Protocol to Collect Control Sample Data

as Part of T2P2

TODAY2 Phase 2
Long-term Post-intervention Follow-up
of the TODAY Cohort

Distributed by
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1 Introduction

TODAY (Treatment Options for type 2 Diabetes in Adolescents and Youth) was a multi-center randomized clinical trial funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). Youth aged 10-17 diagnosed with type 2 diabetes (T2D) <2 years were enrolled. The study compared the efficacy of the three treatment arms: (1) metformin alone, (2) metformin plus rosiglitazone, and (3) metformin plus an intensive lifestyle intervention. The TODAY trial was completed in February 2011. It is followed by TODAY2, a longitudinal study to continue follow-up of the TODAY cohort beyond the end of the TODAY intervention trial to document the progression of diabetes and its complications and related comorbidities. In the last year of TODAY, the cohort was measured using echocardiography. A follow-up echocardiography assessment is scheduled during TODAY2.

The purpose of this study is to collect control sample data and use these data to compare with outcomes in the TODAY/TODAY2 study cohort.

The work is performed by the TODAY/TODAY2 Echocardiography Reading Center (ERC) and the TODAY/TODAY2 Central Biospecimen Laboratory (CBL).

2 Study Design

This is a one-time collection of data in consented volunteers. Enrollment takes place at locations under the direction of Joao Lima, MD, at the Division of Cardiology, Department of Medicine, Johns Hopkins University, and Sam Gidding, MD, at the Alfred I duPont Hospital for Children at Nemours Children's Clinic and at Thomas Jefferson University Hospital.

2.1 Samples and Eligibility

Two control samples have been identified: (1) obese and not diabetic and (2) lean and not diabetic.

Sample 1 Obese Controls Eligibility Criteria

Inclusion

1. Body mass index (BMI) >30 kg/m^2.
2. Age 18-30 years.
3. Allow blood draw for testing HbA1c.
4. Signed informed consent form.

Exclusion

1. Pregnant female.
2. Diagnosed with diabetes (either type 1 or type 2) or HbA1c >6.5% determined by central lab analysis of screening blood drawn.
3. Diagnosed with hypertension or taking anti-hypertensive medication or screening blood pressure ≥130/80.

Sample 2 Lean Controls Eligibility Criteria

Inclusion

1. Body mass index (BMI) 18.5-25 kg/m^2.
2. Age 18-30 years.
3. Allow blood draw for testing HbA1c.
4. Signed informed consent form.

Exclusion

1. Pregnant female.
2. Diagnosed with diabetes (either type 1 or type 2) or HbA1c >6.5% determined by central lab analysis of screening blood drawn.
3. Diagnosed with hypertension or taking anti-hypertensive medication or screening blood pressure ≥130/80.

Both samples include gender and racial-ethnic composition comparable to the TODAY cohort.

2.2 Recruitment

Recruitment is expected to occur from June 1, 2014 to May 31, 2015. Strategies are site-specific and include local advertising and community outreach. Recruitment is monitored to confirm target goals.

2.3 Informed Consent

The relevant Institutional Review Board approves the protocol and informed consent form. The informed consent form has a separate checkbox to indicate whether the individual is willing to undergo an additional blood draw to be stored at the CBL for future study use. Informed consent is administered in an interactive, conversational process with the ultimate goal of ensuring understanding of the study and procedures. Written consent is obtained prior to any research procedures.

2.4 Screening and Enrollment

Screening is performed over the phone, in person, and by lab analysis. Responses are documented on a screening form. Once an individual fails a screening criterion, screening stops. Procedures are:

Initial Contact

- Phone capture includes age, diagnosed with diabetes, diagnosed with hypertension, and taking an anti-hypertensive medication.
- Individuals who pass these criteria are invited to a clinic visit. Participants are advised that if they are eligible and willing to undergo a blood draw at the visit, they must arrive fasting (nothing to eat or drink except water 8 hours prior to the visit).

Clinic Visit

- Informed consent is obtained.
- Eligibility assessment continues using more invasive methods to measure height and weight to determine BMI and to measure blood pressure.
- Individuals who pass the in-person criteria (signed informed consent, BMI in range, BP in range) continue with visit procedures including forms, echocardiogram, and blood draw.
- Blood is collected as follows:
    - Blood to determine hemoglobin A1C is collected in all study participants to detect diabetes. One 5 mL (lavender top) EDTA blood sample is collected and shipped to the CBL for immediate testing. Results are shared with the participant.
    - Blood to determine Fibroblast Growth Factor-23 (FGF-23) is collected in all study participants. FGF-23 is a biomarker for cardiovascular disease and is related to heart muscle growth. One 5 mL (lavender top) EDTA blood sample is collected and stored at

the site. Samples are batched at the completion of the study and sent to Thomas Jefferson University and then forwarded to Lurie Children's Hospital for analysis.
  - Additional fasting blood samples are collected for future testing in only those patients who consent to this optional procedure. Blood is drawn into two 5 mL (tiger top) serum separator tubes and two 5-mL (lavender top) EDTA tubes and sent to the CBL for storage. If the participant is not confirmed fasting for 8 hours, a second visit for fasting blood collection can be scheduled if needed no longer than 1 week later.

