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Review

Subclinical Cushing's syndrome: Current concepts and trends

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ABSTRACT

Clinically inapparent adrenal masses which are incidentally detected have become a common problem in everyday practice. Approximately 5-20% of adrenal incidentalomas present subclinical cortisol hypersecretion which is characterized by subtle alterations of the hypothalamic-pituitary-adrenal axis due to adrenal autonomy. This disorder has been described as subclinical Cushing's syndrome, since there is no typical clinical phenotype. The diagnosis of subclinical Cushing's syndrome is based on biochemical evaluation; however, there is still no consensus for the biochemical diagnostic criteria. An abnormal 1mg dexamethasone suppression test (DST) as initial screening test in combination with at least one other abnormal test of the hypothalamic-pituitary-adrenal axis has been advocated by most experts for the diagnosis of subclinical Cushing's syndrome. DST is the main method of establishing the diagnosis, while there is inhomogeneity of the information that other tests provide. Arterial hypertension, diabetes mellitus type 2 or impaired glucose tolerance, central obesity, osteoporosis/vertebral fractures and dyslipidemia are considered as detrimental effects of chronic subtle cortisol excess, although there is no proven causal relationship between subclinical cortisol hypersecretion and these morbidities. Therapeutic strategies include careful observation along with medical treatment of morbidities potentially related to subtle cortisol hypersecretion versus laparoscopic adrenalectomy. The optimal management of patients with subclinical Cushing's syndrome is not yet defined. The conservative approach is appropriate for the majority of these patients; however, the duration of follow-up and the frequency of periodical evaluation still remain open issues. Surgical resection may be beneficial for patients with hypertension, diabetes mellitus type 2 or abnormal glucose tolerance and obesity.

Key words: Adrenal incidentaloma, Clinical implications, Diagnosis, Laparoscopic adrenalectomy, Subclinical Cushing's syndrome, Treatment

INTRODUCTION

Masses of the adrenal glands are one of the most common tumors in humans, as described in autopsy studies.[1,2] The first report of adrenal masses revealed by computed tomography in patients with unsuspected adrenal disease was published by Korobkin et al. in 1979.[3] Since then, progress in imaging modalities and ever more widespread use of imaging studies have led to increasing detection of these lesions in a

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clinical setting due to imaging evaluation performed for reasons unrelated to adrenal disease. Therefore, clinically inapparent adrenal masses, called adrenal incidentalomas, have become a common problem in everyday practice.[4] It must be mentioned that adrenal masses discovered during staging procedure in patients with malignancy are not considered as incidentally detected. Thus, the definition of adrenal incidentaloma excludes patients with overt adrenal hyperfunction and patients undergoing imaging evaluation as part of staging procedure for malignancy.[4, 5]

Initial diagnostic evaluation of a patient with an adrenal incidentaloma aims to determine the functional status of the mass and the possibility of malignant disease. The vast majority of these lesions are benign nonhypersecreting cortical neoplasms. However, a significant percentage of cases present subclinical hormonal activity, mainly concerning glucocorticoid secretion.[4-6] Subtle cortisol hypersecretion by adrenal incidentalomas is characterized by alterations of the hypothalamic-pituitary-adrenal (HPA) axis due to adrenal autonomy in the absence of the typical clinical phenotype of hypercortisolism, a disorder that has been defined as subclinical Cushing's syndrome (SCS).[5] Therefore, the diagnosis of this disorder is entirely dependent on laboratory evaluation. Because the optimal diagnostic approach is still debated, the prevalence of SCS has not been established.[4-6] Moreover, the variation of biochemical diagnostic criteria applied in relevant studies has resulted in limitations concerning the assessment of the clinical significance of subtle cortisol hypersecretion. Thus, the optimal management of patients with adrenal adenomas and SCS is not yet defined.[4-6] Choices are either close follow-up combined with medical treatment of potentially associated morbidities with subtle cortisol hypersecretion or surgical treatment. In this review we will focus on the diagnostic criteria and clinical implications of SCS as well as surgical treatment of these patients.

OVERVIEW

Subclinical cortisol hypersecretion by adrenal incidentalomas was first described by Beierwaltes et al. in 1974. They reported two patients with unilateral adrenal uptake of ^{131}I-19-iodocholesterol (NP-59) indicating the presence of a hyperfunctioning adrenal adenoma, without clinical or biochemical evidence of Cushing's syndrome. These findings were considered similar to thyroid hot nodules revealed by thyroid scan in the absence of thyrotoxicosis.[7] Further in vivo[8-10] and in vitro studies[11,12] documented the presence of subclinical cortisol hypersecretion in patients with adrenal incidentalomas, and the terms "pre-Cushing's syndrome"[13] and "preclinical" Cushing's syndrome were introduced for its description.[10,14] However, because "preclinical" Cushing's syndrome implies possible progression to overt Cushing's syndrome, which was shown to happen rarely,[15-17] the terms SCS and subclinical autonomous cortisol hypersecretion[18] have been proposed in order to define this hormonal abnormality more adequately, with the former being widely used in the literature. Since 1990, a large number of studies have shown that subclinical cortisol hypersecretion results in various abnormalities of the HPA axis, revealed by detailed hormonal evaluation, at an average range of 5-25% of patients with adrenal incidentalomas.[4-6,14,19] This wide range of prevalence of SCS is mostly due to the use of different diagnostic criteria in relevant studies, in addition to different investigational protocols and series' size as well as referral bias. Therefore, SCS is a common disorder given that the prevalence of adrenal incidentalomas in the general population is estimated at between 1.4-8.7%, based on autopsy studies. SCS prevalence increases with age, with a peak in the eighth decade of life.[20] Subclinical cortisol hypersecretion may be intermittent in some patients, as shown in follow-up studies,[17,21-23] and seems to be related to mass size.[17] Moreover, follow-up studies[15,24,25] have shown that larger adrenal incidentalomas (mass size >2.4 cm according to the most recent study[26]) have a higher risk of developing SCS. The possibility of an increased frequency of SCS in patients with bilateral adrenal incidentalomas has been examined; however, existing data are controversial.[23,26-28]

DIAGNOSIS OF SUBCLINICAL CUSHING'S SYNDROME

The diagnosis of SCS is based on biochemical evaluation.[29] Several tests assessing the hypothalamic-pituitary-adrenal axis, such as the dexamethasone suppression test (DST), 24-hour urinary free corti-

sol (UFC), morning plasma ACTH levels, cortisol rhythm, midnight serum cortisol levels and ACTH and cortisol response to CRH stimulation, used to test overt Cushing's syndrome,[30] have been widely employed in the evaluation of cortisol secretion in patients with adrenal incidentalomas.[14-17,19,21-23,26,28,31-37] However, there is great concern as to whether the sensitivity of these tests is sufficient to reveal subtle cortisol hypersecretion.[4,5,38,39] Moreover, due to lack of clinical symptoms/signs of hypercortisolism by definition, distinguishing between subclinical cortisol hypersecretion and false positive test results is an unresolved issue.[4,5,38,39]

The dexamethasone suppression test, assessing the feedback integrity of the HPA axis, is considered as the most reliable test for the diagnosis of SCS.[4,5,38] Several versions of DST, that relate to the dose of dexamethasone and duration of administration as well as several cut-off levels for adequate cortisol suppression, have been used for the detection of subtle cortisol hypersecretion in patients with adrenal incidentalomas. When using this test, any conditions and medications influencing dexamethasone metabolism should be excluded. Urinary free cortisol, considered an integrated measure of cortisol production, is a test with reduced sensitivity for the detection of slight increases in 24-hour cortisol production[4,5,38] and there might be difficulties in obtaining an adequate urine collection. Morning plasma ACTH levels, indicative of an adrenal cause of increased cortisol secretion when values are in the low level range, is a test influenced by the episodical pattern of ACTH secretion and by the reduced reliability of commercially available ACTH assays in the lowest part of the assay curve.[4,5,38] Midnight serum cortisol measurement, assessing the diurnal cortisol rhythm, is considered a reliable test;[5] however, its main limitation is the requirement of hospitalization. An alternative method assessing diurnal cortisol rhythm is late-night salivary cortisol, performed in an outpatient setting. Existing data support a limited utility of this test to detect subtle cortisol hypersecretion due to low sensitivity.[4,5,29,38,40] A very recent study showed a 31.3% sensitivity of salivary cortisol for diagnosing SCS, measured by liquid chromatography/tandem mass spectrometry (LC–MS/MS), which is the most state-of-the-art laboratory method for measuring steroids.[41] Dehydroepiandrosterone sulfate (DHEAS) levels, indicative of ACTH suppression, when values are in the low level range, is a test with reduced reliability given that DHEA-S secretion decreases with age.

