**Overview of Endocrine Hypertension**

Christian A Koch, MD, PhD, FACP, MACE  
Prof. Koch is presently the Head of the Medcove MVZ Oldenburg and affiliated with the Carl von Ossietzky University as well as the Technical University of Dresden. He also is Adjunct Professor at the University of Louisville, KY. Before June 2017, Koch had served as a tenured professor at the University of Mississippi Medical Center in Jackson, MS.

George P Chrousos, MD, MACE, MACP, FRCP  
Division of Endocrinology, Metabolism and Diabetes (N.C.N., G.P.C., E.C.), First Department of Pediatrics, National and Kapodistrian University of Athens Medical School, Aghia Sophia Children’s Hospital, Athens, 11527, Greece; Division of Endocrinology and Metabolism (N.C.N., G.P.C., E.C.), Center of Clinical, Experimental Surgery and Translational Research, Biomedical Research Foundation of the Academy of Athens, Athens, 11527, Greece.

Last Update: October 26, 2016.

**ABSTRACT**

Endocrine hypertension typically is referred to disorders of the adrenal gland including primary aldosteronism, glucocorticoid excess, and the pheochromocytoma-paraganglioma syndromes. Rare conditions in patients with congenital adrenal hyperplasia and glucocorticoid resistance (Chrousos syndrome) can also lead to hypertension. Nonadrenal endocrine disorders, such as growth hormone excess or deficiency, thyroid dysfunction, testosterone deficiency, vitamin D deficiency, obesity-associated hypertension, insulin resistance and metabolic syndrome are also linked to hypertension. In this chapter, we provide an overview of endocrine hypertension including rare syndromes of mineralocorticoid excess. For complete coverage of all related areas of endocrinology, we invite you to visit our FREE web-book, WWW.ENDOTEXT.ORG.

**INTRODUCTION**

Hypertension affects approximately 31% of Americans (1, 2) and approx. 33% of the Mozambican population (3). The prevalence of hypertension is even higher than 33% in Germany, England, Spain, and Scandinavian countries. The assignment of a diagnosis of hypertension is dependent on the appropriate measurement of blood pressure, the level of the blood pressure elevation, and the duration of follow-up (4). Data from the National Health and Nutrition Examination Survey 2011-2012 showed an increase in the prevalence of hypertension in all age groups compared to 1991 (5). Among adults with hypertension in that survey, 52% achieved a BP of less than 140/90 mm Hg with 76% taking antihypertensives, and with 83% being aware of their hypertension.

The Eight Report of the Joint National Committee for the management of high blood pressure (BP) in adults provides different BP targets for various groups, therefore defines hypertension more broadly and individually (6). BP cutoff / treatment targets are now being controversially discussed after publication of the results of the Systolic Blood Pressure Intervention Trial (SPRINT) (7,8). BP assessment should be based on the mean of 2 or more properly measured seated BP readings on each of 2 or more office visits. Based on expert opinion, the 8th Joint National Committee panel recommends treating a blood pressure exceeding 139/89 mm Hg for adults from age 18 years to 60 and in all patients with diabetes or nondiabetic chronic kidney disease. For individuals aged 60 years or older, the BP goal should be less than 150/90 mm Hg and hypertensive people age 30 through 59 y should have a diastolic goal of less than 90 mm Hg (6). The SPRINT study included 9361 hypertensive patients with a high risk cardiovascular profile who were nondiabetic and older than age 50 y. Randomization was aimed to a target systolic BP of 130 to 140 mm Hg vs. less than 120 mm Hg, identical to the targets of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study (9). Exclusion criteria of the SPRINT study were a history of diabetes or prior cerebrovascular accident. 31% of the study individuals were African American and 28% had chronic kidney disease. The group with a SBP less than 120 mm Hg had a 24% reduction in events such as myocardial infarction, nonmyocardial infarction acute coronary syndrome, acute uncompensated heart failure, or death from cardiovascular disease. There was an increased number of visits to the emergency room for hypotension in the intensive treatment group. Both SPRINT and ACCORD studies showed an adverse effect of intensive BP treatment regarding glomerular filtration rate in people with initial normal renal function, but there was no increase in the incidence of end-stage renal disease in either study in the intensive treatment arm. The ACCORD study showed a reduction in the rate of total stroke by 40%. Summarizing the results of 17,114 participants enrolled in recent BP trials, Krakoff concludes that a SBP in the range of 125-135 mm Hg range is likely to be optimal on treatment for most hypertensive patients (10).

For children, hypertension is defined as an average systolic blood pressure (BP) and/or diastolic BP that is greater than the 95th percentile for age, gender, and height on more than 3 occasions. Normal BP in children is defined as a SBP and DBP smaller than the 90th percentile for age, gender, and height (11,12). Cuff size and arm circumference play a very important role in measuring correct blood pressures. In children and adolescents, BP is classified as normal (<90th percentile for SBP or DBP), prehypertensive, stage 1 hypertensive (90th to the 95th percentile plus 5 mm Hg), and stage 2 hypertensive (>99th percentile plus 5 mm Hg).

The prevalence of hypertension increases with age and most individuals with hypertension are diagnosed with primary (essential) hypertension. Hypertension is a major risk factor for stroke, ischemic heart disease, and cardiac failure. It is the second most common...
reason for office visits to physicians in the United States. Analysis of the Framingham study data suggested that individuals from age 40 to 69 years have a increasing risk of stroke or coronary artery disease mortality with every 20 mm Hg increment in SBP.

