Seminar

Adrenal insufficiency

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Adrenal insufficiency is caused by either primary adrenal failure (mostly due to autoimmune adrenalitis) or by hypothalamic-pituitary impairment of the corticotropic axis (predominantly due to pituitary disease). It is a rare disease, but is life threatening when overlooked. Main presenting symptoms such as fatigue, anorexia, and weight loss are non-specific, thus diagnosis is often delayed. The diagnostic work-up is well established but some pitfalls remain, particularly in the identification of secondary adrenal insufficiency. Despite optimised life-saving glucocorticoid-replacement and mineralocorticoid-replacement therapy, health-related quality of life in adrenal insufficiency is more severely impaired than previously thought. Dehydroepiandrosterone-replacement therapy has been introduced that could help to restore quality of life. Monitoring of glucocorticoid-replacement quality is hampered by lack of objective methods of assessment, and is therefore largely based on clinical grounds. Thus, long-term management of patients with adrenal insufficiency remains a challenge, requiring an experienced specialist. However, all doctors should know how to diagnose and manage suspected acute adrenal failure.

In 1855, Thomas Addison described a clinical syndrome characterised by wasting and hyperpigmentation, and identified its cause as destruction of the adrenal gland. However, life-saving glucocorticoid-replacement therapy for the condition did not become available until 1949, when Kendall, Sarett, and Reichstein first synthesised cortisone. Furthermore, despite this breakthrough, 150 years on there are still many advances and challenges with respect to the management of individuals with adrenal insufficiency.

Epidemiology

There are two types of adrenal insufficiency, primary and secondary (figure 1). Chronic primary adrenal insufficiency has a prevalence of 93–140 per million and an incidence of 4·7–6·2 per million in white populations.[1–4] These recent numbers are higher than those reported during the 1960s and 1970s,[5,6] despite a continuous decline in tuberculous adrenalitis in the developed world, suggesting an increasing incidence of autoimmune adrenalitis.[3,4] The age at diagnosis peaks in the fourth decade of life, with women more frequently affected than men.[1–4]

Secondary adrenal insufficiency has an estimated prevalence of 150–280 per million,[3,7–10] and also affects women more frequently than men. Age at diagnosis peaks in the sixth decade of life.[8,9] Therapeutic glucocorticoid administration is thought to be the most common cause of secondary adrenal insufficiency, since chronic administration exogenous glucocorticoids induces atrophy of pituitary corticotroph cells. However, iatrogenic adrenal insufficiency becomes potentially relevant only during or after glucocorticoid withdrawal. Because iatrogenic adrenal insufficiency is transient in most cases,[11] we suspect its prevalence to be lower than that of endogenous adrenal insufficiency.

Lancet 2003; **361:** 1881–93

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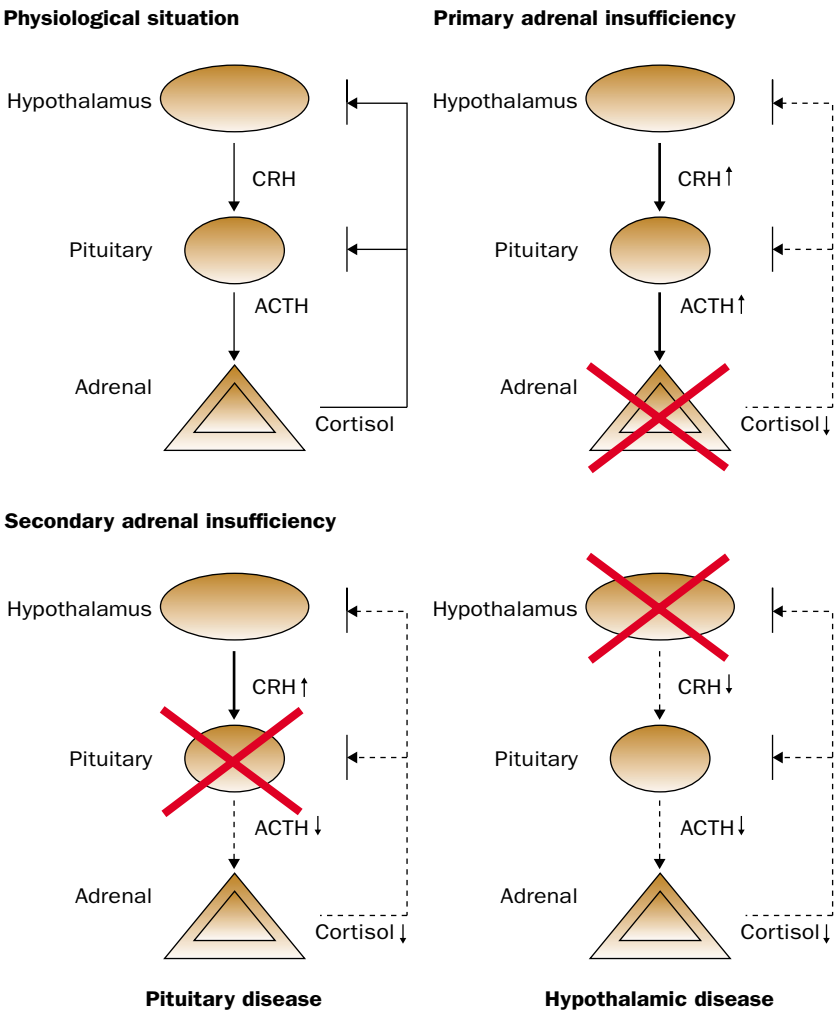
Cause

Primary adrenal insufficiency (panel 1)[12–38]

During the times of Thomas Addison, tuberculous adrenalitis was by far the most prevalent cause of adrenal insufficiency and, in the developing world, it remains a major factor.[39] In active tuberculosis, the incidence of adrenal involvement is 5%.[40] In developed countries, 80–90% of patients with primary adrenal insufficiency have autoimmune adrenalitis, which can arise as isolated (40%; slight male preponderance) or as part of an autoimmune polyendocrine syndrome ([APS]; 60%; female preponderance).[12,41] APS type 1, also termed autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED), arises in up to 15% of patients with autoimmune adrenalitis. It is characterised by adrenal insufficiency, hypoparathyroidism, and chronic mucocutaneous candidiasis with onset during childhood.[12,42] APECED might also comprise the autoimmune disorders seen in APS type 2, and in addition, childhood alopecia (40% of APECD patients), chronic active hepatitis (20%), and malabsorption (15%).[12] APECED is caused by mutations in the autoimmune regulator (*AIRE*) gene[13,14] and is inherited in an autosomal-recessive fashion. APS type 2 is the most frequently seen APS and comprises adrenal insufficiency and autoimmune thyroid disease. The clinical spectrum also includes primary gonadal failure, type 1 diabetes mellitus, and other autoimmune diseases such as vitiligo, chronic atrophic gastritis, or coeliac disease. APS type 2 occurs with autosomal-dominant inheritance with incomplete

Search strategy

We searched Medline and PubMed for reviews and original articles related to adrenal insufficiency and published between 1966 and December, 2002. Keywords used included adrenal insufficiency and incidence, prevalence, cause, origin, diagnosis, function test, imaging, hydrocortisone, glucocorticoid, mineralocorticoid, dehydroepiandrosterone, management, treatment, therapy, replacement, surveillance, crisis, bone mineral density, quality of life, well-being, disablement, pregnancy, prognosis, morbidity, and mortality. Citations were chosen on the basis of relevance to the specific topics covered.



