Surgical remission of Cushing’s syndrome reduces cardiovascular risk

M Terzolo1, B Allasino1, A Pia1, G Peraga1, F Daffara1, F Laino1, A Ardito1, A Termine1, P Paccotti1, P Berchialla2, G Migliaretti2 and G Reimondo1

1Internal Medicine I and 2Statistical Unit, Department of Clinical and Biological Sciences, University of Turin, A.O.U. San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Italy

Correspondence should be addressed to G Reimondo
Email giuseppe.reimondo@unito.it

Abstract

Objective: Recent studies have questioned the reversibility of complications of Cushing’s syndrome (CS) after successful surgical treatment. The aim of this study was to assess the outcome of patients with CS who achieved disease remission compared with those patients with persistent hypercortisolism and matched controls.

Design: A retrospective study of 75 patients with CS followed at an academic center.

Methods: Cardiovascular risk profile was evaluated in 51 patients with CS in remission (group 1) and 24 patients with persistent disease (group 2) and compared with 60 controls. Mortality of patients with CS was compared with the background population.

Results: In group 1, the frequency of cardiovascular risk factors dropped after disease remission even if it remained higher at the last follow-up than in the control group. In group 2, the frequency of cardiovascular risk factors remained unchanged during follow-up. The rate of cardiovascular and thromboembolic events was higher in group 2 than in group 1, as was the mortality rate (two deaths in group 1 and nine in group 2; ratio of two SMRs, 0.11; 95% CI, 0.011–0.512). Survival was significantly longer in group 1 than in group 2 (87 months, 80–98 vs 48 months, 38–62; P<0.0001).

Conclusions: Successful surgical treatment of hypercortisolism significantly improves cardiovascular risk and may reduce the mortality rate. Patients with persistent disease have increased morbidity and mortality when compared with patients in remission.

Introduction

Endogenous hypercortisolism may have severe consequences and cause a number of complications, including obesity, hypertension, hyperglycemia, dyslipidemia, and thrombophilia (1, 2, 3, 4). Cushing’s syndrome (CS) is indeed considered as an archetype of the metabolic syndrome (5), as insulin resistance and the accompanying spectrum of clinical features may occur in about two-thirds of patients (1, 2, 6). Thus, it is not surprising that chronic glucocorticoid excess does significantly affect the quality and duration of life (7), primarily for cardiovascular disease causing a two- to fourfold increase in mortality compared with the general population (8, 9, 10, 11, 12, 13). The evidence that CS is associated with an increased mortality calls for an early diagnosis and prompt cure of hypercortisolism (14). However, diagnosis is often delayed because the clinical phenotype of hypercortisolism overlaps that of the metabolic syndrome (1, 3, 4, 15) as the so-called specific Cushingoid features are slight or lacking in many patients, particularly when the entity of cortisol excess is mild (16, 17). This is an issue of particular relevance, as mild CS may be more common than previously thought, especially among patients with type 2 diabetes and metabolic syndrome (18, 19, 20). In addition, recent studies have questioned the reversibility of complications due to hypercortisolism after its surgical treatment (2, 21, 22, 23, 24). These findings...
suggest that an increased cardiovascular risk may persist despite successful treatment of cortisol excess influencing negative health outcomes in patients who have suffered from CS.

The aim of this study was to investigate the outcome of patients with CS of benign etiology after attainment of disease remission compared with patients with persistent hypercortisolism and the background population.

