

Subclinical Cushing's Syndrome in Adrenal Incidentalomas

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Subclinical Cushing's syndrome is a topic of recent interest and controversy, because the serendipitous discovery of an adrenal mass has become an increasingly frequent event owing to the routine use of sophisticated radiologic techniques. Clinically inapparent adrenal masses are detected inadvertently, in the course of work-up or treatment of unrelated disorders, and they commonly are referred to as adrenal incidentalomas [1–3]. The term adrenal incidentaloma is an umbrella definition encompassing a spectrum of different pathologic entities that share the same path of discovery; adrenal adenoma is the most frequent type of incidental mass [1–3].

That adrenal incidentaloma and the related condition of subclinical Cushing's syndrome are receiving broader attention is justified by the fact that adrenal adenoma is one of the most common tumors in people, and its prevalence increases with age. Therefore, appropriate management of adrenal incidentalomas will be a growing public health challenge for society as it ages, also because there is increased attention toward subclinical diseases [2,3]. Accordingly, the identification of patients who have subclinical Cushing's syndrome may provide an opportunity for early treatment of a notoriously dangerous disease, while recent refinements in the field of minimally invasive surgery have rendered adrenalectomy easier to perform. The financial aspect of

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the problem has to be evaluated carefully, because the serendipitous detection of an adrenal mass will be growing in the future because of further advances in radiologic techniques [4,5].

Definition

Subclinical Cushing's syndrome occurs in patients who have clinically nonfunctioning adrenal adenomas when cortisol secretion becomes autonomous and dysregulated, not fully restrained by pituitary feedback. Previously, the term preclinical Cushing's syndrome often was used interchangeably with subclinical Cushing's syndrome in the literature. As proposed by Ross [6], the term subclinical Cushing's syndrome is probably more accurate, not implying any assumption on the evolution toward clinically overt hypercortisolism. It is unlikely that subclinical hypercortisolism is a preclinical state of a patent glucocorticoid excess, because the prevalence data of Cushing's syndrome caused by adrenal adenoma and silent hypercortisolism in clinically inapparent adrenal adenoma greatly differ [6].

At the recent National Institutes of Health (NIH) State-of-the-Science Conference, it was concluded that a better term for this condition might be "subclinical autonomous glucocorticoid hypersecretion" [2]. Notwithstanding semantic discussions, the definition of subclinical Cushing's syndrome is based upon fulfillment of two criteria.

First, the patient should not present a clear Cushing phenotype, even if some physical stigmata suggestive of hypercortisolism (eg, facial fullness and central obesity) can be identified with a careful second examination after detection of an adrenal mass [7]. This is a critical issue that escapes standardization but depends on individual clinical judgment and personal practice. It may be anticipated that physicians who have less expertise with Cushing's syndrome patients might overlook (mild) signs of hypercortisolism and pursue evaluation of adrenal function only following the (incidental) discovery of an adrenal mass. In the authors' experience, a few patients referred for an adrenal incidentaloma actually displayed a previously unrecognized Cushingoid habitus; in a couple of such patients, Cushing's syndrome was even corticotropin (ACTH)-dependent.

Second, the patient should harbor an adrenal mass detected serendipitously. Although argumentation concerning the clinical consequences of subclinical hypercortisolism may be pertinent also to pituitary incidentaloma [8] and over-replacement of adrenal steroid therapy [9], subclinical Cushing's syndrome commonly is associated with adrenal incidentaloma. Cortical adenoma is by far the leading cause of subtle glucocorticoid excess; however, it also may be demonstrated in some patients who have adrenocortical carcinoma [10,11] and, exceptionally, noncortical mass such as myelolipoma [12]. The study of subclinical endocrine dysfunction is usually less attractive in patients who have adrenocortical carcinoma

because of the natural history of the tumor [13]. In the case of myelolipoma, pathologic examination demonstrates a mixed tumor with interspersed adrenocortical cells [12].