Primary and secondary adrenal insufficiency
CRH=corticotropin-releasing hormone.

penetrance, and shows a strong association with HLA-DR3[12,43] and CTLA-4.[44,45] The combination of adrenal insufficiency with other autoimmune disorders, but without thyroid disease, is classified as APS type 4, and APS type 3 involves autoimmune thyroid disease but not adrenal insufficiency.

X-linked adrenoleukodystrophy is caused by a mutation in the *ABCD1* gene,[46] which encodes a peroxisomal membrane protein (adrenoleukodystrophy protein),[47] leading to accumulation of very-long-chain fatty acids (>24 carbon atoms). The clinical picture comprises adrenal insufficiency and neurological impairment due to white-matter demyelination. The two major forms are cerebral adrenoleukodystrophy (50% of cases; early childhood manifestation; rapid progression) and adrenomyeloneuropathy (35% of cases; onset in early adulthood; slow progression) with restriction of demyelination to spinal cord and peripheral nerves.[16] Adrenal insufficiency can precede the onset of neurological symptoms and is the sole manifestation of disease in 15% of cases.[16]

Other causes of primary adrenal insufficiency—eg, adrenal infiltration or haemorrhage—are rare. Congenital or neonatal primary adrenal insufficiency accounts for only 1% of all cases. However, the elucidation of the genetic basis of underlying diseases has emphasised the importance of specific genes for adrenal development and steroidogenesis (panel 1).

Secondary adrenal insufficiency (panel 2)[48–55]

The most frequent cause of secondary adrenal insufficiency is a tumour of the hypothalamic-pituitary region, usually associated with panhypopituitarism caused by tumour growth or treatment with surgery or irradiation. Autoimmune lymphocytic hypophysitis is less frequent, mostly affecting women during or shortly after pregnancy. Isolated adrenocorticotropic hormone (ACTH) deficiency could also be of autoimmune origin since some patients concurrently have other autoimmune disorders, most frequently thyroid disease.[49] The differential diagnosis of postpartum autoimmune hypophysitis includes Sheehan's syndrome, which results from pituitary apoplexy, mostly due to pronounced blood loss during delivery. Very rarely mutations of genes important for pituitary development or for synthesis and processing of the corticotropin precursor pro-opiomelanocortin cause secondary adrenal insufficiency (panel 2).

Pathophysiology and clinical presentation (panel 3)

Glucocorticoids are secreted from the adrenal zona fasciculata under the control of hypothalamic corticotropin-releasing hormone and pituitary corticotropin. Cortisol secretion is diurnal with maximum concentrations measured early in the morning and trough concentrations noted around midnight.[56] Mineralocorticoids are produced by the zona glomerulosa, mainly under the control of the renin-angiotensin system. Thus, mineralocorticoid secretion is preserved in secondary adrenal insufficiency. Dehydroepiandrosterone secretion by the zona reticularis is also diurnal and is acutely increased by ACTH. However, although cortisol secretion varies little throughout life, dehydroepiandrosterone secretion is age dependent, with an increase noted at age 6–10 years (adrenarche), which continues until age 20–30 years. Thereafter, dehydroepiandrosterone concentrations steadily fall. This pattern suggests the existence of ACTH-independent factors, controlling release of dehydroepiandrosterone.[57]

Patients with acute adrenal insufficiency—ie, life-threatening adrenal crisis—typically present with severe hypotension or hypovolaemic shock, acute abdominal pain, vomiting, and often fever. Such individuals are, therefore, sometimes misdiagnosed as having an acute abdomen. In a series of 91 patients with Addison's disease,[58] adrenal crisis led to the initial diagnosis of adrenal insufficiency in half of them. In children, acute adrenal insufficiency often presents as hypoglycaemic seizures. Deterioration of glycaemic control with recurrent hypoglycaemia can be the presenting sign of adrenal insufficiency in patients with pre-existing type 1 diabetes. In APS type 2, onset of autoimmune hyperthyroidism (or thyroxine replacement for newly diagnosed hypothyroidism) can precipitate adrenal crisis due to enhanced cortisol clearance.

