Addison's disease

Challenges in treatment and follow up

Lisanne Cornelia Catharina Jacoba Smans

Cover: Thomas Addison en de bijnier

Het jaar 1855 kan beschouwd worden als een keerpunt in de geschiedenis van de endocrinologie: Claude Bernard (1813-1878) bedacht het moderne concept van de interne hormoonsecretie, en Thomas Addison (1793-1860) – wetenschapper, docent en arts – leverde de eerste echte bijdrage aan de kennis over de fysiologie van de bijnieren.

In 1855 publiceert Thomas Addison zijn beroemde en fraai geïllustreerde monografie: *On the Constitutional and Local Effects of disease of the Suprarenal Capsules.* Dit was de eerste beschrijving van de ziekte die later naar hem vernoemd zou worden. Hij leverde de eerste echte bijdrage aan de kennis van de fysiologie van de bijnieren, na drie eeuwen van vruchteloze speculatie over hun functie. Daarmee is hij een van de grondleggers van de moderne endocrinologie (Bron: History of Medicine)

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Challenges in treatment and follow up

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht op gezag van de rector magnificus, prof. dr. G.J. van der Zwaan, ingevolge het besluit van het college voor promoties in het openbaar te verdedigen op dinsdag 3 februari 2015 des middags te 2.30 uur

door

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geboren op 27 oktober 1980 te Breda, Nederland

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General introduction and outline of the thesis

General introduction

Addison's disease, or primary adrenal insufficiency, is a rare condition. The first report on the incidence of Addison's disease originates from 1960. This population study in the North East Metropolitan Regional Hospital Board area in The United Kingdom reported an incidence of 39 per million. Since then only a few studies have sought to determine the epidemiology of Addison's disease, reporting quite discordant data on incidence and prevalence, ranging between 0.44-0.83 per 100.000 per year and 39-144 per million respectively.[1-11]

Addison's disease has profound impact on virtually every organ and process in the body. The adrenal cortex is the major site of steroid hormone production and these hormones are pivotal for life. The adrenal glands with a combined weight of 8-10 g lie in the retroperitoneum medial to or above the upper poles of the kidneys and are composed of the adrenal cortex and medulla. The adrenal cortex has three zones: an inner zona reticularis, a zona fasciculata and an outer zona glomerulosa. Aldosterone is produced in the zona glomerulosa. The two inner zones produce cortisol and androgens. These hormones have different functions and exert their effects by binding to steroid receptors (figure 1).

Nowadays, auto-immune adrenalitis is the most common cause of primary adrenal insufficiency. Other causes include infections, hemorrhage or infiltration of the adrenal glands. It can also result from a block in steroid production as in congenital adrenal hyperplasia (CAH) or be part of a genetic syndrome.

Adrenal insufficiency gives rise to various (nonspecific) signs and symptoms but can also lead to a life threatening acute adrenal crisis. Although prognosis of Addison's disease has improved considerably after the introduction of synthetic glucocorticoids and mineralocorticoids, this disease still leads to morbidity and mortality, possibly due to the imperfections of current diagnosis, therapy and follow up.

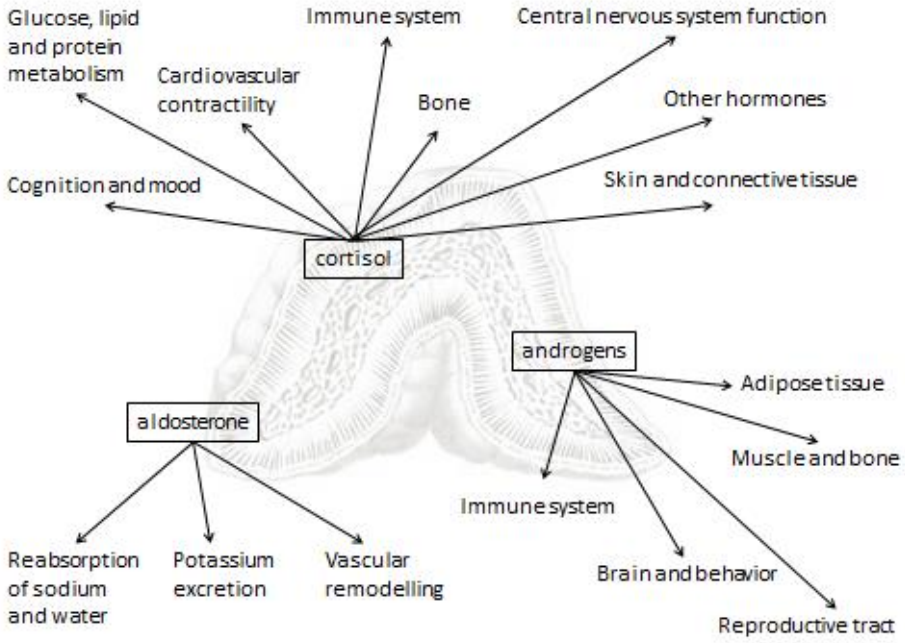

Figure 1 Functions of cortisol, aldosterone and adrenal androgens

Outline of the thesis

This thesis addresses four issues.

The *first* part of this thesis describes the diagnosis and subclassification of adrenal insufficiency. The diagnosis of adrenal insufficiency (AI) is a challenge. Most signs and symptoms are non-specific and vary considerably depending upon the underlying cause and degree of AI. Identification of AI is crucial because the disease may be life-threatening if left unrecognized. **Chapter 1** aims to provide a concise stepwise approach for the diagnostic evaluation of AI, taking into account the possible pitfalls associated with the different tests.

The *second* part of this thesis addresses the treatment of adrenal insufficiency. **Chapter 2** describes the history of glucocorticoid and mineralocorticoid replacement therapy and discusses the current imperfections. In addition, it gives a perspective on future developments and improvements in therapy. In **chapter 3**, our study on the value of salivary

cortisol day curves in optimizing chronic glucocorticoid replacement therapy in Addison's disease is described. The aim of this study was to investigate the use of salivary cortisol day curves in the individual adjustment of therapy, in order to approach normal cortisol levels as closely as possible, reduce over- and under-replacement and study the short term effects on quality of life.

The *third* part of this thesis focuses on several challenges in the follow up of adrenal insufficiency. With the current glucocorticoid replacement therapy restoration of normal physiology cannot be achieved. Periods of over- and under-replacement during the day can occur. We hypothesized that this could have adverse effects on quality of life and in addition could possibly lead to side effects on the long term. In **chapter 4**, the results of our study on quality of life and physical activity in patients with Addison's disease are described. The aim of this study was to explore quality of life and common complaints experienced by patients with Addison's disease in daily life and study factors influencing this quality of life. In addition, we wanted to evaluate the ability of patients with Addison's disease to take part in physical activity because we noted that patients on chronic replacement therapy frequently complain about musculoskeletal pain and fatigue. This seems particularly relevant in these patients, because physical inactivity could result in additional cardiovascular health risks. Previous studies have suggested that infections are an important cause of death in patients with Addison's disease[9-11], but epidemiological studies on the frequency of infections in this population were lacking. Antibiotic prescription patterns and hospital admission for infection in primary adrenal insufficiency are the focus of **chapter 5**. We aimed at studying the incidence of infections among patients with primary adrenal insufficiency and comparing incidence in patients with controls. Furthermore, it has been proposed that excess glucocorticoids can contribute to the metabolic syndrome and cardiovascular disease.[12,13] Patients with Addison's disease have an up to two-fold increased mortality rate from cardiovascular disease.[9,11] Therefore, we studied the prevalence of the metabolic syndrome in patients with Addison's disease (**chapter 6**). Patients with Addison's disease have to increase their glucocorticoid dose in case of illness and severe stress to avert a life threatening adrenal crisis. At present the incidence of adrenal crisis is still substantial[14], but no actual data regarding incidence and precipitating causes of adrenal crisis in Dutch patients with adrenal insufficiency were available. In **chapter 7**, we present our study on the

incidence of adrenal crises in patients with adrenal insufficiency. For this purpose, all patients diagnosed with adrenal insufficiency at the University Medical Center Utrecht from 1980 until 2010 were identified and adrenal crises, potential precipitating causes and possible risk factors were studied.

The *fourth* part deals with the possibility of recovery of adrenal function in auto-immune adrenalitis. We discovered partial recovery in a patient with auto-immune Addison's disease who had been treated with glucocorticoid and mineralocorticoid replacement therapy for 7 years (**chapter 8**). This incited us to find additional patients with (partial) recovery of adrenal function in auto-immune adrenalitis. We conducted a cross sectional study to investigate the possible occurrence of adrenocortical recovery in 27 patients with autoimmune Addison's disease (**chapter 9**).

The *fifth* and final part seeks to discuss these results and gives suggestions for future research.

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PART 1 DIAGNOSIS OF ADRENAL INSUFFICIENCY

Chapter 1: Is diagnosis and subclassification of adrenal insufficiency as easy as it looks?

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Abstract

The diagnosis of adrenal insufficiency (AI) is a challenge. Most signs and symptoms are non-specific and vary considerably depending upon the underlying cause and degree of AI. Identification of AI is crucial because the disease may be life-threatening if left unrecognized. The diagnostic evaluation consists of three steps. The first step is establishing the presence of hypocortisolism. The second step is establishing the level of hypothalamic-pituitary-adrenal (HPA-) axis dysfunction. The third and final step is searching for the exact cause of AI by additional laboratory and imaging techniques. Each diagnostic step can have its own uncertainties. The optimal test in case of intermediate basal cortisol measurements is still a matter of debate. Furthermore, interpretation of the results of the tests is complicated by arbitrary definitions of normal responses, variability in the analytical accuracy of the cortisol assays used and factors influencing cortisol binding globulin (CBG). This chapter aims to provide a concise stepwise approach for the diagnostic evaluation of AI, taking into account the possible pitfalls associated with the different tests.

Classification of adrenal insufficiency

Adrenal insufficiency (AI) results from dysfunction at one or more levels of the hypothalamic-pituitary-adrenal axis (HPA-axis). Primary adrenal insufficiency (PAI) is caused by dysfunction of the adrenal glands, while central adrenal insufficiency results from dysfunction of the hypothalamus or pituitary, also named tertiary (TAI) and secondary adrenal insufficiency (SAI), respectively. Glucocorticoid induced adrenal insufficiency develops after prolonged treatment with exogenous glucocorticoids.

Clinical presentation of adrenal insufficiency

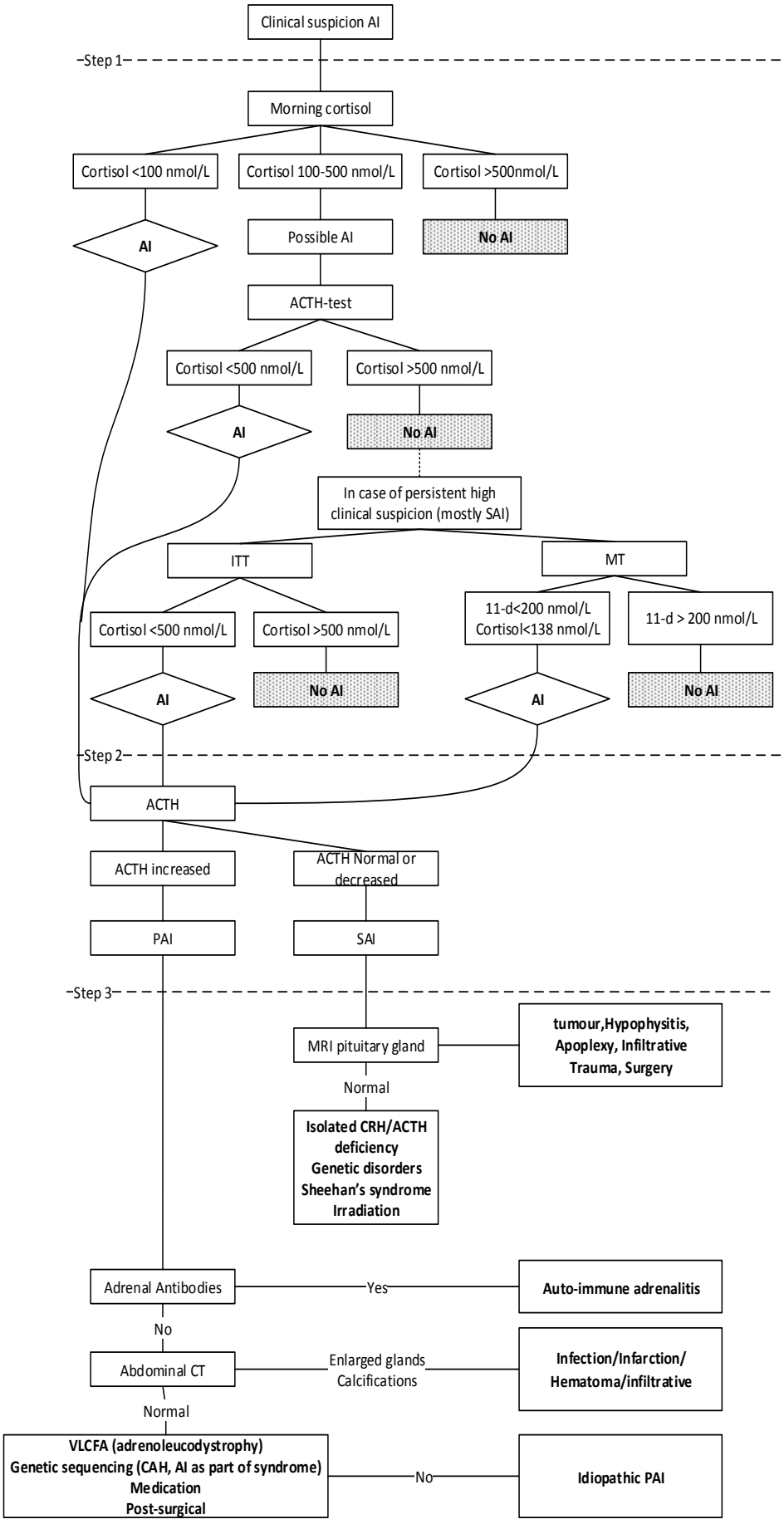
The clinical presentation of AI is variable and depends upon the underlying cause and extent of adrenal dysfunction. The most common clinical features of AI are malaise, fatigue, weakness, anorexia, weight loss, (orthostatic) hypotension, nausea and diffuse myalgia and arthralgia (table 1). Because the onset of AI is often gradual and signs and symptoms are nonspecific, AI may go undetected for a long time.[1] Hyperpigmentation of the skin and mucous membranes is the most classical finding in PAI. Hyperpigmentation is absent in patients with central AI. Other conditions that can lead to hyperpigmentation are hemochromatosis, porphyria cutanea tarda and ingestion of heavy metals, some antineoplastic agents, anti-malarial drugs, tetracyclines, zidovudine and phenothiazines. Another characteristic feature in PAI is salt craving, occurring in up to 78% of patients. Autoimmune destruction of dermal melanocytes, giving rise to areas of depigmented skin (vitiligo), occurs in 10-20% of patients with autoimmune adrenalitis. AI can also present with acute adrenal crisis (AC), mostly triggered by intercurrent illness or severe stress. The principal manifestation of AC is hypotension or hypovolemic shock, but other symptoms and signs such as weakness, anorexia, nausea, abdominal pain, fever, vomiting, fatigue, electrolyte abnormalities, confusion and coma can also occur. AC should be regarded as a medical emergency. Treatment of patients who present in possible AC should not be delayed and therapy with glucocorticoids should be initiated immediately, after drawing blood for plasma cortisol and ACTH.

	Type of AI	
Signs and symptoms	**PAI**	**CAI**
Weakness and fatigue	74-100%	64%
Anorexia	53-100%	29%
Weight loss	25-100%	30%
Hypotension	55-94%	32%
Abdominal pain	21-44%	5%
Nausea, vomiting	36-92%	21-24%
Diarrhea	6-41%	6%
Salt-craving	9-78%	
Depression	20-58%	
Postural symptoms	11-84%	
Hyperpigmentation	41-97%	
Amenorrhea or reduced libido	25-46%	47%
Myalgia, joint pain	6-36%	28%
Headaches	32-44%	45%
Dry skin	32-34%	37%
Loss axillary and pubic hair	24-38%	45%

Table 1 Signs and symptoms of adrenal insufficiency[22-30]

Diagnostic evaluation of suspected AI

The first step in the diagnostic evaluation of a patient with symptoms and signs compatible with AI is to establish whether hypocortisolism is present by measuring basal morning plasma cortisol concentration, if necessary followed by dynamic testing. The next step is to localize the level of HPA-axis dysfunction. The final step is to determine the cause of AI. This is critical because it directs subsequent evaluation, therapy and follow up (flowchart).


Clinical suspicion AI
Step 1
Morning cortisol
Cortisol <100 nmol/L
Cortisol 100-500 nmol/L
Cortisol >500nmol/L
AI
Possible AI
No AI
ACTH-test
Cortisol <500 nmol/L
Cortisol >500 nmol/L
AI
No AI
In case of persistent high clinical suspicion (mostly SAI)
ITT
MT
Cortisol <500 nmol/L
Cortisol >500 nmol/L
11-d<200 nmol/L Cortisol<138 nmol/L
11-d > 200 nmol/L
AI
No AI
AI
No AI
Step 2
ACTH
ACTH increased
ACTH Normal or decreased
PAI
SAI
Step 3
MRI pituitary gland
tumour,Hypophysitis, Apoplexy, Infiltrative Trauma, Surgery
Normal
Isolated CRH/ACTH deficiency Genetic disorders Sheehan's syndrome Irradiation
Adrenal Antibodies
Yes
Auto-immune adrenalitis
No
Abdominal CT
Enlarged glands Calcifications
Infection/Infarction/ Hematoma/infiltrative
Normal
VLCFA (adrenoleucodystrophy) Genetic sequencing (CAH, AI as part of syndrome) Medication Post-surgical
No
Idiopathic PAI

First assessment: hypocortisolism

Several factors are important for the interpretation of plasma cortisol. Cortisol production is pulsatile and has a diurnal pattern with levels being highest in the early morning and declining throughout the day. Cortisol increases in response to physiological and mental stress. The best time to measure plasma cortisol is in the morning between 8 and 9 a.m. Cortisol is bound to cortisol binding globulin (CBG) and albumin, and only around 5% exists in the free state. CBG varies significantly within and between individuals. Decreased and increased CBG can lead to respectively falsely lower or higher plasma cortisol concentrations.[2] CBG can be influenced by several factors. CBG is decreased in hyperthyroidism, cirrhosis and the nephrotic syndrome, whereas it is increased in a high estrogen state. In women using oral contraceptives, for example, CBG increases leading to almost doubling of total plasma cortisol concentration. During pregnancy, cortisol production and secretion increase, its half-life is prolonged due to decreased hepatic clearance and there is a tripling of CBG levels. This leads to increased total plasma cortisol concentrations. These changes underlie the difficulties of the evaluation of AI during pregnancy. Finely, heterophilic antibodies in a cortisol immunoassay can lead to falsely lowered plasma cortisol levels.[3] These factors should all be taken into account when interpreting plasma cortisol.

Basal morning cortisol

A random plasma cortisol can be best measured early in the morning, because overlap between normal and subnormal cortisol levels is least in the early morning. Basal cortisol is affected by stress, exercise and food intake. Stress and exercise should be minimised as much as possible before a blood sample is taken between 8 and 9 a.m. after an overnight fast. Controversy exists about the level of cortisol indicative of AI. Many patients have intermediate levels and require additional (dynamic) tests. Nonetheless, plasma morning cortisol is a good first assessment of adrenal function. It is easy and quick to perform. Very low (<100 nmol/L) or high (>500 nmol/L) morning cortisol levels obviates the need for dynamic tests. Alternatives to plasma total cortisol are plasma free cortisol and salivary cortisol measurement in case of suspected increased or decreased CBG. Salivary cortisol is

easy to collect by absorption into a cotton role (salivette). It reflects the biologically active free form. The analytical sensitivity varies between immunoassays due to the potential for cross-reactivity with other steroids.[4] A disadvantage of plasma free cortisol and salivary cortisol is that it is not widely available and data on the diagnostic accuracy in AI are limited. Hair cortisol is a new approach and has the potential to provide a retrospective view of cortisol levels over a period of several months.[5] Disadvantages of hair cortisol are that it might not detect AI of relatively short duration. It is not clear if it represents the free cortisol fraction. It has been shown to correlate with plasma and salivary cortisol in some but not all studies. The diagnostic value of hair cortisol in diagnosing AI is not known.

Dynamic testing

Different dynamic tests exist for the evaluation of hypocortisolism, such as the ACTH (Synacthen test), the insulin tolerance test (ITT), the metyrapone test (MT) and the glucose tolerance test (GTT).

ACTH test

The ACTH (Synacthen) test is a simple, save and widely used test for AI. The test can be performed on an outpatient basis and side effects are minimal. This test directly measures the functional integrity of the adrenal glands, but it also provides an indirect assessment of hypothalamic and pituitary function.[6] When ACTH production is impaired by pituitary or hypothalamic disease, the adrenals become atrophic and have less capacity to respond to exogenous stimulation. The test must not be used in AI of suspected short (4-6 weeks) duration (such as after recent pituitary surgery), when corticotrope damage may have occurred but the adrenals have not yet atrophied.[7] During the ACTH test cortisol is measured before and after (30 and/or 60 minutes) administration of ACTH. In the literature there is considerable variation in the choice of the cortisol cut-off value, ranging from 400 nmol/L (14.4 µg/dl) to greater than 694 nmol/L (25 µg/dl). However, the majority considers a maximum cortisol value of greater than 500 nmol/L (18 µg/dl) acceptable for determining normality. The increase in cortisol following ACTH administration is an unreliable index of

adrenal function. It does not distinguish normal patients from those with AI. In PAI a 250 microgram ACTH test is performed. However, in central AI controversy exists regarding the diagnostic value of the high (250 μg) versus low dose (1 μg) ACTH test. The low-dose test has been proposed as a more sensitive test. During the high dose test 250 μg ACTH (60000 pg/ml (1320 pmol/L)) is given as compared to 1 μg ACTH (1900 pg/ml (41.8 pmol/L)) during the low dose test. The 250 μg test stimulates maximal secretion and in normal subjects results in a peak plasma ACTH concentration about twice that during ITT.[8] The low dose test gives rise to more physiological plasma concentrations of ACTH and possibly provides a more sensitive index of adrenal responsiveness. The low dose test has a practical disadvantage: commercially available ACTH (vials of 250 μg) has to be diluted and during i.v. injection it can adhere to the tube, leading to administration of a lower ACTH concentration, possibly giving rise to lower cortisol levels. Some studies have reported that the low dose test is more sensitive, but a meta-analysis comparing the high and low dose test found similar sensitivities, concluding that the two tests perform similarly.[9-11] The differences between the studies, such as different populations and cortisol assays could have led to the discrepant conclusions. It is possible that mild or borderline cases of AI could occasionally be missed by 250 μg ACTH. The clinical significance with regard to the risk of AC during intercurrent illness in these cases remains unknown.

Adrenal androgens, secreted by the zona reticularis are regulated primarily by ACTH and thus may be regarded as another parameter of ACTH action on the adrenal cortex. Several studies show that patients with SAI have very low serum DHEAS levels even those who achieved normal cortisol responses to ACTH test.[12,13] In addition, in SAI a higher cortisol to DHEA molar ratio was seen. Cortisol is possibly being secreted preferentially over DHEA, and this becomes more apparent in case of low ACTH secretion. The presence of normal DHEA and DHEAS levels could be indicators of normal ACTH secretion and adequate adrenocortical function.[14] However, interpretation of individual results using age-adjusted references is required. The diagnostic value of this approach in SAI will probably become clearer in future studies.

Insulin tolerance test

The insulin-tolerance test (ITT) is currently considered to be the gold standard when evaluating patients suspected of having SAI. Hypoglycaemic stress stimulates cortisol production by increase of hypothalamic CRH and pituitary ACTH secretion. The aim of the ITT is to induce a hypoglycaemia with a glucose value of <2.2 mmol/L with occurrence of neuroglycopenic symptoms. Short acting insulin is injected i.v. at doses ranging from 0.1 U/kg in patients highly suspected of having AI to 0.2 U/kg or even more in insulin resistant states such as acromegaly, obesity and type 2 diabetes mellitus (DM2). Cortisol and glucose are measured at different time points. In subjects with no adrenal reserve an adrenal crisis can occur. A cortisol >500-550 nmol/L excludes central AI. Disadvantages are that it is contraindicated in patients with cardiovascular disease or epilepsy and that it requires close observation throughout the test to monitor for adrenergic and neuroglycopenic symptoms. Experience with this test in children and elderly people is limited.

Metyrapone test

Metyrapone inhibits 11β-hydroxylase, which converts 11-desoxycortisol to cortisol in the final step of adrenal steroidogenesis. 11-Desoxycortisol does not have glucocorticoid activity and therefore does not inhibit ACTH production. Normally when metyrapone is given, the decline in cortisol stimulates ACTH release, and due to the enzyme blockade, causes 11-desoxycortisol to accumulate. In AI, 11-desoxycortisol fails to increase. The test is performed as an overnight test with a single dose of metyrapone administered orally at 23.00 h. Blood is drawn at 8.00 h the next morning for measurement of ACTH, plasma cortisol and 11-desoxycortisol. Adequate adrenal function is confirmed by an 11-desoxycortisol >200 nmol/L (>7.0 µg/dl), regardless of the cortisol level. AI is diagnosed if 11-desoxycortisol is <200 nmol/L (<7.0 µg/dl) and plasma cortisol is <138 nmol/L (<5µg/dl). If 11-desoxycortisol is <200 nmol/L (<7.0 µg/dl) but cortisol >138 nmol/L (>5µg/dl) the metyrapone test is indeterminate because the hypocortisolemia was not adequate to stimulate pituitary production of ACTH. Phenytoin and phenobarbital increase the metabolism of metyrapone, thereby reducing plasma metyrapone levels and decreasing the 11-β-hydroxylase blockade. Other drugs found to have caused subnormal responses include amitriptyline, chlorpromazine, barbiturates,

chlordiazepoxide, estrogens, somatostatin analogues, diclofenac, furosemide, irbesartan, sodium valproate and zidovudine. The metyrapone test has been validated against the ITT for the diagnosis of SAI with a specificity of 88-100% and sensitivity of 60-100%.[15,16] The risk of an adrenal crisis precipitated by metyrapone should be taken into account during the test.

Glucagon stimulation test

The glucagon stimulation test (GST) is performed by measuring cortisol before and after the administration of 1 mg glucagon. The GST is used almost exclusively in children. Controversy exits about the diagnostic value of the GST in the evaluation of AI, compared to the ITT, metyrapone test and ACTH test. Small studies in healthy controls and pituitary patients initially found that the GST and ITT compared well. These results could not be reproduced by recent larger studies performed in patients after traumatic brain injury and patients following pituitary surgery. These studies found that 30-51% of GST and ITT results were discordant, due to false positive results of the GST.[17,18] Cegla et al showed that against the overnight metyrapone test, the GST had a sensitivity of 87.5% and a specificity of 10.5% at a cortisol cut-off level of ≥440 nmol/L, concluding that the GST has inferior diagnostic utility compared to the metyrapone test.[19] The GST should not be considered as the test of choice in patients with SAI.

In conclusion, for the diagnosis of hypocortisolism in patients with intermediate cortisol values (100-500 nmol/L), the 250 µg ACTH test is the most simple and safe test showing high specificity in the evaluation of PAI and SAI. The evaluation of SAI after pituitary surgery by means of an ACTH test should not be performed within a period of 4-6 weeks after surgery. Interpretation of the results of the tests and defining normal responses should be set regarding the analytical accuracy of the cortisol assays used. In case of discrepant results or with persistent high clinical suspicion of SAI an ITT should be performed. In case an ITT is contra-indicated a metyrapone test could be a valuable alternative.

