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Improvement of cardiovascular risk factors after adrenalectomy in patients with adrenal tumors and Subclinical Cushing 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 Syndrome (SCS) are uncertain. We sought to conduct a systematic review and meta-analysis with the following objectives: 1) determine the effect of adrenalectomy compared to conservative management on cardiovascular risk factors in patients with SCS and 2) compare the effect of adrenalectomy on cardiovascular risk factors in patients with SCS versus those with a non-functioning (NF) adrenal tumor.

Methods: Medline In-Process & Other Non-Indexed Citations, MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trial were searched on November 17th, 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 to 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 as compared to conservative management.

Introduction
Subclinical Cushing syndrome (SCS) is a controversial disorder in name, definition, and management but is currently diagnosed in at least a third of patients with incidentally discovered adrenal masses 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.

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 co-morbid depression and obesity. 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. Previous studies suggest that patients with SCS are at higher risk for developing cardiovascular events and experience an increased cardiovascular mortality. 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. While several authors reported various degrees of improvement in metabolic parameters, others showed no significant metabolic effect of adrenalectomy 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 non-functioning (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.
Insecurity of diagnosis and unclear surgical benefit to patients with SCS leads 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. Until the dilemma of SCS is solved, patients risk progression towards 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 regards 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: 1) determine the effect of adrenalectomy compared to conservative management on cardiovascular risk factors in patients with SCS and 2) compare the effect of adrenalectomy on cardiovascular risk factors in patients with SCS versus 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)\(^\text{25}\). We included studies that evaluated adrenalectomy alone or in comparison to 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 non-comparative studies that enrolled adults with either NF adrenal tumors or adrenal tumors with SCS (as defined by authors), with at least 5 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 non-original studies and case reports. Dichotomous outcomes of interest were: hypertension, pre-diabetes or diabetes.
mellitus, obesity and dyslipidemia. Continuous outcomes were: systolic and diastolic blood pressure, body mass index (BMI), 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 November 17, 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 (Suppl. Table 1) 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 pre-defined inclusion criteria. Many of the identified studies retrieved by our search were non-relevant or non-original 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-effect model to pool estimates from the included studies. A random-effect model was used, rather than a fixed-effects model, in order to account for heterogeneity between studies as well as 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%). I-square values of 25%, 50%, and 75% are thought to represent low, moderate, and high heterogeneity, respectively. Statistical analyses were conducted through OpenMeta[Analyst]. All values were two-tailed and $P < .05$ 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 3 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 $\geq 3 \ \mu g/dL, 83 \ \text{nmol/L}$ (13 studies, DST cortisol cutoff 3-5 $\mu g/dL, 83-138 \ \text{nmol/L}$); subgroup 2 included studies using a cortisol cutoff of $<3 \ \mu g/dL, 83 \ \text{nmol/L}$ (8 studies, DST cortisol cutoff 1-2.5 $\mu g/dL, 28-69 \ \text{nmol/L}$); and subgroup 3 comprised studies that either did not report a DST cortisol cutoff or did not provide how SCS was defined (5 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 were included in this systematic review (Figure 1). Eligible studies included 25 cohort studies (16 retrospective and 9 prospective studies) and one randomized controlled trial. Studies were mostly from European (n=15) or Asian centers (n=9), and 2 were USA-based (Table 1). A total of 584 patients with SCS (mean age 56 yrs, 66.8% women) and 457 patients with NF adrenal tumors (mean age 54.9 yrs, 61.5% women) 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 10 studies provided comparative data for patients with SCS managed conservatively (Table 1). In 6 studies, authors compared the effect of adrenalectomy on outcomes in both SCS and NF adrenal tumor groups. In 3 studies, the effect of adrenalectomy on metabolic parameters in patients with NF was compared to 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” (Table 3). 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 3) 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 4). Improvement in hypertension was observed in 60.5% of patients with SCS; systolic blood pressure decreased by a mean of 12.7 mm Hg (CI95% 7.1-18.3 mmHg) and diastolic blood pressure decreased by a mean of 9.3 mm Hg (CI 95% 3.85-14.83 mm...
Hg). Improvement in DM2 was observed in 51.5% of patients. Only 3 studies examined the effect of adrenalectomy on fasting blood glucose and 4 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 (CI95% 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 and HDL cholesterol, no significant changes following adrenalectomy were noted (Table 4).

