

Subclinical Cushing's Syndrome

revisão

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ABSTRACT

Subclinical Cushing's syndrome (CS) is attracting increasing interest since the serendipitous discovery of an adrenal mass has become a rather frequent event owing to the routine use of sophisticated radiologic techniques. Cortical adenoma is the most frequent type of adrenal incidentaloma accounting for approximately 50% of cases in surgical series and even greater shares in medical series. Incidentally discovered adrenal adenomas may secrete cortisol in an autonomous manner that is not fully restrained by pituitary feedback, in 5 to 20% of cases depending on study protocols and diagnostic criteria. The criteria for qualifying subclinical cortisol excess are controversial and presently there is no consensus on a gold standard for the diagnosis of this condition. An increased frequency of hypertension, central obesity, impaired glucose tolerance, diabetes and hyperlipemia has been described in patients with subclinical CS; however, there is still no clear demonstration of the long-term complications of this condition whose management remains largely empirical. Either adrenalectomy or careful observation associated with treatment of the metabolic syndrome have been suggested as treatment options. (**Arq Bras Endocrinol Metab 2007;51/8:1272-1279**)

Keywords: Adrenal adenoma; Cortisol; Incidentaloma; Subclinical Cushing's syndrome

RESUMO

Síndrome de Cushing Subclínica.

A síndrome de Cushing subclínica (SCS) tem atraído interesse cada vez maior desde que a descoberta casual de uma massa adrenal se tornou um evento freqüente devido ao emprego rotineiro de técnicas sofisticadas de imagem. O adenoma cortical é o tipo mais freqüente de incidentaloma adrenal, correspondendo a cerca de 50% dos casos em séries cirúrgicas e até mais do que isso em séries médicas. Adenomas adrenais descobertos incidentalmente podem secretar cortisol de maneira autônoma ou não controlada totalmente pelo *feedback* hipofisário, em 5 a 20% dos casos, dependendo do protocolo de estudo e dos critérios diagnósticos. Os critérios para qualificar um excesso subclínico de cortisol são controversos e atualmente não existe consenso a respeito de "padrão ouro" para o diagnóstico dessa condição. Em pacientes com SCS, tem sido descrita uma freqüência elevada de hipertensão, obesidade central, intolerância à glicose, diabetes e hiperlipemia; entretanto, ainda não existe uma evidente demonstração de complicações a longo prazo dessa condição, cujo manejo permanece amplamente empírico. Tanto a adrenalectomia como a observação cuidadosa, associada com o tratamento da síndrome metabólica, têm sido sugeridos como opções terapêuticas. (**Arq Bras Endocrinol Metab 2007;51/8:1272-1279**)

Descritores: Adenoma adrenal; Cortisol; Incidentaloma; Síndrome de Cushing subclínica

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DEFINITION

SUBCLINICAL CUSHING'S SYNDROME occurs in patients bearing clinically inapparent adrenal adenoma secreting cortisol in an autonomous and unregulated way that is not fully restrained by pituitary feedback. Although the term "preclinical" Cushing's syndrome has been proposed previously, the term "subclinical" Cushing's syndrome describes more accurately this condition, not implying any assumption on the further development of a clinically overt syndrome. Since the prevalence of overt Cushing's syndrome caused by adrenal adenoma in the general population is exceedingly lower than the prevalence of subclinical Cushing's syndrome in patients with clinically non-functioning adrenal adenoma, it is rather inappropriate to consider subclinical Cushing's syndrome as an early stage of development of overt hypercortisolism (1). Recently, the new definition of "subclinical autonomous glucocorticoid hypersecretion" has been proposed to identify this endocrine disorder (2) even if autonomous cortisol secretion may not be always associated with cortisol excess.

Two criteria should be met to define subclinical Cushing's syndrome. First, the patient should not present a clear Cushing phenotype and, second, the patient should bear an adrenal mass detected serendipitously (3). The first criterion is critical since it depends largely on individual clinical judgment and personal practice. The physicians who have less clinical experience with Cushing's syndrome might overlook (mild) signs of hypercortisolism since some of them, such as facial fullness and central obesity, are specific and of common observation. Thus, it is difficult to decide whether these signs may be attributable to an underlying occult hypercortisolism or are manifestations of the metabolic syndrome. Concerning the second point, the concept of subclinical hypercortisolism may be extended also to patients bearing pituitary incidentaloma (4) and patients who are over-replaced with adrenal steroid therapy (5); anyway, these issues are beyond the scope of this review. Moreover, subtle glucocorticoid excess may also be demonstrated in some patients who have non-adenomatous adrenal masses, such as adrenocortical carcinoma (6) and, exceptionally, myelolipoma (7).

