Muscle mitochondrial dysfunction relates to decreased peripheral insulin sensitivity in female youth with type 2 diabetes

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Target Audience: Researchers in Diabetes and Obesity.

Purpose: The pathology underlying insulin resistance (IR) in youth is not completely understood. IR is associated with mitochondrial dysfunction in adults with type 2 diabetes (T2D) but T2D in youth has a unique phenotype and is more common in females. We hypothesized that muscle IR would be associated with decreased mitochondrial function in girls with T2D as measured with dynamic 31P spectroscopy.

Methods: Subjects included 14 T2D (Age 15.2±0.6 years; BMI%ile 96.1±1.0; mean±SE), 16 normal weight (NW) (Age 15.5±0.6, BMI%ile 54.6±1.7) and 22 obese (OB) females (Age 14.4±0.4, BMI%ile 97.2±0.5). Peripheral IR was assessed with a hyperinsulinemic-euglycemic clamp (80 u/m2/min) and the glucose infusion rate (GIR) calculated. Mitochondrial function was assessed by ^{31}P-MRS during and after a 90 second, 70% maximal volitional contraction (MVC), isometric calf exercise to monitor ATP depletion with exercise and repletion post-exercise. MVC was measured using a custom-built MR-compatible plantar flexion device with force measurement capability as previously described (1-3) and confirmed with a validated force vs. area calculation based on calf area, and force output monitored throughout exercise.

The imaging and spectroscopy data were acquired using a GE 3T/94 with HDx system (GE, Waukesha, WI) equipped with the multi-nuclear spectroscopy (MNS) accessory and a custom 1H/31P leg coil (Clinical MR Solutions, Brookfield, WI) with an inner coil 9 cm in diameter (for 31P) and a 13 cm outer 1H coil for scout imaging and shimming, and measurement of cross-sectional area of the calf. After shimming, a 31P baseline scan was performed using the fidcsi pulse sequence and a hard pulse with TR= 15,000 ms, flip angle 135 degrees, 32 averages, to measure a fully relaxed spectrum. The 31P exercise scan was then performed under partially saturated conditions (TR 1000 ms, flip angle 135, 2048 pts, 2 averages per frame, time resolution 2 s). A representative 31P dataset is shown in **Figure 1**.

Results: Girls with T2D had significantly greater IR than both NW and OB controls (T2D 8.6±1.8 vs. NW 18.5±1.1 mg/kg/min, p=0.003; T2D vs. OB 15.5±1.5; p=0.009, respectively; ANOVA p=0.002). The time for half of the ADP made during exercise to convert to ATP (ADP time constant, ADPTC) was significantly longer in T2D than in both NW and OB controls (T2D 26.2±0.3 vs. NW 15.1±2.1 seconds, p=0.004; vs. OB 18.1±1.5 seconds; p=0.021, respectively; ANOVA p=0.004). GIR was related to oxidative phosphorylation (R=0.40, p=0.04) and maximal mitochondrial capacity (R=0.38, P=0.03) across all groups.

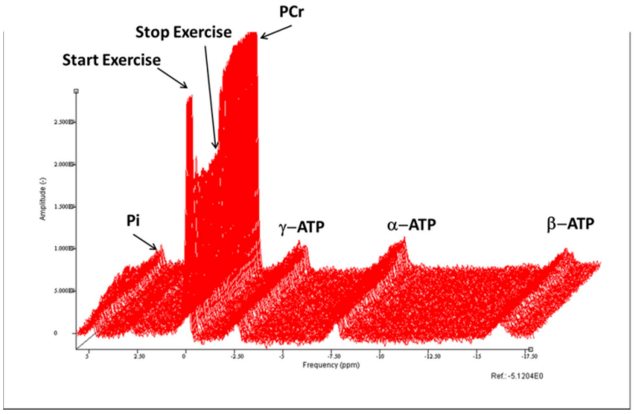

Figure 1: Representative plot of dynamic 31P spectra during and after 70% exercise.

Discussion: T2D girls had slowed post-exercise ATP re-synthesis after exercise at an equal workload, relative to both lean and obese controls indicating decreased mitochondrial function following exercise. Further, rates of oxidative phosphorylation and mitochondrial capacity relate to insulin resistance in youth. Future investigation is needed to determine whether the mitochondrial dysfunction occurs prior to or secondary to development of T2D.

Conclusions: Mitochondrial dysfunction may be a potential treatment target in youth with T2D.

References: 1. Cree-Green M, Newcomer BR, Brown M, et al. Med Sci Sports Exerc 2014. 2. Larson-Meyer DE, Newcomer BR, Hunter GR, et al. NMR in biomedicine 2000;13:14-27. 3. Bamman MM, Caruso JF Journal of strength and conditioning research / National Strength & Conditioning Association 2000;14:45-9

Support: KJN: NIH/NCRR K23 RR020038-05, 1R56DK088971, American Diabetes Association Career Development Award 7-11-CD-08, Juvenile Diabetes Research Foundation 11-2010-343; MCG: T32 DK063687, BIRCWH 2K12HD057022CCTSI; CTRC -5MO1 RR00069, M01-RR00051