THERAPY OF ENDOCRINE DISEASE

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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Abstract

Objective: Beneficial effects of adrenalectomy on cardiovascular risk factors in patients with subclinical Cushing's syndrome (SCS) are uncertain. We sought to conduct a systematic review and meta-analysis with the following objectives: (i) determine the effect of adrenalectomy compared with conservative management on cardiovascular risk factors in patients with SCS and (ii) compare the effect of adrenalectomy on cardiovascular risk factors in patients with SCS vs those with a nonfunctioning (NF) adrenal tumor.

Methods: MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE and Cochrane Central Register of Controlled Trial were searched on 17 November 2015. Reviewers extracted data and assessed methodological quality in duplicate.

Results: We included 26 studies reporting on 584 patients with SCS and 457 patients with NF adrenal tumors. Studies used different definitions of SCS. Patients with SCS undergoing adrenalectomy demonstrated an overall improvement in cardiovascular risk factors (61% for hypertension, 52% for diabetes mellitus, 45% for obesity and 24% for dyslipidemia). When compared with conservative management, patients with SCS undergoing adrenalectomy experienced improvement in hypertension (RR 11, 95% CI: 4.3–27.8) and diabetes mellitus (RR 3.9, 95% CI: 1.5–9.9), but not dyslipidemia (RR 2.6, 95% CI: 0.97–7.2) or obesity (RR 3.4, 95% CI: 0.95–12). Patients with NF adrenal tumors experienced improvement in hypertension (21/54 patients); however, insufficient data exist for comparison to patients with SCS.

Conclusions: Available low-to-moderate-quality evidence from heterogeneous studies suggests a beneficial effect of adrenalectomy on cardiovascular risk factors in patients with SCS overall and compared with conservative management.

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Introduction

Subclinical Cushing's syndrome (SCS) is a controversial disorder in name, definition and management (1, 2, 3, 4, 5, 6) but is currently diagnosed in at least a third of patients with incidentally discovered adrenal masses (7, 8) and therefore could affect up to 2% of the general population. SCS is most commonly described as the presence of inappropriate cortisol production as defined by insufficient suppressibility with dexamethasone and/or subsequent alterations of the hypothalamic pituitary adrenal (HPA) axis without classic, clinically overt signs and symptoms of cortisol excess, such as proximal myopathy, striae, adipose redistribution and cortisol-induced metabolic abnormalities (9, 10). Numerous definitions have been applied to characterize HPA axis alteration, and even when the same diagnostic cutoff criteria are used, interpretation of results is complicated by differences in assay methodology and individual patient factors such as comorbid depression and obesity (1).

Patients with an adrenal mass associated with SCS present with an increased prevalence of several cardiovascular risk factors such as hypertension (HTN), diabetes mellitus type 2 (DM2), dyslipidemia and obesity (11, 12, 13). Previous studies suggest that patients with SCS are at higher risk for developing cardiovascular events (14, 15, 16) and experience an increased cardiovascular mortality (17, 18). However, studies attempting to investigate the beneficial effect of adrenalectomy on cardiovascular risk factors in patients with SCS are characterized by small sample sizes and have generated inconsistent results. Although several authors reported various degrees of improvement in metabolic parameters (19, 20, 21), others showed no significant metabolic effect of adrenalectomy (22, 23) in patients with autonomous glucocorticoid production.

Moreover, several studies have reported a degree of improvement in cardiovascular risk factors after adrenalectomy in patients with so-called nonfunctioning (NF) adrenal tumors; whether this could be due to mild autonomous glucocorticoid production from an adrenal tumor without resultant detectable abnormality of the HPA axis or, possibly, an intrinsic effect of adrenalectomy *per se* is unknown (11, 19).

