Endocrine hypertension

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Aims

- ✓ To understand caused of hypertension by endocrine disorders

- ✓ To understand the role of the renin-angiotensin-aldosterone system in the pathogenesis of endocrine hypertension

Definition and Epidemiology

Criteria

Normal (<120 systolic and <80 mm Hg diastolic)

Elevated (120–129 systolic and <80 mm Hg diastolic))

Stage 1 hypertension (130–139 systolic or 80–89 mm Hg diastolic

Stage 2 hypertension (≥140 systolic or ≥90 mm Hg diastolic

Epidemiology

- **Idiopathic hypertension** (primary or essential) - 85%
- **Secondary hypertension** - identifiable conditions - 15%:

Causes of Secondary Hypertension

Renal	**Glomerulonephritis,** **Renal artery stenosis,** **Renal vasculitis** **Adult polycystic disease** **Chronic renal disease,** **Renin producing tumors**
Endocrine	**Adrenocortical hyperfunction (Cushing syndrome, primary aldosteronism, congenital adrenal hyperplasia)** **Hyperthyroidism/Thyrotoxicosis** **Hypothyroidism/Myxdema,** **Pheochromocytoma** **Acromegaly** **Exogenous hormones (glucocorticoids, estrogen e.g. oral contraceptives)** **Pregnancy-induced**
Vascular	**Coarctation of aorta** **Vasculitis e.g.Polyarteritis nodosa** **Increased intravascular volume** **Increased cardiac output** **Rigidity of the aorta**
Neurogenic	**Psychogenic** **Increased intracranial pressure** **Sleep apnea** **Acute stress, including surgery**

Risk factors for Hypertension

- **Hereditary**,Genetics- family history
- **Race.** African-Americans
- **Gender.** Men & postmenopausal women
- **Age**
- **Obesity**
- **Diet, particularly sodium intake**
- **Lifestyle-stressful**
- **Heavy alcohol consumption**
- **Diabetes**
- **Use of oral contraceptives**
- **Sedentary or inactive lifestyle**

Endocrine Causes of Hypertension

Adrenal Dependent

Mineralocorticoid Excess (AME)

