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Muscle-to-fat interaction: a two-way street?

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In a recent issue of *The Journal of Physiology*, a study by Sitnick *et al.* (2009) sheds new light on the role of muscle and fat in lifestyle-related diseases. They show that chronic high fat feeding impairs the ability of murine skeletal muscle to hypertrophy in response to a mechanical load. If their experimental study can be translated into human biology, it means that the consequence of a high fat diet is not just an increase in fat mass, but a decrease in muscle mass.

Several studies have shown a U-shaped association between body mass index (BMI) and mortality, suggesting that both a high and a low BMI are associated with premature death. It appears that the risk observed at a low BMI is more closely linked with low fat free mass than low fat mass. Also, a large hip circumference relative to BMI and waist circumference appears to be a strong inverse predictor of both morbidity and mortality (Heitmann & Frederiksen, 2009). It seems that it is the lower body muscle mass that is related to the development of type 2 diabetes as impaired insulin resistance could be provoked in lower body muscle, such as leg muscle, but not in arm muscle (Olsen *et al.* 2005).

In continuation, a most recent study shows that a low thigh circumference is associated with an increased risk of developing heart disease and premature death. The authors suggest that the adverse effects of small thighs might be related to too little muscle mass in the region (Heitmann & Frederiksen, 2009). Abdominal adiposity, reflecting accumulation of visceral fat, is associated with cardiovascular disease (CVD), type 2 diabetes and all-cause mortality independently of BMI, even in people with a normal body weight. However, it is also well known that physical inactivity and poor physical fitness, independently of BMI, are associated with an increased risk of CVD, type 2 diabetes, and premature mortality of all causes (Pedersen, 2009). Thus, the health consequences of abdominal adiposity and physical inactivity are similar. In other words, the health consequences of a large abdominal adipose tissue mass and a low muscle mass are similar. Obviously, one interpretation of these facts could be that muscle disuse leads to loss of muscle mass as well as an impairment of fat oxidation capacity, which may lead to accumulation of abdominal adipose tissue. It now appears that 'muscle-to-adipose tissue interaction' is a two-way street. Thus, according to Sitnick *et al.* (2009) a large adipose tissue mass or high fat feeding *per se* influences the ability of muscle to hypertrophy in response to increased mechanical load.

The authors (Sitnick *et al.* 2009) clearly show that the impaired muscle hypertrophy is paralleled by an attenuation in the anabolic pathway, which includes activation of Akt and S6K1. Given that adipose tissues are inflamed and a major source of systemic low-grade inflammation, the possibility exists that obesity induces systemic inflammation that interferes with protein synthesis. An alternative explanation is that saturated fatty acids directly mediate inflammation-induced inhibition of protein synthesis (Kennedy *et al.* 2009). Saturated fatty acids may directly cause inflammation and insulin resistance in muscle. For example, palmitate-mediated lipid accumulation in rat muscle causes insulin resistance via protein kinase C (PKC) signalling. Palmitate increases the expression and secretion of inflammatory cytokines and impairs insulin sensitivity via a nuclear factor-κB (NFκB)/PKC pathway in muscle cells (C2C12). Similarly, palmitate causes insulin resistance in murine L6 myotubes via NFκB signalling. Interestingly, co-supplementation with linoleate prevents palmitate-induced NFκB activation and subsequent expression and secretion of interleukin-6 in human myotubes. Accumulation of 1,2-diacylglycerol (DAG) and ceramide is associated with insulin resistance in muscle. Palmitate, but not oleate, causes the accumulation of DAG and ceramide in C2C12 myotubes (Kennedy *et al.* 2009).

Given the study by Sitnick *et al.* (2009) it would be of interest to know how a high fat diet, mainly consisting of unsaturated fat, such as oils containing oleic acid or (n-3) fatty acid would influence muscle protein synthesis and whether pre-treatment of muscle cells with oleate or (n-3) fatty acid would counteract the effect of saturated fatty acids. Moreover, given that obese individuals with a high fitness level appear to be protected from obesity-related diseases, it would be interesting to know if a trained muscle is resistant to the detrimental effects of a high fat diet rich in saturated fatty acids.

Lay people often claim that they have 'turned fat into muscle' or vice versa. While this is of course physically impossible, needless to say 'nonsense', the myth of turning 'fat into muscle' or 'muscle into fat' may have its background in the fact that not only does physical inactivity cause a decrease in muscle mass and an increase in fat mass, but a chronic high fat diet also exerts differential effects on these two organs.

References

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