Two-Year Effect of Rosiglitazone in Chinese Poorly Controlled Type 2 Diabetic Patients

Jenn-Kuen Lee, MD; Chih-Hsun Chu, MD; Ming-Ju Chuang, MS; Shiu-Chu Lin[1], MS; Mei-Chun Wang, BS; Chih-Chen Lu, MD; Chun-Chin Sun, MD; Hing-Chung Lam, MD

Background: The goal of this study is to assess the 24-week efficacy of the addition of rosiglitazone 4 mg to existing full dose sulfonylurea (SU) and metformin (MET) therapy in patients with inadequately controlled type 2 diabetes, and to observe the continued follow-up efficacy and safety of this drug for up to two years.

Methods: This study consists of 32 patients. Fasting plasma glucose (FPG), free fatty acid (FFA), high sensitive C-reactive protein (HS-CRP), adiponectin, insulin and C-peptide were measured every four weeks up to week 24. After that time, the FPG continued to be checked every month. Glycated hemoglobin (HbA_{1c}) and lipid profiles were also checked every 12 weeks for more than two years.

Results: HbA_{1c} was reduced by 1.4% at week 12 and by 1.1% at week 24. However HbA_{1c} was still above 9% throughout the whole study period. FPG was reduced significantly when comparing the baseline value to the value after treatment. The FPG values after one year and two years follow-up were similar to the value at week 24. The serum total cholesterol and low density lipoprotein (LDL) cholesterol levels increased significantly. Serum triglycerides were reduced significantly. Significant reductions in serum FFA from baseline to week 24 were observed. A gradually decrease of serum HS-CRP was noted from baseline to week 24. Serum adiponectin levels increased maximally at week 12 and then it decreased gradually, showing a significant change. Serum insulin and C-peptide levels showed significant changes from baseline to week 24. There were no acute cardiocerebral peripheral vascular disease events or liver damage within the entire study period.

Conclusions: Clinical improvement in glycemic control was observed after the addition of rosiglitazone to type 2 diabetic patients receiving full dose SU and MET therapy. The maximal effect was observed at week 12 and the effect continued for at least two years. Further, the combination therapy also resulted in an improvement in lipid profiles, decreased HS-CRP and increased adiponectin levels in the short term (24 weeks). This combination therapy is also safe and beneficial for at least two years because no acute episodes of cardiocerebral peripheral vascular disease were seen.

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Key words: rosiglitazone, type 2 diabetes mellitus, HS-CRP, adiponectin.

From the Division of Endocrinology and Metabolism, Department of Medicine, [1]Division of Biochemistry, Department of Pathology and Laboratory, Kaohsiung Veterans General Hospital, and School of Medicine, National Yang-Ming University, Taipei.
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Correspondence to: Dr. Jenn-Kuen Lee, Division of Endocrinology and Metabolism, Kaohsiung Veterans General Hospital. 386, Ta-Chung First Road, Tso-Ying, Kaohsiung, Taiwan 813, R.O.C. Tel.: 886-7-3468089; Fax: 886-7-3468291; E-mail: jklee@isca.vghks.gov.tw

Thiazolidinediones (TZDs), selective and potent agonists of peroxisome proliferator-activated receptor-gamma (PPAR-γ), represent a novel class of antidiabetic agents that improve glycemic control,[1-4] enhance hepatic and muscle insulin sensitivity,[5,6] and improve β-cell function in both human and animal models of type 2 diabetes mellitus (DM).[7-9] The TZDs exert beneficial effects on lipid abnormality, endothelial function, hemostasis and inflammation.[10,11]

There is no report on the long term effects of adding rosiglitazone (one of the TZDs) to poorly controlled type 2 diabetic patients receiving full dose sulfonylurea (SU) and metformin (MET) in Taiwan. Therefore, we observed both the short term (24 weeks) effects of rosiglitazone on plasma glucose, serum lipid profiles, high sensitivity C-reactive protein (HS-CRP) and adiponectin levels, and the long term (two years) efficacy and safety of this drug.

