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Letter to the editor:

MITIGATION OF METABOLIC DYSHOMEOSTASIS BY GLUCOCORTICOID- RECEPTOR ANTAGONISM: INSIGHTS FROM ANIMAL AND HUMAN STUDIES

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Dear Editor,

Glucocorticoid hormones are steroidal signaling molecules produced by cortex of the adrenal gland. While acute glucocorticoid response is critical for immunomodulation and metabolic homeostasis, chronic elevated glucocorticoid levels have been recognized as a risk factor for metabolic syndrome (Wang, 2005). Much of the understanding of consequences of excess glucocorticoids on metabolic homeostasis has come from observations on pathology associated with Cushing's syndrome. While incidence of Cushing syndrome is extremely low (Lindholm et al., 2001), chronic exposure to excess glucocorticoids is a more realistic issue and needs to be taken into consideration. It is now well recognized that abnormalities such as diabetes/impaired glucose tolerance, obesity, hypertension and dyslipidemia are highly prevalent among patients of Cushing's syndrome (Chanson and Salenave, 2010). A cross sectional study involving Cushing's syndrome patients clearly establishes the correlation between endogenous hypercortisolemia and metabolic abnormalities. The said study demonstrates that prompt diabetes was evident in 38 % of patients and fasting blood glucose, oral glucose tolerance test area under the curve (AUC) and HbA1C levels positively correlating with urinary free cortisol (Friedman et al., 1996). The effect of glucocorticoids on metabolic homeostasis can also be discerned by the analysis of effects of corticosteroid therapy on glycemic regulations. Synthetic corticosteroids are the choice of drugs to treat various health issues such as asthma, chronic pulmonary obstructive disorders and rheumatoid arthritis. Panthakalam et al. (2004) reported that 9 of 102 patients receiving glucocorticoid therapy for rheumatoid arthritis developed diabetes while pre-existing state of diabetes in another 6 worsened during the course of treatment (Panthakalam et al., 2004). A retrospective analysis of medical data of patients who were hospitalized at general service of a hospital revealed that 64 % of patients receiving exogenous corticosteroid for at least 2 days developed hyperglycemia. This study demonstrates high prevalence of hyperglycemia among those receiving corticosteroid therapy and indicates that people with a history of diabetes before corticosteroid treatment are likely

to develop hyperglycemia on corticosteroid therapy or due to other multiple co-morbidities (Donihi et al., 2006).

Indeed, many experimental and clinical studies lend strong support to the view that excess glucocorticoid levels share causal relationship with various components of metabolic syndrome. Brunner et al. studied changes in autonomic cardiac activity and neuroendocrine functions in metabolic syndrome patients (n=30 vs. 153 control) of Whitehall II cohort. Interestingly, they observed that excretion (24 h) of a cortisol metabolite and normetanephrine increased in patients, in addition to higher levels of circulating interleukin-6 and C-reactive peptide (Brunner et al., 2002). Analysis of cross-sectional data from the Paris Prospective Study revealed strong association of high systolic blood pressure with cortisol, blood glucose, heart rate, and free fatty acids (Filipovský et al., 1996). A study conducted with young overweight Latino subjects revealed increased cortisol and fasting insulin levels in addition to increased 2 h glucose and insulin (during OGTT) levels among youth with metabolic syndrome. Further, systolic and diastolic blood pressure, fasting glucose levels and intra-abdominal fat tissue mass in subjects with MS were reported to correlate with cortisol levels, indicating that excess cortisol may have far reaching consequences on metabolic homeostasis (Weigensberg et al., 2008). Similarly, another study conducted in obese children and adolescents revealed that circulating ACTH and cortisol levels were higher in metabolic syndrome subjects, who also had higher fasting glucose and insulin, increased systolic and diastolic blood pressure, and increased triglyceride levels (Sen et al., 2008). To summarize, many human-subject based studies demonstrate that the excess glucocorticoid level is associated with many defining components of metabolic syndrome viz., increased waist circumference (Pasquali and Vicennati 2000), increased triglyceride levels (Friedman et al., 1996; Phillips et al., 1998; Ward et al., 2003), hypertension, increased blood glucose (Brunner et al., 2002; Weigensberg et al., 2008; Sen et al., 2008) and insulin resistance (Phillips et al., 1998; Ward et al., 2003; Reinehr and Andler, 2004).

