MINISTRY OF EDUCATION AND SCIENCE OF UKRAINE
SHEF "UZHHOROD NATIONAL UNIVERSITY"
DEPARTMENT OF INTERNAL DISEASES

ENDOCRINE DISORDERS

Part I

Methodological recommendations

Uzhhorod 2021

UDC

Methodological recommendations are purposed for medical students, clinical ordinators and family physicians. Recommendations contain information about main disorders of pituitary and adrenal glands

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METABOLIC SYNDROME

Metabolic syndrome is a clustering of **<u>any 3 out of 5</u>** <u>following conditions</u>:

1. Central obesity*
2. Increased blood preassure (BP≥140/90 mm Hg)
3. Increased blood sugar (≥5.6 mmol/L)
4. Increased serum triglycerides (≥1.7 mmol/L)
5. Decreased level of high-densitylipoproteins (HDL) (<1.03 mmol/L in males; <1/29 mmol/L in females)

*** Normal values of waist circumference:**

<u>American population</u>: less than **102 cm** (males), less than **88 cm** (females)
<u>European population</u>: less than **94 cm** (males), less than **80 cm** (females)

Investigations

BMI Formula

thecalculatorsite.com

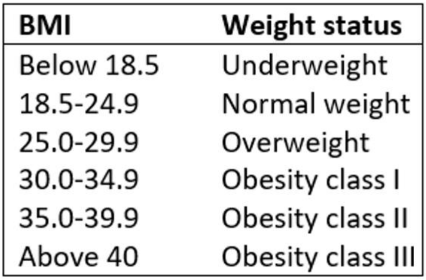
METRIC

BMI = weight (kg) / [height (m)]^2

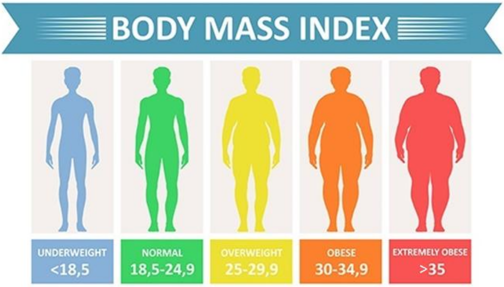
IMPERIAL

BMI = 703 x weight (lbs) / [height (in)]^2

- BMI
- Waist circumference
- Lipid panel
- Fasting plasma glucose/oral glucose tolerance test
- Levels of BP
-



BMI	Weight status
Below 18.5	Underweight
18.5-24.9	Normal weight
25.0-29.9	Overweight
30.0-34.9	Obesity class I
35.0-39.9	Obesity class II
Above 40	Obesity class III



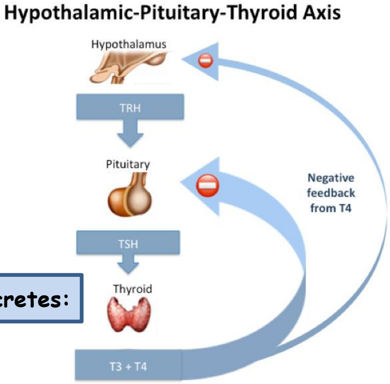
Treatment

- Diet (low fat and carbohydrate intake)
- Physical activity (30-45 min a day 5 days in a week)
- Control of BP (ACE-inhibitors (ex. Lisinopril), or ARB (ex. Losartan, Valsartan), Ca-channel blockers (ex. Amlodipine)
- Control of sugar level in blood (Metformin)
- Control of cholesterol level in blood (statins-atorvastatin, rosuvastatin)

HORMONES OF PITUITARY GLAND

The anterior pituitary (adenohypophysis) secretes:

1. Growth hormone (GH)
2. Prolactin
3. Adrenocorticotrophic hormone (ACTH)
4. Thyroid-stimulating hormone (TSH)
5. Luteinizing hormone (LH)
6. Follicle - stimulating hormone (FSH)



The posterior pituitary (neurohypophysis) secretes:

1. Oxytocin
2. Vasopressin (antidiuretic hormone)

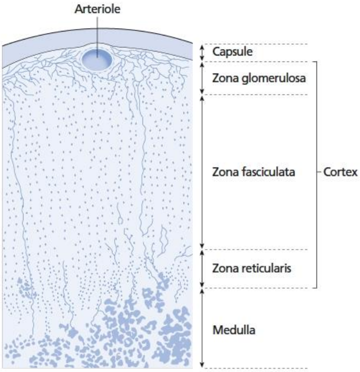
HORMONES OF ADRENAL GLAND

Hormones of adrenal cortex:

