Review Article

Cardiovascular risk and mortality in patients with active and treated hypercortisolism

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Abstract: Patients with hypercortisolism demonstrate high cardiovascular morbidity and mortality, especially if diagnosis is delayed. Hypercortisolism-induced cardiovascular and metabolic comorbidities include hypertension, impaired glucose metabolism, dyslipidemia, and obesity. High prevalence of cardiovascular risk factors leads to increased rate of cardiovascular events and mortality. This risk is reduced, albeit not reversed even after successful treatment of hypercortisolism. In this review we will describe prevalence and mechanisms of cardiovascular comorbidities in patients with hypercortisolism. In addition, we will summarize the effect of therapy on cardiovascular risk factors, events, as well as mortality.

Keywords: Cushing syndrome (CS); mild autonomous cortisol secretion (MACS); hypertension; glucose metabolism; dyslipidemia; cardiovascular events

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Introduction

Cushing syndrome (CS) is a rare endocrine disorder caused by chronic exposure to endogenous cortisol hypersecretion or exogenous administration of glucocorticoids (1). The estimated incidence of endogenous CS is approximately 0.2 to 5.0 cases per million per year with an estimated prevalence of 39 to 79 cases per million in various populations (2-5). CS presents with a wide spectrum of clinical manifestations, which include physical signs such as central obesity, rounded face, facial plethora, dorsocervical and supraclavicular fat pads, striae, thinning of the skin and easy bruising (1), as well as metabolic manifestations, such as hypertension, diabetes mellitus, and dyslipidemia (6,7). The median age of diagnosis with CS is 41.4 years, and women are more frequently affected than men (female-to-male ratio of 3:1) (2-5). Among the different etiologies of CS, adrenocorticotropic hormone (ACTH)-dependent CS is most common affecting around 80% of patients, usually caused by a pituitary adenoma producing ACTH (also called Cushing disease, CD). Rarely, it may be caused by ectopic ACTH or corticotropin-releasing hormone production (ectopic CS) (4,7,8). ACTH-independent CS occurs in approximately 20% of patients, and is caused by autonomous cortisol production from an adrenal cortical adenoma, macronodular or micronodular hyperplasia, or adrenal cortical carcinoma (2,9,10).

Mild autonomous cortisol secretion (MACS) affects around 30% of patients with adrenal tumors (11,12) and is characterized by the presence of metabolic abnormalities in the absence of overt clinical features of CS (12-14). Patients with MACS have been reported to have increased risk of cardiovascular events and higher mortality than those with nonfunctional tumors (6,15). As surgery is not uniformly performed in patients with MACS, these patients are more likely to have longstanding, though mild hypercortisolism.

Table 1 Summary of recent prevalence studies on hypertension in untreated hypercortisolism

Study, year	Patients, n	Etiology of hypercortisolism, n	Prevalence of HTN at baseline, n (%)
Dekkers *et al.*, 2007 (18)	74	CD: 74	58/74 (78%)
Valassi *et al.*, 2011 (5)	481	CD: 317	233/306 (76%), missing data in 11 subjects
		Adrenal CS: 130	103/126 (82%), missing data in 4 subjects
		Ectopic CS: 24	21/24 (76%)
		Other CS: 10	6/10 (60%)
Clayton *et al.*, 2011 (19)	60	CD: 60	22/60(37%)
Dekkers *et al.*, 2013 (20)	343	CD: 211	87/343 (25%), reported for entire cohort
		Adrenal CS: 132	
Lambert *et al.*, 2013 (21)	346	CD: 346	248/346 (72%)
Debono *et al.*, 2014 (15)	206	Adrenal CS: 111	71/111 (64%)
		Adrenal MACS: 95	55/95 (58%)
Di Dalmazi *et al.*, 2014 (6)	69	Adrenal MACS: 69	45/69 (65%)
Clayton *et al.*, 2016 (22)	320	CD: 320	164/320 (51%)
Elhassan *et al.*, 2019 (23)	296	MACS: 296	188/296 (64%)

Selection criteria: publication year: 2005 or after; sample size: above 50 subjects; design: retrospective, prospective studies, or systemic reviews; outcome: hypertension prevalence data available at baseline. CS, Cushing syndrome; CD, Cushing disease; MACS, mild autonomous cortisol secretion.

Untreated hypercortisolism is associated with increased mortality and morbidity, with increase prevalence of cardiovascular events, sepsis, and thromboembolism as the leading causes of death (16). Surgery is the treatment of choice in all subtypes of endogenous CS. If surgery is not possible, medical therapy and radiotherapy may be occasionally used (17). Improvement or resolution of hypercortisolism-induced comorbidities occurs with surgery; however the degree of improvement varies. In this review, we will describe the prevalence and mechanisms behind cardiovascular comorbidities, as well as mortality in patients with untreated hypercortisolism. In addition, we will summarize the effect of therapy on cardiovascular risk factors, cardiovascular events, and mortality.

