Cushing's Disease – Quality of Life, Recurrence and Long-term Morbidity

Isabel Huguet,[1] Georgia Ntali,[1] Ashley Grossman[1] and Niki Karavitaki[2]

1. Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Headington, UK;
2. Centre for Endocrinology, Diabetes and Metabolism, School of Clinical and Experimental Medicine, University of Birmingham, UK

Abstract

Cushing's disease (CD) is a rare disorder caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. Chronic exposure to hypercortisolism leads to significant morbidities, which may be only partially reversible after remission of the disease, as well as to impairment of the health-related quality of life (HRQoL) and an increase in mortality. Transsphenoidal surgery (TSS) is the treatment of choice, and recurrence rates vary widely, confirming the need for lifelong follow-up. This review summarises the studies performed on HRQoL, recurrence rates and morbidities in patients who have CD.

Keywords

Cushing's disease, quality of life, recurrence, morbidity

Disclosure: Isabel Huguet, Georgia Ntali, Ashley Grossman and Niki Karavitaki have no conflicts of interest to declare. No funding was received in the publication of this article.

Received: 18 February 2015 **Accepted**: 16 March 2015 **Citation**: *European Endocrinology*, 2015;11(1):34–8 *DOI:10.17925/EE.2015.11.01.34*

Correspondence: Isabel Huguet, Oxford Centre for Diabetes, Endocrinology and Metabolism, Churchill Hospital, Old Rd, Headington, Oxford, OX3 7LJ, UK.
E: ihm.huguet@gmail.com

Cushing's disease (CD) is a rare condition caused by an adrenocorticotropic hormone (ACTH)-secreting pituitary adenoma. Chronic hypercortisolism is associated with the development of several morbidities that impair health-related quality of life (HRQoL) and contribute to an increased mortality rate.[1–5] Obesity and metabolic alterations, hypertension and cardio-/cerebrovascular complications, neuropsychiatric, muscle/skeletal, hypercoagulability/thromboembolism and immune consequences remain the most challenging.

Despite successful treatment of CD, a number of adverse consequences may persist long after cure or may even be irreversible. Moreover, the remission/cure criteria of CD vary between different studies, making comparison of the results difficult.

This paper aims to review and summarise the studies performed on HRQoL, recurrence rates and morbidities during long-term follow-up in patients who have CD.

Materials and Methods

The available literature was evaluated to address questions on HRQoL, recurrence and morbidities in CD. The literature search was conducted in two stages: (1) identification, review and inclusion of all the most relevant articles published in PubMed having the keywords CD, remission, cure, HRQoL *and* morbidities and (2) additional hand research conducted on the basis of bibliographies of identified articles, with articles referring to paediatric population and case reports excluded and with papers referring to Cushing's syndrome (CS) reviewed and included only if presenting data on CD.

Quality of Life

HRQoL was initially assessed in CD patients using such generic measures as the Short Form (SF)-36[6] and the SF-12[7] and measures of specific symptoms associated with the disease, including the Hospital Anxiety and Depression Scale (HADS).[8] More recently, two disease-specific measures, the CushingQoL[9] and the Tuebingen CD-25[10,11] have been developed. *Tables 1* and *2* present studies evaluating QoL using various questionnaires in CD patients having active disease or in remission.

Quality of life is significantly impaired not only in patients with active CD,[9] but also in those in long-term remission,[12,13] regardless of the presence of hormonal deficiencies[9] or treatment strategies,[14,15] and patients who have CS report more negative illness perceptions than do patients who have other acute or chronic conditions.[16]

Quality of Life Assessed by Generic Questionnaires

Lindholm et al. reported that patients in remission for more than 5 years after initial surgery scored significantly worse in all subscales of SF-36 except for mental health and bodily pain.[17] van Aken et al. evaluated patients cured for a mean period of 13.6 years and showed that general perceived well-being was reduced compared with healthy controls for all subscales in SF-36 and the Nottingham Health Profile (NHP). Moreover, such patients scored worse in all subscales of fatigue (Multidimensional Fatigue Inventory [MFI]-20), anxiety and depression (HADS).[18] In comparison with subjects having other pituitary adenomas, patients who had CD were the most severely affected in all parameters of the SF-36 questionnaire.[8] Sonino et al. studied patients who had CS in remission (the majority of them had CD) for 1 to 3 years and found significantly higher scores in

Table 1: Characteristics of Studies and Questionnaires Used to Assess Quality of Life

