Treatment options for type 2 diabetes in adolescents and youth: a study of the comparative efficacy of metformin alone or in combination with rosiglitazone or lifestyle intervention in adolescents with type 2 diabetes

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Abstract

Despite the increased prevalence of type 2 diabetes mellitus (T2DM) in the pediatric population, there is limited information about the relative effectiveness of treatment approaches. This article describes the rationale and design of a National Institutes of Health-sponsored multi-site, randomized, parallel group clinical trial designed to test the hypothesis that aggressive reduction in insulin resistance early in the course of T2DM is beneficial for prolongation of glycemic control, as well as improvement in associated abnormalities and risk factors. Specifically, the trial compares treatment with metformin with two alternate approaches, one pharmacologic (combining metformin treatment with rosiglitazone) and one combining metformin with an intensive lifestyle intervention program. The in Adolescents and Youth (TODAY) study recruits 800 patients over a 4-yr period and follows them for a minimum of 2 yr and maximum of 6 yr. Patients are 10–17 yr of age, within 2 yr of diagnosis of diabetes at the time of randomization, lack evidence of autoimmunity, and have sustained C-peptide secretion. The primary outcome is time to loss of glycemic control, defined as a hemoglobin A1c >8% for 6 consecutive months. Secondary outcomes include the effect of the alternative treatments on insulin secretion and resistance, body composition, nutrition, physical activity and fitness, cardiovascular risk monitoring, microvascular complications, quality of life, depression, eating pathology, and resource utilization. TODAY is the first large-scale, systematic study of treatment effectiveness for T2DM in youth. When successfully completed, this study will provide critical new information regarding the natural history of T2DM in youth, the benefits of initiating early aggressive treatment in these patients, and the efficacy of delivering an intensive and sustained lifestyle intervention to children with T2DM.

Keywords

Obesity has dramatically increased in prevalence world-wide among children and adolescents, accompanied by the appearance and increasing prevalence of type 2 diabetes mellitus (T2DM). Before the 1990s, it was rare for most pediatric centers to have patients with T2DM. However, by 1994, T2DM patients represented up to 16% of new cases of childhood diabetes in urban diabetes centers (1), and by 1999, depending on geographic location, T2DM accounted for 8–45% of new cases of childhood diabetes, with disproportionate prevalence among minority populations (2,3). Indeed, over the past decade, the increase of T2DM among children and adolescents has been labeled an 'epidemic' (4).

Despite this increased prevalence and the potential short- and long-term risks associated with early onset of T2DM, the most effective approaches to treat youth with T2DM are not known and pediatric diabetologists have had to rely on treatment paradigms derived from research and experience in the care of adults. However, youth with T2DM differ in ways that may have an impact on potential treatment. First, as the environment and care of children with T2DM are highly influenced by parent attitudes, beliefs, and actions, treatment requires a family-centered approach not typical of studies of T2DM in adults. Moreover, the psychological and emotional turmoil and changing family interactions that normally occur during adolescence, as well as the adverse socio-economic conditions frequent in this population, may make achievement of stringent treatment goals especially difficult (5,6). Furthermore, while lifestyle interventions directed at reversing markedly sedentary behaviors and deleterious dietary habits are widely thought to be an important part of therapy for T2DM, the ability to deliver such an intervention to a population of adolescents has never been demonstrated. In addition, the waning efficacy of oral hypoglycemic agents is a concern for youth, given the expected long duration of the condition. The young age at onset and increased risk for later cardiovascular complications heighten the urgency to not only achieve but also sustain optimal metabolic

control of diabetes. Finally, the potential for differential efficacy and/or adverse effects of diabetes treatments in youth require specific assessment in this target population.

This article describes the rationale and design of a National Institutes of Health (NIH)-sponsored multi-site trial designed to test the hypothesis that an aggressive approach of reducing insulin resistance early in the course of T2DM is beneficial for prolongation of glycemic control, as well as improvement in associated abnormalities and risk factors. Specifically, the trial compares treatment with metformin, the most commonly used agent for the treatment of T2DM in youth (7,8), with two alternate approaches providing additional reduction in insulin resistance, one pharmacologic (combining metformin treatment with rosiglitazone) and one combining metformin with an intensive lifestyle intervention program.

Research design and methods

Study design

Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) is a randomized parallel-group trial consisting of a screening visit, a 2- to 6-month single-blind run-in period, and a treatment period of up to 5 yr (Fig. 1). Participants meeting eligibility criteria at the end of run-in are randomized 1:1:1 to (i) metformin alone, (ii) metformin plus rosiglitazone, or (iii) metformin plus an intensive lifestyle intervention called the TODAY Lifestyle Program (TLP). TODAY intends to recruit 800 patients over a 4-yr period and follow patients for a minimum of 2 yr and maximum of 6 yr.

Primary outcome

The primary outcome of TODAY is the time to treatment failure, defined in one of two following ways: (i) all regularly scheduled hemoglobin A1c (HbA1c) values ≥8% over a 6-month period or (ii) the inability to wean from temporary insulin therapy within 3 months following acute metabolic decompensation.

