

**A COMPLETE REVIEW ON ADDISON'S DISEASE****Dr. Daghari Zakieh Jasem\***

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**ABSTRACT**

Addison's disease is a rare condition. Only one in 100,000 people has it. One way the body keeps itself in balance is by using chemical messengers called hormones to regulate various functions. Addison's disease is a disorder that occurs when your body produces insufficient amounts of certain hormones produced by adrenal glands. In Addison's disease, adrenal glands produce too little cortisol and insufficient levels of aldosterone as well. Also called adrenal insufficiency, Addison's disease occurs in all age groups and affects both sexes. Addison's disease can be life-threatening. Just above each of your kidneys is a small adrenal gland. These glands make hormones essential to a

healthy life. When they don't make enough of these hormones, Addison's disease is the result. It can happen at any age to either men or women. In Addison's disease, the adrenal glands don't make enough of a hormone called cortisol, or less often, a related hormone called aldosterone. That's why doctors call the illness "chronic adrenal insufficiency," or hypocortisolism. Cortisol's most important function is to help the body respond to stress. It also helps regulate the body's use of protein, carbohydrates, and fat; helps maintain blood pressure and cardiovascular function; and controls inflammation. Aldosterone helps kidneys regulate the amount of salt and water in your body -- the main way to regulate blood volume and keep blood pressure under control. When aldosterone levels drop too low, kidneys cannot keep salt and water levels in balance. This makes blood pressure drop.

**KEYWORDS:** Addisons Disease, Hypocortism, Kidney.

**INTRODUCTION**

Addison disease is an insidious, usually progressive hypofunctioning of the adrenal cortex. It

Causes various symptoms, including hypotension and hyperpigmentation, and can lead to adrenal crisis with cardiovascular collapse. Diagnosis is clinical and by finding elevated plasma ACTH with low plasma cortisol. Treatment depends on the cause but generally includes hydrocortisone and sometimes other hormones. <sup>[1-2]</sup>

Addison disease develops in about 4/100,000 annually. It occurs in all age groups, about equally in each sex, and tends to become clinically apparent during metabolic stress or trauma. Onset of severe symptoms (adrenal crisis) may be precipitated by acute infection (a common cause, especially with septicemia). Other causes include trauma, surgery, and Na loss from excessive sweating. Even with treatment, Addison disease may cause a slight increase in mortality. It is not clear whether this increase is due to mistreated adrenal crises or long-term complications of inadvertent over-replacement. <sup>[3-4]</sup>

One way the body keeps itself in balance is by using chemical messengers called hormones to regulate various functions. Just above each of your kidneys is a small adrenal gland. These glands make hormones essential to a healthy life. When they don't make enough of these hormones, Addison's disease is the result.

Addison's disease is a rare condition. Only one in 100,000 people has it. It can happen at any age to either men or women. People with Addison's disease can lead normal lives as long as they take their medication. <sup>[5-7]</sup>

There are two forms of Addison's disease. If the problem is with the adrenal glands themselves, it's called primary adrenal insufficiency. If the adrenal glands are affected by a problem starting somewhere else -- such as the pituitary gland -- it's called secondary adrenal insufficiency. <sup>[8]</sup>

### **Etiology:** <sup>[9-11]</sup>

Most cases of Addison's disease result from a problem with the adrenal glands themselves (primary adrenal insufficiency). Autoimmune disease accounts for 70% of Addison's disease. This occurs when the body's immune system mistakenly attacks the adrenal glands. This autoimmune assault destroys the outer layer of the glands.

Long-lasting infections -- such as tuberculosis, HIV, and some fungal infections -- can harm the adrenal glands. Cancer cells that spread from other parts of the body to the adrenal glands also can cause Addison's disease.

Less commonly, Addison's disease is due to secondary adrenal insufficiency, which can be caused by problems with the hypothalamus or pituitary gland, located in the center of the brain. These glands produce hormones that act as a switch and can turn on or off the production of hormones in the rest of the body. A pituitary hormone called ACTH is the switch that turns on cortisol production in the adrenal gland. If ACTH levels are too low, the adrenal glands stay in the off position. <sup>[12]</sup>

Another cause of secondary adrenal insufficiency is prolonged or improper use of steroid hormones such as prednisone. Less common causes include pituitary tumors and damage to the pituitary gland during surgery or radiation.

