Comment on: Høeg et al. Lipid-Induced Insulin Resistance Affects Women Less Than Men and Is Not Accompanied by Inflammation or Impaired Proximal Insulin Signaling. Diabetes 2011;60:64–73

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I read with interest the article by Høeg et al. (1) in the January issue of *Diabetes* in which the authors concluded that there is a sex difference in the response in free fatty acid (FFA)-induced skeletal muscle insulin resistance following a lipid infusion in nonobese healthy humans. This was based on a rather small difference of marginal statistical significance ($P < 0.05$), and it was only the case for the glucose infusion over 120 min (Fig. 1*B*), but not over the last 30 min (which would be of greater value because it is closer to steady state; Fig. 1*A*) or when expressed by overall kilogram of body mass (31 ± 3 vs. 29 ± 4 μmol/min/kg) or as the delta leg glucose uptake (Fig. 1*F*). It is also unclear whether the authors used the glucose infusion rate (as stated in the figures) or meant insulin-stimulated glucose uptake (R_d) from the ^{3}H-glucose reported, which would have been more precise but unlikely in steady state only 5 h after breakfast. I would have indeed expected a greater sex difference from the ~20% higher plasma FFA concentration in men prior to the insulin clamp experiments (statistically not significant per the authors), which was clinically relevant as suggested by their 45% higher plasma triglyceride levels (men: 2,478 vs. women: 1,706 mg/dL, $P < 0.05$). Both the higher plasma FFA and triglycerides persisted until the end of the clamp study.

My colleagues and I have previously reported no sex difference in lipid-induced skeletal muscle insulin resistance after an acute lipid infusion of similar duration than reported in the article by Høeg et al. (1), with plasma FFA ranging in dose-response studies from the physiological (plasma FFA ~700 μmol//L) to the pharmacological (~2,000 μmol/L as in the current study) range (2). Of note, the authors overlooked this work when they stated in the introduction that only one prior study included women (ref. 8 of the article), although they do quote our study in the DISCUSSION section when acknowledging the reported inhibition of insulin signaling by lipid infusion. Intrigued by the work of Høeg et al., my colleagues and I reanalyzed our prior studies to again observe no sex difference to chronic lipid-induced insulin resistance in healthy control subjects after 48 (3) or 96 (4) hours of lipid infusion that raised the plasma FFA concentration by ~twofold (this effect on sex has not been reported before by us).

It is unclear in the article by Høeg et al. (1) the mechanism(s) for the induction of insulin resistance by lipid infusion, since neither insulin signaling was impaired nor was there an accumulation of toxic lipid-derived metabolites (i.e., diacylglycerols, ceramides, other) or induction of inflammatory pathways. This is in contrast to a large body of data in vitro, in vivo, and in humans (2,4, and reviewed in 5,6) suggesting that these mechanisms interact and are likely to play a role in lipid-induced skeletal muscle insulin resistance. While we all know that "current dogma" is not equivalent to the truth, the lack of a strong alternative hypothesis for the observed lipid-induced insulin resistance by Høeg et al. (1) should be a call for caution about the conclusions and stimulate future studies.

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