Despite the increasing understanding of the pathophysiology of hypertension, control of the disease is often difficult and far from optimal. Recent large meta-analyses and genotype studies have identified some “risk genes” for hypertension. Surendran and colleagues (13) found a low frequency nonsense variant in the gene ENPEP, which codes for the enzyme aminopeptidase A that converts angiotensin II into angiotensin III and therefore being part of the regulation of the renin-angiotensin-aldosterone system. Liu and colleagues (14) observed associations for the aggregation of rare and low frequency missense variants in the genes NPR1, DBH, and PTPMT1. The gene DBH codes for the enzyme dopamine beta-hydroxylase, which catalyzes the conversion of dopamine into noradrenaline and, thereby, influences the autonomic nervous system. The gene PTPMT1 codes for the mitochondrial protein tyrosine phosphatase 1, which influences insulin production.

Idiopathic (primary or essential) hypertension accounts for approximately 85% of the diagnosed cases. It is estimated that approximately 15% of hypertensive patients have identifiable conditions that result in blood pressure elevation (secondary hypertension), such as primary renal disease, oral contraceptive use, sleep apnea syndrome, congenital or acquired cardiovascular disease (i.e. coarctation of the aorta) and excess hormonal secretion.

Endocrine Hypertension accounts for approx. 3% of the secondary forms of hypertension and is a term assigned to states in which hormonal derangements result in clinically significant hypertension (15,16). The most common causes of endocrine hypertension are excess production of mineralocorticoids (i.e. primary hyperaldosteronism), catecholamines (pheochromocytoma), thyroid hormone, and glucocorticoids (Cushing syndrome) (17). One important question in this regard is when to screen for secondary causes. Some patients with hypertension, but without primary aldosteronism, demonstrate ACTH-dependent aldosterone hypersecretion by stress (18). The clinician should carefully screen for cardinal signs and symptoms of Cushing syndrome, hyper- or hypo-thyroidism, acromegaly, insulin resistance (acanthosis nigricans), or pheochromocytoma. Hypertension in young patients and refractory hypertension (characterized by poorly controlled blood pressure on > 3 antihypertensive drugs) should alert the physician to screen for secondary causes. The importance of endocrine-mediated hypertension resides in the fact that in most cases, the cause is clear and can be traced to the actions of a hormone, often produced in excess by a tumor, such as an aldosteronoma, in a patient with hypertension due to primary aldosteronism. More importantly, once the diagnosis is made, a disease-specific targeted antihypertensive therapy can be implemented, and, in some cases, surgical intervention may result in complete cure, obviating the need for life-long antihypertensive treatment.

**CLINICAL DIAGNOSIS OF ENDOCRINE HYPERTENSION**

The first step when evaluating a patient with suspected endocrine-related hypertension is to exclude other causes of secondary hypertension, particularly renal disorders. A detailed medical history and review of systems should be obtained. The onset of hypertension and the response to previous anti-hypertensive treatment should be determined. Consideration of adherence to prescribed antihypertensive regimen should be given (? poor compliance). A history of target organ damage (i.e. retinopathy, nephropathy, claudication, heart disease, abdominal or carotid artery disease) and the overall cardiovascular risk status should also be explored in detail.

The prevalence of resistant hypertension is high: 53% of patients in NHANES had a blood pressure < 140/90 mm Hg vs. 48% in the Framingham Heart Study. In NHANES participants with chronic kidney disease, 37% had a BP < 130/80 mm Hg. In ALLHAT, 34% of patients remained uncontrolled after 5 year follow-up on at least 2 antihypertensive drugs (19).

As in other causes of hypertension, the clinician should question the patient about dietary habits (salt intake etc.), weight fluctuations, use of over the counter drugs and health supplements including teas and herbal preparations, recreational drugs, and oral contraceptives. Moreover, a detailed family history may provide valuable insights into familial forms of endocrine hypertension. The review of systems should include disease-specific questions. Most patients harboring a pheochromocytoma are symptomatic. Symptoms may include headaches, palpitations, anxiety-like attacks and profuse sweating, similar to symptoms of hyperthyroidism. The triad headache, palpitations, and sweating in a hypertensive patient was initially found to have a sensitivity of 91% and specificity of 94% for pheochromocytoma (20). More recent studies suggest that this typical triad of symptoms is found much less frequently, for instance, in only 10% of cases (21). Ten or more percent of patients with pheochromocytoma may not have any clinical symptoms and may be normotensive (21-28).

Patients with Cushing syndrome often complain of weight gain, insomnia, depression, easy bruising and fatigue. Acne and hirsutism (in women) can also be observed. The challenge these days is to recognize patients with evolving Cushing’s syndrome amongst the many obese and often poorly controlled diabetic individuals. An Endocrine Society Clinical Practice Guideline can assist in this task (29).

Primary hyperaldosteronism is manifested by mild to severe hypertension. Hypokalemia can be present, but it is not a universal finding and there is normokalemic and normotensive primary aldosteronism (30). Polyuria, myopathy and cardiac dysrhythmias may occur in cases of severe hypokalemia. A thorough physical exam with attention to evidence of target organ injury and features of secondary
hypertension should be conducted.

To better understand the sequelae of disturbed adrenal hormone synthesis, please refer to Figure 1 and also to the following chapters in endotext.com: Section Endocrine Testing Protocols – Chapter 7. Testing for Endocrine hypertension, Melcescu & Koch; Section Adrenal Disease and Function - Chapter 35, Von Hippel-Lindau Disease. Gläsker S, Neumann HPH, Koch CA, Vortmeyer AO.

