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Metabolism Clinical and Experimental 55 (2006) 439–444

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Rosiglitazone improves insulin sensitivity in nonobese subjects with impaired glucose tolerance: the role of adiponectin and C-reactive protein

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Received 14 April 2005; accepted 17 October 2005

Abstract

To evaluate the effects of rosiglitazone (ROS) on serum adiponectin and C-reactive protein (CRP) in nonobese subjects with impaired glucose tolerance (IGT), we enrolled 21 patients with body mass index ≤24 kg/m^2 to receive ROS 4 mg daily for 12 weeks. Fifteen age-, sex-, and body mass index–matched healthy subjects were recruited as controls. A 75-g oral glucose tolerance test (OGTT), hemoglobin A_{1c}, fasting glucose, insulin, C-peptide, lipid profiles, adiponectin, and CRP levels were determined before initiation and at the end of the 12-week ROS treatment. Insulin resistance and beta-cell function were calculated using the homeostasis model assessment method (HOMA-IR and HOMA-β, respectively). Compared with healthy controls, the ROS-treated subjects had significantly higher glycemic indices, HOMA-IR, CRP, and glucose and insulin concentrations in response to OGTT, and lower HOMA-β level. After 12 weeks of ROS therapy, the results showed statistically significant changes from baseline in 2-hour plasma glucose during OGTT (9.4 ± 0.3 vs 8.3 ± 0.4 mmol/L, $P < .05$), HOMA-IR (2.6 ± 0.2 vs 1.9 ± 0.3, $P < .05$), HOMA-β (63.4 ± 12.5 vs 90.1 ± 13.0, $P < .05$), and glucose and insulin concentrations during OGTT in nonobese subjects with IGT. In addition, elevation of serum adiponectin and decrease in CRP levels were significantly found after ROS treatment. Of 21 patients treated with ROS, 5 subjects were converted to normal (converter), 1 progressed to diabetes, and 15 remained in IGT status (nonconverter). There was a significant amelioration in HOMA-IR (−2.10 ± 1.03 vs −0.07 ± 0.33, $P < .05$) without significant changes in adiponectin and CRP levels in converter compared with nonconverter. We conclude that ROS effectively enhanced insulin sensitivity and beta-cell function to improve adiponectin and CRP levels in nonobese patients with IGT. The amelioration of insulin resistance may be a major determinant to predict the conversion of IGT independent of the changes in adiponectin and CRP.

1. Introduction

Adiponectin, mainly synthesized and secreted by adipose tissue, may play an important role in the pathophysiology of metabolic syndrome and cardiovascular disease [1-3]. In humans, the plasma adiponectin was strongly associated with body mass index (BMI), triglycerides, high-density lipoprotein cholesterol (HDL-C), and insulin resistance [4,5]. Recent studies have provided evidences that serum adiponectin can be elevated with enhanced insulin sensitivity achieved by weight reduction through lifestyle modification or gastric surgery [6,7]. This implies that adiponectin has an important role in the regulation of glucose metabolism and insulin resistance and that it may have antiinflammatory and antiatherogenic properties.

C-reactive protein (CRP), a low-grade inflammatory marker, is strongly associated with metabolic syndrome and adverse cardiovascular outcomes [8-12]. A number of studies have found that plasma adiponectin and CRP levels independently predict the risk of diabetes in several different populations [13,14]. Recent studies have demonstrated low plasma adiponectin and high CRP levels coexisted in patients with impaired glucose tolerance (IGT) [9,13,15]. It is now believed that both markers might play a critical role in developing type 2 diabetes mellitus and cardiovascular disease in IGT.

