Review Article

Adrenal Insufficiency - Aetiology, Diagnosis and Treatment

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Abstract

Adrenal insufficiency is caused by either primary adrenal failure or by hypothalamic-pituitary impairment of the corticotropic axis. Adrenal insufficiency, first codified in 1855 by Thomas Addison, remains relevant in 2014 because of its lethal nature. Though, it is a rare disease but is life threatening when overlooked. Main presenting symptoms such as fatigue, anorexia and weight loss are nonspecific, thus diagnosis is often delayed. The diagnostic work-up is well established but some pitfalls remain. The diagnosis is adequately established by the 250 µg ACTH (adrenocorticotropic hormone) stimulation test in most cases. Glucocorticoids provide life saving treatment but long-term quality of life is impaired, perhaps because therapy is not given in a physiologic way. Dehydroepiandrosterone-replacement therapy has been introduced that could help to restore quality of life. It may be useful in pubertal girls, but not in adults. Monitoring of glucocorticoid-replacement is difficult due to 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.

Search strategy

We searched Medline and PubMed for reviews and original articles related to adrenal insufficiency.

Keywords used included adrenal insufficiency and incidence, prevalence, cause, origin, diagnosis, function test, imaging, hydrocortisone, glucocorticoid, mineralocorticoid, dehydroepiandrosterone, management, treatment, therapy, replacement, crisis, quality of life, well-being, pregnancy, prognosis, morbidity and mortality.

Keywords: *Adrenal insufficiency; glucocorticoid.*

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Introduction

The cardinal clinical symptoms of adrenocortical insufficiency, as first described by Thomas Addison in 1855,[1] include weakness, fatigue, anorexia and abdominal pain, with orthostatic hypotension, salt craving and characteristic hyper pigmentation of the skin occurring with primary adrenal failure. The acute syndrome constitutes a medical emergency since it may result in a severe hypotensive crisis and clouded sensorium, together with pain in the muscles, joints or abdomen and fever.[2,3] However, life saving glucocorticoid replacement therapy for the

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condition did not become available until 1949, when Kendall, Sarett, and Reichstein first synthesized cortisone. Furthermore, despite this breakthrough, there are still many advances and challenges with respect to the management of individuals with adrenal insufficiency.[2]

Epidemiology

There are two types of adrenal insufficiency, primary and secondary. Chronic primary adrenal insufficiency has a prevalence of 93-140 per million worldwide and an incidence of 4.7-6.2 per million in white populations.[4-7] These recent numbers are higher than those reported during the 1960s and 1970s,[4,5] despite a continuous decline in tuberculous adrenalitis in the developed world that suggests an increase in incidence of autoimmune adrenalitis.[6,7] The age at diagnosis peaks in the fourth decade of life, with women more frequently being affected than men.[4-7] Secondary adrenal insufficiency has an estimated prevalence of 150-280 per million and also affects women more frequently than men.[6,8-11] Age at diagnosis peaks in the sixth decade of life.[7,8] Therapeutic glucocorticoid administration is thought to be the most common cause of secondary adrenal insufficiency. However, iatrogenic adrenal insufficiency becomes potentially relevant only during or after glucocorticoid withdrawal. Because iatrogenic adrenal insufficiency is transient in most cases,[12] we suspect its prevalence to be lower than that of endogenous adrenal insufficiency.

Cause

Primary adrenal insufficiency -

During the times of Thomas Addison, tuberculous adrenalitis was by far the most prevalent cause of adrenal insufficiency. In the developing world, it remains a major factor.[13] In active tuberculosis, the incidence of adrenal involvement is 5%.[14]

In primary adrenal insufficiency (AI), there is failure of production of all hormones from the adrenal cortex. It is most often caused by autoimmune destruction in developed countries (Table I).[5,6] Adrenal insufficiency may occur alone, with other autoimmune diseases (polyglandular autoimmune syndrome type 2 and polygenic inheritance) or with hypoparathyroidism and mucocutaneous candidiasis (polyglandular autoimmune syndrome type 1) due to autosomal recessive inheritance of mutations in the autoimmune regulator (AIRE) gene.[15]

Table I: Causes of primary adrenal insufficiency

Cause	Frequency
Autoimmune destruction	1 in 10,000 [5,6]
Congenital adrenal hyperplasia	1 in 15,000 [16]
X-linked adrenoleukodystrophy	1 in 20,000 men[17]
Drugs inhibiting steroidogenesis	
Infectious	
Hemorrhagic	

Autoimmune polyglandular syndrome (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.[18,19] Autoimmune polyglandular syndrome 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. Autoimmune polyglandular syndrome type 2 occurs with autosomal-dominant inheritance with incomplete penetrance, and shows a strong association with HLADR3[18,20] and CTLA-4 (cytotoxic T lymphocyte antigen-4).[21,22] 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.[23]

