

Review Article

Persistent Comorbidities in Cushing's Syndrome after Endocrine Cure

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It was assumed that resolution of hypercortisolism in Cushing syndrome (CS) was followed by normalization of morbidity; however, in the last decade evidence is accumulating that patients with cured CS still have increased morbidity and mortality after the biochemical control of hypercortisolism. Patients with CS have an increased cardiovascular and metabolic risk and persistent accumulation of central fat, with an unfavorable adipokine profile, not only during the active phase of the disease but also long after biochemical remission. Clinical management should be particularly careful in identifying global cardiovascular risk, as a primary goal during the followup of these patients, aimed at improving global vascular morbidity. Moreover bone mass is reduced not only due to the endogenous hypercortisolism but also due to duration and dose of exogenous glucocorticoid (GC) replacement therapy after surgery. Thus, therapy in operated patients with inhibition of the hypothalamic-pituitary-adrenal axis should be reduced to the lowest dose and duration possible. Specific treatments should be considered in patients with decreased bone mass, aimed at reducing the increased fracture incidence. Finally, cognitive and health related quality of life impairments, described in active disease, are still abnormal after endocrine cure. Thus, residual morbidity persists in cured CS, suggesting irreversibility of GC-induced phenomena, typical of chronic hypercortisolism.

1. Introduction

1.1. Classification and Epidemiology of Cushing's Syndrome.

Cushing's syndrome (CS) results from chronic exposure to an excess of cortisol produced by the adrenal cortex. Cortisol (a glucocorticoid hormone) is naturally produced by the adrenal glands in response to stress, through the hypothalamic-pituitary-adrenal axis (HPA). Cortisol actions on each tissue are summarized in Figure 1.

CS is caused by excess ACTH production (80–85%), usually by a pituitary corticotroph adenoma (called Cushing's disease (CD)), less frequently by an extrapituitary tumor (ectopic ACTH syndrome), or very rarely by a tumor secreting CRH (ectopic CRH syndrome). CS can also be ACTH-independent (15–20%) when it results from excess secretion of cortisol by unilateral adrenocortical tumors, either benign or malignant or by bilateral adrenal hyperplasia or dysplasia [1, 2]. The incidence of Cushing's syndrome ranges from 0.7 to 2.4 per million-population per year [3]. New data however

suggest that CS is more common than previously thought [4, 5]. It is 3–8 times more frequent in women than in men [4].

In screening studies of obese patients with type 2 diabetes, reported prevalence of CS is between 2% and 5% [6]. Moreover, CS may be also present in adrenal incidentalomas [3].

1.2. Systemic Effects of Chronic Hypercortisolism and Increased Morbidity and Mortality in Cushing's Syndrome.

CS is associated with severe morbidities and increased mortality, due to systemic complications. These include central obesity with a "moon" face and relative limb atrophy, increased fat mass, reduced bone and lean body mass, excessive fatigue, purple striae, easy bruising and skin ulceration, hirsutism, hypogonadism, and decreased libido. Additionally, hypertension, insulin resistance and/or diabetes mellitus, dyslipidemia, prothrombotic state, vascular disease, atherosclerosis with

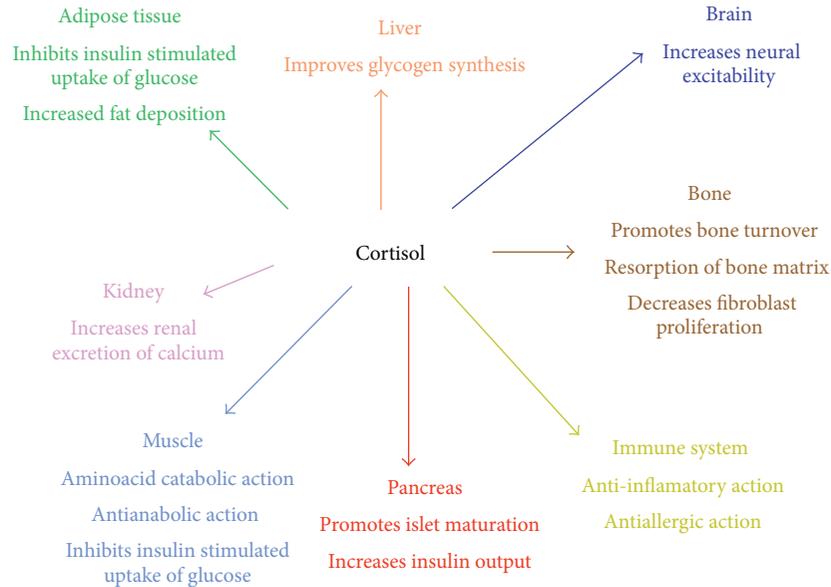


FIGURE 1: Cortisol actions on each tissue.

increased cardiovascular risk in parallel with an acquired metabolic syndrome, depression, loss of brain volume, cognitive decline, and impaired health-related quality of life—HRQoL—may occur [7].

CS patients have an increased cardiovascular and metabolic risk and persistent accumulation of central fat, with an unfavorable adipokine profile.

In women, masculinizing effects such as hypertrichosis, breast atrophy, voice changes, and other signs of virilism are noted. Cessation of linear growth is characteristic in children.

Patients with CS have a mortality rate four times higher than age- and gender-matched subjects, due to complications directly and/or indirectly correlated with glucocorticoid (GC) excess. Therefore, the primary goal in the prevention and treatment of complications is correction of hypercortisolism as soon as possible. For this reason the early diagnosis is the first therapy.