Subjects and methods

Patients

This retrospective study includes and analyzes data of patients suffering from endogenous CS, who have been followed by our institution, a university referral center for endocrine diseases. All these data were retrieved from medical records, from January 1991 to December 2010. Follow-up for this report ended in December 2011. A total of 92 patients with CS of benign etiology were identified. Among them, one patient with pituitary-dependent CS died within a few months from the diagnosis and was excluded, one was on dialysis and was also excluded, while 15 patients were lost to follow-up (Fig. 1). The excluded ones were four men and 13 women, with a median age of 68 years (range, 58–75 years). Etiology of CS was pituitary dependent in 13 cases and adrenal dependent in four cases. The study cohort included 75 patients, of whom 50 (67%) presented with pituitary-dependent CS (Cushing’s disease (CD)), 19 (25%) presented with adrenal-dependent CS (ACS), and six (8%) presented with ectopic ACTH (adrenocorticotropic hormone) syndrome (EAS) caused by a benign neuroendocrine tumor (three differentiated neuroendocrine tumors and three occult EAS). CD was due to a pituitary microadenoma in all but one case. Among the study patients, 51 (68%) achieved remission of hypercortisolism while 24 (32%) had persistent disease (Fig. 1).

The diagnosis of CS was based on clinical features and endocrine workup according to a standard protocol validated at our university center (25). Diagnosis of CS was made in the presence of at least two of the following findings: i) increased daily urinary free cortisol (UFC) excretion; ii) failure to suppress cortisol after 1 mg overnight dexamethasone suppression test (1 mg DST); and iii) elevated midnight serum or salivary cortisol (MSC). Cutoff values of these tests have been reported previously (26). The differential diagnosis of CS among CD, EAS, and ACS was made on the basis of ACTH levels, overnight 8 mg DST (high dose dexamethasone suppression test (HDDST)), corticotropin-releasing hormone stimulation test, and appropriate imaging studies depending on the results of hormonal workup, according to a standard protocol validated at our center (27). Bilateral inferior petrosal sinus sampling for ACTH measurement was carried out in patients with ACTH-dependent CS in whom clinical, biochemical, and radiological studies were discordant or equivocal. Published criteria for central to peripheral ACTH gradients were used to diagnose a non-pituitary source of ACTH (28). None of the patients had been given any drug known to affect the hypothalamic–pituitary–adrenal axis, reporting neither a current nor a previous history of either alcohol abuse or major mood disorders requiring psychiatric assistance. Diagnosis of CD has been confirmed by pathological findings and/or postoperative biochemical evidence of hypoadrenalism, or longstanding normalization of UFC, MSC, and 1 mg DST in all but six patients who did not undergo surgery and in whom diagnosis was based on the results of dynamic tests, imaging, and inferior petrosal sinus sampling (IPSS). Diagnosis of ACS has been histologically confirmed in all but three patients who refused surgery and in whom diagnosis was based on hormonal and imaging data. Diagnosis of EAS has been histologically confirmed in three patients (bronchial neuroendocrine tumor), while the ACTH-secreting tumor remained occult in three patients, in whom the diagnosis was based on the results of dynamic tests and IPSS.

Patients were studied at diagnosis and then they entered a program of proactive follow-up for at least
European Journal of Endocrinology

M Terzolo and others

Effects of surgery in Cushing’s syndrome

Clinical Study

12 months. Duration of hypercortisolism was considered as the period of time between the date of diagnosis and that of surgery, when remission of hypercortisolism was attained, or the date of the last follow-up for patients who did not attain remission. This definition underestimates the actual duration of hypercortisolism, as it does not take into account a variable delay in diagnosis, which is difficult to assess precisely in a retrospective analysis. Remission of CS was defined by resolution of Cushingoid signs along with postoperative adrenal insufficiency or normalization of all hormonal tests including suppression of cortisol <50 nmol/l after a 1 mg DST. Based on the above-mentioned criteria, 51 patients were considered to be in remission at the last follow-up (group 1), while 24 patients had persistent hypercortisolism (group 2). In this study, 60 patients with pituitary incidentaloma were also included as controls. Patients in disease remission (group 1) were younger than either patients with persistent disease (group 2) (39.6±15.6 vs 54.2±16.3 years, P=0.001) or controls (group 3) (39.6±15.6 vs 48.2±14.4 years, P=0.009). The Institutional Review Board approved the study and all patients gave their informed consent in order to take part in the study.