Second assessment: localise level of dysfunction

Once hypocortisolism has been confirmed the next step is to determine the site of the HPA-axis defect. Plasma ACTH level is the best test to distinguish primary AI from central and glucocorticoid induced AI. It fails to separate normal patients from those with secondary AI. In PAI ACTH is usually above 100 pg/ml. An ACTH > 60 pg/ml (13.2 pmol/L) has a sensitivity of 100% and specificity of 98%. There are additional tests that can help in distinguishing the level of defect. The first evidence of autoimmune AI is an increase in plasma renin activity and normal or low aldosterone concentration, followed by a decreased cortisol response to ACTH stimulation, increased basal ACTH and finally decreased basal serum cortisol concentration. AI becomes clinically manifest after at least 90% of the cortex has been destroyed. Finally increased potassium (65%) and decreased sodium (85-90%) concentrations can be seen. In SAI and TAI plasma renin activity and aldosterone concentration are usually normal. Sodium concentration is often decreased due to increased vasopressin levels resulting from decreased inhibition by cortisol. In the past, a CRH stimulation test was proposed to distinguish SAI from glucocorticoid induced AI or TAI. During this test 1 microgram per kg CRH is injected i.v., followed by sampling of ACTH and cortisol over the subsequent 2 h. In SAI low or low normal baseline ACTH was seen, which did not respond to CRH. In glucocorticoid induced AI and TAI low baseline ACTH was seen, which showed an exaggerated response to CRH, and remained elevated for a prolonged period of time.[20] However, overlap in ACTH and cortisol results are frequently seen, making the test less suitable for differentiating between SAI and TAI.

Third assessment: determining the aetiology of AI

Primary adrenal insufficiency

Autoimmune adrenalitis is the most common cause of PAI. Autoimmune adrenalitis is diagnosed in the presence of positive adrenal antibodies. PAI is characterized by the presence of antibodies against the steroidogenic enzymes, mostly 21-hydroxylase and less frequently side-chain cleavage enzyme and 17-alpha-hydroxylase. Antibodies are present in up to 90% of patients, while they are rarely found in normal subjects. Antibodies against

other endocrine glands are commonly seen in patients with autoimmune adrenalitis, possibly leading to autoimmune polyglandular syndrome. PAI can also result from a block in steroid production as in congenital adrenal hyperplasia (CAH) or be part of a genetic syndrome. In the absence of adrenal antibodies abdominal CT should be performed in order to detect adrenal calcifications or enlarged glands suggesting an infectious, metastatic, infiltrative or haemorrhagic cause of AI (table 2). The adrenal glands are invariably small in auto-immune adrenalitis. CT-directed percutaneous fine needle aspiration can ultimately establish the presence of infectious disease or malignancy. In case of haemorrhage in a patient without anticoagulants, measurement of antiphospholipid antibodies should be performed. The presence of adrenoleukodystrophy (ALD) and adrenomyeloneuropathy (AMN) should be excluded in case of accompanying neurologic symptoms.

Central adrenal insufficiency

Any disease, operation or trauma that affects the hypothalamus or pituitary gland can lead to central AI (table 3). Due to destruction of pituitary tissue, the secretion of other pituitary hormones can be decreased as well, leading to (pan)hypopituitarism. Isolated ACTH deficiency or ACTH deficiency due to genetic pituitary abnormalities are rare. Pituitary MRI should always be performed in order to exclude a tumour or other mass lesion.

Causes PAI
Autoimmune adrenalitis
Isolated
APS type 1 (chronic mucocutaneous candidiasis, hypoparathyroidism, other)
APS type 2 (thyroid auto-immune disease, type 1 diabetes mellitus, other)
APS type 4 (auto-immune gastritis, vitiligo, coeliac disease, alopecia)
Genetic
Congenital adrenal hyperplasia (CAH)
Adrenal hypoplasia congenital
Triple A-syndrome (Allgrove's syndrome)
Adrenoleukodystrophy/adrenomyeloneuropathy
Primary generalized glucocorticoid resistance
Familial glucocorticoid deficiency or corticotropin insensitivity syndromes
Sitosterolaemia
Wolman's disease
Kearns-Sayre syndrome
IMAGe syndrome
Smith-Lemli-Opitz syndrome
Infectious adrenalitis
Tuberculous adrenalitis
Fungal (paracoccidiomycosis, cryptococcosis, histoplasmosis)
Syphilis
Trypanosomiasis
Viral (HIV, CMV, HSV)
Drugs
Mitotane, Ketoconazole, Rifampicin, anticoagulants, tyrosine-kinase inhibitors, aminoglutethimide, Fluconazole, Etomidate, Phenobarbital, Phenytoin, Metyrapone
Bilateral adrenal hemorrhage or thrombosis
Waterhouse-Friderichsen syndrome, antiphospholipid syndrome, DIS
Bilateral adrenal metastases
Lung, stomach, breast, colon
Bilateral adrenal infiltration
Sarcoidosis, amyloidosis, hemochromatosis
Bilateral adrenalectomy

Table 2 Causes of primary adrenal insufficiency

Causes CAI
Tumors
adenomas
cysts
craniopharyngiomas
ependymomas
meningiomas
carcinomas
Surgery or irradiation
Infections
Infiltrative processes
Lymphocytic hypophysitis
Hemochromatosis
Sarcoidosis
Histiocytosis X
Wegener's granulomatosis
Pituitary apoplexy
Sheehan's syndrome
Drugs
Antipsychotics
Genetic disorders
Transcription factors involved in pituitary development (obesity, hyperphagia)
Congenital pro-opiomelanocortin deficiency
Prader-Willi syndrome (hypotonia, obesity, mental retardation, hypogonadism)
Trauma
Isolated CRH deficiency
Isolated ACTH deficiency
Autoimmune
Triple H syndrome (hypothalamic-pituitary-adrenal, hair follicle, hippocampus)
Mutation prohormone convertase 1 (ACTH deficiency, impairment of memory and alopecia areata)
DAVID complex (ACTH deficiency and common variable immunodeficiency)

Table 3 Causes of central adrenal insufficiency

Glucocorticoid induced adrenal insufficiency

Suppression of the HPA-axis as a result of treatment with chronic high dose glucocorticoids is by far the most common cause of AI. However the true prevalence is not known. Low dose glucocorticoids can also lead to AI if their metabolism is reduced by drug interactions, for example when inhalation or dermal glucocorticoids and ritonavir are given simultaneously. Glucocorticoids can be taken via various routes, all of which should be considered. Treatment with inhalation and transdermal glucocorticoids as well as glucocorticoid injections are frequently unrecognized causes of glucocorticoid induced AI. Additionally, glucocorticoids can be present in creams or "over the counter" preparations. A thorough history regarding supplements, medications and skin care products should be obtained in every patient suspected of having AI. The type of glucocorticoid, route of administration, dose frequency, duration of glucocorticoid therapy and the (accumulative) glucocorticoid dose are related to the risk of HPA-axis suppression. Probably, an individual sensitivity to glucocorticoids can also play a role. This is hard to predict for the individual patient. The diagnosis of glucocorticoid induced AI is very difficult. Some commonly used glucocorticoid preparations especially prednisolone, cortisone, prednisone and to a lesser extent fludrocortisone and methylprednisolone can potentially cross react in the cortisol assay, giving falsely high cortisol values. Cross-reactivity of dexamethasone, triamcinolone, budesonide and inhalation corticosteroids such as betamethasone, fluticasone and beclomethasone (<1µg/ml) are unlikely.[21] The only way to get a clear picture of AI is to slowly taper glucocorticoid dosage to less than physiological doses and measure morning cortisol before glucocorticoid ingestion. In addition, dose reduction may allow gradual recovery of the HPA axis when it has been suppressed. This is only possible if the underlying disease, for which the glucocorticoids were given, is in remission. If the glucocorticoid dosage is being tapered to below physiologic replacement, signs and symptoms of adrenal insufficiency can occur. These patients should be instructed to double or triple the dose if they suffer from illness or injury. Recovery of the HPA axis from glucocorticoid-induced suppression can take a very long time. If glucocorticoid dosage has been tapered or discontinued, hypocortisolism can be evaluated by measuring morning plasma cortisol and in case of cortisol values between 100-500 nmol/L by performing an ACTH test.

Conclusion

The diagnostic evaluation of AI can be challenging but by following the three proposed steps it will be straight forward and will lead to a correct diagnosis in most cases, provided that the pitfalls described will be taken into account. This method is a fast and reliable diagnostic approach that will help to start treating this potentially life threatening disease as soon as possible yet avoids unnecessary chronic glucocorticoid replacement with its well-known complications in the long run.

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PART 2 TREATMENT OF ADRENAL INSUFFICIENCY

Chapter 2: Glucocorticoid replacement therapy: past, present and future perspectives

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Submitted

Abstract

After Thomas Addison in 1855 had described the adrenal disease that now bears his name, many years had to pass before treatment of patients with Addison's disease was possible. Half a century of intensive research led to the discovery and synthesis of adrenocortical steroids. Effective glucocorticoid replacement therapy became a reality and greatly improved prognosis in patients with Addison's disease. Mortality, however, is still increased in patients on conventional replacement therapy. In addition, many patients suffer from a decreased quality of life. Probably this is, in part, caused by imperfections of glucocorticoid replacement therapy, as it is difficult to imitate normal physiology. Improvements in replacement therapy are needed to optimize quality of life (QoL) and life expectancy of patients with Addison's disease. The newly developed modified-release hydrocortisone formulations seem promising. In this article we review the literature on glucocorticoid replacement therapy in patients with Addison's disease.

History of replacement therapy in Addison's disease

The first landmark in the history of adrenal insufficiency was achieved by Thomas Addison in 1855, 291 years after the discovery of the adrenal glands by Bartolomeo Eustachius.[1] In his classical monograph "On the Constitutional and Local Effects of Disease of the Suprarenal Capsules" Addison described a group of symptoms that he considered to be associated with disease of the adrenal glands.[2-6] After Addison's publications, adrenal gland function remained subject of discussion. In 1856 Brown-Sequard proved that the adrenal glands were essential for life by showing that bilateral adrenalectomy was quickly fatal. He discovered that adrenalectomized guineapigs markedly improved when treated with alcoholic extracts of the adrenal glands.[7] It led to the suggestion that the adrenals were secreting glands and attempts were made to isolate their products. In 1894 the active product of the medulla, adrenalin, was isolated and prepared in pure form by Takamini and Aldrich, making it the first hormone to be isolated.[8] At that time it was commonly accepted that adrenalin was the indispensable hormone of the adrenal gland, the lack of which was responsible for the condition described by Addison. Various attempts were made to treat patients suffering from Addison's disease with these adrenal extracts with varying results. In 1896 Osler

treated a patient with Addison's disease with orally given adrenal extract and found it to be temporarily effective.[9] At the Annual Meeting of the Association of American Physicians in 1925 Rowntree presented encouraging results obtained from the use of what he called the Muirhead treatment in patients with Addison's disease.[10] The principle of the Muirhead treatment was the frequent administration of epinephrine (adrenaline) hypodermically or by rectal administration and of whole gland or suprarenal cortex by mouth to the limit of tolerance. The prognosis of Addison's disease at that time was extremely grave. The Muirhead treatment exceeded expectations. Thirty-one per cent of treated patients survived for two and one-half years. Hereafter, numerous attempts were made to treat Addison's disease with adrenal extracts and by whole adrenal gland, but in the majority of patients only single complaints were relieved and benefit was only claimed in about 7% of reported cases.[11] Later on Biedl proved the importance of the adrenal cortex, by showing that mammals could live with one-eighth or less of their suprarenal substance, provided that the portion left behind was composed of cortical tissue.[12] In 1931, Stewart and Rogoff confirmed his finding that the cortex was the indispensable portion of the adrenal gland. Rogoff demonstrated that the cortex contained a substance, called interrenalin, which could be extracted and was capable of prolonging life in adrenalectomized animals. He treated his patients by administration of oral interrenalin, the extract of interrenal tissue of sheep or beef adrenals. Not only was life prolonged but many symptoms were ameliorated.[11] The preparation of active extracts of suprarenal cortex by Swingle and Pfiffner completely changed the possibilities of treatment.[13] The costs and inconvenience of these extracts, however, were high. In 1932 Loeb discovered that serum sodium and chloride were markedly decreased in patients with Addison's disease and he ultimately demonstrated that the adrenals were involved in mineral metabolism. Since this discovery it was a routine treatment to add sodium to the diet of patients with Addison's disease. Within four years various steroids were isolated. In 1937 Steiger and Reichstein announced the preparation of desoxy-corticosterone acetate. The effectiveness of synthetic desoxy-corticosterone acetate in maintaining bilaterally adrenalectomized dogs prompted Thorn, Howard and Kendall to investigate the possibility of using it in the treatment of Addison's disease. It resulted in marked improvement in the clinical condition of patients with Addison's disease.[14] Pellets of desoxy-corticosterone acetate were developed which could be implanted into the skin of the abdomen. Though life was prolonged, the health of most patients was not restored to

normal. The discovery of desoxy-corticosterone acetate was followed by the production of more potent synthetic adrenal steroids such as cortisone acetate in 1949. Cortisone and hydrocortisone were capable of increasing strength and well-being in patients with Addison's disease. In 1953, aldosterone was crystallised by Simpson and Tait in England and by Reichstein and Wettstein in Switzerland.[15] One year later 9-α-fluoro-hydrocortisone was introduced by Fried and Sabo. From that moment, the majority of patients with Addison's disease was treated with the combination of glucocorticoids and mineralocorticoids. This replacement therapy revolutionized medical care of patients with Addison's disease. A previous lethal disease could now be treated successfully.

Present perspective

From originally targeting on life-sustaining therapy, nowadays our goals have extended to creating a physiologic replacement therapy with glucocorticoids, mineralocorticoids and sometimes dehydroepiandrosterone (DHEA).[16-20] This goal is hard to achieve.[21-24] After starting replacement therapy (RT) patients initially experience great symptomatic improvement. However, many patients on chronic replacement therapy still experience various complaints.[25,26] In addition, patients with Addison's disease have a two-fold increase in mortality compared with age-matched controls, due to cardiovascular, malignant and infectious diseases.[27-29] In order to improve RT knowledge of the HPA-axis and of glucocorticoid preparations is indispensable.

The hypothalamic-pituitary-adrenal-axis and intracellular cortisol regulation

The hypothalamus receives and integrates information from various sources and acts as a sensor of changes in the external and internal environment.[30] Parvocellular neurons release corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP). They work synergistically to trigger the release of adrenocorticotrophic hormone (ACTH) from the pituitary into the systemic circulation.

ACTH acts on high affinity plasma membrane receptors, resulting in activation of intracellular protein kinases including steroidogenic acute regulatory protein (StAR) in the adrenal gland, whereupon steroidogenesis is initiated. The rate-limiting process in steroidogenesis is the transport of free cholesterol through the cytosol to the inner mitochondrial membrane. Cholesterol is ultimately converted into pregnenolone. Pregnenolone is then transported outside the mitochondria before further steroid synthesis occurs to form cortisol (Figure 1).

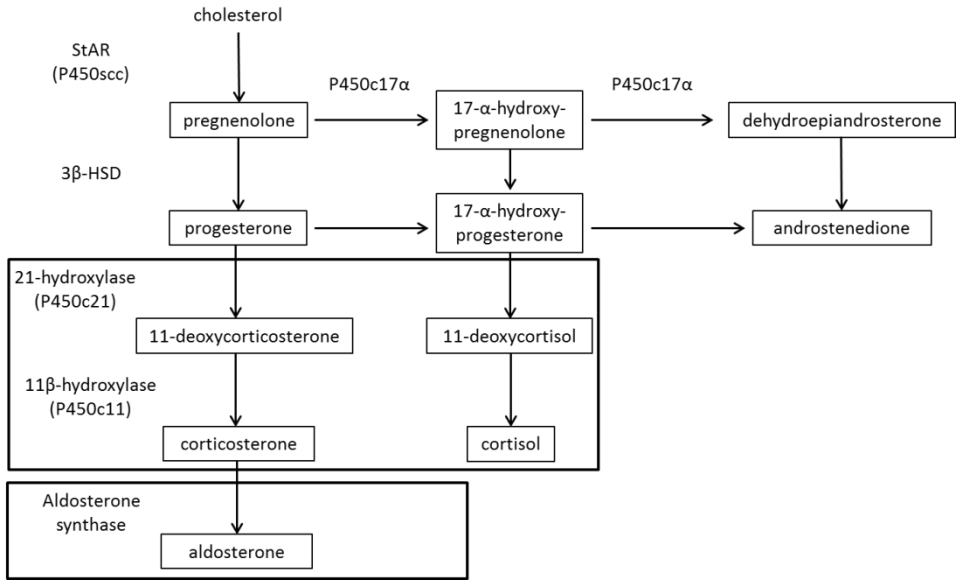
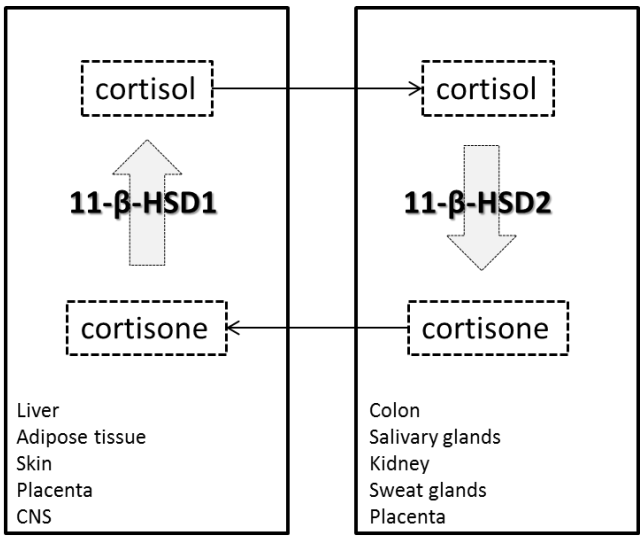


Figure 1 Steroidogenesis

Cortisol is released into the systemic circulation by diffusion and induces negative feedback at the level of the pituitary gland and hypothalamus.[31] Cortisol is transported in the blood predominantly (90%) bound to plasma proteins, of which cortisol binding globulin (CBG) is the most important. CBG-free cortisol readily diffuses across cellular membranes to exert its effect. There is also evidence for cellular uptake of the cortisol-CBG complex, suggesting that this complex plays a role in steroid hormone action.[32,33] Intracellular bioavailability of cortisol is controlled by ' prereceptor ligand metabolism'.[34-36] 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), predominantly expressed in the mineralocorticoid-responsive cells of the kidney, catalyses the conversion of cortisol to cortisone. 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) converts cortisone to cortisol and ensures intracellular cortisol bioavailability in liver, fat, lung and central nervous system (Figure 2).

Glucocorticoids signal through genomic and non-genomic pathways. The genomic actions of glucocorticoids are mediated by an intracellular receptor protein, which functions as a hormone-activated transcription factor of glucocorticoid target genes.[37] The gene of the glucocorticoid receptor consists of nine exons, is located on chromosome 5 and encodes two variants: GRα and GRβ. GRα is the classic glucocorticoid receptor. It transactivates or transrepresses glucocorticoid-responsive promotors.



11-β-HSD1: 11-β-hydroxysteroid dehydrogenase type 1, 11-β-HSD2: 11-β-hydroxysteroid dehydrogenase type 2, CNS: central nervous system

Figure 2 Cortisol-cortisone shuttle

Rapid, non-genomic actions of glucocorticoids are thought to be mediated through interactions with cellular membranes, cytosolic glucocorticoid receptors or membrane-bound glucocorticoid receptors. Thus corticosteroids are able to rapidly alter cellular function by impairing cation transport across the plasma membrane and by increasing the mitochondrial proton leak.[38] Ultradian hormone release is now shown to result in pulsatile gene transcription through dynamic exchange of glucocorticoid receptor with the target gene promoter and glucocorticoid receptor cycling through the chaperone machinery.[39] There is wide inter-individual variability in glucocorticoid sensitivity, modulated by the

number, phosphorylation pattern and hormonal affinity of the glucocorticoid receptor, ultimately influencing the modulation of the transcription of glucocorticoid target genes.[40,41]

Glucocorticoid replacement

Taking the complex actions of the HPA-axis, intracellular cortisol regulation and glucocorticoid sensitivity into consideration, it seems nearly impossible to replicate normal physiology. Nevertheless, much attention has been directed to achieve this goal, studying glucocorticoid type, dosage and regime.

Hydrocortisone and cortisone acetate are the primary agents used as glucocorticoid replacement. Hydrocortisone, which is identical to the native hormone cortisol, is characterized by high bioavailability, a short elimination half-life, low metabolic clearance and small volume of distribution.[42] Cortisone acetate has the disadvantage that it must be metabolized by the liver to cortisol before having any effect.[43] This could lead to treatment failure in case of severe liver disease or 11β-HSD1 deficiency. Some prefer maintenance therapy with equivalent doses of longer-acting corticosteroid preparations, such as dexamethasone or prednisone to avoid excessively high peak levels and periods of inadequate replacement associated with shorter-acting preparations.[44] These agents, however, could result in unfavourably high night-time glucocorticoid activity, due to their longer biological half-lives. Some studies accordingly suggest that the short-acting preparations are to be preferred above long-acting agents.[45] In a study of more than 400 patients with primary and secondary adrenal insufficiency, Bleicken, on the other hand, could not detect a relevant difference between patients on short- or long-acting glucocorticoids with regard to subjective health status and daily performance.[46]

When deciding on glucocorticoid dose, estimates of endogenous cortisol production have to be considered. After original estimates suggesting an endogenous cortisol production of 12-15 mg/m^2 per day, Esteban showed however that the daily production of cortisol was much lower.[47] Subsequently, other investigators reported rates of approximately 5-10 mg/m^2 corresponding to approximately 15-25 mg hydrocortisone and 25-37,5 mg cortisone acetate daily[48-50] Some investigators suggest weight-related dosing. Body weight and body surface

area could play a role in hydrocortisone clearance. Changes in metabolism with increasing weight were described, probably caused by enhanced A-ring reductase activity as well as decreased 11β-hydroxysteroid type 1 activity. Mah studied cortisol pharmacokinetics in patients with Addison's disease and found that weight-related dosing generated a smoother cortisol day profile.[51] They recommend a thrice-daily regimen of hydrocortisone with a total daily dose of 15 mg (8.1 mg/m^2/day) for a 70 kg patient. In order to reduce over-replacement, total daily dose is now believed to be approximately 15-25 mg of hydrocortisone.[52-56]

Due to their pharmacokinetic properties, hydrocortisone and cortisone acetate are not able to replicate the normal pattern of cortisol secretion. The HPA-axis has an ultradian rhythm of about one pulse per hour. ACTH pulses have increased amplitude in the morning. At the same time adrenal sensitivity to ACTH is highest. This results in the circadian rhythm of cortisol.[57,58] Glucocorticoid secretion into the circulation occurs in a continuous pulsatile manner throughout the day. Cortisol secretion is low in the evening and nearly undetectable in the first several hours of sleep. Major secretory episodes begin in the sixth to eighth hour of sleep. Hydrocortisone and cortisone acetate, however, lead to highly fluctuating plasma concentrations with high peaks after ingestion and low through values in between. One could speculate that twice or thrice daily administration achieves a better cortisol day pattern. Riedel investigated the QoL in a small cohort of patients with adrenal insufficiency.[59] He found that a twice daily regime was superior to a single daily dose regarding QoL. It is not clear whether a thrice daily glucocorticoid regimen should be preferred over twice daily administration.[60-64] In 2010 Simon performed a pharmacokinetic analysis to describe the concentration-time courses of hydrocortisone in 50 patients with adrenal insufficiency under their usual replacement therapy.[65] Thereafter simulations were performed with different dosing regimens to assess which regimen was the most appropriate, within average biological targets. Plasma cortisol concentrations showed that 11%, 13% and 31% of patients were under-treated and 68%, 42% and 14% were over-treated at 8.00, 16.00 and 24.00 hour, respectively. The regimen with the highest proportion of simulated patients within the physiological targets was 10-5-5 mg at 07.30, 12.00 and 16.30 hour, respectively. However with this new simulated regimen about 54%, 44% and 32% of patients would remain over-or under-treated at 08.00, 16.00 and 24.00 hour, only 50-70% would reach normal cortisol

levels. Ekman performed a double blind crossover study to assess how an equal dose of hydrocortisone given either four times daily or twice daily influences diurnal profiles of cortisol and ACTH, patient preferences and health related QoL.[66] Compared with the two-dose regime, the four-dose regime gave a significantly higher serum cortisol and lower plasma ACTH before medication intake in the morning. With the four-dose regime, hypercortisolism was less pronounced in the morning and afternoon, but 24-h-cortisol area under the curve was higher. Patients preferred the four-dose regime. The four-dose regime resulted in non-significantly higher QoL scores for all items.

In conclusion, hydrocortisone is still the most commonly used therapy for replacing glucocorticoids in Addison's disease. The total daily glucocorticoid dose in normal, unstressed conditions should be between 15-25 mg, regarding changes in body weight. Unfortunately current therapy is not able to mimic the physiological rhythm of cortisol release and inevitably results in over- or under-replacement.

Monitoring replacement therapy

In daily practice, glucocorticoid replacement therapy (GRT) is most often assessed by clinical judgment. This includes blood pressure, weight and length, sodium, potassium and glucose measurements. At random serum cortisol or ACTH measurements and 24 hour urinary excretion of free cortisol do not offer insight in the fluctuating cortisol concentrations throughout the day.[67-70] Another possibility to assess GRT is performing a serum cortisol day curve. Arlt et al assessed quality of GRT with timed cortisol concentrations. A newly developed quality of glucocorticoid replacement score based on adding and subtracting points for signs and symptoms of under- or over-replacement was compared to results of three cortisol measurements after morning glucocorticoid dose.[71] Arlt et al found that the mean z score of serum cortisol differed significantly between under- and over-replaced patients but neither group differed significantly from well-replaced patients. A disadvantage of obtaining a serum cortisol day curve is that it is time-consuming and that hospitalization is required which makes it expensive. Assessment of cortisol in saliva has been reported to be a good alternative for plasma cortisol measurements.[72] In our study we used salivary cortisol day curves (SCDC) to monitor glucocorticoid replacement. None of the participants

experienced any difficulty in performing a SCDC at home.[73] By using only two salivary cortisol day curves we were able to reduce over-replacement from 32.8 h. nmol/L to 13.3 h. nmol/L (p=0.006) just by small changes in dosage and regime. A SCDC, unlike serum cortisol measurements, can easily be used to detect over-replacement at various moments during the day. In addition, the SCDC is non-invasive, inexpensive and gives a good impression of the free cortisol concentration. Recent studies have established the measurement of cortisol content in scalp hair as a possibility to measure endogenous cortisol exposure. Hair cortisol assesses retrospective systemic cortisol exposure over longer periods of time. Gow measured hair cortisol content as a biomarker of systemic exposure in patients with adrenal insufficiency treated with oral hydrocortisone or cortisone acetate.[74] A significant correlation was found between daily glucocorticoid dose and hair cortisol content. The variability in hair cortisol content however was considerable. Future studies will need to determine the true value of this test and determine to what extent increased hair cortisol content is associated with increased morbidity.

Mineralocorticoid substitution

In primary adrenal insufficiency aldosterone has to be replaced, because it plays an important role in water and electrolyte metabolism.[75] Aldosterone binds to the mineralocorticoid receptor and ultimately leads to sodium reabsorption and potassium excretion. The natural mineralocorticoids aldosterone and 11-deoxycorticosterone can be replaced by the synthetic mineralocorticoid 9alpha-fludrocortisone. Fludrocortisone is given orally at a dose of 0,05 mg/d to 0,20 mg/d. The dose can be adjusted based upon serum electrolyte and renin levels and the presence of postural hypotension or marked orthostasis. The best way of assessing the response to fludrocortisone is by measurement of plasma renin concentration.[75-79]

Androgen replacement

In addition to glucocorticoids and mineralocorticoids, the adrenals also secrete dehydroepiandrosterone (DHEA) and large amounts of dehydroepiandrosterone sulphate

(DHEAS). In androgen target organs DHEAS is converted to DHEA, while DHEAS is mainly formed from DHEA in the adrenal and in the liver by a sulfotransferase. Specific DHEA receptors have not been identified, but neuro- and immunomodulatory properties of DHEA have been suggested, besides a role in sexuality, (bone) metabolism and muscular strength.[80,81] In patients with adrenal insufficiency concentrations of DHEA and DHEAS are very low. DHEA replacement continues to be controversial, with conflicting results regarding QoL.[82-89] Alkatib performed a systematic review and meta-analysis of 10 RCTs of DHEA treatment effects on QoL in women with adrenal insufficiency. DHEA replacement had only a small effect on health related QoL and depression with effect sizes of 0.21 (CI 0.08-0.33) and 0.23 (CI 0.04-0.42) respectively.[90] These results provide insufficient support for the routine use of DHEA replacement. A therapeutic trial of DHEA (25-50 mg a day) could be warranted for patients who experience profound reductions in QoL.

