Intensification of Type 2 Diabetes in Adolescents: Guess What? Exercise Wins!

Reviewed by Jeff Unger, MD

STUDY

TODAY Study Group: A clinical trial to maintain glycemic control in youth with type 2 diabetes. *N Engl J Med* 366:2247–2256, 2012

SUMMARY

Objective. Prompt identification and intensification of glycemic control for adolescents with type 2 diabetes will lower their glycemic burden, establish metabolic memory, and reduce their risk of developing long-term complications as adults.[1–3] This study evaluated the safety, efficacy, and durability of three different treatment protocols (metformin monotherapy, metformin plus rosiglitazone, and metformin plus lifestyle intervention) for young patients with type 2 diabetes who were randomized soon after being diagnosed. The primary objective of the study was to determine whether combination therapy initiated soon after diagnosis would maintain glycemic control better than metformin monotherapy.

Design and methods. The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study was a multicenter, randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases. The study's 699 patients with type 2 diabetes, aged 10–17 years, were initially treated with metformin, 1,000 mg twice daily (or 500 mg twice daily if 1,000 mg twice daily was not tolerated) until achieving an A1C ≤ 8% for a minimum of 2 months. Randomized patients' adherence was documented by pill count and study visit attendance for 6 weeks. The mean duration of type 2 diabetes in these patients was 7.8 months. Subjects were subsequently randomized to one of three treatment groups: *1*) continuation of metformin as monotherapy; *2*) metformin in combination with rosiglitazone, 4 mg twice daily; or *3*) metformin plus lifestyle intervention targeting weight reduction and increased physical activity.

The lifestyle program was designed to augment the pharmacological intervention by promoting moderate weight loss (7–10% of initial body weight or the equivalent for youth still growing in height). Primary behavior-change targets included energy balance behaviors (dietary and physical activity) and family involvement with support. Patients were provided with "Lifestyle Logs," which allowed them to graph weight and behavioral changes. Trained interventionists and behaviorists supervised the lifestyle cohort patients at each study site. The Goldfield and Epstein's Traffic Light Diet[4] targeted a calorie consumption to within 1,200–1,500 kcal/day.

The primary outcome measure was loss of glycemic control defined as a "glycated hemoglobin of ≥ 8% for 6 months or sustained metabolic decompensation requiring insulin." Participants were followed for an average of 3.86 years.

Results. Of the 699 patients, 319 (45.6%) reached the primary outcome, with a median time to treatment failure of 11.5 months (range < 1–66 months). Overall rates of failure were 51.7% (95% CI 45.3–58.2; 120 of 232 participants) with metformin alone; 38.6% (95% CI 32.4–44.9; 90 of 233 participants) with metformin plus rosiglitazone; and 46.6% (95% CI 40.2–53.0; 109 of 234 participants) with metformin plus lifestyle intervention. Metformin plus rosiglitazone was associated with a 25.3% decrease in the occurrence of the primary outcome compared to metformin alone ($P = 0.006$). The outcome with metformin plus lifestyle intervention was intermediate but did not differ significantly from the outcome with either metformin alone or metformin plus rosiglitazone. A secondary covariate analysis with adjustment for sex, race or ethnic group, baseline BMI, and baseline A1C did not modify the relationship between treatment group and primary outcome.

Weight changes among the cohorts differed significantly over a period of up to 60 months. If one were to consider a 7% weight reduction as being clinically significant, the metformin monotherapy and the metformin-plus-lifestyle groups had statistically similar success in achieving this secondary endpoint (24.3 and 31.2%, respectively). Only 16.7% of the metformin-plus-rosigli-

tazone patients were able to achieve similar weight reduction.

