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Autonomous hypercortisolism: definition and clinical implications

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1 **Autonomous hypercortisolism: definition and clinical implications**
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4 Giuseppe REIMONDO¹, Soraya PUGLISI¹, Anna PIA¹, Massimo TERZOLO¹.
5

6 Internal Medicine and Endocrinology Unit, Department of Clinical and Biological Sciences,
7 University of Turin, AOU San Luigi Gonzaga, Orbassano, Italy
8
9

10 Corresponding Author:
11

12 Giuseppe Reimondo
13

14 Internal Medicine and Endocrinology Unit, Department of Clinical and Biological Sciences,
15 University of Turin, AOU San Luigi Gonzaga, Regione Gonzole 10, 10043 Orbassano, Italy
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ABSTRACT

In current practice, an adrenal adenoma usually comes as an unexpected byproduct of an imaging study performed for unrelated reasons, without any prior suspect of adrenal disease. Therefore, these tumors currently represent a public health challenge because they are increasingly recognized due to the widespread use of high-resolution cross-sectional imaging for diagnostic purposes. In radiology series, the prevalence of adrenal adenomas increases steeply with age, from around 3% below the age of 50 years up to 10% in the ageing population. These tumors may have clinical relevance because they are able to secrete cortisol autonomously, independently from the pituitary control, in up to 20% - 30% of patients. In most of the cases the resulting cortisol excess is insufficient to produce a typical Cushing phenotype but may have clinical consequences, such as hypertension, diabetes, obesity, dyslipidemia and osteoporosis.

Despite some controversy on the most effective diagnostic algorithm to define this subtle hypercortisolism, there is mounting evidence that a simple approach by using the 1-mg overnight dexamethasone suppression test (DST) may stratify patients for their cardiovascular risk. Cross-sectional, retrospective studies showed that patients with increasingly higher cortisol following DST have an adverse cardiovascular risk profile and are at increased risk of death. Therefore, also a subtle autonomous cortisol excess is associated with increased morbidity and mortality, mainly of cardiovascular origin.

KEY WORDS

Adrenal adenoma

Hypercortisolism

Cushing's syndrome

INTRODUCTION

Adrenal adenomas are benign tumors with a limited potential of malignant transformation. In current practice, an adrenal adenoma usually comes as an unexpected byproduct of an imaging study performed for unrelated reasons, without any prior suspect of adrenal disease. Therefore, they currently represent a public health challenge because they are increasingly recognized due to the widespread use of high-resolution cross-sectional imaging for diagnostic purposes.

These tumors may have clinical relevance because they are able to secrete cortisol autonomously, independently from the pituitary control, in up to 20% - 30% of patients¹. In most of the cases the resulting ACTH-independent cortisol excess is mild and insufficient to produce a typical Cushing phenotype (facial plethora, easy bruising, proximal muscle weakness, purple striae or weight gain with decreasing growth velocity). Considering the lack of classical external features of Cushing's syndrome (CS), this condition has been defined as subclinical Cushing's syndrome (SCS)² (Table I).

When adrenal adenomas are associated with highly predictive features of CS³, the ACTH-independent cortisol excess is usually promptly recognized. However, endogenous hypercortisolism is a rare disease with an estimated incidence of around 2.4 per million and a prevalence of 39.1 per million⁴ and ACTH-independent cortisol excess due to adrenal adenoma represents only 10% of the overall causes. On the contrary, the epidemiologic relevance of SCS due to adrenal incidentalomas is potentially high, considering that in radiology series the prevalence of adrenal adenomas is around 3% below the age of 50 years, with progressive increase in older patients (up to 10% in the ageing population)¹ and in approximately 20-25% of them an autonomous cortisol secretion is reported.

However, the demonstration of autonomous cortisol secretion could be extremely difficult in practice. The heterogeneity of clinical phenotype and a limited clinical experience make precocious diagnosis a major challenge and frequently SCS remain unrecognized for long time, due its subtle course. In the meanwhile, patients exposed to chronic albeit slight cortisol excess may have significant clinical consequence, such as hypertension, diabetes, obesity, dyslipidemia and osteoporosis.

