The burden of Cushing’s disease: clinical and health-related quality of life aspects

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Abstract

Objective: Cushing’s disease (CD) is a rare endocrine disorder characterized by excess secretion of ACTH due to a pituitary adenoma. Current treatment options are limited and may pose additional risks. A literature review was conducted to assess the holistic burden of CD. Design: Studies published in English were evaluated to address questions regarding the epidemiology of CD, time to diagnosis, health-related quality of life (HRQoL), treatment outcomes, mortality, prevalence of comorbidities at diagnosis, and reversibility of comorbidities following the treatment. Methods: A two-stage literature search was performed in Medline, EMBASE, and Science Citation Index, using keywords related to the epidemiology, treatment, and outcomes of CD: i) articles published from 2000 to 2012 were identified and ii) an additional hand search (all years) was conducted on the basis of bibliography of identified articles. Results: At the time of diagnosis, 58–85% of patients have hypertension, 32–41% are obese, 20–47% have diabetes mellitus, 50–81% have major depression, 31–50% have osteoporosis, and 38–71% have dyslipidemia. Remission rates following transsphenoidal surgery (TSS) are high when performed by expert pituitary surgeons (rates of 65–90%), but the potential for relapse remains (rates of 5–36%). Although some complications can be partially reversed, time to reversal can take years. The HRQoL of patients with CD also remains severely compromised after remission. Conclusions: These findings highlight the significant burden associated with CD. As current treatment options may not fully reverse the burden of chronic hypercortisolism, there is a need for both improved diagnostic tools to reduce the time to diagnosis and effective therapy, particularly a targeted medical therapy.

Introduction

Cushing’s disease (CD) is a rare condition caused by a pituitary adenoma that secretes excess ACTH (1), which promotes excess cortisol production from the adrenal glands. Excess cortisol induces a clinical phenotype that harbors all components of the metabolic syndrome, such as central obesity, diabetes mellitus, dyslipidemia, and hypertension, as well as muscle weakness, hirsutism, increased bruising, psychological dysfunction, and osteoporosis (1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11). Patients with CD experience a significant clinical burden due to comorbidities, increased mortality, and impaired health-related quality of life (HRQoL) due to prolonged exposure to elevated cortisol levels (3, 5, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20). In particular, patients with CD often experience severe fatigue and weakness, physical changes, emotional instability, depression, and cognitive impairments, which have a profound impact on daily life (13, 21).

Although there have been several consensus statements published recently on the definition of remission, diagnosis, and the management of CD, the severity and diversity of the clinical scenario and associated morbidities continue to present a management challenge (1, 22, 23). Additionally, there is recent evidence of persistent deleterious effects after remission, most notably persistent elevated cardiovascular risk (3, 22). The main objective of the current literature review is to describe the current burden of the disease and to summarize data on specific aspects of this burden, which underscores the need for improved diagnostic and therapeutic approaches.
Materials and methods

Available literature were evaluated to address questions regarding the epidemiology of CD, time to diagnosis, mortality, prevalence of comorbidities at diagnosis, reversibility of comorbidities after treatment (in particular, after disease remission), outcomes and complications of current treatment options, and HRQoL associated with CD and interventions.

The literature search was performed in Medline, EMBASE, and Science Citation Index, using keywords related to the epidemiology, treatment, and outcomes of CD. It was conducted in two stages: i) articles published between 2000 and 2012 were identified through a PubMed search using the following keywords: CD, incidence, prevalence, mortality, treatment, remission, cure, excess cortisol, outcomes, cost, QoL, morbidities, transsphenoidal surgery (TSS), adrenalectomy, radiotherapy, steroidogenesis inhibitors, ketoconazole, mitotane, aminoglutethimide, etomidate, metyrapone, pasireotide, and cortisol receptor antagonists; and ii) an additional hand search was conducted on the basis of the bibliographies of identified articles. All studies that provided data (regardless of publication year) related to these research questions were retained.

Definitions

Different criteria for defining the remission of hypercortisolism have been proposed, ranging from the occurrence of definitive or transient postoperative hypocortisolemia to the adequate suppression of cortisol after dexamethasone administration. According to a recent consensus statement (23), persistent postoperative morning serum cortisol levels of <2 μg/dl (≈50 nmol/l) are associated with remission and a low recurrence rate of 10% at 10 years. Persistent serum cortisol levels above 5 μg/dl (≈140 nmol/l) for up to 6 weeks following surgery require further evaluation. When serum cortisol levels are between 2 and 5 μg/dl, the patient can be considered in remission and can be observed without additional treatment for CD. A subset of patients can even develop complete adrenal insufficiency (serum cortisol levels below 2 μg/dl (≈50 nmol/l)) up to 12 weeks postsurgery (24, 25). Therefore, repeated evaluation in the early postoperative period is recommended. However, long-term follow-up is necessary for all patients because no single cortisol cutoff value excludes those who later experience disease recurrence, and up to 25% of patients develop a recurrent adenoma within 10 years after surgery (26, 27, 28).

Results

Incidence and prevalence of CD

Although epidemiologic data on CD are limited, several population-based studies indicate an incidence of 1.2–2.4 per million (14, 19) and the prevalence of diagnosed cases to be ≈39 per million population (14). Lindholm et al. (19) used the case definition as either the presence of a corticotroph adenoma or remission after neurosurgery, which yielded an estimated incidence rate of 1.2–1.7 per million per year. Etxabe & Vazquez (14) reported an incidence of 2.4 per million in Vizcaya, Spain. A large-scale retrospective survey carried out in New Zealand by Bolland et al. (29) found the approximate prevalence of all forms of Cushing’s syndrome (CS) (the majority of these cases were of pituitary origin) to be 79 per million and the incidence to be 1.8 per million per year. Differences in epidemiologic estimates may be attributable to varying case definitions (for instance, the study by Lindholm excluded cases in which the adenoma could not be localized or those that could not achieve remission from surgery), geographical differences, and temporal effects. The prevalence of CD may be underestimated due to unrecognized patients with mild symptoms and patients with a cyclic form of CD (30).