No specific data are available on menstrual irregularities, dermatological manifestations, and effects on immune system after endocrine cure; it seems that there is a recovery of these comorbidities. Moreover, the reappearance of menstrual irregularities after a long period of cure could be considered as a sign of relapse.

The menstrual irregularity in Cushing's disease appears to be the result of hypercortisolemic inhibition of gonadotropin release acting at a hypothalamic level, rather than raised circulating androgen levels [8].

Prevalence of Cushing's syndrome (CS) in patients presenting with hirsutism is not well known; however, a recent study demonstrated that a routine screening for CS in patients with a referral diagnosis of hirsutism is not required; this should be limited to patients who have accompanying clinical signs and symptoms of hypercortisolism [9]. The study included 105 patients with the complaint of hirsutism; all the patients had suppressed cortisol levels following low-dose

dexamethasone administration excluding CS [9], thus not justifying the screening.

1.3. Management of Cushing's Syndrome. Surgery (pituitary adenectomy, adrenalectomy, or excision of the ectopic source of ACTH) can control hypercortisolism in up to 90% of patients in experienced hands and is often followed by a period of inhibition of the adrenal axis, which requires substitution therapy with GC for months or years [10]. The goal of treatment in CD is the complete resection of the pituitary adenoma with correction of hypercortisolism without inducing permanent pituitary deficiencies.

Control of hypercortisolism may be attempted with medical therapy, when surgery is not successful or cannot be used, as it often occurs with ectopic adrenocorticotropic hormone (ACTH) or metastatic adrenal carcinoma. Medical therapy uses drugs that inhibit adrenal cortisol synthesis (mainly ketoconazole or metyrapone) or pituitary ACTH secretion (cabergoline, pasireotide). However, medication failures are common, and adrenalectomy may be indicated in ACTH-mediated Cushing's syndrome. Pituitary radiation may be also useful if surgery fails, in the case of CD.

The prognosis is mainly affected by difficulties in diagnosis and treatment of the disease, which remain a considerable challenge.

1.4. Definition of "Cure" in Cushing's Syndrome. There is still no widespread agreement regarding the definition of cure of CS after surgery. A very low serum cortisol early after surgery seems to be the best index of remission. Dynamic tests cannot predict recurrence in a given individual, although they may suggest increased or decreased risk [1].

Most series from major centers quote remission rates of 70–80%, defining remission as a series of normal postoperative cortisol levels, either as a mean of serial serum cortisol

measurements, obtained throughout the day, between 5.4 and 10.8 $\mu\text{g/dL}$ (150–300 nmol/liter), or as a urinary free cortisol (UFC) in the normal range, associated with resolution of clinical stigmata [1]. However, the long-term followup of such patients shows a significant incidence of recurrence (25% at 10 years) [11–13]. Very low serum cortisol $<1.8 \mu\text{g/dL}$ (50 nmol/liter at 9.00 h) within 2 weeks of surgery is probably the best index of remission, but even when this is the case, late relapses have occurred [14, 15]. Cortisol is usually measured 5–14 days after surgery and at least 24 h after the last dose of hydrocortisone [16] but may take considerably longer to normalize [17]. With the criterion of 1.8 $\mu\text{g/dL}$ of circulating cortisol, surgical remission rate is only 40–65% even in the most experienced hands [1].

1.5. Subclinical Hypercortisolism. Subclinical hypercortisolism (SH) is defined as a status of altered hypothalamic pituitary—adrenal (HPA) axis secretion in the absence of the classical signs or symptoms of an overt cortisol excess [18, 19].

In the last few years, SH became of growing interest, firstly because of its high prevalence, which is thought to be between 0.2 and 2.0% [20]. Indeed, SH is found in 5–30% of patients with incidentally discovered adrenal masses [20]. Secondly, several evidences suggest that SH may lead to long-term consequences of cortisol excess (i.e., diabetes, hypertension, and osteoporosis) [21–25] which may improve after the recovery [3, 26, 27]. However, the correct diagnosis of SH is still a challenge for clinicians [3, 28]. The difficulties are related to the lack of specific signs and symptoms of glucocorticoid excess in these patients and, consequently, of a clinical “gold standard” for the diagnosis. Moreover, the reliability of the commonly used parameters of cortisol secretion in the condition of a subtle glucocorticoid excess is lower than in the overt form of endogenous hypercortisolism (Cushing’s syndrome).

Recently, a multicentric study on long-term followup in adrenal incidentalomas demonstrated that 8.2% of the patients developed SH over time, the risk being particularly increased in patients with an adenoma size $>2.4 \text{ cm}$ [29]. The incidence of cardiovascular events (CVEs) was also higher in patients with SH, regardless of age, the presence of type 2 diabetes mellitus, and the duration of the followup. The authors concluded that the increased risk of incident CVEs has to be taken into account in addressing the treatment of choice [29].

2. Effects of Chronic Hypercortisolism on the Cardiovascular System

2.1. Hypertension. Corticosteroids are critically involved in blood pressure regulation [30] and explain why hypertension is a feature of CS, determining an increase in cardiovascular events. Patients with CD have been shown to lack nocturnal blood pressure dipping and present abnormal heart rate values which do not resolve after short-term remission of hypercortisolism and only partially improve in the long run, both conferring additional cardiovascular risk [31]. Moreover, after control of CS, hypertension persists in approximately 30%

of patients; for this reason the routine detection of blood pressure is useful to early verify the persistence [32].

