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Review article

Possible, probable, and certain hypercortisolism: A continuum in the risk of comorbidity

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INFO ARTICLE

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ABSTRACT

Hypercortisolism may be considered as a continuum in terms of both hormonal and cardiometabolic abnormalities. It ranges from cases with "normal" hormonal profile and low to intermediate risk of comorbidity to florid cases with clear clinical and hormonal evidence of glucocorticoid excess and clearly increased cardiometabolic risk. Even in patients with nonfunctioning adrenal incidentaloma (NFAI), defined as adrenal incidentaloma with normal results on the currently available hormonal test for evaluation of hypercortisolism, cardiometabolic and mortality risk is higher than in the general population without adrenal lesions. Mild hypercortisolism or autonomous cortisol secretion (ACS) is a term used for patients with adrenal incidentaloma and pathological dexamethasone suppression test (DST) results, but without specific clinical signs of hypercortisolism. It is widely known that this condition is linked to higher prevalence of several cardiometabolic comorbidities, including diabetes, hypertension, osteoporosis and metabolic syndrome, than in patients with NFAI or without adrenal tumor. In case of overt Cushing's syndrome, cardiovascular risk is extremely high, and standard mortality ratio is high, cardiovascular disease being the leading cause of death. The present review summarizes the current evidence for a detrimental cardiometabolic profile in patients with possible (NFAI), probable (ACS) and certain hypercortisolism (overt Cushing's syndrome).

1. Introduction

A large amount of evidence indicates that patients with overt Cushing's syndrome are at increased risk of metabolic, cardiovascular, thrombotic, infectious and musculoskeletal complications [1,2], and thus of impaired quality of life because of these comorbidities [3]. In these patients with certain hypercortisolism, increased mortality is primarily due to cardiovascular events induced by the severe metabolic impact of glucocorticoid excess [2]. Overt Cushing's syndrome is in most cases caused by corticotroph pituitary adenoma, also known as Cushing's disease. More rarely it is caused by an extrapituitary tumor secreting adrenocorticotropin hormone (ACTH) or corticotropin-releasing hormone (CRH), or by an adrenal adenoma or carcinoma [4]. It is a rare entity with prevalence of around 40 cases per million and incidence of 0.7–2.4 cases per million per year [5].

Mild hypercortisolism or autonomous cortisol secretion (ACS) is defined by biochemical evidence of abnormal cortisol secretion without the specific clinical manifestations of overt Cushing's syndrome such as myopathy, bone fragility and skin fragility. ACS is frequently discovered in patients with adrenal incidentaloma (AI), in whom prevalence ranges between 5% and 50%, depending on the definition of ACS [6,7]. However, even without specific clinical signs of hypercortisolism and usually with normal urinary and nocturnal serum and salivary cortisol levels, glucocorticoid excess, if untreated, may increase cardiometabolic risk, including risk of diabetes, hypertension, osteoporosis and mortality. Since progression to overt Cushing's syndrome is relatively rare in ACS [8,9], it used to be considered that these patients had "subclinical Cushing's syndrome". However, more recent studies demonstrated that, although hypercortisolism can only be deemed probable, due to the lack of a totally accurate hormonal study compatible with hypercortisolism, the term "subclinical Cushing's syndrome" is inadequate because it does not properly describe the importance

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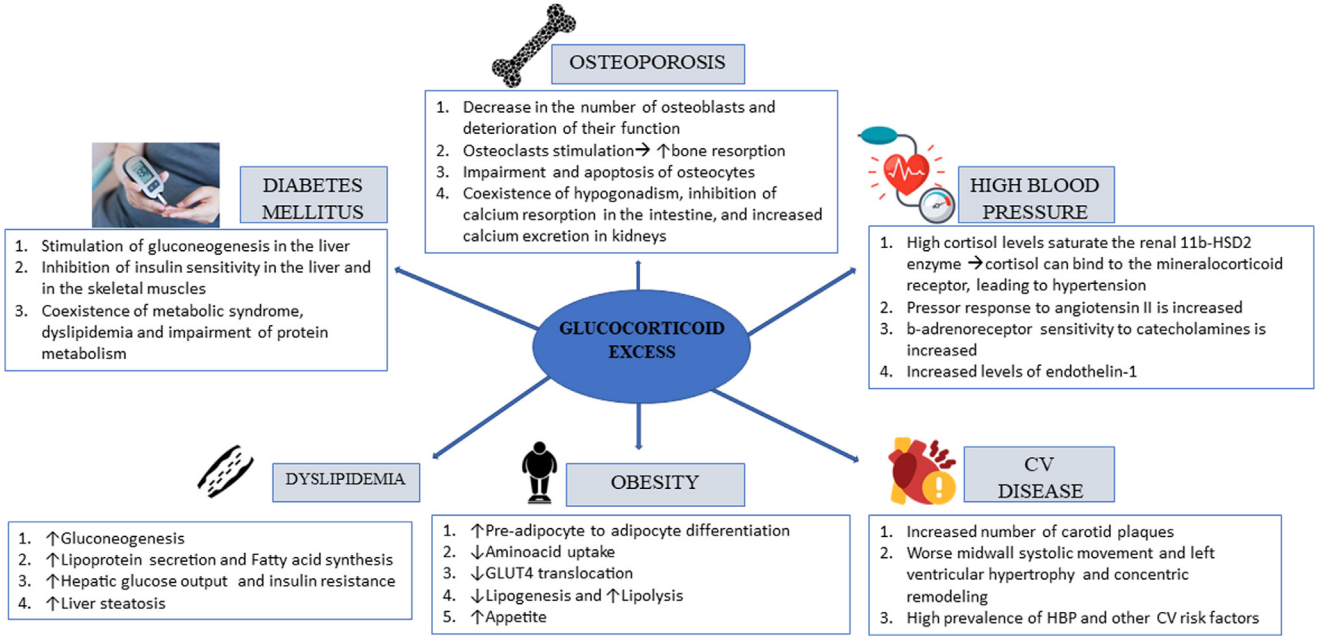

Fig. 1. Pathophysiology of the cardiometabolic risk in patients with hypercortisolism.

of this condition and its link to an unfavorable cardiometabolic profile [10].