METHODS

This trial was approved by the hospital's Human Research Ethic Committees. All participants gave written informed consent before starting the trial. This study was an open-label trial performed between Jan. 2002 and Feb. 2004 in 32 type 2 diabetic patients (12 males, 20 females) with 12.6 ± 5.4 years duration of diabetes. Seven patients had mild background diabetic retinopathy and 30 to 100 mg/dL urine protein. No patient had cerebral vascular accident, myocardial infarction or peripheral vascular disease. All participants had been treated with full dose SU (two tablets twice daily of glibenclamide 5 mg, glipizide 5 mg or glyclazide 80 mg) and MET (two tablets three times daily of metformin 500 mg) for more than six months. Their fasting plasma glucose (FPG) levels remained over 200 mg/dL and their glycated hemoglobin (HbA_{1c}) levels were over 9%, even after they had received instruction from the diabetic dietitian and nurse. The age of eligible patients was 38-78 years (mean 57 ± 11) with a body mass index (BMI) of 23.3 ± 3.3 kg/m^2. Among these 32 patients, four patients had BMI > 27 kg/m^2 and two of these four patients had BMI > 30 kg/m^2. Patients were regarded as ineligible if: (1) they were currently taking lipid-lowering drugs; (2) their serum glutamic pyruvic transaminase (SGPT) was more than three times the upper limit of normal; (3) they had a history of heart failure; (4) they were pregnant or breast-feeding women. During the study, thiazides were allowed to treat edema and, if antihypertensive treatment was indicated, angiotension converting enzyme (ACE) inhibitors, angiotensin II receptor antagonists or calcium antagonists were given so as not to affect glucose homeostasis. Rosiglitazone 4 mg was given to every eligible patient after screening. Patients were seen at screening, and at 4, 8, 12, 16, 20 and 24 weeks, and then they were regularly followed-up at our Outpatients Department (OPD) for at least two more years. At all visits, patients were seen in the morning after at least 10-h fasting. Blood was drawn for FPG, free fatty acid (FFA), high sensitive C-reactive protein (HS-CRP), adiponectin, insulin and C-peptide testing at each visit, and HbA_{1c} as well as lipid profiles total cholesterol, triglyceride, high density lipoprotein (HDL) cholesterol and low density lipoprotein (LDL) cholesterol were checked at 12 week intervals. All patients had their serum glutamic-oxalacetic transaminase (SGOT) and SGPT levels tested at each visit for safety monitoring. After 24 weeks, the FPG was checked each month, and HbA_{1c}, lipid profiles and SGOT/SGPT were tested every three months.

Analysis of SGOT/SGPT, FPG, lipid profiles and FFA was performed in the central laboratories of Kaohsiung Veterans General Hospital. All other analyses were carried out in our endocrinological laboratory. The SGOT/SGPT, FPG and lipid profiles were measured using Hitachi-747 (Hitachi Ltd, Tokyo, Japan), and FFA was measured using Hitachi-7150 (Hitachi Ltd, Tokyo, Japan), by the enzymatic ACS-ACOD (Acyl-CoA synthase-Acyl-CoA oxidase) method (Wako Chemicals, Richmond, Virginia, USA). HbA_{1c} was measured using HLC-723 GHbV high-performance liquid chromatography (Tosoh company, Tokyo, Japan), HS-CRP, insulin and C-peptide were measured using Immulite (Diagnostic Products Co., Los Angeles, CA, USA), and adiponectin was measured using an RIA-IRMA kit (LINCO Research Inc., Charles, MO, USA).

For each subject, the degree of insulin resistance and pancreatic β-cell function were estimated by homeostasis model assessment of insulin resistance (HOMA-IR) and homeostasis model assessment of β-cell function (HOMA-β-cell function), according to the method of Matthews et al.[12] A HOMA-IR score was computed using the following formula:

fasting plasma glucose (mmol/L) x fasting serum insulin (mIU/mL) ÷ 22.5. A HOMA-β-cell function (%) was computed using the following formula: 20 x insulin ÷ (glucose-3.5).

