THE ENIGMA OF THE DIAGNOSIS OF SUBCLINICAL CUSHING

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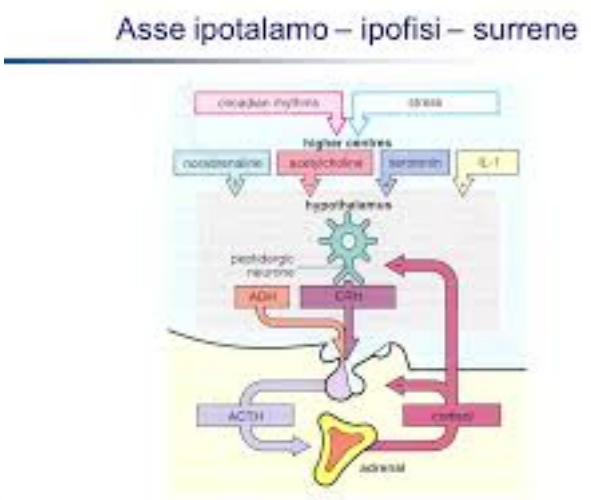
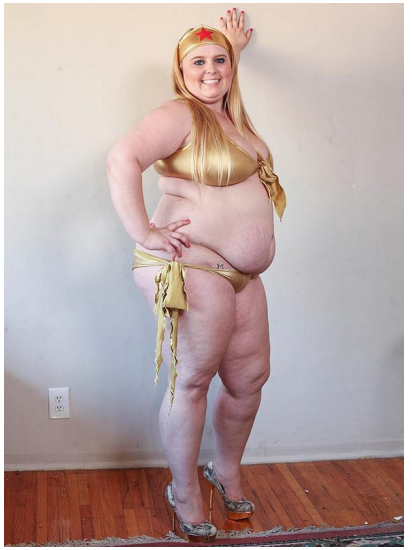
DEFINIZIONE

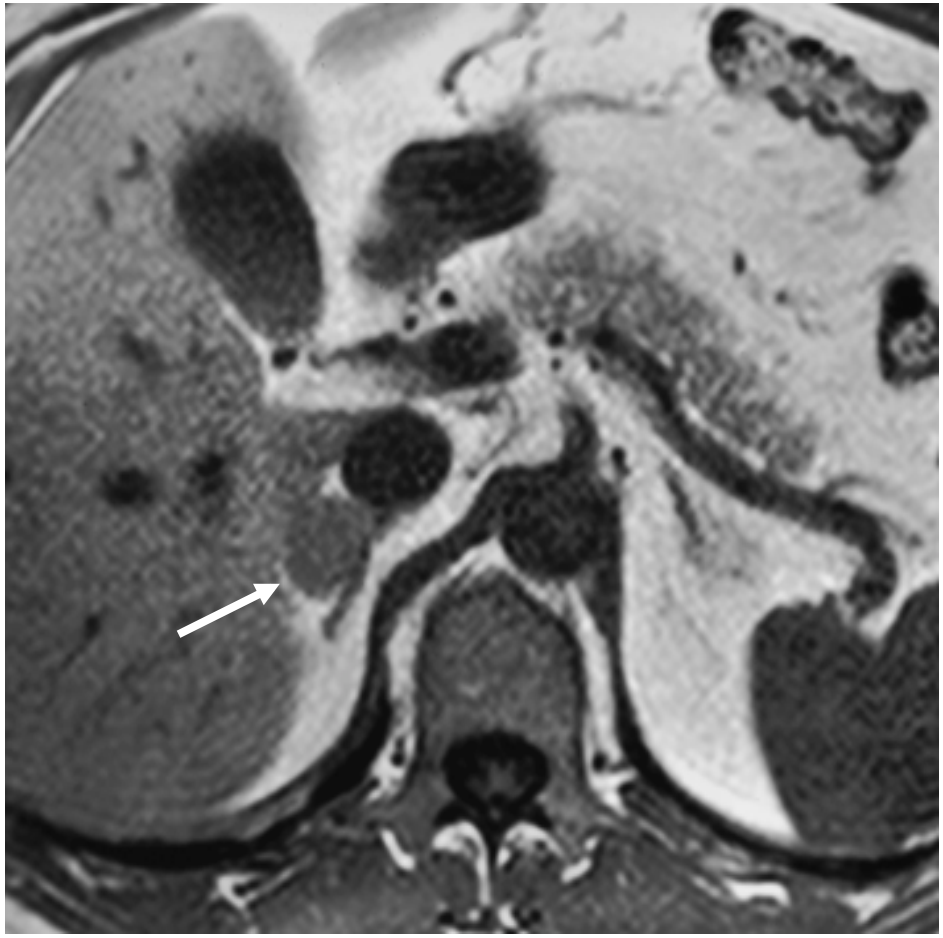
Condizione caratterizzata dalla presenza di alterazioni biochimiche dei parametri di funzione dell'asse ipotalamo-ipofisi-surrene in assenza dei classici segni e sintomi della sindrome di Cushing.





