To evaluate the effects of juvenile glucocorticoid exposure on metabolic disease later in life I administered dexamethasone to juvenile mice and then challenged these mice with a high-fat diet during adulthood and assessed outcomes related to body composition and glucose homeostasis to examine whether factors such as early stress or childhood glucocorticoid treatment impacts metabolic health later in life. Additionally, I, along with Laura Gunder, an MS student involved in this project, assessed the effects of chronically elevated glucocorticoids in the presence or absence of obesity on muscle health.

## Methods

### Cell Culture

C2C12 fibroblasts were cultured in 10% Fetal Bovine Serum and Dulbecco's Modification of Eagle's Medium (DMEM; 4.5 g/L D-glucose; Fisher Scientific; catalog #11965118) with penicillin, streptomycin and glutamine (PSG) until approximately 70% confluence. Once desired confluence was achieved, cells were switched to 2% Horse Serum (HS) media (Sigma-Aldrich; catalog #H1270). Media was refreshed every other day and myotube differentiation was reached around 7-10 days in HS. Cells were kept in an incubator set at 5% $CO_2$ and 37 °C.

### Assessing the Effects of Dexamethasone on Muscle Insulin Signaling *In Vitro*

Differentiated myotubes were treated with 250nM dexamethasone or vehicle (ethanol) in HS media for two days, then 100nM insulin was administered to C2C12 myotubes for 10 or 30 minutes. Following insulin treatment, cells were snap frozen and stored at -80 °C until further analysis.

## qPCR

Cells and tissues were lysed in TRIzol using the TissueLyser II, as described above, and RNA was extracted using a PureLink RNA kit (Life Technologies; catalog #12183025). cDNA was synthesized from 0.5-1ug of RNA using the High Capacity Reverse Transcription Kit (Life Technologies; catalog #4368813). Primers, cDNA and Power SYBR Green PCR Master Mix (Life Technologies; catalog #4368708) were combined in accordance with the manufacturer's guidelines and quantitative real-time PCR (qPCR) was performed as previously described (Lu et al. 2014) using the QuantStudio 5 (Thermo Fisher Scientific). mRNA expression level was normalized to *Actb* and analyzed using the ΔΔCt method after evaluation of several reference genes. Real time qPCR primer sequences are listed in Table 1.

## Protein Extraction and Analysis

Cells and tissues were lysed in RIPA buffer (50 mM Tris, pH 7.4, 0.25% sodium deoxycholate, 1% NP40, 150 mM sodium chloride, 1 mM EDTA, 100 uM sodium orthovanadate, 5 mM sodium fluoride, 10 mM sodium pyrophosphate and 1x protease inhibitor), centrifuged at 14,000rpm for 10 minutes at 4°C. Lysates were heated with loading buffer at 85-95°C and proteins were separated by SDS-PAGE (Life Technologies) and transferred onto nitrocellulose

membranes overnight at room temperature. Membranes were blotted at room temperature using Anti-Akt and anti-pAkt-s473 (Cell Signaling Technologies). Antibody complexes were detected by anti-mouse and anti-rabbit fluorescent conjugated antibodies (Invitrogen) and visualized using an Odyssey CLx image scanner. Blots were quantified using Image Studio software version 5.2 (LiCOR) and pAkt was normalized to total Akt levels.

## Animal Housing and Treatment

To compare the effects of chronic dexamethasone treatment on muscle atrophy and insulin signaling in lean and obese mice, C57BL/6J adult male mice were purchased from the Jackson Laboratory at nine weeks of age (stock #000664). Following a week of acclimation, mice were placed on diets or treated with dexamethasone as described in the figure legends. Mice were treated with vehicle (water) or approximately 1mg/kg/d of water-soluble dexamethasone (Sigma-Aldrich; catalog #2915), a synthetic glucocorticoid, dissolved in their drinking water for up to 12 weeks, as described in figure legends. Additional cohorts of mice used in these experiments either remained on a standard diet (normal chow diet; NCD; 5L0D LabDiet; 13% fat; 57% carbohydrate; 30% protein) or were provided a high fat diet (45% fat from lard; 35% carbohydrate mix of starch, maltodextrin and sucrose; 20% protein from casein; cat# D12451) for either 8 or 12 weeks followed by dexamethasone treatment. Mice remained on their respective diets for the duration of the study. Water intake was measured weekly to determine the concentrations of dexamethasone consumed per cage. Average concentration per mouse was estimated by accounting for number of mice in the cage.

For the juvenile exposure experiment, male and female NON/ShiLtJ mice purchased from the Jackson Laboratory (Stock #002423) and further bred in house. This strain was chosen for the juvenile exposure study is known to develop rapid metabolic disorders when challenged, allowing for a more robust detection of abnormalities due to treatment in a smaller window of time. At 35 days of age mice were either kept on their regular drinking water (vehicle; control group) or had dexamethasone added to their water at an estimated dose of 1mg/kg/day. Dexamethasone water was removed and replaced with regular water following one week of treatment and all mice remained on regular drinking water throughout the remainder of the study. At 70 days, all mice were placed on a high fat diet (HFD; 45% calories from fat; Research Diets) and remained on this throughout the study.

All mice were provided with access to food and water *ad libitum* throughout the study, unless otherwise noted. All mice were kept on a light dark cycle of 12/12 h and were housed at 22 ºC in groups of up to 5 per cage. For all cohorts, weight, body composition (via EchoMRI 2100) and food intake was measured weekly. At the end of studies, mice were fasted for 16 hours beginning a ZT10, dexamethasone water was not removed during this time, and euthanized by cervical dislocation after isoflurane anesthesia at ZT3 of the following day. Immediately following euthanasia, tissues were carefully excised (in some cases weighed) and snap frozen in liquid nitrogen and stored at -80C for further analysis. Additionally, small pieces of tissues were fixed in 10% phosphate-buffered formalin for histology. Animal procedures were approved by the University of Tennessee Health Science Center and University of Michigan Institutional Animal Care and Use Committees.

## Assessment of Grip Strength

Grip strength was measured at baseline and over the course of treatment following treatment for the C57BL/6J mice using a Chatillon digital force gauge (AMETEK). Mice were placed on the grid having all four paws in contact with the apparatus and slowly pulled backwards by the tail. Mice were given five trials with about 10 seconds rest in between trials. Grip strength was measured by the average peak torque (N) over the five trials.

## Hyperinsulinemic Euglycemic Clamp

C57BL/6J adult (70d) male mice were fed HFD for eight weeks and treated with dexamethasone in their drinking water for three weeks or regular drinking water. Animals were anesthetized with an IP injection of sodium pentobarbital (50–60 mg/kg). Indwelling catheters were inserted into the right jugular vein and the right carotid artery, respectively. The free ends of catheters were tunneled subcutaneously and exteriorized at the back of the neck via a stainless-steel tubing connector (coated with medical silicone) that was fixed subcutaneously upon closure of the incision. Animals with healthy appearance, normal activity, and weight regain to or above 90% of their pre-surgery levels were used for the study. Experiments were carried out in conscious and unrestrained animals using techniques described previously (McGuinness et al. 2009; Ayala et al. 2006; Halseth et al. 1999). Briefly, the primed (1.0 uCi)-continuous infusion (0.05 uCi/min and increased to 0.1 $\mu$Ci/min at t = 0) of [3-$^3$H] glucose (50 $\mu$Ci/ml in saline) was started at t = -120min. After a five-hour fast, the insulin clamp was initiated at t = 0, with a prime-continuous infusion (40 mU/kg bolus, followed by 8.0 mU/kg/min) of human insulin (Novo Nordisk). Euglycemia (120~130 mg/dL) was maintained during the clamp by measuring blood glucose

every 10 min and infusing 50% glucose at variable rates, accordingly. A bolus injection of [1-$^{14}$C]-2-deoxyglucose ([$^{14}$C]2DG; PerkinElmer) (10 $\mu$Ci) was given at t = 120 min. At the end of the experiment, animals were anesthetized with an intravenous injection of sodium pentobarbital and tissues were collected and immediately frozen in liquid nitrogen for later analysis of tissue [1-$^{14}$C]-2-deoxyglucose phosphate ([$^{14}$C]2DGP) radioactivity. Blood glucose was measured using an Accu-Chek glucometer (Roche, Germany). Tissue glucose uptake was calculated as described elsewhere (Kraegen et al. 1985; Ayala et al. 2006; Halseth et al. 1999).

