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MILD AUTONOMOUS CORTISOL SECRETION IN ADRENAL INCIDENTALOMAS: FROM BIOCHEMICAL DIAGNOSIS TO THERAPEUTIC DECISION-MAKING: A NARRATIVE LITERATURE REVIEW

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ABSTRACT

Mild autonomous cortisol secretion (MACS) is identified in patients with adrenal incidentalomas who have inadequate cortisol suppression after dexamethasone and lack the clinical features of overt Cushing syndrome. The management decision depends on the reliability of the biochemical finding, the imaging phenotype, and the burden and course of potentially cortisol-related comorbidities. This narrative review synthesises a predefined collection of diagnostic studies, observational cohorts, systematic reviews, and clinical reviews. The 1 mg overnight dexamethasone suppression test remains the initial biochemical assessment. Repeat testing and evidence of adrenocorticotropic hormone independence can strengthen the diagnosis, particularly before surgery. Cardiometabolic associations are most consistently reported for hypertension and diabetes, with heterogeneous findings across cohorts. Comparative treatment studies report improvements in blood pressure after adrenalectomy in selected patients. Results for glycaemia, lipids, body composition, and skeletal outcomes are less consistent, and effects on major cardiovascular events and survival remain uncertain. Frailty and cognitive difficulties may add to the clinical burden, but evidence that either improves after surgery is limited. Management should integrate the persistence of cortisol non-suppression, existing disease control, operative risk, patient preference, and the need to assess adrenal reserve after surgery. When surveillance is chosen, follow-up should focus on the evolution of comorbidities and use the imaging phenotype to guide further radiological assessment.

Keywords: Adrenal incidentaloma, Mild autonomous cortisol secretion, Dexamethasone suppression test, Cardiometabolic risk, adrenalectomy, Adrenal insufficiency

1 INTRODUCTION

An adrenal incidentaloma poses two questions at presentation. The first is whether imaging supports a benign lesion. The second is whether the lesion is hormonally active. Mild autonomous cortisol secretion (MACS) describes adrenal cortisol secretion that escapes normal feedback suppression in the absence of the characteristic clinical features of overt Cushing syndrome. It can occur in an adrenal adenoma with reassuring imaging. Conversely, the demonstration of cortisol non-suppression does not determine the nature of an indeterminate adrenal mass. Evaluating these questions in parallel prevents imaging reassurance from substituting for endocrine assessment and prevents a biochemical label from prematurely resolving an imaging concern. [1, 2]

The clinical problem arises after an abnormal result. Hypertension, diabetes, dyslipidaemia, and fractures are reported more often in some patients with MACS, yet these conditions have several causes and are common among patients whose adrenal lesions suppress normally. The potential contribution of cortisol matters most when it changes the assessment of a comorbidity or the balance between surveillance and adrenalectomy. This review follows that decision from biochemical confirmation through comorbidity assessment, evaluation of comparative treatment evidence, and planning for postoperative adrenal function. [1, 2, 3]

1.1 Scope and approach

This narrative review used a predefined collection of 27 supplied PDFs representing 25 distinct publications. Duplicate copies were consolidated and sources were selected for their relevance to biochemical diagnosis, clinical burden, natural history, and treatment decisions in adults with adrenal incidentalomas. Full-text diagnostic studies, clinical cohorts, and evidence syntheses were used for their respective questions. Clinical reviews provided context for testing and management recommendations. Conference abstracts and reports from atypical clinical settings were assessed for relevance, with case reports used only to illustrate specific diagnostic problems. No external literature search or new quantitative synthesis was performed. Results from primary studies available only through an included review are attributed to that review.