Study population

Eligibility criteria include the following: (i) age10–17 yr inclusive; (ii) diagnosis of T2DM by standard laboratory criteria (9) for less than 2 yr by the time of randomization – for asymptomatic patients with a normal fasting glucose but elevated 2-h glucose during an oral glucose tolerance test (OGTT), HbA1c must be ≥6%, and subjects being treated with diabetes medication for whom diagnostic serum glucose documentation is not available are eligible if HbA1c was ≥8% at the time of diagnosis; (iii) body mass index (BMI) ≥85th percentile; (iv) fasting C-peptide at screening >0.6 ng/mL and absence of pancreatic autoimmunity (both GAD and ICA512); (v) a family member or adult closely involved in the daily activities of the child must consent to participate in the child's treatment [family support person (FSP)] – the inclusion of a parent or caregiver has been shown to be important to the success of lifestyle change (10), particularly in ethnic minority groups (11), and in addition, parental weight change is associated with child weight change (12); and (vi) fluency in English or Spanish due to the intensive personal interactions required for the run-in and lifestyle intervention.

Exclusion criteria are any of the following: creatinine clearance < 70 mL/min; any hepatic transaminase > 2.5 the upper limit of normal; diabetic ketoacidosis at any time after diagnosis, except for a single episode related to a significant medical illness; use of inhaled glucocorticoids at dose above 1000 µg of daily fluticasone equivalent; oral glucocorticoids within the last 60 d or more than 20 d during the past year; use of medication(s) known to affect insulin sensitivity or secretion within the last 30 d, medication(s) known to cause weight gain within the last 30 d, anabolic steroids within the past 60 d, weight loss medication(s) within the last 30 d, or medication(s) known to affect the metabolism of study drug; participation in a formal weight

loss program; participation in another interventional research study protocol in the past 30 d; abnormal reticulocyte count or HbA1c chromatogram indicating abnormal hemoglobin variants other than heterozygosity for S and C; genetic syndrome or disorder known to affect glucose; inability of either participant or family member to comprehend the lowest grade level at which lifestyle intervention materials are prepared; women who are pregnant, planning to become pregnant within 2 yr of enrollment, or who admit sexual activity without appropriate contraception; physical limitations preventing patient from being randomized to the lifestyle intervention; or other significant organ system illness or condition (including psychiatric or developmental disorder) that, in the opinion of the investigator, would prevent full participation.

In addition, patients are excluded from randomization if systolic blood pressure is ≥150 mmHg or diastolic blood pressure is ≥95 mmHg, despite appropriate medical therapy; total cholesterol >300 mg/dL, low density lipoprotein (LDL) > 190 mg/dL or triglycerides .800 mg/dL, despite appropriate medical therapy; hematocrit <30% or hemoglobin ,10 gm/dL, despite appropriate medical therapy; inability to demonstrate mastery of standard diabetes education (SDE) program during run-in; or an episode of diabetic ketoacidosis during run-in.

Treatment

Run-In—The run-in period has the following multiple goals: (i) provide uniform and high-quality SDE to all patients and their family members; (ii) titrate the dose of metformin (single-blind) as tolerated to a target dose of 1000 mg twice a day, with a minimum dose for randomization of 500 mg twice a day; (iii) discontinue all other diabetes medications; and (iv) document adherence to medication by pill count and study visit attendance. To proceed to randomization, patients must demonstrate 80% medication adherence for 6 wk, with no more than two missed study visits. They must also maintain an HbA1c ≤ 8% for a minimum of 2 months on metformin alone. Participants have a maximum of 6 months to complete all run-in goals prior to randomization. Standard diabetes education.

All eligible consenting participants receive SDE delivered by the TODAY certified diabetes educator. SDE was designed by TODAY investigators to provide participants and their family member with the knowledge, skills, and behaviors required for the successful management of T2DM and the ability to follow treatment guidelines in each of the treatment arms. Major topics include diabetes pathophysiology, medication action, nutrition and weight management, physical activity, diabetes self-care, and goal setting. SDE materials are provided in an easy-to-read, youth friendly, and culturally appropriate workbook format and delivered at a minimum of four sessions, each lasting 60–90 min. Both the youth and family member must demonstrate 80% mastery of the material on testing. After randomization, follow-up education is provided at each medical visit, based on the needs of the participants as they arise. Pharmacologic therapy.

Metformin is used in all treatment arms, and the standard treatment group receives metformin alone. The goal is to treat all participants with 1000 mg metformin twice a day, and participants are required to tolerate a minimum of 500 mg twice a day to be eligible for randomization. During run-in, metforminaive participants and participants treated with submaximal doses of metformin have metformin initiated and/or adjusted over 1–4 wk as tolerated. As all patients take two capsules (consisting of metformin and placebo or metformin and rosiglitazone) twice daily after randomization, patients also take two capsules (a combination of capsules containing metformin or placebo) twice daily during the run-in period and are masked to the metformin dose. The doses of insulin and/or other hypoglycemic agents are reduced with the goal of achieving HbA1c < 8% and no ketonuria for a minimum of 2 months on treatment with maximally tolerated doses of metformin alone.

Randomization—Both the investigators and the patients are masked to the pharmacologic treatment group. All patients receive two capsules twice a day containing an appropriate dose of metformin (provided by GlaxoSmithKline, Research Triangle Park, NC, USA) combined with either placebo or rosiglitazone (provided by GlaxoSmithKline) supplied by the Drug Distribution Center in a blister pack. All patients remain throughout the study on the maximum tolerated dose of metformin achieved during run-in. Patients randomized to the metformin plus rosiglitazone arm are started on a dose of 2 mg rosiglitazone twice a day, which is increased after 8 wk to 4 mg twice a day.

