

## REVIEW ARTICLE

# Subclinical Cushing's syndrome: definition and management

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## Summary

Subclinical Cushing's syndrome is an ill-defined endocrine disorder that may be observed in patients bearing an incidentally found adrenal adenoma. The concept of subclinical Cushing's syndrome stands on the presence of ACTH-independent cortisol secretion by an adrenal adenoma, that is not fully restrained by pituitary feedback. A hypercortisolemic state of usually minimal intensity may ensue and eventually cause harm to the patients in terms of metabolic and vascular diseases, and bone fractures. However, the natural history of subclinical Cushing's syndrome remains largely unknown. The present review illustrates the currently used methods to ascertain the presence of subclinical Cushing's syndrome and the surrounding controversy. The management of subclinical Cushing's syndrome, that remains a highly debated issue, is also addressed and discussed. Most of the recommendations made in this chapter reflects the view and the clinical experience of the Authors and are not based on solid evidence.

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Since the early nineties, the serendipitous detection of clinically inapparent adrenal adenomas has been associated with a state of subtle cortisol excess. First described in case reports, subclinical hypercortisolism was then appreciated as a frequent endocrine disorder, being detected in up to 15–20% of patients with adrenal incidentalomas.<sup>1,2</sup> This condition was initially defined as 'preclinical' Cushing's syndrome, but afterward the term 'subclinical' entered in use because it does not imply any assumption on the further development of a clinically overt syndrome. The National Institute of Health, State-of-the-Science Conference concluded that a more precise definition should be 'subclinical autonomous glucocorticoid hypersecretion' but this never gained widespread acceptance.<sup>3</sup> The semantic quarrel underscores the uncertainties about subclinical Cushing's syndrome that has still been recently labelled as a poorly defined entity.<sup>4</sup> In this review, subclinical

hypercortisolism and subclinical Cushing's syndrome will be used synonymously.

## Definition of subclinical Cushing's syndrome

### *The concept of subclinical hypercortisolism*

Subclinical Cushing's syndrome is a common disorder assuming a frequency of up to 20% in patients harbouring incidentally discovered adrenal adenomas, which are found in approximately 4% of middle-age persons and in more than 10% of elderly population.<sup>3,5–7</sup> Ascertainment of subclinical Cushing's syndrome should stand on three criteria: first, the patient bears an adrenal adenoma detected serendipitously without any previous suspect of adrenal disease; second, the patient does not present a clear Cushingoid phenotype; third, the endocrine work-up shows autonomous (ACTH-independent) cortisol secretion.<sup>8</sup>

As to the first point, the concept of subclinical hypercortisolism may apply also to patients bearing pituitary incidentalomas and patients who are on steroid replacement;<sup>8</sup> however, discussion of these conditions is beyond the scope of this review.

The second criterion is elusive depending largely on individual clinical judgment and personal practice. The problem is that Cushing's syndrome is actually a spectrum of clinical presentations that is hard to categorize, because of a continuous variability from the more severe phenotypes to the milder ones. The less-experienced physician may not recognize (mild) signs of hypercortisolism, such as facial fullness that can be identified only after a careful assessment of the patient's photographic material. Thus, what is subclinical for a given physician may actually be obvious for another one. The patients with 'true' subclinical Cushing's syndrome should present only clinical features that are less specific for cortisol excess and are of common observation in the context of the metabolic syndrome (i.e. central obesity, hypertension).

The third point suffers from the inadequacy of current tests to detect minimal cortisol excess. Studies may demonstrate that average results of a specific test are able to differentiate patients with adenomas secreting cortisol autonomously from patients with non-functioning adenomas. However, there is considerable overlap between the different categories and it is usually difficult to qualify an individual patient, unless his or her results fall in the extreme ends of distribution. In this context, cortisol secretion ranges from nonfunctioning adrenal adenomas, to adenomas producing cortisol in overt excess with a manifest clinical phenotype, with

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**Table 1.** Comparison of subclinical Cushing's syndrome and mild Cushing's syndrome.