Due to the aforementioned limitations of any single test, the combination of at least two abnormal tests of the HPA axis has been advocated by most experts for the diagnosis of SCS. Nevertheless, there is still a debate regarding the optimal combination protocol.[4,5,38] DST has been used in the vast majority of studies, in various combinations with other te sts.[14-17,19,21-23,26,28,31-37] Of all versions of DST, the most frequently used is the overnight 1 mg DST (1 mg DST). This test, considered the most reliable and reproducible diagnostic method, as well as being easy to perform, was recommended as the initial screening test by the National Institutes of Health (NIH) State-of-Science Conference panel in 2002[18] and by other panels of experts in the following years.[30,40,42] The 2-days 2mg DST or low-dose dexamethasone suppression test (LDDST) has also been shown to be a sensitive index for subtle glucocorticoid excess in patients with adrenal incidentalomas,[17,33,34,36,37] although less patient-friendly. It can be used as a confirmatory test of autonomous cortisol secretion.[38]

The threshold value for adequate cortisol suppression after dexamethasone administration is still debated, ranging from 1.8-5 μg/dl. A post-dexamethasone cortisol level lower than 1.8 μg/dl virtually excludes autonomous cortisol secretion: the sensitivity of the test is high (>95%) at the expense of a lower specificity (70-80%).[4,30,39,40,43] When the cut-off level of cortisol is raised to 5 μg/dl, as recommended by the NIH State-of-Science Conference panel[18] and the American Association of Clinical Endocrinologists / American Association of Endocrine Surgeons Medical Guidelines (AACE/AAES),[40] autonomous cortisol secretion is highly probable: the specificity of the test is increased to more than 95%; however, sensitivity is reduced.[30,39,43] Cortisol levels between 1.8 and 5 μg/dl have been characterized as indeterminate.[43] It should be noted that there are data showing that normal subjects have post-dexamethasone suppression test cortisol levels lower than 1 μg/dl;[36,37] however, levels greater than 1.8 μg/dl are still compatible with normality.[29,39] It has also been shown that abnormal post-dexamethasone cortisol levels with 1 mg DST[23]

or LDDST[26,36] are positively related to the mass size.

RADIOLOGICAL ASSESSMENT OF ADRENAL INCIDENTALOMAS

Unenhanced computed tomography scan should be the initial imaging procedure for morphological assessment of adrenal incidentalomas.[43] Most adrenocortical adenomas contain abundant intracellular fat, in contrast to malignant lesions.[18,20,44] Given that there is an inverse linear relationship between fat concentration and attenuation on unenhanced CT images, CT densitometry is capable of discriminating adenomas from nonadenomatous lesions. CT attenuation value is expressed in Hounsfield units (HU). A density of <10 HU of the mass on unenhanced CT may diagnose a benign adrenal lesion with a sensitivity of 96-100% and a specificity of 50-100%.[45-50] Diagnostic difficulties are encountered in lipid-poor adenomas, which present attenuation values >10 HU and are estimated as constituting up to 30% of all adenomas.[45-48] It is of note that most adrenal incidentalomas are discovered by CT scans performed with the use of intravenous contrast medium, a technique classified as suboptimal. In effect, an unenhanced CT scan should be obtained in such cases. Delayed contrast-enhanced CT scan should be considered for tumors with baseline attenuation value >10 HU.[46-52] Intravenous contrast medium tends to "wash out" much faster from cortical adenomas than from nonadenomatous lesions on a 15-minute post-contrast administration scan.

The size and appearance of an adrenal mass on CT are two other parameters that may help to characterize the mass as malignant or not. Larger lesions are much more likely to be malignant. Heterogeneity, irregular margins and calcifications are indicators of malignancy.[46]

Magnetic resonance imaging (MRI) is as effective as CT in distinguishing benign from malignant adrenal tumors.[52] However, CT is more commonly performed in everyday practice and MRI should be used in selected cases. Similarly, adrenal scintigraphy and positron emission tomography (PET) scan should be used in cases with diagnostic difficulties.[52-54] The combined use of PET/CT scan is more accurate and more advantageous over PET alone as it offers additional information about the morphology of the lesion. This technique should be considered when CT densitometry and washout analysis are inconclusive or suspicious for malignancy.[43,53]

CLINICAL IMPLICATIONS OF SUBCLINICAL CUSHING'S SYNDROME

Although by definition patients with adrenal incidentalomas and SCS lack the typical stigmata of cortisol hypersecretion (i.e. moon face, truncal obesity, thin extremities, proximal myopathy, easy bruising, cutaneous purple striae), chronic exposure to slight cortisol excess may have clinical implications associated with a state of insulin resistance and a negative effect on bone metabolism. Arterial hypertension (AH), diabetes mellitus (DM) type 2 or impaired glucose tolerance (IGT), central obesity, osteoporosis / vertebral fractures (VF) and dyslipidemia may be considered as detrimental effects of chronic subtle cortisol excess.

Table 1 summarizes the incidence reported in the literature of these morbidities in SCS patients with adrenal incidentalomas. It has also been suggested that subclinical hypercortisolism may be per se an independent risk factor for coronary heart disease,[54] as atherosclerotic plaques are more frequent in these patients than in healthy controls.[34] These parameters constitute an increased cardiovascular risk profile in SCS patients. Yet, data from observational population studies showing increased cardiovascular events are lacking. Most of the existing data are derived from retrospective, cross-sectional, case-control studies, thus carrying the risk of referral bias and being insufficient to establish causality. Finally, most published series are not large and with a limited duration of follow-up. Available data suggest that cardiovascular events are the most frequent cause of death in SCS patients, but it remains unknown whether the mortality rate is higher among these patients than the general population.[43]

It must be noted that an increased prevalence of obesity, hypertension, DM type 2, dyslipidemia and osteoporosis has been found in patients with adrenal incidentalomas irrespectively of adrenal function, being possibly higher in patients with SCS.[14,17,19,33-35,55-61] In addition, an improvement in arterial hypertension,

Table 1. Reported incidence rates of metabolic complications in patients with subclinical Cushing's syndrome

Author	AH	DM or IGT	Obesity	Dyslipidemia	Osteoporosis/VF
Reincke et al[14]	88%	25%*	50%	NR	NR
Morioka et al[123]	83%	33%*	67%	NR	NR
Rossi et al[33]	91.6%	41.6%	50%	50%	NR
Tauchmanova et al[34]	60.7%	64.3%	32.1%	71.4%	NR
Emral et al[95]	100%	50%	75%	NR	NR
Terzolo et al[71]	70.2%	42.5%	NR	NR	NR
Mitchell et al[68]	89%	33%*	NR	NR	NR
Tsuiki et al[67]	45%	65%	25%	65%	NR
Toniato et al[62]	73%	31%*	27%	33%	24%
Vassilatou et al[17]	75%	20%*	NR	NR	NR
Chiodini et al[56]	NR	NR	NR	NR	70.6%**
Alesina et al[107]	79.4%	15.9%*	38%	NR	NR
Morelli et al[69]	61.5%	24.7%	NR	NR	35.1%
Miyazato et al[115]	60%	30.9%*	NR	9.1%	0%
Morelli et al[89]	NR	NR	NR	NR	55.6%**
Akaza et al[73]	56%	25%	19%	50%	NR
Iacobone et al[72]	77.5%	45%	77.5%	48.4%	28.4%***
Oki et al[70]	81.5%	48.1%	NR	NR	NR
Palmieri et al[41]	68.8%	68.8%	NR	NR	87.5% / 68.8%
Morelli et al[28]	NR	NR	NR	NR	50.9%**
Zografos et al[63]	58.6%	41.4%	48.3%	NR	NR

NR: not reported; AH: Arterial Hypertension; DM: Diabetes Mellitus; IGT: impaired glucose tolerance; VF: Vertebral Fractures. *only DM, not IGT patients, **only vertebral fractures, ***only osteoporosis/osteopenia.