Hypertension in hypercortisolism

At the time of diagnosis, around 37–82% of patients with CS and 58–64% of patients with MACS present with hypertension (*Table 1*). Both duration and severity of untreated hypercortisolism contribute to the development of hypertension (5,24). Prevalence, as well as degree of hypertension is higher in patients with ACTH-independent CS when compared to patients with CD, likely due to the differences in demographics and duration of hypercortisolism (5,25-27). The majority of patients with hypertension at baseline are treated with none or one antihypertensive agent, and around a third of patients require 2 or more medications (2,28).

Hypercortisolism-induced hypertension is a multifactorial disease that mainly involves activation of the mineralocorticoid and glucocorticoid receptors, renin-angiotensin system, sympathetic nervous system and an impaired balance between vasodilators and vasoconstrictors (*Table 2*). Aldosterone and cortisol have a similar affinity at the level of mineralocorticoid receptors which are mainly expressed in the kidneys (29). The corticosteroid pathway enzyme 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) is the main regulator of the binding selectivity. It acts by catalyzing the deactivation of cortisol into cortisone (40). In the setting of hypercortisolism, the 11beta-HSD2 capacity to deactivate cortisol is overwhelmed, making cortisol available to act on the mineralocorticoid receptor. This leads to retention of sodium and water in exchange for potassium, causing hypertension and hypokalemia, especially in patients with extremely high cortisol concentrations (41,42). Binding of cortisol to the glucocorticoid receptor also contributes to the development

Table 2 Summary of mechanisms of hypertension in hypercortisolism

Mechanism	Description	Clinical Implication	Reference
Mineralocorticoid Receptor and Glucocorticoid Receptor	↑ 11beta-HSD2 saturation → ↑ cortisol action on mineralocorticoid receptor → sodium and fluid retention	MR antagonists (spironolactone, eplerenone)	(29)
	↑ cortisol action on GR → fluid retention in kidneys	GR antagonist (mifepristone)	(30)
Renin-Angiotensin System	↑ hepatic angiotensinogen → high angiotensin, low/normal renin state	ACEi and ARB	(26,31)
	↑ AT-II 1A receptor → enhanced response to vasoconstrictors		(32)
Sympathetic Nervous System	↑ sensitivity to beta-adrenergic agonists	Unknown	(32,33)
Vasoregulatory System	↑ ET-1 production	Unknown	(34)
	↑ EPO production (only reported in exogenous CS)		(35)
	↓ NO pathway		(36,37)
	↓ Urinary PGE2		(26)
	↓ PGI2 production		(38)
	↓ Urinary kallikrein		(26)
	↑ Urinary kininase		(39)

11beta-HSD2, 11beta-hydroxysteroid dehydrogenase type 2; MR, mineralocorticoid receptor; GR, glucocorticoid receptor; AT-II 1A, angiotensin-II type 1A; ET-1, endothelin-1; EPO, erythropoietin; NO, nitric oxide; PGE2, prostaglandin E2; PGI2, prostacyclin; ACEi, angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker.

of hypertension by enhancing epithelial sodium channel activation and glomerular hyperfiltration (30), and thus spironolactone, a mineralocorticoid receptor antagonist may not be effective as a single agent to normalize blood pressure in hypercortisolism-induced hypertension.

Another mechanism for hypercortisolism-induced hypertension involves the renin-angiotensin system. Hypercortisolism leads to increased hepatic production of angiotensinogen (26,31). Renin is responsible for the conversion of angiotensinogen to angiotensin I, which is then converted to angiotensin II by angiotensin-converting-enzyme. Angiotensin II is a vasoconstrictor, and it also stimulates the production of aldosterone that in turn leads to water retention and sodium reabsorption. In hypercortisolism, renin is suppressed or normal (26,31). Despite the increase of angiotensinogen, the concentrations of circulating angiotensin II in patients with hypercortisolism is reportedly unchanged (32). However, there is upregulation of angiotensin II (Type 1A) receptors, causing an enhanced response to angiotensin II with vasoconstriction (32). Several studies showed that oral administration of the angiotensin-converting-enzyme-inhibitor in patients with hypercortisolism leads to blood pressure improvement (26,43).

Lastly, several vasoactive substances have been reported to contribute to the pathogenesis of cortisol induced hypertension, including endothelin-1, erythropoietin, nitric oxide, prostaglandins, prostacyclins, and the kallikrein-kinin system. Endothelin-1 (a vasoconstrictor) concentrations are increased in patients with hypercortisolism, possibly related to the cortisol-induced endothelial damage and increased vascular permeability (34). Hypercortisolism inhibits the gene expression of nitric oxide synthase and thus leads to decreased concentrations of nitric oxide, a potent vasodilator (36,37,44). Prostaglandin E2 and I2 are two important prostaglandins with strong vasodilatory effects that are inhibited by hypercortisolism through induction of lipomodulin synthesis (26,38,45). In addition, hypercortisolism was associated with low concentrations of urinary kallikrein, another vasodilator, likely due to the inhibitory effect of cortisol (26,46).

