Meet the Expert Session

AACE 25th Annual Scientific and Clinical Congress

Orlando, Florida

Thursday, May 26th, 2016

Mild Hypercortisolism due to Adrenal Adenomas – Is It Really "Subclinical"?

Alice C. Levine, MD

Co-Authors: Gillian M. Goddard, M.D. and Aarti Ravikumar, M.D.

(adapted from "Adrenal Mild Hypercortisolism", Endocrine Clinics of North America, 44(2015), 371-379)

The Hilda and J. Lester Gabrilove Division of Endocrinology, Diabetes and Bone Diseases, Department of Internal Medicine, Icahn School of Medicine at Mount Sinai,One Gustave L. Levy Place, Box 1055, New York, NY 10029-6574

Tel 212-241-7975, Fax 212-241-4218

Email: alice.levine@mountsinai.org

Keywords/Abbreviations : adrenal, adrenal incidentaloma (AI), mild hypercortisolism, subclinical hypercortisolism (SH), subclinical Cushing syndrome, Cushing syndrome, cortisol.

Key Points:

1. Mild hypercortisolism is also known as subclinical Cushing's syndrome and is usually due to benign adrenal adenoma(s)
2. The definition of mild hypercortisolism is debatable but the most sensitive diagnostic test is failure of suppression of AM cortisol after low-dose dexamethasone suppression test (LDDST)
3. Using an AM cortisol < 1.8 ug/dl after LDDST gives high sensitivity but lower specificity as compared to using an AM cortisol level of < 5 ug/dl after LDDST which gives a lower sensitivity but a higher specificity
4. Mild hypercortisolism has been *associated* with the same comorbidities as overt Cushing's syndrome: metabolic syndrome, osteoporosis, increased risk of cardiovascular events and increased mortality but *causality* has not yet been proven.
5. Treatment options include surgical resection of the affected adrenal gland or medical therapies
6. Medical therapies include ketoconazole, mitotane and mifepristone but only mifepristone has been studied specifically for the treatment of mild hypercortisolis

Significance of the Clinical Problem

Adrenal incidentalomas (AI) are increasingly common as more abdominal imaging is performed. The majority of these lesions are benign and cortical in origin. The most common secretory syndrome associated with these adrenal adenomas is that of mild hypercortisolism, also known as subclinical Cushing syndrome. This is a rapidly changing and somewhat controversial subject with no consensus regarding the diagnostic criteria and management recommendations. However, recent reports are beginning to shed light on the prevalence, associated co-morbidities and newer treatment options for adrenal hypercortisolism.

Barriers to Optimal Practice

There is no consensus on the cutoff points that define a state of mild hypercortisolism due to adrenal adenomas. This lack of uniformity also hampers the interpretation of past studies investigating the association between this disorder and various comorbidities as well as the possible benefits of surgical removal. In addition, until recently, there were few medical treatment options and virtually no studies investigating the effects of medical therapy on patients with mild hypercortisolism.

Learning Objectives

As a result of participating in this session, learners should be able to:

1. Identify patients who should be screened for the presence of mild hypercortisolism

2. Appreciate the controversies regarding the biochemical definition of the disorder

3. Recognize the possible sequelae of mild hypercortisolism on bone, metabolic and cardiovascular health.

4. Understand the range of possible therapeutic interventions.

Is Subclinical Cushing Syndrome Really" Subclinical"?

Since its conceptualization, mild hypercortisolism has been referred to as subclinical Cushing syndrome. This is based upon the fact that classical signs and symptoms of Cushing syndrome including moon facies, striae, increased dorsocervical and supraclavicular fat pads and proximal muscle wasting are absent. Additionally, while there may be mild derangements in cortisol production, urinary free cortisol levels 2-3 times the upper limit of normal and grossly abnormal midnight salivary cortisol levels are typically absent. The traditional thinking was that these low levels of excess cortisol were not associated with any co-morbidities (1, 2).