Adrenoleukodystrophy (ALD) is an X-linked recessive disorder caused by mutations in the ABCD1 gene, resulting in defective oxidation of very long chain fatty acids (VLCFAs) and membrane and organelle dysfunction.[17] The clinical features include spastic paralysis and

primary AI which may present in infancy or childhood. The milder ALD phenotype typically presents in adolescence or early adulthood. Other causes of primary adrenal insufficiency e.g. adrenal infiltration or haemorrhage are rare. Congenital or neonatal primary adrenal insufficiency accounts for only 1% of all cases.[24]

Secondary adrenal insufficiency -

The most frequent causes of secondary adrenal insufficiency are hypothalmic-pituitary-adrenal (HPA) axis suppression by chronic glucocorticoid therapy, tumour growth or treatment with surgery or irradiation of the hypothalamic-pituitary region. The condition if often associated with panhypopituitarism. Autoimmune lymphocytic hypophysitis is less frequent, mostly affecting women during or shortly after pregnancy. The differential diagnosis of postpartum autoimmune hypophysitis includes Sheehan's syndrome, which results from pituitary apoplexy, mostly due to pronounced blood loss during delivery.[25]

Pathophysiology and clinical presentation

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.[26] 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.[27]

Patients with acute adrenal insufficiency - i.e. 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.[28] 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.

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 (failure to thrive in children), and can account for muscle and joint 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.[28] In secondary adrenal insufficiency; diagnosis is generally prompted by a history of steroid intake or pituitary disease, but often delayed e.g. 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 e.g. palmar creases, knuckles, scars and oral mucosa.

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.[29]

Mineralocorticoid deficiency, which is present only in primary adrenal insufficiency, leads to dehydration and hypovolaemia, resulting in low blood pressure, postural hypotension, and sometimes even in pre renal 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[30] and reverses cardiac dysfunction.[31] Glucocorticoids contribute to this

improvement not only by mineralocorticoid receptor binding, but also by permissive effects on catecholamine action.[32] Mineralocorticoid deficiency accounts for hyponatraemia (90% of patients with primary adrenal insufficiency), hyperkalaemia (65%), and salt craving (15%).[4,33] 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.[34] 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.[27] Thus dehydroepiandrosterone deficiency could contribute to the impairment of wellbeing noted in patients with adrenal insufficiency despite adequate glucocorticoid and mineralocorticoid replacement.[35]

Diagnosis

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.[36]

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.[37] 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.[37] The impaired ability of the adrenal cortex to respond to ACTH is readily demonstrated by the standard short corticotropin test.[38]

Traditionally, AI is diagnosed biochemically by measuring serum cortisol before[30,45] and/or 60 minutes after intravenous administration of 250 μg synthetic ACTH. Any value ≥ 18 μg/dL usually defines a normal response.[39] It has been suggested that ACTH stimulation testing could also lack sensitivity in chronic secondary adrenal insufficiency, because it achieves supra-physiological levels of ACTH. Instead, a 1 μg dose was proposed and initially was reported to perform similarly to the 250 μg test.[40] Such low specificity may lead to unnecessary lifelong glucocorticoid replacement. Moreover, there is more experience regarding marginal test responses to the 250 μg dose.[41,42] Therefore, we currently favor the use of the 250 μg ACTH stimulation test for diagnosis. Adrenal cortex auto antibodies or antibodies against 21-hydroxylase are present in more than 80% of patients with recent onset autoimmune adrenalitis.[43]

Secondary adrenal insufficiency-

Baseline hormone measurements differ little between patients with secondary adrenal insufficiency and healthy individuals.[24,37] 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 HPA axis.[44-46] Thus, in most instances, dynamic tests of the hypothalmicpituitary- adrenal axis are required to establish a diagnosis of secondary adrenal insufficiency. The insulin tolerance test[47] 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.[48] An intact axis is indicated by a peak cortisol of more than 500 nmol/L at any time during the test.[49,50] Occasionally, however, a patient will pass the insulin tolerance test despite exhibiting clinical evidence for adrenal insufficiency that responds to hydrocortisone substitution.[51] A higher cut-off value (550 nmol/L) for peak cortisol in the insulin tolerance test could help to reduce

misclassification.[50,52] During the test, close supervision is mandatory[48] and cardiovascular disease or history of seizures are contraindications. Sustained secondary adrenal insufficiency leads to adrenal atrophy and also to reduce ACTH receptor expression in the adrenal gland, since ACTH up-regulates its own receptor.[53] 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. Since the administration of 250 µg 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.[54-57] The test has been successfully used to monitor recovery of adrenal function after withdrawal of oral glucocorticoids[12] and to detect subtle impairment of adrenal reserve during inhaled steroid therapy.[58,59] However, the intravenous administration of 1 µg ACTH still results in hormone concentrations greater than those required for maximum cortisol release.[60]

