in HbA1c and FPG within each treatment group. There was no statistical difference in HbA1c among the three groups, but the decrease of FPG in the RSG/MET group was statistically significant compared to the RSG group ($P < 0.05$).

Table 2. Baseline characteristics of subjects

	RSG	MET	RSG/MET	Total
N (male/female)	11 (7/4)	8 (4/4)	8 (3/5)	27 (14/13)
Age (years)	48.1 ± 9.85	52.0 ± 10.7	55.4 ± 3.20	51.4 ± 8.99
Duration of diabetes (years)	1.81 ± 1.72	1.05 ± 2.67	2.38 ± 3.16	1.89 ± 2.42
BW (kg)	65.8 ± 9.16	59.9 ± 8.48	64.4 ± 9.51	63.6 ± 9.06
BMI (kg/m^2)	24.6 ± 2.98	22.8 ± 1.99	24.5 ± 2.03	24.0 ± 2.51
WC (cm)	86.2 ± 6.88	86.4 ± 11.5	83.8 ± 7.54	85.5 ± 8.38
SBP (mmHg)	117.7 ± 11.2	117.9 ± 15.2	117.8 ± 11.7	117.8 ± 12.1
DBP (mmHg)	75.4 ± 9.22	74.4 ± 11.1	77.4 ± 10.4	75.7 ± 9.85
HbA1c (%)	8.78 ± 1.03	8.96 ± 1.25	8.73 ± 1.15	8.82 ± 1.09
FPG (mmol/L)	9.62 ± 2.31	12.3 ± 4.25	9.99 ± 1.95	10.5 ± 3.06
FFA (mmol/L)	0.54 ± 0.15	0.40 ± 0.13	0.49 ± 0.15	0.48 ± 0.15
Insulin (pmol/L)	55.2 ± 29.4	76.5 ± 72.8	71.3 ± 30.2	66.7 ± 46.3
C-peptide (nmol/L)	0.52 ± 0.32	0.67 ± 0.39	0.67 ± 0.13	0.61 ± 0.30

Data are expressed as means ± S.D. BW, body weight; DBP, diastolic blood pressure; FFA, free fatty acid; FPG, fasting plasma glucose; MET, metformin; RSG, rosiglitazone; SBP, systolic blood pressure.

Table 3. The changes of body weight and glycemic control

		0 week	32 week	Mean change	*P* value
BW (kg)	RSG	65.75 ± 9.16	66.2 ± 9.23	0.45 ± 4.62	0.755
	MET	59.9 ± 8.43	58.7 ± 9.82	-1.13 ± 4.67	0.513
	RSG/MET	64.4 ± 9.51	62.8 ± 8.37	-1.56 ± 2.49	0.119
HbA1c (%)	RSG	8.78 ± 1.03	6.91 ± 1.09	-1.86 ± 1.47	< 0.01
	MET	8.96 ± 1.25	6.55 ± 0.57	-2.41 ± 1.46	< 0.01
	RSG/MET	8.73 ± 1.15	6.27 ± 0.66	-2.45 ± 0.90	< 0.01
FPG (mmol/L)	RSG	9.61 ± 2.31	7.33 ± 1.30	-2.29 ± 2.34	< 0.01
	MET	12.31 ± 4.25	7.13 ± 0.66	-5.20 ± 4.14	< 0.01
	RSG/MET	9.98 ± 1.95	6.00 ± 0.83*	-3.99 ± 1.81	< 0.01
HOMA-IR	RSG	1.39 ± 0.76	1.64 ± 1.21	0.25 ± 0.66	0.246
	MET	2.74 ± 3.20	1.19 ± 0.38	-1.55 ± 3.17	0.209
	RSG/MET	1.86 ± 0.43	0.91 ± 0.22	-0.95 ± 0.37	< 0.01

Data are expressed as means ± S.D. BW, body weight; FPG, fasting plasma glucose; HOMA-IR, Homeostasis model assessment insulin resistance; MET, metformin; RSG, rosiglitazone. * $P < 0.05$ vs RSG.

RSG/MET significantly reduced HOMA-IR at week 32 compared to the baseline, but there were no differences among the three groups.

