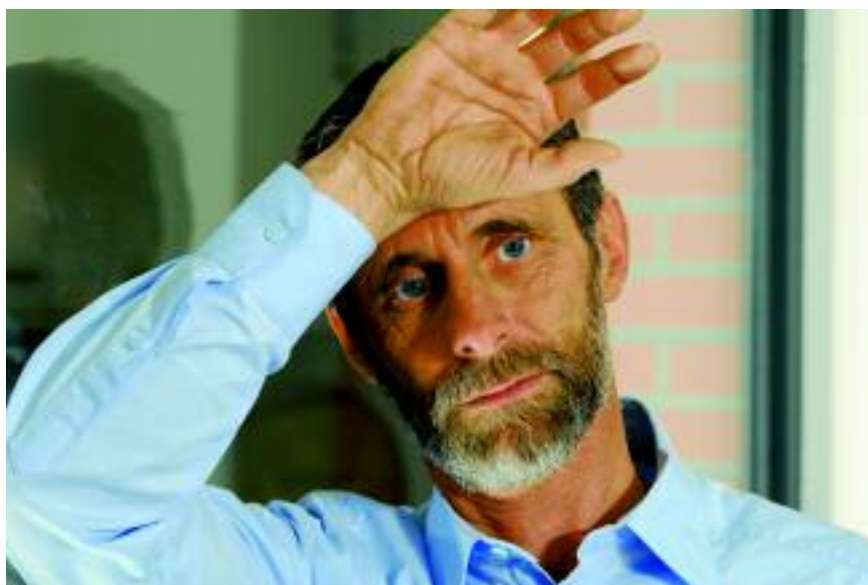


# Addison's Disease



## What is Addison's disease?

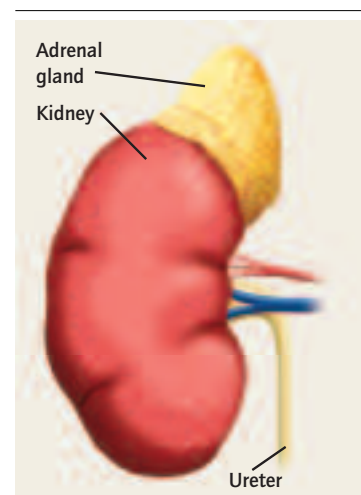
Addison's disease represents an insufficiency or dysfunction of the cortex of the adrenal glands, which fails to release adequate amounts of hormones to meet the physiological needs of the body, despite release of adrenocorticotrophic hormone (ACTH) from the pituitary gland. The onset of the disease occurs when 90 per cent or more of the cortex is dysfunctional or destroyed.

The adrenal glands are situated on top of the kidneys. Their cortex produces several steroid hormones, of which the glucocorticoid cortisol, the mineralocorticoid aldosterone and the sexual hormone dehydroepiandrosterone (DHEA) are important. Addison's disease affects both glucocorticoid and mineralocorticoid function. Cortisol has a major role in the regulation of insulin and blood sugar, and in the inhibition of protein synthesis. It mobilises fatty acids and enhances hepatic amino acid uptake. Cortisol also has a significant anti-inflammatory effect through the moderation of white blood cells and blocking cytokine production. Finally, cortisol enhances appetite and suppresses the synthesis of ACTH.

Aldosterone is released in response to angiotensin 2 (A-2) stimulation in case of increased levels of potassium ions or decreased levels of sodium ions in the blood. Its effect on its primary target organ, the kidney, is to promote re-absorption of sodium and secretion of potassium and hydrogen ions. The net effect is to increase blood volume and blood pressure.

Addison's disease develops over time and is characterised by weakness, fatigue, anorexia, weight loss, and hyperpigmentation. Typically, the skin acquires a bronze tint, resulting from increased blood levels of melanocyte-stimulating hormone (MSH). ACTH and MSH are both components of the same progenitor hormone. When ACTH splits off from the precursor molecule, MSH is concurrently released. In the 1990s, a retrospective survey in the Netherlands showed, that the average time interval between onset of symptoms and correct diagnosis took almost three years. According to the authors, two factors were responsible for the delay: in the first instance, the rarity of Addison's disease and, secondly, the lack of specificity of symptoms which it pro-

**Addison's disease is a rare disease of the adrenal glands. It causes symptoms of weakness and low blood pressure, which seriously affect patients' lives. Research has led to effective therapies which need to be taken for life.**



Adrenal gland and kidney

### The ten most frequently heard complaints and symptoms of untreated Addison's Disease (in %)

Feeling of fatigue or weakness	99
Increased pigmentation of skin or mucous membranes	97
Unintentional weight loss	89
Nausea	86
Postural (orthostatic) dizziness	84
Low blood pressure	82
Feeling of mental fatigue or weakness	80
Loss of appetite	80
Increased need for salt	78
Vomiting	70

Source: Report of the Nederlandse Vereniging voor Addison en Cushing Patiënten (NVACP)

vokes, so that other physical and also psychosomatic causes were first suspected as an explanation.

