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Feasibility of Intravenous Glucose Tolerance Testing Prior to Puberty

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Abstract

Objectives—1) Report the feasibility of completing the 180 minute FSIVGTT in healthy weight, overweight and obese pre-pubertal children and, 2) describe the finalized FSIVGTT protocol after addendums were implemented to decrease the frequency of mild adverse events and improve test completion rates.

Methods—Insulin sensitivity was determined by FSIVGTT.

Results—FSIVGTT was attempted in a total of 22 study participants. Insulin sensitivity was successfully assessed in 15 study participants (8 males, 7 females, 10 Caucasian, 4 African American, 1 Pacific Islander, age range 7-9 years). Mean insulin sensitivity was 15.1±9.8 $(m\mu/l)^{-1}\cdot min^{-1}$ range 4.4 – 43.2 $(m\mu/l)^{-1}\cdot min^{-1}$. Seven study participants, however experienced mild adverse events of hypoglycemia. Several addendums were made to the FSIVGTT protocol to ensure study participant comfort and safety, decrease the frequency of mild adverse events and increase test completion rates.

Conclusion—Addendums made to FSIVGTT protocol allowed successful completion of FSIVGTT in 15 (68%) of the 22 children. These results demonstrate that FSIVGTT is challenging, yet feasible in healthy lean and obese pre-pubertal children.

Keywords

Insulin Resistance; Insulin Sensitivity; Hypoglycemia; Pre-pubertal Children; glucose tolerance

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Introduction

The Frequently Sampled Intravenous Glucose Tolerance Test (FSIVGTT) assesses insulin sensitivity by a computed mathematical analysis of glucose and insulin dynamics (1). FSIVGTT consists of an intravenously administered bolus of glucose and an infusion of insulin 20 minutes after glucose injection. Blood samples are collected periodically for a total test duration of 180 minutes (1). Research has indicated FSIVGTT is an accurate and valid technique for the measurement of insulin sensitivity in adults, adolescents, and children (2). It is also a useful tool for identification of subtle, non-symptomatic metabolic abnormalities prior to the onset of type 2 diabetes (3). However, FSIVGTT is time consuming, invasive, labor intensive, and requires experienced personnel (4) to perform the procedure.

Because early detection of insulin resistance is important to the prevention of type 2 diabetes, FSIVGTT may be a useful procedure to identify at-risk pre-pubertal children. Most pediatric studies using FSIVGTT included overweight children and adolescents and/or healthy children and adolescents during pubertal progression (4-9). Other studies implemented a modified 90-minute FSIVGTT (10, 11). Only one study (12) performed a 180 minute FSIVGTT in healthy weight, pre-pubertal children, however Tolbutamide (a drug used to lower blood glucose) was injected during FSIVGTT rather than insulin. The objectives of this study were to: 1) report the feasibility of completing 180 minute FSIVGTT in healthy weight, overweight and obese pre-pubertal African American and Caucasian children and, 2) describe the finalized FSIVGTT protocol after addendums were implemented to decrease the frequency of mild adverse events and increase test completion rates.

Methods

Study Participants

Children, seven to nine years of age, were recruited to participate in the Study of Insulin sensitivity in Louisiana Low-birth weight Youth (SILLY) through schools, doctors' offices, health fairs, libraries, and other public places throughout southeast Louisiana. SILLY is an ongoing, cross-sectional study exploring markers for the metabolic syndrome in pre-pubertal youth. Prior to enrollment, medical and family history were obtained through a detailed phone interview of the parents/guardians of interested volunteers. If eligible, a complete medical history and physical examination, including Tanner staging were performed on all participants by a physician prior to enrollment into the study. Participants with evidence of significant cardiovascular disease, cardiac arrhythmia, or liver disease, or who chronically used medications were excluded. Those with a maturation level (Tanner) $\geq$2 were excluded. Participants of mothers who reported gestational diabetes were excluded as well as those with a first degree relative with type I or type 2 diabetes.

Data was collected by physicians, pediatric nurses, and trained study staff from the Louisiana State University Health Sciences Center (LSUHSC), School of Public Health and Children's Hospital Clinical Trials Unit (CHCTU) in New Orleans and Pennington Biomedical Research Center (PBRC) in Baton Rouge, LA. Anthropometric measures were

obtained by trained study staff. A medical screening blood test, including a comprehensive metabolic panel and complete blood count with differential was performed on all participants to ensure the child's eligibility to participate in the study. Baseline blood samples including fasting glucose and serum insulin were obtained the morning after a 12 hour fast by a pediatric registered nurse in a private, short stay unit room. Prior to the baseline blood samples, the pediatric registered nurse obtained a urine sample from the study participant to test for the presence of ketones in the urine. A non-violent children's movie was shown throughout FSIVGTT. Bedside blood glucose was checked after each blood draw using a Onetouch Ultra blood glucose meter (LifeScan, Inc., Milpitas, CA) and OneTouch® Ultra® Test Strips (LifeScan, Inc., Milpitas, CA). Insulin and glucose data were entered into the minimal model (MINMOD) computer program (version 6.02; Richard N. Bergman, Los Angeles, CA) to calculate insulin sensitivity.