Data were analyzed using SPSS version 6.1. All data were expressed as means ± SD. Data from before and after treatment were compared using repeated measure ANOVA. For all analyses, the level of statistical significance was set at $p < 0.05$.

RESULTS

Table 1 shows metabolic changes before and after adding rosiglitazone treatment. Reduction in FPG from baseline to week 24 was significant, with the lowest value appearing at week 12. The follow-up FPG was 203 ± 38 mg/dL one year later and 201 ± 63 mg/dL two years later: both were similar to level at week 24 (201 ± 64 mg/dL). Table 1 also shows significant reduction of HbA_{1c}. The follow-up HbA_{1c} was 9.6 ± 1.7% one year later and 9.8 ± 2.5% two years later. However, HbA_{1c} was still above 9% throughout the whole study period.

Changes from baseline in total cholesterol and LDL cholesterol showed significant increases. Although HDL cholesterol also showed a small increase, it was not statistically significant. Triglycerides were significantly reduced. Significant reductions in FFA from baseline were also shown at each follow-up visit. Five cases in the first year and another one in the second year needed statin therapy. Significant reduction in HS-CRP occurred. Adiponectin levels increased to a maximum at week 12 and then decreased gradually thereafter. Serum insulin and C-peptide levels showed significant changes from baseline up to week 24. HOMA-IR and HOMA-β-cell function showed significant changes: HOMA-IR decreased and HOMA-β-cell function increased to maximum levels at week 12.

Eighteen patients showed an increase in body weight of 3.0 ± 1.7 kg, five patients' body weights reduced by 3.2 ± 2.0 kg and nine patients' body weights remained stable. We did not find any cases of edema. Neither did we find any cases of abnormal liver function test or acute episodes of cardiocerebral peripheral vascular disease. During the first year of the study, only three cases required small doses (less than 15 U) of bed-time NPH insulin injection (BTII), one of which shifted to twice daily NPH insulin injection. Another case required BTII in the second year of follow-up.

DISCUSSION

Our results demonstrate that the addition of rosiglitazone in patients insufficiently treated with SU and MET resulted in improved glycemic control throughout the two years of the study period. HbA_{1c}

Table 1. Metabolic Changes Before and After Adding Rosiglitazone Treatment

Week	0	4	8	12	16	20	24	*p*-value
FPG	236 ±33	197 ±47	188 ±52	171 ±55	206 ±63	189 ±64	201 ±64	< 0.0001
HbA_{1c}	11.0 ±1.9			9.6 ±2.2			9.9 ±2.2	< 0.0001
T.C	198 ±28			210 ±38			231 ±41	< 0.0001
HDL	47 ±14			50 ±14			51 ±19	0.115
LDL	116 ±25			131 ±33			145 ±35	< 0.0001
TG	166 ±92			136 ±69			171 ±95	0.021
FFA	0.84 ±0.47	0.48 ±0.25	0.54 ±0.28	0.54 ±0.27	0.38 ±0.22	0.41 ±0.19	0.54 ±0.23	< 0.0001
CRP	0.37 ±0.41	0.17 ±0.19	0.22 ±0.29	0.25 ±0.33	0.20 ±0.19	0.09 ±0.07	0.18 ±0.20	< 0.001
Adipo	1069 ±714	1130 ±660	1150 ±561	1632 ±513	1034 ±561	875 ±485	1070 ±644	< 0.001
Ins	6.7 ±4.4	5.5 ±3.0	5.9 ±3.5	6.2 ±4.0	6.4 ±2.5	6.2 ±4.4	6.7 ±3.6	< 0.001
C-pep	1.1 ±0.8	1.0 ±0.6	1.0 ±0.6	1.1 ±0.7	1.0 ±0.8	1.2 ±0.9	1.6 ±1.0	< 0.0001
HOMA-IR	3.85 ±2.24	2.58 ±1.33	2.62 ±1.36	2.56 ±1.76	3.21 ±2.22	2.84 ±1.65	3.29 ±2.44	< 0.0001
HOMA-β(%)	15.4 ±11.7	17.1 ±13.2	22.1 ±19.6	28.9 ±25.4	20.0 ±16.6	22.0 ±15.4	22.5 ±16.8	< 0.0001

