

Effects of Rosiglitazone, Glyburide, and Metformin on β -Cell Function and Insulin Sensitivity in ADOPT

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OBJECTIVE—ADOPT (A Diabetes Outcome Progression Trial) demonstrated that initial monotherapy with rosiglitazone provided superior durability of glycemic control compared with metformin and glyburide in patients with recently diagnosed type 2 diabetes. Herein, we examine measures of β -cell function and insulin sensitivity from an oral glucose tolerance test (OGTT) over a 4-year period among the three treatments.

RESEARCH DESIGN AND METHODS—Recently diagnosed, drug-naïve patients with type 2 diabetes (4,360 total) were treated for a median of 4.0 years with rosiglitazone, metformin, or glyburide and were examined with periodic metabolic testing using an OGTT.

RESULTS—Measures of β -cell function and insulin sensitivity from an OGTT showed more favorable changes over time with rosiglitazone versus metformin or glyburide. Persistent improvements were seen in those who completed 4 years of monotherapy and marked deterioration of β -cell function in those who failed to maintain adequate glucose control with initial monotherapy.

CONCLUSIONS—The favorable combined changes in β -cell function and insulin sensitivity over time with rosiglitazone appear to be responsible for its superior glycemic durability over metformin and glyburide as initial monotherapy in type 2 diabetes. *Diabetes* 60:1552–1560, 2011

In the UK Prospective Diabetes Study (UKPDS), a progressive decline in β -cell function was the major determinant of loss of glycemic control over time in type 2 diabetes (1). However, differential effects of diet, sulfonylurea, and metformin on insulin sensitivity and β -cell function did not yield substantive differences in the rates of increase in glycated hemoglobin (1).

Subsequently, thiazolidinediones were introduced that primarily improve insulin sensitivity in the peripheral tissues (2), while also affecting β -cell function by reducing the demand to synthesize and release insulin. In contrast,

the biguanide metformin acts primarily to reduce hepatic glucose production, whereas the sulfonylureas stimulate insulin release by binding to their receptor on the β -cell (2).

Given these different mechanisms of action, A Diabetes Outcome Progression Trial (ADOPT) was designed to assess whether initial monotherapy with the thiazolidinedione rosiglitazone could slow the rate of decline of β -cell function in type 2 diabetes and associated loss-of-glucose control, relative to metformin or sulfonylurea (glyburide) (3). In ADOPT, rosiglitazone provided lower rates of monotherapy failure and lower levels of fasting plasma glucose and glycated hemoglobin, yielding superior durability of glycemic control than metformin or glyburide (4).

Measures of insulin sensitivity and β -cell function determined from fasting and 30-min samples during an oral glucose tolerance test (OGTT) allowed examination of mechanisms by which each agent affected glycemic outcomes. Herein, changes over time for these measures are compared among the three treatment groups in the full cohort and separately among those who either successfully completed or failed initially assigned monotherapy over a period of 4 years. Joint vector plots are used to display concomitant changes in secretory response and insulin sensitivity over time with each therapy.

RESEARCH DESIGN AND METHODS

Subjects. ADOPT, a randomized, double-blind, parallel-group trial, enrolled 4,360 individuals with type 2 diabetes of up to 3 years' duration who were drug-naïve for glucose-lowering therapy (3). The protocol was approved by institutional review boards for each center, and subjects gave written, informed consent to participate in the study.

Subjects were randomly assigned to double-blind, twice-daily treatment with rosiglitazone ($n = 1,456$), metformin ($n = 1,454$), or glyburide ($n = 1,441$) as initial monotherapy; nine subjects never received study medication. Medications were titrated, if fasting plasma glucose levels were 7.8 mmol/L or more, to a maximum of 8 mg/day, 2 g/day, and 15 mg/day, respectively. Dose reductions were permitted if adverse events occurred. The primary outcome was the time to monotherapy failure on maximum-tolerated study drug dose, defined as a fasting plasma glucose >10 mmol/L on two successive occasions or by independent adjudication (3).

Analyses were performed in the full cohort and separately in those who completed their metabolic assessments at 4 years (4-year completer cohort) and those who failed monotherapy before 4 years (monotherapy failure cohort).

Methods. Assessments were performed using standardized procedures at baseline and then every 6 months for the duration of the study (3). Fasting blood samples were drawn for measurement of metabolic variables, including plasma glucose, HbA_{1c}, and immunoreactive insulin levels. An abbreviated 75-g OGTT measuring glucose and immunoreactive insulin levels before and 30 min after glucose ingestion was performed at baseline and then every 6 months for the duration of the study.

Assays and calculations. All assays were performed at a central laboratory (3).

Insulin sensitivity and the insulin response obtained from the OGTT were the inverse of the fasting insulin concentration and the insulinogenic index, respectively (5)—the latter a dynamic measure calculated as the ratio of the incremental insulin and glucose responses over the first 30 min of the test

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Received 18 October 2010 and accepted 8 February 2011.

DOI: 10.2337/db10-1392. Clinical trial reg. no. NCT00279045, clinicaltrials.gov.

*A complete list of the ADOPT Study Group can be found in *N Engl J Med* 2006;355:2427–2443.

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(insulin₃₀ - insulin₀/glucose₃₀ - glucose₀). Homeostasis model assessment (HOMA) %S and HOMA %B were estimated using the HOMA2 model calculator (<http://www.dtu.ox.ac.uk/homa>) (6).

Metabolic assessments were not conducted after subjects reached monotherapy failure or withdrew from study medication. Thus treatment group differences in these measures over time may be influenced by the successive culling of subjects reaching monotherapy failure. Thus sensitivity analyses assessed the potential impact of bias.

