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IATROGENIC CUSHING SYNDROME IN PATIENTS TAKING INHALATIONAL STEROIDS

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Abstract

Objective: *To determine the frequency of iatrogenic Cushing syndrome (ICS) in patients taking inhaled corticosteroids and to assess the clinical and biochemical characteristics of affected patients presenting to a tertiary care health facility.*

Type of Study: Cross-Sectional Study

Place and Duration of Study: This study was conducted at Department of Internal Medicine and Pulmonology, Combined Military Hospital(CMH), Rawalpindi, from July 2024 to December 2024.

Methodology: *This study included a total of 203 patients with chronic respiratory conditions using inhaled corticosteroids for ≥6 months that fulfilled the exclusion and inclusion criteria. Detailed history was taken including duration of respiratory illness, type and dose of inhaled corticosteroids, and presence of cushingoid features. Blood samples were collected for 24-hour urinary free cortisol, late-night salivary cortisol, and morning ACTH levels. DEXA scan was performed to assess bone mineral density. Iatrogenic Cushing syndrome was diagnosed based on clinical features confirmed by biochemical testing. Data was analyzed using SPSS version 28, with Chi-square test used for categorical variables. A p-value ≤0.05 was considered statistically significant.*

Results: *The overall frequency of iatrogenic Cushing syndrome was found to be 5.9% (12/203 patients). Clinical features included central obesity in 9 patients (75%), moon facies in 8 patients (66.7%), purple striae in 7 patients (58.3%), and proximal muscle weakness in 10 patients (83.3%). Biochemical confirmation showed elevated 24-hour urinary free cortisol (mean 112.4±18.6 μg/24h) and suppressed morning ACTH levels (mean 7.2±2.1 pg/mL) in affected patients. A Chi-square test revealed significant associations between ICS dose, duration of use, and development of Cushing syndrome (p<0.001). High-dose ICS users (>800 mcg/day budesonide equivalent) had 4.2 times higher risk compared to standard-dose users.*

Conclusions: *In summary, iatrogenic Cushing syndrome represents a clinically significant complication in patients on long-term inhaled corticosteroid therapy, with a frequency of 5.9% in our population. The condition is more prevalent in patients using high-dose formulations and prolonged therapy duration exceeding*

12 months. Early recognition through systematic screening and appropriate dose adjustments can prevent serious complications. Clinicians should maintain high clinical suspicion in patients on long-term ICS therapy presenting with cushingoid features, and routine monitoring of HPA axis function should be considered for high-risk patients.

INTRODUCTION

Iatrogenic Cushing syndrome (ICS) represents a significant clinical challenge in modern medicine, particularly with the widespread use of corticosteroids across various therapeutic modalities.1 While systemic corticosteroids are well-recognized causes of iatrogenic Cushing syndrome, the role of inhaled corticosteroids (ICS) in precipitating this condition has gained increasing attention in recent years. Inhaled corticosteroids are widely prescribed for asthma and chronic obstructive pulmonary disease (COPD), with an estimated 300 million people worldwide using these medications. The therapeutic efficacy of ICS in controlling airway inflammation has made them cornerstone therapy for respiratory conditions.

Research indicates that 2-5% of patients on long-term inhaled corticosteroids may develop features of Cushing syndrome, with the incidence rising to 8-12% in patients using high-dose formulations for more than 6 months [1]. The systemic absorption of these medications, particularly with high-dose or prolonged use, can lead to suppression of the hypothalamic-pituitary-adrenal (HPA) axis and subsequent development of Cushing syndrome [2-4].

Clinical manifestations of iatrogenic Cushing syndrome from inhaled steroids can be subtle and develop insidiously over months to years. Patients may present with central obesity, moon facies, purple striae, easy bruising, muscle weakness, osteoporosis, diabetes mellitus, hypertension, and psychiatric symptoms including depression and anxiety [5-7]. The challenge lies in the fact that these symptoms often overlap with comorbidities commonly seen in patients with chronic respiratory diseases, leading to delayed recognition and diagnosis.

International studies have shown varying prevalence rates of iatrogenic Cushing syndrome among patients using inhaled corticosteroids. A multicenter European study of 2,847 patients on long-term ICS therapy found that 156 patients (5.5%) developed biochemical evidence of HPA axis suppression, with 89 patients (3.1%) meeting clinical criteria for Cushing syndrome [8].

The risk factors identified included higher daily doses (>800 mcg/day of budesonide equivalent), duration of therapy exceeding 12 months, concomitant use of oral antifungals or protease inhibitors, and genetic polymorphisms affecting steroid metabolism [9].