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0026-0495/$ – see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.metabol.2005.10.004

There is a growing evidence that lifestyle modification can reduce the risk of progression to diabetes in subjects with IGT [16]. Despite these encouraging findings, diet and exercise are not fully effective and cannot be implemented in all clinical settings. Therefore, various pharmacologic approaches have been proved to be effective in preventing or delaying the progression from IGT to type 2 diabetes mellitus [16-19]. Thiazolidinediones (TZDs) activate the peroxisome proliferator–activated receptor γ to regulate the expression of several genes involved in insulin resistance. Thiazolidinediones have been shown to be effective in improving insulin sensitivity, enhancing plasma adiponectin levels, and attenuating CRP levels in obese population with IGT, metabolic syndrome, or type 2 diabetes mellitus [20-26]. Nevertheless, the metabolic consequences of these effects on TZDs therapy have not been determined in nonobese patients with IGT. In this study, we investigate the effects of rosiglitazone (ROS) on insulin sensitivity, beta-cell function, serum adiponectin, and CRP levels to determine the major component to affect the metabolic consequence in nonobese patients with IGT.

2. Materials and methods

2.1. Subjects

This study was approved by the Ethics Committee on Human Studies at the Tri-Service General Hospital, Taipei, Taiwan. Informed consents were obtained from the participants before the initiation of the study. Twenty-one participants were selected from the outpatient clinics. Their ages were from 30 to 60 years with BMI less than 24 kg/m^2. Patients were screened for eligibility, and a dietary inquiry was made before initiation of the study. All patients were given healthy eating and exercise advice. Subjects were eligible for the study if their fasting plasma glucose was less than 7.0 mmol/L, and their 2-hour plasma glucose was between 7.8 and 11.1 mmol/L after a 75-g oral glucose tolerance test (OGTT). The definition of IGT was based on the 1999 World Health Organization criteria [27]. Fasting plasma triglyceride concentration should be 4.5 mmol/L or less.

The exclusion criteria were patients using insulin or any oral hypoglycemic agents or lipid-lowering agents within 3 months; women being pregnant or nursing; patients with impaired renal function (serum creatinine $\geq$132.6 μmol/L); patients with abnormal serum aspartate aminotransferase or alanine aminotransferase (2.5 times above the upper reference ranges); patients with acute or chronic pancreatitis; patients with a history of cerebrovascular accident or heart failure (New York Heart Association class III or IV cardiac status); and patients taking concomitant drugs such as β-blocker, diuretics, cholestyramine, or systemic steroids. Subjects in the treatment group were assigned to ROS 4 mg daily for 12 weeks. Efficacy, drug compliance, safety, and adverse effects were evaluated during the monthly visits. The control group consisted of 15 healthy subjects with sex, age, and BMI similar to those of the patient group.

2.2. Methods

2.2.1. Assessment of insulin resistance and beta-cell function

The indices of basal insulin resistance and beta-cell function were assessed using the homeostasis model assessment (HOMA-IR and HOMA-β) originally described by Matthews et al [28], in which HOMA-IR (mmol/L $\times$ μIU/mL) = fasting glucose (mmol/L) $\times$ fasting insulin (μIU/mL)/22.5 and HOMA-β = fasting insulin (μIU/mL) $\times$ 20/[fasting glucose (mmol/L) $-$ 3.5].

2.2.2. OGTT

After a 10-hour overnight fast, an OGTT was performed at 8:30 AM by orally administering 75 g of glucose in 150 mL of free water. Venous blood samples were obtained for determination of plasma glucose and insulin concentrations at 0, 30, 60, 90, and 120 minutes after glucose ingestion.

