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A review on Understanding Addison's Disease: From Early Symptoms to Accurate Diagnosis

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Abstract

Addison's disease, a rare endocrine disorder affecting approximately 1 in 100,000 individuals, is characterized by adrenal insufficiency due to adrenal cortex dysfunction. Initially described by Thomas Addison in 1855, the disease's etiology has shifted from infectious causes, such as tuberculosis, to autoimmune mechanisms, especially in industrialized countries. In children, congenital adrenal hyperplasia (CAH) is a common cause, while autoimmune destruction dominates in adults. Autoimmune adrenal insufficiency is associated with various other autoimmune disorders, often manifesting as polyglandular syndromes. The disease leads to insufficient cortisol and aldosterone production, resulting in symptoms like fatigue, hyperpigmentation, hypotension, gastrointestinal issues, and salt cravings. Diagnosis involves measuring serum cortisol, ACTH levels, and performing the cosyntropin stimulation test. Treatment requires lifelong hormone replacement with glucocorticoids (prednisone or hydrocortisone) and mineralocorticoids (fludrocortisone). Despite advances in research, the condition remains incurable, with management focusing on symptom control and preventing adrenal crises. Moreover, patients require ongoing monitoring for comorbid autoimmune conditions. This review explores the pathophysiology, diagnosis, and multidisciplinary management of Addison's disease, emphasizing the significance of oral manifestations and the need for continuous care.

Keywords: Addison's disease, adrenal insufficiency, autoimmune adrenalitis, cortisol deficiency, and adrenal glands.

INTRODUCTION

A uncommon endocrine condition, Addison's disease affects one in every 100,000 individuals. It affects both men and women equally and is present in all age groups. In his book "On the constitutional and local effects of the disease of supra renal capsule," published in 1855, Thomas Addison initially described people with this

ailment, which bears his name. Because Addison's illness is often overlooked in its early stages, it can manifest as a potentially fatal crisis. Since Addison's disease was first described, its etiology has drastically altered from an infectious cause to an autoimmune pathology. Still, the most common cause of Addison's disease in poorer nations is tuberculosis.

The most prevalent cause of primary adrenal insufficiency in adults from developed nations is autoimmune Addison's disease, however in children, the condition is mostly brought on by a genetic abnormality. The most common cause of primary adrenal insufficiency with a childhood beginning is CAH brought on by 21-hydroxylase deficiency (21OH-D). Although 21OH-D has been extensively studied, there are still gaps in our knowledge of the epidemiology, etiology, and long-term consequences of childhood primary adrenal insufficiency due to the lack of full descriptions of alternative causes. Depending on the underlying ailment, autoimmune adrenal insufficiency can manifest clinically differently and either develop alone or in conjunction with other autoimmune conditions.

The primary cause of Addison's disease, which affects one in 5000–7000 people (with a range of 1000–14,000), is either congenital adrenal hyperplasia in children or the destruction of adrenocortical tissue brought on by mononuclear infiltration of inflammatory cells in 90% of adult cases (pertaining to regions where tuberculosis is not very common). [5] Due to an abnormal T cell profile, autoimmune Addison disease is the primary etiological type.6. Years before the real therapeutic effects manifest, a gradual adrenolytic is registered.

Addison disease is a big concern for any clinician since, if left untreated, it can lead to life-threatening fulminant progression. While alternatives like gene therapy for CAH, stem cell-derived adrenal-like steroid genic cells, and allogeneic adrenocortical cell transplantation are still being developed, glucocorticoid replacement is still the only life-saving option. However, it has several drawbacks, including a lower quality of life, recurrent acute crises, a lack of accurate tools to evaluate adequate hormonal substitution, and long-term effects, with debates surrounding the use of various replacement regimens and formulas.

As is widely known, autoimmune adrenal insufficiency can occur in conjunction with or independently of other autoimmune disorders, and its clinical manifestation varies based on a number of variables, including the underlying ailment. Nevertheless, there is currently a dearth of information on the presentation and prognosis of

the autoimmune diseases that cause AAD in children, despite the fact that numerous writers have detailed the epidemiology, presentation, and long-term consequences of autoimmune forms in adults.

Studies on the physiology of these glands were made possible by the precise observations and interpretations of the pathophysiology of the suprarenal capsules performed by this astute clinical investigator. The role of the adrenal bodies, which must be the foundation of a satisfactory understanding of organ illnesses and their treatment, has not been fully revealed despite the efforts of several researchers, which have produced a vast body of literature.

