Inquadramento Clinico dell'Incidentaloma Surrenalico

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Marta Bondanelli
Sezione di Endocrinologia
Dip. di Scienze Mediche
Università degli Studi di Ferrara
ADRENAL INCIDENTALOMA (AI)

A previously unsuspected adrenal mass discovered on an imaging study performed for an unrelated reason.

**Prevalence**

- **Radiological studies**
  - 0.2 % young age (< 30 yr)
  - 2-4 % middle age
  - 7-10 % elderly

- **Autopsy studies**
  - 2% (ranging from 1 to 8.7%)
  - < 1 % young age (< 30 yr)
  - 7 % elderly (> 70 yr)
CAUSES OF ADRENAL INCIDENTALOMA (AI)

- PHAEOCROMOCYTOMA
- GANGLIONEUROMA
- GANGLIO-NEUROBLASTOMA
- NEUROBLASTOMA
- CARCINOMA

- MYELOLIPOMA
- LIPOMA
- LYMPHOMA
- HAEMANGIOMA
- ANGIOMYOLIPOMA

- ADENOMA
- NODULAR HYPERPLASIA
- CARCINOMA

- CYSTS
- PSEUDOCYSTS

- HAEMATOMA
- HAEMORRHAGE

- metastases
- pseudoadrenal masses

breast, kidney, lung, ovarian cancer, melanoma, lymphoma, leukaemia

stomach, pancreas, kidney, liver, lymphnodal, vascular lesions, technical artefacts

EFE 2012
Frequency of different type of adrenal incidentaloma

<table>
<thead>
<tr>
<th>Type</th>
<th>Average (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>80</td>
<td>33–96</td>
</tr>
<tr>
<td>Non-functioning</td>
<td>75</td>
<td>71–84</td>
</tr>
<tr>
<td>Cortisol secreting</td>
<td>12</td>
<td>1.0–29</td>
</tr>
<tr>
<td>Aldosterone secreting</td>
<td>2.5</td>
<td>1.6–3.3</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>7.0</td>
<td>1.5–14</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>8.0</td>
<td>1.2–11</td>
</tr>
<tr>
<td>Metastasis</td>
<td>5.0</td>
<td>0–18</td>
</tr>
</tbody>
</table>

**Clinical studies**

<table>
<thead>
<tr>
<th>Type</th>
<th>Average (%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenoma</td>
<td>55</td>
<td>49–69</td>
</tr>
<tr>
<td>Non-functioning</td>
<td>69</td>
<td>52–75</td>
</tr>
<tr>
<td>Cortisol secreting</td>
<td>10</td>
<td>1.0–15</td>
</tr>
<tr>
<td>Aldosterone secreting</td>
<td>6.0</td>
<td>2.0–7.0</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>10</td>
<td>11–23</td>
</tr>
<tr>
<td>Carcinoma</td>
<td>11</td>
<td>1.2–12</td>
</tr>
<tr>
<td>Myelolipoma</td>
<td>8.0</td>
<td>7.0–15</td>
</tr>
<tr>
<td>Cyst</td>
<td>5.0</td>
<td>4.0–22</td>
</tr>
<tr>
<td>Ganglioneuroma</td>
<td>4.0</td>
<td>0–8.0</td>
</tr>
<tr>
<td>Metastasis</td>
<td>7.0</td>
<td>0–21</td>
</tr>
</tbody>
</table>

**Surgical studies**

*lung, breast, ovarian, and kidney cancer, melanoma, and lymphoma*  

Bilateral masses in 10-15% of cases

Bilateral adrenal masses (up to 15% of AI)

The most likely diagnoses are

- Metastatic diseases
- Infiltrative diseases
- Congenital adrenal hyperplasia
- Bilateral cortical adenomas
- ACTH-independent macronodular adrenal hyperplasia (AIMAH)
- Infection (tuberculosis, fungal), hemorrhage
- Pheochromocytoma

In oncological patients

50-75% of adrenal incidentalomas are metastases

Unknown primary cancer may present as

- Bilateral adrenal masses in 5.8% of cases
- Monolateral adrenal mass in 0.2%
Discovery of an adrenal mass raises two questions that determine the degree of evaluation and the need for therapy:

1. Is it malignant?

2. Is it functioning?

Over time, in case of conservative approach:

1. Can the adrenal mass become malignant?

2. Can the adrenal mass become hyperfunctioning?
Evaluation for malignancy

<table>
<thead>
<tr>
<th>SIZE</th>
<th>Risk of ACC</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤4 cm</td>
<td>&lt;2 %</td>
</tr>
<tr>
<td>&gt;4 &lt;6 cm</td>
<td>6%</td>
</tr>
<tr>
<td>≥6 cm</td>
<td>25%</td>
</tr>
</tbody>
</table>

NIH Conference 2003

4 cm cut-off
93% sensitivity, 76% sensibility

Imaging phenotype
- Unenhanced CT scan
- Contrast enhanced CT
- MRI
- FDG PET/CT (selected cases, when CT is inconclusive)
- FNAB (selected cases suspicious of metastases)
- NP 59 scintigraphy (unilateral vs. bilateral uptake)
- MIBG, F-DOPA PET, FDA PET (pheochromocytoma)