The TLP is a family-based, behavioral weight loss program with a sustained weight loss goal of 7–10% of initial body weight (13–16). The TLP is standardized but tailored to the developmental stage of the youth (17).

TLP is delivered by an interventionist referred to as the personal activity and nutrition leader (PAL) and consists of three phases of contact between: weekly inperson contact for the first 6 months, biweekly inperson visits alternating with phone contact for the next 6 months, and one monthly in-person contact and one monthly phone contact for the remainder of the participant's involvement in TODAY (16,18). Each TLP visit lasts 45–60 min and includes a combination of the PAL meeting separately and together with the youth and the youth's FSP.

The key components of the TLP include psycho-education, along with dietary, physical activity, and behavior modifications. Concepts and skills previously shown to promote weight loss in youth and adapted for obese youth with T2DM are included in the psychoeducation component (14,19). The dietary component (the traffic light eating plan) was adapted from The Traffic Light Diet (20,21) and the Diabetes Food Guide Pyramid. Foods are divided into the colors of the traffic light; participants decrease the number of servings of red foods (foods that are high in fat and/or sugar) and choose healthy foods based on individual, family, and cultural preferences. Individualized calorie intake recommendations are also made to facilitate weight loss and typically range between 1200 and 1500 calories (22,23). Once initial weight loss goals are achieved, the recommended caloric intake is gradually increased to allow for energy balance.

Two goals of 200 or 300 min per week of moderate-intensity physical activity are used depending on the initial fitness of the subject (24). Increased time spent in preferred physical activities and the gradual introduction of new forms of activity are encouraged, along with a decrease in the amount of time spent in sedentary activities (25) and increased involvement in lifestyle activities. Pedometers are used to help participants estimate and increase their lifestyle activities (24).

Self-monitoring, goal setting, behavioral skills training, and stimulus control have been used in previously successful pediatric weight loss interventions (26). PALs encourage FSPs to actively model healthy eating and physical activity and to restructure the home environment. Positive parenting or behavior change techniques are taught to FSPs, such as the use of praise and a family-based reward system (14). Initially, PALs model the use of contingent reinforcement by directly rewarding achievement of goals by the youth. Participants then transition to a system in which points received for achieving behavior change goals can be exchanged for family-based rewards.

Management of comorbid conditions—Treatment of dyslipidemia, hypertension, and microalbuminuria follow specified treatment algorithms (see www.todaystudy.org). An independent medical consultant reviews lipid, blood pressure, and urine results to assure that treatment goals are met according to the treatment algorithms and provides additional treatment recommendations for individual patients.

Treatment with insulin—When the patient reaches the defined 'primary treatment failure' (see Primary Outcomes below), treatment with insulin is instituted as add-on therapy, in combination with the subject's assigned oral agent(s). In the metformin plus rosiglitazone group, the rosiglitazone dose is lowered to 2 mg twice daily by the central pharmacy. The patients and clinicians remain masked to the original treatment assignment but are unmasked to HbA1c. Initial insulin treatment is 0.2 U/kg glargine insulin each evening, which is increased up to 1.0 U/kg/d (maximum 100 U) until fasting blood glucose values between 70 and 150 mg/dL are achieved. If treatment goals are not achieved with glargine insulin alone, other insulins are used at the clinician's discretion.

Patients may require temporary use of insulin due to hospitalization, intercurrent illness, or conditions leading to metabolic decompensation. In these circumstances, any type or dose of insulin can be used at the discretion of the treatment team. However, acute insulin therapy is weaned within 2–4 wk, and the inability to discontinue insulin within 3 months without decompensation (ketonuria and symptomatic hyperglycemia) is also defined as a 'primary treatment failure'.

Schedule of medical care and research visits (Table 1)

Participants have a medical visit every 2 months in the first year and every 3 months thereafter. Height, weight, blood pressure, Tanner stage, and degree of acanthosis nigricans are recorded. HbA1c and safety monitoring laboratory samples are obtained, and details of all adverse events are documented. Glucose meter memories are downloaded, and adherence estimated with pill counts. More extensive physiologic data are obtained at research visits, termed SuperVisits, which occur at randomization, 6 months, annually, 'primary treatment failure', and the end of study (Table 1). For SuperVisits, patients are studied following a 10- to 14-h fast and are asked to abstain from moderate to vigorous physical activity for 48 h.

Secondary outcomes

Insulin sensitivity and secretion—At SuperVisits, fasting laboratory samples are obtained followed by a standard 75-g OGTT, with glucose, insulin, and c-peptide samples collected every 30 min for 2 h. Insulin sensitivity and secretion are determined based on fasting glucose, insulin, C-peptide, and proinsulin levels, OGTT, homeostasis model assessment (HOMA), and quantitative insulin-sensitivity check index (QUICKI). HOMA-R (resistance) and B (secretion) are calculated using a computer-based model solution (27,28). QUICKI is calculated as $1/(\log[I_0] \; 1 \log [G_0])$ (29).