Reference	Questionnaries	Cushing's Disease Group	Comments
Webb et al. 2014[24]	CushingQoL, BDI-II	n=78, active disease	This study investigated the impact of pasireotide on QoL and the relationship between QoL and UFC
Milian et al. 2013[21]	Tuebingen CD-25	n=17, active disease	All patients were in remission at the second timepoint of investigation. The primary aim of this study was to investigate the value of this questionnaire in assessing the QoL
Alcalar et al. 2013[15]	BDI, SF-36	n=40, 32 cured, 8 active disease	Patients with active CD were compared with cured CD. In addition, CD (active+cured) were compared with healthy controls
Milian et al. 2012[10]	Tuebingen CD-25	n=63, active disease	35 of the patients were evaluated retrospectively, they were asked to imagine themselves in their individual pre-treatment situation. Patients were compared to 1,784 healthy controls
Psaras et al. 2011[22]	SF-36, SCL-90-R	n=24, 19 cured, 5 active disease	Patients with active CD were compared with cured CD. In addition, CD (active+cured) were compared with healthy controls
Webb et al. 2008[9]	SF-36, CushingQoL	n=107	This cross-sectional study recruited 125 patients with CS, 107 (86 %) had CD. At the study visit, 31 % of patients with CS were hypercortisolemic
van der Klaauw et al. 2008[8]	HADS, MFI-20, NHP, SF-36	n=58, cured	Patients with different pituitary adenomas were compared, and also with healthy controls
Sonino et al. 2006[19]	SRT	n=20, cured	Patients with CD were compared with healthy subjects. The presence of latent dysfunctional attitudes was excluded
Lindsay et al. 2006[12]	SF-36	n=23, active disease	Patients were assessed before transsphenoidal surgery and 6 months later
van Aken et al. 2005[18]	NHP, SF-36, MFI-20, HADS	n=58, cured	Patients with CD were compared with 98 healthy controls
Heald et al. 2004[13]	HADS-UK, WHOQOL-BREF, GHQ-8, FACT, SAS-1 and 2	n=15, cured	Patients with CD were compared with other pituitary tumours (NFA: 55; macroprolactinoma: 24; acromegaly: 20), all biochemically stable
Lindholm et al. 2001[17]	SF-36	NA	Results were compared with healthy population

BDI = Beck Depression Inventory; CD = Cushing's disease; CS = Cushing's syndrome; FACT = functional assessment of cancer therapy; GHQ = general health questionnaire; HADS = Hospital Anxiety and Depression Scale; MFI = Multidimensional Fatigue Inventory; NHP = Nottingham Health Profile; NFA = non-functioning adenomas; QoL = quality of life; SAS = Statistical Analysis System; SCL-90-R = Symptom Checklist-90-Revised; SRT = Symptom Rating Test; UFC = urinary-free cortisol; WHOQOL-BREF = World Health Organization Quality of Life-BREF.