Race and sex differences were observed in the overall failure rates within the treatment groups. Metformin plus rosiglitazone was more effective in girls than in boys ($P = 0.03$). In addition, among girls, metformin plus rosiglitazone was more effective than metformin alone ($P = 0.002$) and metformin plus lifestyle intervention ($P = 0.006$), whereas in boys, metformin plus rosiglitazone was not more effective than either metformin alone or metformin plus lifestyle intervention. Overall failure rates among non-Hispanic blacks, Hispanics, and non-Hispanic whites were 52.8, 45.0, and 36.6%, respectively. The failure rate among Native Americans was 39.0%, although these participants were not included in the analysis by race or ethnic group because of their small numbers. Metformin alone was less effective in non-Hispanic blacks, with 66.2% reaching the primary outcome, than in either non-Hispanic whites (44.9%, $P = 0.01$) or Hispanics (44.0%, $P < 0.001$).

Adherence to the medication regimen before the primary outcome was reached or the study was completed ranged from 84% at month 8 to 57% at month 60 but did not differ significantly across treatments. The rate of attendance at lifestyle program visits during the first 24 months was 75.2%; 53.6% of participants met the preplanned target of attending ≥ 75% of visits during these 2 years. Differences in glycemic failure occurrences or changes in BMI were not affected by adherence.

Three study-specific serious adverse events were identified during this trial, including severe hypoglycemia (one in a metformin-monotherapy patient, one in a metformin-plus-rosiglitazone patient, and two in the metformin-plus-lifestyle group), diabetic ketoacidosis (five in the monotherapy group and three each in the other two cohorts), and lactic acidosis. The case of nonfatal transient lactic acidosis was observed in a participant in the metformin-monotherapy cohort who was hospitalized for an exacerbation of bronchial asthma. No deaths occurred.

Conclusions. In young patients (aged 10–17 years) with newly diagnosed type 2 diabetes, rates of drug failure were 51.7% for metformin monotherapy, 38.6% for metformin plus rosiglitazone, and 46.6% for metformin plus lifestyle intervention. Drug effectiveness varied according to race and sex. Monotherapy with metformin was associated with durable glycemic control in approximately half of the children and adolescents with type 2 diabetes. The addition of rosiglitazone, but not an intensive lifestyle intervention, yielded results that were superior to those of metformin alone.

COMMENTARY

How often do patients ask, "When are they going to come up with a cure for diabetes?" The answer should be addressed by informing the petitioner that one must clearly define the etiology of the disease state before one can develop an effective cure.

The TODAY study demonstrates how frustrating diabetes management is even within a well-controlled clinical trial setting designed to treat 699 newly diagnosed patients with type 2 diabetes. Despite having access to metformin as well as expert clinicians and educators, 52% of participants in TODAY progressed toward drug failure (A1C ≥ 8% for 6 months). Metformin plus lifestyle intervention did not significantly improve glycemic control more than metformin monotherapy and achieved transient weight loss in only 31% of patients. Although the addition of rosiglitazone to metformin slightly improved the durability of glycemic control, 39% of those patients still experienced treatment failure. More importantly, the recently published American Diabetes Association/European Association for the Study of Diabetes position statement on the management of hyperglycemia in type 2 diabetes no longer endorses the use of rosiglitazone because the drug is not widely available.[5]

Type 2 diabetes is a multifactorial disease. Both genetic and environmental factors contribute to its development and progression. Specific at-risk population groups have a high prevalence of type 2 diabetes, as do individuals with an afflicted first-degree relative. The most dominant determinant in the development of diabetes appears to be BMI.[6] Of the 699 participants in this study, 78.9% were overweight, based on their baseline BMI scores. In adults with prediabetes, weight reduction and increased physical activity has been demonstrated to improve insulin-mediated glucose disposal, reduce postprandial hyperglycemia, delay β-cell death, and slow progression toward clinical diabetes.[7,8]

The most comprehensive clinical trial that evaluated the importance of lifestyle modification as a deterrent to diabetes was the Diabetes Prevention Program (DPP).[9] This $174 million National Institutes of Health study enrolled 3,234 individuals with impaired glucose tolerance (IGT). Patients were randomly assigned to receive intensive lifestyle intervention or metformin at 27 U.S. centers. The lifestyle-intervention group participated in walking or other moderate-intensity exercise averaging 150 minutes per week. These subjects lost on average 5–7% of their initial body weight

while reducing their risk of diabetes progression by 58%.