Future perspective

In recent years investigators have focused on developing a glucocorticoid replacement that is able to simulate the normal diurnal rhythm of cortisol more closely.

In 2006 Merza explored the potential effectiveness of circadian delivery of cortisol.[91] Patients with apparent poor control of their disease were studied on two occasions. On the first visit they were given their usual oral treatment and on the second visit they were studied during programmed intravenous hydrocortisone infusion based on modelling methods with dose adjustments according to body weight. The infusion regime more closely approximated the normal circadian rhythm. Patients on conventional oral thrice daily hydrocortisone had higher cortisol levels during the day and extremely low cortisol levels overnight. In addition, Lovas studied hydrocortisone administration via a subcutaneous pump.[92] Once the patients used a continuous pump for subcutaneous infusion, the circadian rhythm of cortisol was re-established. They were able to reduce total daily doses without adverse reactions, ACTH levels tended to normalise and they experienced improved levels of subjective health and well-being. New modified-release hydrocortisone formulations were developed to provide more physiological cortisol levels without the invasiveness of intravenous or subcutaneous infusion. In 2008 Newell-Price performed the first proof-of-

principle study to examine $Cortisol_{ds}$,in dexamethasone suppressed healthy volunteers, and compared the profiles with the rhythm of endogenous levels seen in normal individuals.[93] Two formulations were used, A and B, with B having a 50% longer delay time before in vitro drug release (2 hours vs 4 hours). The profiles following both formulations showed significantly delayed release with a significant difference in time delay to the maximum serum cortisol concentration (A 4.5 hours, B 10 hours). Formulation B provided the better match to the normal endogenously generated profile. But following both formulations, serum cortisol fell below the level seen in healthy controls after mid-day. Subsequently, pharmacokinetic and –dynamic studies of *dual*-modified-release formulations were performed. Debono studied replacement profiles of modified-*dual*- release and immediate-release hydrocortisone, comparing them with physiological levels.[94] 20 subjects were randomized to receive three of the following four single-dose regimes: 5 mg modified-release hydrocortisone (MR-HC), 15 mg MR-HC, 2x 15 mg MR-HC or 10 mg immediate-release hydrocortisone. Twelve other subjects were randomized to receive either 2x 5 mg MR-HC or 10 mg immediate-release hydrocortisone. Based on pharmacokinetic modelling, they found that a twice daily regimen of MR-HC given at 23.00 and 7.00 hour can provide levels of cortisol similar to the normal physiological cortisol rhythm. Johannsson published results of a pharmacokinetic phase I study of hydrocortisone modified release tablets in 16 healthy volunteers.[95] Oral modified-release treatments of 5 and 20 mg hydrocortisone were given in random order. The time to reach 200 nmol/L of cortisol in plasma was 17-20 min for the 20 mg tablet. There was no difference in time to reach maximal plasma concentration between the 5 and 20 mg tablet in the fasted state and on average occurred at 40-50 minutes after oral dosing. The mean plasma area under the curve and Cmax increased 2.9- and 2.1-fold respectively, when the dose increased from 5 to 20 mg. Terminal half-life of hydrocortisone was independent of dose and food intake and was 1.0-1.5 hours longer than after administration of a conventional tablet. There was no observation of absorption failure. Furthermore, the gastrointestinal absorption was rapid, bioavailability was high and the variability was equal or better than that previously described with conventional immediate release formulations. In 2010 Verma demonstrated that a delayed- and extended-release form of hydrocortisone achieved good overnight and early morning control of ACTH and improved morning 17-OHP values in patients with classic congenital adrenal hyperplasia.[96] The new formulation was safe and well tolerated with no serious

adverse events. Next Johannsson performed an open, controlled, randomized, two-armed, 12-wk crossover, multicenter trial comparing a once-daily dual-release hydrocortisone tablet (OD), based on an immediate-release coating together with an extended-release core, with a conventional thrice-daily replacement therapy in patients with primary adrenal insufficiency.[97] The OD regime increased serum cortisol in the morning, reduced exposure in the afternoon and evening and reduced 24-h exposure by almost 20%. Weight, blood pressure and glycated haemoglobin were all reduced after OD at 12 weeks. Improvements were observed in some QoL domains at 12 weeks, particularly in those reflecting fatigue. In addition 85% of patients preferred the OD treatment.

These studies show that a modified release formulation of hydrocortisone can potentially replicate cortisol levels under normal unstressed conditions. However, it is unlikely that any future drug regime will be able to replicate the rapid adaptation of cortisol secretion during times of physical and psychological stress.

Conclusion

The future of glucocorticoid replacement lies in the use of modified release hydrocortisone formulations, offering more physiological cortisol replacement ultimately to improve morbidity and mortality in patients with Addison's disease. Longer-term controlled studies are required to evaluate clinical benefits and safety.

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Chapter 3: Salivary cortisol day curves in assessing glucocorticoid replacement therapy in Addison's disease

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Abstract

Objective: Patients with Addison's disease require lifelong treatment with glucocorticoids. At present, no glucocorticoid replacement therapy (GRT) can exactly mimic normal physiology. As a consequence under- and especially overtreatment can occur. Suboptimal GRT could lead to various side effects. The aim of this study was to investigate the use of salivary cortisol day curves (SCDC) in the individual adjustment of GRT, in order to approach normal cortisol levels as closely as possible, reduce over- and under-replacement and study the short term effects on quality of life (QoL).

Design and Methods: Twenty patients with Addison's disease were included in this prospective study. A SCDC was obtained and compared to normal controls; general and disease specific QoL-questionnaires were completed. Based on SCDC assessment of over- and under-treatment (calculated as duration (h) × magnitude (nmol/L) on different time points, glucocorticoid dose and regime were adjusted. After 4 weeks SCDC and QoL assessment were repeated and the effect of adjusting GRT was analysed.

Results: At baseline, under-replacement was present in 3 and over-replacement in 18 patients; total calculated over-replacement was 32.8 h.nmol/L. Over-replacement decreased significantly to 13.3 h. nmol/L ($p = 0.005$) after adjustment of GRT. Over-replacement was found particularly in the afternoon and evening. After reducing over-replacement in the evening, complaints about sleep disturbances significantly decreased.

Conclusions: Individual adjustment of GRT based on SCDC to approach normal cortisol concentrations during the day can reduce over-replacement, especially in the evening. This can lead to a reduction of sleep disturbances and fatigue in patients with Addison's disease. A SCDC is a simple and patient friendly tool for adjusting GRT and can be useful in the follow-up of patients with A Addison's disease.

Introduction

Since synthetic corticosteroids have become available, the life expectancy of patients with Addison's disease treated with lifelong replacement therapy with glucocorticoids and mineralocorticoids has increased dramatically. However, current glucocorticoid replacement therapy (GRT) cannot exactly mimic normal physiology and often leads to overtreatment.[1] Chronic overtreatment can lead to serious side effects on the long term, such as osteoporosis, weight gain or increased cardiometabolic risk and even increased mortality.[2-5] In addition suboptimal GRT could also be the cause of reduced quality of life (QoL).[6] Optimal GRT can probably be achieved by mimicking the physiological circadian cortisol secretion pattern as closely as possible. In daily practice, GRT is most often assessed by clinical judgment only. Random serum cortisol or ACTH measurements and 24 hour urinary excretion of free cortisol do not offer insight in the fluctuating cortisol concentrations throughout the day. One possibility to assess and adjust GRT is performing a serum cortisol day curve, but this is time- consuming and expensive because hospitalization is required.[7] Assessment of cortisol in saliva has been reported to be a good alternative for plasma cortisol measurements.[8,9] A salivary cortisol day curve (SCDC) is inexpensive, easy to perform, non-invasive and can be performed at home. The first aim of this study was to explore cortisol levels throughout the day in patients with Addison's disease by using SCDC in order to detect under- and over-replacement. Secondly, we studied whether adjustments in glucocorticoid therapy based on SCDC were able to create a more physiological cortisol day curve and whether this had short term effects on QoL.

Patients and methods

Patients

We prospectively studied 20 adults with established primary adrenal insufficiency attending the department of Endocrinology of the University Medical Center Utrecht. All subjects had been on stable GRT either with hydrocortisone or cortisone acetate, with a twice or thrice daily regime. Subjects were excluded if they had acute intercurrent disease, unplanned alteration of GRT dose or regime, if they were pregnant or breastfeeding or if they had gingivitis. All additional medical treatment was not changed during the study, including mineralocorticoid replacement and DHEA. None of the 12 women used contraceptives.

QoL assessment

Before and 4 weeks after adjustment of GRT, general and disease specific QoL was assessed using 3 questionnaires. To measure subjective symptoms of fatigue a 14-item visual analogue scale (VAS) was used.[10] It consists of a 100 mm horizontal line, anchored by word descriptors at each end. Participants were asked to mark the line on the point that they felt to represent their perception of their current state. A high score represented a low QoL. The second QoL questionnaire was the Addison questionnaire (ADD), previously used for measuring QoL in Addison patients.[11] It is a self-rating scale containing 11 items of common complaints of Addison patients. It has a total score of 44. Each item consists of a question asking for the intensity of a certain complaint. The possible answers range from "not present" (0) to "severe" (4). A low score indicates absence of complaints and good well-being. Finally the general health questionnaire (GHQ) measures psychological well-being and focuses on three factors: anxiety and depression, social dysfunction and loss of confidence.[12] It contains 12 items and every item has four possible answers: not at all, no more than usual, more than usual, a lot more than usual. For scoring, the Likert scale (0,1,2,3 from left to right) was used. A score of 11-12 is typical. A score of >15 means evidence of distress and > 20 suggests severe problems and psychological distress.

Salivary cortisol day curve

The salivary day curve was performed before (on current GRT) and 4 weeks after adjustment of glucocorticoid dosage and frequency of daily dosage. Saliva was collected by absorption into a cotton roll (Salivettes R, Sarstedt, Numbrecht, Germany).Samples were taken at fixed moments. The first sample was taken shortly after wakening, before the first dosage of glucocorticoids. After 60-120 minutes the second sample was taken. This was also performed before and after the second and (if applicable) third ingestion of glucocorticoids and just before going to sleep. Before a sample was taken and after every dose of glucocorticoid, participants had to rinse their mouth with water. They were not allowed to brush their teeth or drink or eat 15 minutes before taking the sample. The salivettes were send to the laboratory by mail.

Adjustment of salivary cortisol day curve

Glucocorticoid dose and regime were adjusted based on SCDC assessment. We considered overreplacement or under-replacement to be present if cortisol concentrations were respectively above or under the reference range for normal controls (n=59, 20-60 years), i.e. 9-30 nmol/L in the morning (6.00-12.00 a.m.), 4-12 nmol/L in the afternoon (12.00-18.00 p.m.) and 1-6 nmol/L in the evening (18.00-24.00 p.m.). Over- (or under-) replacement was calculated as duration (h) × magnitude (nmol/L) on different time points. The time that the cortisol concentration was above or below the reference value at the different time points was multiplied by the magnitude of deviation. Optimal replacement over 24 hours was defined as under- or over- replacement of 0 h.nmol/L. All patients on a twice daily regime were given a thrice daily regime in order to facilitate optimal adjustment of SCDC. Based upon the SCDC the dose of hydrocortisone or cortisone acetate was reduced or increased by 2.5-5 mg on one or more time points. After 4 weeks SCDC assessment was repeated and the effect of adjusting GRT was analysed.

Saliva cortisol assessment

Cortisol in saliva was assessed using an in-house competitive radioimmunoassay. The lower limit of quantitation was 0.5 nmol/L. The day-to-day variation ranged from 6.5 to 11.5%. Samples were run in duplicate.

Statistical analysis

All values are presented as mean ± SD unless stated otherwise. All statistical analyses were done with IBM SPSS version 20.0. To compare the results of QoL questionnaires, GRT factors, and over-replacement before and after adjustment of GRT repeated measures analysis was performed. In case of violation of the assumption of sphericity values of Greenhouse-Geisser were used. A $P < 0.05$ was accepted as significant for differences between variables and mean scores in all tests.

Results

Baseline characteristics

The baseline characteristics of the studied patients are given in Table 1. The majority of the patients used hydrocortisone and had a trice daily regime at baseline. All participants used fludrocortisone and 55% used DHEA, mostly women (83%). The cause of Addison's disease was autoimmune adrenalitis in 17 (85%) patients. Clinical and laboratory characteristics related to possible under- or overtreatment are given in Table 2.

Patients, *n*	20
Age, *years (range)*	49,3 (32-66)
Sex, *n (m/f)*	8/12
Duration of disease, *years (range)*	18,5 (3-31)
GRT	
Hydrocortisone	12 (60%)
Mean dose, *mg/day*	25,1 ± 6.1
Median (range)	25.0 (15-35)
Cortisone acetate	8 (40%)
Mean dose, *mg/day*	27,2 ± 6.2
Median (range)	27.5 (15-35)
Regime	
Twice / day	6 (30%)
Thrice / day	14 (70%)

GRT = glucocorticoid replacement therapy

Table 1 Patient characteristics

Hypertension	7 (35%)
BMI (mean, SD)	26 ± 6
Fatigue (n, %)	17 (85%)
Anorexia (n, %)	9 (45%)
Nausea (n, %)	9 (45%)
Sodium mmol/L (mean, SD)	139 ± 3
Potassium mmol/L (mean, SD)	4,0 ± 0,3
Glucose mmol/L (mean, SD)	4,8 ± 0,5

BMI= body mass index

Table 2 Clinical and laboratory characteristics suggesting under- or over-replacement

SCDC assessment

At baseline, under-replacement at one or more of the measured time points, was only present in 3 patients. Over-replacement on the other hand was seen in 18 patients, mainly occurring in the afternoon and evening (figure 1). Total calculated over-replacement was 32.8 h.nmol/L. After adjustment of GRT, over-replacement decreased significantly (figure 2) to 13.3 h nmol/L (p=0.005). Over-replacement decreased more in patients already on a thrice daily regime at baseline (from 36,5 to 14,8 h nmol/L, p=0.017) and in patients using hydrocortisone (from 41.0 to 15,1 h nmol/L, p=0.008).

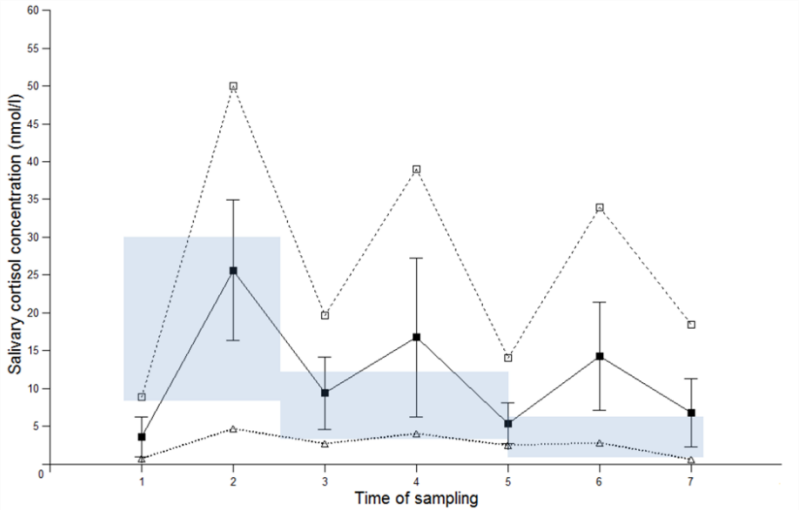

Figure 1 Day curves before adjustment

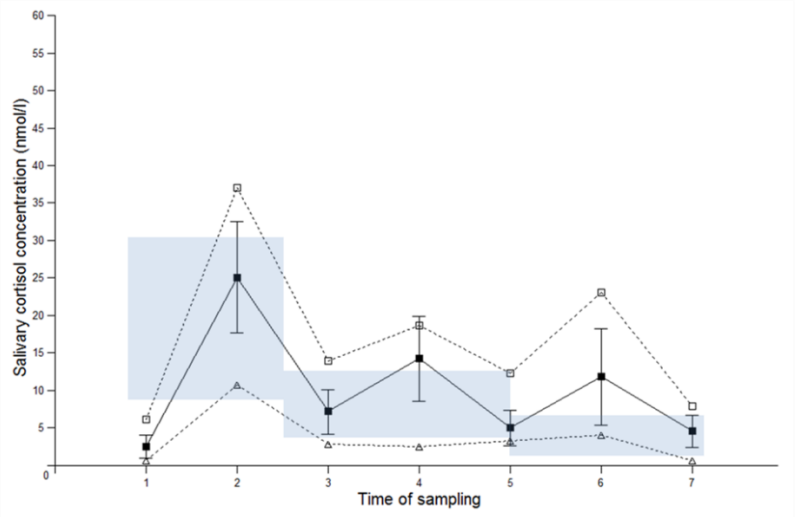

Figure 2 Day curves after adjustment

Glucocorticoid dosage

Mean total daily glucocorticoid dosage did not decrease significantly (26.0 ± 6.1 mg before and 25.4 ± 6.4 mg after adjustment, p= 0.398). After adjustment of GRT there was a significant decrease of the evening glucocorticoid dosage for participants who were on a thrice daily regimen at the start of the study from 7.0 ± 2.6 to 4.8 ±1.8 mg (p= 0.005); for patients on a twice daily regimen the evening dose also decreased from 7.9 ± 3.3 to 4.7 ±1.1 mg (p= 0.017). Tables 3 and 4 show the changes in dose at different time points after adjustment of GRT.

QoL scores

After adjustment of GRT, the ADD changed from 14.4 ± 8.6 to 12.9 ± 7.9 (p=0.131),VAS fatigue improved from 44.4 ±26.0 to 41.8 ± 22.5 (p=0.292) and GHQ scores improved from 12.1± 5.3 to 11.0 ± 3.7 (p=0.349). At the start of the study 70% of patients had a thrice daily regimen.

	Dosage before adjustment GRT	**Dosage after adjustment GRT**
Thrice daily regime at baseline		
Dose 1		
Mean (±SD)	11,8 (±2,4)	12,8 (±2,5)
Median (Range)	10,0 (10,0-15,0)	12,5 (7,5-15)
Dose 2		
Mean (±SD)	7,5 (±2,4)	7,0 (±3,3)
Median (Range)	7,5 (5,0-10,0)	7,5 (2,5-15,0)
Dose 3		
Mean (±SD)	7,5 (±2,9)	5,0 (±2,0)
Median (Range)	6,3 (5,0-12,5)	5,0 (2,5-7,5)
Twice daily regime at baseline		
Dose 1		
Mean (±SD)	12,5 (±3,5)	10,0 (±0,0)
Median (Range)	12,5 (10,0-15,0)	10,0 (10,0-10,0)
Dose 2		
Mean (±SD)	-	5,0 (±0,0)
Median (Range)	-	5,0 (5,0-5,0)
Dose 3		
Mean (±SD)	7,5 (±3,5)	3,8 (±1,8)
Median (Range)	7,5 (5,0-10,0)	3,8 (2,5-5,0)

GRT glucocorticoid replacement regime

Table 3 Hydrocortisone dosage adjustments

	Dosage before adjustment GRT	Dosage after adjustment GRT
Thrice daily regime at baseline		
Dose 1		
Mean (±SD)	14,4 (±4,3)	17,5 (±5,4)
Median (Range)	13,8 (10,0-20,0)	18,8 (10,0-22,5)
Dose 2		
Mean (±SD)	10,0 (±0)	9,4 (±2,4)
Median (Range)	10,0 (10,0-10,0)	8,8 (7,5-12,5)
Dose 3		
Mean (±SD)	5,6 (±1,3)	4,4 (±1,3)
Median (Range)	5,0 (5,0-7,5)	5,0 (2,5-5,0)
Twice daily regime at baseline		
Dose 1		
Mean (±SD)	15,6 (±6,6)	15,6 (±5,2)
Median (Range)	13,8 (10,0-25,0)	16,4 (10,0-20,0)
Dose 2		
Mean (±SD)	-	4,4 (±1,3)
Median (Range)	-	5,0 (2,5-5,0)
Dose 3		
Mean (±SD)	8,1 (±3,8)	4,4 (±1,3)
Median (Range)	7,5 (5,0-12,5)	5,0 (2,5-5,0)

GRT glucocorticoid replacement regime

Table 4 Cortisone acetate dosage adjustments

After the first SCDC assessment, all other patients were given a thrice daily regimen. All QoL scores improved in patients already on a thrice daily regime at baseline, but only the decrease in VAS fatigue score was significant (p=0.026). We found no significant changes in QoL in patients who switched from a twice to a thrice daily regime. There was no significant correlation between general QoL and total daily glucocorticoid dosage, type of GRT and over-replacement. A large number of patients complained about

sleep (65%), concentration (80%) and mood (65%) disturbances before adjustment of GRT. These complaints decreased after adjustment of GRT to 45% (p=0.042), 50% (p=0.010) and 40% (p=0.021) respectively.

Discussion

Patients with Addison's disease are treated with glucocorticoid replacement therapy (GRT) for life. At this time no oral glucocorticoid preparation can precisely mimic normal physiological diurnal variation in cortisol levels. As a consequence, under- and over-replacement occur. We found over- replacement in almost all of our patients, particularly during the afternoon and evening. Under- replacement, on the other hand, was only found in a minority. Inadequate GRT could lead to complications of mild over- replacement with glucocorticoids on the long term such as hypertension, impaired glucose tolerance, immune dysfunction and osteoporosis.[13] These complications could in turn be responsible for the almost twofold increased risk of premature death from cardiovascular and infectious diseases in patients with Addison's disease.[4,5]

Thus optimizing GRT is of great importance, but minor over- or under-replacement is clinically difficult to detect.[14] At present, GRT is assessed mainly by clinical judgment. Various other methods to assess adequacy of GRT have been used, such as random serum cortisol as well as urinary 24-h free cortisol excretion. These are of little value, because they do not give an impression of cortisol concentrations at various moments during the day. Another method of detecting under- or over- replacement is a serum cortisol day curve. Arlt et al assessed quality of GRT with timed serum cortisol concentrations.[15] A newly developed quality of glucocorticoid replacement score based on adding and subtracting points for signs and symptoms of under- or over-replacement was compared to results of three cortisol measurements after morning glucocorticoid dose. Arlt et al found that the mean z score of serum cortisol differed significantly between under- and over-replaced patients but neither group differed significantly from well-replaced patients. Afternoon and evening cortisol measurements were not assessed in their study. A disadvantage of obtaining a serum cortisol day curve is that it is time-consuming and that hospitalization is required which makes it expensive. In our explorative study we used salivary cortisol day curves (SCDC) to monitor GRT. None of the participants experienced any difficulty in performing a SCDC at

home. By using only a single salivary cortisol day curve we were able to reduce over-replacement just by small changes in dosage and regime. The changes did not lead to a significant change of total daily glucocorticoid dose. A SCDC, unlike serum cortisol measurements, can easily be used to detect over-replacement at various moments during the day. In addition, the SCDC is non-invasive, inexpensive and gives a good impression of the free cortisol concentration.[16-18]

An important finding in our study was that over-replacement was found particularly in the afternoon and evening. After reducing over-replacement in the evening, complaints about sleep disturbances significantly decreased. In our patients that switched from a twice to a thrice dosage regime, evening dose significantly decreased. Before adjustment of GRT half of these patients had sleep disturbances, but after dividing and lowering the evening dose sleep disturbances in this group disappeared completely. Sleep disturbances are not unusual in patients with Addison 's disease. Lovas reported sleep disturbances in one third of patients with Addison's disease, characterized by difficulty falling asleep, repeated awakenings and early morning awakenings.[19] A high percentage of patients who took their last glucocorticoid dose after 1800 h reported awakenings and tiredness during daily activities. In addition, we found that small adjustments of GRT resulted in a decrease in VAS fatigue scores in patients on a thrice daily regime, but had little effect on other general QoL scores.

The main limitation of this study is the relatively small number of subjects studied. This could be responsible for the absence of significant changes in some of the QoL scores. In addition we did not assess other clinical endpoints such as cardiometabolic risk factors or adrenal crisis as a results of a short study period. Another limitation is that we did not perform a blinded study to investigate the effect of adjustment of GRT on QoL. However it is reassuring that the reduction in cortisol dose did not seem to be associated with a decrease in QoL.

New pharmaceutical formulations have been developed to provide glucocorticoid replacement that replicates physiology more closely. The reported cortisol profiles of these modified and delayed release glucocorticoids and continuous subcutaneous glucocorticoid infusions seempromising.[20-23] The long-term beneficial effects of physiological glucocorticoid replacement on QoL will have to be determined in future studies.

In conclusion, individual adjustment of GRT based on SCDC to approach normal cortisol concentrations during the day can reduce over-replacement, especially in the evening. This can lead to a reduction of sleep disturbances and fatigue in patients with Addison's disease. A SCDC is a simple and patient friendly tool for assessing GRT and can be useful in the follow-up of patients with Addison's disease.

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PART 3 CHALLENGES IN THE FOLLOW UP OF ADRENAL INSUFFICIENCY

Chapter 4: Decreased physical activity, reduced QoL and presence of debilitating fatigue in patients with Addison's disease

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Submitted

Abstract

Background: Health related quality of life in patients with Addison´s disease has been assessed in various European countries, indicating a reduced quality of life. However, no studies have addressed the impact of Addison´s disease on physical activity.

Objective: The aim of this study was to investigate the ability of patient with Addison's disease to be physically active and to study quality of life in Dutch patients with Addison's disease particularly regarding the presence of fatigue.

Methods: In this cross-sectional study, a postal survey was performed among Dutch patients with Addison's disease on stable glucocorticoid replacement therapy with hydrocortisone or cortisone acetate. For quality of life and physical activity assessment patients completed general and health related quality of life and physical activity questionnaires, and scores were compared to Dutch controls.

Results: A total of 328 patients with Addison's disease were included in this study. In patients with Addison´s disease only 45.7% met the standard of physical activity (Combinorm) compared to 67.8% of Dutch controls ($p<0.01$). Forty-eight percent of patients showed abnormal fatigue, while 61% had severe fatigue. The CIS fatigue scores were significantly higher compared to controls ($p<0.01$). We found reduced general subjective health related QoL scores in both male and female patients, especially in patients <65 years of age.

Conclusion: Physical activity is decreased in patients with Addison´s disease, combined with a reduced subjective health related QoL and increased fatigue.

Introduction

After the report of several cases of adrenal insufficiency by Thomas Addison in 1855, many years had to pass before treatment of patients with Addison's disease (AD) became a reality.[1,2] Effective glucocorticoid replacement therapy (GRT) greatly improved prognosis in patients with AD.[3] However, many patients are still experiencing various complaints, despite treatment with glucocorticoids, mineralocorticoids and sometimes dehydroepiandrosterone (DHEA). In recent years several studies were performed on health related quality of life (HRQoL) in patients with primary and secondary adrenal insufficiency, demonstrating a reduced quality of life (QoL).[4-16] Musculoskeletal complaints, fatigue and reduced vitality seem to be more common in AD.[17,18] This could lead to physical inactivity resulting in additional cardiovascular health risks. No studies in patients with AD have focussed on physical activity. Therefore the aim of this study was to investigate the ability of patients with AD to be physically active. In addition, we studied QoL and common complaints experienced in daily life by patients with AD and we studied factors influencing QoL.