DEFINITION OF AUTONOMOUS ACTH-INDEPENDENT HYPERCORTISOLISM

According to the Endocrine Society guidelines³, overt endogenous hypercortisolism should be investigated when clinical features and history are highly predictive. The recommended screening evaluation includes the following test: 1 mg overnight dexamethasone suppression test, urinary free cortisol (UFC) and late night salivary cortisol. When at least two of them are positive, the diagnosis is confirmed. If an adrenal adenoma is detected by radiological imaging, the diagnosis of ACTH-independent CS requires low ACTH levels (<1.1 pmol/L). This two-step diagnostic procedure is highly effective in presence of high clinical pre-test probability. However, most of the patients may

1 present a mild disease, that is harder to detect. Thus, several studies have been focused on such
2 patients with diabetes mellitus, osteoporosis, hypertension or obesity to screen for mild
3 hypercortisolism. Although a widespread screening is not recommended, interestingly most of the
4 detected cases with confirmed hypercortisolism had an adrenal dependent CS⁵⁻⁷.

7 According to the ESE guidelines¹, the best method to discover autonomous cortisol secretion is the 1
8 mg overnight dexamethasone suppression test (1 mg-DST). Nevertheless, false positive or false
9 negative results are reported, mainly due to variable absorption and metabolism of dexamethasone³.
10 Many drugs cause false positive results, as phenytoin, increasing hepatic metabolism of
11 dexamethasone mediated by CYP3A4 (phenobarbitone, carbamazepine or rifampicin) or raising CBG
12 levels (oral estroprogestinic preparations). On the contrary, false negative results could be due to liver
13 or renal failure, which reduce dexamethasone clearance.

17 Twenty-four hour UFC is widely used in the clinical practice, but considering that it reflects the
18 measure of cortisol circulating levels after CBG saturation, it is less sensitive in patients with mild
19 hypercortisolism or in patients with AI. Moreover, several limits have been reported due to the need
20 of multiple collection, improper collection, high fluid intake or renal insufficiency⁸⁻¹⁰.

25 Although the LC-MS / MS technique is not available in all centers, it appears promising to improve
26 diagnostic accuracy, since interference with other steroids is excluded. Therefore, it is the
27 recommended technique for the evaluation of UFC as first-line screening of CS³ and recent studies
28 have confirmed higher sensitivity and specificity of UFC with LC-MS / MS^{11,12}.

31 The evaluation of the circadian rhythm of cortisol is one of the most important diagnostic clue since
32 the loss of the ultradian pulsatility of cortisol secretion with high nocturnal values is pathognomonic
33 of cortisol excess. However, methodological limits, in addition to the non-uniformity of pathological
34 thresholds, make the consent difficult and the use not widespread, especially for mild
35 hypercortisolism.

39 Newell-Price and colleagues¹³ first suggested the use of midnight serum cortisol as a screening test,
40 and in recent years its higher sensitivity and specificity was reported^{14,15}. Moreover, the midnight
41 serum cortisol threshold of 148 nmol/L has been also documented to be related with an adverse
42 cardiovascular (CV) risk profile in patients with AI¹⁶. However, it requires hospitalization and cannot
43 be proposed for routine clinical practice.

47 The introduction of midnight salivary cortisol has avoided hospitalization and has become one of the
48 most important diagnostic tools in CS. A meta-analysis demonstrated an overall sensitivity of 92%
49 and a specificity of 96%, although there is no agreement on the definition of the cut-off and it is
50 necessary to define the levels of normality in each laboratory^{17,18}. Only few studies have verified the
51 diagnostic accuracy of salivary cortisol at midnight in subclinical hypercortisolism with results that
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1 are mostly lower than other tests. Recently, data published by Ceccato and colleagues¹⁹ have
2 confirmed the reduced accuracy of midnight salivary cortisol in the screening of subclinical
3 hypercortisolism, although measured by LC-MS/MS. Furthermore, it has not been shown to be a
4 strong predictor of accelerated atherosclerosis in patients with subclinical hypercortisolism²⁰.

5
6 Although low ACTH concentrations may support diagnosis of cortisol autonomous hypersecretion,
7 in some cases non-suppressed ACTH levels are associated with pathological value of 1 mg-DST. A
8 possible explanation can be due to analytical errors or interference in ACTH immunoassay.
9 Particularly, negative impact of antibody interference in ACTH measurements was recently reported
10 in adrenal adenomas incidentally detected²¹. As no single routine test is available to identify
11 immunoassay interference, the same authors suggest to ensure collaboration between clinical and
12 laboratory staff to avoid clinical misjudgments.