Statistical methods. Of the 25,196 insulinogenic index values obtained through the 4-year visit, 768 (3.05%) were ≤ 0 . Although mathematically possible, such values are currently considered biologically implausible and were treated as missing values. These implausible responses were observed in 637 subjects (average of 1.17 per such subject), of which 156 had a response ≤ 0 at baseline necessitating their exclusion from the longitudinal analyses. Of the 768 values, the median value was -9.81 , 25% were < -1.34 , 5% were < -152 , and 1% was $< -1,021$, and the minimum was $-5,880$. Finally, no association was observed between the fasting glucose concentration and values ≤ 0 .

Wilcoxon rank sum test compared baseline variables between groups for quantitative variables, and the contingency χ^2 test for qualitative variables (7). Normal errors longitudinal linear models (8) were used to estimate mean levels of the parameters over time within groups up to 4 years of follow-up using all available data. Mean change from baseline to 6 months described the immediate impact of a therapy on outcomes. The average rate of change from 6 months to 4 years was estimated from a linear contrast of the model-estimated means over time.

Analyses of the reciprocal fasting insulin and insulinogenic index used the natural log transformation to better approximate a normal distribution for errors and homoscedasticity of variances, with the results presented as geometric means \pm SE asymmetric limits, the latter obtained as $\exp(\text{means} \pm \text{SE of the log values})$. For these variables, mean percent change over 6 months and mean percent change per year from 6 months to 4 years are presented.

However, the longitudinal model results could be biased because subjects with the most rapid decline in these metabolic measures (i.e., the steepest slopes) have a shorter time to monotherapy failure and, therefore, contribute fewer observations to estimation of the rate of change over time in the cohort.

In this setting, an unweighted average of the subject-specific slopes provides a less biased estimate of the overall rate of change (9).

A two-sided $P \leq 0.05$ was considered statistically significant.

RESULTS

Demographic and metabolic variables. Table 1 presents the baseline values for all 4,351 patients, the 2,112 who completed 4 years of follow-up, and the 526 who failed monotherapy before 4 years, of whom 11% were followed for less than 1 year, 25% for 1–2 years, 30% for 2–3 years, 24% for 3–4 years, and 10% for 4 years or more. The monotherapy failure cohort was younger, more obese, and initially had a greater waist circumference, higher mean fasting plasma glucose and HbA_{1c} levels, and a lower systolic blood pressure than those completing 4 years on study medication. They also had lower median β -cell function scores at baseline, determined as the insulinogenic index and HOMA %B.

Only patients with a baseline and follow-up evaluation of each outcome measure (insulinogenic index and reciprocal fasting insulin) contributed data to the longitudinal analyses of that measure described below. The longitudinal analyses of the HOMA values are not presented because they have been published previously (4). **Early insulin response (insulinogenic index) for the full cohort.** The longitudinal model estimated mean insulinogenic index over up to 4 years of follow-up within each treatment group for the full cohort is presented in Fig. 1A. Table 2 shows the short-term (acute) effect of therapy characterized as the mean percent change from baseline to 0.5 years and the long-term (chronic) effect

TABLE 1

Baseline demographic and metabolic variables in the full cohort, those completing 4 years, and those with monotherapy failure before 4 years

	All subjects	4-Year completer cohort	4-Year monotherapy failure cohort	<i>P</i> value 4-Year completers vs. monotherapy failures
<i>n</i>	4,351	2,112	526	
Age (years)	56.5 \pm 10.0	58.0 \pm 9.4	52.2 \pm 9.7	<0.025
Males (<i>n</i> , %)	2,511 (57.7)	1,251 (59.2)	321 (61.0)	N.S.
Time since diagnosis of diabetes (years)				
<1	1,961 (4.1)	929 (44.0)	237 (45.1)	N.S.
1–2	2,233 (51.3)	1,100 (52.1)	274 (52.1)	N.S.
>2	157 (3.6)	83 (3.9)	15 (2.9)	N.S.
GAD-positive	175 (4.0)	92 (4.4)	25 (4.8)	N.S.
BMI (kg/m ²)	32.2 \pm 6.3	31.8 \pm 6.0	33.2 \pm 6.4	<0.025
Waist circumference (cm)	105.5 \pm 14.7	104.8 \pm 13.7	108.0 \pm 16.1	<0.025
Waist-to-hip ratio	0.95 \pm 0.09	0.95 \pm 0.09	0.96 \pm 0.09	N.S.
Blood pressure (mmHg)				
Systolic	132.9 \pm 15.5	133.3 \pm 15.4	131.1 \pm 15.9	<0.025
Diastolic	79.6 \pm 8.8	79.3 \pm 8.6	79.7 \pm 9.2	N.S.
Fasting plasma glucose (mmol/L)	8.4 \pm 1.5	8.2 \pm 1.3	9.1 \pm 1.7	<0.025
HbA _{1c} (%)	7.4 \pm 0.9	7.2 \pm 0.9	7.7 \pm 1.0	<0.025
Fasting insulin (pmol/L)	150.7 \pm 111.0	147.9 \pm 113.2	148.5 \pm 100.4	N.S.
1/Fasting insulin (pmol/L ⁻¹ \times 10 ⁻³)	122.0 (84.0, 186.0)	120.0 (84.0, 179.4)	126.0 (84.0, 186.0)	N.S.
HOMA %S	8.20 (5.38, 11.90)	8.33 (5.57, 11.90)	7.94 (5.38, 11.90)	N.S.
HOMA %B	33.4 (22.6–48.2)	34.6 (23.5–49.4)	31.5 (21.8–47.7)	N.S.
Insulinogenic index (pmol/L per mmol/L)	32.0 (17.9, 57.4)	33.2 (19.2, 58.9)	26.1 (12.5, 47.7)	<0.025
HOMA %B	68.4 (52.0–88.3)	70.4 (53.4–90.4)	60.3 (44.5–79.7)	<0.025

Continuous data are expressed as means \pm SD and/or median (first, third quartile). For time since diagnosis of diabetes and GAD-positive, data are *n* (%). *P* values were adjusted for two comparisons using the Bonferroni method. HOMA %S and HOMA %B were determined using the HOMA calculator (www.dtu.ox.ac.uk/homa). N.S., nonsignificant.

