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VIEWPOINT

Six controversial issues on subclinical Cushing's syndrome

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Abstract Subclinical Cushing's syndrome is a condition of hypercortisolism in the absence of signs specific of overt cortisol excess, and it is associated with an increased risk of diabetes, hypertension, fragility fractures, cardiovascular events and mortality. The subclinical Cushing's syndrome is not rare, being estimated to be between 0.2–2 % in the adult population. Despite the huge number of studies that have been published in the recent years, several issues remain controversial for the subclinical Cushing's syndrome screening, diagnosis and treatment. The Altogether to Beat Cushing's syndrome Group was founded in 2012 for bringing together the leading Italian experts in the hypercortisolism-related diseases. This document represents the Altogether to Beat Cushing's syndrome viewpoint regarding the following controversial issues on Subclinical Cushing's syndrome (SCS): (1) Who has to be screened for subclinical Cushing's syndrome? (2) How to screen the populations at risk? (3) How to diagnose subclinical Cushing's syndrome in patients with an adrenal incidentaloma? (4) Which consequence of subclinical Cushing's syndrome has to be searched for? (5) How to address the therapy of choice in AI patients with subclinical Cushing's syndrome? (6) How to follow-up adrenal incidentaloma patients with subclinical Cushing's syndrome surgically or conservatively treated? Notwithstanding the fact that most studies that faced these points may have several biases (e.g., retrospective design, small sample size, different criteria for the subclinical Cushing's syndrome diagnosis), we believe that the literature evidence is sufficient to affirm that the subclinical Cushing's syndrome condition is not harmless and that the currently available diagnostic tools are reliable for identifying the majority of individuals with subclinical Cushing's syndrome.

Keywords Subclinical hypercortisolism · Adrenal incidentalomas · Hypertension · Diabetes · Osteoporosis

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Introduction

Subclinical Cushing's syndrome (SCS) is a condition of hypercortisolism in the absence of signs specific of overt cortisol excess (i.e., striae rubrae, moon facies, buffalo hump, proximal muscle weakness, skin atrophy and plethora) [1]. In adults, the SCS prevalence is estimated to be between 0.2–2 % and it is mainly found in patients with incidentally discovered adrenal masses (adrenal incidentalomas, AI) [2]. Although SCS is associated with an

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increased prevalence of metabolic syndrome, hypertension and increased risk of fractures, cardiovascular events and mortality [3–7], its management is debated [8].

The Altogether to Beat Cushing's Syndrome (ABC) Group set up a panel of experts in the field of SCS, for providing a viewpoint on the following questions: (1) Who has to be screened for SCS? (2) How to screen the populations at risk? (3) How to diagnose SCS in patients with an adrenal incidentaloma? (4) Which consequence of SCS has to be searched for? (5) How to address the therapy of choice in AI patients with SCS? (6) How to follow-up AI patients with SCS surgically or conservatively treated? (Table 1).

Question 1: Who has to be screened for SCS?

In AI patients, the SCS prevalence ranges between 5 and 30 %, depending on the screening procedure [1, 2]. Although the fact that patients with more comorbidity are probably more likely to undergo imaging procedures represents an important bias of all studies, currently all AI patients should be screened for SCS [9]. At variance, in patients with pituitary incidentaloma the SCS screening should be performed only in the presence of features of hypercortisolism, although a 4.4 % rate of pituitary SCS has been described in these patients [10].

Although the studies are heterogeneous, the SCS prevalence in diabetics, hypertensive, obese and osteoporotic patients may reach 10.8 % [1], if these patients are screened with sensitive tests for SCS. An indiscriminate screening of SCS among the populations at risk is currently not acceptable. However, since the SCS prevalence is higher in young diabetic and hypertensive patients, and with progressively worsening metabolic features not controlled with conventional therapy [11, 12], the SCS screening could be considered in these subjects. Moreover, the SCS screening is mandatory in patients with low-bone mineral density (BMD) for age and/or if BMD declines overly rapidly and/or fails to respond to therapy and/or in the presence of fragility fractures in eugonadal subjects [8, 13]. In simple overweight patients the SCS prevalence is <1 % and the SCS screening is useless [9].