13
14 The usefulness of DHEAS measurements in the screening of subclinical hypercortisolism is still
15 debated. In the last years DHEAS measurement had a renaissance in this setting also by using LC-
16 MS/MS. Lower DHEAS levels have been confirmed to be correlated to higher cortisol secretion and
17 in some cases with a worsen metabolic profile. However, when compared with the 1 mg DST the
18 sensitivity and specificity in the detection of subclinical hypercortisolism ranges between 70-75%
19^{22,23}. More recently data on 185 patients with AI, of which 29 with subclinical hypercortisolism,
20 DHEAS measurements calculated as age- and sex-specific DHEAS ratios for all patients (derived by
21 dividing the DHEAS by the lower limit of the respective reference range) seem to demonstrate that a
22 single basal measurement of DHEAS offers comparable sensitivity and greater specificity to the
23 existing gold-standard 1 mg DST for the detection of SCS in patients with AI²⁴.

24
25 In conclusion, despite some controversies, use of the 1-mg DST as screening test meets the recent
26 spending-review policies of healthcare systems and limit false positive results. Moreover, there is
27 mounting evidence that the 1-mg DST is useful to stratify patients for their CV and metabolic risk.

28
29 Indeed, it has been demonstrated that patients with impaired suppression of cortisol after 1 mg
30 dexamethasone test have a higher risk of type 2 diabetes mellitus (T2D), hypertension, CV events
31 and vertebral fractures.

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33 Urine steroid metabolomics analysis should be a prospective and promising technique to differentiate
34 secreting and non secreting adrenal tumors.

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52 **MORBIDITY AND MORTALITY IN ADRENAL-DEPENDENT CUSHING'S SYNDROME**
53 **(ACS)**
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1 The effects of hypercortisolism on morbidity and mortality have been extensively studied, but most
2 published papers have focused on patients with Cushing's disease (CD) and fewer on patients with
3 ACS. It is evident that the therapeutic approach to patients with CD is more complex and often
4 requires different and sequential treatments with a persistent risk of hypercortisolism which is
5 maintained for longer periods. As for patients with ACS, the therapeutic approach is by definition
6 surgical and, in absence of clinical contraindications that determine a high operative risk, it results
7 definitive obtaining the cure in 100% of the cases, although the negative effects of pre-surgical
8 hypercortisolism cannot be removed. In this clinical context, however, post-surgical hypoadrenalism,
9 often prolonged, must be considered until it becomes definitive and potentially influences the quality
10 of life and the clinical management of patients who are on steroid replacement therapy.
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20 METABOLIC AND CARDIOVASCULAR MORBIDITY

21 Impaired glucose tolerance, hypertension, CV disease and thromboembolism are very common
22 features of CS and frequently reported as risk factors of mortality²⁵

23 It is known that patients with CS showed abdominal obesity (37–71%) and dyslipidemia
24 (hypercholesterolemia in 16–60% and hypertriglyceridemia in 7–36%)²⁶. This pattern is due to
25 differential effects of GCs on visceral and peripheral adipose tissues. Indeed, the GC excess induces
26 lipogenesis in visceral fat, whereas in peripheral fat it promotes lipolysis²⁷. Moreover,
27 hypercortisolism induces abnormalities in glucose homeostasis, mainly caused by insulin resistance
28 and impairment in insulin secretion, which may persist even after correction of glucocorticoid excess
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37 In addition to metabolic changes, patients with CS are frequently affected by hypertension (55-85%),
38 coagulopathy, structural cardiac alterations (in 70% of cases abnormal left ventricular (LV) mass,
39 with concentric hypertrophy or concentric remodelling) and endothelial dysfunction²⁶.
40

41 Recently, new mechanisms are reported to explain the high CV risk in CS patients.

42 In 2015, Boero and colleagues carried out an open cross-sectional study to identify the presence of
43 atherogenic risk factors in 32 patients with active CS compared with sex- and age-matched controls.
44 Patients with CS showed lower insulin sensitivity, higher waist circumference, high oxidized low-
45 density lipoprotein levels, high sensitive C-reactive protein levels and increased leukocyte count²⁹.
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49 Moreover, in 2017, Gokosmanog and colleagues analyzed prevalence of obstructive sleep apnea
50 (OSA) in 30 female patients with active CS and 30 matched healthy controls. They reported higher
51 prevalence of OSA in patients with CS compared with control subjects with similar ages and BMI
52 levels, identifying hypercortisolemia as an independent risk factor for OSA³⁰.
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1 This multifactorial and variegated pathogenesis of CV morbidity in CS is summarized in Fig 1.
2
3 However, data focused on adrenal-dependent CS are few and mostly collected aiming to evaluate the
4 efficacy of treatment. At diagnosis, the prevalence of CV risk factors in patients with ACS seems to
5 be similar to CD ³¹, and higher than in BMI-matched controls ³².