The exact mechanism by which GC elevates blood pressure appears to be multifactorial, involving increased responsiveness to vasoconstrictors and decreased vasodilator production. Nitric oxide, a vasodilator that plays a key role in blood pressure regulation, may be reduced after GC exposure, contributing to hypertension [33].

Currently available antihypertensive drugs are all indicated in CS patients, with no special indications due to the syndrome.

2.2. Atherosclerosis and Endothelial Dysfunction. Increased atherosclerosis may contribute to the increased rates of cardiovascular morbidity and mortality in patients with glucocorticoid excess. Cortisol favors atherosclerosis, through dyslipidemia, increased visceral fat, hypertension, increased insulin resistance, and the development of reduced glucose tolerance which may result in diabetes mellitus. Endothelial dysfunction is the initiating event for atherosclerosis and may be assessed by flow-mediated dilatation (FMD) of the brachial artery. Recent studies have demonstrated an impairment of endothelium-dependent FMD in CS compared to controls. Assessment of endothelial function may identify high-risk individuals early, allow therapy to reduce or retard endothelial dysfunction to be started, and may lead to decreased cardiovascular morbidity and mortality in these patients with CS [34].

More severe atherosclerotic damage in CS compared to a population matched for similar cardiovascular risk factors has been demonstrated, probably related to multiple effects of long-term cortisol exposure on metabolism at vascular and endothelial sites [35]. Elevated blood endothelin-1 levels and osteoprotegerin levels also appear to be associated with coronary risk in these patients, with a role in the pathogenesis of an early and accelerated atherosclerosis development [36, 37].

It has been also demonstrated that hyperhomocysteinemia and reduced serum folate concentrations are associated with active hypercortisolism, whereas patients in remission may have homocysteine concentrations comparable to healthy subjects [38]. Low serum folate concentrations do not fully account for the increase in homocysteine levels that may be a key to the prothrombotic state and increased cardiovascular risk of CS [38].

Hypertrophic remodelling in subcutaneous small resistance arteries has also been described in CS, probably as a consequence of growth-promoting properties of circulating cortisol and/or increased vascular oxidative stress [39].

Recently it has been demonstrated that increased coronary calcifications and noncalcified coronary plaque volumes are present in patients with active hypercortisolism [40]. This was a prospective case-control study where Agatston scores (a measure of calcified plaque and noncalcified coronary plaque volume) were quantified using a multidetector CT (MDCT) coronary angiogram scan. The paper aimed at evaluating the role of atherosclerosis in the cardiovascular risk of these

patients. However these were preliminary data on fifteen consecutive patients.

The prevalence of coronary artery disease has been also evaluated in CS patients after long-term remission using MDCT coronary angiogram scan demonstrating that patients in remission of hypercortisolism (for a mean duration of 11 years) are still at high risk for cardiovascular disease, especially women and younger patients [41]. Thus, increased cardiovascular risk persists in CS despite remission of hypercortisolism. After these observations, longitudinal studies are now needed to investigate the implications of these coronary abnormalities further in cured CS patients and to determine the effect of aggressive medical therapy and lifestyle modification for these individuals with MDCT-identified coronary artery disease.

2.3. Coagulopathies (Prothrombotic State). In patients with CS doubling of risk was reported for venous thromboembolism (VTE) not provoked by surgery, whereas the risk of postoperative VTE varied between 0 and 5.6%, with one outlier of 20%. VTE was described as the cause of death in up to 1.9% of CS [42].

Glucocorticoid-induced hypercoagulability (suggested by high levels of fibrinogen, factor VIII, factor IX, and von Willebrand factor and by evidence of enhanced thrombin generation), surgery, and obesity almost certainly contribute to this thrombotic tendency [43].

Enhanced metabolic function of endothelial cells has recently been suggested to contribute to the thrombophilic state of patients with active CS, in turn caused by an increased production of thrombin, with secondary hyperfibrinolysis [43]. GC also upregulates the synthesis of plasminogen activator inhibitor type 1 (PAI-1), the main inhibitor of the fibrinolytic system [44].

This hypercoagulability state is a crucial factor predisposing CS patients to thromboembolic events, mostly after surgery or during inferior petrosal sinus (IPS) sampling. Particular attention should be needed in these patients. Therefore, active CS patients should be considered as having a prothrombotic disorder, and antithrombotic prophylaxis should be offered. In the absence of prospective randomized trials, there is general agreement that these patients should be given heparin during IPS sampling, and low-dose heparin treatment when exposed to a thrombophilic condition such as surgery [45]. Thromboprophylaxis with low-molecular weight heparin, low-dose unfractionated heparin, or fondaparinux has been recommended routinely in patients with CS undergoing transsphenoidal or adrenal surgery (open or laparoscopic) [40].

2.4. Heart. Cardiac structural changes associated with reduced mid-wall systolic performance and diastolic dysfunction may contribute to the high risk of cardiovascular events observed in these patients [46]. Hypertension-induced organ damage, particularly cardiac hypertrophy, is frequent. Long-lasting exposure to excess circulating cortisol also may contribute directly to left ventricular concentric

remodelling [47]; however, few data are available on heart comorbidity in CS patients.

Sympathovagal imbalance, characterized by relatively increased parasympathetic activity, has been demonstrated in CS compared to controls. Cardiac autonomic dysfunction is associated with increased cardiovascular mortality. Whether this autonomic alteration is meant to counterbalance cortisol-induced effects on blood pressure and cardiac structure/function or has a different pathophysiological significance is still unknown [48].

