

# Changes Over Time in Glycemic Control, Insulin Sensitivity, and $\beta$ -Cell Function in Response to Low-Dose Metformin and Thiazolidinedione Combination Therapy in Patients With Impaired Glucose Tolerance

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**OBJECTIVE**—In the Canadian Normoglycemia Outcome Evaluation (CANOE) trial, low-dose rosiglitazone/metformin reduced the risk of diabetes in subjects with impaired glucose tolerance by 66% over a median of 3.9 years. We evaluate the temporal changes in glycemic control, insulin sensitivity, and  $\beta$ -cell function during this trial.

**RESEARCH DESIGN AND METHODS**—CANOE participants ( $n = 207$ ) underwent annual oral glucose tolerance testing, enabling temporal comparison of glycemia, insulin sensitivity (Matsuda index), and  $\beta$ -cell function (insulin secretion-sensitivity index-2 [ISSI-2]) between the rosiglitazone/metformin and placebo arms.

**RESULTS**—Glycemic parameters and insulin sensitivity improved in the rosiglitazone/metformin arm in year 1, but deteriorated in the years thereafter as in the placebo arm. Generalized estimating equation analysis confirmed that both insulin sensitivity and  $\beta$ -cell function decreased over time (Matsuda:  $\beta = -0.0515$ ,  $P < 0.0001$ ; ISSI-2:  $\beta = -6.6507$ ,  $P < 0.0001$ ), with no significant time-by-treatment interaction (Matsuda:  $P = 0.57$ ; ISSI-2:  $P = 0.22$ ).

**CONCLUSIONS**—Despite preventing incident diabetes, low-dose rosiglitazone/metformin did not modify the natural history of worsening insulin resistance and  $\beta$ -cell dysfunction.

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Although lifestyle modification and antidiabetic medications can prevent the development of type 2 diabetes (T2D) in patients with impaired glucose tolerance (IGT) (1–7), the long-term durability of these interventions will likely depend on their capacity to modify the insulin resistance and  $\beta$ -cell dysfunction that is characteristic of T2D (8). The recently reported Canadian

Normoglycemia Outcome Evaluation (CANOE) trial was a double-blind, placebo-controlled trial in which low-dose rosiglitazone/metformin therapy was shown to reduce the risk of incident T2D in subjects with IGT by 66% over a median of 3.9 years (9). For insight on the disease-modifying capacity of this intervention, we conducted the current analysis to compare the temporal changes over

time in glycemic control, insulin sensitivity, and  $\beta$ -cell function between the study arms during this trial.

## RESEARCH DESIGN AND METHODS

Detailed descriptions of the CANOE protocol ([www.clinicaltrials.gov](http://www.clinicaltrials.gov): NCT00116922) have been reported (9,10). Briefly, 207 subjects with IGT were randomly assigned to either rosiglitazone/metformin 2/500 mg b.i.d. or identical placebo. All participants received a lifestyle intervention. The study was approved by the institutional research ethics boards, and all subjects provided written informed consent.

During the trial, participants underwent an annual 2-h, 75-g oral glucose tolerance test (OGTT), with sampling at 0, 30, and 120 min. Insulin sensitivity was evaluated with the Matsuda index, and  $\beta$ -cell function was assessed using the insulin secretion-sensitivity index-2 (ISSI-2), an OGTT-derived measure analogous to the disposition index obtained from the intravenous glucose tolerance test (11,12). The Matsuda index and ISSI-2 were calculated from the same OGTT, with formulae as previously described (9,11,12).

All analyses were conducted using SAS 9.2 (SAS Institute, Inc., Cary, NC). The patterns of change over time in glycemic measures, insulin sensitivity, and  $\beta$ -cell function are evaluated in Fig. 1. For each measure, generalized estimating equation (GEE) models were then constructed to assess for 1) a treatment effect of rosiglitazone/metformin versus placebo, 2) an effect of time on each response, and 3) a time-by-treatment interaction (indicating a significant difference between the treatment groups in the rate of change in response over time).

