Rosiglitazone Decreases C-Reactive Protein to a Greater Extent Relative to Glyburide and Metformin Over 4 Years Despite Greater Weight Gain

Observations from A Diabetes Outcome Progression Trial (ADOPT)

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OBJECTIVE — C-reactive protein (CRP) is closely associated with obesity and cardiovascular disease in both diabetic and nondiabetic populations. In the short term, commonly prescribed antidiabetic agents have different effects on CRP; however, the long-term effects of those agents are unknown.

RESEARCH DESIGN AND METHODS — In A Diabetes Outcome Progression Trial (ADOPT), we examined the long-term effects of rosiglitazone, glyburide, and metformin on CRP and the relationship among CRP, weight, and glycemic variables in 904 subjects over 4 years.

RESULTS — Baseline CRP was significantly correlated with homeostasis model assessment of insulin resistance (HOMA-IR), A1C, BMI, waist circumference, and waist-to-hip ratio. CRP reduction was greater in the rosiglitazone group by −47.6% relative to glyburide and by −30.5% relative to metformin at 48 months. Mean weight gain from baseline (at 48 months) was 5.6 kg with rosiglitazone, 1.8 kg with glyburide, and −2.8 kg with metformin. The change in CRP from baseline to 12 months was correlated positively with change in BMI in glyburide ($r = 0.18$) and metformin ($r = 0.20$) groups but not in the rosiglitazone ($r = -0.05$, NS) group. However, there was no longer a significant correlation between change in CRP and change in HOMA-IR, A1C, or waist-to-hip ratio in any of the three treatment groups.

CONCLUSIONS — Rosiglitazone treatment was associated with durable reductions in CRP independent of changes in insulin sensitivity, A1C, and weight gain. CRP in the glyburide and metformin groups was positively associated with changes in weight, but this was not the case with rosiglitazone.

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C-reactive protein (CRP) has been traditionally viewed as one of the acute-phase reactants and is a sensitive systemic marker of inflammation and tissue damage. This acute-phase inflammatory protein is predominantly secreted in hepatocytes, its release being regulated by interleukin-6 and other inflammatory cytokines (1). Other studies have shown that extrahepatic sources of CRP production from adipocytes could point to a more systemic generation of CRP in the body after stimulation by inflammatory cytokines and more specifically, by the adipokine, resistin (1).

Both population-based and prospective studies have demonstrated a clear association between CRP and an increased risk of cardiovascular disease (CVD) and stroke (2). The magnitude of the CRP prediction for future CVD events is similar to that of other traditional CVD risk factors (cholesterol, hypertension, and smoking status) (2). CRP also may be a mediator of atherosclerosis (1,3–6). However, there is no available evidence from clinical trials that a reduction in CRP directly reduces or prevents further CVD events.

The production of CRP by adipocytes may partially explain why CRP levels are elevated in patients with the metabolic syndrome (1), in whom CVD risk is increased. The strong association between CRP and body adiposity has been observed in both diabetic (7) and nondiabetic subjects (8–11) and was only moderately attenuated by adjustment of insulin sensitivity. These results suggest that obesity, insulin resistance, and the metabolic syndrome are interconnected in a proinflammatory state that may be mediated by cytokines and subsequently cause elevated levels of CRP. Elevated CRP concentrations have been shown to predict an increased risk of diabetes (9,12,13). Therefore, CRP may play an active role in the causal relationship among obesity, diabetes, and the high risk of future CVD events. Statins (14) and weight

loss (15–17), which can reduce CRP levels and improve other CVD risk factors, also show benefits in reducing CVD events.

Glucose-lowering agents have different effects on CRP, weight, insulin sensitivity, and glycemic control in the treatment of type 2 diabetes. The thiazolidinediones (TZDs) rosiglitazone and pioglitazone, insulin-sensitizing oral antidiabetic agents, have been shown to be effective in reducing CRP in several short-term (≤6 months) studies (18–21). However, it is not clear whether the weight gain associated with TZDs could attenuate the effect on CRP reduction over larger periods of time. In short-term studies, metformin moderately decreases CRP (16,18), increases insulin sensitivity, and produces weight loss (16). The longer-term relationships among the three commonly used oral antidiabetic agents (TZDs, sulfonylureas, and metformin) with CRP, insulin sensitivity, weight, and glycemic control have not been investigated previously.