Abnormal glucose metabolism in hypercortisolism

Abnormal glucose metabolism has been reported in

Table 3 Summary of recent prevalence studies on glucose metabolism in untreated hypercortisolism

Study, year	Patients, n	Etiology of hypercortisolism, n	Prevalence of DM and IGT at baseline, n (%)
Mancini *et al.*, 2004 (24)	49	CD: 27	DM: 23/49 (46.8%)
		Adrenal Adenoma: 15	IGT: 10/49 (20%)
		Adrenal Carcinoma: 4	
		Ectopic CS:3	
Clayton *et al.*, 2011 (19)	60	CD: 60	DM: 11/60 (18.3%)
Valassi *et al.*, 2011 (5)	481	CD: 317	DM: 96/294 (33%), missing data in 23 subjects
		Adrenal CS:130	DM: 43/127 (34%), missing data in 3 subjects
		Ectopic CS: 24	DM: 17/23 (74%), missing data in 1 subject
		Other CS: 10	DM: 2/10 (20%)
Hassan-Smith *et al.*, 2012 (47)	72	CD: 72	DM: 22/72 (31%)
Dekkers *et al.*, 2013 (20)	343	CD: 211	DM: 45/343 (13.1%)
		Adrenal CS: 132	
Lambert *et al.*, 2013 (21)	346	CD: 346	DM: 95/346 (27%)
Di Dalmazi *et al.*, 2014 (6)	69	Adrenal MACS: 69	DM: 21/69 (30%)
Elhassan *et al.*, 2019 (23)	277	MACS: 277	DM: pooled percentage of 28%

Selection criteria: publication year: 2004 or after; design: retrospective, prospective studies or systematic reviews; outcome: glucose abnormality prevalence data available at baseline. DM, diabetes mellitus; IGT, impaired glucose tolerance; CS, Cushing syndrome; CD, Cushing disease; MACS, mild autonomous cortisol secretion.

14–74% of patients with untreated hypercortisolism, with impaired fasting glucose reported in 21–64% and diabetes mellitus in 21–47% of patients (*Table 3*). Prevalence of glucose abnormalities varies based on the etiology of hypercortisolism. Hyperglycemia in patients with ectopic CS is inconsistently reported with prevalence of as low as 38% and as high as 74% (27,48). Patients with CD have a prevalence of diabetes mellitus between 18% and 36% and in patients with adrenal CS, prevalence of diabetes mellitus at the time of diagnosis ranges between 34% and 41% (*Table 3*). In patients with MACS, prevalence of diabetes mellitus varies between 18% and 30% at the time of initial diagnosis, with another 5% of patients developing new-onset diabetes mellitus during follow-up (6,23,49). As reported in two studies, the majority of patients with hyperglycemia in the setting of CS are not treated with any medications or take oral hypoglycemic agents only; however, around a quarter of patients are treated with insulin at the time of diagnosis (2,28).

The mechanisms of glucose dysregulation in hypercortisolism include stimulation of liver gluconeogenesis (50), interference with glucose transporters leading to increased hepatic and peripheral insulin resistance (51), increased hepatic lipogenesis contributing to steatosis (52), and lastly detrimental effect on pancreatic insulin secretion (53,54). Hypercortisolism-induced visceral adiposity also contributes to glucose dysregulation. The visceral fat accumulation caused by hypercortisolism is hypothesized to occur due to higher expression of 11β-HSD1 in the visceral adipose tissue, allowing higher rates of cortisone conversion to active cortisol (55).

Dyslipidemia in hypercortisolism

The prevalence of dyslipidemia in untreated overt hypercortisolism varies between 12–72% (2,21,27,56). In a population-based study of 190 patients with hypercortisolism and available data at baseline, dyslipidemia was noted in 28% of patients (2). In a smaller study but with more in-depth assessment, dyslipidemia was demonstrated in 64% of patients with CD and 53% of patients with adrenal CS (27). Another larger retrospective study of 346 patients with CS reported dyslipidemia in only 16% of patients (21). Patients with MACS present

with a 26–34% prevalence of dyslipidemia, similar to overt hypercortisolism, likely due to a longer duration of untreated but mild hypercortisolism (23,57). With follow-up, an additional 6% of patients were reported to develop dyslipidemia (23). Dyslipidemia in hypercortisolism usually presents with low HDL and elevated LDL and triglyceride concentrations (2,27).

Several mechanisms of hypercortisolism-induced dyslipidemia have been described. Hypercortisolism promotes lipolysis (58) with subsequent increase of free fatty acids leading to accumulation of hepatic fat, reduction of glucose uptake and insulin signaling (59). Other mechanisms include hepatic overexpression of 11β-HSD1 and polymorphisms at the level of glucocorticoid receptor in the liver, both contributing to the development of hepatic steatosis (60,61). Hepatic steatosis is evident in at least 20% of patients, as was demonstrated on ultrasound in a study of 50 patients with overt CS of various etiologies (62).

Cardiovascular events in hypercortisolism

Patients with hypercortisolism demonstrate high rates of cardiovascular risk factors, cardiac remodeling, dysfunction and vascular atherosclerosis, which contribute to high rates of cardiovascular events (24,63). Left ventricular hypertrophy, decrease in systolic strain and impaired relaxation pattern with a decrease in diastolic filling have been reported in several studies (63-65). In patients with CS, left ventricular enlargement was reported to be more pronounced when compared to patients with hypertension without hypercortisolism, suggesting that factors other than elevated blood pressure contribute to cardiac dysfunction (64). Possible mechanisms include an enhanced response to angiotensin II (32) and hypercortisolism induced activation of the mineralocorticoid receptor (42) leading to myocardial fibrosis, ventricular remodeling, impairment of relaxation and consequently, the development of heart failure (66,67). Additionally, intimal media thickness of common carotid artery, aorta and femoral artery is significantly increased in patients with CS when compared to healthy controls matched for other cardiovascular risk factors (56,68). Vascular damage with increased formation of atherosclerotic plaques has been reported in patients with CS (56,68) and could explain the increased risk of myocardial infarction and stroke reported in patients with CS (20).

