

Addison's Disease

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The adrenal glands are small, triangular-shaped glands located on top of both kidneys. They are composed of two parts: the adrenal cortex and adrenal medulla. The cortex produces cortisol for metabolism and aldosterone for blood pressure. The medulla produces adrenaline and norepinephrine, triggering the fight-or-flight response in stress. The adrenal glands manage metabolism, immunity, and stress, playing a vital role in health.^{1,4}



News-Medical Life Sciences. <https://www.news-medical.net/health/Addisons-Disease-and-Skin-Problems.aspx>³

Addison's Disease (AD), also known as primary adrenal insufficiency or hypoadrenalism, is a rare but potentially life-threatening disorder caused by the inadequate production of adrenal hormones. It is a chronic endocrine disorder characterised by the deficiency of cortisol and aldosterone due to dysfunction or destruction of the adrenal cortex, and can have profound effects on an individual's health and quality of life. The condition affects about 1 in 100,000 people, occurs in all age groups, but usually individuals aged 30-50 years, and affects men and women equally.¹

Cortisol produced by the adrenal glands, belongs to a class of hormones called glucocorticoids, which exert their influence across various organs and tissues throughout the body. Cortisol's main function is to help the body respond to stress. It also helps control blood pressure and cardiovascular function, reduce inflammation in the immune system, balance the effects of insulin in utilising sugar for energy, and helps manage how proteins, carbohydrates, and fats are used by the body. Failure to produce adequate levels of cortisol, or adrenal insufficiency, can occur for a variety of reasons. The problem may be due to a disorder of the adrenal glands called primary adrenal insufficiency or secondary adrenal insufficiency due to inadequate secretion of ACTH by the pituitary gland.^{1, 2, 3}

Aldosterone is part of a group of hormones known as mineralocorticoids, made by the adrenal glands. It helps maintain blood pressure and the water sodium balance in the body by helping the kidney retain sodium and excrete potassium. When aldosterone production falls too low, the kidneys are unable to regulate the sodium and water balance, causing blood volume and blood pressure to drop. ^{1, 2, 3}

Primary Adrenal Insufficiency

The most common causes of Addison's disease are autoimmune disorders and tuberculosis. While TB is the most common cause of Addison's disease in developing countries most cases of AD in the developed world are caused by the gradual destruction of the adrenal cortex by the body's own immune system. In Western Europe, autoimmunity accounts for approximately 85% of Addison's disease diagnoses. Several autoimmune processes can lead to adrenal insufficiency either affecting the adrenal glands exclusively or as part of a more complex inherited autoimmune polyglandular syndrome. Other causes include certain medications, sepsis, and bleeding into both adrenal glands. Less common causes of primary adrenal insufficiency are chronic infections, mainly fungal infections; cancer cells spreading to the adrenal glands; amyloidosis; and surgical removal of the adrenal glands. ^{5,6,7}

Secondary Adrenal Insufficiency

Secondary adrenal insufficiency is caused by insufficient ACTH produced by the pituitary gland or CRH produced by the hypothalamus. It causes a drop in the production of cortisol but not aldosterone. A temporary form of secondary adrenal insufficiency can occur when a person receiving glucocorticoid hormones such as prednisone for a long time abruptly stops taking the medication. Another cause of secondary adrenal insufficiency is the surgical removal of benign ACTH-producing tumours of the pituitary gland. Although less common, adrenal insufficiency can occur when the pituitary gland decreases in size or stops producing ACTH. This can result from tumours or infections of the area, loss of blood flow to the pituitary, radiation for pituitary tumours, or surgical removal of parts of the hypothalamus or the pituitary gland during neurosurgery. ^{5,6,7}

Addison's disease frequently accompanies the emergence of other autoimmune disorders, including type I diabetes, Hashimoto's thyroiditis, coeliac disease, and vitiligo. Additionally, psychiatric manifestations like alterations in mood, decreased motivation, and changes in behaviour are commonly observed in affected individuals. Hyponatremia and hyperkalemia are prevailing indicators in Addison's disease, whereas hypoglycemia is infrequent. Gastrointestinal disturbances manifest as anorexia, nausea, vomiting, and diarrhoea, often with a notable desire for salty foods due to salt depletion. Women may experience irregular or halted menstrual cycles. ^{5,6}

Presentation

Addison's disease can present with various nonspecific symptoms, including weight loss, nausea, abdominal pain, low blood pressure, fatigue, and weakness. Salt craving and

orthostatic hypotension due to aldosterone deficiency are common. One key distinctive symptom of the condition is that it can cause hyperpigmentation of the skin. Darkening of the skin in Addison's disease, sometimes referred to as "bronzing" or "Addison's tan" results from elevated ACTH levels stimulating melanocyte production. It usually develops in the areas of skin that are exposed to direct sunlight, and can also affect the knuckles, knees, palms, soles, armpits, nipples, and areas with folding skin. Skin colour changes are not always present in every patient with Addison's disease. ^{1,2,3,7}