Change in size over time

growth > 1 cm/year
(ACC rapid growth >2 cm/yr)
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Evaluation for malignancy

CT scan
- noncontrast CT: lower attenuation HU ≤ 10 and tumor size ≤ 4 cm
- homogeneous lesion with a smooth border
- high sensitivity for detecting malignancy

MRI
- High signal intensity on T2 weighted MRI (pheochromocytoma)
- can distinguish adenomas from malignancy and pheochromocytoma

FDG PET/CT
- high sensitivity for detecting malignancy
- [93-100% sensitivity; 80-100% specificity]

FNAB
- (Fine-needle aspiration biopsy)
- in selected cases suspicious of metastases
- [81-96% sensitivity; 99-100% specificity]
- Inconclusive biopsies in 6-50% of cases

Imaging phenotype

contrast-enhanced CT:
- rapid washout (absolute > 60%, relative on delayed images > 40%)
- [82-100% sensitivity; 83-100% specificity]
- lesions with liver on both T1 and T2 weighted sequences
- [82-100% sensitivity; 92-100% specificity]
- excluded non adenomatous lesions
- HU ≤ 20 and tumor size ≤ 4 cm homogeneous lesion with a smooth border
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Adrenocortical Carcinoma (ACC)
- a rare tumor with very poor prognosis -

**Prevalence**
- general population ➞ 12 in 1,000,000
- adrenal incidentaloma ➞ 2% (varying widely 0-12%)

The reason for the higher frequency in adrenal incidentaloma compared to population is unclear

**Survival**
- mean ➞ 18 months
- 5-year ➞ < 20%

**Functional**
- Cushing syndrome
- Virilizing syndrome
- Mixed Cushing-Virilizing syndrome
- Estrogen-secreting (rare)
- Aldosterone-secreting (rare)

or

**Non-functional**

Early diagnosis and definitive treatment is critical
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Evaluation for hormonal hypersecretion

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-functioning adenoma</strong></td>
<td>80% (50-95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Functioning adenoma</strong></td>
<td>10-15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cortisol-secreting</td>
<td>10-15% (1-48)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone-secreting</td>
<td>2% (1.5-7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Androgen or estrogen-secreting</td>
<td>0-11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pheochromocytoma</strong></td>
<td>4-7% (1-20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Evaluation for hormonal hypersecretion

Screening for pheochromocytoma

About 30% of all pheochromocytomas are discovered incidentally; this prevalence increases with time.

All patients with adrenal incidentaloma should undergo biochemical testing for pheochromocytoma.

In patients with incidentally detected pheochromocytoma:
- Normal blood pressure in more than 50% of cases
- Mild to moderate hypertension in the other
- No paroxysmal symptoms of adrenergic excess

Even when clinically silent this tumor can be lethal.
Screening for pheochromocytoma

The optimal type of screening test is debated and is institution/laboratory-dependent.

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma-free metanephrines</td>
<td>99%</td>
<td>89%</td>
</tr>
<tr>
<td>Plasma catecholamines</td>
<td>84%</td>
<td>81%</td>
</tr>
<tr>
<td>Urinary catecholamines</td>
<td>86%</td>
<td>88%</td>
</tr>
<tr>
<td>Urinary-fractionated metanephrines</td>
<td>97%</td>
<td>69%</td>
</tr>
<tr>
<td>Urinary total metanephrines</td>
<td>77%</td>
<td>93%</td>
</tr>
<tr>
<td>VMA</td>
<td>64%</td>
<td>95%</td>
</tr>
</tbody>
</table>

Measurements of fractionated metanephrines in plasma and urine provide superior diagnostic sensitivity to measurements of catecholamines.

Measurement of plasma metanephrines is difficult (and not widely available) because their concentration is 2000-fold lower than those of urinary metanephrines.

Because of the continuous high rate of intratumoral catecholamine O-methylation, and because some tumors secrete catecholamines episodically or in low amounts, patients with pheochromocytoma usually have relatively larger and more consistent increases of plasma normetanephrine or metanephrine than of catecholamines.

Eisenhofer G Curr Hypertens Rep 2012, 14:130
Screening for pheochromocytoma

Considering the relatively large number of false-positive results with metanephrine determination, experts suggest to combine measurements of 24-h urinary metanephrines and catecholamines.

