**Glucocorticoid-Induced Metabolic Disturbances are Exacerbated in Obesity**

**Abstract**

Obesity and chronically elevated glucocorticoids result in similar co-morbidities, but the combination of these ailments on metabolic outcomes is unclear. Measures of glucose homeostasis and markers of hepatic lipid accumulations were assessed to determine whether obesity exaggerated the effects of dexamethasone-induced metabolic disturbances. The combination of obesity and glucocorticoids resulted synergistic elevations in hepatic steatosis and insulin resistance and this was matched with synergistic elevations in markers of lipolysis. These findings suggest lipolysis may be a key player in glucocorticoid-induced insulin resistance and fatty liver.

**Introduction**

Obesity has become an epidemic in the US and other developing countries, and though Cushing’s disease is rare, it is estimated that 1-3% of US, UK and Denmark populations are prescribed corticosteroids at any given time (1–4). Comparing this staggering statistic with the fact that many Americans are overweight or obese, it is likely that obesity and glucocorticoid excess are combined in many instances. Given the similar co-morbidities associated with obesity and chronically elevated glucocorticoids, we hypothesized that the combinations of these two conditions would lead to even worse metabolic outcomes than either of them alone. This is supported by studies in rats showing that corticosterone and high-fat diets combine to cause worsened insulin resistance and NAFLD (5,6).

Obesity is often accompanied by a multitude of metabolic complications, such as insulin resistance (7–9) and non-alcoholic fatty liver disease (NAFLD; (10,11)). Similarly, chronically elevated glucocorticoids, such as is seen in Cushing’s disease or corticosteroid treatment, is often matched with impaired glucose tolerance or type 2 diabetes (12,13) and is associated with fatty liver (14,15), and changes in fat mass and distribution (16). Though these diseases and their co-morbidities are well characterized, underlying mechanisms caused by the disease subsequently leading to these metabolic complications have not been identified. Moreover, to our knowledge, the combination of obesity and elevated glucocorticoids on the severity of the aforementioned outcomes has yet to be investigated.

There is an array of physiological changes that occur as a result of elevated glucocorticoids including decreased lean mass (17–19), increased fat mass (18,20,21) and increased lipolysis (22–24), all of which have been associated with decreased insulin sensitivity (25–27). Likewise, obesity, insulin resistance and increased fatty acid flux are associated with NAFLD (10,28–30). Recent tissue-specific knockouts of glucocorticoid signaling molecules have implicated adipose tissue as a central node linking glucocorticoid action and lipolysis to systemic insulin resistance and NAFLD (31–34). Lipolysis is the breakdown of triglyceride into fatty acids and glycerol. It has also been demonstrated that inhibition of lipolysis promotes insulin sensitivity (25,35–37).

Here we show that chronically elevated glucocorticoids in the presence of obesity have synergistic effects on lipolysis, insulin resistance and fatty liver disease. Obese glucocorticoid-treated mice have reduced fat mass compared to all other groups, yet have hyperglycemia and severe insulin resistance; therefore, we speculate that it is the lipolysis drives insulin resistance in obese animals.

**Methods**

**Patient Recruitment and data collection**: Patients were recruited and data was collected as described in Hochberg et al. (18).

**Animal Procedures:** C57BL/6J adult male mice were purchased from the Jackson Laboratory (Bar Harbor, ME, USA) at nine weeks of age. Following a one-week acclimation period, mice were treated as described previously (18) or were either kept on normal chow (NCD) or given high fat diet (45% fat; 35% carbohydrate; 20% protein; Research Diets, New Brunswick, NJ; ID D12451) for 8 or 12 weeks, depending on the experiment. Mice stayed on their respective diets and were treated with 1 mg/kg per day of dexamethasone (Sigma–Aldrich) in their drinking water (NCD n=12; HFD n=32) or used as controls (NCD n=12;HFD n=22) for 3-6 weeks as indicated. For the eight week dexamethasone treatment and prior to sacrifice, sixteen HFD-fed, dexamethasone-treated mice appeared ill and died or were euthanized and were removed from all analyses once symptoms were noticed. Animal body weight and composition was determined weekly using an echoMRI 2100. Food was weighed weekly, with food intake determined as the decrease in food weight per mouse per week per cage. All mice were provided with access to food and water *ad libitum* throughout the study, unless otherwise noted. At the end of treatment, mice were fasted for 16 h and were sacrificed by cervical dislocation at ZT3 after isoflurane anesthesia. Following cervical dislocation, a sagittal incision was made along the medioventral surface of each mouse and the skin was carefully pulled back to expose the subcutaneous fat depots. The incision was extended along the anterior surface of each hind limb to allow careful dissection of the inguinal fat pads. A small incision was then made into the rectus abdominus muscle to expose the abdominal cavity. The epididymal fat pads were identified and carefully dissected out. The right fat pads from each mouse were weighed and snap frozen in liquid nitrogen for later analysis, along with a section of the large lobe of the liver. Small pieces of tissues were placed in 10% formalin for histology. and University of Michigan

