National German Audit of Diagnosis, Treatment, and Teaching in Secondary Adrenal Insufficiency

DOI 10.1055/s-0043-105077
Horm Metab Res 2017;49: 580–588

Publishing House and Copyright:
© 2017 by
Georg Thieme Verlag KG
Rüdigerstraße 14
70469 Stuttgart
ISSN 0018-5043

Thieme

National German Audit of Diagnosis, Treatment, and Teaching in Secondary Adrenal Insufficiency

Autoren
Stephan Petersenn[1*], Jürgen Honegger[2*], Marcus Quinkler[3]

Institute
1 ENDOC Center for Endocrine Tumors, Hamburg, Germany
2 Department of Neurosurgery, University of Tuebingen, Tuebingen, Germany
3 Endocrinology in Charlottenburg, Berlin, Germany

Key words
adrenal insufficiency, pituitary, hydrocortisone, glucocorticoid therapy, patient's teaching

received 29.11.2016
accepted 28.02.2017

Bibliografie
DOI http://dx.doi.org/10.1055/s-0043-105077
Published online: 28.3.2017
Horm Metab Res 2017; 49: 580–588

ISSN 0018-5043

Correspondence
Marcus Quinkler, MD
Endocrinology in Charlottenburg
Stuttgarter Platz 1
10627 Berlin
Germany
Tel.: +49/30/2132 004, Fax: +49/30/2132 005
marcusquinkler@t-online.de

Supporting Information for this article is available online at http://www.thieme-connect.de/products

ABSTRACT

Great heterogeneity seems to exist regarding diagnosis, therapy, and teaching of patients with secondary adrenal insufficiency (SAI) across Germany resulting in different diagnosis and treatment strategies. The aim of the work was to present the first national audit on diagnosis, treatment, and patient teaching of SAI reflecting common clinical practice in Germany. A self-designed questionnaire was sent via e-mail to all members of the German Endocrine Society (approx. 120 centers). Returned questionnaires (response rate 38.3 %) were checked for duplicity of institutions and analyzed. Diagnostic testing focuses on those patients with relevant risk for adrenal insufficiency. Basal serum cortisol is mostly used as screening test. Short synacthen and CRH tests are the preferred confirmatory tests, however, cut-off values vary due to different assays used. Patients with radiation, second surgery, progressive disease or new symptoms are followed by serial re-testing. Perioperative management and frequency of postoperative re-evaluations differ among centers. Hydrocortisone is the preferred glucocorticoid for replacement therapy, but daily doses vary considerably (10–30 mg/day). Some centers perform hormone measurements for dose adjustment of glucocorticoid replacement therapy whereas others rely on clinical judgement. Patients' teaching is done in 84 % of centers, but only half of the centers include patients' relatives. Homogeneity exists in patients' teaching regarding intercurrent illnesses (fever, diarrhoea). Recommendations regarding dose adaptations in situations such as sport-activities, dental-procedures, or coughing are highly variable. This first national audit reveals great heterogeneity among German centers and could improve patients' care in SAI, for example, by initiating new trials and developing clinical practice guidelines.

Introduction

Secondary adrenal insufficiency (SAI) has a prevalence of 150–280 per million [1]. The most frequent cause is a pituitary or hypothalamic tumor with the pituitary macroadenoma being the prevailing tumor entity. No generally accepted recommendations for the diagnostic approach in SAI exist [2]. While diagnosis of glucocorticoid deficiency is straightforward in primary adrenal insufficiency (AI) [3], diagnosis of SAI is difficult and demanding. Basal morning cortisol below 100 nmol/l confirms AI and cortisol greater than 500 nmol/l indicates intact hypothalamic-pituitary adrenal (HPA axis) [1, 4]. Results in the wide range between 100 and 500 nmol/l are equivocal and confirmatory biochemical examinations and stimulation tests are required. The diagnostic procedures [i. e., insulin stimulation test (IST), short synacthen test (SST), and corticotropin releasing hormone (CRH) stimulation test] are not performed uniformly. They differ nationally and between countries [2, 5].

* These authors contributed equally to this work

Treatment of SAI is also a matter of ongoing debate [6]. Standard replacement therapy is mostly performed with hydrocortisone (HC). It is challenging to mimic the physiological requirement of glucocorticoids (GC) with conventional HC tablets [6, 7]. The practice regarding daily total dose, division of the dose during the day, and time points of administration varies considerably among centers and physicians. A modified-release preparation of HC has been developed recently as an alternative [8]. The treatment of SAI is aggravated by the fact that even physicians with training in endocrinology have significant knowledge gaps regarding medical replacement [9].

No randomized controlled studies assess the perioperative need of GC replacement in pituitary surgery [10]. Categorical perioperative replacement minimizes the risk of adrenal crisis. However, most currently used perioperative replacement schemes overtreat the HPA axis and unnecessary GC administration is associated with adverse sequelae [11, 12].

No consensus exists concerning the ideal surveillance of GC therapy in SAI. While the importance of clinical signs and symptoms is generally accepted, the usefulness of hormonal assessment for dose adjustment of GC therapy is an unsettled issue [13–15]. An alarming high incidence of adrenal crises despite patient education has recently been shown in AI. Thus, 8.3 adrenal crises and 0.5 crisis-related deaths were found per 100 patient-years [16]. Emergency cards are supposed to be handed to the patients that he/she can be identified more easily in emergency situations by medical personnel [17]. Besides national emergency cards, a common European emergency card was introduced recently [18, 19]. Patient's teaching has been emphasized recently as cornerstone of adrenal insufficiency therapy [17, 20, 21]. It is especially important to teach the patient how to adapt his glucocorticoid dose during episodes of intercurrent illness, stress [3, 20–22], and especially in life threatening situations such as gastrointestinal infections and infections with fever, which are the most common situations leading to adrenal crisis [16, 23].

Recently, national initiatives have been undertaken to standardize the diagnostic and therapeutic procedures in AI [3, 24]. The aim of our audit was to gain information on daily practice in diagnosis, treatment and teaching in SAI in Germany. We hypothesized that diagnosis, treatment and patient's teaching is handled very differently among German endocrine centers. Based on the findings, it is intended to develop recommendations and to standardize diagnostic procedures, treatment and teaching in SAI in Germany.