All methods and testing procedures were previously approved by the Institutional Review Board (IRB) of LSUHSC, CHCTU and PBRC. Participants' legal guardians read and signed an approved consent form (and children gave their written assent) prior to participation in any study procedures. The flow of participants through the study is described in Table 1.

Finalized FSIVGTT

Prior to the insertion of IV cannulas, a topical anesthetic patch (Synera) was placed on the antecubital area of each arm. Approximately 30 minutes after the patch was applied one IV cannula was inserted into each arm of the participant. IV cannulas were held in place by Tegaderm™ transparent dressings. Three baseline blood samples were drawn at 10 and 15 minute intervals, designated at -30, -15, and -5 minutes. At zero time, 0.3g/kg of 25% dextrose was injected over 1-2 minutes followed by a bolus of insulin, 0.02 U/kg of body weight, 20 minutes later. Additional blood samples (1.1ml) were collected at the following times relative to glucose administration at 0 minutes: 2, 4, 8, 19, 22, 30, 40, 50, 70, 100, and 180 minutes (13). After each blood draw, blood glucose was measured bedside by the glucose meter. Normal saline was used to flush the IV line after each blood draw. FSIVGTT was discontinued if bedside blood glucose was <40 mg/dL and/or the participant exhibited any signs or symptoms of hypoglycemia including shakiness, dizziness, sweating, hunger, headache, irritability, pale skin color, sudden moodiness or behavior changes, clumsy or jerky movements, difficulty paying attention, or confusion and tingling sensations around the mouth. After diagnosis of hypoglycemia, 4 ounces of juice was given to the participant along with a granola bar containing sugar. Blood glucose was rechecked 15 minutes later. The participant remained in the care of the nurse and other study staff 30 minutes to 1 hour after diagnosis of hypoglycemia or after FSIVGTT was completed. Glucose was assayed using a Yellow Springs Instruments analyzer, which uses a membrane bound glucose oxidase technique. Insulin was assayed using an EIA kit from ALPCO. Insulin and glucose values were obtained in all timed samples. A physician was available throughout the duration of FSIVGTT to evaluate participants for signs and symptoms of hypoglycemia.

Results

Insulin sensitivity was determined from 15 participants (8 males, 7 females, 10 Caucasian, 4 African American, 1 Pacific Islander) who completed FSIVGTT. Their physical characteristics are presented in Table 2. Insulin sensitivity ranged from 4.4 to 43.2 (mμ/l)$^{-1}$·min^{-1}. The mean insulin sensitivity calculated for these participants was 15.1±9.8 (mμ/l)$^{-1}$·min^{-1}.

Seven participants experienced hypoglycemia during the FSIVGTT. The first three participants who experienced hypoglycemia were asymptomatic, however their blood glucose was <60 mg/dL and the initial physician orders stated that if blood glucose decreased to <60 mg/dL then FSIVGTT would be stopped immediately. Following these asymptomatic adverse events of hypoglycemia, the criteria for diagnosis of hypoglycemia was changed from <60 to <40 mg/dL (all IRBs were notified). The last four participants who experienced hypoglycemia displayed blood glucose levels <40 mg/dL. Only one of those participants was symptomatic with three asymptomatic. Specific insulin dosage administered during FSIVGTT and demographics of participants who experienced hypoglycemia are reported in Table 3. Due to the events of hypoglycemia and to reduce participant burden even further, several addendums were made to FSIVGTT protocol (Table 4). These addendums were made to ensure study participant comfort and safety, decrease the frequency of mild adverse events and increase test completion rates. Moreover, the 0.02 U/kg of body weight of insulin was selected by the physician for these study participants in order to further reduce the chance of adverse events and to maintain consistency from one test to another. This amount of insulin is similar to the amount used by Ball (7), Goran (6) and Davis (5) in overweight Hispanic 8-13 year old children.

Discussion

Although we successfully completed FSIVGTT in 15 pre-pubertal children, we continued to encounter events of hypoglycemia. Currently we are examining participant characteristics (weight status, ethnicity, gender, etc.) and situational variables (fasting duration, hydration, etc.) in a larger sample of study participants in an effort to explain the diversity of glycemic responses during the procedure.