A Diabetes Outcome Progression Trial (ADOPT) provided the opportunity to evaluate the effects of members of these three classes of oral agents in a randomized, double-blind, controlled trial involving >4,000 patients, treated for a median time of 4 years (22,23). This study compared the efficacy and safety of rosiglitazone, glyburide, and metformin in drug-naive patients with newly diagnosed (≤3 years) type 2 diabetes. We have previously reported the association of CRP, obesity, and insulin resistance in the baseline examination of the ADOPT study (7). We discuss here a subgroup analysis of ADOPT, in which we examined prospectively the long-term effects of rosiglitazone, glyburide, and metformin on CRP reduction and the relationship among CRP, insulin sensitivity, weight, and glycemic variables.

RESEARCH DESIGN AND METHODS

— ADOPT randomized 4,351 subjects from Europe and North America who were drug-naive and in whom type 2 diabetes was recently diagnosed. The study design of this international, multicenter trial has been described previously (23). A subgroup of 904 subjects from investigative centers in the U.S. who had baseline CRP values were included in this analysis. Of those 904 subjects, 304 were randomly assigned to rosiglitazone, 302 to glyburide, and 298 to metformin. A total of 783 subjects had both baseline and at least one on-therapy value for CRP.

In brief, eligible subjects were aged 30–75 years and had a fasting plasma glucose concentration between 7 and 10 mmol/l despite diet and exercise intervention. Eligible subjects were randomly assigned to double-blind treatment with a 1:1:1 ratio of the three glucose-lowering medications. Initial daily doses were 4 mg of rosiglitazone, 500 mg of metformin, or 2.5 mg of glyburide, and the dose was titrated to the maximum effective daily dose (4 mg of rosiglitazone twice daily, 1 g of metformin twice daily, and 7.5 mg of glyburide twice daily). Uptitration of study medication was required at each visit when the fasting plasma glucose level was ≥7.8 mmol/l, whereas a reduction in the dose of study medication was permitted if adverse events occurred. The primary outcome was time to monotherapy failure at the maximum-tolerated dose of the study medication, defined as fasting plasma glucose >10 mmol/l (>180 mg/dl) on two successive occasions or by independent adjudication. The study protocol was reviewed and approved by institutional review boards for each center, and participants gave written, informed consent before participating in the study.

Measurements and assays

Subjects had anthropometric measurements (weight, height, and waist and hip circumference) using standardized procedures across all study centers. Fasting blood samples were drawn for measurement of metabolic variables including plasma glucose, A1C, immunoreactive insulin, and CRP. Metabolic assessments were collected at baseline and every 6 months over 4 years of treatment. Anthropometric measurements were collected at baseline and at yearly visits.

All assays were performed at a central laboratory. Plasma glucose was measured using a hexokinase method (Olympus America, Melville, NY). A1C was determined using the Variant A1C assay (Bio-Rad, Hercules, CA). Serum immunoreactive insulin was quantified using a double-antibody radioimmunoassay (Linco Research, St. Louis, MO). High-sensitivity CRP was measured by fixed-time nephelometry (reporting range 0.2 mg/l to 10 g/l, coefficient of variation <7%; Dade Behring, Deerfield, IL). Insulin sensitivity was estimated with homeostasis model assessment of insulin resistance (HOMA2-IR) using software available at http://www.dtu.ox.ac.uk/homa.

Statistical methods

All statistical analyses were performed with SAS (version 8.2; SAS Institute, Cary, NC). All randomly assigned patients who received at least one dose of study medication and had baseline CRP and at least one postbaseline assessment of CRP were included in the analysis. Although the greatest reduction in CRP was observed at 6 months, 12-month correlations are presented owing to availability of data for all parameters evaluated at this time point.

CRP and HOMA-IR values were log-transformed to achieve a normal distribution before analysis. Results are presented as median (first quartile, third quartile) at baseline and the percent change from baseline at each follow-up time. Changes in CRP and weight over time were analyzed by a normal errors repeated-measures model adjusted for baseline value and sex (24). Partial correlation analyses were performed using the Spearman method; the *P* value for differences between groups was determined by the Wilcoxon test. Other continuous data are presented as mean ± SEM. Two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

— Of 904 participants, 706 remained at month 12 (239 in the rosiglitazone, 220 in the glyburide, and 247 in the metformin group) and 413 at month 48 (153 in the rosiglitazone, 112 in the glyburide, and 148 in the metformin group). As reported previously, major reasons for withdrawals were reaching a monotherapy failure end point, adverse events, and consent withdrawal (22).