Table 2: Main Findings in the Studies Reviewed

Reference	Key Findings
Webb et al. 2014[24]	CushingQoL scores increased (indicating improved HRQoL) as UFC levels declined/improved. The reduction in UFC and improvement in CushingQoL scores from baseline were sustained throughout the 12 months treatment period
Milian et al. 2013[21]	Significant improvement in all scales was found, with the exception of the depression scale. Highest benefits were observed in the domains of eating behaviour, cognition and bodily restrictions
Alcalar et al. 2013[15]	Compared with healthy controls, CD group showed significantly lower scores in SF-36. No differences in depression (BDI) were found. When evaluated according to remission rate, the mean BDI showed significantly higher levels of depression and SF-36 scores were lower in the active CD patients than in both the cured CD patients and the controls
Milian et al. 2012[10]	No correlation was found between Tuebingen CD-25 total score and pre-operative ACTH and serum cortisol levels. 24-hour UFC was significantly correlated to the scale 'Cognition'. Compared with healthy controls, Tuebingen CD-25 score showed significant differences in the perceived QoL in all six domains
Psaras et al. 2011[22]	CD patients scored significantly poorer than the healthy controls in scales of general health, social functioning, mental health (SF-36) and hostility and psychoticism (SCL-90-R). Comparing cured CD with active disease, cured patients scored significantly higher solely in the scale role-emotional of the SF-36
Webb et al. 2008[9]	Current hypercortisolism was associated with worse scores in the CushingQoL questionnaire than patients without. The presence of hypopituitarism or prior pituitary radiotherapy did not determine differences in the CushingQoL score
van der Klaauw et al. 2008[8]	CD was associated with increased impairment in physical functioning (SF-36), increased bodily pain (NHP) and increased anxiety scores (HADS). Impaired physical functioning compared with patients treated for NFA. Hypopituitarism negatively influenced multiple aspects of QoL
Sonino et al. 2006[19]	Patients with CD displayed significantly higher scores in anxiety, depression and psychotic symptoms, with a generalised compromised QoL
Lindsay et al. 2006[12]	All individual SF-36 domains improved after TSS. CD is associated with impaired QoL which partially resolves after treatment (significant improvement in cognitive function)
van Aken et al. 2005[18]	General perceived well-being measured by NHP and SF-36 was reduced for all subscales. Worse scores in HADS depression and anxiety and MFI-fatigue. Hypopitutarism was an important independent predictor of reduced QoL. Not worse QoL in irradiated patients
Heald et al. 2004[13]	Psychological well-being and psychosocial adjustment were significantly impaired in patients with CD compared with all other types of pituitary tumour. Mainly impaired scores for GHQ, HADS depression and anxiety, FACT-F for total score and the fatigue subscale, as were WHO physical, psychological and environment health
Lindholm et al. 2001[17]	The prevalence of health impairment was increased in patients successfully operated for CD compared with healthy controls. Worse results in patients in whom cure was not achieved initially

BDI = Beck Depression Inventory; CD = Cushing's disease; FACT = functional assessment of cancer therapy; HRQoL = health-related quality of life; GHQ = general health questionnaire; HADS = Hospital Anxiety and Depression Scale; MFI = Multidimensional Fatigue Inventory; NHP = Nottingham Health Profile; NFA = non-functioning adenomas; SF-36 = short-form 36 TSS= transsphenoidal surgery; UFC = urinary-free cortisol.

Table 3: Characteristics of Studies Evaluating Recurrence of Cushing's Disease

Reference	n (% Macro)	Mean Follow Up (Months)	Recurrence Rate	Definition of Remission and Recurrence
Dimopoulou et al. 2013[53]	120 (27 %)	79	34 %	RM: UBN or UN or serum cortisol <137 nmol/l on LDDST. RC: UON or serum cortisol >137 nmol/l on LDDST with clinical symptoms
Alexandraki et al. 2013[28]	131 (16 %)	184	24 %	RM: Post-operative serum cortisol level <50 nmol/l or requirement of CGR or UN with resolution of clinical features. RC: UON or serum cortisol >137 nmol/l on LDDST, or elevated serum cortisol concentration with clinical symptoms
Hassan-Smith et al. 2012[4]	80	55	11 %	RM: Morning post-operative cortisol level <50 nmol/l. RC: UON or failure of cortisol suppression on LDDST
Lindsay et al. 2006[12]	331	132	12 %	RM: Two groups of patients, one post-operative cortisol <55 nmol/l; the other <137 nmol/l. RC: Loss of clinical and biochemical eucortisolism (morning cortisol 138–690 nmol/l or UN or cortisol after LDDST <66 nmol/l
Valassi et al. 2011[47]	620 (17 %)	NA	13 %	RM: UN or normal serum levels and/or <138 nmol/l after LDDST. RC: two of: 1) elevated serum cortisol; 2) UON; 3) >138 nmol/l after LDDST; 4) abnormal serum cortisol on LDDST-CRH test
Losa et al. 2009[31]	174 (16 %)	58	11 %	RM: UN and cortisol <138 nmol/l on LDDST. RC: recurrent symptoms of hypercortisolism, UON and no suppression of serum cortisol level aon LDDST
Castinetti et al. 2009[30]	38 (26 %)	60	26 %	RM: UN or maintained cortisol rhythm or cortisol <50 nmol/l on LDDST. RC: UON and losss of cortisol rhythm and no suppression on LDDST
Patil et al. 2008[29]	215	45	17 %	RM: UN or continued need for corticosteroid replacement. RC: UON with clinical symptoms consistent with CD
Atkinson et al. 2005[26]	63	115	15 %	RM: UBN or UN and/or suppression of serum cortisol on LDDST. RC: UON and failure of suppression of serum cortisol on LDDST
Yap et al. 2002[27]	97 (10 %)	92	7 %	RM: Morning post-operative cortisol level <50 nmol/l. **RC:** UON and absence of cortisol suppression on LDDST