Diagnostic strategies

Although the pathophysiologic concept of autonomous cortisol secretion by an adrenal adenoma is straightforward, demonstration of subclinical Cushing's syndrome remains an elusive goal. The diagnostic process of subclinical cortisol excess may prove to be challenging for physicians and their patients for biologic or methodologic reasons.

First, the degree of hypercortisolism only slightly exceeds the physiologic daily production rate of cortisol and is distributed continuously among different patients, because there is a spectrum of variability from non-functioning adenoma to autonomous cortisol-producing adrenal adenoma [2,7]. As a consequence, several different alterations in the endocrine tests aimed at assessing the function of the hypothalamic–pituitary–adrenal (HPA) axis may be found in such patients [7,14–16].

Second, the study of subclinical cortisol excess is pursued by means of the standard biochemical tests used in the screening of Cushing's syndrome that are ill-suited to assessing patients who have only aspecific signs of hypercortisolism, such as hypertension, diabetes, or obesity, if any [6,17]. In the absence of reliable clinical clues, it is hard to distinguish between true-positive and false-positive test results. Moreover, the frequency of subclinical hypercortisolism among patients who have adrenal incidentaloma is roughly comparable with the false-positive rate of the tests used for screening for overt Cushing's syndrome. Therefore, confusion because of methodologic issues adds to the intrinsic biologic variability of silent cortisol excess precluding definition of a uniform entity.

In the literature, the prevalence of subclinical Cushing's syndrome ranged from 5% to 20% [2,14–16,18–22]. This discrepancy is hardly surprising, because the percentage of patients who qualify for this endocrine disorder is highly dependent on the endocrine protocols (testing methods) and criteria used to define subclinical cortisol excess (Table 1). Various endocrine algorithms with disparate assumptions can be found in different series that are also heterogeneous as to sample size and inclusion criteria [1–3,7,22]. Some conclusions, however, can be drawn from the larger series.

Loss of the physiologic circadian rhythm of cortisol, with a blunted nyctohemeral variation, was reported frequently, despite normal baseline cortisol levels [14,16,19,30]. An increase in urinary-free cortisol (UFC) excretion was found less frequently [15,16,21,26,30,33], and this confirms the view that measurement of UFC has insufficient sensitivity to detect mild hypercortisolism [51]. Cortisol excess might be minimal but sufficient to suppress ACTH secretion, as low-to-undetectable ACTH levels were reported repeatedly in clinically inapparent adrenal tumors [14–16,19–21].

Table 1

Alterations of the hypothalamic–pituitary–adrenal axis and prevalence of subclinical Cushing's syndrome in patients who have adrenal incidentaloma