Cushing	Cushing subclinico	Normale

CAUSE di SCS (1)



ALTERAZIONI BIOCHIMICHE (DELL'ASSE IIS)

Alterazione del ritmo circadiano: **cortisolo plasmatico ore 24**
cortisolo salivare ore 24

Aumento del cortisolo urinario

Soppressione dell'ACTH plasmatico

Mancata/ridotta risposta allo stimolo con CRF

Soppressione del DHEAS plasmatico

Mancata soppressione del cortisolo plasmatico dopo DXM

ALTERAZIONI BIOCHIMICHE (DELL'ASSE IIS) PROBLEMATICHE

Alterazione del ritmo circadiano: **Difficile esecuzione variabilità**

Dosaggio problematico, poco sensibile

Dosaggio problematico, poco sensibile

Costosa, risposta variabile, poco eseguita

Valori età dipendenti, poco sensibile

Dose (1, 3, 8 mg), durata (o.n., 2 gg), assorbimento, polimorfismo recettori GC

ALTERAZIONI BIOCHIMICHE DELL'ASSE IIS (2 su 3)

Valori lievemente incrementati di CLU

Valori ridotti/soppressi di ACTH

Anormale soppressione al test di soppressione con Δxm 1 mg on

Mantero F JCEM 2000 85: 637

IL PROBLEMA DEL CUT-OFF

5,0 mg/dl (138nm/L) **3,0 mg/dl (83 nm/L)** **1,8 mg/dl (50nm/L)**

Molto specifico
Poco sensibile

Molto sensibile
Poco specifico

Table 2
Sensitivity and specificity of 1 mg overnight dexamethasone-suppression test at diagnosing subclinical hypercortisolism using various cutoff values for morning serum cortisol measurement

Authors,[Ref.] Year	5 μg/dL Cutoff (Se/Sp)	3 μg/dL Cutoff (Se/Sp)	1.8 μg/dL Cutoff (Se/Sp)	No. of Patients	Criteria for SCS Diagnosis
Barzon et al,[67] 2001	44/100	—	75/72	83	Scintigraphy
Valli et al,[17] 2001	58/83	63/75	100/67[a]	31	Scintigraphy
Eller-Vainicher et al,[68] 2010	33.3/85.7	59/52.4	79.5/23.8	60	Postsurgical hypocortisolism
Morelli et al,[45] 2010	23.8/93.3	52.4/81.4	71.4/49.5	231	Clinical manifestations[b]
Eller-Vainicher et al,[15] 2010	21.7/96.9	—	91.3/56.3[c]	55	Postresection improvement[d]

Starker LF et al. Surg Clin N Am 2014

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Molto specifico
Poco sensibile