### **Pathophysiology**

Addison disease (or Addison's disease) is adrenocortical insufficiency due to the destruction or dysfunction of the entire adrenal cortex.

It affects glucocorticoid and mineralocorticoid function. The onset of disease usually occurs when 90% or more of both adrenal cortices are dysfunctional or destroyed. unless the contamination is promptly removed. <sup>[10]</sup>

### **Epidemiology**

**Frequency:** The prevalence of Addison disease is 40-60 cases per 1 million populations.

### **International**

The occurrence of Addison disease is rare. The reported prevalence in countries where data are available is 39 cases per 1 million population in Great Britain and 60 cases per 1 million populations in Denmark.

### **Mortality/Morbidity**

- Morbidity and mortality associated with Addison disease usually are due to failure or delay in making the diagnosis or a failure to institute adequate glucocorticoid and mineralocorticoid replacement. <sup>[13]</sup>
- If not treated promptly, acute addisonian crisis may result in death. This may be provoked either de novo, such as by adrenal hemorrhage, or in the setting of an acute event superimposed on chronic or inadequately treated adrenocortical insufficiency.
- With slow-onset chronic Addison disease, significant low-level, nonspecific, but debilitating, symptomatology may occur.

- Even after diagnosis and treatment, the risk of death is more than 2-fold higher in patients with Addison disease. Cardiovascular, malignant, and infectious diseases are responsible for the higher mortality rate. <sup>[5]</sup>

### Race

- Addison disease is not associated with a racial predilection.

### Sex

- Idiopathic autoimmune Addison disease tends to be more common in females and children.

### Age

- The most common age at presentation in adults is 30-50 years, but the disease could present earlier in patients with any of the polyglandular autoimmune syndromes, congenital adrenal hyperplasia (CAH), or if onset is due to a disorder of long-chain fatty acid metabolism.

## SIGN AND SYMPTOMS

The symptoms of adrenal insufficiency usually begin gradually. Characteristics of the disease are:

- chronic, worsening fatigue
- muscle weakness
- loss of appetite
- weight loss

About 50 percent of the time, one will notice:

- nausea
- vomiting
- diarrhea

Other symptoms include

- low blood pressure that falls further when standing, causing dizziness or fainting
- skin changes in Addison's disease, with areas of hyperpigmentation, or dark tanning,

Covering exposed and non-exposed parts of the body; this darkening of the skin is most visible on scars; skin folds; pressure points such as the elbows, knees, knuckles, and toes; lips; and mucous membranes.

Addison's disease can cause irritability and depression. Because of salt loss, a craving for salty foods also is common. Hypoglycemia, or low blood glucose, is more severe in children than in adults. In women, menstrual periods may become irregular or stop.

Because the symptoms progress slowly, they are usually ignored until a stressful event like an illness or an accident causes them to become worse. This is called an addisonian crisis, or acute adrenal insufficiency. In most cases, symptoms are severe enough that patients seek medical treatment before a crisis occurs. However, in about 25 percent of patients, symptoms first appear during an addisonian crisis.

#### **Symptoms of an addisonian crisis include**

- sudden penetrating pain in the lower back, abdomen, or legs
- severe vomiting and diarrhea
- dehydration
- low blood pressure
- loss of consciousness

Left untreated, an addisonian crisis can be fatal.

#### **DIAGNOSIS <sup>[14]</sup>**

In Addison's disease, the adrenal glands don't make enough of a hormone called cortisol, or less often, a related hormone called aldosterone. That's why doctors sometimes call the illness "chronic adrenal insufficiency, 'or hypocortisolism.