However, subclinical Cushing syndrome has been shown to be associated with increased insulin resistance and changes in body composition in women (3). In 2014, three studies

found an increased risk of cardiovascular disease and mortality in patients with subclinical Cushing's syndrome (4-6). Given the clinical implications of having even modest elevations of cortisol, we would argue this is not a subclinical disease at all, and that it would best be termed *mild hypercortisolism*.

Frequency of incidentalomas and Mild Hypercortisolism

Adrenal incidentalomas are estimated to be present in approximately 7% of the population (7). With an increase in abdominal imaging, the reported prevalence is higher and the incidence increases with advancing age. The probability of detecting an adrenal incidentaloma in patients between the ages of 20 and 29 years is approximately 0.2% as opposed to approximately 7% in a patient over 70 years of age (8, 9). Previously Cushing's syndrome was estimated to be present in 4-5% of patients with adrenal incidentalomas (7). However, in studies that also include patients with mild hypercortisolism, the incidence is reported to be closer to 30% (5).

Defining Mild Hypercortisolism

Laboratory testing should be performed in patients with known adrenal pathology with or without evidence of clinical signs and symptoms of excess cortisol (1, 7). Particular attention should be paid to those patients with associated co-morbidities including resistant hypertension, obesity, impaired glucose tolerance and lipid derangements (1).

Much of the variability in the reported frequency of mild hypercortisolism among patients with adrenal adenomas can be attributed to differences in the biochemical definition of this disease. There is controversy over which laboratory cutoffs should be used. As with classical Cushing's syndrome a combination of simple lab testing and dynamic testing is helpful.

The most sensitive test for the detection of mild hypercortisolism from adrenal nodules is the 1mg overnight, low-dose dexamethasone suppression test (LDDST) (10). Historically, a morning serum cortisol of more than 5 ug/dl (>138 nmol/L) after 1mg of dexamethasone was considered diagnostic of the disorder (1). This is not intuitive given that in classical Cushing's syndrome, a morning serum cortisol of greater than 1.8 ug/dl (>50 nmol/L)after LDDST is considered diagnostic. The discrepancy is due to the concept that in the case of symptomatic Cushing's syndrome the clinician's index of suspicion is high and there is a high pre-test probability of disease so therefore the likelihood of a false positive test is reduced. In contrast, in patients with mild hypercortisolism symptoms are subtle so the clinician's index of suspicion is lower and therefore a test with greater specificity is preferable, despite the loss of sensitivity.

Currently, the definition of a positive LDDST to confirm mild hypercortisolism is not consistent in the literature. Many investigators use a morning serum cortisol of > 5 ug/dl after LDDST, which has a low sensitivity (44-58%) but a high specificity (83-100%). In contrast, some reports use a lower AM cortisol value after LDDST (cortisol >1.8ug/dl). This definition results in a higher sensitivity (75-100%) but a lower specificity (67-72%)

(1). There is a risk of having false-positive values when using the cutoff of 1.8ug/dl and the potential for over-diagnosis (11). Other values, including a morning cortisol of > 2.2 ug/dl or >3.0 ug/dl after LDDST have been advocated as offering the best balance of sensitivity and specificity when evaluating patients with AI for mild hypercortisolism (1).

1mg Overnight Dexamethasone Suppression Test

	AM Cortisol	
	>1.8 ug/dL	> 5 ug/dL
Sensitivity*	75-100%	44-58%
Specificity*	67-72%	83-100%