<table>
<thead>
<tr>
<th>Sawka AM, JCEM 2003</th>
<th>Sensibility</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma fractionated metanephrines *</td>
<td>97 %</td>
<td>85%</td>
</tr>
<tr>
<td>24-h urinary metanephrines and catecholamines (both elevated)</td>
<td>90 %</td>
<td>98%</td>
</tr>
</tbody>
</table>
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Screening for pheochromocytoma in patients with adrenal incidentaloma

- **Plasma free metanephrines** (sensitivity 97-100%; specificity 85- 89%)
  - the best initial test
  - NIH conference 2003
  - AACE/AAES Adrenal Incidentaloma Guidelines, Endocr Pract. 2009

- **24h Urinary fractionated metanephrines** (sensitivity 95-97%)
  - or
  - **Plasma free metanephrines** (sensitivity 98-99%)
    - Terzolo M et al. AME Position Statement on Adrenal Incidentaloma EJE 2012

- **Plasma free metanephrines** in **patients with high probability** of pheochromocytoma
  - (eg, vascular, dense adrenal mass, with slow contrast washout)
  - or

- **24h Urinary fractionated metanephrines and catecholamines** in **patients with low probability** of pheochromocytoma
  - (eg, hypodense adrenal mass with rapid contrast washout)
  - F Young F et al. 2012 [www.uptodate.com](http://www.uptodate.com)
Normal results rule out pheochromocytoma

An elevation of more than fourfold above the reference interval establishes the diagnosis, requiring further diagnostic and therapeutic management.

False-positive results should be considered in patients with equivocal elevation of plasma or urinary normetanephrine (drugs, dietary interferences, illness requiring hospitalization, inappropriate sampling, other).

<table>
<thead>
<tr>
<th>Analytical methods</th>
<th>Nature of Interference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coffee (including decaffeinated coffee)</td>
<td>HPLC assays: plasma catecholamines</td>
</tr>
<tr>
<td>Labetalol</td>
<td>Spectrophotometric and fluorometric assays urinary catecholamines and metanephrines;</td>
</tr>
<tr>
<td>Sotalol</td>
<td>HPLC assays: plasma catecholamines</td>
</tr>
<tr>
<td>Buspirone</td>
<td>HPLC assays: urinary metanephrines</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>HPLC assays: plasma-free metanephrines</td>
</tr>
<tr>
<td>Levodopa</td>
<td>HPLC assays: catecholamines and metabolites</td>
</tr>
<tr>
<td>α-methylldopa</td>
<td>HPLC assays: catecholamines</td>
</tr>
<tr>
<td>Sympathomimetics (eg, amphetamines, ephedrine)</td>
<td>Spectrophotometric and fluorometric assays plasma and urinary catecholamines</td>
</tr>
</tbody>
</table>

Pharmacodynamic or pharmacokinetic interference:

- **Tri cyclic antidepressants**: Blocks norepinephrine receptors, causing rises in plasma and urinary norepinephrine, normetanephrine, and VMA.
- **Phenothiazine**: Blocks presynaptic α2 adrenoceptors, causing increases in plasma and urinary norepinephrine, normetanephrine, and VMA.
- **Monoamine oxidase inhibitors**: Blocks deamination, causing up to five-fold increases in plasma and urinary metanephrines.
- **Levodopa**: Metaboised by enzymes that also convert catecholamines.
- **α-methylldopa**: Metaboised by enzymes that also convert catecholamines.
- **Stimulants (eg, caffeine, nicotine)**: Increased plasma and urinary catecholamines.
- **Sympathomimetics (eg, amphetamines, ephedrine)**: Increased plasma and urinary catecholamines.
- **Calcium-channel blockers (dihydropyridines)**: Increased plasma catecholamines due to sympathetic activation.

**Terzolo M et al.**
AME Position Statement on Adrenal Incidentaloma
EJE 2012

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Evaluation for hormonal hypersecretion

Screening of primary aldosteronism

Aldosterone-secreting incidentaloma ➔ 2% (1.5-7%)

In all hypertensive or hypokaliemic patients

Normokaliemic primary aldosteronism ➔ up to 40% of cases

Reported cases of normotensive patients with primary aldosteronism

The best screening test

Sensitivity and specificity 90-100%

The ratio (ARR) between morning
➔ plasma aldosterone (PA, ng/dl) and plasma renin activity (PRA, ng/ml/h)
using a diagnostic threshold of 30-50

➔ plasma aldosterone (PA, ng/dl) and direct renin concentration (DRC, mIU/l)
using a diagnostic threshold of 3.7 - 4.9

Tezolo M et al. AME Position Statement on Adrenal Incidentaloma EJE 2012
Arnaldi G et al. Best Pact Clin Endocrinol 2012
AACE/AAES Adrenal Incidentaloma Giudelines 2009
Cawood J et al. EJE 2009

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**Raccomandation for ARR measurement**

- **Correct hypokalemia and liberalize sodium intake**

- **Withdraw agents that markedly affect the ARR for at least 4 wk:**
  - Spironolactone, eplerenone, amiloride, and triamterene
  - Potassium-wasting diuretics
  - Products derived from licorice root

- If the results of ARR off the above agents are not diagnostic, withdraw other interfering medications for at least 2 wk:
  - Beta-blockers, central α-2 agonists, nonsteroidal antiinflammatory drugs
  - Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, renin inhibitors, dihydropyridine calcium channel antagonists

- **Hypertension can be controlled with non-interfering medication** (verapamil slow-release/doxazosin)

- Establish OC and HRT status, because estrogen-containing medications may lower DRC and cause false-positive ARR when DRC (rather than PRA) is measured