2 CONFIRMING THE BIOCHEMICAL PHENOTYPE

2.1 The overnight dexamethasone suppression test

The initial assessment includes a clinical examination for features of overt Cushing syndrome and a review of the circumstances of the adrenal finding. In the diagnostic approach described in the supplied literature, 1 mg oral dexamethasone is given late in the evening and serum cortisol is measured the following morning. A post-dexamethasone cortisol concentration of 1.8 μg/dL or less (50 nmol/L or less) supports adequate suppression. In a patient without features of overt Cushing syndrome, a value above 1.8 μg/dL (above 50 nmol/L) prompts assessment for MACS. Post-test cortisol is a continuous measure. Earlier studies often used separate categories for possible and more pronounced autonomy, which affects how their populations and outcomes compare with those classified under a single threshold. [1, 2, 3, 4]

The threshold is sensitive to modest abnormalities, so the conditions of testing matter, especially near the cut-off. Inadequate dexamethasone exposure may reflect missed administration, altered absorption, or accelerated metabolism with drugs such as phenytoin or carbamazepine. Oral oestrogen can increase cortisol-binding globulin and raise measured total cortisol. When the result is unexpected or would lead to an irreversible intervention, reviewing the dose, timing, and relevant medication exposure allows the test to be repeated under better characterised conditions. Concurrent measurement of dexamethasone, where available, can help establish adequate exposure. The utility of testing itself should be considered in frail patients when the result is unlikely to change management. [1, 2, 4, 5]

2.2 Establishing adrenal autonomy

A low or suppressed morning adrenocorticotropic hormone (ACTH) concentration supports ACTH-independent secretion, interpreted with the repeat dexamethasone suppression test (DST) and the clinical findings. Measurements near the lower analytical limit of ACTH assays are difficult to interpret. Low dehydroepiandrosterone sulfate (DHEA-S) may add evidence of chronic ACTH suppression, although age and sex affect interpretation. A report by Ikeda and colleagues describes an unusual patient with evidence of cortisol autonomy and possible isolated ACTH deficiency. That report illustrates why discrepant results or unexpected impairment of adrenal reserve warrant specialist evaluation. A single case cannot establish the frequency of this presentation. [1, 4, 6]

Ueland and colleagues studied 165 referred patients, including 83 classified as having autonomous cortisol secretion by a DST-based definition. DHEA-S at a cut-off of 40 μg/dL yielded 58% sensitivity and 80% specificity against that classification. Late-night salivary cortisol poorly separated groups, and a conventional prolonged low-dose DST did not

improve discrimination over the overnight test in their study. Twenty-four-hour urinary free cortisol likewise had limited diagnostic value in this setting. The cohort was retrospective and its classification was anchored to the overnight DST. Its results indicate how often adjunctive tests agree with that classification, without resolving whether any marker measures tissue exposure or predicts clinical benefit. [4]

Prinzi and colleagues retrospectively evaluated 171 patients with adrenal incidentalomas, 70 classified as having MACS. They derived a score combining low ACTH and low DHEA-S and reported promising discrimination for late-night **serum** cortisol in the patients assessed. The result concerns a different specimen and sampling setting from late-night salivary cortisol. The study lacked an external validation cohort and defined MACS by the DST. A model derived from that cohort therefore requires validation before it can guide decisions independently. These studies support a role for adjunctive measurements when evaluating a questionable DST, with test selection guided by the specific source of uncertainty. [1, 4, 5]

2.3 Imaging and other sources of hormone excess

The Endotext chapter describes a homogeneous lesion with an attenuation of 10 Hounsfield units or less on unenhanced computed tomography (CT) as having a benign imaging phenotype that ordinarily requires no further imaging. Indeterminate lesions warrant assessment based on attenuation, size, and homogeneity, with additional imaging or multidisciplinary review as appropriate. Hormone evaluation should address pheochromocytoma and primary aldosteronism according to imaging and the clinical context. For example, hypertension is a reason to consider screening for primary aldosteronism. Ravi Kumar and colleagues describe a rare collision tumour containing cortical adenoma and pheochromocytoma in a patient with biochemical evidence of cortisol and catecholamine excess. Its significance is illustrative. When there are discordant findings, cortisol autonomy alone cannot account for the full endocrine presentation. [1, 7]

3 CLINICAL BURDEN AND NATURAL HISTORY

3.1 Cardiometabolic disease and mortality

Pelsma and colleagues included 30 cross-sectional and 16 cohort studies, with 17,156 patients in the comorbidity and prognosis evidence base. Compared with patients with nonfunctioning adrenal incidentalomas, those with MACS had higher pooled prevalence of diabetes (relative risk [RR] 1.44, 95% confidence interval [CI] 1.23–1.69), hypertension (RR 1.24, 95% CI 1.16–1.32), and dyslipidaemia (RR 1.23, 95% CI 1.13–1.34). These estimates describe population-level associations across varying definitions and referral settings. In an individual patient, the temporal course and the degree of control provide information that a diagnosis code or a single measurement cannot supply. [1, 3]