Human subject-based studies clearly establish the association between cortisol and various metabolic aberrations associated with metabolic syndrome. While they offer clear perspectives on these correlations, much of the understanding of mechanisms responsible for the diabetogenic effects of glucocorticoids come from preclinical studies involving *in vitro* systems and experimental animal models. Owing to the fact that GCs are associated with insulin resistance, many authors have investigated the direct effect of GCs on beta cell functions employing isolated islets or insulin producing cell lines. Direct exposure to GCs appears to inhibit insulin release *in vitro* (Barseghian and Levine, 1980; Gremlich et al., 1997; Lambillotte et al., 1997; Jeong et al., 2001; Shinozuka et al., 2001; Ullrich et al., 2005; Zawalich et al., 2006), an outcome which appears to be mediated by post-translational degradation of Glut2 protein (Gremlich et al., 1997). Interestingly, this inhibitory effect is abolished by mifepristone, a glucocorticoid-antagonist, indicating involvement of receptor mediated mechanisms (Lambillotte et al., 1997; Zawalich et al., 2006). Despite compelling *in vitro* evidences for antagonistic effects of GCs on various aspects of beta cell functioning, such results were difficult to reproduce *in vivo*. On the contrary, paradoxically enough, experimental (Haber and Weinstein, 1992; Giorgino et al., 1993; Weinstein et al., 1993; Holland et al., 2007; Rafacho et al., 2009; Protzek et al., 2014) and human studies (Beard et al., 1984; Willi et al., 2002; Nicod et al., 2003; Binnert et al., 2004) demonstrate that administration of glucocorticoids results in hyperinsulinemia as a result of augmented beta cell function to compensate for peripheral insulin resistance.

Glucocorticoids are known for transcriptional activation genes of gluconeogenesis enzymes like G6Pase (Argaud et al., 1996), phosphoenolpyruvate carboxykinase (PEPCK) (O'Brien et al., 1990; Hanson and Reshef 1997) and tyrosine aminotransferase (TAT)

(Schmid et al., 1987; Ganss et al., 1994). In addition, GCs also facilitate muscle protein breakdown and increase the supply of amino acids that serve as gluconeogenesis substrates (Lecker et al., 1999). Using the strategy of subjecting diabetic (insulin dependent) rats to adrenalectomy and glucocorticoid treatment, Exton et al., were able to demonstrate that hepatic glucose output was a consequence of glucocorticoid-dependent gluconeogenesis and was found to be underlined by up-regulation of PEPCK (Exton et al., 1973). Glucocorticoids have been reported to have distinct effects on key mediators involved in the insulin signaling pathway. Cortisone treatment, which caused increase in blood glucose and insulin, was reported to be associated with reduced phosphorylation of insulin receptor without changes in the total levels of it, as well as reduced levels of IRS1 in skeletal muscle (Giorgino et al., 1993). Saad et al., observed that dexamethasone reduced stimulated insulin receptor phosphorylation status in livers of rats, along with reduced phosphorylation of IRS1 and PI3K activity associated with IRS1. Further, dexamethasone was also found to be associated with reduced IRS1-associated PI3K activity in muscle as well (Saad et al., 1993). The glucose transporter, Glut4 is the main insulin-responsive transporter that mediates insulin-induced glucose uptake in skeletal muscle and adipose tissue. The insulin-responsiveness of glut4 is characterized by insulin-induced translocation of the transporter to the plasma membrane from intracellular locations. Short-term treatment of rats with dexamethasone resulted in decrease in insulin stimulated glucose uptake, which was found to be underlined by impairments in cell surface recruitment of glut4 to the plasma membrane (Weinstein et al., 1998).

With extensive research done, it is now apparent that excessive activation of glucocorticoid receptor plays a crucial role in the development of metabolic syndrome/T2D. Therefore glucocorticoid receptor antagonism may offer a viable approach for mitigating abnormalities associated with metabolic syndrome. This review intends to present an account of studies conducted with experimental animals as well as in human subjects that demonstrate efficacy of glucocorticoid antagonism in mitigating metabolic abnormalities typically associated with the metabolic syndrome.