- Collect blood morning, after the patient has been up (sitting, standing, or walking) for at least 2 h and seated for 5–15 min

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*Endocrine Society Guidelines for the diagnosis and treatment of patients with primary aldosteronism. J Clin Endocrinol Metab, 2009*
In patients with HIGH ARR

- $PA (\text{ng/dl}) / PRA (\text{ng/ml/h}) > 30-50$
- or
- $PA (\text{ng/dl}) / DRC (\text{mIU/l}) > 3.7$

**CONFIRMATORY EVALUATION**

(according to the Endocrine Society Guidelines, 2009)

- saline infusion, oral sodium loading, fludrocortisone suppression, or captopril test

Adrenal venous sampling may also be required to localize aldosterone production

Terzolo M et al. AME Position Statement on Adrenal Incidentaloma EJE 2012
Arnaldi G et al. Best Pact Clin Endocrinol 2012
AACE/AAES Adrenal Incidentaloma Guidelines 2009
Cawood J et al. EJE 2009
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Screening of hypercortisolism

Subclinical Cushing Syndrome

Prevalence: 5% -48%
[depending on work-up protocol, diagnostic criteria and screening methods used on different studies]

Autonomous cortisol secretion in patients who do not have the typical signs and symptoms of hypercortisolism

some patients may have

previously undiagnosed mild hypercortisolism

comorbidities
[hypertension, obesity, diabetes mellitus, osteoporosis]
potentially associated with cortisol hypersecretion

EFE 2012
**Definition**
Presence of at least two abnormal tests of HPA axis in patients with adrenal incidentalomas without classic clinical stigmata of cortisol excess

**Tests abnormalities observed in patients with SCS:**
- Lack of cortisol suppression after low-dose dexamethasone suppression test
- Elevated 24 h urinary-free cortisol (UFC)*
- Low morning ACTH levels
- Elevated midnight serum cortisol
- Elevated midnight salivary cortisol (MSC)
- Low DHEAS concentration
- ACTH/cortisol abnormal response to CRH test

*UFC may be normal in mild Cushing syndrome

*Terzolo M et al. AME Position Statement on Adrenal Incidentaloma EJE 2012
Arnaldi G et al. Best Pract Clin Endocrinol Metab 2012*
Subclinical Cushing’s Syndrome (SCS)

The low-dose (1 mg) dexamethasone (DXT) suppression test is the recommended initial test to diagnose Subclinical Cushing’s Syndrome with 73-100% sensitivity and 90% specificity.

- 1.8 mcg/dl (Endocrine Society Guidelines, 2008; French Society of Endocrinology, 2008)
- 3 mcg/dl (Bondanelli et al. 1997; Morelli V et al. 2010; Chiodini et al. 2011)
- 5 mcg/dl (NIH Conference, 2002; AACE/AAES Guidelines, 2009)

References:

- NIH Conference 2002
- Endocrine Society Guidelines 2008
- AACE/AAES Guidelines 2009
- Cawood J et al. EJE 2009
- AME Position Statement 2012
- Arnaldi G et al. Best Pract Clin Endocrinol Metab 2012
## Subclinical Cushing’s Syndrome (SCS)

**Low-dose (1 mg) dexamethasone (DXT) suppression test**

### Cortisol levels after 1 mg DXT

<table>
<thead>
<tr>
<th>&lt; 1.8 mcg/dl</th>
<th>&gt; 1.8 &lt; 5 mcg/dl</th>
<th>&gt; 5 mcg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>exclude</td>
<td>indeterminate</td>
<td>likely indicate</td>
</tr>
<tr>
<td>autonomous</td>
<td>non-diagnostic</td>
<td>subclinical</td>
</tr>
<tr>
<td>cortisol secretion</td>
<td>values</td>
<td>hypercortisolism</td>
</tr>
<tr>
<td></td>
<td>Further testing</td>
<td>(if no interferring condition is present)</td>
</tr>
<tr>
<td></td>
<td>in patients with</td>
<td>Potential SCS</td>
</tr>
<tr>
<td></td>
<td>comorbidities</td>
<td>especially in presence</td>
</tr>
<tr>
<td></td>
<td>(features of Cushing’s Syndrome)</td>
<td>of obesity, hypertension,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>diabetes and osteoporosis.</td>
</tr>
</tbody>
</table>

- Retesting after 3-6 months

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**Further testing**
- Midnight salivary cortisol (MSC)
- ACTH and DHEAS as supportive criteria

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*Terzolo M et al. AME Position Statement EJE 2012*
*Arnaldi G et al. Best Pract Clin Endocrinol Metab 2012*
Clinical features in patients with SCS

Metabolic syndrome
- Central obesity
- Hyperinsulinemia/insulin resistance
- Diabetes mellitus type 2 or IGT
- Systolic and diastolic hypertension
- Dyslipidemia (hypertriglyceridemia, low HDL cholesterol)
- Accelerated atherosclerosis

Increased cardiovascular risk

Skeletal disease
- Osteopenia/osteoporosis

Increased risk of fractures
Impact of surgical intervention on cardiometabolic outcome

