The Effect of Rosiglitazone on Insulin Sensitivity and Midthigh Low Density Muscle in Patients with Type 2 Diabetes

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written by Joo Young Nam

Table of contents

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

The Effect of Rosiglitazone on Insulin Sensitivity and Midthigh Low Density Muscle in Patients with Type 2 Diabetes

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(Directed by Professor Kyung Rae Kim)

We examined the effect of three months of rosiglitazone treatment (4 mg, daily) on insulin sensitivity, abdominal and midthigh fat distribution and plasma concentrations of adipocytokines such as adiponectin, leptin and resistin in patients with type 2 diabetes.

Forty-two type 2 diabetic patients (age: 32-70 years old, BMI 17.48-32.55 kg/m^2, 15 women, 27 men) were enrolled in this study, and designed as rosiglitazone 4 mg, administered daily for 12 weeks. We assessed body composition, and measured the level of plasma adiponectin, leptin, resistin and various biochemical parameters.

Twelve weeks of 4 mg/day rosiglitazone treatment achieved significant increase in BMI from 24.83 ± 3.55 to 25.69 ± 3.44 kg/m^2 ($p = 0.001$), and abdominal subcutaneous adipose tissue area changed from 151.49 ± 75.22 to 177.00 ± 185.01 cm^2 ($p = 0.39$). Abdominal visceral adipose tissue area decreased from 144.69 ± 65.57 to 129.39 ± 73.10 cm^2 ($p = 0.05$). Cross-sectional area of low density muscle (LDM) at the midthigh increased from 23.09 ± 9.58 to 26.12 ± 8.24 cm^2 ($p = 0.009$). Insulin resistance (IR, as measured using the Kitt) was improved (from

2.52 ± 0.98 to 2.85 ± 1.11 %/min, $p < 0.05$). Plasma adiponectin levels increased from 5.58 ± 2.19 to 8.80 ± 3.02 μg/mL ($p < 0.01$). Plasma leptin levels decreased but did not change significantly (7.47 ± 6.44 to 6.63 ± 4.06 pg/mL, $p = 0.10$). Plasma resistin levels decreased from 3.23 ± 2.46 to 1.91 ± 1.93 μg/mL ($p < 0.01$).

In this study, we found that rosiglitazone treatment increased midthigh low density muscle area unexpectedly. But other factor rather than accumulation of fatty acid metabolite in skeletal muscle may be much more important with regard to change of insulin resistance with rosiglitazone treatment. It is also possible the effects of rosiglitazone on low density muscle may be different in Korean patients with type 2 DM. We also examined that rosiglitazone changed plasma level of adiponectin, leptin and resistin.

Key words: rosiglitazone, insulin resistance, adiponectin, leptin, resistin, low density muscle

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I. INTRODUCTION

The pathophysiology of type 2 diabetes involves defects in tissue sensitivity to insulin and decreased insulin secretion. It is generally accepted that resistance to insulin in target tissues (especially muscle and liver) develops initially, followed by decreased insulin secretion as a result of progressive pancreatic beta-cell dysfunction. Insulin resistance is the inability of peripheral target tissues to respond properly to normal circulating concentration of insulin.

Defects in muscle glycogen synthesis play a significant role in insulin resistance. Intracellular defects in glucose transport for insulin-mediated glucose uptake in muscle are likely the result of dysregulation of intramyocellular fatty acid metabolism, whereby fatty acids cause insulin resistance by activation of a serine kinase cascade, leading to decreased insulin-stimulated insulin receptor substrate (IRS)-1 tyrosine phosphorylation and decreased IRS-1–associated phosphatidyl-inositol 3-kinase activity, a required step in insulin-stimulated glucose transport into muscle. Defects in the pathways for fatty acid oxidation

during postabsorptive conditions are prominent, leading to diminished use of fatty acids and increased esterification and storage of lipid within skeletal muscle. Alterations in skeletal muscle substrate metabolism provide insight into the link between skeletal muscle triglyceride accumulation and insulin resistance.

