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PREVALENCE OF METABOLIC ABNORMALITIES AND HPA AXIS SUPPRESSION INPATIENTS WITH EXOGENOUS CUSHING'S SYNDROME

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ABSTRACT

Context: Corticosteroids play an important role in treatment for various inflammatory and autoimmune disorders. However, corticosteroids have a considerable number of side effects, including diabetes, hypertension, lipid disorders, osteoporosis, myopathy, etc which are components of Cushing's syndrome (CS). **Aims:** The present was done to study the prevalence of metabolic abnormalities and status of hypothalamo-pituitary-adrenal (HPA) axis in patients with exogenous Cushing's syndrome. **Material and Methods:** Forty individuals receiving various types of corticosteroids were recruited in this study. Glucose tolerance test (GTT), lipid profile and cortisol were estimated. They were divided into two groups based on 8.00am cortisol levels (Group I < 5mcg/dL; Group II >5mcg/dL to <15mcg/dL). The data were reported as means ± SD. Students't' test was used to study the significant difference between two groups. **Results:** The prevalence of impaired fasting glycemia (IFG), impaired glucose tolerance (IGT) and diabetes was 17.5%, 45% and 30% respectively. Also, the prevalence of systolic and diastolic hypertension was 55% and 35% respectively. The prevalence of complications like acid peptic disease, fractures, avascular necrosis of hip are 30% (12/40), 12.5% (5/40) and 7.5% (3/40) respectively. More than 50% of patients had elevated levels of total cholesterol, triglycerides and LDL cholesterol and decreased HDL-cholesterol levels. However, there was no significant difference in age, BMI, blood pressure, FBS, PPBS and lipid profile between group I and group II. **Conclusion:** The present study showed increased prevalence of abnormal glucose intolerance, hypertension and altered lipid profile in patients with exogenous corticosteroid induced CS.

KEY WORDS: abnormal glucose tolerance, corticosteroids, cushing's syndrome, dyslipidemia, hypertension.

INTRODUCTION

Corticosteroids have been the medication of choice in various disorders, based on their undoubted benefits from their anti-inflammatory and immunomodulatory actions. However, these drugs are complicated by a various of side effects, including Cushing's syndrome (CS).The clinical presentation of CS often strikes with the use of high doses of corticosteroids.[1,2] Symptoms include central obesity, plethora, easy bruising, thin skin, abdominal purple striae, proximal myopathy, depression, glaucoma, hypertension, poor wound healing, and increased incidence of infection.

Synthetic preparations most commonly used are prednisolone, methylprednisolone, dexamethasone, betamethasone, and triamcinolone. These derivatives have the potential adverse effects and lead to CS[2] Adverse effects are dependent on the formulation used, pharmacokinetics, affinity for the glucocorticoid receptor, biologic potency, duration of action, timing and different levels of sensitivity in individual patients.[2]

Oral corticosteroid therapy has been well correlated with CS, and most physicians are aware of the dangers[2] According to available data, topical, aerosol, inhaled, and injectable corticosteroid therapy also have these adverse effects.[2,3–7]

In patients treated with corticosteroids metabolic abnormalities like impaired glucose tolerance, diabetes, dyslipidemia, and fatty liver are commonly noted.[8-10]

In this study, we present the profile of prevalence of abnormal glucose tolerance, dyslipidemia and status of hypothalamo-pituitary-adrenal (HPA) axis in patients with exogenous Cushing's syndrome.

MATERIAL AND METHODS

We retrospectively recruited 40 consecutive patients receiving various types of corticosteroids (duration: 2 months to 4 years) attending the Endocrine outpatient department, Narayana Medical College and Hospital, Nellore between March 2012 and February 2013.

Physical examination included measurements of height (by a wall tape measure with accuracy of 0.1 cm), weight (by an ELPRO electronic weighing machine New Delhi, India] with accuracy of 0.05kg) and blood pressure were recorded. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared.

After a 10-hr overnight fast, venous blood samples were collected for laboratory evaluation of fasting glucose, triglycerides, total cholesterol and high-density lipoprotein (HDL) cholesterol. Serum cortisol sample was also collected between 8.00 and 9.00am. LDL were calculated by Friedewald's formula (LDL = TC – (TGL/5+HDL).[11] A standard 75gm oral glucose tolerance test (OGTT) was performed.

To check whether a relationship between HPA axis suppression and metabolic abnormalities existed, we divided the patients into two groups based on serum cortisol values. Twenty one patients who had cortisol less than 5mcg/dL were assisgned to group I (adrenal insufficiency), while nineteen patients who had cortisol values more 5 and less than 15mcg/dL were assigned to group II (indeterminate). Serum cortisol >15.0mcg/dL (considering normal HPA axis) were excluded from the study. Corticotropin or cortrosyn (ACTH) stimulation test was done to assess HPA axis status in group II. Cortisol values at 30' and 60' (post-corticotropin) more than 20mcg/dL was considered normal. Out of nineteen cases, 18 patients showed cortisol values more than 20mcg/dL and one patient had less than 16mcg/dL (12.7 and 15.8mcg/dL) at 30' and 60' respectively.

