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Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and subclinical Cushing's syndrome: A systematic review and meta-Analysis

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Table 1: Included studies

Author, year	Country	Study type	Data collection	Patients with SCS			Patients with NF adrenal tumors			Analysis arms
				N	Adrenalectomy	Conservative management	N	Adrenalectomy	Conservative management	
Reincke, 1992 ⁴⁵	Germany	cohort prospective	1977-1988	8	7 (1 patient was lost to follow up)	0	0	0	0	SCS adrenalectomy
Rossi, 2000 ⁴⁷	Italy	cohort prospective	1992-1998	12	5	7	38	13	25	SCS adrenalectomy SCS conservative NF adrenalectomy NF conservative
Morioka, 2000 ⁴²	Japan	cohort retrospective	1990-1998	7	7	0	0	0	0	SCS adrenalectomy
Midorikawa, 2001 ³⁹	Japan	cohort prospective	1996-1999	4	4	0	11	11	0	SCS adrenalectomy NF adrenalectomy
Bernini, 2003 ³¹	Italy	cohort prospective	NR	6	6	0	9	9	0	SCS adrenalectomy NF adrenalectomy
Erbil, 2006 ²²	Turkey	cohort retrospective	1995-2005	11	11	0	0	0	0	SCS adrenalectomy
Izaki, 2006 ³⁴	Japan	cohort retrospective	1995-2004	8*	0	0	45	45	0	NF adrenalectomy
Mitchell, 2007 ⁴⁰	USA	cohort retrospective	NR (40 months period)	9	9	0	0	0	0	SCS adrenalectomy
Feng, 2007 ³²	China	cohort retrospective	2001-2006	24	24	0	0	0	0	SCS adrenalectomy
Tsuiki, 2008 ⁴⁹	Japan	cohort retrospective	1995-2006	20	10	10	0	0	0	SCS adrenalectomy SCS conservative
Toniato, 2009 ²¹	Italy	randomized controlled trial	1991-2005	45	23	22	0	0	0	SCS adrenalectomy SCS conservative
Mauclere-Denost, 2009 ³⁸	France	cohort prospective	NR	8	8	0	0	0	0	SCS adrenalectomy
Sereg, 2009 ⁴⁸	Hungary	cohort retrospective	1990-2001	13*	5	8	112	42	70	NF adrenalectomy NF conservative
Alesina, 2010 ³⁰	Germany	cohort prospective	1994-2009	66	66	0	0	0	0	SCS adrenalectomy
Guerrieri, 2010 ³³	Italy	cohort retrospective	NR	47	19	28	0	0	0	SCS adrenalectomy SCS conservative
Giordano, 2010 ²³	Italy	cohort prospective	NR	16	6	10	0	0	0	SCS adrenalectomy SCS conservative
Chiodini, 2010 ¹⁹	Italy	cohort retrospective	2002-2007	41	25	16	67	30	37	SCS adrenalectomy SCS conservative NF adrenalectomy

										NF conservative
Miyazato, 2011 ⁴¹	Japan	cohort retrospective	1994-2008	55	55	0	0	0	0	SCS adrenalectomy
Akaza, 2011 ²⁹	Japan	cohort retrospective	2002-2008	16	8	8	0	0	0	SCS adrenalectomy SCS conservative
Maehana, 2012 ³⁷	Japan	cohort retrospective	1995-2008	13	12 (1 patient refused surgery and was not followed)	0	21	21	0	SCS adrenalectomy NF adrenalectomy
Iacobone, 2012 ²⁰	Italy	cohort prospective	2000-2009	35	20	15	0	0	0	SCS adrenalectomy SCS conservative
Perysinakis, 2013 ⁴⁴	Greece	cohort retrospective	1997-2011	29	29	0	0	0	0	SCS adrenalectomy
Ricciato, 2014 ⁴⁶	Italy	cohort retrospective	2004-2010	33	16	17	0	0	0	SCS adrenalectomy SCS conservative
Kawate, 2014 ³⁶	Japan	cohort retrospective with follow up survey	1995-2013	27	15	12	0	0	0	SCS adrenalectomy SCS conservative
Papierska, 2014 ⁴³	Poland	cohort prospective	2007-2010	25	24	1	0	0	0	SCS adrenalectomy
Kang, 2015 ³⁵	USA	cohort retrospective	2000-2010	15	15	0	35	35	0	SCS adrenalectomy NF adrenalectomy