Materials and Methods

The audit was a joint project of the pituitary working group and the adrenal section of the German Endocrine Society. The questionnaire was initially constructed by the authors (S.P, J.H., M.Q), and presented for discussion both at meeting of the Pituitary Working group and the Adrenal section of the German Endocrine Society. Conceptually, a selection of predefined answers was offered for each queried item. Boxes for additional answers were provided whenever appropriate. Space was provided for comments and explanations. The questionnaire was constructed for digital processing. The questionnaire was sent via e-mail to all members of the German Endocrine Society (DGE) 4 times between April and October 2015. The original German questionnaire is provided as **Supplementary file**.

In Germany, approximately 90 endocrine private practices and 30 endocrine units at university and city hospitals exist. Forty-six of these 120 centers (38.3 %) returned the

questionnaire and participated in the audit. In addition, 2 pediatric endocrine units, 2 neurosurgical units, and one center in Switzerland sent the questionnaire. From each center, only one representatively answered questionnaire was accepted. The centers were contacted in the case of multiple answered questionnaires. In total, questionnaires from 50 centers were eligible for the study. Eleven centers are treating less than 20 patients, 16 centers 20–50 patients, 12 centers 50–150 patients, and 6 centers more than 150 patients with SAI (no information provided from 5 centers).

Results

A total of 50 questionnaires were analyzed. We present each questioned item first in italics, and then an analysis and summary of the responses below.

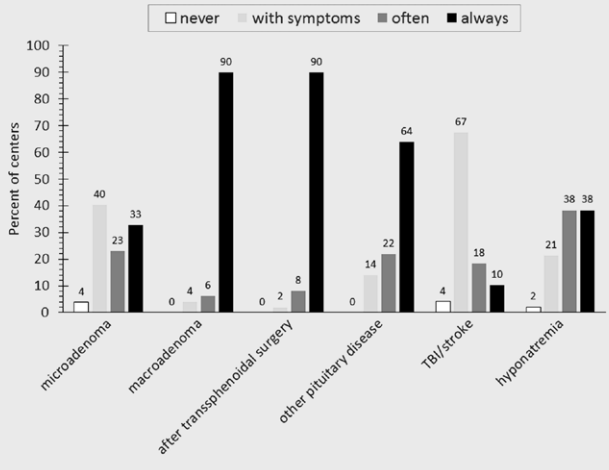
Diagnosis

[Q1.1] In which pathologies and under which clinical circumstances do you test for SAI?

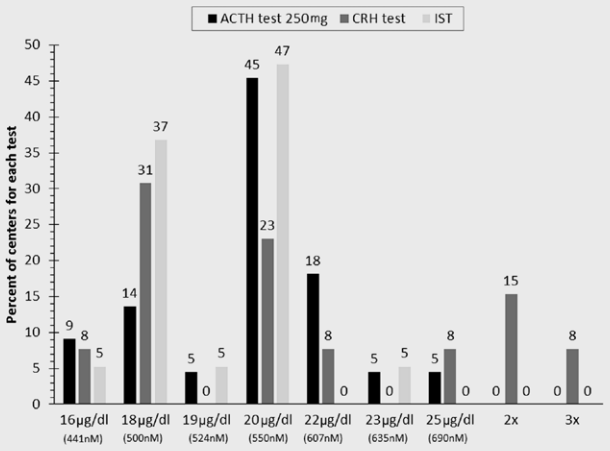
Patients with macroadenomas and patients after pituitary surgery are almost always tested for SAI (▶ **Fig. 1**). In contrast, the majority of centers evaluate patients with microadenomas or patients with TBI (traumatic brain injury)/stroke only in the presence of symptoms. Interestingly, 2 third of the centers screen patients with hyponatremia for SAI independent of the presence of symptoms.

[Q1.2a] Which is your initial test for SAI?

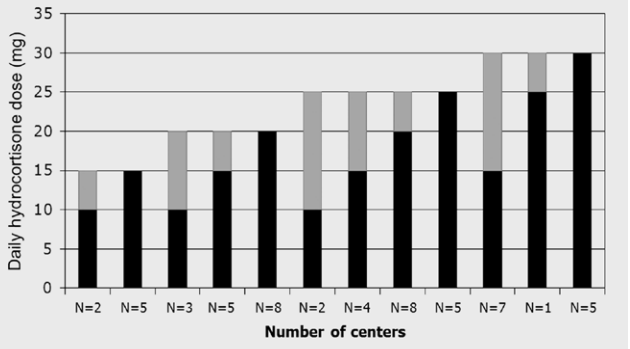
As first line test (screening test) 38 centers use basal serum cortisol, 23 centers basal ACTH, 3 centers the low-dose short synacthen test (SST), 24 centers the 250 µg SST, 11 centers the CRH test, 9 centers the insulin tolerance test (ITT), and 2 centers the metyrapone test.



▶ **Fig. 1** Situations in which to test for secondary adrenal insufficiency according to the 50 responding endocrine centers. TBI: Traumatic brain injury.



▶ **Fig. 2** Cut-off values for commonly used pituitary function tests to assess secondary adrenal insufficiency according to the 50 responding endocrine centers. ITT: Insulin tolerance test.



▶ **Fig. 3** Dose of daily hydrocortisone dose (advised by the physician) according to the 50 responding endocrine centers. Black column: fixed dose; Black and gray column: minimum dose (black) and range from x to y mg.

[Q1.2b] Which is your confirmatory test to confirm or exclude SAI?

As secondary test (confirmatory test) 18 centers use the 250 µg SST, 23 centers the CRH test, 21 centers the ITT, and 3 centers the metopyrone test.

[Q1.3] Which cut-off values do you use for the commonly used functional tests of HPA axis?

With respect to the SST, nearly half of the centers use a cut-off of 20 µg/dl (550 nmol/l) to define AI, with a considerable range of 16–25 µg/dl (441–690 nmol/l) in the remaining centers (▶ **Fig. 2**). Cut-offs for the CRH test vary even stronger, with quite homogenous distribution between 16 and 25 µg/l (441 and 690 nmol/l), or alternatively considering relative stimulation of 2x–3x. In contrast, a narrow range of cut-offs (18–20 µg/dl; 500–550 nmol/l) is used for the ITT by the vast majority of centers.

[Q1.4] Which assay do you use to measure serum cortisol and plasma ACTH levels?

The most commonly used assays are: Diasorin Liason (cortisol n = 4; ACTH n = 6), Roche Cobas (cortisol n = 9; ACTH n = 9), Siemens Advia (cortisol n = 2; ACTH n = 0), Siemens Immulite (cortisol n = 10; ACTH n = 11), CLIA (cortisol n = 3; ACTH n = 3), RIA (cortisol n = 2; ACTH n = 0), other assays (cortisol n = 4; ACTH n = 3).