Group 1 (patients in disease remission)

This group included 51 patients in remission at the last follow-up, ten men (20%) and 41 women (80%) aged between 14 and 72 years (median age, 36 years) (Fig. 1). Of them, 33 patients had CD (65%), 15 had ACS (29%), of whom 11 had adrenal adenoma and four had ACTH-independent macronodular adrenal hyperplasia (AIMAH), and three had EAS (6%) sustained by a bronchial benign neuroendocrine tumor. The median duration of follow-up after remission was 56.5 months (range, 12–192 months) and that of hypercortisolism was 6 months (range, 1–67 months). All patients with CD underwent transsphenoidal surgery; nine patients required a second surgery and eight required bilateral adrenalectomy also. Two patients with CD underwent pituitary radiotherapy and only these two patients underwent medical treatment with ketoconazole or cabergoline for a short period before surgical treatment. The median duration of steroid replacement therapy was 12.5 months (range, 1–192 months). Steroid replacement therapy was done with cortisol acetate at a starting dose of 25 mg/m². The dose was then down-titrated based on clinical presentation, biochemistry, and serum cortisol measurement. Among the patients with ACS, 11 required monolateral adrenalectomy and four bilateral adrenalectomy. Patients with EAS underwent resection of the ACTH-secreting tumor.

Group 2 (patients with persistent disease)

This group included 24 patients with active hypercortisolism at the last follow-up, seven men (29%) and 17 women (71%), aged between 26 and 79 years (median age, 60 years) (Fig. 1). Of them, 17 had CD (71%), four had ACS (17%) due to AIMAH, and three had EAS (12%) due to occult ACTH-secreting tumor. The median duration of follow-up (and hypercortisolism) was 24 months (range, 12–201 months). Among those patients with CD, 11 underwent transsphenoidal surgery (surgery was repeated three times in one patient and twice in one), while the remaining patients did not consent to surgery (n=5) or were not fit for surgery (n=1). After surgical failure, eight patients were treated with medical therapy and one with Gamma Knife radiosurgery, while two of them refused further treatment. The six patients with CD who did not undergo surgery were treated with ketoconazole that was discontinued in five patients for unwanted effects. Patients with ACS refused to undergo bilateral adrenalectomy (monolateral adrenalectomy was performed in one patient) and two of them were treated with ketoconazole. The three patients with occult EAS underwent medical therapy (ketoconazole plus somatostatin analog).

Group 3 (control subjects)

This group included 60 patients with non-functioning pituitary microadenoma discovered serendipitously (pituitary incidentaloma) referred to the outpatient clinic of our institution during the period of 2000–2010. They underwent magnetic resonance imaging for headache or vertigo. Pituitary function was normal in these patients who served as controls to determine hypertension, diabetes, and obesity frequency in a background population. They were 15 men (25%) and 45 women (75%), aged between 18 and 80 years (median age, 49 years).

Study protocol

Clinical evaluation ▶ For all subjects, weight, height, BMI, systolic blood pressure (SBP), and diastolic blood pressure (DBP) were evaluated. A BMI of 25–30 kg/m² was considered as an index of overweight and a BMI above 30 kg/m² was considered as an index of obesity (29). The waist was measured as the minimum abdominal circumference between the xiphoid process and the umbilicus;
waist circumference above 88 cm in women and 102 cm in men defined central obesity (30, 31). According to the ESH and ESC 2007 guidelines (32), blood pressure was measured in the non-dominant arm, with subjects in a relaxed sitting position, using a mercury sphygmomanometer placed at heart level; the average of three measurements was calculated. Hypertension was diagnosed when SBP values were ≥ 140 mmHg and/or DBP values ≥ 90 mmHg, or whether anti-hypertensive treatment was instituted and graded according to the ESH and ESC 2007 guidelines (32).