**Insulin Tolerance Tests and Euglycemic Clamp Experiments:** Insulin tolerance was assessed following five weeks of treatment (27 weeks of age). Mice were given i.p. injections of insulin (Humulin R, Lilly, Indianapolis, IN, USA) at a concentration of 2.5 mU/g following a six hour fast. Blood glucose was determined using a One Touch Ultra Glucometer (Lifescan) prior to and every 15 minutes post injection. For the Clamp experiment C57BL/6J adult (70d) male mice were fed the same HFD as above for eight weeks and treated with dexamethasone for three weeks prior to the experiment. For hyperinsulinemic-euglycemic clamps experiments animals were anesthetized with an intraperitoneal 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 silicon) that was fixed subcutaneously upon the closure of the incision. Animals that had healthy appearance, normal activity, and regained body weight to or above 90% of their pre-surgery levels were used for the study.

The experiments were carried out in conscious and unrestrained animals using techniques as described previously (38–40). Briefly, the primed (1.0 Ci)-continuous infusion (0.05 Ci/min and increased to 0.1 µCi/min at t = 0) of [3-3H] glucose (50 µCi/ml in saline) was started at t = -120min. After 5 hours fast, the insulin clamp was begun at t = 0 with a prime-continuous infusion (16 mU/kg bolus, followed by 2.5 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.  Blood samples were collected at t = 80, 90, 100, and 120 min for determination of glucose specific activity.  Blood insulin concentrations were determined from samples taken at t = -10 and 120 min. A bolus injection of [1-14C]-2-deoxyglucose ([14C]2DG; PerkinElmer) (10 µCi) was given at t = 120 min. Blood samples were be taken at 2, 5, 10, 15, and 25 min after the injection for determination of plasma [14C]2DG radioactivity. 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 [1-14C]-2-deoxyglucose phosphate ([14C]2DGP) radioactivity.

Blood glucose was measured using an Accu-Chek glucometer (Roche, Germany). Plasma insulin was measured using the Linco rat/mouse insulin ELISA kits.  For determination of plasma radioactivity of [3-3H]glucose and [1-14C]2DG, plasma samples were deproteinized with ZnSO4 and Ba(OH)2 and counted using a Liquid Scintillation Counter (Beckman Coulter LS6500 Multi-purpose Scintillation Counter). Glucose turnover rate, hepatic glucose production and tissue glucose uptake were calculated as described elsewhere (39–41).

**Cell culture:** 3T3-L1 fibroblasts (pre-adipocytes) were cultured in 10% newborn calf serum (NCS), high glucose Dulbecco's Modification of Eagle's Medium (DMEM) with 1% penicillin, streptomycin and glutamine (PSG) until confluence. Cells were switched to a differentiation cocktail at two days post confluence including 250nM dexamethasone, 500M 3-isobutyl-1-methylxanthine and 1g/mL insulin in 10% fetal bovine serum (FBS), high glucose DMEM with 1% PSG for four days (42). Media was then replaced including only insulin in the cocktail for an additional three days. For the following three days, cells remained in FBS media with no additional treatment. To assess lipolysis, cells remained in FBS media and were treated with ethanol (vehicle) or 250nM dexamethasone for five days before lysing.

