Arh. farm. 2022; 72: 200 – 211 *Review article/Pregledni rad*

Current challenges in laboratory diagnostics of autonomous cortisol secretion in adrenal incidentalomas

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Abstract

Adrenal incidentalomas are unexpectedly identified adrenal masses without prior suspicion of the existence of adrenal disease. The majority of adrenal incidentalomas are benign adrenal adenomas (80–90%), and they are non-functioning adrenocortical adenomas in more than 70% of cases. Mild hypercortisolemia is the most common finding in hormonally active adrenal incidentalomas. It is defined as autonomous cortisol secretion in up to 15% of patients. Despite a lot of research that anticipated higher cardiometabolic risk in patients with autonomous cortisol secretion, there is still no clear consensus on biochemical criteria for an autonomous cortisol secretion diagnosis in patients with adrenal incidentalomas. This review delineates the advantages and limitations of different laboratory tests recommended for the diagnosis of autonomous cortisol secretion in adrenal incidentalomas.

Keywords: adrenal incidentalomas, cortisol, low-dose dexamethasone suppression test

https://doi.org/10.5937/arhfarm72-36043

Introduction

Adrenal incidentalomas (AI) are incidentally discovered adrenal masses without prior suspicion of the existence of adrenal disorder or adrenal disease (1). It is difficult to define the exact incidence and prevalence of adrenal incidentalomas because data from population-controlled studies are lacking. The available data are mainly based on the results of obduction studies that showed a mean adrenal incidentaloma prevalence of about 2.3% (1 to 8.7%), with no observed differences in gender prevalence (1), and on the results of radiological studies where different imaging methods were used, and a different size of the tumor mass was considered as limiting for the diagnosis (2). The results of previous studies showed that the prevalence of adrenal incidentalomas increased with age, from 0.2% in the population younger than 30 to nearly 10% in the population older than 70 (3). The results of radiological studies have shown a higher prevalence of adrenal incidentalomas in women than men. Still, this difference is explained by the fact that women go through abdominal radiological imagining more often than men. Because the frequency of adrenal incidentalomas increases with the development of technologies used in radiological examinations, the disease is also referred to as a "disease of modern technology" (1). 80–90% of adrenal incidentalomas are benign tumors – adrenal adenomas (1), which are in more than 70% cases non-functional. Autonomous cortisol secretion (ACS) has been diagnosed in 15% of patients with benign adrenal incidentalomas. In comparison, primary hyperaldosteronism is observed in 3% of cases (1). The incidence of pheochromocytoma in adrenal incidentalomas is about 5%, and approximately 6 to 8% of patients with adrenal incidentalomas have adrenocortical cancer. The first step in the clinical approach to adrenal incidentaloma evaluation is the determination of the type of tumor mass by modern imaging techniques, computed tomography (CT), and magnetic resonance imaging (MR) (4). According to the European Society of Endocrinology Guideline, in collaboration with the European Network for the Study of Adrenal Tumors, the second step is the laboratory evaluation of hormone secretion and an individualized approach in patients' therapy (4).

Laboratory evaluation of adrenal incidentalomas

In general, laboratory evaluation of adrenal incidentalomas implies the determination of hormones associated with adrenal function. Screening for autonomous cortisol secretion is recommended for all patients, even though the highest percentage of adrenal incidentalomas are non-functional (4). The recommended screening test for autonomous cortisol secretion is the 1 mg overnight dexamethasone suppression test (4). It is a dynamic test for adrenal gland function assessment. 1 mg dexamethasone is administered orally at 11 p.m. to block the morning adrenocorticotropic hormone (ACTH) surge, and serum cortisol concentration is measured the next morning at 8 a.m. Autonomous cortisol secretion is excluded if serum cortisol concentration is lower than 50 nmol/L (Figure 1). Current guidelines suggest that serum cortisol levels higher than 138 nmol/L after a low-dose dexamethasone suppression test should be taken as evidence

of autonomous cortisol secretion. At the same time, serum cortisol levels after a low-dose dexamethasone suppression test between 51 and 138 nmol/L should be considered evidence of possible autonomous cortisol secretion (Figure 1) (4). According to the current European recommendation, all patients considered to be patients with possible autonomous cortisol secretion should be further screened for hypertension and type 2 diabetes mellitus (4). If some of those hypercortisolism-related comorbidities are diagnosed, further laboratory testing should be performed to confirm autonomous cortisol secretion (4).

