Dana Stoian

CLINICAL ENDOCRINOLOGY

HIPPOCRATE

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Colecţia: HIPPOCRATE

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CONTENT

Writing a textbook on endocrinology in the 3rd millennium is a challenging task. Not only that the amount of medical information is substantial, but also is the number of books published so far. That is, the challenge of imparting the current knowledge on the endocrine system, covering all the major chapters regarding conventional endocrinology, while integrating the newest information from multiple medical disciplines is remarkable. Doing this in only seven well-structured chapters, as Dana Stoian succeeded, is indeed impressive. “Clinical Endocrinology” is a comprehensive textbook, with all the chapters reviewing the physiology of the gland and major hormones, the main syndromes with detailed pathogenic mechanism description, various diagnostic algorithms and differential diagnosis, as well as 1st, 2nd and 3rd line treatment options. I therefore believe that this textbook is very useful not only for young endocrinologists, but also for any young or experienced physician in any other specialty, as it offers an excellent insight into endocrinology, while keeping the text easy to understand and navigate. As nowadays the science is making rapid progress, a textbook that encompasses new discoveries is always welcomed.

Prof. Carmen Panitescu, MD, PhD

I. ENDOCRINE SYSTEM

- *Along the nervous system, the endocrine systems assures the transmission of information between cells/organs*
- *The information coordinate the vast majority of body function*
- *CHEMICAL information*
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- *The information coordinate the vast majority of body function*
- *CHEMICAL information*

DEFINITION

The endocrine system is an integrated network of multiple organs, derived from different embryologic origins that release hormones ranging from small peptides to glycoproteins, which exert their effect in neighboring or distant target

- Closely integrated either the central or peripheral nervous system, as well with the immune system = neuroendocrine/ neuroimmune system.
- 3 COMPONENTS:
  - Endocrine gland
  - Hormones
  - Target organ

GLANDS + HORMONES

- Classical glands:
  - Hypothalamus: producing releasing hormones: GHRN, CRH, TRH, GHRH and inhibitory hormones: Dopamine, Somatostatin, and neurohormones: vasopressin and oxytocin
  - Hypophysis: GH, TSH, FSH, LH, ACTH, PRL
  - Thyroid gland: T3, T4
  - Adrenal gland: cortisol, aldosterone, adrenal androgens, epinephrine, norepinephrine
  - Pancreas: insulin, glucagon, Somatostatin
  - Gonads: estrogen, progesterone (females), testosterone (males)
- Nonclassic endocrine systems
  - Vitamin D
  - Fat tissues
  - Hippocampus
  - APUD cell system
  - Growth factors
  - Malignant cells: producing oncogenes

Target organs are characteristic for each hormone. Some examples are taken into consideration:

- All body structures/tissue: thyroid hormones, growth hormone, and glucocorticoids;
- Bone, gut, kidney: Prohormone, vitamin D, Calcitonin
- Kidney: aldosterone, arginine vasopressin
- Breast, uterus, skin, endothelium, bone: estrogens, progesterone, androgens
- Pancreas: glucagon, insulin
- Liver: estrogens, GH, glucocorticoids, thyroid hormones.

THE ENDOCRINE GLAND is an secretion gland that secrete their products (hormones) into the interstitial space from where they reach the circulatory system ≠ exocrine outside the organism. The systems components are not mechanical interconnected, as cv/respiratory/renal system, but are chemical interconnected. We can have:

- **Endocrine effect** – distant influence: thyroid hormones actions
- **Paracrine effect** = local action, effect on other cells than the secretory cells: ovarian steroids produces by granullosa cells with direct effect on luteal cell growth and oocyte growth
- **Juxtacrine** = local action, juxtacellular action: same cell type as the secretory cells: effects of hematopoietic growth factors
- **Autocrine** = action on self cell: cancerous cells produce oncogene that favor malignant cell growth

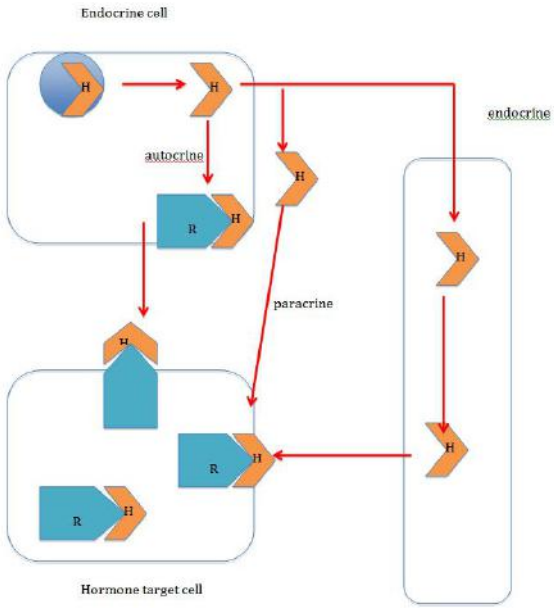


Figure 1. Different mechanism of action in the endocrine system

HORMONES

Hormones are chemical products, release in very small quantities from the cell
They can be released from:

- Endocrine glands: insulin, cortisol
- Brain: CRH, Oxytocin, ADH
- Heart: FNA
- Liver: IGF-1
- Adipose tissue – leptin

From the chemical point of view we have Proteic hormones (the vast majority), steroid hormones and aminic hormones. The main differences are presented in TABLE I.

TABLE I. THE 3 CHEMICAL CATEGORIES OF HORMONES

	PROTEINS	STEROIDS	AMINOACID DERIVATES
Produced from	3-200 AA Pre hormones	Cholesterol	Tyrosine Iodinated Tyrosine Tryptophan
Synthesis	Hypophysis Pancreas	Adrenal cortex Gonads Placenta Teguments	Medulla adrenal gland Hypothalamus Thyroid Pineal gland
Examples	The vast majority ACTH (protein) Insulin Glucagon FSH, LH, TSH, hCG (G Prot) ADH (peptide)	Sexual steroids Glucocorticoids Vitamin D	Catecholamine Noradrenaline Adrenaline Dopamine T3, T4 Serotonin Melatonin
Circulation	Mostly free, unbound	Protein carriers % free, unbound	Protein carriers % free, unbound
Half life	Polypeptides 4-40' Proteins 4-170'	4-170'	Amine 2-3' T3, T4 0.75-6.7 days
Receptors	Cell membrane	Intra cytosolic Nuclear receptor	Cell membrane EXCEPTION thyroid hormones Pass the cell membrane

The most important functional steps in hormone metabolism are:

- *Synthesis*
- *Secretion*
- *Transport*
- *Metabolic clearance*
- *Excretion*

Synthesis process is different in proteic, steroidal and aminic hormones. Proteic hormones synthesis follow the following steps: production at the endoplasmic reticulum level, as preprohormones (long peptide chain), are transported at the level of Golgi apparatus where the prohormone is packed in secretory vesicles, which migrate to the cell periphery, and it is stored at this level until needed. Usually there is also the transformation from the prohormone to active hormone in prepacking step. In the presence of secretion stimuli, the prohormone is release form the endocrine cell in the general blood stream.

All steroid hormones are produced al the cell level from the molecule of cholesterol. Intracytosolic cholesterol esters and cholesterol from the general blood stream are the sources for steroidogenesis. In all cases the first secretion step in the transformation of cholesterol in pregnenolone, activated by Steroid Acute regulatory enzyme, STAR, a saturable/self limited step, which limits the steroidogenesis. The following steps, with final mineralocorticoid, glucocorticoid or sexual steroids are dependent of the active enzymatic apparatus of the gland: adrenal region of gonadal tissue. An exception is represented by vitamin D, also a steroid hormone, which has different synthesis tree.

The 3rd type of hormones, the aminic hormones, is secreted in specific cells, coming form an essential amino acid: Tyrosine for catecholamine and Tyrosyl rest for thyroid hormones, respectively Tryptophan for pineal gland.

Secretion is also dependent of the type of hormones: release from secretory vesicle, in case of stimulation, for the proteic hormones, direct cell release, without any storage in case of steroid hormones, release from secretory vesicles in catecholamine case respectively release from the secretory vesicles, in needed conditions.

The majority of hormones are ***metabolized*** at liver level, in one 1st phase: reduction and hydroxylation, respectively in a 2nd phase, with conjugation. The metabolites will undergo biliary excretion, with a very low proportion remaining for urinary excretion. This is why the majority of urinary metabolites are obtained in 24 hours urine.

The thyroid hormones and steroids are *circulating* in the blood stream bound to carrier proteins, specific for different hormones: thyroxin-binding globulin, sex hormone binding globulin, corticotroph binding globulin and also unspecific, to albumins, and only a minority of the secreted hormone is circulating free, representing the active hormone fraction.

The majority of carrier globulins are synthetized in the liver, with alteration of the production, due to systemic diseases. As in seen in Table II, different systemic disease will influence the production of globulins, indirectly influencing the proportion of free fraction of different hormones.

TABLE II. SYSTEMIC CONDITIONS THAT ALTER CARRIER PROTEINS PRODUCTION

↑ carrier globulins	↓ carrier globulins
Estrogens	Severe hepatic insufficiency
Oral contraceptives	Obesity
Pregnancy	Nephrotic sd.
Hyperthyroidism	Hypothyroidism
	Hypoanabolic sd.

The carrier proteins have the following function in the endocrine system:

- *Pool of hormones*
- *Prolongs the half life of the hormone*
- *Regulates the free fraction of the hormone*
- *Conditionate the metabolic clearance rate*

The aminic hormones, catecholamine, circulate mostly free, unbound.

In order to be active of different target sites, all hormones need to interact with their specific receptor.

The binding of hormones *to their specific receptors* are characterized by the following proprieties:

- AFFINITY = power of the H-R binding (association versus dissociation)
- SPECIFICITY = ability of the R to recognized specific hormones
- BINDING =
  - Saturable phenomenon
  - Biologic response is obtained without 100% receptor occupancy
  - There are always free receptors
  - The distribution/location of the receptors determines the hormonal effect

There are different types of receptors, depending on the chemical structure of the hormone:

1. Proteic hormones, peptide and aminic hormones are active on Cell membrane receptors:
    - G Protein coupled receptor
    - Linase receptors
    - AMPc receptors
    - Guanine nucleotide exchange factors
    - Ligand gated ion channels

2. Thyroid hormones, despite being aminic, act on intranuclear receptors:
    - Binding of the hormone
    - Activation of tyrosine kinase activity
    - Protein phosphorylation
    - Downstream cellular response

3. Steroid hormones, being lipophilic, act on intracellular receptors.

There are 3 major mechanisms that will be discussed when considering the hormone secretion regulation:

- *Neural control* = SNC regulation of the endocrine unit
  Is made by a neuronal structure, producing neurohormones, influencing an endocrine structure: hypothalamus control on anterior hypophysis

- *Hormonal control* = control by another superjacent/subjacent hormone
  Is made by one gland that directly influences another gland: anterior pituitary + peripheral gland

- *Nutrient of ion regulation* = plasma levels of nutrients/ion control, the hormonal release, with best example; kalium level influencing aldosterone production, calcium level influencing Parathormone production or glucose influence on insulin or cortisol production.

In the majority of cases we can see at least 2 mechanisms overlapping with a combined final control.

II. THE HYPOTHALAMUS - HYPOPHYSIS UNIT

This unit represents the paradigm of neuroendocrine interactions = connection between brain and classic endocrine units, where CNS regulates the endocrine system and the endocrine system modulate the CNS activity. The system comprises neuronal cells and glandular cells with both electric and chemical activity. The same chemical substances can be secreted by neurons (neurotransmitters = if circulate between neurons; neuroendocrine hormones if circulating between neurons and cells or hormones) id produced by glandular cells).

Neurons and endocrine cells are both involved in all chemical interactions that are present in the hypothalamus hypophysis axis by the:

1) Release of substances from the hypothalamic neurons transported along the axons in the posterior hypophysis, from where they are secreted directly in the general vascular system
2) Release of substances from the hypothalamic neurons, transported in the anterior pituitary along the pituitary stalk, in the long portal veins, directly in the hypophysis, where they are released and influence only the production of pituitary hormones.

TABLE III. DIFFERENT ROLES IN THE NEUROENDOCRINE UNIT

	Neurotransmitter Neuron→ Neuron	Neurohormon Neuron → Cell	Hormon Cell → Cell/Neuron
Dopamine	+	+	+
Noradrenaline	+	+	+
Adrenaline	+	+	+
Somatostatin	+	+	+
GnRH	+	+	+
TRH	+	+	-
Oxytocin	+	+	+
Vasopressin	+	+	+
VIP	+	+	-
Glucagon	+	-	+
Cholecystokinin	+	-	+
Encephalin	+	-	+

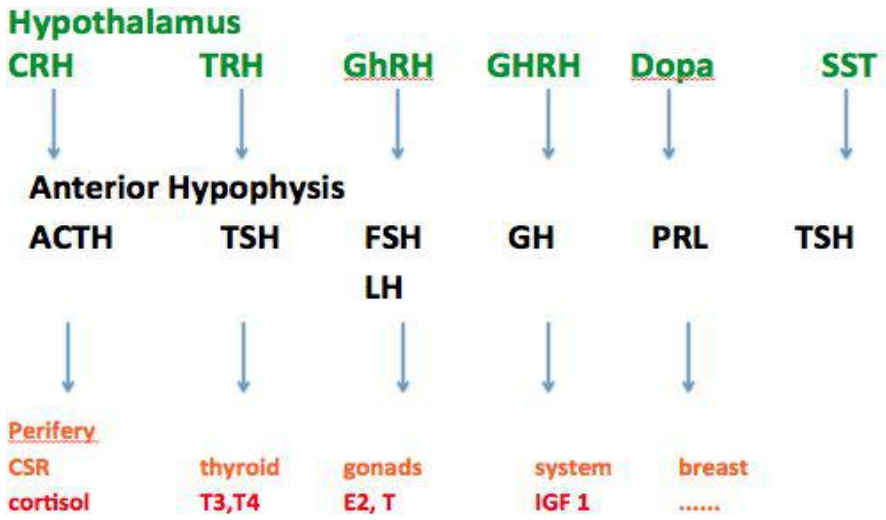


Figure 2. The control model in the neuroendocrine system

II.1. FUNCTIONAL ANATOMY

The hypothalamus is part of the diencephalon, located below the thalamus, the lamina terminalis and the mammillary bodies, forming the lateral walls and the floor of the 3rd ventricle. It is formed from different neurons grouped in many nuclei, which are intricate with neurons from other brain regions. The main clusters of neurons are:

- Anterior: preoptic nucleus, supraoptic nucleus, paraventricular nucleus, anterior hypothalamic nucleus, supraoptic nucleus, suprachiasmatic nucleus, lateral nucleus;
- Tuberal: dorsomedial hypothalamic nucleus, ventromedial hypothalamic nucleus, arcuate nucleus, lateral nucleus, lateral tuberal nucleus;
- Posterior: mammillary nuclei, posterior nucleus, lateral nucleus, tuberomammillary nucleus.

Some of the hypothalamic nuclei have sexual dimorphism in animals; the differences being minimal in humans, where the somatic differences in body mass are not very large between males and females. Also the preoptic area conditions the oflactive attractiveness in many species, an aspect that is blunted in human sexuality.

The 2 symmetric halves of the hypothalamus converge together in a bridge like zone, the median eminence, an important functional region, where the neurons influencing the hypophysis are discharging their secretory compounds, the hypothalamic neurohormones. Also this region is the place where the axons of the hypothalamus neurons traverse on the way to the posterior hypophysis.

The median eminence continues down, to form the pituitary stalk by joining the infundibulary portion of the neurohypophysis.

Some of the neurons in the hypothalamus have the quality of synthetizing hormones, which are called neurohormones because they are secreted by neurons, not by endocrine cells. There are two types of neurons with these properties the **magnocellular** and the **parvicellular** neurons.

The magnocellular neurons are mainly located in the paraventricular and supraoptic nuclei and produce important quantities of Oxytocin (OXT), arginine vasopressin (AVP) and also Neurophysins (NP). Their long axons form the hypothalamo - hypophysial tract, the linked structure between the hypothalamus and hypophysis, which begins in the median eminence and ends at the level of posterior hypophysis. The secretion products are directly released from the posterior hypophysis in response to a stimulatory impulse.

The parvicellular neurons open the axons at the leaves of the median eminence and release their stimulatory or inhibitory neurohormones (hypophysio - trophic hormones) that control the function of the anterior pituitary gland.

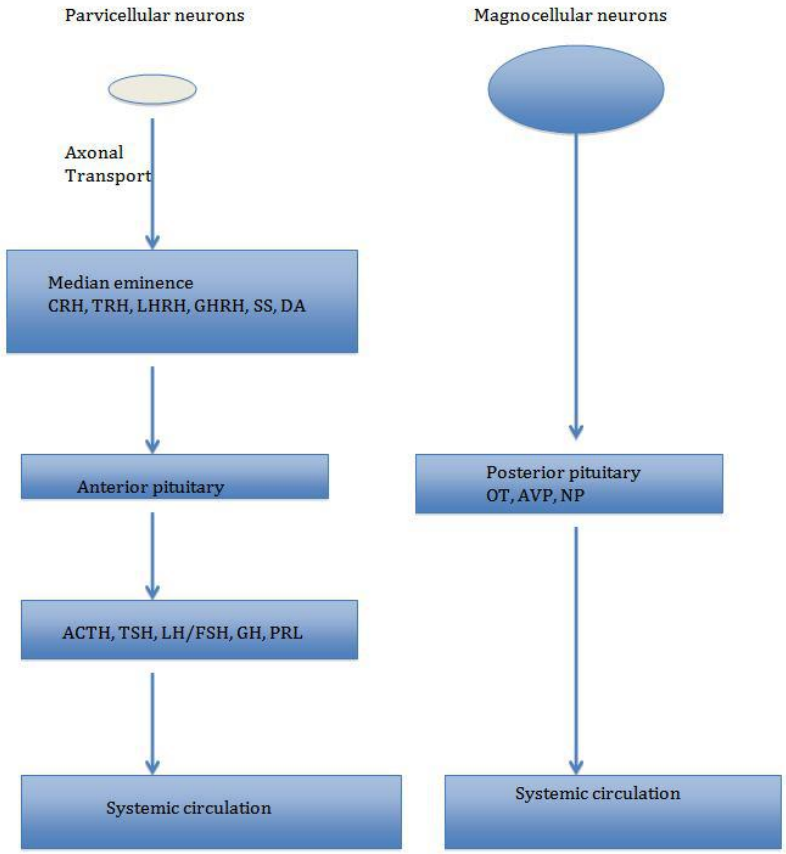


Figure 3. Secretion products of the hypothalamic neurons

Blood supply is part of the functionality of the neuroendocrine system. The vascularization of anterior and posterior hypophysis is totally different:

- The superior hypophysis arteries enter the space at the level of the median eminence where they form a capillary plexus, the first, intra hypothalamic capillary plexus. At this level, the terminal axonal endings of the parvicellular neurons open, and discharge the trophic neurohormones into the local vascularization system.
- The first capillary system vessel do reunite, forming the long portal veins, that will descend along the pituitary stalk and will open in the 2nd capillary structure at the level of anterior hypophysis, forming the second capillary plexus, a sinusoidal system where the neurohormones, brought in by the venous blood from the median eminence, and directly influence the secretion of the anterior pituitary hormones.
- From the second capillary, intrapituitary plexus, the venous blood filled with pituitary hormones, travels through the hypophysis veins into the general circulation.
- It is worth mentioning that the portal circulating system is a typical anatomical vascular structure, typical for the hypothalamic hypophysis axis. Also the hypothalamic neurohormones are present only in the portal venous system, and the pituitary system is present in the general vascular system.

The posterior hypophysis has a different, independent vascularization: arterial supply through the inferior pituitary arteries, that form a capillary plexus in the posterior pituitary and reunite in branches that will open in the hypophysis venous system, part of the general vascular system.

II.2. HYPOTHALAMIC NEUROHORMONES

The neurohormones can be classified in promoting hormones and inhibitory hormones.
The promoting hormones are:

- Corticotroph releasing hormone
- Tireotrop releasing hormone
- Gonadotroph releasing hormone
- Somatotroph releasing hormone
- Dopamine releasing factor = TRH

Inhibitory hormones are:

- Somatostatin
- Dopamine

- **Corticotroph hormone (CRH)**
  - 41 AA peptide, stimulates the POMC secretion in the anterior pituitary
  - biphasic pattern in plasma, lasting 6-10 minutes, and the second spike 40-59 minutes
  - produced by paraventricular neurons and the placenta
  - is released secondary to stress/emotional/physical/organic over load of the body= MEDIATES THE PHYSIOLOGICAL RESPONSE TO STRESS

It is important to note the physiological circadian rhythm of the CRH release, with a maximum at 4.00 AM, a small decrease during morning, an important decrease in the afternoon and with minimum levels during the night.

- **Tyrotroph releasing hormone (TRH)**
  - 3AA
  - The major regulation factor of TSH
  - Produced by neurons located in the medial portion of paraventricular nuclei
  - Very short half life of 6 minutes
  - Synthetic analogue is used for diagnostic purposes: the TRH stimulation test (diagnostic in TSH insufficiency of hypophysis or hypothalamus origin) and also in the preparation of radioiodine treatment in thyroid cancer cases.
  - Major stimulus: cold, hypothyroidism
  - TRH is also the natural stimulator of PRL, but the mechanism is significant mainly in peripheral hypothyroidism, when TRH and TSH values are high, with proportionally increased RPL levels.

- **Gonadotroph releasing hormone (GnRH)**
  - 10 AA peptide
  - Pulsatile secretion with different size and frequency of the secretory peaks
  - Neurons located in the preoptic area
  - Very short half life of 2-4 minutes
  - The only system that becomes functional not at birth, as the other hypothalamic neurohormones, but is inhibited from birth till puberty onset. This pause, called the learning pause, assures that the body is not overwhelmed by sexual steroids (the end product of GnRH mediated by FSH and LH) in order to develop somatically and emotionally before the big changes are induced by the sexual steroids at puberty.
  - The physiological inhibition is not completely known as a pathogenic mechanism, limbic system and central structure, being responsible for a

very sensitive negative feedback, that allows minimal levels of estrogen or androgen, present in children's bodies, to maximally inhibit the hypothalamus. After the spontaneous disinhibition, the system functions constantly: till the menopause in women, till the end in men.

- A continuous secretion of GnRH, after a very short flare up, inhibits the pituitary secretion of FSH and LH, because normal function of the hypophysis is possible only in the presence of secretory pulses of GHRH. In the case of continuous secretion, the inhibition of the pituitary release of FSH and LH determines hypogonadism. This property of the gonadostat is used for medical purposes in the treatment of breast cancer patients, prostatic cancer patients and endometriosis patients, for a limited iatrogenic hypogonadism.

➢ **Somatotroph releasing hormone (GHRH)**

- 44 AA peptide
- Secreted by the neurons located in the arcuate nuclei
- Short half life of 3-7 minutes
- Secretion of GH secretion and synthesis in the pituitary

➢ **Somatostatin (SST)**

- 14 AA peptide
- SST naturally inhibits TSH and GH secretion
- The SST is produced by the neurons located in the paraventricular, and extra cranial D cells of the pancreatic islets, gastrointestinal mucosa and parafollicular thyroidal C cells. There are some structural differences between the hypothalamic and gut SST.
- SST inhibits not only GH but also an important number of nonpituitary hormones: insulin, glucagon, gastrin, secretin and VIP.
- The inhibitory effects of SST are used for medical purposes in the treatment of hormone producing tumors: GH producing tumors, gastrointestinal tumors: gastrinoma, glucagonoma, somatostatinoma.

➢ **Dopamine**

- is an aminic hormone, produced by the neurons from the arcuate nucleus
- very short half life of 1-2 minutes
- it is the principal inhibitor of Prolactin, the control of PRL being mainly an inhibitory one, unlike the other pituitary hormones.
- In cases of disruption of the transmission of Dopamine to the hypophysis: tumor, stalk damage, stalk infiltration or deviation, the levels of PRL increase very rapidly.

II. 3. HYPOPHYSIS

The hypophysis is a gland comprising 2 different structures, from an embryological, functional and vascular point of view. The human pituitary originates from the Rathke pouch, an ectodermal envagination of the oropharynx, that migrates to join the neurohypophysis, that is present on site, in the sella turcica (Turkish saddle) of the sphenoid bone. The bony structures identified in the sella turcica are:

- ❖ Anterior = anterior clinoid processes
- ❖ Lateral =sphenoid wings and apposition of the cavernous sinuses
- ❖ dorsum sellae = posterior wall
- ❖ upper corners = posterior clinoids

The gland is surrounded by the durra, and the roof is formed by a reflection of the durra, attached to the anterior and posterior clinoid processes that prevent the cerebrospinal fluid entering the sella. The distance between the diaphragm sellae and the anterior stalk is 5 to 10 mm.

The functional structure of the hypophysis is very different:

- the anterior hypophysis is a endothelial, glandular structure, that produces the hypophysial hormones;
- the posterior hypophysis is of neuronal origins, being made only by the terminal axons of the magnocellular hypothalamic neurons, that release their hormonal products in the systemic circulation.

The anterior hypophysis comprises different endocrine cells:

- ❖ *Somatotroph* cells, GH secreting, acidophilic, located in the lateral portion of the anterior lobe, accounting for around 50% of all antero hypophysis cells
- ❖ *Lactotrope* cells, PRL secreting, are acidophilic cells randomly distributed in the anterior pituitary, accounting for around 25% of all antero hypophysis cells
- ❖ *Tyrotroph* cells, are basophilic cells, with a period acid Schiff stain. They account for 10% of all antero hypophysis cells, located in the anteromedial and anterolateral portions of the gland.
- ❖ *Corticotroph* cells produce the POMC group, are embryologic, originating from the intermediate lobe and are small basophilic cells, that account for 15 to 20% of all antero hypophysis cells
- ❖ *Gonadotrophs* cells are large basophilic cells accounting for 10-15% of the anterior hypophysis cells, located through to the entire lobe. Their hypertrophy is responsible for the physiological increase of the hypophysis during pregnancy and lactation.
- ❖ *Cromophob* cells do not exhibit any immuno cyto chemical staining for any of the known anterior hypophysis hormones. They are the so called null cells, and are present throughout the gland.

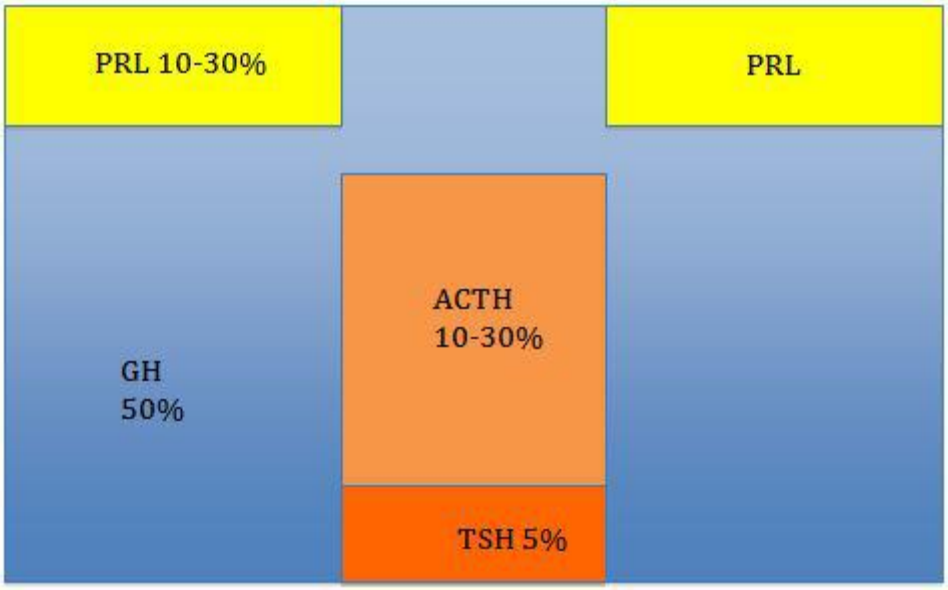


Figure 4. Distribution of the antero-pituitary endocrine cells

II.3.1. PITUITARY HORMONES

According to their biochemical structure, the anterior hypophysis hormones are divided into:

- Glycoproteins: TSH, LH, FSH
- Proopiomelanocrotin: ACTH, MSH
- Proteic: Growth hormone (GH), prolactin

All glycoproteic hormones are the largest known hormones, a heterodimeric glycoprotein consisting of a common α subunit and a unique β subunit, responsible for the biological activity. B HCG, produced by the embryo and the placenta, has a similar structure, and is used in current medical practice for the ovulation inducement in assisted reproduction techniques.