Panel 1: **Causes of primary adrenal insufficiency**

Diagnosis	Clinical features in addition to adrenal insufficiency	Pathogenesis or genetics
Autoimmune adrenalitis		
Isolated autoimmune adrenalitis	No other features	Associations with HLA-DR3, CTLA-4
Auotimmune adrenalitis as part of APS[12]		
APS type 1 (APECED)	Hypoparathyroidism, chronic mucocutaneous candidiasis, other autoimmune disorders	*AIRE* gene mutations (21q22.3)[13,14]
APS type 2	Thyroid disease, type 1 diabetes mellitus other autoimmune diseases	Associations with HLA-DR3, CTLA-4
APS type 4	Other autoimmune diseases, excluding thyroid disease or diabetes	Associations with HLA-DR3, CTLA-4
Infectious adrenalitis		
Tuberculous adrenalitis	Other organ manifestations of tuberculosis	Tuberculosis
AIDS	Other AIDS-associated diseases	HIV-1, cytomegalovirus[15]
Fungal adrenalitis	Mostly in immunosuppressed patients	Cryptococcosis, histoplasmosis, coccidoidomycosis
Genetic disorders leading to adrenal insufficiency		
Adrenoleukodystrophy, adrenomyeloneuropathy	Demyelination of CNS (cerebral adrenoleukodystrophy), spinal cord, or peripheral nerves (adrenomyeloneuropathy)	Mutation of the *ABCD1* gene encoding for the peroxisomal adrenoleukodystrophy protein[16]
Congenital adrenal hyperplasia		
21-hydroxylase deficiency	Ambiguous genitalia in girls	*CYP21* mutation
11β-hydroxylase deficiency	Ambiguous genitalia in girls and hypertension	*CYP11B1* mutation[17]
3β-HSD type 2 deficiency	Ambiguous genitalia in boys, postnatal virilisation in girls	*HSD3B2* mutation[18]
17α-hydroxylase deficiency	Ambiguous genitalia in boys, lack of puberty in both sexes, hypertension	*CYP17* mutation
Congenital lipoid adrenal hypoplasia	XY sex reversal	Mutations in the steroidogenic acute regulatory protein (*SIAR*) gene;[19] mutations in *CYP11A* (encoding P450scc)[20]
Smith-Lemli-Opitz syndrome	Mental retardation, craniofacial malformations, growth failure	7-dehydrocholesterol reductase mutations in gene *DHCR7*[21,22]
Adrenal hypoplasia congenita		
X-linked	Hypogonadotropic hypogonadism	Mutation in *NROB1*[23]
Xp21 contiguous gene syndrome	Duchenne muscular dystrophy and glycerol kinase deficiency (psychomotor retardation)	Deletion of the Duchenne muscular dystrophy, glycerol kinase, and *NROB1* genes[24]
SF-1 linked	XY sex reversal	Mutation in *NR5A1*[25]
IMAGe syndrome	Intrauterine growth retardation, metaphyseal dysplasia, adrenal, insufficiency, and genital anomalies (IMAGe)	Unknown[26]
Kearns-Sayre syndrome	External ophthalmoplegia, retinal degeneration, and cardiac conduction defects; other endocrinopathies	Mitochondrial DNA deletions[27,28]
ACTH insensitivity syndromes (familial glucocorticoid deficiency)	Glucocorticoid deficiency, but no impairment of mineralocorticoid synthesis	
Type 1	Tall stature	ACTH receptor (MC2R) mutations[29]
Type 2	No other features	Unknown[30]
Triple A syndrome (Allgrove's syndrome)	Alacrimia, achalasia; additional symptoms—eg, neurological impairment, deafness, mental retardation, hyperkeratosis	Mutations in triple A gene (*AAAS*) encoding for a WD-repeat protein[31,32]
Bilateral adrenal haemorrhage	Symptoms of underlying disease	Septic shock, specifically meningococcal sepsis (Waterhouse-Friderichsen syndrome); primary antiphospholipid syndrome[33]
Adrenal infiltration	Symptoms of underlying disease	Adrenal metastases[34] primary adrenal lympoma sarcoidosis, amyloidosis, haemochromatosis
Bilateral adrenalectomy	Symptoms of underlying disease	Unresolved Cushing's syndrome
Drug-induced adrenal insufficiency	No other symptoms	Treatment with mitotane,[35] aminoglutethimide, etomidate,[36,37] ketoconazole, suramin,[38] mifepristone

HSD=hydroxy-Δ-5-steroid dehydrogenase.

Panel 2: **Causes of secondary adrenal insufficiency**

Diagnosis	Comment
Pituitary tumours	Secondary adrenal insufficiency mostly as part of panhypopituitarism, additional symptoms (visual-field impairment): generally adenomas, carcinoma is a rarity; consequence of tumour growth, surgical treatment, or both
Other tumours of the hypothalamic-pituitary region	Craniopharyngioma, meningioma, ependymoma, and intrasellar or suprasellar metastases
Pituitary irradiation	Craniospinal irradiation in leukaemia, radiation for tumours outside the hypothalamic-pituitary axis, irradiation of pituitary tumours
Lymphocytic hypophysitis	
Isolated	Autoimmune hypophysitis; most frequently in relation to pregnancy (80%[48]); mostly hypopituitarism, but also isolated adrenocorticotropic hormone deficiency
As part of APS	Associated with autoimmune thyroid disease and, less frequently, with vitiligo, primary gonadal failure, type 1 diabetes, and pernicious anaemia[49]
Isolated congenital ACTH deficiency	Pro-opiomelanocortin cleavage enzyme defect?[50]
Pro-opiomelanocortin-deficiency syndrome	Pro-opiomelanocortin gene mutations;[51] clinical triad adrenal insufficiency, and early-onset obesity, red hair pigmentation
Combined pituitary-hormone deficiency	Mutations in the gene encoding the pituitary transcription factor Prophet of Pit1 (*PROP1*),[52] progressive development of panhypopituitarism in the order GH, PRL, TSH, LH/FSH, (ACTH) Mutations in the homeo box gene *HESX1*,[53] combined pituitary hormone deficiency, optic-nerve hypoplasia, and midline brain defects (septo-optic dysplasia)
Pituitary apoplexy	Onset mainly with abrupt severe headache, visual disturbance, and nausea or vomiting[54]
Sheehan's syndrome	Pituitary apoplexy or necrosis with peripartal onset—eg, due to high blood loss or hypotension
Pituitary infiltration or granuloma	Tuberculosis, actinomycosis, sarcoidosis, histiocytosis X, Wegener's granulomatosis
Head trauma	For example pituitary stalk lesions
Previous chronic glucocorticoid excess	Exogenous glucocorticoid administration for more than 4 weeks[55] endogenous glucocorticoid hypersecretion due to Cushing's syndrome

GH=growth hormone. PRL=prolactin. TSH=thyrotropin. LH=luteinising hormone. FSH=follicle stimulating hormone.

The main symptom of chronic adrenal insufficiency is fatigue, accompanied by lack of stamina, loss of energy, reduced muscle strength, and increased irritability. Additionally, chronic glucocorticoid deficiency leads to weight loss, nausea, and anorexia (anorexia or failure to thrive in children), and can account for muscle and joint

