Mild Autonomous Cortisol Secretion

Approach to Diagnosis, Evaluation, and Management

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KEYWORDS

• Mild autonomous cortisol secretion • Mild autonomous cortisol excess
• Adrenal nodule • Adrenal incidentaloma

KEY POINTS

- Mild autonomous cortisol secretion (MACS) is diagnosed in 20% to 50% of patients with adrenal nodules and is characterized by an abnormal 1-mg dexamethasone suppression test without features of Cushing syndrome.
- MACS is associated with increased risk of cardiometabolic disease, vertebral fractures, and mortality compared to patients with nonfunctioning adrenal nodules.
- Treatment with adrenalectomy may improve cardiometabolic morbidity and reduce the risk of vertebral fractures in select patients with MACS.

INTRODUCTION

Adrenal nodules are common incidental findings reported in 5% to 7% of adults who undergo abdominal imaging scans for reasons other than suspected adrenal disease[1,2] and 1% of adults in an unselected screening population.[3] With the widespread use of cross-sectional imaging scans and improved imaging techniques over the past 2 decades, the incidence of adrenal nodules has increased by 10-fold between 1995 and 2017.[4] In each person with a newly diagnosed adrenal nodule, the evaluation focuses on two main questions: (1) is the adrenal nodule benign or malignant, and (2) is the adrenal nodule producing excess adrenal hormones?

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Abbreviations	
ACTH	adrenocorticotrophic hormone
CS	Cushing syndrome
DST	dexamethasone suppression test
DHEAS	dehydroepiandrosterone-sulfate
ESE-ENSAT	European Society of Endocrinology and the European Network for the Study of Adrenal Tumors
MACS	mild autonomous cortisol secretion
NFAT	nonfunctioning adrenal tumor
PBMAH	primary bilateral macronodular adrenal hyperplasia

The majority of incidentally discovered adrenal nodules or *incidentalomas* are benign adrenocortical adenomas (80%–96% [depending on the study population]) and can be associated with variable cortisol production ranging from nonfunctioning adrenal tumor (NFAT) to overt Cushing syndrome (CS).[3–7] While CS is relatively rare in adrenal nodules, mild autonomous cortisol secretion (MACS)—characterized by inadequate suppression of serum cortisol following the overnight 1-mg dexamethasone suppression test (DST) in the absence of classic signs and symptoms of CS—is much more prevalent.[5] Here, we review the clinical approach to the diagnosis, evaluation, and management of patients with MACS and unilateral adrenal nodules.

BACKGROUND AND TERMINOLOGY

The understanding of the clinical implications of MACS has evolved over time, and with it, the terminology used to describe the condition. MACS has previously been referred to as *subclinical hypercortisolism*, *preclinical hypercortisolism*, or *subclinical CS*.[8] However, these terms are misleading because (1) patients with MACS have an increased likelihood of clinical complications including cardiometabolic disease and vertebral fractures compared to patients with NFAT or referent individuals without adrenal nodules, and (2) MACS is not considered a risk factor for the development of CS.[5,9–11] In a systemic review and meta-analysis of 4121 patients with adrenal adenomas followed for a mean of 50.2 months, less than 1% of patients with MACS progressed to CS during the follow-up period, suggesting that MACS is a separate clinical entity rather than a milder version of CS.[10] The exception are patients with primary bilateral macronodular adrenal hyperplasia (PBMAH) who may progress from NFAT to MACS to CS when the adrenal glands enlarge over time.[12] PBMAH is the focus of article no. 6- *Primary Bilateral Macronodular Adrenal Hyperplasia* by Koukoula and colleagues in this issue and will not be discussed in detail here.