6
7 On the other hand, controversial data are available on the effect of therapy in reducing CV risk
8 factors. When studies are predominantly focused on patients with CD, disease remission appears to
9 have only a moderately positive effect over the long term, while maintaining a higher risk compared
10 to the general population ³³⁻³⁴.

11
12 Although the risk of CV events is not completely eliminated, studies that include patients in
13 remission with ACS demonstrate more successful results. Giordano and colleagues showed that a
14 significant reduction in impaired glucose tolerance was achieved only in patients with ACS after
15 only one year follow-up³². A recent study by Terzolo and colleagues has demonstrated, over a long
16 period of follow-up a complete normalization of CV risk factors in a higher percentage of patients
17 compared to previous publications, having included patients who had already completed the steroid
18 replacement therapy, which had an average duration of about 12 months. In other studies, some
19 patients in remission had ongoing replacement therapy and the possible effect on CV risk outcomes
20 should not be excluded, although further data are needed ³⁵

21 22 23 24 25 26 27 28 29 30 OSTEOPOROSIS AND FRACTURE RISK

31 Osteoporosis is widely documented and up to 80% of patients with CS are reported with an
32 associated risk of fractures exceeding 50% ²⁵. Moreover, unexpected osteoporosis for patient's age
33 or the rapid worsening of bone mineral density, represent relevant signs of CS. Osteoporosis and
34 fracture risk has been well studied in the different etiologies of Cushing following the hypothesis
35 that the suppression of androgens in patients with ACS could determine a reduction of their
36 protective effect on bone mass favoring the negative effect of excess cortisol. Some works have
37 confirmed this hypothesis, demonstrating a correlation between DHEAS levels and bone mineral
38 density ^{36,37}, while others did not highlight differences between etiologies ^{38,39}. It is likely that the
39 controversial data depend on the different selection of patients, in particular regarding the gonadal
40 status and the hormonal replacement therapy in patients with post-surgical pituitary deficiency.

41 42 43 44 45 46 47 48 49 OTHER MORBIDITIES

50 GC excess is associated with neuropsychiatric diseases, probably due to structural and functional
51 changes in brain areas expressing GC receptors, such as the hippocampus, amygdala, and anterior
52 cingulate cortex (limbic system, involved in emotional and cognitive attitudes). Particularly, in
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1 patients with CS is reported an high prevalence of major depression (50–81%), anxiety (66%), and
2 bipolar disorders (30%)⁴⁰. It is worth of note that cognitive, psychiatric and mood disorders may
3 persist also after resolution of cortisol excess, with a significant impact on quality of life ⁴¹.

4 Moreover, hypercortisolism impairs the immune system, causing immunosuppression and,
5 consequently, susceptibility to infections (especially due to opportunistic pathogens). Interestingly,
6 the increase risk of invasive infections appears to be independent of the etiology of CS, but is
7 correlated with the severity of GC excess and the success in treatment of opportunistic infections
8 frequently depends on the rapidity in normalizing cortisol levels ²⁵.

15 MORTALITY

16 Several data have been published in the last decade on mortality in patients with endogenous
17 hypercortisolism confirming the expected excess compared to the general population, mainly due to
18 cardio- and cerebro-vascular events or sepsis. The excessive mortality is described in patients with
19 persistent disease, while patients in remission may have a comparable risk to the general population
20 or at least only a slight increase ²⁵.

21 The investigation of the Standard mortality ratio only in patients with adrenal-dependent benign
22 unilateral adrenal adenoma vary greatly from 1.35 to 7.5 ⁴²⁻⁴⁶. However, recent data from two large
23 series with a prolonged follow-up reported that patients in remission with ACS does not have an
24 excess risk mortality compared to the general population and it is similar or slightly lower than
25 patients with CD ^{45, 46}.