Subsequently the role of intramuscular lipid components in insulin resistance became the subject of attention.[1-3] Low density muscle represents lipid-rich skeletal muscle, which includes fat components between and inside the muscle fibers. Goodpaster et al[4] showed that skeletal muscle attenuation by single-slice CT scans well demonstrate muscle fiber lipid content in percutaneous biopsy specimens. Perseghin et al.[5] used magnetic resonance spectroscopy to report that lipids contained within muscle fibers were strongly correlated with the severity of insulin resistance. The link between insulin resistance and triglyceride content measured in human muscle biopsy samples has also been established.[6]

Thiazolidinediones (TZDs) are antidiabetic agents that improve glucose tolerance in patients with type 2 diabetes mostly through enhancing insulin sensitivity in skeletal muscle.[7-12] Although thiazolidinediones (TZDs) are now widely used to treat type 2 diabetes, their mechanism of action remains largely unknown. However, PPAR-γ is predominantly expressed in adipose tissue, whereas the improvement in insulin sensitivity occurs predominately in skeletal muscle[10,11,13] where PPAR-γ expression is relatively low.[14,15] This paradox suggests that the TZDs may indeed modulate key communication signals between fat and muscle, such as leptin[16], adiponectin,[17] tumor necrosis factor-α (TNF-α),[18]

resistin,[19] and fatty acid.[20-23] In support of fatty acids being an important factor in this regard, recent studies have demonstrated a strong relationship between tissue lipid content and insulin resistance in both skeletal muscle [5,6,24-28] and liver. [24,25,29]

Some investigators have hypothesized that the insulin-sensitizing action of TZDs may involve activation of PPAR-γ in adipocytes resulting in adipocyte differentiation/hyperplasia and partitioning of fat away from skeletal muscle and into adipocytes.[30-35] In contrast, others have argued that TZDs may directly affect skeletal muscle insulin sensitivity by binding to PPAR-γ present in this tissue[36] and altering expression of genes involved in fat and glucose metabolism.[37-42] Recently, Burant et al.[41] demonstrated that troglitazone altered glucose metabolism in ap2/DTA mice that partially lack white and brown adipose tissues and suggested that the insulin-sensitizing action of TZDs may be independent of adipose tissue, therefore supporting the latter hypothesis. In contrast, Chao et al.[42] recently demonstrated that rosiglitazone failed to improve hyperglycemia and glucose intolerance of A-ZIP/F-1 "fatless" mice, which virtually lack white adipose tissue, suggesting that adipose tissue is required for PPAR-γ's insulin sensitizing action.

Mayerson et al. recently demonstrated that rosiglitazone caused no significant decrease in intramyocellular triglyceride content, despite a significant improvement in muscle insulin sensitivity.[32] In contrast, Ye et al.[43] have recently reported that pioglitazone decreases triglyceride and fatty acyl CoA content in skeletal muscle of Zucker rats. In this study, we examined the hypothesis that TZDs improve insulin sensitivity in

patients with type 2 diabetes by promoting the redistribution of fat from muscle to peripheral adipocytes and by altering the concentrations of certain adipocyte-derived hormones, such as leptin, adiponectin, resistin in Korean patients with type 2 diabetes. And we also examined the change of low density muscle area of type 2 diabetic patients with rosiglitazone treatment in Korea.

II. MATERIALS AND METHODS

1. Subjects

Forty-two patients (aged 32-70 years, BMI 17.48-32.55 kg/m^2) with type 2 diabetes, as defined by fasting plasma glucose (> 7.0 mmol/l on at least two separate occasions) and presence of endogenous insulin production (fasting C-peptide > 0.2nmol/l) and who had been stable on sulfonylurea therapy at least 2 months before the screening visit, were included. Patients were excluded in case of fasting plasma glucose < 6.1 or > 10.0 mmol/l) after the screening period, cardiac disease, blood pressure > 160/100 mmHg, hepatic or renal diseases, symptoms of complications of diabetes, history of lactate acidosis, oral corticosteroid treatment, and recent changes in antihypertensive medication or use of ß-adrenergic blocking agents, ACE inhibitors or lipid lowering agents. Their clinical and metabolic profiles are detailed in table 1.