Patients and methods

Patients and reference population

In total 112 patients with confirmed AD on stable replacement therapy with hydrocortisone or cortisone acetate, attending the outpatient clinics of University Medical Center Utrecht and Radboud University Medical Center Nijmegen and 500 members with AD of The Dutch Association of Addison and Cushing patients (NVACP) were requested to participate in a postal survey. The underlying diagnosis of AD (primary adrenal insufficiency) was verified by review of the medical records of participants treated at the University Medical Centers. This was performed by two independent physicians. The underlying cause of adrenal insufficiency of all members of the NVACP is registered and kept up to date. Written informed consent was obtained from all subjects prior to participation and the study was approved by the Committee for Ethics in Medical Research of University Medical Center Utrecht.

Assessment of Quality of life

QoL evaluation was performed using the Short Form 36 (SF 36), the Checklist Individual Strength (CIS) and a general questionnaire comprising questions about age, marital status, education, working abilities, occupational status, duration of disease, co-morbidities and use of medication. Subjects were asked to complete questionnaires without consulting family or friends. The SF36 is one of the most widely used generic health measures. It consists of eight domains: limitations in physical and social functioning (PF,SF), limitations in role activities because of physical or emotional problems (RP, RE), bodily pain (BP), general health perception (GH), vitality (VT) and mental health (MH), completed with physical and mental health component summaries (PCS, MCS).[19,20] Higher scores indicate less pain or less impaired functioning. Missing data in the questionnaires were replaced by the mean scores across the completed items, as recommended for SF 36. The Checklist Individual Strength (CIS) is a 20-item questionnaire that captures four dimensions of fatigue, including subjective experience of fatigue, reduction in motivation, activity and concentration. The person has to indicate on a 7-point scale to what extent the particular statement applies to him or her. High scores indicate a high level of fatigue, a decreased level of concentration, low motivation and a low level of physical activity. A total score of 76 or higher indicates problematic fatigue, a score higher than 27 on the subscale “subjective fatigue” indicates abnormal fatigue and a score higher than 37 on the subscale “subjective fatigue” indicates severe fatigue. The CIS is well validated showing good reliability and construct validity.[21-24]

Physical activity evaluation

Every year trends in physical activity, participation in sports and sports injuries are studied in the Netherlands (OBiN: Ongevallen en Bewegen in Nederland, www.veiligheid.nl). Part of this survey consists of a questionnaire regarding physical activity in daily life (Monitor Bewegen en Gezondheid). For adults the Dutch standard of healthy physical exercise (NNGB Nederlandse Norm Gezond Bewegen) is defined by moderately intensive physical exercise (4-6.5 Metabolic Equivalent of Task (MET)) for 30 minutes during 5 days a week. The Fitnorm is defined by 20 minutes of intensive physical exercise at least 3 times a week. A person meets the Combinorm if he or she meets the criteria of the NNGB and/or Fitnorm. Dutch

control data were provided by TNO, an independent Dutch research organization (www.tno.nl).

Assessment of comorbidity

Additional endocrine or other health problems were explored. Self-reported concomitant disease was regarded as relevant to QoL and defined as pulmonary disease (chronic obstructive lung disease, asthma, bronchitis), cardiovascular disease (heart failure, coronary artery disease, valve disorders, cardiac arrhythmias, deep venous thrombosis), hypertension, hypercholesterolemia, gastro-intestinal disease (gastro esophageal reflux disease, inflammatory bowel disease, hepatitis/cirrhosis, pancreatitis), neurological disease (cerebrovascular disease, polyneuropathy, migraine), psychiatric disease (depression, anxiety/panic disorders), systemic auto-immune disease (rheumatoid arthritis, systemic lupus erythematosus, sarcoidosis), musculoskeletal disease/complaints (osteoporosis, myalgia) or (history of) malignancy.

Statistical analysis

Reference data for SF 36 scores were obtained from a Dutch National Health Survey comprising a representative random sample of 1718 males and females from the Dutch population aged between 18 and 86 years[19]. CIS scores of Dutch AD patients were compared to reported Dutch CIS scores of healthy controls[21] and patients with other chronic diseases, such as multiple sclerosis (MS)[22], chronic fatigue syndrome[25], CVA and cancer survivors[27]. Combinorm scores of our Dutch AD patients were compared to Dutch age and sex matched controls. Additionally, we analyzed the impact of patient characteristics and replacement regime on QoL (SF 36, CIS) and physical activity (Combinorm). Generalized linear models were used for multivariate analysis of SF36 scores to accommodate both non-normal response distributions and transformations to linearity. Estimation of parameters was done using the method of least squares (Maximum Likelihood estimation). Both main effects as well as interaction was studied for each variable. Multivariate analysis for CIS fatigue scores and physical activity Combinorm scores was performed using logistic regression analysis. The

independent variables relevant to the models were selected from univariate analysis (threshold p-value ≤0.2) or in case of clinical relevance. Univariate analysis for categorical variables and QoL was performed using Mann-Whitney U test. Spearman's correlation coefficient was calculated for continuous variables. The following independent variables were included in multivariate analysis: age, disease duration, sex, location (university medical center vs NVACP), comorbidity (present vs absent), partner (no vs yes), education (low vs high), paid work (no vs yes), preparation (hydrocortisone vs cortisone acetate), total daily glucocorticoid dosage, glucocorticoid frequency (2 vs 3 times daily), fludrocortisone (no vs yes), DHEA (no vs yes). For CIS and Combinorm separate comorbidities were included, respectively diabetes mellitus, gastro-intestinal disease, cardiovascular disease, pulmonary disease, psychiatric disease and musculoskeletal disease (no vs yes). Data were presented as mean, median, percentiles and range where appropriate. Analyses were performed using the statistical software package SPSS, version 20. Significance was accepted if $P < 0.05$.

Results

A total of 612 patients with AD were contacted and 343 patients responded (University Medical Centers n= 66, NVACP n= 277 (response rates of respectively 59% and 55%)). Four patients were excluded because they had secondary adrenal insufficiency (NVACP). After exclusion of 11 subjects using prednisone or dexamethasone as glucocorticoid replacement, 328 subjects were eligible for comparison with the normative data. Patient characteristics and replacement regimens are summarized in table 1. More males had isolated AD compared to females, who had accompanying hypothyroidism in almost 50% of cases. The majority of patients used hydrocortisone (74.1%). A total of 87% received fludrocortisone as mineralocorticoid replacement and DHEA replacement was used by 23%. In more than 60% of patients hydrocortisone was used three times a day. In contrast, cortisone acetate was more frequently used twice a day (61.2%). Seventy-seven percent of AD patients had one or more co-morbidities of which hypertension and hypercholesterolemia were present most frequently, followed by pulmonary disease and musculoskeletal diseases/complaints.

	Total (n = 328)	**Men (n = 105)**	**Women (n = 223)**
Age (years, mean ± SD, range**)**	52.6 ± 12.8 18-86	49.5 ± 13.6 18-80	54.1 ± 12.1 19-86
Duration of disease after diagnosis (years, mean ± SD, range)	15.6 ± 12.8 0.5-72	18.5 ± 14.8 1-63	14.2 ± 11.5 1-72
Isolated Addison's disease, n (%) APS type 1, n (%) APS type 2, n (%)	174 (53.0) 5 (1.5) 149 (45.4)	75 (71.4) 3 (2.9) 27 (25.7)	99 (44.4) 2 (0.9) 122 (54.7)
Glucocorticoid replacement Hydrocortisone, n (%) *dose (mg/day, mean*± SD*)* Cortisone acetate, n (%) *dose (mg/day, mean*± SD*)*	 243 (74.1) 25.1 ± 7.4 85 (25.9) 34.5 ± 9.3	 74 (70.5) 26.6 ± 8.9 31 (29.5) 35.2 ±11.5	 169 (75.8) 24.4 ± 6.5 54 (24.2) 34.0 ±7.9
Mineralocorticoid replacement Fludrocortisone (%) *Dose (mcg/day)*	 286 (87.2) 89.7 ± 36.7	 93 (88.6) 91.4 ±37.4	 193 (86.5) 88.9 ± 36.3
Androgen replacement DHEA (%) *dose (mg/day)*	 76 (23.2) 36.1 ± 17.7	 16 (15.2) 45.5 ±12.1	 60 (26.9) 33.6 ± 18.2

APS 1 and APS 2: autoimmune polyendocrine syndrome type 1 and 2; n: number; DHEA: dehydroepiandrosterone

Table 1: Patient characteristics

Physical activity (Combinorm)

In patients with AD 45.7% [95% CI 0.399-0.516] met the standard of physical activity (Combinorm) compared to 67.8% [95% CI 0.622-0.732] of Dutch controls (p<0.01). Multivariate analysis showed no predictors for lower physical activity in patients with AD. Patients who met the Combinorm had significantly lower total CIS fatigue scores (66.2 ±28.1 vs 79.4 ±31.7, p<0.01) and lower "subjective fatigue" scores (28.2± 14.0 vs 34.8 ± 15.3, p<0.01). Regarding general health related QoL we found significantly higher SF36 scores in patients who met the Combinorm (PCS 40.0± 11.4 vs 44.9± 10.9 p<0.01) except for MH (MCS 46.4±11.4 vs 48.9±11.1 p=0.05).

General health related quality of life (SF36)

When comparing SF36 QoL scores between patients and controls we found that in male AD patients under the age of 40 years, QoL scores in all eight SF36 dimensions and physical and

mental health component summaries were significantly decreased compared to Dutch male controls (table 2).

	PF	RP	BP	GH	VT	SF	RE	MH
(a) Total								
Normative	(n=965)	(n=960)	(n=970)	(n=963)	(n=969)	(n=970)	(n=955)	(n=968)
Mean±SD	85.4±21.0	78.7±34.1	77.3±22.7	71.2±20.6	71.9±18.3	86.0±21.1	85.5±29.9	79.3±16.4
Patients	(n=105)	(n=105)	(n=105)	(n=105)	(n=105)	(n=105)	(n=105)	(n=105)
Mean	79.9±22.8	56.4±43.2	71.6±26.8	54.1±25.6	52.3±21.7	74.2±26.0	65.1±43.5	74.0±18.7
P-value	*P=0.02*	*P<0.01*	*P=0.02*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*
b) <40 yrs								
Normative	(n=305)	(n=304)	(n=305)	(n=304)	(n=304)	(n=305)	(n=303)	(n=304)
Mean	95.5±9.3	88.0±25.0	84.1±19.1	79.9±17.4	74.9±14.7	90.1±18.3	90.1±24.0	82.2±13.9
Patients	(n=25)	(n=25)	(n=25)	(n=25)	(n=25)	(n=25)	(n=25)	(n=25)
Mean	87.2±18.3	63.0±44.6	72.9±25.9	57.0±24.3	59.3±21.8	74.5±29.4	62.7±44.4	68.8±25.0
P-value	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*
c) >65 yrs								
Normative	(n=196)	(n=182)	(n=198)	(n=193)	(n=198)	(n=198)	(n=188)	(n=197)
Mean	66.6±27.7	66.0±38.3	78.2±25.1	61.5±21.1	66.7±22.4	81.1±23.8	78.8±35.6	78.2±18.0
Patients	(n=13)	(n=13)	(n=13)	(n=13)	(n=13)	(n=13)	(n=13)	(n=13)
Mean	71.5±27.2	50.0±46.8	71.5±24.9	50.4±29.0	65.8±20.5	76.9±23.9	56.4±49.8	76.6±17.0
P-value	P=0.54	P=0.15	P=0.35	P=0.08	P=0.89	P=0.54	P=*0.03*	P=0.76

PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health

Table 2: SF-36 scores in male AD patients and controls

In male AD patients >65 years of age only RE was significantly decreased compared to controls. In male AD patients <65 years of age we found decreased scores in 6 SF36 dimensions (RP, GH, VT, SF, RE) and in the physical health component summary. In female AD patients we found roughly comparable results: under the age of 40 years QoL scores in all eight SF36 dimensions and physical and mental health component summaries were significantly decreased compared to Dutch female controls (table 3). GH, VT and RE were significantly decreased in female AD patients <74 years of age.

	PF	RP	BP	GH	VT	SF	RE	MH
a) Total								
Normative	(n=753)	(n=733)	(n=759)	(n=742)	(n=746)	(n=759)	(n=731)	(n=746)
Mean	80.4±24.2	73.8±38.5	71.9±23.8	69.9±20.6	64.3±19.7	82.0±23.5	78.5±35.7	73.7±18.2
Patients	(n=223)	(n=222)	(n=223)	(n=223)	(n=222)	(n=223)	(n=223)	(n=222)
Mean	70.0±25.4	49.9±44.4	65.7±25.5	49.5±23.1	51.6±22.8	68.6±27.2	62.6±44.4	72.0±17.5
P-value	*P<0.01*	*P<0.01*	*P<0.01*	P<0.01	*P<0.01*	*P<0.01*	*P<0.01*	P=0.49
b) <40 yrs								
Normative	(n=358)	(n=356)	(n=359)	(n=359)	(n=358)	(n=359)	(n=355)	(n=358)
Mean	91.6±12.9	85.5±29.3	79.2±19.0	77.5±17.1	67.8±16.7	86.2±19.2	81.4±33.5	76.2±15.3
Patients	(n=24)	(n=24)	(n=24)	(n=24)	(n=24)	(n=24)	(n=24)	(n=24)
Mean	78.5±19.5	38.5±36.8	64.8±22.8	45.4±20.3	44.2±15.2	61.5±32.3	59.7±42.8	69.2±16.5
P-value	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P<0.01*	*P=0.03*
c) >65 yrs								
Normative	(n=158)	(n=144)	(n=161)	(n=150)	(n=152)	(n=161)	(n=143)	(n=153)
Mean	55.4±28.5	49.0±43.0	62.9±26.9	56.6±19.3	58.3±20.3	73.6±28.8	72.3±35.7	69.5±19.6
Patients	(n=42)	(n=41)	(n=42)	(n=42)	(n=41)	(n=42)	(n=42)	(n=41)
Mean	57.0±25.0	44.5±43.8	59.6±24.6	45.6±19.4	47.8±21.2	67.3±25.3	54.0±47.1	68.1±16.7
P-value	P=0.74	P=0.56	P=0.47	*P<0.01*	*P<0.01*	P=0.20	*P<0.01*	P=0.73

PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health

Table 3: SF-36 scores in female AD patients and controls

After multivariate analysis of all 8 SF36 dimensions and physical and mental health component summaries in patients with AD, we found significantly lower PF scores in female AD patients (p=0.03). Significantly lower PF (p=0.01), RP (p=0.04), VT (p<0.01), GH (p<0.01) and PCS (p<0.01) scores were found in patients with comorbidities compared with patients without comorbidities . A lower level of education in AD patients was associated with decreased PF (p<0.01) and BP (p=0.02) scores. In patients without paid work lower PF (p<0.01), BP (p=0.01), GH (p<0.01) and PCS (p<0.01) scores were found. Regarding replacement therapy we found significantly lower RP (p=0.04), VT (p=0.03) and PCS (p=0.02) scores in patients with a 3 times daily glucocorticoid replacement regime compared with a 2 times daily regime and lower PF (p<0.01), SF (p<0.01) and PCS (p=0.01) in patients not using fludrocortisone compared to patients with fludrocortisone.

Fatigue (CIS)

Forty-eight percent of patients with AD had a total CIS score of ≥76, indicating problematic fatigue. On the subscale of “subjective fatigue” 61% had a score >27 indicating abnormal

fatigue and 43% had a score >37 indicating severe fatigue. Mean total CIS score in patients with AD was 74.1± 30.8, a score significantly higher compared to healthy controls (difference mean 32.6 [95% CI 24.0-41.4], p<0.01). On the subscale "subjective fatigue" patients with AD had higher scores (32.1 ± 15.0) compared to healthy controls (difference mean 14.8 [95% CI 10.6-19.0] p<0.01). Mean total CIS score and subscale scores for "subjective fatigue" were compared to other patient groups (table 4).

	Total CIS score		**Subscale subjective fatigue**	
	Mean	**sd**	**Mean**	**sd**
Addison, this study (n= 328)	74.1	30.8	32.1	14.9
Healthy controls (n= 53)	41.5	19.8	17.3	10.1
CFS (n= 758)	113.1	14.6	51.7	4.6
MS (n=87)	85.1	21.9	40.2	11.8
CVA (n=73)	93.6	32.2	33.2	5.4
Cancer survivors (n= 84)	49.0	27.2	21.1	13.7

CFS: chronic fatigue syndrome, MS: multiple sclerosis, CVA: cerebrovascular accident, sd: standard deviation,

Table 4: CIS scores in AD, healthy controls and other patients groups (Ref 21)

Patients with AD had a higher total CIS score compared to cancer survivors (difference mean 25.0 [95% CI 17-32] p<0.01), but lower scores compared to patients with multiple sclerosis (MS), chronic fatigue syndrome or patients with stroke. On the subscale "subjective fatigue" patients with AD had higher scores compared to cancer survivors (difference mean 11.0 [95% CI 7.5-14.5] p<0.01), equal scores compared to patients with stroke and lower scores compared to patients with chronic fatigue syndrome or MS. Multivariate analysis for total CIS and the subscale "subjective fatigue" scores showed more fatigue in patients using a 3 times daily glucocorticoid replacement regime (OR 1.9 [95% CI 1.11-3.22] p= 0.02 and OR 2.0

[95% CI 1.11-3.21] p= 0.02, respectively). Patients using fludrocortisone had a lower subjective fatigue score (OR 0.9 [95% CI 0.11-0.79] p=0.02). Patients with comorbidity had higher subjective fatigue scores (pulmonary disease OR 2.3 [95% CI 1.01-5.45] p= 0.04, psychiatric disease OR 4.9 [95% CI 1.14-20.75] p= 0.03). In patients with a higher level of education lower "subjective fatigue" scores were seen (OR 0.57 [95% CI 0.32-0.97] p= 0.04).

QoL	Domain	Dutch AD Mean scores (n=328)	Dutch Normative Mean scores (n=1718)	European AD Range of mean scores (n=222)	European Normative Range of mean scores
Physical health	PF	73.2	83.0	80-92	84-88
	RP	52.0	76.4	46-92	77-87
	BP	67.6	74.9	76-86	66-78
General health	GH	50.9	70.7	56-82	66-76
	VT	53.8	68.6	47-77	58-60
Mental Health	SF	70.4	84.0	78-98	82-87
	RE	63.4	82.3	56-98	56-89
	MH	72.6	76.8	67-89	71-78

AD Addison's disease, QoL quality of life, PF: physical functioning, RP: role physical, BP: bodily pain, GH: general health, VT: vitality, SF: social functioning, RE: role emotional, MH: mental health

Table 5 : Dutch Addison patients mean SF-36 scores compared to published European Addison mean SF-36 scores (Ref: 6, 8, 15, 32)

Discussion

To our knowledge, this is the first study that reports decreased physical activity combined with a reduced subjective health related QoL and increased fatigue in patients with AD. Fatigue is considered to be a major complaint in patients with AD. This was supported by our results of the CIS fatigue questionnaire. A high percentage of our patients showed abnormal or severe fatigue. The CIS total fatigue scores and scores on the subscale "subjective fatigue" were significantly higher compared to controls. In order to be able to contextualize this important complaint we compared scores between patients with AD and other chronic diseases and found higher scores in AD patients compared to cancer survivors, equal scores compared to patients with stroke and lower scores compared to patients with chronic

fatigue syndrome and MS. Considering the burden of fatigue, it is not surprising that patients with AD are less physically active. Only 47.5% of AD patients met the Combinorm compared to 67.8% of Dutch controls. Furthermore, patients with AD complain about myalgia, arthralgia and weakness. This could potentially further compromise the ability to be physically active. At present it is not exactly clear why patients with AD are afflicted by these complaints. Physical exercise represents a stress condition influencing many systems in the body, especially the cardiopulmonary system and the musculoskeletal system. Normally, exercise is a potent stimulus of the hypothalamic-pituitary-adrenal (HPA)-axis.[28,29] The increased endogenous cortisol secretion results in important metabolic and cardiovascular effects. Glucocorticoids play an important role in the mobilization of energy reserves by stimulating gluconeogenesis, promoting lipolysis and increasing protein catabolism. Patients with AD cannot easily meet this increased demand of adrenal steroids in case of physical exercise because they are dependent on glucocorticoid replacement therapy. Moreover, Bornstein et al suggested that high local concentrations of cortisol in the adrenal gland are necessary to produce sufficient catecholamines.[30] It is well known that during physical activity plasma catecholamines are elevated and that catecholamines play an important role during exercise.[31] AD patients may be unable to generate sufficient catecholamine production in the adrenal glands. We speculate that these factors could play an additional role in physical inactivity and musculoskeletal complaints in AD, alongside fatigue and a decreased QoL.

We found reduced general subjective health related QoL scores in both male and female AD patients. There was an inverse relation between age and impaired QoL. QoL was only impaired in patients < 65 years of age. This is probably related to the dispersion of signs and symptoms with increasing age, leading to comparable QoL scores between patients and controls >65 years of age. When comparing mean SF36 scores among AD patients from different European countries (table 5), we found slightly lower scores in our Dutch patients in 4 of 8 domains, respectively PF, BP, GH, and SF.[6,8,15,32] In addition, RP, RE and MH scores were also slightly lower except for those reported by Gurnell[31] (RP, RE) and Hahner[8] (MH score). In contrast, VT in Dutch patients was somewhat higher compared to all other studies. More importantly, the pattern of impairment in general subjective health related QoL between European AD patients seems consistent.

We studied factors possibly predicting decreased QoL, fatigue and physical inactivity. With respect to replacement therapy, two predictors were found: fludrocortisone usage and frequency of glucocorticoid dosage. In patients not using fludrocortisone lower SF36 scores (PF, SF, PCS) and higher CIS fatigue scores were found. In patients on a thrice daily regime we found higher fatigue and lower SF36 scores (RP, VT, PCS scores). Several studies have investigated the effect of replacement regime and total daily glucocorticoid dosage on QoL. Riedel et al investigated QoL in a small cohort of patients with adrenal insufficiency.[4] They found better QoL scores in patients on a twice daily regime compared to a single daily dose. Bleicken et al showed a trend towards a more impaired health status in patients on thrice daily regimes, which reached statistical significance for SF in the 15-20 mg/day group and for PF in the 20-25 mg/day group.[9] Others studies have shown no superiority of a twice, thrice or four times daily regime. An explanation for the observed difference in our study could be confounding by indication between these groups. Patients on a twice daily regime experiencing complaints, are often switched to a thrice daily regime aiming to improve their QoL by mimicking normal physiology as closely as possible. Patients without complaints are more likely to stay on a twice daily regime. This could have generated a bias. The clinical significance of the difference between a twice or thrice daily regime seems small, supported by the fact that all other domains and Combinorm results were comparable in patients on a twice or thrice daily regime. Additional comorbidity, low educational level and not having a paid job led to lower SF36 scores (PF, RP, BP, VT, GH, PCS) and higher CIS fatigue scores.

Our study has several limitations. As a result of our cross-sectional design, bias cannot be ruled out. Recruitment of patients followed up in an academic center or members of a patient support organization based on a postal survey with only measurement of responders, may theoretically lead to bias towards patients with more symptoms. However, QoL and fatigue results did not differ significantly among patients recruited from the NVACP and the University Medical Centers, and the pattern of impaired QoL was nearly identical to the other reported studies on QoL in AD, making it unlikely that these results were influenced by selection bias. Another limitation is that we compared our results in patients with AD with normative data from the general population instead of including our own matched control group.

Interpretation of QoL and fatigue scores is challenging, especially in terms of clinical significance. But the clinical relevance of the impaired QoL and increased fatigue found in our study is supported by the size of the differences in scores and the restriction in physical activity in patients with AD, an important aspect of daily life. Physical inactivity could be very detrimental in AD, because the prevalence of other cardiovascular risk factors is already increased and it has been demonstrated that patients with AD have an up to two-fold increased mortality rate from cardiovascular disease.[33,34] Here lies a challenge for future studies to investigate the possible mechanisms underlying complaints leading to physical inactivity and to apply adjustments in replacement therapy to improve physical activity and ultimately improve QoL of patients with AD.

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Chapter 5: Prevalence of the metabolic syndrome is not increased in Addison's disease, despite more abdominal obesity, hypertension and hypertriglyceridemia in female patients

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Submitted

Abstract

Background: Patients with Addison's disease (AD) are at risk of mild, but structural excessive glucocorticoid exposure, possibly leading to obesity, hypertension and dyslipidemia. The aim of this study was to assess the prevalence of abnormal anthropometric and metabolic parameters and the metabolic syndrome (MetS) in AD.

Methods: Sixty-nine patients with AD attending two university outpatient clinics in The Netherlands were included in this cross-sectional observational study and anthropometric and metabolic parameters were measured. The prevalence of MetS was assessed using NCEP ATP III criteria. The results were compared to age and sex matched controls. Multiple logistic regression analysis was performed to study independent risk factors for MetS.

Results: The prevalence of abdominal obesity, hypertension and hypertriglyceridemia was higher in female, but not in male patients compared to controls. MetS was present in 23% of patients with AD. There was no difference in the prevalence of MetS between male and female patients. MetS was equally present in female patients and controls, but more prevalent in male controls, but this difference was absent above 60 years of age. Age was the only independent risk factor for MetS (odds 1.1, 95% CI 1.0-1.2).

Conclusion: The prevalence of abnormal anthropometric and metabolic parameters is increased in female patients with AD. Cardiovascular risk assessment and intervention are warranted in the management of patients with AD, especially in females.

Introduction

After the discovery and synthesis of adrenocortical steroids, effective glucocorticoid replacement therapy (GRT) greatly improved prognosis in patients with Addison's disease (AD).[1] However, treatment is still far from optimal, possibly leading to co-morbidity in the long run.[2] One of the challenges in optimizing GRT in AD is avoiding mild, but structural glucocorticoid over-replacement. We found over-replacement in almost 70% of patients with AD, based on salivary cortisol day curves.[3] It has been proposed that excess glucocorticoids can contribute to the metabolic syndrome (MetS) and cardiovascular disease.[4,5] Previous studies have indeed reported abnormal anthropometric and metabolic parameters in patients treated with glucocorticoids, such as increased triglycerides (TG), decreased high density lipoprotein cholesterol and a preponderance of small dense low density lipoprotein particles.[6-9] In addition, it has been demonstrated that patients with AD have an up to two-fold increased mortality rate from cardiovascular disease.[10,11] Previous studies have focused on individual cardiovascular risk factors, and so far data on the prevalence of MetS in patients with AD are lacking. Therefore we assessed the metabolic profile and the prevalence of MetS in Dutch patients with AD.

Methods

Subjects

Sixty-nine adult patients with confirmed primary adrenal insufficiency using conventional glucocorticoid and mineralocorticoid replacement, attending the outpatient clinics of University Medical Center Utrecht and Radboud University Medical Center Nijmegen were included in this cross-sectional observational study. The underlying diagnosis of AD was verified by review of the medical records. We studied patient demographics and details on replacement regimes such as type, daily dosage and dose frequency of glucocorticoids, use of mineralocorticoids, sex hormones and dehydroepiandrosterone (DHEA). In case patients used cortisone acetate, hydrocortisone equivalent dosage was calculated (hydrocortisone 20 mg, cortisone acetate 25 mg) and used for further analysis. All concomitant medication was

also documented. Furthermore co-morbidity, including endocrine and cardiovascular disease (myocardial infarction) was assessed. All patients gave their informed consent to participate in the study. The results of anthropometric and laboratory measurements of AD patients were compared to age and sex matched controls from the general Dutch population. In 2009-2010 adults aged 18-70 years were randomly recruited from different regions in the Netherlands (North-East, North-West, Central, South-East, South-West) in order to get a representative picture of the prevalence of cardiovascular risk factors in the Netherlands. Mean age was 52.9 and 51.8 years in males and females, respectively. Demographics were collected using questionnaires and blood samples were taken in the morning after an overnight fast. A total of 2056 males and 2457 females participated (www.RIVM.nl/NLDEMAAT).