Time to diagnosis

Data on the time from onset of symptoms to diagnosis are also limited. In a prospective study by Flitsch et al. (31) of 48 patients with pituitary adenomas, including 19 who had ACTH-secreting adenomas causing CD, the reported time from onset of symptoms to diagnosis was 4.3 years. A study by Martinez Ruiz et al. (32), which was based on only four pediatric CD patients, reported the time between onset of symptoms and diagnosis as ranging from 2.5 to 5 years. Etxabe & Vazquez (14) estimated that the average time from onset of clinical symptoms to diagnosis in 49 CD patients was 45.8 ± 2.7 months (6–144 months), thus 3.8 years. This is corroborated by the findings from a Belgian cross-sectional study on pituitary adenomas including CD, which estimated that patients experienced symptoms for an average of 45 months before diagnosis (33). However, the reliability and generalizability of these data are limited by small sample sizes and the retrospective nature of the studies. Indeed, the New Zealand data from Bolland et al. (29) report that on presentation, patients experienced symptoms for a median of 2.0 years (but ranging up to 20 years) before diagnosis. On the basis of data from the prospective European Registry on Cushing’s syndrome (ERCUSYN) (total number of patients=481, of whom 66% of patients had CD), median delay in diagnosis was 2 years (34).

Mortality in patients with CD

Mortality in patients with CD has been analyzed in several small studies, with overall rates reported as standardized mortality ratio (SMR) ranging from 1.7 to 4.8 (Table 1) (14, 15, 17, 19). In studies in which mortality was assessed among those in remission and
Table 1 Mortality in patients with CD.

<table>
<thead>
<tr>
<th>Study design</th>
<th>n</th>
<th>SMR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population-based study 18-year follow-up (14)</td>
<td>49</td>
<td>3.8 (2.5–17.9)</td>
<td>SMR of vascular disease was 5.0. Older age, persistence of hypertension, and abnormalities of glucose metabolism after treatment were independent predictors of mortality</td>
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<tr>
<td>Retrospective study</td>
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<tr>
<td>Follow-up 1981–1996 (17)</td>
<td>74 CS</td>
<td>1.68 (0.8–30.9)</td>
<td>Mortality risk was moderately increased compared with that of the general population</td>
</tr>
<tr>
<td>National Patient Registry study 11-year period (19)</td>
<td>166 CS</td>
<td>3.68 (2.34–5.33)</td>
<td>The authors in this study reported excess mortality in the first year after diagnosis. After the first year, mortality was not significantly higher than that of the background population</td>
</tr>
<tr>
<td>Single-center study, Mean duration of follow-up was 10.1 ± 7.2 years for the whole cohort (15)</td>
<td>248</td>
<td>2.39 (1.22–3.9)</td>
<td>The SMR in patients with CD with remission after TSS was 1.80 (95% CI: 0.71–3.37), whereas the SMR in patients with persistent disease was 4.38 (95% CI: 1.38–9.07)</td>
</tr>
<tr>
<td>Single-center study, Median duration of follow-up was 15 years (36)</td>
<td>60</td>
<td>4.8 (2.8–8.3)</td>
<td>Vascular disease SMR: 13.8 (95% CI: 7.2–36.5). SMR for persistent disease (n=6): 16 (95% CI: 6.7–38.4) vs remission (n=54): 3.3 (95% CI: 1.7–6.7)</td>
</tr>
<tr>
<td>Systematic review and meta-analysis (40)</td>
<td>7</td>
<td>1.84 (1.28–2.65)</td>
<td>SMR for persistent disease after surgery 3.73 (95% CI: 2.31–6.01)</td>
</tr>
<tr>
<td>Single-center study (38)</td>
<td>80</td>
<td>3.17 (1.70–5.43)</td>
<td>Cure group SMR 2.47 (95% CI: 0.80–5.77)</td>
</tr>
<tr>
<td>Nationwide retrospective survey (29)</td>
<td>253 CS; 158 (62.4%) microadenoma; 30 (11.9%) macroadenoma</td>
<td>Macroadenoma: 3.5 (1.3–7.8); microadenoma: 3.2 (2.0–4.8)</td>
<td>In all 253 patients with CS: SMR 4.1 (95% CI 2.9–5.6)</td>
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</table>

those with persistent disease separately, patients with persistent hypercortisolism consistently had the highest mortality risk (15, 19, 35, 36). In addition, TSS as a first-line treatment has been an important advance as high remission rates after initial surgery have been accompanied by mortality rates that mirror those observed in the general population (17, 35, 37). In a case series from the UK, it was found that the majority of deaths occurred before 1985, which was before TSS was employed as the routine first-line treatment at the center (36). In a recent retrospective study, 80 patients undergoing TSS for CD between 1988 and 2009 were evaluated, and long-term cure (defined as ongoing absence of hypercortisolism at last follow-up) was reported in 72% of patients. However, overall elevated mortality persisted in patients (SMR 3.17 (95% CI: 1.70–5.43)), including those who achieved ‘cure’ (SMR 2.47 (95% CI: 0.80–5.77)), although even higher mortality was seen in those with postoperative recurrence/persistent disease (SMR 4.12 (95% CI: 1.12–10.54) (38)). Additionally, a nationwide, retrospective study in New Zealand reported significantly increased mortality both in macro- and microadenomas (SMR 3.5 (1.3–7.8) and 3.2 (2.0–4.8) respectively), despite long-term biochemical remission rates of 93 and 91% of patients, respectively (29).

In a single-center study designed to assess the impact of hypercortisolism vs the occurrence of a pituitary adenoma in mediating increased mortality risk, patients with CD had higher mortality rates than patients with nonfunctioning pituitary macroadenomas (SMR 2.4 vs 1.4) (15). Patients with persistent hypercortisolism after initial TSS had the highest elevated mortality (SMR 4.4) (15), which suggests that hypercortisolism and the length of exposure to hypercortisolism is associated with increased mortality. This finding is similar to the results of a Danish population study in which patients with persistent hypercortisolism after initial surgery had an SMR of 5 (19). Some deleterious effects of excess cortisol exposure appear to persist as even patients who achieved surgical remission still had elevated mortality (SMR 1.8) (15). Patients with possible CD but whose disease etiology was unproven had the highest reported mortality risk in the literature (SMR 11.5) (19). Among these patients, etiology could not be confirmed because the adenoma could not be localized, patients were unable to achieve remission after surgery, or patients died before a full clinical workup could be done (19).
Mortality has been reported to be higher in females (SMR 4.5) (14), particularly from vascular causes (SMR 5), although it is important to note that this study had a 15:1 female to male preponderance and other studies have not observed gender differences in mortality (14, 19). However, questions remain regarding the relationship between specific dimensions of hypercortisolism in CD, such as the duration of exposure to hypercortisolism and the severity of this exposure, and mortality.

