

## Prevalence of Clinical Iatrogenic Cushing's Syndrome and its Contributing Factors in Patients with Chronic Obstructive Airway Disease

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### ABSTRACT

**Introduction:** Iatrogenic Cushing's syndrome develops due to chronic exposure to excess glucocorticoids and is associated with increased morbidity and mortality if it remains unrecognized and untreated. Cushing's syndrome resulting from long-term use of exogenous glucocorticoids is the commonest cause of iatrogenic Cushing's syndrome. In India, cases of iatrogenic Cushing's syndrome are commonly encountered, owing to the steroid abuse for respiratory conditions and chronic pains along with poor access to health care.

**Method and materials:** This study was conducted in the Department of Respiratory Medicine, Himalayan Institute of Medical Science (HIMS), Swami Ram Nagar, Dehradun. Over a period of 12 months, subjects were recruited from the patients presenting to HIMS, Dehradun with the primary diagnosis of obstructive airway disease after taking written informed consent.

**Result:** After a detailed history and examination and applying the inclusion and exclusion criteria, 384 consecutive patients diagnosed with Obstructive airway disease were enrolled. Demographic data was recorded. Diagnosis of Iatrogenic Cushing syndrome was made on the basis of history of use of glucocorticoids and clinical examination. Most of the patients in the study population were > 60 years of age (34.29%) There was a male predominance in our study with 243 (63.28%) males and 141 (36.72%) females. Smoking was the major risk factor for COPD in comparison to biomass fuel, present in 85.05% and 15.95%, of patients respectively.

**Conclusion:** In our study, prevalence of iatrogenic Cushing syndrome in obstructive airway disease was 7.81%. This study highlights role of screening for iatrogenic Cushing syndrome in patients with obstructive airway disease with early intervention to prevent the side effects of chronic indiscriminate use of steroids.

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## Introduction

Cushing's syndrome was first described by Harvey W Cushing in 1932. It develops due to chronic exposure to excess glucocorticoids and is associated with increased morbidity and mortality if it remains unrecognized or untreated. Iatrogenic Cushing's syndrome resulting from long-term use of exogenous glucocorticoids is the commonest cause of Cushing's syndrome (1).

In humans, hypothalamo-pituitary-adrenal axis follows circadian rhythm. Clinical manifestations of increased level of cortisol are the result of an altered rhythm of cortisol secretion (quality) and increase cortisol level (quantum). Hypercortisolism has a broad spectrum of clinical features, prominent among them being centripetal obesity, proximal muscle weakness, easy bruisability, broad violaceous striae over abdomen (2).

In India, cases of iatrogenic Cushing's syndrome are more commonly encountered, secondary to the overuse of steroids in form of oral/injectable preparations for pains and aches recklessly. Some features such as increased intraocular pressure, cataracts, benign intracranial hypertension, aseptic necrosis of femoral head, osteoporosis, and pancreatitis are more common in exogenous than in endogenous Cushing's syndrome. History of depression, severe obesity or chronic alcoholism are associated with Pseudo-Cushing's syndrome (3).

The tests available for screening of endogenous Cushing's syndrome are 24-hour urinary free cortisol overnight and low dose-dexamethasone suppression test (4, 5). To assess the circadian rhythm and quality of the HPA axis, midnight serum cortisol and late night salivary cortisol tests are useful (6, 7).

The most distinctive features that help to differentiate Cushing's syndrome from simple obesity include signs and symptoms of protein catabolism i.e. proximal muscle weakness, wide dehiscence red-purple striae, easy bruising, cuticular/pulp atrophy and osteoporosis (8, 9). Generally a Cushingoid appearance takes weeks or months to

develop depending upon type and dose of steroid use (10).

Adrenal cortex produces natural steroid hormones. Synthetic steroids are analogues of natural steroid hormones. These synthetic compounds have glucocorticoid, mineralocorticoid and androgenic properties in varied proportion. Mineralocorticoids act on mineralocorticoid receptor present on epithelial cells of the renal tubules and regulate the electrolyte and water balance (11).

In normal individual, plasma cortisol levels are maximum in the morning and reach a minimum (< 50 nmol/L) at about midnight. This circadian rhythm is disturbed in patients with Cushing's syndrome. The midnight cortisol > 200 nmol/L indicates presence of endogenous Cushing's syndrome with sensitivity of 94% and specificity of 100%. However, serum cortisol levels may be low or normal in iatrogenic Cushing's syndrome (12, 13). Hence, history of intake of glucocorticoids is very important in assessment of patients with iatrogenic Cushing's syndrome.

A study conducted by Decramer M and Stas KJ et al. in Belgium in 1992 found that asthmatic patients taking oral steroids developed myopathy. The resultant impairment of respiratory muscle function may lead to reduction in pulmonary inspiratory muscle and pulmonary expiratory muscle function (14).

