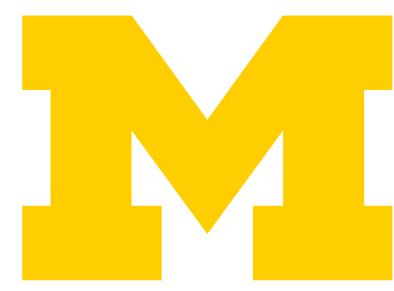


Obesity enhances glucocorticoid action in muscle and adipose tissue



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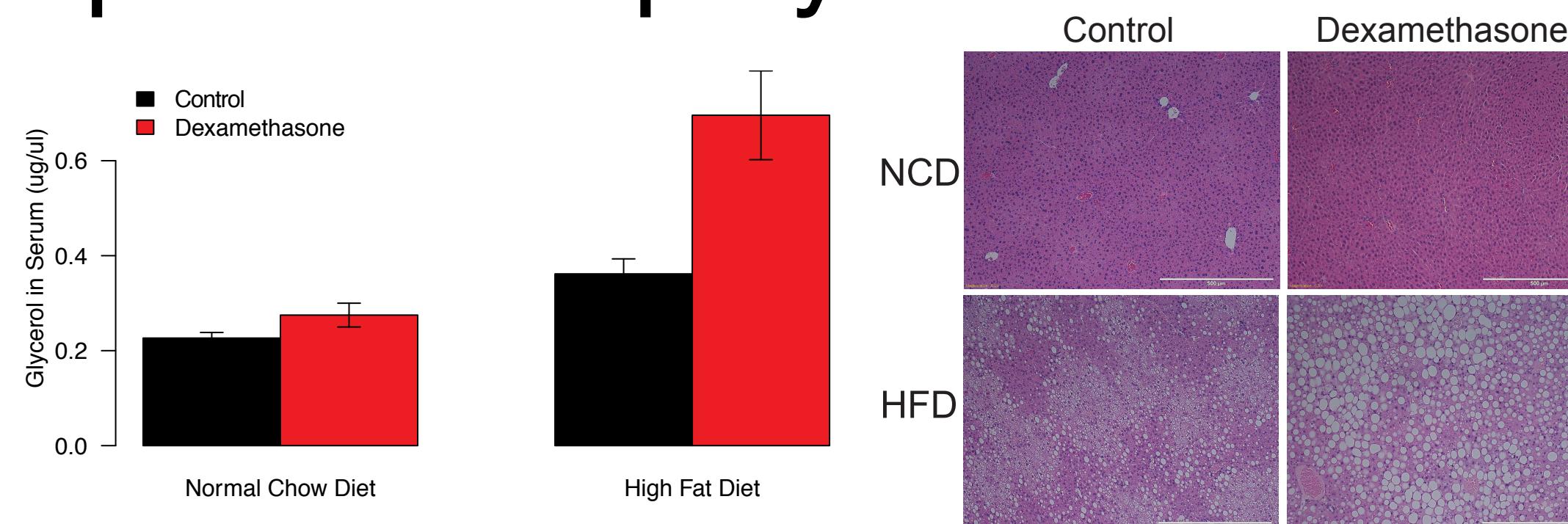