Patients with CD are most likely to die from cardiovascular or cerebrovascular causes (14, 15, 19, 37). In the study by Dekkers et al. (15), the leading causes of death were cardiovascular disease (23.4%), cerebrovascular disease (12.8%), malignancy (19%), and infectious diseases (17%). Additionally, the average age at death in this Dutch study was reported to be 62.4 years, which is significantly lower than the life expectancy of the general population (80 years) (9, 39). Similarly, Hassan-Smith et al. (38) reported that the leading causes of death were cardiovascular disease (n = 8), cancer (n = 3), infection (n = 1), and CD (n = 1), with the median age at death being 57 years. A recent systematic review and meta-analysis of mortality in patients with CS drawing from seven studies estimated that the SMR for patients with CD is 1.84 (95% CI: 1.28–2.65), with patients with persistent disease after surgery having an SMR of 3.73 (95% CI: 2.31–6.01) (40).

These conclusions drawn from small studies and case series with a low number of deaths and variable follow-up time should be interpreted with caution. Studies with longer follow-up time and more analyzable events are needed to assess whether long-term mortality is normalized after long-term remission or whether persistent cardiovascular risk factors translate into an increased mortality risk. The fact that some studies have shown persistent elevated mortality after cure, in particular the study by Hassan-Smith et al. (38) where all patients underwent TSS, may suggest that a stricter definition of ‘cure’ could be applied. Nonetheless, these findings suggest that normalization of cortisol secretion improves mortality, but may be insufficient to normalize mortality as other factors, like adverse cardiovascular risk factors or hypopituitarism, may determine the mortality outcome of patients after successful surgery. In the large retrospective survey from New Zealand, demographic predictors of mortality in patients with a micro- or macroadenoma were older age, hypertension, and diabetes mellitus. It is of note that patients with an adrenal adenoma (n = 37) had an elevated SMR but very good prognosis following the treatment (29). This may suggest that pituitary compromise may account for the persistent elevated mortality in patients with ‘cured’ disease following transsphenoidal intervention. The data reported by Bolland et al. (29) also showed a relatively consistent elevated SMR over four time periods (1960–1980, 1980–1990, 1990–2000, and 2000–present) despite a general shift in pituitary-directed therapy from radiotherapy to TSS, which is at odds with the previously discussed UK data in which the majority of deaths occurred before 1985, before TSS was employed as the standard first-line therapy (36). Nonetheless, early detection and rapid intervention may be key in avoiding long-term sequelae of the disease (41). As CD is a rare disease and, thus, difficult to study, it is hoped that databases such as the ERCUSYN, which now includes more than 500 patients, could become a key resource to further research and aid collaboration (42).

It should be noted that geographic variability in time to diagnosis, the availability of pituitary experts, and the awareness levels of general practitioners who may first encounter patients with undiagnosed CD can all lead to treatment disparities and differences in remission and mortality rates between countries and regions.

**Comorbidities: prevalence and reversibility**

The chronic hypersecretion of cortisol causes central obesity, systemic arterial hypertension, impaired glucose tolerance, dyslipidemia, and hypercoagulability, and is associated with other comorbidities, such as psychological and cognitive dysfunction, osteoporosis, and increased susceptibility to infection (1, 9, 43, 44) (Table 2 and Supplementary Table 1, see section on supplementary data given at the end of this article). When compared with the general population, CD patients showed a greater than twofold increase in hypertension, diabetes, and osteoporosis, and an increase of over five times the rate of major depression and impaired glucose tolerance (Fig. 1) (45, 46, 47). A recent study, using whole-body magnetic resonance imaging (MRI), evaluating body composition and cardiovascular parameters after remission of CD found that cardiovascular risk persisted despite potential dramatic improvements in body composition abnormalities (48).

**Cardiovascular complications** Among all systemic consequences of hypercortisolism, cardiovascular complications are the most dire as these are among the leading causes of death in patients with CD (14, 15). Cardiovascular risk is increased in CD due to complications such as hypertension, atherosclerosis, hypercoagulability, obesity, diabetes, and dyslipidemia, which are all consequences of chronic cortisol hypersecretion (1, 49). In addition, CD is associated with left ventricular hypertrophy and diastolic dysfunction (50).

Years after disease remission, cardiovascular morbidity persists (3, 51). However, despite numerous studies determining the cardiovascular risk in the general population, there are few studies that comprehensively evaluate the cardiovascular risk factors and assess the global risk for patients with CD. A recent paper by De Leo et al. (52) suggests that assessing the global
cardiovascular risk and managing the risk associated with cardiovascular disease such as hypertension, obesity, glucose intolerance, insulin resistance, dyslipidemia, endothelial dysfunction, and the hypercoagulable state should be the important goals of treatment for CD.

### Hypertension

Hypertension has been reported in 55–85% of patients with CD, with most cases being mild to moderate (3, 12, 14, 22, 53). Hypertension remits in a subset of patients (44–75%, Table 2) after successful treatment but persists in ~24–56% (12, 14, 22), presumably due to microvessel remodeling or concomitant underlying essential hypertension (54). The duration of disease has been shown to be longer in hypertensive patients (4.8 ± 3.7 years) than in normotensive (0.7 ± 0.2 years) patients (22) and has been identified as a significant risk factor in several studies (54, 55). Older age and longer duration of hypertension before treatment also negatively influenced the normalization of high blood pressure after resolution of hypercortisolism.

### Hypercoagulopathy

Patients with CD show various abnormalities of hemostatic parameters and those with active CD show an increased thrombotic tendency (56). Increased cortisol levels stimulate the synthesis of several clotting factors, such as fibrinogen by the liver and von Willebrand factor by endothelial cells. Glucocorticoids also upregulate the synthesis of plasminogen activator inhibitor type 1, the main inhibitor of the fibrinolytic system (49). This hypercoagulability state is a crucial factor predisposing CD patients to thromboembolic events, mostly after surgery and during inferior

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### Table 2 Comorbidities, prevalence at diagnosis, and reversibility in patients with CD.