Indiscriminate and excessive use of glucocorticoids in patients with obstructive airway diseases may lead to development of iatrogenic Cushing's syndrome. Presence of Cushing's syndrome may rather make patients with obstructive airway disease prone to increased risk of chest infections and exacerbation of disease due to associated chest muscle weakness and impaired sputum clearance, suppression of immunity and presence of hyperglycemia.

Most of the literature regarding iatrogenic Cushing's syndrome in patients with COPD, bronchial asthma is from western population to the best of our knowledge. There is a need for studying the steroid induced Cushing's syndrome in Indian population as there is an unrestrained use of corticosteroids by untrained medical

practitioners particularly in the rural parts of India.

We aim to study the prevalence of steroid induced Cushing's syndrome among patients with chronic obstructive pulmonary disease and bronchial asthma attending Himalayan Hospital, in Uttarakhand.

### Aims and Objective

To find the prevalence of iatrogenic Cushing's syndrome in COPD/ asthma patients.

To compare demographic, anthropometric, clinical and lab parameter between patients with obstructive airway disease, with and without exogenous Cushing's syndrome.

### Materials and Methods

The present study was conducted in the Department of Respiratory Medicine, Himalayan Institute of Medical Science (HIMS), Swami Ram Nagar, Dehradun. Over a period of 12 months, subjects were recruited from the patients presenting to HIMS, Dehradun with the primary diagnosis of obstructive airway disease after taking written informed consent. Three hundred and eighty four consecutive patients with obstructive airway disease presenting in out-patient department, emergency or admitted in wards during the study period were screened for inclusion and exclusion criteria. The ethical clearance for the study was obtained from the institutional ethics committee.

Type of the study: observational descriptive study

Study protocol: Inclusion Criteria:

- Patients with obstructive airway disease viz. COPD / Asthma.
- Age >18 year
- Exclusion Criteria:
- Pregnancy Active tuberculosis/ disseminated or military tuberculosis
- Patients receiving glucocorticoids for indication other than airway disease such as Rheumatoid arthritis, connective tissue disorder, dermatological disorder etc.

### Data Management and Statistical Analysis

Data was collected as per case reporting form and entered in Microsoft excel 2010. It was analyzed using statistical software SPSS version 22. Categorical variables were represented in form of frequencies and percentage. Continuous variables were represented in form of mean  $\pm$  SD for parametric data and non-parametric data in form of median  $\pm$  inter quartile range. Continuous variables between two groups were compared using Students t-test. Association between categorical variables for two or more categories were done using chi square test. Value of  $p < 0.05$  was considered as statistically significant.

### Results

The study included 384 patients who attended Respiratory Medicine OPD during the study period. Among 384 patients, 257 patients were diagnosed cases of COPD and 127 with Asthma.

Diagnosis of obstructive airway disease (COPD/Asthma) was made according to GOLD guidelines and GINA guidelines. Iatrogenic Cushing's syndrome was diagnosed by presence of history of use of glucocorticoids and clinical features consistent with Cushing's syndrome.

Most of the patients in the study population were more than 60 years of age (34.29%) followed by patients in 51-60 age group which comprised 26.96 % of study population. Mean age in those with Cushing's syndrome was  $53.3 \pm 16.21$  years. Mean BMI was  $22.8 \pm 3.92$  kg/meter<sup>2</sup>. There was a male predominance in our study with 245 (63.80%) males and 139 (36.19%) females (table 1,2).

Prevalence of Iatrogenic Cushing's syndrome in obstructive airway disease (384) was 7.81% (Figure 1).

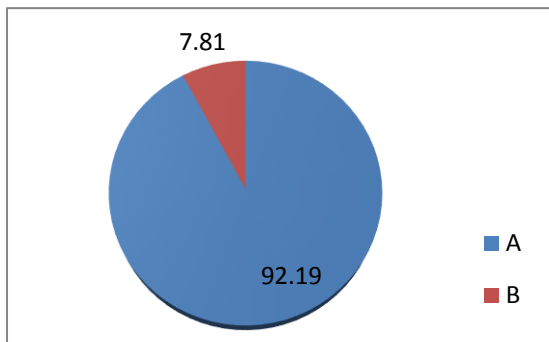
Out of these 30 patients with iatrogenic Cushing's syndrome 19 patients were suffering from Asthma and rest 11 patients had chronic obstructive pulmonary disease. Prevalence of iatrogenic Cushing's syndrome in asthma and chronic obstructive pulmonary disease was 14.96% and 4.28%, respectively (Figure 2).