Molto sensibile
Poco specifico

Table 4 Diagnostic criteria for subclinical Cushing's syndrome

Reference	Diagnostic criteria	Dexamethasone dose (mg)	DST cut-off (nmol/l)
Perysinakis *et al.*[67]	Absence of symptoms + DST + one of: blunted diurnal cortisol circadian rhythm (ratio of plasma cortisol at 24.00 hours to 08.00 hours > 50%), ACTH < 2·2 pmol/l, 24-h UFC > 276 nmol/l	4	> 50
Iacobone *et al.*[66]	Absence of symptoms (facial plethora, striae rubrae, easy bruising and proximal muscle weakness) + DST + ACTH < 2·2 pmol/l + high 24-h UFC	1	> 138
Maehana *et al.*[38]	Absence of symptoms + DST + at least one of: low ACTH, loss of cortisol circadian rhythm, low DHEAS, unilateral uptake at adrenal scintigraphy	1	> 83
Guerrieri *et al.*[65]	Absence of symptoms + at least two of: DST, high 24-h UFC, ACTH < 2·2 pmol/l	1	> 50
Chiodini *et al.*[1]	Absence of symptoms (moon facies, striae rubrae, skin atrophy, proximal muscle weakness) + at least two of: DST, high 24-h UFC, ACTH < 2·2 pmol/l	1	> 83
Toniato *et al.*[35]	Absence of symptoms + DST + at least two of: low ACTH, loss of cortisol circadian rhythm, high 24-h UFC, low DHEAS	1	> 69
Tsuiki *et al.*[64]	Absence of symptoms + DST (low- and high-dose) + at least one of: ACTH < 2·2 pmol/l, blunted ACTH after CRH (< 150% increase with respect to baseline), loss of cortisol diurnal rhythm (>138 nmol/l at midnight), low DHEAS, unilateral uptake at adrenal scintigraphy	1 8	> 83 > 28

DST, dexamethasone suppression test; ACTH, adrenocorticotropic hormone; UFC, urinary free cortisol; DHEAS, dehydroepiandrosterone sulphate; CRH, corticotropin-releasing hormone.

Iacobone et al, BJS 2015; 102: 318

Table 1
Proposed criteria for diagnosis of subclinical hypercortisolism (SCS)

Authors,[Ref.] Year	Criteria	Dexamethasone Dose, DST Cutoff	SCS Prevalence (%)
Reincke et al,[60] 1992	DST alone	1 mg, 3 μg/dL	12
Osella et al,[29] 1994	DST alone	1 mg, 5 μg/dL	16
Ambrosi et al,[28] 1995	DST plus ≥1 of CRH, CCR, ACTH, UFC	1 mg, 5 μg/dL	12
Tsagarakis et al,[31] 1998	Low-dose DST alone	2.5 μg/dL	25
Terzolo et al,[33] 1998	DST plus UFC	1 mg, 5 μg/dL	6
Mantero & Arnaldi,[4] 2000	≥2 of CRH, CCR, ACTH, UFC, DST	1 mg, 5 μg/dL	9.2
Rossi et al,[47] 2000	Low-dose DST plus ≥1 of CRH, CCR, ACTH, UFC	3.0 μg/dL	18.5
Valli et al,[17] 2001	Unilateral uptake on ^{131}I-norcholesterol scintigraphy	N/A	61.3
Emral et al,[25] 2003	DST and high-dose DST	3 mg, 3 μg/dL	5.7
Chiodini et al,[20] 2009	≥2 of ACTH, UFC, DST	1 mg, 3 μg/dL	29.6
Masserini et al,[21] 2009	≥2 of ACTH, UFC, DST	1 mg, 3 μg/dL	21.4
Eller-Vainicher et al,[15] 2010	≥3 of CCR, ACTH, UFC, DST	1 mg, 3 μg/dL	48.3
Di Dalmazi et al,[66] 2012	DST (5 μg/dL) or DST (1.8 μg/dL) plus UFC or ACTH	1 mg, 1.8 μg/dL or 5 μg/dL	21.3

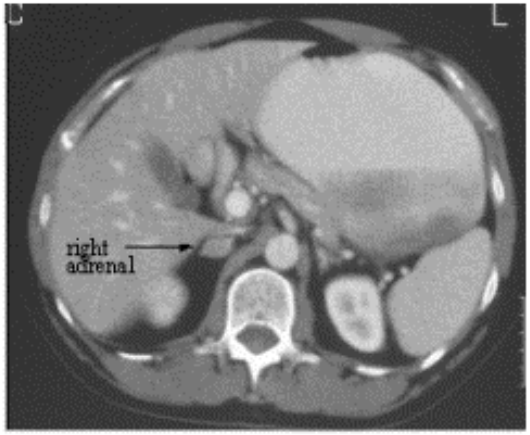
Starker LF et al. Surg Clin N Am 2014

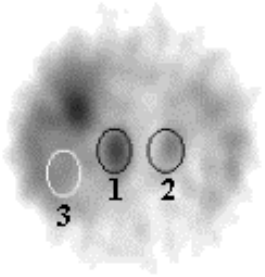
Scintigrafia con iodo-colesterolo

Picciato MP t al. The Role of Adrenal Scintigraphy in the Diagnosis of Subclinica Cushing's Syndrome and the Prediction of Post-surgical Hypoadrenalism World J Surg 2014 38:1328