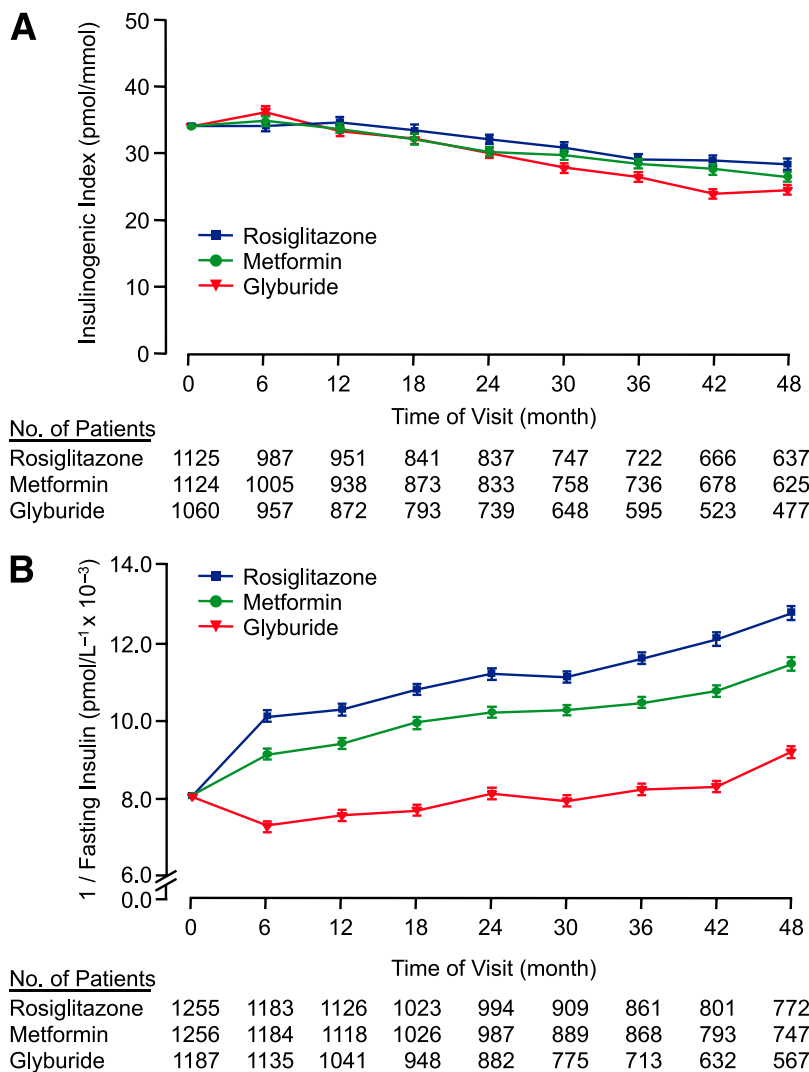


FIG. 1. Baseline adjusted geometric mean levels in the full cohort within each treatment group over 4 years of follow-up for OGTT-derived dynamic measure of the early insulin response (A; insulinogenic index; $\text{insulin}_{30} - \text{insulin}_0 / \text{glucose}_{30} - \text{glucose}_0$) and insulin sensitivity (B; $1/\text{fasting insulin}$). Each was analyzed using the log-transformed values, and the results presented are geometric means (\pm SE asymmetric limits).

characterized as the rate of change (percent per year) from 0.5 to 4 years. The longitudinal analysis of the log values provides estimates of the percent change over time.

A significantly higher acute change in the insulinogenic index over the first 6 months was observed with glyburide versus rosiglitazone, with there being no change with rosiglitazone and an intermediate change with metformin. Thereafter, glyburide was associated with a significantly faster rate of decline (negative slope) versus rosiglitazone (11.1 vs. 6.0% per year), with metformin as the intermediate. The different rates of decline meant that, beyond 24 months, the mean levels with glyburide were lower than those in the other groups. The unweighted mean slope analysis demonstrated similar differences between groups. **Insulin sensitivity ($1/\text{fasting insulin}$) for the full cohort.** Figure 1B presents the longitudinal model estimated mean reciprocal fasting insulin from the OGTT over time for 4 years of follow-up within each treatment group for the full cohort. Table 2 shows the short- and long-term effects of therapy on this measure.

Rosiglitazone produced a significantly greater increase over the first 6 months in the reciprocal fasting insulin than

did either comparator, with glyburide initially decreasing by 9.2% over this period. This ratio then increased over time in all groups with no significant differences between groups. However, the unweighted analysis showed a significantly greater increase over time with rosiglitazone than either comparator, suggesting that the lesser differences between groups observed in the longitudinal model analysis could be attributed to the effects of early termination of follow-up because of monotherapy failure.

OGTT measures in the 4-year completer cohort. Among those in the completer cohort, Fig. 2A and Table 3 indicate that the insulinogenic index did not increase substantially over the first 6 months and then declined at a significantly faster rate with glyburide than with rosiglitazone.

The pattern of changes in insulin sensitivity is shown in Fig. 2B and Table 3. The pattern in the completers was similar to that in the full cohort. There was a significantly greater improvement at 6 months with rosiglitazone than with either glyburide or metformin, and thereafter, there was also a significantly greater rate of increase over time with rosiglitazone than with glyburide, with those with metformin being intermediate.

