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Hydrocortisone dose in adrenal insufficiency

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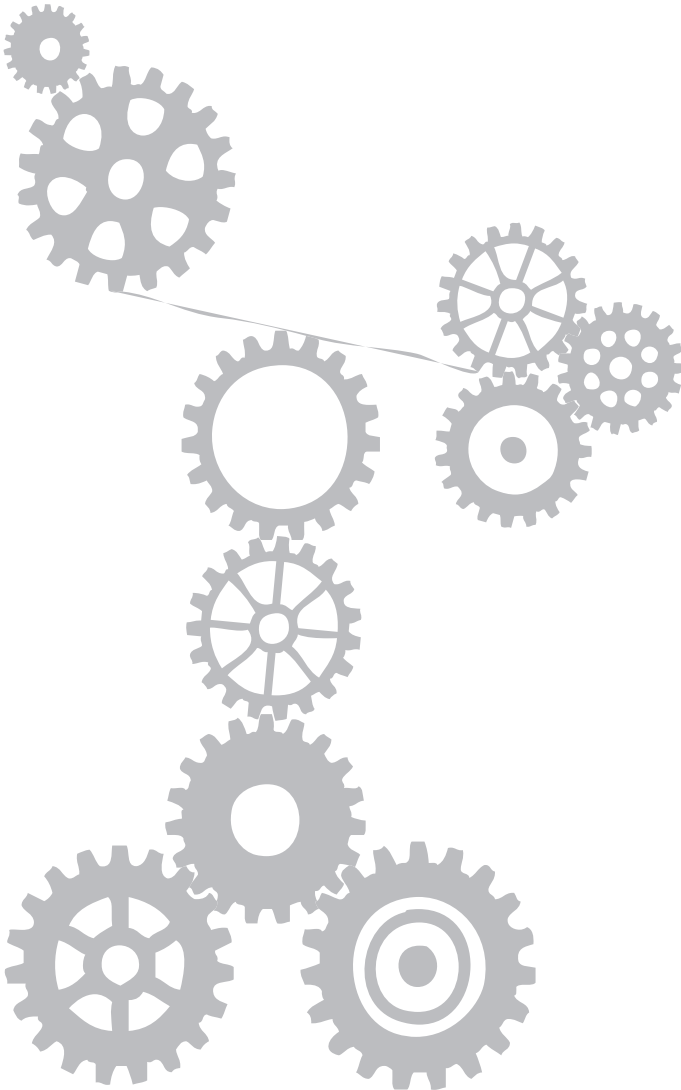
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Chapter 8

General discussion, conclusions and future perspectives



A 67-year-old woman was seen at our endocrine outpatient clinic for her yearly check-up. Two years earlier a non-functioning pituitary adenoma was removed by transsphenoidal surgery due to mass effects on the optic chiasm. After surgery, her vision improved, but her anterior pituitary gland was damaged resulting in pituitary insufficiency, necessitating hormonal supplementation therapy. She received substitution therapy with thyroid hormone, growth hormone and hydrocortisone (HC). The dose of the latter medication was 10 + 5 + 2.5 mg divided over the day. Since her last visit she mentioned that she was not feeling well. She reported regular complaints of headache and muscle and joint pain. She felt tired, restless, emotionally unstable and a bit depressed from time to time. She had trouble falling and staying asleep. She described her overall well-being as “it’s just not right”. Her partner confirmed the reported complaints and insisted that something had to change. Her endocrinologist acknowledged her problems and evaluated her options. Laboratory measurements showed an fT4 level of 16 pmol/L and IGF-1 Z-score of +0.4. Cortisol level measured at 14.15 h was 125 nmol/L after a hydrocortisone dose of 5 mg taken at 12.00 h. She had been treated with hydrochlorothiazide 25 mg once daily for hypertension and this resulted in good control of her blood pressure. After surgery, she gained 5 kg while she already weighed 90 kg, and this increase in body weight was predominantly noticeable in the abdominal region. When reviewing her medical record it was also noticed that her younger sister was diagnosed with osteoporosis.