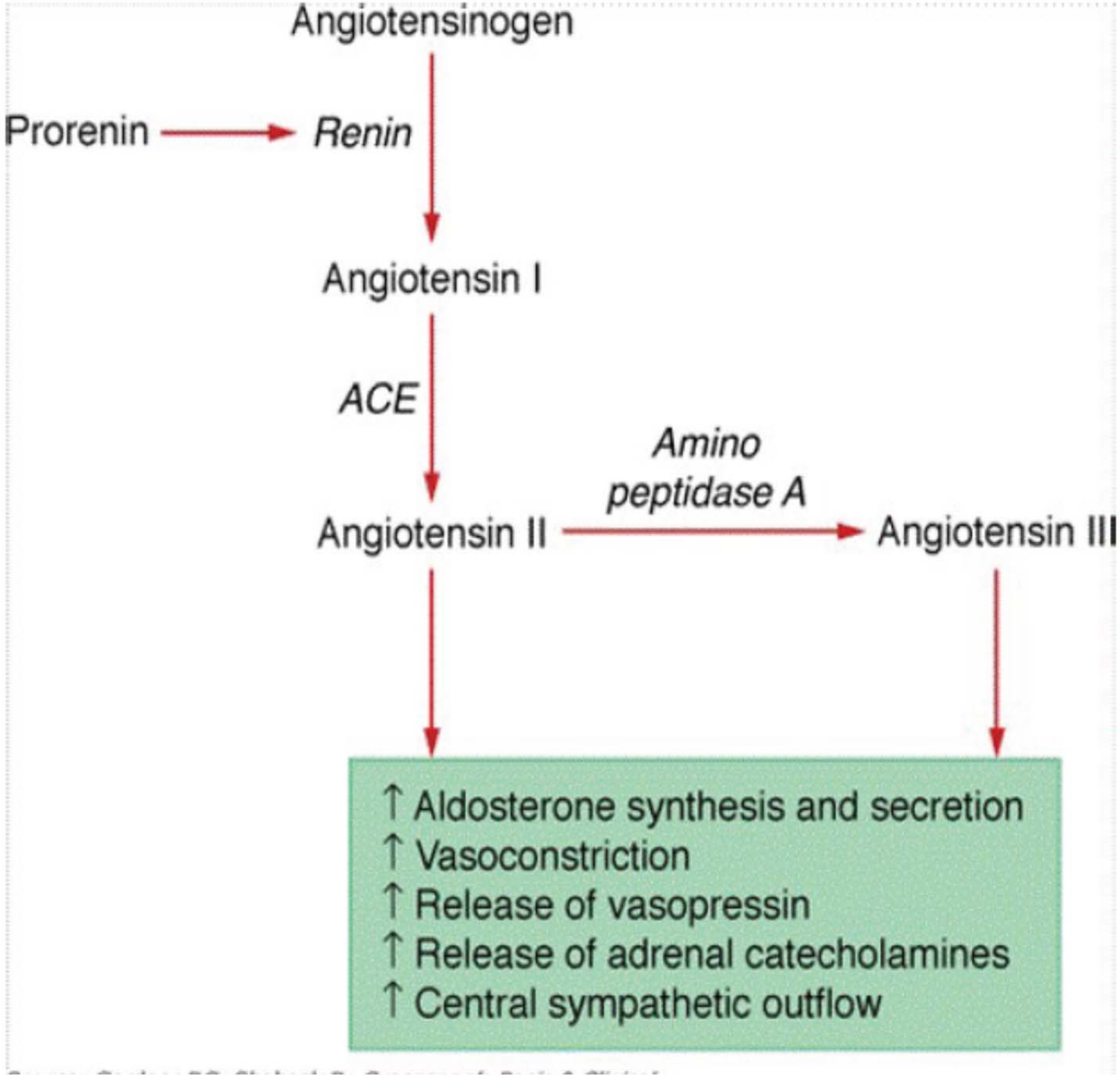
Thyroid Dependent

- Hyper- and hypothyroidism

Pituitary Dependent

- Acromegaly
- Cushing disease

Role of renin- angiotensin- aldosterone in regulating BP



Hypertension of adrenal origin

- Primary aldosteronism
- Cushing's syndrome
- Pheochromocytoma
- Syndromes due to excess deoxycorticosterone production
- Androgen- & estrogen-producing adrenal tumors
- Primary cortisol resistance