## Assessment of Glucose Homeostasis

Following 10 weeks of HFD, NON-ShiLtJ mice were fasted for 6 hours starting at ZT3 and a glucose tolerance was performed using 1g glucose per kilogram of body weight, administered via IP injection. Blood was collected via tail clip and glucose was measured with a OneTouch Ultra glucometer at baseline and every 15 minutes post injection over a two-hour period. The following week glucose stimulated insulin release was determined. Mice were fasted for 6 hours then IP injected with 1g/kg glucose and blood was collected via a retro-orbital bleed at baseline and 15-minutes post injection and insulin was determined using the Ultra Sensitive Mouse Insulin ELISA Kit (Crystal Chem; catalog #90080) according to manufacturer's guidelines. Blood was centrifuged for 20 min at 4 °C and 5,000 rpm following clot and serum was collected and stored at -80 °Celsius until further analysis. At 21 weeks of age mice were euthanized via isoflurane anesthetization prior to cervical dislocation, tissues were collected and snap frozen in liquid nitrogen and stored at -80 °C or placed in 10% formalin for histology until further analysis.

## Serum Glycerol and Fatty Acid Determination

Whole blood was collected following a 16 hour fast starting at ZT10 in 22-week-old NON/ShiLtJ mice. Mice were anesthetized with isoflurane and blood was collected into heparin-coated capillary tubes via retro orbital bleed. Whole blood was allowed to clot on ice then centrifuged at 4 °C at 5000RPM for 20 minutes, serum was extracted and stored at -80 °C until further analysis. Glycerol was assessed via Serum Triglyceride Determination Kit (Sigma-Aldrich; catalog #TR0100-1KT) and fatty acids were quantified using the HR Series NEFA-HR(2) kit (Wako Diagnostics; catalog #276-76491), in accordance with manufacturer's guidelines.

## Muscle Histology

Quadriceps were collected and snap frozen in methyl-butane surrounded by liquid nitrogen and secured to an identifying platform with the patellar tendon facing up. Quadriceps samples were sectioned at -20 °C through the mid belly with a thickness of 12um and mounted on SuperFrost glass slides. Slides were imaged using the 20x objective of an EVOS XL digital inverted microscope. For analysis of fiber cross-sectional area (CSA), fibers were identified by H&E staining and the area of 50 fibers were averaged per mouse quadriceps using Image J.

## Statistics

All data are presented as mean +/- standard error of the mean. For animal studies, two-way ANOVA analyses were performed to test for significance of diet and dexamethasone treatment, as well as their interaction when appropriate. Pairwise comparisons, normality and equal variance were tested using Shapiro-Wilk and Levene's tests, respectively. Pending those results, a Mann-Whitney, Welch's or Student's *t*-test were used. P-values below p=0.05 were considered significant. All statistical tests were performed on Microsoft Excel or using the R software package version 3.30.

## Results

**Table 5: List of Primers for qPCR studies in Chapter 4**

| Gene | Forward 5'-3' Sequence | Reverse 5'-3' Sequence |
|---|---|---|
| *Fbxo32* | CTTCTCGACTGCCATCCTGG | GTTCTTTTGGGCGATGCCAC |
| *Psmd8* | ACGAGTGGAACCGGAAGAAC | CCGTGGTTGGCAGGAAATTG |
| *Trim63* | GAGGGCCATTGACTTTGGGA | TTTACCCTCTGTGGTCACGC |
| *Pgk1* | CAAGCTACTGTGGCCTCTGG | CCCACAGCCTCGGCATATTT |

## Reduced Lean Mass and Strength Following Chronic Glucocorticoid Exposure in Lean Mice

To investigate the effects of chronically elevated glucocorticoids on muscle we treated lean (chow fed) male adult (70d) mice with dexamethasone for 12 weeks and assessed outcomes of muscle atrophy and function. 12 weeks of dexamethasone treatment resulted in significant losses

of lean mass at the end of the study (26.03% increase; p<0.001; Figure 21A), as indicated by echo MRI, with the majority of the effects occurring in the first three weeks of treatment. This is consistent with previously reported effects of glucocorticoids on muscle atrophy (Pleasure, Walsh, and Engel 1970). In support of these findings, dexamethasone treatment led to a 22.47% reduction in mean grip strength at the end of the study (p<0.001; Figure 21B). Since the lean mass loss occurs rapidly following dexamethasone treatment, we measured atrophy and proteasomal transcripts in the quadriceps of another cohort of mice following *one* week of treatment and found nonsignificant elevations in the mRNA of the proteolytic E3 ligase genes *Fbxo32* (encoding Atrogin-1), *Trim63* (encoding MuRF-1) and *Psmd8* a proteasomal subunit (Figure 21C) in dexamethasone mice compared to controls, though these did not reach statistical significance (p>0.05). These data are consistent with the upregulation of proteolytic genes described in the adipose tissue from Cushing's (see Figure 6B-F in Chapter 2).

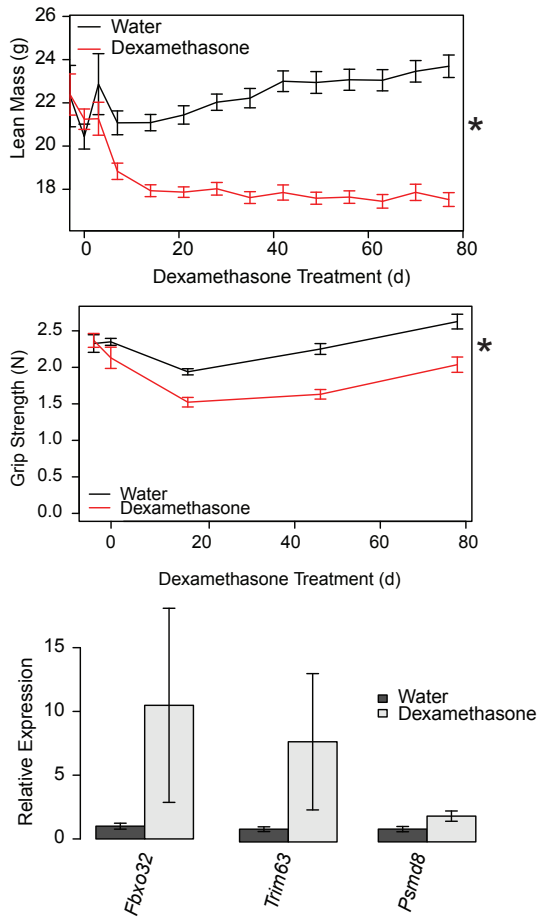


**Figure 21: Twelve weeks of dexamethasone treatment reduces lean mass and strength in mice.** Lean mass throughout study (A) and grip strength (N; B) assessed at baseline, 4, 8 and 12 weeks of dexamethasone treatment in chow-fed mice. Muscle atrogene transcript expression changes in gastrocnemius muscles from mice following 1 week of dexamethasone treatment (C) of mice treated with dexamethasone for 12 weeks. Asterisks indicates p<0.05.