***Patients with SCS were described as a part of NF adrenal tumor cohort**

Abbreviations: SCS, Subclinical Cushing Syndrome, NF, Non-functioning adrenal tumors, NR, not reported

Table 2: Definition of Subclinical Cushing Syndrome

Author, year	Criteria						Rule for SCS diagnosis
	1	2	3	4	5	6	
	Cushingoid features *	Overnight DST, cortisol cutoff (dexamethasone dose) ^{&}	8 mg overnight DST, cortisol cutoff ^{&}	UFC	ACTH	other	
Reincke, 1992 ⁴⁵	none	5 µg/dL (1 mg)	3.3 µg/dL			Adrenal insufficiency after surgery or normal overnight DST after surgery	1+2+3+6
Rossi, 2000 ⁴⁷	none	3 µg/dL (2 mg)		>2 SD above normal range	low	average daily cortisol	1+2+any (4,5,6)
Morioka, 2000 ⁴²	none	4 µg/dL (1 or 2 mg)	2 µg/dL	>160 µg/24 h	<4.4 pg/mL	Loss of circadian rhythm	1+ any 2 of (2-6)
Midorikawa, 2001 ³⁹	none	3 µg/dL (1 mg)	1 µg/dL			Adrenal insufficiency after surgery or normal overnight DST after surgery or one of: low DHEA-S, low ACTH, loss of circadian cortisol rhythm, unilateral uptake on scintigraphy	1+2+3+6
Bernini, 2003 ³¹	none	1.8 µg/dL (1 mg)		>120 µg/24h	<9 pg/mL	loss of circadian rhythm	1+2+any (4,5,6)
Erbil, 2006 ²²	none	3 µg/dL (2 mg)	3 µg/dL				1+2+3
Izaki, 2006 ³⁴							Not defined
Mitchell, 2007 ⁴⁰	at least 3	1 µg/dL (1 mg)		> twice normal range	<15 pg/mL	DHEAS ≤30 µg/dL or evidence of lateralization by adrenal sampling	1+2+any (4,5,6)
Feng, 2007 ³²							Not defined
Tsuiki, 2008 ⁴⁹	none	3 µg/dL (1 mg)	1 µg/dL			Normal basal cortisol AND one of: low DHEA-S, low ACTH, loss of circadian cortisol rhythm, unilateral uptake on scintigraphy	1+2+3+6
Toniato, 2009 ²¹	none	2.5 µg/dL (1 mg)		elevated	low	DHEAS -low	1+2+any (4,5,6)
Mauclere-Denost, 2009 ³⁸	none	2.2 µg/dL (1 mg)		normal	<15 pg/mL	loss of circadian cortisol rhythm	1+2+4 + any (5,6)