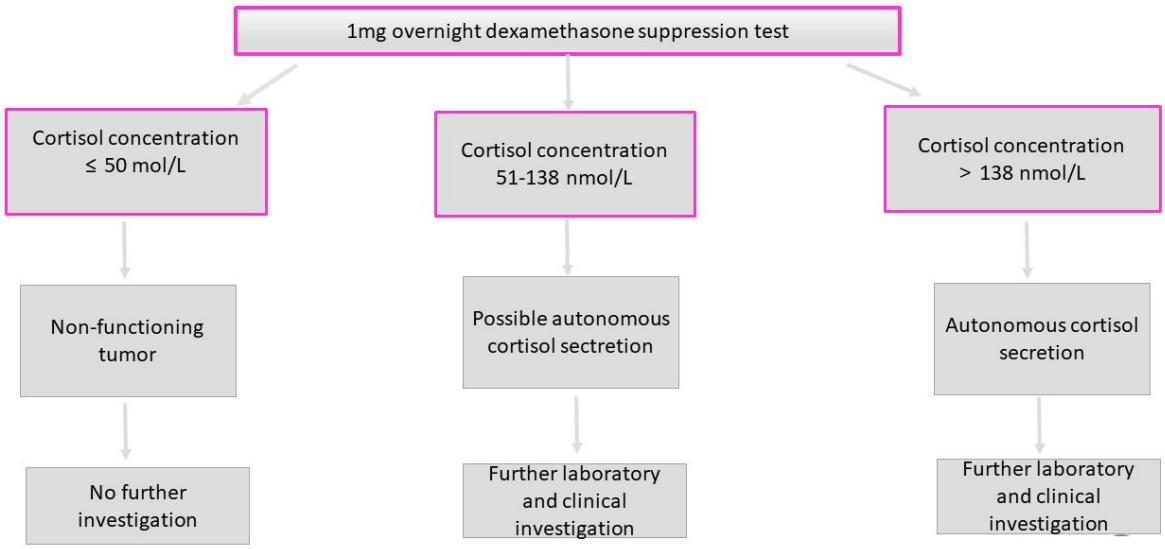

Figure 1. Autonomous cortisol secretion diagnostics in patients with adrenal incidentalomas - graphical algorithm

Slika 1. Autonomna sekrecija kortizola kod pacijenata sa adrenalnim incidentalomima – algoritam

In patients with adrenal incidentalomas, determination of serum catecholamine concentration or measurement of plasma-free metanephrines or urinary fractionated metanephrines is recommended (4). In hypertensive patients, especially patients with hypokalemia, determining aldosterone concentration is recommended (4). If the aldosterone to renin ratio is higher than 25, patients are referred for confirmatory testing for primary aldosteronism (5). In patients with suspected adrenocortical carcinoma, determination of sex hormones and their steroid precursors is recommended (4). The standard laboratory diagnostic approach implies the determination of androstenedione, 17-hydroxyprogesterone, dehydroepiandrosterone sulfate (DHEAS), as well as estradiol concentrations in men and testosterone concentration in women. However, the diagnostic accuracy of these biochemical markers is not high (low test specificity), so current

scientific attention has been focused on panels of urinary steroid metabolites that are thought to have better diagnostic accuracy in the laboratory evaluation of adrenocortical carcinoma. (4). In adrenal incidentaloma patients, 17-hydroxyprogesterone concentration should be measured as a component of primary laboratory testing to exclude congenital adrenal hyperplasia. Congenital adrenal hyperplasia is a group of autosomal recessive diseases characterized by a deficiency of some of the enzymes involved in cortisol biosynthesis. In 95% of cases, the cause of the disease is 21-hydroxylase deficiency. Enzyme deficiency leads to adrenal cortex hyperplasia and, consequently, the accumulation of cortisol precursor, 17-hydroxyprogesterone. However, in patients with adrenal incidentalomas, higher 17-hydroxyprogesterone values may also occur in malignant adrenal tumors.

Laboratory diagnostics of autonomous cortisol secretion in adrenal incidentalomas

As already stated, the initial screening test for autonomous cortisol is the 1 mg overnight dexamethasone suppression test (4). Morning cortisol concentrations lower than 50 nmol/L exclude autonomous cortisol secretion, while concentrations higher than 138 nmol/L indicate autonomous cortisol secretion in adrenal incidentalomas patients. A special challenge in the clinical and laboratory evaluation of adrenal incidentalomas are patients whose morning cortisol concentration after a 1 mg overnight dexamethasone suppression test is between 50 and 138 nmol/L, who are classified as possible autonomous cortisol secretion according to the latest European recommendations (4).