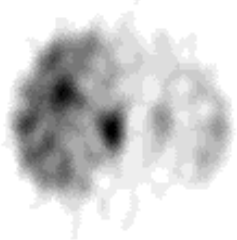
1 – RIGHT ADRENAL ROI
2 – LEFT ADRENAL ROI
3 – LIVER ROI

RIGHT A/L 24 : 0.90
LEFT A/L 24 : 0.55





RIGHT A/L 48 : 1.11
LEFT A/L 48 : 0.78



RIGHT A/L 72 : 1.50
LEFT A/L 72 : 0.90

Iposurrenalismo postchirurgico

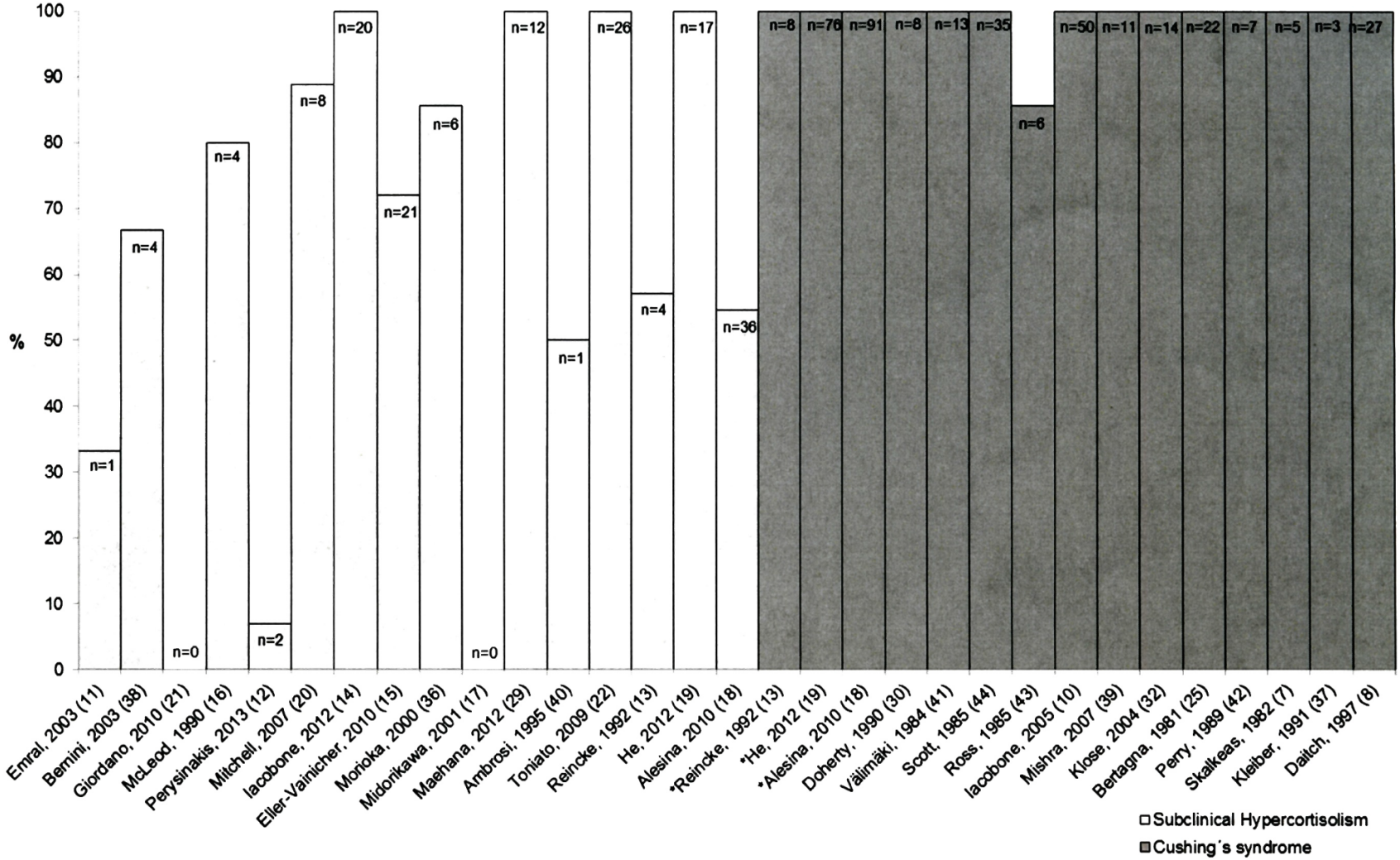


Figure 1. Prevalence of postoperative adrenal insufficiency among different studies. *, Studies reporting data on patients with both SH and Cushing's syndrome. Of 248 patients with SH, 162 (65.3%) experienced postoperative adrenal insufficiency, whereas this was the case in 376 of 377 patients with Cushing's syndrome (99.7%; $P < .001$).

Table 6 Evidence grades for the conclusions in the ES, AACE/AAES and IACE guidelines, grouped as high, moderate or low.

Adjusted evidence grade	ES	AACE/AAES	IACE
Diagnosis	26	4	40
High	0	0	0
Moderate	20	3	34
Low	6	1	6
Treatment		7	18
High	0	0	0
Moderate	0	4	14
Low	0	3	4
Follow-up		1	3
High	0	0	0
Moderate	0	1	0
Low	0	0	3
Total	26	12	52[a]
High	0	0	0
Moderate	20 (76.9%)	8 (66.7%)	42 (80.8%)
Low	6 (23.1%)	4 (33.3%)	10 (19.2%)

ES, Endocrine Society; AACE/AAES, American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; IACE, Italian Association of Clinical Endocrinologists.
[a]Of the 40 evidence included in the IACE guidelines for diagnosis, eight were used to justify the treatment and one was cited regarding follow-up.

Shen et al. EJE 2014, 171:421

Table 4 Domain scores for the clinical practice guidelines for subclinical Cushing's syndrome based on the AGREE-II instrument.

	Guideline					
Domain scores (%)	NIH	ES	AACE/ AAES	FSE	IACE	**Median**
Scope and purpose	94.4	69.4	72.2	77.8	97.2	77.8
Stakeholder involvement	47.2	36.1	38.9	30.6	27.8	36.1
Rigour of development	14.6	51.0	44.8	8.3	46.9	44.8
Clarity of presentation	63.9	75.0	83.3	22.2	91.7	75.0
Applicability	12.5	29.2	22.9	2.0	20.8	20.8
Editorial independence	45.8	54.2	50.0	4.2	100	50.0
Overall assessment	NR	NM	NR	NR	NM	