Sereg, 2009 ⁴⁸	none	3.6 µg/dL (2 mg)				Midnight serum cortisol >5 µg/dL	1+ any 1 of (2-6)
Alesina, 2010 ³⁰	none	3.5 µg/dL (1 mg)					1+2
Guerrieri, 2010 ³³							Not defined
Giordano, 2010 ²³	none	1.8 µg/dL (1 mg)		>100 µg/24h	<5 pg/mL	loss of circadian rhythm	1+2+any (4,5,6)
Chiodini, 2010 ¹⁹	none	3 µg/dL (1 mg)		>70 µg/24 h	<10 pg/mL		1+ any 2 of (2-6)
Miyazato, 2011 ⁴¹							Not defined
Akaza, 2011 ²⁹	none	3 µg/dL (1 mg)	1 µg/dL			Normal basal cortisol AND one of: low DHEAS, low ACTH, loss of circadian cortisol rhythm, unilateral uptake on scintigraphy	1+2+3+6
Maehana, 2012 ³⁷	none	3 µg/dL (1 mg)					1+2+6
Iacobone, 2012 ²⁰	none	5 µg/dL (1 mg)		>76 µg/24h	<10 pg/mL		1+ 2/4/5 (unclear how many criteria needed)
Perysinakis, 2013 ⁴⁴	none	1.8 µg/dL (2 mg)		>100 µg/24h	<10 pg/mL	loss of circadian rhythm	1+2+any (4,5,6)
Ricciato, 2014 ⁴⁶	none	1.8 µg/dL (1 mg)		>137 µg/24 h	<10 pg/mL	Midnight serum cortisol >50 µg/mL	1+ any 2 of (2-6)
Kawate, 2014 ³⁶	none	1.8 µg/dL (1 mg)			<10 pg/mL	9 to 11 pm serum cortisol >5 µg/dL	1+2+5+6
Papierska, 2014 ⁴³	none	3 µg/dL (dose not reported)			<10 pg/mL		1+2+5
Kang, 2015 ³⁵	none	Dose and cutoff not defined					1+2

* Easy bruising, dorsocervical or supraclavicular fat pads, weight gain, proximal muscle weakness, thin skin

& For conversion of µg/dL to nmol/L multiply by 27.59

Abbreviations used: ACTH, corticotropin; DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; UFC, urinary free cortisol.

Table 3: Definition and assessment of measured outcomes:

Author, year	Time of assessment	Hypertension		Overweight/obesity		Pre-diabetes / diabetes mellitus		Dyslipidemia	
		Definition of disease	Definition of improvement	Definition of disease	Definition of improvement	Definition of disease	Definition of improvement	Definition of disease	Definition of improvement
Reincke, 1992 ⁴⁵	Unclear, mean follow up 28 (18-60) months	Not defined	Decrease in the dose, number or discontinuation of medications	Not defined	Weight loss of more than 5 kg	Not defined	Improvement resulting in switch to diet therapy only	Not reported	Not reported
Rossi, 2000 ⁴⁷	Unclear, mean follow up of 38 (12-63) months	Mild/moderate/severe ⁴⁶	Decrease in the dose, number or discontinuation of medications	BMI \geq 25 kg/m ²	Not reported	DM: Fasting glucose > 126 mg/dL or glucose intolerance ⁴⁷	Reduction of oral medications or insulin	Total cholesterol > 240 mg/dL; LDL > 160 mg/dL; and/or triglycerides > 160 mg/dL	Not reported
Morioka, 2000 ⁴²	Not reported	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined
Midorikawa, 2001 ³⁹	1 month	Not defined	Individual SBP and DBP measurements	Not defined	Not defined	OGTT: Diabetes = 0 glucose > 7.7 mmol/l +/- 120 minute glucose > 15.4mmol; Normal 0 glucose < 6.05 60 < 8.8 and 120 minute < 6.6 mmol.	Not defined	Not reported	Not reported
Bernini, 2003 ³¹	12 months	SBP \geq 140 mmHg \pm DBP \geq 90 mmHg or on medications	Normalization and “improvement” in BP Individual patient data for SBP and DBP	Overweight BMI 25-29.9, obese > 30 kg/m ²	Not defined	Per AACE guidelines ⁴⁸	Normalization and “improvement” of IFG/DM, not otherwise defined	Not reported	Not reported
Erbil, 2006 ²²	12 months	SBP \geq 130 mmHg \pm DBP \geq 85 mmHg or on medications	Cessation of medications	BMI > 30 kg/m ²	“improvement” not defined pre/post means for Fasting glucose	IFG: Fasting glucose > 110mg/dL, DM: >126 or medications	Cessation of medications or insulin	Total cholesterol >200 mg/dL, LDL>130 mg/dL, trigs > 150 mg/dL; HDL<40 mg/dL males, <50	Cessation of statins Pre/post mean values for tg, t chol, hdl, ldl