DM type 2 and insulin sensitivity after adrenalectomy has been reported in adrenal incidentaloma patients with[14,33,62-65] and without subclinical Cushing's syndrome.[33,57,64,65] Lastly, transient adrenal insufficiency post-adrenalectomy, considered as an indirect proof of cortisol hypersecretion, has also been described in patients with and without SCS.[33,65,66] These data demonstrate the difficulty in assessing a cause and effect relationship between subclinical cortisol hypersecretion and potentially related morbidities. A contributing factor to this difficulty is the fact that clinical manifestations of cortisol hypersecretion are variable, depending on the degree and duration of cortisol hypersecretion. In addition, there is an interindividual sensitivity to the cortisol excess.[30] Moreover, intermittent subclinical cortisol hypersecretion has been observed in some patients with adrenal incidentalomas in follow-up studies.[17,21,22] These patients may also present adverse effects of subtle cortisol hypersecretion, but because they can present normal adrenal function at a single evaluation they may be considered as patients harbouring non-functioning adrenal incidentalomas. It is noteworthy that obesity, hypertension, DM type 2, dyslipidemia and osteoporosis are not morbidities specific to cortisol excess and are highly prevalent in the general population, especially beyond the sixth decade of life when adrenal incidentalomas are more frequently detected; hence, they cannot be fully attributed to hypercortisolism.

The association of SCS due to an adrenal incidentaloma and hypertension has been shown in several studies.[33,34,41,54,62,67-73] Nitric oxide deficiency and reduced levels of plasma reactive nitrogen intermediate,[74] renal sodium retention,[75] potentiation of vasoconstrictor sensitivity to catecholamines and upregulation of vascular endothelin-1[76,77] are mechanisms which may play an important role in the onset

or progression of cortisol-induced hypertension. Subclinical hypercortisolism appears to have a higher prevalence in patients with resistant hypertension compared to the general hypertensive population.[78]

Cortisol excess has been shown to inhibit insulin secretion, glucose uptake and glycogen synthesis, to worsen insulin sensitivity and to increase gluconeogenesis.[79-83] These mechanisms explain the association between SCS of adrenal origin and DM type 2, which has been found in several studies.[33,34,41,54,62, 67-69,71-73,84,85] The incidence of SCS among patients with DM type 2 ranges from 0 to 9.4%.[83,84] Given this variability, no agreement exists whether screening for SCS is justified in DM type 2 patients.

Hypercortisolism is characterized by a redistribution of adipose tissue from peripheral to central sites of the body, mainly in the truncal region and visceral depots.[86] In effect, SCS is associated with increased body mass index (BMI) and visceral obesity, which is a major cardiovascular risk factor.[33,34,62,67,68,72,73] The prevalence of SCS is considerably higher in obese patients with DM type 2 than in the general population.[87]

Furthermore, an increased incidence of hypercholesterolemia, lower HDL cholesterol levels and hypertriglyceridemia in SCS patients with adrenal incidentalomas has been reported in several studies,[33,34,62,67,73,88] as well as low bone mineral density, high fracture prevalence and reduced bone quality as measured by spinal deformity index.[28,41,54,56,62,69,72,89,90] Most of these studies are cross-sectional, thus demonstrating only associations and not causality. In a longitudinal study, subclinical cortisol hypersecretion was associated with increased lumbar trabecular bone loss rate.[90] In another study by the same authors, the deleterious effect of cortisol on bone tissue was reported to overcome the protective effect of premenopausal hormonal status.[56] It has to be emphasized that data regarding osteoporosis and fractures in SCS patients with adrenal incidentalomas are not homogeneous. Some studies do not report the incidence of vertebral fractures, while other studies have shown that vertebral fractures may occur more often in SCS patients, even in the absence of osteopenia, compared to patients without SCS, as well as healthy controls.[56,89-91] There are also data suggesting that SCS patients do not have an increased risk of osteoporosis.[60]

Recent research has suggested that SCS patients appear to be at greater risk for vascular complications due to higher homocysteine and alpha-1 antitrypsin concentration in comparison to healthy individuals. Both factors intensify the coagulation process, thus representing unquestionable risk factors for venous and arterial thrombosis.[92] SCS also causes abnormalities in hemostatic parameters leading to hypercoagulability.[34]

It has also been hypothesized that cortisol excess exerts deleterious effects on the structure and function of central nervous system, especially the hippocampus.[93] Guldiken et al suggested that SCS is responsible for cognitive functions impairment and that patients with rapidly deteriorating dementia or metabolic dementia should be evaluated for SCS.[94]

Since there is no proven causal relationship between subclinical cortisol hypersecretion and insulin resistance and metabolic syndrome in SCS patients with adrenal incidentalomas,[34,35,64] a hypothesis that nodular adrenals or adrenal incidentalomas may represent a consequence rather than the cause of insulin resistance has been proposed.[26,59,83] This hypothesis is based on in vitro data showing a stimulating effect of insulin on adrenal cells, thus implicating insulin as a pathophysiological mediator in the development of adrenal tumors.[59]

MANAGEMENT OF SUBCLINICAL CUSHING'S SYNDROME

The detection of a clinically inapparent cortisol-secreting adrenal adenoma poses the therapeutic dilemma of careful observation along with medical treatment of morbidities potentially related to subtle cortisol hypersecretion versus surgical treatment, since the benefits of surgery for this condition remain to be clarified. Decision regarding surgery should take into account mass size, imaging phenotype, patient's age and health status.

Surgical management

Several studies have demonstrated an improvement in considered metabolic complications of subtle cortisol hypersecretion after adrenalectomy. The effect of adrenalectomy on blood pressure seems fairly consistent, while conflicting results have been

reported regarding diabetes, obesity and osteoporosis.

Adrenalectomy has been proven superior to medical treatment in SCS patients with hypertension and/or hyperglycemia in a number of underpowered studies.[34,57,68,95,96] Erbil et al. found that adrenalectomy is more beneficial in terms of hypertension among SCS patients than those with overt CS.[97] Tsuiki et al. reported an improvement in hypertension and hyperglycemia in most surgically treated SCS patients; by contrast, associated conditions in the non-operated patients treated medically remained unchanged or even worsened.[67] Toniato et al. conducted the only existing so far prospective randomized study comparing laparoscopic adrenalectomy (LA) to conservative treatment in SCS patients. The authors concluded that LA appears to be more beneficial in improving hypertension and diabetes control.[62] In a recent retrospective controlled study by Chiodini et al, adrenalectomy improved blood pressure and glucose levels not only in SCS patients but in patients with non-functioning adrenal incidentalomas as well, thus raising questions in terms of a potential cause and effect relationship between subtle cortisol hypersecretion and hypertension and disorder of glucose metabolism.[65]

Unfortunately, these studies suffer to a certain degree from several methodological limitations (retrospective and uncontrolled design, small number of patients, variable duration of follow-up, different biochemical criteria for the diagnosis of SCS, inadequate definitions of end-points and outcomes of surgical treatment and lack of comparison with the evidence-based medical treatments).[5,43] Furthermore, even if adrenalectomy was confirmed as being superior to conservative treatment in correcting biochemical abnormalities, its impact on long-term outcome and quality of life would still remain a challenge. Table 2 summarizes the results of adrenalectomy in SCS patients that have been reported in the literature. A significant number of patients with SCS have an improvement in arterial hypertension, DM type 2, impaired glucose tolerance and obesity following surgical management. Improvement rate in hypertension ranges from 50% to 100%. Improvement rate in glucose tolerance ranges between 22.2% and 100%. The wide range (0-100%) in obesity improvement rate reflects the variety of clinical criteria for obesity in small series. There are few data concerning the effect of surgery on dyslipidemia, since several authors have not recorded alterations after adrenalectomy. Tsuiki et al found an improvement in 66.7% of patients, whereas Akaza et al. reported improvement only in 12.5%.[67,73] Scarce data exist concerning the effect of