Panel 3: **Clinical manifestations of adrenal insufficiency**

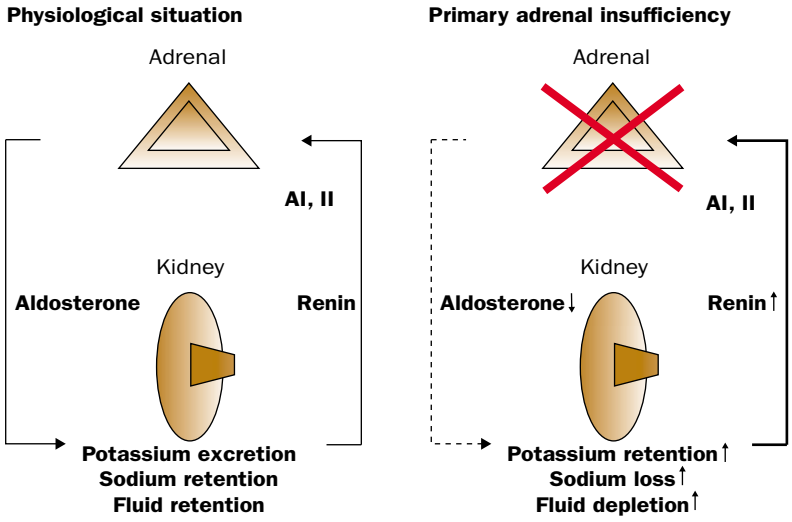
Symptoms	Pathophysiology
Fatigue, lack of energy or stamina, reduced strength	Glucocorticoid deficiency, adrenal androgen deficiency
Anorexia, weight loss (in children failure to thrive)	Glucocorticoid deficiency
Gastric pain, nausea, vomiting (more frequent in primary adrenal insufficiency)	Glucocorticoid deficiency, mineralocorticoid deficiency
Myalgia, joint pain	Glucocorticoid deficiency
Dizziness	Mineralocorticoid deficiency, glucocorticoid deficiency
Salt craving (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Dry and itchy skin (in women)	Adrenal androgen deficiency
Loss or impairment of libido (in women)	Adrenal androgen deficiency
Signs	
Skin hyperpigmentation (primary adrenal insufficiency only)	Excess of pro-opiomelanocortin-derived peptides
Alabaster-coloured pale skin (secondary adrenal insufficiency only)	Deficiency of pro-opiomelanocortin-derived peptides
Fever	Glucocorticoid deficiency
Low blood pressure (systolic RR <100 mm Hg), postural hypotension (pronounced in primary adrenal insufficiency)	Mineralocorticoid deficiency, glucocorticoid deficiency
Raised serum creatinine (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Hyponatraemia	Mineralocorticoid deficiency, glucocorticoid deficiency (leading to SIADH)
Hyperkalaemia (primary adrenal insufficiency only)	Mineralocorticoid deficiency
Anaemia, lymphocytosis, eosinophiliia	Glucocorticoid deficiency
Increased thyroid stimulating hormone (primary adrenal insufficiency only)	Glucocorticoid deficiency (or autoimmune thyroid failure)
Hypercalcaemia (primary adrenal insufficiency only)	Glucocorticoid deficiency (mostly concurrent hyperthyroidism)
Hypoglycaemia	Glucocorticoid deficiency
Loss of axillary or pubic hair (in women), absence of adrenarche or pubarche in children	Adrenal androgen deficiency

RR=R-R interval. SIADH=syndrome of inappropriate antidiuretic hormone secretion.

pain. Unfortunately, most of these symptoms are non-specific. Thus, 50% of patients have signs and symptoms of Addison's disease for more than 1 year before diagnosis is established.[58] In secondary adrenal insufficiency, diagnosis is generally prompted by a history of pituitary disease, but can also be delayed—eg, in isolated ACTH deficiency. A more specific sign of primary adrenal failure is hyperpigmentation, which is most pronounced in areas of the skin exposed to increased friction—eg, palmar creases, knuckles, scars, oral mucosa. Hyperpigmentation is caused by enhanced stimulation of skin MC1-receptor by ACTH and other pro-opiomelanocortin-related peptides. Accordingly, patients with secondary adrenal insufficiency often have pale, alabaster-coloured skin. Laboratory findings in glucocorticoid deficiency can include mild anaemia, lymphocytosis, and eosinophilia. Cortisol physiologically inhibits thyrotropin release. Thus, concentration of thyrotropin is often increased at initial diagnosis of primary adrenal insufficiency, but returns to normal during glucocorticoid replacement unless there is coincident autoimmune thyroid dysfunction.[59] In rare cases, glucocorticoid deficiency can result in hypercalcaemia, which is due to increased intestinal absorption and decreased renal excretion of calcium and generally coincides with autoimmune hyperthyroidism, facilitating calcium release from bone.[60]

Mineralocorticoid deficiency, which is present only in primary adrenal insufficiency (figure 2), leads to dehydration and hypovolaemia, resulting in low blood pressure, postural hypotension, and sometimes even in prerenal failure. Deterioration can be sudden and is often due to exogenous stress such as infection or trauma. Combined mineralocorticoid and glucocorticoid replacement in primary disease reconstitutes the diurnal rhythm of blood pressure[61] and reverses cardiac dysfunction.[62] Glucocorticoids contribute to this improvement not only by mineralocorticoid receptor binding, but also by permissive effects on catecholamine action.[63] The latter could account for the relative unresponsiveness to catecholamines in patients with unrecognised adrenal crisis. Mineralocorticoid deficiency accounts for hyponatraemia (90% of patients with primary adrenal insufficiency), hyperkalaemia (65%), and salt craving (15%).[1,6] Low serum sodium values can also be present in secondary adrenal insufficiency due to syndrome of inappropriate antidiuretic hormone secretion, which results from the loss of physiological inhibition of pituitary vasopressin release by glucocorticoids.[64]

Adrenal insufficiency inevitably leads to dehydroepiandrosterone deficiency. Dehydroepiandrosterone is the major precursor of sex-steroid synthesis and loss of its production results in pronounced androgen deficiency in women. As a consequence, women with adrenal insufficiency frequently show loss of axillary and pubic hair (absence of pubarche in children), dry skin, and reduced libido. Dehydroepiandrosterone also exerts direct action as a neurosteroid with potential antidepressant properties.[57] Thus dehydroepiandrosterone deficiency could contribute to the impairment of wellbeing noted in patients with adrenal insufficiency despite adequate glucocorticoid and mineralocorticoid replacement.[65]



Mineralocorticoid production
AI, II=Angiotensin I and II.

Laboratory assessment of adrenal function (panel 4)

Concentrations of ACTH and cortisol vary throughout the day due to their closely related pulsatile release, which follows a diurnal rhythm. Therefore, the diagnostic usefulness of random samples is limited. Moreover, total cortisol, but not the biologically active free fraction, can increase as a result of hepatic cortisol-binding globulin production, which is increased, for example, by oestrogens.[66] Finally, differences in cortisol assays can affect normative data and interpretation of dynamic tests.[67]

Primary adrenal insufficiency

The combined measurement of early morning serum cortisol and plasma ACTH separates patients with primary adrenal insufficiency from healthy individuals and from those with secondary disease.[68] Plasma ACTH is usually greatly increased and invariably higher than 22·0 pmol/L, with serum cortisol generally lower than the normal range (<165 nmol/L) but sometimes in the lower normal range. Serum aldosterone concentrations are subnormal or within the lower normal range, with plasma renin activity concurrently increased above the normal range.[68] In patients who have adrenal insufficiency, serum dehydroepiandrosterone is consistently low,[69,70] and in women is often lower than the limit of detection.

The impaired ability of the adrenal cortex to respond to ACTH is readily demonstrated by the standard short corticotropin test,[71] which involves measurement of serum cortisol before and after 30 or 60 min intravenous or intramuscular injection of 250 μg 1-24 ACTH.[66,72] In healthy individuals, this challenge leads to a physiological increase in serum cortisol to peak concentrations of greater than 500 nmol/L.[67] In those with primary adrenal insufficiency, in whom the adrenal cortex is already maximally stimulated by endogenous ACTH,[68] exogenous hormone administration usually does not evoke any further increase in serum cortisol.