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,[46,61] 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, and withheld for 24 h before scheduled testing of adrenal function.[62]

Adrenal insufficiency in critically ill patients

In critically ill patients, the corticotropic axis is greatly activated.[63,64] 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.[65] Critically ill patients also have fairly low serum concentrations of aldosterone with concurrently raised plasma renin activity.[66]

Unfortunately, no consensus exists about how to diagnose adrenal insufficiency in these individuals.[67] 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).[67-69]

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,[70] whereas calcifications develop during later stages.[71] 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.[71]

Treatment

Current recommendations for oral replacement doses of hydrocortisone are lower at 10-12 mg/m^2 BSA, although many patients receive higher equivalent doses.[72] 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, equivalent to the oral administration of 15-25 mg hydrocortisone (cortisol) or 25.0-37.5 mg cortisone acetate.[73-78] Initial glucocorticoid treatment provides great symptomatic improvement in AI. However patients taking chronic adrenal hormone replacement report reduced quality of life (QOL) compared with healthy controls.[79] Possible explanations include non physiological glucocorticoid replacement and lack of adrenal androgen replacement. The observation that patients with primary and secondary adrenal insufficiency experience similar impairments[79] suggests that inappropriate mineralocorticoid replacement is unlikely to be the cause.

Normally cortisol levels peak before waking and fall to a nadir during night time sleep.[80] However, even three daily doses of hydrocortisone cannot approximate this rhythm, and a recent study reported no differences in QOL between two or three daily doses.[81] Another option is to use a longer acting glucocorticoid, such as prednisolone or prednisone, in a more convenient single morning dose. However, no differences in QOL were reported between patients taking hydrocortisone or prednisolone.[82] 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.[83]

Dehydroepiandrosterone (DHEA) replacement continues to be controversial, with conflicting reports regarding QOL.[83,84] Some postulate that DHEA insufficiency explains the impaired QOL in AI, particularly in women. Healthy men derive most androgens from the testes so that the androgenic effects of DHEA are presumably less important.[83,84] 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.[37]

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.[85,86] 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. Under replacement bears the risk of incipient crisis and severe impairment of wellbeing. Conversely, chronic over replacement can lead to substantial morbidity, including impaired glucose tolerance,[87] obesity, and osteoporosis.[88,89] With recommended replacement doses of 15-25 mg hydrocortisone osteoporosis is not to be expected. Therefore, bone-mineral-density measurements are not required for regular monitoring in adrenal insufficiency.[90]

Critical illness

Part of the physiological response to critical illness is an increase in serum cortisol. To mimic this increase, patients with AI are advised to double or even triple their glucocorticoids dose for febrile illness and are usually given at least 200 mg hydrocortisone parenterally on the day of major surgery.[91]

Prevention and management of adrenal crisis

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.[92] 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 e.g., 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.[93,94] 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. 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.[37]

Special therapeutic situations -

Thyroid dysfunction

Hyperthyroidism increases cortisol clearance. 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.[78]

Pregnancy

Pregnancy is physiologically associated with a gradual increase in cortisol-binding globulin and, during the last term, also in free cortisol. 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. Peripartum hydrocortisone replacement should follow the requirements for major surgery - i.e., 100 mg per 24 h starting with labour and continuing until 48 h after delivery, followed by rapid tapering.[95]

Conclusion

Prospective data 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.[11] Despite adequate glucocorticoid and mineralocorticoid replacement, health-related quality of life is greatly impaired in patients with primary[35] and secondary adrenal insufficiency.[96] Predominant complaints are fatigue, lack of energy, depression, and anxiety.[35,97] In addition, affected women frequently complain about impaired libido. 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.[98,99] Dehydroepiandrosterone replacement in adrenal insufficiency can improve wellbeing, mood,[97,100] and - in women - libido,[99] and opens up the prospect of improving quality of life for patients with chronic adrenal insufficiency. In critical illness, glucocorticoids may reverse hemodynamic shock independent of adrenal function but do not improve mortality.

References

1. Addison T. On the Constitutional and Local Effects of Disease of the Supra-Renal Capsules. London: Samuel Highley; 1855.
2. Arlt W, Allolio B. Adrenal Insufficiency. Lancet. 2003;361:1881-93.
3. Oelkers W. Adrenal Insufficiency. N Engl J Med. 1996;335:1206-12.