*
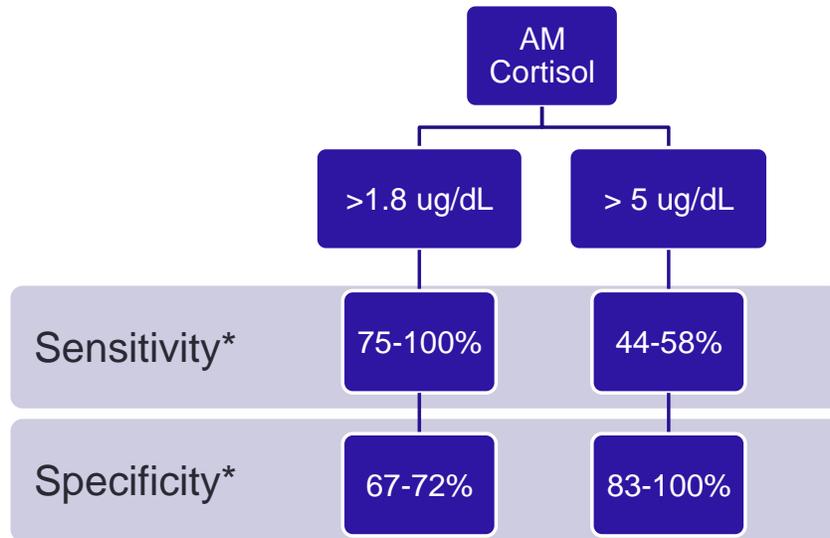
Elevated urinary free cortisol (UFC) from a 24-hour urine collection may support the diagnosis. Mild elevations of up to 2 times the upper limit of normal are often seen. However, not infrequently, patients with mild hypercortisolism may have a normal UFC (2).

The use of midnight salivary cortisol (MSC) has been explored in the diagnosis of mild hypercortisolism, but its utility appears limited. (12, 13). As with UFC, mild elevations of MSC support the diagnosis of mild hypercortisolism, but normal MSC does not rule out the disease.

The majority of published reports define mild hypercortisolism as a disease of the adrenal glands resulting from benign appearing incidentalomas (1). However it is important to confirm this etiology biochemically. Once hypercortisolism is established, a morning ACTH that is suppressed (<10ng/ml) confirms ACTH-independent hypercortisolism due to adrenal pathology. However, in mild adrenal hypercortisolism the degree of excess cortisol production may not be sufficient to entirely suppress the HPA axis and a low-normal

morning ACTH may be seen. In those cases, it is important to check the morning ACTH after LDDST. If the ACTH is not suppressed in the setting of an elevated dexamethasone level, other etiologies such as pituitary or ectopic ACTH overproduction should be considered (14).

Other supportive laboratory testing may include DHEA/DHEAS, two values that are often low in the setting of autonomous adrenal cortisol secretion; however, in older patients non-specific decreases in DHEA/DHEAS are also detected (15).

Mild Hypercortisolism: Associated Co-Morbidities

Recent reports have established that the co-morbidities associated with mild hypercortisolism are similar to those reported in patients with overt Cushing's syndrome: the metabolic syndrome, osteoporosis, increased cardiovascular disease and mortality.

Metabolic Syndrome

In 2002, Terzolo studied patients with adrenal incidentalomas and subclinical Cushing's syndrome (SCS), defined as at least 2 of following criteria: elevated UFC, cortisol > 5ug/dl after LDDST, suppressed ACTH, or disturbed cortisol circadian rhythm. Twelve patients met these criteria and were compared to controls (euthyroid mulitnodular goiter patients). The controls were age, sex and BMI matched. A 120 minute 75gm OGTT was done for both groups. The fasting plasma glucose and insulin levels were similar in the two groups. However, glucose levels were found to be higher and insulin sensitivity lower in the patients with subclinical Cushing's syndrome (SCS) at 60, 90 and 120 minutes after 75 gms glucose ingestion. Fasting triglycerides were higher in the SCS group, which is an indirect measure of insulin resistance. Given that the two groups were BMI-matched, the authors concluded that the observed insulin resistance in the SCS group was likely due to excess cortisol (16).

Osteoporosis

The risk of osteoporosis due to mild hypercortisolism has also been reported. Chiodini published a paper in 2009 which was a multi-center, retrospective study done in Italy evaluating the bone mineral density, prevalence of vertebral fractures and bone quality in patients with adrenal incidentalomas with (SH+) and without subclinical hypercortisolism (SH-). Subclinical hypercortisolism was defined as 2/3 of: UFC > 70ug/24h, cortisol> 3ug/dl after LDDST and ACTH < 10.   The primary endpoint measured was the spinal deformity index (SDI) in which the number and severity of vertebral fractures are integrated; the SDI has been suggested to be associated with vertebral fracture risk over time.   The study demonstrated that the patients with AIs (SH+) were found to have lower BMD at the lumbar spine (trabecular bone) and femoral neck (cortical bone), more metabolic syndrome and increased SDI compared to both those with AI (SH-) and controls. The odds radio (OR) for vertebral fractures was 7.27 (p = 0.0001, CI 3.94 -> 13.41) for patients with SH+ regardless of age, BMD, menopause and gender (17).