In light of her physical complaints that are non-specific, but substantial enough to have an impact on her life and suggestive of under-substitution, it was investigated whether the dose of HC underlay her reported complaints. Her high blood pressure, increase in body weight and the presence of osteoporosis in the family discouraged her specialist from increasing her HC dose thus far. However, her current quality of life was impaired and together with her endocrinologist they decided to experiment with increasing the HC dose.

This anecdote shows that the considerations for the optimal substitution dose can be difficult with several pros and cons for HC dose increments. Therefore, in this thesis we aimed at contributing to the discussion regarding the treatment of secondary adrenal insufficiency (SAI) by adding evidence for current guidelines about substitution doses. In order to do so, we have performed a randomized double-blind crossover trial in which patients with SAI were treated with two different doses of HC.

PART I. THE EFFECT OF HYDROCORTISONE TREATMENT ON PSYCHOLOGICAL OUTCOME MEASURES IN PATIENTS WITH SECONDARY ADRENAL INSUFFICIENCY

Hydrocortisone and cognitive functioning

High levels of cortisol have often been linked to impaired cognitive performance. An inverted “U”-shape relationship between cortisol level and cognitive performance is suggested, with moderate cortisol levels being necessary for proper cognitive functioning, and very low or very high levels being impairing.^{1,2} We assessed cognitive functioning after 10 weeks of treatment with two different doses of HC, and showed that a doubling of the HC dose did not affect cognitive functioning in the domains of memory, attention, executive functioning and social cognition (**chapter 2**). On the higher dose of HC, patients tended to score worse compared to the lower dose on short-term memory for verbal non-coherent information and tended to show increased variability in reaction time for phasic alertness, however, the overall pattern of cognitive performance showed no indication of cognitive deterioration on the higher dose of HC as compared to the lower dose.

Even though these results are reassuring, there are several studies, both in animals and in humans, indicating that prolonged exposure to excessive levels of endogenous or exogenous cortisol is disadvantageous for cognitive functioning and, over time, leads to structural changes in the brain.^{3–5} For instance, patients with active Cushing’s disease report impairments in memory, visual and spatial information processing, reasoning, language performance, verbal learning, and attention,^{6–9} which is accompanied by structural changes in the brain such as cerebral cortical atrophy and hippocampal volume reduction.^{10,11} Moreover, these impairments and structural changes persist even after long-term remission of Cushing’s syndrome.^{12,13} Treatment with exogenous GCs can also lead to changes in brain structure, as white-matter abnormalities and temporal lobe atrophy were reported in patients with primary adrenal insufficiency (PAI) receiving GC substitution therapy.¹⁴ The temporary administration of a higher HC dose might thus not be detrimental for cognitive functioning, however, there is abundant evidence prompting us to be cautious about generalizing our results to longer time periods.

Two receptor types in the brain

Cortisol can bind to glucocorticoid receptors (GRs) and mineralocorticoid receptors (MRs). Both receptors are found in the brain. Neurons in the hippocampus contain both receptor types, whereas other parts of the brain mainly contain GRs. The finding that stress and accompanying high levels of cortisol impair cognitive performance whereas moderate cortisol levels enhance cognition, can be explained by differential activation of these two receptors.

Cortisol has a 6–10 fold higher affinity for the MR,¹⁵ resulting in high MRs occupancy even under basal, non-stressful situations.^{16,17} GRs become activated when cortisol levels increase, i.e. after stress exposure or at the circadian peak. It was found that when cortisol levels are mildly elevated, so when most of the MRs and some of the GRs are activated, long-term potentiation (LTP) is enhanced. LTP is the reinforcement of synaptic contacts contributing to the storage of information.¹⁸ When cortisol levels increase further and GRs become extensively activated, LTP is reduced and instead, long-term depression (reducing synaptic contact) is enhanced, resulting in the opposite effect of LTP.¹⁸