Insecurity of diagnosis and unclear surgical benefit to patients with SCS lead to delaying adrenalectomy until the associated comorbidities develop or progress. Conversely, certain patients undergo a potentially unnecessary surgery, as evidenced by the lack of

post-surgical adrenal insufficiency in at least a third of patients with SCS (24). Until the dilemma of SCS is solved, patients risk progression toward a potentially avoidable clinically significant event (and even premature death) and are exposed to multiple tests and therapies – all of which likely causing undesirable health and economic consequences.

In order to provide a meaningful understanding of existent data in regard to the beneficial effects of adrenalectomy on cardiovascular risk factors in patients with SCS, we sought to conduct a systematic review and meta-analysis with the following objectives: (i) determine the effect of adrenalectomy compared with conservative management on cardiovascular risk factors in patients with SCS and (ii) compare the effect of adrenalectomy on cardiovascular risk factors in patients with SCS vs those with a NF adrenal tumor.

Methods and evidence acquisition

This study was performed based on a protocol that was designed in advance. The results of this review are reported according to the PRISMA statement (preferred reporting items for systematic reviews and meta-analyses) (25). We included studies that evaluated adrenalectomy alone or in comparison with other interventions, for the treatment of SCS and/or NF adrenal tumors.

Inclusion and exclusion criteria

The inclusion criteria were specified in the predefined protocol to include original prospective and retrospective comparative and noncomparative studies that enrolled adults with either NF adrenal tumors or adrenal tumors with SCS (as defined by authors), with at least five patients undergoing adrenalectomy, and reported outcomes of interest before and after adrenalectomy. We included studies regardless of their publication status or language. We excluded all nonoriginal studies and case reports. Dichotomous outcomes of interest were as follows: HTN, pre-diabetes or diabetes mellitus, obesity and dyslipidemia. Continuous outcomes were as follows: systolic (SBP) and diastolic blood pressure (DBP), body mass index, weight, fasting glucose concentrations, glycosylated hemoglobin (HbA1c), total cholesterol, triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol.

Data sources and search strategy

A comprehensive search of several databases was conducted from each database's earliest inception to 17 November 2015, in any language and in adults. The databases included Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus. The search strategy ([Supplementary Table 1](#), see section on [supplementary data](#) given at the end of this article) was designed and conducted by an experienced librarian with input from the study's principal investigator. Controlled vocabulary supplemented with keywords was used to search for comparative studies of surgery in patients with adrenal tumors.

Selection of studies

Initial screening of the identified studies was performed by five independent reviewers (all endocrinologists with adrenal expertise). Titles and abstracts of the identified studies were screened in duplicate, taking into consideration the predefined inclusion criteria. Many of the identified studies retrieved by our search were nonrelevant or nonoriginal and were excluded at this phase. Full-text screening was then performed in duplicate to assess eligibility for final inclusion and discrepancies were resolved through discussion and consensus.

Data extraction

Reviewers extracted data independently from the included studies in duplicate, using a standardized, piloted, web-based form that was developed based on the protocol. Data extracted included demographics of participants, patient inclusion criteria, study design, intervention details and outcomes of interest. Any disagreements or differences in extracted data were resolved by consensus or referral to the full text of the study.

Methodological quality and risk of bias assessment

The quality of each study was assessed in duplicate. Observational studies were evaluated using the Newcastle–Ottawa tool, which included assessment of the following: (i) how the sample represented the population of interest, (ii) how the comparative group was selected, (iii) how the outcome was assessed and (iv) the length and adequacy

of follow-up when applicable. Randomized trials were evaluated independently by the authors using the Cochrane risk of bias assessment tool.

Statistical analysis

We conducted a meta-analysis using the random-effects model to pool estimates from the included studies. A random-effects model was used, rather than a fixed-effects model, in order to account for heterogeneity between-study and within-study variability. We used the I^2 statistic to estimate the percentage of total between-study variation due to heterogeneity rather than chance (ranging from 0 to 100%) (26). I^2 values of 25, 50 and 75% are considered to represent low, moderate and high heterogeneity respectively. Statistical analyses were conducted through OpenMeta[Analyst] (26, 27, 28). All values were two-tailed and $P < 0.05$ was set as the threshold for statistical significance.

