# Comment on: Sitnick et al. Skeletal Muscle Triacylglycerol Hydrolysis Does Not Influence Metabolic Complications of Obesity. Diabetes 2013;62: 3350–3361

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Sitnick et al. (1) provide compelling evidence that skeletal muscle–specific modulations of adipose triglyceride lipase (ATGL) expression in vivo in mice impacts intramyocellular triacylglycerol (IMTG) content with no measurable effects on other lipid species (diacylglycerols [DAG], ceramides, and long-chain acyl-coenzyme A) and insulin sensitivity. The authors speculate that the fatty acid (FA) cycle observed in cardiac muscle, with FA largely trafficking through IMTG before being consumed, may only occur in skeletal muscle during exercise. However, data from Jensen and colleagues (2) elegantly demonstrate that this cycle may be physiologically relevant in resting human skeletal muscle under normal feeding conditions. The findings in mice are also contrasting with the effect of ATGL on fat oxidation and insulin sensitivity observed in vitro in human primary myotubes (3).

The study by Sitnick et al. (1) raises a number of questions. It is first striking that long-term high-fat feeding did not raise DAG and ceramides in skeletal muscle of wild-type and skeletal muscle–specific ATGL knockout (SMAKO) mice, and that only subtle changes in skeletal muscle insulin-mediated activation of Akt were observed. As lipid-induced insulin resistance may occur without noticeable changes in canonical insulin signaling in skeletal muscle (4), future studies should specifically determine glucose uptake and insulin sensitivity in the skeletal muscle of SMAKO mice. Finally and most intriguingly, there is a remarkable discrepancy between muscle-specific (SMAKO) and whole-body genetic deletion (GAKO) of ATGL in terms of muscle insulin sensitivity (5) and glucose tolerance (6). The mechanism by which ATGL deficiency enhances whole-body glucose homeostasis despite massive IMTG accumulation remains an enigma so far. More research efforts are clearly needed to add pieces to this complex puzzle linking ATGL, IMTG, and insulin sensitivity.

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