1. **ALDOSTERON** (Mineralocorticoids)
2. **CORTISOL** (Glucocorticoids)
3. **DEHYDROEPIANDROSTERONE** (Androgens)

Hormones of adrenal medulla:

1. **ADRENALINE AND NORADRENALINE** (Catecholamines)
   (epinephrine and norepinephrine)



ADDISON'S DISEASE

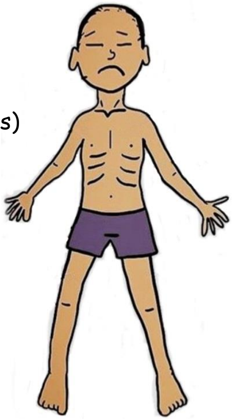
Deficiency of adrenal cortex

Most common cause

Autoimmune destruction of the adrenal cortex

Signs and symptoms

- Fatique
- Nausea / vomiting / diarrhea
- Hyperpigmentation of the skin
- Vitiligo: areas of depigmentation
- Anorexia
- Hypotension
- Alopecia
- Amenorrhoea (females)
- Low libido (females)
- Confusion



Investigations

- **Hypoglycaemia**
- **$\downarrow Na^+$ & H2O**
- **$\uparrow K^+$**
- **ACTH stimulation test**

An increase in cortisol after stimulation by ACTH is typical for healthy person.

Treatment

Lifelong glucocorticoid and mineralocorticoid therapy

In case the daily dose of glucocorticoids is using twice a day two thirds are ingested in the morning, one third in the evening.

Diet: high in protein, carbs and cooking salt

Addisonian Crisis

- Profound fatique
- Dehydration → shock
- Renal failure
- Vascular collapse
- Hyponatremia
- Hyperkalemia

Treat with:

- <u>IV glucocorticoids</u> (high doses of hydrocortisone)

and

- <u>Intravenous fluids</u>
- (to help with the dehydration and low blood pressure)

Differential Diagnosis

- Hemochromatosis
- Acute abdominal pain
- Anorexia nervosa

Normal values:

K^+ 3.5-5.0 mEq/L

Na^+ 135-145 mEq/L

Remember!

Addison's = low measurements (except HYPERkalaemia)

CUSHING'S DISEASE

Excess of cortisol

Signs and symptoms

- Weight gain, especially in the upper body
- Rounded face (**moon face**) and extra fat on the upper back (**Buffalo hump**)
- High blood sugar (**diabetes**)
- High blood pressure (**hypertension**)
- Thin bones (osteoporosis)
- Muscle loss and weakness
- Thin, fragile skin that bruises easily
- **Purple-red stretch marks** (striae) usually over the abdomen and under the arms
- Acne
- Depression, anxiety, irritability and difficulties thinking clearly
- Too much facial hair in women

Investigations

- **Serum cortisol level**
- **Salivary Cortisol Measurements**
- **Hyperglycaemia**
- $\uparrow$ **Na^+**
- $\downarrow$ **K^+ and Ca^+**
- **Urine Test to measure Cortisol Level**
- **Dexamethasone suppression test:**
  Low dose dexamethasone suppression test (exclude/confirm endogenous hypercortisolism)
  High dose dexamethasone suppression test (differentiate Cushing's disease and syndrome)
- **CT/MRI of pituitary and adrenal glands**

Remember! Cushing's = high measurements (except HYPOkalaemia and bones density)

Endogenous Cushing's syndrome can be divided into:

- ACTH-dependent CS:

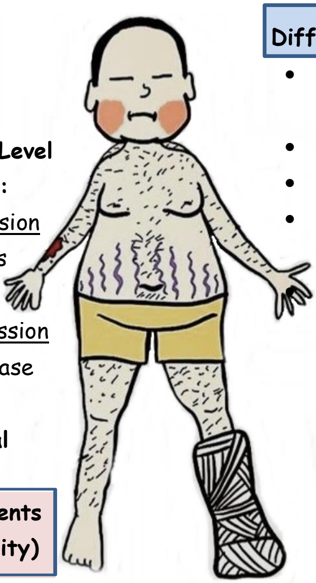
-excess ACTH secreted from a pituitary adenoma = **Cushing's disease**