Symptoms of Addison disease can increase in intensity over time and eventually lead to acute adrenal insufficiency, known as adrenal crisis. Symptoms of Addisonian crisis include sudden penetrating pain in the lower back, abdomen, or legs, severe vomiting and diarrhoea, followed by dehydration, hypotension and loss of consciousness. Adrenal crisis is a medical emergency and must be treated immediately. It can cause cardiac arrest, CVA, hypovolaemic shock and hypoxia. Untreated, adrenal crisis can be fatal leading to coma and death. ^{1,5,6,8}

Diagnosis

Addison disease usually manifests as an insidious and gradual onset of non-specific symptoms, often resulting in a delayed diagnosis. The symptoms may worsen over time, which makes early recognition difficult. A review of the patient's medical history based on the symptoms will lead a doctor to suspect Addison's disease. If Addison's is suspected, blood tests to measure the levels of sodium, potassium and cortisol will be carried out. ⁵ Tests may be carried out to check for a low level of aldosterone, high level of ACTH, low level of glucose, and positive adrenal antibodies. ⁵ A **confirmed diagnosis** is made through a series of specialised biochemical tests including the ACTH stimulation test and insulin-induced hypoglycemia test. X-ray examination of the adrenal and pituitary glands are also useful in helping to establish the diagnosis. Because symptoms progress slowly, the condition is often not detected until a stressful event or illness occurs. In many cases, the diagnosis is made only after the patient presents with an acute adrenal crisis. ^{1,2,5,8}

ACTH Stimulation Test / Synacthen Stimulation Test: ACTH stimulation test measures the ability of the adrenal cortex to respond to ACTH. Blood and/or urine cortisol levels (short/rapid ACTH test) are measured before and 30-60 minutes after a synthetic form of ACTH (Synacthen) is given by 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. If the response to the short ACTH test is abnormal, a "long" ACTH stimulation test is carried out to determine the cause of adrenal insufficiency. ACTH is injected intravenously or intramuscularly over a 48 to 72-hour period, and blood and/or urine cortisol are measured the day before and during the 2 to 3 days of the injection. Individuals with primary adrenal insufficiency do not produce cortisol during the 48 to 72-hour period; however, those with secondary adrenal insufficiency have adequate responses to the test on the second or third day. ^{1,2,9}

Insulin-Induced Hypoglycemia Test: Insulin-induced hypoglycemia is a reliable test to determine how the hypothalamus, pituitary and adrenal glands respond to stress. Blood glucose and cortisol levels are measured, followed by an injection of fast-acting insulin and levels are measured again at 30, 45, and 90 minutes after the insulin injection. The normal response is for blood glucose levels to fall and cortisol levels to rise. ^{1, 2, 5}

Thyroid Function Tests may also be carried out as many people with Addison's disease have hypothyroidism. ^{5, 6}

Other Diagnostic Tests: Once a diagnosis of primary adrenal insufficiency has been made, x-ray of the abdomen may be taken to detect if the adrenal glands have any signs of calcium deposits which could indicate TB. If secondary adrenal insufficiency is determined to be the cause, a CT scan, producing a series of x-ray pictures giving a cross-sectional image may be used to check the size and shape of the pituitary gland. The function of the pituitary gland and its ability to produce other hormones are also tested. ^{5, 6}

Treatment and Management

The primary goal of Addison's Disease management is to replace deficient hormones and prevent adrenal crisis. Glucocorticoid replacement therapy with hydrocortisone or prednisolone is the cornerstone of treatment. Mineralocorticoid replacement with fludrocortisone is often necessary to maintain electrolyte balance.¹¹ A strict balance is required to avoid over- or under-treatment with glucocorticoids and careful monitoring is required. Over-treatment with glucocorticoids may result in obesity, diabetes, and osteoporosis, and over-treatment with mineralocorticoids can cause hypertension. ²

Medication Management: In Ireland, the normal adult requirement is: ¹¹

Hydrocortisone 15mg - 25mg per day usually taken in two or three divided doses. Dosage is dependent on bodyweight, metabolism and absorption. In special circumstances the endocrinologist may recommend alternative forms of glucocorticoid medication. ¹¹

Fludrocortisone 50mcg - 200mcg daily: This replaces aldosterone and is usually taken as either a single morning dose or in two divided doses. Dosage is monitored by measuring blood pressure sitting and standing, serum potassium and plasma renin levels. Dosage is dependent on metabolism and exercise levels, so will alter during the patient's lifespan. Some patients with primary adrenal failure may not require fludrocortisone in the early years post-diagnosis. Patients with secondary adrenal insufficiency normally maintain aldosterone production, so do not require aldosterone replacement therapy. ¹¹

In some cases-DHEA 25mg-50mg per day may be prescribed. If prescribed, DHEA (endogenous steroid) is usually taken as a single morning dose. Although an unlicensed treatment, it may be beneficial in cases of persistent fatigue. DHEA is not recommended for patients where

there is a family history of breast cancer. An endocrinologist is usually best-placed to initiate and monitor DHEA replacement. ¹¹