	Subclinical Cushing	Mild Cushing
Sex	Slight female excess	Clear female excess
Age at diagnosis	Usually >50 years	Usually <50 years
Diagnostic modality	Incidental finding Radiological tests usually prompt further endocrine work-up	Finding based on clinical suspect Endocrine tests usually prompt further radiological work-up
Cause of disease	Usually adrenal adenoma	Usually pituitary adenoma
Clinical presentation	One or more features of the metabolic syndrome No specific Cushingoid signs (slight facial roundness may be present)*	One or more features of the metabolic syndrome One or more specific Cushingoid signs (usually of minimal to mild intensity)*
Biochemical presentation	Altered response to DST UFC usually normal MSC usually normal ACTH usually low	Altered response to DST UFC usually normal or slightly elevated MSC usually elevated Variable ACTH
Disease course	Usually does not progress to overt Cushing's syndrome Hypoadrenalism may occur after removal of the adrenal tumour	Usually progressive to more severe clinical presentation Hypoadrenalism ensues invariably after removal of the causing tumour

UFC, urinary free cortisol; MSC, midnight salivary cortisol; DST, dexamethasone suppression test.

\*For definition of specific Cushingoid signs refers to reference.<sup>11</sup>

adenomas associated with minimal cortisol excess and subclinical Cushing's lying between these extremes. Thus, there is no clear dichotomy between normal and abnormal cortisol secretion, and the process of setting thresholds associated with various outcomes is arbitrary, being related, either implicitly or explicitly, to personal preferences rather than solid evidence.<sup>3,8–10</sup>

In Table 1, we compared subclinical and mild Cushing's syndrome; in general, patients with subclinical Cushing are older, more frequently of male gender and bearing an adrenal instead of pituitary adenoma when compared to patients with mild Cushing's. These differences result from comparison of average data and are of limited help when evaluating an individual patient. The clinical presentation is somewhat different, because the condition is recognized serendipitously in one case and following clinical suspicion in the other, and the specific signs of cortisol excess<sup>11</sup> should not be present in the subclinical variant. Having said this, we have to admit that it is difficult to set precise boundaries separating patients with a mild phenotype from patients with a nonspecific phenotype. Only personal experience and clinical experience may help differentiating, as an example, a slight facial fullness caused by mild cortisol excess from facial roundness associated with obesity. There is also a great overlap in the biochemical presentation, even if endocrine alterations are generally more consistent in mild Cushing's syndrome where ACTH-independent disease is less frequent.

A variety of different approaches to diagnose subclinical Cushing's syndrome can be found in the literature, although many recommendations are in fact minor variations of the same scheme, underlying the concept that there is no consensus on what is the best strategy to confirm subclinical Cushing's syndrome.<sup>3,7–10</sup> A recent revision of the adopted strategies pointed out that the screening tests and relative decisional cut-points that have been

used may result in overdiagnosis of subclinical Cushing's syndrome and in potentially inappropriate treatments. Of particular concern is the fact that is virtually impossible to recognize false-positive results if the disease is defined only by laboratory abnormalities in the absence of specific clinical features that serve to confirm the diagnosis.<sup>10</sup> Moreover, the concomitant use of multiple tests to study the hypothalamic-pituitary-adrenal (HPA) axis may eventually result in a higher probability of finding an altered test result by chance.<sup>10</sup>

A major issue is to differentiate between a functional activation of the HPA axis that may be associated with a number of diseases (severe obesity, uncontrolled diabetes, etc.),<sup>11,12</sup> which are frequent among patients with adrenal incidentalomas, and minimal hypercortisolism produced by an adrenal adenoma. Screening for Cushing's syndrome in patients with type 2 diabetes or osteoporosis has been performed in a number of studies, but results were conflicting, reporting a prevalence of occult (previously unsuspected) Cushing's syndrome ranging from 0% to 10.8%.<sup>13–18</sup> The discrepancy is likely attributable to the choice of different cut-points qualifying a test result as positive and in need of further investigation. Interestingly, adrenal adenomas were the leading cause of hypercortisolism in those series.