To assess whether the benefit of adrenalectomy was influenced by the definition of SCS, a subgroup analysis was performed in three subgroups of patients stratified based on the dexamethasone suppression test (DST) cortisol cutoff (the most common variable used). Subgroup 1 included studies in which the DST cortisol cutoff was $\geq 3 \mu\text{g/dL}$, 83 nmol/L (13 studies, DST cortisol cutoff 3–5 $\mu\text{g/dL}$, 83–138 nmol/L); subgroup 2 included studies using a cortisol cutoff of $< 3 \mu\text{g/dL}$, 83 nmol/L (eight studies, DST cortisol cutoff 1–2.5 $\mu\text{g/dL}$, 28–69 nmol/L) and subgroup 3 comprised studies that either did not report a DST cortisol cutoff or did not provide how SCS was defined (five studies). We selected to perform a subgroup analysis only for outcomes reported for at least 25 patients in each subgroup (HTN and DM2).

Results

Characteristics of included studies

The search yielded 854 references for abstract screening of which 26 studies (19, 20, 21, 22, 23, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49) were included in this systematic review ([Fig. 1](#)). Eligible studies included 25 cohort studies (16 retrospective and nine prospective studies) and one randomized controlled trial. Studies were mostly from European ($n=15$) or Asian centers ($n=9$) and two were US-based ([Table 1](#)). A total of 584 patients with SCS (mean age 56 years, 66.8% women) and 457 patients with NF adrenal tumors (mean age 54.9 years, 61.5% women)

Figure 1

PRISMA flow diagram.

were included. Patients with SCS presented with high prevalence of cardiovascular risk factors (HTN (68%), DM2 (30%), dyslipidemia (25.6%) and obesity (34.6%)). In patients with NF adrenal tumors, prevalence of HTN was 48.4%, DM2 – 8.2%, dyslipidemia – 22.1% and obesity – 18.8%.

Authors reported on various outcome improvements in patients with SCS before and after adrenalectomy in 24 studies; however, only ten studies provided comparative data for patients with SCS managed conservatively (Table 1). In six studies, authors compared the effect

of adrenalectomy on outcomes in both SCS and NF adrenal tumor groups. In three studies, the effect of adrenalectomy on metabolic parameters in patients with NF was compared with conservative management.

As expected, studies used different definitions of SCS (Table 2). Definitions of selected clinical outcomes also varied, as did the definition of outcome ‘improvement’ (Supplementary Table 2). All patients had assessment at baseline and after either adrenalectomy or a period of conservative management. Most studies reassessed patients at least 6 months after the surgery ($n=17$,

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-month 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
Maulere-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 SCS conservative
Miyazato (2011) (41)	Japan	Cohort retrospective	1994–2008	55	55	0	0	0	0	NF adrenalectomy NF conservative
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

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Table 1 Continued.

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	
Iacobone (2012) (20)	Italy	Cohort prospective	2000–2009	35	20	15	0	0	0	SCS adrenalectomy SCS conservative
Perisinakis (2013) (44)	Greece	Cohort retrospective	1997–2011	29	29	0	0	0	0	SCS adrenalectomy SCS conservative
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 SCS conservative
Kang (2015) (35)	United States	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.
NF, nonfunctioning adrenal tumors; NR, not reported; SCS, subclinical Cushing's syndrome.

Supplementary Table 2) with a median follow-up of 28 (1–109) months (median or mean follow-up was reported only in 11 studies).