Body composition—Overweight status is assessed by standardized anthropometric measurements (height, weight, and BMI), as well as waist circumference and abdominal height measured laterally with the patient supine (30). Percent body fat is measured by dual-energy X-ray absorptiometry (DXA). Biological parent height and weight are collected at randomization. FSP weight and height are collected by direct measurement or self-report at randomization and at 2 yr.

Nutrition—Routine dietary habits and nutrient intake are evaluated by use of a food frequency questionnaire (FFQ) (31) that is interview administered and captures the last week of dietary intake.

Physical activity and physical fitness—Routine physical activity is assessed by use of the previous day physical activity recall (PDPAR), a questionnaire that assesses the previous day's activities and their relative intensities for the after school hours (32). However, as lower intensity activities are harder to recall than higher intensity activities, the Computer Science Application (CSA) accelerometer is used to assess patterns of physical activity (33).

Participants wear the accelerometer for 7 d and complete a diary of activities on the days that the monitor is worn.

The most popular methodologies to predict maximal oxygen uptake (VO_2 max) in children utilize cycle ergometry to determine the physical work capacity (PWC) (34). In TODAY, participants undergo PWC 170 testing at SuperVisits. This test effectively predicts VO_2 max in obese children and involves obtaining heart rates at three submaximal workloads, plotting these heart rates against the workload, extrapolating to determine the workload at a given heart rate or at maximal heart rate, and then converting that maximal workload to oxygen uptake.

Cardiovascular risk factors—Fasting blood samples are obtained for measurement of free fatty acids, lipoprotein subclass levels, average LDL particle density, total apolipoprotein B (ApoB), fibrinogen, highly sensitive c-reactive protein, plasminogen activator inhibitor (PAI)-1, homocysteine, vitamin B12, and interleukin-6.

Blood glucose monitoring—Participants are instructed to obtain blood glucose meter readings two times per day – in the morning on awakening (fasting) and at one additional time (e.g., before dinner, lunch, or 2 h after dinner) each day. At all clinic visits, meters are downloaded, and the number of tests performed per day, as well as the 14-d and 30-d average glucose levels, are recorded.

Microvascular complications—Spot urine measurement of microalbumin/creatinine ratio is obtained at randomization and annual visits. Abnormal values (>30 mg/mg creatinine) are confirmed with two additional spot urine samples within 3 months; diagnosis of microalbuminuria is made when there are two out of three positive tests. Estimated creatinine clearance is calculated at randomization and annual visits. The presence of peripheral neuropathy is evaluated using the Michigan Neuropathy Screening Instrument (35) annually. Identification and monitoring for retinopathy are not undertaken as a primary component of TODAY. It is expected that patients will receive retinopathy screening according to American Diabetes Association clinical practice guidelines and reports of retinal screenings are recorded.

Quality of life and psychological measures—Emotional status and quality of life are assessed by the Children's Depression Inventory (up to age 16 yr) (36–40), the Beck Depression Inventory (BDI) (beginning at age 16 yr) (41–44), the Eating Disorders Examination Questionnaire (EDEQ), the Questionnaire on Eating and Weight Pattern – Revised (QEWP-R) (if indicated by the score on the EDEQ) (45). The Pediatric Quality of Life (PedsQL) (46) is used to evaluate health-related quality of life. The biological parent (where available) completes the BDI, EDEQ, and QEWP-R (only if indicated by the score on the EDEQ) at randomization. The FSP completes the BDI, EDEQ, QEWP-R (if indicated by the score on the EDEQ), PedsQL (adult proxy) and the Child Health Questionnaire (P28) at randomization and 2 yr.

Resource utilization and costs—Resource utilization for each of the treatment arms is assessed throughout the trial and considers the intensity of services used in providing care and assuring adherence to each treatment regimen. The frequency of contact with physicians, nurse educators, psychological support staff, dietitians, and the use of drugs, equipment, and supplies are captured through study forms. Information on the time spent by health professionals in treatment provision is obtained through surveys completed periodically by the providers. School absenteeism, work absenteeism (in children and adults), and the time spent in treatment activities by children and caregivers are measured utilizing previously validated questions, as well as academic and employment participation rates and progress. Measurement of quality-adjusted life years is obtained through the Health Utilities Index-2 (47), which provides a preference- based measure of quality of life.

Safety parameters—Data are collected regarding abnormalities in laboratory tests (hemoglobin/hematocrit, liver function tests, and calculated creatinine clearance), episodes of severe hypoglycemia, and incidence of side effects (e.g., gastrointestinal complaints, edema, and weight gain).

Laboratory methods

Samples are processed following standardized procedures and shipped on dry ice to the Northwest Lipid Metabolism and Diabetes Research Laboratories, University of Washington, Seattle, which serves as the Central Biochemistry Laboratory for the study. Details of the assays used are provided at www.todaystudy.org.

Statistical methods

The principal analyses of primary and secondary outcomes employ the 'intent-to-treat' approach (48). The intent-to-treat analyses include all randomized patients, with all participants included in their randomly assigned treatment group; treatment group assignment is not altered based on the adherence to the assigned treatment regimen. All statistical tests are two sided, with the overall significance level of the primary outcome $\alpha = 0.05$. The primary outcome analysis of time to treatment failure uses life-table methodology. Separate product-limit life-table estimated cumulative incidence curves are calculated for each treatment group, and the groups are compared using a log-rank test (49).