2.3. Laboratory measurement

Before and after the treatment, blood samples after a 10-hour fast were obtained for determination of plasma glucose, insulin, C-peptide, hemoglobin A_{1c} (HbA_{1c}), blood urea nitrogen, creatinine, aspartate aminotransferase, alanine aminotransferase, lipid profiles, CRP, and adiponectin concentrations. Serum concentrations of biochemistry and total cholesterol were measured using a dry multilayer analytic slide method with the Fuji Dri-Chem 3000 analyzer (Fuji Photo Film Corporation, Minato-Ku, Tokyo, Japan). Serum HDL-C levels were assessed with an enzymatic cholesterol assay method after dextran sulfate precipitation. Serum low-density lipoprotein cholesterol (LDL-C) concentrations were calculated using the Friedewald formula. The determination of serum triglyceride after enzymatic splitting with lipoprotein lipase was assayed by colorimetric enzymatic test on Hitachi 717 (Biomedilines, San Diego, CA). The plasma glucose concentration was determined by the glucose oxidase method on a Beckman Glucose Analyzer II (Beckman Instruments, Fullerton, CA). Plasma insulin was measured with a commercial radioimmunoassay kit (Coat-A-Count Insulin Kit, Diagnostic Products Corporation, Los Angeles, CA). The intra- and interassay coefficients of variation for insulin are 3.3% and 2.5%, respectively. C-peptide was determined using a Food and Drug Administration–approved radioimmunoassay (DiaSorin Inc, Stillwater, MN). Hemoglobin A_{1c} was measured by Bio-Rad Variant II automatic analyzer (Bio-Rad Diagnostic Group, Los Angeles, CA). Plasma CRP levels were measured using the Tina-quant (Latex) high-sensitivity assay (Roche Diagnostics GmbH, Mannheim, Germany). Serum adiponectin concentrations were assayed with

Table 1
The characteristics of healthy controls and patients with IGT before and after ROS therapy

	Control (n = 15)	IGT (n = 21)	
		Before	After
Female (%)	53	57	
Age (y)	47.1 ± 3.3	49.1 ± 1.9	
Body weight (kg)	58.0 ± 2.8	60.4 ± 2.7	60.2 ± 3.1
BMI (kg/m^2)	22.0 ± 0.8	22.9 ± 0.6	22.8 ± 0.4
Waist-to-hip ratio	0.86 ± 0.01	0.87 ± 0.01	0.86 ± 0.01
Systolic blood pressure (mm Hg)	120.4 ± 2.3	118.8 ± 2.6	122.3 ± 2.2
Diastolic blood pressure (mm Hg)	77.8 ± 1.8	78.3 ± 2.0	79.9 ± 1.6
HbA_{1c} (%)	4.9 ± 0.3**	6.1 ± 0.1	6.1 ± 0.1
Fasting plasma glucose (mmol/L)	5.1 ± 0.1*	5.3 ± 0.2	5.2 ± 0.2
Fasting plasma insulin (pmol/L)	57.1 ± 8.8*	78.3 ± 14.7	60.5 ± 12.5
Fasting plasma C-peptide (nmol/L)	1.2 ± 0.2*	1.7 ± 0.2	1.6 ± 0.2
2-h plasma glucose (mmol/L)	5.8 ± 0.1**	9.4 ± 0.3	8.3 ± 0.4*
2-h plasma insulin (pmol/L)	240.6 ± 18.1**	325.2 ± 51.1	307.7 ± 50.1
HOMA-IR	1.7 ± 0.2*	2.6 ± 0.2	1.9 ± 0.3*
HOMA-β	105.9 ± 16.4*	63.4 ± 12.5	90.1 ± 13.0*
Total cholesterol (mmol/L)	4.2 ± 0.3	4.3 ± 0.2	4.7 ± 0.2**
Triglyceride (mmol/L)	1.7 ± 0.3	1.8 ± 0.2	1.8 ± 0.2
HDL-C (mmol/L)	1.1 ± 0.1	1.2 ± 0.1	1.4 ± 0.1*
LDL-C (mmol/L)	2.6 ± 0.2	2.7 ± 0.2	3.0 ± 0.2*

Data are expressed as mean ± SEM.
* $P < .05$, control and after ROS therapy vs baseline of subjects with IGT.
** $P < .01$, control and after ROS therapy vs baseline of subjects with IGT.

radioimmunoassay established by Linco Research (St Charles, MO). This assay has a sensitivity of 1 ng/mL and intra- and interassay coefficient of variation of less than 8%.