Individual cohorts illustrate the variation behind the pooled results. Adamska and colleagues compared patients with cortisol above 1.8 and up to 5 μg/dL after dexamethasone with patients who suppressed to 1.8 μg/dL or below. In their retrospective series of 295 patients, type 2 diabetes was more frequent in the MACS group, whereas hyperlipidaemia was more frequent in the nonfunctioning tumour group and hypertension did not differ significantly. Turan Erdogan and colleagues reported higher frequencies of diabetes, hypertension, hyperlipidaemia, and coronary artery disease in their MACS group. In Ikram's hospital-based cross-sectional study, 95 of 380 patients met the study criteria for MACS. The association with diabetes persisted after adjustment (adjusted odds ratio 1.68, 95% CI 1.01–2.80). The sample prevalence and effect estimates reflect the populations and definitions studied. They provide a rationale to evaluate specific comorbidities without attributing each finding to cortisol. [8, 9, 10]

Clinical cardiovascular events and measures of cardiac structure should also be distinguished. In a prospectively assessed cohort of 71 patients, Sbardella and colleagues found higher left ventricular mass index and greater arterial stiffness in the group with possible autonomous cortisol secretion. These measures support investigation of cardiovascular burden, while their ability to identify patients who benefit from adrenalectomy remains uncertain. The service evaluation by Heald and colleagues similarly identified differences in cardiovascular history and prescribing across DST categories, illustrating how background treatment can complicate interpretation of measured risk factors. [3, 11, 12]

The mortality findings depend on the population and the comparison. Elhassan and colleagues found similar mortality in conservatively managed patients with and without mild cortisol excess, whereas Pelsma and colleagues pooled adjusted estimates from four studies involving 5,921 patients and reported a hazard ratio (HR) of 1.54 (95% CI 1.27–1.81). In a separate retrospective cohort of 668 patients, Bellach and colleagues reported a fully adjusted HR of 2.51 (95% CI 1.41–4.48) for patients with both MACS and type 2 diabetes compared with those with neither. The formal interaction between MACS and diabetes was not statistically significant. Consequently, the joint-exposure result cannot establish that diabetes modifies the effect of cortisol autonomy. None of these estimates measures the effect of adrenalectomy on survival. [3, 13, 14]

3.2 Fractures, frailty, and cognition

Fracture assessment can add information beyond cardiometabolic status. Pelsma and colleagues found that several studies reported more vertebral fractures in patients with MACS, but differences in ascertainment and outcome definitions precluded a single pooled estimate. A history of fragility fracture and available skeletal findings should therefore inform assessment of disease burden, with attention to the distinction between bone mineral density and fracture outcomes. The evidence that adrenalectomy reduces fractures is limited, even where postoperative bone mineral density findings favour surgery. [1, 3, 15]

In a retrospective study of 168 patients with MACS and 275 with nonfunctioning adrenal tumours, Singh and colleagues reported a higher age-, sex-, and body mass index-adjusted frailty index in the MACS group (0.17 vs 0.15, P = .009). The study used a historical DST band of 1.9–5 μg/dL for MACS and a deficit index that incorporated multiple clinical characteristics. Frailty can help describe the patient's health and functional reserve when weighing surgery. The study does not establish that cortisol caused the observed deficits or that adrenalectomy reverses frailty. [1, 16]

Liu and colleagues identified poorer performance in selected cognitive domains in patients with autonomous cortisol secretion compared with patients with nonfunctioning adenomas. Saini and colleagues also observed lower fluid and total composite cognition scores in MACS compared with referent participants. At reassessment, 37 operated patients and 31 retested referents had similar adjusted changes in most cognitive measures, with a larger comparative increase in attention and executive functioning in the operated group. The longitudinal comparison did not include a randomised surveillance group with MACS. Taken together, these studies support taking cognitive complaints seriously and investigating their causes. Evidence for cognitive recovery as a treatment goal remains preliminary. [17, 18]