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Abstract

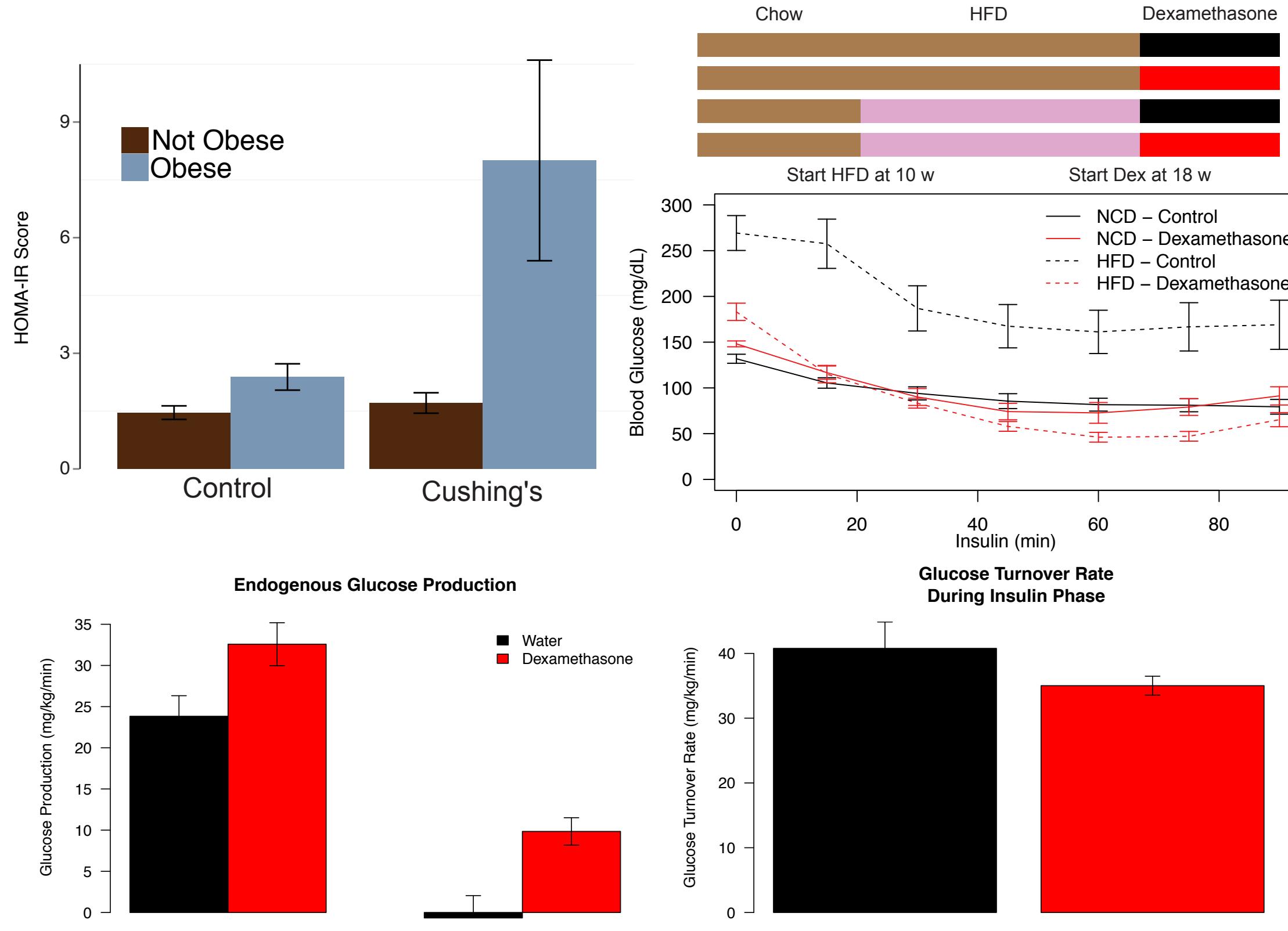
Obesity is a world-wide public health epidemic affecting nearly a third of adult Americans. Both chronic stress and prescription glucocorticoids are increasingly common, but little is known about how stress hormones, such as glucocorticoids, function differentially in lean and obese individuals. Our data in humans and mice demonstrate the sensitizing effects of obesity on glucocorticoid-dependent processes including insulin resistance, NAFLD and muscle atrophy. These data provide support for the hypothesis that **obesity enhances glucocorticoid signaling in muscle and adipose tissue**. Using tissue-specific knockout models we show that adipocyte glucocorticoid action is critical for obesity-enhanced glucocorticoid-induced insulin resistance but that this is independent of effects on muscle atrophy. In terms of molecular mechanisms, we provide data suggesting that obesity modifies the chromatin landscape around select loci enabling more efficient glucocorticoid-dependent transactivation of target genes. It has been established that obesity confers both resistance to anabolism and promotion of catabolism, though the mechanisms underlying the catabolic phenomena are unclear. Our data supports the hypothesis that obesity may enhance the mobilization of fuel from adipocyte and muscle stores as an adaptive process to restore body weight homeostasis.