Question 2: How to screen the populations at risk?

The guidelines on SCS are discordant regarding this point [9, 14–18]. A sensitive screening test in the absence of a high pre-test probability of disease leads to a huge number of false positives, while a very specific test leads to an unacceptable loss of SCS diagnoses [1]. However, if the populations to be screened are correctly selected, thus increasing the SCS pre-test probability, we can use a sensitive test. The screening in the osteoporotic, diabetic and hypertensive patients fulfilling the criteria cited in the question 1 should be performed by assessing cortisol after 1 mg overnight dexamethasone suppression test (1 mg DST) using a cut-off of 1.8 μg/dL. In the presence of drugs interfering with dexamethasone metabolism and/or cortisol determination, other tests should be used [9]. In patients with 1 mg DST > 1.8 μg/dL and with psychological problems and/or alcoholism and/or diabetes, a 2-day low-dose dexamethasone (2 mg/day) suppression test (LDDST, cut-off 1.8 μg/dL) should be used [9].

Question 3: How to diagnose SCS in patients with AI?

Unfortunately, SCS being asymptomatic, specific gold standard parameters to assess the diagnostic accuracy of any test are lacking [19, 20]. However, in AI patients the dexamethasone suppression tests seem the most reliable ones [1, 2, 8], but the cut-off (1.8 or 3 or 5 μg/dL) and the dexamethasone dosage or administration modality (1 or 3 or 8 mg overnight or LDDST) are debated. Since using 1 mg DST with high cut-off (5 μg/dL) increases specificity but decreases sensitivity and vice versa with lower cut-off (1.8 μg/dL), one uses intermediate cut-offs (2.5–3.0 μg/dL) [1]. However, in AI patients the risk of cardiovascular events and mortality increases for 1 mg DST > 1.8 μg/dL [5–7]. Therefore, we should consider this test and cut-off as the gold standard for diagnosing SCS in AI patients. Since the cortisol secretion in AI is fluctuant and several factors influence the 1 mg DST, this test should be repeated at least twice. In patients with alcoholism, psychiatric disease and diabetes the LDDST should be used to confirm the SCS diagnosis [1, 2, 8].

The high-dose (i.e., 3 or 8 mg overnight) dexamethasone suppression tests did not show advantages for the SCS diagnosis [1], while the 24-h urinary-free cortisol (UFC), late-night salivary cortisol, dehydroepiandrosterone-sulphate and adrenocorticotroph hormone (ACTH) levels have low sensitivity and cannot be used as first-line screening tests [1, 8, 9]. The late-night serum cortisol determination requires the hospital admission, and may be used as a confirmative test in patients with severe diseases possibly associated with hypercortisolism [21].

Overall, in AI patients SCS is ascertained or excluded in the presence of 1 mg DST ≥ 5 or <1.8 μg/dL, respectively. Patients with 1 mg DST between 1.8 and 5 μg/dL have a possible SCS. In these patients, the combination of ≥2 altered parameters among 1 mg DST ≥ 3 μg/dL, ACTH levels < 10 pg/mL and increased UFC levels helps to

Table 1 Summary of the viewpoints on the six questions that frequently arise in the clinical practice when leading with subclinical Cushing's syndrome