2. Design

After the baseline studies, subjects took rosiglitazone (4 mg daily p.o.) for 12 weeks. Blood samples and fat measured CT were taken before and after rosiglitazone treatment.

3. Measurement

A. Anthropometric parameters

Body weight and height were measured in the morning, without clothing and shoes. BMI was calculated as body weight in kilograms divided by height in meters squared (kg/m^2).

B. Biochemical profiles

Serum glucose was measured immediately by an autoanalyzer using the hexokinase method (Roche, Hitachi 747). Serum insulin and c-peptide were determined by an enzyme chemiluminescence immuno -assay (ECIA, DPC, Immulite 2000). HbA_{1c} was measured by the high performance liquid chromatography method (Bio-Rad, Variant Ⅱ). Serum total cholesterol, HDL-cholesterol and LDL-cholesterol were assessed by the enzymatic methods (Daiichi, Hitachi 747) and serum triglycerides were measured by the enzymatic colorimetric methods (Roche, Hitachi 747). Serum free fatty acids were measured by the enzymatic colorimetric method (Daiichi, Olympus AU640).

C. Insulin sensitivity

To assess whole body insulin sensitivity, we performed short insulin tolerance test in all subjects. On the day before blood sampling, subjects were instructed not to consume any food after midnight and to avoid strenuous exercise. On the morning of the test day, a 20 G catheter was inserted reversibly into one cephalic vein and another 20 G catheter was inserted for insulin and glucose infusion. In order to obtain an arterialized vein, the temperature at the sampling site was maintained

at 60-70℃ with a heating pad. With the subject at rest, 0.1 U of 100 times diluted short-acting human insulin (Humulin-R, Eli Lilly, US) per kg of body weight equivalent to 5.22 ± 0.44 U/m^2 of body surface was administered via the vein, and a blood sample was collected from the opposite vein 10 and 5 minutes before, and 3, 6, 9, 12 and 15 minutes after insulin injection. Each blood sample was immediately centrifuged and the glucose concentration was determined. Plasma glucose $t^{1/2}$ was calculated from the slope of least-square analysis of plasma glucose concentrations from 3 to 15 minutes after insulin injection, when plasma glucose declined linearly. Kitt represents the percent decline in plasma glucose concentration per minute and is calculated according to the formula: Kitt = $(0.693/t^{1/2})$ x 100, in which $t^{1/2}$ represents the half-life of plasma glucose decay. Lower insulin-sensitivity index (Kitt) scores mean higher degrees of insulin resistance. In order to avoid severe persistent hypoglycemia, 100 ml of 20% glucose was administered immediately after the test.

D. Skeletal muscle lipid contents and regional fat distribution

The abdominal and midthigh adipose tissue areas and the midthigh muscle area were quantified by CT (Tomoscan 350; Philips, Mahway, NJ). With the subject in a supine position, a 10-mm CT slice scan was acquired at the L4–L5 level to measure the total abdominal and visceral fat areas. A cross-sectional scan of the same thickness was obtained for both legs at the midpoint between the anterior superior iliac crest and the patella, as described previously.[44] Skeletal muscle

attenuation was determined by measuring the mean value of all pixels within the range of 0 to 100 Hounsfield units (HU); adipose tissue areas fell in the range of －150 to－50 HU. The midthigh skeletal muscle area was compartmentalized into a normal density muscle area (+31 to +100 HU) and a low density muscle area (0 to +30HU).

E. Adipocytokines

Fasting blood samples were collected in prechilled tubes and immediately separated by centrifugation. Samples were frozen at -70℃ for subsequent analysis. Serum adiponectin levels were determined using a newly developed specific human adioponectin radioimmunoassay (RIA, Linco, USA.). Serum leptin levels were determined using a newly developed specific human leptin radioimmunoassay (RIA, Linco, USA.). Plasma resistin levels were determined using a newly developed specific human resistin enzyme linked immunosolventassay (ELISA, Komed, Korea).