Cardiovascular events, defined as myocardial infarction, unstable angina, ischemic stroke, transient ischemic attack, or other arterial thromboembolic events, were ascertained by reviewing patients’ history, discharge summaries, and source documents; the complementary documentation was requested if necessary. Venous thromboembolic events, defined as deep vein thrombosis or pulmonary embolism, were ascertained using the same method. Smoking status was defined as positive if patients were current or former smokers, while only occasional consumption of alcoholic beverages was reported in some patients.

Biochemical evaluation ► Fasting glucose, triglycerides, and total, LDL, and HDL cholesterol were measured by standard procedures. Diabetes mellitus was diagnosed when fasting blood glucose levels were 7 mmol/l or greater in two consecutive determinations or at least 11.1 mmol/l 2 h after an oral glucose load. Impaired fasting glucose was diagnosed when fasting glucose level was between 6.1 and 7 mmol/l in at least two samples collected on different days (33, 34). Hypertriglyceridemia was diagnosed when triglyceride levels were above 1.69 mmol/l, whereas hypercholesterolemia was diagnosed when LDL cholesterol levels were above 4.13 mmol/l, and low HDL when HDL cholesterol levels were below 1.03 mmol/l (30, 31).

Hormones were measured in-house with commercially available reagents. All samples for an individual subject were batched and run in duplicate. Serum, salivary, and urinary cortisol were measured using commercially available RIA kits. Plasma ACTH was measured by IRMA using commercially available kits. Intra- and inter-assay coefficient of variation values for all hormone variables were <10 and 15% respectively.

Clinical, biochemical, and hormonal assessments were performed at diagnosis and every 6 months during follow-up. Death certificates and medical records were verified for death causes.

Statistical analyses

Descriptive analyses were performed for categorical and continuous data. When data are expressed as percent values, these refer to valid cases. The Kolmogorov–Smirnov test was used to assess the normal distribution of continuous variables. Parametric two-tailed Student’s t-test and the non-parametric Mann–Whitney U-test were used to analyze the differences for normally and non-normally distributed continuous variables respectively. The χ² and Fisher’s exact test were used to analyze the differences for categorical variables. The levels of statistical significance were set at p < 0.05.

Standardized mortality ratios (SMRs) and relative 95% CIs were calculated for groups 1 and 2 using mortality data of the general population of our region, Piedmont counting about 4.5 million inhabitants, as reference (Banca Dati Demografica Evolutiva – Regione Piemonte, http://www.regione.piemonte.it/stat/bdde/info/principi.htm). In order to compare the mortality between groups, the ratio of the two SMRs (RSMRs) and relative 95% CI were computed (35).

Survival analysis was performed using the Kaplan–Meier curves and the relative log-rank tests. A Cox model was carried out to adjust the results for the principal confounding factors.

All statistical analyses were operated using the Stata Statistical Software (StataCorp. Statistical Software, Release 7.0, College Station, TX, USA: Stata Corporation, 2001).

Results

Group 1 (disease remission)

Clinical characteristics of patients either at diagnosis or at the time of last follow-up are given in Table 1. In this group, one deep vein thrombosis and three cardiovascular events (one unstable angina requiring percutaneous transluminal coronary angioplasty and two myocardial infarctions) occurred before the diagnosis of CS. Furthermore, one patient had deep vein thrombosis while awaiting surgery, whereas one stroke and one pulmonary embolism were recorded in the early postoperative period. After remission, one patient had myocardial infarction and one had pulmonary embolism. Two patients died from colorectal and gallbladder cancer respectively and ten patients (19.6%) developed hypopituitarism. Patients with pituitary deficiencies underwent hormone replacement therapy according to the existing protocols available at the time. All patients...
had thyroid-stimulating hormone (TSH) deficiency and were put on 75–100 μg/day l-thyroxine (l-T₄), two men with hypogonadism were administered 250 mg testosterone enanthate i.m. every 2 weeks, and two women were on transdermal estrogen plus oral progesterone. Moreover, five patients were put on recombinant growth hormone replacement therapy at doses ranging from 0.02 to 0.05 mg/kg per week. None of the patients developed clinical or biochemical signs of under- or over-replacement.