Questions	Viewpoint
1 Who has to be screened for SCS	All AI patients
	Patients with pituitary incidentalomas in the presence of other features suggesting hypercortisolism (i.e., fragility fractures, diabetes and hypertension)
	Diabetic and hypertensive patients younger than 50 years with scarce metabolic and blood pressure control
	Patients with low-bone mineral density as compared to age- and weight-matched controls, and/or if bone mineral density declines overly rapidly and/or it fails to respond to therapy and/or in the presence of fragility fractures in eugonadal subjects
2 How to screen the populations at risk	In osteoporotic, hypertensive and diabetic patients (fulfilling the criteria defined in question 1) determine cortisol levels after 1 mg DST using a cut-off of 1.8 μg/dL
	In diabetic patients with 1 mg DST > 1.8 μg/dL perform a LDDST with a cut-off of 1.8 μg/dL
3 How to diagnose SCS in patients with AI	Determine cortisol levels after 1 mg DST
	Ascertained SCS: cortisol levels after 1 mg DST ≥ 5.0 μcg/dL
	Excluded SCS: cortisol levels after 1 mg DST < 1.8 μcg/dL
	Possible SCS: cortisol levels after 1 mg DST between 1.8 and 5 μcg/dL
	SCS is likely in the presence of ≥2 out of: cortisol levels after 1 mg DST ≥ 3 μg/dL, ACTH levels < 10 pg/mL and increased UFC levels
	SCS is unlikely in the presence of <2 out of: cortisol levels after 1 mg DST ≥ 3 μg/dL, ACTH levels < 10 pg/mL and increased UFC levels
4 Which consequence of SCS has to be searched for	In patients with possible or ascertained SCS assess the presence of :
	Diabetes/dyslipidemia
	Hypertension
	Osteoporotic vertebral fractures, performing a bone mineral density determination by dual X-ray absorptiometry and a spinal X-ray
5 How to address the therapy of choice in AI patients with SCS	Ascertained SCS (as defined in question 3): surgical treatment
	Excluded SCS (as defined in question 3): conservative management
	Likely SCS (as defined in question 3): surgery if ≥2 possible complications[a], conservative management if <2 possible complications
	Unlikely SCS (as defined in question 3): conservative management
6 How to follow-up AI patients conservatively or surgically treated	Patients conservatively treated with possible SCS and/or with adrenal lesions ≥2.5 cm:
	Repeat annually cortisol after 1 mg DST for ≥5 years; if changes in cortisol levels after 1 mg DST are observed (re)evaluate UFC and ACTH levels
	Assess annually body weight, blood pressure, cholesterol and glucose levels
	Assess bone mineral density and the presence of asymptomatic vertebral fractures every 2 years
	Manage hypertension, diabetes mellitus and dyslipidemia following specific guidelines and bone consequences as in glucocorticoid-induced osteoporosis
	Patients surgically treated:
	Give a peri- and post-operative steroid replacement therapy
	Clinical revaluation of patients should be performed at 6, 12 and 24 months after surgery
	Verify the changes of the SCS possible complications

AI adrenal incidentaloma, *1 mg DST* 1 mg overnight dexamethasone suppression test, *LDDST* 2-day low-dose (dexamethasone 2 mg/day) dexamethasone suppression test, ACTH adrenocorticoptroph hormone, UFC 24-h urinary-free cortisol, *SCS,* subclinical Cushing's syndrome

[a] Out of obesity, arterial hypertension, diabetes mellitus and dyslipidemia

predict the improvement or worsening of the SCS complications in surgically treated or conservatively managed AI patients, respectively [20, 22, 23]. Therefore, in AI patients with 1 mg DST between 1.8 and 5 μg/dL, SCS could be considered likely or unlikely in the presence or absence of at least two altered parameters among 1 mg DST ≥ 3 μg/dL, ACTH levels < 10 pg/mL and increased UFC levels, respectively.

Question 4: Which consequence of SCS has to be searched for?

In SCS, the increased risk of complications [1–8, 15–21, 24] despite a low degree of cortisol hypersecretion is explained by the long duration of the hypercortisolism [24]. The fractures risk is similar to that of Cushing's syndrome, it is independent of BMD and predicted by 1 mg DST > 2.0 μg/dL [4, 25]. Therefore, in SCS patients we suggest to search for diabetes, hypertension and vertebral fractures, for the latter performing a dual X-ray absorptiometry and an X-ray of the spine. Importantly, in patients with possible SCS, the presence of these complications may help to address the therapy of choice [22].

Question 5: How to address the therapy of choice in AI patients with SCS?