**Figure 1  Adrenal Steroid Synthesis.**

Z Glom = zona glomerulosa; Z Fas = zona fasciculata; Z Ret = zona reticularis; 19-H = 19-Hydroxylase; HSD = Hydroxysteroid dehydrogenase; P450aro = aromatase; 5alpha-Red = 5alpha-Reductase. The 3 adrenal cortex zones Z Glom, Z Fas, and Z Ret stand above the “column” of hormones that are produced in the respective zone. The steroidogenic enzymes on the left starting with P450scc (Desmolase) are listed in order for “vertical and horizontal reading”, i.e. Desmolase converts cholesterol to pregnenolone, 3beta-OH-Steroid Dehydrogenase I/II convert pregnenolone to progesterone, 17-OH-Pregnenolone to 17-OH-Progesterone, and P450c11 converts deoxycorticosterone to 18-OH-Corticosterone and 11-Deoxy cortisol to cortisol, etc. (modified from ref. 31: Koch CA. Encyclopedia of Endocrine Disease, 2004)

**PRIMARY ALDOSTERONISM**

In a community-based study (Framingham Offspring) comprising 1688 nonhypertensive participants, increased plasma aldosterone concentrations within the physiologic range predisposed persons to the development of hypertension (32). Previous studies have reported a prevalence of primary aldosteronism (PA) of 1-2 %. Newer data suggest an overall prevalence of >5% and possibly >10% among the hypertensive population (33-36). In patients with mild to moderate hypertension without hypokalemia, the prevalence of PA has been reported to be 3% (37). In patients with resistant hypertension, the prevalence ranges between 17 and 23 % (36). In a study involving 1616 patients with resistant hypertension, 21% (338 pts) had an Aldosterone/Renin Ratio of > 65 with concomitant plasma aldosterone concentrations of > 416 pmol/L (15 ng). After salt suppression testing, only 11% (182 pts) of these patients had primary aldosteronism (38). In patients with adrenal incidentaloma and hypertension, the prevalence of aldosteronism is low at 2% (36). Many (up to 63%) patients with PA may not present with hypokalemia but are rather normokalemic (36,39-42). Low renin hypertension is not always easy to differentiate from PA (43). Born-Frontsberg and colleagues found that 56% of 553 patients with primary aldosteronism had hypokalemia and 16% had cardio-and cerebrovascular comorbidities (44). In addition to the patient group with resistant hypertension, screening for primary aldosteronism is recommended for those patients with diuretic-induced or spontaneous hypokalemia, those with hypertension and a family history of early-onset hypertension or cerebrovascular accident at young age, and those with hypertension and an adrenal incidentaloma (12,36,45). Recently, a study including 148 hypertensive patients found that a new overnight diagnostic test using pharmaceutical renin-angiotensin-aldosterone system blockade with dexamethasone, captopril and valsartan, has low cost, is rapid, safe and easy to perform with an estimated sensitivity of 98% and specificity of 100% (46).
The **2016 Endocrine Society clinical practice guideline** for the management of primary aldosteronism suggest that patients with hypertension, spontaneous hypokalemia, undetectable renin, and a plasma aldosterone concentration above 20 ng/dl (550 pmol/L) may not need to undergo further confirmatory testing but instead proceed with further imaging and/or adrenal vein sampling or (if unable or unwilling to undergo surgery/adrenalectomy) treatment with a mineralocorticoid antagonist (36).

PA can be a sporadic or familial condition. Most cases of sporadic PA are caused by an aldosterone-producing adrenal adenoma. However, bilateral zona glomerulosa hyperplasia is much more common in sporadic primary hyperaldosteronism than previously thought and is an important differential diagnosis, since it is treated medically with aldosterone antagonists, rather than by adrenalectomy (47,48). Selective use of adrenal venous sampling is helpful in this setting (48-50). Very rarely, PA can be caused by an adrenal carcinoma, or unilateral adrenal cortex hyperplasia (also called primary adrenal hyperplasia).

Familial aldosteronism is estimated to affect 2% of all patients with primary hyperaldosteronism and is classified as type 1, type 2, and type 3 (51-53). Patients with familial aldosteronism type 3 produce amounts of 18-OHF and 18-oxof F10-1,000 times higher than patients with familial aldosteronism type 1 (approx. 20 times normal) or patients with familial aldosteronism type 2 or sporadic aldosteronism (54). Patients with familial aldosteronism type 3 have a paradoxical rise of aldosterone after dexamethasone, atrophy of the zona glomerulosa, diffuse hyperplasia of the zona fasciculata, and severe hypertension in early childhood (around age 7 years) that is resistant to drug therapy but curable by bilateral adrenalectomy (55).

In familial hyperaldosteronism type 1, an autosomal dominantly inherited chimeric gene defect in CYP11B1/CYPB2 (coding for 11beta-hydroxylase/aldosterone synthase) causes ectopic expression of aldosterone synthase activity in the cortisol-producing zona fasciculata, making mineralocorticoid production regulated by corticotropin (56,57). The hybrid gene has been identified on chromosome 8. Under normal conditions, aldosterone secretion is mainly stimulated by hyperkalemia and angiotensin II. An increase of serum potassium of 0.1 mmol/L increases aldosterone by 35%. In familial hyperaldosteronism type 1 or glucocorticoid-remediable aldosteronism, urinary hybrid steroids 18-oxocortisol and 18-hydroxycortisol are approx. 20-fold higher than in sporadic aldosteronomas. Intracranial aneurysms and hemorrhagic stroke are clinical features frequently associated with familial hyperaldosteronism type 1 (58). The diagnosis is made by documenting dexamethasone suppression of serum aldosterone using the Liddle’s Test (dexamethasone 0.5 mg q 6h for 48h should reduce plasma aldosterone to nearly undetectable levels (below 4 ng/dl) (59,60) or by genetic testing (Southern Blot or PCR). In contrast, familial hyperaldosteronism type 2 is not glucocorticoid-remediable. The responsible gene has been linked to chromosome 7p22 but has not yet been identified (61). Familial aldosteronism type 3 is caused by heterozygous gain-of-function mutations in the potassium channel GIRK4 (encoded by KCNJ5) leading to an increase in aldosterone synthase expression and production of aldosterone (51,62).