**Assessment of Triglycerides from Cells and Tissue:** 3T3-L1 ells were grown and treated as described above and a triglyceride assay was performed at the end of the treatment period. Cells were lysed in homogenization buffer (50 mM Tris pH 8, 5 mM EDTA, 30 mM Mannitol, PI inhibitor) undergoing three freeze thaw cycles. Frozen liver tissue was homogenized with 5mm stainless steel pellets in this buffer using a TissueLyser II (Qiagen) set to 30Hz for a duration of 5 minutes. Lipids were extracted using KOH and Chloroform:methanol mixture and left to evaporate overnight. A mixture of butanol, methanol and triton were then used to get the lipids into a solution. Triglyceride content was assessed using the Serum Triglyceride Determination Kit (Sigma) and absorbance was detected as described in (43).

**Histology:** Tissues were kept in 10% formalin for 24 hours and then stored in 70% ethanol until further processing. Following a series of wash steps, tissues were embedded in paraffin wax and sent to either the University of Michigan University of Michigan Comprehensive Cancer Center Tissue Core or the Unit for Laboratory Animal Medicine In-vivo Animal Core (University of Michigan, Ann Arbor) where they were processed and stained with H&E to assess cell morphology.

**Analysis of mRNA:** Cells and tissues were lysed in TRIzol using the TissueLyser II, as decribed above, and RNA was extracted using the PureLink RNA mini kit (Life Technologies). cDNA was synthesized from 0.5-1g of RNA using the High Capacity Reverse Transcription Kit (Life Technologies). Primers, cDNA and Power SYBR Green PCR Master Mix (Life Technologies) were combined in accordance with the manufacturer’s guidelines and quantitative real-time PCR was performed as previously described (44). mRNA expression level was normalized to *Actb* after evaluation of several reference genes (Table 1).

**Protein 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 and 10 mM sodium pyrophosphate) on ice then centrifuged for 15 minutes at 13 000 RPM at 4°C. Clarified lysates were loaded on SDS-PAGE gels, transferred and blotted using ATGL (Cell Signaling Technologies), GAPDH (Fitzgerald), and Actin antibodies. Antibody complexes were detected by anti-mouse and anti-rabbit fluorescent conjugated antibodies (Invitrogen) and visualized using an Odyssey CLx image scanner and blots were quantified using Image Studio software version 5.2 (LiCOR).

**Determination of Glycerol and Fatty Acid Levels:** Twenty-one-week-old *ad libitum* chow fed C57BL/6J male mice were briefly anesthetized with isoflurane at 11 weeks post dexamethasone treatment and blood was taken via retro orbital bleed at baseline and 15 minutes following an i.p. injection of 10mg/kg isoproterenol (Sigma-Aldrich) in PBS. Additionally, serum was taken from these mice as well as from another cohort of twenty-eight-week old mice on HFD or chow six weeks post dexamethasone treatment following an overnight fast, just prior to sacrifice. Glycerol was assessed via Serum Triglyceride Determination Kit (Sigma-Aldrich) in accordance with manufacturer’s guidelines.

**Statistics**: For animal studies, two-way ANOVA analyses were performed to test for significance of diet and treatment, as well as their interaction. For cell culture experiments a Student’s *t*-test was used after confirming equal variance and normality. P-values below p=0.05 were considered significant.

**Results**

# Dexamethasone-Induced Insulin Resistance is Worsened in the Presence of Obesity

Our group has previously published data that suggested different and gene expression in adipose tissue between those with Cushing’s disease (ACTH-secreting pituitary adenoma) and controls (non-secreting pituitary adenoma;(18)). Based on this, we speculated that the glucocorticoid responses may vary according to obesity status. Here we have re-analyzed the data stratifying the Cushingoid and control groups by BMI (Figure 1A), classifying these individuals as “Not obese” (BMI < 30) and “Obese” (BMI ≥ 30). There were no significant differences in BMI in the controls compared to the Cushing’s however, were near-significant interaction between obesity status and Cushing’s diagnosis on HOMA-IR score (p=0.057; Figure 1A-B). We observed only a 17% increase in HOMA-IR score comparing non-obese subjects with and without Cushing’s disease, but a 3.4-fold increase in obese patients.