2.4. Statistical analysis

The unpaired Student t test was used for comparison of the baseline characteristics between the 2 groups (healthy controls and patients with IGT). The paired Student t test was used for comparing the various parameters before and after ROS treatment in patients with IGT. Nonparametric Mann-Whitney U test was used to compare the changes in characteristics from baseline to 12 weeks after ROS treatment with converted or nonconverted subjects with IGT. The χ^2 test was used for comparison of sex-specific difference in both groups. Subjects with plasma CRP levels of 1.5 mg/dL or higher, indicating clinically relevant inflammatory condition, were excluded from the analysis. Analysis was performed using SPSS 10.0 statistical version (Chicago, IL) for Windows. All values are expressed as mean ± SE. Statistical significance was defined as $P < .05$.

3. Results

The ROS-treated subjects had significantly greater glycemic indices, including HbA_{1c}, fasting glucose, insulin and C-peptide levels, 2-hour glucose and insulin during OGTT, HOMA-IR values, and lower HOMA-β level compared with healthy controls. After 12 weeks of ROS therapy, the 2-hour plasma glucose during OGTT and HOMA-IR values demonstrated a significant reduction compared with baseline (9.4 ± 0.3 vs 8.3 ± 0.4 mmol/L, $P < .05$, and 2.6 ± 0.2 vs 1.9 ± 0.3, $P < .05$, respectively). HOMA-β, on the other hand, showed significant increase from baseline (63.4 ± 12.5 vs 90.1 ± 13.0, $P < 0.05$). Total cholesterol (4.3 ± 0.2 vs 4.7 ± 0.2 mmol/L, $P < .01$), HDL-C (1.2 ± 0.1 vs 1.4 ± 0.1 mmol/L, $P < .05$), and LDL-C (2.7 ± 0.2 vs 3.0 ± 0.2 mmol/L, $P < .05$) were significantly elevated without alteration of triglyceride concentration (Table 1). The area under the curve of glucose and insulin was significantly greater in subjects

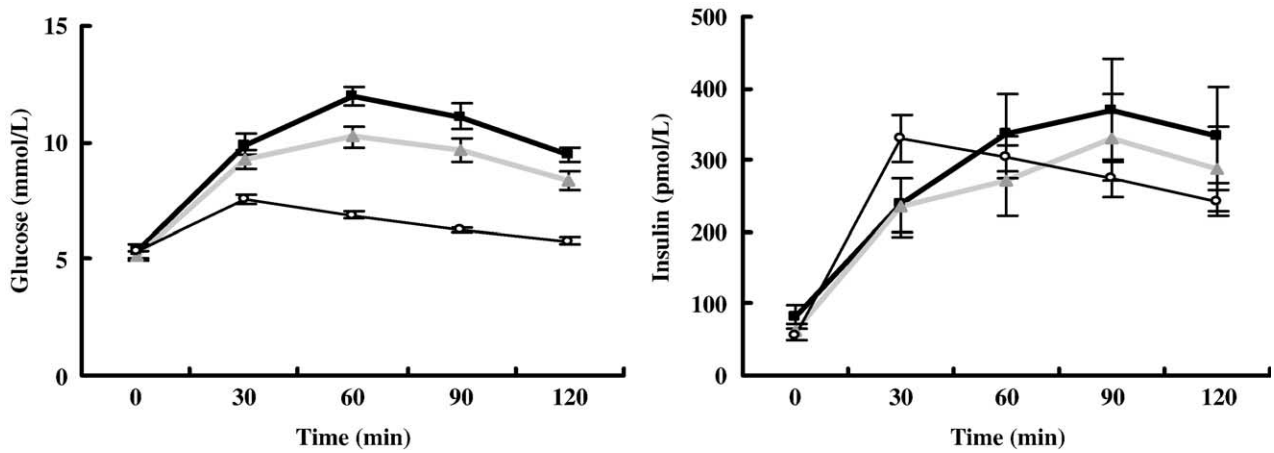

Fig. 1. The area under the curve of glucose and insulin during OGTT were significantly greater in subjects with IGT (filled square) compared with control subjects (open circle) ($P < .05$). The significant decreases in the area under the curve of glucose and insulin on ROS therapy (filled triangle) ($P < .05$) are shown. Values are expressed as mean ± SEM.