Another evolving familial form of primary aldosteronism appears to be linked to germline mutations in **CACNA1D** and **CACNA1H**, genes that encode voltage-gated calcium channels (51).

Primary aldosteronism is screened for by measuring plasma aldosterone (PA) and plasma renin activity (PRA) or direct renin concentration. There are various assays for measuring aldosterone, which can prove to be problematic (63-65). Measuring PRA is complicated and includes generating angiotensin from endogenous angiotensinogen. Quantification of renin’s conversion of angiotensinogen to angiotensin II is performed utilizing radioimmunoassays for PRA, which are not standardized among laboratories. Measuring plasma renin molecules directly by an automated chemiluminescence immunoassay as direct renin concentration also is feasible. A PA/PRA-ratio > 30 with a concomitant PA > 20 ng/dl has a sensitivity of 90% and specificity of 91% for primary aldosteronism (66). Because low renin hypertension can be difficult to distinguish from PA, an upright plasma aldosterone of at least 15 ng/dl may be helpful (43).

As hypokalemia can reduce aldosterone secretion, it should be corrected before further diagnostic work-up. Also, if a patient with hypertension treated with an ACE inhibitor or ARB, calcium channel blocker, and a diuretic (all of which should increase PRA, thereby lower the PA/PRA-ratio or ARR), still has a suppressed renin and 2-digit plasma aldosterone level, primary aldosteronism is likely. Because of medication interference, it is commonly recommended to withdraw betablockers, ACE inhibitors, ARBs (angiotensin receptor blockers), renin inhibitors, dihydropyridine calcium channel blockers, nonsteroidal anti-inflammatory drugs, and central alpha2-agonists approx. 2 weeks before PA/PRA-ratio or ARR testing, and to hold spironolactone, eplerenone, amiloride, and triamterene, and loop diuretics approx. 4 weeks before ARR testing. Licorice root products should also be withheld 4 weeks prior to testing (36). Confirmatory testing can be done by different techniques (36).

To clinically distinguish hyperplasia from unilateral adenoma, imaging with computed tomography and magnetic resonance imaging are helpful but adrenal venous sampling (AVS) with cosyntropin (ACTH) infusion is often essential if the patient desires surgery in case of a unilateral adenoma: cutoff for unilateral adenoma > 4 “cortisol-corrected” aldosterone ratio (adenoma side aldosterone/cortisol: normal adrenal gland aldosterone/cortisol); cutoff for bilateral hyperplasia < 3 “cortisol-corrected” aldosterone ratio (high-side aldosterone/cortisol: low-side aldosterone/cortisol).

If a patient does not desire surgery/adrenalectomy for a unilateral aldosteronoma/hyperplasia (Figure 2), medical therapy should be
initiated. AVS and CT/MRI of the adrenal glands show a unilateral abnormality in 60.5% and 56%, respectively, but were congruent on the involved side in the same patient in only 37% in a recent systematic review (67). If a patient is older than age 40 years, the risk for an adrenal incidentaloma increases (68). Unilateral adrenalectomy can be helpful in some patients with primary aldosteronism and bilateral adrenal hyperplasia (69).

Figure 2  Conn adenoma.

Appearance of a 1 cm right adrenal nodule (arrow) on contrast-enhanced computed tomography in a middle-aged man with hypertension treated for 20 years, initially only with a betablocker before becoming medically refractory and hypokalemic with inappropriate kaliuresis. After laparoscopic right adrenalectomy, the patient required only one antihypertensive to control his blood pressure.

Adrenal adenomas producing aldosterone should be removed. Nearly all patients with such endocrine hypertension have improved blood pressure control and up to 60% are cured (normotensive without antihypertensive therapy) from hypertension (70-72). This outcome is influenced by various factors including age, duration of hypertension, coexistence of renal insufficiency, use of more than 2 antihypertensive drugs preoperatively, family history of hypertension, and others. Bilateral adrenal hyperplasia is treated with spironolactone, eplerenone, and/or amiloride (36,73). Currently under investigation are aldosterone synthase inhibitors, which may not have any nongenomic/non-mineralocorticoid receptor-mediated adverse effects (74). In cases of familial hyperaldosteronism type 1, dexamethasone is also effective by suppressing ACTH and subsequently aldosterone overproduction. Parameters of insulin sensitivity can be restored to normal with treatment of PA (75). A cross-sectional study including 460 pts with primary aldosteronism and 1363 controls with essential hypertension found no significant difference between pre- and postoperative levels of fasting plasma glucose and serum lipids (76). This topic has been extensively reviewed from a pro and contra perspective (77).

PHEOCHROMOCYTOMA

These rare neuroendocrine tumors are composed of chromaffin tissue containing neurosecretory granules (78). Most pheochromocytomas are sporadic but some occur in an inherited form. Recent studies suggest up to 24% of pheochromocytomas are
Patients with multiple endocrine neoplasia type 1 or type 2, von Hippel-Lindau syndrome, neurofibromatosis type 1, and those with germline mutations in the SDHB/C/D genes can develop hereditary pheochromocytomas (28,80,81). There is controversy when genetic testing should be obtained in patients with pheochromocytoma, especially considering cost effectiveness (81,82). Erlic and coworkers (81) used six predictors to develop a screening algorithm in order to find out which patients should be genetically tested for germline mutations. If any of these 6 predictors is present, the patient should be tested, according to these authors (Figure 3).

