

2006 Workshop - Type I & III

TYPE III WORKSHOP REPORT AGSD(UK) CONFERENCE OCTOBER 2006

A dozen Type I and Type III members gathered to hear Catherine's presentation. We were particularly glad to have Raul Mingo with us who had come all the way from Argentina and also Rob Wood who agreed to be the Type III representative. We need some young blood! Dr Phil Lee joined us afterwards and there was some most interesting discussion on dietary regimes as they are much stricter in the USA.

We were also joined by Dr Nick Beauchamp who is Research Fellow in Molecular Biology of Inborn Errors of Metabolism but specialises in the GSDs. He has been establishing a molecular genetic service within the Sheffield Molecular Genetics Service based in Sheffield Children's NHS Foundation Trust for the diagnosis of GSD. He has been able to establish services for all types of GSD. He is now in the process of setting up some research into the defects which underlie GSD type 6.

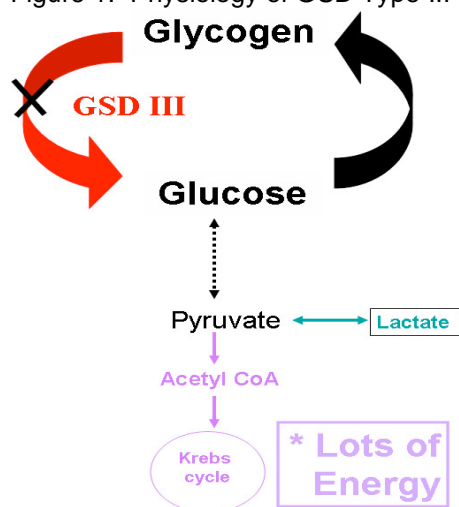
PRESENTATION BY CATHERINE CORRIEA ,UNIVERSITY OF FLORIDA

GSD Type III Exercise Trial and Updates on other current Research Studies at the University of Florida

GSD Type III is caused by a deficiency of the debranching enzyme which leads to incomplete breakdown of glycogen. Glycogen is the principle carbohydrate reserve in the body. Glycogen is stored in most tissue, but is predominantly stored in the muscles (60%) and liver. GSD IIIa patient lack the debranching enzyme in both the liver and muscles and represent approximately 80% of the GSD III population. GSD Type IIIb patients account for an additional 15% of the population and only display liver symptoms. Other rare subtype compose the rest of the Type III population.

Under normal physiology, glycogen is broken down to glucose and other energy containing intermediates to then be used within the cells of our bodies to produce energy for our bodies to do work. The intermediates are used in the Krebs Cycle along with oxygen to make large amounts of energy for fuel. When the Krebs Cycle is over-loaded and available oxygen runs low, the cell shifts to anaerobic respiration (to make energy without oxygen). Anaerobic respiration produces lactate. It is thought that lactate helps in creating metabolic acidosis. Metabolic acidosis makes your muscles more acidic (lower pH) and encourages more oxygen to be dropped off to your muscles so that you can resume making greater quantities of energy through the Krebs Cycle (See Figure 1).

Figure 1. Physiology of GSD Type III



Because a Type IIIa patient cannot break down glycogen in the liver or the muscles, no energy is made through the Krebs Cycle, no lactate is made, and oxygen utilization is different from normal physiology.

Presently, type IIIa patients have progressive myopathy which usually becomes severe by the fourth decade of life. Preliminary studies we have performed demonstrate abnormal oxygen use by muscles during exercise. Lactate levels are very low in Type IIIa.

Goals of Type III exercise study:

1. To characterize and evaluate the response to exercise in Type IIIa and IIIb
2. To better understand what causes muscle damage in Type IIIa
3. To try to find a method to prevent muscle damage

Information known about GSD Type V (McArdles) to help develop a GSD III Study:

Type V GSD patients lack access to muscle glycogen. Published studies that show abnormal use of oxygen during exercise (O'Dochartaigh et. al. Eur. J. Clin. Invest. 2004), and suggest that the use of a sucrose supplement prior to exercise may limit exercise fatigue (Vissing and Haller N. Engl. J Med. 2003).