Based on clinical and physiological research on adrenal insufficiency, I will offer a novel perspective on the diagnosis and management of Addison's disease.

Assuming that Addison's disease is primarily a manifestation of the absence or failure of function of the epinephrine (adrenalin) secretion, this view has previously predominated and is still held by many excellent clinicians who have the opportunity to study and treat this condition. Our experimental research has provided strong evidence that this illness arises not from disruption of epinephrine secretion (from the adrenal medulla) but rather from the absence or dysfunction of the interrenal (adrenal cortex) tissue. Hyperpigmentation in Addison disease is caused by lingual and buccal abnormalities of melanocytes, which are brought on by an elevated amount of adrenocorticotropic hormone.

An acute event that requires a higher amount of cortisol, like an illness or accident, may cause an acute form of adrenal insufficiency, while the patient is still associated with this one hallmark of the underlying condition. Additionally, an intraoral pigmentation may be the only sign of Addison disease.

With an emphasis on oral abnormalities that could have a significant clinical impact, this review emphasizes the interdisciplinary features of Addison disease. Dermatological and dental health aspects are included in the perspective. We looked at two primary aspects of oral manifestations: pigmentation problems associated with particular hormonal abnormalities in Addison's disease, and possible oral lesions in Addison's disease patients, particularly in autoimmune Addison's disease, which are brought on by similar autoimmune mechanisms or diseases related to Addison's disease that share a common genetic background.