Other terms that have been used in the literature include *autonomous cortisol secretion* and *mild autonomous cortisol excess*.[10,13] The use of MACS was first introduced by Di Dalmazi and colleagues in 2020[14] and has emerged as the terminology of choice in recent influential publications, including the 2023 clinical guidelines on the management of adrenal incidentalomas from the European Society of Endocrinology and the European Network for the Study of Adrenal Tumors (ESE-ENSAT).[5,15]

EPIDEMIOLOGY

In patients with adrenal nodules who undergo hormonal workup, MACS is the most common hormone abnormality and is diagnosed in 20% to 50% of patients with adrenal incidentalomas.[3,5,16] Compared to patients with NFAT, patients with MACS are more likely to be women (60%–70%), older (median age 62–65 years), and present

with larger adrenal nodules (median diameter >2.5 cm) and bilateral adrenal disease (20%–40%).[9,17,18]

DIAGNOSIS OF MILD AUTONOMOUS CORTISOL SECRETION

Several biochemical criteria have been used for the diagnosis of MACS over the years. Most have involved an abnormal 1-mg DST with proposed serum cortisol cutoffs ranging from 1.8 to 5.0 mcg/dL, either alone or in combination with elevated late-night salivary cortisol, elevated 24-hour urine free cortisol, and/or suppressed adrenocorticotrophic hormone (ACTH).[17,19] In 2016, the ESE-ENSAT guidelines on the management of adrenal incidentalomas simplified the diagnostic criteria for MACS to the 1-mg DST alone without the need for additional screening tests for hypercortisolism.[19] Patients were initially stratified based on post-DST serum cortisol of 1.8 to 5.0 mcg/dL as *possible autonomous cortisol secretion* and post-DST serum cortisol above 5.0 mcg/dL as *autonomous cortisol secretion*.[19] However, due to accumulating evidence that patients classified as *possible autonomous cortisol secretion* have increased risk of cortisol-mediated comorbidities similar to patients with *autonomous cortisol secretion*, this distinction was removed in the subsequent 2023 ESE-ENSAT guidelines.[5,17]

Current practice guidelines recommend all patients with adrenal nodules undergo screening for MACS with the 1-mg DST.[5,20] MACS is diagnosed when serum cortisol fails to suppress to $\leq$1.8 mcg/dL following the overnight 1-mg DST in patients who lack signs and symptoms of CS.[5,20] Assessment of ACTH-dependency should be performed to confirm ACTH-independent hypercortisolism that would be expected with adrenal nodular disease.[5]

Considerations for the 1-mg Dexamethasone Suppression Test

Several factors can affect the accuracy of the 1-mg DST and should be considered when interpreting test results (**Table 1**). Although not readily available at all centers, the concurrent measurement of a serum dexamethasone level with the 1-mg DST can ensure (1) patients followed test instructions properly and (2) suitable bioavailability of dexamethasone in the serum to interpret test results.[21,22] Implementation of a reflex strategy where only nonsuppressed serum cortisol samples on the 1-mg DST are reflexed for measurement of a serum dexamethasone level may reduce testing costs without loss of DST performance.[23] In patients with inadequate dexamethasone levels, repeating the DST with a higher dose of dexamethasone (2-mg, 4-mg, or 8-mg) can be considered, although data on the use of *nonstandard* DST in adrenal nodules are limited. False-positive results can also occur in patients on oral estrogen (eg, oral contraceptive pill) due to increased cortisol-binding globulin. In patients who do not wish to temporarily stop oral estrogen for testing, alternative strategies may include measurement of a serum free cortisol level with the DST.[24]

Confirming Adrenocorticotrophic Hormone-Independent Hypercortisolism

Patients with abnormal DST should have basal ACTH and basal dehydroepiandrosterone-sulfate (DHEAS) measured to confirm ACTH-independent hypercortisolism.[5] Low-normal or suppressed basal ACTH and DHEAS can help (1) support the diagnosis of MACS and (2) exclude the possibility of non-neoplastic hypercortisolism or ACTH-dependent neoplastic hypercortisolism. In a retrospective study of 464 patients with adrenal nodules, basal ACTH below 10 pg/mL in combination with basal DHEAS below 40 mcg/dL was found to have high accuracy for diagnosing MACS (92% specificity and 87% positive predictive value). Meanwhile, basal

Table 1
Potential pitfalls in the use of the 1-mg dexamethasone suppression test in the diagnosis of mild autonomous cortisol secretion