4. Statistical analyses

All statistical analyses were performed using SPSS Win 11.0 (Statistical Package for Social Science, SPSS, Chicago, II, USA.). All data are presented as means ± SD. Pre- to posttherapy values are compared using a paired t test, with significance reached at $P < 0.05$. Associations between Kitt and regional fat distributions, adipocytokine and kitt were identified using Pearson correlations. Differences were considered to be significant if p-value < 0.05.

III. RESULTS

Table 1. Anthropometric and fasting plasma metabolic concentration before and after 3 months of rosiglitazone treatment

	before	after	p
Body Weight (kg)	68.69 ± 13.58	70.76 ± 13.30	0.001
BMI (kg/m^2)	24.83 ± 3.55	25.69 ± 3.44	0.001
HbA1c (%)	7.96 ± 1.35	7.07 ± 1.41	0.000
Plasma glucose (mg/dl)	152.31 ± 38.94	137.78 ± 45.23	0.005
Insulin (μU/ml)	8.39 ± 4.09	6.51 ± 3.06	0.001
C-peptide (ng/ml)	2.37 ± 0.70	2.38 ± 2.50	0.97
Kitt (%/min)	2.52 ± 0.98	2.85 ±1.17	0.041
Total cholesterol (mg/dl)	201.04 ± 48.18	211.74 ± 56.03	0.06
Triglyceride (mg/dl)	178.51 ± 135.76	172.14 ± 128.51	0.68
HDL cholesterol (mg/dl)	46.08 ± 10.12	48.40 ± 9.98	0.062
LDL cholesterol (mg/dl)	118.56 ± 32.08	129.10 ± 30.40	0.14
Free fatty acid (μmol/l)	561.95 ± 230.36	507.34 ± 214.61	0.216

Data are means ± SD.

Table 1 shows the changes in pertinent fasting laboratory studies before and after therapy. Three months after rosiglitazone treatment body weight increased significantly (68.69 ± 13.58 & 70.76 ± 13.30, p = 0.001). Mean fasting plasma glucose concentrations decreased by 14.53 ± 33.60 mg/dl (P = 0.005), and mean insulin concentrations decreased by 1.88 ± 3.17 uU/ml (P = 0.001). Insulin resistance was improved significantly (Kitt: 2.52 ± 0.98 & 2.85 ± 1.17, p = 0.041) after rosiglitazone treatment. Changes of total cholesterol, triglyceride, LDL and HDL cholesterol were unsignificant. Although free fatty acid decreased after treatment (561.95 ± 230.36 & 507.34 ± 214.61, P = 0.216), the amount was unsignificant. In conclusion, rosiglitazone treatment (4mg,daily), in spite of weight gain (2.06 ± 3.37 kg, p = 0.000),

improved insulin sensitivity without change of beta cell function (no change of c-peptide) and it also improved hyperinsulinemia. Also rosiglitazone had no significant effect on lipid profile in type 2 diabetic patients.

Table 2. Mean values of abdominal and midthigh area before and after 3 months of rosiglitazone treatment

Area (cm^2)	before	after	p
AVFA	144.69 ± 65.57	129.39 ± 73.10	0.050
ASFA	151.49 ± 75.22	177.00 ± 185.01	0.39
TLDMA	23.09 ± 9.58	26.12 ± 8.24	0.009
TNDMA	96.32 ± 27.12	94.17 ± 28.22	0.032
TSFA	48.60 ± 28.82	52.53 ± 31.39	0.007

AVFA: abdominal visceral fat area, ASFA: abdominal subcutaneous fat area, TLDMA: midthigh low density muscle area, TNDMA: midthigh normal density muscle area, TSFA: midthigh subcutaneous fat area