37 MORBIDITY AND MORTALITY IN SUBCLINICAL CUSHING SYNDROME (SCS)

38 An increasing body of evidence suggests association between SCS and metabolic alterations, CV
39 disease and osteoporosis. Long-term exposure to even low-grade cortisol excess may have
40 detrimental effects depending on individual genetic background, associated clinical conditions and
41 degree of hypercortisolism. Moreover, recent studies showed higher mortality in this group of
42 subjects.

49 METABOLIC AND CARDIOVASCULAR MORBIDITY

50 It is known the effect of glucocorticoids on glucose metabolism, including increase of hepatic
51 gluconeogenesis, decrease of insulin-dependent glucose uptake in peripheral tissues and inhibition of
52 insulin secretion from pancreatic β -cells⁴⁷. Therefore, it is not surprising the association between SCS
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1 and impairment of glucose metabolism, including insulin resistance, impaired glucose tolerance
2 (IGT) and T2M. High prevalence of IGT (36%) or previously undiagnosed T2M (5%) has been
3 described since 2002⁴⁸ in patients with AI in comparison with controls. Moreover, the same authors
4 reported higher levels of 2-h glucose after oral glucose tolerance test (OGTT) ($p = 0.03$) and reduced
5 insulin sensitivity index (ISI) ($p < 0.0001$) in the subgroup of patients with adrenal adenoma and SCS
6 compared to subgroup of patients with nonfunctioning adenoma. In the following years, several
7 studies have been conducted in this field and it has been reported T2D roughly in one third of patients
8 with SCS, but with a broad range from 5% to 69%⁴⁹. This variability could depend on different
9 diagnostic criteria used to define SCS, number of examined patients and different method used to
10 evaluate the presence of glucose metabolism impairment. Particularly, it is worth of note that
11 assessment of fasting glucose and fasting insulin in SCS is not sufficient to detect glucose metabolism
12 impairment and an OGTT is required⁵⁰. Due to similar reasons (variability of diagnostic cut-off for
13 SCS), the reported prevalence of mild hypercortisolism in cohorts of patients with T2D is extremely
14 variable. In 2003 Catargi and colleagues described a 3.5% prevalence of SCS in a population of 200
15 diabetic patients⁵¹, while in 2005 Chiodini and colleagues⁵² reported a rough prevalence of 7%, 4.8-
16 fold higher than in non-diabetic group, independently of potentially confounding comorbidities as
17 obesity and hypertension. More recently, a large single center study, conducted in a cohort of 993
18 Asian Indian patients with T2D⁵³, reported in 37 cases (3.72%) a value of cortisol after 1-mg DST $>$
19 50 nmol/L. These patients have been further evaluated with a 48 h, 2 mg low dose DST (LDDST)
20 after a gap of at least 1 week after 1-mg DST and none of them had cortisol $>$ 50 nmol/L, nor did they
21 develop clinically evident CS over a follow-up period of 1 year. Only on the basis of these
22 biochemical and clinical data, the Authors concluded that none of the T2DM patients in their cohort
23 had SCS. Conversely, Costa and colleagues⁵⁴ reported, in a large sample of T2D patients with high
24 CV risk, a prevalence of 8.6% of SCS. Moreover, these patients had more severe hypertension and
25 increased aortic stiffness, despite of a shorter diabetes duration. Regardless this variability of findings,
26 currently it is suggested against systematic biochemical screening for SCS in T2D cohort, while
27 diagnostic investigations should be reserved for cases of clinical suspicion. On the contrary, SCS
28 patients had to be screened for T2D¹. Although less proven, association with dyslipidemia is also
29 plausible. Interestingly, Masserini and colleagues showed that in absence of impaired glucose
30 metabolism a mild hypercortisolism has no effect on lipid pattern⁵⁵. Finally, recent studies showed
31 that patients with SCS have a high prevalence of nonalcoholic fatty liver disease⁵⁶ and visceral fat
32 accumulation (measured by CT-scan)⁵⁷.