3.3 What surveillance is intended to detect

Elhassan and colleagues synthesised 32 studies involving 4,121 conservatively managed patients with nonfunctioning adrenal tumours or mild autonomous cortisol excess. Mean follow-up was 50.2 months. Across 14 studies with data on enlargement of at least 10 mm, the pooled proportion was 2.5% among 2,023 patients. No adrenal cancer developed in the included cohorts, and overt hormone excess was uncommon. New cardiovascular events were reported more frequently in the mild cortisol excess group (15.5% vs 6.4%). These estimates apply to selected, conservatively managed cohorts with heterogeneous definitions. They support focusing follow-up of a clearly benign lesion on the clinical course of comorbidities, while an indeterminate lesion still requires an imaging plan appropriate to its own risk. [1, 13]

4 THERAPEUTIC DECISION-MAKING

4.1 Adrenalectomy and the outcomes it may improve

The most consistent signal across the supplied treatment syntheses concerns blood pressure. Pelsma and colleagues identified two small randomised trials and a larger body of observational evidence. In their account of the larger trial, 62 patients were randomised and 56 could be assessed at least six months later. Blood pressure control improved in 68% of the surgical group and 13.4% of the conservative group. Glycaemic control improved in 28% and 3.3%, respectively. About one-third of participants did not have hypertension and only 11 of 56 assessed patients had diabetes. The findings, as reported in the supplied synthesis, concern improvement under the study definitions. They cannot directly estimate the probability of control in patients with resistant hypertension or remission in patients with established diabetes. [1, 3]

Trandafir and colleagues summarise a later multicentre randomised study by Koh and colleagues. In the comparison reported in that review, 46 patients were analysed in each group, with a median follow-up of 48 months. Blood pressure control improved in 45.7% after adrenalectomy and 23.9% with conservative care. Glucose control improved in 45.7% and 15.2%, respectively, while the between-group difference in improvement of dyslipidaemia was not significant. These results extend the evidence for improvement in selected intermediate outcomes. The primary trial report was not available in the review collection, so this account is limited to what the secondary source reports. [14, 19]

The two additional surgical meta-analyses reach different conclusions about the scope of benefit. Khadembashiri and colleagues reported comparative effects favouring adrenalectomy for systolic and diastolic blood pressure and bone mineral density, with no significant differences across the other comorbidities summarised in their abstract. Ren and colleagues reported differences favouring surgery for blood pressure, fasting glucose, glycated haemoglobin, triglycerides, and measures of adiposity. Several primary studies recur across the reviews. Their findings should be interpreted in light of differences in study inclusion, cortisol thresholds, follow-up, and the way outcomes were defined or measured. A categorical improvement in blood pressure control, a reduction in medication, and a change in mean pressure measure different aspects of response. [3, 15, 20]

The practical implication is to specify the outcome that would justify surgery for the patient. In a patient with persistent cortisol autonomy, a unilateral adenoma, and progressively difficult blood pressure control, improvement in pressure or medication burden can be a concrete treatment goal. Changes in glucose or lipid indices are possible, but the comparative estimates are less consistent. The available studies also leave uncertainty about durable improvement, effects on major cardiovascular events, survival, and functional outcomes. Differences in initial comorbidity severity or treatment between operated and non-operated patients may account for part of the observed benefit in retrospective studies. [1, 2, 3, 15, 20]

4.2 Active surveillance and reassessment

Conservative management includes treatment of comorbidities and a plan to review their trajectory. Blood pressure, glucose status, lipid control, and fracture history can be assessed at baseline and followed according to the patient's clinical needs. An annual review of potentially cortisol-related comorbidities is described in the supplied clinical reviews. New or worsening disease despite appropriate treatment gives a reason to revisit biochemical findings and reconsider surgery. The clinical reviews differ in how routinely they propose repeating hormonal tests in stable patients. The decision should reflect whether the result would change management, especially when previous testing was reliable and the imaging phenotype is clearly benign. Cortisol-lowering medication, including metyrapone, has been explored in the studies discussed by Yozamp and Vaidya and by Bellach and colleagues. The available evidence leaves its routine role in MACS uncertain. [1, 2, 13, 14]