DIAGNOSIS

Although the pathophysiologic concept of autonomous cortisol secretion sustained by an adrenal adenoma is straightforward, demonstration of subclinical Cushing's syndrome is extremely difficult in practice. In

fact, the standard biochemical tests used to screen Cushing's syndrome are generally ill-suited to the assessment of patients who have no, or only mild, signs of cortisol excess (1,8). In this clinical setting, the *a priori* probability of subclinical Cushing's syndrome is roughly comparable with the false-positive rate of the tests used for screening (1,8). In the absence of reliable clinical clues it is indeed challenging to distinguish between true-positive and false-positive test results. Moreover, many tests used to study the HPA axis do not have sufficient sensitivity to recognize a very mild degree of cortisol excess. This is the case for the determination of urinary free cortisol (UFC) that has also the drawback of a remarkable daily variation in either cortisol excretion in the urine or daily urine output (the latter problem is amplified by the difficulty in obtaining complete urine collections) (9).

The reported prevalence of subclinical Cushing's syndrome among patients with adrenal incidentaloma ranges from 5% to 20% (2,3,11-17). The sources of this heterogeneity may be found in the different work-up protocols and variable criteria used to define subclinical cortisol excess as well as in different inclusion criteria and size of the reported series (table 1). Methodological limits add to the intrinsic biological problems associated with identification of subclinical cortisol excess thus explaining the great uncertainty surrounding this entity. A number of alterations of the HPA axis have been associated to clinically inapparent adrenal adenomas (figure 1).

Blunting of the circadian rhythm of cortisol seems more frequent than elevation of UFC and this confirms the view that derangement of the daily secretory pattern of cortisol is an early marker of (subclinical) hypercortisolism (12,13,17). Also low to unde-

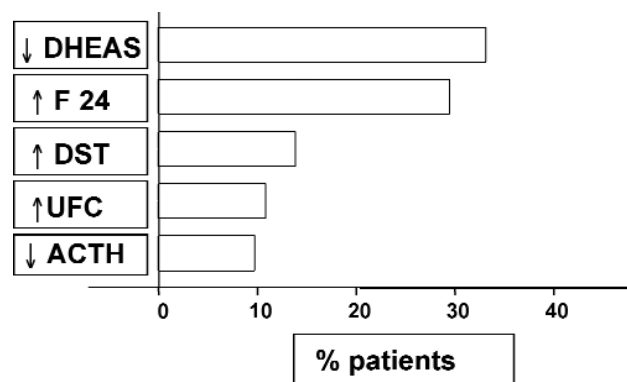


Figure 1. Alterations of the HPA axis observed in 210 patients with clinically inapparent adrenal adenoma. Association of at least two alterations was found in 17.9% of patients. [Terzolo et al., ref. 3]

Table 1. Alterations of the hypothalamic–pituitary–adrenal axis and frequency of subclinical Cushing's syndrome in patients with adrenal incidentaloma.

AUTHOR, YEAR	PATIENTS (no.)	ELEVATED UFC	REDUCED ACTH	NON SUPPRESSION AFTER DST	FREQUENCY OF SCS
Virkkala '89	20	NA	NA	NA	25%
Hensen '90	13	0%	15%	23%	8.0%
Herrera '91	172	NA	NA	1.1%*	1.1%
Jockenhövel '92	18	5.5%	5.5%	50%*	5.5%
Reincke '92	66	1.5%	7.5%	12%**	12%
Aso '92	210	NR	NR	NR	3.3%
Kobayashi '93	14	50%#	NR	50%*	50%
Siren '93	36	NA	NA	NA	5.5%
Caplan '94 (20)	26	NA	11%	NA	11%
Osella '94	45	2%	NA	15%	16%
Seppel '94 (31)	52	NA	NA	NA	1.9%
Flechia '95	24	21%	25%	17%	29%
Ambrosi '95	32	12%	3%	14%	12%
Bencsik '96	63	NA	NA	NA	21%
Bardet '96	35	11%	21%	13%*	8.5%
Linos '96	57	0%	NR	13%	8.8%
Bastounis '97	86	NA	NA	NA	3.5%
Bondanelli '97	38	2.6%	18%	10%**	10%
Kasperlik-Zaluska '97	208	5.2%#	34%	3.0%**	2.9%
Proye '9	103	NR	NR	NR	0%
Terzolo '98	53	7.5%	9.4%	17%	6.0%
Murai '99	59	NR	NR	NR	1.7%
Tutuncu '99	33	NR	NR	NR	6.1%
Rossi '00	65	17%	23%	25%	18.4%
Mantero '00	1004	11%	15%	10%	9.2%
Morioka '00	56	3.6%#	7.1%	11%	12.5%
Favia '00	158	NR	NR	5.1%	5.1%
Tanabe '01	38	NR	26%	47%⊗	47%
Midorikawa '01	20	20%#	15%	25%	20%
Grossrubatscher '01	53	4.0%#	15%	11%	5.7%
Valli '01	31	61%	26%	39%	31.4%
Barzon '02	284	NR	NR	NR	11.3%
Bulow '02	381	0.8%	NR	1.0%	1.0%