Removal of adrenal mass in patients with SCS

is associated with

SIGNIFICANT IMPROVEMENT in ALL (or some=BP) Features of Metabolic Syndrome

Erbil et al. 2006 (n 11, follow-up 1 yr)
Toniato et al. 2009 (n 23, mean follow-up 7.7 yr)
Mauclère-Denost et al. 2009 (n 8, mean follow-up 12 mo)
Guerrieri et al. 2010 (n 19, mean follow-up 4 yr)
Chiodini et al. 2010 (n 25, follow-up 18-48 mo)

No effect on cardiometabolic outcome

only a minority of operated patients had SCS

Sereg et al. 2009 [n 47 (5 SCS) mean follow-up: 9.1 yr (5-16)]
Impact of surgical intervention on cardiometabolic outcome

Conservative approach

Not operated patients with SCS

experienced

worsening of

• blood pressure
• body weight
• glucose and cholesterol levels

Guerrieri et al. 2010
Chiodini et al. 2010
Proposed management of Subclinical Cushing’s Syndrome

The NIH state-of-the-science statement (2002)
- either adrenalectomy or careful observation is a treatment option for patients with SCS

Adrenalectomy has been demonstrated to correct the biochemical abnormalities, but its effect on long-term outcome and quality of life is unknown.

The AACE/AAES Medical Guidelines (2009)
- [until further evidence is available regarding the long-term benefits of adrenalectomy ]
  surgical resection should be reserved for SCS patients with worsening of hypertension, abnormal glucose tolerance, dyslipidemia, or osteoporosis

(recommendation with a low level of evidence)

The AME position statement (2011)
- it seems reasonable to elect for surgery younger patients with SCS who display diseases potentially attributable to excessive cortisol
  (hypertension, diabetes, abdominal obesity, and osteoporosis)
  that are of recent onset, or are resistant to optimal medical treatment or are rapidly worsening
A growing body of evidence supports the notion that also nonfunctioning adrenal incidentalomas (NFAI) are associated with features of metabolic syndrome.

### Clinical features in patients with NFAI

<table>
<thead>
<tr>
<th>Authors (year of publication)</th>
<th>Number of patients examined</th>
<th>Type of AI based on endocrine activity</th>
<th>Cardiometabolic abnormalities associated with AIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ivović et al. (2006)</td>
<td>n = 22</td>
<td>NFAIs</td>
<td>Impaired insulin sensitivity</td>
</tr>
<tr>
<td>Zhang et al. (2006)</td>
<td>n = 24</td>
<td>NFAIs</td>
<td>Abdominal obesity, hypertension, dyslipidaemia, hyperglycaemia</td>
</tr>
<tr>
<td>Comlekci et al. (2009)</td>
<td>n = 376 (predominantly)</td>
<td>NFAIs</td>
<td>Type 2 diabetes, hypertension, hyperlipidaemia</td>
</tr>
<tr>
<td>Yilmaz et al. (2009)</td>
<td>n = 32</td>
<td>NFAIs</td>
<td>Obesity, hypertension, impaired glucose tolerance</td>
</tr>
<tr>
<td>Wagnerova et al. (2009)</td>
<td>n = 92 (predominantly)</td>
<td>NFAIs</td>
<td>Obesity, hypertension, diabetes</td>
</tr>
<tr>
<td>Yener et al. (2009)</td>
<td>n = 49</td>
<td>NFAIs</td>
<td>Increased carotid intima–media thickness</td>
</tr>
<tr>
<td>Yener et al. (2009)</td>
<td>n = 45</td>
<td>NFAIs</td>
<td>Increased D-dimer levels</td>
</tr>
<tr>
<td>Peppa et al. (2010)</td>
<td>n = 29</td>
<td>NFAIs</td>
<td>Impaired fasting and postabsorptive glucose, obesity, hypertension, dyslipidaemia, fatty liver disease, abnormal fat distribution</td>
</tr>
</tbody>
</table>
Impact of surgical intervention on cardiometabolic outcome

Removal of adrenal mass in patients with NFAI is associated with:

**IMPROVEMENT**

of

Metabolic Syndrome Features

or

**NO EFFECT**
on
- Metabolic Syndrome Features
- Cardiovascular Morbidity and Mortality

Rossi et al. 2000 (n 13, median follow-up 30 mo)
Midorikawa et al. 2001 (n 8, follow-up 48 mo)
Bernini et al. 2003 (n 9, follow-up 12 mo)

Sereg et al 2009 (n 7, mean follow up 9 yr)
Giordano et al 2010 (n 102, median follow-up 3 yr, range 1-10)
About 15% of lesions classified as non-functioning demonstrate a single abnormal test of the HPA axis.