When cortisol autonomy is borderline, comorbidities are mild or stable, or the expected benefit is small relative to operative risk, surveillance is a reasonable option. For persistent autonomy with progressive or difficult-to-control comorbidities, the rationale for multidisciplinary surgical discussion is stronger. Age, frailty, general health, laterality, and patient preference influence this balance. By separating the imaging indication from the endocrine indication, a team can also recognise patients for whom suspicious imaging independently drives the decision to operate. [1, 2, 19]

4.3 Adrenal reserve after surgery

Removal of a cortisol-secreting adenoma can reveal inadequate cortisol production from the remaining adrenal gland after chronic suppression of the hypothalamic–pituitary–adrenal axis. Perioperative planning should address glucocorticoid coverage, biochemical assessment, and follow-up for recovery. Endotext describes postoperative glucocorticoid coverage until the axis can be assessed. Trandafir and colleagues review variable approaches using early morning cortisol and, in selected protocols, cosyntropin stimulation to guide the need for ongoing replacement. Differences in definitions, testing time, and replacement strategies help explain variation in reported frequency and duration of adrenal insufficiency. The supplied evidence does not establish a single cortisol threshold or fixed replacement duration that can be applied across protocols. [1, 2, 19]

Table 1: Decision points from biochemical assessment to follow-up

Clinical question	Evidence to review	Implication for the decision
Is cortisol non-suppression reproducible?	Overnight 1 mg DST, test conditions, morning ACTH, and repeat testing where relevant	Confirm the biochemical phenotype before attributing comorbidity or planning surgery. [1, 4, 5]
Is the lesion radiologically benign?	Unenhanced CT attenuation, homogeneity, size, and laterality	Consider any separate imaging indication for intervention. Tailor imaging follow-up to the lesion. [1]
What could improve after surgery?	Course and treatment burden of hypertension or diabetes, skeletal findings, general health, and patient priorities	Discuss the outcome most relevant to the patient and the uncertainty of benefit. [1, 3, 15, 20]
How will surveillance inform reassessment?	Control of comorbidities, interval clinical changes, and the need for targeted retesting	Treat comorbidities and revisit the decision if their course changes. [1, 2]
What care follows adrenalectomy?	Perioperative glucocorticoid plan, postoperative adrenal function, and the original treatment goal	Assess adrenal recovery and clinical response separately. [1, 19]

Adrenal function and clinical response are separate postoperative outcomes. A patient may need temporary glucocorticoid replacement while cardiometabolic treatment is being reassessed. A useful follow-up plan specifies who will assess adrenal recovery and how the comorbidity that prompted surgery will be measured. If the goal was to improve blood pressure control, the assessment should consider both achieved pressure and changes in

antihypertensive treatment. This also improves interpretation of apparent treatment benefit in an individual patient. [1, 3, 19]

4.4 Limitations and research priorities

The predefined collection limits the completeness of this review. The available evidence spans different definitions of cortisol autonomy and mixes cross-sectional comparisons, retrospective cohorts, small randomised trials, and syntheses with overlapping studies. Diagnostic accuracy studies frequently use the overnight DST to define the groups against which proposed new markers are tested. Their estimates describe agreement with that definition and leave open which markers best predict clinical consequences. The limitations are particularly relevant for patients close to the threshold, whose classification can depend on testing conditions and the definition applied. [3, 4, 5, 15, 20]

Future comparative studies should prespecify the degree and persistence of cortisol non-suppression, measure background treatment, and distinguish improvement in a clinical measurement from reduction in treatment burden. Standardised blood pressure and glycaemic outcomes would make studies easier to compare. Longer follow-up is needed to establish the durability of benefit and assess fractures, cardiovascular events, quality of life, and the burden of postoperative glucocorticoid replacement. External validation of proposed biochemical markers should address whether they add information that changes diagnosis or management. [3, 5, 15, 19, 20]

5 CONCLUSION

Management of MACS begins with a reliable demonstration of cortisol non-suppression and assessment of ACTH independence. The treatment decision then turns on the imaging phenotype and the severity, course, and treatment burden of potentially cortisol-related comorbidities. Adrenalectomy can improve blood pressure control in selected patients, while effects on other outcomes vary and longer-term clinical benefits remain uncertain. Surveillance should include an explicit plan for comorbidity assessment and reconsideration if health status changes. Patients who undergo surgery need a plan for perioperative glucocorticoid management and assessment of adrenal recovery.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest regarding this manuscript.

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