**RESULTS**—Detailed baseline and outcome results for the trial have been reported

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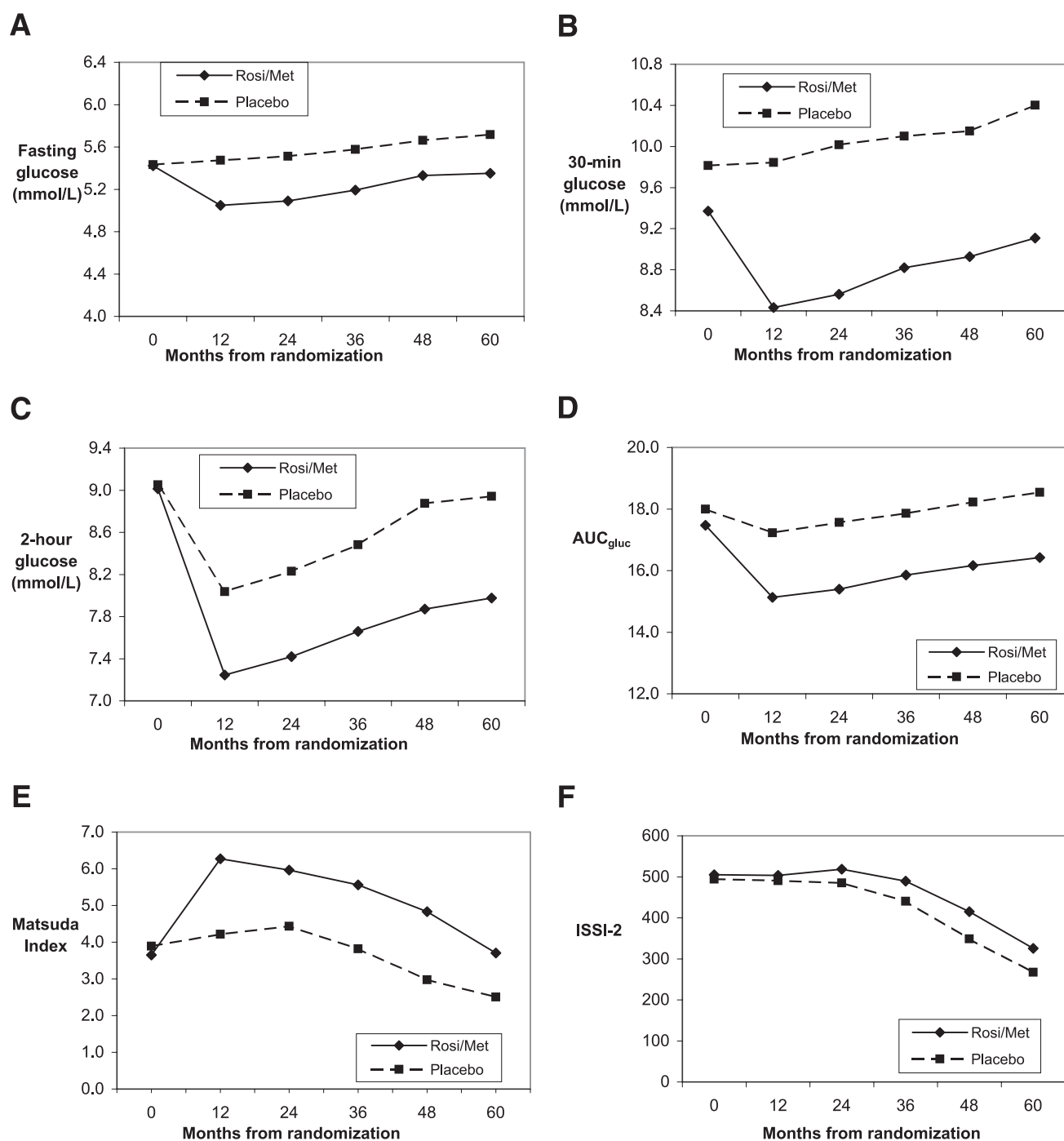
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**Figure 1**—Changes in mean levels of fasting glucose (A), 30-min glucose (B), 2-h glucose (C), AUC<sub>gluc</sub> (D), Matsuda index (E), and ISSI-2 (F) in the rosiglitazone/metformin and placebo arms over 60 months.

(9). At baseline, there were no significant differences between the placebo ( $n = 104$ ) and rosiglitazone/metformin ( $n = 103$ ) arms in age, sex, ethnicity, anthropometry, insulin sensitivity,  $\beta$ -cell function, and glucose homeostasis (Supplementary Table 1). As shown in Fig. 1A–D, all glycemic measures (fasting, 30-min, and 2-h glucose, and area under the glucose curve [AUC<sub>gluc</sub>]) decreased in the first year in

the rosiglitazone/metformin arm, whereas only 2-h glucose and AUC<sub>gluc</sub> declined over this time in the placebo arm (albeit to a lesser degree). Thereafter, from 12–60 months, however, both arms showed a strikingly similar profile of increasing glycemia with all four measures. Furthermore, this pattern of improvement in year 1 followed by subsequent worsening in the years thereafter mirrored that observed

for insulin sensitivity, because the Matsuda index initially increased to a greater extent in the active treatment arm than in the placebo group, before declining similarly in both groups over time (Fig. 1E). In contrast, both groups exhibited relative stability of  $\beta$ -cell function (ISSI-2) for the first 2 years, followed by progressive deterioration in the subsequent years (Fig. 1F). As previously reported, both study arms

showed similar patterns of change in BMI and waist circumference during the trial (9).