Subtle adrenal hormone excess and increased proinflammatory state might explain the development of metabolic syndrome disturbances.
ADRENAL INCIDENTALOMA: CLINICAL AND METABOLIC ASPECTS DURING LONG-TERM FOLLOW-UP

Patients and Methods

78 patients (48 F; aged 35-79 yr) with adrenal incidentaloma
- unilateral mass (37 right, 28 left) in 65 cases
- mass diameter: 27±9.1 mm (range 9-52)

52 assigned to follow-up
- 13 with subclinical Cushing’s syndrome (SCS)
- 39 with normal adrenal function, all with mass diameter < 4 cm and radiological characteristic of benign mass

26 assigned to surgery
- 13 with subclinical Cushing’s syndrome (SCS)
- 13 with normal adrenal function, but mass diameter >4 cm and/or radiological characteristic suspected for malignancy

Exclusion criteria:
- Clinical Cushing’s Syndrome
- Pheochromocytoma
- Primary hyperaldosteronism
- Extra-adrenal malignancy

24 adrenal adenomas
- 1 adrenal pseudocystis
- 1 adrenal mielolypoma

All patients were followed-up for 48-168 months (mean 84±35; median 74) after baseline evaluation and laparoscopic adrenalectomy in 26 cases

Bondanelli et al. JEI 2010 (abstract)
### Clinical and hormonal data at baseline in SCS patients compared with normal adrenal function

<table>
<thead>
<tr>
<th></th>
<th>Subclinical Cushing’s Syndrome</th>
<th>Normal adrenal function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>7M 19F</td>
<td>23M 29F</td>
</tr>
<tr>
<td><strong>Age yr</strong></td>
<td>59.7±9.23</td>
<td>62.8±7.76</td>
</tr>
<tr>
<td><strong>Hypertension</strong></td>
<td>21/26 (81%)</td>
<td>30/52 (55.7%)</td>
</tr>
<tr>
<td><strong>SBP mmHg</strong></td>
<td>144.29±18.3 *</td>
<td>135.24±16.15</td>
</tr>
<tr>
<td><strong>DBP mmHg</strong></td>
<td>86.2±9.86</td>
<td>82.02±8.84</td>
</tr>
<tr>
<td><strong>Well-controlled Hypertension</strong></td>
<td>6/21 (28.6%) **</td>
<td>20/30 (66.6%)</td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>6/26 (23%)</td>
<td>6/52 (11.5%)</td>
</tr>
<tr>
<td><strong>IGT/IFG</strong></td>
<td>11/26 (42.3%)</td>
<td>17/52 (32.7%)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>20/26 (76.9%)</td>
<td>29/52 (55.7%)</td>
</tr>
<tr>
<td><strong>Cardio- or cerebrovascular events</strong></td>
<td>4/26 (15.4%)</td>
<td>7/52 (11.5%)</td>
</tr>
<tr>
<td><strong>BMI (kg/m²)</strong></td>
<td>30.92±6.65</td>
<td>28.8±4.93</td>
</tr>
<tr>
<td><strong>ACTH (pg/ml)</strong></td>
<td>6.96±8.83 **</td>
<td>17.03±10.32</td>
</tr>
<tr>
<td><strong>Morning cortisol (mcg/dl)</strong></td>
<td>18.39±6.07</td>
<td>17.24±6.19</td>
</tr>
<tr>
<td><strong>Midnight cortisol (mcg/dl)</strong></td>
<td>7.03±2.14</td>
<td>5.36±2.92</td>
</tr>
<tr>
<td><strong>Cortisol after DXT 1 mg</strong></td>
<td>5.85±4.55 ***</td>
<td>1.64±0.86</td>
</tr>
<tr>
<td><strong>UFC (mc/24 h)</strong></td>
<td>154.32±103.6 *</td>
<td>106.72±41.2</td>
</tr>
<tr>
<td><strong>DHEAS (mc/dl)</strong></td>
<td>51.73±33.24</td>
<td>68.86±36.62</td>
</tr>
<tr>
<td><strong>Total Cholesterol (mg/dl)</strong></td>
<td>235.05±40.07**</td>
<td>208.95±33.77</td>
</tr>
<tr>
<td><strong>Triglycerides (mg/dl)</strong></td>
<td>142.57±81.04</td>
<td>132.1±79.43</td>
</tr>
<tr>
<td><strong>Glycemia (mg/dl)</strong></td>
<td>142.57±81.04 **</td>
<td>100.67±46.85</td>
</tr>
<tr>
<td><strong>Mass size (mm)</strong></td>
<td>28.3±7.8</td>
<td>26.7±6.9</td>
</tr>
</tbody>
</table>

No significant differences for prevalence of metabolic complications between the two groups.

Patients with SCS had higher total cholesterol, glucose, blood pressure, and body weight.

*<p<0.05, **<p<0.01, ***<p<0.001 vs. normal adrenal function

Bondanelli et al. JEI 2010 (abstract)
Clinical characteristics of Subclinical Cushing's Syndrome (SCS) patients who underwent surgery compared with not-operated SCS patients, at baseline and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Operated</th>
<th>Not-operated</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (pg/ml)</td>
<td>5.9±7.2</td>
<td>26.15±9.9 +</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Morning Cortisol (µg/dl)</td>
<td>17.68±3.9</td>
<td>15.77±3.6</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Cortisol after DXT (µg/dl)</td>
<td>7.84±5.4</td>
<td>1.02±0.3 +</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>UFC (µg/24h)</td>
<td>220.17±110.1</td>
<td>119.01±45.1 +</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

Normalization of cortisol secretion in operated patients was associated with significant improvement in blood pressure levels.