Many classical cardiovascular risk factors known to increase the prevalence of ischaemic heart disease are present in CS patients [49–51]. However, reports on long-term cardiac outcome in these patients are very few. Recent data from the postmarketing surveillance HypoCCS database, which includes patients with GH deficiency treated for 3 years with rhGH therapy, have shown a higher baseline (6.3% versus 2.2%) and 3 year prevalence (7.6% versus 3.9%) of ischaemic heart disease in GH-deficient subjects previously treated for CD, than in subjects with previous nonfunctioning pituitary adenoma (NFPA) not exposed to hypercortisolism [52].

Recently, coronary flow reserve (CFR), an index of coronary microvascular function, has been evaluated in 15 newly diagnosed CS patients with no clinical evidence of ischemic heart disease [53]. Coronary flow velocity in the left anterior descending coronary artery has been evaluated by transthoracic Doppler echocardiography at rest and during adenosine infusion. The author demonstrated that CFR was pathologically reduced in CS patients, even without clinical symptoms of ischemic heart disease and in the absence of epicardial coronary artery lesions. It means that coronary microvascular function is impaired, even without clinical symptoms, contributing to increase the cardiovascular risk of these patients.

All these data suggest that cardiac function has to be routinely evaluated in CS patients, in order to detect cardiovascular risk factors which could impair the prognosis and heart performance.

2.5. Cerebrovascular. Cerebrovascular disease is increased in patients with CS, although little is known on its prevalence [1, 52]. Systemic arterial hypertension, impaired glucose tolerance or diabetes, central obesity, hyperlipidemia, and hypercoagulability probably contribute to cerebrovascular risk [54]. Data from the HypoCCS database have shown that the prevalence of cerebrovascular disease was greater in subjects with previous CD than in subjects with previous NFPA, both at baseline (6.4% versus 1.8%) and after 3 years of rhGH treatment (10.2% versus 2.9%) [52], supporting an irreversible effect of prior hypercortisolism on the cerebrovascular system.

3. Effects of Chronic Hypercortisolism on Glucose and Lipid Metabolism

3.1. Impaired Glucose Tolerance, Insulin Resistance, and Diabetes Mellitus. Glucose intolerance and diabetes mellitus (DM), important cardiovascular risk factors, are common in

CS independently from its etiology and glucose levels are generally higher in patients than in age- and sex-matched controls [49, 54]. Fasting glucose levels are higher in active disease than in remission [50]. Elevated fasting glucose may also be a feature of subclinical CS [51], whereas fasting glucose elevation is a common feature of exogenous GC administration. In fact, fasting glucose consistently rises after 5 days in subjects undergoing GC therapies. Insulin resistance is a feature of cortisol excess, both in clinical [50, 51] and experimental settings [55], and elevated insulin persists 5 years after cure of CD [48]. Short-term cortisol administration in healthy men increased plasma insulin concentration but the homeostasis model assessment (HOMA) score, a measure of insulin resistance, did not increase [51].

There is also a relatively high prevalence of “occult” CS in obesity and DM [56]. In CS the prevalence of diabetes varies between 20% and 50%, but probably this prevalence is significantly underestimated as an oral glucose tolerance test is not always performed in the presence of an apparently normal fasting glycemia [50].

Control of secondary DM is important to reduce cardiovascular risk. Metformin, to reduce insulin resistance, and new insulin analogues could be both useful to reach this important endpoint, together with physical exercise and a healthy lifestyle [57].

It has been recently questioned whether hypercortisolism or another factor could influence the presence of diabetes mellitus in CS [58]. The authors concluded that age, genetic predisposition and lifestyle, in combination with duration and degree of hypercortisolism, strongly contribute to the impairment of glucose tolerance in the natural history of CS. Therefore a more careful phenotypic evaluation of glucose tolerance defects in patients with CS would be useful for the identification of patients at high risk for this metabolic complication.

3.2. Dyslipidemia. Increased very low-density lipoprotein (VLDL), low-density lipoprotein (LDL-cholesterol) triglycerides, and total cholesterol levels with decreased high-density lipoprotein (HDL-cholesterol) have been documented in Cs patients [59]. The mechanisms involved in the dyslipidemia are probably multifactorial, including direct cortisol influences on VLDL synthesis, free fatty acid production, and hepatic endothelial lipase activity [59, 60]. The insulin resistance state induced by GC excess is also likely to play a key role in determining lipid abnormalities [60]. Recently, persistence of dyslipidemia and central obesity after long-term remission of hypercortisolism has been reported [61].

3.3. Metabolic Syndrome. Metabolic syndrome (MS) is a combination of events that increase the risk of developing cardiovascular disease and diabetes. MS is diagnosed if 3 or more of the 5 National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) criteria [62] are present, namely:

- (1) central obesity (waist circumference ≥ 102 cm or 40 inches in males; ≥ 88 cm or 36 inches in females);
- (2) fasting hypertriglyceridemia (TG ≥ 1.7 mmol/L or 150 mg/dL);
- (3) fasting low HDL-cholesterol (HDL-C < 40 mg/dL in males, < 50 mg/dL in females);
- (4) blood pressure $\geq 130/85$ mmHg or current use of antihypertensive medications;
- (5) fasting plasma glucose ≥ 5.6 mmol/L (100 mg/dL), a diagnosis of diabetes or current use of glucose lowering medication.