First author, year [Ref. no.]	No. of patients	%				SCS prevalence
		Increased UFC	Low ACTH	High cortisol after DST ^a	Low ACTH after CRH	
Virkkala, 1989 [23]	20	NA	NA	NA	NA	25
Hensen, 1990 [24]	13	0	15	23	100	8.0
Herrera, 1991 [25]	172	NA	NA	1.1 ^b	NA	1.1
Jockenhövel, 1992 [26]	18	5.5	5.5	50 ^b	NR	5.5
Reincke, 1992 [14]	66	1.5	7.5	12 ^c	7.5	12
Aso, 1992 [27]	210	NR	NR	NR	NR	3.3
Kobayashi, 1993 [28]	14	50 ^d	NR	50 ^b	NR	50
Siren, 1993 [29]	36	NA	NA	NA	NA	5.5
Caplan, 1994 [20]	26	NA	11	NA	NA	11
Osella, 1994 [30]	45	2	NA	15	22	16
Seppel, 1994 [31]	52	NA	NA	NA	NA	1.9
Flechia, 1995 [32]	24	21	25	17	NR	29
Ambrosi, 1995 [15]	32	12	3	14	33	12
Bencsik, 1996 [33]	63	NA	NA	NA	NA	21
Bardet, 1996 [34]	35	11	21	13 ^b	33	8.5
Linos, 1996 [35]	57	0	NR	13	NR	8.8
Bastounis, 1997 [36]	86	NA	NA	NA	NA	3.5
Bondanelli, 1997 [11]	38	2.6	18	10 ^c	8	10
Kasperlik-Zaluska, 1997 [37]	208	5.2 ^d	34	3.0 ^c	17	2.9
Proye, 1998 [38]	103	NR	NR	NR	NR	0
Terzolo, 1998 [16]	53	7.5	9.4	17	NR	6.0
Murai, 1999 [39]	59	NR	NR	NR	NR	1.7
Tutuncu, 1999 [40]	33	NR	NR	NR	NR	6.1
Rossi, 2000 [41]	65	17	23	25	NR	18.4
Mantero, 2000 [42]	1004	11	15	10	17	9.2
Morioka, 2000 [43]	56	3.6 ^d	7.1	11	33	12.5
Favia, 2000 [44]	158	NR	NR	5.1	NR	5.1
Tanabe, 2001 [45]	38	NR	26	47 ^e	31	47
Midorikawa, 2001 [46]	20	20 ^d	15	25	62	20
Grossrubatscher, 2001 [47]	53	4.0 ^d	15	11	NR	5.7
Valli, 2001 [48]	31	61	26	39	NR	31.4
Barzon, 2002 [49]	284	NR	NR	NR	NR	11.3
Bulow, 2002 [50]	381	0.8	NR	1.0	NR	1.0

Abbreviations: DST, dexamethasone suppression test; NA, not available; NR, not reported; SCS, subclinical Cushing's syndrome.

^a DST is the 1 mg overnight test with a threshold for cortisol suppression at 5.0 µg/dL unless specified otherwise.

^b 2 mg DST.

^c 8 mg DST.

^d Urinary 17-hydroxycorticosteroid.

^e Threshold for cortisol suppression at 3.0 µg/dL.

Technical problems concerning measurement of ACTH concentrations close to the detection limits of the assay should be recognized [51]. The response of ACTH and cortisol to CRH also may be blunted in these patients, but CRH challenge did not add significant information to baseline ACTH levels [14–16,30]. In the authors' experience, interpretation of CRH test is confounded by the wide scattering of ACTH and cortisol responses and by their divergent patterns in some patients [30,52]. A reduction in dehydroepiandrosterone sulfate (DHEAS) concentration, which is possibly the most frequent hormonal finding in patients who have adrenal incidentalomas [15,30,32–34,53], was thought to reflect suppression of ACTH secretion by autonomous cortisol production [32,30]. Conflicting data, however, have come from the studies that correlated DHEAS concentration with other test results [33,52,53]. At present, there is insufficient information to conclude that low DHEAS concentration is a reliable, indirect marker of autonomous cortisol secretion [30,53]. Moreover, DHEAS secretion declines with age physiologically, and this may hamper recognition of reduced DHEAS concentrations in an aged population [30].

Dexamethasone suppression tests (DSTs) were employed extensively to screen for subclinical hypercortisolism in patients who had adrenal incidentaloma. Test protocols, however, differed with regard to dexamethasone dose and threshold value for adequate cortisol suppression. The NIH state-of-the-science conference panel recommended the 1 mg DST as the standard for screening autonomous cortisol secretion [2]. Previously, most endocrinologists used either an overnight 1 mg or a standard low-dose suppression test [28,53]. The classical 2-day test may be more accurate than the overnight test [54], but it is also more difficult to perform in everyday practice. Definition of adequate cortisol suppression to dexamethasone is arguably one of the most controversial issues. The traditional threshold of 5 $\mu\text{g}/\text{dL}$ (138 nmol/L) was recommended in the NIH consensus statement [2]; however, some experts proposed using lower cut points to increase the detection of subclinical hypercortisolism [55]. The rationale for this choice is that in most healthy subjects, cortisol is barely detectable following 1 mg of dexamethasone [55,56]; thus, in a recent consensus statement on the diagnosis of Cushing's syndrome, the cut-off level was reduced to below 1.8 $\mu\text{g}/\text{dL}$ (50 nmol/L) [51]. Specificity, however, decreases when lower postdexamethasone cortisol values are used, which may yield more false-positive test results; thus, other authors suggested employing high-dose dexamethasone tests (3 or even 8 mg), because the diagnosis of pituitary Cushing's syndrome is not a consideration [14,17]. At present, there is insufficient evidence to solve these controversies. Using the overnight 1 mg suppression test for screening purposes seems sound, however, because this test is designed specifically for diagnosing hypercortisolism, while there is less experience in using high-dose dexamethasone tests in settings other than the differential diagnosis of Cushing's syndrome.