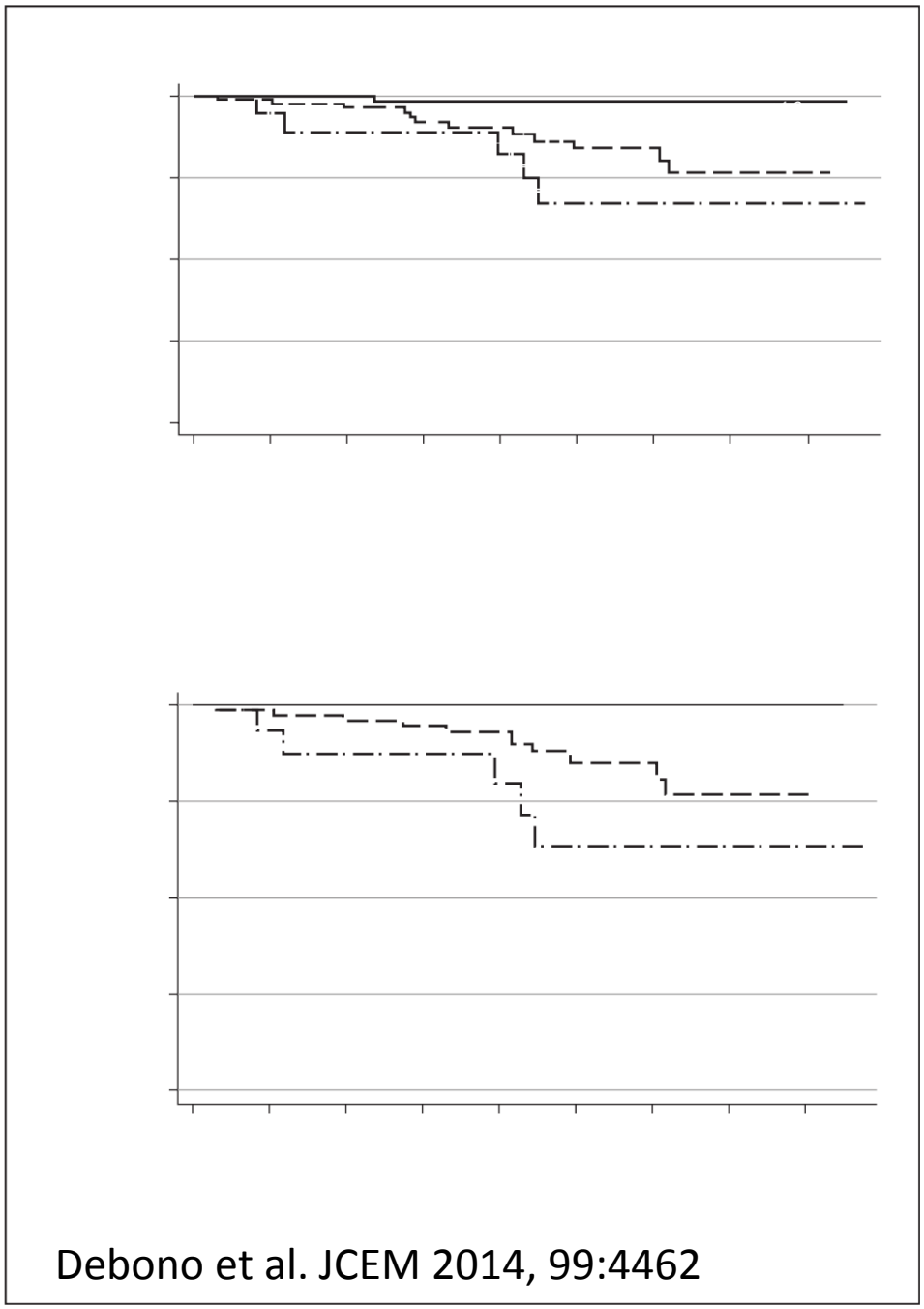
NIH, National Institutes of Health; ES, Endocrine Society; AACE/AAES, American Association of Clinical Endocrinologists/American Association of Endocrine Surgeons; FSE, French Society of Endocrinology; IACE, Italian Association of Clinical Endocrinologists; NR, not recommended; NM, recommended with modification.

Shen et al. EJE 2014, 171:421

KEY POINTS

- SCH is commonly 'diagnosed' in patients with adrenal incidentalomas, but conventional testing has a high rate of false positivity with some of the diagnostic cut-offs used and a formal agreement to define SCH is necessary.
- SCH is associated with multiple complications including an increased prevalence of cardiovascular risk factors, cardiovascular events and bone disease together with an elevated mortality rate.
- Most data assessing complications of SCH are retrospective, and interventional studies are required to establish causation.
- Data from studies comparing conservative with surgical treatment of SCH are mostly retrospective, and prospective, randomized controlled studies to allow individualized stratification of patients towards surgical or medical treatment are vital.