Cortisol's most important function is to help the body respond to stress. It also helps regulate your body's use of protein, carbohydrates, and fat; helps maintain blood pressure and cardiovascular function; and controls inflammation. Aldosterone helps your kidneys regulate the amount of salt and water in your body -- the main way you regulate blood volume and keep your blood pressure under control. When aldosterone levels drop too low, your kidneys cannot keep your salt and water levels in balance. This makes your blood pressure drop. In its early stages, adrenal insufficiency can be difficult to diagnose. A review of a patient's medical history based on the symptoms, especially the dark tanning of the skin, will lead a doctor to suspect Addison's disease. A diagnosis of Addison's disease is made by laboratory tests. The aim of these tests is first to determine whether levels of cortisol are insufficient and then to establish the cause. X-ray exams of the adrenal and pituitary glands also are useful in helping to establish the cause.

**ACTH stimulation test**

This is the most specific test for diagnosing Addison's disease. In this test, blood cortisol, urine cortisol, or both are measured before and after a synthetic form of ACTH is given by injection. In the so-called short, or rapid, ACTH test, measurement of cortisol in blood is repeated 30 to 60 minutes after an intravenous ACTH injection. The normal response after an injection of ACTH is a rise in blood and urine cortisol levels. Patients with either form of adrenal insufficiency respond poorly or do not respond at all.

**CRH Stimulation Test**

When the response to the short ACTH test is abnormal, a "long" CRH stimulation test is required to determine the cause of adrenal insufficiency. In this test, synthetic CRH is injected intravenously and blood cortisol is measured before and 30, 60, 90, and 120 minutes after the injection. Patients with primary adrenal insufficiency have high ACTHs but do not produce cortisol. Patients with secondary adrenal insufficiency have deficient cortisol responses but absent or delayed ACTH responses. Absent ACTH response points to the pituitary as the cause; a delayed ACTH response points to the hypothalamus as the cause. In patients suspected of having an Addisonian crisis, the doctor must begin treatment with injections of salt, fluids, and glucocorticoid hormones immediately. Although a reliable diagnosis is not possible while the patient is being treated for the crisis, measurement of blood ACTH and cortisol during the crisis and before glucocorticoids are given is enough to make the diagnosis. Once the crisis is controlled and medication has been stopped, the doctor will delay further testing for up to 1 month to obtain an accurate diagnosis.

**Other Tests**

Once a diagnosis of primary adrenal insufficiency has been made, x-ray exams of the abdomen may be taken to see if the adrenals have any signs of calcium deposits. Calcium deposits may indicate TB. A tuberculin skin test also may be used.

If secondary adrenal insufficiency is the cause, doctors may use different imaging tools to reveal the size and shape of the pituitary gland. The most common is the CT scan, which produces a series of x-ray pictures giving a cross-sectional image of a body part. The function of the pituitary and its ability to produce other hormones also are tested.

**TREATMENT** <sup>[13-14]</sup>

Hydrocortisone or prednisone

Fludrocortisone

Dose increase during inter current illness

Normally, cortisol is secreted maximally in the early morning and minimally at night. Thus, hydrocortisone (identical to cortisol) is given in 2 or 3 divided doses with a typical total daily dose of 15 to 30 mg. One regimen gives half the total in the morning, and the remaining half split between lunchtime and early evening (eg, 10 mg, 5 mg, 5 mg). Others give two thirds in the morning and one third in the evening. Doses immediately before retiring should generally be avoided because they may cause insomnia. Alternatively, prednisone 5 mg po in the morning and 2.5 mg po in the evening may be used. Additionally, fludrocortisone 0.1 to 0.2 mg po once/day is recommended to replace aldosterone. The easiest way to adjust the dosage is to ensure that the renin level is within the normal range. Normal hydration and absence of orthostatic hypotension are evidence of adequate replacement therapy. In some patients, fludrocortisone causes hypertension, which is treated by reducing the dosage or starting a nondiuretic antihypertensive. Some clinicians tend to give too little fludrocortisone in an effort to avoid use of antihypertensives. Intercurrent illnesses (eg, infections) are potentially serious and should be vigorously treated; the patient's hydrocortisone dose should be doubled during the illness. If nausea and vomiting preclude oral therapy, parenteral therapy is necessary. Patients should be instructed when to take supplemental prednisone or hydrocortisone and taught to self-administer parenteral hydrocortisone for urgent situations. A preloaded syringe with 100 mg hydrocortisone should be available to the patient. A bracelet or wallet card giving the diagnosis and corticosteroid dose may help in case of adrenal crisis that renders the patient unable to communicate. When salt loss is severe, as in very hot climates, the dose of fludrocortisone may need to be increased.