## Dexamethasone-Induced Muscle and Strength Loss is Greater in Obese Mice

To determine whether pre-existing obesity influences glucocorticoid-induced lean mass loss we treated lean and obese male mice with dexamethasone for up to six weeks. These are the same animals described in Chapter 2. Dexamethasone caused a reduction in lean mass in lean and obese mice, with lean mass loss being greater in obese dexamethasone treated mice (Figure 22A), but there was no statistically significant interaction of diet and treatment ($p=0.314$). At sacrifice, the combination of dexamethasone and obesity led to the greatest reductions in both quadriceps ($p<0.001$) and triceps surae ($p=0.003$) muscles (Figure 22B). To ask whether the sensitization by obesity was secondary to adipocyte GR signaling, we performed similar experiments on the adipocyte GR knockout mice. As shown in Figure 22C-D this knockout not significantly attenuate the muscle loss in lean or obese dexamethasone treated animals, indicating that the factors leading to obesity and dexamethasone-induced muscle loss are independent of adipocyte GR signaling, and may be direct effects of glucocorticoid action on muscle tissue.

Consistent with lean mass reductions, dexamethasone treatment led to synergistic reductions in grip strength in both lean and obese mice when compared to controls (Figure 23A-B). Strength reductions were greater in obese dexamethasone-treated mice when compared to their lean counterparts. To understand the mechanisms that may result in increased atrophy of skeletal muscle we assessed both FOXO and the atrogenes, factors previously implicated in dexamethasone-induced muscle atrophy. After one week of dexamethasone treatment, we observed a greater induction of both *Foxo3* and the atrogenes *Trim63* and *Fbxo32*, in obese dexamethasone-treated mice when compared to lean (Figure 23C), though these findings did not

reach statistical significance (p>0.05 for all). After cryo-sectioning staining, and quantification we also observed dramatic reductions in muscle fiber cross-sectional area in obese dexamethasone treated mice (p=0.001 for the interaction of diet and treatment; Figure 23D-E). Taken together, these data provide evidence that obesity exacerbates glucocorticoid-induced muscle wasting. Similar to what we observed with synergistic activation of *Pnpla2* in adipose tissue by obesity and glucocorticoids, obesity is able to enhance muscle tissue's response to glucocorticoids.

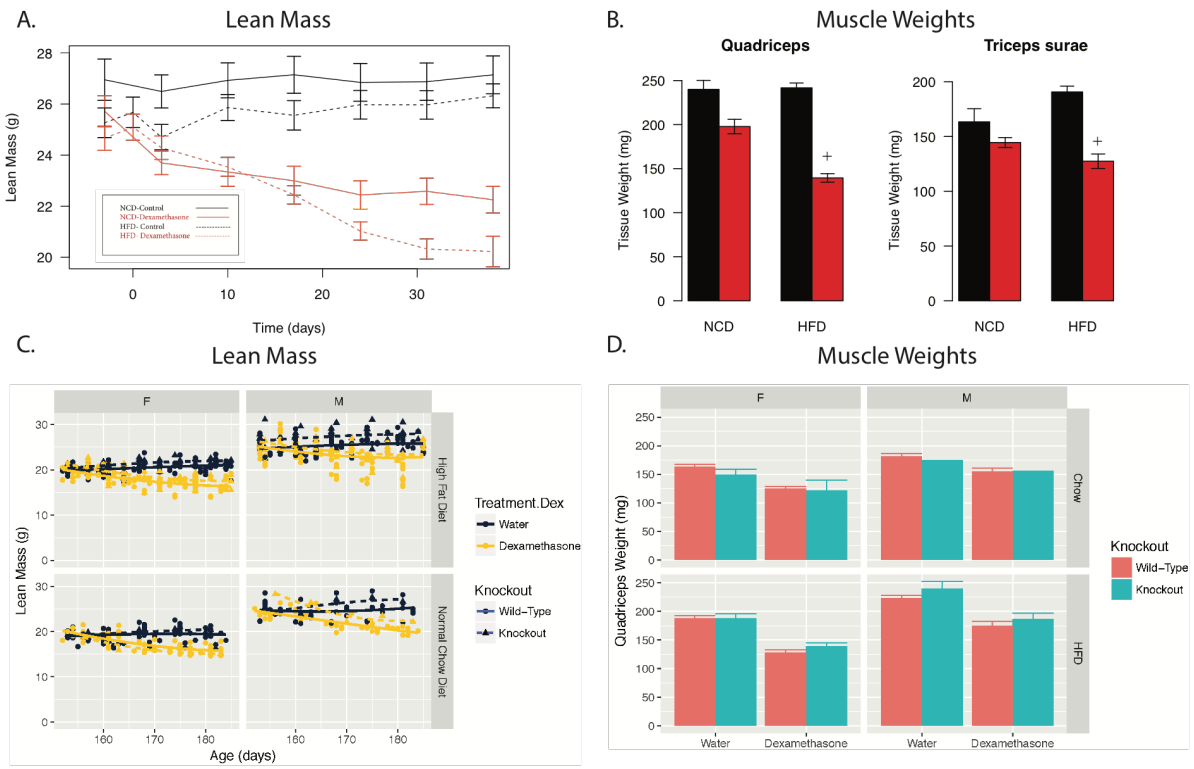


**Figure 22: Glucocorticoid-Induced Muscle Loss is Greater in Obesity and is not Influenced by Adipose Nr3c1 Ablation.** Lean mass via Echo MRI (A) and muscle weights (B) in lean and obese mice following six weeks of dexamethasone treatment. Lean mass (C) and muscle weights (D) in *Nr3c1* knockout and WT mice following three weeks of dexamethasone treatment. (+) indicates p<0.05 for the interaction of diet and treatment

## No Evidence Direct Effects of Glucocorticoids on Akt Phosphorylation in Muscle

Muscle is the primary tissue responsible for insulin-stimulated glucose uptake; therefore, muscle atrophy can lead to reductions in insulin sensitivity. It is well known that glucocorticoids cause insulin resistance, but the underlying mechanisms remain unclear. To determine whether dexamethasone acts directly on muscle to reduce muscle insulin signaling, we treated C2C12 myotubes with dexamethasone or vehicle for 48 hours, stimulated with insulin for 10 or 30 minutes and assessed phosphorylated Akt, a key protein in the insulin signaling pathway. There were no significant differences between dexamethasone- and vehicle-treated cells in serine-473 phosphorylated Akt levels when normalized to total Akt at 10 or 30 minutes ($p>0.05$ for both) of insulin stimulation (Figure 24A-B).

Insulin-stimulated glucose uptake was also assessed in adipose and muscle tissue under hyperinsulinemic euglycemic conditions. Glucose uptake was significantly reduced in lean and obese dexamethasone-treated muscles when compared to controls. Specifically, in lean dexamethasone treated mice glucose uptake was 51.8% lower in gastrocnemius ($p=0.002$) and near-significant differences were noted in iWAT with a 29.1% reduction in the dexamethasone group ($p=0.051$), but glucose uptake reduction in eWAT was not significant when compared to lean controls ($p=0.642$; Figure 24C). As mentioned previously, insulin clearance rates were reduced in lean dexamethasone treated mice (Chapter 2 Figure 10G); therefore, these data are difficult to interpret. Similarly to the findings in lean mice, obese dexamethasone-treated mice had a 67.9% reduction in gastrocnemius glucose uptake when compared to obese controls ($p=0.00002$; Figure 24D) and near-significant reductions in iWAT (30.1%; $p=0.051$), but glucose uptake in eWAT was not significantly different from controls ($p=0.804$). This is consistent with