Pitfall	Example	Impact on Dexamethasone Suppression Test	Suggested Approach
Nonadherence	Missed or incorrect timing of dexamethasone administration	False positive	Obtain simultaneous or reflex dexamethasone level. Careful review of test instructions.
Decreased dexamethasone absorption	Gastric surgery or malabsorptive disorder	False positive	Obtain simultaneous or reflex dexamethasone level. Repeat DST with higher dose of dexamethasone.
Rapid dexamethasone metabolism	Cytochrome P450 inducer	False positive	Obtain simultaneous or reflex dexamethasone level. Repeat DST with higher dose of dexamethasone.
Increased cortisol binding globulin	Oral estrogen use	False positive	Stop oral estrogen for 6–8 wk prior to testing. Obtain serum free cortisol.
Reduced dexamethasone metabolism	Cytochrome P450 inhibitor	False negative	Unlikely to be clinically significant due to nonsuppressibility of cortisol in MACS.
Decreased cortisol binding globulin	Proteinuria	False negative	Obtain serum free cortisol.

DHEAS above 100 mcg/dL with concurrent ACTH above 15 pg/mL can help exclude the possibility of MACS (specificity 96%, positive predictive value 80.4%).[25]

Patients with abnormal 1-mg DST and indeterminate basal ACTH values in the 15 to 20 pg/mL range present a diagnostic challenge. Consideration should be given to (1) potential causes of false-positive DST results; (2) possible causes of non-neoplastic hypercortisolism including alcohol use disorders, advanced kidney disease, and depression; (3) ACTH-dependent hypercortisolism due to Cushing disease; and (4) intranodular production of ACTH in patients with PBMAH. Evidence-based data are limited, but possible strategies that can be employed include obtaining a desmopressin stimulation test[26] or a post-DST ACTH level.[27]

Additional Testing for Hypercortisolism

Late-night salivary cortisol and 24-hour urine free cortisol can be obtained to assess the degree of cortisol excess, particularly for patients with adrenal nodules who have possible features of overt CS. However, they are not required for the diagnosis and are often normal in patients with MACS. Instead of increased total cortisol production, patients with MACS may have subtle flattening of the normal cortisol diurnal rhythm with increased nocturnal steroid production and decreased steroid day/night ratios on 24-

hour urine and blood steroid profiling compared to healthy referent individuals without adrenal nodules.[28] This effect may not be adequately captured by late-night salivary cortisol due to the lower accuracy of salivary cortisol compared to cortisone at the lower limits of detection. A small study has assessed the use of salivary cortisone in the diagnosis of MACS and demonstrated correlation of late-night salivary cortisone with post-DST serum cortisol.[18] However, widespread use of salivary cortisone may be limited by the lack of reference laboratories that currently report out salivary cortisone.[29]

Follow-Up Hormone Testing

Longitudinal studies suggest that MACS is chronic and unlikely to resolve without intervention (<0.1%).[10] Therefore, repeat biochemical testing is not necessary on follow-up, and management decisions should be guided by the presence and/or development of possible cortisol-mediated comorbidities rather than biochemical parameters alone.[5] Similarly, only 4% of patients with NFAT develop MACS over time, and thus, repeat biochemical testing should only be performed in patients initially classified as NFAT if there are clinical concerns for new or worsening comorbidities that may be attributed to cortisol excess.[5,10]

Finally, cosecretion of cortisol has been described in patients with primary aldosteronism and pheochromocytoma and may affect management decisions.[5] Thus, all patients with MACS should undergo complete hormonal evaluation for adrenal hormone excess, which is the focus of article no. 4- *Adrenal Incidentalomas: Modern Tools to Address a Condition of Modern Times* by Bloomgarden and colleagues in this issue.

CLINICAL CONSEQUENCES

MACS is associated with multisystem morbidity with an expanding clinical profile. The data reviewed here focus on studies that use the currently accepted definition for MACS of post 1-mg DST serum cortisol greater than 1.8 mcg/dL.