Table 2. Reported results of adrenalectomy in SCS patients regarding clinical conditions (arterial hypertension, diabetes mellitus / impaired glucose tolerance, obesity, dyslipidemia, osteoporosis)

	Improvement				
Author	**AH (%)**	**DM/IGT (%)**	**Obesity (%)**	**Dyslipidemia (%)**	**Osteoporosis (%)**
Rossi et al[33]	100	100	100	NR	NR
Emral et al[95]	66.7	50	100	NR	NR
Erbil et al[97]	70	33	NR	NR	NR
Mitchell et al[68]	50	66.7	87.5	NR	NR
Tsuiki et al[67]	83.3	22.2	0	66.7	NR
Toniato et al[62]	66.7	62.5	50	37.5	0
Alesina et al[107]	58.1	40	29.2	NR	NR
Chiodini et al[65]	56	48	32	36	NR
Akaza et al[73]	62.5	50	50	12.5	NR
Miyazato et al[115]	66.7	47.1	NR	20	NR
Iacobone et al[72]	53	50	40	20	0
Bernini et al[64]	80	50	0	NR	NR
Zografos et al[63]	70.6	41.7	42.9	NR	NR

NR: not reported; AH: Arterial Hypertension; DM: diabetes mellitus; IGT: impaired glucose tolerance.

surgery on osteoporosis, since most authors have not included osteoporosis in the postoperative follow-up of patients. Two studies showed no improvement in osteoporosis following surgical treatment.[62,72]

Until data from high-quality prospective randomized trials elucidate the optimal management of SCS, clinicians should consider the treatment strategy recommended by three different panels of experts: the NIH State-of-Science and Consensus Statement,[18] the guidelines of AACE / AAES[40] and the most recent Position Statement of AME.[43] All three panels stress the fact that their suggestions are based more on pragmatism than solid evidence. The NIH state-of-the-science statement suggested that either adrenalectomy or careful observation is a treatment option for SCS patients.[18] The AACE / AAES Medical Guidelines for the management of adrenal incidentalomas recommended that surgery should be reserved for SCS patients with worsening hypertension, abnormal glucose tolerance, dyslipidemia or osteoporosis (recommendation with low level of evidence).[40] The AME position statement on adrenal incidentaloma suggested that surgery should be elected for younger SCS patients presenting diseases potentially attributable to cortisol hypersecretion with a recent onset, or a rapid worsening.[43]

In our clinical practice, elderly SCS patients with tumors with benign imaging characteristics are managed conservatively. This also applies for patients with cardiovascular, respiratory and neurologic morbidities, independently of age. Younger patients are evaluated for morbidities potentially related to subtle cortisol hypersecretion and surgery may be recommended if these are poorly controlled with medical therapy.

Post-adrenalectomy adrenal insufficiency in patients with cortisol secreting adenomas is potentially fatal if not treated. Therefore, patients who undergo adrenalectomy for SCS require postoperative glucocorticoid replacement treatment.[18,40,43] The total duration of steroid therapy varies among reported series. The recovery of the HPA axis should be evaluated every 3-6 months and dosage should be tapered accordingly. In a few patients the duration of steroid coverage may exceed six months.[63] Patients with unilateral tumors and normal adrenal function preoperatively do not require routine post-adrenalectomy steroid replacement.[98] However, it has been shown that some of these patients may present post-surgical hypocortisolism.[67] Thus, post-surgical hypocortisolism cannot be predicted by preoperative adrenal function tests in patients with adrenal adenomas. A precautionary steroid treatment has been proposed for all adrenal incidentaloma patients who undergo unilateral adrenalectomy, regardless preoperative adrenal function evaluation.

To date, LA has been the gold standard for the management of SCS, since it is a safe, effective and less expensive procedure than open adrenalectomy.[99-104] Compared to the traditional open resection, LA is associated with less postoperative morbidity, shorter hospital stay and recovery time and better patient satisfaction rates. These clear advantages of LA did not encourage any prospective randomized controlled trials comparing the new technique with the classical 'open', either transabdominal or retroperitoneal technique.[104] Recent data from the American College of Surgeons, National Surgical Quality Improvement Program, further demonstrated the superiority of the laparoscopic approach. In the largest to date comparative study with 3,100 patients assessing laparoscopic versus open adrenalectomy, laparoscopic surgery was associated with reductions in postoperative morbidity and hospitalization.[105] Concomitant conditions as morbid obesity, bleeding disorders or previous abdominal procedures are considered as relative contraindications, depending on the laparoscopic experience of the surgeon.

The transperitoneal laparoscopic peritoneal approach offers better exposure of regional anatomy and safer access to vessels and viscera. Concomitant surgical diseases can be treated in the same operation. The retroperitoneal approach, on the other hand, has been advocated in patients with small adrenal tumors or previous abdominal operations who may have adhesions, rendering difficult the transabdominal approach.[106-108] Potential visceral injury is avoided but limited working space and fewer anatomic landmarks may prolong the learning curve. In our opinion, the transperitoneal resection of adrenal tumors is the preferred method of minimally invasive surgery for the majority of patients. However, the retroperitoneal approach is a useful alternative in patients with small tumors or previous abdominal surgery.

Adrenal-sparing surgery is selectively performed to preserve endogenous steroid production and avoid long-term oral steroid replacement therapy.[107,109-111] This benefit has to be balanced with the risk of tumor recurrence, given that reoperation is associated with increased morbidity. Hereditary pheochromocytomas in von Hippel-Lindau (VHL) and multiple neoplasia type-2 (MEN-2) syndromes have been the standard diseases suitable for adrenal-sparing surgery.[112] Nevertheless, extension of indications in adrenal adenomas and Cushing's syndrome has been advocated by some experts, however, with limited international approval.[113,114]

Although laparoscopic adrenal-sparing surgery is feasible and safe with the use of the harmonic scalpel, the lack of prospective large series evaluating this technique and the risk for postoperative recurrent disease are the limitations of the technique.[113] In our opinion, subtotal adrenalectomy must be considered in patients who undergo either simultaneous or metachronous bilateral adrenal surgery for benign disease.

Follow-up along with medical treatment of associated conditions

Patients with adrenal incidentalomas and SCS who are not treated surgically need careful observation for the detection of any changes in hormonal activity and mass size with time, in addition to monitoring morbidities potentially related to subtle cortisol excess. However, the frequency of biochemical and imaging evaluation and the duration of follow-up in these patients is still a matter of debate[4,5,18,38,40,43,115] due to lack of a clear definition of SCS and solid evidence concerning its natural history.