Functional autonomy of clinically inapparent adrenal adenomas may be depicted *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 correlated the scintigraphic pattern of unilateral uptake with cortisol hypersecretion by the adenoma and consequent pituitary ACTH suppression [1,10,34,57]. Scintigraphic uptake represents a very precocious sign of functional autonomy, because NP-59 uptake on the side of the mass with nonvisualization of the contralateral adrenal gland (concordant uptake) may occur despite overall normal biochemical tests [16,30]. The specificity of this finding was questioned, as it was argued that increased uptake simply reflects the presence of enlarged adrenal tissue [30,58]. Adrenal scintigraphy, however, is a time-consuming and expensive technique that is not widely available; thus, its use has not gained general acceptance outside research settings.

To circumvent the problem of false positivity of biochemical testing, some experts advocated that two concomitant alterations should be demonstrated to diagnose a patient who has subclinical Cushing's syndrome [10,15,16,42]. Several possible combinations of abnormal tests may be found when the HPA axis is studied in detail [14–16,30], and it remains difficult, even with this approach, to define the entity of cortisol excess truly relevant to assume subclinical Cushing's syndrome. The current debate and confusion on what strategy is best suited to detect adrenal cortical autonomy might be concluded by finding at what point cortisol excess does lead to clinical morbidity. The response is shrouded in uncertainty, because there is only limited knowledge on the natural history of adrenal incidentalomas [17].

Long-term consequences

There is a wealth of data on the endocrine features of clinically inapparent adrenal adenomas, but there is still scant information on the detrimental effects, if any, of silent hypercortisolism [7,59–61]. Notwithstanding uncertainty regarding ascertainment of subclinical Cushing's syndrome, there is no doubt that many patients who have clinically inapparent adrenal adenoma can be exposed to a chronic, albeit slight, cortisol excess [5]. Thus, it is biologically plausible to assume that they should suffer, at least to some extent, from the classic long-term complications of full-blown Cushing's syndrome, such as arterial hypertension, obesity, or diabetes, which cluster in the metabolic syndrome [51,62].

The relationship between these diseases and unsuspected adrenal adenomas was investigated in autopsy studies that produced controversial results [1]. In a multi-institutional survey performed in Italy, which collected 1004 patients who had adrenal incidentaloma, the prevalence of arterial hypertension, diabetes, and obesity was remarkably high, with a rate of 41%, 10%, and 28%, respectively [42]. However, the interpretation of these data is partially confounded by the retrospective nature of the study, the possibility