Obesity Enhances Glucocorticoid Dependent Lipolysis and NAFLD



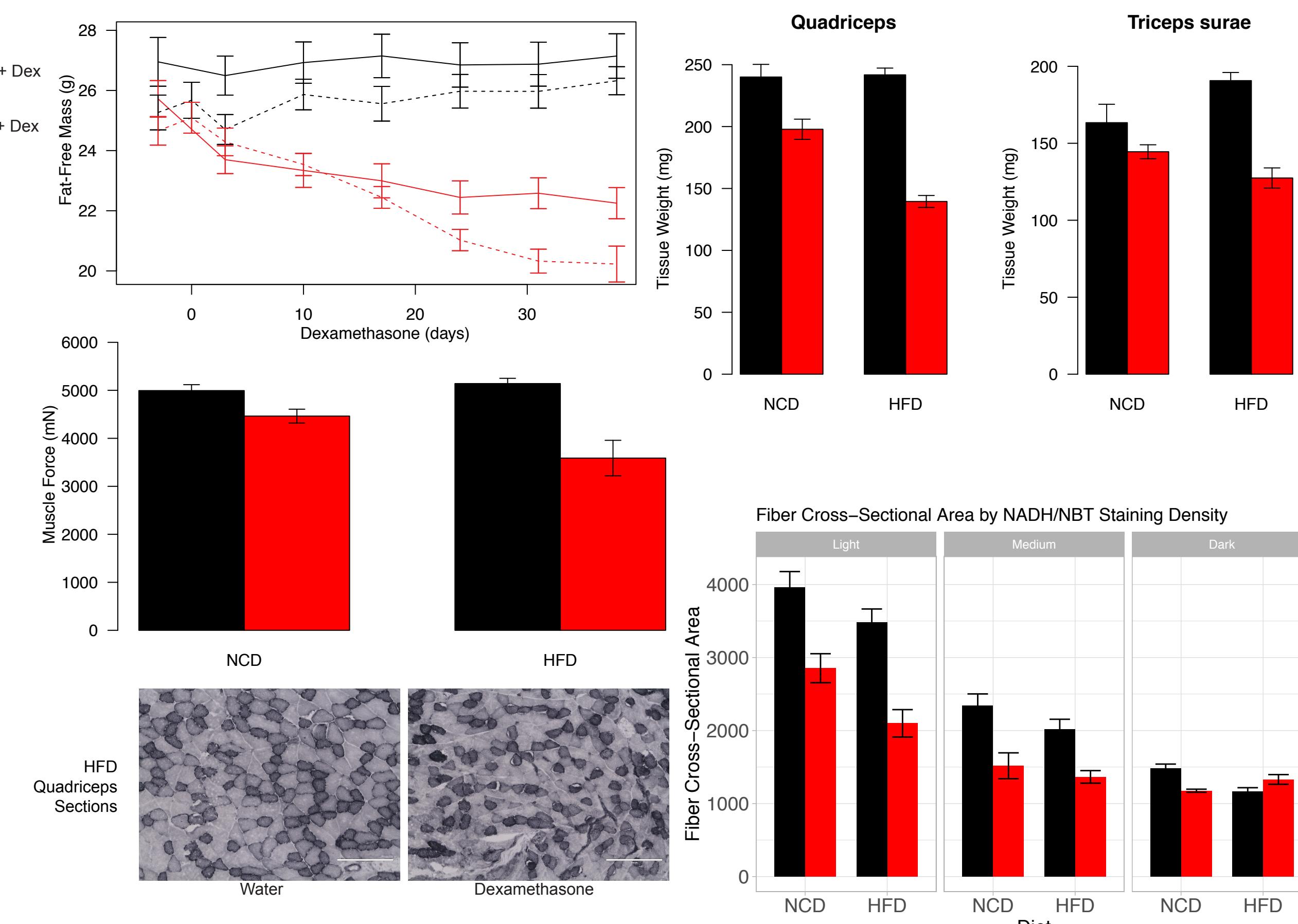
We did not detect any changes in gluconeogenic enzymes, but instead found elevations in lipolysis, and the Adipocyte Triglyceride Lipase in adipose tissue. This elevated lipolysis is also associated with dramatic increases in liver triglyceride levels, and may indirectly promote gluconeogenesis. This is supported by knockout of GR in adipocytes.