Baseline anthropometric and metabolic variables are listed in Table 1. Women were more obese and insulin resistant and had markedly greater CRP levels. However, baseline CRP values among the three treatment groups were comparable (geometric mean 3.9 mg/l in the rosiglitazone group, 3.8 mg/l in the glyburide group, and 3.7 mg/l in the metformin group).

At baseline, CRP was positively correlated with BMI ($r = 0.44$), waist circumference ($r = 0.40$), waist-to-hip ratio ($r = 0.11$), and insulin resistance ($r = 0.30$) (all $P < 0.001$). However, the correlation between CRP and A1C ($r = 0.10$, $P = 0.004$) was relatively weaker.

Percent changes in CRP over time by

Table 1—*Metabolic and anthropometric variables in North American subjects with CRP value at baseline*

	Men	Women	Total
n	467	437	904
CRP (mg/l)*	2.5, (1.3, 5.1)	6.2, (2.9, 10.2)†	4.0, (1.9, 8.4)
HOMA-IR (%)*	3.1, (2.2, 4.5)	3.8, (2.5, 5.3)†	3.5, (2.3, 5.0)
A1C (%)	7.5 ± 0.99	7.4 ± 0.94	7.5 ± 0.97
Age (years)	55.9 ± 10.16	54.5 ± 10.67‡	55.2 ± 10.42
Weight (kg)	100.7 ± 20.7	93.3 ± 20.9†	97.1 ± 21.1
BMI (kg/m^2)	32.1 ± 5.96	35.2 ± 7.59†	33.6 ± 6.97
Waist circumference (cm)§	109.0 ± 15.34	105.8 ± 16.17‡	107.4 ± 15.82
Waist-to-hip ratio	0.97 ± 0.061	0.90 ± 0.079†	0.94 ± 0.080

Data are means ± SD unless indicated otherwise. All data are from subjects who had a baseline CRP value. *Data were log-transformed and are median (25th and 75th quartiles). Wilcoxon test indicated significant differences between men and women (†$P < 0.0001$; ‡$P < 0.01$). §For waist circumference the number of women was 436, giving a total of 903.

treatment group are illustrated in Fig. 1*A*. CRP declined over time in all three treatment groups, with the greatest decrease in the rosiglitazone group, an intermediate decrease in the metformin group, and the least decrease in the glyburide group. CRP declined by >40% within 6 months of initiation of rosiglitazone treatment, compared with <20% with glyburide and metformin. At month 12, CRP was reduced from baseline by 42% in the rosiglitazone group, 10% in the glyburide group, and 26% in the metformin group. After 12 months, CRP continued to decrease gradually in all treatment groups. After 48 months, the CRP reduction was greater in the rosiglitazone group relative to that in the glyburide group (47.6%, $P < 0.001$) and to that in the metformin group (30.5%, $P = 0.004$). Although the absolute changes in CRP were greater in women than in men, the percent changes in CRP over time were comparable between sexes (Fig. 1*B* and *C*).

Weight gain was observed in the rosiglitazone and glyburide groups, whereas weight loss was seen in the metformin group (Fig. 2). At month 12, patients treated with rosiglitazone or glyburide gained an average of 3.6 and 2.8 kg, respectively, whereas patients treated with metformin lost 2.2 kg. At month 48, patients treated with rosiglitazone had significantly greater weight gain compared with those treated with glyburide (3.8 kg, $P < 0.0001$) and metformin (8.5 kg, $P < 0.0001$). Changes from baseline in A1C and HOMA-IR by treatment in this subgroup were similar to those in the entire study population (22). As reported previously (22), subjects treated with rosiglitazone demonstrated greater improvement in HOMA-IR compared with those treated with either glyburide or metformin. Rosiglitazone provided sustained decreases in long-term A1C compared with both glyburide and metformin; however, during the 1st year after commencement of treatment, A1C reduction was greatest with glyburide and least with rosiglitazone. Changes in waist, hip circumference, and waist-to-hip ratio in each treatment group observed in this cohort were similar to those in the entire cohort as well. Subjects treated with rosiglitazone and glyburide had an increase in waist and hip circumference, whereas decreases in both waist and hip circumference were observed in subjects treated with metformin (22). The change in waist-to-hip ratio among the treatment groups was not different (22).

