Aberrant skeletal muscle mitochondrial responses to exercise in overweight women with polycystic ovary syndrome (PCOS)

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Background. Skeletal muscle constitutes 45% of body mass, accounting for 80% of insulin stimulated glucose uptake and is implicated in the pathogenesis of insulin resistance (IR) and type II diabetes mellitus (DM2), although the mechanisms of IR remain unclear. Diminished mitochondrial oxidative capacity and mitochondrial damage have been shown in DM2. Exercise training has been shown to promote mitochondrial biogenesis and function in skeletal muscle, and is currently believed to be a key mechanism for enhancing insulin sensitivity after exercise training. The present study aimed to compare the effects of 12 weeks of exercise training (treadmill) on mitochondrial biogenesis in skeletal muscle of normoglycaemic, overweight women with polycystic ovary syndrome (PCOS; an IR, pre-diabetic condition) to age and weight matched controls.

Materials and Methods. 20 PCOS and 13 control women who met the inclusion criteria began the study, with only 8 PCOS and Control women completing the entire study. These women after a 3 month "wash out" period completed a DEXA scan, VO_{2peak} test and a hyperinsulaemic euglycaemic clamp with *vastus lateralis* muscle biopsies. They then completed 12 weeks of treadmill exercise training (3d wk^{-1}) alternating between 60 min of moderate intensity constant speed exercise and 45-60min high-intensity intermittent exercise. The initial tests were all repeated within 7 d of completing the training. Muscle samples were analysed for gene expression by semi quantitative real-time PCR, protein expression and enzyme activity of key representative mitochondrial proteins.

Results. Exercise resulted in a 17% ($p < 0.05$) and 32% ($p < 0.05$) increase in glucose infusion rate in PCOS and Control women respectively. This was accompanied by a 23% ($p < 0.05$) and 16% ($p < 0.05$) increase in VO_{2peak} in PCOS vs. Controls. Normalised gene expression for Tfam, NRF1, PGC1α and UCP3 remained unchanged or increased to a similar extent in the PCOS and controls in response to training. COX4 gene expression increased to a greater extent in PCOS *vs* Control trained muscle (Fold change; mean ± SEM; 1.9 ± 0.1 *vs* 1.4 ± 0.2; $p < 0.05$). In response to training, protein expression of electron transport chain (ETC) protein complex 2 30 kDa, trended towards an increase in Controls *vs* PCOS muscle (1.8 ± 0.3 fold *vs* 0.9 ± 0.2 fold; $p = 0.06$), with an apparent trend towards this differential effect of exercise seen across the ETC.

Discussion. Markers of mitochondrial biogenesis and function in normoglycaemic, overweight IR women with PCOS showed aberrant gene and protein expression in response to exercise training, compared to age and weight matched controls. Potentially, this is related to the IR state observed in PCOS, impairing mitochondrial response to exercise.