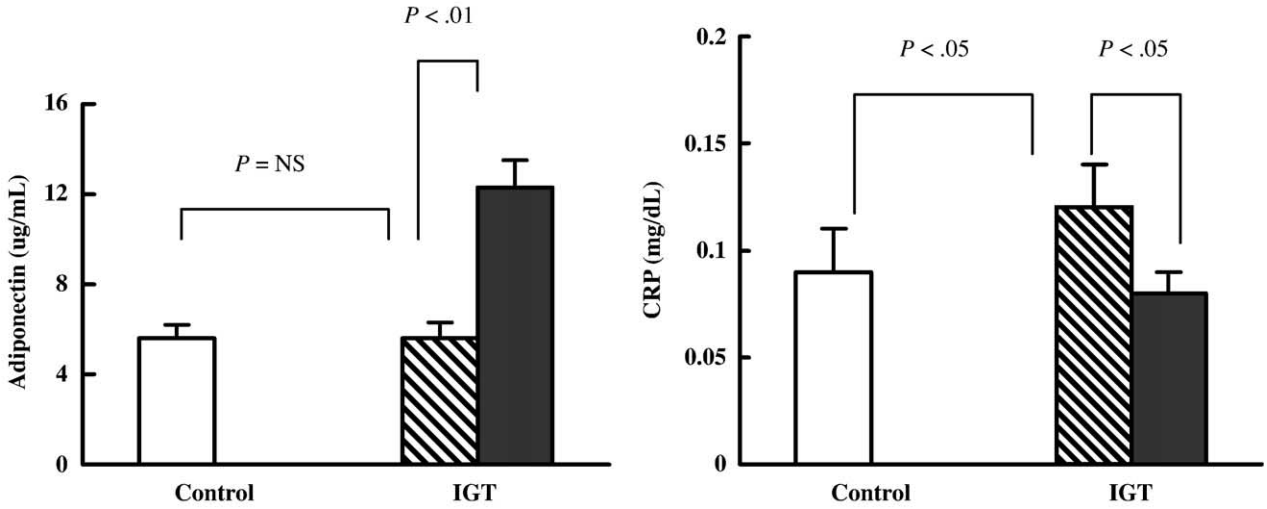

Fig. 2. The CRP level in patients with IGT was significantly higher ($P < .05$) with similar plasma adiponectin level (oblique bar) compared with healthy controls (white bar). Both serum adiponectin and CRP levels on ROS therapy (black bar) were significantly changed ($P < .01$ and $< .05$, respectively). Data are expressed as mean ± SEM. NS indicates not significant.

with IGT compared with control subjects (21.3 ± 0.7 vs 13.1 ± 0.3 [mmol · h]/L, $P < .05$, and 568.3 ± 81.4 vs 528.3 ± 44.5 [pmol · h]/L, $P < .05$, respectively) (Fig. 1). After 12 weeks of ROS treatment, patients with IGT showed improved glucose tolerance with a significant decrease in the area under the curve of glucose and insulin (21.3 ± 0.7 vs 19.1 ± 0.8 [mmol · h]/L, $P < .05$, and 568.3 ± 81.4 vs 501.9 ± 73.1 [pmol · h]/L, $P < .05$, respectively).

In addition, there was a higher CRP level in patients with IGT who have similar plasma adiponectin concentration compared with healthy controls. Both serum adiponectin and CRP levels significantly changed after ROS treatment (Fig. 2). Serum adiponectin showed significant elevation, whereas CRP significantly decreases after ROS treatment.

