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

Ravi Retnakaran, md[1,2]
Ying Qi, msc[1]
Stewart B. Harris, md[3]
Anthony J. Hanley, phd[1,2,4]
Bernard Zinman, md[1,2,5]

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 β-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 β-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 β-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 β-cell dysfunction.

Diabetes Care 34:1601–1604, 2011

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 β-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 β-cell function between the study arms during this trial.

RESEARCH DESIGN AND METHODS

Detailed descriptions of the CANOE protocol (www.clinicaltrial.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 β-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 β-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

From the [1]Leadership Sinai Centre for Diabetes, Mount Sinai Hospital, Toronto, Canada; the [2]Division of Endocrinology, University of Toronto, Toronto, Canada; the [3]Centre for Studies in Family Medicine, University of Western Ontario, London, Ontario, Canada; the [4]Department of Nutritional Sciences, University of Toronto, Toronto, Canada; and the [5]Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada.
Corresponding author: Ravi Retnakaran, rretnakaran@mtsinai.on.ca.
Received 8 January 2011 and accepted 3 March 2011.
DOI: 10.2337/dc11-0046
This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc11-0046/-/DC1.

See accompanying editorial, p. 1678.

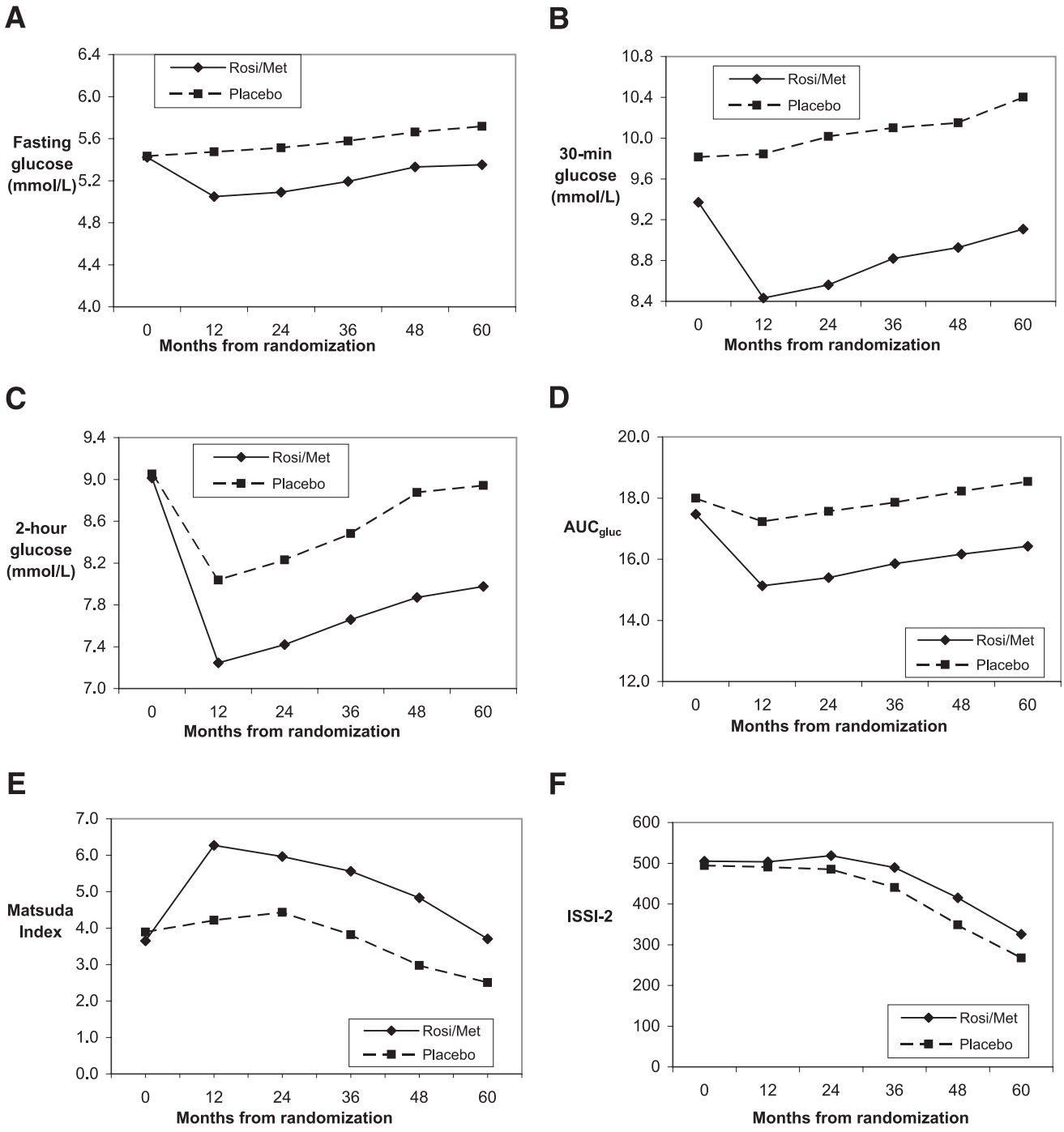

Figure 1—*Changes in mean levels of fasting glucose* (A)*, 30-min glucose* (B)*, 2-h glucose* (C)*, AUC_{gluc}* (D)*, Matsuda index* (E)*, and ISSI-2* (F) *in the rosiglitazone/metformin and placebo arms over 60 months.*

