Skeletal muscle and insulin resistance – a focus on mitochondria

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Skeletal muscle accounts for approximately 80% of insulin-stimulated glucose uptake and a key defect in the aetiology of type 2 diabetes (T2D) is the development of skeletal muscle insulin resistance (DeFronzo *et al.*, 1985). It has been well documented that skeletal muscle of people with T2D have impaired mitochondrial function, with this being due to reduced mitochondrial content (Boushel *et al.*, 2007). Furthermore, many of the regulatory components involved in mitochondrial biogenesis, such as peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) are also known to be reduced in the skeletal muscle of people with T2D (Patti *et al.*, 2003). This led to the popular hypothesis that the reduction in mitochondrial content in T2D was causative in the development of skeletal insulin resistance, via the reduced capacity for lipid oxidation and subsequent accumulation of lipids that may impair insulin-stimulated glucose uptake (Patti *et al.*, 2003). However, many studies who find reduced mitochondrial content in T2D are likely confounded by several factors, such as not controlling for reduced physical activity, which strongly impacts mitochondrial content (van Tienen *et al.*, 2012). Therefore it appears that mitochondrial dysfunction, at least in humans with T2D, is secondary to the development of skeletal muscle insulin resistance.

Although mitochondrial dysfunction may not be causative in the development of skeletal muscle insulin resistance for T2D, it is still quite likely that improving skeletal muscle mitochondrial content and function could be causative in improving insulin resistance. Indeed, people with T2D respond to endurance training with normal increases in insulin sensitivity and skeletal muscle mitochondrial proteins (van Tienen *et al.*, 2012). Furthermore, rodent studies that increase skeletal muscle mitochondria via electrotransfection of PGC-1α also improve skeletal muscle insulin sensitivity (Benton *et al.*, 2010).

Mitochondria are responsible for the majority of skeletal muscle ROS production under basal (non contraction) conditions (Vasilaki *et al.*, 2006) and there is now strong evidence linking mitochondrial ROS and skeletal muscle insulin resistance (Anderson *et al.*, 2009; Hoehn *et al.*, 2009). However, there is currently limited *in vivo* evidence to confirm if mitochondrial ROS levels are elevated in the skeletal muscle of people with T2D. Furthermore, despite the promising evidence of mitochondrial specific antioxidants reducing skeletal muscle insulin resistance in rodents (Anderson *et al.*, 2009; Hoehn *et al.*, 2009), evidence to support antioxidant therapies for the treatment of skeletal muscle insulin resistance in humans is lacking.

The mechanism for reduced ROS levels following increased mitochondrial content (*e.g.* after exercise training) is thought to be due to the elevated mitochondrial content per unit of tissue (*i.e.* more efficient respiration) (Mitsuishi *et al.*, 2008). Importantly, high glucose levels in skeletal muscle cells, which is known to induce insulin resistance, increase mitochondrial ROS levels and this can be reversed *in vitro*, by increasing mitochondrial biogenesis and mitochondrial mass (Mitsuishi *et al.*, 2008). Therefore, it is possible that a similar process may occur in skeletal muscle of people with T2D in response to exercise training. However, studies are now required to test if this also occurs in human or animal skeletal muscle.

Anderson EJ, Lustig ME, Boyle KE, *et al.*, (2009) *Journal of Clinical Investigation* **119**, 573-81.
Benton CR, Holloway GP, Han XX, *et al.*, (2010) *Diabetologia* **53**, 2008-19.
Boushel R, Gnaiger E, Schjerling P, *et al.*, (2007) *Diabetologia* **50**, 790-96.
DeFronzo RA, Gunnarsson R, Bjorkman O, Olsson M & Wahren J. (1985) *Journal of Clinical Investigation* **76**, 149-55.
Hoehn KL, Salmon AB, Hohnen-Behrens C. *et al.*, (2009) *Proceedings of the National Academy of Sciences USA.* **106**, 17787-92.
Mitsuishi M, Miyashita K & Itoh H. (2008) *Biochemical and Biophysical Research Communications* **367**, 840-45.
Patti ME, Butte AJ, Crunkhorn S, *et al.*,(2003) *Proceedings of the National Academy of Sciences USA.* **100**, 8466-71.
van Tienen FHJ, Praet SFE, de Feyter HM, *et al.*, (2012) *Journal of Clinical Endocrinology and Metabolism* **97**, 3261-69.
Vasilaki A, Csete M, Pye D, *et al.*, (2006) *Free Radical Biology and Medicine* **41**, 1719-25.