								mg/dL females	
Izaki, 2006 ³⁴	Not reported	SBP \geq 140 mmHg \pm DBP \geq 90 mm Hg	Decrease in the dose, number or discontinuation of medications	Not reported		Not reported		Not reported	
Mitchell, 2007 ⁴⁰	Not reported	On medications	Decrease in mean arterial BP leading to decrease of the dose, number or discontinuation of medications.	Not defined	Median decrease in BMI before/after surgery	Not defined	Normalization or improvement was decided based on withdrawal or reduction of medication dose	Not reported	Not reported
Feng, 2007 ³²	3-60 months	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined	Not defined
Tsuiki, 2008 ⁴⁹	7-19 months	SBP \geq 140 mmHg \pm DBP \geq 90 mmHg or on medications	Decrease in BP <140/90 mm Hg leading to decrease of the dose, number or discontinuation of medications.	BMI \geq 25 kg/m ²	weight decrease by \geq 3 kg	DM: Fasting glucose > 126 mg/dL IFG: Fasting glucose > 110mg/dL Or on medications	Normoglycemia (glucose <110 mg/dL) on OGTT, HbA1c decreased by >0.3% or discontinuation /decrease of medications	Total cholesterol >220 mg/dL, or on medications	total cholesterol decrease to <220 or decrease/disc ontinuation of medication dose /number
Toniato, 2009 ²¹	Unclear, mean follow up 7.7 (2-17) years	SBP \geq 150 mmHg \pm DBP \geq 90 mmHg or on medications	Decrease in mean arterial BP leading to decrease of the dose, number or discontinuation of medications.	BMI 25 -30 overweight, >30 obese.	BMI drop to <30	DM: Fasting glucose > 126 mg/dL IFG: Fasting glucose > 110mg/dL Or on medications	Normalization or improved based on withdrawal or reduction of medication dose (oral or insulin)	TG >150 mg/dL, HDL <40 mg/dL male, <50 mg/dL female	Normalization resulting in withdrawal of statin therapy
Mauclere-Denost, 2009 ³⁸	12 months	Not defined	Cessation of at least one medication Individual patient SBP and DMP pre/post measurements Individual patient and mean SBP and DBP pre/post surgery	Not defined	Mean BMI pre/post surgery	Not defined	Discontinuation of anti-diabetic treatment Means and individual patient pre/post fasting plasma glucose and HbA1c	Not defined	Not reported
Sereg, 2009 ⁴⁸	9.1 +/-3.1 years	SBP \geq 140 mmHg \pm DBP \geq 90 mm Hg or on	Prevalence of disease before and after based on definitions			Previous dx diabetes, on diabetes medication or:	Prevalence of disease before and after based on definitions	If on lipid-lowering medication / total cholesterol	Prevalence of disease before and after based on