Elevated Insulin Resistance



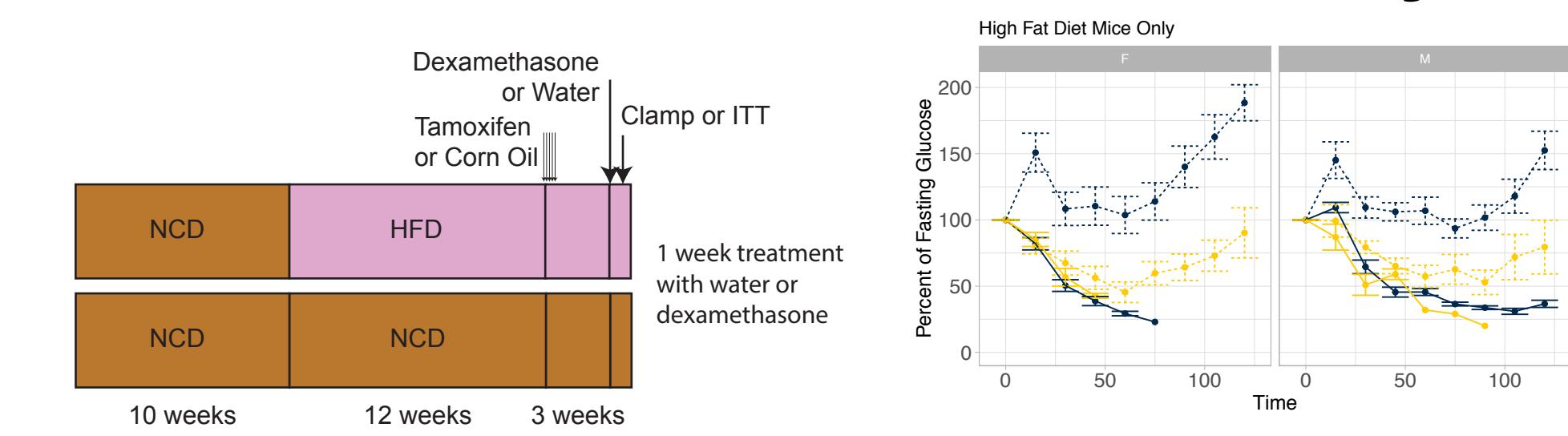
Our transcriptomic studies on Cushing's patients, suggested mRNA differences between individuals with obesity and without in terms of how adipose tissue was affected by chronic glucocorticoid exposure [1]. This lead us to re-analyse the HOMA-IR score of these subjects, which indicated glucocorticoid excess when combined with obesity lead to substantial insulin resistance. We developed a mouse model of diet-induced obesity, followed by dexamethasone treatment (in the drinking water) to evaluate this further. We found that these animals had substantial insulin resistance and hyperglycemia [2]. This was primarily caused by elevated glucose production.