Well-controlled hypertension

Operated vs. Not-operated

P<0.05 vs. respective basal

ADRENAL INCIDENTALOMA: CLINICAL AND METABOLIC ASPECTS DURING LONG-TERM FOLLOW-UP
Clinical characteristics of **Subclinical Cushing Syndrome (SCS)** patients who underwent surgery compared with not-operated SCS patients, at baseline and at follow-up.

- **Fasting glycemia**
  - Normalization of cortisol secretion in operated patients was associated with significant reduction in cholesterol and glucose levels.
  - Not-operated SCS patients showed an increase in body weight.

*EFE 2010*  
Bondanelli et al. JEI 2010 (abstract)
Clinical and hormonal characteristics of patients with normal adrenal function at baseline and at follow-up.

During follow-up:
- Operated patients showed an improvement in blood pressure levels associated with an increase in ACTH levels.
- Not-operated patients showed an increase in body weight, associated with an increase in UFC and persistently low ACTH levels.

EFE 2010

Bondanelli et al. JEI 2010 (abstract)
Changes in adrenal function in 52 not-operated patients during 48-148 months follow-up

- Only one patient (1.9%) with normal adrenal function developed Subclinical Cushing’s Syndrome (SCS)
- No patients with SCS developed Clinical Cushing’s Syndrome (CSC)

No significant increase in average mass diameter:
- Significant increase (≥1 cm) in 3 cases (5.7%) with no signs of malignancy
- Slight increase (<1 cm) in 11 cases (21%)
- Decrease in 4 cases (7.7%)

Bondanelli et al. JEI 2010 (abstract)
The risk of progression from subclinical (SCS) to overt Cushing’s syndrome or non-functioning adenoma (NFA) to SCS is MINIMAL (<1%).

Kaltsas G et al. Trends Endocrinol Metab 2012

Terzolo M et al. Clin Endocrinol 2012
De Leo M et al. Best Pract Clin Endocrinol 2012
Estimated cumulative risk of developing metabolic-cardiovascular disease overtime in patients with adrenal incidentalomas (n=118)

102 NFAI - 16 SCS

The cumulative risk of developing metabolic-cardiovascular abnormalities was globally low (22%), but progressive up to 8 years

New diseases were recorded only in the group of NFAI
(3 dyslipidemia, 4 impaired fasting glucose/impaired glucose tolerance, 3 diabetes mellitus)

None of NF patients developed subclinical or overt endocrine disease
None of SCS patients shifted to overt Cushing’s syndrome

Natural history of AI

Follow-up of adrenal incidentaloma thought to be benign and non-functioning after the initial diagnostic work-up

11 studies (>20 pts/study) including 1410 patients, with mean follow-up of 3.2 yr (range 1-7, median 2.1)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean</th>
<th>Range</th>
<th>Median</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased in size (%)</td>
<td>14.7</td>
<td>0-41.5</td>
<td>14.1</td>
</tr>
<tr>
<td>Decreased in size (%)</td>
<td>7.0</td>
<td>0-44</td>
<td>0</td>
</tr>
<tr>
<td>Became malignant (%)</td>
<td>0.2</td>
<td>0-1.6</td>
<td>0</td>
</tr>
<tr>
<td>Developed ACC (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Developed metastases (%)</td>
<td>0.1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Became functional (%)</td>
<td>0.9</td>
<td>0-8</td>
<td>0</td>
</tr>
<tr>
<td>Developed overt CS (%)</td>
<td>0.3</td>
<td>0-2.7</td>
<td>0</td>
</tr>
<tr>
<td>Developed SCS (%)</td>
<td>0.3</td>
<td>0-4</td>
<td>0</td>
</tr>
<tr>
<td>Developed pheochromocytoma (%)</td>
<td>0.2</td>
<td>0-1.3</td>
<td>0</td>
</tr>
<tr>
<td>Developed aldosteronoma (%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Adapted from Cawood TJ et al Eur J Endocrinol 2009
Estimated cumulative **risk of adrenal mass enlargement** over time in patients with adrenal incidentalomas (n=118)

The cumulative risk of mass enlargement was globally low (25%) but progressive up to 8 years independently of mass size and side at entry

The majority of apparently benign adrenal incidentalomas with no hyperfunction at diagnosis remain functionally and morphologically unchanged over time. The risk of developing malignancy is minimal. The risk of developing pheochromocytoma is minimal. SCS can occasionally occur over time in patients with normal adrenal function at diagnosis. SCS is associated with metabolic abnormalities which ameliorate after normalization of cortisol secretion. Subtle cortisol autonomy of adrenal adenoma may also have a role in the development of metabolic complications of patients with “non-functioning” adenomas.