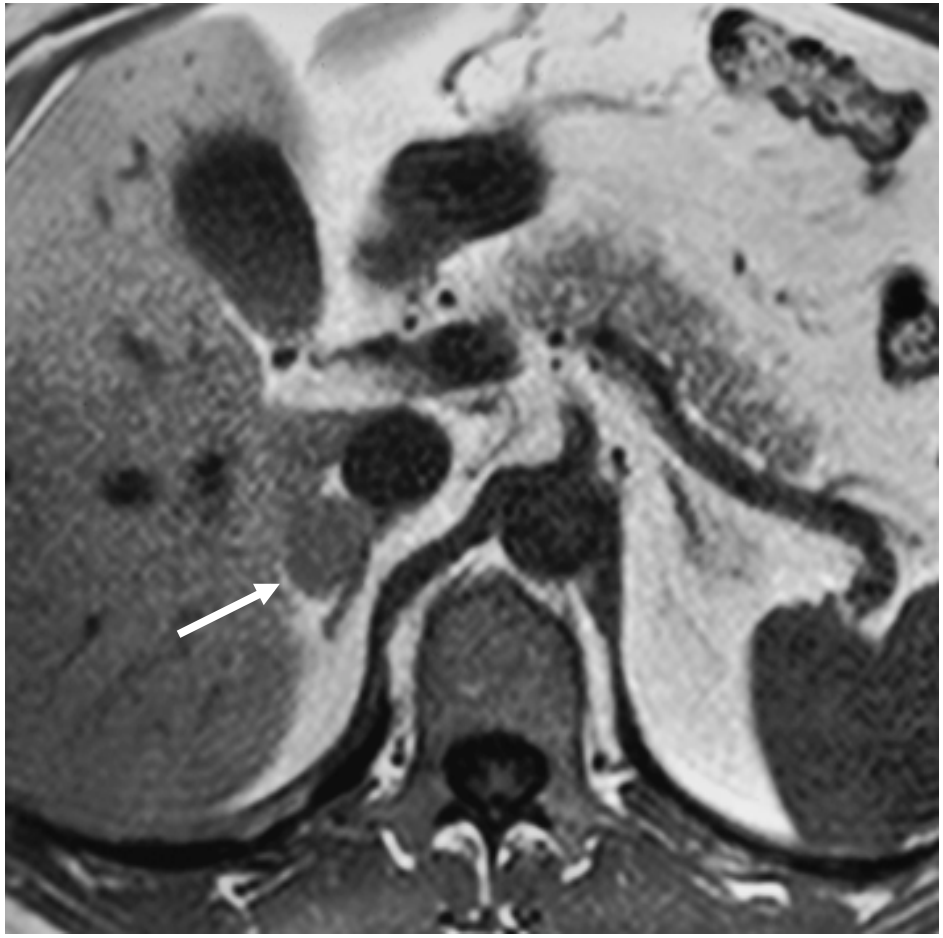
Debono & Newell-Price Curr Opin Endocrinol Diabetes Obes 2015, 22:185



Debono et al. JCEM 2014, 99:4462

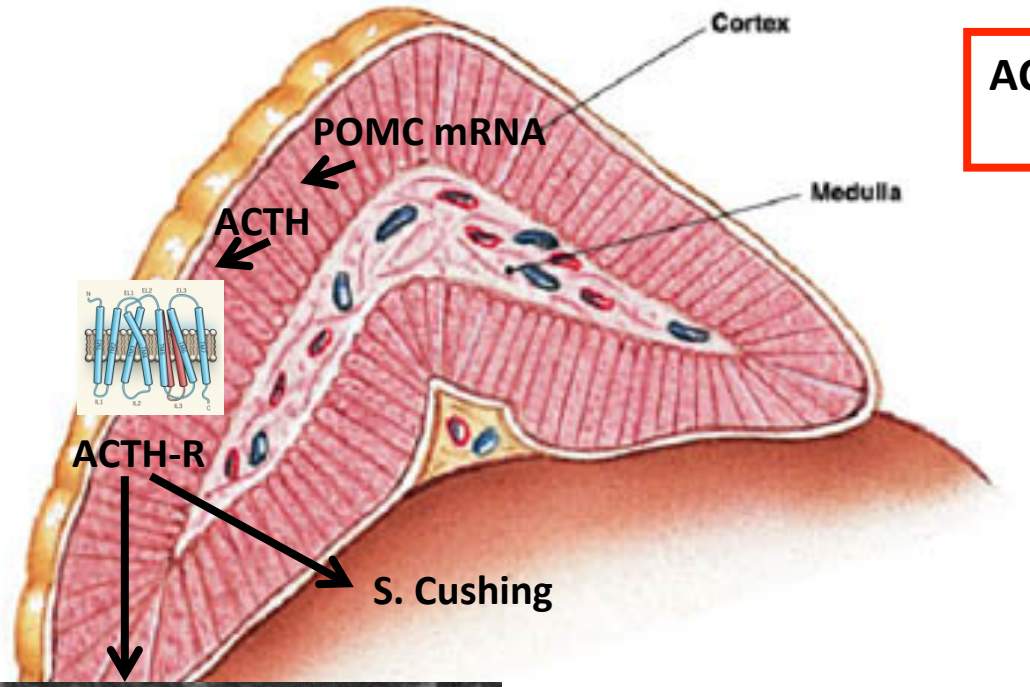
FIGURE 2. Subclinical hypercortisolism (SCH) is associated with an elevated mortality rate. In a retrospective, longitudinal cohort study in 206 patients with a benign, adrenocortical adenoma survival rate decreased with increasing dexamethasone