Patients with both CS and MACS demonstrate an increased risk of cardiovascular events, including coronary artery disease, myocardial infarction, stroke, transient ischemic attack, and heart failure (6,20,28,57). In a study of 343 patients with overt hypercortisolism, the risk for myocardial infarction, stroke, and cardiac failure was high with an age and sex adjusted hazard ratio of 2.2 to 6.8 (20). In patients with persistent CS, rate of cardiovascular events was reported to be as high as 29% (28). In 69 patients with MACS, baseline prevalence of coronary heart disease and stroke was 10% and 7%, respectively (6). During a median follow-up of 7.5 years, patients with MACS demonstrated a higher incidence of cardiovascular events when compared to patients without MACS (16.7% *vs.* 6.7%), with an unadjusted hazard ratio for new cardiovascular events of 3 (6). History of cardiovascular events was reported in 6.3% of patients with MACS at the time of diagnosis, and 15.5% more patients developed new cardiovascular events during 5-year follow-up, which was three times higher than patients without MACS (57).

Treatment of hypercortisolism

Surgery is the treatment of choice in overt hypercortisolism of any etiology, while other therapies, such as radiation therapy (for pituitary tumors) or medical therapy are reserved only when surgery is not possible or not curative (17). Surgical options include transsphenoidal selective tumor resection in CD, laparoscopic unilateral adrenalectomy in adrenal CS, and resection of ACTH-secreting neuroendocrine tumor in ectopic CS (17). Bilateral adrenalectomy may be performed in patients with macronodular and micronodular adrenal hyperplasia presenting with ACTH-independent CS or patients with ACTH-dependent Cushing syndrome where surgical cure is not possible (17). In patients with MACS, adrenalectomy is usually considered for patients with hypercortisolism-induced comorbidities such as hypertension, obesity, diabetes mellitus, dyslipidemia and low bone mass (11,69). Medical therapy includes agents that modulate ACTH release (somatostatin analogs, dopamine agonists), agents that inhibit steroidogenesis (ketoconazole, metyrapone, mitotane, etomidate), and agents that block the glucocorticoid receptor (mifepristone) (17). Medical therapy can be used as monotherapy or in combination, usually as a temporary action to quickly achieve eucortisolism to prevent acute complications, when the surgery has to be delayed (17,70).

Improvement of comorbidities following remission of hypercortisolism

Effect of therapy for hypercortisolism on hypertension

Resolution of hypercortisolism improves blood pressure control in up to 30–70% of patients (*Tables 4,5*). Patients may continue to have persistent hypertension due to cortisol induced irreversible structural cardiovascular changes and vascular remodeling (84), as well as left ventricular hypertrophy (55,85).

It is important to note that studies reporting on improvement in hypertension after surgery or with medical therapy are inconsistent in their definitions of improvement (*Tables 4,5*). In patients with CD after a curative transsphenoidal surgery, multiple studies reported persistent hypertension in 11–40% of the cases after a follow-up period ranging from 1 to 18 years (56,71,74,86,87). In patients treated with bilateral adrenalectomy for ACTH-dependent hypercortisolism from an occult source, 64% of patients improved blood pressure (48). In a cohort of 60 patients with adrenal CS, hypertension was present in 78% of patients and improved in 67% with adrenalectomy (72). Hypertension is also the most likely comorbidity to improve after adrenalectomy in patients with MACS, reported to improve in 60.5% of patients at a median follow-up of 28 months. The mean decrease in blood pressure measurements after surgery in this study was 12.7 and 9.3 mmHg for systolic and diastolic blood pressure, respectively (57).

Several studies reported on the effectiveness of medical therapy for hypercortisolism on hypertension. Most of these studies were of short duration with a small sample size (*Table 5*). Ketoconazole, an inhibitor of 17-alpha hydroxilase and 17, 20 lyase has been reported to improve blood pressure in 40–60% of the patients in three studies (75-77). Therapy with metyrapone, an inhibitor of 11-beta-hydroxylase, led to improvement of hypertension in 73% of patients (78). Notably, 5.5% of the patients treated with metyrapone developed hypokalemia due to activation of the mineralocorticoid receptors and all responded well with potassium supplements, amiloride or triamterene (78). Therapy with mifepristone, a glucocorticoid receptor antagonist, was reported to lead to hypertension improvement in up to 52% of patients, but also led to exacerbation of hypertension in 13.5% of patients, likely due to activation of mineralocorticoid receptor (80). Mitotane, an adrenolytic agent used in patients with adrenocortical carcinoma, was reported to improve hypertension in 63% of patients with severe hypercortisolism (79). Etomidate, another steroidogenesis inhibitor, is the only drug with parenteral administration used in patients with hypercortisolism (88). Due to its fast onset of action with half-life of 75 minutes and mode of administration, it is usually reserved for hospitalized patients with acute and/or life-threatening severe hypertension (88). Dopamine agonist therapy with cabergoline and somatostatin analog therapy with pasireotide have been reported to have a minor effect on hypertension in patients with CS with blood pressure decrease of 4–6 mmHg (81,89).