The study is powered to allow all three possible comparisons between the treatment groups while maintaining the overall significance level at 0.05. If 10% of the metformin group has an HbA1c above the threshold, 250 participants per arm provides at least 90% power to detect a 50% reduction in the treatment failure rates in at least one combination therapy group (i.e., 5% with HbA1c above threshold during a 6-month period). If 20% of the metformin group has an HbA1c above the threshold, 250 participants per treatment arm provides at least 90% power to detect a 40% reduction in hazard rates in at least one of the combination therapy groups (i.e., 12% failing during a 6-month period). Sample size is adjusted for a 10% lost to dropout rate in each 6-month period.

Structure of the study group

The TODAY study group operates under the Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D) cooperative agreement mechanism funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The group is composed of 13 clinical centers, a coordinating center, the project office, and central cores and laboratories. The protocol has been approved by the Institutional Review Board of each participating center. All participants provide written informed consent/assent according to the policies of each local center. A Data Safety Monitoring Board acts as an independent arbiter of study progress and patient safety.

Discussion

There have been no previous large-scale randomized intervention trials examining T2DM in youth. Although rising in prevalence, T2DM remains a relatively uncommon disorder in the pediatric population, and no single center has been able to identify sufficient eligible patients to complete meaningful studies independently. Therefore, the identification and funding of a consortium of centers to develop and undertake these studies represents a significant advance and a potential model for the development of consortia for the examination of other pediatric disorders.

In developing this protocol, the study group was confronted with a large number of unanswered questions. After wide-ranging discussion, investigators agreed that the most pressing issues related to the recognition that these young people can be expected to have a long duration of disease and that the insulin resistance characteristic of puberty provides an additional, although potentially transient, burden. In particular, investigators were interested in determining whether more aggressive therapy aimed at decreasing insulin resistance in adolescents would improve both glycemia and associated abnormalities relative to standard therapy and leads to improved metabolic state when the insulin resistance of puberty has waned. Therefore, TODAY was designed to focus on these primary issues while taking into account the psychosocial and familial characteristics unique to adolescents with T2DM.

Choice of primary outcome

The primary outcome of this study is defined in terms of HbA1c because this measure provides the best index of glycemic control and because previous large-scale studies have established it as a surrogate marker of long-term diabetic complications (50). Given the results of the Diabetes Control and Complications Trial (51), it is no longer acceptable to maintain fixed treatment regimens in the face of chronic elevations in HbA1c levels, and current treatment guidelines in adults with T2DM mandate add-on therapy with insulin or another oral agent if target HbA1c levels are not being met. Consequently, the primary outcome was chosen as the time to treatment failure (i.e., the need for add-on insulin therapy) rather than differences in HbA1c levels between the treatment groups over time. While the treatment target is an HbA1c of 6% or below, it was the consensus of the Study Group that a sustained HbA1c value of 8.0% or greater was a reasonable definition of treatment failure in this population. Acute management of patients with metabolic decompensation utilizes insulin treatment. However, if insulin treatment cannot be withdrawn after 3 months, this is also considered a treatment failure.

Choice of treatment arms

Many youth with T2DM present with marked hyperglycemia, with or without ketoacidosis, and require insulin to correct metabolic status. Nevertheless, following an initial period of insulin therapy, most of these youngsters, as well as those who are diagnosed at an earlier stage of T2DM, are able to achieve satisfactory glycemic control when treated with metformin alone. Metformin remains the most common monotherapy for T2DM in youth in North America (7, 8). Furthermore, metformin was the only oral hypoglycemic agent approved for use in children at the time of study design and has the added advantage of being associated with either weight loss or reduced weight gain in comparison to insulin, sulfonylureas or thiazolidinediones (TZDs). Thus, monotherapy with metformin was chosen as the 'standard treatment' against which other combination therapies would be compared in this trial.

Both metformin and TZDs improve glycemic control but by different mechanisms of action. Therefore, addition of a TZD to metformin offered the potential for additional reduction in insulin resistance relative to standard therapy. A further theoretical advantage in using a TZD as a therapeutic agent in T2DM is the potential that these agents will preserve pancreatic insulin secretion [Diabetes Prevention Program (DPP) and The Troglitazone in Prevention of Diabetes Study] (52–55). Preservation of beta-cell function is a critical aspect of long-term diabetes control, as retention of the ability to compensate for insulin resistance by producing adequate amounts of insulin is important for prevention of hyperglycemia.

Other combinations of drugs were considered but not selected by the Study Group because the estimated number of patients available for recruitment would not support a trial with more than three arms and because there was strong support for inclusion of an intensive lifestyle intervention group. Virtually all youth with T2DM are overweight as a result of the interplay between genetic factors, excess energy intake from high fat, high calorie, low nutrient diets,

and sedentary behaviors with too much time spent watching TV and playing video games (56–59). Adding a third treatment group that combined an intensive lifestyle intervention with metformin was especially attractive because it provided a non-pharmacologic approach to improving insulin sensitivity, physical fitness, and body composition. Moreover, in a number of studies in adults, weight loss associated with improvements in eating behavior, diet, and physical activity has been shown to result in significant reductions in fasting plasma glucose and insulin levels, hepatic glucose output, peripheral insulin resistance, hypertension, and dyslipidemia (60–64). Three uncontrolled trials in adults with T2DM treated with oral agents have shown the benefit of weight loss associated with lifestyle modification on reducing mortality (63,65,66). As the epidemic of T2DM in children and youth is relatively recent, there is little controlled evidence regarding the use of lifestyle modification to improve insulin sensitivity and glycemic control, to induce weight loss, or affect other outcome measures, such as dyslipidemia and hypertension, in pediatric patients with T2DM.