#### ***What work-up should be performed for subclinical hypercortisolism?***

The dexamethasone suppression test (DST) has been extensively employed to assess the integrity of the feedback, and consequently the status of the HPA axis, in adrenal incidentalomas, applying concepts derived by screening of overt cortisol excess. In contrast, however, from overt Cushing's syndrome, no clinical parameter can be assumed as a gold standard to confirm the presence of

subclinical Cushing's syndrome, challenging the evaluation of the diagnostic accuracy of any test used for screening of this elusive disorder. To overcome this problem, several studies have compared the outcome of the DST with an arbitrary gold standard, i.e. nor-cholesterol scintigraphy, postsurgical adrenal insufficiency and improvement of co-morbidities after surgical removal of a cortisol-secreting tumour.<sup>19–22</sup> Regrettably, most studies are heterogeneous as to DST protocols, in terms of either dexamethasone doses or cortisol cut-points to define adequate suppression. Thus, it is not surprising that the resulting figures vary across a wide range of sensitivity (44–100%) and specificity (24–100%).<sup>1–10,23</sup>

These limitations notwithstanding, the DST is considered the most valuable test to screen for subclinical Cushing's syndrome. In 2002, The National Institute of Health, State-of-the-Science conference panel recommended as standard the overnight 1-mg DST with the cut-point of 138 nM (5 mcg/dl) to define adequate suppression.<sup>3</sup> The same recommendation has been expressed by the more recent AACE/AAES Medical Guidelines for the management of adrenal incidentaloma.<sup>4</sup> A controversial voice raised from the French Society of Endocrinology endorsing the cut-off of 50 nM (1.8 mcg/dl) that was recently proposed by the Endocrine Society Clinical Guidelines for the screening of overt Cushing's syndrome.<sup>23</sup> However, this approach is burdened by a great risk of false-positive results, considering that the hormonal work-up is not prompted by a clinical phenotype suggestive of disease as in overt hypercortisolism. Some Authors have proposed the use of the high-dose DST (3 or 8 mg),<sup>24–27</sup> however, a head-to-head comparison made in a recent study did not find any advantage of the 8 mg DST compared to the 1-mg DST in the screening of subclinical Cushing's syndrome.<sup>28</sup> The 2-day low-dose DST has been proposed as a confirmatory test because it should be more accurate, although more time-consuming and demanding, than the overnight DST.<sup>25,29,30</sup> This approach is methodologically sound; however, a definitive evidence of its superiority in this context has still to be proven.

Other tests used to confirm subclinical Cushing's syndrome are 24-h urinary-free cortisol (UFC), plasma ACTH and midnight serum cortisol. Interpretation of either UFC or ACTH results is flawed by technical problems. Determination of UFC is not sensitive enough to detect a minimal increase in the 24-h cortisol production rate, and ACTH measurement is less reliable in the lowermost part of the assay curve to reliably confirm ACTH independence of cortisol secretion.<sup>30–33</sup> A recent study made an assessment of the performance of ACTH assay in different Italian centres and found a low inter-laboratory reproducibility of the assay. It is particularly worrisome that only 60% of the 'low ACTH' samples were correctly assigned to that category.<sup>34</sup>

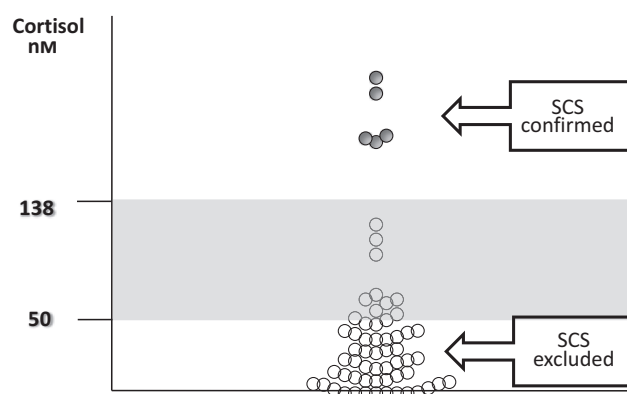
Midnight serum cortisol is a reliable method to detect a disturbance in the cortisol rhythm, which may be an early marker of autonomy and cortisol excess,<sup>11,31,35</sup> and was found to be correlated to an increased cardiovascular risk in patients with clinically inapparent adrenal adenomas.<sup>36</sup> However, it requires hospitalization and cannot be proposed for routine clinical practice.