In addition, it was more recently found that, even in patients with apparently nonfunctioning AI (NFAI), cardiometabolic and mortality risk is higher than in the general population [11–13]. NFAI is the most frequent hormonal presentation of AI, at approximately 65–90% of cases, depending on the dexamethasone suppression test (DST) threshold used to differentiate between NFAI and ACS [14]. Incipient alterations in cortisol metabolism, undetected on classic tests, may explain this higher cardiometabolic risk [15]. We therefore argue that these patients may indeed have hypercortisolism, and that NFAI would better be termed "adrenal lesion of undetermined secretion of adrenal steroids" (ALUSAS) [16]. Several mechanisms are responsible for the greater cardiometabolic risk in patients with hypercortisolism, whether possible, probable or certain, than in those without. Glucocorticoid excess affects a range of metabolic pathways, determining the different manifestations of the metabolic syndrome and other comorbidities (Fig. 1).

Thus hypercortisolism may best be seen as a continuum in terms of hormonal and cardiometabolic abnormalities, ranging from cases with "normal" hormonal profile and low to intermediate risk of comorbidity, to florid cases, with clear clinical and hormonal evidence of glucocorticoid excess and high to very high cardiometabolic risk. The present review summarizes the current evidence for a detrimental cardiometabolic profile in patients with possible hypercortisolism (ALUSAS/NFAI), probable hypercortisolism (ACS) and certain hypercortisolism (overt Cushing's syndrome) (Table 1).

2. Possible hypercortisolism (ALUSAS/NFAI)

2.1. Definition and epidemiology

NFAI is defined as an incidentally discovered >1 cm adrenal mass with normal hormonal values, including normal DST results, urinary or plasmatic metanephrines and aldosterone-to-renin ratio (when hypertension and/or hypokalemia are associated) [17]. Depending on the DST threshold defining NFAI, prevalence ranges from 65% (at a 1.8 μg/dL threshold) to 90% (at a 5.0 μg/dL threshold) of all AIs [14,18].

Overall, NFAI is a common clinical problem: prevalence of AI ranges from 4% to 10% in radiological studies [19]. Prevalence increases with age, with a peak in the sixth decade [20,21]. Some authors reported higher prevalence in women than men [20,22], but others found no difference according to gender [23]. NFAI is also more common in patients with obesity, diabetes or hypertension [24] (Table 2), perhaps due to a link between AI and insulin resistance [11]. However, the pathophysiological link between the two is unclear, since some studies suggest that AI elicits systemic insulin resistance while others suggest that autonomous adrenal cortisol secretion generates insulin resistance and obesity [25].

2.2. Comorbidities in NFAI

Evidence for an association between NFAI and increased cardiometabolic risk has become stronger in recent years (Fig. 2). Several studies [11–13,29–35] found higher cardiometabolic risk in patients with NFAI than in controls without adrenal tumor. Some surgical series reported improvement in cardiometabolic parameters after adrenalectomy in patients with apparently nonfunctioning adrenal tumor [36–41]. Bancos et al., in a meta-analysis [32], reported that 42%, 21.4% and 13% of NFAI patients showed improvements in blood pressure, diabetes and dyslipidemia, respectively, after adrenalectomy. All these studies suggest that subclinical secretion of metabolites of cortisol or other adrenal steroid hormones, not detected on classic tests, is harmful to the cardiometabolic system (Table 3). In addition, some authors even reported postsurgical adrenal failure in up to 30.8% of NFAI patients who underwent adrenalectomy, suggesting that these tumors are not really nonfunctioning [39].

2.2.1. Cardiovascular disease and arterial hypertension

Several studies reported higher risk of hypertension, including resistant [35,42,43] and masked hypertension [44], in patients with NFAI than in those without adrenal lesions. Hypertension prevalence in comparative studies between NFAI and controls was 40–75% vs. 10–55%, depending on the study population and design [35,43]. One study reported that the prevalence of hypertension was similar in patients with ACS and NFAI [45]. Moreover, as mentioned above, several studies reported significant improvement in

Table 1
Comorbidities through the spectrum of hypercortisolism. See text for details and references.

	NFAI (possible hypercortisolism)	ACS (probable hypercortisolism)	Cushing's syndrome (certain hypercortisolism)
Hypertension and cardiovascular disease	Incidence likely higher than in general population. Some evidence suggests higher cardiovascular risk. Benefit from adrenalectomy in some studies.	Increased incidence of hypertension and cardiovascular events. Improvement of hypertension control after adrenalectomy.	Hypertension in 50–90% of patients. Significant increase in cardiovascular events. Improvement/remission of hypertension and reduction of cardiovascular risk with treatment (but remains higher than in background population).
Bone disease	Scarce information. No significant difference in bone mass with respect to ACS	Increased incidence of vertebral fractures, despite no clear decrease in BMD. Scarce data about TBS.	Increased incidence of osteoporosis and osteoporotic fracture. TBS better predictor of fractures than BMD. Significant improvement after hypercortisolism remission.
Obesity and metabolic syndrome	Increased risk of metabolic syndrome compared to controls.	Increased risk of metabolic syndrome compared to controls.	80% suffer weight gain, with abdominal distribution. Increase in total and LDL-cholesterol and triglycerides, decrease in HDL-cholesterol. Improvement in weight and lipids with treatment.
Diabetes	Insulin resistance. Incidence of diabetes probably slightly increased.	Insulin resistance. Incidence of diabetes probably slightly increased (increases with age, size of adrenal adenoma and higher cortisol after 1mg-DST).	High risk of diabetes and prediabetes. Predictor of cardiovascular events, infection and mortality. Significant improvement with medical and surgical treatment.
Mortality	Cardiovascular mortality probably higher than background population.	Mild increase in mortality, mostly from cardiovascular causes (compared to background population or to NFAI)	Mortality 2- to 3-fold increased. Remission lessens but does not normalize mortality.

ACS: autonomous cortisol secretion; BMD: bone mineral density; DST: dexamethasone suppression test; NFAI: non-functioning adrenal incidentaloma; TBS: trabecular bone score

Table 2
Etiology and epidemiology of the various states of hypercortisolism.