- Thyrotroph Releasing hormone, Thyrotropin (TSH) = produced by the tireotrop basophilic cells, under the direct stimulation of TRH, with a direct effect on the thyroid cells: G_s protein cell membrane specific receptor. TSH stimulates all the events in the thyroid:
    - **Iodine thyroid Up take**
    - **Hormones-genesis**
    - **Secretion of T3, T4**
    - **Glandular hypertrophy (Proteic synthesis/ARN)**
    - **Facilitates intra thyroidal vascularisation**

The TSH release for the hypophysis is under the feedback control of the peripheral: inversely proportional with the peripheral T3 and T4 levels = long feedback, direct effect of the hypothalamus: with stimulatory impulses from the TRH and negative control from the SST, integrating the central inhibitory impulses of Dopamine.

Constantly, the hypophysis controls the peripheral thyroid response, in concordance with the current body needs.

Example: in case of an important weight increase, the basic body need of thyroid hormones increases, the peripheral levels of T3 and T4 decrease, so the hypothalamic set point and the hypophysis are signaled by this decrease. The hypothalamus s releases increased quantities of TRH, that stimulate the TSH synthesis and secretion, which increase the thyroid production of T3 and T4 that will compensate for the new needs of the body. After equilibration of the defect, the feedback loop does not transmit any messages till the next change in the needs of the body.

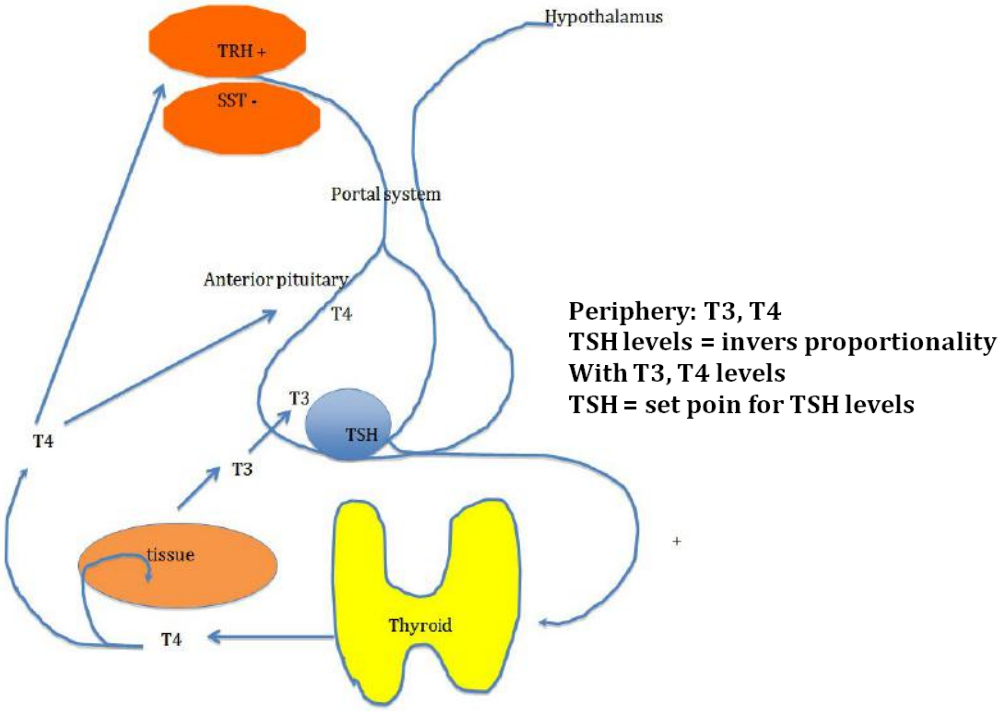


Figure 5. Feedback control of TSH – integrated central and peripheral impulses

TSH measurement:

- Assay: periphery venous blood ($T_{1/2}$ 30-50')
  - I-IV generation assays !!! Different sensibility and quality

- Reference range

1. Adults: 0.5-4.7 mUI/L
2. Children:
   - 1st days of life: 70 mUI/L
   - **day 2 to 3**: **< 10 mUI/L** **neonatal screening**
   - week 2 to 6: 1.7-9.1 mUI/L
   - 2st month: < 6 mUI/L
3. Aging: 0.5 – 7 mUI/L

The assessment of THS is useful in:

1. *Thyroid dysfunction*
2. *Neonatal hypothyroidism screening*
3. *Monitoring of supplemental therapy, in hypothyroidism cases*
4. *Evaluation of hyperthyroidism relapse*
5. *Suppressive therapy in thyroid cancer cases*
6. *Evaluation of hypophysis tireotrop cells performance*
7. *Standard assay in female infertility*
8. *Universal screening> 35 de years, every 5 years*

There are some possible TSH changes, in the absence of any organic hypophysis pathology:

TABLE IV. TSH ALTERATION WITHOUT HYPOPHYSIS PATHOLOGY

TSH increase	TSH decrease
Iodine: Amiodarone	Exogenous thyroid hormones
Lithium	Somatostatin
Dopaminergic antagonist (Metoclopramide)	Dopaminergic agonists (Bromocriptin)
Dopaminergic inhibitors	Adrenergic blockers
H1 histaminic receptor blockers	Serotonin antagonists
Anti estrogens	Glucocorticoids
Spironolactone	Dopamine
Amphetamine	Octreotid
	Opioids
	Clofibrat
	Biotin

- Gonadotrophins: Luteinizing hormone (LH) and Follicle stimulating-hormone (FSH)

The gonadotrophs are produced in the gonadotropic cells, due to the stimulatory pulses of GnRH. The hypophysis secretion and synthesis follows the pulsatile secretion of the GHRH:

- low frequency = preferential FSH secretion
- high frequency = preferential LH secretion

It is clear that FSH and LH secretion begins only after puberty, after the spontaneous/physiological disinhibition of the GnRH producing neurons.

The effects of FSH and LH are different in males and females.

In males:

FSH = is conditioning the spermatogenesis, phenomenon present in the walls of the seminiferous tubules, stimulating:

- Sertolli cell stimulation
- Testicular growth
- Gametogenesis
- Facilitates cell replication

LH = is sustaining the androgen production, required for somatic, sexual and reproductive purposes:

- Leydig cell stimulation
- Testicular steroid genesis
- Very high intra testicular (intraluminal) testosterone levels

In females, the mechanism is more complex, due to the different menstrual cycle phases:

In follicular phases = preferential follicular growth, increase of hormonal ovarian production, till the estrogen levels are high enough in order to auto initiate the ovulation.

In luteal phase = progesterone secretion with sustained activity of luteal corpus with no follicular growth.

FSH = governs the follicular phase sustaining:

1. *Follicular maturation*
2. *Follicular growth*
3. *Indirect hormonal secretion: androgen aromatase*
4. *Inhibine production = follicular protective from over consumption*

LH = governs the luteal phase sustaining:

1. *Direct steroid synthesis in the thecal cells = androgens*
2. *Induces ovulation*
3. *Transformation of ruptured ovulatory follicle in luteal*

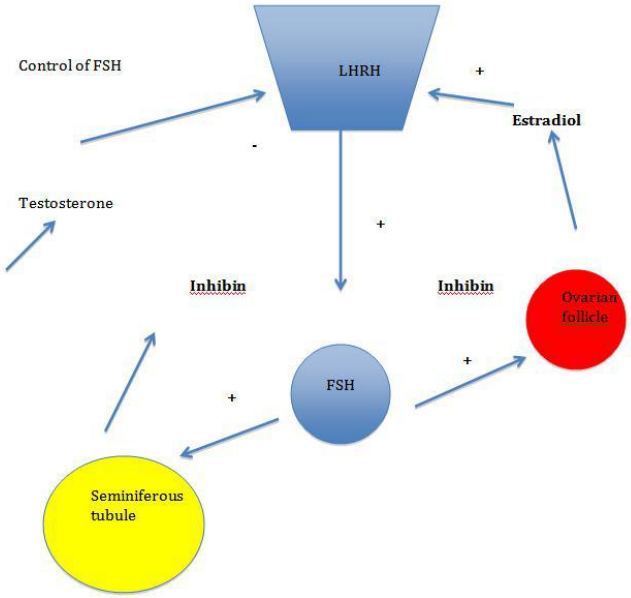


Figure 6. Feedback control of FSH– integrated central and peripheral impulses in males and females

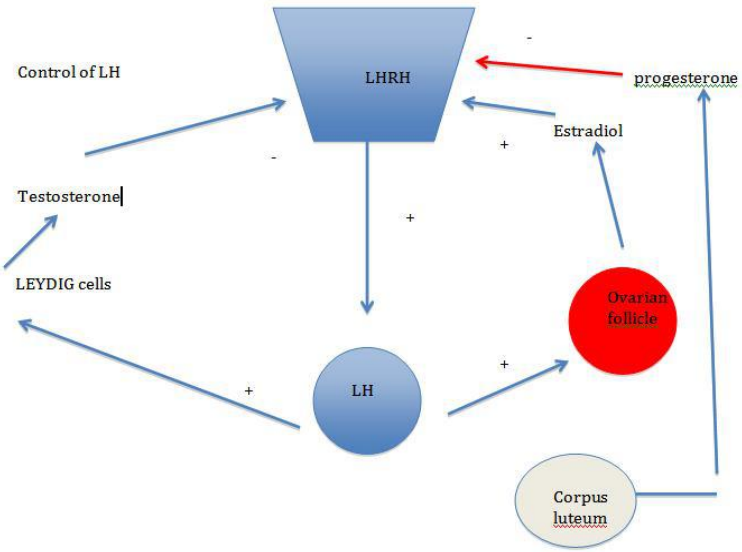


Figure 7. Feedback control of FSH– integrated central and peripheral impulses in males and females

- **Pro Opiomelanocortin group**

POMC is a precursor pro-hormone produced by the corticotroph cells, with the main product: ACTH.

- *Adrenocorticotropic Hormone (ACTH)*

= a peptide hormone, 39 amino acid structure, stimulated by psychological and physical stress such as infection, hypoglycemia, surgery, infection, trauma, being the stress response hormone, that allows our adaptive mechanism to any supra stimulatory situation.

ACTH stimulates the secretion of glucocorticoids, and androgens (all sexual steroids) and to a lesser degree the mineralocorticoids, from the adrenal cortex, by binding to a cell membrane receptor. Also ACTH can bind to the MSH receptor, inducing skin hyperpigmentation when over stimulated.

The release of ACTH follows the circadian rhythm of the CRH.

The control mechanism follows the same feedback rule, with the major impact of the central supra hypothalamic sector: any type of stress: physical, emotional, chemical, that induces many small peaks of ACTH release, superimposed on the general circadian rhythm, congruent with any stress situation.

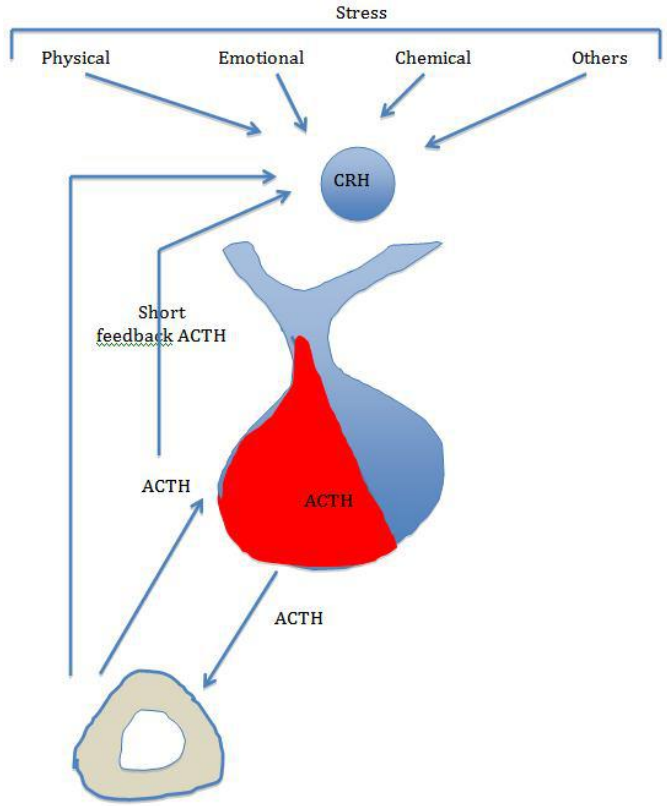


Figure 8. ACTH control in dynamic balance of periphery and central level

The ACTH evaluation follows some general recommendations:

1. ACTH basal unreliable indicator of pituitary function (short $T_{1/2}$)
2. ACTH + cortisol primary ≠ secondary insufficiency

   central peripheral

   ACTH ↓ ACTH ↑
3. Midnight salivary cortisol
4. Stimulatory tests Diagnosis of insufficiencies

   pituitary = hypoglycaemia (Insulin)

   = Metyrapone

   = CRH

   adrenal = ACTH synthetic
4. Inhibition tests Diagnostic of hyper secretion DEXAMETHASON

   = Midnight inhibition

   = 2 days inhibition

   = 2 days high dose inhibition

➢ MSH

In normal conditions, only small amounts of MSH are produced in the pituitary, being responsible for skin pigmentation.

➢ β - endorphin

Is the most abundant endogenous opioid peptide, with a pleiotropic effect, due to the vast distribution of opiate receptors: brain and periphery. The most important biological described effects are: analgesia, behavioral effects and neuromodulator function, with possible implication in chemical addictions.

➢ PRL

PRL is a 198 AA proteic hormone, synthetized and secreted by the lactotrope cells, mainly due to an inhibitory control from the hypothalamus, mediated by Dopamine levels in the portal venous blood:

- PRL stimulates the lactation in the postpartum period
- Increased, during pregnancy for breast development
- Preparation for the milk production

The PRL is released in a peak manner, with no clear etiopathogenic mechanism, increases with sleep, after 1-2 hours of sleep, without being associated with any specific sleep phase.

To the regulatory mechanism of PRL, the major influence is marker by Dopamine, with low stimulatory effect of TRH (important only in untreated hypothyroidism) estrogens have a blunting effect of PRL, explaining why, in pregnancy, despite the high levels of PRL, there is rarely a lactation, because high levels of E2 blunts the direct effect of PRL. Only after parturition, when E2 and progesterone levels decrease dramatically, lactation starts.

PRL is also released after stress (surgery, exercise, hypoglycemia, acute myocardial infarction,), sexual stimulation, explaining the need of correct conditions for PRL measurement. Or after direct neurogenic reflex at thoracic level: mechanical local stress, skin lesion of thoracic dermatomes.

Although PRL, in physiological levels, does not seem to have any role in the human reproduction, persistent high levels of PRL do inhibit the pulsatory secretion of GnRH, respectively FSH and LH, altering the physiology of reproduction: hormonal synthesis and gametogenesis, both in males and females.

The PRL measurements are made according to special blood sampling rules: the patient has to be awake for at least 2 hours, with no food administration, no morning exercise or sexual activity, in order to diminish all the possible natural interferences on morning PRL production.

The utility of PRL screening has to be considered in the following situations:

1. *Galactorhea*
2. *Enlarged sella turcica*
3. *Suspicion of pituitary adenoma*
4. *Amenorhea/oligomenorhea/decrease menstrual bleeding*
5. *Male hypogonadism*
6. *Male erectile dysfunction/loss of libido*
7. *Infertility (female / male)*

TABLE V. PRL ALTERATION IN ABSENCE OF ANY HYPOPHYSIS PATHOLOGY

PRL increase	PRL decrease
Pregnancy, breastfeeding, nursing Mamelonar stimulation Physical effort Sleep Hypoglycaemia	
TRH Estradiol VIP Dopaminergic antagonists Haloperidol, Risperidone, Rezerpin, Methyl Dopa, opiates, Metoclopramid Moaminoxidase inhibitors Cimetidin Verapamil	Dopaminergic afonist Levodopa Apomorfine Bromocriptine Pergolide Cabergoline
Thoracic lesions	Pseudohypoparathyroidism
Medullar lesions	
Hypothyroidism , PCOS	
CDK IV, V	
Hepatic insufficiency	

➢ GH

The Growth hormone is a polypeptide hormone, 191 AA, that is produced by the somatotroph cells, acidophilic cells of the anterior pituitary.

The primary function of GH is to promote growth, mainly mediated by the Insulin growth factor 1 (IGF1) that can be considered the final hormone that mediates the effects of the GH. Despite the other anterior pituitary trophic hormones, GH has not any single organs that it acts on (as TSH = thyroid, ACTH=adrenal or FSH + LH = gonads) but acts almost in the entire body, with:

- direct effect: lipolysis with an indirect protein sparing effect,
  intracellular AA transport,
  gluconeogenesis
  cartilage growth

- indirect effect, IGF1 mediated: bone formation
  proteic synthesis,
  muscular glucose uptake,
  neuronal survival,
  myelin synthesis
  inhibition of proteic degradation

As seen here, GH is more than a growth promoting hormone, it is an anabolic and a survival related agent. We can resume the effects of GH in metabolic and somatic effects. Table V and VI list these effects.

TABLE VI. THE SOMATIC EFFECTS OF GH

Tissue	Effect
BONE	Longitudinal growth – new cartilage/bine formation Condro genesis Epiphyseal plaque widening Bone matrix formation Maintenance bone turnover in adult (osteoblast activity)
MUSCULAR	Anabolic affect AA uptake in cells, protein incorporation with cellular proliferation
LIVER	IGF 1 synthesis and secretion
Immune system	B cell response, Antibody production NK+ , MFG, T lymphocytes activity
CNS	Modulate general mood Myelin synthesis Influence neuronal survival
Blood	+ Fibrinogen, Hb, HT, BAP
Kidney	GFR
Organs	Growth
Skin	Increase body hair growth, sebum and sweat gland secretion

TABLE VII. THE METABOLIC EFFECTS OF GH

Metabolism	Effect
Glycaemic	Decreased intracellular glucose uptake in the extra hepatic cells Decreased glycogen hepatic production Increased hepatic glucose production Decreases insulin sensitivity HYPERGLICEMIANT effect
Lipid	Release/oxidation of FFA Increases plasmatic ketones
Protein	Intracellular AA uptake Proteic synthesis Decreased nitrogen excretion

The GH secretion is made in a peak manner, mediated by the GHRH stimulatory effect and Somatostatin inhibitory effect:

- GHRH binds to pituitary receptors and stimulates the synthesis and secretion of GH, with a maximum peak 30' after the stimulation, with a duration up to 120'
- SST decreases the production of GH in the secretory somatotroph/ tumoral cells, with inhibition of both basal and stimulated GH secretion

Regardless of this main primary regulatory mechanism, the secretion of physiological levels of GH is influenced by:

- Neural control: the nocturnal pattern secretion, with a maximum after 4 hours of sleep, associated with sleep stages 3 and 4, responsible for 70% of the secretion, greater in childhood, with a decrease with age;
- Any type of stress: surgery, trauma, exercise, electric shock therapy, pyrogens, emotional and chemical stress induce GH release, with secondary alteration of the normal GH pattern with impairment of GH secretion on the long run;
- Metabolic control: changes in glucose levels, AA and lipid levels in blood influence the GH secretion: (as seen in table VII)
- Other hormones: hypo or hyperthyroidism blunt the GH response to any stimulus, excess of glucocorticoids (exogenous or endogenous (inhibit the GH secretion, estrogens, enhances the GH response to stimuli

- Secretagogues: Ghrelin is the worst because obesity will disrupt the normal GH secretion pattern
- General body homeostasis: nutritional balance, normal renal function, normal hepatic performance and normal emotional stimuli are required in order for GH secretion to be in the physiological parameters.

Any change in the previous mentioned parameters will disrupt the normal secretory GH pattern, especially in children, with an alteration of growth.

TABLE VIII. GH ALTERATION IN ABSENCE OF ANY HYPOPHYSIS PATHOLOGY

↑	↓
REM phase sleep	Hyperglycaemia
Physical effort	FFA
Stress	
Postprandial hypoglycaemia	
Hypoglycaemia (Insulin)	
H: GHRH, Ghrelin, ACTH, MSH, oestrogen	H: SST, GH, progesterone, GCS
Alpha adrenergic agonists Beta-adrenergic antagonist Dopamine agonists	Alpha adrenergic antagonist Beta-adrenergic agonist Dopamine antagonist
Proteic depletion Starvation	Obesity
Ectopic GHRH production	Thyroid dysfunction
CKD	

II.3.2. PITUITARY ADENOMAS

The major topic of our interest is represented by the **pituitary adenomas**.

They represent 15% of all intracranial neoplasms.

The pathogenesis of the pituitary neoplasia is unclear; hormonal and genetic factors are involved, but still the pituitary adenomas are secondary to a pituitary defect: monoclonal proliferation, isolates the defect, the hyper secretion adenomas do not subscribe to feedback regulations and the hormonal pulsatility pattern is restored only after the adenoma removal.

The vast majority of cases are due to acquired mutation, that favors mutated cell replication, but there are some rare genetic syndromes that generally are associated with pituitary adenomas.

In face of a pituitary tumoral mass, there are 4 major consequences that have to be taken into consideration, every time when we evaluate a case:

1. **Direct effect of tumoral mass = compression effects = functional pituitary syndrome**
2. **Presence of hormone hyper secretion = endocrine syndrome**
   From the endocrine syndrome point of view we can see:
   - Non-secreting adenomas 30%
   - Secreting adenomas 70%
     - PRL secreting 30%
     - GH secreting 10%
     - ACTH secreting 10%
     - TSH secreting < 1%
     - LH/FSH secreting <0.5%
     - Pluri hormonal secretion 10%
3. **Presence of secondary hormonal insufficiencies because of local, pituitary compression**
   There is described: 60% FSH and LH insufficiency, 15% TSH insufficiency and 5% ACTH insufficiency.
4. **Metabolic consequences of tumoral mass = metabolic syndrome.**

II.3.2.1. Pituitary functional syndrome

The functional syndrome, secondary to mechanical compression can appear in almost all cases of hypothalamo-hypophysis disease. The most frequent seen situations are presented in Table IX.

TABLE IX

	Adenoma	benign, epithelial
	Atypical adenoma	
ANTERIOR	Carcinoma	Craniospinal dissemination
	Oncocytoma	Rare tumor
	Pituicytoma	Low grade astrocytoma
	Granular cell tumor	
POSTERIOR	Gangliocytoma	
	Craniopharyngioma	1% neoplasm/10% sellar tumors
	Meningioma	
Nonpituitary	Chordoma	
	Histiocytosis	
	Metastases	
Cystic	Rathke, Arachnois	
	Hypophysitis	
Inflammatory	Granulomatous d.	
	Sarcoidosis	

The described clinical signs and symptoms are directly related to the mechanical compression of the surrounding structures. According to the involved structures, we can observe:

a) Intrasellar tumors commonly manifest with headaches, due to the stretching on the dural plate. **The severity of the headache is not proportional to the tumor size.** Minor lesions with dural distortion can induce a constant important headache. Longstanding **pituitary compression** will induce a different degree of hypopituitarism: the most affected being GH secreting cells (65%), gonadotropin secreting cells (60%), tyrotroph secreting cells (15%) and corticotroph secreting cells (5-10%). In any case of an increase in the intrasellar pressure with stalk deviation, there is an increase in prolactin levels, suggesting the interruption of the portal circulation: delivery of Dopamine to the anterior pituitary.

b) **Stalk** compression will alter the normal access of the anterior pituitary to the hypothalamic neurohormones and determine direct alteration of the pituitary hormones. In this case not only Hyperprolactinemia will be seen but also the inappropriate secretion of other pituitary hormones.

c) **Optic tract** involvement induces gradual signs, according to the degree and the severity of the compression:

- Loss of red perception
- Loss of temporal visual views= bitemporal hemianopia superior
- Bitemporal partial field effects
- Overlaps of the nasal and temporal fields
- Scotoma
- Blindness, in very long standing severe cases

Part of the visual field changes are reversible as the compression disappears, but long standing compression will induce trophic changes in the neural fibers, that are irreversible, despite the mechanical decompression.

d) **Cavernous sinus** comprise the IIIrd, IVth and VIth cranial nerve, and the maxillary branches of the Vth cranial nerve with secondary signs:

a. IIIrd nerve compression = diplopia,

b. IVth nerve = ptosis, ophtalmoplegia

c. VIth nerve = facial numbness.

Even if the internal carotid artery is comprised in the cavernous sinus and in large, lateral extensive tumors, the clinical vascular sequel are very rare.

e) Downward extension in the **sphenoid sinus** may invade the palate with secondary nasopharyngeal obstruction, infection, and cerebrospinal fluid leakage.

f) Upward extension can alter the **hypothalamus** induces temperature deregulation, thirst, sleep or appetite changes, behavioral or autonomic nervous system dysfunction or even metabolic sequel.

g) Rarely, the **temporal or frontal lobe** may be affected, with secondary seizures (temporal lobe), personality disorders, anosmia (frontal lobe).

h) Severe **central** invasion will induce severe headache, hydrocephalus, psychosis, and dementia, laughing seizures.

The degree of compression is evaluated by different measurement scales:

1. HARDY classification system

   noninvasive: limited to the pituitary

   grade 0 intact with normal contour

   grade I bulging the floor

   grade II intact enlarged fossa

   invasive: inferior extension

   grade III sellar destruction

   grade IV diffuse destruction

2. Hardy severity scale of supra sellar tumors
   A = cistern only
   B = recess of the 3rd ventricle
   C = whole anterior 3rd ventricle
   D = asymmetrical intracranial extradural
   E = asymmetrical cavernous sinus involvement

3. Knops classification = lateral extension
   0 = limited to pituitary
   1 = alteration of the sellar bone without involvement of the cavernous sinus
   2 = pushes the medial wall of cavernous sinus
   3 = lateral extension to the internal carotid artery
   4 = total encasement of he intercavernous carotid artery

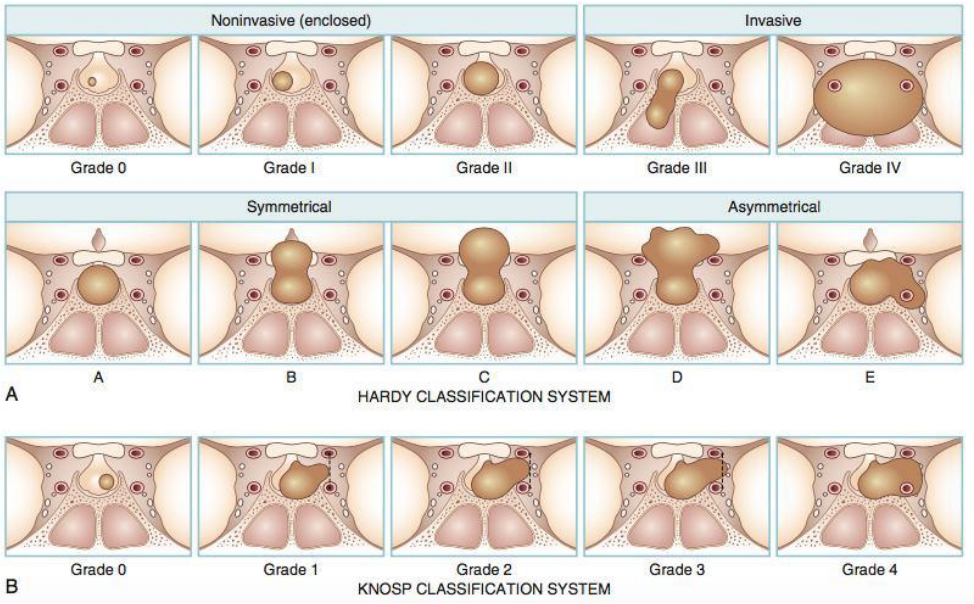


Figure 9. The extension severity classification systems

II.3.2.2. Nonsecreting pituitary adenomas

- 30% of anterior pituitary adenomas
- Mutation of a pituitary cell – proliferation advantage
- No active hormonal secretion
- Micro adenomas < 10 mm
- Macro adenomas > 10 mm

Diagnostic

- ✓ Confirmation – localisation
- ✓ Functionality = Hormonal hyper secretion exclusion:
    1. IGF1, OGTT with GH at 0', 30' and 60' GH <1 ng/mL
    2. PRL 2 assays ! PRL > 200 ng/ml
    3. Midnight salivary cortisol, suppression test
    4. TSH, TT3, FT4
- ✓ Mass impact = functional syndrome
- ✓ Hormonal insufficiency impact:
    1. ACTH + plasmatic cortisol + Insulin tolerance
    2. TSH + TT3 + FT4
    3. FSH+LH + E2/TT
    4. GH, IGF1 +insulin tolerance

Confirmation = localisation is made only by imagistic evaluation.

The best diagnostic tool is represented by Magnetic Resonance imaging (MRI) because of:

- Better resolution
- 1 to 3 mm slices
- Focused on the pituitary
- High resolution T1 weighted coronal+ sagittal sections
- Before/after Gadolinum pentetic acid adm. (paramagnetic agent)
- Normal pituitary up to 12 mm
  (!pregnancy/adolescence/postpartum induce a physiological increase in pituitary volume)
- Stalk = 4 mm diameter
- **Micro**adenomas = **hypo intensity lesion** = low afinity for Ga
- **Macro**adenomas = **hyper intensity lesion** = high afinity for Ga
- Global sensitivity of and specificity of 80-99% and a specificity of 50-65%
- Identifies adenomas higher than 2 mm in diameter.