Metabolic outcome in patients with SCS comparing before and after adrenalectomy

Patients with SCS undergoing adrenalectomy demonstrated an overall improvement in cardiovascular risk factors (Table 3). Improvement in HTN was observed in 60.5% of patients with SCS; SBP decreased by a mean of 12.7 mmHg (95% CI: 7.1–18.3 mmHg) and DBP decreased by a mean of 9.3 mmHg (95% CI: 3.85–14.83 mmHg). Improvement in DM2 was observed in 51.5% of patients. Only three studies examined the effect of adrenalectomy on fasting blood glucose and four studies reported on HbA1c changes, with mild but significant decreases in both. Improvement in obesity was observed in 45% of patients; following adrenalectomy, BMI decreased by a mean of 1.96 kg/m² (95% CI: 0.59–3.32 kg/m²) after adrenalectomy. Adrenalectomy had the least effect on dyslipidemia (24% of patients improved). In three studies examining the effect of adrenalectomy on triglycerides, LDL cholesterol and HDL cholesterol, no significant changes following adrenalectomy were noted (Table 3).

Subgroup analysis based on DST cortisol cutoff criteria was performed only for the outcomes of HTN and DM2. Patients in subgroup 1 (136 with HTN and 61 with DM2), subgroup 2 (71 with HTN and 34 with DM2) and subgroup 3 (58 with HTN and 25 with DM2) experienced similar rates of HTN and DM2 improvement following adrenalectomy (Supplementary Figs 1 and 2). Subgroup analysis of obesity and other outcomes was not performed due to small numbers).

Metabolic outcome in patients with SCS comparing adrenalectomy vs conservative management

Our search identified ten studies that included both patients who underwent adrenalectomy (132 patients with SCS) and were conservatively managed (135 patients with SCS). When compared with conservative management, patients with SCS undergoing adrenalectomy experienced a statistically significant improvement in HTN (RR 11, 95% CI: 4.3–27.8) and DM2 (RR 3.9, 95% CI: 1.5–9.9), but not dyslipidemia (RR 2.6, 95% CI: 0.97–7.2) or obesity (RR 3.4, 95% CI: 0.95–12) (Fig. 2). Data on continuous outcomes derived only from four studies demonstrated a significant decrease in SBP and DBP as well as fasting glucose concentrations in patients with SCS undergoing

Table 2 Definition of subclinical Cushing's syndrome.

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		
Reinke (1992) (45)	5 µg/dL (1 mg)	3.3 µg/dL	>2 SD above normal range	Low	Adrenal insufficiency after surgery or normal overnight DST after surgery	1 + 2 + 3 + 6	
Rossi (2000) (47)	3 µg/dL (2 mg)				Average daily cortisol	1 + 2 + any (4, 5, 6)	
Morioka (2000) (42)	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)	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)	1.8 µg/dL (1 mg)		>120 µg/24 h	<9 pg/mL	Loss of circadian rhythm	1 + 2 + any (4, 5, 6)	
Erbil (2006) (22)	3 µg/dL (2 mg)	3 µg/dL				1 + 2 + 3	
Izaki (2006) (34)						Not defined	
Mitchell (2007) (40)	1 µg/dL (1 mg)		>twice normal range	<15 pg/mL	DHEA-S ≤ 30 µg/dL or evidence of lateralization by adrenal sampling	1 + 2 + any (4, 5, 6)	
Feng (2007) (32)						Not defined	
Tsuiki (2008) (49)	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)	2.5 µg/dL (1 mg)		Elevated	Low	DHEA-S – low	1 + 2 + any (4, 5, 6)	
Maudlere-Denost (2009) (38)	2.2 µg/dL (1 mg)		Normal	<15 pg/mL	Loss of circadian cortisol rhythm	1 + 2 + 4 + any (5, 6)	
Sereg (2009) (48)	3.6 µg/dL (2 mg)				Midnight serum cortisol >5 µg/dL	1 + any one of (2–6)	
Alesina (2010) (30)	3.5 µg/dL (1 mg)					1 + 2	
Guerrieri (2010) (33)						Not defined	
Giordano (2010) (23)	1.8 µg/dL (1 mg)		>100 µg/24 h	<5 pg/mL	Loss of circadian rhythm	1 + 2 + any (4, 5, 6)	
Chiodini (2010) (19)	3 µg/dL (1 mg)		>70 µg/24 h	<10 pg/mL		1 + any two of (2–6)	
Miyazato (2011) (41)						Not defined	
Akaza (2011) (29)	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	
Maehana (2012) (37)	3 µg/dL (1 mg)		>76 µg/24 h	<10 pg/mL		1 + 2 + 6	
Iacobone (2012) (20)	5 µg/dL (1 mg)					1 + 2/4/5 (unclear how many criteria needed)	
Persynakis (2013) (44)	1.8 µg/dL (2 mg)		>100 µg/24 h	<10 pg/mL	Loss of circadian rhythm	1 + 2 + any (4, 5, 6)	
Ricciato (2014) (46)	1.8 µg/dL (1 mg)		>137 µg/24 h	<10 pg/mL	Midnight serum cortisol >50 µg/mL	1 + any two of (2–6)	
Kawate (2014) (36)	1.8 µg/dL (1 mg)			<10 pg/mL	9–11 pm serum cortisol >5 µg/dL	1 + 2 + 5 + 6	
Papierska (2014) (43)	3 µg/dL (dose not reported)			<10 pg/mL		1 + 2 + 5	
Kang (2015) (35)	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. ACTH, corticotropin; DHEA-S, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; UFC, urinary-free cortisol.