GEE analyses revealed that each glycaemic measure was increasing over time in the study population (fasting glucose:  $\beta = 0.0063$ ,  $P < 0.0001$ ; 30-min glucose:  $\beta = 0.0126$ ,  $P = 0.0004$ ; 2-h glucose:  $\beta = 0.0115$ ,  $P = 0.0116$ ;  $AUC_{gluc}$ :  $\beta = 0.0231$ ,  $P = 0.0002$ ). In each case, there was a significant treatment effect, such that the glycaemic measure was lower in the rosiglitazone/metformin arm during the trial (fasting glucose:  $\beta = -0.3234$ ,  $P < 0.0001$ ; 30-min glucose:  $\beta = -0.9025$ ,  $P < 0.0001$ ; 2-h glucose:  $\beta = -0.6402$ ,  $P = 0.0091$ ;  $AUC_{gluc}$ :  $\beta = -1.4141$ ,  $P < 0.0001$ ). There were no significant time-by-treatment interactions (data not shown). Insulin sensitivity and  $\beta$ -cell function also decreased significantly over time in both groups (Matsuda:  $\beta = -0.0515$ ,  $P < 0.0001$ ; ISSI-2:  $\beta = -6.6507$ ,  $P < 0.0001$ ). Again, a treatment effect was apparent because both measures were higher in the rosiglitazone/metformin arm during the trial (Matsuda:  $\beta = 1.8805$ ,  $P < 0.0001$ ; ISSI-2:  $\beta = 79.1788$ ,  $P < 0.0001$ ), but there was no significant time-by-treatment interaction (Matsuda:  $P = 0.57$ ; ISSI-2:  $P = 0.22$ ), indicating no differences between the groups in the rate of change over time.

**CONCLUSIONS**—This analysis shows that the glycaemic improvement in the rosiglitazone/metformin arm in year 1 was not sustained, with all glycaemic parameters worsening thereafter at a similar rate in both arms (Fig. 1A–D). It thus seems that the marked risk reduction for T2D was driven by the glucose-lowering effect of rosiglitazone/metformin in the first year. Indeed, this effect was of sufficient magnitude that it took 4 years for the 2-hour glucose level in the treatment arm to increase to the level seen in the placebo arm at the end of year 1. Overall, this pattern is suggestive of a delay in the development of T2D rather than a disease-modifying preventive effect, consistent with the findings of the Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up (DREAM On) study, which similarly suggested that full-dose rosiglitazone delayed diabetes rather than prevented it (13).

The current analysis further addresses the question of disease modification by considering the changes over time in insulin sensitivity and  $\beta$ -cell function during the trial. These changes (Fig. 1E–F) suggest that the initial glycaemic improvement in

the rosiglitazone/metformin arm was likely due to enhanced insulin sensitivity in year 1, rather than improved  $\beta$ -cell function. After year 1, though, insulin sensitivity declined at a similar rate in both arms. This waning insulin sensitization after the first year is similar to that which was observed with both metformin and lifestyle in the Diabetes Prevention Program (14). Most tellingly, the current GEE analyses confirmed that both insulin sensitivity and  $\beta$ -cell function declined during the CANOE trial, with no difference between the study arms in the rate of change over time for either measure. Taken together, these data suggest that low-dose rosiglitazone/metformin therapy had an early effect that decreased the subsequent development of diabetes during the trial but did not modify the natural history of worsening insulin resistance and  $\beta$ -cell dysfunction over time. As such, at the low doses from this trial, this combination therapy does not seem to have a long-term disease-modifying effect on the development of T2D in patients with IGT.

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R.R. designed the analysis plan, researched data, and wrote the article. Y.Q. performed the statistical analyses. S.B.H., A.J.H., and B.Z. were involved in the design and implementation of the CANOE trial. All authors reviewed and edited the article and contributed to discussion.

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