Subsequently, in 2011, the same group conducted a multicenter, prospective, longitudinal study, evaluating SDI and vertebral fractures at baseline and after 12 and 24 months in patients with adrenal incidentalomas with and without subclinical hypercortisolism (18). The definition was the same as in the retrospective analysis. In the prospective study, Morelli et al reported that the prevalence of fractures and SDI were higher in the SH+ group regardless of age, sex, BMI, BMD and menopausal status. Also, those with subclinical hypercortisolism had a higher risk of vertebral fractures when compared to SH- (OR 12.264, p value 0.001) .

Cardiovascular Disease

Subclinical hypercortisolism has long been reported to be associated with an increased risk of cardiovascular disease. Recently, several studies have reaffirmed this association and further implied that even mild degrees of hypercortisolism are deleterious to overall cardiovascular health. Di Dalmazi et al. performed a retrospective analysis of 198 outpatients with adrenal incidentalomas over 15 years (5). They categorized the AI patients as stable non-secreting (cortisol < 1.8ug after LDDST) (n=114), stable intermediate (cortisol 1.8-5ug/dl after LDDST) or subclinical Cushing's (cortisol > 5ug/dl after LDDST) (n= 61). In addition, 23 patients had a demonstrated worsening of their hypercortisolism during the course of the study, and moved from the non-secreting to intermediate or intermediate to subclinical Cushing's group. The reported incidence of CV events was higher in patients with the stable intermediate or subclinical Cushing's patterns (16.7%, p=0.04) and also in those patients with worsened secreting patterns (28.4%, p=0.02) compared to those with stable non-secreting adenomas (6.7%). Survival rates for all-cause mortality were lower in adenomas with stable intermediate and subclinical Cushing's secreting patterns compared to non-secreting (57% vs. 91.2%, p= 0.005).

Androulakis et al. published a case-control study evaluating cardiovascular risk in patients with apparently non-functioning adrenal incidentalomas and no known cardiovascular risk factors (i.e. hypertension, hyperlipidemia or diabetes) (6). Sixty patients were subdivided into cortisol-secreting adrenal incidentalomas (CSAI) and nonfunctioning adrenal incidentalomas (NFAI). They were both compared to 32 healthy controls with normal adrenal imaging. The definition of cortisol secreting-adrenal incidentalomas was an AM cortisol +2 SD greater than the control group after LDDST, which translated to a cortisol > 1.09 ug/dl, a value that is lower than previously suggested cutoffs even in patients with overt Cushing's syndrome . Twenty-four patients were found to have CSAI and 34 NFAI using this definition. The study measured intimal media thickness (IMT) and flow-mediated vasodilatation (FMD), two measures that are associated with atherosclerosis and cardiovascular risk. The IMT was higher and FMD lower in the cortisol secreting adenomas compared to NFAIs.

Morell et al. studied 206 AI pts >5 yr followup [4]. They defined SH as either a) 1 mg dex with cortisol > 5mcg/dl or b) at least 2: low ACTH, high UFC, 1mg dex cortisol > 3 mcg/dl. They initially identified 24 pts with but 15 additional patients developed SH over time (8.2%). In both the SH+ and SH- many grew and *noted bilateral adenomas.* Of note, in the

SH patients there was more diabetes and CVEs and larger adenomas and they calculated a cutoff size of >2.4 cm as being highly associated with hypercortisolism. The increased CVEs CVEs correlated with dex-suppressed cortisol between 1.5 and 2.0 mcg/dl (best SN and SP).

A study from Debono et al. also confirmed this association. In a retrospective study of 206 patient all with adrenal adenomas, patients were categorized as having cortisol concentrations > 1.8 ug/dl after 1-mg LDDST or having cortisol concentrations < 1.8 ug/dl after 1-mg LDDST. Elevation in cortisol concentration after LDDST was associated with decreased survival. Fifty percent of the deaths in the group were from cardiovascular causes (19).