During **Addisonian crisis**, hypotension, hypoglycaemia, and hyperkalaemia can be life threatening, however, therapy with intravenous hydrocortisone, saline, and dextrose usually provide a 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. ⁸ Early self-administration by the patient of 100mg injected hydrocortisone IM will often stabilise an acute episode of vomiting or diarrhoea without the need for further medical intervention. However, some patients deteriorate rapidly and may require hospital treatment for 24 - 72 hours with IV hydrocortisone and saline. Postural dizziness is a key indicator that IV fluids are necessary. Potentially life-threatening circulatory complications ranging from hypotension to hypovolaemic shock may occur during adrenal crisis. The acutely unwell patient should be stabilised by a saline infusion and a 100mg hydrocortisone injection if possible before transportation to hospital. ¹¹

Essential hypertension is reported in around 10% of treated patients with Addison's. This is best managed through ACE inhibitors or calcium blockers. Diuretics should be avoided. A reduction in fludrocortisone dose may be necessary, requiring monitoring of electrolytes, although it is inadvisable for fludrocortisone to be completely stopped. ¹¹

Patients with chronic adrenal insufficiency who require surgery under general anaesthesia are treated with hydrocortisone injections and saline. Injections commence the evening before surgery and continue until the patient is fully awake and able to take medication orally. The dosage is adjusted until the maintenance dosage given before surgery is reached. ¹

The pregnant patient with Addison's disease will require hospital-based obstetric monitoring. Steroid medication increases may be needed in the latter trimesters and hospital treatment may be required in cases of severe hyperemesis gravidarum.¹¹ Post-diagnosis pregnancies occur in around 20% of female patients with Addison's. Pregnant women with Addison's disease must be thoroughly monitored throughout their pregnancy to ensure the absence of complications. Those with primary adrenal insufficiency 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 like that of patients requiring surgery. Following delivery, the dose is gradually tapered and the usual maintenance doses of hydrocortisone and fludrocortisone acetate by mouth are not reached until about 10 days after childbirth. ¹

Patient Education for Emergency Prevention: Patients with Addison's disease should wear or carry a medical alert such as an ID card, bracelet or necklace. They should be prescribed and carry an emergency injection kit in case of adrenal crises. It is advisable to issue the patient

with 3 - 5 vials injectable hydrocortisone in case of breakages, as an emergency kit for intramuscular injection in case of vomiting, accident or other severe injury. Addison's Ireland Clinical Advisory Panel (AICAP) recommends that all steroid-dependent patients be issued with six-monthly repeat prescriptions of their essential steroid medication to minimise the risk of running out, especially during periodic supply disruptions.¹¹ Each year, approximately 8% of people with Addison's disease experience adrenal crisis requiring extra steroid medication immediately, in the form of an emergency injection of intra-muscular hydrocortisone (100mgs). A person with Addison's disease must be educated about their condition, and know how to increase medication during periods of stress or infections. It is important that patients understand the potentially life-threatening consequences of inadequate glucocorticoid replacement, especially during illness, surgery or severe injury. Patients should be advised that grapefruit juice and liquorice delay hepatic clearance of glucocorticoids and are best avoided or consumed sparingly.¹¹

People with AD are recommended to have an annual flu vaccine, and all patients requiring antibiotic treatment for infection/sepsis should be reminded of the need to double their normal glucocorticoid medication. When travelling away from home, people with Addison's disease must take an extra supply of medication (double what they normally need) plus their injection materials.^{1, 8, 11} Patients should be urged to contact their primary care provider if there are any warning symptoms, and be aware of and follow the 'Sick Day Rules' - available at: <https://www.addisonsdisease.org.uk/newly-diagnosed-sick-day-rules>¹²

Support

Addison's Ireland is the Irish branch of the Addison's Disease Self-Help Group (ADSHG) with approximately 104 members from around the country both north and south. It works to raise awareness of Addison's in Ireland; support people and families affected by the condition and organises regular meetings around the country.¹⁰ For more information visit: <https://www.addisons.org.uk/articles.html/addisons-ireland/>

The Addison's Ireland Clinical Advisory Panel (AICAP) is a group of endocrinologists with an interest in adrenal medicine. It advises the Addison's Ireland group on medical matters. Caring for the patient with Addison's: information for GPs booklet/leaflet is available at:¹¹ <https://www.addisonsdisease.org.uk/caring-for-the-irish-patient-information-for-gps>

Prognosis, Emerging Therapies and Future Outlook

While Addison's disease is a serious illness, the prognosis for many people living with the condition is good. Most people can expect to live relatively normal lives with a good life expectancy, if they receive on going good care and treatment. Recent years have witnessed the exploration of novel therapeutic approaches, including immunomodulatory strategies to halt autoimmune destruction, gene therapy to restore adrenal function, and targeted

interventions to regulate steroidogenesis. These approaches hold promise for more tailored and effective treatments in the future. Addison's Disease remains a challenging endocrine disorder that requires a multidisciplinary approach for effective management. Advances in understanding its pathophysiology, early diagnosis, and personalised treatment regimens have improved patient outcomes. Ongoing research into immunogenetics, molecular mechanisms, and innovative therapies will continue to shape the future landscape of Addison's Disease management.

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