Adrenal cortex autoantibodies or antibodies against 21-hydroxylase are present in more than 80% of patients with recent onset autoimmune adrenalitis.[73] Although 21-hydroxylase has been identified as the major autoantigen in autoimmune adrenalitis,[74] autoantibodies

Panel 4: **Biochemical diagnosis of adrenal insufficiency**

Test	Protocol	Normal range	Definitive adrenal insufficiency	Adrenal insufficiency not excluded	Comment
Primary adrenal insufficiency					
Early morning cortisol and Early morning ACTH	Serum cortisol at 0700–0900 h; Plasma ACTH at 0700–0900 h	165–680 nmol/L; 1·1–11·0 pmol/L	Cortisol <165 nmol/L and ACTH >22·0 pmol/L	Cortisol <300 nmol/L	Cortisol >500 nmol/L usually excludes primary adrenal insufficiency*; ACTH in most cases >45·0 pmol/L*
Standard short corticotropin test	Serum cortisol at 0, 30, and 60 min after 250 µg intravenous or intramuscular 1-24 ACTH	Peak cortisol >500 nmol/L	Peak cortisol <500 nmol/L		In most cases no cortisol increase because of already maximum endogenous ACTH stimulation
Secondary adrenal insufficiency					
Early morning cortisol	Serum cortisol at 0700–0900 h	165–680 nmol/L	Cortisol <100 nmol/L	Cortisol >100 nmol/L or <500 nmol/L	Cortisol >500 nmol/L excludes secondary adrenal insufficiency
Early morning ACTH	Plasma ACTH at 0700–0900 h	1·1–11·0 pmol/L		ACTH <11·0 pmol/L	
Standard short corticotropin test	Serum cortisol at 0 and 30 or 60 min after 250 µg intravenous or intramuscular 1-24 ACTH	Peak cortisol >500 nmol/L	Peak cortisol <500 nmo/L	Peak cortisol <600 nmol/L	Peak cortisol <400nmol/L in most patients with secondary adrenal insufficiency
Insulin tolerance test	Serum glucose and cortisol 0, 15, 30, 45, 60, and 90 min after intravenous insulin (0·1–0·15 U/kg)	Peak cortisol >500 nmol/L	Peak cortisol <500 nmol/L	Peak cortisol <550 nmol/L	Test only valid if symptomatic hypoglycaemia (serum glucose <2·2 nmol/L) is achieved; gold standard test; close supervision mandatory; contraindicated with history of seizures, cerebrovascular, and cardiovascular disease

*Researchers' laboratory; normal values vary dependent on laboratory and assay.

against other steroidogenic enzymes (P450scc, P450c17) and steroid-producing cell antibodies are present in some patients.[12] Measurement of autoantibodies is especially helpful in patients with isolated primary adrenal insufficiency and no family history of autoimmune disease. In APS type 2, autoimmune adrenalitis can be associated with autoimmune thyroid disease or type 1 diabetes, and screening for concomitant disease should involve measurement of thyrotropin and fasting glucose but not of other organ-related antibodies.

In boys and men with isolated primary adrenal insufficiency without unequivocal evidence of autoimmune adrenalitis, serum concentrations of very-long-chain fatty acids (chain length of ⩾24 carbons; C26, C26/C22, and C24/C22 ratios) should be measured to exclude adrenoleukodystrophy or adrenomyeloneuropathy.[16]

Secondary adrenal insufficiency

Baseline hormone measurements differ little between patients with secondary adrenal insufficiency and healthy individuals.[16,68] However, a morning cortisol value below 100 nmol/L indicates adrenal insufficiency whereas a serum cortisol greater than 500 mmol/L is consistent with an intact hypothalmic-pituitary-adrenal axis.[72,75,76] Thus, in most instances, dynamic tests of the hypothalmic-pituitary-adrenal axis are required to establish a diagnosis of secondary adrenal insufficiency.

The insulin tolerance test[77] is regarded as the gold standard in the assessment of suspected secondary adrenal insufficiency, since hypoglycaemia (blood glucose <2·2 mmol/L) is a powerful stressor that results in rapid activation of the hypothalamic-pituitary-adrenal axis.[66] An intact axis is indicated by a peak cortisol of more than 500 nmol/L at any time during the test (panel 4).[78,79] Occasionally, however, a patient will pass the insulin tolerance test despite exhibiting clinical evidence for adrenal insufficiency that responds to hydrocortisone substitution.[80] A higher cut-off value (550 nmol/L) for peak cortisol in the insulin tolerance test could help to reduce misclassification.[79,81] During the test, close supervision is mandatory[66] and cardiovascular disease or history of seizures are contraindications.

Another diagnostic test is the overnight metyrapone test (metyrapone 30 mg/kg [maximum 3 g] administered with a snack at midnight).[82,83] Metyrapone inhibits adrenal 11β-hydroxylase—ie, the conversion of 11-deoxycortisol to cortisol. In healthy individuals, feedback activation of the hypothalmic-pituitary-adrenal axis increases serum 11-deoxycortisol, while serum cortisol remains at concentrations of less than 230 nmol/L. In patients with secondary adrenal insufficiency, however, 11-deoxycortisol does not exceed 200 nmol/L at 0800 h after metyrapone. Shortcomings of the test are limited availability of reliable 11-deoxycortisol assays and the need to order

metyrapone directly from the manufacturer (Novartis, Basel, Switzerland). Since metyrapone can precipitate adrenal crisis in severe cortisol deficiency, a morning cortisol concentration of more than 200 nmol/L should be recorded before doing the test on an out patient basis.[66]

Because both the insulin tolerance test and the metapyrone test pose a great burden to patients and doctors, there have been continuing efforts to replace these tests by more convenient ones.[78,84–86] Sustained secondary adrenal insufficiency leads to adrenal atrophy and also to reduced ACTH receptor expression in the adrenal gland, since ACTH up-regulates its own receptor.[87] Thus adrenal responsiveness to an acute exogenous ACTH challenge is impaired also in secondary disease, facilitating the use of the standard short corticotropin test for the assessment of axis integrity (panel 4). Several studies[72,88] have reported excellent agreement between peak cortisol concentrations in the standard short corticotropin test and in the insulin tolerance test. However, some patients with secondary adrenal insufficiency do pass the standard short corticotropin test but not the insulin tolerance test.[89–91] The use of a higher cut-off value (600 nmol/L) for passing the corticotropin test could keep to a minimum the risk of overlooking secondary disease.[92] Thus the standard short corticotropin test obviates the insulin tolerance test in a substantial proportion of patients with suspected secondary adrenal insufficiency.