TABLE 2

Changes in OGTT-derived measures of β -cell function (insulinogenic index) and insulin sensitivity (1/fasting insulin) for the full cohort from baseline to 0.5 years and rates of change among means from 0.5 to 4 years based on a longitudinal model adjusted for baseline factors

Variable	Rosiglitazone	Metformin	Glyburide	P value	
				Rosiglitazone vs. metformin	Rosiglitazone vs. glyburide
Insulinogenic index (pmol/L per mmol/L)					
<i>n</i>	1,125	1,124	1,060	—	—
Mean %change from 0 to 0.5 years	0.0 (−3.9, 4.1)	2.5 (−1.5, 6.7)	6.6 (2.3, 11.1)	0.3826	0.0249
Rate of change from 0.5 to 4 years (% per year)	−6.0 (−7.2, −4.8)	−7.4 (−8.5, −6.2)	−11.1 (−12.3, −9.8)	0.1133	<0.0001
Unweighted mean slope (% per year)	−8.0 (−9.5, −6.4)	−8.8 (−10.3, −7.2)	−13.2 (−15.0, −11.4)	0.4798	<0.0001
1/Fasting insulin (pmol/L ^{−1} × 10 ^{−3})					
<i>n</i>	1,255	1,256	1,187	—	—
Mean %change from 0 to 0.5 years	25.7 (22.8, 28.7)	13.5 (10.9, 16.2)	−9.2 (−11.4, −7.0)	<0.0001	<0.0001
Rate of change from 0.5 to 4 years (% per year)	6.5 (5.8, 7.2)	5.9 (5.2, 6.7)	5.5 (4.7, 6.3)	0.2898	0.0822
Unweighted mean slope (% per year)	6.9 (6.1, 7.8)	5.3 (4.4, 6.3)	5.2 (4.1, 6.2)	0.0176	0.0128

For the log-transformed insulinogenic index and reciprocal fasting insulin, results are presented as a percentage change from baseline and mean rates of change (percent per year) \pm 95% confidence limits. The unweighted mean rate of change (mean slopes) over 0.5 to 4 years are also listed. Changes from baseline, or rates of change, for which the 95% confidence limits do not bracket zero are statistically significantly different at the 0.05 level, without adjustment for multiple tests of significance.

OGTT measures in the 4-year monotherapy failure cohort. Subjects who ultimately failed had lower levels of the insulinogenic index at baseline (Fig. 3A) than those who completed (Fig. 2A). Glyburide produced a small increase at 6 months, whereas rosiglitazone had little effect (Fig. 3A and Table 3). Thereafter, the insulinogenic index declined, equally so in all groups.

Among failures, there was a much greater acute increase in 1/fasting insulin with rosiglitazone than with either metformin or glyburide, but thereafter, the rate of increase was similar among groups (Fig. 3B and Table 3). The failure cohort started at approximately the same levels as the completer cohort, but the increase with rosiglitazone was less. Thereafter, 1/fasting insulin increased among failures at approximately the same rate as seen with completers.

Vector plots of OGTT measures. Figure 4A–C displays the concomitant changes over time in the relationship between the insulinogenic index and 1/fasting insulin for the full, completer, and monotherapy failure cohorts, respectively. This relationship depicts the pattern of changes in glucose metabolism over time and is termed herein vector plots.

In each case, the concave line represents the known nonlinear relationship between a measure of β -cell function and insulin sensitivity at baseline (10–12) and is based on the linear regression between log-transformed insulinogenic index and 1/fasting insulin values. The single dot on the line, which is the origin for each vector, shows the common mean values for these two measures in all three treatment groups, i.e., for the whole cohort, an insulinogenic index of 33.1 pmol/L per mmol/L and a 1/fasting insulin of 8.2 pmol/L^{−1} × 10^{−3}. This point and each subsequent one is a measure of the joint action of insulin

sensitivity and β -cell function over time and is commonly known as the disposition index (12). The overall mean is used because the baseline covariate-adjusted longitudinal analyses presented in prior figures assume that all groups start with a common baseline value.

Starting from this common point, joint geometric means for insulinogenic index and 1/fasting insulin within each group are plotted for the first 6-month visit and, thereafter, each annual anniversary visit. These are the same means as presented separately in Figs. 1A and B, 2A and B, and 3A and B for the whole 4-year completer and 4-year monotherapy failure cohorts, respectively. Movement of the joint mean values up or down represents changes in β -cell function, and movement of the joint means left or right represents changes in insulin sensitivity over time. Mean values remaining above the concave line represent improvements in glucose metabolism from the level at baseline, whereas those falling below the line represent deterioration in glucose metabolism. Furthermore, the greater the movement away from the concave line, the larger the difference in overall glucose metabolism.

In the full cohort (Fig. 4A), there was a small acute beneficial effect with glyburide on the insulin response (shift upward) but a decrease in insulin sensitivity (shift to the left), so that overall glucose metabolism was not improved relative to the concave line. Thereafter, the insulinogenic index fell (shift downward), whereas 1/fasting insulin increased (shift rightward), but at a rate too slow to compensate for the loss in insulin response (hence, the values remain below the baseline regression line). In contrast, with rosiglitazone and metformin, there is a beneficial effect that continues over time, more so with rosiglitazone. Although rosiglitazone had no acute effect on the insulinogenic index over the first 6 months, it had