33 An increased CV risk profile in SCS subjects was first demonstrated in 2002, with a cross-sectional
34 study including 28 SCS patients compared with 100 controls. Systolic and diastolic blood pressures,
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1 fasting glucose, insulin, total cholesterol, triglycerides, fibrinogen were higher in SCS patients, as
2 were insulin resistance index, waist to hip ratio, mean carotid artery intima-media thickness and
3 prevalence of atherosclerotic plaques. Moreover, among SCS patients it was reported a symptomatic
4 CV disease in six subjects (21.3%) and CV abnormalities (revealed by ultrasound scanning of carotid
5 arteries and/or electrocardiogram records) in 11 cases (39.3%)⁵⁸. In 2005 a multicenter retrospective
6 study including 210 patients with clinically inapparent adrenal adenoma reported higher fasting
7 glucose and systolic blood pressure in patients with elevated midnight serum cortisol concentrations
8 compared to subjects with normal cortisol levels¹⁶. A significance contribute was also provided by a
9 cross-sectional study published in 2012, including 348 patients with AI, classified in 4 subgroups:
10 203 patients with non-secreting adenoma (NSA, with 1 mg DST < 50 nmol/l), 19 patients with SCS
11 (1 mg DST >138 nmol/l) and the remaining patients with intermediate phenotype (1 mg DST between
12 50 and 138 nmol/l), divided in minor (71 patients) or major (55 patients) according plasma ACTH
13 and/or UFC levels. It is worth of note the increase of prevalence of myocardial infarction according
14 to secreting pattern (2.9% in NSA, 11.9% in patients with intermediate phenotype and 26.3% in SCS).
15 Moreover, multivariate logistic regression analysis showed association between prevalence of
16 coronary heart disease and patients with intermediate phenotype or SCS, independently of other
17 potential risk factors⁵⁹. These important findings were confirmed by the same authors in a
18 retrospective analysis of 198 patients, evaluated for their cortisol secreting pattern at baseline and at
19 the last visit, with a mean follow-up of 7.5±3.2 years (range 26 months - 15 years). It was reported
20 that patients with SCS and with worsening cortisol secretion at the last visit (compared to baseline)
21 had higher incidence of CV disease than those with NSA. Moreover, increase of cortisol levels during
22 follow-up was independently associated with higher rate of CV events⁶⁰. Finally, the role of cortisol
23 as a contributing factor to CV diseases was confirmed in other retrospective studies, reporting higher
24 incidence of CV events in patients with SCS than in patients with NSA⁶¹⁻⁶³.
25 More recently Arruda and colleagues, reported the association between hypertension and cortisol
26 levels after 1 mg-DST in patients with NSA⁶⁴. Although there is no indication to a routine screening
27 for cortisol secretion in patients with hypertension, the high prevalence of SCS shown in patients with
28 resistant hypertension, associated with several markers of worse CV prognosis⁶⁵ probably needs
29 further assessments.

30 OSTEOPOROSIS AND FRACTURE RISK

31 In the last decade, several studies investigated the impact of mild hypercortisolism on bone healthy.
32 Retrospective series⁶⁶⁻⁶⁹ reported increased prevalence of bone fractures, mainly in trabecular bone,
33 in patients with SCS compared to patients with NSA or healthy subjects.
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1 In 2011 a first longitudinal study confirmed higher prevalence of vertebral fractures and also reported,
2 using the surrogate tool of spinal deformity index (SDI), worsened bone quality in SCS patients in
3 comparison to patients with AI. Moreover, it was showed that SCS patients had higher risk to develop
4 new vertebral fractures over time despite a stable bone mineral density (BMD)⁷⁰.

7 Deterioration of bone quality in SCS patients was confirmed in a subsequent prospective study, in
8 which trabecular bone score (TBS) was used as surrogate index of damaged bone microarchitecture.
9 It was found that TBS was inversely correlated with 1-mg DST regardless of age, BMD, body mass
10 index (BMI) and gender. Moreover, in patients with SCS, the presence of fractures was associated
11 with low TBS, and its value predicted occurrence of new microfractures, regardless of BMD⁷¹.

15 Correlation between mild hypercortisolism and bone quality was further investigated in OsteoLaus
16 cohort, including 608 women >50 years old, in which salivary cortisol circadian rhythm was assessed.
17 Lower TBS values ($p = 0.02$), more vertebral fractures ($p = 0.012$) and major osteoporotic fractures
18 ($p = 0.042$) were reported in women with 8 PM salivary cortisol in the highest tertile compared to
19 women with salivary cortisol in lowest tertile, without difference in lumbar spine BMD⁷².