Existing data have shown that evolution to overt Cushing's syndrome occurs rarely (Table 3), while the risk of malignant transformation is very rare.[15-17,116] Moreover, the majority of adrenal masses with benign imaging characteristics remain stable over time.[15-17,25,116-118] Based on existing data and a pragmatist approach, panels of experts have proposed protocols of follow-up. According to the NIH state-of-science statement, hormonal screening with an overnight 1mg DST should be performed annually for four years, as the risk of hyperfunction seems to plateau after that period. CT scan should be repeated 6-12 months after the initial imaging study and for lesions that do not increase in size, radiological assessment should be discontinued.[18] The AACE / AAES Medical Guidelines for the management of adrenal incidentalomas recommend hormonal evaluation annually for five years and imaging reevaluation 3-6 months after initial detection of an adrenal mass and then annually for 1-2 years.[40] At variance, the AME position statement on adrenal incidentaloma recommends against a routine follow-up of all adrenal incidentalomas with repeated

Table 3. Reported number of patients with adrenal incidentalomas progressing to overt Cushing's syndrome (from studies with >50 patients and duration of follow-up ≥24 months)

Author / Year	Number of patients	Median duration of follow-up	Overt syndrome (patients)
Grossrubatscher E 2001[24]	53	24	0
Libe R 2002[124]	64	25.5	0
Barzon L 2002[125]	130	56	4
Emral R 2003[95]	60	24	0
Bernini G 2005[126]	115	48	0
Bulow B 2006[16]	229	24	2
Tsvetov G 2007[117]	88	24	0
Vassilatou E 2009[17]	77	60	2
Fagour C 2009[22]	51	52 ± 19 (mean)	3
Giordano R 2010[127]	118	36	0
Yener S 2010[116]	143	24	0
Anagnostis P 2010[118]	60	37 ± 5 (mean)	0
Morelli V 2014[25]	206	72	0

hormonal and imaging evaluation due to limited and incomplete evidence. Hormonal screening with a 1mg DST should be repeated after decision on an individualized basis (i.e. development of clinical signs of hypercortisolism, worsening of metabolic status and/or cardiovascular risk profile). A second CT scan should be performed 3-6 months after diagnosis. In the case of small tumors (<2 cm) that do not increase in size, further imaging is not needed. In the case of larger tumors, repeated imaging evaluation should be judged on an individual basis, taking into consideration the characteristics of the mass, patient's age and history and results of hormonal evaluation.[43] In addition, it is emphasized that SCS patients should be followed up clinically to detect, treat and control morbidities potentially related to subtle cortisol hypersecretion.[43] A review by Young recommended imaging evaluation at 6, 12 and 24 months, although earlier or less frequent evaluation can be proposed depending on how suspicious the mass is at diagnosis. Annual hormonal evaluation for at least four years was also recommended. However, the author recognized that the yield and cost-effectiveness of repeated evaluation at these intervals are uncertain.[119] A committee of expert radiologists advocated against any follow-up of adrenal masses for which a benign diagnosis has been made as well as for those remaining stable in size for over one year.[120] A recent review recommended against routine follow-up of all adrenal incidentalomas, based on data from the literature showing that such tumors rarely undergo malignant transformation; the development of hypersecretion is not a major concern, follow-up with hormonal and imaging evaluation results in significant costs and, finally, frequent CT scan carries the risk of cancer from radiation exposure.[121] Another recent review proposed a follow-up protocol of annual hormonal screening for five years and annual CT scan for the first 2-3 years. In the case of lesions with a mass size 2-4 cm that remain stable, further imaging should take place at 2-3 year intervals.[122] In addition, monitoring of morbidities potentially related to subtle cortisol hypersecretion and evaluation of medical treatment adequacy is also recommended.

Taking into account the aforementioned data, our opinion is that surveillance of SCS patients with adrenal incidentalomas concerning hormonal activity of the mass and putative mass enlargement should be guided by clinical parameters (both at diagnosis and overtime) and by mass size and imaging characteristics, respectively. Initial clinical evaluation (age, presence of potentially related morbidities and assessment of cardiovascular risk factors) and clinical follow-up every 6-12 months (monitoring response to treatment of existing related morbidities and detecting development of new potentially related morbidities and/or clinical signs of hypercortisolism) should guide the frequency and the duration of periodic hormonal evaluation. In the case of SCS patients with stable clinical parameters over time, hormonal evaluation should be repeated only if mass enlargement is detected. Periodic imaging evaluation requires a second CT scan 3-6 months after initial diagnosis and then a short follow-up time of two years with annual CT, for small masses (<2 cm) with imaging characteristics indicative of benignity (CT attenuation values of 10 Hounsfield Units or less, homogeneous, well defined margins), which remain morphologically stable. Prolonged imaging follow-up is needed for small masses (<2 cm) with suspicious imaging characteristics and/or mass enlargement during follow-up, as well as for larger masses, which may be finally managed surgically.

CONCLUSIONS

Approximately 5-20% of adrenal incidentalomas present subclinical cortisol hypersecretion, characterized by subtle alterations of the HPA axis due to adrenal autonomy, a disorder that has also been described as SCS, since there is no typical clinical phenotype. The diagnosis of SCS is based on biochemical evaluation. An abnormal 1mg DST as initial screening test in combination with at least one other abnormal test of the HPA axis has been advocated by most experts for the diagnosis of SCS. Suggested cut-off levels of serum cortisol are either 1.8μg/dl or 5μg/dl, with levels lower than 1.8 μg/dl excluding autonomous cortisol secretion and levels higher than 5μg/dl indicating subclinical hypercortisolism. Although these patients lack many of the usual stigmata of overt Cushing's syndrome, they may have diabetes mellitus, hypertension, dyslipidemia, osteoporosis and obesity, disorders potentially attributable to autonomous glucocorticoid secretion. The optimal management of patients with adrenal incidentalomas and SCS is not yet defined.

Choices are either follow-up combined with medical treatment of potentially associated morbidities or laparoscopic adrenalectomy. The conservative approach is appropriate for the majority of these patients; however, the duration of follow-up and the frequency of periodical evaluation still remain open issues. Surgical resection may benefit patients with hypertension, abnormal glucose tolerance and obesity, without significant comorbidities.

CONFLICT OF INTEREST STATEMENT

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REFERENCES

1. Commons RR, Callaway CP, 1948 Adenomas of the adrenal cortex. Arch Intern Med (Chic) 81: 37-41.
2. Hedeland H, Ostberg G, Hokfelt B, 1968 On the prevalence of adrenocortical adenomas in an autopsy material in relation to hypertension and diabetes. Acta Med Scand 184: 211-214.
3. Korobkin M, White EA, Kressel HY, Moss AA, Montagne JP, 1979 Computed tomography in the diagnosis of adrenal disease. AJR Am J Roentgenol 132: 231-238.
4. Nieman LK, 2010 Approach to the patient with an adrenal incidentaloma. J Clin Endocrinol Metab 95: 4106-4113.
5. Terzolo M, Pia A, Reimondo G, 2012 Subclinical Cushing's syndrome: definition and management. Clin Endocrinol (Oxf) 76: 12-18.
6. Zeiger MA, Siegelman SS, Hamrahian AH, 2011 Medical and surgical evaluation and treatment of adrenal incidentalomas. J Clin Endocrinol Metab 96: 2004-2015.
7. Beierwaltes WH, Sturman MF, Ryo U, Ice RD, 1974 Imaging functional nodules of the adrenal glands with 131-I-19-iodocholesterol. J Nucl Med 15: 246-251.
8. Gross MD, Wilton GP, Shapiro B, et al, 1987 Functional and scintigraphic evaluation of the silent adrenal mass. J Nucl Med 28: 1401-1407.
9. Huiras CM, Pehling GB, Caplan RH, 1989 Adrenal insufficiency after operative removal of apparently nonfunctioning adrenal adenomas. JAMA 261: 894-898.
10. Hensen J, Buhl M, Bahr V, Oelkers W, 1990 Endocrine activity of the "silent" adrenocortical adenoma is uncovered by response to corticotropin-releasing hormone. Klin Wochenschr 68: 608-614.
11. Suzuki T, Sasano H, Sawai T, et al, 1992 Small adrenocortical tumors without apparent clinical endocrine abnormalities. Immunolocalization of steroidogenic enzymes. Pathol Res Pract 188: 883-889.
12. Racz K, Pinet F, Marton T, Szende B, Glaz E, Corvol P, 1993 Expression of steroidogenic enzyme messenger ribonucleic acids and corticosteroid production in aldosterone-producing and "nonfunctioning" adrenal adenomas. J Clin Endocrinol Metab 77: 677-682.
13. Charbonnel B, Chatal JF, Ozanne P, 1981 Does the corticoadrenal adenoma with "pre-Cushing's syndrome" exist? J Nucl Med 22: 1059-1061.
14. Reincke M, Nieke J, Krestin GP, Saeger W, Allolio B, Winkelmann W, 1992 Preclinical Cushing's syndrome in adrenal "incidentalomas": comparison with adrenal Cushing's syndrome. J Clin Endocrinol Metab 75: 826-832.
15. Barzon L, Scaroni C, Sonino N, Fallo F, Paoletta A, Boscaro M, 1999 Risk factors and long-term follow-up of adrenal incidentalomas. J Clin Endocrinol Metab 84: 520-526.
16. Bulow B, Jansson S, Juhlin C, et al, 2006 Adrenal incidentaloma - follow-up results from a Swedish prospective study. Eur J Endocrinol 154: 419-423.
17. Vassilatou E, Vryonidou A, Michalopoulou S, et al, 2009 Hormonal activity of adrenal incidentalomas: results from a long-term follow-up study. Clin Endocrinol (Oxf) 70: 674-679.
18. Grumbach MM, Biller BM, Braunstein GD, et al, 2003 Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann Intern Med 138: 424-429.
19. Mantero F, Terzolo M, Arnaldi G, et al, 2000 A survey on adrenal incidentaloma in Italy. Study Group on Adrenal Tumors of the Italian Society of Endocrinology. J Clin Endocrinol Metab 85: 637-644.
20. Kloos RT, Gross MD, Francis IR, Korobkin M, Shapiro B, 1995 Incidentally discovered adrenal masses. Endocr Rev 16: 460-484.
21. Terzolo M, Osella G, Ali A, et al, 1998 Subclinical Cushing's syndrome in adrenal incidentaloma. Clin Endocrinol (Oxf) 48: 89-97.
22. Fagour C, Bardet S, Rohmer V, et al, 2009 Usefulness of adrenal scintigraphy in the follow-up of adrenocortical incidentalomas: a prospective multicenter study. Eur J Endocrinol 160: 257-264.
23. Olsen H, Nordenstrom E, Bergenfelz A, Nyman U, Valdemarsson S, Palmqvist E, 2012 Subclinical hypercortisolism and CT appearance in adrenal incidentalomas: a multicenter study from Southern Sweden. Endocrine 42: 164-173.
24. Grossrubatscher E, Vignati F, Possa M, Lohi P, 2001 The natural history of incidentally discovered adrenocortical adenomas: a retrospective evaluation. J Endocrinol Invest 24: 846-855.
25. Morelli V, Reimondo G, Giordano R, et al, 2014 Long-term follow-up in adrenal incidentalomas: an italian multicenter study. J Clin Endocrinol Metab 99: 827-834.
26. Vassiliadi DA, Ntali G, Vicha E, Tsagarakis S, 2011 High prevalence of subclinical hypercortisolism in patients with bilateral adrenal incidentalomas: a challenge to