Hypercortisolism condition	Prevalence	Etiology	Female:male sex ratio
Nonfunctioning adrenal incidentaloma	65–90% of AIs [14][a]	Adrenal	1.5–2:1 [20,22]
Autonomous cortisol secretion	30–50% of AIs [26][a]	Adrenal	1.7:1 [10]
Overt Cushing's syndrome	0.7 to 2.4 per million per year [27].	70% pituitary; 15% adrenal; 15% ectopic [4]	3.5:1 in pituitary origin, 1:1 in adrenal origin (4:1 in adenoma) and 1:1 in ectopic origin[b],[4]

AIs: adrenal incidentalomas.
[a] Adrenal incidentaloma prevalence in the general population is estimated at 1.4% (1.6% in men and 1.2% in women) [23].
[b] Sex ratio may vary depending on the etiology of ectopic Cushing's syndrome [28].

Table 3
Surgical series that evaluated cardiometabolic parameters after surgery in NFAI.

Author, date [ref]	Number of NFAIs	Evolution of cardiometabolic profile after surgery
Araujo-Castro, 2022 [38]	486; only 16 underwent adrenalectomy	NFAI with surgery: improvement in SBP vs. NFAI with non-operative treatment (-11.1 ± 15.94 vs. 1.0 ± 17.54 mmHg, $P = 0.009$).
Wang, 2022 [41]	171 cases; all underwent adrenalectomy	130 (76.0%) patients had a resolution of hypertension, and 57 (33.3%) a significant reduction in blood pressure after adrenalectomy.
Chiodini, 2010 [40]	67; 37 underwent adrenalectomy	NFAI with surgery: blood pressure improved more frequently and LDL levels worsened less frequently than in untreated NFAI.
Bernini, 2003 [36]	9 cases; all underwent adrenalectomy	Reduction in body weight and in SBP after adrenalectomy.
Midorikawa, 2001 [37]	11 cases; all underwent adrenalectomy	SBP decreased significantly after adrenalectomy in NFAI (from 148.8 to 136.2 mmHg).
Rossi, 2000 [39]	13 cases; all underwent adrenalectomy	Reduction of the number of antihypertensive and antidiabetic drugs after adrenalectomy in more than half of NFAIs.

NFAI: nonfunctioning adrenal incidentalomas; SBP: systolic blood pressure

blood pressure control after adrenalectomy in patients with NFAI [36–39,41]. The chances of resolving hypertension are better in females with low body mass index (BMI), high systolic blood pressure (SBP), and high aldosterone to plasma renin activity ratio [41]. The mechanism underlying the association between hypertension and NFAI is not fully elucidated, but some studies found that NFAI patients with hypertension had higher mean cortisol levels on 1 mg-DST than those without hypertension (1.3 ± 0.3 vs. 1.0 ± 0.4 μg/dL; $P = 0.03$) [35]. This supports the hypothesis that NFAI patients have a mild excess of cortisol, undetectable on diagnostic tests, but nevertheless harmful [16].

Regarding cardiovascular disease, a recent study found that patients at low to intermediate cardiovascular risk with NFAI had a higher risk of atherosclerosis than those without adrenal tumor

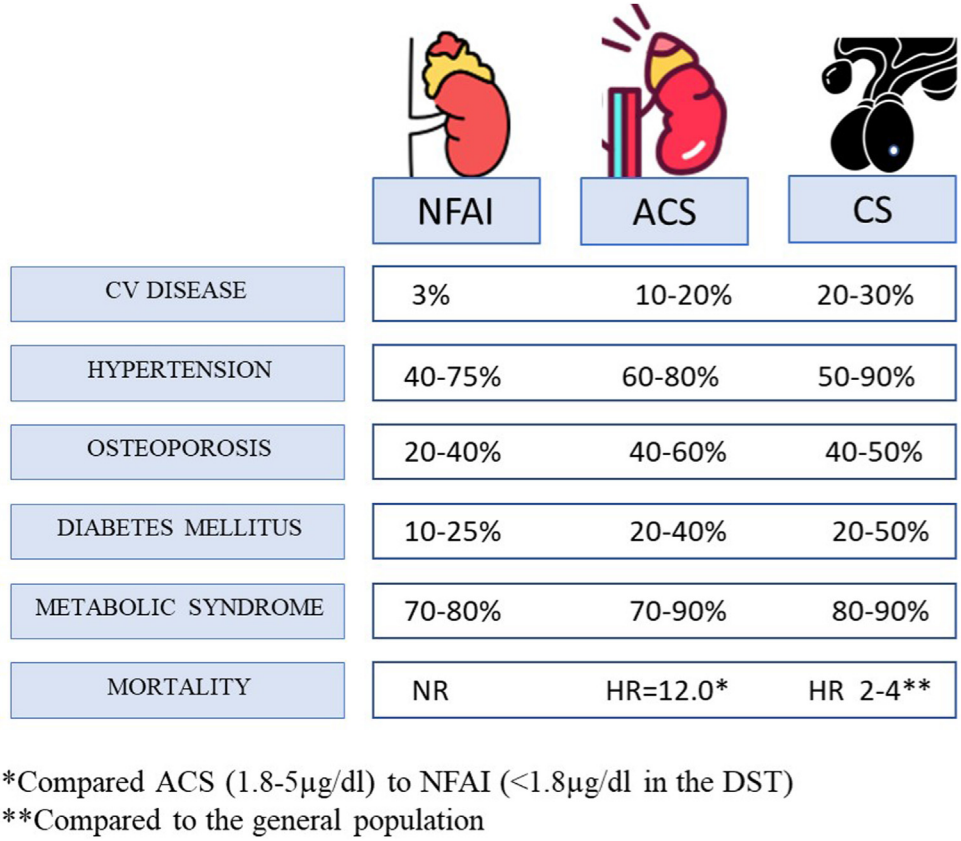

Fig. 2. Effects of hypercortisolism on bone formation. NFAI: non-functioning adrenal incidentaloma. ACS: autonomous cortisol secretion; CS: Cushing's syndrome; CV: cardiovascular disease.; NR: not reported; HR: hazard ratio.