Effect of therapy for hypercortisolism on glucose metabolism

Reversal of hypercortisolism leads to improvement in glucose metabolism (27,28,48,56,72,74,86). Prevalence of diabetes mellitus in patients treated for CS (mostly CD) decreases from 20–47% before treatment to 10–33% (*Table 6*). In a cohort of patients with predominantly adrenal CS but also CD and ectopic CS, treated with adrenalectomy, resolution of hyperglycemia was observed in 79% of patients (72). While both diabetes and impaired fasting glucose persist after cure from CS, improvement in diabetes control (as defined by hemoglobin A1c, fasting glucose, or reduction in number and dose of medications) is poorly reported in patients with overt hypercortisolism. In patients with MACS, adrenalectomy was reported to lead to diabetes mellitus improvement or resolution in 51.5% of patients (57).

Pharmacotherapy for hypercortisolism was reported to lead to improvement in glycemic control. Mifepristone is the agent approved for patients with CS and hyperglycemia, which can reduce fasting glucose concentrations by around 40 mg/dL (80). Improvements in glucose control have also been reported with ketoconazole, metyrapone and cabergoline, and the degree of improvement likely depends on the effectiveness of hypercortisolism control. In a study of 38 patients with CD treated with ketoconazole, HbA1c decreased by 0.5–1% after 6–12 months of therapy (90). Three-month therapy with metyrapone in 7 patients with CD and impaired glucose tolerance was reported to lead to normalization of glucose metabolism in 5 patients (91). In another study of 20 patients with CS, 3-month therapy with cabergoline reduced fasting glucose concentrations by 10 mg/dL (92).

Effect of therapy for hypercortisolism on dyslipidemia

Effect of therapy for hypercortisolism on dyslipidemia

Table 4 Effect of surgical therapy for hypercortisolism on hypertension

Study, year	Patients, n	Etiology of hypercortisolism, n	Hypertension at baseline, n (%)	Therapy, %	Duration of follow up after surgery, mean, month	Hypertension at follow up
Gómez *et al.*, 2007 (71)	71	CD: 50 Adrenal CS: 21	71/71 (100%)	Transsphenoidal surgery: 100% Adrenalectomy: 100%	24	Resolution: 75%
Chow *et al.*, 2008 (48)	68	CD: 42 Ectopic CS: 26	25/42 (60%) 19/26 (73%)	Bilateral adrenalectomy: 100%	Not reported	Resolution: 64 %
Sippel *et al.*, 2008 (72)	60	CD: 17 Adrenal CS: 33 Ectopic CS: 10	46/59 (78%) (missing data in 1 subject)	Unilateral adrenalectomy: 53%, Bilateral adrenalectomy: 47%	24	Improvement: 67%, mean number of antihypertensive medications decreased from 1.6 pre-operatively to 0.4 post-operatively
Alesina *et al.*, 2010 (73)	170	Adrenal CS: 97 Adrenal MACS: 63	68/97 (70%) 50/63 (79%)	Adrenalectomy: 100%	70.9	Resolution: 32%; Improvement: 24% Resolution: 16%; Improvement: 20%
Hassan-Smith *et al.*, 2012 (47)	72	CD: 72	56/72 (78%)	Transsphenoidal surgery: 100%	55.2	Resolution: 32%; Improvement: 30%
Ntali *et al.*, 2013 (74)	311	CD: 311	151/311 (49%)	Transsphenoidal surgery: 99% Medical therapy: 1%	108	Improvement: 11%
Terzolo *et al.*, 2014 (28)	51	CD: 33 Adrenal CS: 15 Ectopic CS: 3	32/51 (63%)	Transsphenoidal surgery: 100% (2 received radiotherapy, ketoconazole/ cabergoline before surgery)	56.5	Resolution: 66%
Bancos *et al.*, 2016 (57)	584	Adrenal MACS: 584	Pooled proportion: 61%	Adrenalectomy: 120	At least 6 months	Improvement: pooled 61%, mean SBP and DBP decreased by 12.7 and 9.3 mmHg

Selection criteria: publication year: 2005 or after; sample size: above 50 subjects; design: retrospective, prospective studies or systematic reviews; intervention: surgical treatment; outcome: hypertension prevalence data available at baseline and after treatment. CS, Cushing syndrome; CD, Cushing disease; MACS, mild autonomous cortisol secretion; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5 Effect of medical therapy for hypercortisolism on hypertension

