REVIEW PAPERS

Subclinical hypercortisolemia – a therapeutic dilemma

Subkliniczna hiperkortyzolemia – dylemat terapeutyczny

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KEYWORDS:

- subclinical hypercortisolemia
- metabolic syndrome
- adrenal adenoma
- adrenal incidentaloma

ABSTRACT

Subclinical hypercortisolemia is the most common secretory function disorder of the adrenal glands caused by the presence of adenoma or hyperplasia of the adrenal cortex. The primary hormonal test performed in the diagnosis of an incidentaloma is a test with 1 mg of dexamethasone. Lack of cortisol suppression after taking 1 mg of dexamethasone is a screening test for hypercortisolemia. Depending on the clinical symptoms, we distinguish between overt and subclinical forms of cortisol excess. Subclinical hypercortisolemia does not cause somatic features of Cushing's syndrome.

However, even a slight excess of cortisol has been found to significantly increase cardiovascular risk, the prevalence of osteoporosis with vertebral fractures, and impair glucose tolerance. In patients with subclinical hypercortisolemia, there are no determined criteria to define strict indications for adrenalectomy. Many studies are showing the beneficial effect of resection of the adrenal adenoma producing cortisol, which led to a reduction in blood pressure and an improvement in the metabolic profile in patients. However, these positive changes do not apply to all patients. As a result, the current European recommendations refer to surgical treatment only when pharmacological treatment fails to achieve good control of hypertension, glucose metabolism, or weight reduction.

Some authors believe that not only the adrenal gland tumor may be a cause of the metabolic syndrome, but on the other hand, hyperinsulinism causes adrenal hyperplasia and excessive secretion of cortisol. In every clinical case, the surgery indication should be carefully analyzed. Primary management is the implementation of pharmacological treatment, regular physical activity, and an appropriate diet.

SŁOWA KLUCZOWE:

- subkliniczna hiperkortyzolemia
- zespół metaboliczny
- gruczolak nadnercza
- incydentaloma nadnercza

STRESZCZENIE

Subkliniczna hiperkortyzolemia jest najczęściej występującym zaburzeniem funkcji wydzielniczej nadnerczy, spowodowanym przez obecność gruczolaka lub rozrostu kory nadnerczy. Podstawowym badaniem hormonalnym wykonywanym przy rozpoznaniu incydentaloma jest test z 1 mg deksametazonu. Brak hamowania wydzielania kortyzolu po przyjęciu 1 mg deksametazonu jest testem przesiewowym w kierunku hiperkortyzolemii. W zależności od objawów klinicznych można rozróżnić jawną i subkliniczną postać nadmiaru kortyzolu. Subkliniczna hiperkortyzolemia nie przyczynia się do wystąpienia cech somatycznych zespołu Cushinga.

Jednakże wykazano, że nawet niewielki nadmiar kortyzolu znacznie zwiększa ryzyko sercowo-naczyniowe, przyczynia się do zaburzeń tolerancji glukozy i zwiększa ryzyko osteoporozy ze złamaniami trzonów kręgowych. W przypadku pacjentów z subkliniczną hiperkortyzolemią, brak jest jednoznacznych kryteriów pozwalających na określenie ścisłych wskazań do adrenalektomii. Istnieje wiele prac, wykazujących korzystne działanie resekcji produkującego kortyzol gruczolaka nadnercza, co prowadziło przede wszystkim do obniżenia ciśnienia tętniczego krwi i poprawy profilu metabolicznego u chorych. Jednak te pozytywne zmiany nie

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dotyczą wszystkich pacjentów – wydaje się, że w przeszłości część pacjentów była poddawanych zabiegowi adrenalektomii niepotrzebnie. W efekcie aktualne zalecenia europejskie mówią o leczeniu zabiegowym jedynie wtedy, gdy leczeniem farmakologicznym nie udaje się uzyskać dobrej kontroli nadciśnienia, gospodarki węglowodanowej czy redukcji masy ciała.

Niektórzy badacze uważają wręcz, że to nie wydzielający autonomicznie guz nadnercza jest najczęściej przyczyną zespołu metabolicznego, ale odwrotnie – że to hiperinsulinizm, występujący w zespole metabolicznym, powoduje rozrost nadnerczy, powstawanie zmian ogniskowych i nadmierne wydzielanie kortyzolu. W takiej sytuacji operacja nie jest wskazana, konieczne jest natomiast wdrożenie leczenia farmakologicznego, regularnej aktywności fizycznej i odpowiedniej diety.