Currently it is considered the best screening and diagnostic tool.
Computer tomography has to be considered the 2nd choice, just in some selected cases, due to a very low sensitivity of less than 30% (17-24%). It also involves exposure to X rays, so is nor recommended in children and contraindicated in women. It has to mention that it directly visualizing the bone structures: sella floor, clinoid processes and evaluates the bony invasion. It also recognize calcification, suggesting: craniopharingioma, meningioma, aneurysms.

- Indications:
  1. Hemorrhagic lesions
  2. Metastatic deposits
  3. Chordomas
  4. Calcifications
  5. Contraindication for MRI (pacemakers)

The historical evaluation, lateral skull conventional X ray, wit or without focusing the sella turcica, has a very low sensitivity or specificity. There are some classical aspects suggesting pituitary adenoma, but the presence or absence of the signs should not be considered in the diagnostic approach of a pituitary adenoma, especially in exclusion of such a lesion. The described signs are:

1. Sella turcica expansion/destruction
2. Enlarged sinus cavities
3. Alteration of clinoids
4. Blurred intrasellar signal
5. Doubled sella floor

Newer imaging techniques are: Receptor imaging SPECT, the used radiolabeled tracers that are actively uptake by specific hormonal receptors. Currently more radiolabel tracers are used:

- Dopamin receptor SPECT
  - ^{131} I-iodobenzamine — PRL secreting tumors
  - ^{123}I epidepride — ACTH secreting tumors
- Somatostatin receptor SPECT
  - - ^{111}In pentetreotide — GH secreting tumors
  - - ^{201}Tl chloride — TSH secreting tumors
  - - ^{111}IN DOTA lanreotide — non-functional tumors

The limitations of these techniques are:

1. Evaluate also healthy pituitary tissue that express receptors
2. Sensitivity of 1 cm
3. Precision depends in the receptor expression in the tumor

We have to bare in mind that this evaluation are mainly functional evaluation:

PRESENCE of TUMOR
REVEALANCE OF DISTANT METASTASIS

Neuro - ophtalmologic assessment of pituitary masses

Because of the position and vulnerability of the optic tract in respect to the pituitary, the evaluation of the neuro-ophtamologic compartment is very important.

The optic nerve comprises fibers coming from the medial half of the retina, sensing the information from the lateral, temporal half of the visual field, and fibers coming from the lateral part of the retina, sensing the information from the medial, nasal half of the visual field, that at the decussation level will change places due to the side change of the medial, nasal fiber. The decussation level, in the optic chiasm is situated only 1 cm higher that the pituitary wall, so any pituitary deformation can impact at the level of the optic chiasm. Depending on the exact place of the compression, different visual field defects are seen.

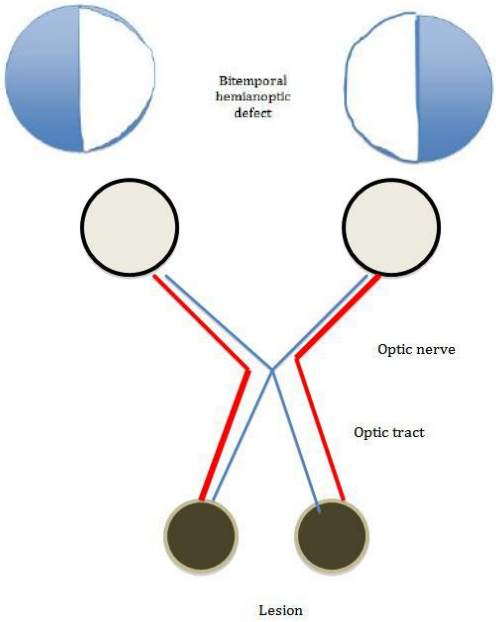


Figure 10. Optic chiasm organization in normal/abnormal conditions

The general evaluation comprises general visual evaluation, colored vision evaluation (red vision lost), and computer assisted visual field evaluation. All the evaluations are done with one eye covered.

Hormonal evaluation

In the presence of a diagnostic of a pituitary adenoma some standard, screening hormonal assays have to be done:

- FSH/LH + E_2/TT
- TSH + TT3+FT4
- ACTH + plasmatic cortisol
- GH + IGF1
- PRL
- in cases where there is a suspicion of tumoral hyper secretion, this aspect has to be confirmed by inhibitory tests (that have to be negative due to the alteration of the normal feedback control in cases of tumoral hyper secretion)
  - **IGF1, OGTT with GH at 0', 30' and 60' GH <1 ng/mL**
  - **PRL 2 assays ! PRL > 200 ng/ml**
  - **Midnight salivary cortisol, DXM suppression test**
  - **TSH, TT3, FT4**

- in cases of suspicion of secondary insufficiency, due to direct compression of the tumor on the healthy secreting pituitary cells, stimulatory tests should be used in order to certify the decreased/absent capacity of the pituitary to secrete the proper amount of hormones.
    - **ACTH + plasmatic cortisol + Insulin tolerance**
    - **TSH + TT3 + FT4**
    - **FSH+LH + E2/TT**
    - **GH, IGF1 +insulin tolerance**

The diagnostic of non-secreting adenoma is made after the exclusion of any hormonal hyper secretion: *Caution - not every elevated PRL level means hyper secretion! In the presence of stalk deviation, PRL levels can be high, despite the nonsecretory effect of the original macroadenoma*. For these cases, the differential diagnosis made with SPECT evaluation is excellent. In cases of no SPECT evaluation, the magnitude of the PRL level is used as an indirect parameter: proportionality between the adenoma size and the level of hyper secretion.

In cases of any pituitary adenoma, the goal of the treatment is to decrease to local compression, to correct the hormonal disbalance (either hyper or hypo secretion) and to reduce as much as possible the tumor per se.

Generally, there are 3 types of curative treatment: surgical, radiotherapy and medical treatment. Supplemental hormonal treatment will be discussed later in the hypopituitarism section:

1. Surgical teatment
    - Trans sphenoidal
    - Craniotomy
2. Medical **NO EFFECT** in nonsecretin lesions
3. Radiotherapy
    - Conventional
    - Radiosurgery

In cases of nonsecreting tumors, the medical treatment is ineffective, due to the lack of the sensitive neurohormones receptor on the proliferating cells (null cells), so the only 2 possibilities left are surgical and radiological management ways.

Surgical management refers to the excision of the mass lesions, decompression, control of the recurrent mass after the initial surgical or radiological treatment. There are 2 described approaches:

- Transsphenoidal approach, minimal invasive technique, that precludes invasion of the cranial cavity, without any brain tissue manipulation, with an approach through the sellar floor, direct visualization of the tumor, microdisection of the tumor, permitting a selective adenomectomy with minimal complications.

  Indication:

  1. Visual tract compression
  2. Decompression after residual/recurrent mass
  3. Tumor recurrence
  4. Cerebrospinal fluid leak
  5. Resistance to medical therapy
  6. Intolerance to medical therapy
  7. Personal choice
  8. Desire for immediate pregnancy in macroadenoma cases

The endoscopic approach is associated with a low complication rate, low morbidity and extremely low mortality rates.

Transient side effects are described:

- Diabetes insipidus
- Cerebrospinal liquid leak, rinorrhea
- Arachnoids
- Meningitis
- Arterial wall damage, epistaxys
- Local abcess

There are some permanent side effects that are present in a maximum of 10% of cases:

- Diabetes insipidus
- Hypopituitarism
- SIADH
- Vascular occlusion
- Nasal septum perforation

In less than 1% of cases mortality can be present, as a consequence of brain injury, or severe vascular damages.

The patient will be supervised for around 6 hours, with electrolyte evaluation, ambulatory after 6 hours, with a total hospitalization of 3 days.

- Craniotomy is recommended only in selected cases:
    1. Invasive suprasellar mass
    2. Invasion of frontal fossa
    3. Invasion of cranial fossa
    4. Extension posterior invasion
    5. Too solid tumors for a successful endoscopic approach.

The number and incidence of side effects is much higher compared with the endoscopic approach due to the aggressiveness of the technique but also due to the dimensions/extension of the treated lesion.
The common described side effects are:

- Allergic reaction
- Injury from the head fixing device
- Injury of the facial muscle
- Injury to the sinuses
- Seizures
- Bleeding
- Brain damage
- Brain swelling
- Stroke, coma
- Hypopituitarism
- Diabetes insipidus/SIADH

After surgery, patients should be kept in bed rest, at an angle of 35-40 degrees with urine, serum electrolytes periodic evaluation, with a cautious evaluation of the posterior hypophysis activity.

Pituitary irradiation

High-energy ionizing radiation delivered to the pituitary region, can inhibit the proliferation of any present adenoma. The big challenge is to obtain the maximum effect on the tumoral tissue with a limited necrotizing reaction of the health pituitary tissue. Conventional radiotherapy cannot deliver a focused X-ray beam. There are high precision newer techniques: gamma knife proton beam procedures can deliver a high energy beam with a minimal effect on the surrounding tissue.

The use of radiation is recommended in selected cases:

1. Macroadenomas – acromegaly, Cushing, nonfunctioning adenoma, PRL
2. Craniofaringyoma
3. Nelson sd = pituitary hyperplasia in ACTH pre-existing adenoma with bilateral adrenalectomy
4. Invasive sellar mass
5. Tumor recurrence
6. Hormone hyper secretion recurrence

Conventional radiotherapy uses a daily regimen, with 18 0 Rad/day, for a total dose of 5000 - 6000 Rad, in 5 to 6 weeks. Unfortunately the number of side effects is notable:

- Hypopituitarism in 100% of cases
- Visual loss, optic neuritis
- Brain necrosis, temporal lobe deficits, cognitive dysfunction
- Up to 10 years for hyper secretion control, the interval in which the patient has to adjust with other treatments
- Risk for a second brain tumor, with a described incidence ratio per person/year of a total of 12 (5 astrocytoma, 4 glioma).

High focused radio surgical procedures are preferred, because of the fewer side effects, with efficacy in 80% of cases, with a shorter period of hyper secretion control, of 2 years, and with a significant lower rate of hypopituitarism of only 25%.

II.3.2.3. Secreting pituitary adenoma

The main characteristics of these tumors are the presence of secretory activity ***= Endocrine syndrome.***

Considering hyper secretion, as mentioned before, the majority of pituitary adenomas are secreting adenomas (70% of cases): with the following prevalence: PRL secreting 30%, GH secreting 10%, ACTH secreting 10%, TSH secreting < 1%, LH/FSH secreting <0.5 and around 10% the multiple hormonal secretion 10%.

We will present the major secretory tumors: PRL secreting, GH secreting and ACTH secreting.

Prolactin secreting adenomas

Hyperprolactinemia is the most frequent endocrine anomaly of the HP unit. The vast majority of causes are related to functional, secondary increase in PRL levels, and only a minority of cases is due to the tumoral production of PRL. The diagnostic challenge is to identify the cases with tumoral hyperprolactinemia.

Prolactinoms are the most frequent pituitary adenoma, with a benign proliferation of the lactotrope cells, comprising over 30% of pituitary adenomas, with a prevalence of 44 cases in 100.000 persons.

It mainly arises from the lateral wings with an anterior progression, with a slow progression and possible compression of the normal anterior and posterior pituitary lobe.

The Prolactinoms is diagnosed early, the vast majority of cases being micro adenomas, with a higher prevalence in women: women to male ratio = 20:1.

Like in all cases of hormonal hyper secretion tumors, the clinical picture can be organized:

a) *Somatic syndrome* – due to increase PRL levels – which directly induces galactorhea, mainly in menstruating women.

b) *Hormonal syndrome* -

- Rapid onset + hypogonadism due to the indirect effect of high PRL levels with the inhibition of gonadostat (by altering the pulsatile secretion), both in males and females
- Late onset = hypopituitarism secondary to mechanic compression

c) *Metabolic syndrome* – not described in Prolactinoma

d) *Functional syndrome* – tumoral sd. described earlier

When we think about genders, the clinical manifestations are different, because the moment of diagnosis is different = earlier in women, later in male.

FEMALE

1. The earliest signs are changes in the menstrual cycle with hypomenorhea (decreased flow), oligomenorhea (spares cycle) and finally secondary amenorrhea (cessation of menstrual cycle), changes seen in over 90% of cases. Another possible manifestation is the post pill amenorrhea, secondary to the same mechanism.
2. Infertility, primary or secondary, can also be a consequence of the prolactinaoma; many a positive diagnosis has been made because of an infertility general check up.

3. The persistence of hypoestrogenemia induces typical manifestation: vaginal dryness, dyspareunia, weight gain, irritability, and hydric retention.
4. The typical considered sign - pathognomonic for Prolactinoma, galactorhea is seen in just 20% of cases. Do not expect the amenorrhea galactorhea syndrome in all cases.
5. Long standing untreated disease will also generate bone demineralization.

Because of the early onset of menstrual cycle changes, the diagnosis of hyperPRL is made quickly

MALE

1. The earliest signs are due to the effect of high PRL levels on male sexual functions: decreased arousal, decreased libido, and followed by erectile dysfunction.
2. Infertility can be a problem in males with prolactinomas, but it is not diagnosed so frequently as in women.
3. Later, due to real hypogonadism the erectile dysfunction aggravates and becomes nonresponsive to classic PDE5i treatment.
4. Bone mineralization is frequently seen.

Because the clinical signs are frequently overseen, the vast majority of prolactinomas are diagnosed in the stage of macro prolactinomas, with typical tumoral sd: headache, visual field defects Etc.
Because of this clinical manifestation an active screening for hyper PRL must be made in cases of:

1. *Galactorhea*
2. *Enlarged sella turcica*
3. *Suspicion of pituitary adenoma*
4. *Amenorrhea/oligomenorhea/decrease menstrual bleeding*
5. *Male hypogonadism*
6. *Male erectile dysfunction/loss of libido*
7. *Infertility (female / male)*

In the presence of a suspicion of hyper PRL the diagnostic steps are the following:

1. Confirmation of hyper PRL – at least 2 assays, in different days, under correct conditions: no food administration, no effort, and no sexual activity in the morning of sampling, with at least 2 hours awakening time.
2. Exclusion of possible functional causes of hyper PRL
    a. Medication
    b. CKD (!!! A normal creatin level does not exclude a decreased GFR)
    c. Peripheral untreated hypothyroidism (low T3 and T4 will increase TRH which stimulates PRL)
    d. Rule out pregnancy
    e. Control, for oral contraceptive use
    f. PCOS, hyperandrogenia

Generally, the values of PRL can orientate in this differential diagnosis: typical tumoral values are considered increased values of PRL higher than 100 ng/ml, lower values being suggestive for a functional/reactive hyper PRL. The general rule in tumoral secretion of PRL is that the hormonal secretion is proportionate with the tumoral volume.

3. Pituitary complete evaluation = to evaluate the magnitude of associated hormonal imbalances:
    LH, FSH + E_2 or TT
    TSH + FT4, FT3
    ACTH, cortisol, stimulation test
    IGHF1
    Diuresis
4. Localization diagnostic:
    - 1st line evaluation = MRI with contrast agent, focused on hypophysis
    - 2nd line = CT in cases where MRI is contraindicated
      (!!! The decreased sensitivity)
    - The profile skull radiography is a overrated evaluation, with no clear value in the diagnostic of prolactinomas. It could have some indirect information, but a quality diagnosis cannot rely on this evaluation.
    - The most difficult differential diagnosis is in the case of hyperprolactinemia associated with an adenoma that deviates the stalk: in these cases it is difficult to say if increased PRL is due to direct tumoral production or due to stalk compression, with decrease of inhibitory Dopamine control.
    - The SPECT with ^{131} I-iodobenzamine is useful in identifying tumors producing PRL.

Treatment

Treatment has to be offered to all patients with prolactinomas, even in cases with very small prolactinomas, that will progress very, very slowly, because of the long term impact on fertility and bone density.

Treatment options:

1st line therapy = medication, Dopamine agonists that control the hyper secretion of PRL, will reduce the tumoral volume and will disinhibit the gonadostat, with fertility restored.

The possible preparations are:

- Bromocriptine (Bromocriptine), that stimulates the Dopamine receptor in the hypothalamus, with an increased inhibitory Dopamine action on PRL production. It has a short half life, with daily administration regimen, with relative tolerance: gastric side effects, dizziness, nystagmus, daily doses of 2.5 -5 mg;
- Cabergoline (Dostinex), a nonergot dopamine agonist, is administered once or twice a week, because of a longer half life time, with excellent tolerance. There were some concerns regarding the long term administration of the medication due to a possible increase in the incidence of Parkinsons' disease (which is described only in the daily regimen) and possible cardiac valvular lesions (due to an affinity for valvular serotonin receptors) with the recommendation of a yearly cardiac ultrasound evaluation in Cabergoline treated patients. Weekly doze of 1=7 mg/week
- Other dopamine agonists: Pergolide mesylate (Permax), Lisuride maleate (Dopergin, REvanil), Quinagolide (Norprolac) that are not used on daily basis.
- The success of the treatment is around 90% of cases in patients with microadenoma and around 60-70% of cases in macroadenoma cases, with a decrease of tumor size days – weeks after the initiation of treatment.

There is a follow up after the first 3 months, establishing the minimal effective dose in the PRL control (to high medication doses with decrease PRL outside the normal range, with secondary behavioral changes, mainly addiction appearance).

2nd line therapy = Surgical approach.

In general, in hormone producing tumors, the indication of surgical treatment is made under the following circumstances:

1. Excision of the mass lesion causing central pressure effects
2. Primary correction of the hormonal secretion
3. Resection of functional tumors resistant/not responsive to medical treatment
4. Hormonal/tumoral recurrence after medical or radiological treatment

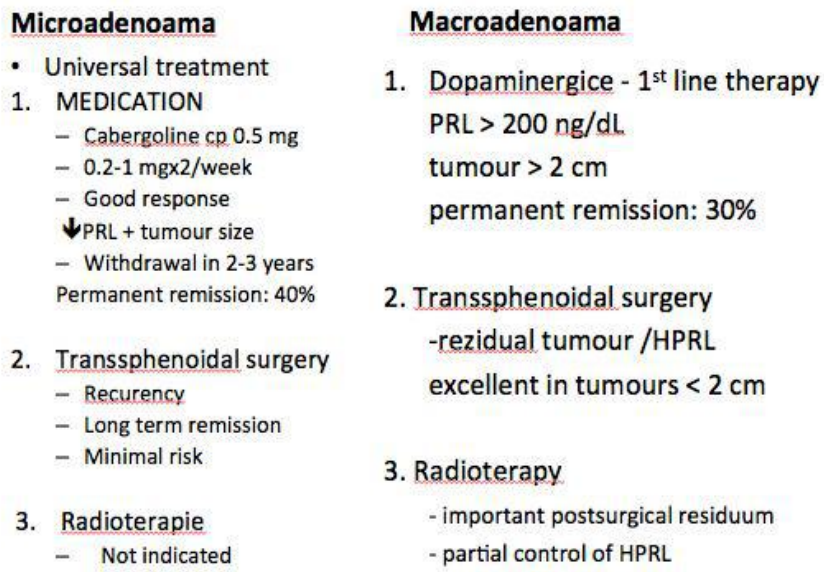
In PRL secreting tumors, the surgical approach can be:

- Transsphenoidal: with excellent results in microadenomas, macradenomas smaller than 2 cm, and PRL levels beow 200 ng/ml, with success in 80 – 95% of cases.
- Transcranial: in big tumors, with suprasellar extension, with a cure rate of only 20%.

3rd line therapy = radiosurgical treatment

Is indicated only in macroadenoma, with severe compression effects, unresponsive to 1st and 2nd line therapy. Radiosurgical approaches are preferred.

Considering micro and macroadenoma the following algorithm is proposed:



The recurrence rate is around 30%, higher in macroadenoma, with important pretreatment PRL levels.

Somatotroph secreting adenomas

The GH secreting adenoma is the second frequent pituitary adenoma in humans.

The incidence is low, around 2 new cases/1 million people per year.

From the pathogenic point of view, the GH producing adenoma is secondary to a mutation of the G protein in the acidophilic pituitary cells, with replication advantage. 15% of tumors are associated with PRL co-secretion. The disease is very rare in childhood. In adults the incidence in males equals the incidence in women, more frequent at 40 years of age.

The vast majority of cases are diagnosed in the stage of macroadenoma, because of the slow development of the symptoms, secondary to exposure to high levels of somatotroph hormone, generally considering that, by the moment of diagnosis, the disease was active for at least 5 to 10 years.

The main problem in pathology is excessive GH secretion, with altered secretion pattern, increase in peak secretion, random secretion, override of the normal regulatory mechanisms, with abnormal response to standard inhibition tests. Secondary to the GH hyper secretion, there is a huge increase in the IGHF1 secretion and release.

Like in all cases of hormonal hyper secretion tumors, we can organize the clinical picture in:

1. *Somatic syndrome* – due to increase GH levels – which directly induces growth, with different patterns depending the moment of onset of GH hyper secretion: before or after growth plate cartilage closure:

Excess before the closure – the increase in growth in length is the main symptom - GIGANTISM

- If the GH excess is before the closure of the growth plate, there is a significant increase in height, due to increased growth of long bones, with increased mean height, Increased growth velocity, accelerated bone age, with associated changes in the soft tissue and changes in facial bones with hard face expression, and also increased soft parts: hands, feet, toes.
- The other changes typical for acromegaly will appear if the GH hyper secretion will persist untreated even after the growth plate closure.

Excess after the closure – the growth in width is the main symptom = ACROMEGALIA

- Symptoms: osteoarticular pain, paraesthesia, excessive sweat, heat intolerance, lethargy, oligomenorhea, galactorhea, erectile dysfunction, infertility

- Signs:

  Soft tissue growth, present in 100% of cases: tongue, ears, nose, hand, fingers, feet, toes.

  Spongious bone growth: calvarium, prognatism, increased space between teeth, frontal bone, zigomatic bone in 100% of cases

Hiperhidrosis due to increase action of skin glands	88%
Weight gain	87%
Hipertricosis with increased hair growth	40%
Papilloma	45%
Goitre	30%
Acanthosis nigricans	30%
Increased blood pressure	24%
Cardiomegaly	16%

2. *Hormonal syndrome* - Associated hypopituitarism: associated hypogonadism in around 60% of cases, hypothyroidism in 13% of cases and only hypocorticotropism in 4%.
3. *Metabolic syndrome* – hyperglycemia, secondary to the hyperglycemia effect of GH excess: increased glycemic levels, in 70% of cases, ATG in 50% of cases and DM in only 20% of cases.
4. *Functional syndrome* – tumoral sd. described earlier, is frequently seen because almost all GH adenomas are diagnosed in advanced cases, due to the compression of the surrounding structures.

In the presence of a suspicion of hypersomatotrophism the diagnostic steps are the following:

1. Basal GH levels - are typically increased 5-500 ng.ml (normal values < 1-5 ng.ml)
2. IGHF1 evaluation – proportionally increase, due to GH excess.

   Normal values have to be considered in concordance to age and sex of the patient.
3. In cases of hyper secretion, inhibition tests are required in order to document the loss of the normal regulatory mechanism. The most useful inhibition test is the hyperglycemic test:
   - 100 g glucose, orally,
   - normally suppresses the GH level below the value of 1 nl/ml.
   - in case of GH excess the decrease of GH is absent or incomplete.

4. Localization of the lesion: MRI with less sensitivity for the pituitary region, with a paramagnetic agent, with images before and after the contrast agent (most adenomas = hyper dense) CT with significant lower sensitivity, with sellar enlargement in 90% of cases, conventional cranial X Ray.

   Conventional X Ray will show some complications of hypersomatotropism: enlargement of the frontal and maxillary sinuses, enlargement of the jaw, tufting of the distal phalanges, cystic changes of carpal bones, with similar changes in feet.

   SPECT imaging, with radiolabeled Somatostatin analogues can be used in GH functional tumoral diagnosis, especially in the paraneoplasic secretion of ectopic GH.

Differential diagnostic has to be made with:

I. Other causes GH/IGF1 secretion

- Anxiety
- Physical activity — **↑↑ GH levels**
- Acute disease — **NO clinical signs**
- Starvation
- CKD
- Proteocaloric malnutrition
- Anorexia nervoasa

II. Ectopic GH / GHRH secretion — **clinical signs**

- pulmonary carcinoma — **normal pituitary**
- carcinoids
- pancreatic C cell

Treatment

All patients with acromegaly / gigantism have to be treated to halt the somatic complication of the disease and prevent the medium and late complication of the disease.

Objective:

1. Removal of the adenoma
2. Controlling/stopping of the somatic changes
3. Correction of the associate hormonal insufficiencies

The criteria for normal secretion control is currently considered: lower GH values than 1 ng/ml (basal or under stimulation) are considered standard value for adequate response to therapy.

1st line therapy = surgery

Generally, in hormone producing tumors, the indication of surgical treatment is made under the following circumstances:

1. Excision of the mass lesion causing central pressure effects
2. Primary correction of the hormonal secretion
3. Resection of functional tumors resistant/not responsive to medical treatment
4. Hormonal/tumoral recurrence after medical or radiological treatment

The surgical approach can be:

- transphenoidal = offered for intrasellar tumors,
- craniotomy = indicated for invasive/suprasellar extension,

The results are excellent in cases of tumors smaller than 2 cm, or GH values < 50 ng/ml, with GH normalization of 60-80% of cases.

The results are moderate in bigger tumors than 2 cm, with higher GH levels > 50 ng/ml.

The recurrence rate is small in a maximum 5% of cases.

2nd line treatment is medical treatment.

It is recommended in cases of:

1. Residual hyper secretion (after radiotherapy or surgery)
2. Contraindication for surgery
3. Small tumours in elderly patients

The used preparations are Somatostatin analogues, Octreotid or Lanreotid, SS2 and SST5 activators that have an antisecretory and antiproliferative effect and will control both tumoral volume and tumoral hyper secretion.

The results are excellent: decrease of GH secretion by 75% and decrease in tumor size by 20%.

Octreotid acetat was the first available preparation, with high-required high doses (up to 500 mcg), with shot half-life time. New preparation, Octreotid acetat LAR and LAnreotid acetat are given sc 1 monthly.

Side effects are gastrointestinal symptoms and gallstones.

If the response to treatment is not good enough, another medical agent can be used: association of dopaminergic agent, Cabergolin, which will further reduce the GH secretion by another 30%.

In resistant cases, with residual important GH secretion, there is another preparation used: Pegvisomant, a GH receptor antagonist, that will block the synthesis and secretion of IGFQ and control the somatic syndrome in resistant disease. The treatment has no effect on the magnitude of GH secretion, nor in the dimensions of the tumoral tissue; it will control only the peripheral effect of GH. It is a last line therapy because of the very high cost of the treatment and also because of controversial opinions regarding a possible tumoral size increase during treatment.

3rd line therapy, is represented, as usual, by radiotherapy.

Conventional irradiation is not recommended, even if the final hyper secretion cure rate is 60-80%. It needs a very long period, of about 10 – 15 years before resuming the hyper secretion. The rate of panhypopituitarism is very high.

Modern radiosurgical focused techniques, as the Gamma knife technique will permit remission in 50 -90% of cases in a significant shorter period of time, of 2 years.

In the interval between the radiotherapy and the control of hyper secretion, medication is imperative.

Response to treatment:

1. normalization of GH secretion
2. cessation of bone overgrowth
3. reduction of the soft tissue hypertrophy
4. decrease of puffiness
5. decrease of weight
6. cessation of skin changes: sebum production, hair growth
7. there is no possible regression in the bone changes.

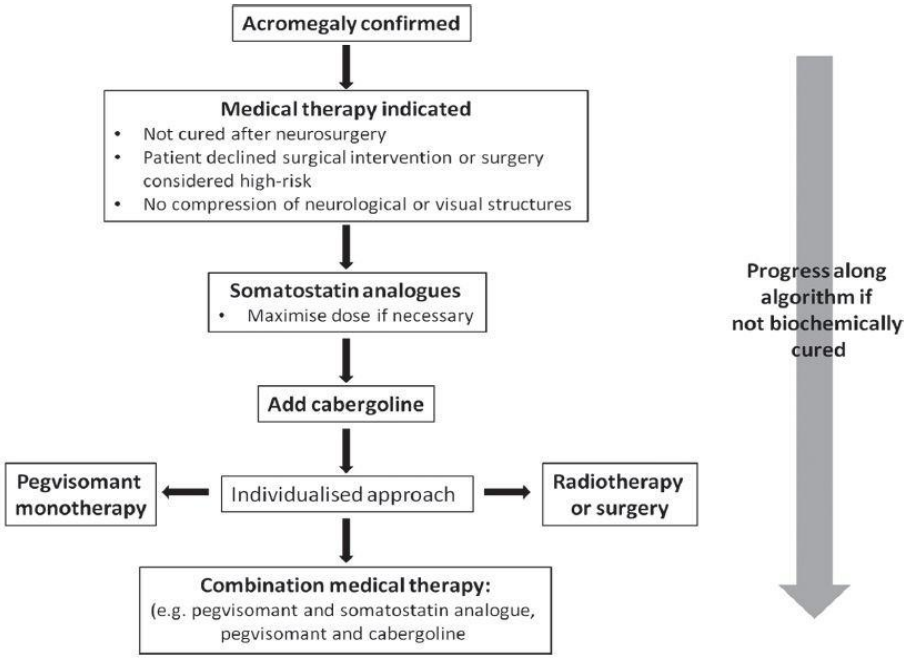


Figure 11. Treatment algorithms in GH secreting tumors

ACTH secreting adenomas are presented in the ADRENAL CHAPTER.