Both receptor types are involved in different aspects of learning and memory. It was found that MRs play a role in the initial behavioral reaction in novel situations, whereas GRs are involved in the consolidation of learned information.¹⁸ In addition, the consequence of activation of MRs and GRs depends on the context, i.e. the environmental input, during the various stages of memory processing: acquisition, consolidation and retrieval.¹⁸ Both effects of GRs and MRs mediate the hippocampal circuits that underlie complex learning paradigms such as spatial learning. Some GR activation is necessary for the consolidation of learned information, but additional activation of GRs due to a stressor that is out of context with respect to the original learning task, disrupts consolidation and favors a more-opportune response. Thus, MRs and GRs mediate different effects, but they interact and proceed in a coordinated manner.¹⁸

Studies assessing the effects of GR and MR occupation were mostly performed in animals or healthy individuals. However, results of these studies cannot uniformly be generalized to patients with AI, since regulation of the hypothalamic-pituitary-adrenal axis is disturbed in these patients. It would be interesting to study receptor activation in patients with AI, in which cortisol levels can be controlled externally. Cooperation between MRs and GRs is necessary to preserve cognitive performance, and even though we did not find differences on the current HC doses used, demands may be different when we expose patients to stress and thereby increase cortisol demand. One could speculate that the lower dose of HC as administered in the present study might not be sufficient to retain cognitive performance.

In conclusion, a higher dose of HC is not harmful for cognitive functioning when administered for a substantial period of time. However, there is evidence that chronic exposure to high cortisol levels leads to impairments in cognitive functioning in the long run.^{12,13} Therefore, we need to be cautious about generalizing our results to longer time periods. Furthermore, it is known that GCs enhance memory consolidation of emotionally arousing experiences, whereas it impairs memory retrieval and working memory in stressful situations.¹⁹ Therefore, the introduction of an (emotional) stressor prior to cognitive assessment may result in different effects.

Hydrocortisone and health-related quality of life

Patients with SAI report a compromised quality of life (QoL). This relationship appears to be dose-dependent, with higher doses of HC being associated with a worse QoL.^{20–22} However, in the present thesis we showed that patients reported increased QoL after receiving the higher dose of HC (**chapter 3**). Particularly improvements in the domains fatigue and energy, pain, somatic complaints, and symptoms of depression were reported. Overall, physical aspects of QoL seemed more affected than mental aspects and most of the reported complaints are related to energy and vitality.

Reduced QoL has a major impact on one's functioning in daily life. In a cross-sectional study in the German AI population, more than 25% of patients with SAI reported to be out of work and 70% experienced that they were restricted in their leisure activities.²² Improving the QoL of patients with AI is a major short- and long-term goal of substitution therapy, but at the same time it was reported to be one of the main challenges associated with conventional GC substitution therapy.²³ Surprisingly, QoL is still not routinely assessed by physicians.²³

Awareness about the importance of QoL is rising, prompting clinicians in the UK to develop an Addison's disease-specific questionnaire aimed at quantifying altered well-being and treatment effects.²⁴ Initially a total of 36 disease-specific items were included in the questionnaire, based on literature research and in-depth interviews with 14 patients with Addison's disease and seven of their partners. Validation of the questionnaire resulted in a revised 30-item AddiQoL questionnaire.²⁵ This questionnaire could be an easy tool for the regular assessment of QoL during GC substitution therapy.

In a study examining the factors affecting QoL in AI, longer time between onset of symptoms and diagnosis turned out to be the most important factor impairing QoL.²⁶ In a German study in 216 AI patients it was found that 47% of patients with AI were diagnosed within the first year of onset of symptoms, whereas for 20% of patients it took more than 5 years before the correct diagnosis of AI was established.²⁷ Furthermore, 85% of patients consulted more than one physician before the diagnosis was made, emphasizing the need for increased awareness of this disease among physicians. Diagnosis is often delayed due to the non-specific signs of AI. This association between delay in diagnosis and impairment in QoL was still present years after manifestation of the disease, indicating the relevance of a timely and adequate diagnosis. Therefore, more attention for this rare disease and an earlier diagnosis should be established as this may contribute to improvements in QoL.