The relationships between the change in CRP from baseline to 1 year and the change over the same time interval in anthropometric and metabolic variables are presented in Table 2. CRP showed a weak, positive correlation with BMI in the glyburide and metformin groups and with waist circumference in the glyburide group. With rosiglitazone, CRP was not correlated with glycemic or anthropometric variables. Of note, the correlation between change in CRP and change in BMI with rosiglitazone treatment trended to be negative but was not significant ($r = -0.052$, $P = 0.464$).

CONCLUSIONS — We have demonstrated for the first time a greater reduction in CRP in patients with newly diagnosed type 2 diabetes treated for 4 years with rosiglitazone compared with that in those treated with glyburide and metformin. These observations occurred in both men and women and are in line with those from several small, short-term studies in patients with type 2 diabetes treated with rosiglitazone (19–21), troglitazone (18), and pioglitazone (19,25). Treatment with rosiglitazone or pioglitazone results in a rapid reduction in CRP that occurs as early as 2 weeks after initiation of treatment (25,26), well before the full effect of TZDs on glucose-lowering, lipid profile changes, and weight gain are manifest. This temporal difference in changes in CRP and metabolic markers with rosiglitazone suggests that an improvement in adipose tissue metabolism could be a prelude for other, later metabolic changes. Unlike with rosiglitazone, the reduction in CRP in the glyburide and metformin groups was smaller and gradual over time. Previous studies with metformin in subjects with type 2 diabetes (18) and impaired glucose tolerance (16) have shown similar results—a modest reduction in CRP levels.

In previous cross-sectional reports CRP was positively associated with obesity in both diabetic and nondiabetic patients (7–11). The current analysis using change in CRP and BMI from baseline to 12 months shows that rosiglitazone treatment disassociates the relationship between CRP and BMI; in contrast, the relationship is positive in both the glyburide and metformin groups as has been shown in observational studies (7,8,10,11). Subjects treated with rosiglitazone experienced weight gain over time; however, this increase in weight occurred gradually and was not accompanied by an increase in CRP. This result may possibly be due to the increase in subcutaneous adipose tissue and fluid retention that can be attributed to rosiglitazone. The correlation between CRP and waist circumference or waist-to-hip ratio followed a similar pattern.

There was a strong positive correlation between CRP and insulin resistance at baseline in all three groups. However, the changes from baseline to 1 year in these parameters in the rosiglitazone group were not significant. This finding was unexpected, because changes in CRP and insulin resistance over time in the rosiglitazone group would have been predicted to be positively correlated. This observation suggests that rosiglitazone regulates CRP and insulin resistance through different mechanisms, which have not yet been elucidated.