**Table-1.** Demographic parameters of study subjects (n=384)

Variable (units)	Mean	SD
Age (year)	53.3	16.21
Height (cm)	164.0	7.58
Weight (kg)	61.1	11.77
History of smoking (Pack-year)	10.5	9.87
Haemoglobin (g %)	12.7	1.40
BMI (kg/meter <sup>2</sup> )	22.8	3.92
Gender (M:F)	245 (63.80%):139(36.19%)	

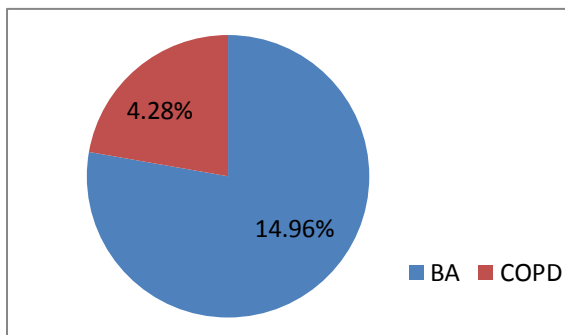
**Table-2 .** Age wise distribution of the cases (n=384)

Age Group (year)	No. of Cases	Percentage
18 – 30	49	12.83
31 – 40	36	9.42
41 – 50	63	16.49
51 – 60	104	27.08
>60	132	34.37

**Figure 1.** Prevalence of iatrogenic Cushing syndrome in obstructive airway disease

A= Obstructive airway disease with Iatrogenic Cushing syndrome.

B= Obstructive airway disease without Iatrogenic Cushing syndrome.

**Figure 2.** Prevalence of iatrogenic Cushing's syndrome in COPD and Asthma

BA= Asthma

COPD=Chronic obstructive airway disease

The most common clinical features of iatrogenic Cushing's syndrome were central obesity followed by moon shaped face (table 3).

Patients with concomitant obstructive airway disease and iatrogenic Cushing's syndrome were younger [age (years) = 46.4 + 13.12 vs 53.9 + 16.33; P value= 0.017] and smoker [smoking in pack year (5.1±6.98 vs 10.9 + 9.94; P value=0.001)] compared to those with obstructive airway disease without iatrogenic Cushing's syndrome. FEV1 was significantly lower in patients with both obstructive airway disease and iatrogenic Cushing's syndrome compared to those with obstructive airway disease without iatrogenic Cushing's syndrome (27.3 ± 12.8 percent vs 43.5 ± 21.6 percent ; P value=0.000) (table 4).

Majority of the obstructive airway disease patients with acute exacerbation of obstructive airway disease, when consulted the nearest health care provider in remote areas, were prescribed oral or injectable glucocorticoids along with other medications, which they continued over long periods or intermittently and repeatedly without supervision.

Among 30 patients with iatrogenic Cushing's syndrome, low morning cortisol (<30 ng/ml) was found in 4 patients suggestive of suppression of hypothalamo-pituitary-adrenal axis in patients giving history of glucocorticoids intake.

## Discussion

Obstructive airway disease is a chronic inflammatory disease of airways which has effects on all the organs of the body. COPD and asthma form the major chunk of obstructive airway disease. Most common causes of acute exacerbation of COPD/Asthma are viral infections, seasonal variations and exposure to irritants. Glucocorticoids are the most potent anti-inflammatory agents used in managing acute exacerbations. Oral or injectable steroids are most commonly used in acute exacerbation of COPD/Asthma. To the best of our knowledge, there is no published study on prevalence of iatrogenic Cushing's syndrome in obstructive airway disease in India.

In our study we have assessed the prevalence of iatrogenic Cushing's syndrome in patients with obstructive airway disease attending a tertiary care hospital and its contributing factors.

Study included a total of 384 patients with obstructive airway disease, among these 243

(63.28%) were males and 141 females (36.71%). We did not find any association of prevalence of iatrogenic Cushing's syndrome with gender. Also patients with obstructive airway disease with low smoking index were found to have higher prevalence of iatrogenic Cushing syndrome which was found to be statistically significant. Patients with obstructive airway disease with iatrogenic Cushing's syndrome were found in younger age group as compared to those with obstructive airway disease without iatrogenic Cushing's syndrome. FEV1 was significantly lower in patients with obstructive airway disease with iatrogenic Cushing's syndrome compared to those with obstructive airway disease without iatrogenic Cushing's syndrome. Probably this group of patients used steroids more frequently and at higher doses owing to the severe and sustained inflammation (symptoms) or repeated exacerbations.