Secondary outcomes

In designing the study, the TODAY Study Group faced a dilemma. On one hand, the study provides a unique opportunity to learn more about the pathophysiology, natural history, and psychosocial impact of T2DM in youth. On the other hand, the burdens of completing secondary outcome assessments could adversely affect patient recruitment and retention. The measures selected provide insight into the mechanism by which the treatment regimens affect durable glycemic control (e.g., effects on insulin resistance, sensitivity, diet, and physical fitness) and provide information concerning the differential risks and benefits of the three treatment arms (e.g., studies of microvascular complications and cardiovascular risk).

Insulin resistance—The efficacy and durability of the successful treatment of T2DM in adults are determined to a great extent by the ability to ameliorate insulin resistance. Yet, little is currently known about how successful drug and lifestyle approaches will be in improving insulin sensitivity in children and youth. In particular, significant questions remain about the impact of pubertal progression on insulin resistance and how changes in insulin sensitivity affect beta-cell function in pediatric patients with T2DM. Therefore, an important component of TODAY is to determine (i) the influence of baseline insulin sensitivity and secretion on the response to therapy and (ii) the effect of each therapy on the progression of changes in insulin sensitivity and secretion.

The glucose clamp technique and the frequently sampled intravenous glucose tolerance test with minimal model analysis are considered the 'gold standard' for determination of insulin sensitivity and secretion. However, these are labor intensive, time-consuming, and costly procedures that are not easily implemented in large clinical trials. A number of simpler methods have been developed that are preferable in the context of large clinical trials such as TODAY. The OGTT, HOMA, QUICKI are used to compare insulin secretion and sensitivity among the three treatment groups. Use of these multiple measures helps compensate for not using the 'gold standard' measures as listed above. Values of glucose and insulin/C-peptide derived from the OGTT, when combined with anthropometric parameters, can predict insulin sensitivity and secretion indices derived from clamp measurements with reasonable accuracy (67–69). The first-phase insulin secretion is estimated with the insulinogenic index (28). The indices, based on fasting measurement of glucose and glucose-regulating hormones such as insulin (including C-peptide) and proinsulin, have also been proven to closely correlate with corresponding clamp-derived indices of insulin sensitivity and secretion in diverse pediatric populations (28,29,69–71).

Body composition—The development of insulin resistance during puberty is most closely correlated to fat mass, independent of insulin, sex steroids, leptin, or insulin-like growth

factor-1 (IGF-1) status (72). Weight loss in overweight adolescents improves both insulin sensitivity (73) and blood pressure (74). However, there are scarce data describing the effects of weight loss on these parameters in children or adolescents with diabetes. Therefore, TODAY will investigate how changes in adiposity relate to glycemic control, insulin sensitivity, cardiovascular risk factors, and blood pressure in children and adolescents with T2DM.

A cross-calibration study of different body composition techniques versus DXA in children has shown that skinfold thickness measurements, bioelectrical impedance, and various combinations of anthropometric measures are highly inaccurate when compared with DXA (75). DXA is also easy to perform and provides minimal radiation exposure. Therefore, DXA was selected as the measure of adiposity. Use of magnetic resonance imaging to assess differential subcutaneous and visceral fat partitioning was considered but felt to be too burdensome and expensive for use in this large cohort.

Nutrition/diet—Diet change has been correlated with a decrease in diabetes risk, as well as weight loss, in a number of prevention and intervention studies, including the DPP (76). Therefore, evaluation of baseline diet characteristics, as well as the effect of treatment interventions on dietary change in participants, will allow us to evaluate the impact of the lifestyle intervention on eating behaviors within this treatment group and in comparison with the other two treatment groups. In addition, dietary assessment over the duration of the trial provides insight into which components of the intervention lead to the most significant and durable change in lifestyle.

A number of tools can be used to assess dietary intake, a variety of which were considered for this trial. Although there are few validity studies of food frequency approaches in adolescent populations, the available data suggest that validity and reproducibility are comparable to results obtained in adults (77). Recently, the Block Kid's Questionnaire was validated in low-income African-American children. This instrument has been further modified to incorporate common food choices among ethnically and regionally diverse youth aged 10–19 yr participating in another large childhood diabetes study, SEARCH [Search for Diabetes in Youth, Centers for Disease Control/NIH], based on previously validated work with FFQ methodology in ethnically diverse populations (31).

Fitness/activity—Physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure. Physical fitness, on the other hand, characterizes the physiologic state of an individual, including aerobic power, muscular endurance, muscular strength, body composition, and/or flexibility. Both physical activity and fitness are independently related to changes in insulin sensitivity and improvement in glycemic control and other abnormalities associated with T2DM. Those who are more active and expend more energy have higher fitness levels. However, there is only a moderate relationship between physical activity and physical fitness (78). Therefore, the effect of the treatment interventions on both of these measures is compared.