DST: dexamethasone suppression test, NA: not available, NR: not reported, SCS: subclinical Cushing's syndrome
 DST is the 1-mg overnight test with a threshold for cortisol suppression at 5.0 µg/dL unless specified otherwise
 * 2 mg DST; ** 8 mg DST; ⊗ Threshold for cortisol suppression at 3.0 µg/dL; # Urinary 17-hydroxycorticosteroid.

tectable ACTH levels have been frequently reported (11-13) even if technical problems associated with measurement of ACTH concentrations close to the detection limits of the assay affect the utility of ACTH determination to demonstrate functional autonomy of an adrenal adenoma (9). Use of CRH test does not seem to add significant information to baseline ACTH levels (11,12,17,18). Low dehydroepiandrosterone sulfate (DHEAS) levels is the most frequent hormonal alteration (11,17,19-22) and was thought to result from suppression of ACTH secretion by autonomous cortisol production (17,19). However, it is presently

unclear whether a reduction in DHEAS secretion may be interpreted as a marker of functional autonomy (17,18,20,22). It has to be considered that the age-related decline in DHEAS secretion may hamper recognition of reduced DHEAS concentrations in an aged population (17).

Not surprisingly, the dexamethasone suppression test (DST) has been widely employed to unmask subtle abnormalities of cortisol secretion in patients with adrenal incidentaloma. It was found that cortisol concentrations after DST are in negative correlation with basal ACTH levels and in positive correlation

with both midnight cortisol concentrations and size of the incidentally discovered adrenal mass (22). However, the results of the published studies are not readily comparable since different protocols and cut-off values to define cortisol suppression have been used (8). The classical 2-day-dexamethasone test is considered more accurate than the overnight 1-mg dexamethasone suppression test (23), but it is more difficult to perform in the clinical practice. The recent NIH state-of-the-science conference panel on adrenal incidentaloma has recommended the overnight 1-mg DST to screen for autonomous cortisol secretion adopting the traditional cortisol threshold of 5 µg/dL (138 nmol/L) to define adequate suppression (2). However, some authors suggest that the proposed cut-off is too high to detect slight cortisol excess and has the drawback of a high rate of false negative results (24). This argumentation comes from the observation that in most healthy subjects cortisol is barely detectable following 1 mg dexamethasone (24,25). The consensus statement on the diagnosis of Cushing's syndrome has indeed proposed a cortisol cut-off level lower than 1.8 mg/dL (50 nmol/L) (9). However, the use of lower cut-off values is inevitably associated with an increased rate of false positive results. The suggestion of giving higher dexamethasone doses, such as 3 mg or 8 mg, has not gained widespread acceptance and has not added significant insight to solve this controversy. At present, the recommendation to use the overnight 1 mg DST seems sound since this test has been extensively employed for screening purposes, whereas there is less experience with the use of high-dose dexamethasone tests in settings other than the differential diagnosis of patient with proven Cushing's syndrome.

To circumvent the problem of false positive results, it has been advocated that two concomitant abnormal results in the tests used for screening should be demonstrated to diagnose subclinical Cushing's syndrome (11,12,26). Many combinations of abnormal tests may be demonstrated when the HPA axis is studied in detail (10-12,17), and it remains difficult, even with this approach, to define subclinical Cushing's syndrome.