A weak correlation between CRP and A1C was observed in the cohort at base-

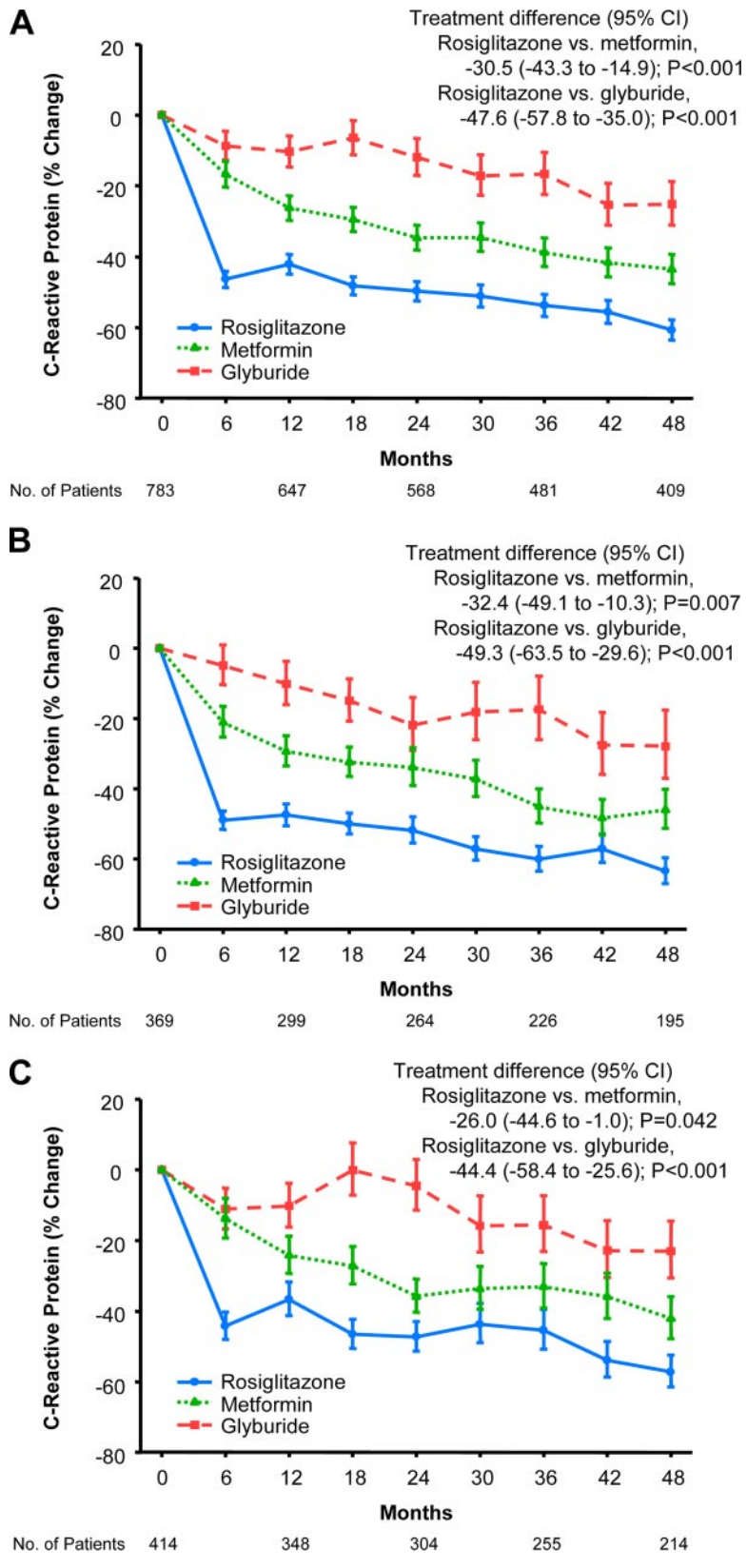

Figure 1—*Percent* (A–C) *changes from baseline in CRP in different treatment groups. Data are percent change ± SEM. Rosiglitazone is in blue, metformin is in green, and glyburide is in red. Data are shown for the whole cohort* (A)*, women* (B)*, and men* (C) *over time in different treatment groups.*

line, in keeping with observations in nondiabetic (27) and elderly type 2 diabetic subjects (28) and probably reflects subclinical microinflammation of the vasculature associated with increased blood glucose. However, in this analysis, improvement in A1C after initiation of glucose-lowering therapy did not correlate with the changes in CRP with all three treatments. In keeping with glucose not being an important determinant of CRP, in ADOPT, over the duration of the study A1C trended upward with both glyburide and metformin, with a slope of 0.24 and 0.14% per year, respectively (22), whereas CRP values trended downward over time in both groups. This observation also suggests that different pharmacological agents affect A1C and CRP through different pathways.

Recently, evidence from large population-based and prospective studies provided support that systemic inflammation biomarkers, such as CRP, may be integrated into the algorithm when the risk of future CVD events (2) is calculated. Some investigators have challenged the importance of CRP in prediction of CHD (29) using an area under the receiver operating curve approach, whereas others have pointed out limitations of the area under the receiver operating curve approach (30). Furthermore, there are few data specifically addressing the role of CRP in predicting future CVD events in patients with type 2 diabetes. CRP might possibly be checked periodically along with other CVD risk factors in patients at higher risk of developing cardiovascular disease but probably should not be used at this time in clinical practice to follow the effect of glycemic interventions.

The discrepancy between the possible benefit in surrogate markers (19–21) and even in atherosclerosis (31) and CVD events with TZDs is not well understood. In a recent meta-analysis of rosiglitazone (32), an increased risk of myocardial infarction and CVD deaths was observed in combined small, short-term trials. However, this increased risk in CVD death was not observed in large, long-term trials. Although ADOPT (22) had a low rate of CVD events, the interim analysis from the Rosiglitazone Evaluated for Cardiovascular Outcomes Study (RECORD) (33) (vs. metformin or sulfonylurea) was based on adjudicated events and showed statistically insignificant increases in myocardial infarction and statistically insignificant decreases in CVD death. In PROspective pioglitAzone Clinical Trial In macroVas-