Abbreviations: FPG: fasting plasma glucose (mg/dL); HbA_{1c}: glycated hemoglobin (%); T.C: total cholesterol (mg/dL); HDL: high density lipoprotein (mg/dL); LDL: low density lipoprotein (mg/dL); TG: triglyceride (mg/dL); FFA: free fatty acid (mmol/L); CRP: C-reactive protein (mg/dL); Adipo: adiponectin (ng/mL); Ins: insulin (mIU/L); C-pep: C-peptide (ng/mL); HOMA-IR: homeostasis model assessment of insulin resistance; HOMA-β: homeostasis model assessment of β cell function.

was reduced by a maximum of 1.4% at 12 week and 1.1% at 24 week, and the effect continued for at least two years. This means that rosiglitazone has an additional blood-glucose-lowing effect that started as early as 12 weeks after its use and the effect can be maintained for at least two years. Rosiglitazone lowered blood glucose by enhancing insulin sensitivity in the skeletal muscle, adipose tissue and liver, in part, by reducing intra-abdominal and intra-hepatic fat.[6] The increase in body weight has been attributed to expansion of the subcutaneous fat depot and, in some patients, to edema, where the mass of visceral fat remains unchanged[13] or decreases.[14] Although we did not find any cases of edema, it has been reported in 4% to 6% of patients undergoing treatment with thiazolidinediones.[31]

Paolisso and Pankow have shown that increased plasma non-esterified (free) fatty acid concentration is a risk factor for development of type 2 DM.[15,16] Boden has demonstrated that FFAs inhibit glucose uptake in a dose-dependent fashion throughout the physiological range of plasma FFA concentration.[17] This study showed that rosiglitazone could reduce FFA levels. These results suggest that the beneficial effects of rosiglitazone on glycemic control are mediated, in part, by the drug's effect on FFA metabolism, a mechanism that is similarly reported by Miyazaki et al.[18] Reduced HDL cholesterol and elevated triglyceride are well-known independent indicators of cardiovascular risk in patients with type 2 DM.[19-21] From epidemiological studies, it is known that a 1% increase in HDL cholesterol is associated with a 2-3% reduction in the risk of coronary heart disease.[21] Improvements in HDL cholesterol (+6% in week 12, +8.5% in week 24) and triglyceride (–18.1% in week 12) were noted in the present study. However, total cholesterol and LDL cholesterol also increased significantly after rosiglitazone treatment, a finding similar to Yki-Jarvinen's review,[31] and this produced six cases that needed additional statin treatment two years later. The cause of the increase in HDL and LDL cholesterol during rosiglitazone treatment is unknown. The effects of rosiglitazone on the size of LDL particles have not been studied in a double blind, placebo-controlled trial.[31] Hence, the long term cardiovascular effect of rosiglitazone requires a longer observation time, though no acute condition of cardiocerebral peripheral vascular disease was noted in this study.

There is increasing recognition that chronic subclinical vascular inflammation plays a role in the pathogenesis of atherosclerosis, insulin resistance and type 2 DM. Markers of subclinical inflammation, in particular HS-CRP, have been shown to be powerful independent predictors of DM and cardiovascular disease risk.[22] During rosiglitazone treatment, the reduction in mean HS-CRP levels was statistically significant compared with the baseline levels. This indicates that rosiglitazone may have potentially beneficial effects on overall cardiovascular risk.[23]

Adiponectin, a plasma protein exclusively synthesized and secreted by adipose tissue, has recently been shown to have anti-inflammatory, antiatherogenic properties in vitro and beneficial metabolic effects in animals. Lower plasma levels of adiponectin have been documented in human subjects with obesity, type 2 DM or coronary artery disease.[24-27] The present study demonstrated that after starting rosiglitazone treatment, the plasma adiponectin levels increased gradually, with a maximal effect noted at week 12. Yang et al. also showed that treatment with rosiglitazone for six months did not further increase the plasma adiponectin level from that measured at the 3rd month, suggesting that the maximal effect of rosiglitazone on adiponectin levels had been attained by the 3rd month.[28] This effect may potentially protect diabetic patients from macrovascular complications, and may improve their insulin sensitivity and glycemic control.