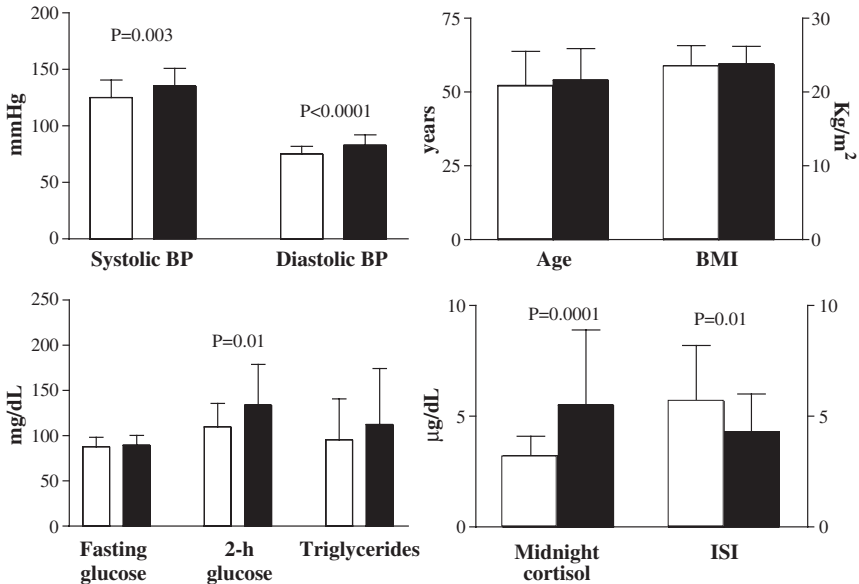


Fig. 1. Comparison of 41 patients who have clinically inapparent adrenal adenoma (*solid bar*) and 41 patients who have euthyroid multinodular goiter, who served as controls (*open bar*), in terms of clinical and biochemical variables. (Data from Terzolo M, Pia A, Ali A, et al. Adrenal incidentaloma: a new cause of the metabolic syndrome? *Clin Endocrinol Metab* 2002;87:998–1003.) BP, blood pressure.

of referral bias, and the large prevalence of these diseases in the general population. In a cross-sectional study, the authors recently 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 (Fig. 1) [63]. Such alterations were not restricted to patients who had subclinical Cushing's syndrome; however, they were more marked in such patients than in those harboring nonfunctioning adenoma (Fig. 2). A significant inverse correlation was found between values of the OGTT-derived insulin sensitivity index and midnight serum cortisol concentrations [63].

The results of this study confirm and extend those previously obtained by Fernandez-Real et al [64] in an uncontrolled study, and by Garrapa et al [65] in a case-control study. Fernandez-Real et al [64] found a remarkably high prevalence of IGT or unknown diabetes among patients who had nonfunctioning adrenal tumors, whereas Garrapa et al [65] found increased visceral fat mass along with IGT and hyperinsulinemia in an analogous cohort of patients. They reported that the degree of metabolic and body fat alterations was intermediate between that of controls and patients who had overt Cushing's syndrome [65]. More recently, Tauchmanova et al [66] found

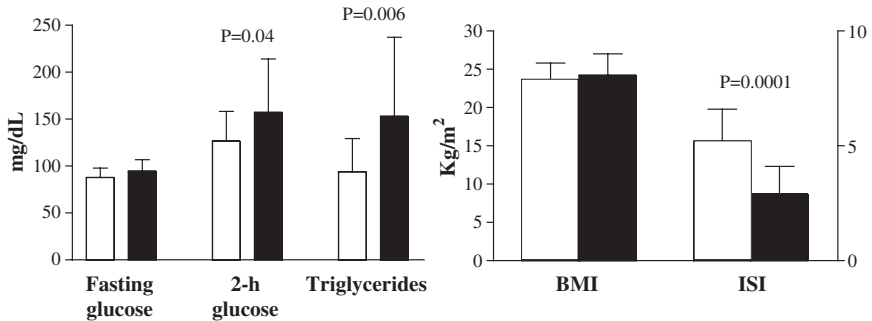


Fig. 2. Comparison of patients who have clinically inapparent adrenal adenoma by the functional status, subclinical Cushing's syndrome ($n = 12$, solid bar) and nonfunctioning adrenal adenoma ($n = 29$, open bar). (Data from Terzolo M, Pia A, Ali A, et al. Adrenal incidentaloma: a new cause of the metabolic syndrome? *Clin Endocrinol Metab* 2002;87:998–1003.)

that 28 of 126 subjects who adrenal incidentaloma and met the criteria for subclinical Cushing's syndrome, sustained an adverse cardiovascular and metabolic risk profile because of elevated blood pressure, greater waist-to-hip ratio, higher triglycerides, total and low-density lipoprotein (LDL) cholesterol and fibrinogen levels, elevation of the homeostasis model assessment (HOMA) index, and an exceedingly high prevalence of IGT or diabetes mellitus compared with matched controls. The impact of these abnormalities upon the vascular system was documented by significant changes in carotid intimal–medial thickness [66].