Assays

The biochemical parameters such as fasting plasma glucose, post prandial plasma glucose, total cholesterol, triglycerides, high density cholesterol (HDL-C) were measured by commercially available in vitro kits from Human GmbH onHumstar600 (fully automated chemistry analyzer), Max-Planck-Ring 21, Wiesbaden, Germany.Cortisol levels were measured by chemilumniscence method on Beckman Coulter Acess 2, CA,USA.

Statistical analysis

The data were reported as means ± SD for the normally distributed variables and as median (range) for the skewed variables. The comparison of the variables between the groups I and II was done by using the 't' test by using a Microsoft Excel spread sheet and SPSS for Windows, version 16.0. P value <0.05 were considered as statistically significant.

RESULTS

Table/Figure 1 shows the characteristics of the study subjects in this study. Of the 40exogenous cushing's syndrome subjects recruited, 26(65%) were female and 14 (35%) were male. The mean age of subjects was 42.74± 12.6yrs (range: 0.5-70yrs). The mean systolic and diastolic blood pressures were 140.58 ± 21.72 and 87.65 ± 11.12 mm of Hg respectively. The mean morning cortisol values were 5.52 ± 1.51mcg/dL.

The prevalence of impaired fasting glycemia (IFG), impaired glucose tolerance (IGT) and diabetes was 17.5% (7/40), 45% (18/40) and 30% (12/40) respectively. Also, the prevalence of SBP and DBP was 55% (22/40) and 35% (14/40) respectively. As shown in table-1, exogenous Cushing's syndrome patients had elevated levels of total cholesterol, triglycerides and LDL-C whereas; HDL-C levels were decreased. The prevalence of complications like acid peptic disease, fractures, avascular necrosis of hip are 30% (12/40), 12.5% (5/40) and 7.5% (3/40) respectively.

As shown in Table -2, there was no significant difference in age, BMI and blood pressure between group I and group II. The FBS and PGBS levels were higher in the group I compared to group II, but the difference was not statistically significant. Similarly, total cholesterol, triglycerides, LDL-C and HDL-C showed no significant difference between two groups.

Table 1: Characteristics of subjects with exogenous Cushing's syndrome

Parameter	Mean ± SD (Range)	Reference values
Age (yrs)	42.74 ± 12.6 (5 months – 70yrs)	-
Sex (F/M)	26/14	-
BMI (Kg/m^2)	30.32 ± 5.10	18.5 – 24.9
SBP (mm Hg)	140.50 ± 21.72	120 ± 80
DBP (mm Hg	87.65 ± 11.40	80 ± 10
8.00 am cortisol (mcg/dL)	5.525 ± 1.51	5-20ug/dl
FBS (mg/dL)	114.12 ± 31.42	70-100
PGBS (mg/dL)	186.61 ± 68.53	<140
Total cholesterol (mg/dL)	214.34 ± 44.21	< 200
Triglycerides (mg/dL)	169.65 ± 58.63	<150
HDL-C (mg/dL)	39.80 ± 2.77	> 40 (male), > 50 (female)
LDL-C (mg/dL)	140 ± 37.1	< 130

SD = standard deviation, FBS = fasting blood sugar, PGBS = Post glucose blood sugar, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol.

Table 2: Comparison of Biochemical parameters between two groups

Variables	Group I (Mean ± SD) (n= 21)	Group I I (Mean ± SD) (n= 19)	P value
Age (yrs)	42.85 ± 15.00	44.10 ± 12.95	0.75
BMI (Kg/m^2)	31.19 ± 6.37	30.14 ± 3.28	0.52
SBP (mm Hg)	141.23 ± 22.89	140.30 ± 20.07	0.75
DBP (mm Hg)	88.57 ± 12.26	90.21 ± 10.01	0.64
FBS (mg/dL)	118.45 ± 30.79	111.5 ± 32.52	0.49
PGBS (mg/dL)	203.81 ± 68.59	172.84 ± 66.56	0.16
Total cholesterol (mg/dL)	212.09 ± 43.67	214.84 ± 39.80	0.83
Triglycerides (mg/dL)	166.66 ± 64.60	175.31 ± 46.83	0.63
HDL-C (mg/dL)	39.42 ± 2.80	40.57 ± 2.69	0.19
LDL-C (mg/dL)	138.95 ± 37.03	139.10 ± 32.88	0.98

SD = standard deviation, FBS = fasting blood sugar, PGBS = Post glucose blood sugar, SBP = systolic blood pressure, DBP = diastolic blood pressure, HDL-C = high density lipoprotein cholesterol, LDL-C = low density lipoprotein cholesterol.