Introduction

Subclinical hypercortisolemia occurs in patients who have diagnose of adrenal adenoma with autonomous cortisol secretion, not fully repressed by pituitary feedback (1, 2). The patients do not present a full Cushing's phenotype, however some physical symptoms can suggest hypercortisolemia (e.g., central obesity). Cortisol excess can be also related to pituitary adenomas or ectopic ACTH-secreting tumors, but in that cases the typical features of Cushing's syndrome are more frequent. It is estimated that approximately 5 to 20% of adrenal adenomas coexist with subclinical hypercortisolemia (1, 2, 3). These changes occur frequently in the population (3-4% in the general population, over 7% after the age of 70) and the prevalence increases with age. They are usually described as *incidentaloma* – found incidentally during imaging of the abdominal cavity or chest performed for clinical reasons other than adrenal glands diagnostics (4).

The cushingoid features require careful examination and evaluation. It is more difficult for physicians who have little experience with patients with Cushing's syndrome. The standardization of Cushing's phenotype evaluation is a persistent medical problem. It may lead to unnecessary diagnostic procedures in some patients or misleading hormonal activity in others. The majority of individuals suffering from subclinical hypercortisolemia do not have any clinical signs and symptoms of the disease (1, 5, 6). Therefore, we should remember to order primary hormonal tests which can easily exclude cortisol excess in patients with adrenal lesions. The main cause of slight glucocorticoid excess is an adrenal adenoma. However, it may also be confirmed in patients with adrenocortical carcinoma and other adrenal tumors (e.g., myelolipomas), but it is not typical for these changes. Adrenocortical carcinomas with hormonal secretion cause more frequently an overt type of Cushing's syndrome. Other adrenal masses usually do not have any hormonal function, but there could be developing some hormone-secreting cells. In each case of finding the adrenal lesion in imaging, we are obligated to perform hormonal tests (5, 7, 8, 9, 10, 11).

Diagnostic approach

The phenotype and metabolic demonstration of subclinical Cushing's syndrome can be quite varied. The diagnostic process may be a challenge for the medicals who not have much experience with these patients. The patients can show a wide spectrum of symptoms. The well-known signs like central obesity, full face, limb muscle weakness and face and neck redness usually are not present, but they may coexist, especially considering the current obesity epidemy. The most important evaluation is to determine the presence and severity of metabolic disorders: hypertension, diabetes or insulin resistance, high level of triglycerides or low HDL-cholesterol level, and obesity. These diseases, which are components of the metabolic syndrome, are often regarded as coexisting processes with the natural aging process and therefore are not an indication for starting hormonal diagnostics (1-3, 5-11).

Several different alterations in the hormonal tests of the hypothalamic–pituitary–adrenal glands axis may be found in patients. The assessment contains every biochemical and endocrine tests used in the diagnosis of Cushing's syndrome. The distinction between true-positive and false-positive test results is difficult in patients with the absence of hypercortisolism signs. Those patients are often under observation due to laboratory abnormalities and lack of clinical symptoms. There is a possibility to develop a disorder after a longer period of acting subtle cortisol excess or even only loss of physiological rhythm of cortisol which normally has a pattern of the highest secretion early in the morning and the lowest at midnight (8, 12, 14).

Except for the cortisol secretion rhythm disruption, the evaluation of morning adrenocorticotropic hormone (ACTH) concentration was reported frequently in the literature. It is important to perform ACTH measurements in the laboratory with available good-quality methods and detection limits. Therefore, it is possible to determine the suppression of ACTH secretion, which is found quite frequently, despite normal baseline cortisol level. The low-to-undetectable ACTH levels were reported in several series. However, the CRH test is not recommended in patients with subclinical hypercortisolemia, as the interpretation of this test can be difficult (1, 3, 7, 13, 14).

A reduction in dehydroepiandrosterone sulfate (DHEAS) concentration could be another indicator of suppression of ACTH secretion, but there is no sufficient data to correlate low DHEAS level with autonomous cortisol secretion. Moreover, DHEAS level decreases with age which can provide to false conclusions (1, 7, 12-14).

An increase in urinary free cortisol (UFC) 24-hour excretion may also be found, but this method has insufficient sensitivity to detect mild hypercortisolism and requires several measurements (at least two) (1, 7, 13, 14). The midnight salivary free cortisol measurement is a useful method as a test that is possible to carry out in outpatients. These two tests are particularly valuable in conditions where other tests (which assess total cortisol concentration) give false results (e.g., in pregnancy) (15, 16).