Other hormones secreting adenomas

The TSH and FSH/LH secreting adenomas are very rare diseases.

The TSH secreting adenoma are big tumors (macroadenoma), secondary to cromophob cells with predominant functional sd., with visual field changes, with excellent response to SST analogues, with efficiency in 70% of cases, with surgical treatment as 2nd line treatment. The hormonal sd. is represented by hyperthyroidism, with high TSH values with high T3 and T4 values.

The LH/FSH producing tumors are extremely rare adenomas, due to the proliferation of cromophob cells that are associated with functional sd. due to dimensions of macroadenoma, with secondary HYPOGONADISM. The particularity of these adenomas are, due to the altered, chaotic FSH and LH secretion, that loosens the normal peak type secretion, continuous exposure to FSH or LH will suppress the normal function of gonads, that will induce hypogonadism, and not, as expected, hypergonadism.

Pituitary carcinomas are extremely rare diseases, most of them having secretary activity, producing ACTH and PRL, with important metastatic potential with secondary low survival rates, after surgery, radiotherapy and chemotherapy.

II.3.3. PITUITARY INSUFFICIENCY

The diminished secretion of at least one of the pituitary hormones defines hypopituitarism.

It can be with

Slow

Insidious

Primary = anterior pituitary destruction

Secondary = hypothalamic deficiency

Inherited

Acquired

Isolated

Multiple

Generally there is a sequence loss: GH, LH and FSH, TSH, GH and PRL. Some of the anterior pituitary insufficiencies are associated with AVP altered secretion.

There are many possible causes for pituitary insufficiency:

Inherited causes, due to:

- Genetic mutation: Kalmann sd (FSH, LG), Prader Willi Sd. (FSH LH), Lawrence Moond Biedl (FSH, LH);
- Receptor mutation: possible mutation of all pituitary receptors; GHRHR, CRHR, GhRHR, TRHR, LeptinR;
- Structural anomalies: pituitary aplasia or hypoplasia, encephalocelel
- Transcription factor defect or
- Hormone mutation.

Acquired hypopituitarism can be secondary to:

- invasive:
  - Space occupying lesions: pituitary adenomas, craniopharingioma,
  - SNC tumors: meningioma, chordoma, optic glioma, epidermoid/dermoid, metastasis
  - Malformations: parasellar aneurysms
- Infarction:
  - Sheehan sd= ↓↓ BP = spasm of the hypophysis arteries = ischemia=infraction
  - ? Pregnancy/postpartum/
  - Simons sd

- Pituitary apoplexy = spontaneous infarction of a pituitary tumor
- Infiltrative
    - Sarcoidosis = DI + alteration of hypothalamus
    - Hemochromatosis = typical hypogonadism IRON DEPOSITS
    - Histiocytosis = DI + anterior hypophysis
- Injury in cases of severe trauma in adults and children
- Immunological: Autoimmune infiltration, during pregnancy, 50% associated endocrine autoimmune diseases
- Iatrogenic causes
    - Surgery
    - radiotherapy: 60% in 4500-5000 cGy;
    - 15-55% proton beam therapy, 25% gamma knife
- Infectious : very rare cause

The clinical picture is usually gradual, due to progressive pituitary insufficiency, following the GH, gonadotropin secretion, then TSH, then ACTH and finally PRL.

Symptoms are directly related to each pituitary hormone deficiency:

- *GH deficiency*: occult in adults: ↓ well being, ↓muscle mass, ↑ fat mass, low energy, tendency for hypoglycemia
- *FSH, LH deficiency*: hypogonadism with amenorrhea, anovulation, low E_2, altered lubrication, depressed mood (in women) and decreased libido, erectile dysfunction, loss of morning erection, changes in general behavior (in males)
- *TSH deficiency:* typical signs of hypothyroidism but less severe than the symptoms seen in the peripheral disease: loss of energy, bradylalia, bradychinesia, bradycardia, edema of extremities, increase in weight, decrease in intestinal transit, decrease in renal filtration rate, tiredness. There are no thyroid lesions in the central disease.
- *ACTH*: deficiency the most severe insufficiency, will cause chronic, baseline symptoms with weakness, tiredness that will increase during the day, decreased blood pressure, decrease in weight, loss of appetite. Under stress situations the deficiency becomes more evident with: weakness, nausea, vomiting, anorexia, weight loss, fever, hypotension, normal BP, with no dehydration and Natrium depletion because of normal function of zona glomerulosa, where the renin-angiotensin-aldosterone will be secreted, independent of ACTH central control. Depigmentation, diminished tanning has been described due to ACTH/MSH deficiency.
- *PRL deficiency*: the only sign in present in postpartum women with absence of lactation.

Following clinical signs can be seen in hypopituitarism:

- Slightly overweight
- Fine, smooth, pale skin
- Fine wrinkling of the face
- Decreased axillary+ pubic hair
- Atrophy of the genitalia
- Decreased pigmentation of mucosa
- Postural hypotension, delayed deep tendon reflex, decrease muscle strength = severe cases

The extreme clinical picture of pituitary insufficiency is called Simmonds syndrome, a profound state of cachexia. In cases of long-standing, untreated panhypopytuitarism, the clinical picture associated with hypothalamic lesions explain the important changes in appetite and weight balance. Sheehan syndrome, has a similar evolution, due to the necrosis of the peripartum hypophysis due to important blood loss, during labor, with rapid onset pan hypopituitarism.

Quality follow up during pregnancy does change the possibility of Sheehan Sd. Appearance. The approach is a prophylactic one with correct evaluation and assessment of dystocic pregnancies.

Another form of hypopituitarism worth mentioning is the acute pituitary apoplexy that appears during the spontaneous liquefaction of a preexisting pituitary tumor. Severe headache, visual impairment, ophtalmoplegia, meningismus and altered consciousness should suggest the tumoral apoplexy. After the acute phase, the clinical picture of acute pituitary insufficiency will appear.

Diagnostic of the pituitary insufficiency evaluates:

- Peripheral gland actions
- Status of pituitary hormones
- Stimulatory test to evaluate the response capacity of the hypophysis and hypophysis

TABLE X. LABORATORY ASSAYS IN HYPOPITUITARISM

Hypophysis hormone	Periphery evaluation	Stimulatory test	Normal response
GH↓	IGF 1↓	Insulin tolerance: 0.1-0.15 UI/kgc	GH > 5 ng/dL
ACTH↓	Cortisol↓	Insulin tolerance: 0.1-0.15 UI/kgc Metyrapone PO 30 mg/kgc	Cortisol > 18 mg/mL Cortisol < 7 mg/mL ACTH > 75 pg/mL
TSH↓	FT3, FT4↓	TRH 200-500 mcg IV	TSH > 2.5- fold, TSH > 5-6 IU/L
LH/FSH↓	E2↓ TT↓	GhRH 100 mcg IV	LH > 2-3 –fold, LH > 10 IU/L FSH > 1.5-2-fold, FSH > 1 IU/L
PRL ↓		TRH 200 mcg IV	PRL > 2.5-fold

Congruent laboratory assays will show:

- Hypoglycemia (ACTH, TSH deficiency),
- Hyponatremia (TSH deficiency),
- Anemia (TSH, GH deficiency),
- Dyslipidemia (GH, TSH deficiency),
- Bone loss (LH, GH deficiency).

The etiological diagnostic of the pan hypopituitarism will comprise all the needed evaluation in order to identify one of the above presented possible causes that altered the normal hypophysis function.

Treatment

After diagnosing that the pituitary lines are deficient, the treatment given is supplemental which will be offered to all patients, with some specific rules.

1. Supplemental therapy is introduced in the order of the severity of the deficiency: corticotroph line ➔ Tireotroph line □➔ □□□□□□□□□□□□□□□□□➔ somatotroph line (if allowed) + AVP line.
2. Follow up has to be done every 6 months
3. General contraindications for steroidal hormonal replacement have to be taken into consideration
4. The treatment is compulsory, lifelong in the most important deficiency: ACTH deficiency and TSH deficiency, the only deficiencies, that if untreated are life threatening.

ACTH LINE

- **Glucocorticoid supplemental therapy** is preferably made with natural, hydrocortisone preparations. There are differences between the basic need doses, which are commonly the following doses:
    - Hydrocortisone – physiological preparation 15-25 mg/day
    - Alternative – Prednisone 5-7.5 mg/day
    - 2/3 morning + 1/3 noon

with NO mineralocorticoid supplementation due to the normal function of Renin Angiotensin Aldosterone regulation, which acts independently of ACTH command.

In stressful conditions there is an imperative need for increasing the doses up to 10 times higher, with orally or mainly parenteral preparation (Hydrocortisone Hemisuccinat preparation) in cases of: acute illness, surgery, trauma, pregnancy, birth, acute infection, diarrhea, vomiting.

- Follow up !!! No use of hormonal blood assays, evaluation of weight, blood pressure, appetite, general well being, essential in the treatment dose changes.

- The supplemental therapy is life long.

TSH LINE

- **Thyroid hormone replacement therapy** with T4 or combined preparation (T3 + T4) is used.
- Commonly T4 preparations are used, in doses around 1.6 mcg/kg/day, total daily dose of 75 – 150 mcg/day, depending on the patients' weight. It must be mentioned that small children, or elderly patients need different doses from the adult patients.

- In selected cases, T4 + T3 preparations are used, but caution must be taken with elderly, patients who have cardiac problems. The combined preparation is contraindicated in pregnant women.
- Always before treatment with thyroid hormones, the quality of the secretion of the corticotroph line has to be checked; thyroid replacement therapy may aggravate the untreated even partial adrenal insufficiency due to the increase in renal metabolism/excretion.
- Follow up will be made for T3 and T4 assays also considering the clinical signs and symptoms.
- The treatment is life long.

GONADOTROP LINE

MALES

- **Androgen supplemental therapy** is used universally, with:
  - Testosterone gels daily 20 mg/day
  - Testosterone cypionate IM 100=200 mg/2 weeks
  - Testosterone undecanoat IM 1000 mg/3 months
  - Oral preparations are avoided due to hepatic side effects.
- In cases of fertility interest, the supplemental testosterone treatment is not preferred, due to the inhibition of the spermatogenesis, long term beta HCG supplemental therapy being temporarily used: 4000 UI/week, for a minimum of 3 months.
- Duration of the substitution is until the senescence
- Follow up – total testosterone/bioavailable testosterone in normal range values

Contraindications:

1. Prostate cancer
2. Breast cancer
3. Untreated vascular/cardiac disease
4. Severe hepatic insufficiency
5. Polycythemia
6. Sleep apnea

FEMALES

- Basic supplemental therapy comprises **estrogen and progesterone treatment**, for women with a preserved uterus. In cases of the absence of the uterus, there is no need for progesterone backup, endometrial safety not being an issue.
- There are many possible treatment alternatives that can be used, but generally they are adapted to the age of the female patients:
  - Young women Combined oral contraceptive
  - Long run 21 days 10 days
    Estradiol 1-2 mg + Progest 100 mg
    Conjugates estradiol 0.3-1.25 mg + Progest 100 mg
    estradiol valerat 1-2 mg + Progest 100 mg
  - Premenopausal alternative administration roots: transdermal/intravaginal.
  - The supplemental therapy will be used until the mean age of menopause onset.

- Follow up – absence of hypoestrogenemia deprivation symptoms, no estradiol blood assay.

Absolute contraindications:

1. Breast cancer
2. ovarian cancer
3. Endometrial cancer
4. Unknown vaginal bleeding
5. Hepatic insufficiency
6. Unevaluated endometrial hyperplasia
7. Pulmonary thromboembolism**,** deep venous thrombosis arterial thrombotic disease
8. Untreated hypertension
9. Hyper sensibility to any preparation
10. Chronic porphyria
11. SLE

In the presence of pregnancy desire, the total supplemental therapy should be used with recombinant FSH, for follicular growth stimulation and beta HCG for ovulation induction.

SOMATOTROP LINE

- Somatotroph supplemental therapy can be used in adults for a better body composition, bone density, psychological well-being.
- Administration = rGH I 2-5 mcg/kg
- Monitoring efficacy = normal IGF1 levels
- Long-term benefits are still under debate, with secondary possible morphologic changes. Common side effects are: edema, parenthesis, arrhythmias, glucose intolerance, and diabetes.

Contraindications:

1. Present malignancy
2. Diabetic retinopathy
3. Intracranial hypertension
4. Airway obstruction

GH deficiency in children

The GH deficiency in children has special clinical characteristics and treatment regulations that are different from the adult GH deficiency. This is why we are presenting this deficiency separately from the other possible pituitary deficiencies in children.

Incidence: 1:3500- 1:4000, with higher incidence in boys.

Etiopathogenic mechanism:

1. Congenital growth deficiency secondary to various GHN gene, isolated, associated with hypogammaglobulinemia, combined pituitary hormone deficiency.

Particularities:

The birth length is almost normal, with no striking difference.

The growth speed is decreased, with a growth deficiency present in the 1st year of age, clear in the first 2 years of age. The children have special features: besides short stature, increased fat mass, chubby appearance, immature facial characteristics, high pitched voice, delayed skeletal growth and maturation, micro phallus. The intelligence is normal) if there is no concomitant TSH deficiency).

Associated midline anatomic defects are frequent: optic hypoplasia, absence of septum pellucidum, cleft palate, oral dysraphism.

The metabolic changes due to GH deficiency are almost always striking: neonate hypoglycemia and seizures.

2. Acquired growth deficiency

There is a normal growth development until the deficiency appears. The clinical picture is different corresponding to the age of onset of the deficiency, mainly late childhood or adolescence.

Clinically there is a

- Decreased growth speed
- Growth retardation compared with peers
- Slow bone maturation
- Delayed bone age
- Decreased final height
- Childish voice
- Decrease effort tolerance
- Delayed cartilage closure (20 years)

There are some differences suggestive of a pathogenic substrate:

- Empty sella sd. appears more frequent in children than in adults
- Constitutional delay may be associated with a transient GH deficiency, that will disappear when associated secretion of testosterone starts
- CNS irradiation will be associated in 12=18 months post treatment with GH deficiency
- Chemotherapy can also induce GH deficiency
- Acute lymphoblastic leukemia can induce GH deficiency
- Theoretically, all causes of hypopituitarism in adults can lead to GH deficiency in children
- Lower rates of posttraumatic pituitary deficiency in children compared with adults

Diagnostic

STEP I Evaluation should be made under some conditions:

1. Severe short stature (T < -3 SD)
2. Severe growth deceleration (velocity < -2 SD in 1 year)
3. Height < -2 SD **and** height velocity < -1 SD in 1 years
4. Height < -1.5 SD **and** height velocity < -1.5 SD in 1 year
5. Active screening in the presence of Risk factors:
    - History of brain tumor, cranial irradiation, organic/congenital hypothalamic hypophysis disorder
    - Incidental finding of a problem in the pituitary region = MRI

STEP II Screening for IGF deficiency/other anomalies

1. Bone age, TSH + FT4, cariotyp, general health evaluation
2. IGF1- level + IGFBP 3 level = exclusion of GH receptor deficiency
3. Ca, phosphate, PTH, 25 OH vitamin D level
4. FSH, LH, estradiol, total testosterone
5. Cortisol,
6. IGHF1, IGFBP!!! Adjusted for chronological age, sex.

In the absence of any possible secondary causes of growth deficiency move forward to the following step.

STEP III Testing GH secretion

Because basal values of GH levels are totally insensitive, and the GH response to any stimulating tests are variable, due to nutritional status, age, puberty stage, levels of endogenous steroids secretion,

2 stimulating tests:

- Insulin: Insulin hypoglycaemia test- 0.075-0,1 U/kg iv bolus with GH measurement at 0, 20' and 40' = GH > 10 ng/mL
- Arginine
- Clonidine: 0.15 mg/m^2 GH at 0.30',60',90'
- Glucagon: 0.03 mg/kg GH at 0.30',60',90'

If stimulated GH < 10 ng/mL step 4

If stimulated GH > 15 ng/ml Step 1 in 6 months

If stimulated GH between 10-15 ng/ml Step 2 in 6 months

STEP IV Imagistic evaluation

1. MRI
2. Test the HPA axis = CRH evaluation
3. ? Genetic testing

STEP V Treatment initiation = synthetic GH preparation

- Subcutaneous, 0.3 mg/kg/wk in daily doses: around 0.07-0.1UI/Kgc/day
- The therapy response is the highest in the first year of treatment
- Higher doses are using during puberty
- The final height is better than in the absence of treatment but will never achieve the mean, usually being 1/.4 SD below the mean.
- Treatment monitoring is usually made by the evaluation of the height and the growth rate/ growth speed, with normal IGF 1. Additional evaluations can monitor the process of growth: urinary hydroxiproline, deoxypyridinolin.
- Used preparations: Norditropin/Genotropin/Nutropin/Omnitrop.

Possible side effects of r GH

1. Return of tumor/cancerous growths
2. Hyperglycaemia
3. Intracranial hypertension
4. Knee/hip/limb pain
5. Worsening of the pre-existing spine curvature
6. Middle ear infection, hearing or ear problems
7. Increases in PO_4, FAL, PTH
8. Joint stiffness
9. Decrease of thyroid hormone levels

Differential diagnosis

1. Psychosocial dwarfism – poor growth, pot-bellied, immature appearance, odd eating behavior: bagging for food, eating from garbage cans, odd drinking habits: drinking from inappropriate sources, big family, with excessive discipline or complete ignorance from the parents, with emotional deprivation with or without caloric deprivation. The deficiency is functional, due to emotional distress, or to maternal deprivation and will return to normal after resuming the normal familial habits.

2. Hypothyroidism – will cause growth retardation, in the absence of any GH deficiency. Always it is associated with decreased intellectual capacities: hypofrenism - olygofrenism – cretinism, with associated hypothyorididsm signs: bradycardia, constipation, coarsening of hair and skin, apathetic.
3. Glucocorticoid excess – endogenous or exogenous, will affect the rate of growth, due to direct suppression of GH action. The degree of deficiency depends on the age of onset of the GCS excess.
4. Pseudohypoparathyroidism – children are short and overweight, with round face, short 4th and 5th metacarpal bones. Because of the mutation in the PTH receptor, hypocalcaemia and hyperphosphatemia are present and condition the bone growth rate.
5. Vitamin D disorders = severe vitamin D deficiency can cause short stature and growth delay, besides the typical clinical signs of rickets: bowing of the legs, chest deformities, decreased bone mass.
6. Diabetes mellitus = the growth deficiency is present only in bed treated cases; well-controlled DM cases do not show any growth delay. There is a blocked IGHF1 stimulation with decreased of physiological GH effects, not a typical GH deficiency.
7. Diabetes insipidus = can induce poor growth due to decrease caloric intake, not due to a GH deficiency
8. Nutritional deprivation will affect the growth rate and the growth speed without any typical GH deficiency
9. Sexual deficiency sd will affect the final growth, during and after puberty. The growth delay is present only after the puberty, due to the lack of growth spur that is estrogen dependent, both in girls and boys.
10. Prematurity and SGA are also associated with decreased growth spur, especially in early childhood
11. Other forms of GH deficiency
    - IGF-1 deficiency – lack of GH effect, with nor patent GH deficiency
    - GH receptor defects
    - GH post receptor defects
    - Congenital IGF 1 production
    - IGF1 receptor defects

II. 4. RETROHYPOPHYSIS

The posterior pituitary is a independent neuronal structure, comprised in the posterior part of the sella turcica. The posterior hypophysis is formed from the axons of the magnocellular neurons and from the paraventricular and supraoptic hypothalamus nuclei. The blood supply of the posterior hypophysis is totally separated and different from the inferior hypophysis, capillary system in the posterior hypophysis, where the axons termination will release the neurohormones from the secretory vesicles, capillary that will confluence in a venous system, posterior hypophysis veins ➔intercavernous sinus ➔ internal jugular vein general ➔ circulation.

The magnocellular neurons have a typical secretion process:

1. in the presence of the stimulus (suckling, osmotic change) Generate and propagate action potentials
2. Produce membrane depolarization
3. Release the contents of the secretory granules: OXT (oxytocin) and AVP (arginine vasopressin) in the blood system = posterior hypophysis veins ➔intercavernous sinus ➔ internal jugular vein

Arginine vasopressin and oxytocin are nonapeptides synthetized by the neurons, produced from the cell, traversing the endoplasmic reticulum and the Golgi apparatus will package the secretory vesicles. The neurosecretory vesicles descend in the axons and are released in the interstitial space in condition of stimulation. 2 hormones are produced by different neurons, organized in separate clusters in the hypothalamic clusters.

II.4.1. RETROHYPOPHYSIS HORMONES

Oxytocin is produce in response to:

- Suckling (nipple stimulation)
- Parturition (cervix stimulation)
- Orgasm (nipple + cervix stimulation)

The main target organs:

- LACTATING BREAST – milk ejection due to contraction of myoepithelial cells in the alveoli and ducts in the mammary gland
- UTERUS – rhythmic contraction
  - to help induce the labor
  - Progression of the fetus
  - Regression of the uterus after delivery (safety contractions)

Apart from the classical effects of OXT, there is a recognized effect at brain level, OXT being considered the bonding hormone, responsible for maternal behavior in postpartum period/amnesia of labor pain, but also the attachment/bonding feelings in a couple. The effect of OXT in males is not clear, but the bonding effect and the role in ejaculation effect are described.

The OXT receptors are cell membrane receptors located on the uterine muscle level and myoepithelial glandular breast cell. The uterine receptors expression and sensitivity are estrogen dependent: high estrogen level will increase the number and sensitivity of OXT receptors (seen in pregnancy – with a density increase of around 200 times), but will blunt the OXT effect permitting small quantities of OXT to be active in the immediate postpartum period.

The most powerful stimuli are the mechanical manipulation of cervix, important stimulation during natural labor, and minimal stimulation during sexual stimulation, and secondary the manipulation of the nipple.

OXT is also regulated by a positive feedback mechanism: small quantities of OXT will favor, by juxtacrine mechanism, the release of OXT.

The physiological effects of OXT regulation are used as a clinical application: labor inducing by administering small amounts of OXT that will stimulate the uterine muscle contraction and further central OXT release, and in postpartum period OXT administration will assure a proper smooth muscle uterine contraction that will control the postpartum blood loss = the safety uterine contractions – which is a normal process in the natural labor but it is a problematic process in C section surgical labor.

Arginine vasopressin is the man hormone that controls the water balance in the body. The water balance in the body is influenced by:

- Thirst, conditioned by the receptors in the hypothalamus
- Osmotic changes that will influence the osmoreceptors in the hypothalamus
- Bariatric changes that will influence the pressure receptor.

AVP will regulate the reabsorption of free water, at the level of distal convoluted tubules and medullary collecting ducts, will influence the periphery vascular resistance (important effect especially in haemorrhagic shock, sepsis and water deprivation. The effects of AVP are mediated by a system of receptors, cell membrane, G protein coupled:

liver

- V_1R responsible for VASOPRESSOR effects — smooth muscle, brain, adrenals
- V_2R responsible for EABSORPTIVE effects — kidney
- V_3R responsible for increase intracellular calcium: corticotrop hormone, thymus, heart, spleen, uterus, breast

The most important AVP effect is mediated by the V2R, present at the renal level, that coordinate the reabsorption of free water at the level of collecting ducts, after the site of renin angiotensin aldosterone (proximal ducts, responsible for water reabsorption secondary to the active sodium reabsorption).

Normally, the water balance at kidney level is maintained by reabsorption:

- 90% in the proximal tubule = Renin Angiotensin Aldosterone dependent
- 10% in the collecting ducts = AVP dependent.

In special conditions, Osm changes or hypovolemia, the permeability of collecting ducts can change dramatically = important changes in free water reabsorption. AVP controls the expression of AQP2 = modulates the permeability of water exclusively in collecting ducts, even if 10% seems a small number in comparison with the effect of RAA mechanism, a loss of the 10%, in cases of absent AVO, secretion will have a dramatic impact in the urinary outflow: Average glomerular filtrate = 180 L/day, Normal urinary output – 1.5 - 2 L/day

Loss of AVP activity = urinary output = 10% = 18 L/day (collecting ducts impermeable for water). The effect of V2R is generated by the expression in the basal lamina, after the coupling of AVP with the v2R receptor, of the aquaporin 2, active water reabsorption gates that will allow the circulation/reabsorption of free water from the tubular level through the collecting duct cell into the interstitial space and directed into the hypertonic medullar region.

Normal urinary output – 1.5 -2 L/day

The V1R mediated mechanism is a facultative effect of AVP, concurring in the maintaining volemic/pressure effect of AVP: vasoconstriction of the vascular smooth muscle = increased peripheral vascular resistance with increased renal medullary blood flow.

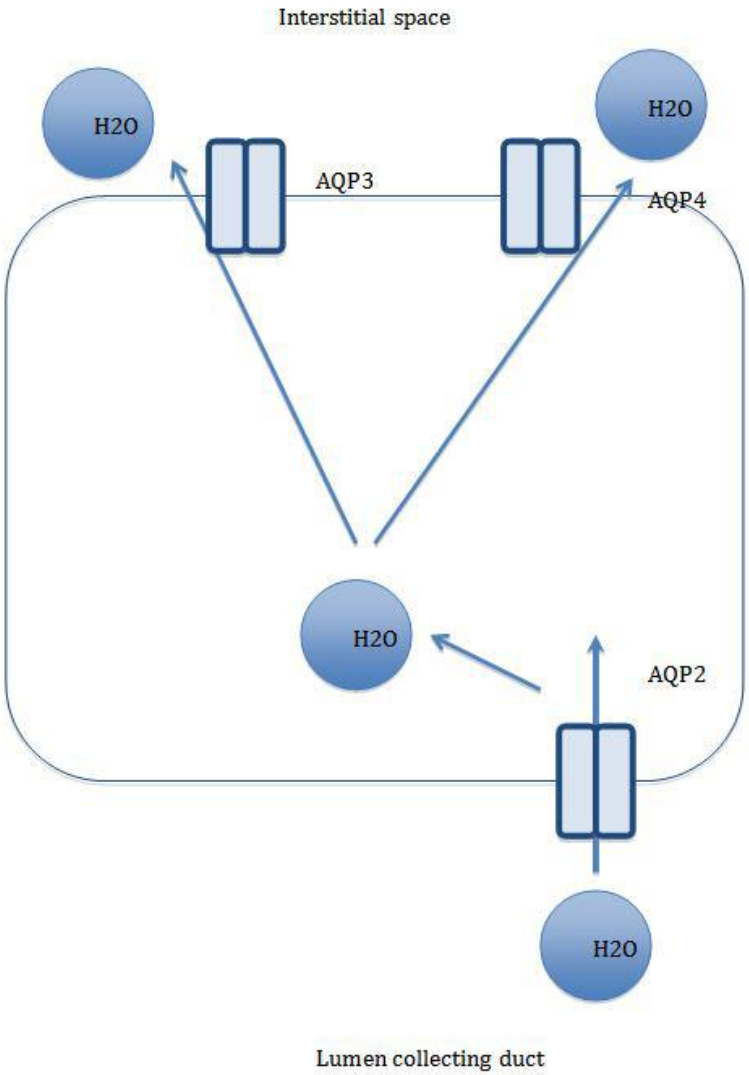


Figure 12. Effect of AVP at renal level

The control mechanism of AVP release is different from the anterior pituitary hormones, with no feedback loops, no peripheral target gland effect.

Receptors involved in the regulatory mechanism are:

- Osmoreceptors are present at the hypothalamic level, anterior of the third ventricle, that regulates the thirst and AVP production
- Baroreceptors are present and located in the carotid sinus and aortic arch (high pressure) and at the low-pressure volume in the atria and pulmonary venous system.

Chain effect:

1. Trigger = Osmolality change 1%

↓

2. Osmolality receptor = Osmoreceptor neurons in the hypothalamus + lamina terminalis

↓

3. Loss of cellular water= dehydration↓ = cell shrinkage = signal for AVP magnocellular neurons

↓

4. AVP release **before sensation of thirst**

↓

5. Increased water reabsorption: AQP2 expression and activation.

In order for the same activation to be induced, by volemic changes, a decrease of more than 10% will be needed in order to stimulate the V1R receptors, that will generate the contraction of the vascular smooth muscle, with an increase in blood pressure and secondary, a reduction of intravascular volume.