Post-Visit

- CBL returns the value of HbA1c to complete screening. If HbA1c >6.5% then the individual is ineligible and any data collected are destroyed.
- Findings are conveyed to participants and their designated healthcare provider in a follow-up letter. Alert values may initiate a more immediate response – see the section on Safety.

2.5 Participant Management

- The following incentive and visit reimbursement amounts are distributed:
  - Individuals who attend a clinic screening visit and sign informed consent form but are determined not eligible due to values of BMI or BP receive $25 to cover incentive plus visit reimbursement (travel, parking, etc.).
  - Individuals who attend the clinical screening visit, sign informed consent form, have an echocardiogram, provide blood for HbA1c and FGF-23, and complete study forms receive $75.
  - Individuals who attend the clinical screening visit, sign informed consent form, have an echocardiogram, provide blood for HbA1c and FGF-23, complete study forms, and provide additional blood for storage receive $100.

- Participants who have a fasting blood draw are provided with a light breakfast after the draw and before the echocardiogram.

2.6 Data Collection and Management

Data are collected for screening and eligibility, to document the echocardiogram, to document the blood draw and shipment, and to characterize the participant in terms of gender, race-ethnicity, and smoking behaviors. Blood is processed and sent to the CBL and to Thomas Jefferson University. The CBL runs HbA1c and stores the frozen samples. Thomas Jefferson University performs the FGF-23 test.

Participants are assigned a study ID modeled after the TODAY study ID formatted as:

☐☐☐-☐☐☐

The first 3 numbers are '222' to indicate a participant in this data collection; the second 3 numbers are assigned by the data collection site to be unique to each participant. All data are labeled with the study ID, including forms and specimens.

Data are entered by the research study staff into a central database maintained by the TODAY Coordinating Center at George Washington University Biostatistics Center. No personal contact information or identifiers are kept in the central database.

The coordinating enter applies the Biostatistics Center's data backup and security policies to ensure the safety and confidentiality of the data. Backup procedures include: twice-weekly

system backup, daily incremental backup, and off-site fire proof storage. Security procedures include: logon and link password protection, remote password logon and dial-back modems, and for internet access, separate Web servers which use SSL and encryption algorithms. Regularly updated virus scanning software is used routinely to check personal computers for computer viruses. University computing facilities provide support in the event of a disaster.

The coordinating center maintains confidentiality of patient data and emerging results per a confidentiality policy, which every staff member is required to sign annually.

Coordinating center statisticians perform data analysis in collaboration with the study group.

2.7 Sample Size

To estimate control group sample sizes, we use data (mean/SD) from CARDIA and TODAY for a measure of left ventricular diastolic function (E/Em ratio):

- CARDIA obese control sample – no diabetes, BMI >30 8.20 (2.31)
- CARDIA lean control sample – no diabetes, BMI <25 7.23 (1.97)
- TODAY cohort 5.83 (1.82)

These measures are age dependent – the heart gets stiffer as we age. At follow-up echo, the TODAY cohort will not be as old as the CARDIA sample, so the sample means will not be equivalent to the CARDIA samples but are expected to show the same clinically meaningful differences. That is, the difference between the TODAY cohort and TODAY obese controls will be on the order of what we see between the CARDIA diabetes sample versus the CARDIA obese sample, and similarly for the diabetic versus lean sample comparison. Also, although CARDIA does not have the same racial-ethnic distribution as TODAY, that should not be a factor in the measures of interest.

Therefore, we use the CARDIA data to estimated sample size needed to detect the clinically meaningful differences we anticipate seeing in the TODAY cohort and control samples at follow-up. The method of analysis is a two-sample t-test and sample size is based on detecting an 'effect size' computed as the difference in means relative to the standard deviation. We compute sample size for the two comparisons (1) diabetes versus obese and no diabetes and (2) diabetes versus lean and no diabetes. Because we are not projecting sample size to address the definitive objective of a clinical trial but are estimating data needed to perform meaningful statistical analysis for an observational data collection, we use a significance level α of 0.05 for each comparison. We use a common estimate of variability.

Sample sizes needed for 90% power are 200 obese controls and 50 lean controls.