One of our most striking results from **chapter 3** was the reported increase in pain symptoms after treatment with the lower dose of HC. In healthy individuals, stress leads to secretion of cortisol, which in turn reduces pain levels due to its pain-dampening effects.²⁸ Correspondingly, low levels of cortisol are associated with high pain

levels.²⁹ However, it has recently been questioned whether low cortisol levels are the consequence rather than the cause of these high pain levels.³⁰ To study this cause-effect relationship, we have investigated the possible mediating role of cortisol levels in the association between perceived stress and pain (**chapter 4**). We did not find evidence for a mediating role of cortisol in the association between perceived stress and pain, which was in accordance with a recently conducted large longitudinal study.³⁰ It should be noted that overall reported stress levels in this study were relatively low. It is conceivable that the role of HC in the association between stress and pain is particularly evident in stressful situations and that the relationship between stress and pain is different when a mild stressor is applied. Therefore, the introduction of a mild stressor in addition to a change in HC substitution dose would be suggested for future research.

In conclusion, QoL should be regularly assessed in GC substitution treatment since reduced QoL has a major impact on daily life functioning. Endocrinologist should be aware that patients might benefit from a higher dose of HC with regard to several aspects of QoL. We suggest to start with the lowest dose to relieve the symptoms of adrenal insufficiency (AI), but consider to increase the dose when QoL is impaired.

PART II. THE EFFECT OF HYDROCORTISONE TREATMENT ON SOMATIC OUTCOME MEASURES IN PATIENTS WITH SECONDARY ADRENAL INSUFFICIENCY

Hydrocortisone and somatosensory functioning

As described earlier (**chapter 3**), after receiving the lower HC dose, patients reported more pain symptoms. Elaborating on this, we investigated whether the two HC doses also altered somatosensory functioning. To study this, the Quantitative Sensory Testing (QST) battery of the German Research Network on Neuropathic Pain was used to establish detection and pain threshold in response to mechanical stimuli.^{31,32} We applied several sensory stimuli, ranging from modified von Frey hairs to pinpricks, on the dorsal hand and patients had to indicate whether they felt the stimulus or not, or how much pain they experienced when the stimulus was applied. We did not find differences in sensitivity in response to mechanical stimuli between the two treatment doses (**chapter 5**). However, even though the QST has proven to be valid, reliable and sensitive in quantifying sensory abnormalities,^{33–35} it was mainly developed to study inter-individual differences in pain diagnoses and it might be questioned whether it was sensitive enough to assess potentially much smaller intra-individual differences. The QST can be used as a tool for discriminating between groups (pain versus no pain), however, its ability to predict pain intensity in patients based on pain thresholds seems limited.³⁶

Mechanisms regulating cortisol exposure

It is well established that high levels of GCs increase risk factors for cardiovascular disease and can even increase cardiovascular mortality. In the present thesis it was found that 10 weeks of treatment with a higher dose of HC resulted in an increase in blood pressure, accompanied by suppression of the renin-angiotensin-aldosterone system (**chapter 6**), indicating MR activation. The mechanisms underlying these relationships are complex; exposure to cortisol is not just the equivalent of the dose of HC administered. This was illustrated in **chapter 7**, where we showed that administration of the same weight-adjusted dose of HC led to large inter-individual differences in cortisol exposure. Furthermore, tissue specific cortisol levels are not only determined by circulating plasma or serum cortisol levels. This system is much more complex and additional factors play a role. For instance plasma proteins that bind cortisol and steroid metabolism within target tissues both regulate tissue specific cortisol exposure.

CBG and albumin

Most of the cortisol is bound to the plasma proteins corticosteroid-binding-globulin (CBG) and albumin. Approximately 80% of cortisol is bound to CBG (with high affinity but low binding capacity) and 10% to albumin (with low affinity but high binding capacity), leaving approximately 10% of cortisol unbound, i.e. free cortisol. As cortisol levels increase, the relative amount of albumin-bound cortisol and free cortisol increases, while the relative CBG-bound cortisol fraction decreases.³⁷ This is probably due to saturation of CBG at higher concentrations of cortisol.