		medications	provided			DM if 0 glucose on OGTT > 7.0 mmol or 120 minute > 11.1 mmol; IGT if 120 minute glucose 7.8-11.0 mmol	provided	> 5.2mmol / LDL > 2.6 mmol / TG > 1.7 mmol	definitions provided
Alesina, 2010 ³⁰	At least 6 months (6-171 mo)	Not defined	Amelioration or normalization of HTN, not defined	Not defined	Mean BMI before and after surgery, n "improved"	Not defined	Not defined	Not defined	Not reported
Guerrieri, 2010 ³³	Not reported	SBP≥150 mmHg ± DBP≥ 90 mm Hg	Before and after SBP and DBP means/SD, P values and magnitude of change reported	27-30kg/m ² defined as overweight, > 30kg/m ² obese	Before and after mean BMI/SDs P values and magnitude of change reported	DM: Fasting glucose > 126 mg/dL IFG: Fasting glucose > 110mg/dL	P values and magnitude of change reported to fasting plasma glucose	TG ≥ 150, HDL <40 male, <50 female	P values and magnitude of change reported for HDL
Giordano, 2010 ²³	Not reported	SBP≥125 mmHg ± DBP≥ 80 mmHg	Not defined	overweight / obesity > 25 kg/m ²	Not defined	DM: Fasting glucose > 126 mg/dL IGT: 2 hours post OGTT glucose 140-200 mg/dL	Not defined	Triglyceride > 150 mg/dL; Total cholesterol > 240 mg/dL	Not defined
Chiodini, 2010 ¹⁹	18 months	SBP≥135 mmHg ± DBP≥ 85 mmHg or on medications	Change of HTN grade (European Society Cardiology ⁴⁹ Mean SBP and DBP before and after	BMI > 30 kg/m ²	Improvement = greater than 5% decrease in body weight Body weight before and after mean	type 2 DM by WHO criteria or if on diabetic medication	Fasting plasma glucose considered changed if move from one category to another according to Adult Treatment Panel III criteria ⁵⁰ Fasting plasma glucose mean before and after	TG ≥ 150 mg/dL, HDL <40 mg/dL male, <50 mg/dL female, or on medication.	move from one category to another based on Adult Treatment Panel III criteria LDL means before and after
Miyazato, 2011 ⁴¹	Not reported	SBP≥150 mmHg ± DBP≥ 90 mm Hg	Not defined	BMI ≥25 kg/m ²	Number of overweight patients pre/post as %	DM: Fasting glucose > 126 mg/dL IFG: Fasting glucose >	Normalization or "improvement" not defined Mean Hb A1c pre/post	Hyperlipidemia if TG ≥ 172 mg/dL or Total cholesterol. >220 mg/dL or	Not defined.

						110mg/dL Or on medications Or HbA1c>6.1%		if on statin.	
Akaza, 2011 ²⁹	Unclear, mean follow up 28±7 months for surgical and 40±19 months for nonsurgical groups	SBP≥140 mmHg ± DBP≥ 90 mmHg or on medications	Decrease in BP <140/90 mm Hg leading to decrease of the dose, number or discontinuation of medications.	BMI ≥25 kg/m ²	weight decrease by ≥ 3 kg	DM: Fasting glucose > 126 mg/dL or 2h glucose after 75 g oral glucose >200 mg/dL or HbA1C>6.1% or on medications IFG: Fasting glucose > 110mg/dL, 2h glucose after 75 g oral glucose 140-199 mg/dL	Normoglycemia (glucose <110 mg/dL) on OGTT, HbA1c decreased by >0.3% or discontinuation /decrease of medications	LDL>140 mg/dL, trigs > 150 mg/dL; HDL<40 mg/dL or medications	LDL<140 mg/dL, trigs < 150 mg/dL; HDL>40 or discontinuation/ decrease of medications
Maehana, 2012 ³⁷	Not reported	Not defined	Decrease in the dose, number or discontinuation of medications	Not defined		Not defined	Cessation or reduction of insulin dose	Not defined	Not defined
Iacobone, 2012 ²⁰	At least 6 months	SBP≥140 mmHg ± DBP≥ 90 mm Hg or on medications	Decrease in the category of BP or decrease of the dose, number or discontinuation of medications	Overweight defined as BMI 25-29.9 and obesity as BMI ≥30.	Change in BMI and moving between categories of normal, overweight and obese.	DM: Fasting glucose > 126 mg/dL IFG: Fasting glucose > 110mg/dL	Improvement or worsening defined as either decrease or increase HbA1c by at least 1% and/or achievement/loss of usually recommended targets, or if meds decreased/stopped or increased.	Defined as TG ≥ 150 mg/dL HDL <40 mg/dL male, <50 mg/dL female, or on medication.	Not defined
Perysinakis, 2013 ⁴⁴	6 and 12 months	SBP≥135 mmHg ± DBP≥ 85 mmHg or on medications	Decrease in mean arterial BP leading to decrease of the dose, number or discontinuation of medications.	BMI > 30 kg/m ²	Reduction in BMI (not defined)	Fasting glucose > 126 mg/dL or on medications	Development of euglycemia	Not defined	Not reported