Surgery is the only cure of SCS, since the medical therapy of hypercortisolism has important side-effects [9]. All studies on the effect of adrenalectomy in SCS have limitations (i.e., retrospective not randomised design and small sample size). However, in AI patients with SCS surgically treated hypertension, diabetes, obesity and risk of fractures improve in more than half of cases, while they worsen or remain unchanged in SCS patients conservatively managed [1, 3, 8, 26, 27]. Therefore, we suggest the surgery or the conservative management in patients with ascertained SCS or without SCS (as defined in question 3), respectively. In AI patients with likely SCS (as defined in question 3) and ≥2 complications surgery is generally effective and it should be the first choice, while in AI patients with likely SCS but with <2 complications and in those with unlikely SCS a conservative management could be chosen [22]. Finally, young patients with worsening metabolic features and deteriorating hypercortisolism should be considered for surgery.

Question 6: How to follow-up AI patients conservatively or surgically treated?

In ~14 % of patients with AI ≥ 2.4 cm without SCS at the first evaluation, the SCS may appear after 5 years of follow-up [5, 28]. Therefore, in AI patients conservatively treated with possible SCS and/or with AI ≥ 2.5 cm, the hormonal screening should be repeated annually for at least 5 years, by performing the 1 mg DST. In patients with 1 mg DST > 1.8 μg/dL, we suggest (re)evaluating UFC and ACTH levels. In these patients, we suggest to assess annually body weight, blood pressure, cholesterol and glucose levels, and to evaluate BMD and the presence of vertebral fractures every 2 years, following the guidelines for hypertension, diabetes, dyslipidaemia and glucocorticoid-induced osteoporosis.

After the adrenalectomy, the hypoadrenalism occurs in about half of the patients with possible or ascertained SCS before surgery [29], but it is not pre-operatively predictable [30]. Therefore, we give a peri- and post-operative steroid replacement therapy to surgically treated AI patients with ascertained or possible SCS. We suggest revaluating these patients at 6, 12 and 24 months after surgery, for verifying the improvement of the SCS complications.

Conclusions

In SCS patients, the subtle hypercortisolism is not harmless. Since most data come from retrospective and cross-sectional studies, it is essential that prospective randomised trials are set up. Hopefully, the amelioration of the hormonal assays and the development of safe medical treatments for controlling the cortisol secretion will improve our capability in the SCS diagnosis and therapy.

Compliance with ethical standards

Conflict of interest The author declares that he has no conflict of interest.

References

1. I. Chiodini, Clinical review: diagnosis and treatment of subclinical hypercortisolism. J. Clin. Endocrinol. Metab. **96**, 1223–1236 (2011)
2. M. De Leo, A. Cozzolino, A. Colao, R. Pivonello, Subclinical Cushing's syndrome. Best Pract. Res. Clin. Endocrinol. Metab. **26**, 497–505 (2012)
3. R. Rossi, L. Tauchmanova, A. Luciano, M. Di Martino, C. Battista, L. Del Viscovo, V. Nuzzo, G. Lombardi, Subclinical Cushing's syndrome in patients with adrenal incidentaloma: clinical and biochemical features. J. Clin. Endocrinol. Metab. **85**, 1440–1448 (2000)
4. V. Morelli, C. Eller-Vainicher, A.S. Salcuni, F. Coletti, L. Iorio, G. Muscogiuri, S. Della Casa, M. Arosio, B. Ambrosi, P. Beck-Peccoz, I. Chiodini, 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 (2011)
5. V. Morelli, G. Reimondo, R. Giordano, S. Della Casa, C. Policola, S. Palmieri, A.S. Salcuni, A. Dolci, M. Mendola, M. Arosio, B. Ambrosi, A. Scillitani, E. Ghigo, P. Beck-Peccoz, M. Terzolo, I. Chiodini, Long-term follow-up in adrenal incidentalomas: an Italian multicenter study. J. Clin. Endocrinol. Metab. **99**, 827–834 (2014)
6. G. Di Dalmazi, V. Vicennati, S. Garelli, E. Casadio, E. Rinaldi, E. Giampalma, C. Mosconi, R. Golfieri, A. Paccapelo, U. Pagotto, R. Pasquali, Cardiovascular events and mortality in patients with adrenal incidentalomas that are either non-secreting or associated