CBG is the principal transport protein of GCs. Cortisol is hydrophobic and it therefore requires a transport system in plasma to circulate and reach target tissues.³⁸ In addition, CBG also acts as a reservoir of circulating cortisol. Upon interaction with target proteinases, the binding activity of CBG is lost and cortisol is released.³⁹ This mechanism regulates local delivery of cortisol to tissues, for instance during inflammation.⁴⁰ CBG concentrations and its binding capacity are affected by several factors such as sex (CBG levels are higher in women compared to men⁴¹), concomitant medications (for instance estrogen are known to increase CBG levels and consequently increase total cortisol levels⁴²⁻⁴⁴) and physiological changes in body temperature (in response to fever or external heat, CBG releases cortisol⁴⁵). Changes in CBG have an impact on total serum cortisol levels, but concentrations of serum free cortisol, i.e. the biologically active part of cortisol, are believed to be unaffected. Nevertheless, total cortisol is usually measured in clinical practice as a reflection of free cortisol. However, free cortisol levels are not always dose proportional to total cortisol, as was shown in **chapter 7**. A doubling of the HC dose did result in a doubling of plasma free cortisol levels, whereas total cortisol levels increased less. This non-proportional increase in total cortisol could be attributed to saturation of CBG, leading to increased

free cortisol levels and in order to compensate for this, resulting in increased total cortisol clearance and thus a relatively less increase in total cortisol levels.⁴⁶ Serum free cortisol could potentially be a useful biomarker in the monitoring of GC replacement therapy, however, measurement of free cortisol is time-consuming and cumbersome as no commercial assays are available yet. Therefore, it is not used in daily clinical practice. It should be mentioned that even though free cortisol levels more closely reflect the biologically active part of cortisol, it still does not represent intracellular cortisol levels.⁴⁷

Alternatively cortisol in saliva is suggested as a potential marker for monitoring HC substitution. Salivary cortisol is believed to reflect the free fraction of cortisol in plasma because of the absence of substantial amounts of CBG and albumin in saliva.⁴⁸ Furthermore, the measurement of cortisol in saliva is non-invasive and convenient for the patient because it can be collected at home. However, it has some limitation as well. Salivary cortisol is undetectable when serum cortisol levels are low,⁴⁹ samples are easily contaminated by oral HC intake resulting in very high salivary cortisol levels,⁵⁰ and correlations with serum cortisol are variable.⁵⁰⁻⁵⁴ Therefore, its utility in the monitoring of HC substitution therapy remains uncertain. In contrast, salivary cortisone is not affected by contamination with oral HC. In addition, due to the activity of 11 β -hydroxysteroid dehydrogenase type 2 (11 β -HSD2) in the salivary gland, cortisone levels exceed cortisol levels in saliva, making them easier to measure even at low concentrations of serum cortisol. Furthermore, salivary cortisone is presumed to be generated during the production of saliva from free serum cortisol.⁴⁹ With saliva being considered a post-enzyme tissue, salivary cortisone levels could thus reflect tissue specific cortisol exposure. However, results thus far are inconclusive about whether salivary cortisone can be used as a biomarker for monitoring HC substitution therapy.^{51,55,56}

11 β -hydroxysteroid dehydrogenase

Another mechanism involved in the targeted tissue exposure is the pre-receptor metabolism of cortisol by 11 β -hydroxysteroid dehydrogenase type 1 (11 β -HSD1) and type 2 (11 β -HSD2). 11 β -HSD2 is highly expressed in mineralocorticoid target tissues such as the salivary gland, kidney and colon.⁵⁷ In vitro, cortisol has the same binding affinity to the MR as the mineralocorticoid aldosterone, but 11 β -HSD2 protects the MR from unwanted activation by cortisol by converting cortisol to cortisone.⁵⁸ In the absence of 11 β -HSD2 or when its activity is reduced, the MR is activated by cortisol, leading to increased blood pressure, sodium retention, potassium loss with low renin and aldosterone concentrations. In **chapter 6** we have shown that even GC substitution doses considered to be within the physiological range have an effect on blood pres-

sure and decrease renin and aldosterone concentrations, suggesting MR activation by cortisol.