Functional autonomy of clinically inapparent adrenal adenomas may be demonstrated *in vivo* by iodocholesterol scintigraphy with a typical imaging pattern of unilateral tracer uptake in the adenoma and absent uptake in the contralateral adrenal gland. Several studies have correlated the scintigraphic pattern of unilateral uptake with cortisol hypersecretion by the adenoma and consequent pituitary ACTH suppression (15,21,26). Scintigraphic uptake may represent a very

early sign of functional autonomy, because NP-59 uptake on the side of the mass without visualization of the contralateral adrenal gland (concordant uptake) occurs even with normal biochemical tests (12,17). An alternative explanation is that the increased uptake simply reflects the presence of enlarged adrenal tissue (17). Notwithstanding this uncertainty in the interpretation, adrenal scintigraphy has become progressively less popular because it is time-consuming, expensive and not widely available.

The current uncertainty on what strategy is best suited to detect adrenal cortical autonomy might be solved by finding at what point cortisol excess becomes clinically significant causing clinical morbidity. We are presently unable to answer this question because we do not know to which extent subclinical Cushing's syndrome may affect patients' health and may affect life expectancy (27).

NATURAL HISTORY

Since many patients with clinically nonfunctioning incidentaloma are exposed to a chronic, even if only minimal to mild, cortisol excess, it is biologically plausible to anticipate that they should suffer, at least to some extent, from the classic long-term consequences of overt Cushing's syndrome, such as arterial hypertension, obesity, or diabetes (8,27,28) (figures 2 and 3). Several data from autopsy series (2,15), cross-sectional studies (12,26) and case-control studies (29,30) consistently point to an association between clinically inapparent adrenal adenoma and some manifestations of the metabolic syndrome (table 2). In a multi-institutional study of 1,004 patients with incidentally detected adrenal masses, the prevalence of arterial hypertension, diabetes, and obesity was remarkably high among patients with adrenal adenomas, with a rate of 41%, 10%, and 28%, respectively (30).

In a cross-sectional study, we have previously demonstrated that nonobese, normoglycemic patients who had clinically inapparent adrenal adenoma had frequent occurrence of impaired glucose tolerance (IGT), elevated blood pressure, and reduced insulin sensitivity compared with matched controls (29). Such alterations were also found in patients who had non-functioning adenoma even if metabolic alterations were more pronounced in the patients who qualified for subclinical Cushing's syndrome. A significant inverse correlation was found between the values of an OGTT-derived insulin sensitivity index and midnight serum cortisol concentrations (29).

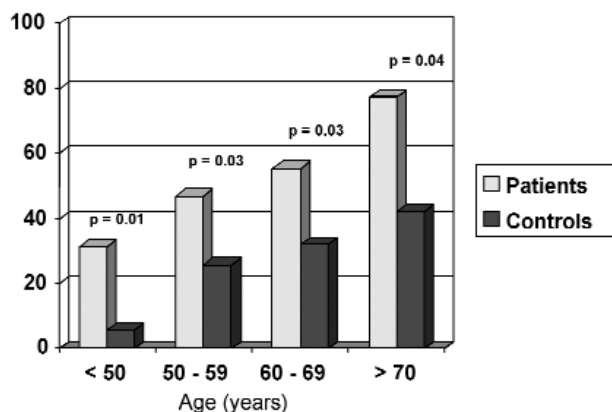


Figure 2. Prevalence of hypertension in patients with non functionally adrenal adenoma. [Data from the National Italian Study Group of adrenal tumors, 2004]

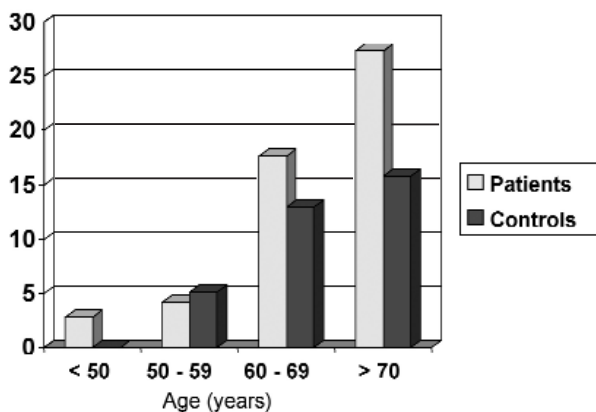


Figure 3. Prevalence of diabetes in patients with non functionally adrenal adenoma. [Data from the National Italian Study Group of adrenal tumors, 2004]

Table 2. Characteristics of the metabolic syndrome described in patients with clinically inapparent adrenal adenoma (highlighted in bold).