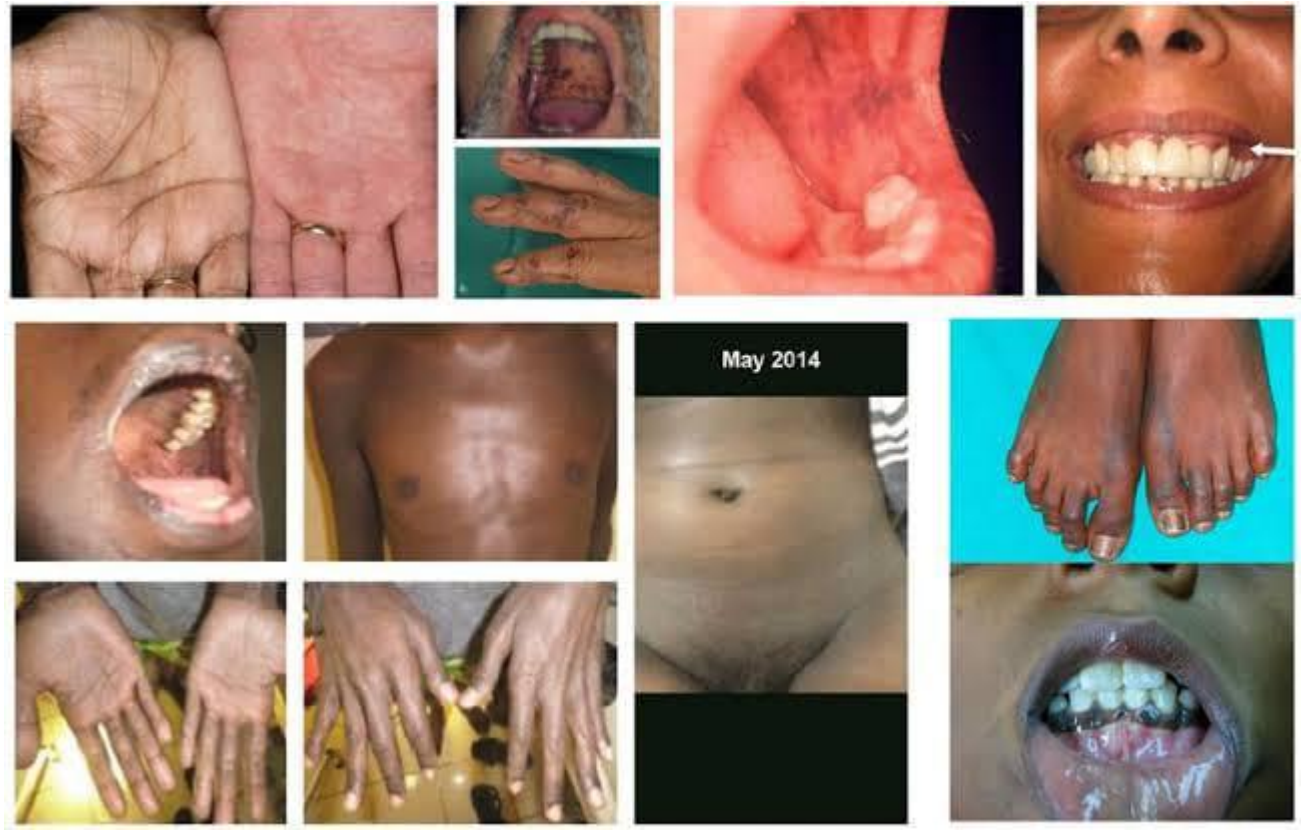


Figure 1: Disease of Adrenal gland

HISTORY

Bartolomeo Eustachio made the discovery of the adrenal glands in 1553. Prior to the recovery and publication of a significant portion of Eustachio's original anatomical 47 tables in 1714, his work did not receive much attention. When Thomas Addison released his paper on the Constitutional and Local Effects of Disease of the Suprarenal Capsules in 1855, he revealed the clinical and anatomical results of 11 people who passed away from what would later be known as heart disease.

Addison identified a set of symptoms linked to adrenal gland dysfunction in 1855, the year he first raised awareness of the syndrome. From the perspective of interpreting the physiological abnormalities that ensue from the loss of adrenal function, the meaning of these symptoms has remained rather unclear. Up until recently, clinical observation and experimental research had contributed relatively little useful information to our understanding and management of this illness. Failure to recognize that the adrenal body is made up of two glands that are morphologically linked yet differ in origin, structure, and function has led to a great deal of confusion.

They exist as distinct structures in some lower animals (some fishes), with the chromaffin tissue representing the medulla of the mammalian adrenals and the internal bodies representing the cortex.

Oliver and Schafer discovered in 1895 that if given to an animal's circulation, adrenal extracts made by massaging the glands with a salt solution may cause a substantial increase in blood pressure. These researchers found that extracts from the glands' medulla alone produce this effect, with the cortical section being useless.

ETIOLOGY

Although there are other contributing factors to Addison's disease, autoimmunity is the main cause in developed nations, accounting for 70–90% of cases. The development of autoantibodies against steroidogenic enzymes, namely 21-hydroxylase, is a characteristic of autoimmune adrenolytic. Additional pertinent causes include infections, adrenal hemorrhage, cancer, hereditary factors, especially in male patients, and adrenal TB, which is still a significant cause in endemic area

Insufficient production of adrenocortical hormones by the adrenal cortices is the etiology of Addison's disease. Adrenal insufficiency is categorized as either primary or secondary.

1. Primary Adrenal Insufficiency

Primary adrenal insufficiency (Addison disease) can be caused by any disease process that directly damages the adrenal cortex, including autoimmune, infectious, hemorrhagic, pharmacologic, and infiltrative etiologies.

➢ Autoimmune

The most frequent cause of Addison's disease is autoimmune destruction of the adrenal glands. As antibodies are formed against the adrenal cortex, this damage takes place.

Autoimmune damage can occur in type 1 and type 2 autoimmune polyglandular endocrinopathies or as a single finding. Polyglandular autoimmune syndromes are more common in patients with autoimmune adrenal illness.

• Type 1: Ectodermal dysplasia, candidiasis, and autoimmune polyendocrinopathy are symptoms of autoimmune polyglandular syndrome. Addison's disease, mucocutaneous candidiasis, and hypoparathyroidism make up the typical triad.

• Type 2: A number of disorders are linked to autoimmune polyglandular syndrome:

o Thyroid autoimmune disease (Schmidt syndrome)

o Carpenter syndrome (type 1 diabetes)

o Autoimmune diseases (such as vitiligo, alopecia, or pernicious anemia)
o Celiac disease has been linked to Addison's disease.

➢ Infections

The cytomegalovirus, HIV, tuberculosis, and sepsis are examples of infectious etiologies. HIV is now the leading cause of adrenal insufficiency linked to adrenal necrosis, while tuberculosis has become less common. Syphilis, histoplasmosis, and widespread fungal infections are additional infectious causes. Another cause of Addison's disease, especially in South America, is blast mycosis.

➢ Adrenal Hemorrhage

Bilateral adrenal hemorrhages can be caused by DIC, trauma, meningococcemia, and neoplastic events. The Waterhouse-Frederickson syndrome, an adrenal crisis brought on by meningococcemia, is more prevalent in youngsters and asplenia patients.