Hypothesis:

Since lactate stimulates oxygen to be released by hemoglobin, increasing lactate will increase oxygen utilization by the muscle and decrease muscle damage

Will giving sucrose prior to exercise, provide the muscles glucose (fuel) to produce energy and lactate?

Description of Study:

A 2 night, 2 day inpatient study is presently taking place in which a subject will perform two exercise tests on consecutive days. One test will follow the administration of a drink containing sucrose and the other test will follow the administration of a drink containing an artificial sweetener. All air inhaled and exhaled while exercising will be measured. Blood labs measuring glucose, lactate, and muscle enzymes will be recorded before, during, and after exercise. Oxygen utilization will also be measured with a non-invasive monitor and cardiac function will be examined before, during, and after exercise through the use of a Holter monitor, an echocardiogram, and an EKG. The study is open to ages 8 years and older. Type IIIa and IIIb subjects are still needed for completion of study.

Other Research Projects at the University of Florida:

11 Ongoing Project teams:

1. GSD III exercise study
2. Treatment Trial – A collaboration with UK GSD researchers Dr. Lee and Dr. Bhattacharya. The study is goal is to find a new treatment to maintain normal blood sugars for extended periods of time which will last longer than the presently used cornstarch and will allow a full nights sleep (7-10 hours).
3. Inflammatory Bowel Disease Research – Inflammatory Bowel Disease (IBD) occurs in over 70% of patients with GSD Ib. Studies are on-going investigating the cause of IBD and new treatments.
4. Attention Deficient and Hyperactivity Disorder in GSD – Lead by an adolescent psychologist at UF. Aimed at determining prevalence of ADHD and the psychosocial impact of having a chronic disease in the GSD I and III populations.
5. Stem Cell – Lead by UF PhD. He and his research team are working to cure GSD Ia mice through the use of bone marrow derived stem cells

6. Gene Therapy – Gene therapy has now been successfully performed in mice. Researchers at UF and US National Institutes of Health are attempting to cure GSD using gene therapy in the dog model of GSD Ia.
7. Adenoma – A collaboration with researchers at Stanford and NIH to better understand the genetic components of hepatic adenomas. Microarray technology is used to evaluate the genes that are turned on or off in hepatic adenomas.
8. Anemia – A collaboration with researchers at Children’s Hospital Boston. Working to better understand Anemia in GSD and the link to the hormone hepcidin produced by hepatic adenomas.
9. Cardiovascular – UF Endocrinology and Cardiology. A large study to evaluate the prevalence of markers of early heart disease in the GSD population.
10. Pregnancy in GSD – The first population of GSD mothers are having babies. We are working with the different GSD centers around the world to document the successful pregnancies in the medical literature.
11. Genetic Screening for Type 0 GSD and Type IX GSD – Screening to better understand the prevalence GSD0 and GSD IX.

Questions:

- How much ‘exercise’ causes muscle damage in Type III?
 - Any repetitive movement can cause muscle damage.
- How much cornstarch and protein is recommended per day for a Type III patient?
 - The UF GSD program recommends 3g of protein per kg body weight to be consumed throughout the day. In addition to meals and protein snacks, as little cornstarch as possible should be used to maintain normal blood sugars throughout the day and night. Excess cornstarch can cause increased glycogen to be stored in the cardiac tissue, muscles, and liver.
- Is exercise recommended for Type III patients?
 - The UF GSD program recommends that the patient dictate how much exercise they participate in. The patient will know their own limitations. A snack can be consumed before exercise as a source of energy.
- Do different Brand name cornstarches/corn-flours have different results?
 - Yes. Every cornstarch brand is made from different types of corn and blends of corn. The amount of time that your blood sugar is maintained at normal can vary from brand to brand. It is also possible that products (flour, sugar, etc) other than cornstarch are added to the cornstarch that you are buying. In the United States, we use Argo® brand cornstarch.