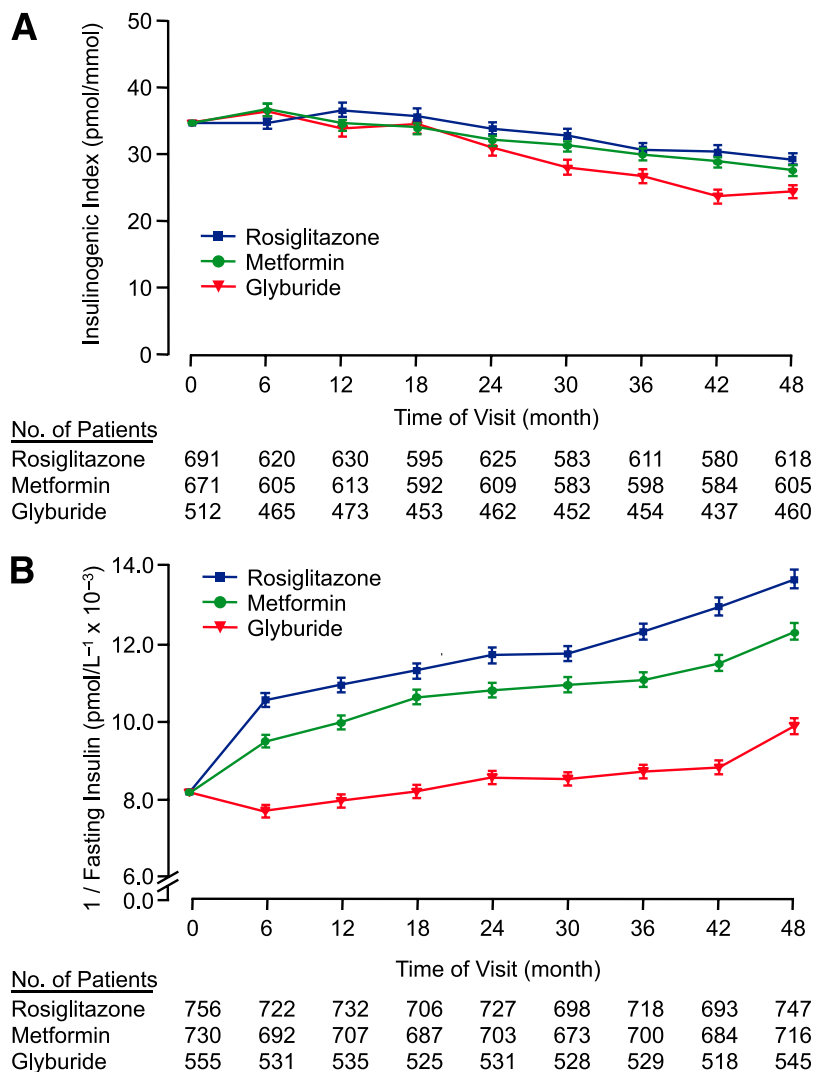


FIG. 2. Baseline adjusted geometric mean levels in the 4-year completer cohort within each treatment group over 4 years of follow-up for OGTT-derived dynamic measure of the early insulin response (A; insulinogenic index; $\text{insulin}_{30} - \text{insulin}_0 / \text{glucose}_{30} - \text{glucose}_0$) and insulin sensitivity (B; $1/\text{fasting insulin}$). Each was analyzed using the log-transformed values, and the results presented are geometric means (\pm SE asymmetric limits).

a dramatic beneficial effect on $1/\text{fasting insulin}$, and thereafter, the rate of further increase in the reciprocal insulin more than compensated for the decline in the insulinogenic index. Thus, the joint means show the greatest distance from the baseline level in keeping with the observation that rosiglitazone produced a more favorable long-term improvement in glucose metabolism than either comparator.

The vector plot for the 4-year completer cohort (Fig. 4B), as in the full cohort, shows that rosiglitazone produced a more favorable long-term improvement in glucose metabolism than either of the comparators. These results are similar both qualitatively and quantitatively to those observed in the full cohort.

The vector plot for the 4-year monotherapy failure cohort (Fig. 4C) shows an initial improvement in glucose metabolism in all three groups that then rapidly dissipates, with the subjects returning to their baseline status, on average, by 18–24 months, and then worsening further. The fall below the baseline regression line with all treatments is in keeping with disease progression and these subjects ultimately reaching the monotherapy failure end

point. These results are both qualitatively and quantitatively different from those of the 4-year completer and full cohorts.

DISCUSSION

Type 2 diabetes is characterized by a progressive loss of β -cell function that is represented by deteriorating measures of insulin response relative to the prevailing insulin sensitivity (10–13), resulting in deteriorating glycemic control (1,13). This is best demonstrated by the loss of β -cell function over time in individuals who progress from states of impaired glucose metabolism to diabetes (14,15). Thus, preserving the ability of the β -cell to secrete insulin is thought to be critical to preventing the inexorable loss of glucose control.

ADOPT allowed the systematic, prospective evaluation of changes in glucose metabolism over a period of 4 years in a large cohort of recently diagnosed type 2 diabetic subjects randomized to initial monotherapy using rosiglitazone, metformin, or glyburide. In the first 6 months, as anticipated, glyburide increased stimulated insulin release during the OGTT but did not change insulin sensitivity.

Metformin primarily improved insulin sensitivity, with a small beneficial effect on β -cell function following glucose ingestion. Rosiglitazone had similar effects to metformin, but of greater magnitude. Whether the beneficial effects of rosiglitazone and/or metformin on the β -cell are indirect as a result of their ability to improve insulin sensitivity or result from a direct action on the β -cell, as suggested by some in vitro studies (16,17), cannot be determined from these analyses.

Further differences emerged beyond the first 6 months. The insulinogenic index fell at the greatest rate with glyburide but at the lowest rate with rosiglitazone, whereas metformin was intermediate. Concurrently, insulin sensitivity showed a long-term beneficial change with all three medications, although the change with glyburide was less than with rosiglitazone. This change with glyburide may be the result of alleviation of glucose toxicity (18).