CRH = corticotropin-releasing hormone; GCR = glucocorticoid replacement; LDDST = low-dose dexamethasone suppression test; RM = remission; UBN = 24-hour urinary-free cortisol (UFC) below normal range; UN = 24-hour UFC within normal range; UON = 24-hour UFC over normal range. Recurrence (RC) rates apply to the total number of patients included in each series.

anxiety, depression, anger, hostility and psychotic symptoms in the Symptom Rating Test (SRT) questionnaire in comparison with healthy controls.[19] When the Beck Depression Inventory (BDI), SF-36 and the multidimensional body-self relations questionnaire (MBSRQ) were used, patients who had CD demonstrated lower QoL, lower body image perception and higher levels of depression compared with healthy controls, particularly in cases of persistent disease.[15]

Quality of Life Assessed with Disease-specific Questionnaires

Since 2008, two disease-specific questionnaires have been developed: CushingQoL and Tuebingen CD-25. The CushingQoL questionnaire was evaluated by Webb et al. in a multicentre European study. Active CD was associated with worse scores, but the presence of hypopituitarism or prior pituitary radiotherapy did not determine differences in the scores.[9] Similarly, Santos et al. found that active CD patients scored worse on the CushingQoL questionnaire than did cured subjects.[20] Wagenmakers et al. found that CD patients in remission without hormonal deficiencies scored significantly better than those having hormone deficiencies but significantly worse than the control group on 50 % of the items of the questionnaires.[14]

The Tuebingen CD-25 also demonstrated significant differences in all subscales and the total score between active CD patients and healthy controls.[10,11]

The post-operative improvement in HRQoL could be predicted by the presence of pre-operative HRQoL impairment, and younger patients were more likely to improve. Patients without post-operative pituitary deficiencies improved significantly in the cognition scale.[21,22]

QoL does not change after short-term biochemical remission induced by medical therapy but may improve after sustained control of the hypercortisolism.[23,24]

To summarise, most of the results on HRQoL in CD derive from generic questionnaires raising concerns about how appropriate these are for the reliable and accurate assessment of the HRQoL of patients with this rare condition. Interestingly, despite the use of the same type of questionnaire in some studies, the subscales mainly affected show variation among them, suggesting that either CD affects several dimensions in QoL in a heterogeneous way in different patient groups, or these questionnaires are not specific enough. The newly developed questionnaires focus on important disease-specific aspects of the QoL, and their sensitivity in detecting changes renders them a very promising and useful tool in clinical practice.

Recurrence

Transsphenoidal surgery is the treatment of choice in CD, with immediate post-operative remission rates ranging from 59 % to 94 % and recurrence rates from 3 % to 46 %, both depending upon the definition criteria, the duration of follow-up, the number of patients studied and the inclusion of macroadenomas (see *Table 3*).[2,25–29] A small number of studies have used undetectable or very low post-operative serum cortisol levels as a strict criterion of remission, but most have defined effective remission as the resolution of clinical features and the reversal of hypercortisolism (in serum or urine), along with the recovery of cortisol suppressibility on dexamethasone administration or a normal cortisol circadian rhythm. Predictors of remission in CD include age at diagnosis, presence of hypertension or diabetes,[4,5] response to desmopressin testing,[30] identification of tumour at surgery and an adenoma histology positive for ACTH.[31–33]

Out of concern about recurrence of CD after initial remission, several parameters have been evaluated and are still matter of debate. Factors that have been associated with a low (but not zero) risk of CD recurrence include undetectable or low early morning serum levels of cortisol,[33] low plasma levels of ACTH and prolonged requirement for glucocorticoid replacement after pituitary surgery. The effects of serum cortisol levels in the early post-operative period on predicting relapse have been assessed in various studies. No recurrences were found by Trainer et al.[34] during a median follow-up of 40 months in patients with a post-operative serum cortisol of <50 nmol/l; similar results were reported after a median follow-up of 58 months by McCance et al.[35] In contrast to these findings, several series have reported recurrence rates of 11.5 % and 15 % despite a serum cortisol <50 nmol/l post surgery.[27,28] Another possible parameter is the length of adrenal insufficiency post-TSS. Thus it has been suggested that patients who have a shorter duration of adrenal insufficiency have a significantly higher risk of relapse.[36]

Accordingly, after successful treatment of CD, there is no accurate criterion that can ensure lifelong cure, and although the evidence shows a more optimal outcome in patients who achieve severe cortisol deficiency after TSS, lifelong follow-up is mandatory.