Study, year	Study Drug	Drug dose	Patient, n	Etiology of hypercortisolism, n	Hypertension at baseline, n (%)	Duration of follow-up, month	Hypertension at follow-up
Sonino *et al.*, 1991 (75)	Ketoconazole	Range: 400–800 mg QD Mean: 564.3 mg QD Median: 600 mg QD	34	CD: 28 Adrenal CS: 4 Ectopic CS: 2	21/34 (62%)	Range: 0.13–36; Mean: 8.1 Median: 5	Resolution: 33% Improvement: 62%
Moncet *et al.*, 2007 (76)	Ketoconazole	Range: 200–1200 mg QD Median: 600 mg QD	54	CD: 37 Adrenal CS: 5 Ectopic CS: 1 Unclear: 11	43/54 (80%)	Range: 0.5–156 Mean: 9.6	Resolution: 44% Improvement: 37%
Castinettiet *et al.*, 2014 (77)	Ketoconazole	Range: 200–1200 mg QD Mean: 774.6 mg QD Median: 600 mg QD	174	CD: 174	116/174 (67%)	Range:0.03–135 Mean:20.6	Improvement: 42%
Verhelst *et al.*, 1991 (78)	Metyrapone	Range: 500–4000 mg QD	91	CD: 57 Adrenal CS: 16 Ectopic CS: 18	74/91(81%)	Range: 0.25–140	Improvement: 73 %
Donadille *et al.*, 2010 (79)	Mitotane	Mean: 3.3±1.2 g Lysodren equivalent daily	23	Ectopic CS: 23	19/23(83%)	Range: 3.6–408 Mean: 96.48	Resolution: 16 % Improvement: 47 %
Fleseriu *et al.*, prospective, open-label study, 2012 (80)	mifepristone	Range: 300–1200 mg daily	50	CD: 43 Adrenal CS: 3 Ectopic CS: 4	40/50 (80%)	6	Improvement: 53 %
Colao *et al.*, RCT, 2012 (81)	Pasireotide	Range: 600–900 BID	162	CD: 162	56/72 (78%) (missing blood pressure data in 90 subjects)	12	Mean SBP and DBP decreased by 6.1 and 3.7 mmHg
Feelders *et al.*, prospective, open-label study, 2013 (20)	Pasireotide Cabergoline Ketoconazole	Pasireotide: range: 100–250 mcg TID, if UFC not normalized: added: Cabergoline (day 28) range: 0.5–1.5 mg QOD, Ketoconazole (day 60) 200 mg TID	17	CD: 17	Not reported	2.6	Mean SBP and DBP decreased by 12 and 8 mmHg

Table 5 (*continued*)

Table 5 (*continued*)

Study, year	Study Drug	Drug dose	Patient, n	Etiology of hypercortisolism, n	Hypertension at baseline, n (%)	Duration of follow-up, month	Hypertension at follow-up
Bertagna *et al.*, prospective, open-label study, 2013 (82)	Osilodrostat (LCI699)	Range: 2–50 mg BID	12	CD: 12	Not reported	2.5	At day 70: SBP decreased by 10 mmHg, DBP decreased by 6 mmHg
Fleseriu *et al.*, prospective, open-label study, 2016 (83)	Osilodrostat (LCI699)	Range: 4–60 mg QD	19	CD: 19	13/19 (68%)	5.5	SBP decreased by 1.0 mmHg, DBP increased by 1.3 mmHg

Selection criteria: publication year: 1990 or after; design: retrospective, prospective studies or randomized control trials; intervention: medical therapy as main therapy; outcome: hypertension prevalence data available at baseline and after treatment. mg, milligram; QD, once daily; CS, Cushing syndrome; CD, Cushing disease; g: gram; BID, twice daily; RCT, randomized control trial; SBP, systolic blood pressure; DBP, diastolic blood pressure; TID, thrice daily; UFC, urinary free cortisol; QOD, once every other day.

is variable but usually mild. In a population-based study of 190 patients with CS and available data, prevalence of dyslipidemia at follow-up was similar to baseline (2). No improvement in lipid profile was observed in patients with CD in remission during 5 years of follow-up with total cholesterol and LDL concentrations higher than controls matched for sex and age (86). In another study of 25 patients with CD, LDL concentrations improved only by a mean of 0.6 mmol/L after 1 year of remission (56). Prevalence of dyslipidemia decreased in 15 patients with adrenal CS (from 53% to 27%) and 14 patients with CS (from 64% to 50%) with treatment for hypercortisolism (27). A more significant improvement was reported in a study of 51 patients with CS, when hypercortisolism remission led to normalization of LDL and HDL in 60% and 78% of patients, respectively (28). In patients with MACS, adrenalectomy did not result in statistically significant improvement of dyslipidemia after a median of 28 months following surgery (57).

Effect of therapy for hypercortisolism on cardiovascular events

Remission from CS leads to a decrease in frequency of cardiovascular risk factors and decrease in rate of cardiovascular events (27,28,57). In a study of 51 patients with CS, rate of cardiovascular events in patients with CS in remission was 3.9%, as opposed to 29% in patients with persistent CS (28). However, risk for cardiovascular events remains elevated despite remission when compared to controls, suggesting that achieving eucortisolism does not completely eliminate cardiovascular risk (18,20,93). In a study of 25 patients with CS followed for 1 year after remission, despite improvement in vascular parameters, patients continued to demonstrate increased stiffness of carotid arteries wall and persistence of atherosclerotic plaques (56). In 71 patients with history of CS, structural changes with abnormal left ventricular mass and concentric remodeling were still seen after a median of 46 months following curative surgeries (85). At a median of 11 years after curative therapy, patients with history of CS were reported to have higher prevalence of coronary calcifications and evidence of atheroma plaques on cardiac computed tomography angiograms when compared to controls (94). Of 15 patients with history of CD followed 5 years after curative surgeries, 26.7% had evidence of atherosclerosis based on echo-Doppler ultrasonography (versus 0% in controls matched for age and sex) (86). In a study of 160 patients with CS in remission with at least 3 years of