<table>
<thead>
<tr>
<th>Morbidity</th>
<th>Prevalence at diagnosis</th>
<th>Reversibility</th>
</tr>
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<tbody>
<tr>
<td>Hypertension</td>
<td>55–85% (12, 14, 22, 53)</td>
<td>18-Year follow-up: posttreatment 24% (12/49); diagnosis 55% (27/49) (14) After 5 years’ cortisol normalization: CD 40% (6/15); BMI-matched controls 20% (6/30) (3) After 1 year’s cortisol normalization, hypertension was reversed in 44% (12) Less than 2 years after successful remission, 75% had normalized BP (55)</td>
</tr>
<tr>
<td>IGT</td>
<td>21–64% (12, 14, 22, 53)</td>
<td>18-Year follow-up: posttreatment 4% (2/49); diagnosis 24% (12/49) (14) After 5 years’ cortisol normalization: CD 27% (4/15); BMI-matched controls 27% (8/30) (3)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20–47% (12, 14, 22, 53)</td>
<td>18-Year follow-up: posttreatment 18% (9/49); diagnosis 39% (19/49) (14) After 5 years’ cortisol normalization: CD 33% (5/15); BMI-matched controls 7% (2/30) (3) After 1 year’s cortisol normalization, diabetes was reversed in 40% of patients (12)</td>
</tr>
<tr>
<td>Overweight (BMI 25–30 kg/m²)</td>
<td>21–48% (12, 22, 53)</td>
<td>After 5 years’ cortisol normalization: CD 33% (5/15); sex- and age-matched controls 20% (6/30) (3)</td>
</tr>
<tr>
<td>Obesity (BMI &gt; 30 kg/m²)</td>
<td>32–41% (12, 22, 53)</td>
<td>After 5 years’ cortisol normalization: CD 40% (8/15); 0 in controls (3) After 1 year’s cortisol normalization, 38% were no longer obese (12)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>38–71% (22, 53)</td>
<td>After 5 years’ cortisol normalization, the prevalence was 27% (3)</td>
</tr>
<tr>
<td>Hypercoagulopathy/hemostatic abnormalities</td>
<td>Hemostatic abnormalities (53.6%) (53) Vascular morbidity (10%) (49) VTE (incidence 2.5–3.1 per 1000 persons per year) (57) Adequate prophylaxis with anticoagulants can reverse the prothrombotic state and greatly reduce the risk of postoperative thromboembolic events (49)</td>
<td></td>
</tr>
<tr>
<td>Kidney disease</td>
<td>Nephrolithiasis: 50% (116) Prevalence in patients achieving remission 27% (116) Only partially reversible 2 years after normalization of cortisol levels (67)</td>
<td></td>
</tr>
<tr>
<td>Osteoporosis/compression fractures</td>
<td>Osteoporosis: 38–50% (6, 71) Fractures: 15.8% (71) Prevalence of MD at 3 months: 54%; at 6 months: 36%; at 12 months: 24% (5) About 70% of patients fully recovered from their depression (75)</td>
<td></td>
</tr>
<tr>
<td>Major depression/psychopathology</td>
<td>MDD/MD/MAD: 54–81% (10, 72, 73) Overall psychopathology: 67% (5) Atypical depression: 51.5% (5)</td>
<td></td>
</tr>
<tr>
<td>Cognitive deficits/loss of brain volume</td>
<td>Subjective loss of brain volume: 86% (80) Partially reversible (based on retrospective study in 38 patients only) (80)</td>
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</table>
operative phases. Therefore, prophylaxis is not routinely used in individuals with fasting plasma glucose of

Figure 1 Prevalence of morbidities in patients with CD vs the general population in the USA, 2006. Prevalence rates in the general population are derived from Centers for Disease Control and Prevention (USA) statistics and National Health and Nutrition Examination Survey III findings.

Petropoulos et al. (57) have summarized the literature on the effects of endogenous hypercortisolism on coagulation and fibrinolysis. Venous thromboembolism (VTE) was reported as the cause of death in 0–1.9% of CS patients (57). The incidence of VTE in CD has been reported as 2.5–3.1 per 1000 persons per year (57), whereas the incidence in the general population is 1.0–2.0 per 1000 persons per year (58). A recent retrospective cohort study among 473 Dutch patients with CS showed an incidence of 14.6 pretreatment VTE cases per 1000 persons per year. In addition, it was found that the postoperative risk of VTE (3.4%) in patients with CD is greater than that of patients with nonfunctional pituitary adenomas (0%). Most postoperative VTE occurred between 1 week and 2 months after surgery (59). It is not entirely clear yet how long and to what extent patients remain at risk of VTE after remission. A recent study showed that short-term biochemical remission (i.e. 3 months) induced by medical therapy is not accompanied by normalization of procoagulant and fibrinolytic parameters (60). Manetti et al. (61) observed an improvement in these parameters 1 year after successful surgery, although hemostasis did not completely normalize. Persistence of abdominal obesity may in part maintain activation of the coagulation cascade. Future studies should further examine the time to reversal of the hypercoagulable state after successful treatment of CD. Because exogenous glucocorticoids can influence components of pro- and anticoagulative pathways, the risk of VTE should be evaluated in patients who are chronically treated with supraphysiological glucocorticoid dosages (62).

Before introduction of anticoagulant prophylaxis, 10% of CD patients died due to thromboembolism and 10% had vascular morbidity. Since the introduction of prophylaxis, however, morbidity and mortality due to thromboembolic events were reduced to 6 and 0.4% respectively (49). However, prophylaxis is not routinely applied in all centers. There is a clear need for guidelines on the dose and duration of thromboprophylaxis in patients with CD, both in the pre- and the post-operative phases.

Overweight and obesity Obese and overweight patients with CD were also exposed to hypercortisolism for a longer duration (5.6±3.5 and 5.7±3.9 years respectively) than normal-weight patients (2.1±3.5 years) (22). The prevalence of overweight (defined as a BMI of 25–30 kg/m²) ranged from 21 to 48% (12, 22, 53), but can be reduced after cortisol normalization (3).