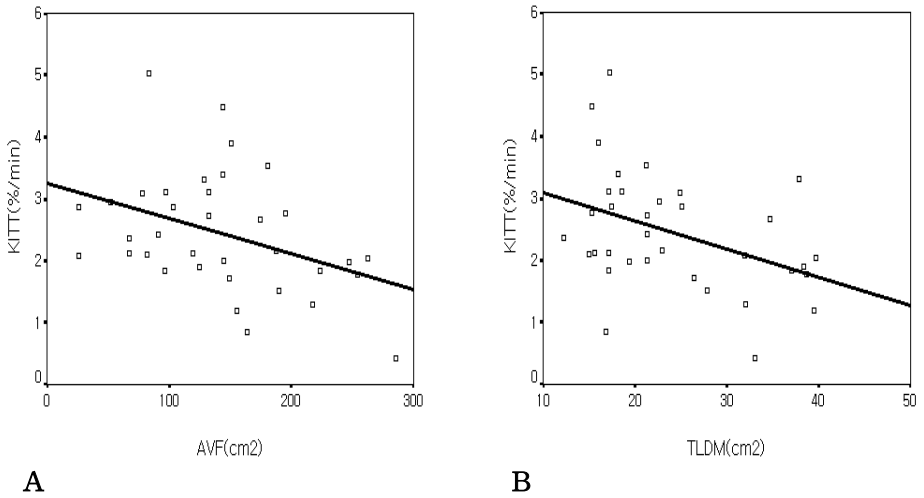
After treatment, AVFA decreased significantly (144.69 ± 65.57 & 129.39 ± 73.10, p = 0.050). Change of ASFA was unsignificant although it increased. In midthigh area, TLDMA increased significantly unexpectedly (23.09 ± 9.58 & 26.12 ± 8.24, p = 0.009) and TSFA increased after treatment (48.60 ± 28.82 & 52.53 ± 31.39, p = 0.007).

Table 3. Adipocytokine concecntrations before and after 3 months of rosiglitazone treatment

adipocytokine	before	after	p
Adiponectin (μg/ml)	5.58 ± 2.19	8.80 ± 3.02	0.000
Resistin (μg/ml)	3.23 ± 2.46	1.91 ± 1.93	0.000
Leptin (pg/ml)	7.47 ± 6.44	6.63 ± 4.96	0.10

After rosiglitazone treatment, plasma level of adiponectin increa-

sed (5.58 ± 2.19 & 8.80 ± 3.02, p = 0.000) and plasma level of resistin and leptin decreased respectively (3.23 ± 2.46 & 1.91 ± 1.93, p = 0.000 , 7.47 ± 6.44 & 6.63 ± 4.96, p = 0.10).



A B

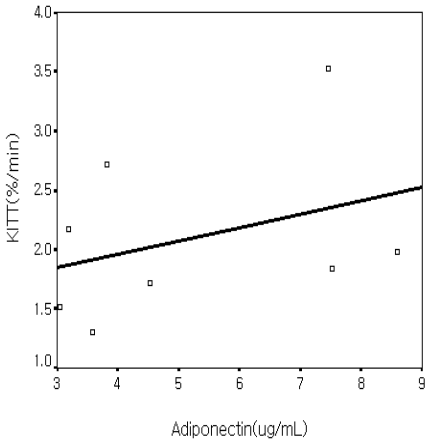
Fig.1 Correlation between regional adiposity and insulin resistance. A: Abdominal visceral fat area and Kitt (P = 0.014) B: Midthigh low density muscle area and Kitt (P = 0.033).

In consistent with other previous studies, abdominal visceral fat area and midthigh low density muscle area were linealy correlated with Kitt (r = -0.364, p = 0.014 & r = -0.318, p = 0.033). The abdominal subcutaneous fat area did not correlate with Kitt. Although midthigh subcutaneous fat area increased significantly (48.60 ± 28.82 & 52.53 ± 31.39, p= 0.007), it did not correlate with Kitt.