To investigate if obesity status influences insulin sensitivity in the presence of elevated glucocorticoids we performed an insulin tolerance test (ITT) on lean (NCD) and diet-induced obese (HFD) mice that were untreated (Control) or treated with glucocorticoids (Dexamethasone; Figure 1C). HFD-fed, dexamethasone-treated mice were significantly more resistant to insulin-stimulated glucose uptake when compared to all other groups (Figure 1D. Additionally, HFD dexamethasone-treated mice exhibited dramatic fasting hyperglycemia, with a significant interaction between diet and drug (p=0.00009; Figure 1E). While HFD animals had a 24% increase in fasting glucose when compared to NCD animals, in the presence of Dexamethasone, HFD-fed animals had a 122% increase in fasting glucose relative to NCD controls not treated with dexamethasone. In the lean, NCD-fed animals, dexamethasone caused a 18% decrease in fasting glucose.

To evaluate glucose homeostasis in more detail we performed a hyperinsulinemic, euglycemic clamp in obese mice (11 weeks of HFD) treated with dexamethasone for the final three weeks. This shorter HFD/dexamethasone exposure still caused dramatic insulin resistance, hyperglycemia and reductions in lean mass, but no differences in fat mass between the groups (Supplementary Figures 1A-F). During the hyperinsulinemic phase, the glucose infusion rate was 39% lower in obese dexamethasone-treated mice when compared to obese controls indicating insulin resistance at euglycemia (Figure 1E). Basal endogenous glucose production (EGP) was 37% higher in the dexamethasone treated group (p=0.026). Moreover, In the dexamethasone group, EGP was reduced to near zero by insulin but only 70% in the control group (p=0.0091) resulting in EGP being 5-fold higher during the insulin phase in dexamethasone treated mice (p=0.014) when compared to controls (Figure 1F). Overall glucose turnover was slightly decreased in the presence of insulin (p=0.141; Figure 1H). However, there were significant reductions in 2-deoxyglucose uptake in subcutaneous white adipose (p=0.019), heart (p=0.0003) and gastrocnemius tissues (p=0.00001; Supplementary Figures 1F-H). These data suggest that increased EGP and impaired suppression of EPG by insulin are the primary causes of the observed insulin resistance and hyperglycemia in obese, dexamethasone treated animals.

# HFD-Induced Liver Steatosis in Dexamethasone Treated mice

Obesity and chronic elevations in glucocorticoids have been associated with increased liver fat and even NAFLD (10,14). We observed slight but non-significant increases in plasma ALT, a liver enzyme associated with liver disease, in obese Cushing’s patients (38% increase in non-obese subjects versus a 2.8 fold increase in obese subjects, p=0.13 for the interaction of disease and obesity status; Figure 2A). In our mouse model of HFD-fed, dexamethasone treated mice we observed drastically elevated liver triglycerides when compared to all other groups with a significant interaction of drug and diet (p=0.000068; Figure 2B). In support of this, H&E staining of hepatic tissue clearly depicts exacerbated lipid levels in the obese, glucocorticoid-treated group when compared to HFD-fed or dexamethasone-treated controls (Figure 2C).

Genes involved in hepatic *de novo* lipogenesis, *Srebf1* and *Fasn*, were assessed via qPCR in these liver lysates (Figure 2D). There was a significant effect of diet and drug on *Fasn* expression (p=0.014). Though both transcripts were somewhat elevated in response to HFD alone, there was no significant synergism with dexamethasone. This finding indicates that lipid accumulation resulting from dexamethasone treatment is likely occurring via a different mechanism than accelerated glucocorticoid-dependent upregulation activation of *de novo* lipogenesis.

# Dexamethasone Causes Decreased Fat Mass in HFD-Fed Mice

We evaluated body mass in mice via EchoMRI. Contrary to expectations, we observed reductions in fat mass in the HFD-fed dexamethasone treated group (Figure 3A,B). These reductions do not appear to be depot specific, as we observed reductions in both inguinal (65% reduced) and epididymal adipose tissue (59% reduced) from the HFD-fed animals (Figure 3C). There was no significant reduction in fat mass, either by MRI or dissection weights of iWAT or eWAT in response to dexamethasone treatment in the chow-fed groups (Figure 3B-C). Due to these changes in body composition we next asked whether this could be explained by changes in food consumption throughout this study (Figure 3D). Surprisingly we found that the dexamethasone-treated HFD animals ate slightly more food, even though they lost substantial fat mass throughout the study (11% increase, p=0.032). These data suggest that the weight loss in obese animals provided dexamethasone is not due to reductions in food intake. These data also suggest that glucocorticoids may promote a lipodystrophy-like phenotype in obese animals by causing substantial fat reductions.