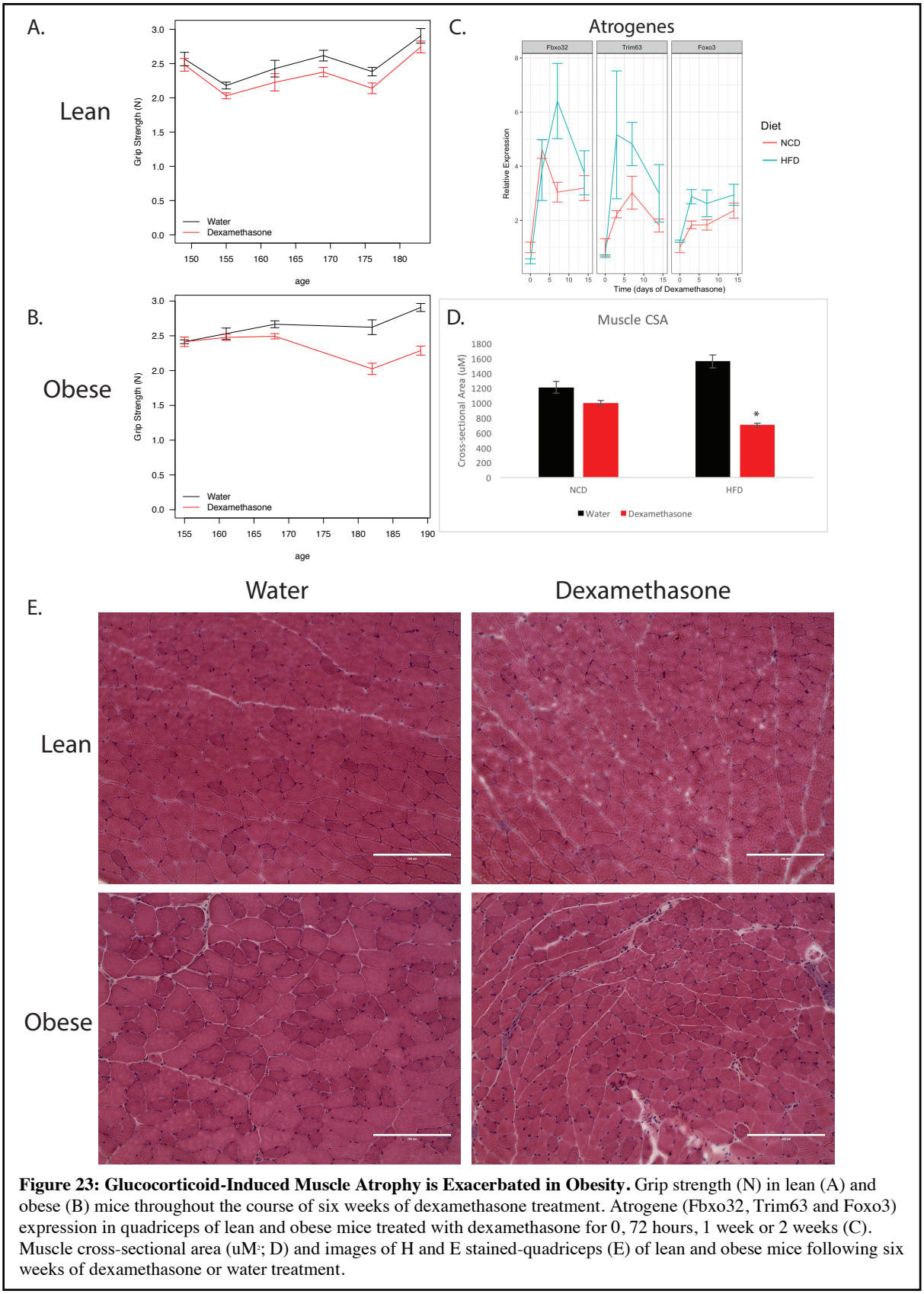


**Figure 23: Glucocorticoid-Induced Muscle Atrophy is Exacerbated in Obesity.** Grip strength (N) in lean (A) and obese (B) mice throughout the course of six weeks of dexamethasone treatment. Atrogene (Fbxo32, Trim63 and Foxo3) expression in quadriceps of lean and obese mice treated with dexamethasone for 0, 72 hours, 1 week or 2 weeks (C). Muscle cross-sectional area (uM$^2$; D) and images of H and E stained-quadriceps (E) of lean and obese mice following six weeks of dexamethasone or water treatment.

the modest reductions in insulin-stimulated glucose disposal observed during the euglycemic

hyperinsulinemic clamps in the obese dexamethasone-treated mice (see Figure 10 in Chapter 2).

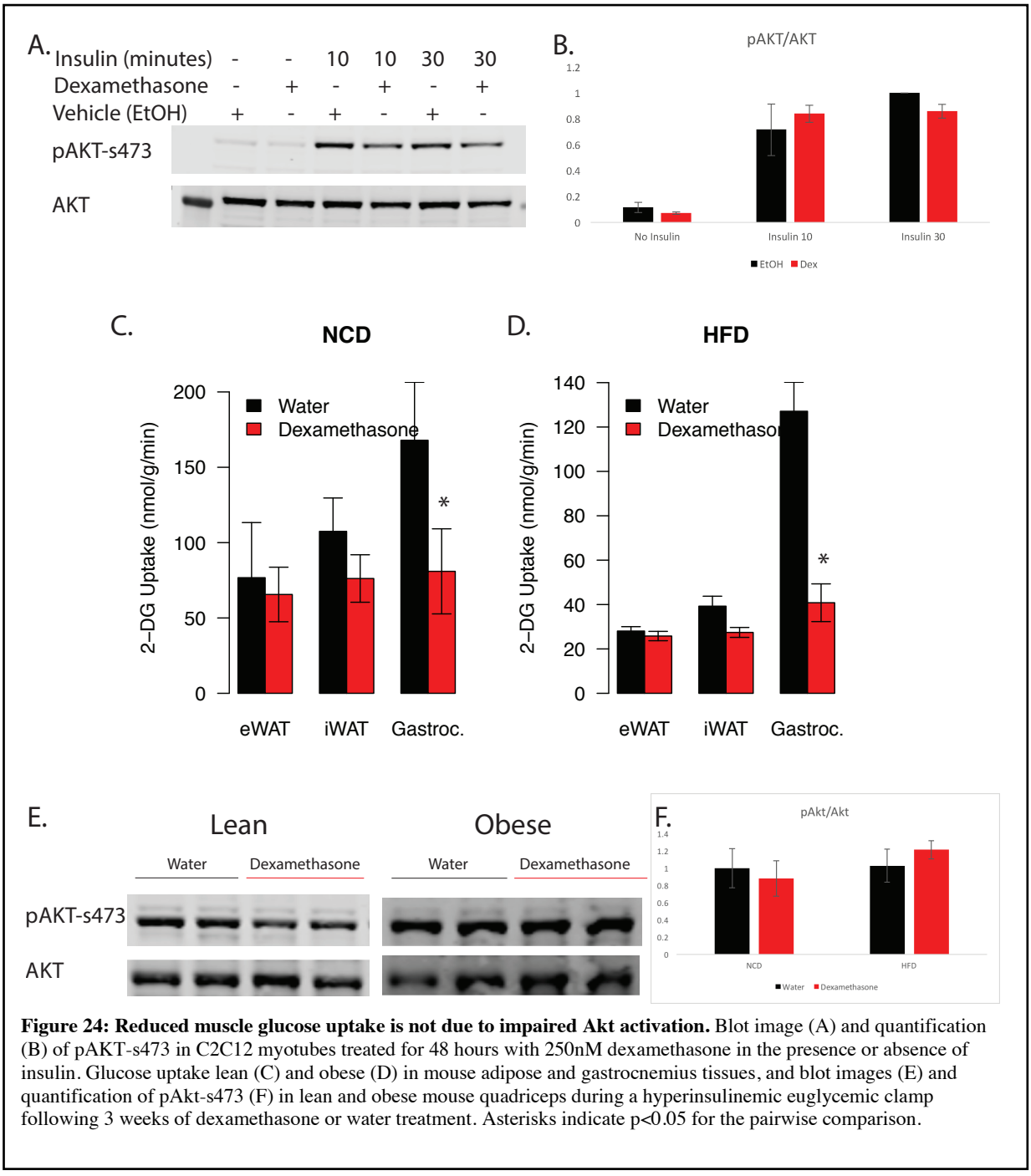


**Figure 24: Reduced muscle glucose uptake is not due to impaired Akt activation.** Blot image (A) and quantification (B) of pAKT-s473 in C2C12 myotubes treated for 48 hours with 250nM dexamethasone in the presence or absence of insulin. Glucose uptake lean (C) and obese (D) in mouse adipose and gastrocnemius tissues, and blot images (E) and quantification of pAkt-s473 (F) in lean and obese mouse quadriceps during a hyperinsulinemic euglycemic clamp following 3 weeks of dexamethasone or water treatment. Asterisks indicate $p<0.05$ for the pairwise comparison.