A similar pattern is seen in obese patients. However, reversibility of body composition is limited. In a case–control study conducted in Spain, patients whose endogenous hypercortisolism had been controlled for an average of 11 years exhibited higher total fat mass and central obesity than age-adjusted controls. In addition, these patients also expressed an unfavorable adipocytokine profile (increased inflammatory markers and reduced adiponectin), which is implicated in increased coronary heart disease risk and has been hypothesized to be a link between adiposity and increased cardiovascular risk (2).

Insulin resistance, impaired glucose tolerance, and diabetes mellitus Insulin resistance is another important cardiovascular risk factor and glucocorticoids seem to play a key role in its development (3, 12, 63). Insulin resistance is a well-known complication of CD and also seems to persist after biochemical remission (3, 12). Studies demonstrate that even a slight cortisol excess, as in adrenal incidentaloma, could be associated with insulin resistance in the metabolic syndrome (64). The high values of homeostatic model assessment (HOMA) (51) and low values of the insulin sensitivity index (ISI) (64) in patients with CD confirm the decrease in insulin sensitivity in this condition without significant differences between obese, overweight and normal-weight patients, suggesting that the alteration in insulin sensitivity is due not to obesity but to the state of hypercortisolism per se (22). Barahona et al. (51) observed that although patients achieving remission had lower levels of insulin compared with those with active disease, insulin levels in both groups were elevated when compared with population controls (P<0.05). Insulin resistance as measured by HOMA also exhibited this trend. However, patients with complications (diabetes and/or hypertension and/or dyslipidemia) presented a higher BMI than patients without the respective complications. Epidemiological studies have shown a variable prevalence of abnormalities of glucose metabolism: 20–47% of patients suffer from overt diabetes mellitus, whereas impaired glucose tolerance is present in 21–64% of patients (12, 14, 22, 53).

As patients with CD are likely to have impaired glucose tolerance, assessment by an oral glucose tolerance test (OGTT) may have utility in monitoring changes in glucose homeostasis. OGTT is the only means of identifying people with impaired glucose tolerance. The WHO recommends that OGTT should be used in individuals with fasting plasma glucose of
6.1–6.9 mmol/l (110–125 mg/dl) to determine the glucose tolerance status (65).

**Dyslipidemia** The prevalence of dyslipidemia in patients with CD ranges from 38 to 71% in the literature (22, 53). A study by Mancini et al. (22) has shown dyslipidemia to occur less frequently than the other metabolic complications and that it was not correlated to the degree of hypercortisolism or duration of the disease. The majority of patients examined presented with three or more risk factors and a ‘high’ or ‘very high’ global cardiovascular risk, calculated according to WHO/ISI guidelines (22). However, the causative role of cortisol excess for dyslipidemia is not extensively described in the literature and the findings are controversial. In some study populations, the prevalence of hypertriglyceridemia was lower than in BMI-matched controls (12). It is recommended that the prevalence of osteoporosis ranging from 31.6 to 62.9% in women (34). Both overt and subtle endogenous hypercortisolism affect bone, leading to vertebral fractures in up to 70% of patients (16).

**Psychopathology** Studies show that 54–81% of patients with CD meet Diagnostic Statistics Manual (DSM) criteria for major depressive disorder or generalized anxiety disorder (10, 72, 73). Despite remission, many patients exhibit residual symptoms in the first postoperative year or longer. Although the common belief is that depression abates with the ‘cure’ of CD and the correction of hypercortisolism, few studies have prospectively examined the psychological profiles of patients with CD after correction of the hypercortisolemic state. In general, these studies reported that symptoms of depression decreased but were not eliminated after remission in some, but not all, patients (5, 20, 74, 75, 76).

In the study by Dorn et al. (5), however, after remission, overall psychopathology decreased significantly (based on DSM-III criteria) to 54% at 3 months, 36% at 6 months, and 24% at 12 months. Dorn et al. (5) assessed the longitudinal psychological course of patients at 3, 6, and 12 months after surgical correction of hypercortisolism, whether the recovery of the hypothalamic–pituitary–adrenal (HPA) axis was related to psychological recovery, and finally whether psychopathology (as evaluated with a single questionnaire) before or during CD or the duration of CD was related to the occurrence or intensity of psychopathology following remission. The authors observed that the prevalence of atypical depression progressively decreased after correction of hypercortisolism. In addition, the authors reported that having a psychiatric diagnosis after remission of CD was not related to the recovery of the HPA axis. The recovery of the HPA axis did increase from 13.6% at 3 months posttreatment to 54.6% at 12 months. During this time, there was a parallel decrease in the presence of psychiatric diagnoses. However, results of the long-term study by Tiemensma et al. (77) suggest irreversible effects of previous cortisol excess on the central nervous system rather than an effect of pituitary tumors and/or their treatment in general, as CD patients achieving long-term remission showed an increased prevalence of psychopathology and maladaptive personality traits.

**Cognitive impairment** Cognitive deficits were reported in several studies (76, 78, 79) and ranged in severity from mild (29%) to moderate/severe (34%) when English language and other language study results
were compared (79). Mental disturbances can be associated with structural modification of the brain, namely, atrophy or specific cerebral areas. Subjective loss of brain volume has been reported in 86% of patients with CD in a case–control study with four groups: patients with proven CS secondary to CD (n=21) or primary adrenal causes (n=17), along with control groups composed of patients with other (non-ACTH-secreting) sellar tumors (n=18 patients) and normal controls with no sellar tumors (n=20) (80). The normalization of cortisol secretion following remission has been demonstrated to reverse cerebral atrophy, at least partially (80). Forget et al. (81) found persistent cognitive impairment among CD patients in remission, which suggests that prolonged exposure to high levels of glucocorticoids can cause chronic deleterious effects to the cognitive function. In this study, 13 subjects presented with CD were investigated 1 year after surgical treatment to determine the extent to which the effects of hypercortisolism on cognitive function are reversible. The return to normal levels of cortisol following surgical treatment was not accompanied by significant improvement in cognitive performance. Thus, the data suggest that correction of hypercortisolism is not directly correlated with short-term improvement in cognitive function. However, it is noteworthy that there may be a delay of several months or even years from the correction of elevated cortisol levels to the remission of cognitive deficit.