[46]. Other studies reported higher prevalence of coronary artery or endothelial disease [46,47], increased epicardial fat thickness and higher prevalence of left ventricular (LV) hypertrophy [48,49]. Sokmen et al. [50] reported that patients with NFAI had higher LV mass index and worse LV myocardial performance than healthy controls. In addition, intra- and inter-atrial electromechanical delay was significantly longer in patients with NFAI. Greater carotid intima-media thickness in subjects with NFAI than healthy subjects was also reported in several studies [34,43,48,51]. One study [52] found that peripheral and central blood pressure and arterial stiffness were negatively affected in patients with NFAI and no traditional cardiovascular risk factors. Another study reported that, even after matching for BMI, NFAI patients had more cardiovascular risk factors than those without adrenal tumor [53]. Furthermore, in one of our recent studies we observed that at least two categories of cardiovascular risk could be established based on DST in patients with NFAI: patients with DST 0.9–1.8 µg/dL had higher cardiovascular risk than those with DST < 0.9 µg/dL (adjusted odds ratio (OR), 2.23 [1.10–4.53]) [54].

2.2.2. Bone disease

Although no studies compared prevalence of osteoporosis and bone quality in NFAI versus controls, some studies reported osteoporosis prevalence up to 64.9% in NFAI patients. Patients with ACS had lower trabecular bone scores (TBS) than those with NFAI, but prevalence of osteoporosis did not differ between NFAI (64.9%) and ACS (75%) ($P = 0.55$) [55]. Likewise, another study showed that patients with ACS presented significantly lower TBS, but not bone mineral density (BMD), than patients with NFAI [56]; overt fragility fractures tended to be associated with low TBS ($P = 0.07$) but not low BMD. According to some studies, TBS correlates inversely with 1-mg DST, regardless of age, lumbar BMD, BMI or gender [57]. Nevertheless, several studies highlighted that both ACS and NFAI patients show low levels of osteocalcin, probably due to reduced bone formation induced by a subtle excess of glucocorticoids [58]. Studies comparing bone density and quality in NFAI versus subjects without adrenal tumor are needed to determine whether NFAI is also associated with a higher risk of osteoporosis and fracture.

2.2.3. Diabetes and insulin resistance

Regarding insulin resistance in NFAI patients, Androulakis et al. [59] showed that NFAI was associated with higher insulin resistance indices than in healthy controls without adrenal tumor. Likewise, some authors argued that increased carotid intima-media thickness (IMT) index in NFAI was a consequence of the insulin-resistant state associated with subtle cortisol autonomy [51]. Notably, Lopez et al.'s cohort study, at a minimum 3 years' follow-up, found that NFAI patients had significantly higher risk of incident composite diabetes than those without adrenal tumor (adjusted risk ratio (RR), 1.87 [95% CI, 1.17–2.98]) [60]. Moreover, NFAI was associated with 15.6% (95% CI, 6.9–24.3%) greater risk of developing incident diabetes [61]. In another longitudinal cohort study of 154 NFAI patients and 1:3 age- and gender-matched controls without AI ($n = 462$), covariate-adjusted logistic regression showed a significantly higher OR for diabetes in the NFAI group (adjusted OR, 1.89 [95%CI 1.17–3.06]). Moreover, NFAI subjects with diabetes showed larger adrenal lesions at follow-up than those without ($P = 0.048$) [62]. Supporting these findings, a recent meta-analysis found that patients with NFAI had a 2-fold greater OR for type 2 diabetes and higher fasting plasma glucose levels than controls [13].

Table 4
Thresholds (mcg/dL) in the 1 mg dexamethasone suppression test for the diagnosis of possible ACS and ACS proposed by the various guidelines.

	ESE/ENSAT	SEEN	FES	AME	AACE/AAES	NIH
Author, date [ref.]	Fassnacht, 2016 [6]	Araujo-Castro, 2020 [77]	Tabarin, 2008 [68]	Terzolo, 2011 [67]	Zeiger, 2009 [92]	Grumbach, 2003 [70]
Possible ACS	1.9–5	1.9–5	1.9–5	1.9–5	> 5	> 5
ACS	> 5	> 5 or > 3 + other criteria[a]	> 5	> 5	> 5 + other criteria[a]	> 5 + other criteria[a]

ACS: autonomous cortisol secretion; AACE/AAES: American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; AME: Italian Association of Clinical Endocrinologists; ESE/ENSAT: European Society of Endocrinology/European Network for the Study of Adrenal Tumors; FES: French Endocrinology Society; NIH: National Institutes of Health; SEEN: Spanish Society of Endocrinology and Nutrition.

[a] At least one of the following criteria: elevated urinary free cortisol, low ACTH, elevated midnight serum or salivary cortisol, or low DHEAS.

2.2.4. Obesity and metabolic syndrome

Increasing evidence supports an association between NFAI and several parameters of metabolic syndrome: insulin resistance, obesity, hypertension, hyperglycemia and dyslipidemia [63]. Metabolic syndrome is significantly more frequent in NFAI patients than in the general population [64]. Depending on the definition, prevalence ranges from 81.7% based on the NCEP-ATP III definition to 69.2% based on the WHO criteria, compared to 44.9% and 31.0% in controls, respectively [65]. Another recent study evaluating body composition using dual-energy X-ray absorptiometry (DXA) found that the prevalence of metabolic syndrome on WHO criteria was 80.6% in NFAI vs. 43.6% in controls ($P < 0.001$), and 85.5% vs. 46.4% based on AACE criteria ($P = 0.001$) [64]. A previous study that evaluated body composition by DXA and quantitative CT showed that premenopausal patients with NFAI had a higher percentage of total body fat and trunk fat than premenopausal controls [59]. The authors suggested that subtle disturbances of steroid secretion are probably also present in NFAI, although they cannot yet be detected with a sufficient degree of specificity. On this hypothesis, we recently demonstrated that the profile of urinary steroid metabolites observed in adrenal tumor, with low excretion of androgen metabolites and high excretion of glucocorticoid metabolites, was associated with less lean and bone mass and more visceral mass in patients with adrenal tumor [66]. Central obesity and insulin resistance are among the main pathogenic factors of metabolic syndrome, and their prevalence was reported to be higher in NFAI than in controls in several studies [64,65]. However, NFAI has also been reported to be an independent risk factor for metabolic syndrome [64].