**Group 2 (active disease)**

Clinical characteristics of patients either at diagnosis or at the time of last follow-up are given in Tables 1 and 2. In this group, one cardiovascular event and one thromboembolic venous event were observed before the diagnosis. During follow-up, four myocardial infarctions, one stroke, one deep vein thrombosis, and one pulmonary embolism were observed. Nine patients (37%) died, of whom four from cardiovascular events, three from sepsis, and two from malignancies. Three patients who underwent pituitary surgery developed TSH deficiency (14%) and were put on 75–125 mg/day L-T₄. Primary hypogonadism was diagnosed in two men who were treated with testosterone replacement therapy (250 mg testosterone enanthate i.m. every 2 weeks).

**Changes in cardiovascular risk factors and mortality**

In group 1, the frequency of all cardiovascular risk factors dropped significantly after disease remission and the percentage of patients achieving target levels for blood pressure and HbA₁c increased remarkably (Table 1). However, the frequency of diabetes, central obesity, and dyslipidemia at the last follow-up remained higher than in the control group (Table 1). In group 2, the frequency of cardiovascular risk factors did not change, or increased, from baseline to the last follow-up, remaining greater than that in control groups (Table 1). The percentage of patients achieving target levels for blood pressure and HbA₁c did not change remarkably during follow-up (Table 1).

The rate of cardiovascular and thromboembolic events during follow-up was higher in group 2 than in group 1 (29.2 vs 3.9%; \(P=0.006\)), notwithstanding that duration of follow-up was longer for subjects in group 1. Death was observed in nine patients (37%) of group 2 (SMR = 2.56; 95% CI, 0.76–3.06), of whom seven died from causes possibly related to cortisol excess, and in two patients (4%) of group 1 (SMR = 0.28; 95% CI, 0.13–2.22) for unrelated causes. Assessment of the ratio of the
two SMRs confirmed the reduced mortality risk in patients attaining disease remission (RSMR = 0.11; 95% CI, 0.011–0.512). The survival analysis demonstrated a median survival of 87 months (95% CI, 80–98 months) in group 1 and 48 months (95% CI, 38–62 months) in group 2. The Kaplan–Meier curves showed a difference between groups for all follow-up time, with a survival probability at the end of follow-up of 75% in group 1 and 48% in group 2 (log-rank test $Z = 17.96$, $P < 0.0001$; Fig. 2). The results of the mortality ratio and the survival probability continue to show a statistically significant difference between the groups after adjustment for age and sex.

**Discussion**

Chronic hypercortisolism causes a number of associated features, such as hypertension, central obesity, hyperglycemia, dyslipidemia, and thrombophilia, which determine an elevated cardiovascular risk (1). This study confirms that central obesity and hypertension are the most frequently observed complications, being found in 82 and 63% of patients at diagnosis respectively. In our cohort, hypertension was usually slight to moderate, but often resistant to treatment, as only 44% of patients had blood pressure at target. Dyslipidemia was also common, presenting as reduced HDL cholesterol and mixed dyslipidemia in most cases. Overt diabetes was found in 27% of patients with target Hba1c levels attained in about one-third only. These observations fit completely with the clinical presentation reported by ERCUSYN (European Register on Cushing’s Syndrome), a large European database including 481 patients of different etiologies (36). The clustering of multiple cardiovascular risk factors observed in the majority of our patients, as is usual for CS (2), may confer a high probability of future cardiovascular events. However, in CS, the risk profile is not explained completely by the conventional risk factors but also by disease-specific factors that are still inadequately defined and partly related to a hypercoagulable state (37, 38, 39). Interestingly, these risk factors reverted following remission of hypercortisolism in a significant number of patients; thus, on average, surgical cure was able to abate significantly the cardiovascular risk of patients with CS. Conversely, in patients with persistently active CS, the overall cardiovascular risk remains unchanged. Furthermore, a lower frequency of cardiovascular and venous thromboembolic events was recorded in patients who underwent remission compared with those patients with persistently active disease, as a clear demonstration of