These five criteria are common in active CS patients; however, MS persists in patients cured from CS for at least 5 years [49]. More central obesity and hypertension are reported in both long-term cured (for a mean of 11 years) and active CS patients compared to controls. Furthermore, active CS fulfilled criteria for the MS more frequently than cured CS and controls [63]. Although abnormal body composition is characteristic of active CS (increased total and trunk fat mass and low lean body mass), persistence of body composition abnormalities, with an unfavorable adipokine profile, and persistent low-grade inflammation have been confirmed also in cured CS [52, 63, 64].

Cushing’s syndrome must be considered as a state of low-grade inflammation, even after long-term remission of hypercortisolism, because central fat mass and consequent increased levels of adipokines persisted after cure of CS, leading to a situation of increased cardiovascular risk in these patients [63].

4. Effects of Chronic Hypercortisolism on Body Composition

4.1. Lean Body Mass, Fat Mass, and Its Relation with Inflammatory Markers. Active CS is associated with changes in body composition, in particular central fat accumulation and reduced lean body mass [65]. It was assumed that resolution of hypercortisolism was followed by normalization of body composition; in fact, a decrease in fat mass has been reported early in recovery after successful treatment of CS [66, 67]. However, patients who have suffered CS, either exogenous or endogenous, often complain of obesity, despite successful treatment that may even have rendered them adrenal insufficient. Persistently increased total and central body fat are reported in patients with cured CS, whose disease began in childhood or adolescence [68, 69].

Persistent accumulation of central fat despite long-term cure of CS, for over 10 years, has been described, with an unfavorable adipokine profile, including low adiponectin, elevated plasma Soluble Tumor Necrosis Factor Receptor 1 (sTNF-R1) and interleukin-6 (IL-6), as in active hypercortisolemia [63]. When women were separated by estrogen status, those in the estrogen-deficient group had more total and trunk fat mass than healthy controls; these differences were not observed in the estrogen-sufficient group. Thus, postmenopausal women who have lost the protective effects of estrogens on the cardiovascular system and have more total and trunk fat related to their prior CS, would be at even higher cardiovascular risk. Therefore, absent estrogens in patients

who have suffered CS appears to play a major role in the persistent fat accumulation [63].

The real mechanism is still unclear; however, possible explanations for the persistent increased trunk fat may be the effect of cortisol on omental adipose tissue, due to hyperactivation of the 11β -hydroxysteroid dehydrogenase type 1, stimulating differentiation of more preadipocytes to adipocytes. After hypercortisolism has disappeared, the increased number of fat cells remains and contributes to explain the persistent increase in abdominal fat deposits [70–72].

Moreover, a dysregulation in the hypothalamic-pituitary-adrenal axis namely hyperactivation of this axis, may lead to visceral distribution of body fat and other manifestations of the metabolic syndrome [73–75]. Another novel mechanism that explains deposit of visceral adipose tissue and central obesity in patients with iatrogenic or endogenous CS is the inhibition of AMP-activated protein kinase activity in adipose tissue by GC [64], leading to increased lipid stores, enhanced lipolysis, release of free fatty acids and an “inflammatory state” which may contribute to vascular damage, atherosclerosis and cardiovascular disease (Figure 2). In fact, sTNF-R1 correlated positively with central fat mass in cured CS patients, and could be another link between central fat mass and persistence of high cardiovascular risk in long-term cured CS patients [63].

4.2. Bone. It is known that any chronic GC excess reduces bone mass [76–79]. This is caused by direct and indirect effects of GC on bone, such as reduction of osteoblastic and increase of osteoclastic activity, induction of hypogonadism, reduced intestinal calcium absorption, and increased urinary calcium excretion.

Whereas the increased risk of fractures and bone loss in active CS is well known, conflicting data have been reported in cured patients. Some studies reported complete recovery of bone mass after cure of CS [80–82], with normalization of bone mineral density (BMD) in multiple skeletal compartments in endogenous CS after a prolonged recovery time (mean of 6 years) [80]. Other studies reported complete BMD recovery 9 years after cure of CS [81], increased fracture risk in patients with CS in the 2 years immediately before diagnosis but not after diagnosis and treatment [82]. However, the time required for total bone mass recovery is unclear because there are data showing incomplete recovery as well [83–85]. Infact, incomplete restoration of bone mass after treatment for CS after shorter follow-ups of 2 [83] and 3 [84] years have been described. Moreover, increased prevalence of spine damage in patients cured of CS for 4 years has been evidenced using spine X-rays [85]. Biochemical parameters have also been evaluated and a persistence of low bone mineral content (BMC) and BMD and depressed levels of osteocalcin despite 11 years of remission of CS has been reported [86]. Several reasons may explain these discordances: only women were included, whereas other studies included both sexes; duration of endogenous hypercortisolism differed. Finally, duration of GC replacement therapy, a main predictor for long-term low bone mass, was not evaluated in all the studies. Exogenous

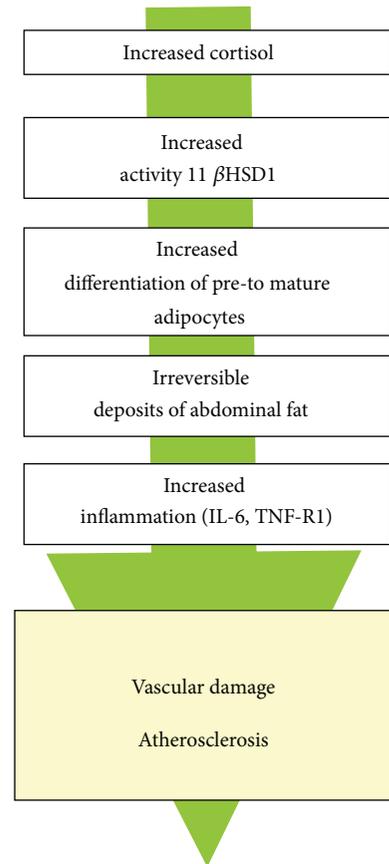


FIGURE 2: Inflammatory state as a contributor to vascular damage, atherosclerosis, and cardiovascular disease in CS patients.