Ricciato, 2014 ⁴⁶	30.9 +/- 16 mo	SBP≥135 mmHg ± DBP≥ 85 mmHg	Before and after BP measurements, reduction or discontinuation of BP meds	BMI ≥30,	Before and after mean BMIs	IFG: Fasting glucose > 110mg/dL	Change in glucose level	TG >150 mg/dL = hyperTG, HDL <40 mg/dL male <50 mg/dL female = low HDL	Before and after mean HDL and TG
Kawate, 2014 ³⁶	5.3 years	SBP≥140 mmHg ± DBP≥ 90 mm Hg or on medications	Decrease in BP <140/90 mm Hg or decrease of the dose, number or discontinuation of medications.	BMI ≥25 kg/m ²	Not defined	DM: Fasting glucose > 126 mg/dL or random glucose >200 mg/dL or HbA1C>6.5% or on medications IFG: Fasting glucose > 110mg/dL or random glucose 140-199 mg/dL	Normalization or amelioration of laboratory data, or decrease in the dose, number or discontinuation of medications	Hyperlipidemia if TG ≥ 150 mg/dL or total cholesterol ≥220 mg/dL or LDL cholesterol ≥140 mg/dL or HDL cholesterol <40 mg/dL or if on medication.	Normalization or amelioration of laboratory data, or decrease in the dose, number or discontinuation of medications
Papierska, 2014 ⁴³	At least 6 months	Not defined		Not defined		Not defined		Not defined	
Kang, 2015 ³⁵	Average follow up 34.5 months	Not defined	Decrease in the dose, number or discontinuation of medications or improved control on the same medications	Not reported		Not defined	Decrease in the dose, number or discontinuation of medications or improved control on the same medications	Not defined	Decrease in the dose, number or discontinuation of medications or improved control on the same medications

Abbreviations used: BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; HbA1C, glycosylated hemoglobin; HDL, high density lipoprotein; IFG, impaired fasting glucose; LDL, low density lipoprotein; OGTT, oral glucose tolerance test; SBP, systolic blood pressure; TG, triglycerides;

Table 4 Effect of adrenalectomy on outcomes in patients with subclinical Cushing syndrome

Outcome	Number of studies	% improved	CI 95% lower limit	CI 95% upper limit	I², %
<i>Hypertension (n=265)</i>	21	60.5%	50%	71%	72%
<i>Diabetes mellitus type 2 (n=120)</i>	20	51.5%	39%	64%	59%
<i>Dyslipidemia (n=102)</i>	13	24%	13%	35.5%	58%
<i>Obesity (n=128)</i>	16	45%	32%	57%	64%
Outcome	Number of studies	Difference in means	CI 95% lower limit	CI 95% upper limit	I², %
<i>Systolic blood pressure (mm Hg)</i>	8	-12.72	-18.33	-7.1	61%
<i>Diastolic blood pressure (mm Hg)</i>	7	-9.34	-14.83	-3.85	76%
<i>BMI (kg/m²)</i>	7	-1.96	-3.32	-0.59	68%
<i>Fasting glucose (mmol/L)</i>	4	-7.99	-13.9	-2.09	27%
<i>HbA1C (SMD)*</i>	3	-0.96	-1.43	-0.49	53%
<i>LDL cholesterol (mg/dL)</i>	2	-0.12	-37.7	37.5	53%
<i>HDL cholesterol (mg/dL)</i>	3	2.9	-3.4	9.2	53%
<i>Triglycerides (mg/dL)</i>	3	-23	-36.7	-9.2	0%

Abbreviations used: BMI, body mass index; HbA1C, glycosylated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SMD, standardized mean difference, I², Study heterogeneity