**Table 2** Characteristics of patients who remained with active disease at the last follow-up.

<table>
<thead>
<tr>
<th>No.</th>
<th>Etiology</th>
<th>Medical treatment</th>
<th>1 mg DST (nmol/l)</th>
<th>UFC (nmol/24 h)</th>
<th>ACTH (pmol/l)</th>
<th>MSC (nmol/l)</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EAS</td>
<td>KC + SSRa</td>
<td>906</td>
<td>5500</td>
<td>14</td>
<td>150</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>CD</td>
<td>KC</td>
<td>201</td>
<td>607</td>
<td>12</td>
<td>317</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>CD</td>
<td>KC</td>
<td>176</td>
<td>243</td>
<td>11</td>
<td>237</td>
<td>No</td>
</tr>
<tr>
<td>4</td>
<td>CD</td>
<td>KC</td>
<td>524</td>
<td>299</td>
<td>14</td>
<td>772</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>CD</td>
<td>KC</td>
<td>160</td>
<td>359</td>
<td>5</td>
<td>207</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>AIMAH</td>
<td>KC</td>
<td>599</td>
<td>657</td>
<td>&lt;1</td>
<td>155</td>
<td>Yes</td>
</tr>
<tr>
<td>7</td>
<td>CD</td>
<td>No</td>
<td>174</td>
<td>607</td>
<td>6</td>
<td>168</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>CD</td>
<td>KC</td>
<td>229</td>
<td>698</td>
<td>8</td>
<td>210</td>
<td>No</td>
</tr>
<tr>
<td>9</td>
<td>CD</td>
<td>No</td>
<td>342</td>
<td>925</td>
<td>9</td>
<td>281</td>
<td>No</td>
</tr>
<tr>
<td>10</td>
<td>EAS</td>
<td>KC + SSRa</td>
<td>450</td>
<td>792</td>
<td>5</td>
<td>441</td>
<td>Yes</td>
</tr>
<tr>
<td>11</td>
<td>AIMAH</td>
<td>KC</td>
<td>94</td>
<td>348</td>
<td>2</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>12</td>
<td>AIMAH</td>
<td>KC</td>
<td>337</td>
<td>1200</td>
<td>&lt;1</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>13</td>
<td>CD</td>
<td>KC</td>
<td>–</td>
<td>662</td>
<td>4</td>
<td>442</td>
<td>No</td>
</tr>
<tr>
<td>14</td>
<td>EAS</td>
<td>KC + SSRa</td>
<td>$&gt;1380$</td>
<td>1611</td>
<td>24</td>
<td>$&gt;1380$</td>
<td>Yes</td>
</tr>
<tr>
<td>15</td>
<td>AIMAH</td>
<td>No</td>
<td>580</td>
<td>1780</td>
<td>&lt;1</td>
<td>497</td>
<td>No</td>
</tr>
<tr>
<td>16</td>
<td>CD</td>
<td>KC</td>
<td>–</td>
<td>336</td>
<td>12</td>
<td>441</td>
<td>No</td>
</tr>
<tr>
<td>17</td>
<td>CD</td>
<td>No</td>
<td>–</td>
<td>905</td>
<td>3</td>
<td>773</td>
<td>Yes</td>
</tr>
<tr>
<td>18</td>
<td>CD</td>
<td>KC</td>
<td>364</td>
<td>679</td>
<td>12</td>
<td>–</td>
<td>Yes</td>
</tr>
<tr>
<td>19</td>
<td>CD</td>
<td>No</td>
<td>171</td>
<td>–</td>
<td>8</td>
<td>94</td>
<td>No</td>
</tr>
<tr>
<td>20</td>
<td>CD</td>
<td>No</td>
<td>414</td>
<td>831</td>
<td>10</td>
<td>944</td>
<td>Yes</td>
</tr>
<tr>
<td>21</td>
<td>CD</td>
<td>No</td>
<td>237</td>
<td>1131</td>
<td>8</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>22</td>
<td>CD</td>
<td>No</td>
<td>130</td>
<td>1018</td>
<td>11</td>
<td>902</td>
<td>Yes</td>
</tr>
<tr>
<td>23</td>
<td>CD</td>
<td>KC</td>
<td>221</td>
<td>477</td>
<td>5</td>
<td>–</td>
<td>No</td>
</tr>
<tr>
<td>24</td>
<td>CD</td>
<td>No</td>
<td>152</td>
<td>960</td>
<td>5</td>
<td>–</td>
<td>No</td>
</tr>
</tbody>
</table>