The other enzyme, 11β -HSD1, is more widely expressed throughout the body, with highest expression detected in key metabolic tissues including adipose tissue, liver, and skeletal muscle.⁵⁹ 11β -HSD1 is bidirectional *in vitro*, it can activate GCs by converting cortisone to cortisol (reductase) and it can inactivate GCs by converting cortisol to cortisone. However, the reductase activity (activating GCs) predominates *in vivo*.

In healthy men, the amount of cortisol regenerated through 11β -HSD1 is greater than endogenous secretion by the adrenal gland.⁶⁰ Three pathways have been identified by which cortisol activates GRs and 11β -HSD1 plays a role in these mechanisms. Firstly, active cortisol is able to diffuse through the cell and bind to the GR. Secondly, excess active cortisol in the circulation is converted to inactive cortisone by 11β -HSD2, and once it has reached the target tissue, is transformed back into cortisol by 11β -HSD1 to enable activation of the GR. Thirdly, activation of the GR by GCs stimulates the expression and activity of 11β -HSD1 within the cell, resulting in a feed forward loop in which more cortisone is being reactivated to cortisol.⁵⁸

It is suggested that 11β -HSD1 plays a role in the adverse metabolic features of GC excess. Two case reports describe patients with GC excess due to Cushing's disease, but who lack the typical Cushingoid phenotype.^{61,62} In both these patients, a defect in 11β -HSD1 activity was identified. This led to the assumption that tissue regeneration of cortisol by 11β -HSD1, rather than circulating delivery, is the major determinant of the adverse metabolic manifestations of circulatory GC excess. This was replicated in a mouse model, in which 11β -HSD1 knock-out mice receiving exogenous GCs remained protected from the adverse metabolic side effects of GC excess such as glucose intolerance, hyperinsulinemia, hypertension, hepatic steatosis, myopathy and dermal atrophy.⁵⁸

11β -HSDs are also expressed in the brain and are suggested to be involved in the cognitive consequences of GC overexposure. 11β -HSD2 can be found in the developing brain, where it protects the brain from the negative effects of GC excess, but its expression in the adult brain is very limited and restricted to the hippocampus, lateral septum, and some brain stem nuclei.^{17,63} In contrast, 11β -HSD1 is more widely expressed in the brain, particularly in the hippocampus, prefrontal cortex and cerebellum.⁶⁴ Local regeneration of cortisol by 11β -HSD1 may cause neurotoxicity and this can result in age-related cognitive decline.⁶⁰ In the mouse brain, 11β -HSD1 levels rise with age and correlate with impaired cognitive performance. Accordingly, 11β -HSD1 knockout mice are protected from the age-related impairment in cognitive performance.⁶⁵ This was associated with reduced intrahippocampal glucocorticoid levels whereas circulating glucocorticoid levels remained stable or were modestly elevated.⁶⁵ This shows that

11 β -HSD1 in the brain is more important for GC action in the brain than circulating cortisol levels.

Inhibition of 11 β -HSD1 has been suggested as a potential target for therapy in disorders in which local cortisol regeneration plays a key role, such as type 2 diabetes, obesity and age-related cognitive decline. A number of selective and non-selective 11 β -HSD1 inhibitors have been developed and studied, but results are inconclusive. A few studies described the effects of a selective 11 β -HSD1 inhibitor in patients with type 2 diabetes and those not responding to metformin treatment and reported modest improvements in blood glucose control, insulin sensitivity and lipid profile.⁶⁶⁻⁶⁸ However, due to the small magnitude of their glucose lowering effect, these inhibitors have not been further developed as antidiabetic agents, and are therefore not commercially available yet. With regard to cognition, the non-selective 11 β -HSD inhibitor carbenoxolone improved verbal fluency and memory in healthy elderly and men with type 2 diabetes.⁶⁴ However, a phase II clinical trial studying the selective 11 β -HSD1 inhibitor ABT-384 in patients with mild to moderate Alzheimer's disease was terminated prematurely due to lack of efficacy.⁶⁹

One might speculate that 11 β -HSD1 inhibition could also be used to counteract the negative side effects of GC excess in GC substitution therapy as treatment for SAI. However, none of these selective inhibitors have been tested in this application. Furthermore, the effects of long-term 11 β -HSD1 inhibition on, for example, the immune system are unclear.⁵⁸ Clinical studies are needed to further elucidate these long-term effects and to investigate the potential role in neutralizing the negative side effects of potential GC excessive exposure in the substitution therapy of SAI.