### Outcomes and complications of current treatment options

Surgery is the first-line treatment for CD and, in the hands of an experienced pituitary surgeon, surgical remission can be achieved for 65–100% of patients (37, 82, 83, 84) (Table 3). Remission rates are considerably lower in patients with a nonvisible adenoma, a microadenoma with unfavorable localization (e.g. the parasellar region), or a macroadenoma (27, 35, 37, 85). Comorbidities can also negatively affect postoperative outcomes in neurosurgery: patients with two comorbidities are nearly twice as likely to experience a complication than those with no comorbidities (86). Disease recurrence is more likely in patients with a macroadenoma than patients with a microadenoma, with overall recurrence rates (for all tumor sizes) ranging between 5 and 36% (37, 83, 87).

If remission is not achieved or if patients experience a relapse, a second surgery, radiation therapy, or a combined approach with medical therapy may be utilized. Regarding remission criteria, normalization of urinary free cortisol (UFC) is frequently used as a measure of remission after surgery (23); however, the quality of UFC assays varies widely and the lack of availability of good normative data also poses a problem. Other criteria include normal cortisol suppression after dexamethasone administration and normalization of midnight plasma or salivary cortisol concentrations. Outcomes of subsequent treatments are considerably poorer, which adds to the burden that patients with resistant or recurrent disease bear. Second surgery has far lower success rates (61–73%) (88, 89) than first surgery and bears risks of complications such as hypopituitarism (26, 90).

Radiation therapy controls tumor growth in 80–98% of patients with nonsecreting adenomas and 67–89% for endocrine-active pituitary tumors (91). Control of hypercortisolism in ~43–83% of patients can be achieved within 8 months to 5 years (92, 93, 94). Hypopituitarism is the most common side effect of pituitary irradiation, with an incidence of 13–56% (91). Although bilateral adrenalectomy (BA) offers effective permanent treatment (95–100% achieve disease control (95, 96, 97, 98)), permanent replacement with glucocorticoids and mineralocorticoids is required, with the inherent risks of acute adrenal insufficiency.

### Medical therapy

Adrenal-blocking drugs, including ketoconazole, metyrapone, and mitotane, all competitively inhibit adrenal enzyme activity and decrease cortisol secretion. In addition, the efficacy of agents with other mechanisms of action, such as cabergoline, has been studied in CD. Comparison among these agents is difficult due to the use of varying remission criteria and lack of definitive published data. A wide range of efficacy is reported in the literature due to differing definitions of control. None of the adrenal-blocking agents nor cabergoline has been approved for the treatment of CD and reported outcomes may bear selection bias as they are not derived from randomized clinical trials. All pose significant side effects that limit their broad use. In addition, outcomes from these reports cannot be directly attributed to these medical treatments, as patients in many studies had received other treatments, such as adjunctive radiotherapy.

An effective tumor-targeted medical therapy would be an important advance in the management of CD. In a Phase III clinical trial, pasireotide significantly reduced elevated cortisol levels in patients with CD (99) and 88% of patients at month 6 had some decrease in UFC (100). On the basis of these results, pasireotide has been approved for use in the EU for the treatment of adult patients with CD for whom surgery is not an option or for whom surgery has failed. Pasireotide has a high affinity for somatostatin receptor subtypes sst2 and sst5, the targeting of which may allow for a reduction in cortisol levels and inhibition of ACTH secretion (101). The dopamine D₂ receptor is expressed in >75% of corticotroph pituitary adenomas (102) and its activation leads to inhibition of ACTH secretion. In some patients with a corticotroph tumor expressing the D₂ receptor, the dopamine agonist cabergoline has been
reported to normalize UFC in a subgroup of patients (103). Combination therapy with pasireotide and cabergoline may provide a greater inhibitory effect than with either agent alone (104).

The glucocorticoid receptor antagonist mifepristone has recently been approved by the Food and Drug Administration for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous CS. An uncontrolled, open-label, 24-week multicenter study found that mifepristone decreased HbA1c levels in CS patients with glucose intolerance and was generally well tolerated. Patient cortisol and ACTH levels increased during this study (105).

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Table 3 Reported outcomes of surgery and radiotherapy in patients with CD.

<table>
<thead>
<tr>
<th>Treatment option</th>
<th>Control/remission</th>
<th>Incidence of complications and adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSS (in patients with microadenomas)</td>
<td>Remission: 73–100% (37, 82, 83, 84)</td>
<td>Hypopituitarism: 34% (84)</td>
<td>TSS induces remission in about 80% of patients (minimum of 6 months’ follow-up), the remission rate ranged from 73 to 100% and the recurrence rate from 5 to 13%</td>
</tr>
<tr>
<td></td>
<td>Recurrence: 5–13% (37, 83)</td>
<td>CSF leak: 1.8–13% (83, 84) DI: 5–57% (83, 84)</td>
<td>Results from studies highlighting the differences of outcome by size of adenoma are equivocal</td>
</tr>
<tr>
<td>TSS (in patients with macroadenoma)</td>
<td>Remission: 65–100% (37, 82, 84)</td>
<td>Hypopituitarism: 24% (84)</td>
<td>The odds of failure for repeat TSS is 3.7-fold greater vs initial TSS (89)</td>
</tr>
<tr>
<td></td>
<td>Recurrence: 18–36% (37, 87)</td>
<td>CSF leak: 14% (84)</td>
<td>Can be successful when residual tumor is detectable on MRI (88)</td>
</tr>
<tr>
<td>Repeat surgery</td>
<td>Remission: 61–73% (88, 89)</td>
<td>Hypopituitarism: 50% (88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Recurrence: 9–13% (88, 89)</td>
<td>Pan-hypopituitarism: 7% (89)</td>
<td></td>
</tr>
<tr>
<td>Conventional radiotherapy</td>
<td>Remission: 49–83% (89, 92, 93, 117)</td>
<td>Hypopituitarism: 3–21% (93, 117)</td>
<td>Average (mean or median) time to normalization usually 6–36 months (92, 93, 94)</td>
</tr>
<tr>
<td></td>
<td>Probability of remission as a function of follow-up time: 100% (2 years), 82% (5 years), 72% (7 years), 65% (10 years) (118)</td>
<td>Central hypopituitarism: 20% (93)</td>
<td>Remission usually occurs during first 2 years after irradiation (118)</td>
</tr>
<tr>
<td></td>
<td>Recurrence: 0–11% (93, 117)</td>
<td>i) Prevalence increases to 77% 10 years after irradiation (119)</td>
<td></td>
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<td></td>
<td></td>
<td>ii) Leads to reduced life expectancy, mainly caused by cardiovascular diseases (120)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>iii) Increases risk for vascular mortality by 50% (120)</td>
<td></td>
</tr>
<tr>
<td>SRS, GKRS</td>
<td>Remission: 43–66% (94, 121, 122, 123)</td>
<td>Pan-hypopituitarism: 7.5% (94)</td>
<td>Remission usually occurs within the first 2 years following radiotherapy (123)</td>
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<tr>
<td></td>
<td></td>
<td>Quadrantanopsia: 2% (123)</td>
<td></td>
</tr>
<tr>
<td>Adrenalectomy</td>
<td>95–100% (95, 96, 97, 98)</td>
<td>Operative mortality: 0–3.6% (95, 96, 97, 124, 125, 126)</td>
<td>The proportion of patients presenting corticotroph tumor progression reached 39% and plateaued at 47% after 7 years (124)</td>
</tr>
<tr>
<td></td>
<td>Life-long glucocorticoid and mineralocorticoid replacement therapy, osteoporotic fractures Nelson’s syndrome (NS): i) Expanding pituitary tumor; absence of negative feedback on corticotroph tumor cells by high cortisol levels ii) Progressive cutaneous hyperpigmentation iii) Risk of developing NS after BA is relatively high; 8–46% (117, 127) iv) Presentation time varies from 0.5 to 24 years postoperatively; prophylactic RT of the sellar region after BA may prevent development</td>
<td></td>
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</tr>
</tbody>
</table>