Systolic and diastolic hypertension
Hyperinsulinemia / Insulin resistance
Endotelial dysfunction
Low HDL cholesterol
Elevated triglycerides
LDL remnants
Elevated fibrinogen
Hypercoagulability
Increase of PCR and other inflammatory markers
Microalbuminuria
Non-dipping BP pattern
Increase of uric acid
Left ventricular hypertrophy
Accelerated atherosclerosis

In a recent multi-institutional retrospective study of 210 patients with clinically inapparent adrenal adenoma, we have observed hypertension in 53.8% of patients, obesity in 21.4% and hyperglycemia in 22.4%, respectively. The patients with elevated midnight serum cortisol concentrations displayed higher fasting glucose and systolic blood pressure than the subjects with normal cortisol levels (30). These data support the view that clinically inapparent adrenal adenomas may be associated with an increased risk of metabolic and cardiovascular diseases (27), and extend the results previously obtained by Tauchmanova et al. (33). They found that 28 of 126 subjects with adrenal incidentaloma, who qualified for subclinical Cushing's syndrome, showed an adverse risk profile compared with matched controls; these patients also showed a significant increment in the carotid intimal-medial thickness (31).

The results of the above-mentioned studies are in an overall agreement and argue in favor of the view that subclinical Cushing's syndrome may be associated with the clinical phenotype of the insulin resistance syndrome. However, the interpretation of these data must be considered with a note of caution. First, it may be not completely correct to generalize results from series gathered in academic centers and, additionally, referral bias is an obvious limit since these studies are not population-based. Second, there is a potential for confounding in the case-control design since an accurate matching between patients and controls for the many factors that may affect cardiovascular risk is difficult to achieve. Third, in none of the studies the assessment of insulin sensitivity was pursued by using the gold standard test, the glucose clamp, even if the surrogate markers employed have been validated previously for epidemiologic studies (32). Fourth, the published series are not large, but protocols are similar, and data are remarkably consistent across studies.

An alternative hypothesis that adrenal incidentaloma may be a consequence rather than cause of the metabolic syndrome could not be ruled out (33); however, a causal link between subclinical Cushing's syndrome and insulin resistance is the most plausible explanation for the available data (27). In this line, the presence of a relationship between elevated midnight cortisol concentration and metabolic or vascular alterations does not establish causality; however, these data are suggesting that midnight serum cortisol may be viewed as a surrogate marker of insulin sensitivity in patients who have clinically inapparent adrenal adenoma (30).

Even if there is evidence that subclinical Cushing's syndrome may promote development of insulin resistance, that is known to be associated with enhanced all-cause and cardiovascular mortality (34), it is presently unknown whether mortality is increased in patients with clinically inapparent adrenal adenoma, with or without subclinical Cushing's syndrome (28). The scarce available data suggest that most patients with adrenal incidentaloma die of causes not strictly related to the adrenal mass itself but mostly from cardiovascular events, but it is unknown whether the mortality rate is higher than the general population (35,36). Prospective studies of adequate power to address disease-specific or all-cause mortality should address this issue. These studies may be unfeasible, however, if not by means of multi-institutional collaboration, because of the low frequency of disease-specific outcomes.

Osteoporosis is another well-established consequence of overt cortisol excess (9), but data on bone mineral density in patients who have clinically inapparent adrenal adenoma are somewhat controversial (3). Differences in the devices used to estimate bone density and in selection criteria of either patients or controls, along with the small number of subjects studied, are likely explanations for the divergent results. An increased risk of osteoporosis has been documented by the most recent studies that addressed this issue (37-40). Moreover, in a recent study an increased prevalence of vertebral fractures in women with subclinical Cushing's syndrome was found, corroborating the notion that even subtle glucocorticoid excess can exert a detrimental effect on bone quality, particularly in condition of estrogen deficiency (41). Longitudinal studies of adequate statistical power are urgently needed to estimate the risk of osteoporotic fractures and their attendant impact on outcome and quality of life.