Since the administration of 250 μg 1-24 ACTH represents a massive supraphysiological challenge, a low-dose corticotropin test that uses only 1 μg ACTH has been proposed as a more sensitive test for the diagnosis of secondary adrenal insufficiency.[93–96] The test has been successfully used to monitor recovery of adrenal function after withdrawal of oral glucocorticoids[11] and to detect subtle impairment of adrenal reserve during inhaled steroid therapy.[97,98] However, the intravenous administration of 1 μg ACTH still results in hormone concentrations greater than those required for maximum cortisol release.[99] Accordingly, in healthy individuals, serum cortisol concentrations measured 30 min after the challenge do not differ between the standard short corticotropin test and the low-dose corticotropin test. Results of several studies, comparing the two tests for the assessment of patients with secondary adrenal insufficiency, have indicated a slightly improved sensitivity of the low-dose corticotropin test.[95,96] However, this advantage is offset by handling difficulties caused by the need to dilute the test amount from the commercially available 250 μg 1-24 ACTH ampoule and because of the potential binding of the hormone to the surface of injection devices.[100]

Corticotropin releasing hormone has been used to differentiate hypothalamic from pituitary disease in secondary adrenal insufficiency. However, stimulation of the hormone is not of great help in actually diagnosing the condition, because individual responses to exogenous corticotropin releasing hormone are highly variable and cut-off values or even normal ranges are still not well defined.[66]

Finally, a word of caution: none of the tests, including the insulin tolerance test, classify all patients correctly. Mild secondary adrenal insufficiency can pass as intact hypothalamic-pituitary-adrenal axis, and healthy individuals might fail any single test by a small margin. Thus, clinical judgment remains important. Persisting symptoms such as fatigue, myalgia, or reduced vitality should lead to reassessment.

Special diagnostic situations

Adrenal insufficiency after pituitary surgery

Screening for adrenal insufficiency with the standard short corticotropin test or with the low-dose corticotropin test should be done 4–6 weeks or more after surgery for pituitary surgery,[76,101] since adrenal atrophy can develop only gradually after onset of ACTH deficiency. Until then, patients with a morning cortisol not excluding secondary adrenal insufficiency (<450 nmol/L at 3 days and <350 nmo/L at 7 days after surgery) should receive hydrocortisone replacement, withheld for 24 h before scheduled testing of adrenal function.[102] The impairment of other hormonal axes after pituitary surgery increases the likelihood of ACTH deficiency,[103] whereas isolated corticotropin deficiency is uncommon.

Adrenal insufficiency in critically ill patients

In critically ill patients, the corticotropic axis is greatly activated.[104,105] Moreover, patients in intensive care are less sensitive to dexamethasone suppression and achieve higher peak ACTH and cortisol concentrations after administration of corticotropin-releasing hormone.[106] Critically ill patients also have fairly low serum concentrations of aldosterone with concurrently raised plasma renin activity.[107] Cortisol concentrations correlate with illness-severity scores and are highest in individuals with the highest mortality.[106,108] However, cytokine activation might impair the adequate responsiveness of pituitary corticotrpic cells leading to secondary adrenal insufficiency in some patients with severe illness, thus putting them at risk of dying from adrenal crisis.

Chronic inhibition of cortisol production by etomidate has been associated with increased mortality in patients in intensive care.[36,37] Unfortunately, no consensus exists about how to diagnose adrenal insufficiency in these individuals.[109] In patients with primary or severe secondary adrenal insufficiency the standard short corticotropin test will establish a diagnosis by indicating a low baseline cortisol (<165 nmol/L) not responding to corticotropin (peak cortisol <500 nmol/L). However, partial secondary adrenal insufficiency might be present in some critically ill patients, characterised by a poor cortisol response (increment <248 nmol/L[110]) to ACTH despite normal baseline cortisol. These patients often present with catecholamine-dependent hypodynamic shock that responds to treatment with hydrocortisone.[109,111] Findings of a study showed decreased mortality in patients with septic shock and abnormal cortisol response in the standard short corticotropin test (increment <248 nmol/L) after treatment with replacement doses of hydrocortisone and fludrocortisone.[112]

We recommend that a random sample of serum cortisol and plasma ACTH is obtained from critically ill patients with suspected adrenal insufficiency followed by immediate hydrocortisone administration. Dependent on the results of these hormone measurements (serum cortisol >700 nmol/L rules out adrenal insufficiency) hydrocortisone therapy should be terminated or a more detailed assessment with the standard short corticotropin test undertaken.

Imaging

Adrenal imaging is not indicated in patients with an unequivocal diagnosis of autoimmune adrenalitis or adrenomyeloneuropathy. If infection, haemorrhage, infiltration, or neoplastic disease is suspected, abdominal CT scans should be done. In adrenal tuberculosis, bilateral enlargement is present in the subacute phase,[113] whereas calcifications develop during later stages.[114]

	Number (%)				
	All (n=53)	Men (n=23)	Women (n=30)	Primary adrenal insufficiency (n=28; 19 female, 9 male)	Secondary adrenal insufficiency (n=25; 11 female, 14 male)
Symptoms					
Fatigue	21 (40%)	8 (35%)	13 (43%)	10 (36%)	11 (44%)
Lack of energy	14 (28%)	7 (30%)	8 (27%)	7 (25%)	8 (32%)
Reduced strength	13 (26%)	6 (26%)	8 (27%)	5 (18%)	9 (36%)
Insomnia	11 (20%)	4 (17%)	7 (23%)	4 (14%)	7 (28%)
Muscle pain	7 (13%)	3 (13%)	4 (13%)	4 (14%)	3 (12%)
Recurrent infections	3 (6%)	0	3 (10%)	3 (11%)	0
Nausea	3 (6%)	0	3 (10%)	3 (11%)	0
Signs					
Weight gain	11 (20%)	4 (17%)	7 (23%)	3 (11%)	8 (32%)
Truncal obesity	10 (19%)	3 (13%)	7 (23%)	4 (14%)	6 (24%)
Hyperpigmentation	9 (17%)	2 (7%)	7 (23%)	9 (32%)	0
Arterial hypotension	8 (15%)	4 (17%)	4 (13%)	3 (11%)	4 (16%)
Increased serum sodium or decreased potassium	4 (9%)	1 (4%)	4 (13%)	4 (13%)	1 (4%)
Decreased serum sodium or increased potassium	3 (6%)	0	3 (10%)	2 (7%)	1 (4%)
Arterial hypertension	3 (6%)	0	3 (10%)	2 (7%)	1 (4%)
Peripheral oedema	2 (4%)	1 (4%)	1 (3%)	0	2 (8%)
Weight loss	1 (2%)	0	1 (3%)	1 (4%)	0

Mean age 51 (SD 14) years and mean duration of disease 10 (7) years.