Dexamethasone Treatment Results in Increased Lipolysis

One potential mechanism of these alterations in lipid deposition is accelerated adipocyte lipolysis. Lipolysis has previously been associated with insulin resistance (25,35), is known to be elevated NAFLD in patients with (28), and has been shown to increase with glucocorticoid treatment (18,22–24). We first assessed whether there was a direct effect of dexamethasone on adipocyte lipolysis in cultured adipocytes. 3T3-L1 fibroblasts were undifferentiated (pre-adipocytes), differentiated (mature adipocytes) or treated with dexamethasone following differentiation (mature adipocytes +dexamethasone) over a 15-day period. Dexamethasone treatment following differentiation led to decreased lipid content (p=) and a 71% increase in the amount of glycerol in the media (p=0.001), suggesting increased lipolysis (Figure 4B). In order to identify a potential GR-dependent lipolytic target we evaluated the levels of ATGL, the rate limiting enzyme in lipolysis. Expression of ATGL (encoded by the *Pnpla2* gene) was enhanced following dexamethasone treatment in 3T3-L1 cells at both the transcript (2.7 fold, p=0.002; Figure 4C) and protein (8.4 fold; Figure 4D-E) levels. These data show that glucocorticoids elevate both ATGL levels and lipolysis in cultured adipocytes.

To assess the effects of glucocorticoid-induced lipolysis *in vivo,* we glycerol levels in animals chronically exposed to glucocorticoids, in basal and stimulated conditions (Figure 4E). Stimulation of lipolysis was achieved via isoproterenol, a -adrenergic receptor agonist, or by a 16-hour fast. Dexamethasone treatment led to significant increases in the fed (2.9 fold), fasted (1.5 fold) and isoproterenol-stimulated (1.4 fold, all groups p<0.05) conditions, indicating that dexamethasone enhances basal and stimulated lipolysis *in vivo* in chow-fed mice, as has been previously reported (45). Consistent with these findings, mRNA analysis from inguinal white adipose tissue (iWAT) of these mice showed an upregulation of *Pnpla2* transcripts in the dexamethasone-treated mice compared to controls (2.1 fold, p=0.016; Figure 4F).

Since the HFD-fed, dexamethasone-treated mice are subject to more severe insulin resistance and hepatic lipid accumulation, we tested whether lipolysis was elevated by measuring serum glycerol following a 16-hour fast (Figure 5A). We observed a nearly two-fold increase in serum glycerol levels by dexamethasone in the HFD-fed animals. compared with only a 18% increase in chow-fed mice. There was a significant interaction between dexamethasone exposure and diet (p=0.017) on glycerol levels, suggesting synergistically elevated lipolysis.

We quantified mRNA and protein expression of the lipolytic enzymes, ATGL, in the iWAT of these mice (5B,C). Consistent with the hypothesis that ATGL activation could drive increased lipolysis in HFD and dexamethasone treated mice, expression of ATGL was elevated in both dexamethasone-treated groups, with a significant synergistic effect of glucocorticoids and obesity at both the transcript (p=0.02 for the interaction) and protein (p=0.003) level. These data support the hypothesis that glucocorticoid-stimulated lipolysis is augmented in the context of obesity, potentially via increased transactivation of *Pnpla2*/ATGL.

**Discussion**

Chronic glucocorticoid elevations are associated with many co-morbidities such as increased fat mass (18,20,21), decreased muscle mass (17–19), insulin resistance (12,13) and non-alcoholic fatty liver disease (NAFLD; (14,15)), all of which can have a negative effect on health (46–49). These side effects are similar those seen in obesity; however, the combination of chronically elevated glucocorticoids in the context of pre-existing obesity has not been assessed. Here we show that glucocorticoid-induced insulin resistance and NAFLD are exacerbated when paired with obesity, more than the sum of their individual effects.