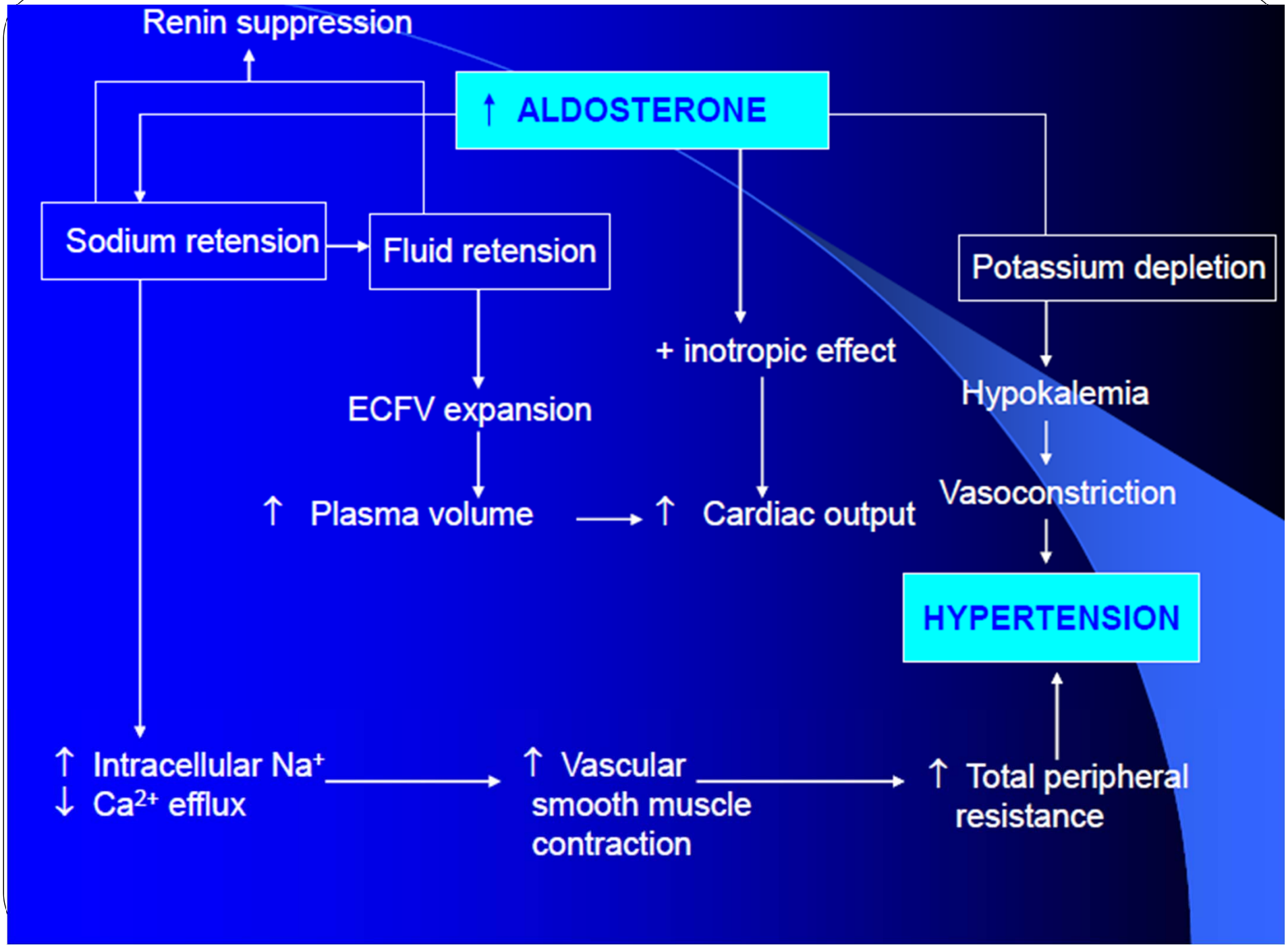
Primary aldosteronism

- prevalence:- 4-10%
- sporadic or familial
- adenoma (Conn's syndrome): 30-40%
- hyperplasia (uni- or bilateral) of zona glomerulosa tissue: 60%
- aldosterone-producing adrenocortical carcinoma: 0.5-1%
- dexamethasone (glucocorticoid)-remediable aldosteronism: 1-3%
- ectopic secretion (ovarian, renal and intestinal carcinoma) < 1%

Primary aldosteronism

should be considered in patients with:

- early-onset hypertension
- suppressed PRA
- strong family history of early cerebral hemorrhage (< 35 yr)


Renin suppression
↑ ALDOSTERONE
Sodium retension
Fluid retension
Potassium depletion
+ inotropic effect
ECFV expansion
Hypokalemia
↑ Plasma volume
↑ Cardiac output
Vasoconstriction
HYPERTENSION
↑ Intracellular Na+
↓ Ca2+ efflux
↑ Vascular smooth muscle contraction
↑ Total peripheral resistance

Hyperaldosteronism - clinical features

- Hypertension (severe)
- Hypokalemia (< 3.5 mEq/l), alkalosis

Symptoms of K+ depletion

Fatigue, weakness

thirst

Polyuria (especially nocturnal)

Paresthesias

Headaches

Primary hyperaldosteronism - diagnosis

- Biochemical assays: ▪K+ (< 3.5 mEq/l), ▪K+ in urine (> 50 mmol/24h)
- Hormonal assays:

  24-hour urine collection for aldosterone (>20 ▪g/24h)

Primary hyperaldosteronism - diagnosis

Aldosterone (PA, ng/dL) to renin activity (PRA, ng/ml/h) ratio:

< 20 - normotensive or essential hypertension

≥20 - suspicion for primary aldosteronism

≥30 (with a PA > 15 ng/dl) - 90% sensitivity and 91% specificity for the diagnosis of primary aldosteronism

≥50 - diagnostic of primary aldosteronism

Primary hyperaldosteronism - treatment

MR antagonist

- Spironolactone: side effects (at doses >100 mg/day) - especially in males (gynecomastia and erectile dysfunction) and females (menstrual dysfunction)
- Eplerenone - no anti-androgen activity