4. Kong MF, Jeffcoate W. Eighty-Six Cases of Addison's Disease. Clin Endocrinol (Oxf). 1994;41:757-61.

5. Willis AC, Vince FP. The Prevalence of Addison's Disease in Coventry, UK. Postgrad Med J. 1997;73:286-88.

6. Laureti S, Vecchi L, Santeusanio F, Falorni A. Is the Prevalence of Addison's Disease Underestimated? J Clin Endocrinol Metab. 1999;84:1762.

7. Lovas K, Husebye ES. High Prevalence and Increasing Incidence of Addison's Disease in Western Norway. Clin Endocrinol (Oxf). 2002;56:787-91.

8. Bates AS, Van't Hoff W, Jones PJ, Clayton RN. The Effect of Hypopituitarism on Life Expectancy. J Clin Endocrinol Metab. 1996;81:1169-72.

9. Nilsson B, Gustavasson-Kadaka E, Bengtsson BA, Jonsson B. Pituitary Adenomas in Sweden Between 1958 and 1991: Incidence, Survival, and Mortality. J Clin Endocrinol Metab. 2000;85:1420-25.

10. Regal M, Paramo C, Sierra SM, Garcia-Mayor RV. Prevalence and Incidence of Hypopituitarism in an Adult Caucasian Population in Northwestern Spain. Clin Endocrinol (Oxf). 2001;55:735-40.

11. Tomlinson JW, Holden N, Hills RK, Wheatley K, Clayton RN, Bates AS, et al. Association between Premature Mortality and Hypopituitarism. Lancet. 2001;357:425-31.

12. Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and Recovery of Adrenal Response after Short-Term, High-Dose Glucocorticoid Treatment. Lancet. 2000;355:542-45.

13. Soule S. Addison's Disease in Africa: A Teaching Hospital Experience. Clin Endocrinol (Oxf). 1999;50:115-20.

14. Lam KY, Lo CY. A Critical Examination of Adrenal Tuberculosis and a 28-Year Autopsy Experience of Active Tuberculosis. Clin Endocrinol (Oxf). 2001;54:633-39.

15. Wolff AS, Erichsen MM, Meager A, Magitta NF, Myhre AG, Bollerslev J, et al. Autoimmune Polyendocrine Syndrome Type 1 in Norway: Phenotypic Variation, Autoantibodies, and Novel Mutations in the Autoimmune Regulator Gene. J Clin Endocrinol Metab. 2007;92:595-603.

16. Merke DP, Bornstein SR. Congenital Adrenal Hyperplasia. Lancet. 2005;365:2125-36.

17. Mosser J, Douar AM, Sarde CO, Kioschis P, Feil R, Moser H, et al. Putative X-linked Adrenoleukodystrophy Gene Shares Unexpected Homology with ABC Transporters. Nature. 1993;361:726-30.

18. Betterle C, Dal Pra C, Mantero F, Zanchetta R. Autoimmune Adrenalinsufficiency and Autoimmune Polyendocrine Syndromes: Autoantibodies, Autoantigens, and Their Applicability in Diagnosis and Disease Prediction. Endocr Rev. 2002;23:327-64.

19. Ahonen P, Myllarniemi S, Sipila I, Perheentupa J. Clinical Variation of Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal Dystrophy (APECED) in a Series of 68 Patients. N Engl J Med. 1990;322:1829-36.

20. Weetman AP. Autoimmunity to Steroid-Producing Cells and Familial Polyendocrine Autoimmunity. Baillieres Clin Endocrinol Metab. 1995;9:157-74.

21. Donner H, Braun J, Seidl C, Rau H, Finke R, Ventz M, et al. Codon 17 Polymorphism of the Cytotoxic T Lymphocyte Antigen 4 Gene in Hashimoto's Thyroiditis and Addison's Disease. J Clin Endocrinol Metab. 1997;82:4130-32.

22. Kemp EH, Ajjan RA, Husebye ES, Peterson P, Uibo R, Imrie H, et al. A Cytotoxic T Lymphocyte Antigen-4 (Ctla-4) Gene Polymorphism is Associated with Autoimmune Addison's Disease in English Patients. Clin Endocrinol (Oxf). 1998;49:609-13.

23. Kasznicki J, Żurawska-Kliś M, Drzewoski J. Autoimmune Polyglandular Syndrome Type 3 Associated with Autoimmune Thyroiditis (Hashimoto's Disease), Type 1 Diabetes Mellitus, Vitiligo and Autoimmune Urticaria: A Case Report. Diabetologia Doświadczalna i Kliniczna. 2011;11(2):96-100.