Physical activity is comprised of activities that span a spectrum of intensity levels and can be assessed using activity recall questionnaires and/or objective measures of activity, such as pedometers and accelerometers. The most popular activity questionnaire currently used with youth is the PDPAR (32). However, the PDPAR analyzes the activity level over a short time frame and may not reflect activity levels that vary with seasons or as a result of an acute illness or time commitment (79). The activity questionnaire may also not accurately quantify changes in lower intensity lifestyle activities. However, in combination with accelerometer data, it offers a valuable comparison of differential activity levels across treatment arms.

The accelerometer allows the collection and storage of daily patterns of physical activity and is a more complex instrument than the pedometer. In adults, correlation coefficients ranging from $r = 0.66$ to $r = 0.89$ between CSA counts and metabolic measures (33) have been obtained. In 7- to 15-yr-old boys and girls, the CSA was validated against heart rate telemetry, with correlation coefficients between the two ranging from $r = 0.50$ to 0.74 (80). Comparisons with oxygen consumption during treadmill exercise and self-selected speed on a track found that the CSA was highly related to both and was highly sensitive to change in speed but not changes in grade (81). As the CSA has been found to successfully detect bouts of moderate-intensity physical activity such as brisk walking (82), this monitor was chosen for TODAY where moderate-intensity activity is the goal.

Cardiorespiratory fitness is defined as the ability to absorb, transport, and use oxygen. Higher VO_2 max values indicate better cardiorespiratory fitness. However, measurement of VO_2 max is a challenging task in children (83,84). Motivating youth to exercise maximally is difficult, they may have difficulty obtaining VO_2 max, the tests require expensive metabolic measuring systems, and take approximately an hour to complete.

In contrast, the PWC method of predicting VO_2 max has several advantages (34). First, the PWC equipment and space needs are modest. Second, the PWC can be administered in 12–15 min and requires only the measurement of heart rate. Third, the PWC is ideal to use in a test–retest protocol because learning, practice, or training have little effect on results.

Cardiovascular markers—The development of cardiovascular risk is an important consideration in comparing the efficacy and long-term implications for the treatment interventions in TODAY. To address this, the differential effects of the three treatment arms on both traditional and non-traditional markers are compared.

Obesity, T2DM, hypertension, and dyslipidemia are associated with a significantly increased risk of cardiovascular morbidity and mortality in adults, and insulin resistance has been considered the underlying pathologic mechanism (85–87). However, these traditional risk factors account for only approximately 50% of the cardiovascular risk associated with hyper-insulinemia and insulin resistance, an observation that has led to the identification of a number of 'non-traditional' risk factors (88), including alterations in hemostasis and markers of acute and chronic systemic inflammation.

Very little is known about the relationship between obesity, insulin resistance, T2DM, and non-traditional cardiovascular risk factors in children. Several large epidemiologic studies in youth have shown an association between obesity, traditional risk factors (e.g., hypertension and dyslipidemia), and cardiovascular disease (89,90). However, less is known about non-traditional risk factors. In small series, obese children and adolescents have been found to have increased levels of fibrinogen, PAI-1, and D-dimer, as well as abnormalities in factor VIIc, von Willebrand factor, PAI-1, fibrinogen, and tissue plasminogen activator (91–93). Following weight loss interventions, decreased levels of PAI-1 and interleukin-6 (IL-6) have been demonstrated (92–94), suggesting that lifestyle interventions may be able to alter cardiovascular risk in young patients.

Microvascular complications associated with diabetes produce significant burdens for the individual patient and are responsible for considerable healthcare costs. Microvascular complications are more common among children with T2DM at the time of presentation than among those with type 1 diabetes mellitus (95,96). There is evidence, although limited, which suggests that progression rates of microvascular complications are also greater in youth with T2DM. Therefore, a comparison of the effect of the treatment interventions on the prevention and slowing of rates of development of microvascular complications associated with T2DM

is an important secondary outcome of TODAY and could significantly modify the interpretation of the primary outcome results.

Psychosocial outcomes—The psychological, emotional, and social status of a patient interacts with his or her chronic illness in complex ways. Difficulties in the family social or psychological structure can hasten onset of lifestyle-related disorders, such as T2DM, and then further interfere with treatment. Onset of a chronic illness, particularly one that requires significant personal change, can adversely affect many aspects of a patient's and family's emotional wellbeing. This trial examines whether psychological characteristics of patients and families influence treatment outcome and whether the interventions have an effect on psychological problems and quality of life. The following questions are of interest: (i) whether the participant's and/or parents' psychological characteristics at baseline affect the success of the three treatment arms, (ii) whether the treatment assignment has an effect on psychological outcomes related to the diagnosis of diabetes, and (iii) whether changes in the family FSP's psychological status during the intervention affect outcomes.

Cost—Rising healthcare costs and limited healthcare resources have increased the focus placed on the economic aspects of health care. Analyses of resource utilization and costs contribute to decisions made by health service providers and policy makers regarding diabetes care. By incorporating measures of resource utilization, cost, and an intervention's effectiveness, cost-effectiveness analysis has become an important tool in decision making about the use of different treatments for the same condition. Several large trials of diabetes care interventions have demonstrated that enhanced treatment of diabetes improves health at an acceptable cost (97–99).