Patients with autonomous cortisol secretion generally have morning cortisol values that are in the range of the reference interval; however, most of them lose cortisol circadian rhythm and have higher cortisol concentrations in the evening (6). Moreover, these patients do not have the classical phenotype characteristics that indicate clinically manifested Cushing's syndrome (6), so this pathological condition was categorized in the literature as subclinical hypercortisolism or subclinical Cushing's syndrome. However, this terminology has been voted as insufficiently precise. European Society of Endocrinology Guideline, in collaboration with the European Network for the Study of Adrenal Tumors, recommended the term autonomous cortisol secretion (4). Although autonomous cortisol secretion in adrenal incidentalomas rarely progresses into clinically manifested Cushing's syndrome, the results of previous studies indicate that patients with autonomous cortisol secretion often have at least one component of metabolic syndrome (hypertension, obesity, dyslipidemia), insulin resistance, or type 2 diabetes (7,8) which implies that they are at higher risk for cardiovascular disease (CVD) development and require special clinical and laboratory monitoring. Furthermore, these patients are at risk for osteoporosis development (9).

With the recommended exclusion criteria for autonomous cortisol secretion in adrenal incidentalomas (cortisol concentration 50 nmol/L), high sensitivity of the test is achieved (almost 100%). Still, the specificity is not adequate (70–80%), which indicates a significant percentage of false-positive results. On the other hand, the upper critical test

value of 138 nmol/L gives high specificity and low sensitivity, so a significant percentage of patients with moderate hypercortisolism could be missed for further monitoring. Because of that, all patients with cortisol concentrations between 50 and 138 nmol/L after a 1 mg overnight dexamethasone suppression test and at least one cardiometabolic risk factor are recommended for further laboratory testing. Moreover, the 1 mg overnight dexamethasone suppression test has its limitations that should be acknowledged during the evaluation of adrenal incidentaloma patients. The results of previous studies have shown that almost 30% of patients hospitalized for different pathological conditions, but not related to endocrine diseases, had a positive result of this test (10). This fact is explained by a faster dexamethasone metabolism in those patients, which implies that the biologically active dose of dexamethasone is lower and, accordingly, there is no suppression in cortisol secretion. In addition, patients who receive therapy with drugs that induce heme biosynthesis (enzyme P450, which cooperates in dexamethasone metabolism) experience faster metabolic degradation of dexamethasone. In patients with kidney and liver disease, dexamethasone metabolism is slowed down, while the bioavailability of the dexamethasone is higher, which also affects the diagnostic accuracy of the 1mg overnight dexamethasone suppression test (10). In patients with possible autonomous cortisol secretion and at least one cardiometabolic risk factor, three different laboratory tests are used for further laboratory evaluation: plasma ACTH concentration, 24-h urinary-free cortisol (UFC), and midnight serum cortisol concentration (11,12). All these tests have limitations (Table I), so there is no clear scientific consensus about the recommended test combinations for clinical practice use. Various clinical practice guidelines for autonomous cortisol secretion in adrenal incidentalomas have been proposed in Europe and the USA. However, the 1 mg overnight dexamethasone suppression test, morning ACTH plasma concentration, and UFC ("UFC-ACTH-DST criteria") are the most often used combination of laboratory tests (11). This combination of laboratory tests is used in Serbia as well. The Japan Endocrine Society has recommended the 1 mg overnight dexamethasone suppression test, morning ACTH plasma concentration, and midnight serum cortisol concentration in the laboratory evaluation of autonomous cortisol secretion in adrenal incidentalomas (12).

Table I The major limitations of available laboratory tests for autonomous cortisol secretion diagnosis in adrenal incidentaloma patients

Tabela I Najznačajnija ograničenja laboratorijskih testova koji se koriste u dijagnostici autonomne sekrecije kortizola kod pacijenata sa adrenalnim incidentalomima

Laboratory test	**Major limitations**
1mg overnight dexamethasone suppression test	High percentage of false-positive results in hospitalized patients Different diagnostic accuracy in patients who received therapy with drugs that induce heme biosynthesis
Plasma ACTH concentration	Pulsatile secretory rhythm Very short plasma half-life Result variability related to the used test methodology
UFC	Cortisol metabolite and conjugate interference Day-to-day result variability Not recommended for renal failure patients
Midnight serum cortisol	Results depend on psychological stress There is no consensus about the most appropriate cut-off value

While morning plasma ACTH concentration is considered a key laboratory marker in Cushing's syndrome differential diagnosis, its diagnostic accuracy for autonomous cortisol secretion is more limited. Cortisol concentrations in autonomous cortisol secretion in adrenal incidentalomas are moderately high. Consequently, there is no significant suppression of ACTH excretion. The usually used cut-off value is 10 ng/ml, and the specificity of the test is about 50% (38–60%), which implies that this parameter cannot be used for autonomous cortisol secretion diagnosis on its own, but only in combination with the 1 mg overnight dexamethasone suppression test (13). The main limitations of this laboratory test are reflected in its highly pulsatile secretory rhythm and very short plasma half-life (15 minutes), as well as result variability related to the used test methodology (lack of international reference standard, high coefficient of variation between results obtained by different tests) (14). ACTH concentration is marginally lower in women compared to men. It has been shown that the use of oral contraceptives may be associated with lower ACTH values (15).