Forty-five percent of the DPP subjects came from high-risk minority groups that have a disproportionate prevalence of type 2 diabetes (African Americans, Hispanics, Asian Americans, Pacific Islanders, and Native Americans). Other high-risk subjects in the DPP included patients > 60 years of age, women with a history of gestational diabetes, and individuals with a first-degree relative with type 2 diabetes.

Ten years after the initial randomization within the DPP, the modest weight loss within the metformin cohort was maintained. Diabetes incidence in the 10 years after DPP randomization was reduced by 34% in the lifestyle group and 18% in the metformin group compared to placebo. The DPP extension proves that the prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years.[10]

The most cost-effective and rational approach to diabetes management in adolescents may require targeting preventive care. Primary care providers should identify patients who are at highest risk for developing diabetes based on their race, activity level, BMI, family history, blood pressure, and lipid panel assessments. Prevention of diabetes progression must target restoration of normal glucose tolerance in any individual with impaired fasting glucose or IGT.

Weight reduction appears to be the most important component of intensive lifestyle modification that predicts regression from prediabetes to normal glucose regulation.[11] Every kilogram of weight lost can reduce the risk of clinical diabetes progression by 16%.[12] Intensive lifestyle intervention targeting weight reduction should be addressed urgently after patients are initially diagnosed with prediabetes.[11] The ultimate goal is to preserve and restore pancreatic β-cell function. Although lifestyle intervention might be useful in preventing or reducing diabetes risk, the adaptation of intensive interventional strategies may be expensive or unacceptable to certain ethnically, socially, and culturally diverse populations.

Certainly, one should not disregard the potential benefits of metformin as an effective restorative intervention for adolescents with type 2 diabetes. Freemark and Bursey[13] demonstrated that metformin improved both fasting glucose (reduced from a baseline of 84.9 to 75.1 mg/dl compared to an increase from 77.5 to 82.5 mg/dl with placebo) and fasting insulin levels in obese adolescents predisposed to type 2 diabetes during 6 months. Average BMI declined 1.3% from baseline, whereas the placebo group's average BMI increased 2.3% from baseline. Metformin also reduced serum leptin concentrations in girls in this trial, suggesting a reduction in fat mass and overall improvement in insulin resistance.

The TODAY study began enrollment in 2004, before U.S. Food and Drug Administration approval of dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. GLP-1 receptor agonists are indicated as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes, but not in patients < 18 years of age. A single pharmacokinetic and safety study has been published using single doses of exenatide, 2.5 and 5.0 μg, in 13 adolescents aged 10–16 years with type 2 diabetes and a baseline A1C of 8.2%.[14] As expected, postprandial glucose and glucagon concentrations were normalized, and no hypoglycemic events were noted. To date, no studies of the safety or efficacy of liraglutide use in pediatrics have been published. The safety and efficacy of DPP-4 inhibitors and pramlintide have not been evaluated in patients < 18 years of age.

Given the ability of these drugs to reduce A1C by 0.5–1.5 percentage points in adults with little risk of hypoglycemia or weight gain, safety and efficacy trials in select pediatric subgroups might be warranted. The newer agents may be effective at restoring and maintaining β-cell function over time when initiated shortly after type 2 diabetes diagnosis.

Another crucial point identified by the TODAY study is the collective failure of adolescents to adhere to a lifestyle that encourages consumption of healthful foods and active participation in physical activity. More tweens and teens would rather text their friends than participate in mixed martial arts, volleyball, or dance. An active lifestyle becomes even less attractive for those who are overweight or obese and may be subject to disparaging remarks from their peers.

Fifty years ago, children lived in a society that provided fewer calories, included more physical activity, and offered fewer technological distractions. Hopes for a "nanny state" led by government agencies that swoop into school districts and restrict bake sales are more likely to make our communities mean than lean, however. Unless individual families begin working together to identify potential customized risk factors that may affect their long-term health outcomes, the diabetes epidemic likely has just begun.

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