While several studies performed FSIVGTT in overweight children (4-8), only one performed 180 minute FSIVGTT in healthy weight children; however, Tolbutamide was administered not insulin (12). Symptomatic hypoglycemia was not observed in the 11 children who participated in FSIVGTT with Tolbutamide. However, these children ranged in age from 7-20 years, therefore not all were pre-pubertal. Moreover, Cutfield (12) did not provide their criteria for hypoglycemia only stating that none of the study participants experienced symptomatic hypoglycemia.

To date, only one study examined the incidence of hypoglycemia during FSIVGTT in young children. Cruz (14) observed the incidence of hypoglycemia (defined as a plasma glucose <50 mg/dL) during FSIVGTT in 210 overweight Hispanic children (mean age 11±1.7 years, range 8-13 years). An insulin dosage of 0.02 U/kg of body weight was administered. Only

one participant (<0.5% participants) displayed plasma glucose <50 mg/dL, while only four participants (1.9%) had a plasma glucose <60 mg/dL at any time during FSIVGTT. Compared to the present study, the percentage of hypoglycemia reported in the study by Cruz (14) was much lower; however the children were older, 8-13 years, and were all overweight. The children in the present study were younger, 7-9 years, all pre-pubertal with a tanner stage < 2, and five of the seven children who experienced hypoglycemia were healthy weight.

To the authors' knowledge this is the first investigation to conduct FSIVGTT in exclusively healthy pre-pubertal lean and obese children using insulin. The adverse events encountered with the initial protocols made it difficult to conduct FSIVGTT procedure in these healthy pre-pubertal children. However, changes made to FSIVGTT protocol allowed successful completion in 15 (68%) children. Furthermore, study participant characteristics and situational variables continue to be investigated in order to explore these hypoglycemic events. The results of this study demonstrate that FSIVGTT is challenging, yet feasible in healthy weight, overweight, and obese pre-pubertal children. Future research will investigate insulin sensitivity by FSIVGTT in a larger cohort of multi-ethnic, pre-pubertal children.

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Table 1

Study participants' visit description

Visit 1: Screening

- Consent Obtained
- History & physical exam (including Tanner staging)
- Medical screening blood test

Visit 2: FSIVGTT

- Ketone urine analysis
- Topical anesthetic patches applied for 30 minutes
- IV cannulas inserted
- 3 baseline blood samples obtained (designated as time points -30, -15, -5)
- Dextrose administered at timepoint 0
- 4 blood samples obtained (designated as time points 2, 4, 8, 19)
- Insulin infused at timepoint 20
- 7 blood samples obtained (designated as time points 22, 30, 40, 50, 70, 100, 180)

Table 2

Physical characteristics of study participants who successfully completed the FSIVGTT (n=15).

	Mean ± SD
Age	7.93 ± 0.8
Weight (kg)	32.2 ± 7.1
Height (cm)	129.3 ± 8.2
Body Mass Index ([wt(kg)]/ht[m]^2)	19.0 ± 2.4
Total Body Mass (kg)	32.1 ± 7.4
Fat Body Mass (kg)	8.0 ± 3.6
Lean Body Mass (kg)	24.1 ± 4.8
Percent Fat (%)	24.3 ± 6.3

Table 3

Demographics and insulin dosage for study participants who experienced hypoglycemia.

Sex	Age	Weight (kg)	BMI (wt(kg)/ht(m)^2)	Total Insulin Dosage (U/kg of body weight)	FSIVGTT Time point of Hypoglycemia Occurrence	Lowest blood glucose experienced
F	8	65.4	32.4	1.96	80	50
F	8	61.4	25.4	1.8	100	40
M	8	28	13.6	0.56	35	36
F	7	23.9	16.7	0.5	40	13
F	9	31	17.7	0.62	50	19
F	8	28.7	17.7	0.6	30	21
M	9	40.8	21.5	0.82	40	38

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Table 4

Addendums made to the FSIVGTT protocol.

Addendum #	Description of Addendum
1	Decreased insulin dosage from 0.03U/kg of body weight to a range of 0.02 – 0.03U/kg of body weight
2	Medical screening blood test
3	Decreased insulin dosage from range of 0.02 – 0.03 to 0.005 – 0.030U/kg of body weight
4	Increased # of time points from 18 to 26, decreased amount of blood drawn at each time point from 1.5mL to 1.1mL
5	Ketone urine analysis
6	Decreased # of time points from 26 to 14