We demonstrated that there were significant changes in the serum insulin and C-peptide levels before and after 24 weeks of rosiglitazone treatment. This was also correlated with significant decreases in HOMA-IR and increases in HOMA-β-cell function, although the maximal effect showed at week 12.

In summary, although the results of the present study are from a single medical center with a relatively small number of Chinese poorly controlled type 2 DM subjects, the additional glucose-lowering effect and generalized multiple effects of rosiglitazone in these subjects is similar to that of Yki-Jarvinen's review.[31] These findings suggest that rosiglitazone is an effective combination regimen for type 2 DM patients insufficiently treated with SU and MET. From this point of view, earlier usage of rosiglitazone in the combination therapy may have a better and longer effect on the blood sugar control

than later usage of this drug. At the end of the second year, only four cases received NPH insulin injection. This means that the addition of rosiglitazone may delay the use of insulin treatment.[29] From the report of the Taiwanese Association of Diabetes Educators (TADE) 2004 survey,[30] compared with 2002, the same phenomenon was also noted. Tsai et al. have shown that TZD combined therapy increased from 6% to 20%, whereas insulin treatment decreased from 22.6% to 18.2%. Furthermore, the decrease in triglycerides, FFA and HS-CRP, as well as the rise in HDL cholesterol and adiponectin, suggest that additional benefits may be obtained in terms of reducing the risk of complications from the addition of rosiglitazone to patients with type 2 DM. However, there was also an increase in total cholesterol and LDL cholesterol, which resulted in some cases requiring statin treatment. Hence, the overall influence of this drug requires longer term observation. The long-term effects of rosiglitazone on cardiovascular morbidity and mortality currently are being evaluated in several large randomized controlled trials.[32] Nevertheless, no subject in the present study had an acute event of cardiocerebral peripheral vascular disease, or any acute or chronic side effects when observed for more than two years. These findings suggest that rosiglitazone is safe and effective in both short-term (six months) and long-term (two years) use in Chinese type 2 DM patients.

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REFERENCES

1. Mudaliar S, Henry RR. New oral therapies for type 2 diabetes mellitus: The glitazones or insulin sensitizers. Annu Rev Med 2001;52:239-57.
2. Saltiel AR, Olefsky JM. Thiazolidinediones in the treatment of insulin resistance in type II diabetes. Diabetes 1996;45:1661-9.
3. Wolffenbuttel BH, Sels JP, Huijberts MS. Rosiglitazone. Expert Opin Pharmacother 2001;2:467-8.
4. Aronoff S, Rosenblatt S, Braithwaite S, Egan JW, Mathisen AL, Schneider RL. Pioglitazone hydrochloride monotherapy improves glycemic control in the treatment of patients with type 2 diabetes: a 6-month randomized placebo-controlled dose-response study. Diabetes Care 2000;23:1605-11.
5. Miyazaki Y, Mahankali A, Matsuda M, Glass L, Mahankali S, Ferrannini E, Cusi K, Mandarino L, DeFronzo RA. Improved glycemic control and enhanced insulin sensitivity in type 2 diabetic subjects treated with pioglitazone. Diabetes Care 2001;24:710-9.
6. Mayerson AB, Hundal RS, Dufour S, Lebon V, Befroy D, Cline GW, Enocksson S, Inzucchi SE, Shulman GI, Petersen KF. The effects of rosiglitazone on insulin sensitivity, lipolysis and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. Diabetes 2002;51:797-802.
7. Shimabukuro M, Zhou YT, Levi M, Unger RH. Fatty acid induced β cell apoptosis: a link between obesity and diabetes. Proc Natl Acad Sci USA 1998;95:2498-502.
8. Miyazaki Y, Matsuda M, DeFronzo RA. Dose-response effect of pioglitazone on insulin sensitivity and insulin secretion in type 2 diabetes. Diabetes Care 2002;25:517-23.
9. Finegood DT, McArthur MD, Kojwang D, Thomas MJ, Topp BG, Leonard T, Buckingham RE. β-cell mass dynamics in Zucker diabetic fatty rats. Rosiglitazone prevents the rise in net cell death. Diabetes 2001;50:1021-9.
10. Dandona P, Aljada A. A rational approach to pathogenesis and treatment of type 2 diabetes mellitus, insulin resistance, inflammation, and atherosclerosis. Am J Cardiol 2002;90(5A):27G-33G.
11. Bays H, Mandarino L, DeFronzo RA. Role of the adipocyte, free fatty acids, and ectopic fat in pathogenesis of type 2 diabetes mellitus: perioxisomal proliferator-activated receptor agonists provide a rational therapeutic approach. J Clin Endocrinol Metab 2004;89:463-78.
12. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-9.
13. Carey DG, Cowin GJ, Galloway GJ. Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients. Obes Res 2002;10:1008-15.
14. Miyazaki Y, Mahankali A, Matsuda M, Mahankali S, Hardies J, Cusi K, Mandarino LJ, DeFronzo RA. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87:2784-91.
15. Paolisso G, Tataranni PA, Foley JE, Bogardus C, Howard BV, Ravussin E. A high concentration of fasting plasma non-esterified fatty acids is a risk factor for the development of NIDDM. Diabetologia 1995;38:1213-7.
16. Pankow JS, Couper DJ, Duncan BB, Hoogeveen RC, Schmidt MI, Golden SH, Ballantyne CM. Fasting plasma free fatty acids and risk of type 2 diabetes: the atherosclerosis risk in communities study. Diabetes Care 2004;27:77-82.
17. Boden G. Fatty acids and insulin resistance. Diabetes Care 1996;19:394-5.
18. Miyazaki Y, Glass L, Triplitt C, Matsuda M, Cusi K,