Overall, several lines of evidence from different studies consistently support the view that subclinical Cushing's syndrome may be associated with the clinical phenotype of the insulin resistance syndrome that fosters several unwanted metabolic and vascular manifestations [5]. There are limitations, however, in the studies that should be addressed for a meaningful appraisal of the data. First, caution should be taken in generalizing results from series gathered in academic centers. Additionally, referral bias is an obvious issue, because they are not population-based studies. Second, there is the potential of confounding because of the case–control design. The complexity of an accurate matching between patients and controls for the many factors that may affect cardiovascular risk should be disclosed. Third, in none of the studies was assessment of insulin sensitivity based on the use of the glucose clamp technique, which is considered the gold standard [67]. The surrogate markers employed, however, were validated previously for epidemiologic studies. Fourth, the published series are not large, but protocols are similar, and data are remarkably consistent across studies. An alternative hypothesis that adrenal incidentaloma itself may be an unrecognized manifestation of the metabolic syndrome cannot be ruled out [68], even if a causal link

between subclinical Cushing's syndrome and insulin resistance is the most plausible explanation for the available data [5].

Demonstration of end-organ complications linked to silent hypercortisolism adds strength to the concept of subclinical Cushing's syndrome, which otherwise remains a condition whose definition is somewhat arbitrary, being established only on a biochemical basis [5]. In this line of research, the authors tried to correlate endocrine data and clinical phenotype of patients who had incidentally detected adrenal adenoma. Preliminary results suggest that some features of the metabolic syndrome cluster in the patients who have elevated midnight cortisol concentration [69]. The presence of a relationship between elevated midnight cortisol concentration and metabolic and vascular alterations does not establish causality; however, these data are in agreement with previous observations of the authors' group, suggesting that midnight serum cortisol may be viewed as a surrogate marker of insulin sensitivity in patients who have clinically inapparent adrenal adenoma [63]. Interestingly, the authors found that elevation of midnight serum cortisol was one of the most frequent alterations of the HPA axis in such patients. This is biologically plausible, because high late-night cortisol levels appear to be the earliest and most sensitive marker for Cushing's syndrome, so that it has been exploited as a diagnostic tool [51,70–72]. Moreover, silent hypercortisolism may be characterized more frequently by a qualitative rather than quantitative alteration of cortisol secretion [30].

There is evidence that the slight amount of cortisol excess caused by clinically inapparent adrenal adenomas, even if insufficient to give a full-blown Cushingoid phenotype, may promote development of insulin resistance and its attendant clinical manifestations. Subclinical hypercortisolism may prove to be harmful, particularly to individuals who express other (genetically determined or acquired) risk factors, and it may play an important role in accelerating the atherosclerosis process [5]. Even if it is held that the metabolic syndrome is associated with enhanced all-cause and cardiovascular mortality [73,74], evidence of increased morbidity and mortality in patients who have clinically inapparent adrenal adenoma and subclinical Cushing's syndrome or not, is lacking. The (scarce) available data suggest that most patients who have adrenal incidentaloma remain asymptomatic throughout life [7,75], but the existing follow-up studies have focused almost exclusively on imaging and endocrine work-up protocols. Prospective studies addressing more appropriate outcome measures, such as disease-specific or all-cause mortality, are needed. 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 established consequence of overt cortisol excess [51], but data on bone mineral density in patients who have clinically inapparent adrenal adenoma are controversial. A research group reported that patients who have subclinical Cushing's syndrome have reduced bone mass in eugonadal and hypogonadal subjects [76–78], while another research

group published conflicting data [41,79]. Additionally, the authors did not find any difference in bone mass density between patients and controls, or between patients who had or did not have subclinical hypercortisolism [80]. 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. There is limited evidence that women who have subclinical Cushing's syndrome are exposed to a higher risk of vertebral fractures independent of their gonadal status [81]. Longitudinal studies of adequate statistical power are mandatory to estimate the risk of osteoporotic fractures that affect outcome and quality of life.