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Table 3 Effect of adrenalectomy on outcomes in patients with subclinical Cushing's syndrome.

Outcome	Number of studies	% improved	Difference in means	CI 95% lower limit	CI 95% upper limit	<i>P</i> (%)
Hypertension (<i>n</i> =265)	21	60.5%		50%	71%	72
Diabetes mellitus type 2 (<i>n</i> =120)	20	51.5%		39%	64%	59
Dyslipidemia (<i>n</i> =102)	13	24%		13%	35.5%	58
Obesity (<i>n</i> =128)	16	45%		32%	57%	64
Systolic blood pressure (mmHg)	8		−12.72	−18.33	−7.1	61
Diastolic blood pressure (mmHg)	7		−9.34	−14.83	−3.85	76
BMI (kg/m ²)	7		−1.96	−3.32	−0.59	68
Fasting glucose (mmol/L)	4		−7.99	−13.9	−2.09	27
HbA1c (SMD)*	3		−0.96	−1.43	−0.49	53
LDL cholesterol (mg/dL)	2		−0.12	−37.7	37.5	53
HDL cholesterol (mg/dL)	3		2.9	−3.4	9.2	53
Triglycerides (mg/dL)	3		−23	−36.7	−9.2	0

BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SMD, standardized mean difference, *P*, study heterogeneity.

adrenalectomy when compared with conservative management. No significant change in BMI decrease was noted between groups (Fig. 3).

Patients with NF adrenal tumors

Metabolic outcome in patients with NF adrenal tumors comparing before and after adrenalectomy

Our search identified eight studies reporting on clinical outcomes before and after adrenalectomy in patients with NF adrenal tumors (19, 31, 34, 35, 37, 39, 47, 48). In five of these studies (54 patients with HTN), 21 patients had improvement of BP control after adrenalectomy (42%, 95% CI: 21–63%), [Supplementary Fig. 3](#). In four studies, 3/14 and 3/23 patients with DM2 and dyslipidemia respectively improved after adrenalectomy, [Supplementary Fig. 3](#).

Metabolic outcome in patients with NF adrenal tumors comparing adrenalectomy vs conservative management

In two studies, metabolic outcomes of adrenalectomy were compared with conservative management (19, 48). Meta-analysis was not performed due to small numbers and studies are discussed individually. When compared with conservative management, the adrenalectomy effect on HTN was variable among the studies. In the study by Chiodini *et al.*, a statistically significant improvement of SBP was found between surgical and nonsurgical NF groups (9/30 vs 5/37, *P*=0.05) (19). However, in a larger study by Sereg *et al.*, no differences were found when the prevalence of cardiovascular events, HTN, obesity, dyslipidemia and DM2 in patients with surgically treated NF adrenal tumors was compared with patients with NF

adrenal tumors followed conservatively. Patients also had similar BMIs, cholesterol concentrations and glucose concentrations at follow-up assessment (48).