Morbidities

CD is associated with significant comorbidities – metabolic and vascular complications, osteoporosis, neuropsychiatric dysfunction and immunosuppression – that increase mortality and affect daily life. A number of these may persist long after cure or may even be permanent.[37]

Metabolic and Vascular Complications

It is well recognised that CD increases cardiovascular risk, with hypertension and obesity the most common associated risk factors. The cardiovascular complications are part of the metabolic syndrome, but hypertension related to endogenous hypercortisolism is not simply a component of the CS-related metabolic syndrome. The renin–angiotensin system, mineralocorticoid activity, the sympathetic nervous system and the vasoregulatory systems have been reported to be involved in the pathophysiology of hypertension, but the mechanisms are only partially understood.[38]

The adverse cardiovascular risk profile of patients who have CD[39] is attributed to metabolic and vascular aberrations, as well as to changes in cardiac structure and function. Patients who have CD have increased leptin,[40,41] resistin[42] and pro-inflammatory agents, such as tumour necrosis factor-α and interleukin-6, C-reactive protein and low ghrelin levels.[40] Moreover, they are characterised by a prothrombotic phenotype attributed to various abnormalities of coagulation and fibrinolysis: these include shortened activated partial thromboplastin time,[43] increased factor VIII, von Willebrand factor, fibrinogen and plasminogen activator inhibitor-1,[43] decreased fibrinolytic capacity[44] and increased α2-antiplasmin.[45] Endothelium-dependent flow-mediated vasodilatation is impaired, and several humoral markers of endothelial dysfunction (such as endothelin, homocysteine, vascular endothelial growth factor, osteoprotegerin and cell adhesion molecules) are elevated. Cardiac echocardiograms demonstrate left ventricular hypertrophy, concentric remodelling and diastolic and systolic dysfunction.

Persistent clinical abnormalities have been documented in terms of cardiovascular complications, showing that remission of hypercortisolaemia reduces, but does not completely eliminate them. Colao et al. reported that 27 % of patients having CD in remission for 5 years had persistently atherosclerotic plaques, compared with only 3 % of gender-, age- and body mass index–matched controls.[45] Faggiano et al. also found persistence of the metabolic syndrome, vascular damage and atherosclerotic plaques after disease remission.[46]

Thus it is likely that disease remission does not entirely reverse cardiovascular morbidities affecting long-term survival and that lifelong follow-up is needed, with particular emphasis on cardiovascular risk factors.

Bone

Bone loss is attributed to decreased osteoblastic activity, increased osteoclastic bone resorption and impaired enteral calcium absorption. In the ERCUSYN study, osteopenia at the spine and hip was reported in 40 % and 46 % of patients who had CD, respectively, and osteoporosis at the spine and hip in 22 % and 12 %, respectively.[47,48] Bone mineral density (BMD) does not completely recover following remission,[49,50] though normalisation in some skeletal sites has been reported in the long-term.[51]

Glucocorticoid-induced vertebral fractures may develop even in the presence of normal or slightly low BMD. The risk of fractures at comparable BMD values with controls suggests that components of bone strength, not assessed by routine densitometric approaches, are also affected by glucocorticoids (including bone architecture, geometry and remodelling). Methods of assessment other than measurement of BMD are required, because despite the improvement of BMD after correction of hypercortisolism, the quality of the bone likely remains compromised.

Immune System

Hypercortisolism induces reversible immunosuppression. During hypercortisolaemia, autoimmune disorders improve but may worsen during remission and new ones develop.[52] There is a high risk of superficial fungal, opportunistic or bacterial infections.

Neuropsychiatric Manifestations

Glucocorticoids are known to influence many functions of the central nervous system. Hypercortisolaemia is associated with depression, disrupted sleep and a wide range of cognitive impairments (derangement of memory – especially short-term – irritability and decreased concentration). High anxiety levels and low externalising behaviour are common emotional disorders.[53] Smaller hippocampal volumes and generalised brain atrophy have been described.[54] Functional magnetic resonance imaging studies in patients having CD have demonstrated emotion-processing difficulties and hyperactivity in the frontal and subcortical regions, similar to major depressive disorders. After remission, hippocampal volumes increase and emotional and cognitive functions improve,[53–55] but profound structural alterations in the brain remain such as smaller volumes in the anterior cingulate cortex, a structure involved in cognitive–affective processes and behavioural adaptation.[56]

The new data on persistent changes in the central nervous system after cure of CD support the hypothesis that psychiatric symptoms and cognitive impairment could be related to structural changes, providing the basis for future research on the neurobiological background of psychological dysfunction in this complex condition.