The studies that evaluated the risk of progression from subclinical to overt Cushing's syndrome are as a whole reassuring and demonstrate that the clinical evolution of silent hypercortisolism occurs rarely, if ever. Development of the overt clinical syndrome during follow-up was observed in a negligible number of cases, while appearance of silent biochemical alterations was reported in a percentage ranging from 0% to 11% across different studies [22]. 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 [75,82]. On the other hand, the authors observed spontaneous normalization of subclinical hypercortisolism in some patients, and this finding raises the possibility that cortisol output by an adrenal adenoma may be variable over the course of time [16]. 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. The limited and incomplete evidence available precludes making any stringent recommendation for periodic hormonal testing. One current approach is an overnight 1 mg DST at yearly intervals, or earlier if clinically indicated [2]. Also the issue of progression over time of metabolic derangements that could be attributable to subclinical Cushing's syndrome remains unsolved by the available studies.

Management strategies

In the era of evidence-based medicine, the long-term complications of incidentally discovered adrenal adenomas remain virtually unknown and, consequently, the management of such tumors is largely empirical. There is little evidence of a relatively high mortality rate caused by cardiovascular disease in patients who have adrenal incidentaloma, but the studies have limited power and suffer from several methodologic limits [83,84]. Either adrenalectomy or careful observation was suggested as a treatment option in patients who have clinically inapparent adrenal adenoma. Patients who have subclinical hypercortisolism should receive perioperative glucocorticoids after removal of the functioning mass, because they are at risk for hypo-

adrenalism [1–3]. They should be monitored for subsequent HPA axis recovery and clinical improvement. It is difficult, however, to predict the risk of postoperative adrenal insufficiency on the basis of endocrine and scintigraphic data; thus, a short course of steroid coverage is recommended in all patients after adrenalectomy [60]. Steroids should be discontinued after demonstration of an intact HPA axis according to established work-up protocols [85]. Guidelines for follow-up of patients who do not undergo adrenalectomy have not been defined.

Although adrenalectomy has been demonstrated to correct the biochemical abnormalities, its effect on long-term outcome and quality of life is unknown [4]. Preliminary results suggest that adrenalectomy may ameliorate the cardiovascular risk profile of patients who have subclinical Cushing's syndrome, but data remain inconsistent [7,46,66]. Even if these data were confirmed in larger prospective series, it is unlikely that any patient who has subclinical Cushing's syndrome would benefit from surgery [5,60].

As previously mentioned, autonomous cortisol secretion by the tumor and its attendant detrimental effects may vary greatly across different individuals. Moreover, if the aim is to prevent metabolic and cardiovascular events, 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 for patients, but this is not the case with adrenalectomy, even when performed by laparoscopic technique. Indeed, in experienced hands laparoscopic adrenalectomy has relatively little morbidity and minimal (but not zero) mortality, but experience is critical, and there is a learning curve [86]. Thus, performing surgery on more people has the potential to cause considerable morbidity, even if it is a safe procedure [4]. Conversely, there is ample evidence of the benefits of drug intervention for treating several clinical manifestations of the metabolic syndrome.