CAUSE di SCS



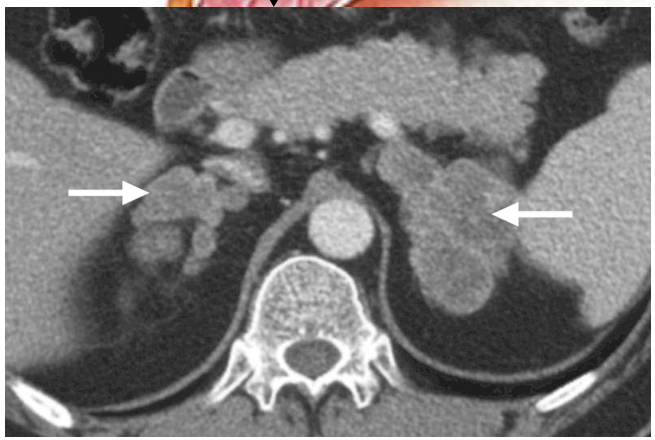
Solo incidentalomi?

CAUSE di SCS



ACTH-independent macronodular adrenal hyperplasia (AIMAH)

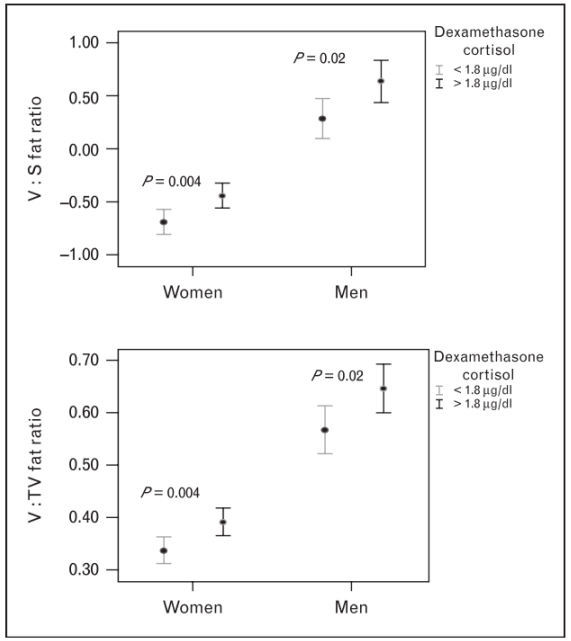
Lefevbre Eur J Endocrinol 2013



AIMAH o ADMAH
(ACTH dependent macronodular adrenal hyperplasia)?

CAUSE di SCS

Una aumentata attività 11-beta-idrossisteroidodeidrogenasi di tipo 1 è stata dimostrata nel tessuto adiposo ed implicata nella patogenesi dell'obesità, ipertensione, intolleranza glicidica, sindrome metabolica. La inibizione selettiva dell'enzima è considerato un target terapeutico per tali condizioni.



Debono et al. JCEM 2013, 98:2383

Cushing | **Cushing subclinico** | **Normale**

CONCLUSIONI

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