[Q1.5] When do you pause hydrocortisone replacement before re-evaluation of HPA axis?

The duration of the hydrocortisone pause varies strongly among the centers: 8 h (n = 2), 12 h (n = 7), 16 h (n = 6), 24 h (n = 23), 48 h (n = 2), 72 h (n = 4), >120 h (n = 1).

[Q1.6] How often do you re-evaluate patients who are post-operatively evaluated a) as adrenal-sufficient, b) with SAI?

For patients who are adrenal-sufficient after surgery (a), the majority of centers will limit re-evaluation to a yearly schedule [in detail: 3-monthly (n = 10), 6-monthly (n = 10), yearly (n = 25), other (n = 5)]. In contrast, patients initially tested with SAI (b) will be re-evaluated mostly either every 3 or 6 months [3-monthly (n = 16), 6-monthly (n = 17)), yearly (n = 5), or depending on symptoms (n = 8), (other (n = 4)].

[Q1.7] How do you re-evaluate patients who are post-operatively evaluated a) as adrenal-sufficient, b) with SAI?

Both for adrenal-sufficient patients and for patients with SAI, the vast majority of centers (a: 36 centers, b: 34 centers) will rely on clinical signs of hypocortisolism and measure basal hormone levels. Salivary cortisol (a: 2, b: 0), low-dose SST (a: 3, b: 1), SST (a: 6, b: 5), and CRH test (a: 4, b: 2) are used with a low frequency.

[Q1.8] In which situation do you repeat pituitary function tests?

The majority of centers (n = 26) re-assess with function tests if new symptoms occur, 10 centers after radiotherapy/radiosurgery, 8 centers in the case of tumor re-growth, 7 centers if tests did not show clear results at initial testing, 6 centers after repeated neurosurgical operation, 3 centers on patients requesting to stop hormone substitution, 2 centers in the case of macroadenomas (on a yearly basis), and one center if changes in the basal hormone levels occur.

Hormone replacement therapy

[Q2.1] What is the average daily dose (range) of hydrocortisone, which you prescribe to patients with SAI?

The doses varied widely among the centers (▶ **Fig. 3**). Some centers mentioned fixed doses [15 mg (n = 5), 20 mg (n = 8), 25 mg (n = 5), 30 mg (n = 5)], whereas others varied their doses ranges by 5–15 mg (variation of dose ranges: 10–15 mg up to 15–30 mg).

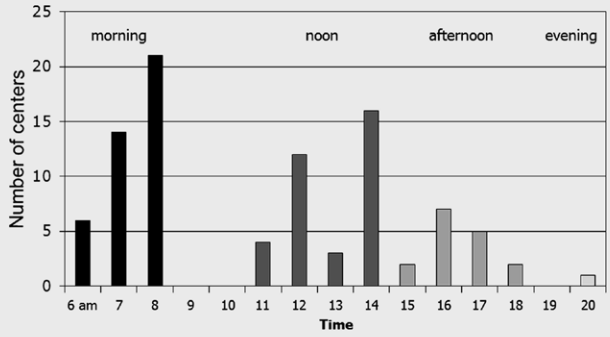
[Q2.2] In how many doses do you divide the daily glucocorticoid dose?

Hydrocortisone is prescribed in 2 daily doses by 33 centers, and in 3 doses daily in 17 centers. Prednisolone is given once daily by 3 centers, and twice daily by 2 centers. Modified-release hydrocortisone is given once daily by 23 centers, and twice daily by 2 centers. Dexamethasone is given once daily by one center.

[Q2.3] Which are the time points of hydrocortisone tablet intake in your patients?

Morning doses are given between 6 AM and 8 AM, midday doses between 11 AM and 2 PM, and afternoon doses between 3 PM and 6 PM (▶ **Fig. 4**).

[Q2.4] Do you measure hormones to evaluate the required glucocorticoid dose in your patients with SAI?



▶ **Fig. 4** Time of hydrocortisone intake (advised by the physician) according to the 50 responding endocrine centers.

Thirty-three centers stated that they do not measure any hormones to adjust the appropriate glucocorticoid replacement dose, whereas 17 centers responded that they do.

[Q2.5] If you do measure hormones to evaluate the glucocorticoid replacement dose in your patients with SAI, which hormones do you measure?

The hormonal parameters used were morning serum cortisol (n = 9), 24-h urinary cortisol excretion (n = 4), plasma ACTH (n = 3), serum cortisol profile (n = 2), salivary cortisol profile (n = 2), single salivary cortisol (n = 1).

[Q2.6] If you do measure hormones to evaluate the glucocorticoid replacement therapy dose in your patients with SAI, do you measure before or after glucocorticoid intake?

Sixteen centers responded that they evaluate hormones before glucocorticoids are taken in the morning, whereas 15 centers take blood after tablet intake.

[Q2.7] If you do measure hormones after glucocorticoid intake, after which time interval following tablet intake do you draw blood?

2 centers stated that they perform blood sampling after 4 h, and one center each at 30 min, 2 h, 3 h and 12–24 h.

[Q2.8] In which dosage steps do you lower the hydrocortisone daily dose if dose reduction is required?

Seven centers prefer dose reduction in steps of 2.5–5 mg hydrocortisone, 24 centers in steps of 5 mg, 13 centers in steps of 5–10 mg, and 4 centers in steps of 10 mg.

[Q2.9] In which dosage steps do you increase the hydrocortisone daily dose?

Four centers use dosage steps of 2.5–5 mg of hydrocortisone, 26 centers increase hydrocortisone by 5 mg steps, 17 centers by 5–10 mg steps, and 2 centers by 10 mg steps.

[Q2.10] What is the usual time interval between clinical control visits in your patients with SAI?

The range of clinical follow-up intervals is broad. Scheduled intervals are 3–6 months in 14 centers, 6 months in 14 centers, 6–12 months in 12 centers and 12 months in 6 centers.

[Q2.11] What is the usual time interval between laboratory control visits in your patients with SAI?

The range of intervals between laboratory controls is similar to the intervals between clinical follow-up visits. Laboratory controls are scheduled every 3–6 months in 12 centers, every 6 months in 12 centers, every 6–12 months in 13 centers, and every 12 months in 4 centers.

[Q2.12] Which clinical or biochemical signs do you use as indicator of an insufficiently low daily glucocorticoid replacement dose?