➢ Infiltration

With hemochromatosis, amyloidosis, and metastases, adrenal infiltration is common. Sarcoidosis, lymphoma, and genetic conditions such congenital adrenal hyperplasia and adrenal leukodystrophy are additional reasons. [28] Wolman disease is an uncommon inborn metabolic mistake that manifests as hepatosplenomegaly, failure to thrive, diarrhea, and adrenal gland calcification. Adrenal insufficiency has been linked to antiphospholipid antibody syndrome.

➢ Medications

Adrenal insufficiency can result from some pharmaceutical etiologies that inhibit the manufacture of cortisol. For example, intimidate can have a dose-dependent effect by specifically inhibiting 11β-hydroxylase, which reduces the conversion of deoxycortisol to cortisol, and ketoconazole directly inhibits adrenal enzymes.

2. Secondary Adrenal Insufficiency

The most frequent cause of secondary insufficiency is exogenous steroid treatment, which suppresses the synthesis of ACTH. The pituitary-dependent reduction of ACTH secretion that results from secondary adrenal insufficiency lowers the synthesis of glucocorticoids. Aldosterone and other mineralocorticoid secretions, however, continue to function largely normally. The symptoms of secondary adrenal insufficiency typically appear after stopping a steroid, and it is more prevalent than primary insufficiency.

- Primary: autoimmune-mediated intrinsic adrenal gland dysfunction, which leads to cortisol and aldosterone deficiency
- Secondary: chronic glucocorticoid administration resulting in hypothalamic-pituitary dysfunction and cortisol deficiency alone.

SIGN AND SYMPTOMS

Table 1 : Sign and Symptoms

Sign and symptoms	Prevalence (%)
Anorexia	100
Weakness fatigue	100
Hyperpigmentation	94
Gastrointestinal symptoms (e.g. nausea vomiting, diarrhea)	92
Hypotension	~90
Salt craving	16
Postural dizziness	12
Vitiligo	10 to 20
Muscle or joint pain	~10

CAUSE

Adrenal insufficiency (Addison disease) can be caused by any disease process that directly damages the adrenal cortex. The most common cause of Addison's disease in the majority of the developed world is autoimmune destruction of the adrenal glands. Autoimmune destruction may occur alone or as a component of type 1 and type 2 autoimmune polyglandular endocrinopathies. Polyglandular autoimmune syndromes are more common in patients with autoimmune adrenal illness.

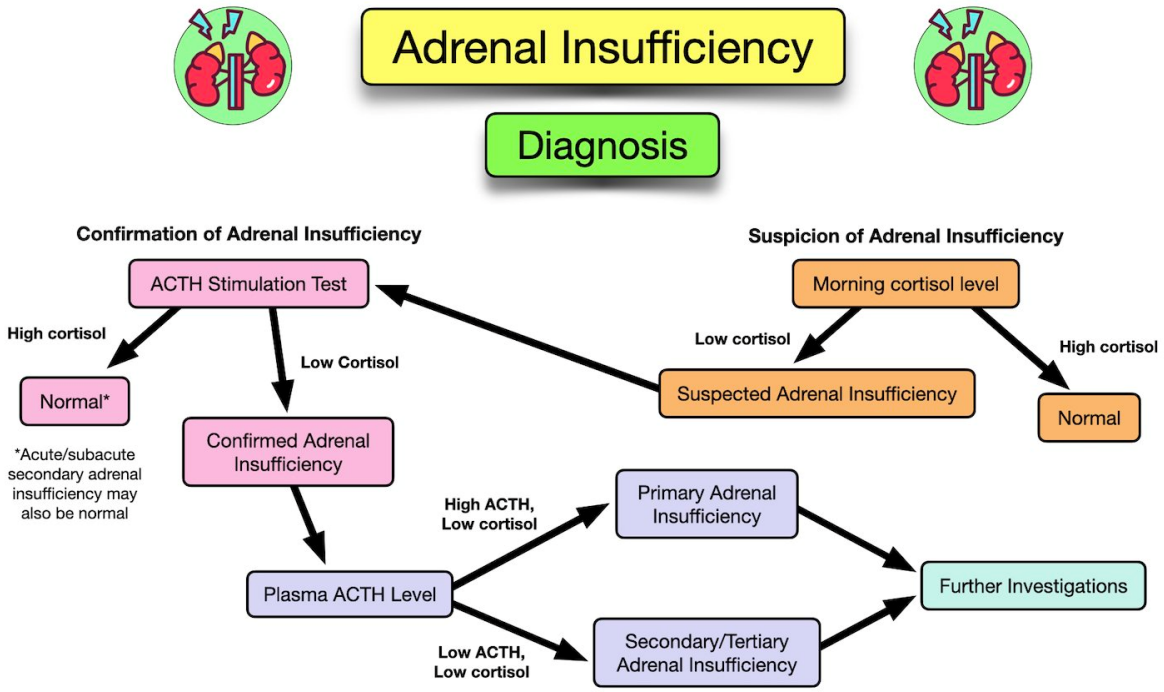
Bilateral adrenal hemorrhages (caused by coagulopathy, trauma, meningococcemia, and neoplastic processes involving the adrenal glands) and infections (including sepsis, TB, and HIV) are other causes. Sarcoidosis, amyloidosis, fungal infections, and hereditary conditions such Wolman disease and adrenal leukodystrophy are less common causes.