The most important test for subclinical hypercortisolemia is the dexamethasone suppression test (DST). The Endocrine Society guidelines recommend the 1 mg DST as the basic test for autonomous cortisol secretion. Patients are receiving one tablet of 1 mg dexamethasone at about 11:00 PM,

then in the next day morning the cortisol level is determined. Sometimes the 2 mg short DST can be provided (i.e., 2 mg instead of 1 mg in one dose). The classical 2-days (0,5 mg every 6 hours) test may be more difficult to perform in everyday practice as it requires a hospital stay. The definition of adequate cortisol suppression to dexamethasone was quite controversial (17). A commonly used standard is that if cortisol serum concentration after dexamethasone is less than 1.8 ug/dl (50 nmol/l), the suppression of cortisol secretion is considered normal and adequate. Some authors proposed using lower cut points to increase the detection of subclinical hypercortisolemia. However, when lower post-DST cortisol values are used, the specificity of the method decreases, which can lead to more frequent false-positive test results (3, 7, 13, 14, 17).

Apart from the laboratory tests, the autonomic function of adrenal adenoma may be determined by iodocholesterol scintigraphy where we may detect unilateral tracer uptake in the adrenal adenoma and lack of uptake in the contralateral adrenal gland. Several studies show a correlation between the unilateral tracer uptake in adenoma with cortisol hypersecretion and ACTH suppression. The specificity of N-59 scintigraphy was questioned, because some experts claimed that increased tracer uptake may reflect the presence of enlarged adrenal tissue. The main problems with iodocholesterol adrenal scintigraphy are the cost and the availability. Therefore, this test is not frequently performed (3, 7).

Two concomitant biochemical tests should be performed to confirm autonomic cortisol secretion and to avoid a false-positive diagnosis of subclinical Cushing's syndrome. In patients without any clinical symptoms of hypercortisolemia, the diagnosis is not simple and requires medical experience. Sometimes the hormonal tests, UFC, and SFC should be repeated multiple times every few months. Moreover, the metabolic state assessment should be performed on each visit to check if suspected cortisol excess affects metabolic disorders (1, 7, 13, 14, 17).

Therapeutic dilemma

The overt Cushing's syndrome has well-known clinical consequences, but there is still not enough information on the subclinical hypercortisolemia and its impact on human body. Many patients have clinically inapparent adrenal adenomas and who can be exposed to chronic subtle cortisol excess. However, not everyone diagnosed with subclinical Cushing's syndrome suffers from long-term complications of hypercortisolism, such as visceral obesity, diabetes, impaired glucose tolerance or insulin resistance, arterial hypertension, hypercholesterolemia, or osteoporosis with vertebral fractures. Commonly available diagnostic tools do not allow an unequivocally correct qualification for surgical treatment. A decision about surgery is made depending on age, prognosis, and severity of metabolic disorders (18, 19, 20, 21, 22). Patients are often followed up for years without a decision on surgery.

There were many studies regarding the relationship between metabolic disorders and adrenal adenomas. In a multi-institutional survey performed in Italy, with 1004 patients having adrenal incidentaloma, the prevalence of hypertension, obesity, and diabetes was remarkably high, with a rate of 41%, 28%, and 10%, respectively (11). These data may be partially adulterated by the retrospective nature of the study, the possibility of referral bias, and the high frequency of assessed diseases in the general population. The last one is a main problem occurring in data from studies regarding subclinical hypercortisolemia. There is no easy way to determine if hypertension is definitely related to slight cortisol excess as it can be essential hypertension which is remarkably more common disorder. The prevalence of diabetes, hypertension, obesity, and osteoporosis among patients with subclinical hypercortisolemia may reach 10.8% (1). The screening should include especially young people with those disorders or low bone mineral density. In obese patients with no other diseases, screening is not necessary (7). Majority of patients with adrenal incidentaloma remain asymptomatic throughout life. Some studies showed that even when symptoms of hypercortisolemia are not present, patients with adrenal lesions and subclinical hypercortisolism have an increased risk of cardiovascular events and mortality (23). Disturbed circadian cortisol secretion rhythm is also related to increased cardiovascular risk (24).

Another consequence of hypercortisolemia is osteoporosis. Several authors reported that patients who have subclinical hypercortisolemia have reduced bone mass and density. The negative impact of subclinical cortisol excess on BMD was observed in eugonadal men with adrenal incidentalomas who had also vertebral fractures more frequently (25). Women who have subclinical hypercortisolism are exposed to a higher risk of vertebral fractures independent of their gonadal status (pre- or postmenopausal) (26).