Evolution of silent hypercortisolism to the overt clinical syndrome occurs rarely, while appearance of silent biochemical alterations was reported in a percentage ranging from 0% to 11% across different studies (14) (table 3). It was found that masses of 3 cm or greater are more likely to develop silent hyperfunction than smaller tumors, and the risk seems to plateau after 3 to 4 years, even if it does not subside completely (35). In other series, no case of evolution from subclinical to overt Cushing was observed (12,42,43) even if several endocrine modifications occurred during follow-up. In some cases, a spontaneous regression of the alterations of the HPA axis may be observed and this finding suggests that cortisol hypersecretion may have a cyclical pattern (12,43).

The interpretation of these follow-up studies is affected by their small sample size, variable length of follow-up, and variable follow-up strategies. The potential for ascertainment bias also should be disclosed, because many of these observations are made in small, retrospective series. Also the issue of the potential progression over time of metabolic derangements that could be attributable to subclinical Cushing's syndrome remains unsolved by the published studies. The currently available evidence does not allow to make any stringent recommendation for periodic hormonal testing. In the NIH state-of-the-science statement, however, it is reported that it is reasonable to repeat hormonal screening by means of the 1 mg DST annually for at least 4 years (2).

MANAGEMENT GUIDELINES

Data from randomized trials are lacking to guide the appropriate management of subclinical Cushing's syndrome, thus, the therapeutic approach remains largely empirical. Since an increased frequency of hypertension, central obesity, impaired glucose tolerance, diabetes and hyperlipemia has been described in patients with subtle glucocorticoid excess, the management of clinically inapparent adrenal adenoma may have a great deal to do with cardiovascular prevention (27). However, a clear demonstration of long-term consequences of subclinical Cushing's syndrome is still lacking.

Reasonably, adrenalectomy should be considered for younger subjects (below 40 years of age) and for patients with metabolic derangements and hypertension, or both, of recent onset, or for patients with the metabolic syndrome resistant to medical intervention, or rapidly decompensating (3,44). Steroid replacement therapy after adrenalectomy should be reserved for patients with subclinical Cushing syndrome because of the risk for adrenal insufficiency. Patients undergoing adrenalectomy for non-secreting adrenal adenomas do not usually require chronic post-operative steroid replacement (45). It is difficult, however, to predict the risk of postoperative adrenal insufficiency on the basis of pre-operative data; thus, steroid coverage in the early post-operative period may be recommended in all patients after adrenalectomy (8). Steroids should be discontinued after demonstration of an intact HPA axis according to established work-up protocols (46).

Although adrenalectomy has been demonstrated to correct the hormonal abnormalities due to

Table 3. Natural history of adrenal incidentaloma in series of more than 25 patients with a mean follow-up of at least 12 months.

AUTHORS	No	FOLLOW-UP (months)	SUBCLINICAL CUSHING (n)	OVERT CUSHING (n)	REGRESSION (n)
Terzolo et al., 1998	48	12	0	0	3
Mantero & Arnaldi, 2000	53	>12	1	1	0
Rossi et al., 2000	32	9-78	1	0	0
Grossrubatscher et al., 2001	53	6-78	0	0	0
Barzon et al., 2002	130	12-144	5	4	0
Libè et al., 2002	64	12-120	0	0	0
NISGAT, 2004	154	12-120	4	0	4
Bernini et al., 2005	115	12-84	nd	0	nd
TOTAL	649		11 (2.0%)	5 (0.7%)	7 (1.3%)

autonomous cortisol secretion, its effect on long-term outcome and quality of life is not established (3,46,47). Preliminary results suggest that adrenalectomy may benefit patients who have subclinical Cushing's syndrome, but these data should be confirmed in large prospective trials (3,31). At the present time, there is insufficient evidence to recommend adrenalectomy to any patient who qualifies for subclinical Cushing's syndrome (3,28,46). The decision between surgery and conservative management has to be considered individually on the basis of the physician's best clinical judgment and expertise as well as patient's preference. Surgery should be compared in terms of risk, cost, and outcome with the other possible interventions, including life-style changes and pharmacologic intervention. An optimal preventive measure should be harmless but this is not the case with adrenalectomy, even when performed by laparoscopic technique. Indeed, in experienced hands laparoscopic adrenalectomy has minimal (but not zero) morbidity and mortality, but experience is critical depending on a learning curve (48).

Most patients are not candidates for surgery and should be enrolled in a program of regular and careful follow-up to detect, treat, and control the manifestations of the metabolic syndrome. However, precise guidelines for follow-up of patients who do not undergo adrenalectomy have yet to be defined.

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