Obese patients with Cushing’s disease were found to have a trend toward increases in HOMA-IR score, indicating increased insulin resistance, as well as increases in the liver enzyme ALT, a marker of liver disease. In line with these findings, increased in central adiposity, such as is seen in people with obesity, has been previously associated with enhanced fatty acid flux (i.e. lipolysis) when compared to lower body fat stores (50), which is thought to contribute to insulin resistance and fatty liver (25,51). There are two limitations to this human study, one is the small sample size and the second is that it was not possible to determine the physiological status of the patients before they developed a tumor; therefore, we could discern whether obesity was present prior to or after development of Cushing’s disease. For this reason, we designed a mouse study to investigate whether being obese prior to glucocorticoid treatment leads to worsened outcomes.

We found that HFD-fed, dexamethasone-treated mice exhibited hyperglycemia and severe insulin resistance. This was primarily due to increased endogenous glucose production in these animals. Significant elevations in liver fat were also observed in HFD-fed, dexamethasone-treated mice, consistent with a trend towards elevated ALT levels seen in the obese Cushing’s patients. Cushing’s disease is often paired with increased fat mass, which has been proposed to contribute to fatty liver (52,53). Indeed, obesity is a known risk factor of NAFLD (10,11). Previous work from our lab shows increased fat mass, specifically in the iWAT, following 12 weeks of dexamethasone treatment (18) in chow-fed mice, in accordance with what others have reported (54). However, to our surprise, the glucocorticoid treatment in obese mice led to an overall reduction in adiposity. Therefore, when comparing HFD control mice to HFD dexamethasone-treated mice, increased fat mass is not cause of the observed exacerbations in insulin resistance and increased liver fat.

Lipolysis has been linked to increased gluconeogenesis by several studies (55–58). One potential mechanism is that the increased flux of fatty acids, oxidized in the liver to acetyl-CoA, activate pyruvate carboxylase and gluconeogenesis (57,58). Glucocorticoids are known to stimulate lipolysis (18,22–24), possibly as a way to promote gluconeogenesis to maintain blood glucose levels, a key function of these hormones. Lipolysis has been implicated in insulin resistance (25,35) and NAFLD (28) and there is evidence to support it is enhanced in the obese state (59). However, hepatic *de novo* lipogenesis is also associated with NAFLD (60). We found synergistic elevations in glycerol, indicative of enhance lipolysis, as well as in hepatic fat accumulation in the HFD-fed dexamethasone-treated mice, but there was no data to support enhanced hepatic *de novo* lipogenesis. These findings suggest that lipolysis is driving enhanced hepatic lipid accumulation in these mice.

There is some debate as to which genes glucocorticoids are acting on to promote lipolysis. Downregulation of *Pde3b* (61) and upregulation of -adrenergic receptors (62) and lipase transcripts (63) have been proposed as possible mechanisms. We assessed all of the previously proposed targets and found adipose triglyceride lipase (ATGL), the rate limiting enzyme for adipose triglyceride lipolysis, to be synergistically activated by obesity and glucocorticoid-treatment. These findings bear a striking resemblance to elevations in glycerol levels in obese, dexamethasone-treated mice when compared to diet or glucocorticoid-alone controls. The mechanisms by which obesity and glucocorticoids synergize to activate ATGL expression are not clear at this time.

Further research is needed to determine whether the insulin resistance observed is due to obesity or the high fat content of the diet. We evaluated glucocorticoid treatment in obesity; however, Riddell and colleagues have reported similar findings when giving HFD and glucocorticoids in concert to rats, prior to the onset of obesity (5,6,64). It is possible that HFD lends to elevated FFAs, leading to a similar phenotype as elevated adipose tissue lipolysis. Further studies are needed to determine whether diet or obesity status or both are the source of this elevated metabolic risk.

In summary, glucocorticoids are commonly prescribed drugs used to treat a multitude of health issues, but are known to induce a variety of metabolic side effects. Their actions in persons with obesity are not yet clear, in spite of a huge number of obese individuals on prescription glucocorticoids. The data presented here shows that obesity does in fact pose a greater risk for the harmful co-morbidities associated with chronically elevated glucocorticoids and this might be considered when determining treatment options. More work is required in the area to assess whether blocking glucocorticoid/lipolytic action in the fat tissue would be beneficial to prevent or enhance recovery of the afore-mentioned glucocorticoid-induced comorbidities.

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