3. Lipid Parameters and Other Markers

There were no differences in lipid parameters at week 32 compared to baseline, except for a decrease in triglyceride in the RSG/MET group ($P < 0.05$) (Table 4).

RSG/MET significantly decreased hs-CRP at week 32, compared to baseline. There were increases in adiponectin from baseline to week 32 in the RSG and RSG/MET groups, and the increase in the RSG/MET group was statistically significant compared to the MET group ($P < 0.05$).

At week 32, there was a significant decrease in PAI-1 in each of the three treatment groups, but there was no statistical difference among these groups.

RSG/MET significantly decreased urinary ACR at week 32, compared to baseline.

Discussion

This study found that treatment with RSG/MET in Korean type 2 diabetes patients improved glycemic control and insulin resistance. In each of the RSG, MET, and RSG/MET groups, an significant improvements were

observed in terms of HbA1c and FPG, after 32 weeks of treatment. FPG improvement in the RSG/MET group reached statistical significance when compared to the MET group.

It is the β-cell dysfunction and insulin resistance that are two central, interrelated defects inherent in the pathophysiology of type 2 diabetes[9]. Insulin resistance is initially compensated by an increase in insulin secretion, which normally maintains normoglycemia; however, if an increased insulin production fails to keep pace, the glucose tolerance becomes impaired. Sustained insulin resistance with a further loss of β-cell function gives rise to higher hyperglycemia and accompanying vascular complications[10,11]. Obesity is an important factors in insulin resistance and it frequently exacerbates insulin resistance. However, approximately 65% of type 2 diabetes subjects in Korea are not obese, even when obesity is defined as a body mass index (BMI) ≥ 25 (kg/m^2)[12]. The relative β-cell volume correlated with BMI in diabetes patients; a decrease in β-cells in the islet suggests that impaired insulin secretion is more prominent than insulin resistance in the pathogenesis of Korean type 2 diabetes[13].

The subjects of this study had a relatively short duration of diabetes (1.89 ± 2.42 years) and moderately increased HbA1C levels (8.82 ± 1.09). Treatment with only an insulin sensitizer in Korean type 2 diabetes patients showed a significant reduction of HbA1C and FPG. This suggests that insulin resistance is also an important factor in the non-obese Korean type 2 diabetes. The use of metformin and rosiglitazone generally does not induce hypoglycemia; furthermore, rosiglitazone maintains long-term glycemic control better than metformin and glyburide in type 2 diabetes[14]. It might therefore be reasonable to start an initial treatment with an insulin sensitizer such as metformin or rosiglitazone, or a combination thereof, both in Korean type 2 diabetes subjects.

Whereas metformin does not cause weight gain and may induce modest weight loss in overweight and obese type 2 diabetes patients, TZD use generally results in weight gain[14,15]. In this study, although the number of study subjects was not large, RSG was found not to induce significant weight gain, while RSG/MET induced non-significant modest weight loss in Korean type 2 diabetes patients (Table 3). This suggests that metformin has a mitigating effect on weight gain when administered in combination with rosiglitazone. However, the long term health effect of increases in weight and changes in body composition with TZD use should be further explored.

The effects of metformin on the lipid profile are generally favorable but rosiglitazone tends to increase

Table 4. The changes of lipid profile

		0 week	32 week	Mean change	*P* value
TC (mmol/L)	RSG	5.21 ± 0.66	5.21 ± 0.89	-0.01 ± 0.56	0.975
	MET	4.98 ± 0.74	4.63 ± 0.77	-0.36 ± 1.27	0.455
	RSG/MET	5.04 ± 0.82	4.53 ± 0.65	-0.51 ± 0.95	0.174
TG (mmol/L)	RSG	1.28 ± 0.36	1.19 ± 0.45	-0.09 ± 0.51	0.577
	MET	1.97 ± 0.89	2.01 ± 1.26	0.04 ± 1.09	0.917
	RSG/MET	1.99 ± 0.97	1.42 ± 0.71	-0.57 ± 0.60	< 0.05
HDL-C (mmol/L)	RSG	1.29 ± 0.20	1.43 ± 0.31	0.14 ± 0.17	0.246
	MET	1.09 ± 0.51	1.16 ± 0.33	0.08 ± 0.39	0.60
	RSG/MET	1.12 ± 0.24	1.11 ± 0.24	-0.01 ± 0.11	0.743
LDL-C (mmol/L)	RSG	3.34 ± 0.57	3.23 ± 0.74	-0.11 ± 0.52	0.504
	MET	2.88 ± 0.61	2.58 ± 0.95	-0.29 ± 1.05	0.453
	RSG/MET	2.99 ± 0.92	2.76 ± 0.50	-0.23 ± 1.18	0.605
FFA (mmol/L)	RSG	0.54 ± 0.15	0.45 ± 0.15	-0.09 ± 0.20	0.198
	MET	0.40 ± 0.13	0.41 ± 0.17	0.04 ± 0.15	0.906
	RSG/MET	0.49 ± 0.15	0.49 ± 0.08	-0.00 ± 0.12	1.000