RISK FACTORS

The annual incidence is 0.6 per 100,000 people. There are 4 to 11 cases of this condition for every 100,000 people in the population. Women are more impacted than men, and those between the ages of 30 and 50 are most affected.

Risk factors for the autoimmune (most common) type of Addison's disease include other autoimmune diseases:

- Type I diabetes
- Hypoparathyroidism
- Hypopituitarism
- Pernicious anemia
- Graves' disease
- Chronic thyroiditis
- Dramatis herpetiformis
- Vitiligo
- Myasthenia gravis



DIAGNOSIS

Figure 2: Adrenal Insufficiency

- Clinical diagnosis

Addison disease typically manifests as shock, hypotension, and volume depletion (adrenal or Addisonian crisis) after a major illness or stress reveals a cortisol and mineralocorticoid shortage. Hypotension, orthostatic, and shock are caused by deficits in cortisol and aldosterone; nevertheless, primary adrenal insufficiency is more likely to result in an adrenal crisis than secondary adrenal insufficiency.

- Metabolic Test

Documenting a low cortisol level and identifying primary or secondary adrenal insufficiency are the objectives of laboratory testing. Adrenal insufficiency is suggested by low serum cortisol levels at 8 a.m. (less than 3 mcg per dL [83 nmol per L]). Whereas hyperkalemia is exclusively caused by a deficiency of mineralocorticoids, hyponatremia can be caused by shortages in both cortisol and mineralocorticoids.

The levels fluctuate because the adrenal hormones are gradually eliminated over years or decades. An increased plasma renin level is one of the early signs of adrenal cortex impairment.

The decrease of adrenal hormones is accompanied by an increase in ACTH levels. When at-risk individuals' ACTH levels are monitored annually, readings higher than 50 pg per mL (11 pmol per L), which above the upper limit of normal, are suggestive of cortisol shortage.

When diagnosing adrenal insufficiency, a cosyntropin stimulation test is the first test that is used. Prior to giving 250 mcg of ACTH, the levels of serum cortisol, plasma ACTH, plasma aldosterone, and plasma renin should be assessed. The serum cortisol level should be checked again 30 and 60 minutes following intravenous ACTH injection. Peak cortisol levels over 18 to 20 mcg per dL (497 to 552 nmol per L) indicate a normal response; a smaller or nonexistent response indicates adrenal insufficiency.