In the majority of cases, osmolar changes and volume changes are synergic, with an appropriate additive mechanism: V2R receptor for free water reabsorption, V1R receptor for pressure maintenance.

II.4.2. AVP DEFICIENCY

Four etiopathogenetic mechanisms are described:

1. Absolute AVP deficiency = Diabetes insipidus
2. Increased needs = relative AVP deficiency
3. Increased metabolism = relative AVP deficiency
4. Decrease end organ response = Nephrogenic diabetes insipidus

Central diabetes insipidus is secondary to:

- Familial disorder = autosomal dominant mutation of the vasopressin gene with the pathology of the neurons develop over time
- Pathologic lesions = all possible causes in the anterior pituitary can also induce AVP deficiency: tumors: craniopharingioma/metastatic lesion: breast/lung, trauma (the triphasic DI), Granulomatous disease, Lymphocytic infundibulohypophysitis, essential hypernatremia = absent of osmoreceptor function, cerebral anoxia, infections: tubercolosis, enchephalitis, syphilis.

The special evolution of posttraumatic Diabetes insipidus is:

1. Axon shock = inhibition of any AVP release = 5-10 days
2. Necrosis of axons = uncontrolled/exaggerated AVP release = SIADH = fluid retention + hyponatremia = 5-10 days
3. Residual AVP leaks
4. Branching of axons may regenerate = AvP returns to normal

Relative deficit of AVP due to increased needs are present in primary polydipsia, excessive parenteral administration of fluids, behavioural abnormality = psychiatric patients, In cases of pregnancy, due to the increased metabolism of the AVP, there is a resetting of the osmostat, 10 mOsm/kg H2O less than the value in the nonpregnant women. The changes are limited only during pregnancy.

Nephrogenic diabetes appears in cases of:

- Congenital nephrogenic diabetes - X linked V2R mutation or rA AQP2 channels mutation, both mutation generating a diabetes that occurs in the first weeks of life with: dehydration symptoms: vomiting, constipation, failure to thrive, fever, polyuria, hypernatremia + low urine Osm + AVP ↑
- Acquired nephrogenic diabetes is related to architectural changes with the altering of the hyper osmolality of the inner medulla, essential for the reabsorption of free water. The main causes of nephrogenic diabetes are: alteration of the inner medulla, polycystic renal disease, infarcts, sickle cell anemia, hypercalcemia, nephrotoxicity.

The typical clinical picture is the polyuro - polydipsic syndrome, considering that the acute onset, characteristics for central DI, and chronic onset are characteristics for nephrogenic DI.

The characteristics of polyuria are: permanent polyuria, high diluted urine, the volume increase will characterise the minor DI (4-5 l/day), medium DI (6-10 l/day), respectively severe (over 10 l/day).

Polydipsia is compensatory for the urinary losses, with increased consumption of cold fluids that will better compensate the increased thirst.

Contextual signs have to be taken into consideration: history of trauma/surgery, visual field defects/pan hypopituitarism, acute headache and aanorexia/bulimia will suggest the pathogenetic context of the onset of DI.

Diagnostic approach has to follow the steps:

1. *Documenting the polyuria*
2. *Plasmatic Osm* n, ↑
3. *Urinary Osm* ↓ < 200 mOsm/kgH_2O
4. *Urinary density* ↓ < 1005
5. *Free water Clearance* = POSITIVE

   $C_{H2O} = V - U_{osm}/P_{osm} V = V (1- U_{osm}/P_{osm})$

   Normally $U_{osm} >>>> P_{osm}$ C_{H2O} = negative

   DI $U_{osm} <<< P_{osm}$ C_{H2O} = positive

6. Confirmation test = Dehydration test = **Water restriction**

- The patient is weighed ed at the beginning
- Initial evaluation: Na^+ and P_{osm}
- Recording of the weight +V + U_{osm} after each liter of urine
- In case of 2% loss of body weight = Na^+ and P_{osm}
- Administration of 2 mcg synthetic AVP
- Measurement of V + U_{osm} after 2 hours

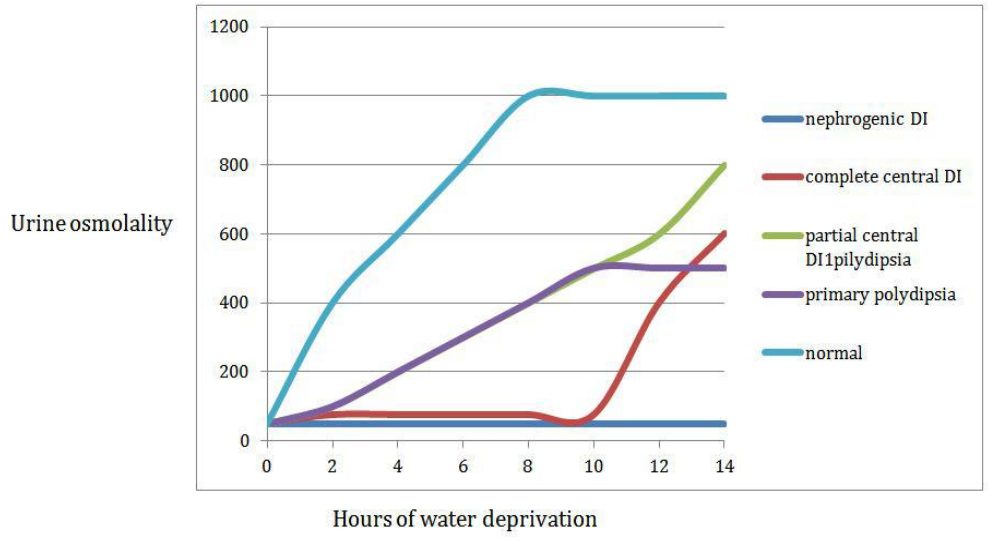


Figure 13. Results of the dehydration test in different instances

1. DI
    a. Undetectable AVP concentration
    b. No urine concentration
    c. Positive response to AVP administration: Uosm increase of at least 50% = up to 400%
2. Primary polydipsia
    a. Low AVP
    b. Concentration of urine
    c. Lack of response to AVP administration
3. DI nephrogenic
    a. No response at all: dehydration/AVP administration

7. Imaging tests will suggest the context of DI appearance.

Differential diagnosis

Excessive water intake	AVPn, ↑	U_{osm}↓	P_{osm}↓
Inappropriate tubular resorption:			
AVP deficiency	AVP↓	U_{osm}↓	P_{osm} ↑
AVP insensitivity	AVPn, ↑	U_{osm} ↓	P_{osm} ↓
Renal pathology	AVP n, ↑	U_{osm} ↓	P_{osm} ↑
Osmotic diuresis	AVP n U_{osm}↑		P_{osm}↑↑

Treatment

1. *Supplemental therapy* = AVP analogue Desmopressin DDAVP 1st line

- Highly selective for V2R 2000x
- Increased half life

• Orally	1 tb = 0.1-0.2 mg	1-2/day
• Nasal instillation	1% 0.1 mg/mL	1-4 drops/x1-2
• Parenteral solution	4 mcg/mL	0.5-1 ml/day

- iv push or SC
- ? Poor intranasal absorption/pre surgery/loss of consciousness

Response should be estimated by: adequate duration of sleep and adequate water turnover.

- Caution should be used in the condition of concomitant use of: Chlorpropramide, Carbamazepine, Clofibrate, Indomethacin, that will prolong action/release of AVP.

2. *Reducing urine volume* through low sodium diet + thiazide diuretic, potassium sparring diuretics: Amiloride, Indomethacin favours AVP action/enhances AVP response.

II.4.3. SIADH

The hyper secretion of AVP generates increased water retention with secondary hypo osmolality, mainly hyponatremia. Hyponatremia is associated with increased morbidity and mortality, because hyponatremia is an indicator of the severity of the underlying disease.

The SIADH appears only in **severe diseases**, as seen in TABLE XI.

TABLE XI. Causes of SIADH

Ectopic producing AVP - **Bronchogenic carcinoma** - **Duodenal/pancreatic carcinoma** - **Ureteral, prostate, bladder carcinoma** - **Carcinoma of the uterus** - **Thymoma** - **Lymphoma, leukaemia**
Disruption of neural control - Pulmonary disorders: pneumonia, tuberculosis, fungal infection, positive pressure ventilation - CNS disorders: infections, degenerative disease, porphyria
Nephrogenic SIADH - V2R mutation
Rare causes = AIDS =extreme strenuous exercise = acute psychosis
Drug induced AVP/ OXT/Carbamazepin, Clofibrate, Ectasy, antidepressants, MAOI, SSRI

In the presence of inappropriate/uncontrolled secretion of AVP (ADH) there is a volume expansion due to the uncontrolled/unbalanced free water reabsorption, with a decrease of the water in the urine. Thirst is not inhibited, so continuous ingestion of water + free water reabsorption will increase the extracellular volume, with a decrease of osmolality.

The body is trying to compensate for the hypervolemia, by natriuresis, at the level of the proximal tubule, renin angiotensin aldosterone mediated, with a decrease of body water, in parallel with a decrease of Natrium, that will partially compensate the hypervolemia, but will not compensate the hyponatremia.

Despite the attempts to normalise the total body fluid, it will remain increased due to the high, uncontrolled free water reabsorption and uncontrolled thirst.

The last adaptation is the decrease of kidney to the AVP action, a water spearing effect, due to reduce the number of AQ2P.

The differential diagnosis comprises all other causes of hyponatremia:

1. Dehydration with fluid loss (gastrointestinal/blood losses) with decreased volume, decreased natremia and low urinary NA losses
2. Dehydration with increased urinary sodium losses: renal disease, chronic Diuretic use, untreated Addison disease, cerebral salt wasting sd.
3. Expanded volume, with normal natriuresis, in cases of hyper Aldosteronism due to inadequate perfusion, chronic hepatic disease (CHF) or congestive heart failure
4. Expanded volume associated with increased natriuresis: SIADH.

   Correct evaluation of natremia, natriuresis and volemia will make the correct diagnosis of the 4 major forms of hyponatremia.

The symptoms of hyponatremia are universally the same, dependent on the degree of hyponatremia and the onset of the decrease: cerebral oedema, herniation of brain stem, neurogenic pulmonary oedema, seizures, coma, respiratory arrest, with typical appearance of the symptoms at Natrium levels below 120 mEq/L.

From the biological point of view, SIADH consists of:

1. P_{osm} ↓
2. Inappropriate urine concentration (concentrated urine)
3. Euvolemia (no hypovolemia)
4. Absence of other euvolemic hypo osmolar causes: sever hypothyroidism, adrenal insufficiency, and diuretic use.

The treatment will follow 2 directions:

1. *Correction of hyponatremia,* life threatening condition: with restricted water intake and Na^+ correction: 1st day: 0.5-1 mEq/L/h, total of 12mEq/L; 2nd day: 1-1.5 mEq/L, total of 18 mEq/L, continued for the following days until the Na^+ will increase over 120 mEq/L.

Chronic hyponatremia, usually asymptomatic, will be corrected slowly. Acute hyponatremia, with significant clinical signs, will be corrected more rapidly, with the remark that rapid correction will induce an osmotic demyelination with more severe neurological consequences than the hyponatremia per se.

2. *Vasopressin antagonist* = Vaptans = increase free water excretion (aquaresis) without natriuresis, administered chronically, in cases with decreased natremia (below 125 mEq/L)

CONIVAPTAN = V1 + V2R

TOLVAPTAN = selective V2R

an excellent control of the SIADH in the long run.

III. THYROID

III.1. GENERAL INFORMATION

Thyroid is an acinar gland, with ductless alveolar structure, 10-25 g total weight, butterfly shaped, composed of two cone-like lobes: right + left, connected via isthmus, with additional pyramidal lobe. It is placed in the anterior neck; in front of the trachea; with posterior margins abut the oesophagus. It starts cranially at the oblique linen the thyroid cartilage (just below the laryngeal prominence, or "Adam's Apple" and extends inferiorly to approximately the fifths or sixth tracheal ring. It is difficult to demarcate the gland-s upper and lower border with the vertebral levels because it moves position in relation to these during swallowing.

Histology the gland consists of many indistinct lobules containing follicles and many blood vessels enmeshed in fine connective tissue. The follicles contain a homogeneous, acidophilic material, called colloid. The follicles are lined by simple cuboidal epithelium but the epithelium may be columnar or squamous depending upon the function activity of the gland.

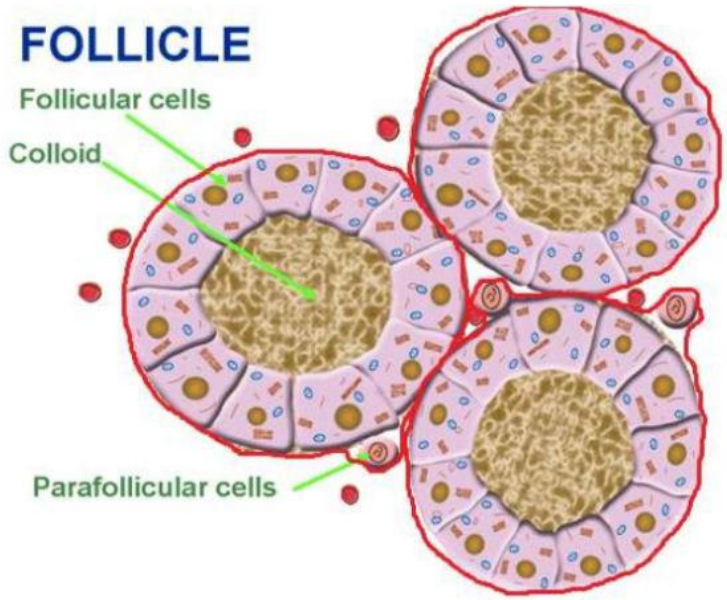


Figure 14. Thyroid follicle structure

The thyroid is the 1st gland that is formed in the embrio, starting about 24 days after fertilization, appearing as a median endodermal thickening in the floor of the primordial pharynx between tuberculum impar and copula. The site from

which it originated persists as the foramen cecum at the base of the tongue. As the embryo and tongue grow, the developing thyroid gland descends in the neck in front of pharyngeal gut, passing ventral to the developing hyoid bone and laryngeal cartilages. At the lower end of the thyroid gland, from the foramen cecum the thyroglossal duct will develop. The thyroglossal duct will ensure the migration of the thyroid, from the tongue to the final, pretracheal position. When the gland reaches the position it occupies in the adult, the gland has assumed its definitive shape. By this time, the thyroglossal duct normally degenerates and disappears, or, in some cases the pyramidal lobe.

It has a rich blood supply, assured by:

- Superior thyroidal arteries (branch of the common carotid artery)
- Inferior thyroidal arteries (branch of the brachiocephalic artery)

Middle/inferior cervical ganglia of the sympathetic nervous system assure innervation.

Thyroid secretes 2 type of hormones: thyroid hormone, T3 and t4, produced by the follicular cells, and Calcitonin, produced by the parafollicular cells.

Calcitonin is produces by C parafollicular cells, is a poplipeptidic hormone, involved in phosphocalcic metabolism/homeostasis, being a contra regulatory hormone of PTH. More details will be presented in parathyroid section.

III.2. THYROID HORMONES

The thyroid follicular cells are producing the thyroid hormones, aminic hormones, following these steps:

1. Active transport of iodine across the basement membrane, from the blood stream, transporting it through the thyroid follicular cell.
2. Intracellular, there is the oxidation of the iodine, which is than transported through the apical into the colloid, where the iodination of tyrosyl residues takes places. The products of the iodination are the iodothyrosine on the Thyroglobulin surface

   = tyrosyl + 1 iodine molecule = Monoiodthyronine

   = tyrosyl + 2 iodine molecule = Diiodothyronine
3. The iodothyrosine couple themselves to form the iodothyrosine

   = Monoiod-thyronine + Diiod-thyronine = Triiodo-thyrosine = T_3

   = Diiod-thyronine+ Diiod-thyronine = Tetraiodo-thyrosine = T_4

   There is to mention that all the thyronines and thyrosines are present at the colloid level, in the centre of each thyroid follicle.
4. Under TSH stimulation, whenever needed, there is a pinocytosis/ proteolysis of the thyroglobulin with direct release of free thyrosines and thyronines in the circulation (secretion).
5. The non-used iodothyrosines molecules undergo a process of deiodination for iodine and thyrosyl conservation.
6. Intrathyroidal, there is also a process of deiodination of T4 to T3, the most active form of the 2 thyroid hormones.

Considering the thyroid hormone secretion some important details/steps have to be considered:

- **Iodine**
- **NIS** = iodine transmembranar transporter (TSH mediated) = natrium iodine symporter. The NIS activity is responsible for an intrathyroidal iodine concentration 30=40 times higher than in the blood stream.
- **Thyroglobulin (Tg)** = globulin produces by the follicular cell, TSH mediated, at the Rough endoplasmatic reticulum, glycosylate in the Golgi apparatus, incorporated in vesicles and released at the colloidal level.

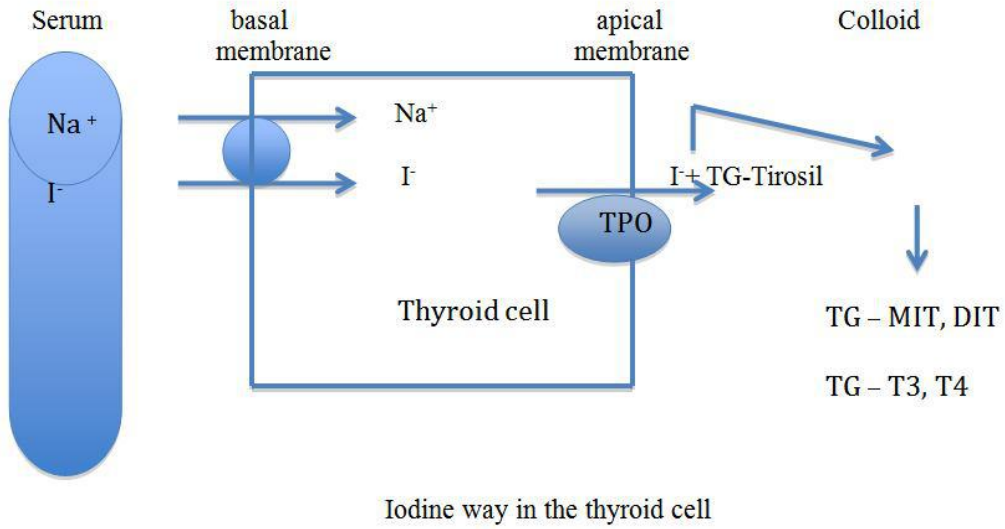
  Each Tg molecule is presenting 140 tyrosine residues.

Iodine is not produced in the human body, thyroid hormone producing relies on the external iodine intake.

The principal iodine sources are: water, iodized salt, preservatives in baked goods, dairy products, food containing iodophore antibacterial agents: milk collection, food coloring, seafood, especially raw. The current WHO recommendations for sufficient daily iodine intake for normal thyroid hormone secretion are:

- Adults 150 mcg iodine intake (food+ water)
- Pregnancy 200 mcg iodine
- Lactating 200 mcg iodine
- Children 50-250 mcg iodine

A daily intake lower than 50 mcg/day induces the incapacity of thyroid gland of sustained thyroid hormone synthesis and secretion.



Iodine way in the thyroid cell

Figure 15. Iodine way in the thyroid cell

As all hormones, only a small fraction of thyroid hormones is circulating free: 0.03% of T4 respectively 0.3% of T3. The majority fraction circulate bound to: Thyroxin binding globulin (TBG), 70% Transthyretin, a prealbumin 10-15% and albumin 15-20%. The functions of this bound fraction are:

1. Pool of hormones
2. Prolongs the half life of the hormone
3. Regulates the free fraction of the hormone
4. Conditionate the metabolic clearance rate

The most important binding globulin, TBG, is produced, as other transporter globulin, at liver level, with the concentration influenced by different systemic diseases or conditions:

TABLE XII. SYSTEMIC CONDITION THAT INFLUENCE TBG PLASMATIC CONCENTRATION

Increased TBG	Decreased TBG
Pregnancy	**Androgens**
Estrogen secreting tumors	**Glucocorticoids**
Estrogens	**Danazol = antiandrogen**
5 Fluorouracil	**L Asparaginase**
Acute intermittent porphyria	**Nephrotic sd.**
	Chronic renal failure
	Chronic liver disease
	Malnutrition
	Cushing sd.
	Acromegaly
Salicylates, phenytoin, furosemide	**Displace T3 and t4 from TBG**

The systemic effects of thyroid hormones are due to:

- Receptor activation = genomic/intranuclear receptor present in the majority of cells
- Enzymatic effect = nongenomic
    - Mitochondrial proteins
    - Glucose transporters
    - Calcium ATPasa
    - Adenilat cyclase

Triiodothyrosine (T3) is the active hormone al cellular level, mainly from T4 transformation = deiodination:

Extrathyroidal	T4 → T3	ACTIVATION	1 deiodinase
CNS	T4 → T3	ACTIVATION	2 deiodinase
Placenta brain	T4 → rT3	DEACTIVATION	3 deiodinase

We can describe the following effects of the thyroid hormones:
TABLE XIII. THYROID HORMONE EFFECTS

LEVEL	EFFECT
Basal metabolism	Direct stimulation of mitochondrial activity Heat production ↑Basal metabolic rate
Glycemic metabolism	↑Intestinal absorption ↑Peripheral consumption ↓ hepatic glycogenolysis ↓ Insulin sensitivity
Proteic metabolism	↑Proteic synthesis (small doses) ↑ Protein degradation
Lipid metabolism	↑Lipogenesis ↑Triglyceride synthesis ↑LDL hepatic clearance
Calcium metabolism	Facilitate diuresis Urinary/fecal Ca loss Bone turnover
Iodine metabolism	Almost exclusively controled by thyroid: NIS
Immunity	↑IgG synthesis
Cardiovascular	↑Inotropism, ↑Cardiac output ↑Cronotropism ↑Adrenergic sensitivity
Pulmonary	Maintain ventilatory response to hypoxia/hypercapnia ↑Respiratory muscle function
Hematopoiesis	↑Erytropoetin /erythropoiesis Favours 2 dissociation from Hb
Gastrointestinal	↑ gut motility
Skeletal	B□□□□□□□□□□□□□
Skin	T□□□□□□□□□□
Neuromuscular	Normal development of CNS Conditionate the muscle contraction/relaxation Emotional balance
Endocrine	Normal function of gonadostat facilitates glucocorticoids metabolism
Fetal development	Sustain brain development Sustain skeletal growth/maturation

Looking to these effects, we an also describe to general effect in case of thyroid hormone dysfunction.

The control of thyroid function is part of the neuroendocrine mechanism: hypothalamus- hypophysis-thyroid axis.

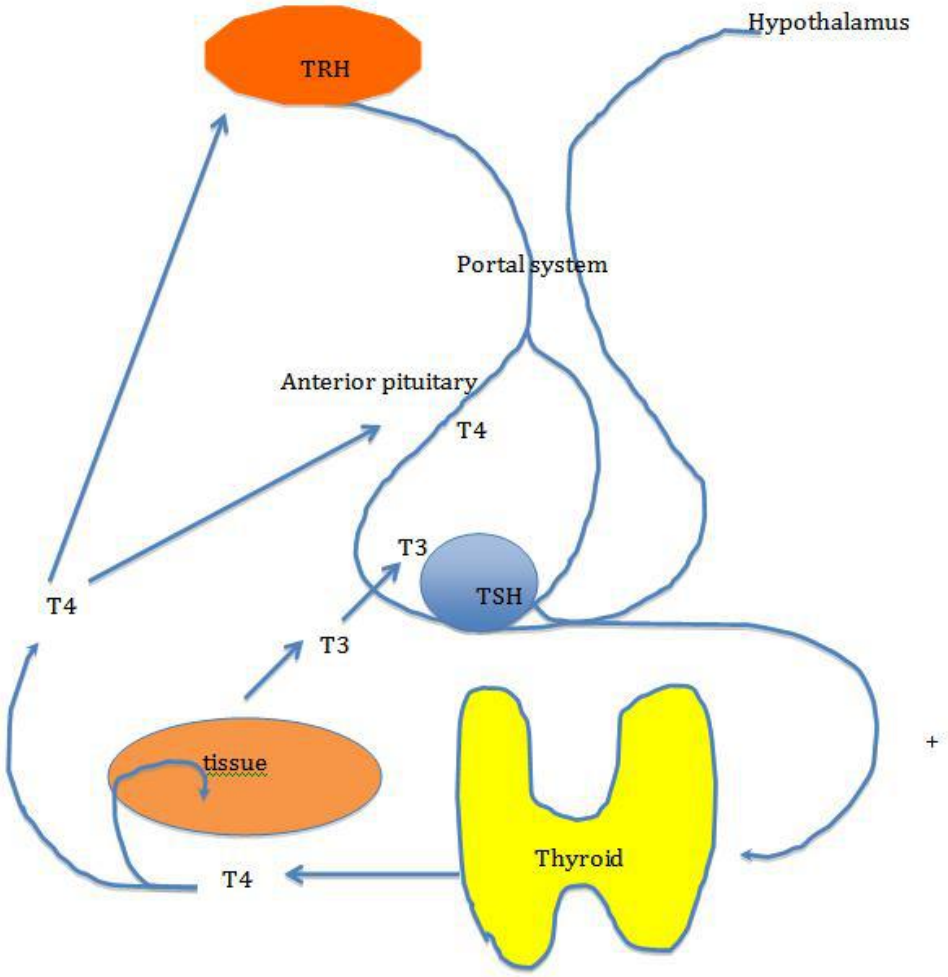


Figure 16. The neuroendocrine control of the thyroid gland

III.2. THYROID EVALUATION

Regardless the type, of thyroid pathology, the used evaluations are the following:

- Hormonal evaluation: TSH, Ft3, Ft4
- Immunological evaluation: ATPO Ab, ATg Ab, TRAB
- Morphologic: Ultrasound evaluation
- Morpho-functional : Scintigraphy
- Dynamic tests: stimulatory = TRH
- Additional test – Calcitonin, Thyroglobulin
- FNAB
- Clinic symptoms scale
- Basal metabolic rate

➢ ***Functional assays:***

TSH, TT4, TT3, TBG, FT4, FT3, FT4i, FT3i, precursor and degradation products. On the common basis TSH, FT3 and FT4 are usually used.

1. Thyroid hormone assays

Total concentrations of the thyroid hormones, total triiodothyronin and total tetraiodothyronin are unusual used. Their serum level is not only influenced by rate of thyroid production, but also from the protein bound fraction and also tissues distribution, and degradation.

Commonly, the free fractions of T3 and T4 are determined because they are independent from the previous mentioned factors. Direct measurement of T3 and T4 free fractions is a much simpler and more accurate evaluation of thyroid function. Physiologically about 0.04% in T4 and 0.4% in T3 are found free in the blood. Measurement of FT3 and FT4 are indispensable in the evaluation and follow up after treatment susbtitution in children diagnosed with hypothyroidism.

Ideally, each country should determine reference for pediatric population, by sex, but for ethical reasons, are used blood samples obtained from hospitalized children.

2. Thyroid stimulating hormon (TSH)

Determination of TSH is one of the basic assessments of thyroid pathology. Over time there were used several tests:

First generation tests, have low sensitivity to TSH values <1 mIU / L and can not identify situations with TSH inhibited. These tests have cross-reactivity with FSH, LH and βhCG due to the similarity in glycoprotein chain.

Second generation tests, allow the identification of inhibited TSH values, sensitivity threshold being 0.3-0.4 mIU/L.

Third generation tests, permit the differentiation between the clinical and subclinical hyperthyroidism with a sensitivity of around 0.1 mIU / L.

Fourth generation tests reduced lower limit sensitivity threshold of 0.005 to 0.01 mIU / L, with changing the lower limit of normal TSH.

Blood sample for TSH dosage can be taken at any time of day.

In general terms, the determination of TSH is used in the following situations:

a. Thyroid dysfunction
b. Neonatal hypothyroidism screening
c. Monitoring of supplemental therapy, in hypothyroidism cases
d. Evaluation of hyperthyroidism relapse
e. Suppressive therapy in thyroid cancer cases
f. Evaluation of hypophysis tireotrop cells performance
g. Standard assay in female infertility
h. Universal screening > 35 de years, every 5 years

The limit of TSH use as single seeing tool, in thyroid pathology, are in cases of pituitary pathology, which can cause abnormal TSH values, independent of the thyroid pathology

TSH evaluation is done together with the measurement of peripheral hormones, in order to have a clear picture of the hypothalamic-pituitary activity.

FT3, FT4 capture the moments of assay and TSH evaluation show axis function in the last 4 to 5 weeks.

If the lower limit of normal TSH, is generally accepted as 0,3-0,4mUI/L, the upper limit is subject to controversy. It is known that TSH value increases with age, higher values of TSH being associated with long survival with all these there is no consensus on these values. Value of 2.5 to 3 mIU / L is considered optimal limit for women at reproductive age, and it must be obtained and maintained in case of pregnancy, respectively in preconceive status, before in vitro fertilization techniques. In the elderly, in the context of supplemental therapy, the TSH threshold value should be 6-7 mIU / L.