![Proposed Algorithm for Genetic Testing in pheochromocytoma. Modified from Erlic et al., 2009 (ref. 81)](image)

The 2014 Endocrine Society clinical practice guideline recommends that all patients with pheochromocytoma-paraganglioma should be engaged in shared decision making for genetic testing (28). All patients with paraganglioma should undergo testing for succinate dehydrogenase (SDH) mutations and those patients with metastatic disease should be tested for $SDHB$ mutations. Recognizing the distinct genotype-phenotype presentations of patients with hereditary tumors, the guideline recommends a personalized approach to patient management.

The biochemical profile of pheochromocytomas associated with the aforementioned hereditary syndromes varies (83). Patients with MEN 2 and VHL syndrome may have clinically “silent” pheochromocytomas. Normotensive patients may also have sporadic pheochromocytomas (24). It appears that approx. 15% of patients with pheochromocytoma are normotensive (22-27). Blood pressure does not correlate with circulating catecholamines in patients with pheochromocytoma (84).

Although in older textbooks one finds still the term Sipple syndrome for multiple endocrine neoplasia type 2, it now appears that the original description of classic MEN-2 was made by Felix Fraenkel in 1886 (85).

Hypertension is paroxysmal in approximately 50% of patients with pheochromocytoma. The diagnosis can be established by measuring free plasma or fractionated urinary metanephrines and normetanephrines (28). When plasma free metanephrines cannot be measured by
HPLC with electrochemical detection or high-throughput automated liquid–chromatography-tandem mass spectrometry (LC-MS/MS), measuring plasma free metanephrines by RIA or measuring plasma chromogranin A may represent good markers for pheochromocytoma (86-89). In rare circumstances, pheochromocytomas release large amounts of dopamine (90). In patients with renal failure, plasma concentrations of free metanephrines can be increased several fold (91-93).

Approximately 35% of extra-adrenal pheochromocytomas are malignant (metastasizing) as opposed to approximately 10% of those arising in the adrenal gland. The risk for malignancy increases when the tumor exceeds 5 cm in size and when there is a germline mutation in the SDHB gene (94-96). Therefore, for such tumors exceeding 6 cm in size, open adrenalectomy is the suggested procedure for tumor removal rather than laparoscopic or retroperitoneoscopic minimally invasive tumor removal, to ensure complete tumor resection, prevent tumor rupture, and avoid local recurrence (page 1931 in ref. 28; Koch, Figure 4a,b, unpublished observation in a patient with MEN2-related bilateral pheochromocytomas and unilateral tumor recurrence 11 years after bilateral adrenalectomy, photo: courtesy of Prof. Andrea Tannapfel).
CT or MR imaging can localize the tumor in approx. 95 % of cases. For malignant pheochromocytomas, 18F-Fluorodopamine and 18F-FDG PET appears to be more helpful than 123I-MIBG or 131I-MIBG scintigraphy (28,97). In fact, MIBG scintigraphy should nowadays only be used in selected patients (98,99). Many medications can interfere with 123I-MIBG or 131I-MIBG uptake (for instance, calcium channel blockers, antipsychotics) and should be discontinued before the scan/imaging. The 2014 Endocrine Society guideline (28) recommends the use of 123I-MIBG in patients with metastatic pheochromocytoma-paraganglioma when radiotherapy with 131I-MIBG is planned and occasionally in some patients with an increased risk for metastatic disease (large tumor size, extra-adrenal tumor, multifocal or recurrent disease).

For patients with head and neck paragangliomas, 111In-octreotide has a very good sensitivity (100). Approx. 50% of patients with malignant pheochromocytomas respond to 131I-MIBG therapy by partial remission or at least stable disease (94). Chemotherapy is usually administered according to the so-called Averbuch protocol from 1988. New therapies may include tyrosine kinase inhibitors in selected patients (101-103).

CONGENITAL ADRENAL HYPERPLASIA: 11BETA-HYDROXYLASE DEFICIENCY

The most common cause of congenital adrenal hyperplasia (CAH) is 21-hydroxylase deficiency. Hypertension per se has not been regarded as a component of this syndrome. Recent data have suggested that hypertension may be more prevalent in this patient population than previously thought (104-106).

Approx. 5% of all cases of CAH care caused by 11beta-hydroxylase deficiency. 11beta-hydroxylase is responsible for the conversion of deoxycorticosterone (DOC) to corticosterone (precursor of aldosterone) and 11-deoxycortisol to cortisol. In approximately 2/3 of individuals affected by a deficiency of this enzyme, monogenic low renin hypertension with low aldosterone levels ensues caused by accumulation of 11-deoxycortisol and DOC (107,108). The earliest age of onset of hypertension was reported at birth (109). The inheritance mode is autosomal recessive. The responsible gene CYP11B1 is located on chromosome 8 and mutated (110). Since corticotropin (ACTH) is chronically elevated and precursors such as 17-OH progesterone and androstendione accumulate, androgen production is increased and may lead to prenatal virilization with resulting pseudohermaphroditism in females. Males may develop
CONGENITAL ADRENAL HYPERPLASIA: 17ALPHA-HYDROXYLASE DEFICIENCY

This enzyme deficiency is rare and leads to diminished production of cortisol and sex steroids. Chronic elevation of ACTH causes an increased production of DOC and corticosterone with subsequent hypertension, hypokalemia, low aldosterone concentrations with suppressed renin as well as pseudohermaphroditism in XY males (114), and sexual infantilism and primary amenorrhea in females (115,116). Diagnosis may be delayed until puberty. Plasma adrenal androgen levels are low as are cortisol, aldosterone, plasma renin activity, and 17alpha-hydroxypregosterone. DOC, corticosterone, and 18-hydroxycorticosterone are elevated. Blood pressure is reduced by glucocorticoid replacement. The responsible gene for cytochrome P450C17 is located on chromosome 10q24.