- excess ACTH secreted from an ectopic source

- ACTH-independent (excess cortisol secreted from a benign adrenal adenoma or an adrenal carcinoma)

Treatment

- **Surgery** to remove the tumour that is causing high cortisol levels
- **Radiation therapy** to destroy any tumour cells that are left behind.
- Medications to lower cortisol, if surgery/radiation is not effective: **adrenal enzyme inhibitors** (ketoconazole, metyrapone)



Differential Diagnosis

- Essential hypertension
- Alimentary obesity
- Metabolic syndrome
- Pseudo-Cushing's syndrome
- Exogenous Cushing's Syndrome (due to glucocorticoid intake)

SIADH

Syndrome of inappropriate antidiuretic hormone secretion

Excessive secretion or action of antidiuretic hormone

Signs and symptoms

- Hypertension
- Tachycardia
- Weight gain without edema
- Nausea & vomiting
- Low urinary output
- Fluid volume overload
- **HYPONATREMIA that causes:**
- Headache
- Anorexia, nausea, vomiting
- Muscle cramps
- Depressed reflexes
- Confusion, restlessness, disorientation
- Lethargy
- Seizures
- Coma, death

Investigations

- **↓ Na^+ (<135 mEq/L)**
- **↑ Urine osmolality (>100 mosmol/kg)**
- ↑ Urinary specific gravity (>1.030)
- ↓Serum osmolality (<280 mOsm)
- **Serum osmolality** – low results
- **Urine osmolality** – high results
- **Urine sodium concentration** - high results (> 20 mmol/L)
- **Thyroid function tests**
- **Morning cortisol level** if hyponatremia is potentially related to Addison's disease
- **Computed tomography** of the head if a neurosurgical condition is suspected; **chest X-ray** if pulmonary causes of SIADH are suspected

Differential Diagnosis

- **Hypothyroidism**
- **Cortisol deficiency**
- **Diuretics**
- **Marked hyperproteinemia**

Hypokalaemia that causes

Treatment

- **Patients with minor symptoms (headache, nausea)**

- **Fluid restrictions**

Start 800-1200 ml/24 hours

- **Patients with severe symptoms (Vomiting, confusion, seizures, respiratory arrest, cerebral herniation)**

- **Hospital admission**
- Monitored fluid restriction, consideration of **hypertonic (3%) saline** bolus via central line

Remember!
In patients with SIADH water remains

DIABETES INSIPIDUS

Decreased secretion or action of antidiuretic hormone

Signs and symptoms

- Polydipsia
- Polyuria
- Nocturia
- Signs of volume depletion (Tachycardia, hypotension)

Investigations

- **↑ Na^+ (>145 mEq/L)**
- **↓ Urine osmolality**
- **↓ Urinary specific gravity**
- **24 hours urine collection** (volume) – typically 3-20 L of urine per day
- **Urine osmolality** – low results <300 mmol/kg
- **Serum osmolality** – normal or elevated (Normal ranges: 285-295 mOsm)
- **Elevated serum sodium (↑ Na^+)**
- **Water deprivation test/dehydration test**
  Desmopressin stimulation test – differentiating CDI or NDI – responds to desmopressin = central DI (respond by reduction in urine output and increase urine osmolality of >50%)

Normal urine specific gravity
1.005-1.030

Remember!
Patient with diabetes insipidus <u>loses water</u>

Central DI (also known as neurogenic DI) caused by insufficient synthesis or release of ADH from the central nervous system
Nephrogenic DI caused by ineffective response to ADH in the kidneys, such as defective ADH receptors caused by genetic defects.
Dipsogenic DI (also known as **primary polydipsia**) results from excessive fluid intake practiced over an extended period.