Table 6 Effect of therapy for hypercortisolism on glucose metabolism

Study, year	Patients, n	Etiology of hypercortisolism, n	Prevalence of DM and IGT at baseline, n (%)	Therapy	Duration of follow up after therapy, mean, month	Prevalence of DM and IGT at follow up, n (%)	Resolution or improvement of DM and IGT at follow up
Etxabe *et al.*, 1994 (87)	49	CD: 49	DM: 19/49 (38%) IGT: 12/49 (24%)	Transsphenoidal surgery: 28 Bilateral adrenalectomy: 18 Pituitary radiotherapy: 16 Other: 1	76.1	DM: 9/49 (18%) IGT: 2/49 (4%)	Not reported
Colao *et al.*, 1999 (86)	15	CD: 15	DM: 7/15 (46.7%) IGT: 6/15 (40%)	Transsphenoidal surgery: 15	59.9	DM: 5/15 (33%) IGT: 4/15 (27%)	Not reported
Faggiano *et al.*, 2003 (56)	25	CD: 25	DM: 5/25 (20%) IGT: 16/25 (64%)	Transsphenoidal surgery: 25	12	Not reported	DM resolution: 2/5 (40%)
Chow *et al.*, 2008 (48)	68	CD: 42 Ectopic CS: 26	DM: 10/42 (24%) DM: 10/26 (38%)	Bilateral adrenalectomy: 68	Not reported	Not reported	DM resolution: 2/5 (29%)
Sippel *et al.*, 2008 (72)	60	CD: 17 Adrenal CS: 33 Ectopic CS: 10	DM: 24/59 (41%) Reported for entire cohort Missing data in 1 subject	Unilateral adrenalectomy: 31 Bilateral adrenalectomy: 27	44.4	Not reported	DM resolution: 15/19 (79%)
Giordano *et al.*, 2011 (27)	29	CD: 14 Adrenal CS: 15	DM: 5/14 (36%) IGT: 2/14 (14%) DM: 2/15 (13%) IGT: 6/15 (40%)	Transsphenoidal surgery: 14 Laparoscopic surgical Resection: 15	12 12	DM: 2/14 (14%) IGT: 2/14 (14%) DM: 0/15 (0%) IGT: 1/15 (7%)	Not reported Not reported
Ntali *et al.*, 2013 (74)	311	CD: 311	DM or IGT: 67/311 (22%)	Surgery: 308 Medical therapy: 3	108	DM/IGT: 53/311 (17%)	Not reported
Terzolo *et al.*, 2014 (28)	51	CD:33 Adrenal CS: 15 Ectopic CS: 3	DM: 14/51 (27%)	Transsphenoidal surgery: 33 Radiotherapy: 2 Medical therapy: 2 Bilateral adrenalectomy: 8 (Some patients received more than 1 treatment) Unilateral adrenalectomy: 11 Bilateral adrenalectomy: 4 Surgical resection: 3	56.55	DM: 5/51 (10%)	Not reported
Bancos *et al.*, 2016 (57)	584	Adrenal MACS: 584	DM: pooled proportion 52%	Adrenalectomy: 132	At least 6 months	Not reported	DM improvement: pooled 52%

Selection criteria: publication year: 1994 or after; design: retrospective, prospective studies or systematic reviews; intervention: surgical or medical therapy; outcome: glucose abnormality prevalence data available at baseline and/or after treatment. DM, diabetes mellitus; IGT, impaired glucose tolerance; CS, Cushing syndrome; CD, Cushing disease; MACS, mild autonomous cortisol secretion.

Table 7 Mortality in hypercortisolism

Type of hypercortisolism	Active hypercortisolism (persistent, untreated or recurrent)			Treated hypercortisolism			
	Patients, n	SMR (95% CI)/or mortality (%)	Citations	Patients, n	SMR (95% CI)	Follow-up after treatment, years	Citations
Cushing Disease	766	4.6 (2.9–7.3)	van Haalen *et al.*, 2015 (95)	766	2.5 (1.4–4.2)	Range: 1.3–12.8	van Haalen *et al.*, 2015 (95)
	40	6.9 (4.3–10)	Ragnarsson *et al.*, 2019 (96)	419	1.9 (1.5–2.3)	13	Ragnarsson *et al.*,2019 (96)
Ectopic Cushing syndrome	11	66.7 (21.2–160.8)	Ntali *et al.*, 2013 (74)	11	83.3 (4.2–411)	12	Ntali *et al.*, 2013(74)
Adrenal Cushing syndrome	No studies reported			109	1.9 (0.9–3.1)	Range: 7.4–11.2	Graversen *et al.*, 2012 (97)
Mild autonomous cortisol secretion	431	11.5%	Elhassan *et al.*, 2019 (23)	No studies reported			
Endogenous Cushing syndrome of any etiology, combined	386	2.4 (0.87–8.19)	Yaneva *et al.*, 2013 (98)	386	1.7 (0.6–3.6)	7.1	Yaneva *et al.*, 2013 (98)