GC “replacement” therapy negatively affected bone mass, which questions the concept that this is truly a “replacement” dose [86]. Nevertheless, there is still a debate in literature. A previous study performed in patients with primary or secondary adrenal insufficiency, treated with GC replacement for a mean of 12 years, found no differences in BMD compared with controls, or any correlation with duration or dose of GC replacement [87]. The authors concluded that regular monitoring of BMD measurements was not required, since patients with adrenal insufficiency receiving replacement doses (15–20 mg daily of hydrocortisone) were not at increased risk of osteoporosis [87]. By the contrast, it has been recently evidenced that in cured CS patients receiving a median of 20 mg/day of hydrocortisone, BMC and BMD values are lower than controls and the strongest determinant was duration of GC treatment [86]. Although some reports have found more severe bone loss in primary adrenal than in pituitary-dependent CS [88, 89], others have not [90]. Some studies reported more severe bone damage in postmenopausal than premenopausal CS women [91]. Others have shown the opposite [86, 90, 92], suggesting that the protective effect of estrogens on bone mass is lost in CS, since BMC and BMD in estrogen-sufficient CS women were lower than in the respective controls; thus supporting the idea that bone loss in estrogen-sufficient women is caused by the negative effect of GC excess on bone.

5. Effects of Chronic Hypercortisolism on the Brain

5.1. Structural and Functional Abnormalities. The effects of chronic hypercortisolism on the brain were poorly evaluated and few data were available; however, in the last few years new data have been arised, due to new advances in imaging techniques and therefore the possibility to investigate brain activity *in vivo*. Hypercortisolism in CS was associated with loss of cerebral volume, although a loss of brain cells (i.e. atrophy) was not been clearly demonstrated [93]. Increased widths of the 3rd ventricle or the bicaudate diameter were also described as partially reversible after control of hypercortisolism [94–96].

The hippocampus, a subcortical brain area, critical for learning and memory, is rich in GC receptors and for this reason particularly vulnerable to GC excess [97]. Animal studies showed that hippocampus was sensitive to both deficiency [98, 99] and elevation of GC [100, 101]. Administration of exogenous GC or exposure to endogenous hypercortisolism due to chronic social and experimental stress also induces changes in hippocampal pyramidal cell morphology and loss [100–102], impairing memory performance in animals [103]. Thus hippocampus was a structure particularly studied in CS patients. Loss of volume of the hippocampus and of the right caudate partially has been demonstrated to recover 1 year after surgery, in parallel with improvements in depression, anxiety, obsessive-compulsive and paranoid subscales of the SCL-90 questionnaire [104, 105].

In children with CS loss of volume of the amygdala did not improve after control of hypercortisolemia [106], while in adolescents, functional imaging (that reflects not structure but brain functional activations) showed greater activation in the left amygdala (related to emotional memory) and right anterior hippocampus (usually associated to verbal and visual memory) [107].

CS is a good human model to characterize relationships between cognitive performance and chronic exposure to elevated levels of GC [108] and hippocampus a good start point. A recent study has demonstrated that verbal and visual memory performance are worse in CS patients than controls, but only the patients with severe memory impairments also have reduced hippocampal volumes (HV) [109], Figure 3. In this study brain atrophy and reduction in total and cortical gray matter volumes have been also observed in CS patients compared with controls, but subcortical gray matter reduction has been seen only in those patients with severe memory impairment, in parallel to the findings of reduced hippocampla volumes (HV). The negative effect of GC excess on memory and HV seems to be not totally reversible after biochemical cure because there were no differences between active and cured CS, neither in HV nor in memory performance [109]. Less exposure to hypercortisolism by earlier diagnosis and successful treatment of CS would probably avoid the progression of memory problems and the reduction of HV and this is an important take home message for clinicians for the daily management of these patients.

Furthermore, HV reduction has been found only in CS patients with severe memory impairments, however it was

reasonable that initial functional abnormalities would precede structural abnormalities after GC overexposure, since memory was generally impaired in all CS patients. Consequently, there was a need to detect brain functional abnormalities, with a no invasive technique. ^1H -MR-spectroscopy (^1H -MRS) is a sensitive, non-invasive imaging technique. It provides information on biochemical composition of brain tissue *in vivo*, by measuring metabolites containing protons, allowing functional evaluation of the brain. It is routinary preceded by magnetic resonance imaging (MRI), used to select a volume of interest (VOI), where proton spectra of brain metabolites will be acquired. Thus, ^1H -MRS may detect and identify subtle functional alterations in the brain, despite an apparently normal structure, by assessing concentrations of neuronal components, it can indirectly deliver information on glial and neuronal integrity, potential cell loss and metabolic alterations in the brain. For this reason it has been used to study hippocampal metabolites in CS patients [110].