Table 1: Summary of experimental reports on the effect of glucocorticoid antagonism on metabolic aberrations

Key findings	Reference
Mifepristone was observed for its ability to prevent obesity and hyperphagia in Zucker (*fa/fa*) rats along with suppression of glucocorticoid-dependent genes in the hippocampus. The glucocorticoid receptor antagonism was reported to increase total body protein content while causing hypercorticosteronemia.	Langley and York, 1990)
Mifepristone prevented weight gain caused by high fat feeding in Osborne-Mendel rats along with reduction in adipose tissue weights. Further, mifepristone also reduced fasting glucose and hepatic TAT activity in both high fat- and normal-diet fed rats, albeit causing hypercorticosteronemia and increase in adrenal gland weights.	Okada et al.,1992
Mifepristone reversed (significantly, but not fully) the decrease in glucose infusion rates (during euglycemic clamp) in Wistar rats fed high fat diet, with concomitant improvements in insulin-stimulated glucose metabolism in extensor digitorum longus and red quadriceps.	Kusunoki et al., 1995
Oral administration of mifepristone for a brief period of 9 days has been reported to be associated with reduction in systolic blood pressure in hypertensive obese Zucker rats, albeit without any impact on hyperinsulinemia and hypercorticosteronemia.	Clapham and Turner, 1997
Mifepristone was found to suppress the up-regulated activities of PEPCK, TAT and G6Pase in *db/db* mice, along with reducing glucose and insulin levels. However, mifepristone was associated with HPA axis activation.	Friedman et al., 1997

Table 1 (cont.): Summary of experimental reports on the effect of glucocorticoid antagonism on metabolic aberrations

Key findings	Reference
Mifepristone administration was found to be efficient in abrogating hyperglycemia and hyperinsulinemia in *ob/ob* mice, albeit it had no impact on suppressed G-alpha (subunit of the heterotrimeric complex) or glut-4 levels in adipocytes. Further, mifepristone partially restored beta-3 adrenergic receptor expression levels, while offering a minimal but significant increase in adenylate cyclase activation under the influence of isoprenaline.	Gettys et al., 1997
In view of adverse effect of systemic GR antagonism (characterized by HPA axis activation), Jacobson et al., investigated the effect of liver-specific GR antagonism on metabolic homeostasis. A molecule created by conjugating mifepristone with a bile acid meant for hepatic delivery was found to antagonize glucocorticoid-induction of GR-responsive genes and was associated with improvements in blood glucose as well as normalization of free fatty acid levels in a type 2 diabetic mouse model. Further, the liver specific GR antagonist failed to elicit HPA activation, which was observed due to treatment with mifepristone.	Jacobson et al., 2005
Liver-specific reduction of glucocorticoid receptor using targeted antisense technology resulted in decreased blood glucose and triglyceride levels with improvement in insulin sensitivity in *ob/ob* and *db/db* mice. Further, the *db/db* mice receiving antisense technology demonstrated lower PEPCK activity in liver without HPA activation. Importantly, treatment of *db/db* mice with anti-sense oligonucleotide was also associated with improved glucose infusion rates and reduced endogenous glucose production during hyperinsulinemic-euglycemic clamp.	Liang et al., 2005
Reduction of liver and adipose glucocorticoid receptor, using antisense oligonucleotide, has been reported to exert antidiabetic effects in various rodent models without hypercorticosteronemia.	Watts et al., 2005
Mifepristone has been reported to reduce blood glucose levels in *ob/ob* mice along with reduced expression of 11-BHSD1 and gluconeogenesis enzyme gene expression in liver. The protective effects of mifepristone also reflected in improved glucose tolerance with reduced area under the curve for oral glucose tolerance test.	Taylor et al., 2009
Mifepristone has been reported to exert antidiabetic effects in obese mice fed high fat diet. Mifepristone was found to reduce glucose levels in the diabetic mice along with improved sensitivity to insulin. Further, mifepristone was effective in restoring total adiponectin and HMW adiponectin-total adiponectin ratios, which were suppressed in diabetic mice. High fat diet feeding was found to be associated with adipocyte area, which was abrogated by mifepristone.	Hashimoto et al., 2013
Effect of mifepristone was studied on metabolic abnormalities in a type 2 diabetes model DS/obese (a cross between Dahl sensitive rats and Zucker fatty rats). GR antagonism achieved by 4 week administration of mifepristone (2 mg/kg/d) was found to reduce fasting glucose, fasting insulin levels. Further mifepristone improved glucose tolerance and insulin sensitivity. Diastolic dysfunction and left ventricular (LV) fibrosis in the DS/obese rats were abrogated by GR antagonism.	Takeshita et al., 2015
Mifepristone treatment was effective in ameliorating increase in body weight, adiposity index, plasma glucose and insulin levels in high fructose fed rats. GR antagonism was also effective in reducing hepatic glucose-6-phosphatase and fructose1,6-bisphosphatase activities.	Priyadarshini and Anuradha, 2017

The data on efficacy of GR antagonism in mitigating metabolic abnormalities is not limited to only preclinical studies. Human-subject based studies demonstrate that GR antagonism holds realistic promise in reducing the burden of metabolic abnormalities associated with excess glucocorticoids. It is important to recognize that much of our understanding of effect of mifepristone on glucocorticoid-related abnormalities has come from treatment of patients with Cushing's syndrome.