Treatment of Mild Hypercortisolism

Surgery

The usual treatment of adrenal Cushing's syndrome is unilateral adrenalectomy to remove the gland that contains the hyperfunctioning adrenal nodule. There have been several studies assessing the effectiveness of unilateral adrenalectomy in patients with mild hypercortisolism. One such retrospective, longitudinal study evaluated 108 subjects all with adrenal incidentalomas, of which 55 underwent unilateral adrenalectomy and 53 did not undergo surgery.
The data demonstrated that metabolic improvements after surgery were seen in those patients with two or more of the following preoperatively: UFC >70 mcg/24 hrs, ACTH <10 pg/ml, or cortisol >3.0 ug/dl (83 nmol/L) after LDDST (sensitivity 65% specificity 69%) (20).

A review of the surgical literature assessed ten studies with a total of 101 patients meeting the criteria for mild hypercortisolism. The definition of mild hypercortisolism did vary between studies ranging from cortisol > 1 ug/dl to cortisol > 5ug/dl after LDDST. Outcomes including improvements in blood pressure, body weight and fasting glucose were mixed. Only one of the 10 studies looked at possible improvements in bone health and showed no significant improvement in bone density after unilateral adrenalectomy (1).

A prospective randomized controlled trial was performed over 15 years assigning patients with adrenal incidentalomas to either conservative management or surgical resection with laparoscopic adrenalectomy (21). Conservative management was = carried out by 2 experienced endocrinologists monitoring who treated the patients for diabetes mellitus, hypertension, hyperlipidemia, obesity and osteoporosis if necessary. It should be noted that no medical therapy was given that specifically targeted the hypercortisolism in either group. Forty-five patients enrolled: 23 underwent surgery and 22 were treated conservatively. Mean follow-up was 7.7 years (2 - 17 years). Surgery proved beneficial for patients with mild hypercortisolism that was accompanied by any of the following: diabetes (5/8 normalized or improved, 62.5%), arterial hypertension (12/18 normalized or improved, 67%) and central obesity (3/6 normalized, 50%). However, the only statistically significant improvement in metabolic parameters was improvement in BP (p = 0.046).

Medical Treatment of Mild Hypercortisolism

Historically, medical treatment options for Cushing's syndrome have been limited, both in the number of options available and in their efficacy. Ketoconazole has been used for many years, though it does not have an FDA-approved indication for the treatment of Cushing syndrome. More recently, mifepristone, a glucocorticoid receptor antagonist, was approved for the treatment of hyperglycemia due to Cushing syndrome. More medical options are under active investigation.

Mifepristone acts as a potent glucocorticoid receptor blocker. It does not lower cortisol levels and actually may cause a rise in serum cortisol measurements. To determine efficacy, surrogate markers of cortisol action, such as improvement in insulin sensitivity, must be followed. Side effects include nausea, fatigue and muscle aches (22). Rarely, adrenal insufficiency can occur due to excessive glucocorticoid receptor blockade. Additionally, patients may experience hypertension and hypokalemia due to cortisol activity at the mineralocorticoid receptor as it is not blocked by mifepristone.

Mifepristone has been used in the only small study of medical treatment of *mild* hypercortisolism. DeBono, et al, conducted a pilot study of mifepristone in 6 patients all with mild hypercortisolism (defined as a serum cortisol >1.8ug/dl after both a 1-mg overnight, and 2-mg 48 hour dexamethasone suppression test) and normal glucose parameters (3). After 4 weeks of treatment with mifepristone, insulin sensitivity measured by HOMA-IR, Matsuda index and insulin area under the curve (AUC) all improved as did fasting insulin levels. Fasting glucose levels were not improved but were not noted to be elevated at baseline.

Ketoconazole, an anti-fungal agent has been the most widely prescribed medication for Cushing's syndrome. The medication has not been FDA approved for this indication and the FDA recently issued a safety warning about the use of ketoconazole for the treatment of fungal infection and the risk of liver toxicity. As of this publication ketoconazole is still available.