Metabolic outcome comparing adrenalectomy in patients with SCS vs patients with NF adrenal tumors

Only six studies aimed to compare the effect of adrenalectomy on comorbidities in both SCS and NF populations (19, 31, 35, 37, 39, 47). Taking into consideration the small sample size, we did not find statistically significant differences between patients with SCS and NF adrenal tumors with regard to impact of adrenalectomy on HTN (39 SCS and 43 NF patients), DM2 (19 SCS and 14 NF patients), obesity (16 SCS and 14 NF patients) and dyslipidemia (22 SCS and 23 NF patients) (data not shown). There were insufficient data to evaluate any difference between patients with SCS and patients with NF adrenal tumors on any continuous outcomes.

The largest comparative study of both surgical and nonsurgical patients with SCS and NF adrenal tumors contained only 16–37 patients in each arm (19). In this study, surgical patients with SCS experienced greater improvements in several outcomes when compared with surgically treated patients with NF adrenal tumors, including more weight loss after surgery (32% vs 10%), improved BP (56% vs 30%) and improved fasting glucose concentrations (48% vs 10%) (19). In a smaller study, more than half of the 13 patients with NF adrenal tumors treated with adrenalectomy experienced improvements in BP and DM2 control. However, it is important to mention that four patients developed postoperative temporary adrenal insufficiency, raising the question of

Figure 2

Adrenalectomy vs conservative management in patients with subclinical Cushing's syndrome: Dichotomous outcomes. Grp 1, adrenalectomy group; Grp 2, conservative management group.

whether these patients were misclassified as having a NF adrenal mass (47).

Risk of bias assessment

Except for one randomized controlled trial, all of the studies were observational. The observational studies were of moderate risk of bias. Samples were not representative enough in most studies. Most of the included studies

had good ascertainment of the exposure but not of the outcome. Additionally, many studies were judged to lack a period of sufficient length of follow-up for the change in outcome to occur.

Discussion

This systematic review and meta-analysis summarizes the available evidence of adrenalectomy effects on

Figure 3

Adrenalectomy vs conservative management in patients with subclinical Cushing's syndrome: Continuous outcomes.

cardiovascular risk factors in patients with SCS. Based on the limited and heterogeneous published data, we demonstrate that a significant proportion of patients with SCS improve their cardiovascular morbidities (HTN, DM2, dyslipidemia and obesity) after adrenalectomy. The beneficial effect of adrenalectomy persists for HTN and DM2 in the comparative analysis of patients with SCS treated with adrenalectomy vs conservative management. Notably, the stringency of SCS criteria varied between the studies. Despite the fact that subgroup analysis has not shown higher benefit of adrenalectomy in patients with a DST cortisol of $\geq 3 \mu\text{g/dL}$, the number of patients in each subgroup was small and could have accounted for the absence of significant differences in the benefit of adrenalectomy in relation to the SCS definition used.

Interestingly, we have also found that a proportion of patients with NF adrenal tumors experienced an improvement of HTN after adrenalectomy. One of the likely explanations for this observation could be a potential misclassification of patients; for example, one study described that a significant proportion of patients with NF adrenal tumors developed adrenal insufficiency after surgery, clearly suggesting that autonomous glucocorticoid production was not recognized preoperatively (47). Overall glucocorticoid production has been linked to HTN, abnormal glucose tolerance and increased BMI (50). Thus, it is also possible that a temporary reduction of the overall glucocorticoid load caused by unilateral adrenalectomy could have contributed to a short-term BP improvement described in patients with NF adrenal tumors.