This analysis represents the first longitudinal assessment of measures involved in determining glucose metabolism in a cohort of individuals with type 2 diabetes followed for a prolonged period in a large, multicenter, clinical trial. The effective evaluation of the time course of β -cell function and insulin sensitivity was allowed by the selection of a glycemic level of 10 mmol/L to unequivocally represent monotherapy failure.

It is now well accepted that knowledge of the concomitant insulin sensitivity is required to accurately evaluate β -cell function (10–13). Thus, vector plots of the joint changes in OGTT measures of insulin response and insulin sensitivity were used to describe changes in β -cell function over time. These highlight the importance of this interplay between the insulin response and insulin sensitivity and how the relationship between these two parameters changes over time with all three treatments. These changes are different not only in magnitude but also in nature, with the most favorable changes occurring with rosiglitazone in keeping with improvements in both β -cell function and insulin sensitivity.

These analyses used indirect measures of the β -cell and insulin sensitivity. The dynamic measure of insulin release was computed from two glucose and insulin pairs and the estimate of insulin sensitivity from the fasting insulin level. Although both these measures include fasting insulin, they failed to show a substantial correlation at baseline, $R^2 = 0.29$, a level far below what would be considered as collinearity (19). Thus, this OGTT measure of insulin release alone is far from redundant with the measure of insulin sensitivity, and examination of joint changes in the two measures provides a more complete picture of disease progression over time than does examination of either in isolation. Furthermore, joint changes in the OGTT measures are in keeping with different responses to therapy and an overall preservation of β -cell function that is greatest with rosiglitazone and least with glyburide.

Additional analyses were performed by examining the 526 subjects who failed monotherapy and the 2,112 that did not during 4 years of follow-up. At baseline, those who ultimately failed were younger and metabolically in a more advanced state. The results among those who did not fail closely resemble those for the full cohort, whereas among those who ultimately failed monotherapy, all three medications demonstrated a short-term improvement in glucose metabolism manifest as a change in the vector plot, such that it was above the concave line. In those who failed monotherapy, the final point in each treatment group is equidistant from the curve determined using the baseline

TABLE 3
Changes in OGTT-derived measures of β -cell function (insulinogenic index) and insulin sensitivity (1/fasting insulin) for the 4-year completer and monotherapy failure cohorts from baseline to 0.5 years and rates of change among means from 0.5 to 4 years based on a longitudinal model adjusted for baseline factors

Variable	4-Year completer cohort			4-Year monotherapy failure cohort		
	Rosiglitazone	Metformin	Glyburide	Rosiglitazone	Metformin	Glyburide
Insulinogenic index (pmol/L per mmol/L)	691	671	512	93	128	215
Mean %change from 0 to 0.5 years	0.2 (–4.5, 5.2)	5.2 (0.2, 10.5)	4.2 (–1.5, 10.1)	–8.0 (–21.5, 7.9)	8.3 (–5.3, 24.0)	13.5* (2.2, 25.9)
Rate of change from 0.5 to 4 years (% per year)	–5.3 (–6.6, –4.0)	–6.6 (–7.9, –5.4)	–10.6* (–12.0, –9.2)	–20.0 (–27.2, –12.2)	–16.9 (–22.9, –10.6)	–19.9 (–25.1, –14.4)
1/Fasting insulin (pmol/L ^{–1} × 10 ^{–3})	756	730	555	108	153	244
Mean %change from 0 to 0.5 years	26.1 (22.5, 29.8)	14.5* (11.2, 17.9)	–5.2* (–8.3, –1.9)	20.1 (11.3, 29.6)	3.6* (–2.8, 10.4)	–13.5* (–17.8, –9.0)
Rate of change from 0.5 to 4 years (% per year)	6.6 (5.8, 7.4)	6.0 (5.2, 6.8)	5.4* (4.4, 6.3)	4.5 (0.0, 9.3)	5.9 (2.8, 9.2)	4.6 (1.3, 8.0)

For the log-transformed insulinogenic index and reciprocal fasting insulin, results presented as a percent change from baseline and mean rates of change (percent per year) \pm 95% confidence limits. Changes from baseline, or rates of change, for which the 95% confidence limits do not bracket zero are statistically significantly different at the 0.05 level, without adjustment for multiple tests of significance. * $P < 0.05$ for metformin or glyburide vs. rosiglitazone.