3. Probable hypercortisolism

3.1. Definition of possible ACS and ACS

ACS is a diagnostic challenge, given the lack of consensus on its definition and on the cut-off points to be used in the various screening tests. The most widely accepted test for initial screening of ACS is the 1mg-DST [6,67–70], but there is still no consensus on which cut-off point should be used (Table 4). In addition, conditions and drugs that may interfere with the test results must be taken into account, and some experts recommend simultaneous measurement of cortisol and dexamethasone for this test to ensure that dexamethasone plasma concentrations allow assessment of false-positives due to abnormal metabolism or drug absorption [71–74]. Potential causes of false-positives should be ruled out: oral estrogens, CYP3A4 inducers, exogenous glucocorticoids, poorly controlled diabetes, alcoholism, psychiatric disorders, liver and/or kidney failure, morbid obesity, etc. [10,73,75,76]. Several clinical guidelines recommend DST for initial screening of ACS and, in case of a pathological result, completing with other tests: nocturnal serum or salivary cortisol, urinary free cortisol (UFC), and ACTH [6,76,77]. Suppressed or low basal morning plasma ACTH, elevated midnight serum or salivary cortisol and/or increased UFC support the diagnosis of ACS. Low DHEAS also reinforces diagnosis of ACS [78–80]. However, in mild ACS, UFC is usually normal and the accuracy of midnight salivary cortisol is low [81–89].

The ESE-ENSAT guidelines define possible ACS by post-DST serum cortisol 1.9-5.0 mcg/dL, and ACS by > 5.0 μg/dL [6]. On the other hand, the Adrenal Diseases Group of the Spanish Society of Endocrinology and Nutrition has the same definition for possible ACS but defines ACS by post-DST serum cortisol > 5.0 μg/dL or > 3.0 μg/dL with other associated hormonal criteria [77] (Table 4). Mild ACS is diagnosed in up to 30% to 50% of patients with AI [6,29,90]. However, for clinical management, potentially cortisol-related comorbidities such as high blood pressure, type 2 diabetes or osteoporosis and the age of the patient are of major importance [91].

3.2. Comorbidities in ACS and possible ACS

In patients with possible or confirmed ACS without typical signs or symptoms of overt Cushing's syndrome, the frequency of several cardiometabolic disorders associated with cortisol excess is higher: arterial hypertension, type 2 diabetes, obesity, dyslipidemia, osteoporosis, and increased mortality [93,94] (Fig. 2).

3.2.1. Cardiovascular diseases and arterial hypertension

Patients with ACS are at higher risk of cardiovascular disease and hypertension [29,59,95–100]. Furthermore, patients with mild hypercortisolism are also at risk of new cardiovascular events such as coronary heart disease and ischemic or hemorrhagic stroke [96]. Patrova et al. [101] showed that patients with post-DST cortisol > 1.8 μg/dL were more affected by cardiovascular disease and hypertension, and Prete et al. [39] demonstrated that the prevalence and severity of hypertension increased in patients with cortisol levels > 5 μg/dL on 1 mg-DST. On the other hand, Zhang et al. [102] found no notable differences in the prevalence and incidence of cardiometabolic disease between patients with NFAI and mild ACS. However, previous studies reported a higher prevalence of atherosclerosis and impaired vessel dilation and structure, with potential cardiac dysfunction as a consequence, demonstrating the adverse effect of cortisol excess on cardiovascular risk and increased morbidity and mortality in these patients [59,103–106].

For this reason, the ESE guidelines recommend screening for high blood pressure in all patients with possible ACS or ACS [6]. Moreover, intensive treatment of hypertension and of all cardiovascular risk factors is recommended in patients with ACS (taking into account the risk/benefit ratio), with the aim of reducing overall cardiovascular risk [6,10]. It should be borne in mind that hypertension is the disorder that improves the most after surgery in patients with ACS [32]. In fact, in Bancos et al.'s meta-analysis [32], patients with ACS or possible ACS undergoing adrenalectomy as compared with conservative management experienced significant improvement in hypertension (RR 11, 95% CI: 4.3–27.8) and type 2 diabetes (RR 3.9, 95% CI: 1.5–9.9), but not in other cardiometabolic parameters.

3.2.2. Bone disease

Patients with ACS are also at significantly higher risk of osteoporosis and vertebral fracture than patients with NFAI [107–110].

Chiodini et al. [111] reported that more than 10% of patients referred for evaluation of osteoporosis had subclinical hypercortisolism. The level of cortisol secretion correlated positively with the rate of bone loss [112]. The incidence of vertebral fracture is significantly higher in patients with ACS [57,110,113–117], and Salcuni et al. [94] found that adrenalectomy reduced the risk of vertebral fracture in patients with ACS.

The pathophysiology of glucocorticoid-induced osteoporosis is complex, and includes direct effects such as decrease in number and worsening of function of osteoblasts, stimulation of osteoclasts that enhances bone resorption, and impairment and apoptosis of osteocytes, and indirect effects such as hypogonadism, inhibition of calcium reabsorption and increased calcium excretion. Consequently, cortisol excess induces a decrease in BMD and deterioration in bone quality [108]. Since microarchitecture shows more severe deterioration than BMD, the role of DXA in fracture risk prediction is unknown and study results are inconclusive. Some studies found no difference in BMD in the lumbar spine and femoral neck between patients with and without mild ACS [39,110,113], while other studies found the opposite [57,107–109,114–116]. Another tool for assessing bone quality is TBS, which appears to be a better option when diagnosing osteoporosis in ACS and could help assess fracture risk in osteoporosis when BMD results are inconclusive [118], although data for TBS in mild ACS are scarce [56,57]. Vinolas et al. found that fracture was associated with low TBS but not with low BMD [56], and McCloskey et al. reported that TBS could be a significant predictor of fracture risk independently of fracture risk assessment on FRAX score [119]. The spinal deformity index can also provide additional information on bone microarchitecture and could be a good indicator of bone condition, although data in mild ACS are limited [107,110,120,121]. Finally, ACS has also been shown to be associated with decreased blood levels of osteocalcin, but with no consistent changes in other markers of bone formation or markers of bone resorption [122].