To investigate insulin signaling in the intact muscle in response to dexamethasone and obesity we assessed insulin signaling by measuring pAkt-s473 in the gastrocnemius muscle of animals

under euglycemic hyperinsulinemic clamp conditions. We found no significant differences in the lean or obese dexamethasone-treated animals when compared to controls (pval; Figure 24E-F). As a whole, these data suggest that impairment of muscle Akt phosphorylation is not the cause of dexamethasone-induced insulin resistance either *in vitro* or *in vivo*.

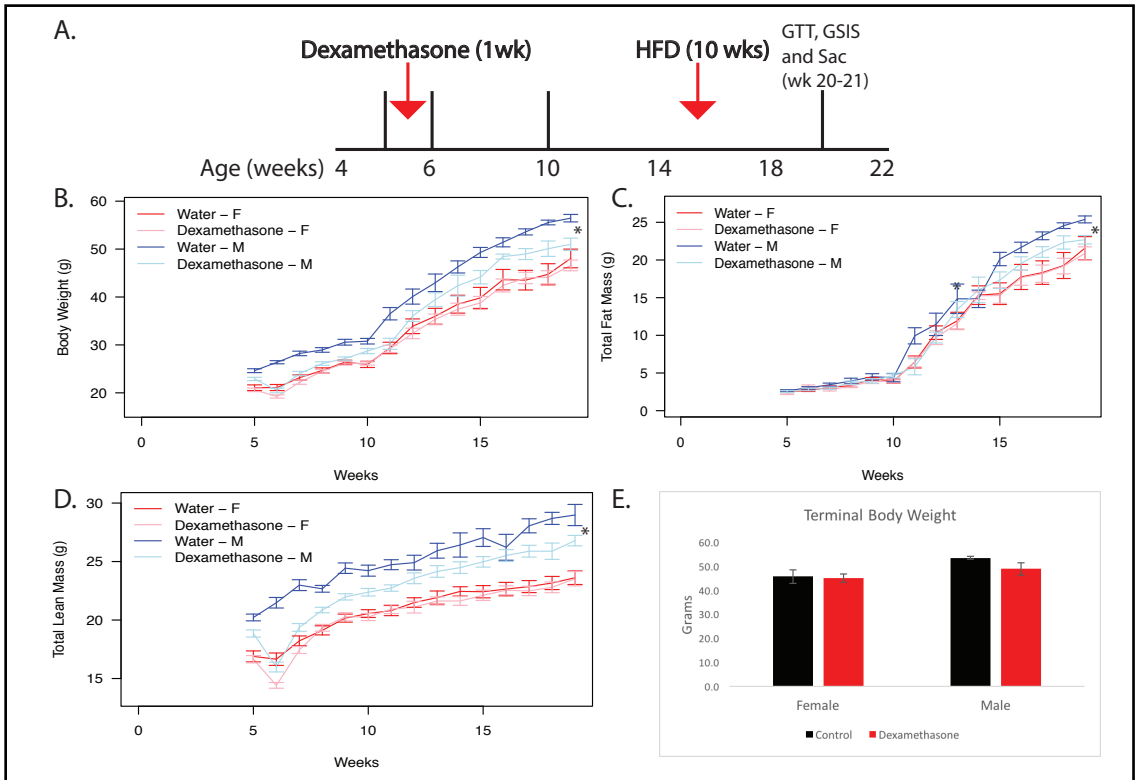


**Figure 25. Recovery from dexamethasone-induced lean mass loss is prolonged in male mice.** Study design schematic (A), body weight (B), fat mass (C) and lean mass (D) for juvenile dexamethasone- or water-treated mice. Terminal body weights in mice following overnight fast (E). Asterisks indicate p<0.05 for the pairwise comparison.

## Dexamethasone-Induced Lean Mass Loss is More Pronounced and Recovery is Slower in Young Male Mice

Based on the effects of glucocorticoids on muscle stability and insulin sensitivity, we wondered what the effects of short-term glucocorticoid exposure may have in a developing animal where muscle growth is occurring. To test this, NON-shiltJ mice were treated with dexamethasone at five weeks of age for one week and then challenged with HFD as adults (70 days) for 10 weeks