Data are expressed as means ± S.D. FFA, free fatty acid; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; MET, metformin; RSG, rosiglitazone; TC, total cholesterol; TG, triglyceride.

Table 5. The changes of other marker

		0 week	32 week	Mean change	*P* value
hs-CRP (mg/L)	RSG	0.86 ± 0.89	0.64 ± 0.83	-0.23 ± 1.16	0.53
	MET	1.71 ± 2.69	0.29 ± 0.30	-1.43 ± 2.62	0.168
	RSG/MET	1.13 ± 0.97	0.56 ± 0.64	-0.56 ± 0.65	< 0.05
ADP (ug/mL)	RSG	5.56 ± 3.00	19.5 ± 11.7	13.9 ± 13.0	< 0.01
	MET	4.63 ± 4.25	4.88 ± 4.19	0.25 ± 1.02	0.168
	RSG/MET	4.08 ± 1.94	14.78 ± 9.22†	10.7 ± 8.89	< 0.05
PAI-1 (IU/mL)	RSG	26.8 ± 12.8	12.8 ± 7.69	-14.0 ± 13.0	< 0.01
	MET	20.4 ± 16.5	8.53 ± 9.97	-11.9 ± 11.4	< 0.05
	RSG/MET	28.0 ± 24.9	8.55 ± 7.70	-19.5 ± 17.6	< 0.05
ACR (mg/mmol)	RSG	1.06 ± 0.52	0.85 ± 0.54	-0.21 ± 0.51	0.228
	MET	2.74 ± 3.20	1.19 ± 0.38	-1.56 ± 3.17	0.209
	RSG/MET	1.85 ± 1.14	0.96 ± 0.43	-0.89 ± 0.85	< 0.05

Data are expressed as means ± S.D. ACR, albumin creatinine ratio; ADP, adiponectin; hs-CRP, high sensivity C-reactive protein; MET, metformin; PAI-1, plasminogen activator inhibitor-1; RSG, rosiglitazone. † $P < 0.05$ vs MET.

LDL-cholesterol by 5~10%. On the other hand, TZDs are known to reduce plasma FFA and change the distribution of LDL particles, to reduce the number of more atherogenic small dense particles[16,17]. In this study, rosiglitazone, metformin, and RSG/MET did not change lipid profile, except RSG/MET significantly decreased triglyceride (Table 4).

Microalbuminuria in diabetes is associated with diabetic retinopathy, amputation, cardiovascular disease, and increased cardiovascular mortality[18,19]. Among the oral hypoglycemic agents, rosiglitazone, in comparison to glyburide, has been shown to decrease urinary albumin excretion in type 2 diabetes patients. This suggests a beneficial effect of rosiglitazone in the prevention of renal complications related to type 2 diabetes[20]. In the RSG/MET group, there was a reduction in urinary ACR compared to baseline, but it was not significant when compared to those of the RSG and MET groups. In the current study, RSG/MET significantly reduced hs-CRP and PAI-1 and increased adiponectin (Table 5). Type 2 diabetes is associated with a marked increase (i.e., by a factor of two to four) in the risk of coronary heart disease[21]. Diabetes patients without previous myocardial infarction have as high a risk of incurring myocardial infarction as non-diabetes patients with previous myocardial infarction[22]. In this sense, type 2 diabetes is therefore regarded as being equivalent to coronary artery disease. Among the coronary artery disease risk markers, C-reactive protein level is a stronger predictor of cardiovascular events than the LDL cholesterol level, in that it offers prognostic information additional to that conveyed by the Framingham risk score[23]. RSG/MET showed beneficial effects on hs-CRP, adiponectin, and PAI-1; for this reason, RSG/MET is thought to have a favorable effect on cardiovascular disease.