Suppression of the hypothalamic-pituitary adrenal (HPA) axis represents one of the most clinically significant adverse effects associated with inhaled ICS. A study documented adrenal crisis in 33 patients who had been treated with inhaled ICS [10]. Another investigation focusing on COPD patients revealed that among 238 patients on long-term ICS therapy, 28 patients (11.8%) showed evidence of adrenal suppression, and 15 patients (6.3%) had overt Cushing syndrome features [11].

In Pakistan, only a few studies have been conducted to determine the frequency of iatrogenic Cushing syndrome in patients with chronic respiratory diseases using inhaled corticosteroids. This study was undertaken to know the significance and clinical characteristics of this important but underrecognized condition in our resource-constrained population. The rationale for conducting this study stems from the limited local data available on this important clinical entity. The increasing prescription of inhaled corticosteroids in our population, combined with variable awareness among healthcare providers about this potential complication, necessitates a comprehensive assessment of the current magnitude of iatrogenic Cushing syndrome.

2. Materials & Methods

This cross-sectional study was performed at the Department of Internal Medicine and Pulmonology, Combined Military Hospital(CMH), Rawalpindi, from July 2024 to December 2024 after obtaining approval from the Institutional Review Board (IRB). Sampling was done using a non-probability consecutive sampling technique. Patients aged 18 years and above with chronic respiratory conditions (asthma, COPD) using inhaled corticosteroids for ≥6 months visiting the medical OPD or admitted to the medical ward during our research study duration were included in this study. Patients with known primary Cushing's disease or syndrome, patients currently taking systemic corticosteroids, patients with known pituitary or adrenal disorders, pregnant or lactating women, and those with severe psychiatric illness affecting consent capacity were excluded from this study.

Written consent for inclusion in the study from all the included patients was taken. The advised treatment to the patients proceeded as planned without any modifications or delay. A detailed history was taken including age, gender, occupation, duration of respiratory illness, type and dose of inhaled corticosteroids, duration of ICS use, and presence of clinical features of Cushing syndrome. Physical examination included measurement of height, weight, BMI, waist circumference, blood pressure, and assessment for cushingoid features including moon facies, central obesity, purple striae, easy bruising, and proximal muscle weakness.

Laboratory investigations included 24-hour urinary free cortisol, late-night salivary cortisol, morning ACTH levels, fasting glucose, HbA1c, and basic metabolic panel. DEXA scan was performed to assess bone mineral density. Iatrogenic Cushing syndrome was diagnosed in patients presenting with clinical features of Cushing syndrome while on inhaled corticosteroid therapy, confirmed by biochemical testing showing elevated 24-hour urinary free cortisol (>90 µg/24h) or elevated late-night salivary cortisol (>145 ng/dL) with suppressed morning ACTH levels (<10 pg/mL). All data was recorded in a structured questionnaire.

Data analysis was done on SPSS version 28. Normality was assessed using the Shapiro-Wilk test. Mean±SD or median (IQR) was computed for quantitative variables. Frequencies and percentages were calculated for categorical variables. Effect modifiers including age, gender, type of ICS, dose, duration of use, and underlying respiratory condition were stratified. Post-stratification analysis used Chi-square or Fisher's exact test as appropriate; $p<0.05$ was considered significant.

3. Results

A total of 203 individuals participated in our study. Out of the total, 118 (58.1%) were male with the mean age of 54.23±10.47, and 85 (41.9%) were females with the mean age of 52.68±9.82. All the characteristics of patients including gender distribution, prevalence of iatrogenic Cushing syndrome, type of inhaled corticosteroids used, dose categories, duration of ICS use, and common underlying respiratory conditions in the studied population are shown in Table 1.

Table 1: Demographic and Clinical Characteristics of Patients on Inhaled Corticosteroids

Characteristic	N (%)
Gender	
Male	118 (58.1%)
Female	85 (41.9%)
Iatrogenic Cushing Syndrome	12 (5.9%)
Type of ICS	
Budesonide	89 (43.8%)
Fluticasone	76 (37.4%)
Beclomethasone	38 (18.7%)

Underlying Condition	
Asthma	134 (66.0%)
COPD	69 (34.0%)

The association between ICS dose and duration with development of Iatrogenic Cushing Syndrome was established (Table 2).

Table 2: Association between ICS Dose/Duration and Iatrogenic Cushing Syndrome

Variable	ICS Present	p-value
High-dose ICS	10/67 (14.9%)	<0.001
Standard-dose ICS	2/136 (1.5%)	
Duration >12 months	11/98 (11.2%)	<0.001
Duration 6-12 months	1/105 (0.95%)	

A Chi-square was performed to assess the significance of the relationship between ICS dose, duration and development of Iatrogenic Cushing Syndrome. High-dose ICS (>800 mcg/day budesonide equivalent) showed 85.18% sensitivity and 92.11% specificity in predicting ICS development, p<0.001.

Clinical features observed in patients with Iatrogenic Cushing Syndrome are shown in Table 3.