Selection criteria: publication year: 2001 or after; design: retrospective, prospective studies, systematic reviews or meta-analyses; outcome: all-course mortality. SMR, standardized mortality ratio; CI, confidence interval.

follow-up compared to 879 patients with nonfunctioning pituitary adenoma, the prevalence of cardiovascular disease and cardiovascular risk factors was significantly higher in patients with CS despite remission (93). Risk of myocardial infarction and stroke remained elevated in a population study of 343 patients with CS in remission who were followed for 1–30 years with age and sex adjusted HR of 3.6 and 1.5 respectively (20).

Mortality in patients with hypercortisolism

Mortality in untreated or persistent hypercortisolism

Untreated or persistent hypercortisolism of any cause is associated with increased mortality (*Table* 7). In a meta-analysis of studies on mortality in CD published in 2015, a pooled standardized mortality ratio (SMR) was 4.6 and the range was between 2.4 and 16 (95). In a more recent study of 40 patients with persistent CS, SMR was 6.9 (96). Causes of death in patients with persistent CD and adrenal CS were reported to be primarily cardiovascular but also from infection or malignancy (74,96).

Mortality is highest in patients with ectopic CS, with SMR of 66.7 if remission is not achieved (74). Causes of death in patients with ectopic CS were reported to be mainly metastatic disease and sepsis, in 40% and 30% of patients respectively (74). In another study of patients with ectopic CS, poor survival was mainly due to cardiovascular (43%) and infectious (29%) causes (98). Patients with small cell lung carcinoma have the worst prognosis, whereas those bronchial carcinoid tumors have better survival (74,99).

Patients with MACS were reported to have a higher mortality, proportional to the severity of hypercortisolism. In a study of 206 patients diagnosed with an adrenal mass followed for a mean of 4.2 years, mortality was reported to be highest in patients with cortisol concentrations following the overnight dexamethasone suppression (DST) >5 mcg/dL (26%), followed by mortality in patients with DST between 1.8 and 5 mcg/dL (13%), as compared to only 1% mortality in patients with DST<1.8 mcg/dL (15). In patients with DST >1.8 mcg/dL, primary cause of death was cardiovascular (50%), followed by respiratory and infectious causes of death (33%) (15). A recent meta-analysis of patients with adrenal adenomas reported that mortality in patients with MACS is similar to patients with nonfunctioning adenomas at 11%, despite higher rate of new cardiovascular events in patients with MACS. It is important to note that very few studies reported on mortality of patients with untreated MACS, and duration of

follow up was insufficient for confident conclusions (23).

Mortality in cured hypercortisolism

Mortality in patients with hypercortisolism in remission is lower when compared to patients with persistent hypercortisolism, but is still increased with a pooled SMR of 2.5, as reported in a meta-analysis of studies of patients with CD (95) (*Table* 7). A similar finding was reported in a multicenter study in the UK, which found that those patients with CD in remission for more than 10 years still had increased risk of mortality (22). In a more recent study of 419 patients with CD and confirmed remission, SMR was 1.9 (96) with increased mortality mainly due to cardiovascular causes. Scarce data exist on mortality in treated adrenal CS. A meta-analysis of several studies on mortality in patients with treated adrenal CS demonstrated no statistically significant increase in mortality (97).

Possible contributors to persistent mortality after cure include co-existing pituitary deficiency (especially secondary adrenal insufficiency), prolonged duration of hypercortisolism leading to irreversibility of some of the metabolic consequences, persistence of pro-inflammatory cytokines and left ventricular hypertrophy (19,21,63,96,100). Older age at the time of diagnosis and time in remission were significantly associated with mortality (96). Another study reported that older age, male sex, and depression predicted mortality in patients with CD in remission (21). Post-treatment pituitary dysfunction in patients with CD was also demonstrated to play a role in mortality despite correction of hypercortisolism (96). For example, glucocorticoid replacement therapy was associated with HR of 2.6 for mortality, while levothyroxine and growth hormone supplementation demonstrated a HR of 1.2 and 0.4, respectively (96). Treatment modality for CD also plays a role in mortality. For example, in 102 patients with CD who were treated with bilateral adrenalectomy, SMR was 2.7; whereas in patients treated with pituitary surgery or radiotherapy SMR did not increase (96). Presence of hypertension and diabetes mellitus was associated with higher mortality in one study (19), but not demonstrated in another study (96).

Conclusions

Patients with untreated overt CS and MACS present with high prevalence of cardiovascular risk factors such as hypertension, abnormal glucose metabolism, dyslipidemia, and ultimately a high rate of cardiovascular events and increased mortality. Treatment of hypercortisolism is primarily surgical, although medical therapy or radiation may occasionally be used with the goal to achieve eucortisolism. Optimal treatment can lead to improvement or reversal of cardiovascular risk factors and decrease the incidence of new cardiovascular events. Even with successful treatment of hypercortisolism, patients in remission continue to demonstrate higher mortality than the general population.

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Footnote

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