DISCUSSION

Corticosteroids are one of the most common causes of drug-induced diabetes mellitus.[12] However, not everyone treated with corticosteoids develops diabetes. Predictors of development of diabetes on corticosteroids are age, weight, type, dose, duration, timing, family history of diabetes mellitus, or a personal history of gestational diabetes. Also, there is evidence that patients with decreased insulin secretory reserve are much more likely to develop diabetes.[13]

Welbourn et al, reported the occurrence of abnormal glucose tolerance in up to 90% of patients with Cushing's syndrome, but only 10% to 29% of these patients develop frank diabetes mellitus.[14] In agreement with this, our study showed the prevalence of abnormal glucose tolerance in 62.5% [IFG = 17.5% (7/40), IGT = 45% (18/40) and diabetes in 30% (12/40) respectively.

The mechanism by which corticosteroids cause abnormal glucose tolerance and diabetes predominantly involves insulin resistance rather than decreased insulin production. Corticosteroids induce insulin resistance in skeletal muscle by directly interfering with the insulin signaling cascade.They also inhibit glucose uptake in muscle and fat, reducing insulin sensitivity as much as 60% in healthy volunteers. This seems primarily due to a post receptor effect, ie, inhibition of glucose transport.[15-17] Corticosteroids also induce hepatic insulin resistance directly by interference with insulin signaling and indirectly by elevating free fatty acid and triglyceride supply to the liver.[18]

Hypertension is a prominent feature in patients with corticosteroid induced CS, occurring in up to 20% of cases, and is dose dependent.[1, 2, 19, 20] However, in our study the prevalence of SBP and DBP (55%; 35%) was higher than the previous studies.[19, 20] which are depend on dose, duration and type of corticosteroid. With corticosteroids, an imbalance occurs between vasoconstriction and vasodilation, favouring vasoconstriction, resulting in hypertension.[19, 20] Increased vasoconstriction is in large part mediated by increased endothelin-1 synthesis and secretion.[21-23] Data also suggest that increased sympathetic activity, reflected in the increased synthesis of catecholamines and a1β-adrenergic receptor expression, is an important underlying pathogenetic mechanism as well.[19,20] The increased synthesis of catecholamines is due to increased expression and activity of various enzymes involved in the catecholamine biosynthesis, including tyrosine hydroxylase and phenylethanolamine N-methyltransferase (PNMT).

On the other hand, corticosteroids have negative effect on various vasodilatory systems.[19, 20] Corticosteroid-

induced hypertension has been associated with nitric oxide (NO) deficiency through a range of negative influences on the NO biosynthetic pathways. Also, corticosteroids seem to negatively affect the production of other vasodilatory substances as well, such as prostacyclin, prostaglandin E2 (PGE2) and kallikrein.[24-26] Coexisting metabolic abnormalities like diabetes mellitus and dyslipidemia also appear to mediate and accentuate the corticosteroid-induced hypertension as shown in this study.

In our study, corticosteroids showed elevated total cholesterol, triglyceride, LDL-C and decreased HDL-C compared to normal reference levels. Ettinger et al, showed a 22% increase in HDL-C and a 40% increase in triglycerides, but no change inLDL-C in healthy men with a dose of 0.35 mg/kg/d of prednisone for 15 to 28 days.[27] In another short study done by Taskinen et al, showed a 27% increase in HDL-C and no change in triglycerides or LDL-C with 30mg of prednisolone for a week.[28] Decreased level of HDL- C and increased level of triglycerides in our study is due to higher dose of corticosteroids and abnormalities like impaired glucose tolerance and diabetes mellitus. Therefore, dyslipidemia with exogenous corticosteroids depend on dose, duration of corticosteroid intake and other associated metabolic abnormalities.

Suppression of the HPA axis occurs rapidly with exogenous glucocorticoid therapy. When glucocorticoid therapy is continued for several days, the HPA axis hypothalamic–pituitary–adrenal axis response is more impaired. Traditionally, the withdrawal schemes begin by reducing the glucocorticoid from supraphysiologic to physiologic doses. The physiologic dose is approximately 5 to 7.5 mg a day of prednisone, 15 to 20 mg a day of hydrocortisone, or the equivalent.

During this stage of withdrawal, it is appropriate to begin checking the morning cortisol levels, which can be useful as a screening test for the basal adrenal sufficiency. Morning (8.00am) cortisol level measuring less than 5µg/dL, indicates a deficient basal cortisol secretion and the need for a continued replacement therapy. If the morning cortisol level is greater than 20µg/dL, the patient can be assumed to have a recovered HPA axis and can be withdrawn entirely from the glucocorticoid therapy.[29]

We acknowledge the limitations of this study, 1) important factor being the small sample size, 2) selection bias of including patients on corticosteroids for some other comorbidities (respiratory, inflammatory and rheumatology disorders).

In conclusion, the results of the present study showed alteration of metabolic profile i.e, glucose intolerance, hypertension, dyslipidemia with corticosteroid induced CS. Before starting corticosteroids, a careful plan regarding formulation, route, dose, and time of exposure should be properly evaluated for each individual. Corticosteroid induced complications should be treated appropriately, and prevention strategy involves changes in lifestyle and treatment with appropriate agents.

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