with intermediate phenotype or subclinical Cushing's syndrome: a 15-year retrospective study. Lancet Diabetes Endocrinol. **2**, 396–405 (2014)
7. M. Debono, M. Bradburn, M. Bull, B. Harrison, R.J. Ross, J. Newell-Price, Cortisol as a marker for increased mortality in patients with incidental adrenocortical adenomas. J. Clin. Endocrinol. Metab. **99**, 4462–4470 (2014)
8. V. Morelli, I. Chiodini, Subclinical hypercortisolism: how to deal with it? Front. Horm. Res. **46**, 28–38 (2016)
9. L.K. Nieman, B.M. Biller, J.W. Findling, J. Newell-Price, M.O. Savage, P.M. Stewart, V.M. Montori, The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J. Clin. Endocrinol. Metab. **93**, 1526–1540 (2008)
10. A. Toini, A. Dolci, E. Ferrante, E. Verrua, E. Malchiodi, E. Sala, A.G. Lania, I. Chiodini, P. Beck-Peccoz, M. Arosio, A. Spada, G. Mantovani, Screening for ACTH-dependent hypercortisolism in patients affected with pituitary incidentaloma. Eur. J. Endocrinol. **172**, 363–369 (2015)
11. A. Gungunes, M. Sahin, T. Demirci, B. Ucan, E. Cakir, M.S. Arslan, I.O. Unsal, B. Karbek, M. Caliskan, M. Ozbek, E. Cakal, T. Delibasi, Cushing's syndrome in type 2 diabetes patients with poor glycemic control. Endocrine **47**, 895–900 (2014)
12. I. Chiodini, M. Torlontano, A. Scillitani, M. Arosio, S. Bacci, S. Di Lembo, P. Epaminonda, G. Augello, R. Enrini, B. Ambrosi, G. Adda, V. Trischitta, Association of subclinical hypercortisolism with type 2 diabetes mellitus: a case-control study in hospitalized patients. Eur. J. Endocrinol. **153**, 837–844 (2005)
13. I. Chiodini, M.L. Mascia, S. Muscarella, C. Battista, S. Minisola, M. Arosio, S.A. Santini, G. Guglielmi, V. Carnevale, A. Scillitani, Subclinical hypercortisolism among outpatients referred for osteoporosis. Ann. Intern. Med. **147**, 541–548 (2007)
14. J. Shen, M. Sun, B. Zhou, J. Yan, Nonconformity in the clinical practice guidelines for subclinical Cushing's syndrome: which guidelines are trustworthy? Eur. J. Endocrinol. **171**, 421–431 (2014)
15. M.M. Grumbach, B.M. Biller, G.D. Braunstein, K.K. Campbell, J.A., Carney, P.A. Godley, E.L. Harris, J.K. Lee, Y.C. Oertel, M.C. Posner, J.A. Schlechte, H.S. Wieand, Management of the clinically inapparent adrenal mass ("incidentaloma"). Ann. Intern. Med. **138**, 424–429 (2003)
16. M.A. Zeiger, G.B. Thompson, Q.Y. Duh, A.H. Hamrahian, P. Angelos, D. Elaraj, E. Fishman, J. Kharlip, American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons Medical Guidelines for the Management of Adrenal Incidentalomas: executive summary of recommendations. Endocr. Pract. **15**, 450–453 (2009)
17. A. Tabarin, S. Bardet, J. Bertherat, B. Dupas, O. Chabre, E. Hamoir, F. Laurent, F. Tenenbaum, M. Cazalda, H. Lefebvre, N. Valli, V. Rohmer, Exploration and management of adrenal incidentalomas. French Society of Endocrinology Consensus. Ann. Endocrinol. **69**, 487–500 (2008)
18. M. Terzolo, A. Stigliano, I. Chiodini, P. Loli, L. Furlani, G. Arnaldi, G. Reimondo, A. Pia, V. Toscano, M. Zini, G. Borretta, E. Papini, P. Garofalo, B. Allolio, B. Dupas, F. Mantero, A. Tabarin, AME position statement on adrenal incidentaloma. Eur. J. Endocrinol. **164**, 851–870 (2011)
19. P.M. Stewart, 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 (2010)