A recently published meta-analysis suggests a significant increase in the risk of myocardial infarction associated with treatment with rosiglitazone treatment and an increase of similar magnitude, albeit non-significant, in the risk of death from cardiovascular disease[24]. As a result of the publication of this data, the steering committee of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial undertook an unplanned interim analysis of some of the cardiovascular end-points in that trial. The interim findings were inclusive regarding the effect of rosiglitazone on the overall risk of hospitalization or death from cardiovascular causes; RECORD found no evidence of any increase in death from any particular cause, including cardiovascular causes[25].

Although RSG/MET had favorable effects on glycemic control and cardiovascular risk markers in this study, a study regarding cardiovascular outcomes in Korean diabetes patients treated with rosiglitazone will be needed, as there is continued uncertainty surrounding the cardiovascular safety of rosiglitazone.

The main adverse reaction with metformin is gastrointestinal disturbance; with rosiglitazone, it is edema due to fluid retention. In this study, there were no specific adverse reactions to the drugs, and no drop-out subjects in the course of the study.

A limitation of this study is the small number of study subjects; as such, these subjects cannot be considered to represent the general population of Korean type 2 diabetes subjects. In addition, we did not assessed the subject's cardiovascular functions during the study.

In conclusion, rosiglitazone and metformin combination therapy was effective in glycemic control as an initial therapy, and it improved cardiovascular risk markers in Korean type 2 diabetes patients.

요 약

연구배경: 제2형 당뇨병은 발병 전에 일반적으로 오랜 기간 동안 임상적으로 증상이 나타나지 않는 인슐린저항성이 선행한다. 본 연구의 목적은 한국인 제2형 당뇨병환자를 대상으로 초기 치료로 고정 용량의 로지글리타존/메트포르민 복합 투여와 로지글리타존, 메트포르민 단독 투여를 비교하여 혈당 강하 유효성을 평가하고자 하였다.

방법: 본 연구는 32주 동안 다기관, 무작위, 이중 맹검 방법으로, 27명의 제2형 당뇨병환자를 대상으로 하였다. 대상환자들은 로지글리타존, 메트포르민, 로지글리타존/메트포르민 복합제 3군으로 무작위 배정하였다. 본 연구의 일차 목표로 약제 투여 32주 후 기준 시점으로부터의 당화혈색소 변화를 보고자 하였고, 이차 목표는 공복 혈장 혈당, HOMA-IR (Homeostasis model assessment insulin resistance), 기타 심혈관계 위험 인자의 변화를 비교하는 것이었다.

결과: 약제 투여 32주 후, 3군 모두에서 당화혈색소, 공복 혈장 혈당이 기준 시점에 비해 의미 있게 감소하였다. 당화혈색소 감소에 대해 각 군 간에 의미 있는 차이는 없었지만 공복 혈장 혈당 감소는 복합제군에서 메트포르민군 보다 의미 있게 감소하였다 ($P < 0.05$). 복합제군에서 HOMA-IR이 기준 시점에 비해 감소하였지만 다른 군과는 차이가 없었다. hs-CRP (high sensitive C-reactive protein)는 복합제군에서 기준 시점에 비해 감소하였다. 로지글리타존군과 복합제군에서 adiponectin이 증가하였고 복합제군의 경우 메트포르민군에 비해 의미 있게 증가하였다 ($P < 0.05$). 각 군 간의 차이는 없었지만 PAI-1 (plasminogen activator inhibitor-1)은 3군 모두에서 기준 시점에 비해 감소하였다 ($P < 0.05$).

결론: 로지글리타존과 메트포르민 복합 제제는 한국인 제2형 당뇨병환자에서 초기 치료로써 혈당 조절에 효과적이었고 심혈관계 위험 인자들을 개선시켰다.

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