For children, the TSH reference values are variable, dependent on the age:

- in the first 30 minutes after birth, it can be perceived a physiological increased level of TSH, secondary to birth stress and exposure to different temperature from extrauterine environment. Can be reach values of up to 70 mIU / L and persist for at least 24 hours.
- in the first days of life the TSH value returns to normal, below 10 mIU / L.
- the optimum period for hypothyroidism screening is represented in the first 48-72 hours after birth
- TSH values greater than 20 mIU/L from venous blood dictate initiation of therapy, even if the FT4 value is in normal range. TSH values between 6-20 mIU/L, allow monitoring of the newborn in the first 21 days and clinical and biological reassessment after 3 weeks of age.
- in the first 2 to 6 weeks of life, TSH values that are considered normal are between 1.7-9.1 mIU / L
- after the neonatal period, normal TSH values are considered less than 6 mIU/L.

TABLE XIV. TSH CHANGES WITHOUT ANY ACTIVE PATHOLOGY

↑TSH	↓TSH
Iodin	Thyroid hormones
LITHIUM	Dopamine agonists
dopamine antagonists	L-Dopa
Dopamine blocking agents	Cabergoline, Bromocriptine
L-Dopa inhibitors	Fumaric acid
H1 histamine receptor blockers	Ddrenergic blockers
Antiestrogens	Serotonin antagonists
Spironolactone	Glucocorticoids
Amphetamines	Growth hormone
	Somatostatin
	Octreotid
	Opioid
	Clofibrat
	Biotin

TABLE XV. TSH + TH POSSIBLE CHANGES

TSH	FT4	FT3	Interpretation
↑	N	N	Subclinical hypothyroidism !!!!!Pregnancy/Preconception
↑	↓	N, ↓	Primary hypothyroidism
↓	N, ↑	N, ↑	Hyperthyroidism
↓	N,↓	N,	Central hypothyroidism Non-thyroidal illness
N	↑	↑	Resistance to thyroid hormone, Recent hyperthyroidism

3. TBG (Thyroxin binding globulin)

Thyroxin binding globulin is synthesized in the liver and represents the main carrier of thyroid hormones. Only 0.05% of T4 and 0.4% of T3 are found free in plasma circulation and regulate the biologic effect on the peripheral tissues. If the clinician uses the assay of TT4 or TT3 he must require the measurement of TBG.

Physiologically, TBG levels tends to vary with age, sex, position and pregnancy. These conditions generate changes TT4 and TT3 values, without any active thyroid disease.

TABLE XVI. TBG CHANGES IN DIFFERENT NONTHYROID PATHOLOGY

↑	↓
Pregnancy	**Androgens**
Estrogen secreting tumors	**Glucocorticoids**
Estrogens	**Danayol**
5 Fluorouracil	**L asparaginase**
Acute intermittent porphyria	**Nephrotic sd.**
Liver disease	**Chronic renal failure**
	Chronic liver disease
	Malnutrition
	Cushing sd.
	Acromegaly
Salicylates, phenytoin, furosemide = displace T3 and T4 from TBG	

➢ ***Dynamic tests***

Axis stimulation test

TRH stimulation test is used to:

1. Resistance to TSH, secondary to TSH receptors mutations = exaggerated response to TSH is observed;
2. Secreting pituitary tumor differentiation, where we see a slow response or no response after TRH stimulation, due to TSH insufficiency;
3. Differentiation between secondary hypothyroidism (pituitary), where there is no response from TSH, and tertiary hypothyroidism (hypothalamic) with exaggerated TSH response;
4. Facilitated radioiodine therapy in patients with differentiated thyroid carcinoma to avoid the negative effects of thyroid hormone treatment break (doses used are much higher than stimulation test itself).

The technique:

- initial determination of TSH and FT4
- injection of TRH (7 mcg / kg),
- repeating TSH and FT4 at 20 and 60 minutes after the injection
- standard doses = 200 and 400 mcg /1.73m^2 s.c.
- normal response = prompt increase of TSH (peak at 15-40'), up to 16 mIU/L and with a decrease at the previous stimulation values in the next 3-4 hours.
- In addition the central pathology, TSH response to TRH ↓↓↓

Apart from TRH test, the TSH reserve evaluation can be done with stimulation tests (L-Dopa or metoclopramide), with limited clinical application.

Axis Inhibition tests

Thyroid suppression = administration of exogenous thyroid hormones with suppression of TSH.

The test is used in suspicion of increased TSH producing tumor.

If there are functional autonomy thyroid, the pituitary-thyroid suppression mechanism does not occur.

Test technique:

- 100 mcg T3 for 7-10 days,
- evaluation in day 11 of the 24 hours iodine uptake.
- normal response is represented by its decrease of thyroid uptake of 50%.

- ***Immunoassay***

a. TSH autoantibody

The stimulating antibodies of TSH receptors are found only in Graves' disease Basedow.

Actually are described two categories of TSHR antibodies, enhancers and inhibitors, which are attached to different epitopes in the thyroid cells, but, often are not distinguished during the measurement and most often they coexist**.**

TRAB evaluation is essential:

1. to follow the development of Graves Basedow disease
2. differential diagnosis of hyperthyroidism,
3. monitoring the response to treatment,
4. differential between remission and relapse of disease,
5. assessment of risk exacerbation in Graves ophthalmopathy

b. Thyroid autoantibodies

Commercial available Ab are: antitiroglobulina antibodies (anti-Tg) and antithyroperoxidases (anti-TPO). T3 and T4 antibodies or antigen anti colloid are not used in the routine clinical practice.

TPO antibodies (anti TPO Ab)

The prevalence of antibodies against TPO vary in different ethnic and geographic groups. The prevalence of high titers of Ac anti TPO is higher in iodine replete areas, about 11% compared to the areas with iodine deficiency (about 6%).

Increased Anti TPO Ab titers are suggestive for:

- diagnostic of autoimmune thyroid disease,
- not recommended for monitoring autoimmune thyroid disease under treatment
- predictor of subsequent thyroid dysfunction in interferon , amiodarone, interleukin and lithium therapy
- Increased TPO-Ab titers in pregnancy may suggest an increased risk of obstetric complications.

Thyroglobulin antibodies (anti TG Ab)

The thyroglobulin antibodies belong to the IgG class.

It is considered that there are healthy individuals who have elevated TG-Ab titers, but their meaning is unclear on long term

Typically, the TG-Ab titers increased accompany those of TPO-Ab, only about 3% of patients with autoimmune thyroid disease have isolated TG-Ab titer increased.

Clinical utility of TG-Ab:

- follow up differentiated thyroid carcinoma cases whether is absolutely necessary to identify the interference of TG by TG-Ab, TG being considered a surrogate marker of tumor relapse
- TG-Ab titers are elevated in about 20% of patients with differentiated thyroid carcinoma, especially in cases of papillary carcinoma
- independent factor of evolution outstanding or recurrent tumor mass.

➢ ***Malignancy markers***

a. Thyroglobulin (TG)

Thyroglobulin (TG) is a glycoprotein, produced directly by the follicular cells, being essential for thyroid hormone production. Under physiological conditions, only minimum trace amounts can be detect in the serum. Functional thyroid tissue is the only source of serum TG. Increased Tg values in the serum suggest increased follicular activity. Low TG values mean the absence or virtual absence of functional thyroid tissue (by surgical or iatrogenic inhibition).

TG is really known as an important marker in monitoring the evolution of thyroid cancer, but not any elevated TG means thyroid cancer., almost all thyoird disease are associated with increased Tg levels.

TABLE XVII. SITUATIONS ASSOCIATED WITH MODIFIED VALUES OF TG

Increase	
TSH dependent	***TSH independent***
After TSH or TRH administration	Basedow disease (TRAB)
Neonatal period	Trophoblastic disease
Iodine deficiency	Massive thyroid trauma
Endemic goiter	Sub acute thyroiditis
Goitrogenic use	Postpartum thyroiditis
Lingual thyroid	Intrathyroid nodules
TSH secreting pituitary adenoma	Differentiate carcinoma
Resistance to thyroid hormones	Acromegaly
TBG deficiency	
Decrease	
Suppressive therapy with thyroid hormones	Thyroidectomy
	Thyroid agenesis

TG can be used as a marker in differentiated thyroid cancer screening, but only after total thyroidectomy. Presurgical Tg evaluation has no indication and utility. If it is not done total thyroidectomy, TG cannot be used to follow the evolution/recurrence of thyroid cancer.

Expected postoperative and radioablation treatment, TG values are nearly undetectable: <2 ng/mL.

Periodically active follow up are made every 6 to 12 months, under system defrenation (2 weeks no administration of suppressive LT4 treatment) with possible values:

- undetectable TG under elevated TSH conditions exclude residual cancer or metastases in 99% of cases;
- increased TG indicate tumor recurrence / metastasis away.

The significance of TG values in patients follows up with thyroid cancer

- under suppressive therapy with thyroid hormones:

- TG> 5 ng / ml indicates the need and standard protocol assessmen
- TG value between 2-5 ng / ml, involves therapy withdrawal and remeasurement of TG
- TG value <2 ng / ml requires different attitudes depending on the risk category in which the patient was engaged.

- withdrawal therapy suppression:

- TG <2 ng / ml or an increase <1 ng / ml compared to the previous assessment recommends retesting over 1 year;
- TG <2 ng / mL, but with an increase > 1 ng / ml compared to the previous evaluation, requires scintigraphic assessment of the whole body;
- TG> 2 ng / ml requires of whole body scintigraphy and suggests the possibility of a residual form of the disease;
- TG> 10 ng / ml require imaging studies, whole body scintigraphy and administration of an appropriate radioiodine dose . The threshold of 10 ng / ml has been suggested as a predictor of recurrent disease and the need for whole body scintigraphy.

b. Calcitonin

Calcitonin is a polypeptide hormone produced by parafollicular C-cells. In current practice it is used as medullary thyroid carcinomas marker.

Without a well defined screening recommendation in all cases with nodular thyroid disease, the measurement of serum calcitonin is mandatory in cases with a family history of medullary carcinoma, multiple endocrine neoplasia type 2 or Personal pathological conditions framed picture MEN 2 or FNA splitting cytology elements that suggest medullary thyroid carcinoma

Calcitonin presents a large range of variability, being increased in the presence of: smoking, chronic alcohol consumption, endocrine tumors (pancreatic or lung), hypergastrinemia, chronic use of proton pump inhibitors, chronic infections, calcitonin antibodies, autoimmune thyroid disease, chronic hypocalcemia.

Currently it is considered threshold a value of 10-20 pg / ml as a screening value in thyroid nodules evaluation.

- ***Morphological investigations***

a. Thyroid ultrasonography

Thyroid ultrasonography is the first choice imaging technique in evaluation of thyroid pathology. High resolution ultrasound is the most sensitive test for detecting thyroid abnormalities, identifying structure details and give a precise measurement of thyroid dimensions.

It is recommended to use only linear transducers with a frequencies between 7.5-12 MHz, that allows evaluate lesions biger than 1-2 mm.

Ultrasonography is indicated in the following situations:

1. to correlate a thyroid disease with clinical symptoms and follow up autoimmune thyroid disease in dynamics,
2. search for potential not palpable nodules,
3. in the presence of anamnestic risk factors for thyroid cancer
4. enlargement of a nodular formation in the cervical region
5. apearance of a cervical adenopathy
6. monitor thyroid nodules in dynamics (nodule characteristics and dimensions)
7. to guide fine needle aspiration
8. postoperative long term follow up
9. screening of children with risk factors: cervical /regional irradiation, total body irradiation, exposure to ionized radiation.

Thyroid ultrasonography – normal aspect

Conventional gray scale ultrasound, show thyroid as a as homogeneous, frosted glass, with an elevated echogenic structure compared to surrounding muscles. The structure of tracheal cartilage rings are central revealed and lateral it can be observed the common carotid and jugular vein with transonic aspect. Often intrathyroidal, either transverse or sagittal section, thyroid blood vessels are seen. Lower, paratracheal, anteromedial to "longus colli" muscle, in most cases on the left side, stands esophagus, with the corresponding layers of walls, that move when the patient swallows. Parathyroid glands are not normally not seen. Only enlarged parathyroid gland are visible on cervical ultraspund.

In general, the recorded parameters are: homogeneity, echogenicity, parenchyma pattern, the presence of focal lesions, thyroid capsule integrity and lymph nodes presence, appearance and number.

Thyroid dimensions

Without a very clear threshold value it is considered a normal value of thyroid lobe dimensions: 4 x 2 x 1cm, the total volume resulting by summing both lobes. If the isthmus dimension exceeding 3 mm, than it is added in total thyroid volume calculation.

Normal thyroid volume depend also on gender, height, intake of iodine, the geographical origin (endemic area / non- endemic area) should be considered.

The following formula is more commonly used:

V = width x length x thickness x / 6

On average, a volume up to 15-16 ml (women) and 18 to 20 ml (males) are considered as normal

In general, a reduced thyroid volume in adults may suggest a thyroid atrophy, most common autoimmune etiology and an increased thyroid volume may suggest a diffuse goiter with or without degenerative-regressive changes.

Diffuse goiter, defined as a significant increase in the upper limit of normal is associated with iodine deficiency or autoimmune pathology, both situations must be properly identified in order to an appropriate therapeutic approach.

In children, there was not established a general consensus on average values of thyroid volume. In Romania the data comes from the study "Thyromobil" ran until the early 2000s. The values of national averages are shown in the tables below.

TABLE XVIII. THYROID VOLUME IN SCHOOL CHILDREN

The European mean values

Age	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Volume (ml)boys	5,4	5,7	6,1	6,8	7,8	9	10,4	12	13,9	19
Volume (ml) girls	5	5,9	6,9	8	9,2	10,4	11,7	13,1	14,6	16,1

The Romanian mean values

Age	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Volume (ml) boys	4	3,2	3,7	4,9	6,5	7,1	6,4	7,9	12,3	12
Volume (ml) girls	3,1	3,4	4,5	5,4	6,3	8,3	8,3	9,8	11	10,7

Normal thyroid volumes in children will define the normal thyroid volume in adults.

Hypoechogeneity is associated with:

- Iodine deficiency
- Autoimmune thyroid disease
- Need to go into evaluation, to confirm the diagnosis
- Particular attention should be given to obese patients, where hipoechogenicity may be strictly linked to interposition of adipose tissue, Inhomogeneous pattern is the prerogative of autoimmune thyroid disease.

Evaluation of nodule formations is an extremely important aspect of the thyroid ultrasound The ultrasound will divide nodules in risk categories, according the number of suspicious US patterns found. Currently, it is a consensus that ultrasound divide nodules into different categories of risk: very lw risk, low risk, moderate risk and increased risk. The assessment of each node include evaluation of:

- size,
- shape (oval/round, taller than wide)
- margins
- echogeity
- omogenicuty
- vascularization
- presence calcifications.

TABLE XIX. SUSPICIOUS ULTRASOUND FEATURES FOR MALIGNANCY

Characteristic	***Benignity features***	***Malignancy features***
Shape	Oval	*"Taller than wide"*
Edges/borders	smooth	Unclear/ill defined
Echogenity	Isoechoic, homogenous	heterogenous
Calcification	Microcalcification points- in old nodules, post haemorrhage	Microcalcifications < 2 mm Macrocalcifications > 2 mm - Round - Egg shell - Unclear peripheral/edge
Vascularity	Perilesional/absent	Intralesional
Capsule	Intact	Disrupted by node
Lymph nodes	Absent Oval, with central hilum hyperechoic Thin cortical	Round Peripherel hyperechoic hilum Absent hilum Thickened cortical> 3 mm

The diagnostic accuracy of different ultrasound parameters is variable. The sensitivity, specificity, positive and negative predictive values are summarized in the table below.

TABLE XX. ULTRASOUND FEATURES ASSOCIATED WITH THYROID CARCINOMA

Feature	*Aappearance*	*Sensitivity*	*Specificity*	*PPV*	*NPV*
Node					
Appearance	Solid	26 - 59%	86 - 95%	24-71%	42-94%
Echogenity	low	26 - 87%	43 - 94%	11-68%	73-94%
Halou / margins	Absent/ irregular	17 - 77%	39 - 85%	9-60%	39-98%
Vascularity	Intralesional	54 - 74%	79 - 81%	24-42%	86-97%
Shape	Taller than wide	33%	92%	67%	75%
Lymph node					
Hilum area	Absent	100%	29%		
Calcification	Pointed	46%	100%		
Crystallization	Present	11%	100%		
shape	ball	46%	64%		
Vascularity	Peripheral Pointed	86%	82%		

Doppler ultrasonography

Provides information on the dynamics of intrathyroidal blood flow.

Doppler Ultrasonography related information are controversial because they are useful only if are read in conjunction with the information provided by grey scale ultrasound.

TABLE XXI. COMMONLY SITUATIONS ASSOCIATED WITH CHANGES IN THE THYROID VASCULARITY

Increased vascularization	***Decreased vascularization***
Active Graves disease	Thyrotoxicosis factitia
Untreated hhypothyroidism	Thyroid marked atrophy
Hashitoxicosis - in the beginning	Sub acute thyroiditis - hyperthyroid phase

The presence only of hipervascular thyroid nodule, in the absence of any suspicion signs, it is not sufficient to switch node in to increased risk category.

Elastography

Elastography is an application of classic ultrasound, which is based on the different behavior of nodular structures tumor to the adjacent tissue based on the finding that a malignant tumor is much tougher than the healthy perilesional tissues.

There are two main types of elastography:

Static (Strain) - the elastic wave is fixed and the technician produce the transducer motion. Elastic wave propagation in the underlying structures makes possible the evaluation of tumor lesion, which is hard, compressing it less than the surrounding healthy tissues. The difference compression is visualized in a color scheme with different colors corresponding to the different hardnesses. Besides this, the color map, which assesses the quality of tumor anelasticity, can make a semiquantitative evaluation with intralesional anelasticity/surrounding healthy parenchyma ratio. The higher the ratio is the greater anelasticity injury has.

Dynamic (Share wave), elastic wave is generated by the device, the examiner's hand being fixed. The speed wave spread through tumor structures is higher than the surrounding healthy structures. This technique also presents the evaluation results as a color code which assess the quality or measuring the velocity wave through the lesion (m.sec) or lesion elasticity(kPascali) as quantitative assay.

Even if, for now, endocrine society's guidelines do not include elastography in the algorithm of thyroid nodule assessment, the results are impressive and suggestive: sensitivity 92%, specificity: 90%. The quality of the results is independent of nodule size, the quality of diagnosis remains in lesions with intermediate quantitative cytology. Quantitative versions has greater diagnostic value than qualitative ones, higher ratio than 3-4 or 2.5 in lesions with intermediate cytology have 93% diagnostic sensitivity, 92% specificity and 89.5% accuracy.

Disadvantages of each method:

- large cystic lesions not allow intranodular movement of elastic wave,
- presence of major calcification lesion influences the anelasticity by summation effect.

In addition share wave elastography is excellent in assessing diffuse diseases, autoimmune thyroiditis being the main condition assessed by this alternative method.

b. Computer tomography (CT)

CT evaluation is not part of routine endocrine examinations. Most often, when a neck CT scan finds thyroid anomalies, endocrine evaluation is recommended.

Useful in:

1. Evaluation of substernal extension (thoracic CT)
2. Presence of extrathyeroidal invasion: postero-inferior metastatic lymph nodes (cervical CT)
3. Advanced disease with massive locoregional extension (cervical CT).

c. Magnetic resonance imaging (MRI)

Incidental discovery of thyroid nodular formations during an MRI assessment (cervical or thoracic) should be completed with ultrasound.

Brain and spinal metastases, are well visualized on MRI. Is not part of clinical routine evaluation.

- ***Morpho functional evaluation***

a. Thyroid Scan (scintigraphy)

Scintigraphy represents a morphofunctional evaluation, because it is based on the unique ability of the thyroid to concentrate iodine. Scintigraphy does not provide information with precise anatomical location such as ultrasound or other imaging techniques (CT or MRI), but provide details on cellular level activity in various thyroid lesions/ segments.

Principle of the method is based on the normal iodine concentration in the thyroid, due to the activity of Na-Iod symporter, responsible for active capitation 10-35% of the administered iodine. This symporter behaves the same with both, the natural and the radiolabeled iodine. After administration, external detectors measures the amount of radiation (usually gamma) issued by the evaluated region. The result is an indicative that can locate different thyroid territories with different functional behavior, but can not predict with precision the exact dimensions of these lesions.

Several types of isotopes are used:

- I^{123}, orally administrated, with images obtained at 4 to 24 hours. Recommended for thyroid nodules.
- Technetium ^{99m}, with intravenous administration, is traped but not organificated at thyroid level, in salivary glands or stomach mucosae. It is preferred for the speed (low dose exposure and low cost.

- I^{131} is used in evaluation distant metastasis in differentiated thyroid cancer lesion.
- In-Pentreotid111 is a Somatostatin analogue used in the diagnosis of medullary thyroid carcinoma and other neuroendocrine tumors.

Current scintigraphy indications are:

1. Hyperthyroidism , subclinical or clinic, with or without goiter:
   - to identify the source of hyperthyroidism
   - for differential diagnose between diffuse functional and localized autonomy
   - source of hyperthyroidism in uninodular goiter (parenchyma or node)
   - the evaluation of remnant thyroid volume after curative treatment with ablative radioiodine;
2. suspicion of ectopic goiter,
3. suspicion of sub sternal goiter,
4. postoperative assessment in differentiated thyroid cancers.
   - the evaluation of thyroid remnants or loco regional lymph nodes
   - if is necessary administration of therapeutic doses of radioactive iodine,
   - dosing the amount of radioactive iodine required for therapeutic effect
   - the reassessment of the patient (over 6 or 12 months)
   - used in parallel with the whole body scintigraphy to identify distant metastases;
5. coexistence of thyroid and parathyroid nodules.

Contraindications of he method:

- pregnancy
- lactation
- limited indication in newborns, infants and children: nodular autonomy/ectopic thyroid gland.

The scintigraphy may be performed immediately after menstruation, with a check up in advance for beta hCG (human chorionic gonadotropin) levels. Urine test is not preferred due to false negative range in the first 7-10 days after conception.

b. Radioiodine uptake/24h (RAIU 24)

This assessment should not be confused with the usual scintigraphy. Even though the principle is the same, it relates to the assessment of the quantitative measurement of the total absorption of radioactive iodine in the thyroid parenchyma in 24 hours.

RAIU assess the overall avidity of the thyroid to iodine or indicate a thyroid clearance rate related to renal clearance.

Following oral administration of radioactive tracer (I131, I123, I125, I132, 99m Tc) periodic measurements of gamma ray emission are take. To calculate the percentage capture / 24h depends on the amountof radioactive tracer adminsitrated.

Normal thyroid capture/24h is between 5-30%, depending on the daily intake of iodine.

In areas with more intensive iodine uptake RAIU is lower while in areas with deficiency of iodine uptake RAIU is higher. Exposure to large amounts of iodine (> 5 mg / day) completely suppresses iodine uptake (eg iodine contrast agents, antiseptics, vitamins, amiodarone).

TABLE XXII. SITUATIONS THAT ASSOCIATES VARIATIONS OF RAIU

Increased RAIU	**Decreased RAIU**
- Basedow disease, - Toxic adenoma. - Multinodular goiter, - Trophoblastic disease, - Resistence to thyroid hormones - TSH thyrotoxicosis	- thyrotoxicosis factitia, - iod Basedow effect, - subacut thyroiditis, - painless thyroiditis, - struma ovari
Nontoxic goiter - endemic - Enzime deficiency	Thyroid dysgenesis NIS malfunction Malfunction in iodine concentration
Iodine deficiency	Iodine excess
TSH administration	Chemical substance administration: - dopaminergic, L Dopa, - piridoxin, - dopamin antagonists, - serotonin agonists, - glucocorticoids, - somatostatin, Octreotid, - opioid.

c. Single-photon emission computed tomography (SPECT)

This imaging technique requires higher doses of radioactive isotopes compared with usual Tc ^{99m} scintigraphy and provide tridimensional images of the region of interest. The fallowing radioactive tracers are used: I123, or I131.

The method has limited indications, beeing used in:

- estimating the functional volume,
- to identify the ectopic tissue, especially in the retrosternal area
- accurate detection of whole body metastases.

➢ ***Cytology investigation***

Fine needle aspiration (FNA)

Fine needle aspiration is a basic evaluation technique for nodular thyroid diagnosis, beeing considered the golden standard method in the diagnostic of thyroid nodular disease.

The eco guided FNA is recommended, for significant increase in sensitivity and specificity of the method.

The diameter of the thyroid nodule at the point the FNA is recommended is different nodules:

- More than 1 cm in case of increased risk nodules and intermediate risk nodules,
- More than 1.5 cm in low risk nodules
- More than 2 cm in very low risk nodules.

The sensitivity of the method varies between 63-98% (mean = 83%) and specificity between 72-100% (average 92%) and depends on the FNA material quality and the experience of the practician.

FNA technique: The patient must be positioned with the neck in hyperextension, prior skin sterilization, ideally with medicinal alcohol and cyproheptadine skin solutions. Local or depth anesthesia is not required. 5% Betadine gel may be used in place of the normal ultrasound gel.Most of the times the puncture can be performed without any gel by changing the ultrasound gan's.

The assistant positioned the transducer as perpendicular to the skin and reveals nodular formation using cross section of the thyroid and the ipsilateral jugular carotidian package

Using a very thin needle, 25-27 gauge, attached to a syringe of 10 ml., the needle is insert parallel to transducer, so can have a view of the needle path that goes successively through the layers. When nodular lesion was reached, negative pressure can be make with specific movements to "go forth" without leaving nodular, with subsequent withdrawal of the needle, but maintaining negative pressure. Some technicians do not use suction technique, but enters with needle already prepared when tegumantare penetration occurs. The maneuver is repeated several times, addressing to different portions of the target node. Immediately after the harvest smear stretches are put between two blades, and fixed with 95% ethanol. Subsequently the smears are stained with Papanicolau and Hematoxylin Eosin technique.

The results are detailed according to Bethesda reporting system:

I. = nondiagnostic / unsatisfactory (exclusive fluid content, acellular specimen, artifact, thrombus);

II. = Benign (follicular adenoma, autoimmune thyroiditis, subacute granulomatous thyroiditis, other situations);

III. = Atypia of undetermined origin

IV. = Follicular neoplasm,

V. = suspicion of malignancy (papillary carcinoma, medullary carcinoma, metastatic carcinoma, lymphoma)

VI. = Malignant (papillary carcinoma, poorly differentiated, medullary, undifferentiated cell carcinoma, mixed)

This reporting system indicates the risk of malignancy, quantifying the following: category I 1-4%, category II 0-3%, category III 5-15%, IV category 15-30% category V 60-75%, respectively to 99% in category VI.

Indications:

1. Therapeutic attitude in case of uninodulare formations:

- no attitude(keeping in place) if the nodule is benign with no compression
- unilaterally lobectomy in case of benign nodule with surgical indications,
- total thyroidectomy on suspicion of malignancy

2. Assessment of dominant nodule in multinodular goiter,

3. Reassement a node with intermediate cellularity after 3-6 months of development.

As a conclusion, thyroid FNA avoids unnecessary surgical interventions, decreses the unnneded surgical procedures in nodular goiters and increases operative accuracy in case of highly suspicious lesion of malignancy.

➢ ***Molecular diagnosis***

Molecular diagnosis is useful for understand some particular cases in thyroid pathology:

- Resistance to thyroid hormones,
- TBG alteration,
- TSH secreting pituitary tumors
- Dysalbuminemia
- Prealbumin Hyperthyroxinemia
- TBG mutation
- Abnormalities of sodium iodine symporter.
- Impaired thyroperoxidase
- Dyshormonogenesis
- Abnormalities of TSH receptor
- Abnormalities of the thyroid hormone receptor.

Main thyroid pathology can be systematised as following:

- Autoimmune disease = Antithyroid Ab

- stimulatory TSH R Ab → HyperThyroidism
- A TPO Ab, A TG Ab → euThyroidism, hThyroidism, HyperTyroidism

Nodular disease = cell proliferation uninodular/multinodular → euThyroidism, hypoThyroidism, HyperThyroidism

Iodine deficiency → hypoThyroidism, HyperThyroidism, euThyroidism

III.3. THYROID PATHOLOGY

The main functional syndromes in thyroid pathology are euthyroidism, hyperthyroidism and hypothyroidism.