Signs indicating a too low glucocorticoid replacement dose were weakness, loss of energy, exhaustion (74 % of the responding endocrine centers), tiredness (50 %), weight loss (24 %), nausea (20 %), listlessness (14 %), frequent adrenal crisis (8 %), muscle pain/aching (6 %), sleep (4 %), abdominal pain (4 %), dizziness, loss of appetite, joint pain, paleness, exsiccosis, depressive mood (each 2 %).

[Q2.13] Which clinical or biochemical signs do you use as indicator of a too high daily glucocorticoid replacement dose?

Regarding clinical signs, weight gain (n = 41) was the mostly mentioned sign followed by cushingoid features (n = 27), sleep disturbances (n = 6), thin skin and easy bruising (n = 3), muscle weakness (n = 3), depression and psychological problems (n = 3) and edema (n = 2). Measurable variables were hypertension (n = 29), blood glucose increase (n = 21), increase of sodium levels (n = 7), worsening of bone mineral density (n = 6), hypokalemia (n = 4), worsening of lipid profile (n = 4), impaired growth in children (n = 2).

[Q2.13] Do you use peri-operative glucocorticoid substitution during transsphenoidal surgery?

Thirty centers answered yes, whereas 14 centers only use a peri-operative substitution scheme in patients with pre-operative adrenal insufficiency.

[Q2.14] Do you use peri-operative glucocorticoid substitution during transsphenoidal surgery for Cushing's disease?

Twenty-four centers use peri-operative glucocorticoid substitution, whereas 21 do not.

[Q2.15] If you do not use a peri-operative glucocorticoid substitution during transsphenoidal surgery for Cushing's disease, when do you start with glucocorticoids after transsphenoidal surgery?

Twelve centers start to give glucocorticoids directly after operation. Others start at post-op day 1 (n = 4), post-op day 2 (n = 1), post-op day 3 (n = 1), if cortisol is below < 2 µg/dl (n = 1), or depending on the neurosurgeon's preference (n = 3).

[Q2.16] What is your average hydrocortisone dose at the time of postoperative discharge after surgery for Cushing's disease?

The daily hydrocortisone doses vary considerably: 200 mg (n = 3), 150 mg (n = 1), 100 mg (n = 2), 60 mg (n = 1), 50 mg (n = 8), 30–50 mg (n = 2), 40 mg (n = 3), 30 mg (n = 9), 25 mg (n = 3), 20 mg (n = 1), and 15 mg (n = 2).

[Q2.17] What do you prescribe to your SAI patient as emergency kit?

For an emergency kit, 61 % of the centers prescribe additional hydrocortisone tablets, 59 % prescribed prednisone/prednisolone suppositorium, 65 % a 100 mg hydrocortisone ampoule, 2 % a 50 mg prednisolone ampoule, 4 % hydrocortisone suppositorium, and 5 % betamethasone liquid.

[Q2.18] Which emergency card do you hand out to your patients?

Sventy-three percent of the centers hand out the emergency card of the German patient's selfhelp network (Netzwerk für Hypophysen- und Nebennierenerkrankungen eV), whereas 16 % use emergency cards distributed from 4 different pharmaceutical companies. Six percent use self-made emergency cards, 2 % the Swiss emergency card and 2 % do not hand out any card.

[Q2.19] Do you hand out also the European emergency card (German version) to your patients?

Fifty-one percent of the centers distribute the German version of the European emergency card [19] to their patients, whereas 49 % did not.

Patient's teaching

[Q3.1] Do you offer and perform teaching in your patients with adrenal insufficiency?

Eighty-four percent of the centers answered that they perform teaching, whereas 12 % of the centers do not teach their patients. Four percent did not answer the question.

[Q3.2] If you perform teaching of your patients regarding adrenal insufficiency, who is the teaching person?

In 47.8 % of the centers it is done by the doctor, in 28.8 % of the centers by the doctor's assistant, in 14.5 % by a trained endocrine nurse, in 7.4 % of the centers by a nurse or study nurse, and in 2.5 % of centers by a diabetes nurse.

[Q3.3] Do you incorporate relatives into the teaching process of your SAI patient?

Relatives are involved in the teaching on adrenal insufficiency in 52 % of the centers, but are not in 34 % of the centers. Fourteen percent of the centers are not able to teach the relatives, but wish to be capable.

[Q3.3] Does the teaching of your patients also include the symptoms and signs of hypocortisolism?

Ninety percent of the centers marked "yes", 10 % answered "no".

[Q3.4] Does the teaching of your patients incorporate the adaptation of the glucocorticoid dose in different situations?

Ninety-four percent of the centers marked "yes", 6 % answered "no".

[Q3.4] Does the teaching of your patients incorporate the use of the emergency set?

Sixty-eight percent of the centers marked "yes", 32 % answered "no". However 11 % of the centers who marked "yes", did not prescribe an emergency kit to their patients.

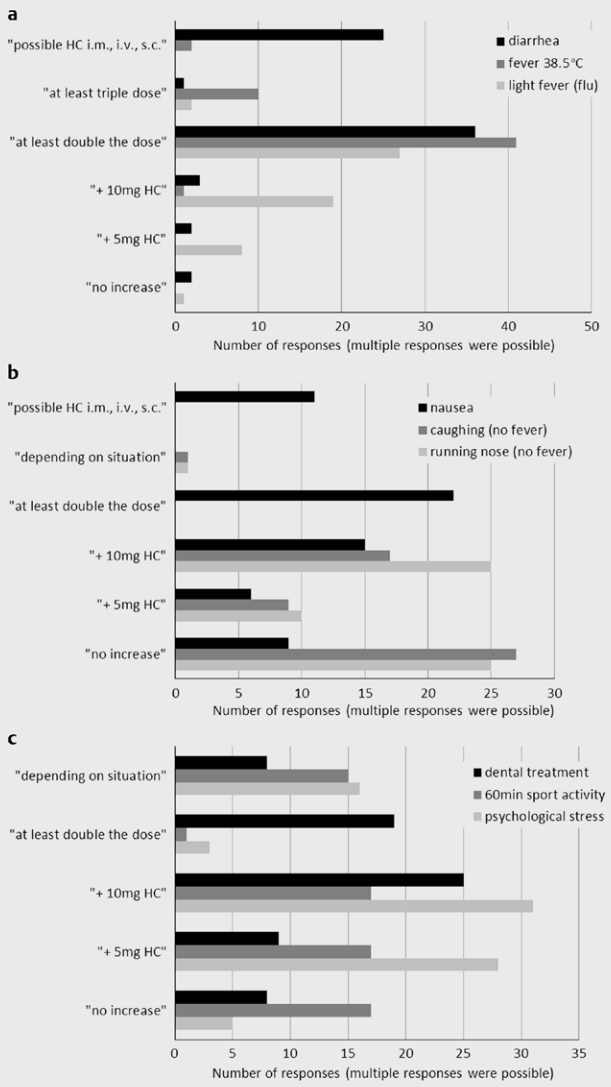
[Q3.5] In the event of reduced gastrointestinal resorption (diarrhoa, vomiting), which advise do you give to your patients?