2.8 Safety and Confidentiality

- No risks or safety issues are anticipated. All procedures – physical measurements, echocardiogram, and blood draw – are performed by trained experience staff.

- Female participants of childbearing potential who meet the eligibility criteria are enrolled. Pregnant females are excluded because pregnancy can affect the echocardiography outcome measures. There are no risks; therefore, pregnancy status will be obtained by participant report only and pregnancy testing will not be needed.

- As stated in the informed consent form, a participant may refuse to answer any question or engage in any procedure.

- A light breakfast is provided to participants who arrived fasting for blood draw.

- Participants are identified in the central database only by a study identification code, and the link between that code and personal identifying information remains at the clinical site in a secure location as dictated by local privacy and confidentiality regulations.

- Once a participant has been determined to be ineligible, any data from form or procedure, including blood and echocardiogram, are destroyed.

- 'Alert' levels that have been established for TODAY2 Phase 2 are also applied in this study. Notification of an alert value may be by follow-up visit summary letter or by more immediate action.

    - Blood Pressure. The procedure for measuring BP is (1) measure after 5 minutes sitting at rest, (2) measure 1 minute later, (3) measure 1 minute later.
        - If the average of the 2nd and 3rd BP > 130/80, then note in the follow-up letter.
        - If either the 2nd or 3rd BP > 140/100, then the clinic study MD asks the participant about symptoms and at his/her discretion either note in the follow-up letter or escort to ER or clinic for immediate follow-up.
    - HbA1c. The CBL notifies the clinic staff of alert levels as analyzed.
        - If value 5.8-6.5, then note in the follow-up letter with interpretation of pre-diabetes.
        - If value >6.5, then note in the follow-up letter with recommendation to be tested to confirm diagnosis of diabetes.

    - Echocardiogram
        - Alerts and referrals are identified and confirmed by a reading center physician and are considered an official interpretation of the echocardiogram.
        - All results that meet criteria for a referral or alert are reported to the participant via a results letter after the visit.
        - Alerts include aortic aneurysm, flail leaflet, severe LV dysfunction, significant arrhythmia, suspected pericardial tamponade, thrombus, tumor, or vegetation.
        - The on-site sonographer may identify a condition during the echocardiogram; the sonographer notifies the study MD and study staff. Because the study is performing this procedure to identify findings of immediate and urgent interest that may have clinical relevance, we are responsible for appropriate follow-up.

            If there is a good well engaged primary care provider (PCP), the plan could be that the study MD calls the PCP and they decide together how to proceed. If the participant is going to a free clinic, then the study MD needs to take responsibility for discussing with someone who can give a clinical judgment on the echo that was done and making a plan that is appropriate.

            It may or may not be appropriate to send the echo to a referral clinic or have them talk to the reading center – the study echo may not be considered sufficient for clinical practice and a follow up echo may be needed if indicated for clinical purposes.

Action: Immediate attention and plan for response.	
Left ventricular internal dimension in diastole • The most likely cause is obesity, regardless an LV this big is a risk factor for future heart failure.	> 6.0 cm
Interventricular septal thickness in diastole • Walls these thick are suggestive of chronic hypertension or possible cardiomyopathy	> 1.4 cm
Left ventricular posterior wall in diastole • Walls these thick are suggestive of chronic hypertension or possible cardiomyopathy	> 1.4 cm
Ejection fraction (fraction of blood pumped out of ventricles with each heart beat) • Values below this threshold are definite ventricular dysfunction and need cardiology assessment	≤ 45%
Left ventricular dysfunction • See ejection fraction above, needs cardiology referral right away	Moderate or severe
Aortic root dimension • Values above this threshold are consistent with an ascending aortic aneurysm	> 4.5 cm
Left atrial dimension • Most likely causes are obesity, hypertension, and diabetes; could also be a marker for LV dysfunction	> 4.5 cm

Action: Note in letter to PCP for follow-up.	
Right ventricular systolic pressure • Could be indicative of PA hypertension, possibly secondary to sleep apnea, needs to be confirmed as these values often vary a lot day to day	> 40 mmHg
Mitral or aortic regurgitation • These findings would suggest intrinsic heart disease (unlikely this would be a new finding as these conditions have significant heart murmurs)	*Moderate or severe*
Stenosis of any valve	*Mild, moderate, or severe*
Mitral valve prolapse	*Moderate or severe*
Left ventricular hypertrophy • Might suggest the need for intensification of antihypertensive therapy (starting medication in a borderline individual or making sure BP is at goal in someone on treatment), otherwise the most likely cause is obesity.	*≥ 51 g/m$^{2.7}$*
Clinical findings (i.e., pericardial effusion, wall motion abnormality, severe arrhythmias, bicuspid aortic valve, etc.)	*Significant*