(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, β-cell function, and glucose homeostasis (Supplementary Table 1). As shown in Fig. 1*A–D*, all glycemic measures (fasting, 30-min, and 2-h glucose, and area under the glucose curve [AUC_{gluc}]) decreased in the first year in the rosiglitazone/metformin arm, whereas only 2-h glucose and AUC_{gluc} 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. 1*E*). In contrast, both groups exhibited relative stability of β-cell function (ISSI-2) for the first 2 years, followed by progressive deterioration in the subsequent years (Fig. 1*F*). 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 glycemic 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 glycemic 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 β-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 glycemic improvement in the rosiglitazone/metformin arm in year 1 was not sustained, with all glycemic parameters worsening thereafter at a similar rate in both arms (Fig. 1*A–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 β-cell function during the trial. These changes (Fig. 1*E–F*) suggest that the initial glycemic improvement in the rosiglitazone/metformin arm was likely due to enhanced insulin sensitivity in year 1, rather than improved β-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 β-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 β-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.

Acknowledgments—R.R. is supported by a Canadian Institutes of Health Research New Investigator Award and Canadian Diabetes Association Clinician-Scientist incentive funding. A.J.H. holds a tier two Canada Research Chair in Diabetes and Epidemiology. B.Z. holds the Sam and Judy Pencer Family Chair in Diabetes Research at Mount Sinai Hospital and University of Toronto. S.B.H. holds the Canadian Diabetes Association Chair in Diabetes Management and the Ian McWhinney Family Medicine Chair at the University of Western Ontario.

GlaxoSmithKline provided the study medication and funding for the CANOE trial but had no role in study design, data collection, data analysis, data interpretation, or article preparation. B.Z. has received consulting fees, honoraria, and grant support from GlaxoSmithKline. S.B.H. has received consulting fees, travel and lecture fees, and grant support from GlaxoSmithKline. No other potential conflicts of interest relevant to this article were reported.

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.

The authors thank the research staff at the study sites in Toronto (Jan Neuman, Stella Kink, and Annette Barnie) and London (Sheila Porter, Mario Bueno, and Susan Webster-Bogart).

Parts of this work were submitted for presentation at the 71st Scientific Sessions of the American Diabetes Association, San Diego, California, 24–28 June 2011.

References

1. Knowler WC, Barrett-Connor E, Fowler SE, et al.; Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393–403
2. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care 1997;20:537–544
3. Tuomilehto J, Lindström J, Eriksson JG, et al.; Finnish Diabetes Prevention Study Group. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. N Engl J Med 2001;344:1343–1350
4. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). Diabetologia 2006;49:289–297
5. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M; STOP-NIDDM Trail Research Group. Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. Lancet 2002;359:2072–2077
6. Gerstein HC, Yusuf S, Bosch J, et al.; DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators. Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. Lancet 2006;368:1096–1105
7. Buchanan TA, Xiang AH, Peters RK, et al. Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. Diabetes 2002;51:2796–2803
8. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003;46:3–19
9. Zinman B, Harris SB, Neuman J, et al. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomised controlled study. Lancet 2010;376:103–111
10. Zinman B, Harris SB, Gerstein HC, et al. Preventing type 2 diabetes using combination therapy: design and methods of the CAnadian Normoglycaemia Outcomes Evaluation (CANOE) trial. Diabetes Obes Metab 2006;8:531–537

11. Retnakaran R, Shen S, Hanley AJ, Vuksan V, Hamilton JK, Zinman B. Hyperbolic relationship between insulin secretion and sensitivity on oral glucose tolerance test. Obesity (Silver Spring) 2008;16:1901–1907
12. Retnakaran R, Qi Y, Goran MI, Hamilton JK. Evaluation of proposed oral disposition index measures in relation to the actual disposition index. Diabet Med 2009;26:1198–1203
13. DREAM On (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication Ongoing Follow-up) Investigators. Long-term effect of rosiglitazone and/or ramipril on the incidence of diabetes. Diabetologia 2011;54:487–495
14. Kitabchi AE, Temprosa M, Knowler WC, et al.; Diabetes Prevention Program Research Group. Role of insulin secretion and sensitivity in the evolution of type 2 diabetes in the diabetes prevention program: effects of lifestyle intervention and metformin. Diabetes 2005;54:2404–2414