Measurements

Anthropometric parameters in AD (weight, height, blood pressure, body mass index (BMI) and waist circumference) were measured. Height and body weight were measured to the nearest 1.0 mm and 0.1 kg, respectively. Waist circumference measurement was made at minimal inspiration, midway between the lowest rib and the iliac crest. Blood pressure was measured according to guidelines from the World Health Organization International Society of Hypertension.[12] The following laboratory parameters were measured: glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides. Blood samples were taken at fast in the morning, between 8.00 and 9.00 a.m. Serum determinations were performed by standard laboratory methods. Glucose (mmol/L), total cholesterol (mmol/L), HDL cholesterol (mmol/L) and triglycerides (mmol/L) were measured using the Beckman-Coulter AU5811 analyser. Between run CV: cholesterol 3.5 ± 1.4%; 7.0 ± 1.05%, HDL cholesterol: 0.98 ± 1.4%; 2.2 ± 1.0%, Glucose: 4.8 ± 2.1%; 19.5 ± 1.6%. LDL cholesterol (mmol/L) was calculated (LDL-cholesterol = total-cholesterol – HDL-cholesterol – 0.45 x triglycerides (mmol/L)).

Defining overweight and obesity

Body mass index (BMI) was calculated as body weight in kilograms divided by body height in meters squared. A BMI between 25 and 29.9 was considered overweight and a BMI of 30 or higher was considered obese.[13] Abdominal adiposity was defined by a waist circumference ≥ 102 cm in males and ≥ 88 cm in females.

Defining hypertension

Patients and controls with a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mm Hg or when treated with antihypertensive drugs were considered to have hypertension.

Defining abnormal lipid level, fasting glucose and diabetes mellitus

Abnormal lipid concentrations were defined as follows: total cholesterol ≥6.5 mmol/L, triglycerides ≥1.7 mmol/L, HDL cholesterol <1.03 mmol/l in males and <1.3 mmol/l in females, LDL cholesterol > 3.5 mmol/L. Impaired glucose tolerance was defined as glucose < 5.6 mmol/L, and diabetes mellitus as fasting glucose ≥7.0 mmol/L. In addition, patients and controls using lipid-lowering drugs or antidiabetic drugs were considered to have abnormal lipid levels or diabetes mellitus, respectively.

Criteria for the clinical diagnosis of MetS

According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria, as modified by the American Heart Association/National Heart, Lung and Blood Institute[15], the following criteria were used for the presence of the metabolic syndrome (any 3 of 5 constitute diagnosis of MetS): abdominal obesity was defined as waist circumference greater than or equal to either 102 cm (men) or 88 cm (women), elevated fasting glucose as glucose levels ≥ 5.6 mmol/L (≥ 100 mg/dl) or on drug treatment for elevated glucose, elevated triglycerides as triglyceride levels of ≥1.7 mmol/L (≥ 150 mg/dl) or

on drug treatment for elevated triglycerides, reduced HDL cholesterol as HDL cholesterol levels <1.03 mmol/L (<40 mg/dl) in men or <1.3 mmol/L (<50 mg/dl) in women or on drug treatment for reduced HDL, elevated blood pressure as blood pressure ≥130 mm Hg systolic or ≥85 mm Hg diastolic or on antihypertensive drug treatment in a patient with a history of hypertension.

Statistical analysis

Comparison of means was performed by One Sample T-test. Additionally, we analyzed the impact of patient characteristics and replacement regime on components of the metabolic syndrome. Univariate analysis for categorical variables was performed using Mann-Whitney U test. Spearman's correlation coefficient was calculated for continuous variables. Multivariate analysis was performed using logistic regression. The independent variables relevant to the models were selected from univariate analysis (threshold p-value ≤0.2: age, history of cardiovascular disease, glucocorticoid preparation, midday dosage 12.00-13.00 h.) or based on clinical relevance (sex, duration of disease, total daily glucocorticoid dosage, glucocorticoid frequency, use of DHEA). Data were presented as mean, median, percentiles and range where appropriate. Analyses were performed using the statistical software package SPSS, version 20. Significance was accepted if P <0.05.

Results

Sixty-nine patients with primary adrenal insufficiency participated in our study (Table 1). Adrenal insufficiency was caused by auto-immune adrenalitis in at least 94% of patients, with a mean duration after diagnosis of 16.7 years. Twenty percent of patients used antihypertensive medication, 22% used statins and 17% had a history of a cardiovascular event. The majority of patients used hydrocortisone (78%), 22% used cortisone acetate as glucocorticoid replacement. The mean glucocorticoid dosage was 23.2 ± 6.3 mg/day and 33.5 ± 4.4 mg/day for hydrocortisone and cortisone acetate, respectively.

	N (%) **Mean ± SD**
Age (years)	51.8 ± 12.0
Female sex	40 (58.0)
Duration of disease after diagnosis (years)	16.7 ± 11.1
Glucocorticoid replacement	
Hydrocortisone	54 (78.3)
Dosage (mg/day)	23.2 ± 6,3
2 versus 3 times daily (%)	30 vs. 65
Cortisone acetate	15 (21.7)
Mean dosage (mg/day)	33.5 ± 4.4
2 versus 3 times daily (%)	60 vs. 40
Fludrocortisone (%)	69 (100)
DHEA (%)	28 (40.6)
Antihypertensive drugs (%)	14 (20.3)
Statins (%)	15 (21.7)
History of cardiovascular disease (%)	12 (17.4)

Table 1 Baseline characteristics of 69 patients with Addison´s disease

Overweight, obesity and abdominal obesity

There were no significant differences in the prevalence of being overweight or obese between AD patients and controls. Thirty-two percent and 7% of male patients were overweight or obese, respectively, compared to 47% and 13% of male controls. In female patients these percentages were 28% and 18%, compared to 30% and 14% in controls. The prevalence of abdominal adiposity was not significantly different in male patients and controls (18% vs 27%). There was, however, a significant difference in the occurrence of abdominal adiposity between female AD patients and controls (64% [95% CI 49.5-77.9] vs 39% [95% CI 36.9-41.2]. The frequency of abdominal obesity was also significantly higher in female patients compared to male patients (64% [95% CI 48.5-77.0] vs 18% [95% CI 8.1-35.4]). Prevalence of abdominal obesity increased with age in both patients and controls. There was a correlation between BMI and waist circumference in both female (correlation coefficient 0.78, P <0.01) and male (correlation coefficient 0.87, P <0.01) patients.

Hypertension

Hypertension was equally present in male patients and controls (38% [95% CI 22.7-56.1] vs 37% [95% CI 34.8-39.3]). However, female patients had more hypertension than female controls (50% [95% CI 35.2-64.8] vs 26% [95% CI 24.1-27.9]). There was no relation between fludrocortisone dose and systolic (correlation coefficient -0.07, P=0.55) or diastolic blood pressure (correlation coefficient 0.03, P=0.82). The prevalence of hypertension increased with age in both patients and controls. In addition, in women with AD there was a correlation between waist circumference and presence of hypertension (correlation coefficient 0.34, P= 0.03).

Abnormal lipid profile, impaired fasting glucose and DM

When comparing the mean lipid concentrations of male and female AD patients with controls we found no significant differences. We also looked at the percentage of male and female patients with abnormal lipids. Increased total cholesterol, triglycerides and LDL cholesterol and decreased HDL cholesterol were respectively present in 28%, 41%, 61% and 28% of males and in 18%, 35%, 30% and 20% of females. Comparing patients and controls we found that more female AD patients had abnormal triglycerides (35% CI 22.5-50.5%) compared to female controls (20% CI 18.3-21.8). No significant differences were found between male patients and controls Mean fasting glucose levels in male and female patients with AD were comparable to controls. Impaired fasting glucose was equally present in male and female AD patients. None of the male patients had diabetes mellitus. In females 5% had diabetes mellitus. This was comparable to female controls (4%).

Metabolic syndrome

The metabolic syndrome was present in 23% of patients with AD. The prevalence of MetS was not significantly different between male and female patients. In male controls (34% [95% CI 31.8-36.2]) MetS was more prevalent than in female controls (24% [95% CI 22.2-26.1]). MetS was equally present in female patients and controls. MetS was more prevalent in male controls (34% [95% CI 31.8-36.2]) compared to male patients with AD (17.2% [95% CI

7.6-30.5]). However, this difference between male patients and controls was absent above 60 years of age. Regarding the prevalence of the different components of the MetS in patients with AD, we found that blood pressure was the most frequent abnormal component in males, whereas in females this was abnormal waist circumference. The frequency of the remaining abnormal components was equal in male and female patients. AD patients with a positive cardiovascular history had significantly more MetS compared to AD patients without a cardiovascular history (58% vs 15%, P<0.01) .

Univariate and multivariate analysis in AD patients

Univariate analysis showed more MetS with increasing age (p <0.01), with a history of cardiovascular disease (p <0.01), in patients treated with cortisone acetate (p= 0.02) and in patients with a higher mean midday glucocorticoid dosage (p= 0.04). When comparing patients using hydrocortisone or cortisone acetate we found that patients with cortisone acetate were older (p=0.02), had higher fasting glucose (p= 0.02), higher total daily glucocorticoid (HC equivalent) dosage (p= 0.02), higher morning glucocorticoid (HC equivalent) dosage (p= 0.01) and were treated more frequently with a twice daily glucocorticoid regime (p= 0.05). After multiple logistic regression analysis only age was an independent risk factor for MetS (odds 1.1, 95% CI 1.01-1.22).

Discussion

The results of the present study show that female patients with AD have a higher prevalence of abdominal obesity, hypertension and hypertriglyceridemia, when compared to female Dutch controls. In contrast, these differences between patients and controls were not found in males. Our results are in accordance with results of others studies showing an increased prevalence of abnormal anthropometric parameters and dyslipidemia in both ACTH-deficient hypopituitary patients and patients with AD.[6-9,16-17] However, despite the higher prevalence of abdominal obesity, hypertension and hypertriglyceridemia, prevalence of MetS in our female patients with AD was the same as in age matched controls. In male patients with AD the prevalence of MetS was even lower when compared to male controls, but this difference

disappeared with increasing age. As expected, the prevalence of MetS in our study increased with age. When comparing the prevalence of MetS using ATP III criteria versus the criteria proposed by the International Diabetes Federation we found more central obesity and consequently higher prevalence of MetS in males using IDF criteria (28% vs 17%). By using these criteria the difference between male patients and controls disappeared.

The 23% prevalence of MetS that we found in our patients is lower than the 36.8% prevalence reported by Dullaart et al in 117 ACTH-deficient hypopituitary patients.[18] However, their patients had additional hormonal deficiencies probably explaining the higher prevalence of MetS.

The fact that despite the higher prevalence of abdominal obesity, hypertension and hypertriglyceridemia in females the prevalence of MetS was not increased and in male patients even lower than in controls may be related with the low frequency of decreased HDL cholesterol in AD. Other studies also found that despite higher serum triglycerides and LDL cholesterol, HDL cholesterol was not decreased in glucocorticoid-replaced patients.[9,18] Supra-physiological doses of glucocorticoids may increase HDL concentrations. This may be due to reduction of hepatic lipase activity and increased apoprotein A1, both resulting in higher HDL-cholesterol.[19] In addition, glucocorticoid replacement therapy is associated with lower cholesteryl ester transfer protein (CETP) activity possibly leading to higher HDL cholesterol.[20] Mutations in the CETP gene, which result in partial or complete CETP deficiency are associated with a higher HDL cholesterol. Dullaart et al found that glucocorticoid replacement may modify the relationship of HDL cholesterol concentration with CETP polymorphism, leading to lower serum CETP action and consequently higher HDL cholesterol.[18]

Abdominal obesity was highly prevalent in our female patients. Our results are in line with Leonsson et al. They also found more abdominal obesity in female hypopituitary patients compared to controls.[21] Several factors could explain this increased prevalence. Firstly, cortisol affects 11β-HSD type 1 activity, thereby amplifying local cortisol production. Cortisol promotes the differentiation of pre-adipocytes into mature adipocytes.[22] Increased activity of 11β-HSD type 1 in adipose tissue is more marked in women than in men.[23] Secondly, androgens play a pivotal role in the regulation of body fat distribution. They reduce early-

stage adipocyte differentiation.[24] Normally, the adrenals are major sources of androgens in females. However, female AD patients lack androgen precursors from the adrenals.[25] This can lead to reduced circulating and cellular levels of androgens, especially with increasing age. In addition, a cross talk exists between glucocorticoids and androgens at both hypothalamic-pituitary and peripheral level. Glucocorticoid induced androgen inactivation, could partially remove the inhibitory effect on adipogenesis. It is well accepted that the decrease in estrogen levels in menopausal women is associated with an increase in abdominal fat.[26]

We found more hypertension in our female patients compared to female controls. No correlation was found with fludrocortisone dosage. Hypertension in patients with AD has been reported before. Lovas et al showed that AD patients are prescribed more antihypertensive drugs than controls.[27] In our female patients, abdominal obesity correlated positively with BMI. Both are strongly related to higher blood pressure. An additional hypothesis could be the effect of mild over- replacement of glucocorticoids on salt- and water reabsorption and vascular function and remodeling.

We found normal fasting glucose concentrations in AD patients. Normal fasting glucose concentrations were also found in patients on conventional glucocorticoid replacement in a study by Al-Shoumer.[28] However, it is not clear what the effects are of current non-physiological replacement with two or three cortisol peaks after ingestion of glucocorticoids on glucose tolerance or HbA1C and risk of impaired fasting glucose or diabetes mellitus in the long run.

Mild glucocorticoid over-replacement frequently occurs in AD. Although cortisol excess has been associated with central obesity, hypertension, insulin resistance and dyslipidemia, we did not find a correlation between anthropometric and metabolic parameters and glucocorticoid replacement dose, regime or frequency. In contrast, Filipsson et al found that in hypopituitary patients, hydrocortisone doses above 20-30 mg/day were associated with adverse consequences with respect to waist circumference, serum cholesterol and triglycerides.[29] Dullaart et al also showed that hypertriglyceridemia and higher non-HDL cholesterol levels were related to glucocorticoid treatment.[18] However, two studies performed in patients with AD, showed similar results compared to ours.[6,9] Ross et al

showed that despite higher doses of hydrocortisone replacement, the cardiovascular profile in their Swedish AD patients was more favorable than in AD patients in South Africa, despite the use of lower doses of hydrocortisone in the latter patients.[9] They speculated that other factors are likely more important in modifying cardiovascular risk factors associated with AD than hydrocortisone total daily dosage.

Normally, ultradian hormone stimulation induces cyclic glucocorticoid receptor mediated pulses of gene transcription allowing an individual interpretation of glucocorticoid signals at tissue level. Current replacement therapy gives rise to a more continuous glucocorticoid delivery to target tissues. We speculate that this could be an additional explanation for the alterations in metabolic parameters in our patients with AD.

Another factor of interest could be the difference in individual sensitivity to the effects of glucocorticoids. Glucocorticoid gene polymorphisms are found throughout the gene with variable impact on function.[7,8] Due to the incongruity of results in these studies it is at present not clear what the actual influences of these polymorphisms are and if they can be used for individual adjustment of GRT in patients with AD.

Buscemi et al studied the association between lifestyle and components of MetS.[30] MetS was associated with physical inactivity. We found that in patients with AD only 46% met the standard of physical activity compared to 68% of Dutch controls (data not published). In addition, female patients were less physically active compared to male patients.

Our study has some limitations that result from the cross sectional design and the small sample size. It did not allow us to determine any causal relationship between GRT and MetS. The results of anthropometric and laboratory measurements of AD patients were compared to controls from the general Dutch population. Demographics and lifestyle factors such as educational level, diet and physical activity were not evaluated in our study, thus patients and controls were only matched according to sex and age. We recruited patients from two university medical centers which may have resulted in selection bias.

Despite these limitations, the results of our study are in concordance with other studies in patients with adrenal insufficiency and show that the prevalence of cardiovascular risk factors are more prevalent, but we could demonstrate this only in female and not in male

patients. We state that cardiovascular risk assessment and intervention are warranted in the management of patients with AD. It will be of interest to prospectively study the effects of new therapeutic approaches, such as continuous hydrocortisone infusion and dual release formulation, on abdominal obesity, blood pressure and other metabolic parameters in patients with AD.

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Chapter 6: Increased use of antimicrobial agents and hospital admission for infections in patients with primary adrenal insufficiency: a cohort study

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Abstract

Background: Previous studies have suggested that infections are an important cause of death in patients with Addison's disease, but epidemiological studies on the frequency of infections in this population are lacking.

Objective: To assess and compare the incidence risk of infections in patients with primary adrenal insufficiency with controls.

Design and setting: We conducted a cohort study, using data from the Dutch PHARMO record linkage system, that links patients' demographics and medication histories to hospital admissions.

Patients: From a cohort of oral glucocorticoid users, 390 patients with primary adrenal insufficiency were identified by assessing concurrent use of glucocorticoids and mineralocorticoids using pharmacy dispensing records. A reference cohort (*n*=1933) with the same age and sex distribution was sampled from patients not using glucocorticoids.

Outcome measure: Incidence rates and incidence rate ratios (IRR) were calculated of infections, defined by use of antimicrobial agents, as well as hospital admissions for infection.

Results: The incidence of infectious episodes, defined by usage of antimicrobial agents, among patients with primary adrenal insufficiency (incidence rate 59.2/100 person-years) was 1.5 times higher compared with controls, yielding a crude IRR of 1.61 (95% CI 1.51–1.72). The IRR decreased slightly to 1.58 (95% CI 1.47–1.70) after adjustment for co-medication and co-morbidity also associated with infection risk. Also with respect to hospital admissions for infection, the incidence rates observed for patients with primary adrenal insufficiency was higher compared with controls (3.8/100 vs 0.8/100 person-years): crude IRR 5.02 (3.66–6.87) and adjusted IRR 4.34 (95% CI 3.04–6.22).

Conclusion: Patients with primary adrenal insufficiency had an increased use of antimicrobial agents and hospital admissions related to infection.

Introduction

Addison's disease is an autoimmune disease, leading to destruction of the adrenals and subsequent adrenal insufficiency. Its prevalence is relatively low with a reported prevalence of 93–140 per million[1]. Since the introduction of glucocorticoids in 1948 life expectancy of patients with Addison's disease has increased considerably. However, even in recent studies, an increased risk of premature death in patients with Addison's disease is reported, attributed to cardiovascular diseases, neoplasms, and infections[2].

Erichsen reported infections as cause of death in 10% of Addison patients, compared with 6% in the general population.[3] In addition, Bergthorsdottir found a five times higher mortality rate resulting from infectious disease in patients with Addison's disease compared with an age-adjusted background population.[4] While this higher mortality could be explained by the concurrent occurrence of a life-threatening Addison crisis in these patients, it is also possible that patients with Addison's disease suffer from a higher frequency of infections or have more severe infections compared with controls.

To our knowledge, data on the incidence or severity of infectious disease in patients with Addison's disease are currently lacking. This information could be important in the treatment and follow-up of patients with Addison's disease, in order to reduce morbidity and mortality due to infections. Therefore, the objective of this study was to assess and compare the incidence of infections among patients with primary adrenal insufficiency with controls.

Materials and methods

Setting

Data were obtained from the PHARMO record linkage system (Pharmo Institute, Utrecht, The Netherlands; available at: http://www.pharmo.nl). The PHARMO RLS includes the demographic details and complete medication history of more than two million community-dwelling residents of more than 25 population-defined areas in The Netherlands from 1985 onward, further linked to hospital admission records as well as several other health registries, including pathology, clinical laboratory findings, and general practitioner data.[5] As virtually all patients in The Netherlands are registered with a single community pharmacy,

independent of prescribers, pharmacy records are virtually complete with regard to prescription drugs. For this study, drug dispensing data and hospitalization data (discharge records, ICD-9) were used. Laboratory data were not available for this study. The computerized drug dispensing histories contain information concerning the dispensed drug, dispensing date, the prescriber, amount dispensed, prescribed dosage regimen, and the estimated duration of use. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospitalization register comprises all hospitalizations in The Netherlands, including detailed information concerning: the primary and secondary discharge diagnoses; diagnostic, surgical, and treatment procedures; type and frequency of consultations with medical specialists; and dates of hospitalization and discharge. All diagnoses are coded according to the International Classification of Diseases, 9th edition (ICD-9-CM). Hospitals are currently in a transition phase with respect to coding. The objective is that in January 2013, all Dutch hospitals are coding diagnoses according to the ICD-10 (http://www.icd-10.nl/home/-in Dutch). For the current study, all codes are in ICD-9. All PHARMO-linked research is in accordance with Dutch privacy and ethical regulation. The study had no external funding source.

Cohort selection

Community pharmacy records do not contain indications for drug use. However, as the preferred treatment of primary adrenal insufficiency requires suppletion of both glucocorticoids (to replace cortisol) and mineralocorticoids (to replace aldosterone), concurrent use of both drugs is a good marker for the presence of primary adrenal insufficiency. In The Netherlands, most patients with primary adrenal insufficiency are treated with hydrocortisone or cortisone acetate but very few patients are treated with prednisolone instead.[6] From the PHARMO RLS, we identified all users of glucocorticoids between January 1998 and December 2008. The theoretical duration of each prescription was assessed by dividing the number of dispensed units by the prescribed daily dose. Prescribed daily doses were subsequently expressed as the number of defined daily doses (DDDs) per day. Primary adrenal insufficiency was defined as concurrent use of glucocorticoids (hydrocortisone, cortisone acetate, or prednisone ≤10 mg daily) and

mineralocorticoids (fludrocortisone). This definition was required because we aimed to include patients with primary adrenal insufficiency only, thereby excluding patients with secondary adrenal insufficiency. Thus, patients with primary adrenal insufficiency were selected based only on the combination of glucocorticoid and mineralocorticoid usage. No ICD-9 codes were available in this selection. The first date that both types of drugs were used concomitantly marked the start of follow-up. Distinction was made between prevalent and incident patients, where the latter were those patients who were at least 365 days without gluco- and mineralocorticoid usage before the start of the follow-up. The resulting cohort of primary adrenal insufficiency patients was restricted to those who were 18 years or older and had a minimum of two dispensings of glucocorticoids and mineralocorticoids. A reference cohort, about five times the size of the index cohort (*n*=1933), with the same age and sex distribution was sampled from patients not using glucocorticoids.

Outcome definition

We identified all prescriptions for antibacterial, antiviral, or antifungal medication. For anti-infective agents, episodes were calculated, defined as a cluster of subsequent refills, independent of changes in dose regimen or drug switches within the same class. A new episode was assumed if an interval of 14 days or more occurred between the theoretical end date of one prescription and new prescription. Each episode was considered a separate event. Furthermore, we identified hospital admissions for respiratory (ICD 1–137, 460–466, 480–489, 510, 513), urinary (ICD 580, 590, 595, 597, 599, 601, 604, 614, 615, 616), musculoskeletal (ICD 711, 720, 730), cutaneous (ICD 681, 682), CNS (ICD 320–321), and other (ICD 320–321, 380.1, 381, 382, 324, 421) infections. For this, we used hospital discharge records (ICD-9 codes).

A relapse was defined by a hospital admission for infection occurring during the first 21 days between subsequent hospitalizations. New prescriptions for antibacterial, antiviral, or antifungal medication were not regarded as a new infection when prescribed in the following 14 days after hospital discharge.

Comorbidity

Several medical conditions are associated with decreased immune response and increased risk of infection. For each subject, presence of diabetes (defined by use of insulin and/or oral antidiabetic agents), statins, asthma, chronic obstructive pulmonary disease (COPD) (defined by use of inhalation glucocorticoids), immunodeficiency disorders (defined by use of immunoglobulins and/or immunosuppressants), rheumatoid arthritis, and vasculitis was identified.

Statistical analysis

Incidence rates for infectious events, defined by use of antimicrobial agents, and hospital admission for infection were calculated as the number of infectious events or admissions divided by person-time. Crude incidence ratios (IDRs) and 95% CI were calculated by dividing the incidence rate in the primary adrenal insufficiency cohort by the incidence rate in the control group. Poisson regression analysis was used to adjust for other conditions and drugs associated with an increased risk of infection. We stratified according to age (<40, 40–59, and ≥60 years) and sex. Risk estimates were calculated for all anti-infective drug prescription subtypes, as well as subtypes of hospital admissions for infection. Time-varying analyses, where follow-up time was divided in 90-day periods, were conducted to study the effect of (cumulative) glucocorticoid dose, as well as the frequency of dosing. Data analysis was conducted with STATA, version 10.1, and SPSS version 17.0.

Results

A total of 390 patients met the definition of primary adrenal insufficiency and were included in the primary adrenal insufficiency cohort. The reference cohort consisted of 1933 controls. The cohort characteristics are depicted in Table 1. The use of medication represents co-morbidity at cohort entry, for both newly diagnosed primary adrenal insufficiency and patients with long disease duration.

Characteristics	Adrenal insufficiency patients (n=390)		Control patients (n=1933)	
	No.	(%)	No.	(%)
Sex				
Men	156	(40.0)	775	(40.1)
Women	234	(60.0)	1158	(59.9)
Age (years)				
18-29	40	(10.3)	198	(10.2)
30-39	60	(15.4)	300	(15.5)
40-49	75	(19.2)	367	(19.0)
50-59	68	(17.4)	340	(17.6)
60-69	63	(16.2)	313	(16.2)
70-79	61	(15.6)	302	(15.6)
80+	23	(5.9)	113	(5.9)
Type of glucocorticoid				
Prednisone	34	(8.7)		
< 0.67 DDD/day	16			
0-67-1.33 DDD/day	17			
Hydrocortisone	223	(57.2)		
< 0.67 DDD/day	20			
0-67-1.33 DDD/day	149			
> 1.33 DDD/day	24			
Cortisone acetate	133	(34.1)		
< 0.67 DDD/day	7			
0-67-1.33 DDD/day	117			
> 1.33 DDD/day	8			
Drugs indicating comorbidity at cohort entry				
Statins	30	(7.7)	123	(6.4)
Insulin	16	(4.1)	22	(1.1)
Oral antidiabetic drugs	12	(3.1)	72	(3.7)
Thyroid hormone	69	(17.7)	36	(1.9)
Respiratory drugs	34	(8.7)	60	(3.3)
Dehydroepiandrosterone	4	(1.0)	0	(0.0)

DDD: defined daily doses; <0,67 DDD = <20 mg of hydrocortisone, 0,67-1,33 DDD= 20-40 mg of hydrocortisone, >1,33 DDD=>40 mg of hydrocortisone

Table 1 Characteristics of primary adrenal insufficiency patients and controls

In over 90% of patients in the primary adrenal insufficiency cohort, glucocorticoid replacement was provided by hydrocortisone or cortisone acetate. Only a small proportion of primary adrenal insufficiency patients (1.0%) used DHEA in addition to gluco- and mineralocorticoids. The prevalence of insulin use, thyroid hormone replacement therapy, and use of respiratory drugs was statistically significantly higher in the primary adrenal

insufficiency cohort compared with the reference cohort. The incidence of infectious events was 59.2/100 person-years in the primary adrenal insufficiency cohort, about one and a half times the rate in the reference cohort (34.8/100 person-years; crude incidence rate ratio (IRR) of 1.61, 95% CI 1.51–1.72). Adjustment for age, sex, co-medication, and co-morbidity had only marginal effects on the risk estimate: adjusted IRR 1.58 (95% CI 1.47–1.70). IRRs were consistently increased across anti-infective drug prescription subtypes (Table 2).

	Number of episodes	**Rate/100 person-years**	**Crude IRR (95% CI)**	**Adjusted IRR (95% CI)[a]**
Antibacterial				
Reference	3340	34.8	1	1
Addison	1157	55.0	1.58 (1.48-1.69)	1.56 (1.45-1.68)
Antifungal				
Reference	159	1.6	1	1
Addison	67	3.2	1.98 (1.47-2.65)	1.99 (1.46-2.72)
Antiviral				
Reference	38	0.4	1	1
Addison	18	0.9	2.23 (1.27-3.90)	1.99 (1.05-3.79)

IRR incidence rate ratio, CI confidence interval; [a] Adjusted for age, sex, insulin, inhalation glucocorticoids, COPD

Table 2 Incidence rates of infectious episodes according to antimicrobial drug prescription in primary adrenal insufficiency and reference cohort

The highest risk estimates were found for antifungal and antiviral drugs with adjusted IRRs of 1.99 (95% CI 1.46–2.72) and 1.99 (95% CI 1.05–3.79) respectively. Stratification according to age showed the highest IRRs among primary adrenal insufficiency patients aged 60 years and older. The incidence of serious infection events requiring hospital admission was five times higher among patients with primary adrenal insufficiency compared with controls (3.8/100 vs 0.8/100 person-years). For subtypes of infection, the rates for pneumonia and urinary

tract infection were respectively more than nine and four times higher in primary adrenal insufficiency patients compared with controls (Table 3).