In coexisting diabetes mellitus and Addison disease, the hydrocortisone dose usually should not be > 30 mg/day; otherwise, insulin requirements are increased.

Emergency medicine physicians should be able to identify and treat patients whose clinical presentations, including key historical, physical examination, and laboratory findings are consistent with diagnoses of primary, secondary, and tertiary adrenal insufficiency, adrenal crisis, and pheochromocytoma. Failure to make a timely diagnosis leads to increased morbidity and mortality. As great mimickers, adrenal emergencies often present with a

constellation of nonspecific signs and symptoms that can lead even the most diligent emergency physician astray. Treatment of Addison's disease involves replacing, or substituting, the hormones that the adrenal glands are not making. Cortisol is replaced orally with hydrocortisone tablets, a synthetic glucocorticoid, taken once or twice a day. If aldosterone is also deficient, it is replaced with oral doses of a mineralocorticoid called fludrocortisone acetate (Florinef), which is taken once a day. Patients receiving aldosterone replacement therapy are usually advised by a doctor to increase their salt intake. Because patients with secondary adrenal insufficiency normally maintain aldosterone production, they do not require aldosterone replacement therapy. The doses of each of these medications are adjusted to meet the needs of individual patients.

During an Addisonian crisis, low blood pressure, low blood glucose, and high levels of potassium can be life threatening. Standard therapy involves intravenous injections of hydrocortisone, saline (salt water), and dextrose (sugar). This treatment usually brings rapid improvement. When the patient can take fluids and medications by mouth, the amount of hydrocortisone is decreased until a maintenance dose is achieved. If aldosterone is deficient, maintenance therapy also includes oral doses of fludrocortisone acetate.

### **Surgery**

Patients with chronic adrenal insufficiency who need surgery with general anesthesia are treated with injections of hydrocortisone and saline. Injections begin on the evening before surgery and continue until the patient is fully awake and able to take medication by mouth. The dosage is adjusted until the maintenance dosage given before surgery is reached.

### **Pregnancy**

Women with primary adrenal insufficiency who become pregnant are treated with standard replacement therapy. If nausea and vomiting in early pregnancy interfere with oral medication, injections of the hormone may be necessary. During delivery, treatment is similar to that of patients needing surgery; following delivery, the dose is gradually tapered and the usual maintenance doses of hydrocortisone and fludrocortisone acetate by mouth are reached by about 10 days after childbirth.

### **Patient education**

A person who has adrenal insufficiency should always carry identification stating his or her condition in case of an emergency. The card should alert emergency personnel about the need



to inject 100 mg of cortisol if its bearer is found severely injured or unable to answer questions. The card should also include the doctor's name and telephone number and the name and telephone number of the nearest relative to be notified. When traveling, a needle, syringe, and an injectable form of cortisol should be carried for emergencies. A person with Addison's disease also should know how to increase medication during periods of stress or mild upper respiratory infections. Immediate medical attention is needed when severe infections, vomiting, or diarrhea occur. These conditions can precipitate an Addisonian crisis. A patient who is vomiting may require injections of hydrocortisone.

People with medical problems may wish to wear a descriptive warning bracelet or neck chain to alert emergency personnel. A number of companies manufacture medical identification products. Education is paramount for patients and their caregivers to anticipate, recognize and provide proper early treatment to prevent or reduce the occurrence of ACs.

### Key Points

- Addison disease is primary adrenal insufficiency.
- Weakness, fatigue, and hyperpigmentation (generalized tanning or focal black spots involving skin and mucous membranes) are typical.
- Low serum Na, high serum K, and high BUN occur.
- Usually, serum ACTH is high and cortisol levels are low.
- Replacement doses of hydrocortisone and fludrocortisone are given; doses should be increased during intercurrent illness.

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