Thirteen centers advise to use hydrocortisone parenteral, 7 centers to use prednisolone suppositorium, 7 centers recommend immediate presentation to a physician, and 2 centers advise to double or triple the glucocorticoid dose.

[Q3.6] After an intercurrent illness period, which recommendation is given to your patients regarding dose reduction?

Eight centers advise to reduce speedily, 5 centers recommend to reduce the dose over the next 3–4 days, 4 centers state to do it depending on the situation, another 4 centers emphasize to reduce it directly to normal dose in the case of only light stress, 3 centers advise to reduce the dose over 2–3 days, 2 centers recommend that it should be done over one week, and one center reduces by 50 % after 3 days and to the normal dose after one week.

[Q3.7] Which advise do you give to your patients in the case of diarrhoea, light fever (flu) or fever of 38.5 °Celsius: a) no increase, b) + 5 mg HC, c) + 10 mg HC, d) at least double the dose, e) at least triple the dose, f) possible HC i.m., i. v., s.c.?



▶ **Fig. 5** Patient's teaching in the event of **a** diarrhea, fever 38.5 °C, or light fever; **b** nausea, coughing (no fever), or running nose (no fever); **c** dental treatment, 60 min sport activity, or psychological stress in secondary adrenal insufficiency according to the 50 responding endocrine centers. HC = Hydrocortisone.

The majority of centers advise their patients to at least double the dose in case of diarrhea and fever of 38.5 °Celsius (▶ **Fig. 5a**).

[Q3.8] Which advise do you give your patients in the case of nausea, coughing (no fever), or running nose (no fever): a) no increase, b) + 5 mg HC, c) + 10 mg HC, d) at least double the dose, e) depending on the situation, f) possible HC i.m., i. v., s.c.?

The answers of the centers varied widely in the advice how to behave in these situations (▶ **Fig. 5b**).

[Q3.9] Which advise do you give your patients in the case of dental treatment, 60 min sports activity, or psychological stress: a) no increase, b) + 5 mg HC, c) + 10 mg HC, d) at least double the dose, e) depending on the situation?

The answers of the centers varied widely in the advice how to behave in these situations (▶ **Fig. 5c**).

Discussion

Our survey reveals a very heterogeneous approach of the different centers to nearly all aspects of care of patients with SAI in Germany. This is clearly visible with respect to the diagnosis of SAI, where a large variety of tests are applied during initial evaluation and follow-up with different cut-offs and at variable time points. Such heterogeneity may result in the same patients being considered adrenal sufficient in one center and adrenal insufficient in another center. Potential explanations are the huge variety of tests and assays available [1, 25–28], as well as the small number of well-founded recommendations by endocrine societies or health care authorities for SAI [24, 29]. Any study evaluating tests, assays and specific cut-off is also hindered by the lack of a well-established gold standard to define SAI. Although the ITT is considered as a reference by some authors [30], the test is unpleasant for patients, is resource-consuming, is not without risk, and most importantly, lacks patients' outcome correlation [5]. Furthermore, some studies have questioned its reproducibility [31, 32]. The potential problems with the ITT are mirrored by the results of our survey, with less than half of the centers using the ITT. Instead, when combining screening and confirmatory investigation, the SST is the stimulatory test used most frequently. Indeed, this is the only test, for which long-term outcome correlation has been published, supporting its use in clinical practice [33]. On the contrary, a meta-analysis found low sensitivity of the SST to diagnose SAI and suggests to use instead tests involving stimulation of the hypothalamus [25] supported by a recent study comparing ITT and SST [34].

Interestingly, most centers perform initial screening for SAI by measuring morning serum cortisol, with few centers applying salivary cortisol. Considering the advantages of salivary cortisol, such as its simple and cost-effective collection, as well as its independency of binding proteins like albumin or cortisol binding globulin (CBG), which are often adversely affected by diseases or drugs, this most probably relates to difficulties in measurement. However, recent studies have supplied cut-offs by comparison to the ITT [4], and studied measurement by automated assay [35], hopefully improving the availability for screening purposes.

In general, dynamic testing for ACTH reserve is performed after an interval of 2–3 months after pituitary surgery to allow recovery of altered pituitary function, determining the need for life-long replacement therapy. Quite interestingly, in our survey many centers will perform post-operative re-evaluation, especially in those patients initially tested with SAI. For postoperative re-evaluation, only basal hormones were measured in the majority of centers. This most frequently relates to patients with new symptoms, but also to patients with progressive tumor, after second surgery, and after radiation. In agreement, many studies have demonstrated new pituitary insufficiency even many years after radiation [36, 37] or after second surgery [38]. However, recent data also suggests that there is potential for subsequent improvement of pituitary function due to surgical decompression of the normal pituitary gland and stalk, justifying re-evaluation of patients with initial SAI [39–41]. This would prevent unnecessary life- long substitution in a number of patients, which in itself may be harmful.

Replacement therapy

Hydrocortisone (HC) is the preferred replacement therapy for AI [7]. Our survey showed that the administered daily HC dose varies considerably between the centers. Inconsistent replacement doses have also been shown in a UK survey, although the majority use 20 mg/day or more [2]. Daily cortisol production rates are lower than previously believed. They vary between 5 and 10 mg/m²/day [13, 42], which corresponds to 15–20 mg oral HC. An increase in morbidity, mortality and impairment of quality of life has been shown with HC doses above 30 mg/day [15, 43]. Despite these facts, 30 mg HC or even more are still widely used [15]. We would suggest re-evaluation of the replacement dose in those German centers that use 25 mg daily or more.