Mahankali A, Mahankali S, Mandarino LJ, DeFronzo RA. Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in Type II diabetic patients. Diabetologia 2001;44:2210-9.
19. Manninen V, Tenkanen L, Koskinen P, Huttunen JK, Manttari M, Heinonen OP, Frick MH. Joint effects of serum triglyceride and LDL cholesterol and HDL cholesterol concentrations on coronary heart disease risk in the Helsinki Heart Study. Implications for treatment. Circulation 1992;85:37-45.
20. Hokanson JE, Austin MA. Plasma triglyceride level is a risk factor for cardiovascular disease independent of high-density lipoprotein cholesterol level: a meta-analysis of population based prospective studies. J Cardiovasc Risk 1996;3:213-9.
21. Gordon DJ, Probstfield JL, Garrison RJ. Neaton JD, Castelli WP, Knoke JD, Jacobs DR Jr, Bangdiwala S, Tyroler HA. High-density lipoprotein cholesterol and cardiovascular disease. Four prospective American studies. Circulation 1989;79:8-15.
22. Frohlich M, Boeing H, Imhof A, Muche R, Berg G, Brenner H, Hutchinson WL, Koenig W, Pepys MB. Association between C-reactive protein and features of the metabolic syndrome: a population-based study. Diabetes care 2000;23:1835-9.
23. Haffner SM, Greenberg AS, Weston WM, Chen H, Williams K, Freed MI. Effect of rosiglitazone treatment on nontraditional markers of cardiovascular disease in patients with type 2 diabetes mellitus. Circulation 2002;106:679-84.
24. Ouchi N, Kihara S, Arita Y. Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. Circulation 1999;100:2473-6.
25. Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, Hotta K, Shimomura I, Nakamura T, Miyaoka K, Kuriyama H, Nishida M, Yamashita S, Okubo K, Matsubara K, Muraguchi M, Ohmoto Y, Funahashi T, Matsuzawa Y. Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem Biophys Res Commun 1999;257:79-83.
26. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K, Nishida M, Kihara S, Sakai N, Nakajima T, Hasegawa K, Muraguchi M, Ohmoto Y, Nakamura T, Yamashita S, Hanafusa T, Matsuzawa Y. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000;20:1595-9.
27. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, Tataranni PA. Hypoadiponectinemia in obesity and type 2 diabetes: close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab 2001;86:1930-5.
28. Yang WS, Jeng CY, Wu TJ, Tanaka S, Funahashi T, Matsuzawa Y, Wang JP, Chen CL, Tai TY, Chuang LM. Synthetic peroxisome proliferator-activated receptor-gamma agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. Diabetes Care 2002;25:376-80.
29. Dailey GE 3rd, Noor MA, Park JS, Bruce S, Fiedorek FT. Glycemic control with glyburide/metformin tablets in combination with rosiglitazone in patients with type 2 diabetes: a randomized, double-blind trial. Am J Med 2004;116:223-9.
30. Tsai ST. Diabetes care in Taiwan. Symposium of optimal diabetes management-treat to target Taipei, Taiwan. July 3 2004.
31. Yki-Jarvinen H. Thiazolidinediones. N Engl J Med 2004;351:1106-18.
32. Chiquette E, Ramirez G, Defronzo R. A meta-analysis comparing the effect of thiazolidinediones on cardiovascular risk factors. Arch Intern Med 2004;164:2097-104.

