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Iatrogenic Cushing's Syndrome with Inhaled Steroids

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Abstract
Long-term usage of exogenous corticosteroids is linked to the uncommon but severe adverse impact known as iatrogenic Cushing's syndrome. For the treatment of respiratory disorders like asthma and chronic obstructive pulmonary disease (COPD), inhaled corticosteroids (ICS) are frequently given. With regard to iatrogenic Cushing's syndrome specifically associated with the use of inhaled steroids, this review paper seeks to offer a thorough analysis.

ICS works by modulating the transcription of genes that promote inflammation, which reduces airway inflammation and improves respiratory symptoms. The risk of iatrogenic Cushing's syndrome can, however, increase as a result of increased exposure to corticosteroids caused by systemic absorption of ICS.

Due to underdiagnosis and underreporting, the prevalence of iatrogenic Cushing's syndrome with ICS treatment may be underestimated. Its development is influenced by a number of risk factors, such as high-dose ICS therapy, protracted treatment, and individual vulnerability.

Iatrogenic Cushing's syndrome caused by inhaled steroids presents clinically similarly to endogenous Cushing's disease, making diagnosis difficult. For a precise diagnosis, close observation, hormonal evaluations, and imaging modalities are necessary.

The goal of management is to address the underlying respiratory condition while reducing or stopping corticosteroid therapy. Effective management requires regular patient monitoring, dose titration, and alternate therapy choices. Additionally, precautionary precautions and approaches to reduce the chance of getting iatrogenic Cushing's syndrome from using ICS should be taken into account.

Iatrogenic Cushing's syndrome is a serious issue connected to the usage of inhaled steroids, to sum up. To ensure early discovery and effective care, clinicians should be aware of this potential risk and regularly follow patients.

1. Introduction

An excessive exposure to glucocorticoids, whether from exogenous injection or endogenous overproduction, is a defining feature of iatrogenic Cushing's syndrome [1]. Numerous symptoms, such as central obesity, moon facies, hirsutism, hypertension, and glucose intolerance, are present with the condition [2]. Even while inhaled corticosteroids (ICS) are a lesser-known contributor to the development of iatrogenic Cushing's syndrome, systemic corticosteroids are a well-known cause of the condition [3]. By lowering airway inflammation and ameliorating symptoms, ICS are very successful in treating respiratory disorders [4]. They are frequently used for ailments like COPD and asthma [5]. Iatrogenic Cushing's syndrome risk is raised by the systemic absorption of ICS, which can result in considerable exposure to corticosteroids [6]. Due to underdiagnosis and underreporting, the frequency of iatrogenic Cushing's syndrome specifically linked to ICS use may be underestimated [7]. This raises questions regarding how long-term ICS medication may affect how quickly this illness develops. Understanding the incidence of and risk factors for iatrogenic Cushing's syndrome with ICS use is

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essential for determining the most effective therapy approaches. This review paper seeks to offer an in-depth analysis of the most recent research on iatrogenic Cushing's disease, particularly as it relates to the use of inhaled steroids. We seek to deepen our awareness of this significant clinical entity by analyzing the mechanisms of action of ICS, investigating the prevalence and risk factors, talking about the clinical presentation and diagnostic evaluation, and addressing the management and prevention efforts. Clinicians must actively monitor patients to ensure early diagnosis and proper management and be aware of the potential danger of iatrogenic Cushing's syndrome with ICS use. We intend to advance understanding of this iatrogenic problem connected to the use of inhaled steroids by addressing this issue.

2. Mechanism of Action

Through the reduction of airway inflammation and the amelioration of symptoms, inhaled corticosteroids (ICS) are incredibly effective in treating respiratory conditions [5]. These drugs work through a complicated method of action that involves controlling the transcription of genes that promote inflammation. When inhaled, ICS are deposited in the airways and have a localized effect on the respiratory tract's immune cells and airway epithelial cells [6]. These cells have a high expression of glucocorticoid receptors, which the corticosteroids bind to. The corticosteroid-receptor complex is moved into the cell nucleus as a result of this interaction, where it functions as a transcription factor [7]. The complex controls the transcription of numerous pro-inflammatory genes implicated in the pathophysiology of respiratory disorders by binding to particular DNA sequences known as glucocorticoid response elements [8]. Through the regulation of gene expression, ICS block the production of pro-inflammatory cytokines, chemokines, and adhesion molecules while promoting the synthesis of anti-inflammatory proteins including secretory leukocyte protease inhibitor and lipocortin-1 [9]. The control of airway inflammation, a decrease in airway hyperresponsiveness, and enhanced lung function are all results of this general anti-inflammatory effect [10]. Although ICS are primarily intended to have local effects, it is significant to remember that some of the inhaled dose can be absorbed systemically [11]. In particular with high doses or long-term use, systemic absorption, which primarily occurs through the pulmonary capillaries, might result in considerable exposure to corticosteroids [12]. Iatrogenic Cushing's syndrome may occur as a result of this systemic exposure. The lipophilicity of the medication, particle size, inhaler technique, airway inflammation, and unique patient features are the factors that affect systemic absorption of ICS [13]. Compared to hydrophilic corticosteroids like beclomethasone, lipophilic ICS like fluticasone propionate and budesonide have a higher potential for systemic absorption [14]. Additionally, using spacers or valved holding chambers with metered-dose inhalers can boost lung deposition while decreasing oropharyngeal deposition, hence reducing systemic exposure [15]. In conclusion, ICS treat respiratory disorders by modifying the transcription of genes that cause inflammation. Lung health and respiratory symptoms are improved by local anti-inflammatory actions. However, ICS can be absorbed systemically, which could expose the body to corticosteroids. Drug properties and patient-specific factors are some of the factors that affect systemic absorption. Recognizing the possible danger of iatrogenic Cushing's syndrome linked with the use of ICS requires an understanding of the mechanism of action and variables affecting systemic absorption.