Conclusions

CD is associated with significant adverse sequelae affecting long-term morbidity, mortality and quality of life. To some extent, the

duration and severity of hypercortisolism determine the possibility of reversion of the morbidities, but a number of manifestations may persist long after cure – possibly permanently. Generic questionnaires and disease-specific measures have evaluated many aspects of the quality of life impaired, not only during the active state, but also when in remission.

Despite initial successful treatment, there is a risk of relapse, and post-operative hypocortisolism is the most significant predictor of remission. These long-term and persistent changes are challenging to our understanding of hypercortisolaemia but in a clinical context suggest that long-term follow-up is essential in all patients having CD, even those apparently cured. ■

1. Feelders RA, Pulgar SJ, Kempel A, et al., The burden of Cushing's disease: clinical and health-related quality of life aspects, *Eur J Endocrinol*, 2012;167:311–26.
2. Ntali G, Asimakopoulou A, Siamatras T, et al., Mortality in Cushing's syndrome: systematic analysis of a large series with prolonged follow-up, *Eur J Endocrinol*, 2013;169:715–23.
3. Yaneva M, Kalinov K, Zacharieva S, Mortality in Cushing's syndrome: data from 386 patients from a single tertiary referral center, *Eur J Endocrinol*, 2013;169:621–7.
4. Hassan-Smith ZK, Sherlock M, Reulen RC, et al., Outcome of Cushing's disease following transsphenoidal surgery in a single center over 20 years, *J Clin Endocrinol Metab*, 2012;97:1194–201.
5. Clayton RN, Raskauskiene D, Reulen R C, et al., Mortality and morbidity in Cushing's disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature, *J Clin Endocrinol Metab*, 2011;96:632–42.
6. Hawn MT, Cook D, Deveney C, et al., Quality of life after laparoscopic bilateral adrenalectomy for Cushing's disease, *Surgery*, 2002;132:1064–8; discussion 1068–9.
7. Thompson SK, Hayman AV, Ludlam WH, et al., Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience, *Ann Surg*, 2007;245:790–4.
8. van der Klaauw AA, Kars M, Biermasz NR, et al., Disease-specific impairments in quality of life during long-term follow-up of patients with different pituitary adenomas, *Clin Endocrinol*, 2008;69:775–84.
9. Webb SM, Badia X, Barahona MJ, et al., Evaluation of health-related quality of life in patients with Cushing's syndrome with a new questionnaire, *Eur J Endocrinol*, 2008;158:623–30.
10. Milian M, Teufel P, Honegger J, et al., The development of the Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25), part I: construction and psychometric properties, *Clin Endocrinol*, 2012;76:851–60.
11. Milian M, Teufel P, Honegger J, et al., The development of the Tuebingen Cushing's disease quality of life inventory (Tuebingen CD-25), part II: normative data from 1784 healthy people, *Clin Endocrinol*, 2012;76:861–7.
12. Lindsay JR, Nansel T, Baid S, et al., Long-term impaired quality of life in Cushing's syndrome despite initial improvement after surgical remission, *J Clin Endocrinol Metab*, 2006;91:447–53.
13. Heald AH, Ghosh S, Bray S, et al., Long-term negative impact on quality of life in patients with successfully treated Cushing's disease, *Clin Endocrinol*, 2004;61:458–65.
14. Wagenmakers MA, Netea-Maier RT, Prins JB, et al., Impaired quality of life in patients in long-term remission of Cushing's syndrome of both adrenal and pituitary origin: a remaining effect of long-standing hypercortisolism? *Eur J Endocrinol*, 2012;167:687–95.
15. Alcalar N, Ozkan S, Kadioglu P, et al., Evaluation of depression, quality of life and body image in patients with Cushing's disease, *Pituitary*, 2013;16:333–40.
16. Tiemensma J, Kaptein AA, Pereira AM, et al., Negative illness perceptions are associated with impaired quality of life in patients after long-term remission of Cushing's syndrome, *Eur J Endocrinol*, 2011;165:527–35.