III.3.1. HYPERTHYROIDISM

Definition = Clinical sd = exposure to high levels of circulating thyroid hormones with

- Generalised acceleration of metabolic process
- Increased adrenergic sensitivity

Etiopathogeny:

1. Diffuse toxic goiter (Graves Basedow disease)↑ production
2. Toxic adenoma (Plummer diseases) ↑ production
3. Toxic multinodular goiter ↑ production
4. Hashitoxicosis acute ↑release
5. Subacute thyroiditis ↑release
6. Postpartum thyroiditis ↑release
7. Iatrogenic: to high T4/ T3+T4 medication
8. Rare forms:
   - struma ovari, hydatiform mole (beta HCG = TSH like)
   - metastatic thyroid carcinoma: increased production
   - hamburger thyrotoxicosism: ingestion of thyroid tissue
   - TSH secreting tumors
   - Amiodarone induced

III.3.1.1. Graves Basedow disease

- The most common form
- F: M = 5:1
- Peak incidence 20-40 years
- Autoimmune disease (familial cluster) HLA-B8, HLA-DR3
- Triggers:
  - Stress
  - Postpartum/breast feeding/menopause
  - Tobacco use, iodine exposure
- **T lymphocytes = sensitized to thyroid Ag = TSHR = stimulating all thyroid functions = thyrotoxicosis**
- **TSHR Ab = positively correlated with active disease + relapse**
  = positive diagnostic criteria
  = criteria for cure of disease

TABLE XXIII. SIGNS/SYMPTOMS OF HYPERTHYROIDISM

EUTHYROIDISM	HYPERTHYROIDISM
↑Inotropism, ↑Cardiac output ↑Cronotropism	Tahicardia, tahiarythmias, Atrial Fibrillation Increased hyper contractility
↑Respiratory muscle function	Breathless (weakend of resporatory muscle)
↑Erytropoetin / erythropoiesis	Increased Hb
↑ Gut motility	Hyperdefecation
Bone turnover	Demineralisation, hypercalciuria, ↑Ca^{2+}
Muscle contraction/ relaxation Emotional balance	Hyperactivity, Hyperreflexia Anxiety/agitated/insomnia
Normal function of GhRH, GCS metabolism	Androgen aromatisation, hyperE_2, SHBG, GCS metabolism
Glicemic metabolism	Hyperglicemia
Lipidic metabolism	Hypocholesterolemia
Proteic metabolism	Proteic loss/muscle loss
Basal metabolism	Increased sensitivity to heat

In order to have a clinical diagnostic, we need at least 1 out of the 4 major signs of hyperthyroidism:

1. Tachycardia
2. Goiter
3. Ophthalmopathy

Cytotoxic L (NK), proliferation of fibroblast, action of cytotoxic Ab = TSH receptor antibodies and preadipocytes inflammations are some of the involved mechanisms. Inflammation is present al the level of orbital fibroblast and also orbital muscle.

Eye disease: is not universally present. Risk categories are recognised:

- Males
- Smoking
- Long standing disease
- Relapses
- Iatrogenic hypothyroidism

4. Dermatopathy = pretibial oedema

It has a typical localisation - Lower tibia, secondary to an accumulation of glycosaminoglycans with tickening of the skin (peau d'orange aspect), typical but very rare, seen in up to 2-3% of cases.

Subperiostal inflammation = acropathy hands/feet, is even more rare than dermatoptahy, but is a pathognomonic sign of hyperthyroidism, which is not considered MAJOR due to very low prevalence in the clinical picture of Graves disease.

All possible combination of the MAJOR signs of hyperthyroidism but also minor sigs of hyperthyroidism are seen in Graves disease:

- Increased skin temperature
- Wet, soft, smooth, sweat skin
- Hand hand tremor
- Tachykinesia
- Emotional sings: lability, stress, anxiety,
- Physical asthenia (muscle loss)
- Weight loss
- Increased intestinal transit
- Oligomenorhea
- Premature ejaculation
- Bone pain

Thyroid evaluation has the following steps:

- Inspection = patient swallowing = butterfly shape gland, possible increased volume/increased isthmus/asymmetry
- Palpation
  = the thumb anterior along the trachea
  = hand on the lobe
  = Normal – barely palpable, smooth surface, soft – rubber consistency
  diameter 1cm/2cm
  = Diffuse goiter/nodular goiter = symmetrical/asymmetrical increase
  = purr = due to increased blood speed
- Auscultation
  = increased blood strain continues systolic/diastolic.

Eye change evaluation needs to quantify the ophthalmic protrusion, the severity of complications, and also to be able to follow the evolution. The degree of proptosis is measured with an exophtalmometer, a device with prism mirrors, than projects the eye in.

Several classifications are used for this:

TABLE XXIV. INVOLVEMENT SCALE

Class		Definition
O	N	No signs or symptoms
1	O	Only signs = upper lid retraction, stare, lid lag
2	S	Soft tissue involvement
3	P	Proptosis 25 mm Hertel
4	E	Extraocular muscle involvement – diplopia
5	C	Corneal involvement
6S	S	Sigh loss (optic nerve involvement)

There is also an activity scale, quantified as the number of present signs out of 7:

- Spontaneous pain
- Pain with movement
- Lid edema
- Lid redness
- Conjunctiva redness
- Chemosis
- Swollen caruncula

The severity scale Grade of proptosis

- Low severity = intermittent diplopia, with proptosis less than 25 mm
- Moderate severity = permanent diplopia and/or proptosis less than 30 mm
- Important severity = associated signs

Positive diagnostic:

1. Hormonal evaluation: Ft3 ↑ +Ft4 ↑
2. Immunological evaluation: ATPO Ab, ATg Ab, TRAB
    a. ↑↑↑↑ TRAB = confirmation of Graves disease
    b. Indication of disease activity/aggressively
    c. Evaluation of diseases stage: active/inactive
    d. Estimation of relapse risk
    e. In pregnant women: evaluate the risk of neonate Graves disease

3. Associated complication:
    a. Hypercalcemia, hypercalciuria, ↑ FAL
    b. ↓LDL-C, TG, TC
    c. ↑ glycaemia !!!! DM patients
4. Morphologic: Ultrasound evaluation
    a. Volume = normal/increased
    b. Hypoecogenity = sign of autoimmune process
    c. Increased vascularisation = TRAB dependent
    d. Exclusion of other forms of HT
5. Scintigraphy is commonly used, being reserved just for cases with associated nodular disease (to identify the hyperactive tissue= diffuse or nodular tissue)

COMPLICATION = EMERGENCY = THYROID STORM

- Acute exacerbation of all signs and symptoms
- Life - threatening complication
- Context = after surgery, after RAIU therapy, parturition in an **INADEQUATE controlled** thyrotoxicosis
    – Hypermetabolism
    – Excessive adrenergic response
    – **Fever 38-41 OUT of PROPORTION**
    – Flushing, sweating
    – Marked tachycardia. ATRIAL FIBRILLATION, high pulse pressure, heart failure
    – ↑↑TT4, ↑↑FT4, ↑↑FT3 ↓↓↓TSH

Differential diagnostic:

- Different form of hyperthyroidism: toxic adenoma, multinodular hyperactive goiter, debut of autoimmune thyroid disease, initial phase of subacute thyroiditis, painless thyroiditis, postpartum thyroiditis, iatrogenic hyperthyroidism, other rare forms of hyperthyroidism.
- Excess of catecholamine
- Paraneoplasic sd.
- Psychiatric diseases, especially hyperactive states

Treatment options:

*1st line medication = **antithyroid drug therapy***

- Methimazole — competitive TPO inhibitors
- Carbimazole — immunosuppressive effects
- PropylTioUracyl (PTU) — have also effect of the peripheral conversion T4 ➔T3, blocking the process.

Regardless the used preparations, there is an initial attack dose of 10 - 40 mg MTM/ 150- 600 mg PTU with euthyroidisation in 4 to 12 weeks of treatment. Afterwards there is a pprogressive decreased doses: 5 -10 mg MTM/50-150 mg PTU.

The correct treatment evaluates:

- Changes of clinical signs, Heart rate, weight gain, quality of sleep.
- Hormonal assays: **FT3 + FT4**. The TSH value is not used for following the progression of disease, because the values can remain inhibited for months, as a sign of Graves disease per se.
- The follow up has to check for adverse effects:

  MTM> skin rush (5%), leucopenia, agranulocitosis (0.5%), liver cytolysis

  PTU: hepatic toxicity, vasculitis (< 0.1%)

Under treatment, there is a remission in the vast majority of cases, in 20-50% after 1 year. The mean treatment duration is around 1-2 years, interval in wchih the majority of cases will cure.

*1st line adjuvant **therapy***

- <u>Beta adrenergic blockers</u>

  Control the adrenergic symptoms better/quicker than ATD

  unselective blocker — PROPRANOLOL 2x10-40 mg/day

  selective blockers

- Adequate Nutrition
- Calcium preparation
- Anxiety control

2nd line **Radioactive iodine therapy** 80-200microCi/thyroid g

The principle of action of radioiodine treatment is the capacity of thyroid to uptake iodine, the intense the activity of thyroid parenchyma, the higher the uptake. Using radioactive iodine compounds, these will inactivate the functional thyroid tissue.

It is used in adults only patients: orally single capsule administration, with euthyroidisation in 2-6 months in all cases. The principal complication is represented by hypothyroidism: HYPOTHYROIDISM, described in 80% 6-12 months after the treatment.

Indications for radioiodine treatment:

1. cases with normal/small thyroids
2. no associated nodular lesions
3. younger patients
4. no response to 1st line treatment
5. no pregnancy plan in the next 2 years

Contraindications/limited indications

1. increased thyroid volume
2. Associated nodular lesions (!increased cancer risk)
3. old patients
4. associated ophthalmopathy
5. pregnancy
6. 2 years before a planned pregnancy
7. children

3rd line **Surgery = total / near total thyroidectomy**

1. Large glands
2. Multinodular glands
3. Concomitant suspicious of cancer
4. Allergic/noncompliant to therapy
5. Refuse of 2nd line therapy
6. Pregnant women with allergies to 1st line treatment – 2nd trimester

SPECIAL PREPARATION = withdrawal of medication 2 weeks prior, administration of saturated solution of potassium iodide for a maximum of 7-10 days = vascularisation of thyroid

Special situations

1. Thyrotoxicosis crisis (thyroid storm)
   - Betablockers = iv = ideally Propranolol (betaadrenergic + inhibits T4 ➔T3)
   - Severe cardiac insufficiency = Calcium blockers: Verapamil 5=10 mg
   - PTU preferable = more effective > MTM 2400 mg/day RECTAL adm
   - IODINE acute – sodium ipodate/ iopanoic acid
   - HHC 4x500 mg/zi inhibits peripheral conversion
2. Pregnancy
   - Medical treatment, PTU preferred = in the 1st trimester than switch to MTM
   - MTM = teratogenic effect = aplasia cutis, choanal atresia, tracheoesophageal fistulae
   - !!! TRAB evaluation = risk of neonate Graves
   - Breastfeeding is possible with treatment
   - !! All medication will cross the placeta
   - !!! No betablockers = SGA
3. Ophthalmopathy
   - The majority will decreased as the Graves disease will diminished
   - Head elevated at night
   - Reduce/cessation of smoking
   - Selenium suppressive treatment 200 mcg/day, 6 months
   - Corticotherapie is selected cases CAS > 4/7 moderate/severe
     - Orally = Prednison 60 mg/day, reducing 10 mg.weekn every 2 weeks
     - Pulse therapy: total of 4.5g Metilprednisolone 0.5 mg/week, 9 weeks
   - External X ray therapy to the retrobulbar area = 2000 cGY,

Prognostic of disease

- Life long evolution
  - Relapses
  - Long term natural hypothyroidism 25%
  - Iatrogenic hypothyroidism
    - post RAIU 80%
    - postsurgical 100%

III.3.1.2. Toxic adenoma

Is the 2nd cause of overt hyperthyroidism, Isolated, benign adenoma secreting T3 /T4 in a uncontrolled manner, with a gradually suppression of TSH, with moderate intense hyperthyroidism signs, never with ophthalmic disease, without any autoimmune context, more frequent in women (F:M ratio = 4:1).

Solitary overactive nodule can appear in a normal thyroid or in a preexisting goiter, but, regardless the initial thyroid hormone, because of the somatic mutation in the gene encoding TSH receptor, there is a increased activation of TSH receptor with over activity of the affected thyroid cells. The degree of hyperthyroidism increases with time, with subsequent decrease of the activity of the surrounding, unaffected parenchyma,. In the first stages the hyperactivity of toxic adenoma is contra balanced by the suppressed surrounding parenchyma, with no signs or symptoms of hyperthyroidism. In the next stages, this compensatory mechanism is overstepped, becomes inefficient, and hyperthyroidism appears.

Clinical signs = typical hyperthyroidism, without ophthalmic disease, no acropathy and no tibia edema.

Positive diagnostic:

1. Hormonal evaluation: borderline Ft3, FT4 with ↓ TSH
2. Immunological evaluation: ATPO Ab, ATg Ab, TRAB = 0
3. Associated complication: less severe
    a. Hypercalcemia, hypercalciuria, ↑ FAL
    b. ↓LDL-C, TG, TC
    c. ↑ glicemia !!!! DM patients
    d. Morphologic: Ultrasound evaluation
4. Presence of a unique nodule, typically increased vascularisation
5. Morph functional = scintigraphy = ELECTION DIAGNOSTIC
    a. Hyperactive unique nodule with suppressed surrounding tissue

Diferential diagnostic:

- Different form of hyperthyroidism: Graves disease, multinodular hyperactive goiter, debut of autoimmune thyroid disease, initial phase of subacute thyroiditis, painless thyroiditis, postpartum thyroiditis, iatrogenic hyperthyroidism, other rare forms of hyperthyroidism.
- Excess of catecholamine
- Paraneoplasic sd.
- Psychiatric diseases, especially hyperactive states

Treatment options:

After a pre treatment with antithyroid preparations, around 2 months with the symptomatic control of thyrotoxicosis symptoms, 2 possible treatment line can be followed:

1st line Radioiodine therapy preferred in cases with:

- Older patients (> 45 years)
- Small nodules
- No planned pregnancy

Alternative treatment = 2nd line treatment = Surgical approach = Lobectomy, in cases with:

- Very large nodule with obstructive symptoms
- Younger patients (< 45 years)

Both after radioiodine and lobectomy, no iatrogenic hypothyroidism is described.

III.3.1.3. Toxic multinodular goiter

Is pathology reserved seen in older patients, special in longstanding diseases, especially when coming from an iodine deficiency region with secondary exposure to iodine. Even if all signs and symptoms of hyperthyroidism are seen, as in toxic adenoma, there is no autoimmune involvement with co ophthalmic component. The major landmark of this disease is the cardiac symptoms. The hyperthyroidism has an gradual onset, first with subclinical hypothyroidism and than with clinical, overt hyperthyroidism.

Clinical signs = typical hyperthyroidism, without ophthalmic disease, no acropathy and no tibia edema, with visible goiter, or not, although in the majority of cases there is an old goiter, known before the appearance of hyperthyroid signs and symptoms.

Positive diagnostic

1. Hormonal evaluation: borderline Ft3, FT4 with ↓ TSH or overt hyperthyroidism

2. Immunological evaluation: ATPO Ab, ATg Ab, TRAB = 0

3. Associated complication: less severe

   a) Hypercalcemia, hypercalciuria, ↑ FAL
   b) ↓LDL-C, TG, TC
   c) ↑ glicemia important in !!!! Diabetes mellitus cases
   d) EKG: tachycardia, premature depolarisation, fibrillation, flutter

4. Morphologic evaluation: Ultrasound evaluation

- presence of a multiple nodule, typically increased vascularisation of at least 2 nodules, wtouth significant vascularisation of the nonnodular tissue

5. Morphofunctional evaluation = scintigraphy = ELECTION DIAGNOSTIC

Hyperactive nodules with suppressed surroundings

Differential diagnostic:

- Different form of hyperthyroidism: toxic adenoma, Graves disease, onset of autoimmune thyroid disease, initial phase of subacute thyroiditis, painless thyroiditis, postpartum thyroiditis, iatrogenic hyperthyroidism, other rare forms of hyperthyroidism.
- Excess of catecholamine
- Paraneoplasic sd.
- Psychiatric diseases, especially hyperactive states

Treatment options

After a pre treatment with antithyroid preparations, around 2 months with the symptomatic control of thyrotoxicosis symptoms, 2 possible treatment lines can be followed:

Radioiodine therapy

- Older patients (> 45 years)
- Reasonable big goiter

Surgical treatment Total Thyroidectomy

- Very large nodule with obstructive symptoms
- Younger patients (< 45 years)

Because of the extension of hyper functional tissue, regardless if the treatment type (surgical or radioiodine) iatrogenic hypothyroidism will follow, with needed supplemental therapy, with thyroid hormones.

There is a time span between the treatment moment and presence of hypothyroidism:

- after the first 7 days after total thyroidectomy – the introduction of LT4 supplemental therapy has to be started, in medium doses: 1 mcg LT4/lg body weight
- in cases of radioiodine treatment – evaluation 5 weeks after radioiodine, with introduction, if needed of supplemental therapy. The risk of hypothyroidism is proportional with the amount of hyperactive thyroid tissue

III.3.1.4 Other causes of hyperthyroidism

A. Amiodarone induces hyperthyroidism

Amiodarone is a well knows, widely used antiarrhythmic, that due to its high quotient of iodine, is associating thyroid dysfunction. The spectrum of thyroid-induced diseases is wide, with hyper functional states but also hypo functional states.

Each Amiodarone tablet contains 37.3% Iodine = 75 mg Iodine representing 100 time higher iodine that the daily requirements. The excess amount of iodine is stored in the body at the thyroid level, but alos at the level of fat, myocardium, liver and lung. The half-life of the used iodine is around 50 days, but the iodine stores last up to 9 months after total treatment discontinuation.

Hyperthyroidism is induces by 2 possible mechanisms.

TABLE XXV

Iodine induced HT	**Amiodarone induces thyroiditis**
Latent/pre-existing thyroid disease	Normal pre-existing thyroid
↑Synthesis ↑Release	Destructive inflammation = AIT Temporarily ↑Release
F:M = 1.5:1	F:M = 1:3
Acute cardiac symptoms	Acute cardiac symptoms
Increased vascularisation Other US changes	Decreased/absent vascularisation No US pathology
Antithyroid drugs + beta adrenergic blockade	GCS therapy NO antithyroid drug therapy
Long standing hyperthyroidism	Short duration hyperthyroidism

Correct identification of the form of Hyperthyroidism – overproduction or acute cellular destruction is mandatory for a correct treatment.

B. Hashitoxicosis

In 10% of the autoimmune diseases, the onset of the disease is characterised by a a destructive phase, with cellular destruction and active release of the thyroid hormones in the general blood flow, with signs and symptoms of hyperthyroidism. There is no hyper production of thyroid hormones, just a release from the stores in the general blood flow. The intensity of HT symptoms is medium to low, and the duration of this phase is up to 3 months. The use of antithyroid drug therapy is inadequate, and will induce a severe hypothyroidism. Only medication for reduction of inflammation, even glucocorticoids in severe cases, is needed. Associated beta-blockers and calcium preparation can be used.

The diagnostic is an exclusion diagnostic:

1. Hormonal evaluation: ↑ Ft3, FT4 with ↓ TSH

2. Immunological evaluation: ↑↑ATPO Ab, ↑ATg Ab, TRAB = 0 = other autoimmune disease than Graves disease

3. Associated complication: less severe
   a) Hypercalcemia, hypercalciuria, ↑ FAL
   b) ↓LDL-C, TG, TC
   c) ↑ glycaemia !!!! DM patients
   d) EKG: tachycardia, premature depolarisation, fibrillation, flutter

4. Morphologic: Ultrasound evaluation
   - Autoimmune disease (with or without goiter)
   - ABSENT hyper vascularization (!!! Destruction NO hyper secretion)

5. Morph functional = Typical DIAGNOSTIC
   No RAIU activity at all due to important diffuse parenchyma inflammation/aggression = DESTRUCTION

C. Sub acute/silent thyroiditis

Sub acute thyroiditis is an inflammation secondary to an viral infection. The 1st phase of the disease is characterized also by a hyperthyroid phase, due to the release of the thyroid hormones in the general circulation, after the diffuse post viral inflammation process. The intensity of hyperthyroidism is variable, the duration of the lesional phase is limited to maximum 2-3 months, and the process is self limited with or without treatment. Silent thyroiditis has he same mechanism, but typically appears after in the first 2 to 3 months postpartum, favored by a preexisting thyroid disease, but not universally needed.

The diagnostic *steps are the same:*

1. Hormonal evaluation: borderline ↑Ft3, FT4 with ↓ TSH

2. Immunological evaluation: ATPO Ab, ATg Ab, TRAB = 0

3. Associated complication: less severe
   a) Hypercalcemia, hypercalciuria, ↑ APH
   b) ↓LDL-C, TG, TC
   c) ↑ glycaemia !!!! DM patients
   d) EKG: tachycardia, premature depolarisation, fibrillation, flutter

4. Morphologic: Ultrasound evaluation
   - presence of a inhomogeneous hypo echoic thyroid gland with alternation of different hypo echoic intensities, similar to a chess table. No nodules are to be seen.

5. Morphofunctional evaluation = ELECTION DIAGNOSTIC
   NO iodine concentration secondary to the diffuse inflammation/aggression and destruction.

As in other aggression form of hyperthyroidism, there is no need of antithyroid drugs, but only anti-inflammatory drugs and beta blockers have to be used.

Whenever we have sign or symptoms of hyperthyroidism, the following algorithm is recommended:

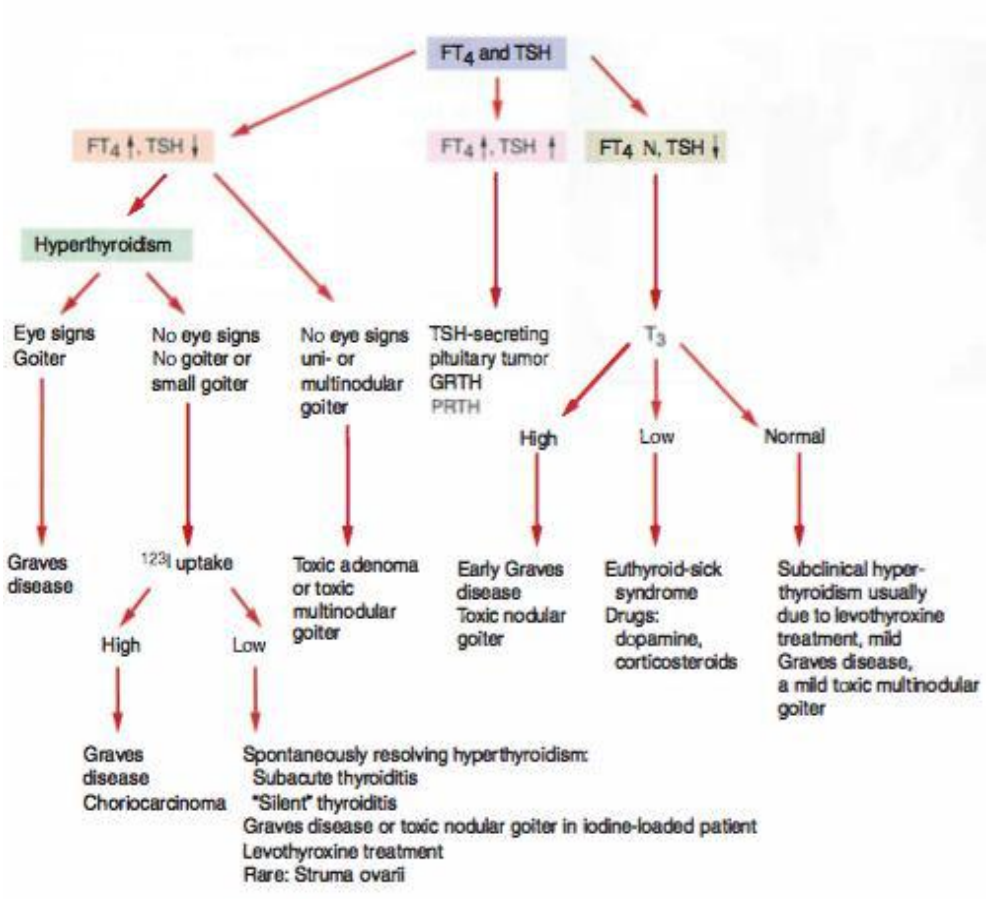


Figure 17. Hyperthyroidism diagnostic steps

III.3.2. HYPOTHYROIDISM

Hypothyroidism is characterized by low production of thyroid hormones, due with generalized slowdown of all metabolic processes.

The clinical picture is different in adults versus children, since thyroid hormones have a great important and influence in the growth process, not only somatic growth but also neurocognitive development:

- In children =
  - Marked slowing growth and development
  - Mental retardation
- In adults =
  - Generalised decrease in metabolism
  - Deposition of glycosaminoglycan's in intracellular spaces

Depending on the location of the functional defect we describe:

Primary disease = thyroid failure = low T3 and T4 production

Secondary disease = pituitary failure = low TSH production

Tertiary disease – hypothalamus failure = low TRH production

Peripheral disease = thyroid hormones receptor resistance

Primary form of the disease represent 95% of all cases of hypothyroidism, due to different thyroid diseases:

- Autoimmune thyroid disease
  - With goiter = asymptomatic
  - Without goiter = atrophic – end stage disease
  - With goiter = Hashimoto
  - Neonatal = transplacental inhibitory TRAB passage
- Iodide deficiency
- Sub acute thyroiditis
- Inborn errors of thyroid hormones
- Iatrogenic
  - Post RAIU in diffuse HT
  - Postsurgery
  - Drugs: Amiodarone, lithium, INF α
- Iodide exposure: kelp, radiocontrast agents, Amiodarone

Each type of thyroid disease will alter thyroid hormones production or release by different mechanism listed in the following Table:

TABLE XXVI. MECHANISM OF PRIMARY HYPOTHYROIDISM

Thyroid disease	Observed m**echanism**
Autoimmune disease	Blocking Ab: aTPO = no organification, linkage, MIT/DIT aTG = altered substrate for thyroid hormones synthesis
Iodine deficiency	< 50 mcg/day = inability to secrete T3, T4
Sub acute thyroiditis	Late phase of disease = remnant post aggression phase
Inborn errors	Impaired NIS activity Deficient TPO = no MIT/DIT Impaired coupling = no T3, T4 Absence of deiodinaze = no peripheral T3 Excessive T3, T4 inactivation
Iodine excess	No escape from Wolff Chaikoff effect
Iatrogenic	surgical/radioiod destruction of follicular cells lithium – block TH synthesis Amiodarone/IFN = autoimmune disease

Secondary hypothyroidism is seen in different pituitary lesions:

- Tumors, infiltration, surgery, ablative therapy, autoimmune, apoplexy, traumatism

I can be with isolated or associated pituitary hormones insufficiencies, generally TSH producing acidophilic cells have a moderate resilience to trauma. In case of trauma or tumor, the order of hormone insufficiencies is the following: GH ➔LH/FSH ➔TSH ➔ACTH ➔PRL

Tertiary hypothyroidism is a rare disease, secondary to hypothalamic dysfunction.

According to the moment of onset of hypothyroidism we have neonatal hypothyroidism, juvenile hypothyroidism and adult onset hypothyroidism.

The important of thyroid hormone in fetal development is well known. What is to mention is that the fetal thyroid is full functional starting week 20 of gestation, till this period, the thyroid, even in present from the anatomical point of view is nonfunctional. The lack of thyroid hormones will affect de neural development with important impairment of the intelligence of the newborn. The more severe the thyroid hormone deficiency during intra natal phase, the more severe the clinical picture at birth.

Clinical signs and symptoms

Newborn hypothyroidism = neonatal cretinism can be seen due to:

- Iodine deficiency
- Undescendent thyroid = ectopic gland with poor function
- TSH R blocking AB (trans placental passage)
- Inherited TH alteration
- Exposure to iodide, antithyroid drugs, RAIUS during pregnancy, insufficiency supplemental therapy in hypothyroid mothers

Presentation at birth:

- Respiratory difficulty
- Cyanosis
- Jaundice
- Poor feeding
- Hoarse cry
- Umbilical hernia
- Marker retarded bone maturation = absence of proximal tibia epiphysis + distal femoral epiphysis

Because of the severity of the disease the screening for neonatal hypothyroidism is made in the first 2 or 3 days after birth, when every increased TSH value higher than 10 mUI/L should be evaluated carefully.

If untreated hypothyroidism is inducing on the long run:

- Important growth deficiency
- Intellectual deficiency ..... cretinism
- Delayed puberty

The later the supplemental therapy tis started, the smaller the benefits.

Childhood hypothyroidism is characterized with normal development up to the moment of onset of hypothyroidism:

- Retarded growth
- Short stature
- Choking episode
- Dry, brittle hair
- Lack of muscle tome (floppy aspect)
- Low hairline
- Sleepiness
- Sluggishness
- Short legs + arms
- Declining school performance with altered intelligence, depending of the severity of hypothyroidism.

Also in this case, the later the introduction of supplemental treatment, the more sever and irreversible symptoms.