Limitations and strengths

The strengths of this review include an in-depth and comprehensive literature search, a focused review question and predefined group and subgroup analyses. Our review mainly includes retrospective cohort studies of small sample size. Our results are limited by the heterogeneous definitions of SCS. One may dispute the legitimacy of combining patients diagnosed with SCS using different criteria. However, comparative analysis showed similar improvement in most cardiovascular factors. Moreover, we have performed a subgroup analysis using different DST cortisol cutoffs. In contrast to our expectations to find more benefit in the higher DST cortisol cutoff subgroup, no significantly different outcomes from the overall analysis were noted. Various SCS definitions used in the included studies bring to surface the still-ongoing debate on the best diagnostic cutoffs for diagnosing SCS. Even when the same definition of SCS is used across the studies, differences in assay methods and presence of individual factors contributing to possible false-positive or false-negative results (51) may lead to subsequent misclassification of patients (40, 47). Most clinicians do not rely solely on the results of biochemical cutoffs to make a diagnosis, but also on clinical suspicion and existence of comorbidities.

A significant limitation of this review stems from the significant differences in how and when the outcomes of interest were assessed (Table 3). Inconsistent definitions of comorbidities as well as degrees of improvement, in many cases applied retrospectively, limit our ability to provide accurate estimates of the benefits resulting from adrenalectomy. It was also unclear how aggressive the conservative management was in nonsurgical patients and what factors influenced the decision not to undergo adrenalectomy, with all but one study not applying randomization. In addition, we were not able to perform any analysis of age, gender and tumor size influence on cardiovascular outcomes, as individual variables were not consistently reported.

Comparison with previous studies

To our knowledge, only one previous systematic review of the literature assessed the effect of adrenalectomy in patients with SCS (52). Iacobone *et al.* limited their review of studies to those published in English consisting of at least ten operated patients and only including patients with SCS. They identified only seven publications, which are also reviewed in our work. Our current systematic

review provides additional value by including smaller cohort studies, as well as studies published in languages other than English ($n=2$), allowing for a larger total cohort size. Our current review also includes comparative NF adrenal tumor studies.

Review implications

This review raises several important questions needing further clarification. The first question mirrors the ongoing debate on the best SCS definition. The overnight 1-mg DST is most consistently used among the included studies; however, the best cutoff distinguishing patients with clinically relevant autonomous glucocorticoid production is still undetermined. It could be useful to adopt a retrospective approach and examine only patients with SCS who indeed experienced a predefined degree of improvement in their comorbidities with adrenalectomy to gain more insight; however, this was technically not feasible to perform in the current review. Secondly, conservative management differs in its intensity among the studies included. Data from a well-designed randomized controlled trial comparing adrenalectomy to aggressive management of HTN, DM2 and obesity in patients with SCS is needed. Thirdly, it is unclear whether the improvement in cardiovascular risk factors noted after adrenalectomy in patients with SCS actually persisted (or influenced cardiovascular outcomes and mortality) as most studies had short follow-up. Nevertheless, despite many unanswered questions, and bearing in mind the heterogeneity of SCS and outcome definitions, the findings from our review demonstrate improvement of cardiovascular risk factors with adrenalectomy in comparison to conservative management in patients with SCS. Until more data are available, the potential favorable impact of adrenalectomy on patients with SCS should be discussed with the patient in the context of informed medical decision making.

Conclusions

Available low-to-moderate-quality evidence derived from heterogeneous studies, most with at least six months follow-up, suggests a beneficial effect of adrenalectomy on cardiovascular risk factors in patients with SCS overall and as compared with conservative management.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-16-0465>.

Declaration of interest

The authors have no conflicts of interest to declare. I B, W A and M T are members of the European Society of Endocrinology and European Network for the Study of Adrenal Tumors Clinical Guideline Panel.

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Author contribution statement

I B, R K C, V C, D D, D E and N N were involved in data extraction; I B, F A and M H M were involved in data analysis; I B, F A, R K C, V C, D D, D E, N N, M T, W A, W F Y and M H M were involved in manuscript writing; M H M were involved in methodology expertise; I B, M T, W A and W F Y were involved in subject matter expertise; I B was involved in overall project supervision.

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