17. Lindholm J, Juul S, Jørgensen JO, et al., Incidence and late prognosis of Cushing's syndrome: a population-based study, *J Clin Endocrinol Metab*, 2001;86:117–23.
18. van Aken MO, Pereira AM, Biermasz NR, et al., Quality of life in patients after long-term biochemical cure of Cushing's disease, *J Clin Endocrinol Metab*, 2005;90:3279–86.
19. Sonino N, Bonnini S, Fallo F, et al., Personality characteristics and quality of life in patients treated for Cushing's syndrome, *Clin Endocrinol*, 2006;64:314–8.
20. Santos A, Resmini E, Martínez-Momblán MA, et al., Psychometric performance of the CushingQoL questionnaire in conditions of real clinical practice, *Eur J Endocrinol*, 2012;167:337–42.
21. Milian M, Honegger J, Teufel P, et al., Tuebingen CD-25 is a sensitive tool to investigate health-related quality of life in Cushing's disease patients in the course of the disease, *Neuroendocrinology*, 2013;98:188–99.
22. Psaras T, Milian M, Hattermann V, et al., Predictive factors for neurocognitive function and Quality of Life after surgical treatment for Cushing's disease and acromegaly, *J Endocrinol Invest*, 2011;34:e168–77.
23. van der Pas R, de Bruin C, Pereira AM, et al., Cortisol diurnal rhythm and quality of life after successful medical treatment of Cushing's disease, *Pituitary* 2013;16:536–44.
24. Webb SM, Ware JE, Forsythe A, et al., Treatment effectiveness of pasireotide on health-related quality of life in patients with Cushing's disease, *Eur J Endocrinol*, 2014;171:89–98.
25. Aranda G, Enseñat J, Mora M, et al., Long-term remission and recurrence rate in a cohort of Cushing's disease: the need for long-term follow-up, *Pituitary*, 2015;18:142–9.
26. Atkinson AB, Kennedy A, Wiggam MI, et al., Long-term remission rates after pituitary surgery for Cushing's disease: the need for long-term surveillance, *Clin Endocrinol*, 2005;63:549–59.
27. Yap LB, Turner HE, Adams CB, et al., Undetectable postoperative cortisol does not always predict long-term remission in Cushing's disease: a single centre audit, *Clin Endocrinol*, 2002;56:25–31.
28. Alexandraki KI, Kaltsas GA, Isidori AM, et al., Long-term remission and recurrence rates in Cushing's disease: predictive factors in a single-centre study, *Eur J Endocrinol*, 2013;168:639–48.
29. Patil CG, Prevedello DM, Lad SP, et al., Late recurrences of Cushing's disease after initial successful transsphenoidal surgery, *J Clin Endocrinol Metab*, 2008;93:358–62.
30. Castinetti F, Martinie M, Morange I, et al., A combined dexamethasone desmopressin test as an early marker of postsurgical recurrence in Cushing's disease, *J Clin Endocrinol Metab*, 2009;94:1897–903.
31. Losa M, Bianchi R, Barzaghi R, et al., Persistent adrenocorticotropin response to desmopressin in the early postoperative period predicts recurrence of Cushing's disease, *J Clin Endocrinol Metab*, 2009;94:3322–8.
32. Acebes JJ, Martino J, Masuet C, et al., Early post-operative ACTH and cortisol as predictors of remission in Cushing's disease, *Acta Neurochir*, 2007;149:471–7; discussion 477–9.
33. Dimopoulou C, Schopohl J, Rachinger W, et al., Long-term remission and recurrence rates after first and second transsphenoidal surgery for Cushing's disease: care reality in the Munich Metropolitan Region, *Eur J Endocrinol*, 2013;170:283–92.
34. Trainer PJ, Lawrie HS, Verhelst J, et al., Transsphenoidal resection in Cushing's disease: undetectable serum cortisol as the definition of successful treatment, *Clin Endocrinol (Oxford)*, 1993 Jan;38(1):73–8.
35. McCance DR, Besser M, Atkinson AB, Assessment of cure after transsphenoidal surgery for Cushing's disease, *Clin Endocrinol (Oxford)*, 1996 Jan;44(1):1–6.
36. Bochicchio D, Losa M, Buchfelder M, Factors influencing the immediate and late outcome of Cushing's disease treated by transsphenoidal surgery: a retrospective study by the European Cushing's Disease Survey Group, *J Clin Endocrinol Metab*, 1995 Nov;80(11):3114–20.