24. Moser HW. Adrenoleukodystrophy: Phenotype, Genetics, Pathogenesis and Therapy. Brain. 1997;120:1485-508.

25. Kasperlik-Zaluska AA, Czarnocka B, Czech W, Walecki J, Makowska AM, Brzeziński J, et al. Secondary Adrenal Insufficiency Associated with Autoimmune Disorders: A Report of Twenty-Five Cases. Clin Endocrinol (Oxf). 1998;49:779-83.

26. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-Four Hour Pattern of the Episodic Secretion of Cortisol in Normal Subjects. J Clin Endocrinol Metab. 1971;33:14-22.

27. Allolio B, Arlt W. DHEA Treatment: Myth or Reality? Trends Endocrinol Metab. 2002;13:288.

28. Zelissen PM. Addison Patients in the Netherlands: Medical Report of the Survey. The Hague: Dutch Addison Society; 1994.

29. Hangaard J, Andersen M, Grodum E, Koldkjaer O, Hagen C. Pulsatile Thyrotropin Secretion in Patients with Addison's Disease during Variable Glucocorticoid Therapy. J Clin Endocrinol Metab. 1996;81:2502-507.

30. Fallo F, Fanelli G, Cipolla A, Betterle C, Boscaro M, Sonino N. 24-hour Blood Pressure Profile in Addison's Disease. Am J Hypertens. 1994;7:1105-109.

31. Fallo F, Betterle C, Budano S, Lupia M, Boscaro M, Sonino N. Regression of Cardiac Abnormalities after Replacement Therapy in Addison's Disease. Eur J Endocrinol. 1999;140:425-28.

32. Allolio B, Ehses W, Steffen HM, Muller R. Reduced Lymphocyte Beta 2-Adrenoceptor Density and Impaired Diastolic Left Ventricular Function in Patients with Glucocorticoid Deficiency. Clin Endocrinol (Oxf). 1994;40:769-75.

33. Nerup J. Addison's Disease: Clinical Studies - A Report of 108 Cases. Acta Endocrinol (Copenh). 1974;76:127-41.

34. Oelkers W. Hyponatremia and Inappropriate Secretion of Vasopressin (Antidiuretic Hormone) in Patients with Hypopituitarism. N Engl J Med. 1989;321:492-96.

35. Lovas K, Loge JH, Husebye ES. Subjective Health Status in Norwegian Patients with Addison's Disease. Clin Endocrinol (Oxf). 2002;56:581-88.

36. Clark PM, Neylon I, Raggatt PR, Sheppard MC, Stewart PM. Defining the Normal Cortisol Response to the Short Synacthen Test: Implications for the Investigation of Hypothalamic-Pituitary Disorders. Clin Endocrinol (Oxf). 1998;49:287-92.

37. Oelkers W, Diederich S, Bahr V. Diagnosis and Therapy Surveillance in Addison's Disease: Rapid Adrenocorticotropin (ACTH) Test and Measurement of Plasma ACTH, Renin Activity, and Aldosterone. J Clin Endocrinol Metab. 1992;75:259-64.

38. Wood JB, James VHT, Frankland AW, Landon J. A Test of Adrenocortical Function. Lancet. 1965;1:243-45.

39. Speckart PF, Nicoloff JT, Bethune JE. Screening for Adrenocortical Insufficiency with Cosyntropin (Synthetic ACTH). Arch Intern Med. 1971;128:761-63.

40. Dorin RI, Qualls CR, Crapo LM. Diagnosis of Adrenal Insufficiency. Ann Intern Med. 2003;139:194-204.

41. Stewart PM, Clark PM. The Low-Dose Corticotropin-Stimulation Test Revisited: The Less, The Better? Nat Clin Pract Endocrinol Metab. 2009;5:68-69.

42. Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM. The Long-Term Predictive Accuracy of the Short Synacthen (Corticotropin) Stimulation Test for Assessment of the Hypothalamic-Pituitary-Adrenal Axis. J Clin Endocrinol Metab. 2006;91:43-47.

43. Betterle C, Volpato M, Pedini B, Chen S, Smith BR, Furmaniak J. Adrenal-Cortex Autoantibodies and Steroid-Producing Cells Autoantibodies in Patients with Addison's Disease: Comparison of Immunofluorescence and Immunoprecipitation Assays. J Clin Endocrinol Metab. 1999;84:618-22.

44. Stewart PM, Corrie J, Seckl JR, Edwards CR, Padfield PL. A Rational Approach for Assessing the Hypothalamo-Pituitary-Adrenal Axis. Lancet. 1988;1:1208-10.

45. Hagg E, Asplund K, Lithner F. Value of Basal Plasma Cortisol Assays in the Assessment of Pituitary-Adrenal Insufficiency. Clin Endocrinol (Oxf). 1987;26:221-26.