3.2.3. Diabetes and insulin resistance

Mild ACS may impair glucose metabolism, although results were inconclusive. The prevalence of mild ACS in patients with type 2 diabetes ranges from 0 to 9.4% [123–130], probably depending on study design and the cut-off points in the tests performed (DST and/or late-night salivary cortisol). In addition, some studies reported higher prevalence of type 2 diabetes in patients with mild ACS, at 20–75%, depending on the diagnostic criteria [39,96,131–134]. The risk of type 2 diabetes was higher in patients with impaired cortisol suppression after 1 mg-DST and increased further during follow-up [7,29,96], proportionally to the degree of hypercortisolism, the age of the patient and the size of the adenoma [135]. In contrast, other studies reported that the prevalence of type 2 diabetes was not significantly greater in patients with pathologic cortisol secretion [82,97,98,101,136]. This discrepancy could be due not only to the lack of clear criteria for mild ACS, but also to different methods of diagnosis of diabetes. Lastly, some studies reported poorer metabolic control in diabetic patients with mild ACS [124,137]. Regarding insulin resistance, some studies found a correlation between insulin resistance and mild ACS [138]. Reincke et al. found that most patients with AI were insulin-resistant [139]. Other studies found increased insulin resistance and lower insulin sensitivity in non-diabetic patients with either mild ACS or NFAI [140,141].

3.2.4. Obesity and metabolic syndrome

ACS can cause metabolic syndrome, mediated directly by cortisol excess or indirectly by insulin resistance associated with ACS, especially in case of dyslipidemia and specifically hypertriglyceridemia (considered to be a surrogate marker of insulin resistance) [134,142]. Reincke et al. [139], in a series of 13 patients with incidentally detected adrenal tumor, reported that the majority were insulin-resistant with obesity and abdominal fat tissue distribution, and suggested that the AI was a manifestation of the metabolic syndrome [139]. Subsequent studies showed an association between AI and cardiometabolic morbidity and highlighted the need for metabolic syndrome screening during initial workup in AI [11,63]. Abnormalities in serum lipid concentration were also found in patients with mild ACS [39,134]. However, some studies linked dyslipidemia with insulin resistance associated with mild ACS: in the study by Masserini et al. [142], in the absence of alterations of glucose metabolism, a mild excess of cortisol had no effect on lipid pattern. On the other hand, Morelli et al. [96] did not find a significant difference in the prevalence of dyslipidemia between patients with and without mild ACS. Thus, patients with AI, who may also have mild ACS, are more likely to develop metabolic syndrome. Furthermore, mild ACS can be associated with lipid abnormalities, although the connection appears to be indirect, via insulin resistance.

3.2.5. Mortality

ACS is associated with increased mortality, mainly related to cardiovascular disease and infection [7,93,101]; therefore it is important to identify it. Several studies showed that patients with mild ACS have an increased risk of mortality, mostly from cardiovascular causes [29,93]. Moreover, previous studies demonstrated that patients with ACS have higher rates of cardiovascular disease and death than those with NFAI [29,101].

3.2.6. Other associations

ACS may also be associated with nonalcoholic fatty liver disease (NAFLD). Several studies reported an association between cortisol excess and NAFLD [143–146], while others found no association between NAFLD and plasma cortisol concentration [147] or AI (including mild ACS) [148]. Other possible associations found by different authors include thromboembolic disease [149] and psychiatric disorders [150]. However, since there are few studies, further research is needed to clarify these possible associations with ACS.

Treatment of ACS is not consensual. In general, a conservative approach is suggested, which implies treating comorbidities. The European Society of Endocrinology recommends an individualized approach when surgical removal of the adrenal lesion is required [6] (Table 5).

4. Certain hypercortisolism (Overt Cushing's syndrome)

4.1. Definition and epidemiology

Certain hypercortisolism (overt Cushing's syndrome) is characterized by clearly excessive and autonomous secretion of glucocorticoids, documented by elevated UFC and loss of both the suppressive response to exogenous glucocorticoids and the circadian rhythm of cortisol secretion. ACTH-secreting pituitary tumors are the leading etiology of this syndrome, at 65-70% of cases, but ectopic ACTH-secreting tumors (around 10%) and adrenal adenomas or carcinomas (15-20%) can also be found (Table 1). In contrast to adrenal adenomas with possible and probable hypercortisolism, which are quite common, overt Cushing's syndrome is rare, with prevalence of around 40–80 cases per million and incidence of 0.2–5 cases per million per year [4]. Women are more frequently affected than men, especially when the underlying cause is a pituitary tumor.

Table 5
Studies that reported improvement in cardiometabolic conditions after surgery in adrenal incidentalomas with ACS.

Author [ref.], date	*n* (total)	Results
Raffaelli et al. [151], 2017	29 (29)	Improvement in hypertension and diabetes.
Bancos et al. [32], 2016	429 (584)	Improvement in hypertension, diabetes, obesity and dyslipidemia. Only hypertension and diabetes when compared with conservative management
Salcuni et al. [94], 2016	32 (55)	Improvement in BMD and reduction in risk of vertebral fracture.
Iacobone et al. [152], 2012	20 (35)	Improvement in blood pressure, glycemic control, BMI and quality of life.
Chiodini et al. [40], 2010	25 (108)	Improvement in weight, blood pressure, and glucose levels.
Toniato et al. [153], 2009	23 (45)	Improvement in diabetes, hypertension, hyperlipidemia and obesity. No improvement in osteoporosis.
Tsuiki et al. [154], 2008	10 (20)	Improvement in cardiovascular risks (hypertension, impaired glucose metabolism and dyslipidemia).
Mitchell et al. [155], 2007	9 (24)	Improvement in blood pressure, glycemic control and BMI.
Bernini et al. [36], 2003	6 (15)	Improvement in glucose profile and hypertension.
Emral et al. [156], 2003	3 (70)	Improvement in blood pressure, glycemic control and BMI.
Midorikawa et al. [37], 2001	4 (15)	Improvement in insulin resistance and blood pressure.
Rossi et al. [39], 2000	5 (50)	Improvement in blood pressure, glucose and lipid values.

BMD: bone mineral density. BMI: body mass index. N (total): number of cases with ACS adrenal incidentalomas who underwent adrenalectomy and total study population.