APPARENT MINERALOCORTICOID EXCESS

Low-renin hypertension (undetectable aldosterone, hypokalemia) can present in various forms, one of them is apparent mineralocorticoid excess (AME), an autosomal recessive disorder caused by deficiency of the 11beta-hydroxysteroid dehydrogenase type 2 (11beta-HSD2) enzyme (117-120). This enzyme converts cortisol to the inactive cortisone in renal tubular cells.

In 1977, New et al. (121) first described this syndrome and in 1995 Wilson et al. (122) first reported mutations in the 11beta-HSD2 gene located on chromosome 16q22 cause AME. The 11beta-HSD2 enzyme is co-expressed with the mineralocorticoid receptor in renal tubular cells and leads to conversion of cortisol to cortisone (123). Cortisol does not bind to the mineralocorticoid receptor. Cortisol and aldosterone bind with equal affinity to the mineralocorticoid receptor but normal circulating concentrations of cortisol are 100 to 1000 fold higher than those of aldosterone (124). If 11beta-HSD2 is oversaturated or defective, more cortisol will be available to bind to the mineralocorticoid receptor (125). Diminished 11beta-HSD2 activity may be hereditary or acquired. Acquired deficiency of this enzyme may result from inhibition by glycyrrhetinic acid which may occur with use of licorice, chewing tobacco, and carbenoxolone. In childhood, AME often causes growth retardation/short stature, hypertension, hypokalemia, diabetes insipidus renalis, and nephrocalcinosis. Diminished 11beta-HSD2 activity may play a role in the pathogenesis of preeclampsia (126). The diagnosis of AME can be established by measuring free unconjugated steroids in urine (free cortisol/free cortisone ratio), and/or steroid metabolites (tetrahydrocortisol + allotetrahydrocortisol/tetrahydrocortisone) (127). Affected individuals have low renin and aldosterone levels, normal plasma cortisol levels, and hypokalemia. Treatment of AME consists of spironolactone, eplerenone, triamterene, or amiloride. Renal transplant is an option for patients with advanced renal insufficiency.

CONSTITUTIVE ACTIVATION OF THE MINERALOCORTICOID RECEPTOR (GELLER SYNDROME)

The MC receptor can be mutated leading to the onset of hypertension before age 20 (128). In vitro experiments demonstrate that progesterone and spironolactone, usually antagonists of the mineralocorticoid receptor, become agonists in Geller syndrome, suggesting “gain of function” mutations in the MC gene on chromosome 4q31. The inheritance pattern is autosomal-dominant.

LIDDLE SYNDROME

In 1963, Liddle (129) described patients with severe hypertension, hypokalemia, and metabolic alkalosis, who had low plasma aldosterone levels and plasma renin activity. An improvement of the hypertension occurred after salt restriction and triamterene therapy. Spironolactone is ineffective in this autosomal-dominant inherited syndrome. So-called “gain of function” mutations in the genes coding for the beta- or gamma-subunit of the renal epithelial sodium channel, located at chromosome 16p13, lead to constitutive activation of renal sodium reabsorption and subsequent volume expansion. The 24-h urine cortisone/cortisol ratio is normal.

PSEUDOHYPALDOSTERONISM TYPE 2

Pseudohypoaldosteronism type 2 or Gordon’s syndrome (130) is a rare Mendelian disorder, transmitted in an autosomal dominant fashion, and can cause low renin hypertension (131). It has an unknown prevalence, since many patients remain undiagnosed. Published families with this condition (hypertension, hyperkalemia, metabolic acidosis, normal renal function, low/normal aldosterone levels) are predominantly from Australia (Gordon et al.) or the United States (Lifton et al.). Hypertension in these patients may develop as a consequence of increased renal salt reabsorption, and hyperkalemia ensues as a result of reduced renal K excretion despite normal glomerular filtration and aldosterone secretion (132). The reduced renal secretion of potassium makes this condition look like an aldosterone-deficient state, thus the term “pseudohypoaldosteronism”.

These features are chloride-dependent. Infusion of sodium chloride instead of sodium bicarbonate corrects the abnormalities, as does the administration of thiazide diuretics, which inhibit salt reabsorption in the distal nephron. Gordon and coworkers found that all features could be reversed by very strict dietary salt restriction (130). Gordon syndrome is an autosomal, dominantly inherited disorder with
genes mapping to chromosomes 1, 12, and 17 (133,134). Mutations have been identified in WNK kinases WNK1 and WNK4 on chromosomes 12 and 17, respectively (133). Abnormalities such as activating mutations in the amiloride-sensitive sodium channel of the distal renal tubule are responsible for the clinical phenotype (135,136). Severe dietary salt restriction, antihypertensives, with preferably use of thiazide diuretics, can control the hypertension in this syndrome. Interestingly, common variants in WNK1 contribute to blood pressure variation in the general population (137). Figure 5 lists conditions with low renin levels.