Cardiometabolic Disease

Patients with MACS present with higher rates of cardiovascular risk factors including hypertension (60%–80%), obesity (30%–50%), dyslipidemia (26%–68%), type 2 diabetes mellitus (15%–40%), and chronic kidney disease (48%) compared to patients with NFAT.[9,10,17,30–32] On longitudinal follow-up, patients with untreated MACS are more likely to develop new or worsening hypertension, new or worsening dyslipidemia, weight gain, worsening glycemic control, and new cardiovascular events compared to patients with NFAT.[10] While several individual studies have suggested that the risk of cardiometabolic disease increases with higher post-DST values, a meta-analysis of 46 studies and 17,156 patients in 2023 did not find any specific cortisol cutoff threshold (above 1.8 mcg/dL) to be helpful in predicting prevalent or incident outcomes in patients with MACS.[17]

Bone Disease and Frailty

Patients with MACS have a higher prevalence of vertebral fractures (34%–63%) compared to patients with NFAT (24%–29%), primarily due to the presence of mild morphometric vertebral fractures, and a higher incidence of vertebral fractures on longitudinal follow-up (36% MACS vs 10% NFAT, mean duration 25 months).[11,33] Sex- and age-related disparities in fracture risk may exist, with 1 study noting increased risk of fractures in postmenopausal women but not in younger women or men with MACS.[11]

Assessing who is at risk for fractures in MACS can be challenging, because areal bone mineral density by standard dual-energy X-ray absorptiometry scan may not adequately capture fracture risk.[34] Instead, MACS may disproportionally affect bone quality rather than areal bone density with a few studies demonstrating reduced trabecular bone score—an indirect measure of vertebral microarchitecture—in patients with MACS compared to patients with NFAT and referent individuals without adrenal nodules.[35,36]

Reflecting multisystem morbidity, patients with MACS have also been reported to have higher rates of frailty (based on a cumulative deficit model) compared to patients with NFAT (24% vs 18%).[37] Frailty scores in patients with MACS have been demonstrated to correlate with measures of physical performance including the 6-minute walk test, gait speed, and hand-grip strength.[38]

Mortality

A meta-analysis published in 2023 included 4 studies (n = 5292) assessing all-cause mortality (adjusted for confounders) and found that MACS was associated with an increased risk of mortality compared to NFAT (hazard ratio, 1.54; 95% confidence interval, 1.27–1.81).[17] Cardiovascular disease and malignancies were the most common causes of death.[17] Sex- and age-dependent disparities in mortality may exist among patients with MACS, with one study finding that women younger than 65 years are at the highest risk, while men over the age of 65 years were not affected.[39]

Emerging Clinical Outcomes

The impact of MACS on cognition, mood, and quality of life are still being explored. A recent study of 84 patients with MACS reported lower cognitive performance, increased depressive symptoms, and impaired quality of life in patients with MACS compared to 201 referent individuals without adrenal nodules.[40] Other small studies on cognition in MACS have been discrepant with one reporting higher verbal fluency and executive function scores in patients with MACS compared to NFAT.[41]

Outcomes After Adrenalectomy

In a meta-analysis published in 2023 that reported eleven studies (2 randomized control trials and 9 observational studies, n = 856), treatment with adrenalectomy in patients with MACS was associated with improvement in hypertension, glycemic control, and dyslipidemia.[17] In a recent longitudinal study published after the meta-analysis, patients with MACS who underwent adrenalectomy also had a lower risk of incident vertebral fractures on follow-up compared to those managed conservatively, despite bone density being comparable between the 2 groups.[42] No studies to date have reported on the effect of adrenalectomy on cardiovascular events or mortality in MACS yet. In addition, limitations to the current data include the mostly retrospective nature of the studies and lack of standardized assessment and treatment of comorbidities, particularly in patients undergoing conservative management.

EVALUATION AND MANAGEMENT

Patients who are diagnosed with MACS should undergo assessment for relevant comorbidities including hypertension, obesity, diabetes, dyslipidemia, and fragility fractures (**Table 2**).[5] As bone quality may be disproportionately affected compared to bone density, use of trabecular bone score (if available) could be considered in the assessment of bone health in patients with MACS.