Other mechanisms regulating cortisol exposure

Binding of cortisol and the interconversion between cortisol and cortisone are not the only mechanisms influencing cortisol exposure. Cortisol is metabolized by cytochrome P450 3A4 (CYP3A4). CYP3A4 is the major enzyme metabolizing various substances made by the body (e.g. cholesterol and cortisol) and substances foreign to the body (e.g. several medications). The inhibition or induction of CYP3A4 by drugs often causes unfavorable and long-lasting drug-drug interactions. CYP3A4-inhibiting drugs (e.g. ketoconazole, clarithromycin, cimetidine) decrease the activity of the enzyme, resulting in decreased clearance and increased half-life (hence increased exposure) of cortisol. On the other hand, CYP3A4 inducing drugs (e.g. carbamazepine, barbiturates, rifampin) can increase enzyme activity and consequently increase clearance and decrease half-life of cortisol.⁷⁰ When such interfering medications are used concomitantly with GCs, GC doses should be adjusted accordingly.

Cortisol exerts its effect through binding with GRs within the cell. After binding with a GR, the GR-complex enters the nucleus of the cell where it binds to a GC response

element to up-regulate and down-regulate certain genes. Several single nucleotide polymorphisms (SNPs) have been identified in the human GR gene which can influence receptor sensitivity for GCs.⁷¹ The main polymorphisms studied in the GR-gene are *Tth1111* (rs10052957), ER22/23EK (rs6189 + rs6190), N363S (originally rs6195, currently listed as rs56149945), *BclI* (rs41423247) and GR-9 β (rs6198). The *Tth1111* was originally reported to be associated with elevated basal cortisol levels,⁷² but other studies suggested that this SNP coincides in haplotypes with either the 9 β SNP, the 9 β SNP and the ER22/23Ek SNP, or the *BclI* SNP.⁷³ The *BclI* and the N363S SNP are associated with a phenotypes indicating increased GC sensitivity, whereas the ER22/23EK and GR-9 β are associated with decreased GC sensitivity.⁷¹ Furthermore, the 11 β -HSD1 SNP (rs11119328) was associated with increased salivary cortisol levels and increased susceptibility for depression.⁷⁴ Most associations between SNPs and clinical outcome have been reported in body composition, metabolism, the cardiovascular system, the immune system and psychiatric illnesses.⁷⁵ We know from patient experience and reported in this thesis that there is a large variation in the clinical response to GC treatment. Some patients reported to experience large differences in well-being between the two treatment doses, whereas others reported no change whatsoever. Genetic variation in the GR-gene may underlie this variation⁷¹ and it would be interesting to study whether genetic variation mediates the effect of the GC substitution dose.

Should we treat them all with dual-release hydrocortisone?

One of the shortcomings of the currently available substitution treatments for SAI is that it does not mimic the normal diurnal cortisol rhythm seen in healthy people very well, which is a consequence of the pharmacokinetic properties of the oral immediate release tablets. New developments in timed-release HC preparations enable the mimicking of the daily rhythm in cortisol production. Plenadren® (dual-release HC) is one of those new formulations. It consists of a modified-release HC tablet with combined immediate and extended release characteristics, allowing only once daily administration.⁷⁶ Initial studies showed that a more physiological cortisol profile could be established, leading to decreased overall cortisol exposure accompanied by improvements in blood pressure, body weight, body mass index, hemoglobin A1c, and QoL.⁷⁷⁻⁷⁹ Even though modified-release HC is able to create a more physiological cortisol profile during the day, patients still lack the nocturnal rise in cortisol and the peak upon awaking. Early morning fatigue as a consequence of low cortisol levels is a major problem with current replacement regimen.⁸⁰⁻⁸² In order to overcome this limitation, another modified-release preparation of cortisol (also known as Chronocort®) was designed to provide nocturnal cortisol levels comparable to healthy individuals.⁸³ Indeed, administration of 30 mg of Chronocort® at 2200 h with a delayed release of cortisol of 4 h, resulted in close to normal concentration-time curves, with time