Frequency of signs and symptoms during chronic replacement therapy for adrenal insufficiency in a series of our patients (n=53)

In secondary adrenal insufficiency of unknown origin, MRI of the hypothalamic-pituitary region is the method of choice to reveal a space-occupying lesion. Only pituitary adenomas with a diameter of greater than 1 cm will cause secondary adrenal insufficiency; smaller microadenomas are coincident. Lymphocytic hypophysitis might initially present as pituitary enlargement, sometimes leading to the misdiagnosis of a pituitary tumour, whereas the long-term course leads to pituitary atrophy and subsequent empty sella.

Treatment

Chronic replacement therapy

Glucocorticoid replacement is usually given in two or three daily doses, with a half to two-thirds of the daily dose administered in the morning to mimic the physiological cortisol secretion pattern. Findings of studies indicate that daily cortisol production rates vary between 5 mg/m^2 and 10 mg/m^2,[115–118] equivalent to the oral administration of 15–25 mg hydrocortisone (cortisol) or 25·0–37·5 mg cortisone acetate.[119–120] Cortisone acetate requires conversion to cortisol by 11β-hydroxysteroid dehydrogenase type 1. Administration of hydrocortisone or cortisone acetate results in peak serum cortisol concentrations that vary substantially between individuals but that are generally within the supraphysiological range, followed by a rapid decline to below 100 nmol/L 5–7 h after ingestion.[120–122] Whether a three-times-daily regimen of glucocorticoid administration should be preferred over a twice-daily one is not clear. The only study addressing this issue[123] claimed improved effects of a three-times-daily regimen on measures of quality of life.[123] However, the number of patients included (seven) was small, with six switched from three times to twice daily, but only one from twice to three times daily. Furthermore, the intervention was open-label and not blinded. Additionally, the second dose in the twice-daily regimen was administered at 2000 h and thus is unusually late. In general, if a twice daily regimen is applied, the second dose should be administered about 6–8 h after the first. Long-acting glucocorticoids are also used for replacement (1 mg hydrocortisone=1·6 mg cortisone acetate=0·2 mg prednisolone=0·05 mg dexamethasone). Prednisolone and dexamethasone have much longer biological half-lives than hydrocortisone and cortisone acetate, which could result in unfavourably high night-time glucocorticoid activity.

Treatment surveillance of chronic glucocorticoid replacement is mainly based on clinical grounds because no objective assessment has proven to be reliable for monitoring replacement quality. ACTH cannot be used as a criterion for glucocorticoid dose adjustment, since in primary adrenal insufficiency it is invariably high before the morning dose and rapidly declines with increasing cortisol concentrations after glucocorticoid ingestion.[122,124] Aiming at morning ACTH values continuously within the normal range would, therefore, lead to chronic over-replacement. However, in case of reappearance of skin hyperpigmentation in primary adrenal insufficiency, concentrations of plasma ACTH should be measured.

Urinary 24 h free cortisol excretion has been advocated for monitoring replacement.[125,126] However, after exogenous glucocorticoid administration, urinary cortisol excretion shows considerable between-individual variability.[120] More importantly, after glucocorticoid absorption cortisol-binding globulin will be rapidly saturated,[127] resulting in transient but pronounced increases in renal cortisol excretion. Thus, one cannot refer to normal ranges for healthy individuals when judging urinary cortisol excretion during replacement therapy in adrenal insufficiency. However, in cases of suspected under-replacement—eg, due to non-adherence—urinary cortisol measurements could be helpful.

To measure a random serum cortisol without knowing the exact time of preceding glucocorticoid administration is not helpful in monitoring glucocorticoid replacement. Some researchers have suggested regular measurements of serum cortisol day curves during replacement therapy, aiming at serum cortisol concentrations within the normal range.[126,128] However, due to their pharmacokinetic properties, none of the exogenous glucocorticoids currently used is suitable to mimic the diurnal cortisol pattern noted in healthy individuals.

Thus, in the absence of objective variables to measure replacement quality, the doctor has to rely primarily on clinical judgment, taking into account signs and symptoms potentially suggestive of glucocorticoid over-replacement or under-replacement (table). Under-replacement bears the risk of incipient crisis and severe

Panel 5: **Replacement regimen and treatment surveillance in chronic adrenal insufficiency**

Glucocorticoid replacement
- Hydrocortisone 15–25 mg daily (or cortisone acetate 25·0–37·5 mg)
- Given in two to three doses with half to two-thirds of the total dose given in the morning (immediately after rising)
- Surveillance: history of glucocorticoid dose adjustment and potential adverse events, including any crisis since last visit bodyweight, signs and symptoms suggestive of over-replacement or under-replacement, and ability to cope with daily stress (optional, fasting glucose)

Mineralocorticoid replacement (only in primary adrenal insufficiency)
- Fludrocortisone 0·05–0·2 mg daily taken as one dose in the morning
- Surveillance: blood pressure, peripheral oedema, serum sodium, serum potassium, plasma renin activity

Dehydroepiandrosterone replacement (optional)
- Dehydroepiandrosterone 25–50 mg daily taken as one dose in the morning
- Surveillance: serum dehydroepiandosterone sulphate, in women also free testosterone (or total testosterone and sex-hormone binding globulin)

Additional monitoring requirements
- Primary adrenal insufficiency: thyrotropin (in patients with autoimmune adrenalitis)
- Secondary adrenal insufficiency: monitoring of underlying hypothalamic-pituitary disease, including replacement of other axes
- Yearly outpatient visits in a specialised centre
- Verification of steroid emergency card or bracelet
- Reinstruction of patient on stress-related glucocorticoid dose adjustment

impairment of wellbeing. Conversely, chronic over-replacement can lead to substantial morbidity, including impaired glucose tolerance,[129] obesity, and osteoporosis.[130,131] With recommended replacement doses of 15–25 mg hydrocortisone osteoporosis is not to be expected.[132] Therefore, bone-mineral-density measurements are not required for regular monitoring in adrenal insufficiency.