4.2. Comorbidities

Overt Cushing's syndrome is often diagnosed from external changes such as abdominal obesity, muscle wasting in the limbs and buttocks and skin atrophy, with striae and hirsutism. However, comorbidities are sometimes the diagnostic clue: worsening diabetes or hypertension or a thrombotic event (Fig. 2). In this section, we review recent data about the prevalence of these complications and the increased mortality in Cushing's syndrome.

4.2.1. Hypertension and cardiovascular disease

Hypertension is one of the most common symptoms in the clinical presentation of Cushing's syndrome, found in 50–93% of patients. Systolic and diastolic blood pressure are raised equally, and the physiological nocturnal decrease is frequently lost. The prevalence of hypertension increases with age and with longer exposure to hypercortisolism [3,157–160]. Remission of hypercortisolism can improve but does not always normalize hypertension: hypertension was reported in 25–54% of patients in remission [3,161,162].

Cushing's syndrome incurs high cardiovascular risk, and cardiovascular events are a leading cause of mortality in these patients. The high rates of hypertension, dyslipidemia and diabetes in Cushing's syndrome underlie the increase in atherosclerosis, seen as increased intima-media thickness in both carotid and aortic arteries, but the development of myocardial fibrosis, related to enhanced responsiveness to angiotensin II and activation of the mineralocorticoid receptor in response to cortisol excess, has been suggested to be another underlying cause of cardiac damage. The procoagulant state promotes cardiovascular events, and hypokalemia can increase the risk of arrhythmia [3,163]. In a recent Mexican series of 172 patients with Cushing's disease followed for a median 7.5 years, ischemic heart disease occurred in 3.4% and cerebrovascular disease in 7% of cases [157].

Since cardiovascular diseases are so prevalent in the general population and a leading cause of death in developed countries, studies of the incidence of cardiovascular events in patients with Cushing's syndrome in comparison with the background population are of special interest. A study comparing 343 patients with benign Cushing's syndrome versus the general Danish population found an increased risk of myocardial infarction (hazard ratio (HR) 3.7, 95%CI 2.4–5.5) and stroke (HR 2.0, 95%CI 1.3–3.2) at diagnosis [164]. The risk of myocardial infarction remained elevated during long-term follow-up. A recent analysis of the Swedish National Patient Register, in which 502 patients with a diagnosis of Cushing's disease were compared to the general Swedish population, found that, in the three years before diagnosis, the standardized incidence ratio (SIR) of myocardial infarction was 4.4 (95%CI 1.2 to 11.4). In the long term, these patients likewise showed higher risk of cardiovascular disease, with 3-fold higher SIR for stroke and 2-fold higher SIR for myocardial infarction, risk being especially high for patients not achieving remission (SIR for stroke, 8.2 (95%CI 3.8–15.6) [165].

4.2.2. Thrombotic events

Hypercoagulability is a clinical characteristic of active Cushing's syndrome [166,167]. Thrombotic events are significantly more prevalent after pituitary and adrenal surgery to treat Cushing's syndrome than in other indications [168]. This hypercoagulable state reverses after successful surgery [169].

Analysis of the Swedish National Patient Register, found an increased risk of thromboembolism throughout the course of the disease, being maximal from diagnosis to remission, most likely due to hospitalization and surgical treatment (SIR 13.8 in the three years before diagnosis, 18.3 from diagnosis to remission, and 4.9 once remission was achieved) [165]. A single-center retrospective study of 208 patients with Cushing's syndrome documented a thrombotic event in 18.2% of patients, with some suffering more than one event: lower-limb deep venous thrombosis (38%), stroke (27%), myocardial infarction (21%), and pulmonary embolism (14%); most occurred in the 60 days following surgical treatment [69]. A similar study was undertaken in all the university hospitals in the Netherlands: 7.8% of the 473 patients suffered a thrombotic event in the three years before and the three years after first treatment (14.6 events per 1,000 person-years) [170]. A systematic meta-analysis that included 7142 patients with Cushing's syndrome concluded that the odds ratio for spontaneous thromboembolism in Cushing's syndrome is 17.82 (95% CI 15.24–20.85, $P < 0.00001$) compared to a healthy population.

4.2.3. Bone disease

Chronic hypercortisolism is related to persistent hyperactivity of osteoclasts and a decrease in the number and function of osteoblasts, which can lead to bone mass loss [166]. Bone formation markers are diminished and bone resorption markers are elevated [3]. Hypercortisolism can induce hypogonadotropic hypogonadism and growth hormone/IGF1 deficiency, both further reducing bone mass (Fig. 2). Osteopenia and osteoporosis are frequent comorbidities in overt Cushing's syndrome. Fractures occur even in patients with BMD in the normal or osteopenic range. The risk of osteoporosis and fracture is higher in men than in women. Remission of Cushing's syndrome improves the situation but does not always restore normal bone mass [3].

A 2022 analysis of the more than 1,550 patients in the European Register on Cushing's Syndrome found spine and hip osteoporosis in 23% and 12% of patients, respectively; vertebral fractures were reported in 41% of patients, rib fractures in 39% and hip fractures in 5%, and these numbers may be underestimated, because systematic screening for bone fracture is not usually performed and many fractures may be almost asymptomatic, remaining undiagnosed [160]. The Swedish National Patient Register also showed increased SIR for fractures (4.9, 95%CI 2.7–8.3) in the three years before diagnosis in patients with Cushing's disease, remaining slightly elevated after remission [165]. Rates of osteoporosis and clinical fracture were even higher in studies with systematic evaluation of bone mass and fracture in Cushing's syndrome. Randazzo et al. [171] published a densitometric evaluation of 20 patients with Cushing's syndrome, at baseline and after remission: at baseline all patients showed osteopenia/osteoporosis and the spine appeared more damaged than the femur; spine and femur bone parameters correlated with disease duration and severity of hypercortisolism, but did not differ between patients with or without deficiencies in GH or other pituitary hormones. After cure of hypercortisolism, there was significant progressive improvement in all patients, with normalization of bone mass in 3 cases. Bisphosphonates did not influence the recovery of bone mineralization. Braun et al. [172] evaluated 89 patients with Cushing's syndrome, at diagnosis and two years after surgical treatment, and compared them to 71 matched controls. At diagnosis 52% had osteopenia, an additional 17% had osteoporosis, and 9% had a history of osteoporotic fracture. BMD improved after surgery in 78% of cases and no clinical fractures occurred after successful treatment of the Cushing's syndrome.