**Table-3.** Clinical manifestation's in iatrogenic Cushing's syndrome (n=30)

clinical features	Yes (n=30)	Percentage
Central Obesity	28/30	93.33
Moon Face	27/30	90
Abdominal Striae	4/30	13.66
Easy Bruisability	3/30	10
Irregular Menstrual cycle	6/18	33
Increased Supraclavicular and dorsocervical fat pad	13/30	43.33
Proximal Myopathy	6/30	20

**Table-4 .**Comparison of demographic data in patients with and without Cushing's syndrome

Demographic variable	Cushing syndrome		P value
	Present (n=30)	absent (n=354)	
Age (year)	46.5±13.1	53.9±16.3	0.017
Height (cm)	163.1±5.5	163.7±7.7	0.680
Weight (kg)	63.5±6.2	60.9±12.1	0.227
BMI (kg/meter <sup>2</sup> )	23.9±2.1	22.7±4.0	0.099
History of smoking (Pack-year)	5.1±6.9	10.9±9.9	0.001
Hemoglobin (g% )	13±1.0	12.7±1.4	0.214
FEV1 (%) (Post bronchodilator)	27.3±12.1	43.5±21.6	0.000
FEV1/FVC (%)	67.3±16.3	66.0±12.8	0.617
Sex ratio M:F (number)	12:18	233:121	

Most of the females with COPD in our study had biomass fuel exposure (68.18%) as the risk factor. As our hospital is situated in a hill state patients coming from the remote areas are still using biomass fuel as a cooking medium. This remains the major risk factor for COPD among the females of our state.

Among 384 study objects with obstructive airway disease, 72 subjects gave history of intake of glucocorticoids. Among these 72 patients, 30 had clinical features suggestive of iatrogenic Cushing's syndrome. Thus, prevalence of iatrogenic Cushing's syndrome was 7.8% in present study.

Among 30 patients with iatrogenic Cushing's syndrome, four patients were found to have suppression of hypothalamic-pituitary-adrenal axis.

Corticosteroids are useful drugs, if prescribed for an evidence based indication; but if used irrationally, troublesome adverse effects may be noted. The corticosteroids should be used for a specific indication, a proper duration, and with an appropriate dosage schedule. The risk-benefit ratio should be evaluated before starting therapy. The physicians must also explore the alternative modes of treatment of various diseases, where steroids are indicated as primary drugs, and these alternative modalities may be used, if troublesome side effects appear following glucocorticoids treatment and warrants discontinuation of the same.

As per available literature, there was no study available on prevalence of iatrogenic

Cushing's syndrome in obstructive airway disease, to compare our study.

Iatrogenic Cushing's syndrome in obstructive airway disease results from chronic exposure to glucocorticoids and irrational use of steroids in form of tablet, Ayurvedic, Unani medicine and any other form of alternative medicine. In our study, patients with iatrogenic Cushing syndrome had truncal obesity in 93.33% of cases, Moon face in 90% of cases, buffalo hump in 43.37%, myopathy in 20%, abdominal striae in 13.66% and easy bruisability in 10% of cases. The frequency of various clinical features of iatrogenic Cushing's syndrome in our study compared with earlier studies by Singh et al, Srivastav et al and Venkateshwarlu Nandyala et al in the following table. These studies were carried out in patient with rheumatoid arthritis, asthma, connective tissue disorders, joint pains and dermatological disorders (table 5) (15, 16, 17).

### Conclusion

- Patients with obstructive airway disease with iatrogenic Cushing's syndrome were found in younger age group as compared to those with obstructive airway disease without iatrogenic Cushing's syndrome.
- Among the 384 patients with obstructive airway disease, there were 243 (63.28%) males and 141 females (36.71%). We did not find any association of iatrogenic Cushing's syndrome with gender.

**Table-5** .Comparison of Clinical features of Cushing's syndrome with earlier studies

Sr. no.	Clinical features	Singh, Kotwal et al in 2011 [Percentage]	Srivastav et al 2015 [Percentage]	Venkateshwarlu Nandyala1 et al 2014 [Percentage]	Present study [Percentage]
1	Moon shaped facies	89	92.6	95.74	90
2	Buffalo hump	79.2			43.37
3	Truncal obesity	97		78.72	93.33
4	Myopathy	20		21.27	20
5	Ecchymosis	75	12.1	17.02	10
6	Striae	08	9.8	8.51	13.66

- Among 30 patients with iatrogenic Cushing's syndrome, four patients were found to have suppression of hypothalamo-pituitary-adrenal (HPA) axis.

Thus, we conclude that the prevalence of iatrogenic Cushing's syndrome in obstructive airway disease was 7.81% in our study.

To the best of our knowledge, this is first study from India to assess prevalence of iatrogenic Cushing's syndrome in patients with obstructive airway diseases. This helps to understand the importance of screening all the obstructive airway disease patients for symptoms of iatrogenic Cushing syndrome and history of steroid use to prevent the side effects of steroid abuse early in the disease course. Prevention of iatrogenic Cushing syndrome can improve the quality of life and save patients from potentially harmful complications.

There is a need for studying a larger population for finding more accurate prevalence of iatrogenic Cushing syndrome in obstructive airway disease in Indian population.

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