MSC, midnight serum cortisol; KC, ketoconazole; SSRa, somatostatin analog. Normal values are 1 mg DST, <50 nmol/l; UFC, 414 nmol/24 h; ACTH, 1.1–13.2 pmol/l; and MSC, <207 nmol/l.
benefit of resolved hypercortisolism. These findings are consistent with a cortisol-induced activation of coagulation and demonstrate the beneficial effects that can be attained with the elimination of hypercortisolism (2, 37, 38, 39, 40). However, our data confirm that the risk of venous thromboembolic events is not limited to the early postoperative period (3).

In our cohort, the benefits of surgery were more apparent than reported previously in two series of 25 and 29 patients, respectively, assessed 1 year following remission (22, 24). We observed normalization of body weight, blood pressure, and lipid levels in higher percentages of cases, whereas figures for diabetes were similar. It is possible that a progressive improvement in the metabolic profile may develop with a longer follow-up after resolution of hypercortisolism (41), although there are studies showing that cardiovascular risk remains high after many years (7, 13, 21). Improvement may require time particularly in patients given postoperative replacement therapy. The duration of glucocorticoid replacement therapy might be long (the median was 12.5 months in our cohort) and some patients in the previous series were still on replacement therapy at the time of assessment (22, 24). This condition may contribute to the residual cardiovascular risk, as it is known that conventional glucocorticoid replacement therapy may induce metabolic alterations in patients with hypopituitarism, even if it has received scarce attention (42).

Some patients refused to undergo surgical treatment although it has been strongly recommended for all of them, in particular when bilateral adrenalectomy was considered (i.e. in case of AIMAH). An incomplete compliance with surgical recommendations has already been observed. Only 66% of patients with CD studied by Yaneva et al. (43) underwent transphenoidal surgery (TSS) as first-line treatment, and 36% of patients with AIMAH refused to undergo surgery.

Other factors predicting a worse outcome after surgery are the use of pituitary radiotherapy, which is a known risk factor for mortality in patients with pituitary tumors (44), and development of pituitary hormone deficiencies, which also portends an increased mortality. Treatment of hypopituitarism is a major clinical problem and replacement therapies may worsen the cardiovascular risk profile per se (42). In our cohort, pituitary radiotherapy was rarely used and pituitary deficiency was less frequently observed than in previous series (13, 22, 24). The incidence/frequency of hormone deficiencies was comparable between patients in remission and those with persistent disease, as was the modality of replacement therapy. The number of patients is too small to assess the contribution of replacement therapies to a patient’s outcome. It is pertinent to consider that studies showing persistence of metabolic and cardiovascular damage have included only patients with pituitary-dependent CS (13, 22, 23) and, as Giordano et al. (24) clearly pointed out, such patients may be characterized by a less favorable outcome than patients with cortisol-secreting adrenal adenoma for the above-mentioned considerations.