Metyrapone, an 11β-hydroxylase inhibitor, has long been used for the treatment of Cushing's syndrome in Europe. It is not easily available in the United States. Another more potent 11 β-hydroxylase inhibitor under investigation is LCI699 (Novartis) [24,25]. Both of these medications block the conversion of 11-deoxycortisol to cortisol, thus lowering serum concentrations of cortisol. The inhibition of cortisol synthesis does lead to a build-up of steroid precursors that are shunted into other steroid synthesis pathways potentially resulting in undesirable, androgenic side effects such as hirsutism in women. Recent proof-of-concept studies of LCI699 have been promising but the compound is not yet commercially available. The chemotherapeutic agent mitotane is cytotoxic to adrenal cortical tissue.

To date there is very little evidence for or against the use of medical therapies for the treatment of mild hypercortisolism due to adrenal adenomas. Future studies may help determine which medications are most effective and which patients may benefit most from surgical intervention.

Summary

Adrenal incidentalomas are becoming increasingly more common and nearly one-third may be producing low levels of excess cortisol. The definition of mild hypercortisolism is much debated. Utilizing a cortisol cut-off of >1.8ug/dl after LDDST results in a higher sensitivity (90%) but with a trade-off of lower specificity (70%). Recent studies have demonstrated as association between mild hypercortisolism and the metabolic syndrome, CV disease, osteoporosis and increased mortality. These association studies make a compelling argument that *any* degree of hypercortisolism, over time, is deleterious to bone, metabolic and cardiovascular health; However, these studies have *not* established causality. There are surgical and medical options available to treat mild hypercortisolism due to adrenal adenomas, including mifepristone and ketoconazole. Additional further medical therapies are being evaluated.

The data regarding the efficacy of various treatments in patients with only mild degrees of hypercortisolism is sparse. In addition, most of the previous reports utilize varying definitions of the disorder, further complicating the interpretation of the data. Prospective studies are sorely needed in order to better define the disorder and determine whether therapy, either medical or surgical, should be considered in patients with adrenal adenomas and mild hypercortisolism.

Bibliography

1. Chiodini I. Clinical review: Diagnosis and treatment of subclinical hypercortisolism. J Clin Endocrinol Metab. 2011;96(5):1223-36.
2. De Leo M, Cozzolino A, Colao A, Pivonello R. Subclinical Cushing's syndrome. Best Pract Res Clin Endocrinol Metab. 2012;26(4):497-505.
3. Garrapa GG, Pantanetti P, Arnaldi G, Mantero F, Faloia E. Body composition and metabolic features in women with adrenal incidentaloma or Cushing's syndrome. J Clin Endocrinol Metab. 2001;86(11):5301-6.
4. Morelli V, Reimondo G, Giordano R, Della Casa S, Policola C, Palmieri S, et al. Long-term follow-up in adrenal incidentalomas: an Italian multicenter study. J Clin Endocrinol Metab. 2014;99(3):827-34.
5. Di Dalmazi G, Vicennati V, Garelli S, Casadio E, Rinaldi E, Giampalma E, et al. Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. 2014;2(5):396-405.
6. Androulakis, II, Kaltsas GA, Kollias GE, Markou AC, Gouli AK, Thomas DA, et al. Patients with apparently nonfunctioning adrenal incidentalomas may be at increased cardiovascular risk due to excessive cortisol secretion. J Clin Endocrinol Metab. 2014;99(8):2754-62.
7. Young WF, Jr. Clinical practice. The incidentally discovered adrenal mass. N Engl J Med. 2007;356(6):601-10.
8. Young WF, Jr. Management approaches to adrenal incidentalomas. A view from Rochester, Minnesota. Endocrinol Metab Clin North Am. 2000;29(1):159-85, x.
9. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B. Incidentally discovered adrenal masses. Endocr Rev. 1995;16(4):460-84.
10. Morelli V, Masserini B, Salcuni AS, Eller-Vainicher C, Savoca C, Viti R, et al. Subclinical hypercortisolism: correlation between biochemical diagnostic criteria and clinical aspects. Clin Endocrinol (Oxf). 2010;73(2):161-6.
11. Stewart PM. Is subclinical Cushing's syndrome an entity or a statistical fallout from diagnostic testing? Consensus surrounding the diagnosis is required before optimal treatment can be defined. J Clin Endocrinol Metab. 2010;95(6):2618-20.
12. Masserini B, Morelli V, Bergamaschi S, Ermetici F, Eller-Vainicher C, Barbieri AM, et al. The limited role of midnight salivary cortisol levels in the diagnosis of subclinical hypercortisolism in patients with adrenal incidentaloma. Eur J Endocrinol. 2009;160(1):87-92.
13. Ceccato F, Barbot M, Zilio M, Ferasin S, Occhi G, Daniele A, et al. Performance of salivary cortisol in the diagnosis of Cushing's syndrome, adrenal incidentaloma, and adrenal insufficiency. Eur J Endocrinol. 2013;169(1):31-6.
14. Newell-Price J, Trainer P, Besser M, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome and pseudo-Cushing's states. Endocr Rev. 1998;19(5):647-72.
15. Rossi R, Tauchmanova L, Luciano A, Di Martino M, Battista C, Del Viscovo L, et al. Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab. 2000;85(4):1440-8.