Differential Diagnosis

- Diabetes Mellitus Type I and Type II
- Excessive fluid intake
- Pituitary adenoma
- Hyperaldosteronism
- Medications (Diuretics overdose)
- Hypercalcaemia
- Hyperosmolar hyperglycaemic state

Treatment

Hypernatraemia management

(regular complication of Diabetes insipidus)

- IV hypotonic fluids (5% dextrose and 0.45% saline)
- Frequent monitoring of electrolytes

Central Diabetes insipidus

- Desmopressin or Vasopressin
- Oral or IV fluid replacement (only in acute settings)

Nephrogenic diabetes insipidus

- Maintenance of adequate PO fluid
- NSAIDs
- Hydrochlorothiazide
- Sodium restriction
- Treat underlying cause

PHEOCHROMOCYTOMA

Excess of epinephrine & norepinephrine

Signs and symptoms

- ↑ **Blood pressure** (episodic or persistent)
- ↑ **Heart rate**
- Palpitations
- **Headache**
- **Hyperglycemia**
- Tremors
- Flushing / diaphoretic
- Pain the chest or abdomen
- Anxiety
- Weight loss due to ↑ basal metabolism

Differential Diagnoses

- Cushing's syndrome
- Hyperthyroidism
- Essential hypertension
- Anxiety attack
- Adrenal adenoma
- Use of cocaine or amphetamine

Investigation

1. **Plasma tests:**
   - Catecholamines
   - Metanephrine
   - Chromogranin A
2. **24-hour urine samples for catecholamines** and their metabolites (**fractionated and total metanephrine**)
3. **CT/MRI** of thorax, abdomen and pelvis to localize pheochromocytomas/paragangliomas

Treatment

- **Adrenalectomy** (if a tumor is present)
- **alpha-blocker** (phenoxybenzamine)
- **beta-blocker** (propranolol)
- Other antihypertensives,

such as **calcium channel blockers** or **angiotensin-converting enzyme inhibitors**

CONN’S SYNDROME

Primary hyperaldosteronism due to unilateral adrenal adenoma

Signs and symptoms

- **Hypertension**
- **Hypokalaemia that causes:**
  - Fatigue
  - Muscle weakness
  - Cramps
  - Polydipsia
  - Polyuria

Investigations

- **↓ serum K^+** (<4 mmol/L)
- **24 hours urine collection:**

inappropriate potassium wasting
(> 30 mmol/L in a patient with hypokalaemia)

- **plasma aldosterone concentration**
- **plasma renin activity**
- **<u>Salt loading test:</u>**

Failure of aldosterone suppression following a sodium load confirms primary hyperaldosteronism.

- **<u>Captopril suppression test:</u>**

An inability to reduce plasma aldosterone levels after administration of captopril suggests primary hyperaldosteronism.

- **CT/MRI imaging of adrenal glands**

Differential Diagnoses

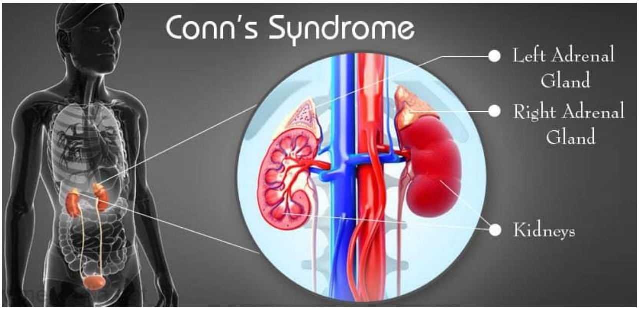
- Essential hypertension
- Congenital adrenal hyperplasia
- Ectopic ACTH syndrome

Conn’s Syndrome should be excluded in hypertensive patients with:

- a young age of onset (< 40 years)
- severe or resistant hypertension
- hypokalaemia: spontaneous or diuretic-induced hypokalaemia that does not respond to potassium replacement.

Treatment

- **Spironolactone** – potassium-sparing diuretic
- **Other antihypertensives** (e.g. ACE inhibitors and calcium channel blockers)
- ***Adrenalectomy***



HYPERPROLACTINEMIA

Excess of prolactin

Causes

- Physiological (Pregnancy, Lactation, Stress)
- Tumours and other sellar/parasellar lesions
- Primary hypothyroidism
- Chronic renal failure (reduced clearance of prolactin)
- Severe liver disease (disordered hypothalamic regulation)
- Polycystic ovary syndrome
- Drugs (some of antipsychotics, antidepressants, metoclopramide, domperidone, oestrogens, opiates etc)