Table 4. Mean values of abdominal and midthigh area before and after 3 months of rosiglitazone treatment in BMI < 25kg/m^2 group and AVFA < 100 cm^2 group

	AVFA			TLDMA		
	before	after	p	before	after	p
BMI <25	119.70±56.25	103.58±66.95	0.17	88.55±22.41	86.39±23.57	0.02
AVFA <100	75.93±20.27	68.68±23.38	0.33	19.17±5.25	21.46±6.00	0.16

We divided our patients into 2 groups: BMI < 25 kg/m^2 , AVFA < 100 cm^2. In each group, AVFA decreased unsignificantly (p = 0.17, p = 0.22) but midthigh low density muscle area increased variably (p = 0.02 , p = 0.16). It is possible that rosiglitazone may have different effect on low density muscle of relatively lean, less cental obese patients with type 2 diabetes in Korea.



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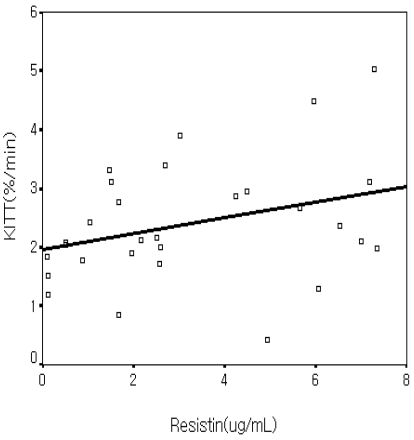

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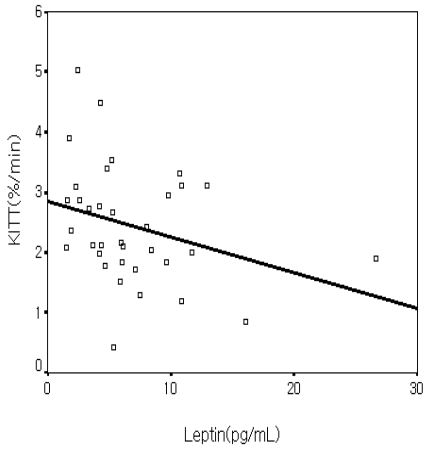

C

Fig.2 Correlation between adipocytokine and insulin resistance.

A: plasma adiponectin concentration and Kitt (r = 0.22, P = 0.247). B: plasma resistin concentration and Kitt(r = 0.328, P = 0.082). C: plasma leptin concentration and Kitt (r = -0.24, P = 0.139).

It is well known that rosiglitazone increases plasma adiponectin level and we also examined it. But in this study any adipocytokine level did not correlate with insulin resistance.

IV. DISCUSSION

The 3 months of rosiglitazone treatment in this study resulted in a significant improvement in fasting plasma glucose, hyperinsulinemia and insulin sensitivity (Kitt). These results are similar to the results from previous rosiglitazone treatment in patients with type 2 diabetes in Korea.[45]

This improvement in insulin responsiveness was associated with fat redistribution of abdomen and midthigh. After treatment, AVFA decreased significantly (144.69 ± 65.57 & 129.39 ± 73.10, p = 0.050). Kim et al[46] showed correlation between midthigh low density muscle and inslin resistance in obese nondiabetic patients in Korea, but surprisingly in midthigh, low density muscle area increased significantly (23.09 ± 9.58 & 26.12 ± 8.24, p = 0.009) and normal density muscle area decreased unsignificantly (96.32 ± 27.12 & 94.17 ± 28.22, p = 0.032) and subcutaneous fat area increased remarkedly (48.60 ± 28.82 & 52.53 ± 31.39, p = 0.007) in this study.