3. Prevalence and Risk Factors

The frequency of iatrogenic Cushing's syndrome, which is especially linked to the use of inhaled steroids, is unknown, and there is scant information on its precise incidence. However, new data point to the possibility that this illness is more widespread than previously thought [15]. The use of inhaled steroids has been linked to a number of risk factors that can lead to the development of iatrogenic Cushing's syndrome. Since higher doses result in more systemic exposure to corticosteroids, high-dose ICS therapy has been linked to an elevated risk [16]. The duration of the medication is also a significant risk factor because long-term corticosteroid exposure can cause adrenal suppression, which can then result in Cushing's syndrome [17]. A significant factor in the emergence of iatrogenic Cushing's syndrome is individual sensitivity. Due to differences in drug metabolism, genetics, or underlying disorders that impact the hypothalamic-pituitary-adrenal (HPA) axis, certain patients may be more susceptible to the negative effects of corticosteroids [18]. Patients who concurrently take drugs such ritonavir or

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ketoconazole, which impede the metabolism of corticosteroids, may be more susceptible to developing iatrogenic Cushing's syndrome [19]. It is important to remember that ICS generally carries a lesser risk of iatrogenic Cushing's syndrome than systemic corticosteroid therapy. This is because ICS is delivered locally and has a lower systemic bioavailability. But with increasing doses, continued usage, and personal vulnerability, the danger rises [20].

Determining the true prevalence of iatrogenic Cushing's syndrome with ICS use is difficult because it is underdiagnosed and underreported. This is made worse by the fact that iatrogenic Cushing's disease caused by inhaled steroids can have a clinical presentation that resembles endogenous Cushing's syndrome, complicating diagnosis [21]. Weight gain, moon facies, and hirsutism are examples of symptoms that may be ignored entirely or linked to the underlying respiratory illness.

Clinicians should keep a high index of suspicion and consider hormonal testing such morning cortisol levels, adrenocorticotropic hormone (ACTH) stimulation tests, and measurements of urinary free cortisol in order to correctly identify iatrogenic Cushing's syndrome [22]. To assess the underlying cause and severity of adrenal suppression, imaging techniques like MRI of the pituitary or imaging of the adrenal glands may also be required. Conclusion: Although the frequency of iatrogenic Cushing's syndrome especially linked to the use of inhaled steroids is not fully understood, mounting evidence points to its importance. Important risk factors include high-dose ICS therapy, protracted treatment, and individual susceptibility. To identify and manage this potential consequence of ICS use, there is a need for enhanced awareness and precise diagnostic procedures. Underdiagnosis and underreporting are difficulties that need to be addressed.

Clinical Presentation and Diagnostic Evaluation

Iatrogenic Cushing's syndrome caused by inhaled steroids can show clinically in a variety of ways and without any clear pattern, frequently coexisting with the symptoms of the underlying respiratory illness being treated [15]. Weight gain, especially in the middle of the body, facial rounding (moon facies), an increase in facial hair development (hirsutism), and skin abnormalities like thinning and easily bruised skin are common signs [1]. Additionally, patients may develop osteoporosis, glucose intolerance, and hypertension [19].

A thorough strategy that includes clinical examination, hormonal assessment, and imaging testing is necessary for the diagnosis of iatrogenic Cushing's syndrome. To determine the usage of inhaled steroids, including the precise medication, dosage, and length of therapy, a thorough medical history is required. The hypothalamic-pituitary-adrenal (HPA) axis and any concurrent drugs that can alter corticosteroid metabolism should also be discussed by doctors [21]. To definitively diagnose iatrogenic Cushing's syndrome, laboratory tests are essential. The HPA axis can be studied by measuring morning cortisol levels and performing suppression tests, such as the overnight dexamethasone suppression test or the low-dose ACTH stimulation test [20]. Even after using exogenous steroids, elevated cortisol levels still point to adrenal suppression and iatrogenic Cushing's syndrome. Imaging tests may be necessary in addition to hormonal evaluations to determine the root cause and degree of adrenal insufficiency. Adrenal gland imaging techniques like computed tomography (CT) or magnetic resonance imaging (MRI) can spot structural problems such adrenal gland atrophy that are brought on by long-term corticosteroid use [22]. Pituitary MRI may also be required to check for secondary adrenal suppression brought on by hypothalamic-pituitary axis suppression.