to reach maximum concentrations and area under the curve being similar to levels found in healthy volunteers with intact endogenous cortisol production.^{83–86} However, despite the more physiological profile during the night and the early morning, very low cortisol levels were observed at around midday after administration of Chronocort®, indicating the remaining need for a morning administration of GCs.

Alternatively, continuous subcutaneous hydrocortisone infusion (CSHI) has been proposed as a treatment option, and it proved to allow accurate regulation of GC delivery restoring the biological daily rhythm.⁸⁷ It was able to normalize morning cortisol levels and to restore GC metabolism close to normal.⁸⁸ CSHI proved safe and might be a treatment option for selected patients who function poorly on regular oral HC treatment. Particularly patients with issues in first-pass hepatic metabolism or gastrointestinal diseases might benefit from CSHI. It has the potential to reduce risk of acute adrenal crisis in case of vomiting or diarrhea. If pump technology improves and costs will be reduced, CSHI has the potential to become an affordable treatment choice for patients who fail conventional treatment.

In conclusion, results from initial studies with modified-release HC preparations and CSHI are promising. They provide a more physiological cortisol profile and metabolic parameters improve. Furthermore, adherence might be better compared to thrice daily dosing which is necessary with immediate release tablets.⁸⁹ However, studies assessing long-term safety and effectiveness are still needed. In case of persistent compromised well-being or in patients that are poorly controlled by conventional therapy, dual-release HC or CSHI should be considered a treatment option in order to improve disease control and outcomes.

CONCLUSION AND FUTURE PERSPECTIVES

In this thesis we looked into the effects of two different doses of HC on several psychological and somatic outcome measures. Treatment with a higher dose of HC was not harmful for cognitive functioning and it increased several components of QoL. However, it also increased blood pressure and affected several blood pressure regulating mechanisms. No differences were found for somatosensory functioning between the two HC doses and there was no evidence for a mediating role of cortisol in the relationship between perceived stress and pain. Large differences in cortisol exposure were found between individuals, which can be attributed to the many factors in the complex system that coordinate and mediate cortisol exposure. The data of this thesis support the use of a personalized approach in the treatment of SAI, taking into account the short- and long-term benefits and harms. A “one dose fits all” approach does not suffice. We suggest to start with the lowest dose that relieves symptoms of AI, but urge

that QoL should be taken into account in determining the appropriate substitution dose because patients might benefit from a higher HC dose. In case of persistent impaired QoL or other factors resulting in failed treatment with immediate release tablets, dual-release HC preparations or CSHI might be a treatment option.

During previous years, more insight has been gained into factors that have an impact on or are influenced by HC substitution therapy. Nevertheless, additional research is needed to evaluate long-term effects of HC treatment, and whether outcomes will be different in the presence of a stressor. Furthermore, other markers should be explored that could assist in the monitoring of currently used and new treatments. Therefore, future research should include the following:

- The effects of long-term HC use on cognition.
- The effects of the introduction of a mild stressor in the relationship between HC substitution and several clinical outcome measures.
- The potency of selective 11β -HSD1 inhibitors in the prevention of negative side effects of GCs excess.
- The number of daily doses (in contrast to a change in dose), in certain subgroups of patients (e.g. with high cortisol clearance).
- The influence of cortisol exposure, or GC-sensitive biomarkers on clinical outcome measures.
- Studies to identify better methods to estimate cortisol tissue exposure, for instance by salivary cortisol measurements or by dedicated sensor technology.

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