The late-night salivary cortisol holds promise to become an easier-to-do alternative to midnight serum cortisol maintaining a similar reliability, as it happened for screening of overt Cushing's syndrome.<sup>11,32</sup> Surprisingly, the late-night salivary cortisol failed to

distinguish between subclinical Cushing's syndrome and normality in patients with incidentally discovered adrenal adenomas in a number of studies.<sup>37–40</sup> However, it has been recently argued that late-night salivary cortisol may be more specific than the 1-mg DST, identifying patients with a more than minimal cortisol excess.<sup>41</sup>

Recognizing the limitations of any single test of the HPA axis, many studies have used several combinations of tests to get more solid evidence of ACTH independence (and eventually excessive quantity) of cortisol secretion: most panels of tests included the 1-mg DST, although with different cut-points, ACTH and UFC; sometimes, CRH test, high-dose DST, DHEAS or mid-night serum cortisol were also performed in variable combinations.<sup>7–10,22,25,30,36–38,42–46</sup>

We have recently proposed a flexible approach guided by clinical judgment to the diagnosis of subclinical Cushing's syndrome, suggesting the 1-mg overnight DST as the first step.<sup>47</sup> Post-DST cortisol levels of <50 nM clearly exclude, whereas cortisol levels higher than 138 nM definitively indicate subclinical Cushing's syndrome.<sup>68</sup> Cortisol values between the two cut-points fall in a grey area that has to be interpreted considering the clinical phenotype.<sup>47</sup> The presence of features of the metabolic syndrome or osteoporotic fractures should prompt further investigation to confirm subclinical Cushing's syndrome<sup>68</sup> because these conditions are associated with cortisol excess.<sup>11,31,47</sup> We believe that there is sufficient evidence to support the concept that a cortisol value lower than 50 nM following 1-mg DST reflects an intact HPA axis, while a cortisol value higher than 138 nM is a hallmark of hypercortisolism, if no interfering conditions are present. Conversely, we do not think that there is sufficient evidence to set a cut-point between these two limits, as it has been proposed at 69 nM (2.5 mcg/dl)<sup>29</sup> or 83 nM (3.0 mcg/dl),<sup>26,42,46</sup> to categorize subclinical Cushing's syndrome, and we consider more logical to consider as undefined the values in-between (Fig. 1). When the results of the 1-mg DST are undefined and the clinical context is appropriate, subclinical Cushing's syndrome may be definitively demonstrated with additional



**Fig. 1** Proposed definition of subclinical Cushing's syndrome by using different cut-off levels of cortisol after 1-mg overnight dexamethasone suppression test. Cortisol levels <50 nM exclude the condition, while levels  $\geq 138$  nM are confirmatory. Cortisol levels in between are indeterminate and should be interpreted with clinical data (see text for further details). Data from a personal series of 100 consecutive patients with an adrenal adenoma discovered serendipitously.

work-up, i.e. measurement of ACTH, UFC or late-night salivary cortisol. We are not using adrenal scintigraphy anymore to detect autonomous cortisol secretion because this test causes a high radiation exposure to the patient and has insufficient specificity in this context.<sup>43</sup>

### Management of subclinical Cushing's syndrome

Because of the uncertainties surrounding the definition of subclinical Cushing's syndrome, it is no wonder that its management remains also poorly fixed. The therapeutic dilemma is the choice between surgery and conservative management or, say it in other words, to select the patients who can benefit from surgical removal of their adrenal mass from those who are better managed with their tumour left in place. If surgery has the potential for a definitive solution and can be curative in the event of overt hormonal secretion, its benefits are more difficult to predict when cortisol excess is modest and is not associated with a clear phenotype. Moreover, even if laparoscopic adrenalectomy, the surgical technique of choice for removing benign adrenal tumours, is considered a safe procedure,<sup>4,48</sup> it carries a small risk of major complications; thus, expanding the indications of surgery is doomed to induce considerable morbidity.<sup>49</sup> The dimensions of the problem adrenal incidentaloma impose a careful selection of the patients to refer to surgery also for the need of limiting health care spending.