	Admissions	Rate/100 person-years	Crude IRR (95% CI)	Adjusted IRR (95% CI)[a]
All cause				
Reference	79	0,8	1	1
Addison	80	3,8	5,02 (3.66-6.87)	4.34 (3.04-6,22)
Respiratory infections				
Reference	19	0.2	1	1
Addison	40	1.9	9.9 (5.73-17.09)	8.25 (4.52-15.07)
Pneumonia				
Reference	14	0.1	1	1
Addison	30	1.4	10.08 (5.34-19.00)	9.42 (4.91-18.05)
Urinary tract infections				
Reference	13	0.1	1	1
Addison	11	0.5	3.98 (1.78-8.88)	4.56 (2.03-10.25)

IRR incidence rate ratio, CI confidence interval; [a] Adjusted for age, sex, insulin, inhalation glucocorticoids, COPD

Table 3 Hospital admissions for infection

Subsequently, we stratified the primary adrenal insufficiency cohort in prevalent and incident patients, where an incident primary adrenal insufficiency patient was defined by no history of gluco- and mineralocorticoid usage before the index date. In general, incidence rates were marginally higher in incident cases compared with prevalent primary adrenal insufficiency patients (data not shown). Furthermore, we explored within the primary adrenal insufficiency cohort whether the presence of an additional autoimmune disorder

would lead to an increased risk of infection. Patients with both primary adrenal insufficiency and type 1 diabetes mellitus had a twofold increased risk of an infectious event (adjusted IRR 2.00, 95% CI 1.52–2.65) and a more than threefold increased risk of admission for infection (adjusted IRR 3.53, 95% CI 1.42–8.8) compared with patients having primary adrenal insufficiency alone. In a similar analysis for thyroid disease, no differences were found. Assessment of seasonal differences in the occurrence of infectious events showed that highest risk estimates were observed during the winter months.

In order to study the effect of glucocorticoid dosage on infection risk, we performed time-varying analysis, classifying patients in three cumulative dosage groups based on tertiles of cumulative dose. No obvious effect of cumulative dose on the risk of infectious events was found with adjusted IRRs for the medium and high cumulative dose compared with low cumulative dose of 1.64 (95% CI 1.25–2.16) and 1.42 (95% CI 1.05–1.97) respectively. To study potential effects on fluctuating levels during the day, we assessed the influence of the frequency of glucocorticoid dosing. No differences in infection risk were found for patients on a once-daily regimen vs patients using glucocorticoids multiple times daily (data not shown).

Discussion

In this cohort study, we found that the risk of infectious episodes, defined by the use of antimicrobial agents, among patients with primary adrenal insufficiency was 1.5 times higher and the risk of hospital admission as a result of infection was 4.5 times higher compared with sex- and age-matched controls. To our knowledge, this is the first study to report on increased risk of infections in patients with primary adrenal insufficiency.

It is unclear whether the observed association between primary adrenal insufficiency and infectious events is related to adrenal replacement therapy or the underlying disease itself. Primary adrenal insufficiency patients are treated with low-dose glucocorticoids for life. Glucocorticoid replacement therapy cannot mimic normal physiology, and as a result, over replacement frequently occurs, which ultimately leads to high cumulative dosages. The fact that the incidence of antifungal and antiviral drug prescriptions is higher than antibacterial

drugs, prescriptions suggest a defect in the adaptive cellular immunity, a well-known side effect of glucocorticoids.[7,8] Stuck *et al*. evaluated the risk of infectious complications in patients taking glucocorticoids.[9] In a meta-analysis of 71 trials involving over 2000 patients with different diseases and different dosages, they found that infection rates were significantly increased in patients given an average dose of prednisone of more than 10 mg/day or a cumulative dose of >700 mg. Our results do not support the hypothesis that the cumulative dose of glucocorticoids in patients with primary adrenal insufficiency is associated with the increased risk of infection, given the absence of a clear dose–effect relationship. We speculate that the substitution dosage used in primary adrenal insufficiency, although leading to somewhat higher average cortisol concentrations throughout the day, probably does not lead to an increased risk of infection as seen in patients treated with high pharmacological glucocorticoid dosages. This is further supported by our finding that frequency of daily dosing did not seem to have an effect on infection risk.

The increased risk of infectious episodes already present in incident primary adrenal insufficiency patients suggests that other factors like decreased resistance to infections in the scope of (active) autoimmunity could play a role. Diabetes mellitus type 1, a comparable endocrine autoimmune disease, has also been associated with increased rates of infections.[10] This is partially due to defects in cellular innate immunity such as decreased chemotaxis, phagocytosis of polymorphonuclear cells, monocytes, and macrophages.[11] Studies on defects in immunity in patients with Addison's disease are lacking.

A speculative alternative explanation for the increased infection risk in autoimmune adrenalitis and some types of congenital adrenal hyperplasia (CAH) could be DHEA deficiency. There is evidence that DHEA may play a role as a regulator of immune function.[13] DHEA has been shown to enhance immune function directly by regulating cytokine production and immune cell cytotoxicity as well as to have indirect benefits by counteracting the immune suppressive effects of glucocorticoids. In our adrenal insufficiency cohort, only 1% of patients used DHEA replacement. Laboratory results on DHEA and DHEAS were not available to us. This would have enabled us to speculate more on the role of DHEA in the increased risk of infection.

Several studies have shown an increased risk of infection in patients with diabetes mellitus.[11,12,14] Our results are in line with these findings, as we found a twofold increased risk of infectious events and a more than threefold increased admission risk for infection in patients with both primary adrenal insufficiency and diabetes mellitus compared with patients with primary adrenal insufficiency alone.

The strengths of this study are its population-based nature, the substantial sample size, and the reliable longitudinal data collection on both drug exposure and hospitalization. There are some limitations as well. As we had no data on medical diagnoses, identification of patients with primary adrenal insufficiency was based on pharmacy records only, which could have resulted in misclassification. Due to the selection of patients using both glucocorticoids and mineralocorticoids, it is possible that a small number of patients with primary adrenal insufficiency not using mineralocorticoids were missed, but we expect this to be a very small number as primary adrenal insufficiency patients in The Netherlands are mainly treated with the combination of glucocorticoids and mineralocorticoids. The patients among our prevalent primary adrenal insufficiency cohort are in fact patients with different types of primary adrenal insufficiency such as autoimmune adrenalitis, salt-wasting CAH, or patients after bilateral adrenalectomy. In the incident Addison cohort, however, probably no salt-wasting adrenogenital syndrome patients are included because we excluded patients under the age of 18 and the vast majority of adult patients with adrenogenital syndrome are being treated with dexamethasone instead of hydrocortisone or cortisone acetate.[15]

A limitation of our study might be diagnostic suspicion bias. It could be that general practitioners and medical specialists are more likely to initiate treatment or admit patients with primary adrenal insufficiency to hospital under suspicion of infection due to a fear of a potential adrenal crisis in case of stress and disease. This could have resulted in an overestimation of observed effect. However, admission rates were based on discharge records after thorough diagnosis and treatment in the course of the disease. In addition, Dutch physicians have a renowned low tendency to treat patients with antimicrobial drugs to decrease the risk of resistance, treating only patients with a proven or very high suspicion of infection.[16]

In conclusion, our results show an increased use of antimicrobial agents and infection-related hospital admissions in patients with primary adrenal insufficiency compared with controls. In order to gain more insight into the possible increased risk of infections in patients with primary adrenal insufficiency, likely underlying causes of increased risk of infection should be studied. In addition, the potential positive effects of DHEA replacement and preventive strategies such as vaccination on the incidence of infections should be explored in future studies.

Declaration of interest

All authors declare no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Chapter 7: Incidence of adrenal crisis in adrenal insufficiency

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Submitted

Abstract

Background: An adrenal crisis (AC) is a potential life threatening event in patients with adrenal insufficiency (AI). This study aims to determine the incidence, causes and risk factors of AC in AI.

Methods: Patients with AI diagnosed and treated at the University Medical Center Utrecht for the past 30 years were identified and all medical records were assessed by two independent investigators. The observed frequency of AC was determined as incidence rate, calculated as the number of AC divided by person years (PY). In addition, precipitating factors and risk factors were assessed.

Results: We observed an incidence rate of 5.2 AC (95% CI 4.3-6.3) per 100 PY in primary adrenal insufficiency (PAI) and 3.6 AC (95% CI 3.1-4.1) per 100 PY in secondary adrenal insufficiency (SAI). Patients with an established diagnosis of tertiary (glucocorticoid-induced) adrenal insufficiency had an incidence rate of 15.1 AC (95% CI 11.0-19.9) per 100 PY. The most important risk factor was the existence of co-morbidity. Gastro-enteritis and other infections were the most common precipitating factors for AC.

Conclusion: AC still occurs relatively frequent in patients with AI, mostly precipitated by infections and particularly in patients with high co-morbidity. This should be taken into account in the education and follow up of patients with AI.

Introduction

Adrenal crisis (AC) is a potential life threatening event in patients with adrenal insufficiency (AI).[1] In the past it was the main cause of death in patients with AI.[2] Fortunately, due to the use of glucocorticoids in the treatment of AI and increased knowledge among caregivers and patients, a lethal outcome is rather exceptional nowadays. At present the incidence of AC is still substantial.[3] AC occurs when patients with AI are challenged by illness, pain or severe psychological stress and are not able to meet the increased demand of cortisol. In case of physical and severe psychological stress, patients with AI have to increase their glucocorticoid replacement dose appropriately in order to avoid symptoms, such as fatigue, weakness, anorexia, nausea, vomiting and orthostatic dizziness, and in that way to prevent a life threatening AC. The clinical signs of impending crisis are non-specific and this can lead to delay of additional glucocorticoid administration. Patient education about risks and precipitating causes, next to training in how to adjust glucocorticoid medication during physical and severe mental stress as well as training in injection technique of high doses of parenteral glucocorticoids, are considered the most important preventive measures.[4,5] To date, no data regarding incidence and precipitating causes of AC in a Dutch cohort with AI are available. In addition, none of the previous reported studies on the epidemiology of AC included patients with glucocorticoid induced tertiary AI. The aim of this study was to determine the incidence, causes and risk factors of AC in Dutch patients with AI.

Methods

Study design

All patients diagnosed with AI at the University Medical Center Utrecht from 1980 until 2010 were identified using subsequent ICD-9 diagnostic codes 017.6, 036.3, 191.0, 194.0, 194.3, 225.2, 227.0, 227.3, 253, 255, 377.5. A retrospective analysis was performed on all medical records (outpatient records, hospital admission and discharge records, correspondence between specialists and primary care physicians). The diagnosis of AI was verified by review of medical records. We studied patient demographics (age, sex, BMI) and details on replacement regimes such as type, daily dosage and dose frequency of glucocorticoids, use

of mineralocorticoids and dehydroepiandrosterone (DHEA). Furthermore co-morbidity, including endocrine-metabolic (obesity, diabetes mellitus, diabetes insipidus, hypothyroidism, hypopituitarism), neurological (cerebrovascular events, dementia, epilepsy, neuromuscular disorders, encephalopathy, Parkinson's disease), cardiopulmonary (myocardial infarction, congestive heart failure, arrhythmias, valvular disorders, chronic obstructive pulmonary disease, asthma), musculoskeletal, malignant and psychiatric disorders, was assessed. Adrenal crisis was defined as an acute impairment of general health requiring hospital admission and administration of intravenous saline and glucocorticoids in patients with AI. For each crisis the precipitating factor was determined and categorized into infection, presentation (AC was first manifestation of AI), perioperative, trauma, severe illness, other factors (such as mental or physical stress) or unknown (precipitating cause was not reported or not clearly identified). Potential risk factors that we evaluated included replacement therapy (glucocorticoid type, dosage and frequency, mineralocorticoids, DHEA, sex hormones, desmopressin), duration of disease, use of other medication (antihypertensive medication, inhalation or dermal glucocorticoids) and other co-morbidity as described above. All medical data were extracted from medical records and interpreted by two independent investigators before start of analysis.

Statistical analysis

Patients were divided into groups according to the presence of primary, secondary or tertiary AI. Continuous variables were expressed as median with interquartile range and categorical variables were expressed as percentages. All patients with a disease duration equal to or less than one year were analyzed as having disease duration of one year. The observed frequency of AC was determined as incidence rate, calculated as the number of AC divided by person-years (PY). In each group (PAI, SAI, TAI) we reported the number of events per 100 PY including 95% confidence intervals (CI). Patients with PAI and patients using hydrocortisone were used as reference. To identify possible risk factors, negative binomial regression was used for univariate risk estimates of all relevant factors. Factors of great clinical relevance were used for multivariate analysis and if statistical significance of univariate analysis was $p<0,2$. Stepwise forward multivariate regression was performed and

each new predictor was tested for multicolinearity and risk ratios (RR) were calculated. P values are considered statistically significant at a level of <0.05. Analyses were performed using the statistical software package SPSS, version 20.0.

Results

Patients

A total of 458 patients with AI were included in our study. Patient characteristics are shown in **table 1.** There were 111 (24%) patients with PAI comprising 86 patients with autoimmune Addison's disease. Other causes of PAI were tuberculous adrenalitis, bilateral adrenalectomy, congenital adrenal hyperplasia (CAH), adrenoleukodystrophy, or adrenal destruction due to hemorrhage, metastatic disease or thrombosis. Of 319 patients with SAI 312 (98%) had hypopituitarism due to pituitary adenoma, pituitary surgery or irradiation. Four hundred and twenty-four patients used hydrocortisone or cortisone acetate, mostly twice or thrice daily (98%). Only 4% used long-acting glucocorticoids such as predniso(lo)ne or dexamethasone. Mean (equivalent) total daily hydrocortisone dosage was 20 mg. We identified 28 patients with a diagnosis of tertiary adrenal insufficiency (TAI), caused by chronic glucocorticoid use for inflammatory diseases, chronic inhalation corticosteroids (ICS) or chronic topical corticosteroid use (TCS).

Occurrence of adrenal crisis

In the studied time period a total of 357 AC were recorded, leading to 4.1 (95% CI 3.7-4.6) AC/100 PY. In the group of PAI the frequency of AI was 5.2 (95% CI 4.3-6.3) and in SAI this was 3.6 (95% CI 3.1-4.1) AC/100 PY. In TAI we found 15.1 (95% CI 11.0-19.9) AC/100 PY. Two hundred and forty-nine (58%) patients experienced no AC at all, 149 (35%) had one or two AC and 7% had more than two AC.

Patient Characteristics	**n (%)** **mean, ±SD, range**
Demographics	
Age (years)	55.3±17.6, 6-92
Disease duration (years)	17.5±11.6, 1-63
Sex, male	230 (54%)
Type of AI	
Primary AI	111 (24%)
Secondary AI	319 (70%)
Tertiary AI	28 (6%)
Medication use	
Hydrocortisone Twice daily Thrice daily	342 96 (27%) 241 (71%)
Cortisone acetate Twice daily Thrice daily	82 53 (65%) 28 (34%)
Long-acting glucocorticoids	18 (4%)
Total daily equivalent dose of HC (mg)	21.6±17.3
Comorbidity	
Pulmonary	63 (15%)
Cardiac	81 (19%)
Neurological	103 (24%)
Malignancy	44 (10%)
Musculoskeletal	31 (7%)
Psychiatric	49 (11%)
Other auto-immune diseases	61 (14%)
Diabetes insipidus	93 (22%)
Insulin dependent diabetes mellitus	29 (7%)
Obesity (BMI>30)	68 (16%)
Number of AC	
No adrenal crisis	249 (58%)
1-2 crises	149 (35%)
>2 crises	32 (7%)
IQR= Interquartile range, Long-acting GRT= glucocorticoid replacement therapy with predniso(lo)ne or dexamethasone, HC= hydrocortisone, other auto-immune disorders = coeliac disease, primary hypothyroidism, Graves' disease, vitiligo, type 1 diabetes mellitus, premature menopause	

Table 1 Baseline characteristics of 458 patients with adrenal insufficiency

Precipitating factors

Precipitating factors for AC are summarized in **figure 1**. The most common precipitating factor for AC was infection, including 61 (32%) ACs precipitated by gastro-enteritis, 56 (29%) by bronchopulmonary infections, 22 (11%) by urinary tract infections and 54 (28%) by other infections, including viral infections, erysipelas and meningitis. In 17 patients the AC was preceded by cessation or reduction of glucocorticoids, either by the patient himself or after

tapering glucocorticoids in TAI (in 7 patients). AC was precipitated by severe mental stress in 3 patients, physical stress in 1 patient and a dental procedure without adequate steroid coverage in 3 patients. AC as first presentation of AI occurred in 14% of patients with PAI and in 4% in patients with SAI.

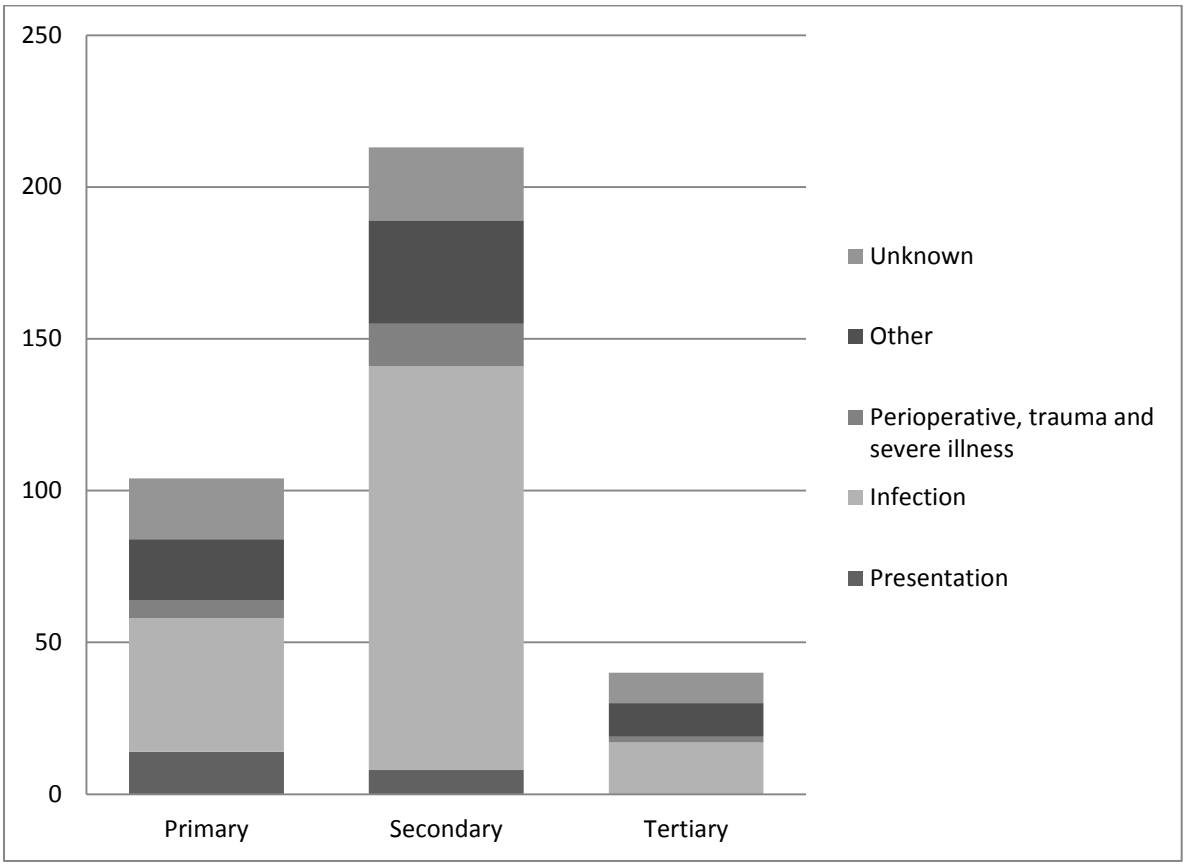

Figure 1 Precipitating factors AI

Risk factors

After univariate analysis type of AI, type of glucocorticoid preparation, use of mineralocorticoids, diabetes mellitus, diabetes insipidus and other co-morbidity (cardiac, pulmonary and neurological disease, malignancy), use of inhalation corticosteroids, age and sex were included in multivariate analysis (**table 2**).

Predictor	Subgroups (n)	Observed amount of AC's (95% CI)	P-value
Type of AI	PAI (111) SAI (319) TAI (28)	5.2 (4.3-6.3) 3.6 (3.1-4.1) 15.1 (11.0-19.9)	0.024
Age	0-42 yr, (114) 42-54 yr, (80) 55-63yr, (99) >64, (165)	5.7 (4.6-6.9) 4.3 (3.2-5.6) 3.3 (2.5-4.2) 4.4 (3.7-5.1)	NS*
Sex	Male (241) Female (217)	4.5 (3.9-5.2) 4.2 (3.6-4.9)	NS*
GRT preparation	Hydrocortisone (342) Cortisone acetate (82) Predniso(lo)ne (12) Dexamethasone (6) In case of stress (16)	4.7 (4.2-5.3) 3.0 (2.2-3.8) 9.3 (5.4-14.6) 2.7 (0.8-6.8) 20.8 (10.8-34.1)	NS*
GRT frequency	Once daily (27) Twice daily (146) Thrice daily (269)	6.2 (4.1-8.9) 3.3 (2.7-4.0) 4.7 (4.1-5.4)	0.053
Equivalent HC dose (mg/day)	<12.5 (47) 12.5-30 (344) >30 (67)	5.3 (3.6-7.5) 4.1 (3.6-4.6) 5.2 (4.1-6.4)	NS*
Mineralocorticoids	No (355) Yes (103)	4.2 (3.7-4.7) 5.1 (4.1-6.1)	0.086
DHEA	No (394) Yes (64)	4.3 (3.8-4.8) 4.8 (3.6-6.3)	NS
Sex hormones	No (273) Yes (185)	5.0 (4.4-5.7) 3.6 (3.0-4.3)	NS
Diabetes insipidus	No (365) Yes (93)	4.3 (3.8-4.8) 4.7 (3.7-5.9)	0.015
Inhalation glucocorticoids	No (438) Yes (20)	4.2 (3.7-4.6) 9.7 (6.7-13.5)	0.075
Cardiac history	No (370) Yes (88)	4.0 (3.5-4.5) 6.0 (4.9-7.3)	0.000
Pulmonary history	No (384) Yes (74)	4.0 (3.5-4.5) 6.6 (5.3-8.1)	0.001
Neurological history	No (351) Yes (107)	3.8 (3.4-4.4) 6.0 (5.0-7.2)	0.000
Psychiatric history	No (405) Yes (53)	4.3 (3.9-4.8) 4.6 (3.4-6.2)	NS
Diabetes mellitus	No (426) Yes (32)	4.2 (3.7-4.7) 6.9 (5.00-9.3)	0.074
Malignancy	No (411) Yes (47)	4.0 (3.6-4.5) 7.4 (5.6-9.4)	0.005
BMI>30	No (351) Yes (73)	4.3 (3.8-4.8) 5.5 (4.3-6.9)	NS
Musculoskeletal disease	No (416) Yes (42)	4.4 (3.9-4.9) 5.1 (3.6-7.1)	NS

AI= adrenal insufficiency, PAI= primary adrenal insufficiency, SAI= secondary adrenal insufficiency, TAI= tertiary adrenal insufficiency, yr= years, DHEA= dehydroepiandrosterone, BMI= body mass index, NS= not significant, *CR= clinical relevant

Table 2 Results of univariate analysis

Results of forward multivariate regression analysis are displayed in **table 3.** As compared to primary AI, secondary AI carried a reduced risk of AC, whereas tertiary AI had an increased risk. Factors significantly increasing the risk were cardiac, neurological or pulmonary comorbidity and malignancy. The use of cortisone acetate was associated with a significantly reduced risk for AC (RR 0.6 (95% CI 0.4-0.9), p=0.03). In the subgroup of auto-immune Addison's disease we observed no increased risk of AC in the presence of other associated auto-immune diseases such as diabetes mellitus type 1, thyroid disease, coeliac disease, vitiligo or auto-immune premature menopause.

Factors	**Relative risks**	**95%CI**	**P-value**
Age	0,99	0,98-1,00	0,10
Female	0,90	0,66-1,24	0,52
PAI	1 (ref)		
SAI	0,49	0,33-0,71	0,00
Neurologic comorbidity	1,84	1,28-2,63	0,00
Malignancy comorbidity	1,78	1,11-2,85	0,02
Cardiac comorbidity	1,99	1,33-2,98	0,00
Pulmonary comorbidity	1,77	1,17-2,70	0,01
Diabetes insipidus	1,49	0,99-2,23	0,05
Hydrocortisone	1 (ref)		
Cortisone acetate	0,62	0,41-0,94	0,03
Long-acting	0,66	0,21-2,04	0,47
PAI= primary adrenal insufficiency, SAI= secondary adrenal insufficiency, Ref= reference category			

Table 3 Risk ratios for predictors after multivariate analysis

Discussion

In our retrospective study on the incidence, precipitating causes and risk factors of AC in Dutch patients with AI, we found an incidence rate of 5.2 AC/100 PY in PAI and 3.6 AC/100 PY in SAI as compared to 15,1 AC/100 PY in TAI (overall 4.1 AC/ 100 PY). The incidence of AC in PAI and SAI patients in our study are roughly comparable to previously reported studies. Hahner et al analyzed the epidemiology of AC in a large cohort of patients with PAI and SAI with a frequency of 6.6/100 PY in PAI and 5.8/100 PY in SAI (overall frequency of 6.3 AC/100

PY).[4] In addition, Reisch et all performed a cross-sectional study next to a detailed retrospective assessment on AC in CAH patients and revealed 5.8 AC /100 PY from evaluation of questionnaires, while patient charts documented 4.9 AC/100 PY. After correction for neonatal salt wasting crisis the frequency was still respectively 4.9 AC/100 PY and 3.8 AC/100 PY.[6] In our patients 45% experienced at least one crisis, which is also similar to other studies (29-58%)[3,4,6,7]

The most important precipitating factor for AC was infection (194 out of 357 crises), mostly gastro-enteritis and bronchopulmonary infection. These results are in line with our previous report on increased use of antimicrobial agents and hospital admissions for infections in patients with PAI.[8] In three patients AC was precipitated by a dental procedure. Khalaf et al performed a systematic search of the literature to identify the frequency and factors associated with AC after dental procedure.[9] Six cases met the criteria of AC (3 in PAI and 3 in SAI). Risk was associated with unrecognized AI, poor health status, pain, infection, having undergone an invasive procedure and having received a barbiturate general anesthetic. In 3 out of 6 cases, additional peri-operative glucocorticoid coverage was not provided. Another important finding is that some patients have a crisis after cessation or reduction of medication. This offers another opportunity for prevention of AC. This is especially true for TAI patients, as in 6 out of these 17 TAI patients AC occurred after glucocorticoid dose reduction.

Patients with concomitant pulmonary, cardiac, malignant or neurological disease face a significantly higher risk for AC. It is conceivable that these patients are exposed to more (mental and physical) stress due to their co-morbidity. In addition, certain disorders such as severe neurological impairment like dementia and stroke may cause difficulties in self-management. Surprisingly, the use of CA was associated with less AC as compared to HC (RR 0,62 (95% CI 0,41-0,95), p=0,03). To our knowledge this has not been reported before. A speculative explanation could be that CA due to its properties will lead to lesser periods of glucocorticoid under-substitution and consequently less AC in case of physical or mental stress. No conclusions could be drawn about long-acting glucocorticoids, because of the low number of patients on prednisone or dexamethasone. In the last decades increased knowledge about the possible effects of mild glucocorticoid over-substitution have led to a lower daily glucocorticoid dosage in patients with AI. Theoretically, this could lead to an

increased risk of AC, although our study does not support an inverse relationship between total glucocorticoid dose and the incidence of AI (<12.5 mg a day AC 5.3 (95% CI 3.6-7.5), 12.5-30 mg a day AC 4.1 (95% CI 3.6-4.6), >30 mg a day AC 5.2 (95% CI 4.1-6.4).