management. Clin Endocrinol (Oxf) 74: 438-444.
27. Androulakis II, Kaltsas GA, Markou A, et al, 2011 The functional status of incidentally discovered bilateral adrenal lesions. Clin Endocrinol (Oxf) 75: 44-49.
28. Morelli V, Palmieri S, Salcuni AS, et al, 2013 Bilateral and unilateral adrenal incidentalomas: biochemical and clinical characteristics. Eur J Endocrinol 168: 235-241.
29. Arnaldi G, Boscaro M, 2012 Adrenal incidentaloma. Best Pract Res Clin Endocrinol Metab 26: 405-419.
30. Nieman LK, Biller BM, Findling JW, et al, 2008 The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab 93: 1526-1540.
31. Barzon L, Scaroni C, Sonino N, et al, 1998 Incidentally discovered adrenal tumors: endocrine and scintigraphic correlates. J Clin Endocrinol Metab 83: 55-62.
32. Valli N, Catargi B, Ronci N, et al, 2001 Biochemical screening for subclinical cortisol-secreting adenomas amongst adrenal incidentalomas. Eur J Endocrinol 144: 401-408.
33. Rossi R, Tauchmanova L, Luciano A, et al, 2000 Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J Clin Endocrinol Metab 85: 1440-1448.
34. Tauchmanova L, Rossi R, Biondi B, et al, 2002 Patients with subclinical Cushing's syndrome due to adrenal adenoma have increased cardiovascular risk. J Clin Endocrinol Metab 87: 4872-4878.
35. Terzolo M, Pia A, Ali A, et al, 2002 Adrenal incidentaloma: a new cause of the metabolic syndrome? J Clin Endocrinol Metab 87: 998-1003.
36. Tsagarakis S, Kokkoris P, Roboti C, et al, 1998 The low-dose dexamethasone suppression test in patients with adrenal incidentalomas: comparisons with clinically euadrenal subjects and patients with Cushing's syndrome. Clin Endocrinol (Oxf) 48: 627-633.
37. Piaditis GP, Kaltsas GA, Androulakis, II, et al, 2009 High prevalence of autonomous cortisol and aldosterone secretion from adrenal adenomas. Clin Endocrinol (Oxf) 71: 772-778.
38. Kaltsas G, Chrisoulidou A, Piaditis G, Kassi E, Chrousos G, 2012 Current status and controversies in adrenal incidentalomas. Trends Endocrinol Metab 23: 602-609.
39. Stewart PM, 2010 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 95: 2618-2620.
40. Zeiger MA, Thompson GB, Duh QY, et al, 2009 The American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons medical guidelines for the management of adrenal incidentalomas. Endocr Pract 15 Suppl 1: 1-20.
41. Palmieri S, Morelli V, Polledri E, et al, 2013 The role of salivary cortisol measured by liquid chromatography-tandem mass spectrometry in the diagnosis of subclinical hypercortisolism. Eur J Endocrinol 168: 289-296.
42. Tabarin A, Bardet S, Bertherat J, et al, 2008 Exploration and management of adrenal incidentalomas. French Society of Endocrinology Consensus. Ann Endocrinol (Paris) 69: 487-500.
43. Terzolo M, Stigliano A, Chiodini I, et al, 2011 AME position statement on adrenal incidentaloma. Eur J Endocrinol 164: 851-870.
44. Mansmann G, Lau J, Balk E, Rothberg M, Miyachi Y, Bornstein SR, 2004 The clinically inapparent adrenal mass: update in diagnosis and management. Endocr Rev 25: 309-340.
45. Hamrahian AH, Ioachimescu AG, Remer EM, et al, 2005 Clinical utility of noncontrast computed tomography attenuation value (hounsfield units) to differentiate adrenal adenomas/hyperplasias from nonadenomas: Cleveland Clinic experience. J Clin Endocrinol Metab 90: 871-877.
46. Lee MJ, Hahn PF, Papanicolaou N, et al, 1991 Benign and malignant adrenal masses: CT distinction with attenuation coefficients, size, and observer analysis. Radiology 179: 415-418.
47. Korobkin M, Brodeur FJ, Francis IR, Quint LE, Dunnick NR, Londy F, 1998 CT time-attenuation washout curves of adrenal adenomas and nonadenomas. AJR Am J Roentgenol 170: 747-752.
48. Pena CS, Boland GW, Hahn PF, Lee MJ, Mueller PR, 2000 Characterization of indeterminate (lipid-poor) adrenal masses: use of washout characteristics at contrast-enhanced CT. Radiology 217: 798-802.
49. Caoili EM, Korobkin M, Francis IR, et al, 2002 Adrenal masses: characterization with combined unenhanced and delayed enhanced CT. Radiology 222: 629-633.
50. Szolar DH, Kammerhuber FH, 1998 Adrenal adenomas and nonadenomas: assessment of washout at delayed contrast-enhanced CT. Radiology 207: 369-375.
51. Blake MA, Kalra MK, Sweeney AT, et al, 2006 Distinguishing benign from malignant adrenal masses: multi-detector row CT protocol with 10-minute delay. Radiology 238: 578-585.
52. Low G, Dhliwayo H, Lomas DJ, 2012 Adrenal neoplasms. Clin Radiol 67: 988-1000.
53. Lumachi F, Marchesi P, Miotto D, Motta R, 2011 CT and MR imaging of the adrenal glands in cortisol-secreting tumors. Anticancer Res 31: 2923-2926.
54. Di Dalmazi G, Vicennati V, Rinaldi E, et al, 2012 Progressively increased patterns of subclinical cortisol hypersecretion in adrenal incidentalomas differently predict major metabolic and cardiovascular outcomes: a large cross-sectional study. Eur J Endocrinol 166: 669-677.
55. Hadjidakis D, Tsagarakis S, Roboti C, et al, 2003 Does subclinical hypercortisolism adversely affect the bone mineral density of patients with adrenal incidentalomas? Clin Endocrinol (Oxf) 58: 72-77.
56. Chiodini I, Morelli V, Masserini B, et al, 2009 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 94: 3207-3214.
57. Midorikawa S, Sanada H, Hashimoto S, Suzuki T, Watanabe T, 2001 The improvement of insulin resistance in patients with adrenal incidentaloma by surgical resection. Clin Endocrinol (Oxf) 54: 797-804.
58. Erbil Y, Ozbey N, Barbaros U, Unalp HR, Salmaslioglu A, Ozarmagan S, 2009 Cardiovascular risk in patients with nonfunctional adrenal incidentaloma: myth or reality? World J Surg 33: 2099-2105.
59. Reincke M, Fassnacht M, Vath S, Mora P, Allolio B, 1996 Adrenal incidentalomas: a manifestation of the metabolic syndrome? Endocr Res 22: 757-761.
60. Osella G, Reimondo G, Peretti P, et al, 2001 The patients with incidentally discovered adrenal adenoma (incidentaloma) are not at increased risk of osteoporosis. J Clin Endocrinol Metab 86: 604-607.
61. Yener S, Ertilav S, Secil M, et al, 2012 Increased risk of unfavorable metabolic outcome during short-term follow-up in subjects with nonfunctioning adrenal adenomas. Med Princ Pract 21: 429-434.
62. Toniato A, Merante-Boschin I, Opocher G, Pelizzo MR, Schiavi F, Ballotta E, 2009 Surgical versus conservative management for subclinical Cushing syndrome in adrenal incidentalomas: a prospective randomized study. Ann Surg 249: 388-391.
63. Perysinakis I, Marakaki C, Avlonitis S, et al, 2013 Laparoscopic adrenalectomy in patients with subclinical Cushing syndrome. Surg Endosc 27: 2145-2148.
64. Bernini G, Moretti A, Iacconi P, et al, 2003 Anthropometric, haemodynamic, humoral and hormonal evaluation in patients with incidental adrenocortical adenomas before and after surgery. Eur J Endocrinol 148: 213-219.
65. Chiodini I, Morelli V, Salcuni AS, et al, 2010 Beneficial metabolic effects of prompt surgical treatment in patients with an adrenal incidentaloma causing biochemical hypercortisolism. J Clin Endocrinol Metab 95: 2736-2745.
66. Eller-Vainicher C, Morelli V, Salcuni AS, et al, 2010 Post-surgical hypocortisolism after removal of an adrenal incidentaloma: is it predictable by an accurate endocrinological work-up before surgery? Eur J Endocrinol 162: 91-99.
67. Tsuiki M, Tanabe A, Takagi S, Naruse M, Takano K, 2008 Cardiovascular risks and their long-term clinical outcome in patients with subclinical Cushing's syndrome. Endocr J 55: 737-745.
68. Mitchell IC, Auchus RJ, Juneja K, et al, 2007 "Subclinical Cushing's syndrome" is not subclinical: improvement after adrenalectomy in 9 patients. Surgery 142: 900-905.
69. Morelli V, Masserini B, Salcuni AS, et al, 2010 Subclinical hypercortisolism: correlation between biochemical diagnostic criteria and clinical aspects. Clin Endocrinol (Oxf) 73: 161-166.
70. Oki K, Yamane K, Nakanishi S, Shiwa T, Kohno N, 2012 Influence of adrenal subclinical hypercortisolism on hypertension in patients with adrenal incidentaloma. Exp Clin Endocrinol Diabetes 120: 244-247.
71. Terzolo M, Bovio S, Pia A, et al, 2005 Midnight serum cortisol as a marker of increased cardiovascular risk in patients with a clinically inapparent adrenal adenoma. Eur J Endocrinol 153: 307-315.
72. Iacobone M, Citton M, Viel G, et al, 2012 Adrenalectomy may improve cardiovascular and metabolic impairment and ameliorate quality of life in patients with adrenal incidentalomas and subclinical Cushing's syndrome. Surgery 152: 991-997.
73. Akaza I, Yoshimoto T, Iwashima F, et al, 2011 Clinical outcome of subclinical Cushing's syndrome after surgical and conservative treatment. Hypertens Res 34: 1111-1115.
74. Liu Y, Mladinov D, Pietrusz JL, Usa K, Liang M, 2009 Glucocorticoid response elements and 11 beta-hydroxysteroid dehydrogenases in the regulation of endothelial nitric oxide synthase expression. Cardiovasc Res 81: 140-147.
75. Hamm LL, Hering-Smith KS, 2010 Pivotal role of the kidney in hypertension. Am J Med Sci 340: 30-32.
76. Rossi GP, Andreis PG, Colonna S, et al, 2002 Endothelin-1[1-31]: a novel autocrine-paracrine regulator of human adrenal cortex secretion and growth. J Clin Endocrinol Metab 87: 322-328.
77. Xiao D, Huang X, Bae S, Ducsay CA, Zhang L, 2002 Cortisol-mediated potentiation of uterine artery contractility: effect of pregnancy. Am J Physiol Heart Circ Physiol 283: H238-246.
78. Martins LC, Conceicao FL, Muxfeldt ES, Salles GF, 2012 Prevalence and associated factors of subclinical hypercortisolism in patients with resistant hypertension. J Hypertens 30: 967-973.
79. Lambillotte C, Gilon P, Henquin JC, 1997 Direct glucocorticoid inhibition of insulin secretion. An in vitro study of dexamethasone effects in mouse islets. J Clin Invest 99: 414-423.
80. Plat L, Byrne MM, Sturis J, et al, 1996 Effects of morning cortisol elevation on insulin secretion and glucose regulation in humans. Am J Physiol 270: E36-42.
81. Vegiopoulos A, Herzig S, 2007 Glucocorticoids, metabolism and metabolic diseases. Mol Cell Endocrinol 275: 43-61.
82. Van Raalte DH, Ouwens DM, Diamant M, 2009 Novel insights into glucocorticoid-mediated diabetogenic effects: towards expansion of therapeutic options? Eur J Clin Invest 39: 81-93.
83. Giordano R, Guaraldi F, Berardelli R, et al, 2012 Glucose metabolism in patients with subclinical Cushing's syndrome. Endocrine 41: 415-423.
84. Murakami H, Nigawara T, Sakihara S, et al, 2010 The frequency of type 2 diabetic patients who meet