Obesity Increases Muscle Atrophy



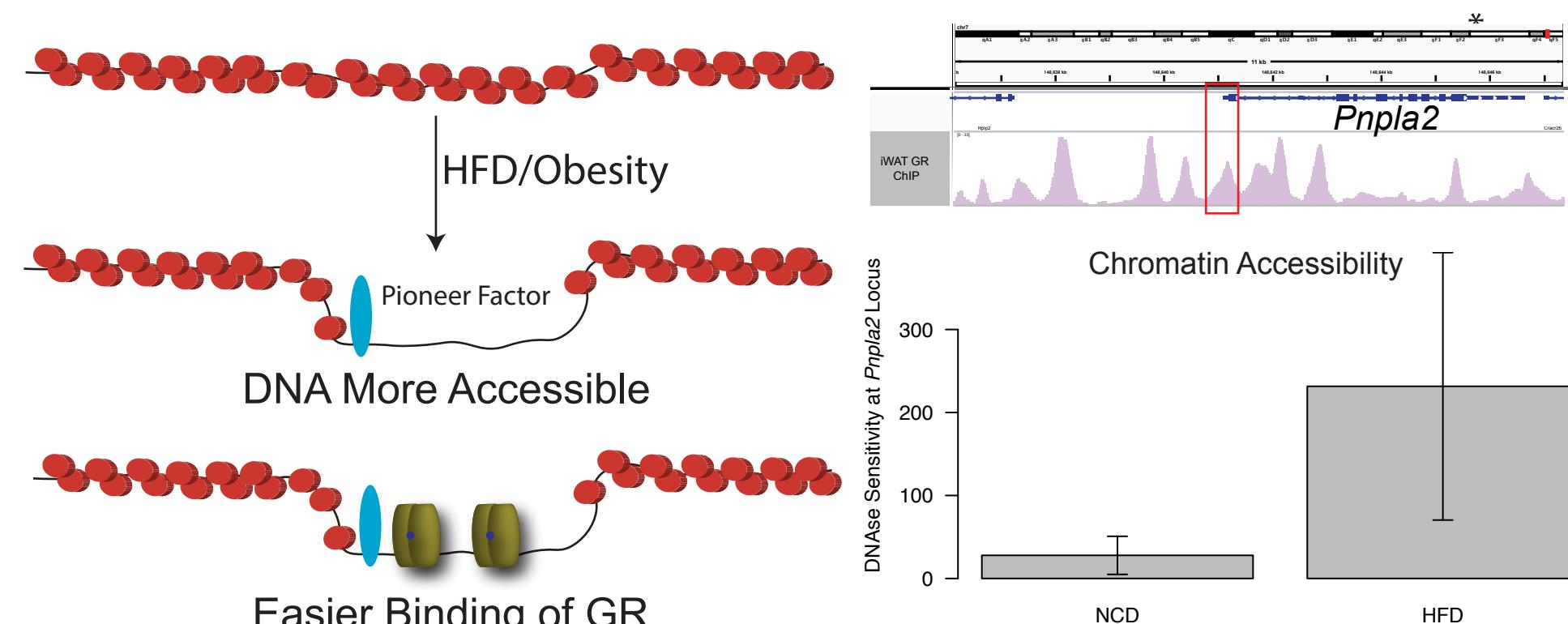
We noticed that mice not only had substantial diabetes and insulin resistance, but also had much stronger steroid-induced muscle atrophy than their lean counterparts. This was largely due to reductions in type II muscle fiber cross-sectional area. Functionally, the combination of obesity and steroid treatment resulted in very reduced muscle function as assessed by isometric force testing.

Knockout of Adipocyte GR and Insulin Sensitivity



To isolate adipocyte glucocorticoid action, we used an inducible GR knockout model which first were made obese via HFD, then were induced with tamoxifen, then finally treated with dexamethasone. These knockout of GR in adipocytes largely recovered the insulin resistance induced by obesity and glucocorticoid treatment.

Proposed Mechanism



We observed synergistic elevations of ATGL in adipose tissue, and the atrogenes in muscle tissue, but no changes in GR expression. We propose that the mechanism for this synergy is that obesity alters the chromatin state around GRE sites and this then promotes transcription of GR-dependent targets. This is supported by DNase sensitivity assays near key GR target genes.

Funding and References

1. Harvey I, Stephenson EJ, Redd JR, Tran QT, Hochberg I, Qi N, Bridges D. Glucocorticoid-Induced Metabolic Disturbances Are Exacerbated in Obese Male Mice. *Endocrinology* 159: 2275–2287, 2018.
2. Hochberg I, Harvey I, Tran QT, Stephenson EJ, Barkan AL, Saltiel AR, Chandler WF, Bridges D. Gene expression changes in subcutaneous adipose tissue due to Cushing's disease. *J Mol Endocrinol* 55: 81–94, 2015.

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