BA, bilateral adrenalectomy; CSF, cerebrospinal fluid; DI, diabetes insipidus; GKRS, gamma knife radiosurgery; NS, Nelson’s syndrome; RT, radiotherapy; SRS, stereotaxic radiosurgery.
Health-related QoL

Chronic exposure to hypercortisolism has a significant impact on HRQoL in CD (Table 4) (1, 20, 81, 106, 107). This impact is mediated through physical and psychological features and social and role-functioning impairments (13, 17, 21, 108). In a patient survey study by Gotch (21), issues that were most often reported by patients were fatigue and weakness (85%), interference in family life and relations with their partners (80%), changes in physical appearance (63%), emotional instability (61%), impaired

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Table 4 Reported health-related QoL in patients with CD.

<table>
<thead>
<tr>
<th>Study frame</th>
<th>Assessment tool</th>
<th>n</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective analysis Follow-up: 1981–1996 (17)</td>
<td>VAS</td>
<td>74</td>
<td>Many of the symptoms experienced by the patients persist even years after therapy. Likewise, the ability to work is not always regained after clinical recovery</td>
</tr>
<tr>
<td>Prospective study (108)</td>
<td>SF-36</td>
<td>42</td>
<td>Impairment in all but one measure was observed compared with population controls and patients with other types of pituitary adenomas</td>
</tr>
<tr>
<td>Single-center, 15-year follow-up study (18)</td>
<td>HADS-UK, WHO-QoL-BREF, GHQ-28, FACT, SAS1 and 2</td>
<td>114</td>
<td>Evidence that patients with CD continue to experience impaired HRQoL in multiple domains of HRQoL, even when they had apparently achieved biochemical remission</td>
</tr>
<tr>
<td>Case–control study (20)</td>
<td>SF-36, MFI-20, NHP, HADS</td>
<td>58</td>
<td>Enduring physical and psychological impairments may affect HRQoL in patients with CD despite long-term biochemical remission. Hypopituitarism was an important predictor of reduced HRQoL</td>
</tr>
<tr>
<td>Case–control and cross-sectional study (111)</td>
<td>SF-36</td>
<td>23</td>
<td>CS is associated with impaired HRQoL, which partially resolves after treatment. At longer-term follow-up, however, there is residual impairment of HRQoL</td>
</tr>
<tr>
<td>Single-center, controlled, prospective case–control study (113)</td>
<td>TPQ, SRT</td>
<td>24</td>
<td>There were no significant differences in personality dimensions as measured by TPQ between patients and controls. However, with regard to psychological distress and HRQoL, patients with CD displayed higher scores on SRT anxiety, depression, and psychotic symptoms</td>
</tr>
<tr>
<td>Retrospective review (128)</td>
<td>SF-12v2</td>
<td>39</td>
<td>Based on a Cushing’s disease-specific questionnaire, the study showed that 89% of patients experienced improvement in symptoms after bilateral adrenalectomy and also improved HRQoL</td>
</tr>
<tr>
<td>Multinational, cross-sectional study (13)</td>
<td>CushingQoL, SF-36</td>
<td>125</td>
<td>A greater impairment of HRQoL in active disease than in patients achieving remission was observed. There was no correlation between CushingQoL score and time elapsed since surgery</td>
</tr>
<tr>
<td>Case–control study (112)</td>
<td>SF-36, MFI-20, NHP, HADS</td>
<td>403, of which CD 58</td>
<td>Compared to population controls, patients with CD reported impairment in physical functioning and experienced increased anxiety. Hypopituitarism negatively influenced multiple aspects of HRQoL</td>
</tr>
</tbody>
</table>

FACT, Functional Assessment of Cancer Therapy; GHQ-28, General Health Questionnaire; HRSD, Hamilton Rating Scale for Depression; HADS, Hospital Anxiety and Depression Scale; MFI, Multidimensional Fatigue Inventory; NHP, Nottingham Health Profile; POMS, Profile of Moods Scale; QoL, quality of life; SADS-LA, Schedule for Affective Disorders and Schizophrenia – Lifetime Version; SAS1 and SAS2, Social Adjustment Scale; SF-36, Short Form Health Survey; SRT, symptom rating test; TPQ, Tridimensional Personality Questionnaire; VAS, visual analogue scale; WHOQoL-BREF, World Health Organization Quality of Life Scale – abbreviated version.

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school/work performance (56%), cognitive problems (49%), depression (32%), and sleeping difficulties (12%).