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Table 2: Human-subject based studies demonstrating effect of glucocorticoid antagonism on metabolic aberrations

Key findings	Reference
A patient with Cushing's syndrome caused by ectopic ACTH production was subjected to oral mifepristone treatment. Treatment with mifepristone was associated with decrease in 2 h glucose levels during OGTT, fasting glucose levels, and mean blood pressure. Further, increase in TSH, free and total testosterone levels were observed during the treatment. The antiglucocorticoid was reported to elicit no adverse effect during the treatment period of 9 weeks, during which resolution of a few Cushingoid features was observed. The dosage of mifepristone was increased from 5 mg/kg/day to 20 mg/kg/day during the treatment.	Nieman et al., 1985
Prolonged treatment with mifepristone elicited over activation of HPA axis.	Bertagna et al., 1986
Mifepristone was explored as an alternative to removal of adrenals for treating a 27-months old girl. The patient exhibited Cushingoid appearance, growth failure, obesity, osteoporosis, hyperglycemia and hypertension. With hypercortisolemia and increased ACTH levels that were non-responsive to dexamethasone-suppression, the patient was subjected to treatment with mifepristone. Administration of GR antagonist resulted in weight loss, reduction in blood pressure, normalization of glucose levels. Interestingly, urinary and plasma cortisol levels were reduced. No side effect was observed and no relapse of clinical conditions was reported at two months after discontinuation of mifepristone.	Beaufrère et al., 1987
A severely ill patient with pituitary ATCH-related Cushing's syndrome received treatment with mifepristone for a period of 18 months. The dosage ranged from 6 mg/kg/d to 25 mg/kg/d, with dosage being tapered downwards during the later stages to deal with signs of adrenal insufficiency. During the course of treatment, the ACTH levels reduced and patient experienced decrease in fasting triglycerides levels and reduced dependence on insulin. Treatment with mifepristone also led to improvement in heart health and resolution of depression.	Chu et al., 2001
Mifepristone was studied for safety and evaluation of therapeutic effects in patients with Cushing's syndrome. Among those who were diabetic, mifepristone reduced blood glucose and glycated hemoglobin levels. Among hypertensive patients, 38 % of patients exhibited improvements in diastolic pressure. In addition to causing weight loss and decrease in waist circumference, mifepristone was associated with improvements in quality of life and cognition. Mifepristone was effective in resolving insulin resistance and depression. Fatigue, hypokalemia, joint pain and endometrial thickening in women were observed due to mifepristone.	Fleseriu et al., 2012
Mifepristone has been reported to improve insulin resistance in subjects with adrenal incidentaloma, and five out of six patients were reported to exhibit improvements in area under the curve for insulin.	Debono et al., 2013
In a follow-up study, the participants of a phase III trial of efficacy of mifepristone in Cushing's patients, who benefited from weight loss during the trial, were subjected to mifepristone treatment. Treatment with mifepristone was associated with persistence of weight loss achieved at the end of the preceding phase III trial.	Fein et al., 2015

From studies conducted with various diabetic animal models, and studies conducted on Cushing's patients, it appears that GR antagonists have the potential to mitigate metabolic abnormalities associated with diabetes/metabolic syndrome. Despite its observed efficacy in alleviating anomalies associated with Cushing's syndrome, mifepristone has the disadvantage of lack of specificity (due to progesterone antagonism) and is associated with hypokalemia as a result of counter-regulatory activation of HPA axis-induced hypercortisolism (Castinetti et al., 2010). While mifepristone is of great value in treating severe cases of Cushing's syndrome, selective GR antagonists that are devoid of propensity to cause activation of HPA axis are

likely to be evaluated more for the possibility of therapeutic management of metabolic dysregulations associated with metabolic syndrome.

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Conflict of interest

None.

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