Until the risks and benefits of surgical removal of silent hyperfunctioning adrenal adenomas are elucidated, clinicians should elect to surgery patients who have subclinical Cushing's syndrome who display diseases potentially attributable to cortisol excess that are of recent onset or are resistant to medical intervention. This strategy is based purely on pragmatism and not evidence. The time course of the attendant disorders may be important for the surgical choice, however, because it is held that established complications of overt Cushing's syndrome do not resolve fully after successful surgery [87]. Patients who are not candidates for surgery (possibly most patients) should be enrolled in a program of regular and careful follow-up to detect, treat, and control hypertension, diabetes, dyslipidemia, and other manifestations of the metabolic syndrome. These disorders should be treated aggressively with drugs that are of proven benefit in preventing cardiovascular events [5]. Because the metabolic syndrome is directly responsible for the cardiovascular risk of patients who have clinically

inapparent adrenal adenoma, therapeutic efforts should be directed toward the real culprit.

Summary

The incidental discovery of an adrenal mass is a frequent event owing to the routine use of sophisticated radiologic techniques. The potential harm to health associated with incidentally discovered cortical adenoma, the most frequent tumor among adrenal incidentalomas, is unclear at present. As a consequence, diagnostic algorithms and management strategies vary widely across different centers. Incidentally discovered adrenal adenoma may secrete cortisol autonomously, in a way that is no longer under close control by pituitary feedback in 5% to 20% of cases. Exhaustive endocrine evaluation may provide a wide spectrum of results, because subclinical Cushing's syndrome is a heterogeneous condition.

Data are insufficient to estimate the outcome of patients who have subclinical Cushing's syndrome. Evidence, however, is gathering that subclinical Cushing's syndrome may contribute to developing the phenotype of insulin resistance, thus portending to atherosclerosis and relevant cardiovascular complications. It is tempting to speculate that subclinical Cushing's syndrome represents a very mild variant of endogenous glucocorticoid excess syndrome sharing similar target organ damages and long-term complications with the full-blown variant (Fig. 3). Even if progression to overt glucocorticoid excess is rare, subclinical Cushing's syndrome has the potential to carry an adverse prognosis. A critical issue, however, is whether precocious diagnosis and treatment are more effective in paucisymptomatic patients and whether the beneficial effects justify the costs incurred. Data are insufficient to indicate the superiority of a surgical

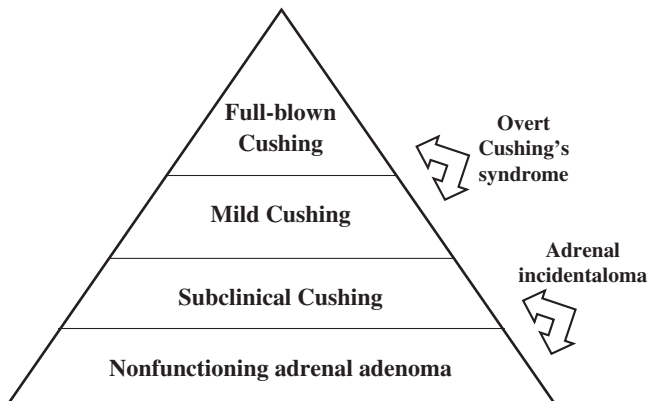


Fig. 3. The spectrum of hypercortisolism.

Box 1. Research agenda

- Identify biochemical markers of cortisol excess predictive of target-organ damage
- Identify a subset of patients at increased risk of adverse outcome
- Compare surgery versus medical treatment on predefined outcomes (cardiovascular morbidity or surrogate endpoints)
- Establish cost-effective follow-up schedules for imaging and biochemical work-up of patients managed conservatively

or nonsurgical approach to manage patients who have subclinical hyperfunctioning adrenal cortical adenoma.

As was concluded at the NIH consensus conference, additional research is needed to guide practice [2]. It is of the utmost importance to establish collaborative prospective studies with clearly defined entry criteria and standardized evaluation protocols and treatment modalities to appraise the natural history and long-term morbidity of clinically inapparent adrenal adenoma and subclinical Cushing's syndrome. A possible research agenda is drafted in (Box 1).

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