Table 2
Changes in characteristics from baseline to 12 weeks after ROS treatment with converted and nonconverted subjects with IGT

	Converter (n = 5)	Nonconverter (n = 16)
HbA_{1c} (%)	−0.12 ± 0.17	−0.06 ± 0.14
Fasting plasma glucose (mmol/L)	−0.85 ± 0.25*	0.003 ± 0.23
Fasting plasma insulin (pmol/L)	−49.4 ± 25.8*	−4.9 ± 10.2
Fasting plasma C-peptide (nmol/L)	−0.16 ± 0.11	0.18 ± 0.18
2-h plasma glucose (mmol/L)	−2.79 ± 0.86*	−0.45 ± 0.55
2-h plasma insulin (pmol/L)	−64.8 ± 60.7	−0.5 ± 50.5
HOMA-IR	−2.10 ± 1.03*	−0.07 ± 0.33
HOMA-β	25.6 ± 42.4	33.2 ± 35.8
Total cholesterol (mmol/L)	0.27 ± 0.05	0.43 ± 0.13
Triglyceride (mmol/L)	0.05 ± 0.28	0.07 ± 0.11
HDL-C (mmol/L)	0.12 ± 0.18	0.13 ± 0.05
LDL-C (mmol/L)	0.28 ± 0.18	0.23 ± 0.12
Adiponectin (μg/mL)	9.06 ± 3.21	5.65 ± 0.59
CRP (mg/dL)	−0.68 ± 0.38	−0.39 ± 0.21

Data are expressed as mean ± SEM.

* $P < .05$ compared with the nonconverted subjects by nonparametric Mann-Whitney U test.

Of the 21 patients with IGT treated with ROS, 5 subjects converted to normal (converter), 1 progressed to diabetes, and 15 remained in IGT status (nonconverter). There were significant changes in fasting glucose, insulin, and 2-hour plasma glucose during OGTT and HOMA-IR (−2.10 ± 1.03 vs −0.07 ± 0.33, $P < .05$) in converter compared with nonconverter (Table 2).

4. Discussion

In our study, we demonstrated that nonobese subjects with IGT were associated with insulin resistance and impaired beta-cell secretory function compared with the healthy nonobese population in Taiwan. Although these values were calculated by the simple method of HOMA, data obtained using HOMA-IR and HOMA-β have been shown to be similar to the standard euglycemic insulin clamp [29,30]. Plasma CRP concentration was elevated in nonobese patients with IGT, which was consistent with obese subjects in previous studies [9,13,15]. In the meanwhile, several studies have shown that CRP levels were positively correlated with the degree of insulin resistance. This implies the insulin resistance may play a crucial role in regulating CRP levels in subjects with IGT with various weights. In addition, some authors propose the CRP should be included as a component of the metabolic syndrome because glucose intolerance and insulin resistance are the cardinal features of metabolic syndrome, and CRP significantly correlates with each component of the syndrome [9,31]. Therefore, these results suggest IGT to be a risk factor for the development of cardiovascular disease. However, the plasma adiponectin concentrations of healthy controls and patients with IGT in our study were lower compared with previous literatures [4,32]. This difference could be attributed to the older age of our subjects,

population-based differences, and the different assays used for determining adiponectin concentrations. It was also likely that concentrations of adiponectin may vary in different ethnicity. In addition, the plasma adiponectin levels in nonobese patients with IGT did not differ significantly from those of BMI-matched healthy population. This result was identical with obese African Americans with IGT, although insulin resistance was present in both obese and nonobese patients with IGT [26]. The explanation of this observation remained to be defined.