An important finding of our study is that TAI patients had an increased incidence of AC (15,1/100 PY). We identified in the literature studies evaluating the occurrence of AC in glucocorticoid-induced AI and found studies in patients with inhalation and topical glucocorticoids and in patients using high dose glucocorticoids in the treatment of acute lymphoblastic leukemia and rheumatic diseases. Due to substantial differences in diagnostic criteria for AI and AC in these heterogenic studies, assessment of a clear incidence of the risk of AC in patients with TAI is not possible.[10-16] Most of these studies used biochemical parameters to evaluate AI itself but only seldom mention the occurrence of crisis. The high risk of AC in TAI patients, found in our study, should be interpreted with caution. Besides the relatively low number of patients with TAI, we have only included patients with an established diagnosis of TAI, and thus analyzed a selection of more vulnerable patients. This study does however emphasize the fact that AC is a serious threat to patients who are treated for glucocorticoid induced AI. High-quality studies regarding the occurrence of AI and AC in TAI are needed in order to formulate adequate guidelines for treatment and follow up in patients with TAI.[10]

The incidence of AC in Dutch patients with AI points out an important hiatus in current chronic treatment in AI patients. A number of studies have clearly indicated important deficits in knowledge on emergency measures in patients regarding AI and AC management or prevention. Reisch et al found that patients reported to increase glucocorticoid dosage in case of infection with fever and in the peri-operative setting in only 85% and 67% respectively. Only 22% had emergency medication. Hahner et al found comparable results, only 30% of patients had of an emergency kit.[4] In addition, only 12% of patients in the study of White et al had given themselves an emergency steroid injection in case of AC.[3] Most patients relied on medical personnel for their first line emergency treatment. Other studies show inadequate management of AC by caregivers. In almost 25% of hospitalizations for AC, the medical team did not provide the right glucocorticoid stress dosage as reported in a study performed by Leblicq et al.[10] Only 70% of surveyed patients had received a written guideline sheet with proper stress dosing procedure.[11] These studies emphasize the need for

quick and proper adjustment of glucocorticoid education and treatment during stress. To assess efficacy of improved education, Repping-Wuts et al studied the effect of a group meeting.[12] At follow-up both knowledge how to act in different situations and use of self-management tools increased. It remains to be seen if this eventually leads to fewer hospitalizations for AC in patient with AI.[20,21]

A limitation of our study is its retrospective nature in which only medical records for determining and scoring the occurrence of AC were used. This could have led to an underestimation of AC because some AC could have been treated in other hospitals and have possibly not been documented in the medical records. To further increase the accuracy a prospective study is required, which also gives better opportunities to study the various precipitating factors. On the other hand the strength of our study is that it provides an overview of objectively diagnosed AC instead of self-reported AC. We were able to follow patients for a long time, covering all patients diagnosed with AI in a single university medical center for the last 30 years. In our study, the total number of AC that occurred per patient was taken into account, while other studies only reported whether or not an AC occurred at all. Using this continuous outcome measure allowed for a more specific estimation of the influence of risk factors. Furthermore our study is the first study observing all AI patients without exclusions, and many possible risk factors were studied. This study adds to the limited and heterogeneous amount of data that is available for TAI patients. For these reasons our study is applicable to clinical practice.

In conclusion, AC in Dutch patients with AI is relatively common. Since each episode can be dangerous, appropriate care must be taken to educate patients with known AI to prevent and treat acute AC. Since infections seem to impose an important threat to patients with AI we emphasize the need for more research on the underlying cause of the increased risk of infections and efficiency of preventive strategies, such as vaccination, to reduce the incidence of infections in AI and thus decrease the incidence of AC in the future.

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PART 4: RECOVERY OF ADRENAL FUNCTION IN ADDISON'S DISEASE

Chapter 8: Partial recovery in a patient with autoimmune Addison's disease

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Abstract

Objective: To our knowledge, no case of remission in autoimmune Addison's disease has previously been reported. We describe a patient with primary adrenal insufficiency caused by autoimmune adrenalitis in whom partial remission was observed after 7 yr.

Case: A 39-yr-old male was referred because of extreme fatigue, weight loss, anorexia, nausea, and bouts of fever. During physical examination hyperpigmentation was seen. Laboratory tests showed a plasma cortisol of 0.02 µmol/l (08:30 h). Cortisol failed to increase during the ACTH stimulation test (0.02 to 0.03 µmol/l) and ACTH was markedly elevated (920 pmol/l). Adrenal auto-antibodies were weakly positive. A CT-scan showed no evidence of calcifications or other abnormalities of the adrenal glands. The diagnosis of autoimmune Addison's disease was made and replacement therapy with hydrocortisone and fludrocortisone was started. During the following years the dose of hydrocortisone was gradually decreased. Eventually, the patient decided to stop his medication completely. A repeated ACTH stimulation test revealed a basal cortisol of 0.25 µmol/l and a peak cortisol of 0.30 µmol/l with a basal ACTH of 178 pmol/l. The patient did not have any complaints.

Conclusion: Recovery of adrenal insufficiency, due to causes other than autoimmune adrenalitis, has been reported in the past. If our case of partial recovery of autoimmune adrenalitis is not unique this could have profound effects on treatment and follow-up of Addison's disease.

Introduction

Addison's disease, which is considered to be chronic and incurable, is a rare disorder with a reported prevalence of 117-140 per million population. In Addison's disease, autoimmune adrenalitis causes destruction of the adrenal cortex and lifelong treatment with glucocorticoids and mineralocorticoids is necessary. We present a case of complete clinical and partial biochemical recovery of adrenal insufficiency in a 39-yr-old male with Addison's disease.

Case report

A 39-yr-old male was referred because of progressive fatigue and weight loss of 20 kg in the past 12 months. He also complained of anorexia, nausea, bouts of fever, and salt craving. Occasional attacks of extreme fatigue and vomiting occurred. He had noticed a brown discolouration of his hands. His previous medical history was unremarkable and he did not use any medication. On physical examination no abnormalities were found except for hyperpigmentation of the hands. His blood pressure was 130/75 mmHg without orthostatic hypotension and a regular pulse of 96 beats per min. Routine laboratory tests showed a normal sodium of 138 (normal values: 136-146 mmol/l) and a slightly increased potassium of 5.2 (normal values: 3.8-5.0 mmol/l). There was no lymphocytosis, eosinophilia or hypoglycemia. TSH was slightly increased (5.5; normal values: 0.35-5.0 mU/l) with normal free T4 (12; normal values: 9-27 pmol/l). Plasma aldosterone was low (80 pmol/l). Chest x-ray, and abdominal ultrasound were unremarkable. Abdominal computed tomographyscan showed no adrenal calcifications or other abnormalities. Plasma cortisol was very low 0.02 (0.20-0.65 µmol/l) 08:30 am. Cortisol failed to increase during the 250 µg ACTH-stimulation test (Fig. 1).

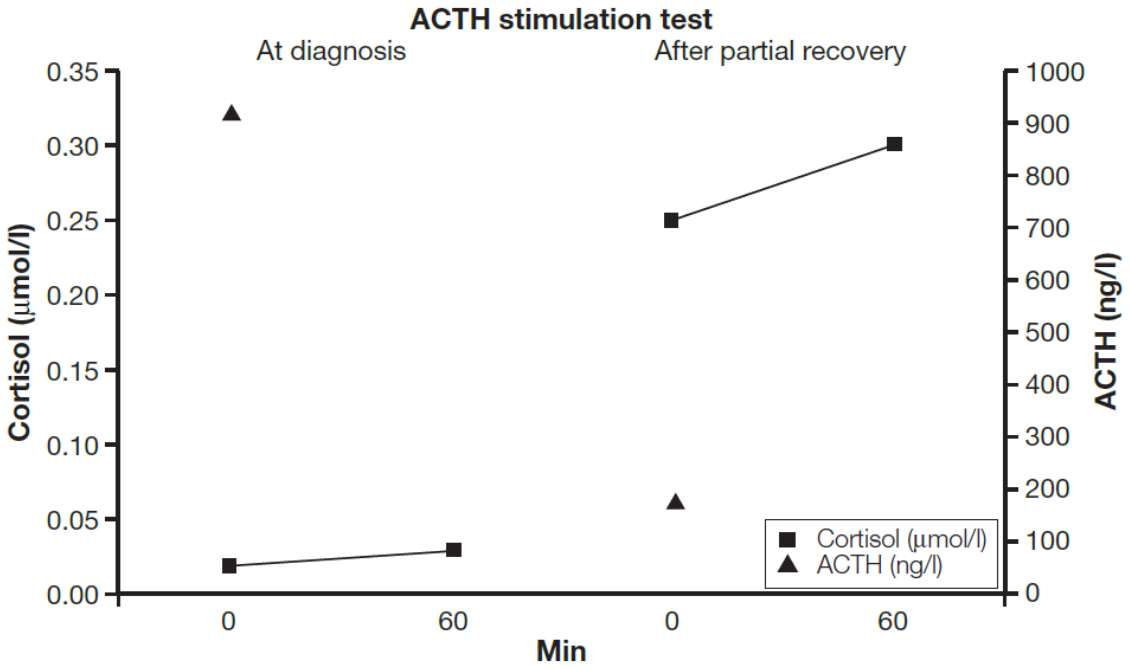

Figure 1 Results of basal ACTH and cortisol before and after ACTH stimulation at diagnosis and after partial recovery

Tetracosactide (Novartis) was given iv at 08:00 h. Cortisol was determined before, 30, and 60 min after administering ACTH. Basal ACTH was markedly elevated (920 pmol/l; normal values: 20-60 pmol/l). Adrenal auto-antibodies were weakly positive (ACA, Indirect Immunofluorescence, Substrate Monkey adrenal cryosections INOVA Diagnostics, Uniprom, Capelle aan de IJssel, the Netherlands). There were no indications of adrenal hemorrhage, infectious disease (TBC, HIV, fungal infection), infiltrative disorders or malignancy. No other organ-specific antibodies were found (thyroid antibodies, islet cell antibodies, antibodies to glutamic acid decarboxylase). The family history was unremarkable. The patient did not have any signs of adrenoleukodystrophy, such as cognitive dysfunction, behavioural problems, visual or gait disturbances, emotional lability, urinary retention or impotence. The diagnosis of autoimmune Addison's disease was made and replacement therapy with hydrocortisone and fludrocortisone was started. His complaints disappeared completely. During the following years the dose of hydrocortisone was decreased. At first, the dosage was gradually decreased from 30 to 20 mg hydrocortisone a day. During this time, his wife, who claimed to have paranormal gifts, started to treat her husband with "energy therapy" in order to cure him. Eventually, he stopped using fludrocortisone and hydrocortisone, against medical advice. He was, however, advised to use hydrocortisone at times of illness, fever or stress.

Six months after discontinuation of steroid replacement therapy a second ACTH stimulation test revealed a basal cortisol of 0.25 µmol/l and a peak cortisol of 0.30 µmol/l with a basal ACTH of 178 pmol/l. Sodium and potassium were normal, aldosterone remained low at 50 pmol/l and the adrenal antibodies were still weakly positive. During an outpatient visit he found himself in excellent health. During the past 2 yr he has not experienced an Addisonian crisis and reports no complaints. He did not have any intercurrent illness and has not used hydrocortisone.

Discussion

We described a patient with primary adrenal insufficiency caused by autoimmune adrenalitis in whom, after 7 yr, partial remission was observed. To our knowledge, no case of remission in autoimmune Addison's disease has previously been reported. Primary adrenocortical insufficiency is caused by destruction or dysfunction of the cortex. The etiology of primary adrenal insufficiency has changed over time. In the past, tuberculosis was the major cause of adrenocortical insufficiency. At the present time, autoimmune adrenalitis accounts for more than 80% of cases in the western world. Other causes are adrenal hemorrhage, infections, metastatic malignancy or lymphoma, infiltrative disorders, adrenoleukodystrophy or drugs.[1,2] Adrenocortical insufficiency is considered to be irreversible and therefore requires permanent glucocorticoid replacement therapy. But sometimes recovery of primary adrenal insufficiency can occur. Feuerstein was the first to report recovery of adrenal function after hemorrhage-induced adrenal insufficiency.[3] In 2004 Guichelaar also described recovery of adrenocortical function in a trauma patient with bilateral adrenal hemorrhage.[4] Jahangir-Hekmat retrospectively reviewed the follow-up of 4 patients with acute bilateral adrenal hemorrhage and subsequent adrenal insufficiency.[5] They reported improvement in baseline and/or cosyntropin-stimulated serum cortisol levels in 3 out of 4 patients. One patient was able to function normally without hydrocortisone replacement.

Mycobacterial, bacterial, viral, and fungal infections may also lead to adrenal insufficiency. Prompt diagnosis and treatment of these infections is necessary to avoid further adrenocortical damage. Recovery of adrenal function was observed after treatment of tuberculosis, histoplasmosis, paracoccidioidomycosis, and trypanosomiasis.[6-9] The mechanism by which the adrenal cortex is damaged in autoimmune Addison's disease is not completely clear.

Autoantibodies against adrenocortical antigens are often found. The reported prevalence of autoimmune adrenalitis as a cause of Addison's disease ranges from 25 to 84%.[10] The level of adrenocortical auto-antibodies correlate with the degree of adrenal dysfunction.[11] Antibodies may destroy cells by initiating antibody-dependent cellmediated immunity or by activating the cytolytic complement cascade. Antibody-mediated cytotoxic responses by T lymphocytes is another possible mechanism. Addison's disease can remain subclinical for a long time.[12] De Bellis et al. studied the relation between adrenal auto-antibodies and adrenal functional reserve in patients without clinical evident disease.[13] They found that spontaneous recovery of subclinical adrenal insufficiency can occur in the early stages. These results are in contrast with the belief that the natural course of destruction of the adrenal cortex in Addison's disease is a chronic, progressive, and irreversible process.

We have observed partial remission in a patient with clinical evident autoimmune adrenalitis. A comparable situation has been found in Hashimoto´s disease, also previously considered to be an incurable disease. Takasu found long-term remission in Hashimoto thyroiditis. Substitution therapy with levothyroxine could be discontinued successfully in 10-30% of patients.[14] Comtois studied 79 patients with Hashimoto's thyroiditis.[15] After 1 yr of treatment, levothyroxine was stopped for 3 weeks. In 11.4% normalization of thyroid blood tests occurred. These results show that hypothyroidism caused by Hashimoto's thyroiditis is not always permanent. What could be a possible explanation for partial recovery of adrenal function in our patient? Regeneration of adrenocortical cells could have occurred because of high plasma ACTH concentrations caused by decreased dosages of hydrocortisone. Another possibility lies in the critical size of residual functional adrenal tissue. Animal studies have shown a compensatory growth of adrenal tissue after subtotal bilateral adrenalectomy. Some authors reported on recovery of functionally impaired adrenal remnants. Brauckhoff investigated the early postoperative function of adrenal remnants (15-30% of adrenal tissue was left *in situ*).[16] After subtotal bilateral adrenalectomy functional recovery could be observed in all 10 patients. Perhaps not the entire adrenal cortex was destroyed in our patient and recovery and/or compensatory growth of adrenal tissue occurred. The role of autoantibody status and recovery is not clear. In our patient antibodies were weakly positive. Laureti and other investigators found a positive correlation between levels of adrenal autoantibodies and severity of adrenal dysfunction. However, this correlation was found in the pre-clinical period.[17] They also saw spontaneous remission of early stages of

adrenal dysfunction but this was associated with disappearance of adrenal autoantibodies. In our patient, autoantibodies remain weakly positive. This was also the case in a substantial number of patients with Hashimoto's disease in whom remission occurred. If adrenocortical destruction in auto-immune adrenalitis does not always lead to total or permanent dysfunction of adrenocortical cells and if recovery is possible, this could have important consequences for treatment and follow-up of patients with Addison's disease. Nowadays patients are treated with glucocorticoids for life. Glucocorticoids, at too high accumulative dosages, might lead to side-effects in the long term. Further investigation of occurrence and identification of remission in a group of Addison patients seems justified.

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Chapter 9: Does recovery of adrenal function occur in patients with autoimmune Addison's disease?

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Clinical Endocrinology 2011 74: 434-437

Abstract

Objective: We earlier discovered partial recovery in a patient with autoimmune Addison's disease. The aim of this study was to assess the occurrence of adrenocortical recovery in patients with autoimmune adrenalitis.

Design: Cross-sectional study.

Patients: Twenty-seven adult patients with autoimmune Addison's disease on stable glucocorticoid and mineralocorticoid replacement therapy (RT) attending the Department of Endocrinology of a university teaching hospital were included in this study.

Methods: Adrenocortical function was assessed by performing an adrenocorticotrophic hormone (ACTH) (250 μg Synacthen) stimulation test (SST) after interruption of current glucocorticoid and mineralocorticoid RT. A normal adrenal response was defined as a serum cortisol concentration >500 nm 30 or 60 min after stimulation. Partial recovery was defined as a cortisol concentration ≥100 and ≤500 nm after stimulation.

Results: In 17 patients (63%), serum cortisol concentrations remained undetectable 30 and 60 min after the administration of ACTH. None of the remaining 10 participants had a normal response. Only one patient reached a cortisol concentration of 100 nm after 60 min, but this could not be confirmed during a second SST.

Conclusions: In this cross-sectional study among 27 patients with autoimmune adrenalitis, no new cases of adrenocortical recovery were found.

Introduction

Addison's disease, mostly because of autoimmune adrenalitis, is a relatively uncommon disease with a reported prevalence of approximately 93–140 per million.[1-7] Autoimmune adrenalitis is probably caused by both humoral and T-cell-mediated immune responses, leading to adrenocortical destruction.[8] It can develop slowly through different stages from subclinical dysfunction to clinically manifest disease.[9] It is believed that Addison's disease will only become clinically apparent if more than 90% of the adrenals are destroyed. spontaneous remission of subclinical adrenocortical dysfunction can occur.[10,11] Clinically manifest autoimmune adrenocortical failure on the other hand is still considered to be a chronic, incurable disease leaving patients requiring lifelong glucocorticoid and mineralocorticoid replacement therapy (RT) with possible side effects of mild over-replacement in the long term. We however have documented partial recovery of adrenocortical function in a patient with autoimmune Addison's disease who had been treated with glucocorticoid RT for 7 years.[12] We conducted this cross-sectional study to investigate the possible occurrence of adrenocortical recovery in patients with autoimmune Addison's disease.

Methods

Participants and study design

Twenty-seven adult patients with autoimmune Addison's disease attending the Department of Endocrinology of a university teaching hospital with stable glucocorticoid and mineralocorticoid RT were included in this cross-sectional study. Subjects were excluded if they had acute intercurrent disease or if they were pregnant. The study was approved by the medical ethical review committee and board of the University Medical Center Utrecht, and all participants gave written informed consent prior to participation.

Study procedures

Adrenal function was assessed by performing a Short Synacthen stimulation test (SST). The day before, the SST participants discontinued their current RT. They were protected against adrenal crisis by taking 0.5 mg of dexamethasone in the morning, directly after awakening, on the day before and on the day of the SST and were allowed to take more salt if needed. In case of the use of dehydroepiandrosterone, this was discontinued a week before the SST. All tests were performed in the morning, between 8.00 and 10.00 am. A venous catheter was placed in the forearm and just before administering 250 μg Synacthen, blood was drawn for the measurement of cortisol, adrenocorticotrophic hormone (ACTH), dehydroepiandrosterone sulphate (DHEAS) and aldosterone. Cortisol, DHEAS and aldosterone were measured 30 and 60 min after stimulation. A second SST was performed under the same conditions in those patients who showed partial or complete recovery after the first SST. Prior to discontinuation of RT, ACTH measurements were collected early in the morning to get an impression of the extent to which the pituitary was still suppressed after the last glucocorticoid dosage the night before.

Main outcome measures

A normal adrenal response was defined as a cortisol concentration of 500 nm 30 or 60 min after stimulation. Partial recovery was defined as a cortisol concentration ≥100 and ≤500 nm after stimulation.

Laboratory assessments

Blood samples were centrifuged and stored directly after the SST before analysis in a single laboratory of Endocrinology (University Medical Center Utrecht, The Netherlands). All samples were run in duplicate. Cortisol was measured using an electrochemiluminescence immunoassay on the Modular E170 (Roche Diagnostics GmbH, D-68298 Mannheim, Germany). The lower limit of detection was 0.5 nm, and interassay variation was <5%. ACTH was measured by an Elecsys E170 chemiluminescence's immunoassay analyser (Roche). The interassay CV for the range of 4.6–160 ng/l was 5.5–8%. Aldosterone and DHEAS were measured by using a RIA (DPC; Siemens healthcare Diagnostics, Firmley, UK). The interassay CV for aldosterone concentrations of 61, 350 and 1100 pm were 15%, 7% and 5%,

respectively. For DHEAS concentrations of 1.3, 5.5 and 13 µm, interassay CV were 9%, 6% and 9.5%, respectively.

Statistical analysis

Continuous variables were expressed as mean with standard deviation and range, and categorical variables were expressed as percentages. Patients were divided into two groups according to the cortisol response after SST. Comparisons between the two groups were calculated by Mann–Witney U for continuous variables and Chi-square tests for categorical variables. All P-values are reported to be two-sided and considered statistically significant at a level of <0.05. Analyses were performed using the statistical software package spss Statistics 17.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Thirteen men and 14 women with confirmed autoimmune Addison's disease, based on positive adrenal antibodies, participated in our study. The mean age at enrolment was 50.1 ± 11.9 years (range 20–68 years). Most participants had longstanding Addison's disease (mean 15.7 ± 9.1 years, range 4–32 years) with a mean age at time of diagnosis of 34.5 ± 11.7 years (range 13–63 years). All patients were on glucocorticoid and mineralocorticoid RT. Participants used either hydrocortisone (89%, mean 24.4 ± 7.2 mg/day, range 12.5–40 mg) or cortisone acetate (11%, mean 26.7 ± 2.9 mg/day, range 25–30 mg). In addition, 55.% also used dehydroepiandrosterone. ACTH concentrations before and after temporary discontinuation of RT were 293.6 ± 418.9 ng/l (3–1930) and 385.5 ± 921.9 ng/l (2–4290), respectively. In 11 patients, adrenal insufficiency was accompanied by autoimmune hypothyroidism (40.7%) and in one patient by diabetes mellitus type 1 (3.7%). None of the 27 participants experienced any complaints after temporary replacement of hydrocortisone or cortisone acetate by dexamethasone.

Cortisol concentration before SST was 4.3 ± 14.5 (0–67.4) nm. In 20 of 27 participants (74.1%), morning cortisol was undetectable. Surprisingly, two patients had cortisol concentrations in the morning of 67.4 and 36.7 nm in spite of discontinuation of RT. In the remaining five, cortisol concentrations were very low. Aldosterone was undetectable in all 27 patients. DHEAS concentrations before and after stimulation are depicted in Table 1.

	Men		Women	
	≤60 years	>60 years	≤50 years	>50 years
DHEAS (µmol/L)				
T= 0	0,9 ± 0,3 (0,5-1,3)	1,5 ± 1,1 (0,7-2,3)	0,1 ± 0,1 (0-0,2)	0,2 ± 0,2 (0-0,5)
T= 30	0,9 ± 0,3 (0,5-1,2)	1,4 ± 1,2 (0,6-2,3)	0,1 ± 0,1 (0-0,2)	0,1 ± 0,2 (0-0,5)
T= 60	0,9 ± 0,2 (0,5-1,2)	1,4 ± 1,1 (0,6-2,2)	0 ± 0,1 (0-0,2)	0,1 ± 0,2 (0-0,5)

Reference values: men ≤60 years 1-12 µmol/L, men> 60 years 0,5-5, women ≤50 years 1-9 µmol/L, women >50 years 0,5-5

Table 1: DHEAS measurement before and 30, 60 minutes after stimulation with 250 µg ACTH

In 17 patients (63%), cortisol concentrations remained undetectable 30 and 60 min after the administration of 250 µg Synacthen. The remaining 10 participants showed a slight increase in cortisol concentration, but none had a normal response (Fig. 1).

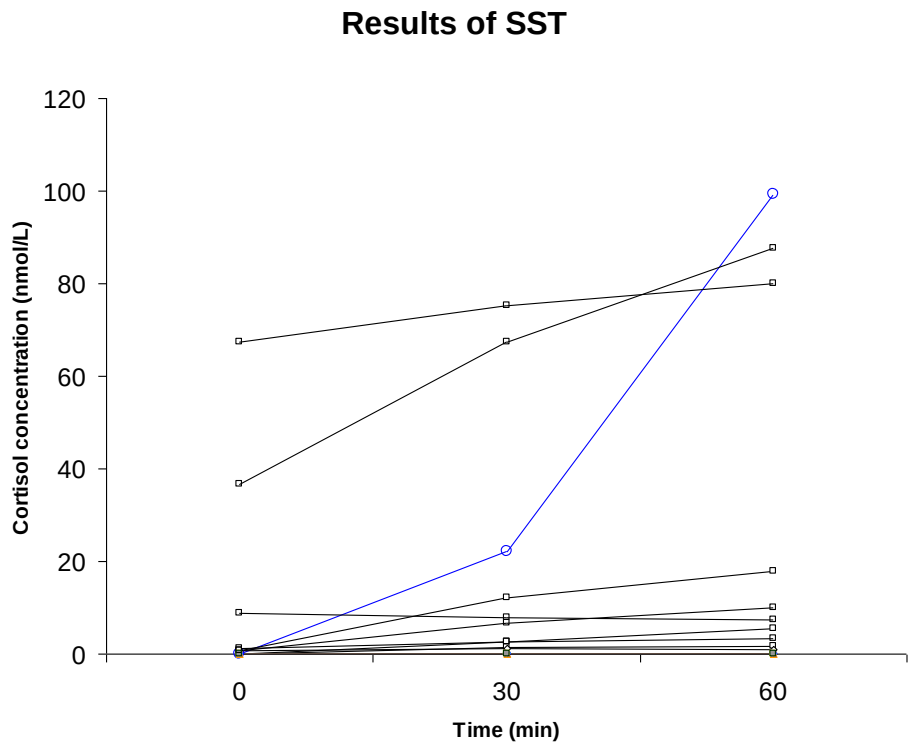

Figure 1: Results of SST

When comparing patients with and without a cortisol response after Synacthen, no differences were detected between the two groups regarding sex (chi-square 3.04; P-value 0.081), type of RT (chi-square 1.99; P-value 0.159), presence of hypothyroidism (chi-square 0.76; P-value 0.384) or other variables (Table 2). In the two participants with relatively high cortisol concentrations in the morning, cortisol increased after SST but did not reach 100 nm. Only one patient reached a cortisol concentration of 100 nm after 60 min [T = 0 undetectable, T = 30 22.1 nm; ACTH 12.0 ng/l (reference range 5–70 ng/l)]. A second SST in this patient showed no relevant cortisol rise [0.6, 2 and 3 nm at 0, 30 and 60 min, respectively, ACTH 8.0 ng/l (reference range 5–70 ng/l)].