Mayerson et al.[32] recently showed that 3 months of rosiglitazone treatment in patients with type 2 diabetes resulted in lowering of plasma fatty acids and intrahepatic triglyceride content, which was associated with enhanced insulin action in peripheral adipocytes and an increase in extramyocellular lipid content. Theses findings are consistent with rosiglitazone's effects in promoting adipocyte differentiation and suggests that extramyocellular adipocytes behave similarly to peripheral adipocytes in response to TZDs. Theses findings are also consistent with the results

of Kelley et al.[47], who found that 3 months of troglitazone therapy in subjects with type 2 diabetes improved fasting plasma glucose concentrations while increasing total body fat mass. Body composition analysis by computed tomography revealed that this increase was exclusively attributable to an increase in peripheral adiposity, while visceral fat stores decreased. Similar results have been achieved by other group with troglitazone[48-51] and pioglitazone[52] in patients with type 2 diabetes and lipodystrophy.[53] This redistribution of body fat may result from the predilection for certain PPAR-γ agonists to induce pre-adipocyte differentiation in subcutaneous rather than visceral fat depots.[54]

Although body composition analysis by computed tomography has some limitation in differentiate intramyocellular lipid content from extramyocellular lipid content and genetic difference should be considered, in our study improvement of insulin sensitivity after rosiglitazone treatment is not associated with decreased midthigh low density muscle area. Our results are similar with those of Clinton T et al.[55] They found that skeletal muscle TG was markedly elevated in type 2 diabetic patients but skeletal muscle oxidative capacity was a better predictor of insulin sensitivity than either TG concentration or long-chain fattyacyl CoA content. Another report consistent with us: rosiglitazone treatment resulted in decreased TG content of cardiac muscle, but increased TG content of skeletal muscle in *ob/ob* mice with improvement of insulin sensitivity.[56]

It is also possible that rosiglitazone improves insulin sensitivity in type 2 diabetes by altering the concentrations of certain adipocyte -derived hormones, such as leptin,[16] TNF-α,[18] adiponectin,[17] or resistin.[19]

With regard to leptin, we found no significant effects of rosiglitazone on leptin concentrations. Previous in vitro and in vivo studies on the effects of TZDs on leptin production by adipocytes have yielded conflicting results.[54,57,58] Nolan et al.[54] showed that co-incubation of adipocytes with troglitazone abolished the usual twofold increase in insulin-stimulated leptin productionin vitro. In contrast rosiglitazone had no effect on plasma leptin concentrations in obese Zucker rats.[57] In obese, non-diabetic human subjects, troglitazone caused no change in leptin levels, but has been shown to decrease leptin concentrations in diabetic subjects.[58,59] Based on our results, an alteration in circulating leptin concentrations does not appear to play a major role in mediating the insulin-sensitizing effects of rosiglitazone.

We also found PPAR-γ agonist increase plasma level of adiponectin in type 2 diabetic patients consistent with previous other studies. In regard to resistin, Steppan et al.[60] reported that serum concentrations of resistin are markedly increased in obese mice and are decreased by treatment with thiazolidinediones. However, subsequent studies in rodent models[62-64] have produced different findings. In humans, the expression of resistin in adipocytes is very low compared with that in rodents, but resistin mRNA is readily detectable in circulating mononuclear cells, which suggests that human resistin may be regulated by a different mechanism or has a different role from that in rodents.[64] Furthermore, the expression of resistin in adipocytes does not differ among normal, insulin-resistant, and type 2 diabetic individuals.[65-67] However, some genetic case-control studies have demonstrated that

genetic variations in the resistin gene are associated with insulin resistance and obesity in human.[67,68] Youn et al[69] demonstrate for the first time that plasma resistin concentrations are elevated in patients with type 2 diabetes. They also concluded that plasma resistin concentrations are related to insulin resistance in human. In this study, we examined that rosiglitazone treatment decreased plasma resistin concentrations significantly, but it was not associated with insulin resistance.