Mineralocorticoid replacement (only required in primary adrenal insufficiency) consists of oral administration of 0·05–0·2 mg fludrocortisone. Monitoring includes measurement of blood pressure, serum sodium, and potassium and plasma renin activity, aiming at concentrations within the middle or upper normal range (panel 5).[68] If primary hypertension develops during the long-term course of adrenal insufficiency, mineralocorticoid replacement can be gradually reduced, accompanied by monitoring of serum sodium and potassium. Glucocorticoids also contribute to the mineralocorticoid pool, since they bind to the mineralocorticoid receptor. However, excessive binding is prevented by 11β-hydroxysteroid dehydrogenase type 2, which inactivates cortisol to cortisone. With respect to mineralocorticoid potency, 20 mg hydrocortisone is equivalent to 0·05 mg fludrocortisone.[68]

Replacement of dehydroepiandrosterone has positive effects on wellbeing and mood in patients with primary and secondary adrenal insufficiency.[69,70,133] Treatment is hampered by the lack of pharmaceutically controlled preparations and larger-scale studies are underway. In the meantime, dehydroepiandrosterone should be reserved for patients whose wellbeing is greatly impaired despite optimimum glucocorticoid and mineralocorticoid replacement. Doses of 25–50 mg dehydroepiandrosterone should be taken as one dose in the morning. Treatment surveillance should include measurement of serum dehydroepiandrosterone sulphate, aiming at the middle normal range for healthy young people (panel 5). Dose recommendations for elderly patients with adrenal insufficiency, who would physiologically experience an age-associated decline in serum dehydroepiandrosterone sulphate, remain to be established.

Prevention and management of adrenal crisis

In a series of 53 patients with chronic adrenal insufficiency, representing 511 replacement-years, we noted an overall risk of adrenal crisis needing hospital admission of 3·3 per 100 years. Risk of crisis was much higher in primary adrenal insufficiency (3·8 per 100 *vs* 2·5 per 100 years) and in women (4·4 per 100 *vs* 1·6 per 100 years) with the highest overall risk in women with autoimmune adrenalitis (6·5 per 100 years). Most crises were due to glucocorticoid dose reduction or lack of stress-related dose adjustment by patients or family practitioners. Inappropriate stress-related glucocorticoid adjustment occurs more often in patients older than age 60 years.[134] All patients and their partners should receive regular crisis prevention training, including verification of steroid emergency card or bracelet and instruction on stress-related glucocorticoid dose adjustment. Patients should add 5–10 mg hydrocortisone to their normal regimen shortly before strenuous activities—eg, hiking. More severe physical stress such as fever requires doubling of daily doses until recovery. In instances of vomiting or diarrhoea, glucocorticoids should be administered parenterally. Some doctors advocate a hydrocortisone emergency supply for rectal or parenteral self-administration.[135,136] For major surgery, trauma, and diseases that require monitoring in intensive care, patients should receive intravenous infusions of 100–150 mg hydrocortisone in 5% glucose per 24 h. Results of some studies[137,138] advocate lower doses (25–75 mg per 24 h) for minor or moderate surgical stress.

Management of acute adrenal crisis consists of immediate intravenous administration of 100 mg hydrocortisone followed by 100–200 mg per 24 h and continuous infusion of larger volumes of physiological saline solution (initially 1 L/h) under continuous cardiac monitoring. With daily hydrocortisone doses of 50 mg or more, mineralocorticoid replacement in primary adrenal insufficiency can be reduced because this dose is equivalent to 0·1 mg fludrocortisone.[68] In case of newly diagnosed (or suspected) adrenal insufficiency, treatment must not be delayed by diagnostic work-up. Baseline blood samples for ascertainment of cortisol and ACTH (optional: plasma renin activity, aldosterone, dehydroepiandrosterone sulphate) should be drawn immediately before hydrocortisone administration.

Special therapeutic situations

Thyroid dysfunction

Hyperthyroidism increases cortisol clearance.[120] In patients with adrenal insufficiency and unresolved hyperthyroidism, glucocorticoid replacement should be doubled or tripled. To avoid adrenal crisis, thyroxine replacement for hypothyroidism should only be initiated after concomitant glucocorticoid deficiency has either been excluded or treated.

Pregnancy

Pregnancy is physiologically associated with a gradual increase in cortisol-binding globulin and, during the last term, also in free cortisol.[139] Serum progesterone concentrations also increase, exerting antimineralocorticoid action. Therefore, during the third trimester, hydrocortisone replacement should be increased by 50%. Mineralocorticoids should be adjusted according to blood pressure and serum potassium. Plasma renin activity cannot be used in monitoring because it physiologically increases during pregnancy.[140] Peripartum hydrocortisone replacement should follow the requirements for major surgery—ie, 100 mg per 24 h starting with labour and continuing until 48 h after delivery, followed by rapid tapering.

Drug interactions

Treatment of tuberculosis with rifampicin increases cortisol clearance[141] but does not affect aldosterone clearance.[142] Thus, glucocorticoid replacement should be doubled during rifampicin treatment.

Mitotane decreases bioavailable glucocorticoid concentrations because of an increase in cortisol-binding globulin and enhanced glucocorticoid metabolism. During chronic mitotane treatment—eg, in adrenal carcinoma—usual glucocorticoid replacement doses should, therefore, be doubled or tripled.[35]

Quality of life, disablility, and prognosis

Prospective data[10] indicate excess mortality in hypopituitarism, including secondary adrenal insufficiency, mainly due to vascular and respiratory disease. However, deficiencies of other hormonal axes could also contribute. Mortality in patients with primary adrenal insufficiency has not been studied. Nevertheless, life expectancy may be reduced as a consequence of unrecognised adrenal crisis, underlying illness—eg, adrenomyeloneuropathy—and other as yet unidentified causes.[4]

Despite adequate glucocorticoid and mineralocorticoid replacement, health-related quality of life is greatly impaired in patients with primary[65] and secondary adrenal insufficiency.[143] Predominant complaints are fatigue, lack of energy, depression, and anxiety.[65,69,70] In addition, affected women frequently complain about impaired libido. In a survey of 91 individuals, 50% of patients with primary adrenal insufficiency considered themselves unfit to work and 30% needed household help.[144] In another survey of 88 individuals the number of patients who received disablility pensions was two to three times higher than in the general population.[65] The adverse effect of chronic adrenal insufficiency on health-related quality of life is comparable to that of congestive heart failure.[65] However, fine-tuning of glucocorticoid replacement leaves only a narrow margin for improvement, and changes in timing or dose do not result in improved wellbeing.[145,146] Dehydroepiandrosterone replacement in adrenal insufficiency can improve wellbeing, mood,[69,70,133] and—in women—libido,[69] and opens up the prospect of improving quality of life for patients with chronic adrenal insufficiency.

Conflict of interest statement

W Arlt and B Allolio serve as consultants to Paladin Labs, Montreal, Canada, and to Euphar Corporation, Piacenza, Italy, which are both involved in the development of a pharmaceutically controlled dehydroepiandrosterone preparations.

Acknowledgments

W Arlt is a DFG Heisenberg Senior Clinical Fellow (Ar 310/3-1) and B Allolio is the recipient of DFG project grant Al 293/7-4. The funding source had no role in the writing of this Seminar.

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