Variable	No response	Response	Mann-Whitney U	P-value
Glucocorticoid dosage (mg/day)	23,6 ± 5,9	26,3 ± 8,3	69,0	0,44
Age at enrolment	49,1 ± 11,2	52,1 ± 13,6	71,5	0,50
Age at time of diagnosis	32,4 ± 10,1	38,1 ± 13,9	74,5	0,597
Duration of Addison's disease	16,7 ± 9,0	14,0 ± 9,6	68,5	0,41
ACTH (ng/L)before RT change	239,0 ± 312,7	386,3 ± 563,8	66,0	0,34
ACTH (ng/L) T=0	398,4 ± 1069,9	363,7 ± 647,6	56	0,15

Table 2: Comparison of patients with and without cortisol response after SST

Discussion

In the present study, we found no new cases of adrenocortical recovery among 27 patients with autoimmune adrenalitis after our previous report of partial recovery in one patient with autoimmune Addison's disease,12 who is presently in excellent health without glucocorticoid or mineralocorticoid RT after more than 5 years. Based upon this observation, we hypothesized that recovery of adrenocortical function in patients with autoimmune Addison's disease could not be excluded and it prompted us to perform this study. Recovery of endocrine function in a more or less comparable autoimmune disease, namely Hashimoto's thyroiditis, has been reported previously. Comtois assessed the incidence of remission of hypothyroidism and found recovery in 9 of 79 patients (11.4%).[13] Takasu studied 92 patients with Hashimoto's thyroiditis and, based upon a positive response to a

TRH test, identified patients who no longer required thyroxine. Twenty-two patients remained clinically and biochemically euthyroid after discontinuation of thyroxine for 1–8 years.[14] Similarly, we used the 250 μg SST as it is recognized as the best diagnostic test in the assessment of adrenocortical insufficiency.[15,16] In contrast to Comtois and Takasu, who stopped thyroxine in all study participants, we obviously could not stop RT completely, because of the risk of adrenal crisis. By replacing hydrocortisone and cortisone acetate by a low dose of dexamethasone, this was in our opinion the best feasible test to observe a possible increase in plasma cortisol. We found no new cases of (partial) adrenocortical recovery. More than 60% of participants did not have any response after a supraphysiological dosage of ACTH. Suppression of the hypothalamic pituitary adrenal axis (HPA axis), because of chronic glucocorticoid over-replacement, could be a possible explanation for the absence of cortisol response, but is unlikely, considering the nonsuppressed ACTH values during RT. In addition, total daily glucocorticoid dosage was, albeit slightly higher than recommended, not excessive in the majority of patients. Apart from the most plausible explanation for the absent cortisol response, namely complete destruction of cortisol-producing adrenocortical tissue, another possible explanation could be downregulation of ACTH receptors on adrenocortical cells. Incomplete ACTH suppression by pharmacological doses of glucocorticoids has been reported in patients with Addison's disease.[17,18] Inappropriately high ACTH concentrations at various moments during the day could, in the long term, lead to diminished sensitivity of adrenocortical cells to ACTH. Two of our patients had cortisol concentrations in the morning of 67.4 and 36.7 nm in spite of discontinuation of RT, but cortisol did not reach 100 nm after SST. Possibly, these patients have some residual adrenocortical cells that are capable of producing a very low quantity of cortisol, but are unable to respond properly to ACTH stimulation. Only one patient reached a cortisol concentration of 100 nm during the first SST. A second SST in this patient showed no relevant cortisol rise. We do not know why this patient showed different results on the second SST. All the test conditions were identical on both occasions, and the same immunoassay was used. We could speculate that in this patient, a few residual vital adrenocortical cells might be preserved with a variable response to ACTH stimulation.

In conclusion, in this study, we could not demonstrate adrenocortical recovery among 27 patients with autoimmune Addison's disease. Recovery of adrenocortical function is probably very rare, as opposed to recovery of Hashimoto's thyroiditis, found in about 10–20% of patients. Based upon our results, we cannot recommend routinely testing patients with Addison's disease for adrenocortical recovery.

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Competing interests/financial disclosure

The authors have nothing to declare.

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PART 5: SUMMARY AND CONCLUSIONS

Chapter 10: General discussion and summary

After the first description of Addison's disease in 1855 and one and a half century of intensive research on the adrenals and adrenocortical steroids, the diagnosis and treatment of Addison's disease still remains a challenge. This is in part caused by our current inability to imitate and influence the complex actions of the hypothalamic-pituitary-adrenal axis, intracellular cortisol regulation and glucocorticoid sensitivity. In clinical practice we noticed that many patients with Addison's disease experience persistent complaints influencing their daily life activities. This inspired us to explore the pitfalls in the diagnosis and the imperfections of current treatment and to illuminate important issues encountered during the follow up of patients with Addison's disease and finely to study the possibility of recovery of adrenal function in Addison's disease.

Part 1: Diagnosis of adrenal insufficiency

Part 1 of this thesis described the diagnosis and subclassification of adrenal insufficiency (**chapter 1**). The onset of adrenal insufficiency is usually gradual and signs and symptoms are often nonspecific. Therefore, adrenal insufficiency may go undetected for a long time. In this chapter we aimed at providing a concise stepwise approach and we discussed the pitfalls associated with the different tests. The first step we defined was establishing the presence of hypocortisolism by measuring basal morning plasma cortisol concentration. We pointed out that it is important to take into account possible changes in cortisol binding globulin, because this could lead to falsely lower or higher plasma cortisol concentrations. The finding of very low (<100 nmol/L) or high (>500 nmol/L) morning cortisol levels obviates the need for dynamic tests. In patients with intermediate results we proposed to perform a 250 microgram ACTH test, because it is a simple, save and accurate test, showing high specificity. We feel that in case of doubtful results or in patients with persistent high clinical suspicion of secondary adrenal insufficiency an insulin tolerance test should be performed or, if an insulin tolerance test is contraindicated, a metyrapone test. We discussed that the interpretation of the results of the test, and the definion of a normal cortisol response, should be set regarding the analytical accuracy of the cortisol assay used. Once hypocortisolism is

confirmed the next step is to determine the site of the hypothalamic-pituitary-adrenal axis defect by measuring plasma ACTH, which is the best test to distinguish primary from central adrenal insufficiency. The final step is to determine the exact etiology of adrenal insufficiency by performing additional blood tests and if needed adrenal or pituitary imaging. In our opinion this diagnostic approach is straightforward and will lead to a correct diagnosis in the majority of cases, thereby helping to start treating this potentially life-threatening disease as soon as possible.

Part 2: Treatment of Addison's disease

Part 2 of this thesis started with a review (**chapter 2**) aimed at describing the past, present and future perspectives of replacement therapy in patients with Addison's disease. We discussed the first landmarks in the history of adrenal insufficiency. It started with the discovery of the adrenal glands by Bartolomeo Eustachius, followed by the description of the first cases of adrenal insufficiency by Thomas Addison, and subsequently the demonstration of the pivotal role of the adrenal glands for life by Brown-Sequard. Extensive research eventually led to the synthesis of cortisone in 1949 and fludrocortisone in 1954. This revolutionized medical care of patients with Addison's disease. A previous lethal disease could now be treated. Hydrocortisone and cortisone acetate are still the most commonly used glucocorticoid preparations. Total daily dose is now believed to be approximately 15-25 mg of hydrocortisone, regarding changes in body weight. There is insufficient evidence that a thrice daily glucocorticoid dosage regime should be preferred over a twice daily regime. However, there is some evidence that a four times daily regime leads to less over-replacement in the morning and afternoon and leads to better quality of life scores. Unfortunately current therapy is still not able to mimic the physiological rhythm of cortisol release and inevitably results in over- and under-replacement. In our study, described in **chapter 3,** we aimed at investigating the use of salivary cortisol day curves in the individual adjustment of glucocorticoid replacement therapy, in order to approach normal cortisol levels as closely as possible, thereby reducing over- and under-replacement. Twenty patients with Addison's disease were included in this prospective study. At baseline, under-replacement was present in 3 and over-replacement in 18 patients, particularly in the

afternoon and evening. Over-replacement decreased significantly after adjustment of therapy. After reducing over-replacement in the evening, complaints about sleep disturbances significantly decreased. We believe that a salivary cortisol day curve is a simple and patientfriendly tool for adjusting glucocorticoid therapy and can be useful in the follow-up of patients experiencing persistent complaints in daily life.

Part 3: Challenges in the follow up of Addison's disease

With current replacement therapy many patients with Addison's disease still experience complaints. Especially musculoskeletal complaints, fatigue and reduced vitality seem to be common. In order to evaluate quality of life we performed a postal survey among 328 patients with Addison's disease (**chapter 4**) and studied their ability to be physically active. Sixty-one percent of patients with Addison's disease had severe fatigue and we found reduced general subjective health related quality of life scores in both male and female patients, especially in younger patients. In addition, we found that patients with Addison's disease are less physically active compared to controls. This seems particularly relevant in these patients, because besides being physically inactive they could have additional cardiovascular risk factors due to mild, but structural excessive glucocorticoid exposure. We assessed the prevalence of abnormal anthropometric and metabolic parameters and the metabolic syndrome in Addison's disease (**chapter 5**). We found that the prevalence of abdominal obesity, hypertension and hypertriglyceridemia was higher in female patients compared to healthy controls. The metabolic syndrome was not more prevalent in patients with Addison's disease compared to controls. Besides an up to two-fold increased mortality rate from cardiovascular disease, previous studies have also suggested that infections are an important cause of death in patients with Addison's disease, but epidemiological studies on the frequency of infections in this population were lacking. In our cohort study we found that the risk of infectious episodes, defined by the use of antimicrobial agents, among patients with Addison's disease was 1.5 times higher and the risk of hospital admission as a result of infection was 4.5 times higher compared to sex and age matched controls (**chapter 6**). In case of an infection or other forms of illness or stress patients with Addison's disease have to increase their glucocorticoid dose to avoid a life threatening adrenal crisis. No data

regarding incidence and precipitating causes of adrenal crisis in Dutch patients with adrenal insufficiency were available. We performed a retrospective analysis on the incidence, precipitating causes and risk factors of adrenal crisis in Dutch patients with adrenal insufficiency (**chapter 7**). We found an incidence rate of 5.2 adrenal crises/100 person years in primary, 3.6 adrenal crises/100 person years in secondary as compared to 15,1 adrenal crises/100 person years in tertiary adrenal insufficiency (overall 4.1 adrenal crises/ 100 person years). The most important precipitating factor for adrenal crisis was infection, mostly gastro-enteritis and bronchopulmonary infection. Patients with concomitant pulmonary, cardiac, malignant or neurological disease had a significantly higher risk for adrenal crisis. We concluded that adrenal crisis still occurs relatively frequent in patients with adrenal insufficiency and this points out that appropriate care must be taken in the follow up to educate patients with adrenal insufficiency to prevent and treat acute adrenal crisis.

Part 4: Recovery of adrenal function in Addison's disease

Part 4 of this thesis was introduced by an interesting case-report (**chapter 8**). We described a patient with primary adrenal insufficiency caused by autoimmune adrenalitis in whom partial remission was observed after 7 years of treatment. After he was diagnosed with Addison's disease, this 39 year old male was treated with hydrocortisone, which was gradually decreased during the following years. Eventually, he decided to stop his medication completely. A repeated ACTH stimulation test revealed a basal cortisol of 0.25 µmol/l and a peak cortisol of 0.30 µmol/l with a basal ACTH of 178 pmol/l. Remarkably, he did not have any complaints. We hypothesized that, if our case of partial recovery of autoimmune adrenalitis was not unique, this could have profound effects on treatment and follow-up of Addison's disease. It prompted us to perform a study aimed at finding more cases of (partial) recovery of adrenal function in patients with Addison's disease (**chapter 9**). We performed a cross-sectional study including 27 males and females with longstanding Addison's disease and performed ACTH stimulation tests after temporary discontinuation of glucocorticoid and mineralocorticoid replacement therapy. More than 60% of participants did not have any response after a standard dosage (250 microgram) of ACTH. Ten patients

only showed a slight increase in cortisol. In our study we found no new cases of (partial) adrenocortical recovery. In our opinion, the most plausible explanation for the absent cortisol responses was complete destruction of cortisol producing adrenocortical tissue. We concluded that recovery of adrenocortical function is probably very rare as opposed to the more frequently occurring recovery of Hashimoto's thyroiditis. Based on our results, we cannot recommend to routinely test Addison's patients for adrenocortical recovery.

Main conclusions and recommendations for further research

Adrenal insufficiency has a major impact on quality of life and daily life activities. Therefore, it is important to recognize adrenal insufficiency as soon as possible. With our diagnostic algorhythm we intended to accommodate all physicians who regularly encounter patients suspected of having adrenal insufficiency, in order to reduce the time that patients are withheld from treatment. In treating patients with Addison's disease, we are currently faced with our inability to catch and imitate normal physiology. It would be advantageous to develop markers of cortisol activity to be able to better assess individual replacement with glucocorticoids. In our opinion, these shortcomings result in the persistent reduced quality of life and morbidities in the long run. Unfortunately, recovery of adrenocortical function is probably very rare in patients with Addison's disease, making it a chronic disease that has to be treated for life. In the follow up of patients with Addison's disease, appropriate care must be taken to educate patients to prevent and treat acute adrenal crisis. Since infections seem to impose an important threat and seem to be more prevalent in patients with Addison's disease we emphasize the need for more research on the underlying cause of the increased risk of infections and efficiency of preventive strategies, such as vaccination, to reduce the incidence of infections in Addison's disease and thus decrease the incidence of adrenal crisis in the future. Furthermore, cardiovascular risk assessment and intervention are warranted in the management of patients with Addison's disease, especially in females, since the prevalence of abnormal anthropometric and metabolic factors is increased in female patients. In recent years, investigators have focused on developing new ways of glucocorticoid replacement, such as subcutaneous hydrocortisone infusion and modified release hydrocortisone. These regimes more closely approximate the normal circadian

rhythm and limited data available sofar suggest that patients experience improved levels of subjective health and well-being. However, long-term studies are required to further evaluate the clinical benefits and safety of these new preparations.

Chapter 11: Algemene discussie en samenvatting

Hoewel de eerste beschrijving van de ziekte van Addison al dateert van 1855 en er hierna gedurende anderhalve eeuw intensief onderzoek heeft plaatsgevonden naar de functie van de bijnieren en de werking van bijnierschorshormonen, zijn het stellen van de diagnose en de behandeling van de ziekte van Addison nog steeds een uitdaging. Dit wordt voor een deel veroorzaakt door het feit dat wij thans nog onvoldoende in staat zijn om de complexe werking van de hypothalamus-hypofyse-bijnieras na te bootsen en de intracellulaire cortisolregulatie en de glucocorticoïdgevoeligheid te beïnvloeden.

In de dagelijkse praktijk viel het ons op dat veel patiënten met de ziekte van Addison klachten houden die grote invloed hebben op het dagelijks functioneren. Dit inspireerde ons om de valkuilen in de diagnostiek en de onvolkomenheden van de huidige behandeling te exploreren en dÍe onderwerpen te onderzoeken die belangrijk zijn tijdens de follow up van patiënten met de ziekte van Addison. Tenslotte wilden we onderzoeken of herstel van bijnierfunctie mogelijk is bij de ziekte van Addison.

Deel 1: Diagnostiek van bijnierschorsinsufficiëntie

Deel 1 van dit proefschrift beschrijft de diagnostiek en de subclassificatie van bijnierschorsinsufficiëntie (hoofdstuk 1). Bijnierschorsinsufficiëntie ontstaat meestal geleidelijk en de klachten en verschijnselen zijn vaak aspecifiek. Daarom kunnen deze klachten al lang aanwezig zijn voordat de diagnose wordt gesteld. Het doel van dit hoofdstuk was het beschrijven van een effectieve, stapsgewijze methode voor het stellen van de diagnose bijnierschorsinsufficiëntie en het bespreken van de valkuilen van de verschillende diagnostische testen. De eerste stap die we hebben gedefiniëerd was het aantonen van hypocortisolisme door het meten van een basale ochtend cortisolwaarde. Hierbij hebben we het belang besproken van het in acht nemen van veranderingen in het cortisol bindend globuline, omdat die kunnen leiden tot een foutief lage of hoge cortisolconcentratie. Een lage (<100 nmol/L) of hoge (>500 nmol/L) basale cortisolwaarde maakt het uitvoeren van een dynamische test overbodig. Bij patiënten met basale cortisolconcentraties tussen 100

en 500 nmol/L, achten we het noodzakelijk een 250 microgram ACTH test uit te voeren. De ACTH test is een simpele, veilige en accurate test met een hoge specificiteit. In het geval van een twijfelachtig resultaat bij de ACTH test of bij blijvend hoge klinische verdenking op secundaire bijnierschorsinsufficiëntie, moet worden overgegaan tot het uitvoeren van een insulinetolerantietest, of indien deze gecontraindiceerd is, een metyrapon test. Het interpreteren van de resultaten van iedere test en het definiëren van de normaalwaarden, moet gebeuren met inachtneming van het type cortisolassay dat wordt gebruikt. Als hypocortisolisme eenmaal is bevestigd, moet vervolgens bepaald worden op welk niveau van de hypothalamus-hypofyse-bijnieras de dysfunctie gelocaliseerd is, door het meten van ACTH. Dit is de beste manier om een primaire van een centrale bijnierschorsinsufficiëntie te onderscheiden. De laatste stap is het bepalen van de exacte oorzaak van de bijnierschorsinsufficiëntie door het uitvoeren van aanvullend bloedonderzoek of indien nodig beeldvorming van de bijnieren of hypofyse. Het voorgestelde diagnostische plan is naar onze mening duidelijk en leidt tot een correcte diagnose in het overgrote deel van de gevallen. Zo kan snel gestart worden met het behandelen van deze potentieel levensbedreigende ziekte.

Deel 2: De behandeling van de ziekte van Addison

Deel 2 van dit proefschrift begint met een review (**hoofdstuk 2**) van de historie van en recente ontwikkelingen in de behandeling van bijnierschorsinsufficiëntie. Als hoogtepunten in de geschiedenis van de behandeling van bijnierschorsinsufficiëntie kunnen genoemd worden het ontdekken van de bijnieren door Bartolomeo Eustachius, gevolgd door de eerste beschrijving van de ziekte door Thomas Addison en het aantonen van de centrale functie van de bijnieren voor het in leven blijven door Brown-Sequard. Uitgebreid onderzoek heeft uiteindelijk geleid tot de synthese van cortison in 1949 en fludrocortison in 1954. Dit bracht een revolutie teweeg in de behandeling van mensen met de ziekte van Addison. Het werd mogelijk om een voorheen dodelijke ziekte te behandelen. Hydrocortison en cortisonacetaat zijn nog steeds de meest gebruikte preparaten. De totale dagdosering ligt meestal tussen de 15 en 25 mg per dag, waarbij veranderingen in lichaamsgewicht in ogenschouw genomen moeten worden.

Er is onvoldoende bewijs dat een driemaal daags regime beter is dan een tweemaal daags regime. Er zijn echter wel aanwijzingen dat een viermaal daags regime leidt tot minder oversuppletie in de morgen en middag en mogelijk tot een betere kwaliteit van leven. Met de huidige behandeling is het echter nog steeds niet mogelijk om het normale cortisolritme te imiteren en dit leidt onvermijdelijk tot over- en ondersuppletie. In onze studie, beschreven in **hoofdstuk 3**, onderzochten we of het gebruik van speekselcortisoldagcurves bij de individuele aanpassing van de glucocorticoïdbehandeling leidt tot het beter imiteren van de normale cortisolconcentraties met als doel onder- en oversuppletie te verminderen. Twintig patiënten met de ziekte van Addison werden geïncludeerd in deze prospectieve studie. Bij de start van de studie vonden we ondersuppletie bij 3 en oversuppletie bij 18 patiënten, met name in de middag en avond. Er was een significante afname van de oversuppletie na aanpassing van de behandeling op basis van de speeksel cortisol dagcurve. Na het reduceren van de oversuppletie in de avond namen klachten van slapeloosheid significant af. Wij zijn van mening dat een speeksel cortisol dagcurve een simpele en patiëntvriendelijke methode is voor het aanpassen van de glucocorticoïd behandeling en bruikbaar is in de follow up van patiënten met persisterende klachten in het dagelijkse leven.

Deel 3: Uitdagingen in de follow up van de ziekte van Addison

Ondanks de huidige behandeling blijven veel patiënten met de ziekte van Addison klachten houden. Met name klachten van het bewegingsapparaat, moeheid en verminderde vitaliteit komen veel voor. Om de kwaliteit van leven bij mensen met de ziekte van Addison te evalueren, verrichtten we een enquête onder 328 patiënten met de ziekte van Addison (**hoofdstuk 4**). Ook bestudeerden we het vermogen van mensen met de ziekte van Addison om fysiek actief te zijn. Ernstige moeheid was aanwezig bij 61% van de patiënten en er was sprake van verminderde kwaliteit van leven bij zowel mannelijke als vrouwelijke patiënten, met name bij jongeren. Daarnaast bleek dat patiënten met de ziekte van Addison minder fysiek actief waren. Het is aannemelijk dat dit met name in deze patiëntengroep relevant is, omdat naast fysieke inactiviteit er ook een verhoogde kans bestaat op andere cardiovasculaire risicofactoren door een structureel te hoge blootstelling aan glucocorticoïden. Om dit nader in beeld te brengen deden we onderzoek naar de prevalentie

van abnormale antropometrische en metabole parameters en het voorkomen van het metabool syndroom (**hoofdstuk 5**). We vonden een verhoogde prevalentie van abdominale obesitas, hypertensie en hypertriglyceridemie bij vrouwelijke patiënten. Onder patiënten met de ziekte van Addison was de prevalentie van het metabool syndroom niet hoger vergeleken met een controlegroep.

Naast een bijna twee maal verhoogd risico op sterfte door cardiovasculaire ziekte, blijkt uit eerdere studies dat infecties een andere belangrijke oorzaak voor sterfte zijn onder patiënten met de ziekte van Addison, maar epidemiologisch onderzoek naar de frequentie van infecties in deze populatie was nog niet eerder uitgevoerd. In onze cohortstudie vonden we dat het risico op een infectieuze episode, gedefinieerd als het gebruik van antibiotica, onder patiënten met de ziekte van Addison 1,5 keer hoger en het risico op een ziekenhuisopname als gevolg van een infectie 4,5 keer groter was vergeleken met op geslacht en leeftijd gematchte controles (**hoofdstuk 6**).

In geval van een infectie of een andere vorm van ziekte of stress moeten patiënten met de ziekte van Addison hun glucocorticoïddosering verhogen om een levensbedreigende bijniercrisis te voorkomen. Tot aan dit onderzoek waren geen gegevens bekend met betrekking tot de incidentie van en oorzaken voor een bijniercrisis bij Nederlandse patiënten met bijnierschorsinsufficiëntie. We verrichtten een retrospectieve analyse naar de incidentie van bijniercrises en keken daarbij naar predisponerende factoren en risicofactoren (**hoofdstuk 7**). We vonden een incidentiecijfer van 5,2 bijniercrises/100 persoonsjaren bij primaire, 3,6 bijniercrises/100 persoonsjaren bij secundaire en zelfs 15,1 bijniercrises/100 persoonsjaren bij tertiaire bijnierschorsinsufficiëntie (totaal 4,1 bijniercrises/100 persoonsjaren). De belangrijkste predisponerende factor voor bijniercrisis was infectie, met name gastro-enteritiden en luchtweginfecties. Patiënten met pulmonale, cardiale, maligne of neurologische comorbiditeit hadden een significant verhoogd risico op een crisis. We concludeerden hieruit dat bijniercrises nog steeds relatief vaak voorkomen bij patiënten met bijnierschorsinsufficiëntie hetgeen wijst op het belang van adequate instructies aan patiënten met bijnierschorsinsufficiëntie om bijniercrises te voorkomen en te behandelen.

Deel 4: Herstel van bijnierfunctie bij de ziekte van Addison

Deel 4 van dit proefschrift wordt ingeleid met een interessante ziektegeschiedenis **(hoofdstuk 8)**. We beschreven een patiënt met primaire bijnierschorsinsufficiëntie veroorzaakt door een auto-immuun adrenalitis waarbij partiële remissie werd aangetoond na 7 jaar behandeling. Na de diagnose werd deze 39 jarige man behandeld met hydrocortison, welke langzaam werd afgebouwd in de daarop volgende jaren. Uiteindelijk besloot hij zijn medicatie geheel te staken. Een nieuwe ACTH stimulatie test liet een basaal cortisol van 0,25 µmol/l en een maximaal cortisol van 0,30 µmol/l zien bij een basaal ACTH van 178 pmol/l. Zeer opvallend was dat hij hierbij geen klachten had. Wij hadden het idee dat als onze casus niet uniek was dit van groot belang zou zijn voor de behandeling en follow-up van mensen met de ziekte van Addison. Dit was voor ons de reden een vervolgonderzoek te verrichten gericht op het vinden van meer gevallen van (partieel) herstel van bijnierfunctie (**hoofdstuk 9**). We verrichtten een cross-sectionele studie met 27 mannen en vrouwen met de ziekte van Addison waarbij we ACTH-stimulatietesten deden na het tijdelijk staken van de glucocorticoïden en mineralocorticoïden. Meer dan 60% van de deelnemers had geen enkele respons na 250 microgram ACTH. Bij 10 patiënten vonden we een geringe stijging van het cortisol. We vonden geen enkele nieuwe casus met (partiëel) herstel van bijnierfunctie. De meest waarschijnlijke verklaring voor de afwezige cortisolrespons is complete destructie van het cortisol-producerend bijnierschorsweefsel. We concludeerden dat herstel van bijnierschorsfunctie waarschijnlijk zeer zeldzaam is in tegenstelling tot het vaker voorkomen van herstel bij een Hashimoto thyreoïditis. Op basis van onze resultaten raden wij het routinematig testen op herstel van de bijnierschors af bij patiënten met de ziekte van Addison.

Belangrijkste conclusies en aanbevelingen voor nader onderzoek

Bijnierschorsinsufficiëntie heeft een grote invloed op de kwaliteit van leven en de dagelijkse activiteiten. Daarom is het erg belangrijk om bijnierschorsinsufficiëntie snel te herkennen. Onze diagnostische flowchart biedt artsen die mensen onderzoeken met een verdenking op bijnierschorsinsufficiëntie een snelle en duidelijke procedure, zodat bij mensen die inderdaad bijnierschorsinsufficiëntie hebben snel gestart kan worden met behandeling.

Bij de huidige behandeling van mensen met de ziekte van Addison worden we geconfronteerd met ons onvermogen om de normale fysiologie met de thans beschikbare medicijnen te imiteren. Daarom is het van groot belang om markers van cortisolactiviteit te ontwikkelen zodat we veel beter in staat zullen zijn de behandeling individueel aan te passen. We zijn van mening dat deze tekortkomingen van de huidige behandeling resulteren in het aanwezig blijven van een verminderde kwaliteit van leven en op lange termijn leiden tot morbiditeit. Waarschijnlijk is herstel van bijnierschorsfunctie zeldzaam in patiënten met de ziekte van Addison en dit maakt dat mensen behandeld moeten worden gedurende het gehele leven. Tijdens de follow-up van patiënten met de ziekte van Addison moet aandacht besteed worden aan de educatie van patiënten t.a.v. het voorkomen en behandelen van een acute bijniercrisis. Aangezien het erop lijkt dat infecties een belangrijk gevaar vormen en die meer voor lijken te komen bij patiënten met de ziekte van Addison, willen we benadrukken dat er meer onderzoek uitgevoerd moet gaan worden naar de onderliggende oorzaak van het toegenomen risico van infecties en dat onderzocht moet worden wat de efficiëntie is van preventieve strategieën zoals vaccinatie, om de incidentie van infecties en daarmee in de toekomst het voorkomen van bijniercrisis bij de ziekte van Addison te reduceren. Bovendien is cardiovasculaire risico analyse en interventie gerechtvaardigd tijdens de follow up van mensen met de ziekte van Addison, vooral bij vrouwen, aangezien de prevalentie van afwijkende antropometrische en metabole factoren bij vrouwen hoger is. In de afgelopen jaren is een begin gemaakt met het ontwikkelen van nieuwe manieren van glucocorticoïdsuppletie zoals subcutane hydrocortison infusie en toepassing van modified release hydrocortison. Deze behandelingen benaderen het normale circadiane ritme beter en patiënten lijken zich hierbij beter te voelen. Lange termijn studies zijn nodig om de klinische voordelen en de veiligheid verder te evalueren.

Curriculum vitae

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