46. Watts NB, Tindall GT. Rapid Assessment of Corticotropin Reserve After Pituitary Surgery. JAMA. 1988;259:708-11.

47. Landon J, Greenwood FC, Stamp TCB, Wynn V. The Plasma Sugar, Free Fatty Acid, Cortisol, and Growth Hormone Response to Insulin and the Comparison of this Procedure with Other Tests of Pituitary and Adrenal Function. II. In Hypothalamic or Pituitary Dysfunction or Anorexia Nervosa. J Clin Invest. 1966;45:437-48.

48. Grinspoon SK, Biller BM. Clinical Review 62: Laboratory Assessment of Adrenal Insufficiency. J Clin Endocrinol Metab. 1994;79:923-31.

49. Nelson JC, Tindall DJ Jr. A Comparison of the Adrenal Responses to Hypoglycemia, Metyrapone and ACTH. Am J Med Sci. 1978;275:165-72.

50. Tuchelt H, Dekker K, Bahr V, Oelkers W. Dose-Response Relationship between Plasma ACTH and Serum Cortisol in the Insulin hypoglycaemia Test in 25 Healthy Subjects and 109 Patients with Pituitary Disease. Clin Endocrinol (Oxf). 2000;53:301-307.

51. Tsatsoulis A, Shalet SM, Harrison J, Ratcliffe WA, Beardwell CG, Robinson EL. Adrenocorticotrophin (ACTH) Deficiency Undetected by Standard Dynamic Tests of the Hypothalamic-Pituitary-Adrenal Axis. Clin Endocrinol (Oxf). 1988;28:225-32.

52. Stewart PM, Clark PM, Sheppard MC. Comparison of the Short ACTH Stimulation Test with the Insulin Tolerance/Glucagon Test. Clin Endocrinol (Oxf). 1998;48:124-26.

53. Lebrethon MC, Naville D, Begeot M, Saez JM. Regulation of Corticotropin Receptor Number and Messenger RNA in Cultured Human Adrenocortical Cells by Corticotropin and Angiotensin II. J Clin Invest. 1994;93:1828-33.

54. Dickstein G, Shechner C, Nicholson WE, Rosner I, Shen-Orr Z, Adawi F, et al. Adrenocorticotropin Stimulation Test: Effects of Basal Cortisol Level, Time of Day, and Suggested New Sensitive Low Dose Test. J Clin Endocrinol Metab. 1991;72:773-78.

55. Tordjman K, Jaffe A, Grazas N, Apter C, Stern N. The Role of the Low Dose (1 Microgram) Adrenocorticotropin Test in the Evaluation of Patients with Pituitary Diseases. J Clin Endocrinol Metab. 1995;80:1301-305.

56. Thaler LM, Blevins LS Jr. The Low Dose (1-Microg) Adrenocorticotropin Stimulation Test in the Evaluation of Patients with Suspected Central Adrenal Insufficiency. J Clin Endocrinol Metab. 1998;83:2726-29.

57. Tordjman K, Jaffe A, Trostanetsky Y, Greenman Y, Limor R, Stern N. Low-Dose (1 Microgram) Adrenocorticotrophin (ACTH) Stimulation as a Screening Test for Impaired Hypothalamo-Pituitaryadrenal Axis Function: Sensitivity, Specificity and Accuracy in Comparison with the High-Dose (250 Microgram) Test. Clin Endocrinol (Oxf). 2000;52:633-40.

58. Broide J, Soferman R, Kivity S, Golander A, Dickstein G, Spirer Z, et al. Low-Dose Adrenocorticotropin Test Reveals Impaired Adrenal Function in Patients Taking Inhaled Corticosteroids. J Clin Endocrinol Metab. 1995;80:1243-46.

59. Kannisto S, Korppi M, Remes K, Voutilainen R. Adrenal Suppression, Evaluated by a Low Dose Adrenocorticotropin Test, and Growth in Asthmatic Children Treated with Inhaled Steroids. J Clin Endocrinol Metab. 2000;85:652-57.

60. Mayenknecht J, Diederich S, Bahr V, Plockinger U, Oelkers W. Comparison of Low and High Dose Corticotropin Stimulation Tests in Patients with Pituitary Disease. J Clin Endocrinol Metab. 1998;83:1558-62.

61. Auchus RJ, Shewbridge RK, Shepherd MD. Which Patients Benefit from Provocative Adrenal Testing after Transsphenoidal Pituitary Surgery? Clin Endocrinol (Oxf). 1997;46:21-27.