Subgroup analysis based on DST cortisol cutoff criteria was performed only for the outcomes of HTN and DM2. Patients in subgroup 1 (136 with hypertension, 61 with DM2), subgroup 2 (71 with HTN, 34 with DM2) and subgroup 3 (58 with HTN and 25 with DM2) experienced similar rates of HTN and DM2 improvement following adrenalectomy (Supplemental figure 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 10 studies that included both patients who underwent either adrenalectomy (132 patients with SCS) or were conservatively managed (135 patients with SCS). When compared to conservative management, patients with SCS undergoing adrenalectomy experienced a statistically significant improvement in hypertension (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)), (Figure 2A). Data on continuous outcomes derived only from 4 studies demonstrated a significant decrease of systolic blood pressure (SBP) and diastolic blood pressure (DBP) as well as fasting glucose concentrations in patients with SCS undergoing adrenalectomy when compared to conservative management. No significant change in BMI decrease was noted between groups (Figure 2B).

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

Our search identified 8 studies reporting on clinical outcomes before and after adrenalectomy in patients with NF adrenal tumors. In 5 of these studies (54 patients with hypertension), 21 patients had improvement of BP control after adrenalectomy (42%, 95%CI 21 to 63%), Supplemental Figure 3. In 4 studies, 3/14 and 3/23 patients with DM2 and dyslipidemia respectively improved after adrenalectomy, Supplemental figure 3.

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

In 2 studies, metabolic outcomes of adrenalectomy was compared with conservative management. Meta-analysis was not performed due to small numbers and studies are discussed individually. When compared to conservative management, the adrenalectomy effect on hypertension was variable among the studies. In the study by Chiodini et al, a statistically significant improvement of systolic blood pressure was found between surgical and non-surgical NF groups (9/30 versus 5/37, \(P=0.05\)). However, in a larger study by Sereg et al., no differences were found when the prevalence of cardiovascular events, hypertension, obesity, dyslipidemia and DM2 in patients with surgically treated NF adrenal tumors was compared to patients with NF adrenal tumors followed conservatively. Patients also had similar BMIs, cholesterol concentrations and glucose concentrations at follow up assessment.

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

Only 6 studies aimed to compare the effect of adrenalectomy on comorbidities in both SCS and NF populations. Taking into consideration the small sample size, we did not find statistically significant differences between patients with SCS vs. 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 vs. patients with NF adrenal tumors on any continuous outcomes.

The largest comparative study of both surgical and non-surgical patients with SCS and NF adrenal tumors contained only 16 to 37 patients in each arm. In this study, surgical patients with SCS experienced greater improvements in several outcomes when compared to 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%). 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 4 patients developed postoperative temporary adrenal insufficiency, raising the question of whether these patients were misclassified as having a NF adrenal mass.

**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 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 versus 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 $\geq 3 \, \mu g/dL$, 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 glucocorticoid autonomous production was not recognized preoperatively.\textsuperscript{47} Overall glucocorticoid production has been linked to HTN, abnormal glucose tolerance and increased BMI.\textsuperscript{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 includes mainly 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 brings 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 negative results may lead to subsequent misclassification of patients. 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 non-surgical 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. Iacobone et al limited their review of studies to those published in English consisting of at least 10 operated patients, and only including patients with SCS. They identified only 7 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 in 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 6 months follow up, suggests a beneficial effect of adrenalectomy on cardiovascular risk factors in patients with SCS overall and as compared to conservative management.

**Declaration of interest:** The authors have no conflicts of interest to declare. IB, WA, and MT are members of the European Society of Endocrinology and European Network for the Study of Adrenal Tumors Clinical Guideline Panel.

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**Figure Legends:**

**Figure 1.** Prisma Flow Diagram.

**Figure 2.** Adrenalectomy versus conservative management in patients with Subclinical Cushing Syndrome.

2A Dichotomous outcomes

2B Continuous outcomes

Grp 1 –Adrenalectomy group

Grp 2 – Conservative management group
**Supplemental figure 1.** Effect of adrenalectomy on hypertension in patients with SCS (Subgroup analysis)

Subgroup 1: DST cortisol of 1-2.5 mcg/dl

Subgroup 2: DST cortisol of 3-5 mcg/dl

Subgroup 3 – DST cortisol cutoff not reported

**Supplemental figure 2.** Effect of adrenalectomy on diabetes mellitus type 2 in patients with SCS (Subgroup analysis)

Subgroup 1: DST cortisol of 1-2.5 mcg/dl

Subgroup 2: DST cortisol of 3-5 mcg/dl

Subgroup 3 – DST cortisol cutoff not reported

**Supplemental figure 3.** Effect of adrenalectomy on hypertension, diabetes mellitus and dyslipidemia in patients with NF adrenal tumors

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