Long term follow-up is needed for all patients with adrenal incidentalomas.
### Summary of management strategy for patients with adrenal incidentaloma

<table>
<thead>
<tr>
<th>Experts opinion</th>
<th>Endocrine tests</th>
<th>Tests and frequency</th>
<th>Duration</th>
<th>Imaging</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>NIH Consensus statement 2002⁴</td>
<td>1 mg DST, plasma free metanephrines, K and PRA/aldo in hypertensive patients</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor mass &lt;4 cm. In addition to size use additional criteria in 4–6 cm mass</td>
<td>Two CTs, at least 6 months apart, no data to support continued imaging if size remain stable</td>
</tr>
<tr>
<td>Young, 2007¹³</td>
<td>1 mg DST, urinary metanephrines and catecholamines, K and PRA/aldo in hypertensive patients</td>
<td>Annual</td>
<td>4 years</td>
<td>Monitor mass &lt;4 cm</td>
<td>CT at 6, 12 and 24 months</td>
</tr>
<tr>
<td>French Society of Endocrinology Consensus, 2008⁶²</td>
<td>1 mg DST, glycemia, plasma and urinary metanephrines, K and PRA/aldo in hypertensive patients</td>
<td>1 mg DST, plasma and urinary metanephrine at 6 months then 1 mg DST at 2 and 5 years</td>
<td>5 years</td>
<td>Monitor mass &lt;4 cm</td>
<td>CT at 6 months and then at 2 and 5 years</td>
</tr>
<tr>
<td>AACE/AAES Medical Guidelines, 2009²³</td>
<td>1 mg DST, plasma and urinary metanephrines/catecholamines and PRA/aldo in hypertensive patients</td>
<td>Annual</td>
<td>5 years</td>
<td>Monitor mass &lt;4 cm</td>
<td>Imaging reevaluation at 3–6 months and then annually for 1–2 years. Imaging reevaluation at 1–2 years (or more) and for intermediate mass at 3–12 months. CT or MRI at 3–6 months. No further imaging if mass is &lt;2 cm with clear benign features. If mass &gt;2 cm judge on individual basis.</td>
</tr>
<tr>
<td>Nieman, 2010²⁷</td>
<td>1 mg DST or late-night cortisol test, plasma and urinary metanephrines/catecholamines and PRA/aldo in hypertensive patients</td>
<td>Annual No repeat screening for aldosteronism if previously excluded</td>
<td>4 years if mass &lt;3 cm, nonfunctional and benign at imaging 1–2 years (or more)</td>
<td>Monitor mass &lt;4 cm, in addition to size use additional criteria</td>
<td></td>
</tr>
<tr>
<td>AME Position³</td>
<td>1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldo in hypertensive and/or hypokalemic patients</td>
<td>To be judged on individual basis after clinical monitoring</td>
<td>To be judged on individual basis after clinical monitoring</td>
<td>Monitor 2–4 cm mass; in addition to size use additional criteria</td>
<td></td>
</tr>
<tr>
<td>Arnaldi, 2012</td>
<td>1 mg DST, urinary metanephrines or plasma free metanephrines, PRA/aldo in hypertensive patients</td>
<td>Annual No repeat screening for aldosteronism if previously excluded</td>
<td>5 years</td>
<td>Monitor mass &lt;4 cm; in addition to size use additional criteria</td>
<td>CT or MRI at 6 months (before if suspect mass) then after 3 and 5 years</td>
</tr>
</tbody>
</table>

 Arnaldi G & Boscaro M. Best Pract Clin Endocrinol Metab 2012

EFE 2012
An abdominal CT scan is estimated to cause one cancer-related death for every

- 1000
- 2000

abdominal CT scans

Epidemiological evidence from human populations demonstrated that acute exposure to ionizing radiation at doses of 10-50 mSv (i.e. the organ dose range typically delivered by two or three CT scans) increases the risk of some cancers

Brenner DJ et al. 2003

Cawood J et al. EJE 2009
Management strategy for patients with adrenal incidentaloma

History and physical examination
Hormonal testing
  Overnight dexamethasone (1 mg) suppression test
  Measurement of fractionated metanephrines and catecholamines in a 24-hr urinary specimen
If hypertension and/or hypokaliemia, plasma aldosterone and plasma renin activity (or direct renin) measurement

Positive results
Confirmatory testing
Lack of autonomous secretion of cortisol, aldosterone, or catecholamines

Negative results
Imaging phenotype

Benign appearance ≤4 cm
Unenhanced CT attenuation ≤10 Hounsfield units
CT contrast-medium washout ≥50% at 10 min

Suspicious appearance >4 cm
Unenhanced CT attenuation >10 Hounsfield units
CT contrast-medium washout <50% at 10 min

Consider:
  Fine-needle aspiration biopsy if metastatic disease or infection suspected
  Surgery
  Close follow-up (e.g., repeating imaging at 3 mo)

Consider:
  Repeating imaging at 6 mo (before if suspected), at 1 - 2 yr, and at 5 yr *
  Hormonal testing annually for 5 yr *

Consider:
  Surgery

Mass ≥4
Growth ≥1 cm
Autonomous hormonal secretion

Consideration of hormonal testing

* To be judged on individual basis after clinical monitoring
Grazie per l'attenzione