23 In a recent study including 110 patients with overt Cushing (OC: UFC > 1.5 ULN and 1 mg DST >
24 50 nmol/L) or mild autonomous cortisol secretion (MACE: normal UFC associated with 1 mg DST
25 > 50 nmol/L), a group of 29 patients with MACE due to AI was compared with a group 18 patients
26 with NSA (normal UFC associated with 1 mg DST < 50 nmol/L). Patients with MACE had lower
27 TBS than patients with NSA ($p < 0.04$), despite similar BMD, age, BMI and female predominance.
28 Moreover, 52% of patients with MACE and 33% of patients with NSA ($p = 0.05$) had impaired bone
29 microarchitecture (as indicated by their TBS)⁷³.

36 MORTALITY

38 Recent studies have also shown that SCS is associated with an increase in mortality rate. A 15-year
39 retrospective study⁶⁰ showed that in 198 patients followed up for a mean 7.5 years 21 patients died,
40 48% attributable to CV disease and 43% due to cancer. All-cause (57 vs. 91%) and CV specific
41 mortality (78 vs. 98%) survival rate was worse in SCS patients compared with NSA. Another
42 retrospective, longitudinal cohort study⁶² involving 206 patients (mean follow-up 4.2 ± 2.3 years),
43 confirmed the relationship between a low-grade excess cortisol and an increased mortality rate. It is
44 worth of note that patients with SCS showed higher mortality rate related to cardiovascular disease
45 and infection when compared with UK population.

52 CONCLUSION

54 Since the first years of the new millennium, the growing number of incidentally discovered adrenal
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1 masses increased the interest on their clinical management, primarily in identifying malignancy, but
2 also in demonstrating a potential increase in cortisol secretion and its consequences in patients who
3 did not show any of the typical signs and symptoms of hypercortisolism. While in overt Cushing's
4 syndrome it is clearly demonstrated that associated co-morbidities (CV events, metabolic syndrome,
5 osteoporosis, psychiatric disorders, and infective diseases) contribute to an increase mortality risk,
6 which is not always completely reversible after disease remission, in patients referred to the clinician
7 for incidentally discovered adrenal masses, without any signs and symptoms of hypercortisolism, the
8 diagnostic evaluation and the potential clinical implications were more complex to study and there
9 are still unresolved questions. Although the measure of cortisol after overnight 1 mg DST is currently
10 the most accurate, less expensive and easiest test to identify patients with an autonomous cortisol
11 secretion, there are still areas of uncertainty in patients with cortisol levels higher than 50 nmol/L.
12 The addition of further hormone evaluations does not provide sufficient specificity, thus it is still
13 crucial to identify new diagnostic methods, which allow to better measure the chronic exposure to a
14 slight cortisol excess. The assessment of potential co-morbidities is essential in identifying the best
15 therapeutic approach. Many studies confirm a correlation between a progressive increase of impaired
16 glucose metabolism, CV events and osteoporosis with higher cortisol secretion and early data seem
17 to demonstrate an increasing effect on mortality. Actually, further extensive studies are needed to
18 better discriminate the effect of hypercortisolism, especially in older patients who have an age related
19 co-morbidity risk. The prospective aim will be to accurately identify and to categorize, from the initial
20 clinical and biochemical assessment, patients who can benefit from specific treatments for
21 hypercortisolism.
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Tab I. Relevant differences between Subclinical Cushing Syndrome and Overt Cushing Syndrome.

	SUBCLINICAL CUSHING SYNDROME	OVERT CUSHING SYNDROME
Age at diagnosis	Frequently > 50 years	Frequently < 50 years
Sex	Slight prevalence in women	Clear prevalence in women
Presentation and cause of disease	Usually, adrenal mass incidentally finding during radiological exams, in patients with characteristics of metabolic syndrome,	Clinical suspect on the basis of

	without specific features of Cushing	specific signs of Cushing, followed by radiological exams frequently showing a pituitary adenoma
Disease course	Usually does not progress to overt Cushing's syndrome	Usually progressive to more severe clinical presentation
Prevalence of hypoadrenalism after surgery	Hypoadrenalism may results after removal of adrenal tumor	Hypoadrenalism invariably follow removal of causing tumor

Modified from Terzolo et al.²

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