By using UFC in the laboratory diagnosis of autonomous cortisol secretion, the problem of cortisol pulsatile secretory rhythm and effect of corticosteroid-binding protein (CBG) concentration on the result are eliminated. The most common pathological conditions followed by changed CBG concentrations are thyroid disease, liver disease, kidney disease, and pathological conditions with hormone therapy (estrogen therapy). In these pathologies, UFC is the recommended test for autonomous cortisol secretion diagnosis. The cut-off values used for hypercortisolism diagnosis depend on the

methodology used for UFC determination. If UFC is determined by immunometric tests, the critical values are higher than cut-off values obtained by sensitive methods, such as liquid or gas chromatography, followed by mass or tandem mass spectrometry (13). However, the UFC as a marker for the diagnosis of hypercortisolism, especially in conditions of moderately elevated cortisol secretion, which most often occurs in patients with adrenal incidentalomas, also shows weaknesses that should be discussed. The critical problem-related methodology of UFC determination is related to cortisol metabolites and conjugates which interfere with accurate cortisol measurement (14). This problem has been overcome mainly by highly sensitive and specific methods used for UFC determination, gas chromatography, or liquid chromatography coupled with mass spectrometry with adequate sample preparation (maximum possible removal of interference by extraction methods). Both methodologies are expensive and require special technical expertise, so they are not applicable in routine laboratory practice. The day-to-day variability of UFC is the next problem regarding this biochemical marker (estimated around 40 %) (14). For this reason, one value is never taken as significant, two or three UFC determinations are needed, and the calculated mean value is considered to be the obtained result. There are literature data indicating that it is sometimes necessary to make ten UFC determinations to obtain a completely satisfactory reliability of measurements of adrenocortical hormones (16). Moreover, UFC measurement depends on renal function (this parameter is not recommended for hypercortisolism diagnosis in renal failure patients), as well as on urine flow rate and adequate sample collection (some laboratories express UFC as ng/mg creatinine and urinary creatinine is measured to ascertain the competence of sample collection) (14).

High midnight serum cortisol concentration and the loss of a diurnal rhythm are the first indicators of endogenous hypercortisolism. According to the previous clinical research results, midnight serum cortisol determination is a diagnostic test with high sensitivity and specificity (depending on the cut-off values taken, they can go up to 90%). However, only the Endocrinological Society of the United States (17) recommends this test as the first screening test to diagnose autonomous cortisol secretion. Most of the leading international guidelines recommend this test in patients with possible autonomous cortisol secretion as an additional test for diagnosis (13). To avoid the effects of psychological stress during hospitalization, patients need to be hospitalized at least 48 hours before sampling for midnight serum cortisol concentration, which is the main reason why this test is not recommended as a screening test. Most endocrinological societies considered midnight cortisol concentrations above 200 nmol/L pathological (18). On the other hand, midnight serum cortisol concentration lower than 50 nmol/L is considered to be an exclusion criterion for autonomous cortisol secretion. A high percentage of false-positive results are observed, especially in patients hospitalized for less than 48 hours (19) and in patients older than 40 years, due to age-affected diurnal cortisol rhythm. Modern technologies in laboratory diagnostics have provided tests for cortisol in saliva. The main convenience of saliva as a biological sample is that the sampling is not invasive for the patient, and cortisol concentration results do not depend

on CBG concentrations. On the other hand, there is a problem with the methodology, which is reflected as a lack of harmonization between the assays. In addition, different research results have shown that midnight salivary cortisol concentrations are higher in obesity and diabetes, and this parameter cannot be used for autonomous cortisol secretion diagnosis in those conditions (14).