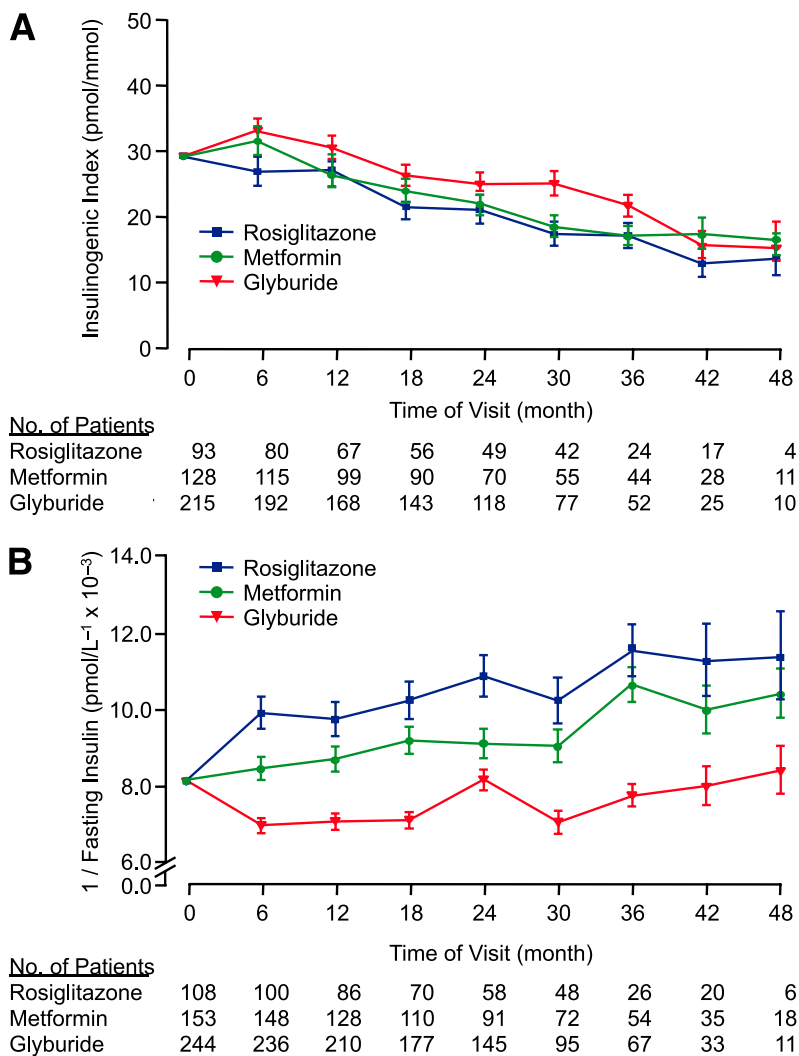


FIG. 3. Baseline adjusted geometric mean levels in the 4-year monotherapy failure cohort within each treatment group over 4 years of follow-up for OGTT-derived dynamic measure of the early insulin response (A; insulinogenic index; $\text{insulin}_{30} - \text{insulin}_0 / \text{glucose}_{30} - \text{glucose}_0$) and insulin sensitivity (B; $1/\text{fasting insulin}$). Each was analyzed using the log-transformed values, and the results presented are geometric means (\pm SE asymmetric limits).

data from the whole cohort and is the position at which the pair of insulin release and insulin sensitivity measures represent a deterioration in glucose metabolism associated with a fasting glucose of 10 mmol/L.

Analyses of the 4-year completer and 4-year monotherapy failure cohorts demonstrated beneficial effects of rosiglitazone versus either comparator or the lack of beneficial effects among those who failed. These outcomes are directly explained by the presence or absence, respectively, of beneficial effects jointly on both β -cell function and insulin sensitivity. Thus, the beneficial effects of rosiglitazone on the durability of glycemic control are explained by changes in determinants of glucose metabolism over time.

The longitudinal analyses within the full cohort may be biased because of the truncation of follow-up assessments in those who failed monotherapy. Additional sensitivity analyses conducted to allow for such bias showed little difference from those in the longitudinal analyses. The analyses within the completer and failure cohorts also suggest that had there been complete follow-up of all subjects up to 4 years, regardless of monotherapy failure or not; the overall beneficial effects observed with rosiglitazone

would be expected to be diluted by the lack of a sustained beneficial effect among those who failed. However, given the smaller number of such subjects, the overall beneficial effects observed in the full cohort would still apply.

In ADOPT, we chose to obtain measures of β -cell function and insulin sensitivity that were the most practical to institute across the many clinics involved in the study. This approach, of course, meant that we did not use more sophisticated and precise measures of insulin sensitivity. However, we do not believe that this severely limits our findings because, although glyburide stimulates insulin release and we may have overestimated the decrease in insulin sensitivity, the rate of change in the insulinogenic index over time was greatest with the sulfonylurea. This change can be associated with the most rapid decrease in β -cell function and thus more monotherapy failure.

In 3% of tests, the value for the insulinogenic index was ≤ 0 , with a similar percentage applicable to the values at each visit and with a minority of subjects having only one such value (if any). However, it did not appear to be occurring in subjects who had more severe diabetes because we failed to demonstrate a relationship between the fasting