Persistently abnormal metabolites have been recently demonstrated for the first time in the head of both hippocampi of CS patients, using ^1H -MR-spectroscopy, despite endocrine cure of hypercortisolism [110]. Low levels of NAA indicate neuronal dysfunction and/or loss, while high levels of Glx suggest concomitant glial proliferation, as a repair mechanism. These altered brain metabolites could be considered early markers of GC neurotoxicity, would precede hippocampal volume reduction and could be involved in the memory impairments evidenced in these patients [110]. These alterations would explicate the lower memory performance in CS patients with normal hippocampal volumes. Thus, an earlier diagnosis and a rapid normalization of hypercortisolism would avoid the progression of hippocampal damage and memory impairments.

Longitudinal studies would be needed to clarify all the points opened after these preliminary observations. Future researches in the field should evaluate if these metabolites impairments would be present in the whole brain of CS patients and if patients using high levels of glucocorticoid drugs have the same brain alterations, causing memory problems. These would be a new challenge in this endocrine field, connecting neuroendocrinology to daily life clinical practice.

5.2. Psychological and Neuropsychological Features. Hypercortisolism predisposes to depression, mania and anxiety disorders [111]. Most CS patients have depression or emotional lability [112] especially if they are older, females and have severe hypercortisolism [93, 113]. Even though, biochemical control improves these symptoms, 25% may still present psychopathology 1 year after cure [114, 115]. No differences of personality traits have been reported between cured CS patients and controls [116].

By investigating the relationship between brain and behaviour, neuropsychologists can evaluate cognitive functions (i.e. intellectual capacities that allow an individual to interact with the environment by picking up information, processing it and communicating back with the environment). Cognitive functions include, among others, attention,

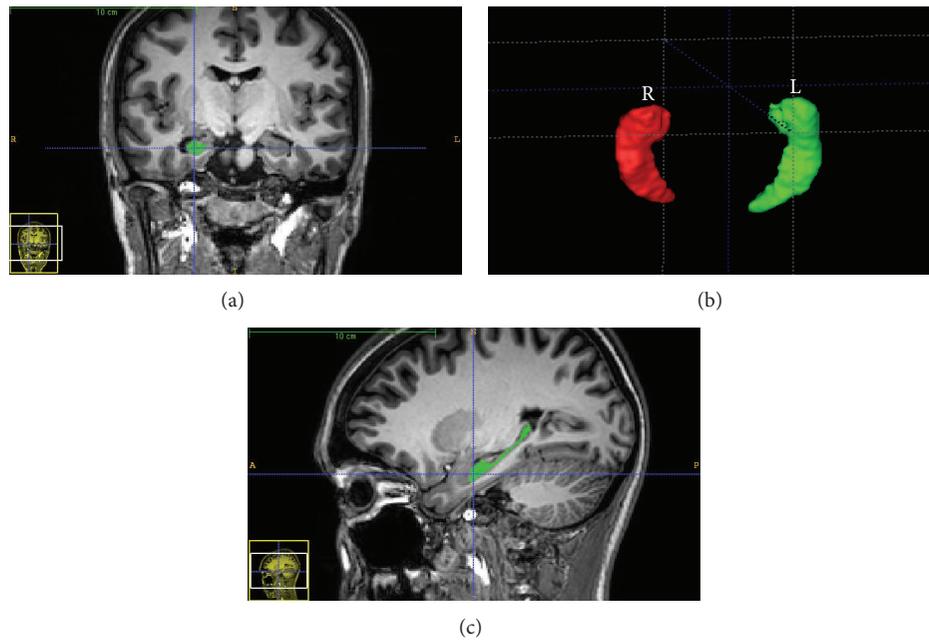


FIGURE 3: Examples of automatically segmented hippocampi using FreeSurfer (L = left and R = right). FreeSurfer provides automated measurements of cortical and subcortical gray matter volumes, the latter including the hippocampi (<http://surfer.nmr.mgh.harvard.edu/>).

memory, language and executive functions (the abilities that control and regulate other abilities and behaviours, as planning, inhibition, rule acquisition, abstract thinking, flexibility or selecting relevant information). Neuropsychological evaluation in CS is controversial, although impairment in attention and memory and alterations in the frontal lobes (related to executive functions) have been reported [117, 118]. More specifically, impairment in 2/3 of the patients in visual and verbal memory functions was reported, although there was no control group [119]. Subjective cognitive impairment in of CS [120] or impaired concentration, impaired memory [96] and problems in attention or visuomotor functions [121] have also been reported.

Prior to surgery, worse scores in tests related to visuospatial processing, reasoning, verbal and language tests, nonverbal aspects of memory and attention have been reported [117], suggesting frontal area involvement [122, 123]. Finally, endogenous hypercortisolism has been suggested to determine premature aging, since cognitive performance similar to controls aged 15 years older has been observed [124].

Little is known on the impact of hypercortisolism control on cognitive function. Partial improvement of several memory functions have been observed in small groups [121, 125], correlated in one study with recovery of hippocampus volume [126], but not in the other [127]. Another study only found improvement in a visuospatial organization task [128]. A recent more extensive study of 74 cured CS patients compared to both normal controls and treated Non-Functioning Pituitary Adenoma (not exposed to hypercortisolism) observed subtle cognitive deficits in the hippocampus, suggesting that the impact of prior hypercortisolism is not totally reversible [129].

Future studies would be needed to investigate neuropsychological features in CS.

5.3. Health-Related Quality of Life Impairment. Health-related Quality of life (HRQoL) is impaired in CS, even after biochemical cure [104, 130–132]. Impairment is greater than in other pituitary adenomas [133], especially with concomitant hypopituitarism [7]. These patients do not completely return to their pre-morbid level of functioning, and HRQoL is persistently impaired despite long-term cure.