37. Ntali G, Grossman A, Karavitaki N, Clinical and biochemical manifestations of Cushing's, *Pituitary*, 2015 Jan 10 [Epub ahead of print].
38. Isidori AM, Graziadio C, Paragliola RM, et al., The hypertension of Cushing's syndrome: controversies in the pathophysiology and focus on cardiovascular complications, *J Hypertens*, 2015 Jan;33(1):44–60.
39. Mancini T, Kola B, Mantero F, et al., High cardiovascular risk in patients with Cushing's syndrome according to 1999 WHO/ISH guidelines, *Clin Endocrinol*, 2004;61:768–77.
40. Libè R, Morpurgo PS, Cappiello V, et al., Ghrelin and adiponectin in patients with Cushing's disease before and after successful transsphenoidal surgery, *Clin Endocrinol*, 2005;62:30–6.
41. Veldman RG, Frölich M, Pincus SM, et al., Hyperleptinemia in women with Cushing's disease is driven by high-amplitude pulsatile, but orderly and eurhythmic, leptin secretion, *Eur J Endocrinol*, 2001;144:21–7.
42. Krsek M, Silha JV, Jezková J, et al., Adipokine levels in Cushing's syndrome: elevated resistin levels in female patients with Cushing's syndrome, *Clin Endocrinol*, 2004;60:350–7.
43. Manetti L, Bogazzi F, Giovannetti C, et al., Changes in coagulation indexes and occurrence of venous thromboembolism in patients with Cushing's syndrome: results from a prospective study before and after surgery, *Eur J Endocrinol*, 2010;163:783–91.
44. van der Pas R, Leebeek FW, Hofland LJ, et al., Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment, *Clin Endocrinol*, 2013;78:481–8.
45. Colao A, Pivonello R, Spiezia S, et al., Persistence of increased cardiovascular risk in patients with Cushing's disease after five years of successful cure, *J Clin Endocrinol Metab*, 1999;84:2664–72.
46. Faggiano A, Pivonello R, Spiezia S, et al., Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission, *J Clin Endocrinol Metab*, 2003;88:2527–33.
47. Valassi E, Santos A, Yaneva M, et al., The European Registry on Cushing's syndrome: 2-year experience—baseline demographic and clinical characteristics, *Eur J Endocrinol*, 2011;165:383–92.
48. Toth M, Grossman A, Glucocorticoid-induced osteoporosis: lessons from Cushing's syndrome, *Clin Endocrinol*, 2013 Jul;79(1):1–11, doi: 10.1111/cen.12189.
49. Di Somma C, Pivonello R, Loche S, et al., Effect of 2 years of cortisol normalization on the impaired bone mass and turnover in adolescent and adult patients with Cushing's disease: a prospective study, *Clin Endocrinol*, 2003;58:302–8.
50. Barahona MJ, Sucunza N, Resmini E, et al., Deleterious effects of glucocorticoid replacement on bone in women after long-term remission of Cushing's syndrome, *J Bone Miner Res*, 2009;24:1841–6.
51. Kristo C, Jemtland R, Ueland T, et al., Restoration of the coupling process and normalization of bone mass following successful treatment of endogenous Cushing's syndrome: a prospective, long-term study, *Eur J Endocrinol*, 2006;154:109–18.
52. da Mota F, Murray C, Ezzat S, Overt immune dysfunction after Cushing's syndrome remission: a consecutive case series and review of the literature, *J Clin Endocrinol Metab*, 2011;96:E1670–4.
53. Dimopoulou C, Ising M, Pfister H, et al., Increased prevalence of anxiety-associated personality traits in patients with Cushing's disease: a cross-sectional study, *Neuroendocrinology*, 2013;97:139–45.
54. Toffanin T, Nifosì F, Follador H, et al., Volumetric MRI analysis of hippocampal subregions in Cushing's disease: a model for glucocorticoid neural modulation, *Eur Psychiatry*, 2011;26:64–7.
55. Bourdeau I, Bard C, Noël B, et al., Loss of brain volume in endogenous Cushing's syndrome and its reversibility after correction of hypercortisolism, *J Clin Endocrinol Metab*, 2002; 87:1949–54.
56. Andela CD, van der Werff SJ, Pannekoek JN, et al., Smaller grey matter volumes in the anterior cingulate cortex and greater cerebellar volumes in patients with long-term remission of Cushing's disease: a case–control study, *Eur J Endocrinol*, 2013;169:811–9.