the endocrinological screening criteria of subclinical Cushing's disease. Endocr J 57: 267-272.
85. Ivovic M, Marina LV, Vujovic S, et al, 2013 Nondiabetic patients with either subclinical Cushing's or nonfunctional adrenal incidentalomas have lower insulin sensitivity than healthy controls: clinical implications. Metabolism 62: 786-792.
86. Androulakis, II, Kaltsas G, Piaditis G, Grossman AB, 2011 The clinical significance of adrenal incidentalomas. Eur J Clin Invest 41: 552-560.
87. Caetano MS, Silva Rdo C, Kater CE, 2007 Increased diagnostic probability of subclinical Cushing's syndrome in a population sample of overweight adult patients with type 2 diabetes mellitus. Arq Bras Endocrinol Metabol 51: 1118-1127.
88. Garrapa GG, Pantanetti P, Arnaldi G, Mantero F, Faloia E, 2001 Body composition and metabolic features in women with adrenal incidentaloma or Cushing's syndrome. J Clin Endocrinol Metab 86: 5301-5306.
89. Morelli V, Eller-Vainicher C, Salcuni AS, et al, 2011 Risk of new vertebral fractures in patients with adrenal incidentaloma with and without subclinical hypercortisolism: a multicenter longitudinal study. J Bone Miner Res 26: 1816-1821.
90. Chiodini I, Torlontano M, Carnevale V, et al, 2001 Bone loss rate in adrenal incidentalomas: a longitudinal study. J Clin Endocrinol Metab 86: 5337-5341.
91. Chiodini I, Viti R, Coletti F, et al, 2009 Eugonadal male patients with adrenal incidentalomas and subclinical hypercortisolism have increased rate of vertebral fractures. Clin Endocrinol (Oxf) 70: 208-213.
92. Swiatkowska-Stodulska R, Kaniuka-Jakubowska S, Wisniewski P, et al, 2012 Homocysteine and alpha-1 antitrypsin concentration in patients with subclinical hypercortisolemia. Adv Med Sci 57: 302-307.
93. Csernansky JG, Dong H, Fagan AM, et al, 2006 Plasma cortisol and progression of dementia in subjects with Alzheimer-type dementia. Am J Psychiatry 163: 2164-2169.
94. Guldiken S, Guldiken B, 2008 Subclinical Cushing's syndrome is a potential cause of metabolic dementia and rapidly progressive Alzheimer-type dementia. Med Hypotheses 71: 703-705.
95. Emral R, Uysal AR, Asik M, et al, 2003 Prevalence of subclinical Cushing's syndrome in 70 patients with adrenal incidentaloma: clinical, biochemical and surgical outcomes. Endocr J 50: 399-408.
96. Terzolo M, Osella G, Ali A, et al, 1996 Different patterns of steroid secretion in patients with adrenal incidentaloma. J Clin Endocrinol Metab 81: 740-744.
97. Erbil Y, Ademoglu E, Ozbey N, et al, 2006 Evaluation of the cardiovascular risk in patients with subclinical Cushing syndrome before and after surgery. World J Surg 30: 1665-1671.
98. Shen WT, Lee J, Kebebew E, Clark OH, Duh QY, 2006 Selective use of steroid replacement after adrenalectomy: lessons from 331 consecutive cases. Arch Surg 141: 771-774.
99. Ogilvie JB, Duh QY, 2005 New approaches to the minimally invasive treatment of adrenal lesions. Cancer J 11: 64-72.
100. Kwok KC, Lo CY, 2003 Applicability and outcome of laparoscopic adrenalectomy. Asian J Surg 26: 71-75.
101. Bonjer HJ, Sorm V, Berends FJ, et al, 2000 Endoscopic retroperitoneal adrenalectomy: lessons learned from 111 consecutive cases. Ann Surg 232: 796-803.
102. Zografos GN, Markou A, Ageli C, et al, 2006 Laparoscopic surgery for adrenal tumors. A retrospective analysis. Hormones (Athens) 5: 52-56.
103. Bjornsson B, Birgisson G, Oddsdottir M, 2008 Laparoscopic adrenalectomies: A nationwide single-surgeon experience. Surg Endosc 22: 622-626.
104. Lezoche E, Guerrieri M, Crosta F, et al, 2008 Perioperative results of 214 laparoscopic adrenalectomies by anterior transperitoneal approach. Surg Endosc 22: 522-526.
105. Elfenbein DM, Scarborough JE, Speicher PJ, Scheri RP, 2013 Comparison of laparoscopic versus open adrenalectomy: results from American College of Surgeons-National Surgery Quality Improvement Project. J Surg Res 184: 216-220.
106. Ramacciato G, Nigri GR, Petrucciani N, et al, 2011 Minimally invasive adrenalectomy: a multicenter comparison of transperitoneal and retroperitoneal approaches. Am Surg 77: 409-416.
107. Alesina PF, Hommeltenberg S, Meier B, et al, 2010 Posterior retroperitoneoscopic adrenalectomy for clinical and subclinical Cushing's syndrome. World J Surg 34: 1391-1397.
108. Kiriakopoulos A, Economopoulos KP, Poulios E, Linos D, 2011 Impact of posterior retroperitoneoscopic adrenalectomy in a tertiary care center: a paradigm shift. Surg Endosc 25: 3584-3589.
109. Iacobone M, Albiger N, Scaroni C, et al, 2008 The role of unilateral adrenalectomy in ACTH-independent macronodular adrenal hyperplasia (AIMAH). World J Surg 32: 882-889.
110. Young WF Jr, du Plessis H, Thompson GB, et al, 2008 The clinical conundrum of corticotropin-independent autonomous cortisol secretion in patients with bilateral adrenal masses. World J Surg 32: 856-862.
111. Kawasaki Y, Ishidoya S, Kaiho Y, et al, 2011 Laparoscopic simultaneous bilateral adrenalectomy: assessment of feasibility and potential indications. Int J Urol 18: 762-767.
112. Grubbs EG, Rich TA, Ng C, et al, 2013 Long-term outcomes of surgical treatment for hereditary pheochromocytoma. J Am Coll Surg 216: 280-289.
113. He HC, Dai J, Shen ZJ, et al, 2012 Retroperitoneal adrenal-sparing surgery for the treatment of Cushing's syndrome caused by adrenocortical adenoma: 8-year experience with 87 patients. World J Surg 36: 1182-1188.