### Conditions with low renin concentrations
- Mineralocorticoid Excess
  - Primary aldosteronism
  - Cushing’s syndrome
  - Glucocorticoid/cortisol resistance
- Apparent mineralocorticoid excess syndrome
- Licorice or carbenoxolone in excess
- Congenital adrenal hyperplasia (11beta- and 17alpha-hydroxylase deficiencies)
- 11-Deoxycorticosterone (DOC), 18-hydroxy-DOC excess
- Salt retention (Gordon and Liddle syndrome)
- Geller syndrome
- Salt loading (oral or intravenous)

### Other conditions leading to low renin levels
- Increasing age
- Low renin essential hypertension
- Hyporeninemic hypoaldosteronism
- Hyperkalemia
- Therapy with beta-adrenergic blockers
- Catecholamine deficiency
- Autonomic dysfunction
- Decrease of renal tissue or being anephric

Figure 5  Low renin conditions

### Insulin Resistance
The metabolic syndrome is characterized by hypertension, abdominal/visceral obesity, dyslipidemia, and insulin resistance (138). At least 24% of adults in the United States meet the criteria for the diagnosis of metabolic syndrome, and this number may even be higher for individuals over the age of 50 years (139). Insulin resistance is significantly associated with hypertension in Hispanics and can cause vascular dysfunction (140,141). Patients with essential hypertension often are insulin resistant (142). Interestingly, not all insulin resistant patients are obese. Excess weight gain, however, accounts for as much as 70% of the risk for essential hypertension and also increases the risk for end stage renal disease (143). In insulin-sensitive tissues, insulin can directly stimulate the calcium pump leading to calcium loss from the cell (144). In an adipocyte, elevated cytosolic calcium concentrations can induce insulin resistance. In a cell resistant to insulin, the insulin-induced calcium loss from cells would be decreased. With the subsequent increase in intracellular calcium, vascular smooth muscle cells respond more eagerly to vasoconstrictors and thus lead to rising blood pressure. Other mechanisms possibly explaining the association of insulin resistance and hypertension are increased sodium retention and increased activity of the adrenergic nervous system (145). In obesity, increased production of most adipokines (bioactive peptides secreted by adipose tissue) impacts on multiple functions including insulin sensitivity, blood pressure, lipid metabolism, and others (146-148).

### Hyperparathyroidism
Parathyroid hormone levels in hypertensive patients usually are in the normal range and appropriate for the serum calcium
concentration. However, patients with essential hypertension excrete more calcium compared to normotensive people, suggesting an enhanced parathyroid gland function (149). When infused, PTH is a vasodilator, although chronic infusion of PTH raises blood pressure in healthy subjects (150,151). High-calcium intake may lower blood pressure (152,153). However, hypercalcemia is associated with an increased incidence of hypertension (1). In patients with primary hyperparathyroidism, hypertension is observed in approximately 40% of cases. The mechanisms of these observations/associations are unclear. Hypertension is usually not cured or better controlled after parathyroidectomy (154,155). In patients with asymptomatic primary hyperparathyroidism, surgery/parathyroidectomy did not show any benefit regarding blood pressure or quality of life when compared to medical management (156). On the other hand, severe hypertension may improve in patients with primary HPT who undergo parathyroidectomy (157). Arterial stiffness measured in the radial artery seems to be increased in patients with mild primary hyperparathyroidism (158). Patients with primary hyperparathyroidism have carotid vascular abnormalities (159). Another contributory factor to hypertension in patients with primary HPT may be endothelial dysfunction (160). In MEN syndromes, hypertension in patients with hyperparathyroidism may be related to an underlying pheochromocytoma or primary aldosteronism. Criteria for parathyroidectomy have recently been revisited at the Fourth International Workshop on the management of asymptomatic primary hyperparathyroidism, including now skeletal and/or renal involvement (nephrocalcinosis on imaging) (161).

**Cushing Syndrome**

Hypercortisolemia is associated with hypertension in approximately 80% of adult cases and half of children (162-166). A recent workshop consensus paper attempts to rationalize the treatment of hypertension in patients with Cushing syndrome (167). In patients with Cushing disease, night-time blood pressure decline is significantly lower than that in patients with essential hypertension (168). After cure of Cushing syndrome, approximately 30% of patients have persistent hypertension (169). In children and adolescents, blood pressure normalization occurs in most patients within a year and seems to be dependent on the degree and duration of presurgical hypercortisolemia (164,165). In patients with Cushing disease, renin and DOC levels are usually normal, whereas in ectopic corticotropin syndrome, hypokalemia is common and related to an increased mineralocorticoid activity with suppressed renin and elevated DOC levels.

There are several mechanisms of blood pressure elevation in Cushing syndrome: increased hepatic production of angiotensigen and cardiac output by glucocorticoids, reduced production of prostaglandins via inhibition of phospholipase A, increased insulin resistance, and oversaturation of 11beta-HSD activity with increased mineralocorticoid effect through stimulation of the mineralocorticoid receptor (170,171). Screening studies for Cushing’s syndrome include measuring 24-h urinary free cortisol excretion on at least 2 occasions, performing a 1 mg dexamethasone suppression test, checking a midnight salivary cortisol and diurnal rhythm of cortisol secretion, and others listed in the recent Endocrine Society Clinical Practice Guideline (29). Therapy should be directed at removing glucocorticoid excess (172). Hypokalemia (especially in patients with ectopic ACTH production) can be treated with mineralocorticoid receptor antagonists such as spironolactone or eplerenone. Thiazide diuretics may also be helpful.