The high variability of treatment regimens and suggested time points of HC intake [6] are confirmed by our survey. Simon et al. [6] calculated a model for best treatment. They found that HC 10-5-5 mg taken at 7.30, 12.00, and 16.30 h, respectively, is the best calculated regimen to achieve cortisol levels in the physiological target range. Mah et al. [7] showed that weight-adjusted HC with a morning dose of 0.12 mg/kg decreased interpatient variability of cortisol profiles.

Prednisolone and dexamethasone are less suitable to replicate the circadian rhythm of cortisol secretion due to their long half-life and could result in unfavorable night-time GC levels [1] and probably in an adverse lipid profile [44].

A modified-release formulation of HC has been developed to obtain a more physiological circadian cortisol profile [8]. A decrease of BMI and HbA1c with modified-release HC compared with conventional HC has been shown [45]. Despite a more recent marketing approval of this HC formulation, half of our centers already have experience with this preparation.

There is general agreement that clinical assessment is pivotal for monitoring of the appropriate replacement dose [1]. The usefulness of hormone measurements for adjustment of HC replacement therapy is still a matter of debate [13, 15]. Objective biochemical parameters would be most helpful to avoid over-treatment or under-treatment. Cortisol day profile, time-point serum cortisol measurement, urinary cortisol secretion and salivary cortisol have been proposed to monitor replacement therapy in AI [14]. Each of these methods has well-known limitations for monitoring of replacement therapy [13, 15]. Regarding time-point measurement, Jung et al. [15] found that plasma, salivary and urine cortisol at 2 h after oral HC seems to provide good information of peak cortisol concentration. Mah et al. [7] have shown that a plasma cortisol level at 4 h after a single morning HC dose correlates well with the cortisol AUC. For a thrice daily regimen, Rousseau et al. [14] found that a cortisol measurement 2 h after morning HC intake best correlates with the cortisol AUC.

No guidelines or generally accepted recommendations exist concerning follow-up intervals for patients with SAI. In our audit, the reported intervals for clinical follow-up were not different from the intervals for biochemical re-assessment. The range was from 3 to 12 months. In the long-term follow-up with stable insufficiency, tight control intervals of 6 months or less are too prudent and might be caused by a lack of recommendations and guidelines. In the UK, patients not ACTH-deficient by pituitary surgery who received postoperative radiotherapy (RT) are usually tested annually

[2]. In patients without RT, 29 % of the endocrinologists did no routine biochemical testing unless the patient was symptomatic or had tumor recurrence on imaging.

Perioperative replacement

Surprisingly, the majority of centers use perioperative replacement therapy in every patient undergoing pituitary surgery. Postoperative assessment of hypothalamo-pituitary-adrenal (HPA) axis is difficult while on replacement therapy and patients with normal pituitary function may unnecessarily stay on GC treatment after postoperative discharge [12, 46]. Transsphenoidal surgery without perioperative GC replacement was found to be safe in patients without evidence of adrenal insufficiency and with normal SST prior to surgery [12]. We support this concept to abstain from GC replacement in adrenal sufficient patients. However, the neurosurgeon must be experienced and confirm selective adenomectomy [10]. The need of postoperative replacement therapy can be guided by early postoperative morning cortisol levels [10].

Great variations exist regarding postoperative tapering of GC replacement following successful pituitary surgery in Cushing's disease (CD) [47]. This finding was confirmed by our audit. The dose at the time of discharge after pituitary surgery for CD was highly variable with a range from 15 to 200 mg daily. Again, the heterogeneity is most likely caused by a lack of concise recommendations. There is no good evidence from the literature that supraphysiological GC replacement prevents or ameliorates GC withdrawal syndrome following transsphenoidal surgery for CD [48]. However, some patients have symptoms of hypoadrenalism after successful surgery for CD if HC is tapered too rapidly. Therefore, we suggest to discharge on 40–60 mg daily.

Emergency set

Only 60 % of the endocrine centers in Germany prescribe their patients additional hydrocortisone tablets or suppositorium or a hydrocortisone ampoule for their emergency kit. This results that nearly 40 % of patients have no medications in the case of emergency and rely completely on the emergency personnel, which often gives extra glucocorticoids too late or are even refusing it [49]. This situation needs to be improved. Besides the emergency kit it seems to be necessary to avoid too many different national emergency cards which might result in a lower recognition rate among emergency personnel. In addition, the new European emergency card [18, 19] should be promoted and distributed more thoroughly.

Teaching

Teaching of patients is performed in over 80 % of the centers. Considering the tight time schedules of doctors in hospitals and endocrine practices, the time used for patient teaching by doctors is probably minimal and mainly takes place during the short consulting time (average appointment time 5–15 min). We suggest that more endocrine trained medical personal is needed and extra time slots (e. g., 2–3 h) should be implemented for small group teaching for adrenal insufficiency. Small patient's group teaching has been reported to be a useful tool [21] for prevention and treatment of adrenal emergency. It is advisable to include also relatives into the teaching process to guarantee patient's emergency treatment in cases of unconsciousness, severe sleepiness or weakness.

The content of the teaching seems to vary considerably across Germany. In one Dutch center teaching consisted of a lecture about the disease, its treatment and instructions on 'sick rules', that is, the recommended stress-related glucocorticoid dose adjustment [21]. Among the German centers there was a broad agreement on advices given to patients regarding behavior in conditions, such as diarrhoea, fever 38.5 °C and light fever (flu). However recommendations and teaching varied considerably regarding situations involving psychological stress, 60 min sport activity, common cold (no fever), coughing (no fever), or dental treatment. Recently the first study was published addressing the question if pre-exercise HC dose increases short-term physical performance in female patients with PAI [50]. The patients did not benefit from an extra dose of HC in short strenuous exercise in this setting. In general, we think that more studies should be performed to investigate possible dose-adaptation in these situations. In addition, we believe that it is necessary to implement a structured education and treatment program for patients with AI.

A limitation of our survey is that we did not gather data regarding further analysis on academic vs. peripheral practices and younger vs. older physicians and internists vs. endocrinologists. In addition our self-designed questionnaires may lack specificity by not describing an exact context (a case vignette), but rather relate to general practice.

In conclusion, this first national German audit reveals great heterogeneity among German centers in diagnosis, treatment and teaching of patients with SAI. We believe that this survey could be used to improve patient's care and therapy in SAI.

First of all, this audit gives the centers an important feedback and insight how colleagues in other centers diagnose and treat patients with SAI. Regarding diagnostic procedures this audit, for example, might initiate new trials to clarify and validate different tests and cut-offs used for different assays. But it also might initiate investigations, for example, regarding the necessary hydrocortisone dose adjustment in cases of psychological stress, sport activities, common cold (no fever), coughing (no fever), or dental treatments. Overall we hope that this first national German audit might be a start for the development of clinical practice guidelines for SAI patients.