- Dihydropyridine calcium channel antagonists - effectively ↓ blood pressure and may ↓ aldosterone secretion
- Dietary sodium restriction (<100 mmol/day), regular aerobic exercise, maintenance of ideal body weight

Pheochromocytoma

- Catecholamine-producing tumors of chromaffin cells
- Present at any age (more commonly in the 4-5th decades)
- Located in adrenals - 90% in adults, 70% in children
- Unilateral - 90% – more frequent in the right adrenal (65% vs. 35%)
- Bilateral – 10% in adults, 35% in children, (common in familial syndromes)

Pheochromocytoma - clinical presentation

Hypertension	>98%
Hypertension sustained	50-60%
Hypertension paroxysmal	50%
Headache	70-90%
Palpitations+tachycardia	50-70%
Diaphoresis	60-70%
Fever	>66%
Nervousness	35-40%
Hyperglycemia	42%

Headaches + palpitations + sweating in patient with hypertension – suspicion for a pheochromocytoma

Pheochromocytoma - diagnosis

- 24-h urine collection for metanephrines
- metanephrines in plasma
- plasma or urine free catecholamines (less sensitive and specific)
- ultrasound scanning
- CT and MRI imaging

Pheochromocytoma - treatment

preoperative management:

calcium channel blockers

alpha-adrenergic blockers

ACE inhibitors

beta-adrenergic blockers (not prescribed without alpha-blockers)

surgical management

Other Forms of Mineralocorticoid Excess

Hyperdeoxycorticosteronism

- Deoxycorticosteronism - second most important mineralocorticosteroid hormone

- Excess deoxycorticosteronism should be suspected in any hypertensive patient with hypokalemia and suppression of renin and aldosterone production

Syndromes due to excess deoxycorticosteronism production

Congenital Adrenal Hyperplasia

- 17‣-hydroxylase deficiency
- 11‣-hydroxylase deficiency

Androgen- and estrogen-producing adrenal tumors

Primary cortisol resistance

17▪-hydroxylase deficiency

- Single gene mutation
- Impaired synthesis of cortisol, sex steroids
- Secretion of large amounts of deoxycorticosterone and corticosterone
- Decreased aldosterone secretion, suppression of renin

A Rare Condition: Apparent Mineralocorticoid Excess (AME)

- Caused by a problem that lets cortisol act like aldosterone.
- Can also be caused by eating too much licorice!
- Treated with medicine to block aldosterone effects.

17α-hydroxylase deficiency

recognized at the time of puberty in young adults

presenting symptoms:

- Hypertension

(High 11-deoxycorticosterone, low renin, low aldosterone)

- hypokalemia
- primary amenorrhea
- pseudohermaphroditism
- cortisol deficiency
- no virilization or retarded growth

11β-hydroxylase deficiency

- mutations of genes on chromosome 8
- recognized in newborns and infants
- classic, mild, late-onset forms (usually mild, with partial defect of cortisol production)
- High androgens, 11-deoxycortisol, 11-deoxycorticosterone, 17-hydroxyprogesterone, urinary 17-ketosteroids and 17-hydroxycorticosteroids
- Low cortisol

11β-hydroxylase deficiency

- virilization
- hypertension (high 11-deoxycorticosterone, hypokalemia, low renin)
- diagnosis: high 11-deoxycortisol, 11-deoxycorticosterone, urinary excretion of their metabolites

Androgen and estrogen producing adrenal tumors

- malignancies originating in the zona reticularis
- features of mineralocorticoid excess: hypertension, hypokalemia, renin supression
- inhibition of 11▪-hydroxylase with increased production of androgens, 11-deoxycorticosterone, 11-deoxycortisol
- enzymatic inhibition probably is due to high intra-adrenal concentration of androgens (pseudosubstrate for the reaction)

Syndrome of apparent mineralocorticoid excess (11β-hydroxysteroid dehydrogenase deficiency)

- Rare disorder
- Mutation in gene encoding 11-hydroxysteroid dehydrogenase type 2, which is present in the renal tubule
- Peripheral metabolism of cortisol: impaired conversion to cortisone in the renal tubule ・accumulation of cortisol and occupancy of MR
- Diagnosis: free steroids in urine (cortisol/cortisone) or steroid metabolites
- Treatment: spironolactone, eplerenone, triamterene, amiloride