Given the increasing improvement in imaging and laboratory (assays etc.) techniques/modalities, one can expect an increasing number of incidentally discovered tumors and nodules in various organs including the adrenal glands. The future challenge will be when and to which extent to test individuals for disease conditions (173,174). For those individuals with adrenal incidentalomas but clearly lack of clinical features of Cushing syndrome, subclinical hypercortisolism may be detected biochemically depending upon which cutoff values and assays will be used. For the latter population, the American Association of Clinical Endocrinologists recommend using a cutoff for (8 AM) serum cortisol of 5 mcg/dl after 1 mg overnight (11 PM) dexamethasone which reveals approx. 58% sensitivity at a 100% specificity (175). A lower cutoff for serum cortisol suppression, i.e. 1.8 mcg/dl, usually rules out Cushing syndrome (173). A prospective, randomized study including 45 patients with subclinical hypercortisolism and adrenal incidentalomas was divided into 23 pts who underwent adrenalectomy and 22 pts under surveillance. Monitoring included glycemic control, blood pressure, lipid profile, obesity, and bone mineral density. In the surgical group, diabetes mellitus improved in 62% and hypertension in 67% of pts, whereas the conservative group showed worsening of glycemic control, blood pressure and lipid profiles (176).

**Glucocorticoid Resistance (Chrousos syndrome)**

This autosomal recessive or dominant inherited disorder is rare and caused by inactivating mutations of the glucocorticoid receptor gene (177,178). Cortisol and ACTH are elevated but there are no clinical features of Cushing syndrome. Permanent elevation of ACTH can lead to stimulation of adrenal compounds with mineralocorticoid activity (corticosterone, DOC), along with elevated cortisol secretion may lead to stimulation of the mineralocorticoid receptor, resulting in hypertension. In women, hirsutism and oligo-amenorrhea may develop through stimulation of androgens (androstendione, DHEA 5-androstendiol,). Clinically, children may present with ambiguous genitalia and precocious puberty. Men may be infertile and/or oligospermic. Women may have acne, excessive hair, menstrual irregularities with oligo-anovulation, as well as infertility (177,179).

Treatment entails suppression of ACTH secretion with high doses of dexamethasone (1-3 mg/day). Mineralocorticoid receptor-dependent hypertension may be treated with blockade of the receptor, for instance spironolactone or eplerenone.
Hyperthyroidism

Hyperthyroidism increases systolic blood pressure by increasing heart rate, decreasing systemic vascular resistance, and raising cardiac output (180,181). In thyrotoxicosis, patients usually are tachycardic and have high cardiac output with an increased stroke volume and elevated systolic blood pressure (182,183). Approx. one third of patients with hyperthyroidism have hypertension which often resolves after achieving euthyroidism (184,185). Subclinical hyperthyroidism may contribute to left ventricular hypertrophy and thereby lead to hypertension (186), although it has not yet been found to be associated with hypertension (187).

Hypothyroidism

Hypothyroid patients have impaired endothelial function, increased systemic vascular resistance, extracellular volume expansion, and an increased diastolic blood pressure (188,189). Hypothyroid patients have higher mean 24-h systolic blood pressure and BP variability on 24-h ambulatory BP monitoring (190). In 32% of hypertensive hypothyroid patients, replacement therapy with thyroxine leads to a fall in diastolic blood pressure to 90 mm Hg or less (191). There is a positive association between serum TSH and blood pressure within the normal serum TSH range, statistically significant for diastolic hypertension (192). Subclinical hypothyroidism may or may not be associated with hypertension (193-195). Hypothyroidism can lead to volume-dependent blood pressure elevation with low plasma renin concentrations (196-198).

Acromegaly

The prevalence of hypertension in patients with growth hormone excess is approximately 46% and more frequent than in the general population (199-201). Growth hormone has antinatriuretic actions and may lead to sodium retention and volume expansion (201-203). Increased systolic output and high heart rate as manifestations of a hyperkinetic syndrome may lead to congestive heart failure (201,204). Blood pressure values are increased in patients with acromegaly associated with reduced glucose tolerance or diabetes compared to those with normal glucose tolerance (201). The RAAS system appears to be implicated in the pathogenesis of hypertension in patients with growth hormone excess (200-206). Comorbidities in acromegals, such as hypertension, hyperlipidemia, diabetes mellitus, and cardiomyopathy, all may improve even with partial biochemical control of growth hormone excess (207-210).

Other potential endocrine conditions causing endocrine hypertension

There is accumulating evidence that vitamin D deficiency may be linked to an increased cardiovascular risk and hypertension (reviewed in ref. 211,212). Potential mechanisms in this setting are concurrent insulin resistance and direct vitamin D action through the renin-angiotensin-aldosterone system (Figure 6).
Testosterone deficiency is frequently identified in obese individuals and those with diabetes mellitus and/or metabolic syndrome including hypertension. Replacement therapy in selected patients may be beneficial not only related to their symptomatology of androgen deficiency such as low libido, poor erections, fatigue, and others, but also in regards to their metabolic profile and blood pressure (213-220).

Similarly, individuals with growth hormone deficiency may be at risk for developing hypertension, mostly because of their body composition being more “fat” and “inflamed” when compared to subjects with growth hormone sufficiency, as assessed by serum IGF-1 levels matched to gender and age. The key in such patients will be to replace them with growth hormone individually to an IGF-1 level at which no features of growth hormone excess develop and to increase physical activity. In obese subjects who are willing to take on major lifestyle changes with the goal to lose weight, eat and live healthier, temporary medication assistance (phentermine, topiramate, liraglutide, lorcaserin, orlistat, naltrexone-bupropion) including administration of growth hormone may be acceptable (221-228).

Individual tissue-dependent sensitivity of the glucocorticoid receptor and actions of endogenous glucocorticoids may play a major role in the development of hypertension, obesity, and diabetes mellitus (229-231).

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Hypertens Res. 2011 Oct;34(10):1098-105


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Bookshelf ID: NBK278980  PMID: 25905214