From a theoretical point of view, the management strategy of subclinical Cushing's syndrome should be planned after reviewing data on its natural history and impending complications or risks, and results of intervention studies reporting the outcome of adrenalectomy compared to nonsurgical attitudes. Regretfully, we lack solid data on both issues.

### The burden of subclinical hypercortisolism

The working hypothesis is that even the minimal cortisol excess typically observed in cases of subclinical Cushing's syndrome may contribute to the development of an insulin-resistance state, leading to the phenotype of the metabolic syndrome,<sup>50</sup> and may also affect bone health leading to osteoporosis and enhanced susceptibility to fractures.<sup>51,52</sup> The hypothesis that subclinical hypercortisolism causes harm to the patients is mostly supported by the results of retrospective, cross-sectional studies.<sup>7–9,23,30,36,51–54</sup> Such studies are prone to referral and ascertainment bias and cannot definitively prove a cause and effect relationship between cortisol excess and metabolic, cardiovascular and bone diseases.<sup>50</sup>

Few data are available on the long-term outcome of patients with subclinical hypercortisolism.<sup>2,8,9,50</sup> In principle, these patients should be considered at elevated risk of cardiovascular events, but a convincing demonstration of increased mortality associated with this endocrine disorder has been never obtained because of the difficulties in carrying on prospective studies of adequate power with long-term follow-up of large patient cohorts. The available studies suffer to one degree or another from limitations because of limited sample size, insufficient duration of follow-up, retrospective design and are inconclusive as to whether mortality is higher than the general population.<sup>2,53–56</sup>

Most of the observational studies focused on the risk of evolution from subclinical to overt Cushing's syndrome, which was likely overestimated in early studies.<sup>57</sup> More recent studies confirmed the concept that alterations of the HPA axis are dynamic, as they can appear, progress or disappear over time.<sup>7,42,55</sup> However, most of these newly detected endocrine abnormalities do not have clinical relevance and may be transient. If it is true that the disturbance of cortisol secretion may become more evident with time, development of definitive Cushing's syndrome has almost never been observed.<sup>8–10</sup>

### What management for subclinical hypercortisolism?

A number of small studies reported that adrenalectomy may lead to cure or better control of the diseases potentially associated with subclinical Cushing's syndrome, such as hypertension, diabetes and obesity.<sup>30,58–60</sup> However, also the studies including more than 20 patients suffer from some of the following limitations: (i) heterogeneous definition of subclinical Cushing's syndrome; (ii) retrospective and uncontrolled design of the study; (iii) variable duration of follow-up; and (iv) inadequate definition of end-points and outcomes of surgical treatment. Of particular concern is the fact that the results of adrenalectomy have not been compared with the evidence-based medical treatments of the specific conditions.

An example of the first limit is offered by a study<sup>61</sup> comparing the effects of adrenalectomy between patients with subclinical and overt Cushing's syndrome, where values of UFC and cortisol after DST were superimposable between the two groups, casting doubts on the definition of 'subclinical' hypercortisolism.