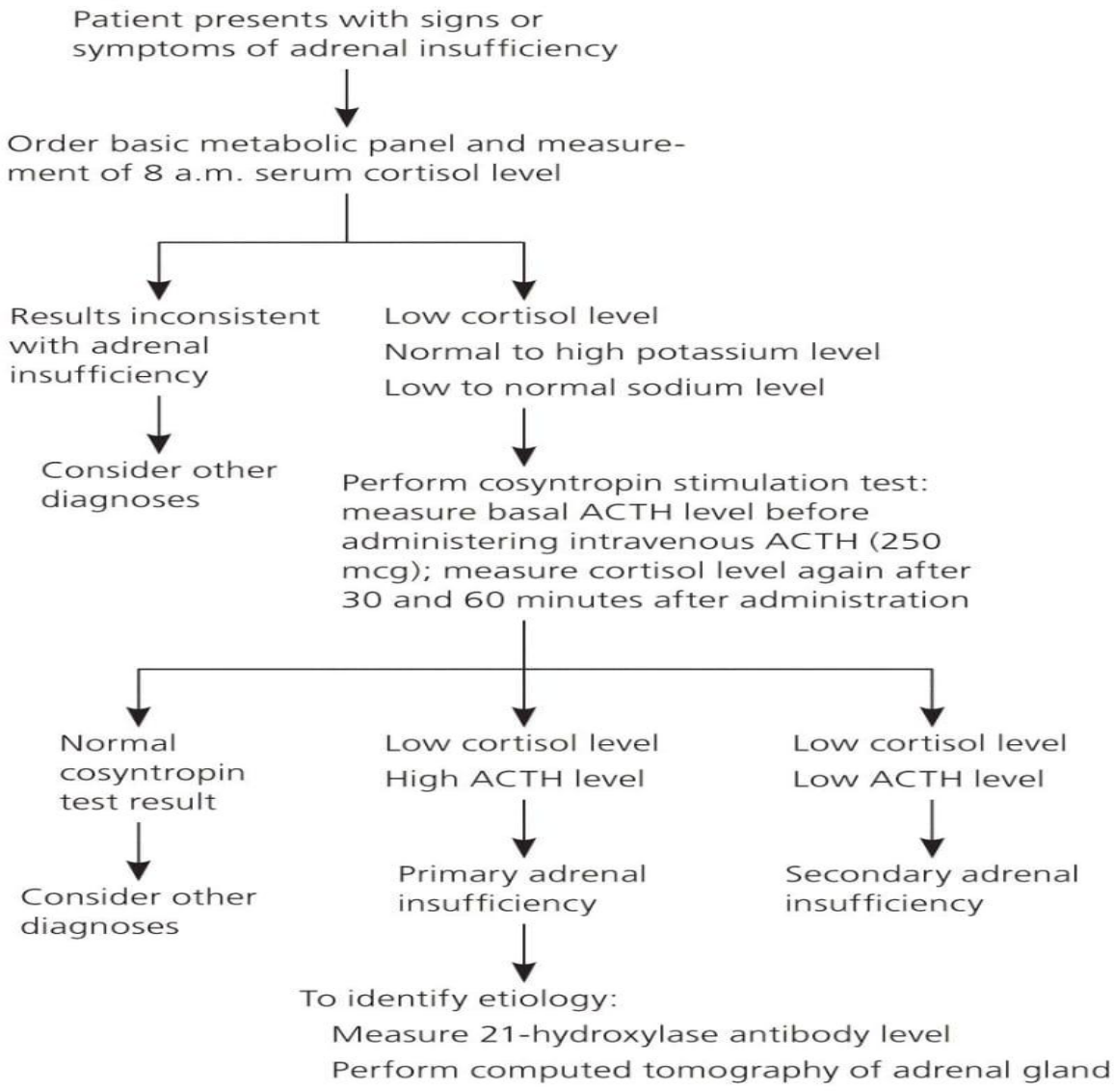


Figure 3: Diagnosis of Adrenal Insufficiency

TREATMENT/ MANAGEMENT

- Hormone Therapy

Lifelong hormone therapy using glucocorticoids and mineralocorticoids is the treatment for Addison's disease. There is currently no treatment to halt the immune system's underlying damage of the adrenal cortex. Typically, oral prednisone or hydrocortisone is part of glucocorticoid replacement. [40]

While hydrocortisone is administered in two or three doses daily, prednisone can be taken once daily.

Fludrocortisone is used in place of mineralocorticoids at a dose that maintains the plasma renin level within the upper limit of the normal range.

While women can benefit from androgen replacement since the adrenal glands are the primary source of androgen production in women, men with Addison disease do not require androgen replacement because their testes can create sufficient levels of testosterone. Dehydroepiandrosterone (DHEA) supplementation led to modest improvements in depression and health-related quality of life in women with adrenal insufficiency, according to a meta-analysis of ten randomized placebo-controlled trials.