62. Inder WJ, Hunt PJ. Glucocorticoid Replacement in Pituitary Surgery: Guidelines for Perioperative Assessment and Management. J Clin Endocrinol Metab. 2002;87:2745-50.

63. Drucker D, McLaughlin J. Adrenocortical Dysfunction in Acute Medical Illness. Crit Care Med. 1986;14:789-91.

64. Lamberts SW, Bruining HA, de Jong FH. Corticosteroid Therapy in Severe Illness. N Engl J Med. 1997;337:1285-92.

65. Reincke M, Allolio B, Wurth G, Winkelmann W. The Hypothalamicpituitary- Adrenal Axis in Critical Illness: Response to Dexamethasone and Corticotropin-Releasing Hormone. J Clin Endocrinol Metab. 1993;77:151-56.

66. Findling JW, Waters VO, Raff H. The dissociation of renin and aldosterone during critical illness. J Clin Endocrinol Metab. 1987; 64: 592–95.

67. Beishuizen A, Thijs LG. Relative Adrenal Failure in Intensive Care: An Identifiable Problem Requiring Treatment? Best Pract Res Clin Endocrinol Metab. 2001;15:513-31.

68. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol Response to Corticotropin and Survival in Septic Shock. Lancet. 1991;337:582-83.

69. Briegel J, Forst H, Kellermann W, Haller M, Peter K. Haemodynamic Improvement in Refractory Septic Shock with Cortisol Replacement Therapy. Intensive Care Med. 1992;18:318.

70. Kawashima A, Sandler CM, Fishman EK, Charnsangavej C, Yasumori K, Honda H, et al. Spectrum of CT Findings in Nonmalignant Disease of the Adrenal Gland. Radiographics. 1998;18(2):393-412.

71. Sawczuk IS, Reitelman C, Libby C, Grant D, Vita J, White RD. CT Findings in Addison's Disease Caused by Tuberculosis. Urol Radiol. 1986;8:44-45.

72. Erichsen MM, Lovas K, Skinningsrud B, Wolff AB, Undlien DE, Svartberg J, et al. Clinical, Immunological, and Genetic Features of Autoimmune Primary Adrenal Insufficiency: Observations from a Norwegian Registry. J Clin Endocrinol Metab. 2009;94:4882-90.

73. Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, et al. Daily Cortisol Production Rate in Man Determined by Stable Isotope Dilution/Mass Spectrometry. J Clin Endocrinol Metab. 1991;72:39-45.

74. Kerrigan JR, Veldhuis JD, Leyo SA, Iranmanesh A, Rogol AD. Estimation of Daily Cortisol Production and Clearance Rates in Normal Pubertal Males by Deconvolution Analysis. J Clin Endocrinol Metab. 1993;76:1505-510.

75. Kraan GP, Dullaart RP, Pratt JJ, Wolthers BG, Drayer NM, de Bruin R. The Daily Cortisol Production Reinvestigated in Healthy Men: The Serum and Urinary Cortisol Production Rates are Not Significantly Different. J Clin Endocrinol Metab. 1998;83:1247-52.

76. Brandon DD, Isabelle LM, Samuels MH, Kendall JW, Loriaux DL. Cortisol Production Rate Measurement by Stable Isotope Dilution Using Gas Chromatography-Negative Ion Chemical Ionization Mass Spectrometry. Steroids. 1999;64:372-78.

77. Kehlet H, Binder C, Blichert-Toft M. Glucocorticoid Maintenance Therapy Following Adrenalectomy: Assessment of Dosage and Preparation. Clin Endocrinol (Oxf). 1976;5:37-41.

78. Allolio B, Kaulen D, Deuss U, Hipp FX, Winkelmann W. Comparison between Hydrocortisone and Cortisone Acetate as Replacement Therapy in Adrenocortical Insufficiency. Akt Endokr Stoffw. 1985;6:35-39.

79. Hahner S, Loeffler M, Fassnacht M, Weismann D, Koschker AC, Quinkler M, et al. Impaired Subjective Health Status in 256 Patients with Adrenal Insufficiency on Standard Therapy Based on Cross-Sectional Analysis. J Clin Endocrinol Metab. 2007;92(10):3912-22.

80. Weitzman ED, Fukushima D, Nogeire C, Roffwarg H, Gallagher TF, Hellman L. Twenty-Four Hour Pattern of the Episodic Secretion of Cortisol in Normal Subjects. J Clin Endocrinol Metab. 1971;33(1):14-22.

81. Bleicken B, Hahner S, Loeffler M, Ventz M, Decker O, Allolio B, et al. Influence of Hydrocortisone Dosage Scheme on Health Related Quality of Life in Patients with Adrenal Insufficiency. Clin Endocrinol (Oxf). 2010;72(3):297-304.