Signs and symptoms

- **Galactorrhoea** (spontaneous flow of milk from the breast, unassociated with childbirth or nursing)
- **Hypogonadism**: menstrual irregularities (**oligomenorrhoea/amenorrhoea** or delayed menarche).
- **Infertility** (even when there is no abnormality of the menstrual cycle)
- Men present with reduced libido, impotence or infertility (galactorrhoea is rarely)

Investigations

- **Exclude pragnancy**
- **Level of prolactin** (if the level of prolactin is elevated, thyroid hormone should be tested. If thyroid hormone levels are normal, hyperprolactinemia is not caused by hypothyroidism).
- **Magnetic Resonance Imaging**: Of the brain and pituitary is done to see the location and size of the pituitary tumour.

Differential Diagnosis

- Pregnancy
- Polycystic Ovarian Syndrome
- Primary hypothyroidism
- Chronic renal failure
- Severe liver disease

Treatment

- **Dopamine agonists (cabergoline or bromocriptine)**
- **Surgery** to remove the tumour if medicines are ineffective. Surgery is needed if the tumour reduces vision.
- **Radiation therapy** to shrink the tumour destroy any tumour cells that are left behind.

POLYCYSTIC OVARIAN SYNDROME (PCOS)

Presence of multiple follicular cysts in the ovaries (>12 cysts)

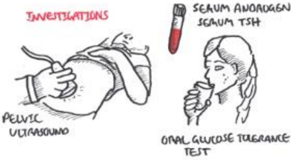
The Rotterdam criteria for the diagnosis of polycystic ovary syndrome include two out of the following three:

- Ovulatory dysfunction (**oligomenorrhoea or amenorrhoea**)
- Hyperandrogenism: clinical (**acne, hirsutism, male - pattern hair loss**) and/or biochemical (**elevated serum androgen levels**)
- Polycystic ovaries on USG (**at least one ovary with 12 follicles 2-9 mm and volume >10 ml)**

Signs and Symptoms

Clinical Presentation is often of a young women who **experiences irregular periods / weight gain / hirsutism.**

- **Hyperandrogenism:**
  - Acne
  - Hirsutism (excess hair growing in a male distribution)
  - Male-pattern hair loss
- **Menstrual disturbance:**
  - Oligomenorrhoea
  - Secondary amenorrhoea
  - Cystic ovaries
  - Infertility
- **Obesity:**
  - Hyperglycaemia
  - Insulin resistance
  - Dyslipidaemia
  - Hypertension



Differential Diagnosis

- Congenital adrenal hyperplasia
- Hypothyroidism
- Hyperprolactinaemia
- Cushing's syndrome

Investigations

- **Androgens**: testosterone, androstenedione and dehydroepiandrosterone sulphate (usually raised)
- **Luteinizing hormone** (usually raised)
- **Follicle stimulating hormone** (to rule out premature ovarian failure)

Exclude other causes of menstrual irregularity or hyperandrogenism by performing the following tests:

- **Hyperprolactinaemia**: serum prolactin.
- **Hypo/hyperthyroidism**: free thyroxine and thyroid – stimulating hormone.
- **Congenital adrenal hyperplasia**: 17 - hydroxyprogesterone
- **Cushing's syndrome**: dexamethasone suppression test
- **Androgen** - secreting ovarian or adrenal tumours: serum testosterone

Treatment

- **Weight reduction** through exercise and diet
- **Clomifene citrate** – induces ovulation (<u>if woman plans pregnancy</u>)
- **Oral contraceptive** (<u>if woman doesn't plan pregnancy</u>)

For hyperandrogenism and hirsutism:

- **Spironolactone** - has anti-androgenic properties
- **Antiandrogens** (Flutamide, Finasteride, Cyproterone acetate

List of abbreviations

ACE-inhibitors – angiotensin-converting enzyme inhibitors

ACTH – adrenocorticotrophic hormone

ARB – angiotensin receptor blockers

BMI – body mass index

BP – blood pressure

CT – computer tomography

DI – diabetes insipidus

FSH – follicle - stimulating hormone

GH – growth hormone

IV – intravenous

LH – luteinizing hormone

MRI – magnetic Resonance Imaging

NSAIDs – non-steroidal anti-inflammatory drugs

PO – oral administration

TSH – thyroid-stimulating hormone

USG – ultrasonography