Tabel 1. Medication for the Treatment of Addison Disease

Medication	*Dosage*	*Comments*	*Monitoring*
Glucocorticoids			
Prednisone	3 to 5 mg once daily	Use stress doses for illness, surgical procedures, and hospitalization	Symptoms of adrenal insufficiency; low to normal plasma adrenocorticotropic hormone levels indicate over-replacement
Hydrocortisone	15 to 25 mg divided into two or three doses per day	Use stress doses for illness, surgical procedures, and hospitalization	
Dexamethasone	0.5 mg once daily	Use intramuscular dose for emergencies and when unable to tolerate oral intake	
Mineralocorticoid			
Fludrocortisone	0.05 to 0.2 mg once daily	Dosage may need to increase to 0.2 mg per day in the summer because of salt loss from perspiration	Blood pressure; serum sodium and potassium levels; plasma renin activity in the upper normal range
Androgen			
Dehydroepiandrosterone (DHEA)	25 to 50 mg once daily	Available as an over-the-counter supplement; can improve mood and quality of life in women	Libido, mood, and sense of well-being

➢ Treatment of Confirmed Addison Disease

In order to receive the proper hormone therapy, patients with Addison's disease should be treated in collaboration with an endocrinologist and regularly checked. To reduce the negative effects of too much glucocorticoid, doses should be titrated to the lowest tolerated dose that manages symptoms.

It is necessary to maintain lifelong vigilance for related autoimmune illnesses since around 50% of people with Addison disease, which is characterized by autoimmune adrenalitis, go on to acquire another autoimmune

problem during their lives. The relative occurrence of concomitant autoimmune disorders is described in [44], along with the proper autoantibodies and metabolic testing for Addison disease patients who exhibit symptoms of one of these conditions. [45]

In their reproductive years, 10% of women with Addison disease develop autoimmune premature ovarian failure, also known as primary ovarian insufficiency, accompanied by symptoms of estrogen shortage, such as amenorrhea, flushing, exhaustion, and difficulty concentrating. Offering these patients assessment and guidance on other family-building alternatives is appropriate.

Table 2. Autoimmune Disorder Occuring with Addison Disease

Medication	*Dosage*	*Comments*	*Monitoring*
Glucocorticoids			
Prednisone	3 to 5 mg once daily	Use stress doses for illness, surgical procedures, and hospitalization	Symptoms of adrenal insufficiency; low to normal plasma adrenocorticotropic hormone levels indicate over-replacement
Hydrocortisone	15 to 25 mg divided into two or three doses per day	Use stress doses for illness, surgical procedures, and hospitalization	
Dexamethasone	0.5 mg once daily	Use intramuscular dose for emergencies and when unable to tolerate oral intake	
Mineralocorticoid			
Fludrocortisone	0.05 to 0.2 mg once daily	Dosage may need to increase to 0.2 mg per day in the summer because of salt loss from perspiration	Blood pressure; serum sodium and potassium levels; plasma renin activity in the upper normal range
Androgen			
Dehydroepiandrosterone (DHEA)	25 to 50 mg once daily	Available as an over-the-counter supplement; can improve mood and quality of life in women	Libido, mood, and sense of well-being

➢ Treatment Consideration

- Glucocorticoid secretion does not rise in Addison disease patients under stress. Therefore, to account for a potential stress reaction, the dosage of hydrocortisone should be raised in the presence of fever, infection, or other diseases.

- Two to three times the daily maintenance dose of hydrocortisone is typically the typical stress dose.
- Because rifampin increases the elimination of hydrocortisone, patients on this medication need to take higher doses of hydrocortisone.
- An adrenal crisis may be triggered by thyroid hormone's increased hepatic clearance of cortisol.
- Thyroid-stimulating hormone may return to normal with glucocorticoid replacement.
- Glucocorticoid medication may exacerbate diabetes insipidus in those who also have it.
- Free-water clearance depends on cortisol, and polyuria may be avoided by a cortisol shortage.
- The need for corticosteroids rises throughout pregnancy, especially in the third trimester.

FUTURE PROSPECT

1. Improved Diagnosis and Awareness
2. Better Hormone Replacement Therapies
3. Technological Advances
4. Crisis Prevention and Emergency Care
5. Research in Autoimmune Disease

CONCLUSION

Addison's disease is a rare endocrine disorder primarily caused by autoimmune destruction of the adrenal glands, leading to cortisol and aldosterone deficiencies. The condition manifests with symptoms such as fatigue, hyperpigmentation, gastrointestinal disturbances, and hypotension. Diagnosis is confirmed through clinical assessment and hormonal tests, including the cosyntropin stimulation test. Lifelong hormone replacement therapy with glucocorticoids and mineralocorticoids is the primary treatment. Close monitoring is required, particularly for associated autoimmune disorders. Early detection and appropriate management are critical to prevent life-threatening complications.

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