HRQoL detriment as assessed by the SF-36 for CD patients is notably worse than for population controls and is comparable to the detriment reported for patients with multiple sclerosis (Fig. 2) (109, 110). A prospective study of HRQoL using the SF-36 health survey before and after TSS has demonstrated that active CD is associated with impaired HRQoL (111). Impaired QoL in CD patients partially resolves after successful treatment; however, at long-term follow-up, despite apparent clinical remission, there was still evidence of residual impairment of HRQoL. In a cross-sectional validation study for a new disease-specific HRQoL questionnaire for CS, regression analysis identified elevated UFC as the risk factor associated with impaired HRQoL. This association was also observed with the SF-36, a general HRQoL instrument that was concurrently administered (13).

Studies with longer follow-up suggest that prolonged exposure to high levels of cortisol may cause persistent negative effects. Studies of the long-term impact of remission on HRQoL in patients with CD confirmed that patients still experienced a considerable decrease in QoL with physical and psychosocial impairment, especially in the presence of hypopituitarism, suggesting that both the sequelae of treatment and the direct effects of the disease can contribute to the HRQoL detriment (5, 13, 18, 20).

Hypopituitarism was found to be associated with reduced HRQoL in a study comparing HRQoL among patients with different types of pituitary adenomas. In a multivariate regression model, the presence of hypopituitarism was negatively associated with total HRQoL score as well as multiple subscales, such as general health perception, energy and physical ability, and depression (112). Another study of only CD patients reported that any degree of hypopituitarism was associated with increased anxiety, depression, and worse total HRQoL scores (20).

Because cognitive function is also impaired by hypercortisolism, especially the declarative system, these impairments explain the patients’ demoralization and psychological distress after remission of CD and, consequently, the great impact on HRQoL (1). Sonino et al. (113) evaluated characteristics and QoL in a single-center prospective study in 24 patients with CD and found no differences with regard to personality dimension between patients and controls, but patients with CD displayed significantly higher scores in anxiety, depression, and psychotic symptoms, with a generalized compromised QoL.

**Economic implications of CD**

There were only two studies identified in the literature that attempted to estimate costs associated with CD; these studies indirectly assessed the economic burden of CD (86, 114). Patil et al. (2007) (86) analyzed data from 3525 patients with CD who had undergone TSS, from a representative sample of US hospitals. Rates of complications, duration of hospitalization, hospital charges, and discharges to facilities other than home and death were analyzed. The authors found that only one postoperative complication increased the mean length of stay by 3 days, more than tripled the odds of an adverse outcome, and increased hospital charges by more than one-third. More than 30% of the patients had ≥1 complication. Swearingen et al. (114) analyzed data from a US administrative claims database (Thomson Medstat Marketscan Commercial and Medicare Supplemental Database) for the period 2004–2008, which includes data on hospital admissions, physician visits, emergency room visits, and medication use. Each CD patient was age and gender matched to four nonfunctioning pituitary adenoma (NFPA) patients and 10 population controls. In comparison with NFPA patients and population controls, CD patients incurred significantly higher health care costs for every bucket of health care expenditure, including outpatient, inpatient, emergency room, and pharmacy costs. Total health care costs for CD patients were fourfold greater than that of population controls and twofold greater than that of NFPA patients. In 2008, total health care costs for CD patients were $26,440, compared with $13,708 for NFPA patients and $5,954 for population controls (14, 22, 54, 114). In a subanalysis of surgical patients pre- and post-surgery, total annual costs more than doubled postoperatively compared with preoperatively in the nonremission cohort (from $15,829 to $36,795; P = 0.02). In contrast, in patients whose surgery was successful, outpatient costs decreased significantly from $16,983 to $12,465 (P < 0.01) and there was a trend for reduced total costs (from $28,501 to $19,896, although not statistically significant) (114).

A third study assessed costs of hypopituitarism explicitly from causes other than acromegaly or CD, but it is important as it does raise the question regarding the sequelae of treatment for CD and potential for additional costs (115). This Swedish study found that patients with hypopituitarism incur, on average, nearly double the costs of the general population, primarily due to inpatient care, and they were more likely to draw

![Figure 2 SF-36 results for patients with Cushing's disease, multiple sclerosis, and cancer vs the general population.](https://www.eje-online.org)
disability benefits and have longer periods of work leave than population controls. These studies, particularly the study by Swearingen et al., suggest that the annual costs of CD are considerably higher per capita than for population controls and other pituitary disorders. Decreased working ability and increased sick leave are presumably also present in the long period before the diagnosis of CD is made.

Conclusions

Although CD is a rare disease, the clinical, HRQoL, and economic burden is significant. Several questions still remain, such as what is the association between the duration and severity of hypercortisolism and morbidity and how do these dimensions affect the possibility of morbidity reversibility. The literature suggests that although mortality is elevated in CD, particularly in persistent disease, surgical remission and optimal follow-up can essentially normalize mortality. However, there is also a growing body of evidence that suggests that many risks and morbidity persist, including the risks that determine global cardiovascular risk, which to a large extent determines mortality. These findings can be reconciled through larger studies with longer follow-up, increased awareness, and earlier diagnosis. As second-line treatments are limited and pose considerable risks such as hypopituitarism, new medical treatments targeting the pituitary adenoma are urgently needed to address the persistent unmet medical needs in CD. With the advent of new therapeutic techniques, it is hoped that long-term outcomes will be improved and the burden of CD will be minimized.

Supplementary data

This is linked to the online version of the paper at http://dx.doi.org/10.1530/EJE-11-1095.

Declaration of interest

S J Pulgar was an employee of Novartis during the preparation of this manuscript and is now an employee of GlaxoSmithKline. A Kempel has received consulting fees from Novartis with regard to this manuscript. All other authors have no conflicts of interest.

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References


5 Dorn LD, Burgess ES, Friedman TC, Dubbert B, Gold PW & Chrousos GP. The longitudinal course of psychopathology in Cushing’s syndrome after correction of hypercortisolism. Journal of Clinical Endocrinology and Metabolism 1997 82 912–919. (doi:10.1210/jcem.82.3.3912)


127 Invitti C, Pecori GF, De Martin M & Cavagnini F. Diagnosis and management of Cushing’s syndrome; results of an Italian multicentre study. Study Group of the Italian Society of Endocrinology on the Pathophysiology of the Hypothalamic–Pituitary–Adrenal Axis. *Journal of Clinical Endocrinology and Metabolism* 1999 **84** 440–448. (doi:10.1210/jc.84.2.440)


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