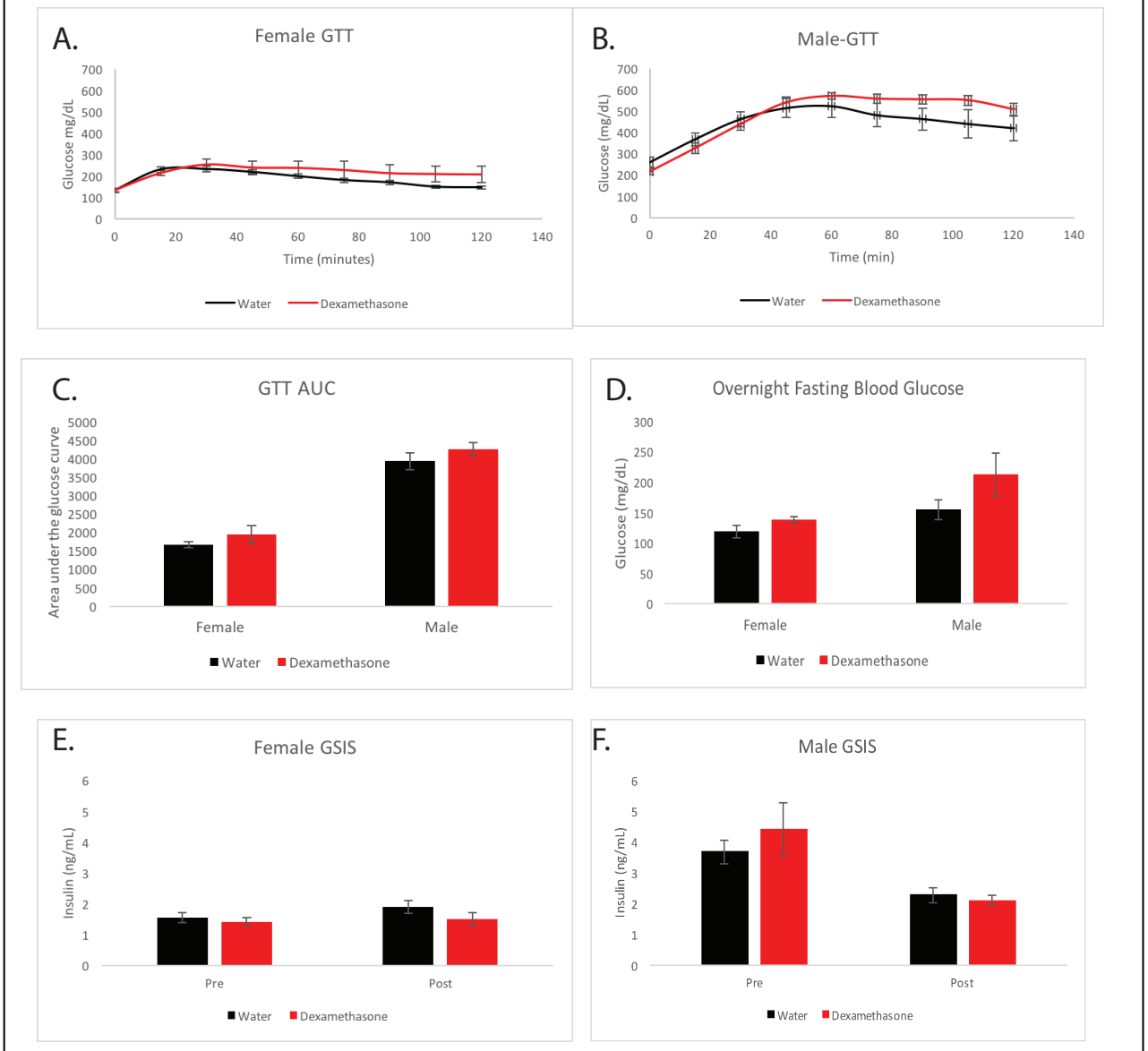


**Figure 26: Juvenile Dexamethasone Treatment Leads to Imaried Glucose Tolerance:** Female (A,C) and male (B,D) glucose values and area under the glucose curve during glucose tolerance test after 10 weeks of HFD. Glucose was administered following a 6-hour fast via IP injection at 1g/kg body weight. Female (E) and male (F) fasting blood glucose (FBG) at sacrifice following 11 weeks of HFD. Female (G) and male (H) glucose stimulated insulinsecretion (GSIS) after a 6-hour fast, pre and 15 minutes post 1mg/kg glucose injection after 10 weeks of HFD.

(see Figure 25A). There was no significant effect of treatment on body weight or fat mass within sex; however, there was a significant interaction of sex and treatment on fat mass $p<0.0001$ with male mice gaining less weight after earlier dexamethasone exposure, but no differences observed in female mice. (Figure 25B-D). Likewise, there was no observable effect of juvenile

dexamethasone treatment on lean mass in the females. However, MRI measures revealed there was a greater loss in lean mass following one week of dexamethasone treatment in males when compared to females from which they never fully recovered. Similar to fat mass, there was a significant interaction of sex and treatment on lean mass $p<0.0001$ with male mice being smaller after juvenile dexamethasone exposure. Terminal weights were not statistically different for either sex following dexamethasone treatment (females $p=0.84$; males $p=0.13$; Figure 25E).

## Glucose Homeostasis is Altered in Response to Juvenile Dexamethasone Exposure

To assess glucose homeostasis in these mice we performed glucose tolerance tests. In female mice, there was no significant difference in glucose tolerance following a six-hour fast (Figure 26A-C). Similarly, there were no significant differences for area under the glucose curve (females, $p=0.282$; males, $p=0.284$), though there was a trend of higher glucose levels during the GTT in the dexamethasone-treated males, indicating reduced glucose clearance (Figure 26B-C). Additionally, dexamethasone treated males tended to have lower fasting blood glucose at baseline (Figure 26B), but this effect did not reach statistical significance ($p=0.119$). Early life dexamethasone treatment in both sexes tended to result in higher fasting blood glucose following an overnight fast when compared to controls, though this did not reach statistical significance (females $p=0.09$; males $p=0.16$; Figure 26D).

To assess whether juvenile dexamethasone exposure impaired glucose-stimulated insulin secretion we IP injected mice with glucose and measured insulin before and 15-minutes post

injection (Figure 26E-F). In females, insulin secretion was elevated in response to glucose challenge in the water-treated group, as expected; however, glucose did not lead to greater insulin secretion in the dexamethasone-treated females. Interestingly in males, the bolus of glucose did not induce greater insulin secretion in either treatment group, in fact insulin levels were reduced below basal for both groups; though fasting insulin tended to be higher and insulin secretion was lower in the dexamethasone treatment group. Taken together, these data suggest that brief juvenile exposure to glucocorticoids leads to impairments in glucose homeostasis as well as body composition in male but not female mice.

## Discussion

### The Effects of Dexamethasone and Obesity on Muscle Stability and Function

Maintenance of proper muscle function is pertinent to overall health and wellness as it plays a major role in stability, mobility, strength, energy production and glucose metabolism. Muscle function has been reported to be reduced in obesity (Maffiuletti et al. 2007; Blimkie, Sale, and Bar-Or 1990; Hulens et al. 2001; Zoico et al. 2004) and following chronic elevations of glucocorticoids (Blom et al. 2017; Barry and Gallagher 2003) in juveniles and adults; however, to my knowledge no one has studied the effects of juvenile glucocorticoid exposure on adult metabolic health, nor has the combination of excess glucocorticoids and obesity on muscle health been assessed. Here I show that both short-term juvenile exposure to and chronic elevations of glucocorticoids in adulthood lead to impairments in glucose homeostasis and affect muscle health in general. Furthermore, I show that dexamethasone-induced muscle atrophy is exacerbated in obesity, as evidenced by synergistic reductions in muscle function, mass and

muscle fiber cross-sectional area. These findings provide functional outcomes that are consistent with previous data revealing multiple dysregulated pathways associated with muscle stability in models of excess glucocorticoids, such as upregulated muscle degradation pathways and impairments in protein synthesis (Menconi et al. 2007; Price et al. 1994; Wing and Goldberg 1993; Dominique Dardevet et al. 1995; Rayner 2001; Beaufrere et al. 1989). Mechanistically, this is consistent with synergism between obesity and glucocorticoid exposure on elevations in atrogene mRNA expression in skeletal muscle.

Systemic insulin resistance is common with elevated glucocorticoids, but the mechanism by which this occurs is unclear. Here I investigated the effects of dexamethasone on insulin signaling in muscle. In both lean and obese animals, dexamethasone treatment resulted in reduced muscle glucose uptake that could not be fully explained by the loss in mass. Though it is apparent that insulin signaling is disrupted in the muscles of dexamethasone treated mice as evidenced by reduced responsiveness to insulin in muscle as well as systemically, the activation of Akt, a key protein in insulin signaling in muscle, was not reduced either *in vitro* or *in vivo* in response to diet-induced obesity or treatment, suggesting that the insulin signaling pathway is intact up to this point. This is not in agreement with other data that has shown reduction in Akt activation in muscles from obese rats (Sishi et al. 2011). Dexamethasone-induced reductions in pAkt have previously been observed in C2C12 myotubes, however at a much higher dose (S. a Morgan et al. 2009). The concentration of dexamethasone that we gave to our mice was comparable to the high end prescribed to patients, since we did not observe reductions in pAkt at this dose, it is likely that dexamethasone-induced impairment of insulin-stimulated glucose uptake occurs downstream of Akt. Other groups have assessed various components downstream

of the insulin signaling pathway in response to glucocorticoid treatment such as Glut4, a protein responsible for insulin-stimulated glucose uptake in muscle. Evidence indicates that while Glut4 protein is not reduced, translocation to the membrane is impaired in muscle (Dimitriadis et al. 1997) and in adipocytes (Sakoda et al. 2000); however, the mechanism responsible for glucocorticoid impairment on Glut4 translocation has not been evaluated. Therefore, further research in this area should may on Glut4 translocation.

It was striking that we noted dramatic reductions in glucose disposal in muscle, but only very modest reductions in whole body glucose turnover under glucose clamp conditions. These data suggest that some other tissue must be using more glucose after glucocorticoid exposure. Although we were unable to measure this in these studies we suspect that this tissue may be the brain, and that glucocorticoids may promote glucose oxidation in neural tissues, while impairing it in skeletal and adipose depots. This would be consistent with a primary physiological role of glucocorticoids to shift glucose to brain tissues. Again, whether these effects are direct neuronal effects, or indirect do to peripheral glucose intolerance require further study.