V. CONCLUSION

We found that 3 months of rosiglitazone treatment resulted in improvement of insulin responsiveness in type 2 diabetic subjects that was associated with a change of abdominal visceral fat area, but increase of midthigh low density muscle area. It is possible that in Korean patients with type 2 diabetes, rosiglitazone may have different effect on fat metabolism of skeletal muscle, therefore it increased midthigh low density muscle area. It is also possible that accumulation of fatty acid metabolism in skeletal muscle is just a phenomenon of insulin resistance and rosiglitazone improve insulin resistance through other effect. Although we cannot find any correlation between insulin resistance and any adipocytokine, rosiglitazone treatment made a change of plasma concentrations of adipocytokines such as adiponectin, leptin and resistin. Further study should be necessary on insulin resistance of skeletal muscle and mechanism of rosiglitazone especially on association between adipocytokine and insulin resistance.

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국문요약

제2형 당뇨병 환자에서 Rosiglitazone의 인슐린 저항성과 저밀도근육에 미치는 영향

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제2형 당뇨병 환자를 대상으로 3개월 동안 rosiglitazone을 매일 4 mg을 투여하여 인슐린 저항성과 복부, 근육에서의 지방 분포의 변화, adiponectin, leptin, resistin 등의 아디포싸이토카인의 농도 변화에 미치는 영향을 알아보고자 하였다.

42명의 제 2형 당뇨병 환자(나이: 32세-70세. BM1: 17.48 - 32.55 $kg/m^{2,}$ 15 명의 여자환자, 27 명의 남자환자)를 대상으로 하루 4 mg의 rosiglitazone을 12주간 투여하였다. 투여 전, 후에 체지방 분석과 혈청 adiponectin, leptin, resistin의 농도를 측정하였고 그 외에도 여러 생화학적 변수들을 측정하였다.

12주간의 rosiglitazone 투여후 체질량지수는 24.83 ± 3.55 에서 25.69 ± 3.44 kg/m^2 로 의미 있게 증가하였고(p=0.001), 복부의 내장 지방은 144.69 ± 65.57 에서 129.39 ± 73.10 cm^2 로 감소하였고, 피하 지방은 151.49 ± 75.22 에서 177.00 ± 185.01 cm^2 로 증가하였으나 통계학적 의미는 없었다(p=0.39). 허벅지 중간 부위의 저밀도 근육량의 변화는 23.09 ± 9.58 에서 26.12 ± 8.24 cm^2 으로 증가하였다(p=0.009). 인슐린 저항성은 Kitt를 이용하여 측정하였는데, 2.52 ± 0.98 에서 2.85 ± 1.11 %/min 으로 의미있게 개선되었다($p < 0.05$). 혈청 adiponectin은 5.58 ± 2.19 에서 8.80 ± 3.02 $\mu g/mL$ 으로 의미있게 증가하였으며(p

< 0.01), leptin 농도는 감소하였으나 통계학적 의미는 없었다(7.47 ± 6.44 & 6.63 ± 4.06 pg/mL, p=0.10). resisin의 농도는 3.23 ± 2.46 에서 1.91 ± 1.93 μg/mL 으로 의미있게 감소하였다(p < 0.01).

본 연구에서는 rosiglitazone 투여로 저밀도 근육량이 증가하는 결과를 얻었으며 이는 기대했던 연구 결과와는 다른 것이다. 근육내 지방산의 대사 산물의 축적이 근육 조직에서의 인슐린 저항성의 주요 기전이며 rosiglitazone이 이를 감소시킴으로써 인슐린 저항성을 개선시킨다고 생각되어져 왔다. 저자의 연구결과를 토대로, 서양인보다 비교적 덜 비만한 한국인 제 2형 당뇨병 환자에 있어서 rosiglitazone의 효과가 서양인과는 다를 수 있다는 것을 유추할 수 있겠다. 또한 지방산의 대사 산물인 중성지방의 근육 내 축적으로 저밀도 근육량이 증가하는 것은 인슐린 저항성의 한 현상에 불과하고 rosiglitazone의 근육 내 인슐린 저항성의 개선을 이루는 다른 기전이 존재 할 수 있다는 것을 유추할 수 있다.

핵심되는 말: rosiglitazone, 인슐린 저항성, adiponectin, leptin, resistin, 저밀도 근육