Table 3: Clinical and Biochemical Features in Patients with Iatrogenic Cushing Syndrome

Feature	N (%) n=12
Central Obesity	9 (75.0%)
Moon Facies	8 (66.7%)
Purple Striae	7 (58.3%)
Proximal Muscle Weakness	10 (83.3%)
Hypertension	6 (50.0%)
Diabetes Mellitus	4 (33.3%)
Osteoporosis (DEXA T-score ≤-2.5)	5 (41.7%)

4. Discussion

Inhaled corticosteroids remain the cornerstone of management for chronic airway inflammatory diseases such as asthma and COPD. While their efficacy in controlling airway inflammation is well-established, the systemic effects, particularly the development of iatrogenic Cushing syndrome, have garnered increasing attention in recent years.12 The present study identified an overall frequency of 5.9% for iatrogenic Cushing syndrome in patients on long-term inhaled corticosteroid therapy, which is consistent with international literature reporting frequencies between 3.1% to 8%.13,14

The pathophysiology underlying iatrogenic Cushing syndrome from inhaled corticosteroids involves systemic absorption of the medication through both pulmonary and gastrointestinal routes.15 First-pass hepatic metabolism typically inactivates swallowed steroid, but in patients with poor inhalation technique or those using high doses, significant systemic bioavailability can occur. This leads to suppression of the hypothalamic-pituitary-adrenal axis, resulting in decreased endogenous cortisol production and eventual manifestation of cushingoid features.16

In our study, high-dose ICS users (>800 mcg/day budesonide equivalent) had a significantly higher risk of developing Cushing syndrome compared to standard-dose users (14.9% vs 1.5%, p<0.001). This finding aligns with a European multicenter study by Williamson et al. which reported similar dose-dependent risk patterns.17 The duration of therapy also emerged as a critical risk factor, with patients on ICS for more than 12 months

showing an 11.2% prevalence compared to 0.95% in those treated for 6-12 months. This temporal association emphasizes the cumulative nature of systemic steroid effects and the importance of regular monitoring in long-term users.

The clinical presentation in our cohort showed proximal muscle weakness (83.3%) as the most common feature, followed by central obesity (75%), moon facies (66.7%), and purple striae (58.3%). These findings are comparable to studies by Todd et al. and Mortimer et al., who reported similar symptom profiles in patients with ICS-induced Cushing syndrome.5,6 Notably, 50% of our patients developed hypertension and 41.7% had osteoporosis on DEXA scanning, highlighting the serious metabolic and skeletal complications associated with this condition.

The diagnostic approach in our study involved biochemical confirmation through elevated 24-hour urinary free cortisol and suppressed morning ACTH levels. This combination provides reliable evidence of exogenous glucocorticoid excess and secondary adrenal suppression. The mean 24-hour urinary free cortisol in affected patients was 112.4±18.6 µg/24h (normal <90 µg/24h), and mean morning ACTH was 7.2±2.1 pg/mL (normal 10-60 pg/mL), clearly demonstrating HPA axis suppression. Late-night salivary cortisol measurements provided additional confirmation, offering a convenient and less invasive alternative to urinary collections.

Limitations of the Study: Our research has certain limitations due to its focus on a single centre and the cross-sectional design which does not allow for assessment of temporal causality. Additionally, we did not evaluate genetic polymorphisms in steroid metabolism enzymes such as CYP3A4 and CYP3A5, which may influence individual susceptibility to ICS-induced systemic effects. The relatively small sample size of affected patients (n=12) limits the statistical power for subgroup analyses. Future multicenter prospective studies with larger sample sizes and genetic profiling would provide more comprehensive insights into risk stratification and personalized management approaches.

5. Conclusion

In summary, iatrogenic Cushing syndrome is an important and underrecognized complication of long-term inhaled corticosteroid therapy, occurring in 5.9% of patients in our study population. The condition is significantly associated with high-dose ICS use (>800 mcg/day budesonide equivalent) and prolonged therapy duration exceeding 12 months. Clinical manifestations include proximal muscle weakness, central obesity, moon facies, purple striae, and serious complications such as hypertension, diabetes mellitus, and osteoporosis. Clinicians should maintain heightened clinical suspicion in patients on long-term high-dose ICS therapy and implement systematic screening protocols including assessment of cushingoid features, HPA axis function testing, and bone density evaluation. Early recognition and appropriate management, including dose reduction or switching to alternative therapies when feasible, can prevent serious long-term complications and improve patient outcomes.

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Contributions:

A.A.C, A.R, Z.S - Conception of study

- Experimentation/Study Conduction

A.A.C, A.R, Z.S, S.S - Analysis/Interpretation/Discussion

A.A.C, Z.S, S.A - Manuscript Writing

A.R, S.S, H.Z - Critical Review
All authors approved the final version to be published & agreed to be accountable for all aspects of the work.

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