It is crucial to distinguish between endogenous and iatrogenic Cushing's syndromes since they can have comparable clinical manifestations. Endogenous Cushing's syndrome is brought on by an excessive amount of cortisol being produced by the body, typically as a result of pituitary or adrenal tumors [23]. Additional tests, such as measuring ACTH levels, monitoring late-night salivary cortisol levels, and imaging scans to look for lesions in the pituitary or adrenal glands may be required for a differential diagnosis. For long-term problems to be avoided, iatrogenic Cushing's syndrome must be diagnosed as soon as possible. Once the diagnosis has been made, the recommended course of action is to decrease or, if possible, stop using inhaled steroids while maintaining adequate treatment of the underlying respiratory illness [29]. To prevent adrenal insufficiency, the dose

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of corticosteroids should be gradually decreased under medical supervision. Alternative non-steroidal treatments might be thought of in some circumstances. In conclusion, iatrogenic Cushing's syndrome caused by inhaled steroids can appear clinically in a variety of ways. A thorough evaluation that includes a clinical assessment, hormone tests, and imaging procedures is necessary for an accurate diagnosis. It is essential to distinguish between endogenous Cushing's syndrome and iatrogenic Cushing's syndrome. The risk of long-term problems associated with this iatrogenic illness must be kept to a minimum through prompt identification and proper care, including corticosteroid dose reduction.

4. Management

The primary goal of using inhaled steroids to treat iatrogenic Cushing's syndrome is to reduce the side effects of corticosteroid therapy while maintaining appropriate control of the underlying respiratory disease. Reduced systemic exposure to corticosteroids and reduced risk of long-term consequences are the main objectives. If possible, tapering or stopping the use of inhaled steroids gradually while keeping a careful eye on the respiratory symptoms is one of the primary management techniques for iatrogenic Cushing's syndrome. To make sure that the underlying respiratory problem is kept under good control during the tapering process, this should be done in cooperation with a healthcare expert. Alternative non-steroidal therapy may be taken into consideration in situations where total withdrawal of inhaled steroids is not feasible. Depending on the health of the patient and their reaction to treatment, these may involve the use of bronchodilators, leukotriene modifiers, or immunomodulatory drugs [15].

When treating iatrogenic Cushing's syndrome, close attention to adrenal function must be paid. Regular evaluation of the hypothalamic-pituitary-adrenal (HPA) axis, including measurements of morning cortisol levels and ACTH stimulation tests, can aid in assessing the recovery of adrenal function and direct future therapeutic choices. The management process must include patient counseling and education. The possible dangers of prolonged corticosteroid therapy should be explained to patients, along with the value of following the recommended course of treatment. Additionally, they should be made aware of the warning signs and symptoms of adrenal insufficiency, such as weakness, exhaustion, and postural hypotension, and urged to seek medical help right once if they manifest. Referral to an endocrinologist or specialist facility for additional assessment and management may be required in some circumstances, particularly if there are worries about the return of adrenal function or the existence of other endocrine problems [25].

In general, iatrogenic Cushing's syndrome care with inhaled steroids necessitates a personalized strategy that strikes a balance between the need for respiratory symptom control and reducing the systemic effects of corticosteroids. To improve results and lower the risk of complications related to this illness, collaboration between healthcare professionals and patient education is crucial.

5. Conclusion

An important and sometimes underappreciated side effect of using inhaled steroids is iatrogenic Cushing's disease. Although the precise prevalence is still unknown, recent research indicates that this illness may be more widespread than previously thought. There are known risk factors, including individual predisposition and long-term usage of high doses of inhaled steroids. Iatrogenic Cushing's syndrome must be correctly diagnosed in order to be managed and long-term consequences to be avoided. A thorough evaluation that involves a clinical assessment, hormone tests, and imaging procedures is necessary because the clinical presentation can be nonspecific. For the management strategy to be effective, iatrogenic Cushing's syndrome must be distinguished from endogenous Cushing's syndrome. A multidisciplinary strategy is required for the treatment of iatrogenic Cushing's syndrome, including, if practical, the gradual reduction or elimination of inhaled steroids while maintaining adequate control of the underlying respiratory problem. In circumstances where total discontinuation of inhaled steroids is not practicable, alternative non-steroidal therapy may be taken into consideration. Patient counseling and education are essential for encouraging adherence to treatment regimens and identifying potential side effects. The risk of long-term consequences related to iatrogenic Cushing's syndrome is reduced with regular monitoring of adrenal function and consultation with medical practitioners. To better identify and manage iatrogenic Cushing's syndrome with inhaled steroids,

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improved awareness, early recognition, and reliable diagnostic techniques are required. To improve our knowledge of the prevalence, risk factors, and ideal management approaches for this significant iatrogenic illness, more study is necessary.

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