Therefore, an important secondary outcome of TODAY is an investigation of the resources, related costs, and cost-effectiveness of the three treatment arms. The cost-effectiveness analysis considers the resources used and associated costs for each treatment arm throughout the time of the trial. The time frame of the analysis is short term. The main analysis is based on the primary glycemia outcome in the trial and, thus, examines the costs of each treatment relative to the glycemia benefits obtained. By incorporating costs incurred by participants and caregivers, the analysis adopts a societal perspective, following the accepted standard for such studies (100,101).

Conclusions

TODAY is the first large-scale, systematic study of treatment effectiveness for T2DM in youth, an emerging disease with significant long-term healthcare and social implications for this population. When successfully completed, TODAY will provide critically needed new information regarding broad questions of treatment approach in youth T2DM, particularly regarding the benefits of initiating early aggressive treatment in these patients. Furthermore, TODAY will address the efficacy and feasibility of adapting intensive and sustained lifestyle interventions previously shown to be successful in weight loss programs to the needs of children with T2DM.

At the same time, TODAY will capitalize on the recruitment of this cohort of patients to examine in relative depth the pathophysiology of patients with recently diagnosed T2DM, the natural history of early stages of the disorder, the effect of alternative treatment interventions on T2DM physiology, and the pathophysiology of treatment failure. This information promises to provide an improved foundation for informed clinical management of children with T2DM and has the potential to allow analysis of patient characteristics, including both biologic and behavioral/social, that determine differential benefit of different treatment approaches. Finally, an extensive parallel analysis of cost of the intervention will provide policy makers with critical

information regarding the efficacy and cost-effectiveness of intensive medical and lifestyle interventions in these young patients.

TODAY was designed as an efficacy trial, and the Study Group recognizes that clinicians do not generally have the means available to study sites for delivery of the labor- and resource-intensive interventions described. However, it is hoped that successful proof of principle by TODAY, along with the analysis of secondary outcomes that may allow delineation of which components of the intervention were most critical, will provide the basis for future effectiveness studies examining the translation of these findings into routine clinical practice.
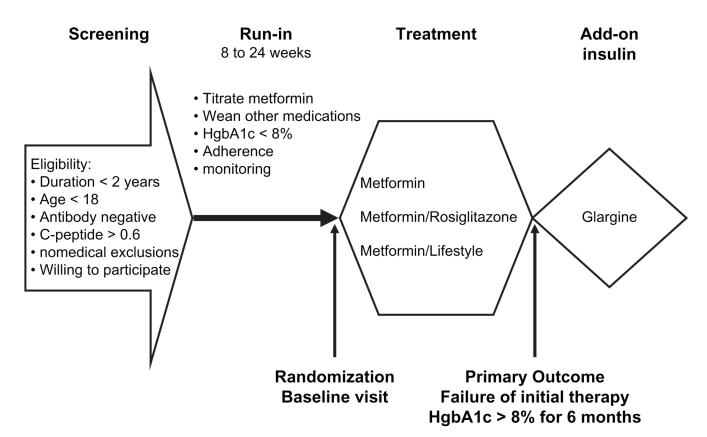
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Screening

Run-in
8 to 24 weeks

Treatment

Add-on insulin

Eligibility:
• Duration < 2 years
• Age < 18
• Antibody negative
• C-peptide > 0.6
• nomedical exclusions
• Willing to participate

• Titrate metformin
• Wean other medications
• HgbA1c < 8%
• Adherence
• monitoring

Metformin

Metformin/Rosiglitazone

Metformin/Lifestyle

Glargine

**Randomization
Baseline visit**

**Primary Outcome
Failure of initial therapy
HgbA1c > 8% for 6 months**

Fig. 1.
Schematic of TODAY trial.

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Table 1

Outcome data collection

Measurement/assessment	Eligibility Initial screen	Run-in	Baseline	Yr 1 X = every 2 months	Post-Yr 1 follow-up
Primary outcome					
Hemoglobin A1c	X	X	X	X	Quarterly / Primary treatment failure / End of study
Secondary outcomes					
Insulin sensitivity and secretion	Primary treatment failure / End of study		X	6, 12	Annually
Serum creatinine	X		X	12	Annually / Primary treatment failure / End of study
Liver function tests	X		X	X	Quarterly / Primary treatment failure / End of study
Hemoglobin and hematocrit	X		X	2, 6, 12	Annually / Primary treatment failure / End of study
Anthropometrics	Primary treatment failure / End of study		X	6	24 months
Dual-energy X-ray absorptiometry	Primary treatment failure / End of study		X	6	24 months
Lipids	X		X	6, 12	Annually / Primary treatment failure / End of study
Fitness, nutrition, and activity			X	6	24 months

Measurement/assessment	Eligibility — Initial screen	Run-in	Baseline	Yr 1 (X = every 2 months)	Post-Yr 1 follow-up
Psychosocial and quality of Life	Primary treatment failure; End of study		X	6	24 months
Cardiovascular risk factors	Primary treatment failure; End of study		X	6, 12	Annually
Neuropathy (Michigan Neuropathy Screening Instrument)	Primary treatment failure; End of study		X	12	Annually
Microalbumin	Primary treatment failure; End of study				
Adverse events		X	X	X	Quarterly; Primary treatment failure; End of study
Resource utilization costs	Primary treatment failure; End of study		X	X	Quarterly
Blood and urine for storage	Primary treatment failure; End of study		X	6, 12	Annually