Only one randomized controlled study is available,<sup>62</sup> but this study is not free of methodological shortcomings. Inclusion of patients took 15 years, medical treatment was not standardized either before or after surgery, and the outcome of patients was poorly described (the number of patients at target for hypertension and diabetes is not given). Nevertheless, the result that about one-quarter of patients showed normalization of either blood pressure or glucose levels is of interest.<sup>62</sup>

The best evidence in favour of the concept that adrenalectomy is more beneficial than conservative management for patients with subclinical Cushing's syndrome comes from a retrospective study by Chiodini *et al.*<sup>46</sup> who recommended adrenalectomy to all patients with subclinical Cushing's syndrome and all patients with nonsecreting adenomas of size >4 cm, or size increasing by >1 cm during follow-up. Because a number of patients refused surgery, the study could compare four different groups (subclinical operated, subclinical not operated, nonsubclinical operated and non-subclinical not operated). In comparison with patients treated conservatively, adrenalectomy was found to improve blood pressure and glucose levels in patients with subclinical Cushing's syndrome and, quite surprisingly, also in patients without subclinical Cushing's syndrome.<sup>46</sup> Evidence that the benefits of surgery were not limited to patients with subclinical Cushing's syndrome is casting some doubts on a causal relationship between cure of the endocrine disorder and amelioration of the cardiovascular risk profile.

There is also evidence at variance with the superiority of surgery. Sereg *et al.*<sup>63</sup> did not find any difference in the rate of



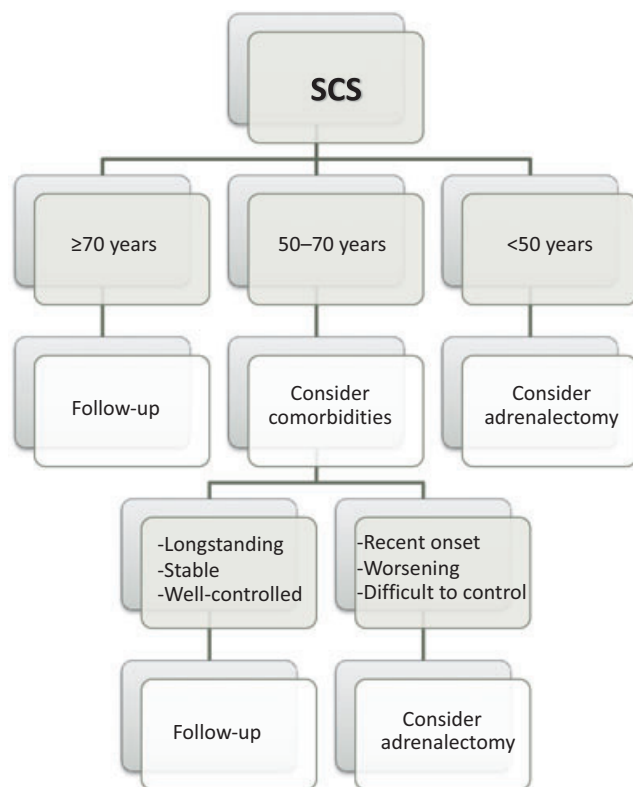


Fig. 2 Proposed management strategy of subclinical Cushing's syndrome.

cardiovascular or cerebrovascular events after a long-term follow-up of two groups of patients with clinically nonfunctioning adrenal adenomas, one who underwent adrenalectomy and one followed conservatively. However, the study was retrospective and uncontrolled, and adrenalectomy was not recommended for the treatment of subclinical Cushing's syndrome.

It is our opinion that evidence is insufficient to conclude whether surgery is preferable to a nonsurgical approach that in our experience is able to control adequately blood pressure and metabolic parameters in most patients, following the published guidelines for the management of hypertension, diabetes and dyslipidaemia (M. Terzolo, G. Reimondo, pers. obs.). Until data from high-quality prospective studies will become available, we should recommend surgery to younger patients with subclinical Cushing's syndrome and to patients who present vascular, metabolic or bone disorders potentially linked to cortisol excess and are of recent onset, are difficult to control, or are progressively deteriorating (Fig. 2).<sup>47</sup> Although this commonsense strategy is based more on pragmatism than solid evidence, it has been shared by previous reviews of the topic.<sup>2,4,8,9,49</sup> It is indeed held that advanced age, long history of associated diseases with established target organ damage are factors predicting unsuccessfulness of surgery in overt Cushing's syndrome.<sup>64,65</sup>

### Declaration of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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