Table 2
Suggested approach to the evaluation and management of patients with mild autonomous cortisol secretion

Screen for relevant clinical comorbidities	Comorbidities to consider: • Hypertension • Obesity • Dysglycemia • Dyslipidemia • Cardiovascular event(s) • Fragility fracture(s)	Obtain: • Blood pressure • Body mass index • Hemoglobin A1c • Lipid panel • Bone density scan with trabecular bone score (if available) • Thoracic and lumbar spine x-rays
Individualize management decisions	Options: • Adrenalectomy • Conservative follow-up with focus on treating relevant comorbidities • Medical therapy for hypercortisolism (select cases)	Considerations: • Presence and severity of comorbidities • Patient age, sex, and general health status • Adrenal nodule characteristics • Patient preference • Availability of surgical expertise

Adrenalectomy

Decisions about surgical treatment with adrenalectomy in MACS should be individualized.[5] Evidence to date suggests that patients with MACS, as a group, have improvement in cardiometabolic comorbidities.[17] However, the benefit in an individual patient is more challenging to quantify due to the high prevalence of cardiometabolic disease in the general population with unclear contribution of MACS, individual susceptibility to the deleterious effects of hypercortisolism, and the often unclear duration of cortisol excess prior to diagnosis, which may affect reversibility of complications after treatment.

Currently, the 2023 ESE-ENSAT clinical guidelines recommend discussing the option of adrenalectomy in patients with MACS who have an unilateral adrenal nodule and relevant comorbidities. Additional factors that should be considered include age, sex, general health, and preference of the patient as well as adrenal nodule characteristics (see **Table 2**).[5]

Patients who undergo adrenalectomy should be counseled on the possibility of developing postoperative adrenal insufficiency (around 50% in patients with MACS who do not receive empiric preoperative glucocorticoid coverage) and glucocorticoid withdrawal syndrome.[43–45] In patients who do develop postoperative adrenal insufficiency, more than 50% have recovery of their hypothalamic-pituitary-adrenal axis within 4 months of surgery.[44]

Conservative Management

Patients with MACS who do not undergo adrenalectomy should have regular follow-up with proactive screening and treatment of relevant comorbidities. However, no studies to date have examined whether this approach may mitigate the increased risk of cardiometabolic disease and morbidity in patients with MACS.

Medical Therapy for Mild Autonomous Cortisol Secretion

Data on the use of medical therapy for hypercortisolism in patients with MACS are scarce and comes primarily from small case series reporting on the use of

metyrapone, mifepristone, and 11β-hydroxysteroid dehydrogenase type 1 inhibitor.[46–48] The 2023 ESE-ENSAT clinical guidelines on adrenal incidentalomas were unable to provide any consensus recommendations given the paucity of evidence.[5] In clinical practice, medical therapy could be considered for treatment of MACS in very select cases when (1) patients have relevant comorbidities but are either not interested or are not suitable candidates for surgery, (2) patients with bilateral adrenal cortisol excess (eg, PBMAH), or (3) as short-term therapy to determine the effect of MACS on patient symptoms and comorbidities.

SUMMARY

MACS is the most common hormone abnormality diagnosed in patients with adrenal nodules and is associated with increased risk for cardiometabolic disease, vertebral fractures, and mortality. While adrenalectomy may improve cardiometabolic complications in select patients with MACS, decisions about management should be individualized based on the presence of relevant comorbidities and patient characteristics. Patients with MACS who undergo conservative monitoring should have proactive screening and treatment of cortisol-mediated comorbidities.

CLINICS CARE POINTS

- Mild autonomous cortisol secretion (MACS) is diagnosed when serum cortisol fails to suppress to $\leq$1.8 mcg/dL following the overnight 1-mg dexamethasone suppression test in patients who lack signs and symptoms of Cushing syndrome.
- Low-normal or suppressed basal adrenocorticotrophic hormone and dehydroepiandrosterone-sulfate can help confirm the diagnosis of MACS and exclude the possibility of non-neoplastic hypercortisolism.
- Patients with MACS should undergo evaluation for relevant comorbidities including hypertension, dysglycemia, obesity, dyslipidemia, and fragility fractures.
- Decisions about treatment in MACS should be individualized based on the severity of possible cortisol-mediated comorbidities and patient characteristics including age, sex, and general health.

DISCLOSURE

The authors declare they have no relevant disclosures.

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