114. Diner EK, Franks ME, Behari A, Linehan WM, Walther MM, 2005 Partial adrenalectomy: the National Cancer Institute experience. Urology 66: 19-23.
115. Miyazato M, Ishidoya S, Satoh F, et al, 2011 Surgical outcomes of laparoscopic adrenalectomy for patients with Cushing's and subclinical Cushing's syndrome: a single center experience. Int Urol Nephrol 43: 975-981.
116. Yener S, Ertilav S, Secil M, et al, 2010 Prospective evaluation of tumor size and hormonal status in adrenal incidentalomas. J Endocrinol Invest 33: 32-36.
117. Tsvetov G, Shimon I, Benbassat C, 2007 Adrenal incidentaloma: clinical characteristics and comparison between patients with and without extraadrenal malignancy. J Endocrinol Invest 30: 647-652.
118. Anagnostis P, Efstathiadou Z, Polyzos SA, et al, 2010 Long term follow-up of patients with adrenal incidentalomas--a single center experience and review of the literature. Exp Clin Endocrinol Diabetes 118: 610-616.
119. Young WF, Jr, 2007 Clinical practice. The incidentally discovered adrenal mass. N Engl J Med 356: 601-610.
120. Berland LL, Silverman SG, Gore RM, et al, 2010 Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. J Am Coll Radiol 7: 754-773.
121. Cawood TJ, Hunt PJ, O'Shea D, Cole D, Soule S, 2009 Recommended evaluation of adrenal incidentalomas is costly, has high false-positive rates and confers a risk of fatal cancer that is similar to the risk of the adrenal lesion becoming malignant; time for a rethink? Eur J Endocrinol 161: 513-527.
122. De Leo M, Cozzolino A, Colao A, Pivonello R, 2012 Subclinical Cushing's syndrome. Best Pract Res Clin Endocrinol Metab 26: 497-505.
123. Morioka M, Fujii T, Matsuki T, et al, 2000 Preclinical Cushing's syndrome: report of seven cases and a review of the literature. Int J Urol 7: 126-132.
124. Libe R, Dall'Asta C, Barbetta L, Baccarelli A, Beck-Peccoz P, Ambrosi B, 2002 Long-term follow-up study of patients with adrenal incidentalomas. Eur J Endocrinol 147: 489-494.
125. Barzon L, Fallo F, Sonino N, Boscaro M, 2002 Development of overt Cushing's syndrome in patients with adrenal incidentaloma. Eur J Endocrinol 146: 61-66.
126. Bernini GP, Moretti A, Oriandini C, Bardini M, Taurino C, Salvetti A, 2005 Long-term morphological and hormonal follow-up in a single unit on 115 patients with adrenal incidentalomas. Br J Cancer 92: 1104-1109.
127. Giordano R, Marinazzo E, Berardelli R, et al, 2010 Long-term morphological, hormonal, and clinical follow-up in a single unit on 118 patients with adrenal incidentalomas. Eur J Endocrinol 162: 779-785.