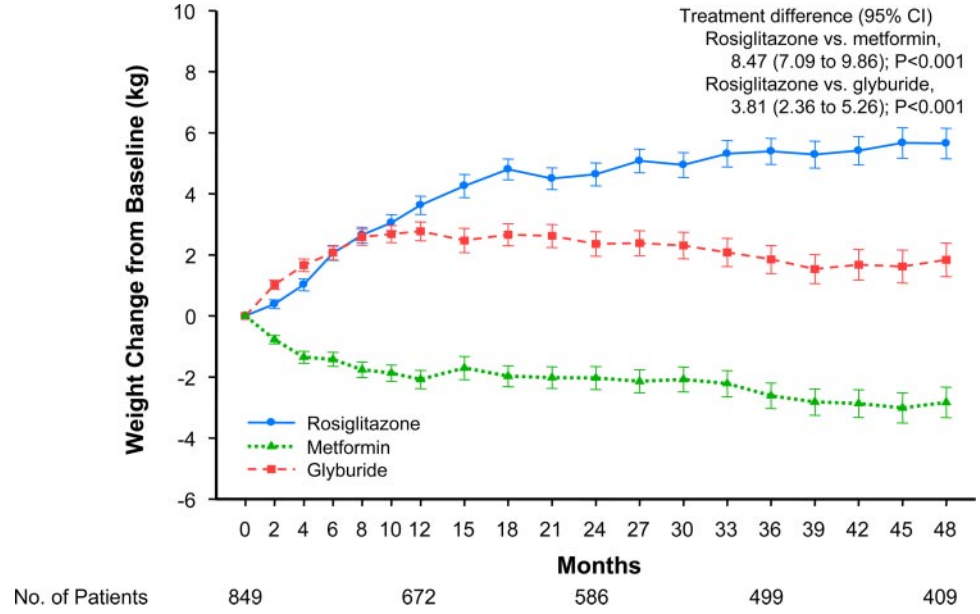

Figure 2—*Change from baseline in weight in different treatment groups. Rosiglitazone is in blue, metformin is in green, and glyburide is in red.*

cular Events (PROACTIVE) (34), pioglitazone improved glycemic control and lipoproteins relative to placebo, but these benefits did not translate to expected significant decreases in CVD outcomes as defined for the primary end point (although a secondary cardiovascular end point was significantly reduced with pioglitazone). The CRP concentration was not assessed in PROACTIVE. Several possibilities for the discrepancy between the lack of positive effects on CVD and the beneficial effects on surrogate markers exist, including chance due to low power and short duration of many studies; alternatively, surrogates such as CRP or measures of atherosclerosis may not be informative for TZDs, as was the case with the HDL-raising medication torcetrapib (35,36). Another possibility is that TZDs may have other effects that are not understood and could potentially counterbalance the effects of reducing inflammation. Any benefits of CRP reduction by TZDs may only be adequately evaluated in a long-term study for CVD outcomes in which variables such as glucose and lipids are well controlled with therapy. Thus, at this time, we believe the long-term effect of TZDs should be viewed largely for their improvement in adipose tissue metabolism, modulation of endocrine functionality of adipocytes, and durability of glycemic control, therefore partially reducing the long-term burden for atherogenesis in patients with type 2 diabetes.

In summary, we have reported the long-term differential effects of three commonly used oral antidiabetes agents on the systemic inflammatory biomarker CRP in subjects with recently diagnosed type 2 diabetes. Treatment with rosiglitazone was associated with a rapid and durable reduction in CRP independent of changes in insulin sensitivity, A1C, and weight gain. Treatment with glyburide and metformin was associated with a moderate and gradual reduction in CRP and was partly associated with changes in weight but independent of glycemic control and insulin sensitivity. The possible value of CRP reduction by glucose-lowering therapy for future CVD events needs to be considered with other CVD risk factors in patients with type 2 diabetes. This issue needs to be evaluated in larger, longer-term clinical trials with adequate samples and adjudication of cardiovascular events.

Table 2—*Correlations of changes from baseline to 12 months in CRP with like changes in metabolic and anthropometric parameters*

	Rosiglitazone	*P*	Glyburide	*P*	Metformin	*P*	Total	*P*
HOMA-IR	−0.035	0.631	0.083	0.285	0.0052	0.940	0.090	0.031
A1C	0.089	0.210	0.048	0.513	0.0052	0.454	0.046	0.255
BMI	−0.052	0.464	0.176	0.016	0.201	0.003	0.055	0.178
WC	−0.002	0.972	0.236	0.001	0.124	0.071	0.090	0.024
WHR	0.052	0.460	0.017	0.813	0.008	0.898	0.032	0.423

Data are % change. WC, waist circumference; WHR, waist-to-hip ratio.

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