16. Terzolo M, Pia A, Ali A, Osella G, Reimondo G, Bovio S, et al. Adrenal incidentaloma: a new cause of the metabolic syndrome? J Clin Endocrinol Metab. 2002;87(3):998-1003.

17. Chiodini I, Morelli V, Masserini B, Salcuni AS, Eller-Vainicher C, Viti R, et al. Bone mineral density, prevalence of vertebral fractures, and bone quality in patients with adrenal incidentalomas with and without subclinical hypercortisolism: an Italian multicenter study. J Clin Endocrinol Metab. 2009;94(9):3207-14.

18. Morelli V, Eller-Vainicher C, Salcuni AS, Coletti F, Iorio L, Muscogiuri G, et al. Risk of new vertebral fractures in patients with adrenal incidentaloma with and without subclinical hypercortisolism: a multicenter longitudinal study. J Bone Miner Res. 2011;26(8):1816-21.

19. Debono M, Bradburn M, Bull M, Harrison B, Ross RJ, Newell-Price J. Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas. J Clin Endocrinol Metab. 2014;99(12):4462-70.

20. Eller-Vainicher C, Morelli V, Salcuni AS, Battista C, Torlontano M, Coletti F, et al. Accuracy of several parameters of hypothalamic-pituitary-adrenal axis activity in predicting before surgery the metabolic effects of the removal of an adrenal incidentaloma. Eur J Endocrinol. 2010;163(6):925-35.

21. Toniato A, Merante-Boschin I, Opocher G, Pelizzo MR, Schiavi F, Ballotta E. Surgical versus conservative management for subclinical Cushing syndrome in adrenal incidentalomas: a prospective randomized study. Ann Surg. 2009;249(3):388-91.

22. Fleseriu M, Biller BM, Findling JW, Molitch ME, Schteingart DE, Gross C, et al. Mifepristone, a glucocorticoid receptor antagonist, produces clinical and metabolic benefits in patients with Cushing's syndrome. J Clin Endocrinol Metab. 2012;97(6):2039-49.

23. Debono M, Chadarevian R, Eastell R, Ross RJ, Newell-Price J. Mifepristone reduces insulin resistance in patient volunteers with adrenal incidentalomas that secrete low levels of cortisol: a pilot study. PLoS One. 2013;8(4):e60984.

24. Trainer PJ. Next generation medical therapy for Cushing's syndrome--can we measure a benefit? J Clin Endocrinol Metab. 2014;99(4):1157-60.

25. Bertagna X, Pivonello R, Fleseriu M, Zhang Y, Robinson P, Taylor A, et al. LCI699, a potent 11beta-hydroxylase inhibitor, normalizes urinary cortisol in patients with Cushing's disease: results from a multicenter, proof-of-concept study. J Clin Endocrinol Metab. 2014;99(4):1375-83.