## The Effects of Juvenile Dexamethasone Exposure on Metabolic Parameters in Adulthood

In this chapter I also assessed the effects of juvenile glucocorticoid exposure on metabolic outcomes in adulthood in mice. Based on the studies above, we expected to observe changes in both lipolysis and muscle proteolysis, and predicted that if this occurred during key the developmental window of adolescence there may be chronic effects in adulthood. As stated in the beginning of this chapter, data from studies on excess glucocorticoids during childhood

suggest that children exposed to glucocorticoids early in life have an increased risk of becoming obese as adults. Contrary to our expectations, I did not observe this outcome in the juvenile dexamethasone-treated mice, as mice gained fat mass at a similar or lower rate, suggesting strong resilience of adolescent exposures, even in the context of a fairly rapid drop in muscle mass during the exposure window (see Figure 23C). The epidemiological data reported have many confounding factors that could have impacted their results. It is possible that childhood glucocorticoid treatment was not the culprit for the increased risk for obesity in adulthood given that the reasons for treatment included cancer and asthma, both of which can have a major impact on activity levels. Not to mention the psychological issues that come along with childhood cancer or those observed with poor living conditions, another juvenile glucocorticoid model.

There are several limitations to our exposure model, which did not result in apparent differences in adiposity. First, I assessed what happens following the onset of high fat diet feeding in adults. It is possible had the mice remained on chow following short-term dexamethasone treatment we would have seen increases in adiposity. This is supported by the data provided in Chapter 2 where we saw increased fat mass in the lean mice following 12 weeks of dexamethasone treatment, whereas I observed reduced adiposity in obese dexamethasone treated mice. In our model, however, we chose a brief exposure to mimic a brief period of chronic stress, rather than a prolonged sustained exposure to dexamethasone. We used the NON/ShiltJ mouse strain to study the effects of glucocorticoids early in life since they are known to develop metabolic dysfunction more rapidly than other strains. These mice became severely obese and glucose intolerant quite rapidly following the introduction of HFD, far more than we observed for

C57BL/6J mice in Chapters 2 and 3. It is possible that these mice achieved a maximum increase in adiposity and glucose intolerance thereby preventing observation of any differences due to treatment. It would be interesting to investigate whether differences in adiposity are observed in other strains that are less apt to developing rapid obesity and metabolic disease.

Similar to adiposity measures, there was no evidence of chronic changes in lean mass after dexamethasone-induced muscle atrophy for females, as lean mass was not different at the end of the study. However, I did observe a rapid drop in lean mass during the treatment week in the dexamethasone group for both sexes, which male mice did not fully recover from. This drop in lean mass due to treatment was also more pronounced in male mice. Consistent with these findings, there is evidence to suggest that females have higher rates of protein synthesis when compared to males of similar age (Henderson et al. 2008). Similar observations have been found with combination of aging and obesity in rats, where female rats are less susceptible to muscle loss (Kob et al. 2015). These findings suggest that sex largely influences muscle metabolism outside of additional stressors. Further research needs to be conducted to investigate how excess glucocorticoids influence these findings, as well as the mechanisms involved.

In addition to the modest changes from juvenile glucocorticoid exposure on body composition in adults, glucocorticoid-induced impairments in glucose homeostasis were observed at the end of the study. Dexamethasone treatment led to slight decreases in glucose tolerance for both sexes, fasting insulin was elevated males and glucose-stimulated insulin secretion was reduced in both males and females, indicating glucose handling is impaired in both sexes. It is worth noting that the reduction in glucose tolerance is not due to increased adiposity, as there was no statistically

significant effect of treatment in fat mass in either sex. This is similar to what I reported in Chapter 2, showing obesity and dexamethasone combined lead to reduced fat mass and increased insulin resistance when compared to the obese water-treated group. The observed reduction glucose-stimulated insulin secretion in the dexamethasone treatment groups is possibly due to severe dysfunction of pancreatic beta cells. Indeed, there is evidence of elevated glucocorticoid signaling resulting in reduced insulin release from pancreatic beta cells (Delaunay et al. 1997) and dexamethasone has been shown to promote cell death in insulin-secreting cells of mouse islets (Ranta et al. 2006). It is important to note the possibility that dexamethasone-induced glucose intolerance in males is likely even greater than reported as we observed glucose values above 600mg/dL, the highest concentration our instruments can read in many of the dexamethasone-treated mice. This is a major limitation to our study, going forward we will reduce the glucose load in male mice to observe true measurements. In the future, our group plans to assess pancreatic function in more detail as well as determine the factors influencing sex-dependent differences in early-onset lean mass loss and glucose homeostasis.

An alternate outcome that we considered was that juvenile glucocorticoid exposure may lead to substantial adipogenesis during development, consistent with my *in vitro* studies presented in Chapter 3. In studies not completed at the time of writing, we utilized adipocyte tracing models to monitor adipogenesis after this exposure. We do not predict, based on our data that this was a physiologically significant effect for two reasons. First, we did not observe any increases in fat mass with the exposure. Second, given roughly equal adiposity, we would predict that increased adipogenesis would improve glucose tolerance, but instead we observed signs of intolerance at least in male mice.

The data presented in this chapter support the hypothesis that there are direct effects of glucocorticoids on skeletal muscle that affect insulin sensitivity and muscle proteolysis, and that these effects are positively modified by obesity. As previously mentioned, obesity has become a major epidemic in developing countries and glucocorticoids are among the top prescribed drugs given to children and adults, indicating that individuals with obesity are commonly exposed to elevated glucocorticoids. Therefore, it is important to continue to investigate the underlying mechanisms responsible for glucocorticoid-induced metabolic disease, including the role of muscle in this process, so that we can develop better therapeutic strategies.

# Chapter 5: Conclusion

Our findings lend insight into the detriments of excess glucocorticoids and illustrate the importance of continued study in both juvenile and adult populations, as well as across the BMI spectrum. A substantial amount of data has been generated aiding our understanding of glucocorticoids on metabolism over the past several decades; however, glucocorticoid signaling occurs in virtually every tissue in the body and there are still may unanswered questions. In this chapter, I highlight some implications of my data and discuss the areas which need further focus to provide a more intricate understanding of the issues at hand and improve overall health in persons with chronically elevated glucocorticoids

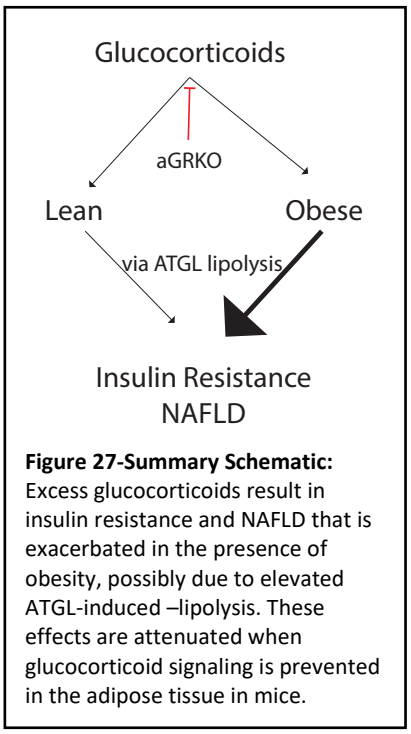


**Figure 27-Summary Schematic:** Excess glucocorticoids result in insulin resistance and NAFLD that is exacerbated in the presence of obesity, possibly due to elevated ATGL-induced –lipolysis. These effects are attenuated when glucocorticoid signaling is prevented in the adipose tissue in mice.