Rosiglitazone 對控制不良之台灣第 2 型糖尿病人兩年的作用

李鎮堃 朱志勳 莊明儒 林秀珠[1] 王玫君 呂志成 孫群欽 林興中

背 景： 由於台灣本土在使用最高劑量的磺基尿素及雙胍類治療後，仍屬血糖控制不良的糖尿病患者，加上 rosiglitazone 後，對其治療果效及其他影響的醫學報告缺乏，故本研究評估最高劑量磺基尿素及雙胍類使用後血糖仍控制不良的患者，再添加 rosiglitazone 4 毫克治療 24 週後的臨床生化及內分泌反應，並繼續觀察其療效及安全性達兩年。

方 法： 這個研究，包含 32 位糖尿病患。觀察 12 週及 24 週糖化血色素及血脂的變化，並每 4 週的空腹血糖、游離脂肪酸、C 反應蛋白、adiponectin、胰島素、C 肽胜的反應。第 24 週後，空腹血糖每一個月測一次，糖化血色素及血脂每三個月測一次超過兩年的時間。

結 果： 在第 12 週時糖化血色素下降 1.4%，第 24 週時下降 1.1%，但第二年糖化血色素仍大於 9%。空腹血糖與最初治療前比較都呈有意義下降，之後空腹血糖在第一年及第二年也維持與第 24 週相同的程度。總膽固及低密度膽固醇呈有意義的上升。三酸甘油脂呈有意義下降，至於游離脂肪酸則由開始至第 24 週均呈現有意義的下降。C 反應蛋白由開始至第 24 週，呈現有意義的下降，adiponectin 逐漸上升，在第 12 週時達到最高值，之後再逐漸降到治療前數值，但呈有意義的改變。至於血清胰島素及 C肽胜由開始至第 24 週呈現有意義變化。這二年中的追蹤，這些患者中，沒有發生任何急性心臟、腦部、及周邊血管疾病事件，也沒有肝臟傷害發生。

結 論： 在添加 rosiglitazone 治療後，可見血糖控制的改善，且最好的效果在第 12 週發生，雖糖尿病控制仍屬不良，但其果效可一直維持到二年時間。在短期 24 週內，此藥添加亦對血脂有一定的果效並使 C 反應蛋白下降及 adiponectin 上升。總而言之，再添加 rosiglitazone 治療，對於控制不良的糖尿病患者應有長期二年以上安全並額外有益的效果，因爲在這段期間內，患者均沒有急性的心、腦、周邊血管疾病的發生。

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關鍵詞：rosiglitazone，第 2 型糖尿病，C 反應蛋白，adiponectin。

高雄榮民總醫院 內科部 新陳代謝科；病理檢驗部 生化科，[1]國立陽明大學 醫學院
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索取抽印本處：李鎮堃醫師，高雄榮民總醫院 新陳代謝科。高雄市813左營區大中一路386號。Tel.: (07)3468089; Fax: (07)3468291; E-mail: jklee@isca.vghks.gov.tw