20. V. Morelli, B. Masserini, A.S. Salcuni, C. Eller-Vainicher, C. Savoca, R. Viti, F. Coletti, G. Guglielmi, C. Battista, L. Iorio, P. Beck-Peccoz, B. Ambrosi, M. Arosio, A. Scillitani, I. Chiodini, Subclinical hypercortisolism: correlation between biochemical diagnostic criteria and clinical aspects. Clin. Endocrinol. **73**, 161–166 (2010)
21. M. Terzolo, S. Bovio, A. Pia, P.A. Conton, G. Reimondo, C. Dall'Asta, D. Bemporad, A. Angeli, G. Opocher, M. Mannelli, B. Ambrosi, F. Mantero, Midnight serum cortisol as a marker of increased cardiovascular risk in patients with a clinically inapparent adrenal adenoma. Eur. J. Endocrinol. **153**, 307–315 (2005)
22. C. Eller-Vainicher, V. Morelli, A.S. Salcuni, C. Battista, M. Torlontano, F. Coletti, L. Iorio, E. Cairoli, P. Beck-Peccoz, M. Arosio, B. Ambrosi, A. Scillitani, I. Chiodini, Accuracy of several parameters of hypothalamic-pituitary-adrenal axis activity in predicting before surgery the metabolic effects of the removal of an adrenal incidentaloma. Eur. J. Endocrinol. **163**, 925–935 (2010)
23. H. Raff, J.W. Findling, A physiologic approach to diagnosis of the Cushing syndrome. Ann. Intern. Med. **138**, 980–991 (2003)
24. A. Faggiano, R. Pivonello, S. Spiezia, M.C. De Martino, M. Filippella, C. Di Somma, G. Lombardi, A. Colao, Cardiovascular risk factors and common carotid artery caliber and stiffness in patients with Cushing's disease during active disease and 1 year after disease remission. J. Clin. Endocrinol. Metab. **88**, 2527–2533 (2003)
25. A.S. Salcuni, V. Morelli, C. Eller-Vainicher, S. Palmieri, E. Cairoli, A. Spada, A. Scillitani, I. Chiodini, Adrenalectomy reduces the risk of vertebral fractures in patients with monolateral adrenal incidentalomas and subclinical hypercortisolism. Eur. J. Endocrinol. **174**, 261–269 (2015)
26. I. Chiodini, V. Morelli, A.S. Salcuni, C. Eller-Vainicher, M. Torlontano, F. Coletti, L. Iorio, A. Cuttitta, A. Ambrosio, L. Vicentini, F. Pellegrini, M. Copetti, P. Beck-Peccoz, M. Arosio, B. Ambrosi, V. Trischitta, A. Scillitani, Beneficial metabolic effects of prompt surgical treatment in patients with an adrenal incidentaloma causing biochemical hypercortisolism. J. Clin. Endocrinol. Metab. **95**, 2736–2745 (2010)
27. A. Toniato, I. Merante-Boschin, G. Opocher, M.R. Pelizzo, F. Schiavi, E. Ballotta, Surgical versus conservative management for subclinical Cushing syndrome in adrenal incidentalomas: a prospective randomized study. Ann. Surg. **249**, 388–391 (2009)
28. L. Barzon, F. Fallo, N. Sonino, M. Boscaro, Development of overt Cushing's syndrome in patients with adrenal incidentaloma. Eur. J. Endocrinol. **146**, 61–66 (2002)
29. G. Di Dalmazi, C.M. Berr, M. Fassnacht, F. Beuschlein, M. Reincke, Adrenal function after adrenalectomy for subclinical hypercortisolism and Cushing's syndrome: a systematic review of the literature. J. Clin. Endocrinol. Metab. **99**, 2637–2645 (2014)
30. C. Eller-Vainicher, V. Morelli, A.S. Salcuni, M. Torlontano, F. Coletti, L. Iorio, A. Cuttitta, A. Ambrosio, L. Vicentini, V. Carnevale, P. Beck-Peccoz, M. Arosio, B. Ambrosi, A. Scillitani, I. Chiodini, 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 (2010)