Liddle's syndrome

- Familial disorder, autosomal dominant pattern of inheritance
- Defect in the epithelial Na channel resulting in constitutive activation
- Symptoms: hypertension, hypokalemia, renal K wasting, metabolic alkalosis, suppressed plasma renin activity, low aldosterone
- Treatment: administration of amiloride or triamteren (inhibitors of Na channel), salt restriction

Glucocorticoid resistance

- Autosomal recessive or dominant
- Inactivating mutations of the glucocorticoid receptor gene
- ↑ cortisol and ACTH
- No clinical features of Cushing's syndrome
- Permanent ↑ ACTH → production of compounds with mineralocorticoid activity
- ↑ cortisol stimulates mineralocorticoid receptor

Cushing's syndrome

- chronic glucocorticoid excess
- ACTH-dependent (90%)
  - pituitary adenoma (Cushing's disease) – 80%
  - nonpituitary neoplasm (ectopic ACTH secretion) – 10%

ACTH-independent (10%)

- iatrogenic (glucocorticoids)
- adrenal neoplasm (adenoma, carcinoma)
- nodular adrenal hyperplasia

Cushing's syndrome - clinical features

- obesity – central, mainly affecting the face („moon like face"), neck („buffalo hump"), trunk, abdomen, with relative sparing of the extremities
- skin changes – easy bruising, striae (red to purple, most commonly abdominal), acne, slow healing of minor wounds, mucocutaneous fungal infections, hyperpigmentation in case of ectopic ACTH secretion

Cushing's syndrome – clinical features

- hirsutism
- gonadal dysfunction
- psychologic disturbances – emotional lability, anxiety, depression, poor concentration, psychosis
- muscle weakness (more often proximal)
- osteoporosis
- diabetes mellitus
- hypokalemia
- hypertension

Cushing's syndrome – associated hypertension

- hypertension in approximately 80% of cases of endogenous hypercortisolemia (only in 10-20% in case of exogenous)

- night-time RR decline is significantly lower than that in patients with essential hypertension

Cushing's syndrome – associated hypertension

mechanisms of RR elevation:

- ↑ hepatic production of angiotensinogene
- ↑ cardiac output
- ↑ production of prostaglandins (inhibition of phospholipase A)
- ↑ insulin resistance

oversaturation of 11▪-HSD activity with increased mineralocorticoid effect

- ↑ vascular sensitivity to catecholamines
- ↑ extra- and intravasular volume

ectopic ACTH production – frequently associated with ▪DOC and corticosterone – mineralcorticosteroid excess state

Cushing's syndrome - diagnosis

- diurnal rhythm of cortisol secretion
- urinary free cortisol (24 h urine collection)
- plasma ACTH

Dexamethasone suppression test:

- screening test (short test) with 1 mg at bedtime (determination of cortisol at 8.00 a.m. – in healthy subjects < 1.8 µg/dl)
- low- and high-dose
- pituitary MRI
- CT and MRI of adrenal glands

Hyperparathyroidism and hypertension

- hypercalcemia - associated with ▪ incidence of hypertension
- in patients with primary hyperparathyroidism, hypertension is observed in approximately 40% of cases
- hypertension is not cured or better controlled after parathyroidectomy

Hyperthyroidism and hypertension

↑ **systolic blood pressure by:**

- ↑ heart rate (tachycardia)
- ↓ systemic vascular resistance
- ↑ cardiac output
- ↑ stroke volume

Hypothyroidism and hypertension

positive association between serum TSH and blood pressure

hypothyroid patients often have:

↑ diastolic blood pressure

impaired endothelial function

↑ systemic vascular resistance

extracellular volume expansion

subclinical hypothyroidism seems not to be associated with hypertension

Acromegaly and hypertension

prevalence of hypertension- 46%

GH - antinatriuretic actions, may lead to sodium retention and volume expansion

↑ systolic output and high heart rate (may lead to congestive heart failure)

the RAAS system appears to be implicated in the pathogenesis of hypertension in patients with acromegaly (▪ PRA, disturbances in dopaminergic regulation of aldosterone secretion)

Thank You!

- Questions and discussion