After normalization of cortisol excess, all the risk factors returned to a level comparable to control subjects, apart from obesity and triglyceridemia (which may itself relate directly to central obesity), as observed previously (23, 24, 41). The comparison with a control group including patients who had to seek medical advice is a more appropriate match than normal subjects, to avoid the healthier comparator bias, and strengthens the value of observing a residual cardiovascular risk. Although analyses have been adjusted for the age difference, we disclose younger age as a limit for group 1 patients. Obviously, older age implies a higher risk of death and may be associated with a reduced probability to get into remission (13, 43, 45). In our study, patients with

![Figure 2](https://www.eje-online.org)

**Figure 2**

Survival curves of the two groups of patients with Cushing’s syndrome. The dashed line represents patients in remission, while the solid line represents patients with active disease.
persistent disease showed an increased mortality when compared with patients in remission, whose mortality rate was comparable to the reference population, despite the fact that their cardiovascular risk was not completely normalized following resolution of hypercortisolism. However, we should be cautious concluding that successful treatment of hypercortisolism restores the mortality risk to the level of the reference population. In this case, a longer follow-up may be needed to unmask a slight increase in the mortality rate due to residual cardiovascular risk. Usually previous studies with longer follow-up date back to the 1960s or 1970s, when treatment of hypercortisolism was much different, particularly for the frequent use of pituitary radiotherapy, which is an independent predictor of morbidity and mortality (44).

The issue of whether cure of CS may reset the excess mortality associated with the condition at levels observed in the background population remains controversial. A Danish survey showed that a higher mortality rate is confined to patients in whom cure was not achieved, whereas in patients free of disease it is comparable with the general population (8). In addition, a Dutch study confirmed a significant increase in the SMR only in patients with CD and persistent disease (12). By contrast, a survey in New Zealand showed that chronic cortisol excess is associated with an excess mortality notwithstanding the large number of patients who achieved cure during follow-up (11). A single-center study in the UK confirmed that the higher death risk of CD does not completely revert to the normal level after resolution of hypercortisolism. However, patients with disease remission had a far better outcome than those with persistence of hypercortisolism (10). A recent contribution to this conflicting topic is a population-based study demonstrating that successful surgical treatment does not normalize cardiovascular and mortality risk in a cohort of operated patients only (13).

This existing discrepancy may be explained by a number of factors, such as a small number of observed deaths, variable duration of follow-up, heterogeneous inclusion criteria (i.e. selection of patients with CD only), different modalities of data extraction (national registries, institutional records, etc.), and variable, and often unclear, definition of remission. A recent meta-analysis has concluded that patients with CD in remission do not appear to have an increased mortality than the reference population, although the statistical power of this analysis was limited (46).

The strengths of our study are the inclusion of all patients with CS followed proactively at a single center, with a clear definition of disease remission and careful recording of cardiovascular and thromboembolic events. We think that population-based studies have the advantage of a larger series but information on biochemical data and cure after surgery may not be as detailed as in reports of monocentric cohorts. However, we recognize the limits of a retrospective analysis of a small cohort size including different etiologies of CS. In this real life setting, the two groups presented different ages (in favor of a possible increased cardiovascular risk in patients with persistent CS) and follow-up, which does not influence the results, as a greater number of cardiovascular events and deaths occurred in the group of patients with a shorter follow-up.

To conclude, our study shows that resolution of hypercortisolism induces a significant improvement in a number of cardiovascular risk factors, such as hypertension, diabetes, obesity, and dyslipidemia. However, these conditions remain more evident when compared with control subjects in agreement with the concept of a residual cardiovascular risk after disease remission. These findings do not downplay the importance of attaining cure as quickly as possible and by no means make an argument against surgery, as successful surgical treatment of hypercortisolism may reduce the mortality rate in our series. However, our study cannot demonstrate that mortality after cure is comparable to that of the reference population.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References


Received 4 July 2013
Revised version received 11 April 2014
Accepted 30 April 2014