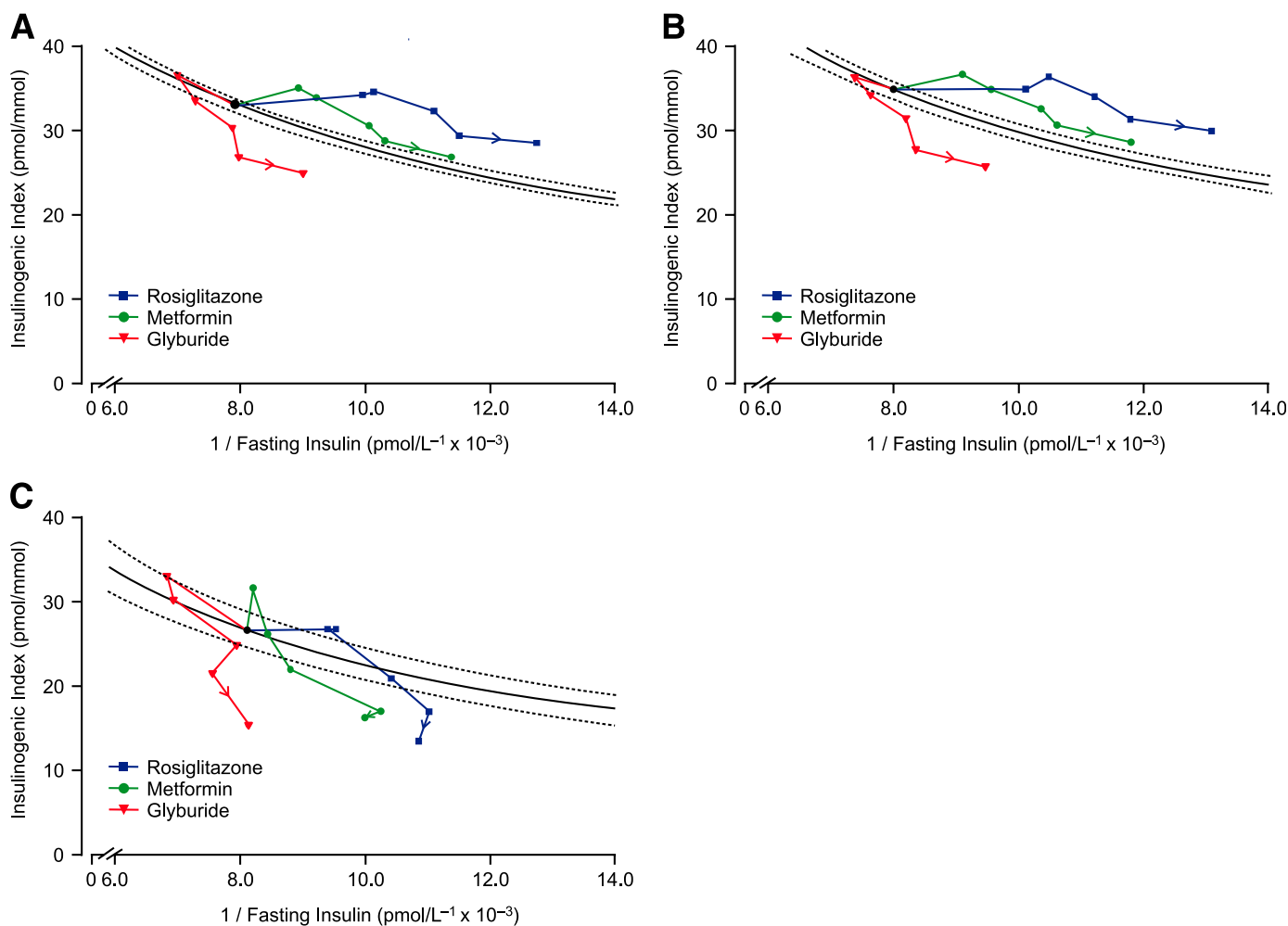


FIG. 4. Vector plot of the joint changes in the baseline adjusted geometric mean levels (\pm SE asymmetric limits) of the OGTT-derived dynamic measure of the early insulin response (insulinogenic index; $\text{insulin}_{30} - \text{insulin}_0 / \text{glucose}_{30} - \text{glucose}_0$) and insulin sensitivity ($1/\text{fasting insulin}$) over time within each treatment group over 4 years of follow-up in the full (A), 4-year completer (B), and 4-year monotherapy failure (C) cohorts. The changes are plotted relative to the regression line of the baseline levels (the concave line). The dots represent the baseline measurements, that after 6 months and each annual assessment thereafter, and the arrow the directional change with time. The 95% confidence bands for the baseline relationship are illustrated. The SE limits for the individual time points have been omitted for clarity.

glucose level and the magnitude of this negative response. This is in line with a previous observation of ours demonstrating that these negative responses occur not only in subjects with diabetes but also in those with normal and impaired glucose tolerance (20). It is noteworthy that a negative first-phase insulin response to intravenous glucose has been observed in diabetic subjects with the greatest elevation in glucose (21), suggesting that, in this instance, it may be a manifestation of severely impaired β -cell function. Although further studies will be required to better understand whether there is a physiological explanation for an insulinogenic index ≤ 0 , we believe that for the purpose of estimating insulin release for large clinical studies, these responses are not likely to represent a major limitation and that the measure should be used.

Although the study cohort was broadly representative of patients with type 2 diabetes diagnosed within 3 years, they were selected to have a fasting glucose concentration between 7.0 and 10.0 mmol/L without medication. Thus, individuals who were more hyperglycemic or already required oral therapy would have been excluded. Furthermore, since ADOPT was initiated, there has been a move toward tighter glucose control. Despite this, we believe

that our findings regarding β -cell function and insulin sensitivity would have been similar if a fasting glucose < 10 mmol/L was used and would, thus, be applicable to therapy today. This belief is based on our observation that the monotherapy failure outcome was similar if we restricted the analysis to an outcome of a fasting glucose > 7.8 mmol/L in subjects who started below this threshold (4).

In summary, the different evolving relationships between β -cell function and insulin sensitivity observed over time explain the propensity to either maintain adequate glycemic control with the initial monotherapy or to fail. Differential changes in β -cell function and insulin sensitivity, i.e., in glucose metabolism, are responsible for the different degrees of glycemic durability observed with rosiglitazone, metformin, and glyburide in ADOPT, with rosiglitazone providing the most favorable changes in both parameters and greatest durability over time.

ACKNOWLEDGMENTS

The study was supported by GlaxoSmithKline. Academic members of the ADOPT Steering Committee have received honoraria, consulting fees, and/or grant/research support

from GlaxoSmithKline. R.P.A., G.P., and B.G.K. are employees of the company. No other potential conflicts of interest relevant to this article were reported.

S.E.K. researched data, contributed to the discussion, and wrote the manuscript. J.M.L. researched data, contributed to the discussion, and reviewed and edited the manuscript. B.Z., S.M.H., and R.P.A. contributed to the discussion and reviewed and edited the manuscript. G.P. researched data, contributed to the discussion, and reviewed and edited the manuscript. B.G.K., W.H.H., G.V., and R.R.H. contributed to the discussion and reviewed and edited the manuscript.

ADOPT was overseen by a steering committee (S.E.K., G.V. [co-chairs], S.M.H., W.H.H., R.R.H., Nigel Jones [GlaxoSmithKline], J.M.L., Colleen O'Neill [GlaxoSmithKline], and B.Z.), and day-to-day operations were conducted under the auspices of the ADOPT Study Team (B.G.K., Dahong Yu, Rosemary Fowler, Suzanne Evans, Darlene Steele-Norwood, Mark Heise, G.P., Karen Huckel, Josephine Koskinas, Andrea McClatchy, and Doreen Woodward). Without the effort of the study participants and study staff, these analyses would not have been possible.

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