4.2.4. Diabetes and insulin resistance

Glucocorticoid excess interferes with the action of insulin through downregulation of the intracellular signaling pathways, and promotes a state of insulin resistance characterized by excessive liver gluconeogenesis and diminished glucose uptake in muscle cells, due to decreased translocation of glucose transporters (GLUT4) to the plasma membrane. Diabetes was found in 20–45% of patients with Cushing's syndrome and an additional 10-30% met the criteria for prediabetes [3,135,157–159,161]. Diabetes is a strong predictor of cardiovascular events, infection and increased mortality; whether better glycemic control can reduce these risks is not known. The prevalence of diabetes in Cushing's syndrome was higher than in BMI-matched controls, and glucose and insulin concentrations after oral glucose loading were higher, suggesting that some effects on insulin resistance are independent of weight [173]. Glucose metabolism improved with medical or surgical treatment of Cushing's syndrome, with the exception of the somatostatin analog pasireotide, which impaired glycemic control [3,135,161,173].

4.2.5. Obesity and dyslipidemia

Weight gain is a very common complaint in patients with Cushing's syndrome, affecting over 80% of them, but mean BMI is not very high (mean, 31.7 in 1,564 patients in the European Register on Cushing's Syndrome) and the percentage of obese patients varies greatly between series, from 25% to 100% [3,159,160]. The characteristic distribution of fat, with a clear predominance of visceral over subcutaneous fat, is linked with insulin resistance, metabolic syndrome and atherosclerosis. Significant improvements in BMI are observed after remission, and also after pharmacological treatment [3,159].

Lipid profile in Cushing's syndrome is characterized by high levels of total and LDL-cholesterol and triglycerides, and low HDL-cholesterol, increasing cardiovascular risk. There is no unanimously accepted definition of dyslipidemia, whence the wide range of prevalence, from 12% to 72%, in series of patients with Cushing's syndrome, with missing data in many other reports [3,174]. Although dyslipidemia usually improves following remission of Cushing's syndrome, a more adverse lipid profile than in healthy controls may persist [161,173]. Pharmacological treatment can also improve lipid parameters, apart from mitotane, which markedly raises the cholesterol level.

4.2.6. Mortality

A considerable number of studies in recent years reported increased overall and cardiovascular mortality in patients with Cushing's syndrome, not only during the active phase of the disease but also after remission. Most data came from patients with pituitary-dependent hypercortisolism, but there is no evidence that other causes of benign endogenous Cushing's syndrome have a different prognosis. Mortality is undoubtedly higher in patients with adrenocortical carcinoma and ectopic ACTH-secreting tumor [3].

Mortality was twice as high in a series of 343 Cushing syndrome patients (HR 2.3, 95%CI 1.8–2.9) as in more than 34,000 controls in the general Danish population. The HR for mortality was higher in the first year after diagnosis (5.2, 95%CI 2.7–9.7) than in subsequent years (2.1, 95%CI 1.7–2.7) [164]. Similar results were found in a Mexican series of 172 patients with Cushing's disease, with a median follow-up of 7.5 years, with an all-cause standardized mortality ratio (SMR) of 3.1 (95%CI 1.9–4.8, $P < 0.001$). Cardiovascular disease was the main cause of death (SMR = 4.2, 95%CI 1.5–9.3, $P = 0.01$) [157]. Active disease, diabetes and higher afternoon cortisol increased the mortality risk on multivariate analysis.

A recent matched analysis of 371 patients with Cushing's disease found higher overall mortality in patients than in matched controls (HR 2.1, 95%CI 1.5–2.8). HR was 1.5 (95%CI 1.02–2.2) for patients in remission at last follow-up and 5.6 (95%CI 2.7–11.6) for those not in remission. Cardiovascular disease (48.5%) and infection (18.2%) were the most frequent causes of excess death [175]. A systematic review and meta-analysis of all-cause and specific mortality in patients with benign endogenous Cushing's syndrome, including 14 articles and 3,691 patients, found an SMR of 3.0 (95%CI, 2.3-3.9; $I^2 = 80.5\%$). The major contributor to excess mortality was cardiovascular disease, implicated in 43.4% of all deaths [176]. The results were similar to those found in a previous meta-analysis seven years previously [177].

Finally, a multinational multicenter retrospective cohort study from referral centers in the UK, Denmark, the Netherlands and New Zealand, including patients cured of hypercortisolism for a minimum 10 years at study entry, with a median follow-up of 11.8 years from study entry, found an SMR of 1·61 (95%CI 1.23–2.12; $P = 0{\cdot}0001$) in comparison to the general population. The SMR for cardiovascular disease was increased, at 2.72 (95%CI 1.88–3.95; $P < 0{\cdot}0001$). Diabetes, but not hypertension, was an independent risk factor for mortality (HR 2·82, 95%CI 1.29–6.17; $P = 0{\cdot}0095$). Life expectancy was normal for the subgroup of patients in remission after pituitary surgery alone. The authors speculated that this might be related to factors such as less severe hypercortisolism, shorter time from diagnosis to cure, less complex treatment and less hypopituitarism, including less post-treatment requirement for replacement therapy with glucocorticoids [178].

5. Conclusion

Hypercortisolism may be considered a continuum in terms of both hormonal and cardiometabolic abnormalities. The milder cases are those with "normal" hormonal parameters (nonfunctioning adrenal incidentaloma: NFAI) but increased cardiometabolic risk compared to the general population, so that hypercortisolism is also possible in NFAI. In the middle of the spectrum are patients with probable hypercortisolism (possible autonomous

cortisol secretion (ACS) and ACS), who show increased prevalence of several cardiometabolic comorbidities, including diabetes, hypertension, osteoporosis and metabolic syndrome, compared to patients with NFAI or without adrenal tumor. Lastly, the more severe cases correspond to patients with overt Cushing's syndrome, with clear clinical and hormonal evidence of glucocorticoid excess and clearly increased cardiometabolic risk and mortality than in ACS, NFAI or the general population.

Human and animal rights

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Informed consent and patient details

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