Acknowledgements

The study was performed by the Arbeitsgemeinschaft "Hypophyse und Hypophysentumoren" and the Section "Nebenniere, Steroide und Hypertonie" of the German Endocrine Society (DGE).

Funding: This research was not supported by any funding.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

[1] Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003; 361: 1881–1893

[2] Reynolds RM, Stewart PM, Seckl JR, Padfield PL. Assessing the HPA axis in patients with pituitary disease: a UK survey. Clin Endocrinol (Oxf) 2006; 64: 82–85

[3] Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA, Torpy DJ. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016; 101: 364–389

[4] Deutschbein T, Unger N, Mann K, Petersenn S. Diagnosis of secondary adrenal insufficiency: unstimulated early morning cortisol in saliva and serum in comparison with the insulin tolerance test. Horm Metab Res 2009; 41: 834–839

[5] Petersenn S, Quabbe HJ, Schofl C, Stalla GK, von WK, Buchfelder M. The rational use of pituitary stimulation tests. Dtsch Arztebl Int 2010; 107: 437–443

[6] Simon N, Castinetti F, Ouliac F, Lesavre N, Brue T, Oliver C. Pharmacokinetic evidence for suboptimal treatment of adrenal insufficiency with currently available hydrocortisone tablets. Clin Pharmacokinet 2010; 49: 455–463

[7] Mah PM, Jenkins RC, Rostami-Hodjegan A, Newell-Price J, Doane A, Ibbotson V, Tucker GT, Ross RJ. Weight-related dosing, timing and monitoring hydrocortisone replacement therapy in patients with adrenal insufficiency. Clin Endocrinol (Oxf) 2004; 61: 367–375

[8] Johannsson G, Nilsson AG, Bergthorsdottir R, Burman P, Dahlqvist P, Ekman B, Engstrom BE, Olsson T, Ragnarsson O, Ryberg M, Wahlberg J, Biller BM, Monson JP, Stewart PM, Lennernas H, Skrtic S. Improved cortisol exposure-time profile and outcome in patients with adrenal insufficiency: a prospective randomized trial of a novel hydrocortisone dual-release formulation. J Clin Endocrinol Metab 2012; 97: 473–481

[9] Harbeck B, Brede S, Witt C, Sufke S, Lehnert H, Haas C. Glucocorticoid replacement therapy in adrenal insufficiency – a challenge to physicians? Endocr J 2015; 62: 463–468

[10] Inder WJ, Hunt PJ. Glucocorticoid replacement in pituitary surgery: guidelines for perioperative assessment and management. J Clin Endocrinol Metab 2002; 87: 2745–2750

[11] Tohti M, Li J, Zhou Y, Hu Y, Yu Z, Ma C. Is peri-operative steroid replacement therapy necessary for the pituitary adenomas treated with surgery? A systematic review and meta analysis. PLoS One 2015; 10: e0119621

[12] Wentworth JM, Gao N, Sumithran KP, Maartens NF, Kaye AH, Colman PG, Ebeling PR. Prospective evaluation of a protocol for reduced glucocorticoid replacement in transsphenoidal pituitary adenomectomy: prophylactic glucocorticoid replacement is seldom necessary. Clin Endocrinol (Oxf) 2008; 68: 29–35

[13] Arlt W, Rosenthal C, Hahner S, Allolio B. Quality of glucocorticoid replacement in adrenal insufficiency: clinical assessment vs. timed serum cortisol measurements. Clin Endocrinol (Oxf) 2006; 64: 384–389

[14] Rousseau E, Joubert M, Trzepla G, Parienti JJ, Freret T, Vanthygem MC, Desailloud R, Lefebvre H, Coquerel A, Reznik Y. Usefulness of time-point serum cortisol and acth measurements for the adjustment of glucocorticoid replacement in adrenal insufficiency. PLoS One 2015; 10: e0135975

[15] Jung C, Greco S, Nguyen HH, Ho JT, Lewis JG, Torpy DJ, Inder WJ. Plasma, salivary and urinary cortisol levels following physiological and stress doses of hydrocortisone in normal volunteers. BMC Endocr Disord 2014; 14: 91–94

[16] Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F, Willenberg HS, Quinkler M, Allolio B. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab 2015; 100: 407–416

[17] Quinkler M, Beuschlein F, Hahner S, Meyer G, Schofl C, Stalla GK. Adrenal cortical insufficiency – a life threatening illness with multiple etiologies. Dtsch Arztebl Int 2013; 110: 882–888

[18] Quinkler M, Hahner S, Johannsson G, Stewart PM. Saving lives of patients with adrenal insufficiency: a pan-European initiative? Clin Endocrinol (Oxf) 2014; 80: 319–321

[19] Quinkler M, Dahlqvist P, Husebye ES, Kampe O. A European emergency card for adrenal insufficiency can save lives. Eur J Intern Med 2015; 26: 75–76

[20] Husebye ES, Allolio B, Arlt W, Badenhoop K, Bensing S, Betterle C, Falorni A, Gan EH, Hulting AL, Kasperlik-Zaluska A, Kampe O, Lovas K, Meyer G, Pearce SH. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med 2014; 275: 104–115

[21] Repping-Wuts HJ, Stikkelbroeck NM, Noordzij A, Kerstens M, Hermus AR. A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis. Eur J Endocrinol 2013; 169: 17–22

[22] Grossman A, Johannsson G, Quinkler M, Zelissen P. Therapy of endocrine disease: Perspectives on the management of adrenal insufficiency: clinical insights from across Europe. Eur J Endocrinol 2013; 169: R165–R175

[23] Allolio B. Extensive expertise in endocrinology. Adrenal crisis. Eur J Endocrinol 2015; 172: R115–R124

[24] Yanase T, Tajima T, Katabami T, Iwasaki Y, Tanahashi Y, Sugawara A, Hasegawa T, Mune T, Oki Y, Nakagawa Y, Miyamura N, Shimizu C, Otsuki M, Nomura M, Akehi Y, Tanabe M, Kasayama S. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: a Japan Endocrine Society clinical practice guideline [Opinion]. Endocr J 2016; 63: 765–784