The availability of a new disease-generated specific QoL questionnaire for patients with CS (CushingQoL, a unidimensional tool with 12 questions with good reliability, validity and feasibility) has allowed confirming worse scores in hypercortisolism than in normocortisolemic patients [134]. The CushingQoL questionnaire is a useful tool for the evaluation of HRQoL in CS patients in clinical practice due to its simplicity, reduced number of items, and ability to detect clinically relevant changes over time. In fact, CS probably determines impaired HRQoL in a multifactorial way, including physical and psychological problems, as well as the necessity to undergo repeated testing and check-ups and the need for chronic medication. The psychometric properties of test-retest reliability and sensitivity to change of the CushingQoL questionnaire have been evaluated in clinical practice conditions, demonstrating a good test-retest reliability and sensitivity to change [135]. The authors also pointed out that biochemical cure of hypercortisolism after treatment for CS is not associated with complete normalization of HRQoL and clinicians need to manage this point.

Illness perceptions are determinants of quality of life and factors contributing to persisting impaired QoL after CS.

It has been recently demonstrated that patients after long-term remission of CS report more negative illness perceptions compared with patients with other acute or chronic conditions [136].

These new findings suggest that the effects of previous cortisol excess on the central nervous system can be long-lasting and to a certain extent even be irreversible, impairing the HRQoL.

6. Conclusions

The assumption that resolution of hypercortisolism normalized morbidity is currently questioned since evidence is accumulating that cured CS patients still have increased morbidity and mortality despite endocrine control. In patients with persistent moderate hypercortisolism despite treatment, standard mortality ratio is increased 3.8- to 5.0-fold, compared with the general population [137].

Greater cardiovascular risk typical of active CD was reported high 5 years after remission [49]. These patients still had increased prevalence of clinical and biochemical abnormalities typical of the active phase, as atherosclerosis, obesity, hypertension, impairment of glucose tolerance, hyperlipidemia, and hypercoagulability. Moreover, they have significantly reduced caliber, increased stiffness of carotid artery walls, and increased prevalence of carotid atherosclerotic plaques compared to sex- and age-matched control populations [49, 138].

Most patients with CS develop some manifestations of the metabolic syndrome, which may persist after remission of the hypercortisolism, contributing to increased cardiovascular risk and deserves to be treated according to common standard practice [1]. Persistent accumulation of central fat and other features of the metabolic syndrome are common in both active hypercortisolemia and in endocrine biochemical control, leading to an unfavourable adipokine profile, a state of low-grade inflammation, vascular damage, and cardiovascular disease [63].

Hypertension improves in most patients after successful treatment but may persist, presumably because of microvessel remodelling and/or concomitant underlying essential hypertension [49, 61, 139].

Awareness of this persistent increase in cardiovascular risk in CS patients after endocrine cure should lead to strict control of improvable factors, which include blood pressure, dyslipidemia, hyperglycemia, smoking, obesity, and protrombotic state [140]. Oral glucose tolerance test, 24-hour ambulatory blood pressure monitoring, echocardiography, electrocardiogram, and carotid ultrasound have been proposed in the followup to establish the cardiovascular risk in cured CS [31, 141]. A combination of treatments directed both against hypercortisolism and aimed at controlling cardiovascular risk factors seems appropriate to reduce cardiovascular events in these patients [1, 2, 59].

Low bone mass does not recover completely after endocrine control of hypercortisolism [86]; whether this determines an increase in fracture rate is currently unknown

but seems probable and should alert the clinicians to prescribe currently available therapy for osteoporosis, if BMD is in the osteoporotic range. Lean body mass, mainly reflecting muscle mass, also tends to be lower after long-term cure of hypercortisolemia, explaining the common complaint of reduced exercise capacity in cured CS patients [129].

Subtle cognitive defects [128] and impaired quality of life [130] are common in cured CS and psychopathology is reported in 25% of the patients after endocrine control [114, 115].

Verbal and visual memory performance is impaired in CS patients compared to controls, but only the patients with severe memory impairments also had reduced HV. The negative effect of GC excess on memory and HV was not totally reversible after biochemical cure because there were no differences between active and cured CS, neither in HV nor in memory performance.

Persistently abnormal metabolites have been also recently demonstrated for the first time in the head of both hippocampi of CS patients, using ^1H -MR-spectroscopy, despite endocrine cure of hypercortisolism [110]. These altered brain metabolites could be considered early markers of GC neurotoxicity, would precede hippocampal volume reduction, and could be involved in the memory impairments evidenced.

Impaired HRQoL in a multifactorial scenario, including physical and psychological problems, as well as the necessity to undergo repeated testing and checkups and the need for chronic medication, is present in CS patients, despite long-term cure.

There are few speculations on the literature regarding the possible explanation behind “residual” morbidity in CS patients; the topic is still open to debate; this is an intriguing point for future investigations. In the last few years this residual morbidity has been described in some comorbidities, something new for the clinicians; further studies are needed to explain the physiopathology of long-term damage of hypercortisolism. However it seems reasonable that a long-term damage of specific sensible organs would persist, depending on the possibility of each tissue to recover and to the disease duration.

In summary, prior exposure to chronic hypercortisolism induces irreversible effects, determining “residual” morbidity at many levels. An earlier diagnosis and successful treatment would reduce this morbidity, reducing the harmful effect of the long term exposition to hypercortisolism. Longitudinal databases to follow these patients should provide further insight into their long-term prognosis.

Disclosure

The author Eugenia Resmini has M.D. and Ph. D. degrees.

Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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