CASES WITH QUESTIONS

Case 1

A 66 year old woman was referred to an endocrinologist by her primary care physician after a 2.8 cm left adrenal mass was incidentally noted on an abdominal CT performed for non-specific abdominal pain. It measured 6 Houndsfield Units without contrast and was read by the radiologist as consistent with a benign adrenal adenoma.

Her past medical history was significant for hypertension that was well controlled on a single anti-hypertensive agent (a calcium channel blocker), hyperlipidemia and osteopenia. Upon further questioning the patient noted that she had gained 25 pounds in the previous 18 months. She had her last menses 16 years earlier at age 50 and had not received any estrogen replacement therapy.

On physical exam the patient was well-appearing with some central obesity but no other stigmata of Cushing syndrome. Her blood pressure was 158/88 mmHg and her pulse was 80 beat/min. She had no scalp hair loss, hirsutism or acne. Cardiovascular exam revealed regular heart rate and rhythm, with no murmurs. Lung exam was clear to auscultation with no wheezes. Abdomen was obese with waist circumference of 37 inches. She did not have abdominal striae, lower extremity edema, or proximal muscle weakness or wasting.

Biochemical workup revealed a fasting glucose of 78 mg/dl, creatinine of 0.7 mg/dl, BUN of 16 mg/dl, AST 19 U/l, and ALT of 15 U/l (all normal). The patient's late afternoon serum cortisol level was 6.5 mcg/dl, ACTH was <10 pg/ml and DHEA-S was 31 mcg/dl (normal 35-430 mcg/dl). Her hemoglobin A1C was 6.2%. Her aldosterone/renin ratio was normal as were plasma free metanephrines.

QUESTIONS:

1. What factors in the case history, physical exam and laboratory tests point to a diagnosis of possible mild hypercortisolism?

Although this patient does not have any features of classic Cushing syndrome, she does have several features of the metabolic syndrome including increased waist size, hypertension, hyperlipidemia and prediabetes. In the presence of an adrenal adenoma, particularly one that is >2.5 cm in diameter, there may well be an association with mild hypercortisolism.

2. What is the best test to rule out hypercortisolism in this patient?

In mild hypercortisolism due to benign adrenal adenoma (s), the usual Cushing screening tests such as 24 hour urinary free cortisol and midnight salivary cortisols may be

normal or only slightly elevated. The most sensitive test for ruling out mild hypercortisolism in this patient would be a 1 mg overnight dexamethasone suppression test with measurement of early AM cortisol, ACTH and dexamethasone levels. Although some earlier studies accepted a cortisol suppression to < 5mcg /dl after 1 mg dexamethasone as a rule out of adrenal hypercortisolism, recent studies indicate that any degree of hypercortisolism may be deleterious to cardiovascular, bone and metabolic health. Therefore, in adrenal Cushing as in pituitary or ectopic Cushing, the cortisol cutoff after 1 mg dexamethasone the night before of <1.8 mcg/dl would be the most sensitive.

3. What are the sequelae of mild hypercortisolism due to benign adrenal adenomas?

Although causality has not been proven, most studies indicate that any degree of mild hypercortisolism is associated with deleterious effects on bone, glucose metabolism, and hypertension. Several large retrospective studies have recently been published demonstrating that mild hypercortisolism is particularly deleterious to cardiovascular health and mortality. Although these studies only prove association, there have been some surgical studies demonstrating a beneficial effect of adrenalectomy on metabolic parameters. However, most of the surgical studies have been hampered by poor design or too much variability in the definitions of mild hypercortisolism.

4. What are the treatment options for mild hypercortisolism due to benign adrenal disease?

Surgical adrenalectomy has been studied but, as mentioned above, in the absence of concern for malignancy, there is no solid evidence to support this treatment for mild hypercortisolism. Newer medical therapies such as the glucocorticoid receptor blocker, mifepristone, can be utilized in patients with hypercortisolism and glucose intolerance or diabetes . Cortisol synthesis inhibitors such as ketoconazole and 11 beta-hydroxylase inhibitors (if available) are options. Finally, as in any patient with features of the metabolic syndrome, treatment of co-morbidities with diet, exercise, statins, antihypertensives and anti-diabetic drugs should be considered.