A limited number of studies have specifically addressed the effects of ROS on the insulin resistance and beta-cell failure underlying type 2 diabetes mellitus [20,21]. In our study, we demonstrated that ROS could significantly improve insulin sensitivity and beta-cell function in subjects with IGT. Notably, our results seem to be consistent with the Troglitazone in Prevention of Diabetes study, which targets improving insulin sensitivity leading to the preservation of beta-cell function and the delay or prevention of diabetes in Hispanic women with previous gestational diabetes [17]. Furthermore, ROS attenuates the circulating insulin and glucose levels during OGTT, as well as significantly decreases fasting glucose and insulin concentrations. This further supports the fact that the improvement of insulin sensitivity can reduce the requirement of insulin and thus reduce postchallenged glucose concentrations. This suggests improving insulin sensitivity could restore beta-cell function and prevent or delay the progression of type 2 diabetes mellitus. However, there were no significant changes in beta-cell function in obese subjects with IGT treated with ROS regardless of the improvement in insulin sensitivity [26]. We hypothesized that less insulin resistance existed in nonobese patients with IGT, which was readily overcome to restore beta-cell function, but further studies are needed to address this hypothesis.

In previous studies, ROS therapy has lead to the improvement of insulin sensitivity with 2- to 2.5-fold increase in plasma adiponectin and attenuation of CRP levels in obese patients with IGT or type 2 diabetes mellitus [20,21,23,26]. Our data found ROS therapy to have the similar effects on both markers in nonobese patients with IGT with lower baseline adiponectin concentrations. Hence, ROS therapy could raise adiponectin levels by the similar magnitude independent of obesity. The mechanism of increased plasma adiponectin by ROS treatment was secondary to increased transcription of adiponectin gene by activating peroxisome proliferator–activated receptor γ mainly in adipocyte. It is still not yet determined whether gene expression of adiponectin with ROS therapy between obese and nonobese subjects was equivalent. Further studies in assessing the expression of the adiponectin gene in adipose tissue in those subjects are warranted.

In our study, of the 21 patients treated with ROS, 5 subjects converted to normal (converter), 1 progressed to diabetes, and 15 remained in IGT status (nonconverter). In the converted group, the levels of insulin sensitivity were profoundly enhanced compared with the nonconverted group. These findings also compared favorably with the Troglitazone in Prevention of Diabetes study [17], although the TZDs used and the subjects involved were different in the 2 studies. In our study, the plasma adiponectin and CRP had minimal changes without statistical significance in the converted group compared with the nonconverted subjects. It implies the beneficial effect of ROS treatment on insulin sensitivity is independent of changes in adiponectin and CRP levels. The effect of ROS therapy on insulin sensitivity is the major determinant in predicting diabetes progression in subjects with IGT rather than the changes in adiponectin and CRP. Therefore, our results supported the hypothesis that type 2 diabetes mellitus can be prevented or delayed through improvement of insulin sensitivity in subjects with IGT.

There are some limitations to our study. First, our results simply reflect the effects of ROS therapy in nonobese subjects with IGT and do not claim any definite outcome from short duration of treatment and the variability and poor reproducibility of OGTT results. Although the reproducibility of OGTT is low, our main thrust is to highlight the changes in insulin sensitivity, plasma adiponectin, and CRP levels from ROS treatment and its metabolic consequence especially in nonobese patients with IGT. Second, this study lacks standard methods to determine insulin sensitivity and beta-cell secretory function. Our result of improved insulin sensitivity in patients with IGT on TZDs therapy was similar to the previous report using a standard method [17]. This consistency allowed us to consider HOMA as an alternative assessment of the role and metabolic effects of adiponectin and CRP in nonobese subjects with IGT. However, the standard methods of the measurement would provide more accurate results.

In conclusion, ROS treatment significantly improved insulin sensitivity, beta-cell secretory function, and reduced postloaded glucose and insulin concentrations with improvement of plasma adiponectin and CRP concentrations in nonobese patients with IGT. The status of IGT could be reversed to normal response to OGTT as a result of ROS therapy. The changes in insulin sensitivity may play a crucial role in determining the progression of IGT independent of changes in CRP and adiponectin. However, it is necessary to conduct additional long-term prospective studies with larger sample size to elucidate whether ROS can reduce cardiovascular morbidity and mortality in patients with IGT.

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