82. Bleicken B, Hahner S, Loeffler M, Ventz M, Allolio B, Quinkler M. Impaired Subjective Health Status in Chronic Adrenal Insufficiency: Impact of Different Glucocorticoid Replacement Regimens. Eur J Endocrinol. 2008;159:811-17.

83. Arlt W, Callies F, van Vlijmen JC, Koehler I, Reincke M, Bidlingmaier M, et al. Dehydroepiandrosterone Replacement in Women with Adrenal Insufficiency. N Engl J Med. 1999;341:1013-20.

84. Neary N, Nieman L. Adrenal Insufficiency - Etiology, Diagnosis and Treatment. Curr Opin Endocrinol Diabetes Obes. 2010;17(3):217-23.

85. Feek CM, Ratcliffe JG, Seth J, Gray CE, Toft AD, Irvine WJ. Patterns of Plasma Cortisol and ACTH Concentrations in Patients with Addison's Disease Treated with Conventional Corticosteroid Replacement. Clin Endocrinol (Oxf). 1981;14:451-58.

86. Groves RW, Toms GC, Houghton BJ, Monson JP. Corticosteroid Replacement Therapy: Twice or Thrice Daily? J R Soc Med. 1988;81:514-16.

87. al-Shoumer KA, Beshyah SA, Niththyananthan R, Johnston DG. Effect of Glucocorticoid Replacement Therapy on Glucose Tolerance and Intermediary Metabolites in Hypopituitary Adults. Clin Endocrinol (Oxf). 1995;42:85-90.

88. Zelissen PM, Croughs RJ, van Rijk PP, Raymakers JA. Effect of Glucocorticoid Replacement Therapy on Bone Mineral Density in Patients with Addison Disease. Ann Intern Med. 1994;120:207-10.

89. Florkowski CM, Holmes SJ, Elliot JR, Donald RA, Espiner EA. Bone Mineral Density is Reduced in Female but Not Male Subjects with Addison's Disease. N Z Med J. 1994;107:52-53.

90. Braatvedt GD, Joyce M, Evans M, Clearwater J, Reid IR. Bone Mineral Density in Patients with Treated Addison's Disease. Osteoporos Int. 1999;10:435-40.

91. Melby JC, Spink WW. Comparative Studies on Adrenal Cortical Function and Cortisol Metabolism in Healthy Adults and in Patients with Shock Due to Infection. J Clin Invest. 1958;37:1791-98.

92. Flemming TG, Kristensen LO. Quality of Self-Care in Patients on Replacement Therapy with Hydrocortisone. J Intern Med. 1999;246:497-501.

93. Braatvedt GD, Newrick PG, Corrall RJ. Patients' Self Administration of Hydrocortisone. BMJ. 1990;301:1312.

94. de Vroede M, Beukering R, Spit M, Jansen M. Rectal Hydrocortisone during Stress in Patients with Adrenal Insufficiency. Arch Dis Child. 1998;78:544-47.

95. Allolio B, Hoffmann J, Linton EA, Winkelmann W, Kusche M, Schulte HM. Diurnal Salivary Cortisol Patterns During Pregnancy and after Delivery: Relationship to Plasma Corticotrophin-Releasinghormone. Clin Endocrinol (Oxf). 1990;33:279-89.

96. Rosen T, Wiren L, Wilhelmsen L, Wiklund I, Bengtsson BA. Decreased Psychological Well-being in Adult Patients with Growth Hormone Deficiency. Clin Endocrinol (Oxf). 1994;40:111-16.

97. Hunt PJ, Gurnell EM, Huppert FA, Richards C, Prevost AT, Wass JA, et al. Improvement in Mood and Fatigue after Dehydroepiandrosterone Replacement in Addison's Disease in a Randomized, Double Blind Trial. J Clin Endocrinol Metab. 2000;85:4650-56.

98. Riedel M, Wiese A, Schurmeyer TH, Brabant G. Quality of Life in Patients with Addison's Disease: Effects of Different Cortisol Replacement Modes. Exp Clin Endocrinol. 1993;101:106-11.

99. Wichers M, Springer W, Bidlingmaier F, Klingmuller D. The Influence of Hydrocortisone Dubstitution on the Quality of Life and Parameters of Bone Metabolism in Patients with Secondary Hypocortisolism. Clin Endocrinol (Oxf). 1999;50: 759-65.

100. Johannsson G, Burman P, Wiren L, Engström BE, Nilsson AG, Ottosson M, et al. Low Dose Dehydroepiandrosterone Affects Behavior in Hypopituitary Women: a Placebo-Controlled Trial. J Clin Endocrinol Metab. 2002;87:2046-52.