Addison's disease was first described in 1855 by British physician Thomas Addison in his paper *"On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules"*, while working at Guy's Hospital in London. Originally, the disorder resulted from an infection of the adrenal glands; the most common was tuberculosis, which is still the predominant cause in developing countries. In industrialised countries, Addison's disease most often results from non-specific autoimmune destruction. The expression of adrenal cortex antibodies in individuals represents a significant risk of acquiring the disease. Other precipitating events include infections, malignancies, trauma, medication, vascular disturbances or metabolic events.

### Who does Addison's disease affect?

While it is a rare condition, Addison's disease is well known because of one of its famous sufferers, former US President John F. Kennedy. In Europe, prevalence is estimated to be around 60 cases per million of the population, which is equivalent to about 24,000 cases. The reported prevalence in countries where data have been collected is 39 cases per million in the UK and 60 cases per million in Denmark. The reported incidence is five to six cases per million per year.

The most common age at presentation in adults is 30-50 years, but the disease can present earlier in patients. Idiopathic autoimmune Addison's disease tends to be more common in females and children. The male-to-female ratio has been shown to be 1:2.5. The disorder is not associated with a racial predilection.

Morbidity usually is due to delay in diagnosing the disease or a failure to institute adequate replacement therapy. The mortality rate for Addison's disease is estimated to be around one death per million.

### Present treatments

Lifelong, continuous treatment with steroid replacement therapy is required. With the right balance of daily medication, most people with the disease are able to continue life much as it was before their illness.

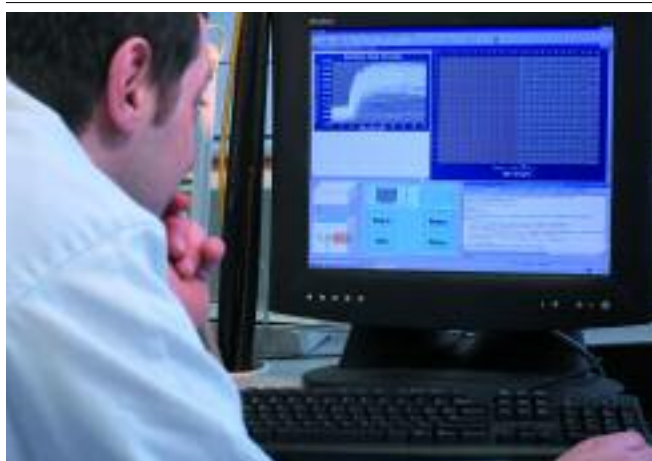
Cortisol is replaced orally with tablets containing a synthetic glucocorticoid, taken once or twice a day. If aldosterone is also deficient, it is replaced with oral doses of a mineralocorticoid, which is taken once a day. Patients receiving aldosterone replacement therapy are usually advised to increase their salt intake.

### What's in the development pipeline?

A phase 1 clinical trial is ongoing with a sustained release tablet for the medical replacement of corticosteroids according to the circadian rhythm, i.e. with high levels in the morning and low levels at night. The therapy aims to provide a viable alternative to current steroid therapies that do not mimic the natural circadian rhythm of the native steroid hormone. The medicine has already obtained orphan medicinal product designation in the EU.

For diagnosing adrenal abnormalities, scientists are investigating the option of using I-131 iodocholesterol which is an experimental chemical compound spiked with radioactive iodine, currently in phase 3 clinical trials. When injected into the vein of a patient, the molecule is picked up in the adrenal glands and permits visualisation with gamma imaging devices.

Currently, the associated failure of DHEA synthesis in patients with Addison's disease is not corrected. Several research groups are studying the effect of substitution therapy with DHEA. According to the first results, psychological assessment showed enhancement of self-esteem with a tendency for improved overall well-being in both sexes. The findings suggest that DHEA may act directly on the central nervous system, rather than by augmenting peripheral male sexual hormone biosynthesis. As DHEA replacement in Addison's disease is controversial, these effects warrant further studies to understand the role for DHEA substitution.



Research is being conducted to clarify the relationship between Addison's disease and autoimmune diseases of the endocrine glands and other organs. Apparently, there is an association between the disorder and malabsorption syndromes. Antibodies against adrenal cortex are found in about 15 per cent of patients with coeliac disease.

Clinical investigators are studying the function of the adrenal glands after living kidney transplantation. As the success of transplantation is hampered by the shortage of organs, an attractive strategy is the use of kidneys from living donors. During the donor operation, the kidney artery and vein have to be interrupted as far as possible from the organ to have sufficient length for the reconnection in the transplant operation. As the venous drainage of the left adrenal gland is closed during this procedure, the gland is most likely to be functionally impaired. This is compared to a right-sided kidney donation, where the adrenal vein is left intact.

### **The longer-term future**

Recently, research groups have shown that the target antigens of the autoimmune process in the adrenal cortex belong to enzymes which are crucial for the synthesis of steroid hormones, notably 21-hydroxylase, 17-hydroxylase, and the side-chain cleavage enzyme. These key findings have opened up new insights into the understanding of Addison's disease and associated autoimmune disorders. The new approaches include: (i) preparation of recombinant adrenal and related auto-antigens; (ii) characterisation of the T-helper leukocytes and cytotoxic T-cells' responses toward such antigens; (iii) generation of animal models for the disease in order to create new immunodiagnostic tests and immunotherapeutic regimes.

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