[25] Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003; 139: 194–204

[26] Schmidt IL, Lahner H, Mann K, Petersenn S. Diagnosis of adrenal insufficiency: Evaluation of the corticotropin-releasing hormone test and Basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. J Clin Endocrinol Metab 2003; 88: 4193–4198

[27] Alaioubi B, Mann K, Petersenn S. Diagnosis of adrenal insufficiency using the GHRP-6 Test: comparison with the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. Horm Metab Res 2010; 42: 198–203

[28] Berg C, Meinel T, Lahner H, Yuece A, Mann K, Petersenn S. Diagnostic utility of the glucagon stimulation test in comparison to the insulin tolerance test in patients following pituitary surgery. Eur J Endocrinol 2010; 162: 477–482

[29] de Miguel NP, Vela ET, Garcia NP, Rodriguez MM, Guerras IS. Martinez de Salinas Santamaria Mde, Maso AA. Guidelines for the diagnosis and treatment of adrenal insufficiency in the adult. Endocrinol Nutr 2014; 61 (Suppl 1): 1–35

[30] Erturk E, Jaffe CA, Barkan AL. Evaluation of the integrity of the hypothalamic-pituitary-adrenal axis by insulin hypoglycemia test. J Clin Endocrinol Metab 1998; 83: 2350–2354

[31] Pfeifer M, Kanc K, Verhovec R, Kocijancic A. Reproducibility of the insulin tolerance test (ITT) for assessment of growth hormone and cortisol secretion in normal and hypopituitary adult men. Clin Endocrinol (Oxf) 2001; 54: 17–22

[32] Vestergaard P, Hoeck HC, Jakobsen PE, Laurberg P. Reproducibility of growth hormone and cortisol responses to the insulin tolerance test and the short ACTH test in normal adults. Horm Metab Res 1997; 29: 106–110

[33] Agha A, Tomlinson JW, Clark PM, Holder G, Stewart PM. The long-term predictive accuracy of the short synacthen (corticotropin) stimulation test for assessment of the hypothalamic-pituitary-adrenal axis. J Clin Endocrinol Metab 2006; 91: 43–47

[34] Deutschbein T, Unger N, Mann K, Petersenn S. Diagnosis of secondary adrenal insufficiency in patients with hypothalamic-pituitary disease: comparison between serum and salivary cortisol during the high-dose short synacthen test. Eur J Endocrinol 2009; 160: 9–16

[35] Deutschbein T, Broecker-Preuss M, Flitsch J, Jaeger A, Althoff R, Walz MK, Mann K, Petersenn S. Salivary cortisol as a diagnostic tool for Cushing's syndrome and adrenal insufficiency: improved screening by an automatic immunoassay. Eur J Endocrinol 2012; 166: 613–618

[36] Minniti G, Scaringi C, Poggi M, Jaffrain Rea ML, Trillo G, Esposito V, Bozzao A, Enrici MM, Toscano V, Enrici RM. Fractionated stereotactic radiotherapy for large and invasive non-functioning pituitary adenomas: long-term clinical outcomes and volumetric MRI assessment of tumor response. Eur J Endocrinol 2015; 172: 433–441

[37] Xu Z, Lee VM, Schlesinger D, Sheehan JP. Hypopituitarism after stereotactic radiosurgery for pituitary adenomas. Neurosurgery 2013; 72: 630–637

[38] Jahangiri A, Wagner J, Han SW, Zygourakis CC, Han SJ, Tran MT, Miller LM, Tom MW, Kunwar S, Blevins LS Jr., Aghi MK. Morbidity of repeat transsphenoidal surgery assessed in more than 1000 operations. J Neurosurg 2014; 121: 67–74

[39] Arafah BM. Reversible hypopituitarism in patients with large nonfunctioning pituitary adenomas. J Clin Endocrinol Metab 1986; 62: 1173–1179

[40] Webb SM, Rigla M, Wagner A, Oliver B, Bartumeus F. Recovery of hypopituitarism after neurosurgical treatment of pituitary adenomas. J Clin Endocrinol Metab 1999; 84: 3696–3700

[41] Berg C, Meinel T, Lahner H, Mann K, Petersenn S. Recovery of pituitary function in the late-postoperative phase after pituitary surgery: results of dynamic testing in patients with pituitary disease by insulin tolerance test 3 and 12 months after surgery. Eur J Endocrinol 2010; 162: 853–859

[42] Esteban NV, Loughlin T, Yergey AL, Zawadzki JK, Booth JD, Winterer JC, Loriaux DL. Daily cortisol production rate in man determuned by stable isotope dilution/mass spectrometry. J Clin Endocrinol Metab 1991; 72: 39–45

[43] Bleicken B, Hahner S, Loeffler M, Ventz M, Decker O, Allolio B, Quinkler M. Influence of hydrocortisone dosage scheme on health-related quality of life in patients with adrenal insufficiency. Clin Endocrinol (Oxf) 2010; 72: 297–304

[44] Quinkler M, Ekman B, Marelli C, Uddin S, Zelissen P, Murray RD. Prednisolone is associated with a worse lipid profile than hydrocortisone in patients with adrenal insufficiency. Endocr Connect 2017; 6: 1–8

[45] Quinkler M, Miodini NR, Zopf K, Ventz M, Oksnes M. Modified-release hydrocortisone decreases BMI and HbA1c in patients with primary and secondary adrenal insufficiency. Eur J Endocrinol 2015; 172: 619–626

[46] Agha A, Liew A, Finucane F, Baker L, O'Kelly P, Tormey W, Thompson CJ. Conventional glucocorticoid replacement overtreats adult hypopituitary patients with partial ACTH deficiency. Clin Endocrinol (Oxf) 2004; 60: 688–693

[47] Bhattacharyya A, Kaushal K, Tymms DJ, Davis JR. Steroid withdrawal syndrome after successful treatment of Cushing's syndrome: a reminder. Eur J Endocrinol 2005; 153: 207–210

[48] Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO, Tabarin A. Treatment of cushing's syndrome: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2015; 100: 2807–2831

[49] Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C, Allolio B. Timelines in the management of adrenal crisis – targets, limits and reality. Clin Endocrinol (Oxf) 2015; 82: 497–502

[50] Simunkova K, Jovanovic N, Rostrup E, Methlie P, Oksnes M, Nilsen RM, Henno H, Tilseth M, Godang K, Kovac A, Lovas K, Husebye ES. Effect of a pre-exercise hydrocortisone dose on short-term physical performance in female patients with primary adrenal failure. Eur J Endocrinol 2016; 174: 97–105