## Potential Guidelines for Reducing Glucocorticoid-Induced Metabolic Disease

As mentioned previously, many individuals are prescribed glucocorticoids in developed countries where obesity is at epidemic levels, this suggests that obesity and glucocorticoid use is combined in many instances. Results from Chapter 2 provide evidence to suggest that elevated glucocorticoids in the presence of obesity amplifies glucocorticoid-induced insulin resistance and

NAFLD in human Cushing's patients and mouse models of Cuhsing's syndrome (see summary figure xx). It is well appreciated that glucocorticoids are used to treat many serious

conditions and I am not here to argue that their use should be discontinued. However, the data are clear that there are many adverse side effects associated with long-term treatment, which is likely exacerbated in individuals with obesity, and efforts to reduce the metabolic consequences may be beneficial. In addition, data from Chapter 4 suggests that short-term dexamethasone exposure early in development leads to disturbances in glucose homeostasis later in life. Though these data are preliminary and require more research, they are important to contemplate given that children with asthma, autoimmune disease and cancer are frequently prescribed some form of glucocorticoids. The outcomes from glucocorticoid treatment and the potential effects on special populations including children and individuals with obesity should be warrant discussion and further examination. One possibility is that the doses of prescribed glucocorticoids should consider extant metabolic syndrome and/or obesity with individuals at elevated risk for diabetes and NAFLD being prescribed lower doses and monitored carefully. In terms of supplemental treatments, below I present some suggestions for reducing adverse side effects from chronically elevated glucocorticoids.

## Exercise May Ameliorate Effects of Glucocorticoids

Exercise is known to enhance health and there is evidence that this is also true for populations with metabolic disease. For example, exercise enhances muscle insulin sensitivity following six weeks of resistance training in patients with Type 2 diabetes (Holten et al. 2004). Moreover, aerobic and resistance exercise has been shown to be effective in lowing hepatic lipid

accumulation in individuals with NAFLD without apparent changes in body weight (Sullivan et al. 2013; Zelber-Sagi et al. 2014; Hallsworth et al. 2011). As mentioned previously, lipolysis is elevated in response to glucocorticoids and is associated with insulin resistance and NAFLD. Our preliminary data support these statements as *Nr3c1* knockout mice had improved insulin sensitivity, reduced markers of lipolysis and appear completely rescued from NAFLD. Exercise improves insulin stimulated glucose uptake in adipose tissue and muscle, and enhances insulin suppression of lipolysis during a hyperinuslinemic euglycemic clamp in trained males when compared to untrained (Stallknecht et al. 2000). Likewise, basal lipolysis was reduced in obese adipose tissue following three months of aerobics training (De Glisezinski et al. 1998).

Though exercise has been found to activate the HPA axis leading to elevated cortisol during exercise, it has also been shown to improve glucocorticoid-induced metabolic disturbances (Hill et al. 2008) . In fact, four weeks of wheel running in hamsters led to reduced local cortisol activity by attenuating 11βHSD1 protein levels in metabolically active tissues, including the liver and muscle, and reductions in circulating glucocorticoids (Coutinho et al. 2006). Consistent with this, Barel and colleagues compared the effects of exercise training in concert with glucocorticoid treatment (Barel et al. 2010). They found that eight weeks of treadmill running significantly attenuated fasting blood glucose and insulin levels, as well as muscle glycogen loss and muscle atrophy following 10 days of dexamethasone treatment when compared to sedentary dexamethasone treated rats. Likewise, another study reported that 12 weeks of running attenuated glucocorticoid-induced muscle atrophy from 10 days of cortisone acetate treatment in both castrated and normal rats when compared with controls (Hickson and Davis 1981). Beaudry et al. show similar data on exercise improving outcomes from rats fed HFD in concert

with glucocorticoids (Beaudry et al. 2015). They reported that 2 weeks of wheel running led to significant improvements overall glucose homeostasis and reductions in lipolysis in HFD-fed rats treated with corticosterone compared to the sedentary group; however, there was no improvement in ectopic fat deposition.

There is less data regarding resistance training but one study by Macedo et al. reported that eight weeks of ladder climbing following 10 days of dexamethasone treatment prevented glucocorticoid-induced elevations in fasting blood glucose, muscle atrophy proteins (MuRF-1 and Atrogin-1) when compared to sedentary dexamethasone treated rats (Macedo et al. 2014). Moreover, they report reduced loss in body mass and increased muscle strength even above that of the control training groups, suggesting reduced muscle atrophy but did not specifically measure muscle weight or lean mass. Likewise, the same group show that high-intensity resistance training in glucocorticoid-treated rats yield similar results of reduced muscle atrophy and increased strength (Krug et al. 2016).

There is some evidence to suggest that exercise training is also beneficial in humans exposed to excess glucocorticoids with improvements in overall muscle function noted in rheumatoid arthritis patients; however, this study did not stratify patient outcomes by treatment and several were not taking corticosteroids making it difficult to determine (Häkkinen et al. 2001). While the data are sparse, these findings support exercise as a potential treatment for metabolic symptoms resulting from excess glucocorticoids.

## Dietary Manipulation and Pharmacological Changes

To my knowledge, there has been no research on potential diets or dietary supplements for the improvement of glucocorticoid-induced metabolic disease. We performed a study of high protein feeding and found no moderation of dexamethasone-induced muscle atrophy (data not shown). My data discussed in Chapter 2 and those mentioned above, that report diets high in fat and sugar, similar to common western diets, lead to exacerbated glucocorticoid-induced lipolysis, insulin resistance and NAFLD (D'souza et al. 2012; Beaudry et al. 2013; Shpilberg et al. 2012; Harvey et al. 2018; Beaudry et al. 2015); hence, avoiding obesogenic diets may help attenuate some of the unwanted effects. Low carbohydrate diets would be predicted to be ineffective as they have been shown to raise cortisol levels, likely in an attempt to support gluconeogenesis (Ryan et al. 2018; Hall et al. 2016).

Outside of diet and exercise there are promising drugs to combat the metabolic effects of glucocorticoids, such as Mifepristone (Fleseriu et al. 2012), a GR antagonist, which has been shown to improve glucose homeostasis in Cushing's disease patients. However, as outlined here, the majority of individuals have Cushing's syndrome as a result of therapeutically prescribed glucocorticoids as treatment for serious medical conditions; therefore, blocking global glucocorticoid signaling would not be beneficial. More promising are the 11βHSD1 inhibitors, which still are not selective but could reduce local activity of cortisol, some studies have shown improved glucose homeostasis in patients with diabetes (Anderson and Walker 2013; Rosenstock et al. 2010). Another approach is LXRβ antagonists that can be used in combination with glucocorticoids. These antagonists that have been reported to reduce unwanted metabolic side effects of glucocorticoid treatment while still allowing for the anti-inflammatory actions to

remain intact (Petty, Huckins, and David 2002). There are no data on how the effectiveness of LXRβ antagonists in this context may be moderated by obesity.

These data provide evidence to suggest exercise, regardless of the type, as a potential modifier to glucocorticoid-induced metabolic disease. Research needs to be conducted on whether dietary modifications could potentially alleviate glucocorticoid-induced symptoms, while still supporting the clinically relevant anti-inflammatory actions. Likewise, future research is warranted to develop therapeutic agents that can retain anti-inflammatory properties, while blocking the unwanted metabolic-effects of glucocorticoid treatment, but may be available in the near future.

## Summary and Future Directions

Taken together, the data presented in this dissertation provide clear evidence that excess glucocorticoids lead to a multitude of metabolic complications. These include but are not limited to, impairments in glucose homeostasis, insulin sensitivity, elevated lipolysis, NAFLD and muscle atrophy, all of which are exacerbated by HFD-induced obesity. Additionally, I show that adipocyte GR signaling is responsible, at least in part, for the majority of these findings in obese mice, excluding muscle atrophy. Lastly, I show that short-term glucocorticoid exposure in juvenile mice leads to impairments in glucose homeostasis in adulthood and has sex-specific effects on lean mass loss. These findings along with the presented evidence highlighting the high prevalence of glucocorticoid use across sex, age and body type reveal the importance for continued research, especially among special populations and in the pursuance of improved therapeutics.

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