Potential new laboratory diagnostic marker in autonomous cortisol secretion in adrenal incidentalomas

All the above-mentioned laboratory tests used in diagnosing autonomous cortisol secretion in adrenal incidentalomas have their limitations in diagnostic accuracy. There is a need for further investigations for potential new laboratory markers which could be used alone or in combination with already proposed tests. The role of dehydroepiandrosterone sulfate (DHEAS) has been studied in different pathological conditions caused by the dysfunction of the hypothalamic-pituitary-adrenal axis (HHA axis), such as adrenal insufficiency, chronic glucocorticoid exposure, and Cushing syndrome (20). Adrenal androgens (dehydroepiandrosterone and androstenedione) are secreted by the zona reticularis of the adrenal cortex. The secretion of adrenal androgens is regulated by ACTH, which controls the hypothalamic-pituitary axis. Hypothalamic corticotropin-releasing hormone (CRH) is a major stimulator of ACTH secretion. In addition to CRH, ACTH secretion is stimulated by antidiuretic hormone (ADH) and by inflammatory cytokines. Cortisol has negative feedback effects on the hypothalamus, and it inhibits the secretion of CRH, as well as the secretion of ACTH. In pathological conditions followed by elevated cortisol concentration, ACTH is suppressed, the adrenal gland is less stimulated, and there is consequently a reduced biosynthesis of adrenal androgens (21,22). A short plasma half-life (25 minutes) and pulsatile secretory rhythm similar to ACTH have limited the investigation of dehydroepiandrosterone in autonomous cortisol secretion diagnosis. DHEAS is a metabolite of dehydroepiandrosterone produced in the adrenal cortex, liver, and kidneys. The plasma half-life of DHEAS is much longer (10–16 hours), and irrelative variation in the daily concentration of this metabolite has been observed. These biological characteristics indicate that DHEAS could be an interesting marker for the laboratory assessment of chronically suppressed ACTH activity seen in autonomous cortisol secretion (23). Previous study results regarding the diagnostic accuracy of DHEAS in laboratory diagnostics of autonomous cortisol secretion in adrenal incidentalomas are not consistent (23–25). The reasons for inconsistent results are probably a relatively small number of patients, different analytical methods used for DHEAS concentration determination, and different cut-off values marked as critical that have been used. The National Institutes of Health (NIH), the Endocrine Society (ES), the French Society of Endocrinology (FSE), and the Italian Association of Clinical Endocrinologists (IACE) do not recommend determining DHEAS concentration in autonomous cortisol secretion in adrenal incidentalomas (12). A decrease in concentration with age and undefined critical values are highlighted as the main limitations of this parameter. However, the latest recommendations of the Japan

Endocrine Society (JES) from 2018, as well as the American Association of Clinical Endocrinology/American Association of Endocrine Surgeons (AACE/AAES) suggest low DHEAS concentrations as one of the recommended diagnostic criteria for adrenal autonomous cortisol secretion in patients with possible autonomous cortisol secretion (12). Low DHEAS concentrations are those less than the lower limit of class interval for age and sex group (12).

Conclusion

A higher incidence of pathological conditions related to autonomous cortisol secretion (diabetes mellitus, osteoporosis, cardiovascular diseases) in patients with adrenal incidentalomas suggests the need for improved protocols for diagnosis and assessment of autonomous cortisol secretion in adrenal incidentalomas. The 1 mg overnight dexamethasone suppression test is currently the recommended screening test. Morning ACTH plasma concentration and UFC are the most often used tests for further laboratory testing of patients with possible autonomous cortisol secretion. All the used tests have certain limitations that should be considered during laboratory result interpretation.

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Izazovi u laboratorijskoj dijagnostici autonomne sekrecije kortizola kod pacijenata sa adrenalnim incidentalomima

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Kratak sadržaj

Adrenalni incidentalomi predstavljaju vizuelizacionim tehnikama slučajno otkrivene tumore nadbubrežne žlezde, bez prethodne sumnje na postojanje poremećaja funkcije ili bolesti nadbubrega. 80-90% adrenalnih incidentaloma predstavljaju benigne tumore, koji su u preko 70% slučaja nefunkcionalni, dok je kod oko 15% pacijenata sa benignim adrenalnim incidentalomima dokazana autonomna sekrecija kortizola. Iako su rezultati većeg broja istraživanja ukazali na veći kardiometabolički rizik kod pacijenata sa autonomnom sekrecijom kortizola, još uvek ne postoji jasan konsenzus o biohemijskim kriterijumima za postavljanje dijagnoze autonomne sekrecije kortizola kod pacijenata sa adrenalnim incidentalomima. U ovom radu su opisane osnovne prednosti i nedostaci različitih laboratorijskih testova koji se koriste za postavljanje dijagnoze autonomne sekrecije kortizola.

Ključne reči: adrenalni incidentalomi, kortizol, niskodozni deksametazon supresioni test