Nowadays, management strategies of subclinical hypercortisolemia treatment are based on general surgery indications for adrenalectomy. There are no determined criteria related to hormonal test results or severity of metabolic complications. The prediction of surgery effects and their impact on metabolism is difficult. Eller-Vainicher et al. concluded that using criteria based on UFC, 1 mg dexamethasone test and suppressed ACTH concentration seems to be the best choice for predicting the metabolic outcome in patients with adrenal adenomas treated by surgery (27). However, like in other rare diseases, more research is needed because of small study groups. Petramara et al. showed a significant reduction in the number of antihypertensive medications needed to reach target blood pressure levels and a decrease in major cardiovascular events in a group of patients with subclinical hypercortisolemia treated with surgery (compared to pharmacological treatment) (28). Pogorzelski et al. performed unilateral laparoscopic adrenalectomy in patients with Cushing's syndrome and subclinical hypercortisolemia getting positive results in both groups (29). The same conclusions were made in many other studies, i.a., in work of Raffaelli et al. (30) and the systematic review performed by Iacobone et al. (31).

Some patients who have adrenal adenoma coexisting with subclinical cortisol excess may not benefit from unilateral adrenalectomy (25,27,32). There are many possible explanations, e.g. surgery may affect an adrenal gland with found adenoma, but due to imaging methods limitations, the other adrenal gland may contain very small adenoma responsible for cortisol excess not visible at the CT scan or MRI. The N-59 iodocholesterol scintigraphy may be useful to reveal this fact, however, the method is still not enough available. Most experts have proven that in patients with adrenal adenomas, hyperinsulinism, prediabetes, or diabetes are caused by the presence of subclinical hypercortisolemia.

But there are studies concerning other theories: hyperinsulinism may cause enlargement of adrenal tissue and occurring adrenal adenoma. Therefore maybe it is a cause of different metabolic effects of surgical treatment in patients with subclinical hypercortisolemia (31, 32, 33, 34, 35). Midorikawa et al. observed patients with adrenal tumors, both non-functioning and having subclinical hypercortisolemia. The prevalence of impaired glucose tolerance, insulin resistance, and hypertension was comparable in two groups (i.e., with functioning and non-functioning adrenocortical tumors). Moreover, the fasting glucose levels decreased after the surgery in both patient groups (33).

The bilateral adrenal incidentalomas coexisting with subclinical hypercortisolemia are a good example of complexity of this issue. Patients with unilateral adrenal adenomas have lower prevalence of subclinical Cushing's syndrome compared with those with bilateral adrenal incidentalomas (36). Papierska et al. followed up fifty patients with bilateral adenoma, among which 24 underwent the surgery. In all patients, cortisol excess retreated after unilateral adrenalectomy. However, only in 14 patients (58%) the clinical improvement was observed (improved control of glucose metabolism, cholesterol level, and hypertension, as well as body mass loss). There are more research and trials needed to evaluate which patients with adrenal adenomas should be surgically treated (37).

Patients who have subclinical hypercortisolism should receive perioperative injections of glucocorticoids, followed by oral hydrocortisone after adrenalectomy because of the insufficiency of the second gland. Those who are not candidates for surgery should be observed with regular follow-up to detect and treat every possible metabolic disorder which may be related to subclinical hypercortisolemia (30).

There are several drugs acting in the mechanism of steroidogenesis inhibition (e.g., metopirone, osilodrostat), but all of them are expensive, not widely available and they are preserved for patients with overt Cushing syndrome after surgery treatment failure or those who have contraindications to the surgery (38).

Conclusions

The regular use of accurate imaging techniques provides to the high prevalence of incidentally detected adrenal adenoma. They may be related to cortisol excess, generally to subclinical hypercortisolemia. The adrenal adenoma may secrete cortisol in 5% to 20% of cases. Subclinical hypercortisolemia is a heterogeneous condition, therefore the biochemical and hormonal results as well as symptoms and diseases reported by patients may widely vary depending on the individual. Mild cortisol excess may lead to insulin resistance, osteoporosis, atherosclerosis, and cardiovascular complications.

There are still insufficient data to decide whether surgical treatment is better than nonsurgical management. It appears that it depends on the individual patient. We should keep trying to define the patients at increased risk of cardiovascular diseases. The additional studies are needed to improve the algorithms of follow-up schedules for hormonal tests and imaging for patients treated without surgery. The steroidogenesis inhibitors may play a more important role at subclinical hypercortisolemia management in the future, however, there should be performed more studies determined the safety and efficacy of this treatment.

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