Hypothyroidism in adults

The main symptoms are presented in the TABLE XVII

TABLE XXVII. CARDINAL SYMPTOMS OF ADULT ONSET HYPOTHYROIDISM

EUTHYROIDISM	HYPOTHYROIDISM
↑Inotropism, ↑Cardiac output ↑Chronotropism	Bradycardia, decreased BP, cardiac insufficiency
↑ Respiratory muscle function	Hypoventilation
↑Erythropoietin /erythropoiesis	Anaemia, dizziness
↑ Gut motility	Slow bowel transit, constipation
Renal	↓ RFG: altered excretion of water load
Bone turnover	-
Muscle contraction/relaxation Emotional balance	Sluggishness Depression
Normal function of GhRH, GCS metabolism	Hypogonadism, hyperPRL, precocious puberty, infertility
Glycaemic metabolism	Hypoglycaemia
Lipidic metabolism	Dyslipidaemia
Skin	Brittle nails, dehydrated skin/nails/hair
Basal metabolism	Decreased, intolerance to cold

- **Cardiac clinical picture**
  - Impaired ventricular contraction
  - Bradycardia
  - Diminished cardiac output
  - EKG = low voltage QRS, P and T waves
  - Cardiac enlargement = myofibrillary swelling
  - Pericardial effusion
  - Increased CAD = ↑LDLC, lipoprotein A, Homocystein
  - May “protect” the angina pectoris !!! when supplemental therapy is introduced it will increase the oxygen needs to the normal, with increased risk of angina pectoris development.
- **Anemia**
  - Impaired Haemoglobin synthesis
  - Iron deficiency (↑losses, ↓intestinal absorption)
  - Folic acid deficiency (↓intestinal absorption)
  - Pernicious anaemia (cluster autoimmune disease)

From the degree of clinical symptoms we can see:

Subclinical disease	**Clinical disease**
• Minimum symptoms • Increased TSH • Normal FT3,FT4 • Atherogenetic risk • Procreation risk • Treatment in all situations except old, cardiac patients • !!!! Pregnant women	• Typical symptoms • Increased TSH • Decreased FT3, FT4 • Multiple complications • Procreation risk • Treatment - universally • Special rules for elderly/pregnant women

Diagnostic

1. Hormonal evaluation: TSH + FT3 and FT4

Always measurement of free fraction, independent of Tiroglobulin levels

Always measure together at least TSH + FT4

Primary hypothyroidism
↑ TSH + ↓ FT4/FT3

Secondary + Tertiary hypothyroidism
↓ TSH + ↓ FT4/FT3

2. Immunological evaluation : anti thyroid antibodies
   Present = autoimmune thyroid disease
   Absent = all non autoimmune diseases

3. Associated complication
a) Total blood count: ↓Hematocrit, ↓Hemoglobin
b) EKG: bradycardia, delayed depolarisation, low voltage aspect

4. Morphologic evaluation – ultrasound evaluation
- IDD = diffuse/nodular disease
- AIT = normal, increased (Hashimoto AIT), decreased (atrophy)
- With or without nodular lesions
- Surgical intervention: partial/total lobectomy/subtotal/ total thyroidectomy
- Vascularisation
  - Decreased in atrophic thyroid
  - Increased (due to ↑ TSH) in goiters
  - Normal – in treated cases

5. Morphofunctional evaluation = of NO USE in any case with hypothyroidism

6. Dynamic tests
   - Primary disease = No response to TRH test (altered peripheral synthesis capacity)
   - Secondary disease = No response to TRH test (altered hypophysis transmission via TSH)
   - Tertiary disease = Positive response to TRH test

Treatment

Regardless the etiology of hypothyroidism, or the moment of the diagnostic of hypothyroidism, the only medication used is supplemental treatment with synthesis analogues of thyroid hormones.

Usually tetraiodithyronine are used, limited cases need combined tetraiodothyronine plus triiodothyronine treatment.

The treatment onset is gradually, with slow onset up to the final needed dose. The thyroid hormone need is dependent on the degree of deficiency but also on the needs of different patient categories higher in children than in adolescents, lower in adults with the lowest needs in elderly.

TABLE XXVIII. MEAN LT4 NEEDS FOR DIFFERENT AGE GROUPS

Age	Lt4 doze (μg/kg/d)
0 – 6 mo	**10-15**
7 – 11 mo	**6-8**
1-5 y	**5-6**
6-10 y	**4-5**
11-20 y	**1-3**
Adult	**1-2**

Because, at the time of diagnostic, the real moment of onset of the disease is unknown, and because normalization of thyroid hormone level will increased the metabolic processes, the introduction of supplemental therapy is made slowly, with progressive increment of the dose up to the total needed dose: 12.5 mcg every 2-7 weeks, dependent on the age and severity of the hypothyroidism. Oral administration of T4 preparation is mostly used, using a unique morning administration, ideally between 06.00-08.00 AM, at least half an hour before any food intake, and at least 2-hour difference from any calcium preparation.

Caution regarding gastric absorption should be in case of associated treatment/diet with:

- Soy products
- Aluminium hydroxide antacids
- Bile acid resin: colestyramine/colestipol
- Sucralfat
- Iron compound

When a safe 4 hour interval should be used.

Combined T3 + t4 preparation are used in cases with difficult to balance cases, when the patient has altered capacity of synthetizing T3 out of used T4.

T3 only preparations with parenteral administration are used in myxedema coma where quick increase of the thyroid hormone strode is imperious needed.

Chronic use od estrogen (oral contraceptive treatment or supplemental therapy) or Carbamazepin increase the thyroid hormone needs.

Treatment follow up = is easy to be done by:

- Clinical evaluation – disappearance of hypothyroidism signs
- Hormonal evaluation:
    - In primary disease = **normal TSH < 4 mUI/L + normal FT4**
    - In secondary disease = normal FT4 , no evaluation of TSH
    - In tertiary disease = normal FT4 , no evaluation of TSH
    - !!! TSH = needs at least 4-5 weeks to change
    - !!! FT4 = changes in only a few days

  how often?
    - Every 4-6 months
    - Monthly in pregnant women
    - On demand in case of + symptoms

Special situations

1. <u>Myxedema coma</u>

- End stage of untreated hypothyroidism
- **? Winter** (increased needs) **older women**, with associated pulmonary + vascular disease
- Mortality rate $\approx 50\%$
- Progressive weakness/stupor/hypothermia (24°/hypoventilation/hypoglycaemia/hyponatremia/shock/death
- Gradual onset of lethargy ➔stupor ➔coma
- Yellowish skin, puffy eyes, hoarse voice, large tongue, thin hair, ileus, slow reflexes
- Seizures, bleeding, hypocalcaemia.
- Pathophysiology: CO_2 retention + hypoxia; Fluid, electrolytes imbalance; Hypothermia
- Precipitating factors: Heart failure; Pneumonia; Administration of sedatives/narcotics; Adrenal insufficiency

Treatment:

Emergency = Intensive Care Unit

- Parenteral T4 administration (impaired gastric absorption)
- 300 – 400 μg T4
- Additional Parenteral T3 preparations + 5 μg every 6 hours

Co administration of glucocorticoids (prophylaxis of associated GCR insufficiency)

- HHC 100 mg, + 50 mg every 6 hours = 300 mg 1st day
- HHC 50 mg every 6 hours 200 mg 2nd + 3rd day

!!! Cardiac support – angina pectoris precipitation (rebalance the real O2 needs of the body)

2. Hypothyroidism and heart disease

- Supplemental therapy can bring to light subclinical underlying cardiac disease
- Cardiac symptoms + sufficient LT4 treatment need cardiologic revaluation + active treatment
- Safety supplemental doses = lower doses than for conventional supplemental treatment = follow up TSH = 5-7 mUI/L

3. Neuropsychiatric disease

- Frequent associated with depression
- Rarely: confusion, paranoid thoughts, maniac (myxedema madness)
- Screening for thyroid disorders in psychiatric patients
- Excellent response to T3/T4 ± psychopharmacologic agents

4. Hypothyroidism and pregnancy Urgently to be addressed and treated

FETAL/NEONATE RISK

- *Altered cognition of the fetus = decreased IQ (6-8 Units) ➔ congenital cretinism*
- *SGA (small for gestational age)*
- *Respiratory neonate insufficiency*

MATERNAL RISK

- ↑ *frequency of spontaneous abortion*
- *Prematurity risk (5%)*
- *? Preeclampsia*
- *Anaemia*
- *Postpartum haemorrhage*

- Supplemental therapy of the hypothyroid mother will sustain also the fetus
- Only T4 preparation
- Special TSH target:
    - < 2.5 UI/L 1st trimester
    - < 3 UI/L in 2nd + 3rd trimester
    - < 2-2.5 UI/L before FIV procedures
- Monthly follow up: TSH, FT3, FT4 = normal range
- Permanent dose adjustment
- !!! Thyroid ill mother with TSH 2.5-4 UI/L need supplementary T4 doses in pregnancy compared with nonpregnant state
- Breastfeeding is allowed

Adverse effects of replacement therapy

◆ T4

- No reported allergies to T4 (only excipients)
- AE only in cases of over dosage = partial thyrotoxicosis
- Symptoms disappear after 3 days without treatment

◆ T3

- More active agent
- No administration in elderly
- Limited administration in cardiac patients
- No use in pregnancy (short T1/2, risk of SGA)
- Selected cases: impaired peripheral/central T4➔ T3 conversion

III.3.3. THYROIDITIS

There major forms of thyroiditis are:

Acute, sub acute and chronic forms, with postpartum thyroiditis, silent/painless thyroiditis and iodine induce thyroiditis variants for cornic thyroiditis.

Acute thyroiditis is an acute infection, which frequently evolves with abscess. Is a very rare form of thyroiditis, that is favored by:

- contextual factors:

    ? Septicaemia/acute infective endocarditis

    ? Extension of pharyngeal infection

    ?? HIV patients

- in special cases of:

    ✓ Piriform sinus fistulae

    ✓ Pharyngeal space infections

    ✓ Persistent Thyroglossal remnants

    ✓ Thyroid surgery wound infection

    ✓ Rare complication of FNAB

- 68% bacterial infections: S. aureus, S. pyogenes
- 15% fungal infections
- 9% Mycobacterium

Suggestive clinical signs are:

- Thyroid pain/tenderness
- Fever
- Dysphagia
- Dysphonia
- Warm, tender, enlarged thyroid

There should be always awareness of associated preexisting situations, favored by a systemic infection, which associated to the mentioned clinical signs should suggest acute thyroiditis.

Diagnostic:

1. hormonal evaluation – normal thyroid function
2. immunological evaluation-negative
3. additional evaluation – positive inflammatory changes
4. FNA- only needed to drain abscess and obtain culture
5. Morphological evaluation: thyroid ultrasound = abscess formation – pseudonodular lesion, solid appearance, markedly inhomogeneous, avascular, increased vascularization in the healthy surrounding tissue.
6. Morphofunctional evaluation – scintigraphy – normal uptake, in abscess formation – the region of abscess appears as a cold nodule

Treatment

1. IV Antibiotics: Gentamycin/Rochephin/Nafcillin
2. Search for fistulae
3. With correct treatment, recovery is complete
4. High mortality without treatment

Sub acute thyroiditis

- is an acute inflammatory disorder, secondary to a viral infection
- secondary to the inflammatory disorder there is limited destruction of the thyroid parenchyma due to phagocytic cells and giant cells.
- The disease is more frequent in female, up to 5 time more frequent
- With seasonal variations, in accordance to seasonal respiratory infections
- Age 20-60 years of age

Clinical aspects:

I Prodromal phase = myalgias, fever, pharyngitis

II Free of disease period = 1-14 days

III Acute lesion phase – thyrotoxic phase

- Fever, severe neck pain
  - Aggravated by swallowing/head turning
  - Radiates to the ear/jaw/occiput
  - Changes from one side to the other side
- Dysphagia, odynophagia, hoarseness
- Thyroid enlarged, firm, nodular, tender, asymmetrical
- Duration of 2-3 weeks

- Rare cases – relapse after 1-2 weeks free of symptoms
- Hyperthyroidism due to RELEASE of thyroid hormones from the follicular thyroid cells in the inflammatory process

IV Euthyroid phase

- Short auto limited phase = transient phase between the thyrotoxic phase to the hypothyroid phase, after the washout of the released thyroid hormones.

V Hypothyroid phase

- Recovery phase - hypothyroidism phase
- Hypothyroidism phase
  - Severity depending on the remnant unaffected thyroid parenchyma
  - Duration of up to several months
  - Recovery phase – the increase in TSH is needed for recovery/ growing of the previous attacked thyroid parenchyma
  - In some cases complete cure of the disease is not possible

Diagnostic:

1. hormonal evaluation – dependent on the phase of the disease
   - hyperthyroidism: ↓TSH + ↑T4 > T3,
   - hypothyroidism ↑TSH + n, ↓T3, T4
2. immunological evaluation-negative during the whole evolution of the disease
3. additional evaluation – positive inflammatory changes:

   especially in the acute, aggression phase:
   - ESR > 100 mm/h
   - Anaemia
   - + Inflammation parameters

   ↑↑↑ Tiroglobulin DESTRUCTION
4. Morphological evaluation: thyroid ultrasound = patchy aspect
5. Morph functional evaluation – scintigraphy

   Lesional phase = no RAIU = no uptake because of the diffuse destruction of the thyroid parenchyma

   Recovery phase = present RAIU = reappearance of thyroid functional activity

Differential diagnosis

1. Viral infection
2. Other forms of hyperthyroidism

Prognosis

- Resolves completely in weeks-months
- 10% - permanent hypothyroidism

Treatment

1. Non Steroidal Anti-inflammatory Drugs and salicylates, in the majority of cases
2. Oral steroids in severe cases: 40-60 mg, tapered, 6-8 weeks, severe cases
3. Beta-blockers for hyperthyroidism symptoms relief
4. Antithyroid medication – NOT RECOMMENDED (there is no effective hyper production of thyroid hormones)
5. TSH + FT4 monitoring every 2-4 weeks
6. Symptoms can recur requiring repeat treatment
7. Levothyroxine replacement in the hypothyroid phase LOW doses = **TSH mediated recovery**

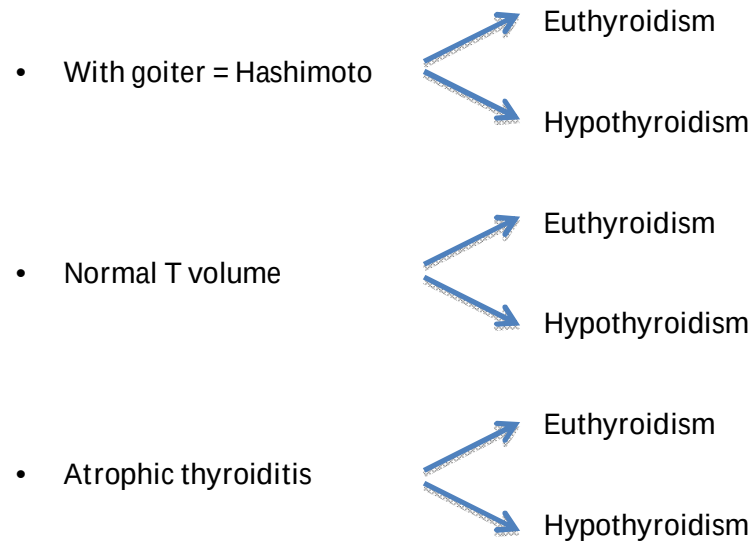
Chronic thyroiditis

- Most common cause of goiter and hypothyroidism
- Is an autoimmune disease, induced by overproduction of antithyroid antibodies; the most frequent being anti thyroglobulin antibodies and anti thyroperoxidase antibodies/
- Lymphocytes sensitized to thyroidal antigens
- Antithyroid Ab: TG Ab, TPO Ab, TSH-R-blocking
- Hypothyroidism lifelong

Predisposing factors:

- Autoimmune disease (familial cluster): HLA –B8 (atrophic), HLA-DR5 (Hashimoto)
- Post pubertal/premenopausal/postpartum = female sex hormones are involved in the pathogenesis
- High iodine intake = highly iodinated TG = more immunogenic
- Therapeutic lithium = interfere the suppressor cell function = precipitate AIT

There are different forms of chronic, autoimmune thyroid disease:



As mentioned in the previous chapter, at the beginning of the disease, or, very rare, in postpartum period, there can be a short, auto limited thyrotoxic phase, due the inflammation and destruction of the thyroid structures in contact to antithyroid antibodies.

Clinical picture can be as following:

- Functional point of view
  - = no signs and symptoms in euthyroid cases (diagnosed by chance due to active screening autoimmune or ultrasound evaluation)
  - = typical clinical picture of hypothyroidism
- Mechanical point of view = only in cases with enlarged goiters
- Combination of functional + mechanical clinical picture

A lot of cases are discovered incidentally, in absence of any typical symptoms.

The positive diagnostic is made following the same general steps of positive diagnostic:

- Hormonal evaluation: euthyroidism/hypothyroidism
- Immunological evaluation: ATPO Ab, ATg Ab, TRAB
  - ↑↑↑↑
  - in order to be diagnostic, the values have to be significantly increased, at least 2-3 time higher than the upper normal value
  - the Diagnostic value no prognostic value
- Associated complication: secondary to hypothyroidism
  - Morphologic: Ultrasound evaluation

  - Volume = decreased/normal/increased

  - Hypoecogeneity = sign of autoimmune process

  - Exclusion of other forms thyroiditis: sub acute/acute/ Amiodarone induced

Complication

1. Progressive hypothyroidism
2. Frequently subclinical hypothyroidism (increased TSH values with normal Ft3 and FT4 values): risk for atherogenic disease, renal impairment, conception risk

Treatment

- The presence of ATPO Ab alone does not need supplemental treatment
- Subclinical hypothyroidism has to be treated in the circumstances:
  - Mild symptoms
  - Dyslipidaemia
  - Positive ATPO Ab which suggest the higher change for progression to overt hypothyroidism
  - Renal impairment
  - Associated thyroid nodules

Riedel's thyroiditis

Is a rare form of chronic thyroiditis, mostly seen in middle aged women, characterized by an important goiter, with compressive signs and symptoms due to the marked fibrosis present at the thyroid level, mostly without functional impairment. The clinical landmark is considered to be the "woody" consistency, which often is associated with other focal sclerosis lesions: retroperitoneal, mediastinal, retroorbital, sclerosing cholangitis fibrosis.

Diagnosis

- Thyroid Ab are present in 2/3 cases
- Painless goiter "woody"
- Open biopsy often needed to diagnose
- Associated focal sclerosis sd. (retroperitoneal, mediastinal, retroorbital, sclerosing cholangitis)

Treatment options are limited to resection for compressive symptoms, if needed chemotherapy with Antiproliferative agents: Tamoxifen, Methotrexate, steroids, with use of thyroid hormones only in cases with hypothyroidism.

Drug induces thyroiditis

Destruction of the thyroid can be induced by the chronic use of the following drugs:

- Amiodarone
- Il-2, interferon alpha
- Lithium
- GnRh agonist Leuprolide
- Sunitinib = multitargeting kinase inhibitor

The lesion type is an inflammatory Lesional disease, with secondary hypothyroidism. Previous autoimmune thyroid disease can favor the appearance of chemical induced hypothyroidism, but not necessarily. Because of no predictive model for at risk patients, all cases use long term treatment with the previous mentioned medication should be screened periodically, ideally every 3 to 6 months for the function of thyroid.

In all cases, supplemental treatment for hypothyroidism should be offered for the patients. After stopping the aggressive medication, thyroid function should be periodically also screened, because there is a partial process of thyroid recovery, with decrease of the needed supplemental doses.

A special remark about Amiodarone, which, secondary to it's high amount of Iodine can induce 2 total different types of thyroid diseases, as shown in Table XIX.

TABLE XXIX. SPECTRUM OF THYROID DISEASE INDUCE BY AMIODARONE

TYPE I	TYPE II
Iodine induced HT	Amiodarone induces thyroiditis
Latent/pre-existing thyroid disease Graves disease/nodular goiter	Normal pre-existing thyroid
↑Synthesis ↑Release	Thyrotoxic phases: Destructive inflammation = AIT Temporarily ↑Release Hypothyroid phase:
F:M = 1.5:1	F:M = 1:3
Acute cardiac symptoms	Acute cardiac symptoms
Increased vascularisation Other US changes	Decreased/absent vascularisation No US pathology
Antithyroid drugs + beta adrenergic blockade	GCS therapy NO antithyroid drug therapy
Long standing hyperthyroidism	Short duration hyperthyroidism

III.3.4. IODINE DEFICIENCY DISORDERS (IDD)

The spectrum of iodine deficiency disorders is very vast. Comprising different presented entities.

The important impact of iodine of thyroid function and morphology, is due to the dependence of the thyroid hormone synthesis and secretion on the exogenous iodine intake. There is no natural endogen iodine production, only conservation of the preexisting deposits.

As already mentioned, the current WHO recommendations for sufficient daily iodine intake for normal thyroid hormone secretion are:

- Adults 150 mcg iodine intake (food+ water)
- Pregnancy 200 mcg iodine
- Lactating 200 mcg iodine
- Children 50-250 mcg iodine

A daily intake lower than 50 mcg/day induces the incapacity of thyroid gland of sustained thyroid hormone synthesis and secretion.

Sources of iodine in areas where is no iodine added to the water supply or food products, the primary sources of dietary iodine are saltwater fish, seaweed, and trace amounts in grains. The upper limit of safe daily iodine intake is 1100 mcg/day for adults. Other major iodine sources are egg yolks, milk, milk products because of iodophore cleaners and supplemental dietary iodine to prevent hoof rot.

Mechanism of IDD:

- When dietary iodine is inadequate for thyroid hormone synthesis, the serum T3 level initially falls and a number od processes ensue to restore adequate thyroid hormone production.
- The pituitary gland senses low levels of circulating T4, will increase TSH in order to reestablish the normal thyroid function.
- TSH will stimulate the iodine intake and functional activity of follicular thyroid cells.
- Also there is a shift in the thyroid hormone production, with a preferential T3 secretion, because T3 is 20-100 times more biologically active than T4 and requires less iodine atoms for biosynthesis. The increase in T3 production is the first adaptive mechanism that appears in iodine deficiency.
- The 2nd adaptive mechanism is goiter development. The goiter is initially diffuse, but eventually becomes nodular. Some nodules may become autonomous and secrete thyroid hormone regardless of the TSH level.
- When iodine deficiency is more severe or longstanding, thyroid hormone falls and hypothyroidism appears.

Mild to moderate IDD can cause thyroid dysfunction abnormalities and endemic goiter. In areas with severe endemic IDD the rates of miscarriage and infant mortality are increased. Cretinism is rare, but populations with severe iodine deficiency is prevalent children are at risk for reduced intelligence and mental retardation. In fact, iodine deficiency is the leading cause of preventable mental retardation worldwide.

Where iodine deficiency causes an increase risk for thyroid cancer is not clear, but higher rate of more aggressive thyroid cancers (follicular carcinoma) and an increase thyroid cancer mortality rate are found in areas where iodine deficiency is endemic. Also there is a shift, after water iodination, in differentiated thyroid cancer spectrum, with a higher proportion of papillary thyroid carcinoma.

Clinical picture

The most frequent clinical finding is represented by goiter: children diffuse goiter, adult diffuse and nodular goiter. Compression symptoms are seen, according to the volume of goiter and localization of the nodules.

Hypothyroidism with typical signs and symptoms is also present.

Cretinism, as presented before, is the most severe manifestation of IDD, and appears in untreated congenital and neonatal hypothyroidism. Cretinism can be divided in neurological and myxedematous subtypes.

Neurological cretinism (mother hypothyroidism during pregnancy = mental retardation, abnormal gait, deaf-mutism, no goiter or hypothyroidism in the child

Myxedematous cretinism (hypothyroidism in fetus during late pregnancy/ neonatal period) = mental retardation, short stature, goiter, hypothyroidism

Reduction of IQ has been noted in affected youth from regions of severe and mild iodine deficiency. Concomitant deficiency of Selenium or vitamin A will exaggerate this deficiency. If untreated, IDD in children will associate all the complications of untreated hypothyroidism, with different degree and severity of clinical picture according to the severity of hypothyroidism, moment of onset and length un untreated period.

If IDD appears after the childhood period, the possible clinical picture is represented by:

- Diffuse goiter = increased in volume goiter, higher than the validated thyroid volumes: 200 ml in males and 16 ml in females
- Nodular goiter = uninodular/multinodular lesion
- Different degrees of hypothyroidism
- Combination of goiter and hypothyroidism
- Exceptional hyperthyroidism (in cases with long standing nodular lesion, moving from and iodine deficient area to an iodine replete area).

Summarizing, we can conclude that the clinical spectrum of IDD is vast, as seen in TABLE XX.

TABLE XXX. THE SPECTRUM OF IDD

Life period	Pathology
Fetus	Spontaneous abortion Death "in utero" Congenital malformations Increased perinatal mortality Cretinism
Neonate	Goiter Neonatal hypothyroidism Mental retardation Increased sensitivity to ionized radiation
Children/adolescents	Goiter Subclinical hypothyroidism Mental deficit Decreased growth Increased sensitivity to ionized radiation
Adults	Endemic goiter Hypothyroidism Increased sensitivity to ionized radiation

In case of clinical suspicion, the diagnostic is made with the following evaluations:

1. hormonal evaluation – dependent on the phase of the disease
    a. euthyroidism : normal TSH, Ft3, FT4
    b. hypothyroidism ↑TSH + n, ↓T3, T4
    c. very rare: hyperthyroidism: ↓TSH + preferential FT3 secretion = (↑T4 < T3)

2. immunological evaluation-negative during the whole evolution of the disease

3. Additional evaluation – possible metabolic changes due to altered thyroid function

4. Morphological evaluation: thyroid ultrasound =
    a. increased volume,
    b. with or without nodules,
    c. increased vascularization (in cases with increased TSH),
    d. hypoecogeneity = suggestive for iodine deficiency

5. Morph functional evaluation – scintigraphy
    a. Reversed just the cases with suppressed TSH
    b. Not indicated in euthyroid or hypothyroid cases, regardless the aspect of thyroid on ultrasound

6. Confirmation of iodine deficiency:
    a. Ioduria - evaluation of urinary iodine excretion
    90% of iodine content absorbed is cleared through the urine. The measurement of iodine is considered a way to asses recent iodine intake, although the concentration may vary from day to day and even during the same day. This is why 24 hours sample are used for research purposes. The screening purposes morning sample ioduria are preferred.
    - urinary iodine threshold of 100 mcg Iodine/L urine is considered to define iodine deficiency intake, because the iodine excretion rate correspond to an daily intake of 150 mg Iodine.

Differential diagnostic of IDD:
- all causes of goiter
- all causes of hypothyroidism
- iatrogenic thyroid dysfunction

Treatment
1. Iodine supplementation:
    - Universal salt iodination: bread, milk products
    - Kalium iodide – orally daily 100 – 200 mcg/zi

2. Hypothyroidism treatment – supplemental treatment

3. Surgical treatment in case of:
    a. Compressive treatment
    b. Autonomy:
    c. Malignancy suspicion

    The surgical approach is:

Lobectomy	**Total thyroidectomy**
+ uninodular confirmed benign lesion	+ bilateral disease
+ absence of any increased risk indicators	+multinodular goiter
	+ huge diffuse goiter

4. Radioiodine is reserved to selected cases with functional autonomy (TSH < 0.1 mUI/l)

Summarizing, in case of a nodule with autonomous function we can rely of surgery or radioactive iodine treatment, as following:

SURGERY	RAIU
Younger patients	Adult patient
Children/adolescents	Nodule < 5 cm
Large nodules > 5 cm	Associated surgical risk
Compressive symptoms	No compressive symptoms

III.3.5. NODULAR GOITER – THYROID CANCER

When we consider nodular disease there are some general **epidemiological data:**

- 3-5 % of the general population have palpable thyroid nodules
- 50% of the general population had ultrasound detectable nodules
- Cancer is detected in 4.5-23.4% of thyroid surgeries
- 10% of thyroid cancer patients are under 21 years
- Thyroid cancer will be the 3rd cancer in females starting 2019
- Correct identification of cancer lesions is still a challenge for the clinicians

As in the case of diffuse goiter, the **etiopathogeny** of disease comprises one of the following:

- IDD
- Hashimoto autoimmune disease
- Dyshormonogenesis
- Somatic gene mutation = isolated thyroidal cell proliferation
  - Activating mutation of the Gs protein
  - Thyroid cell proliferation

Considering thyroid cancer, there are **different forms**:

- Differentiated thyroid cancer form, derived form follicular cells, sensitive to TSH action and having iodine concentration capacity
- Undifferentiated thyroid cancer, derived form follicular cells, but with lost of any normal follicular cell behavior: papillary thyroid cancer and follicular thyroid cancer
- Medullary thyroid carcinoma, derived from parafollicular C cells, unrelated to differentiated thyroid carcinomas.

Clinical picture:

1. Compression signs:
   - Dysphagia = oesophagus compression
   - Dysphonia = laryngeal nerve compression
   - Inspiratory dyspnoea = tracheae compression
   - Claude Bernard Horner sd: ptosis, miosis, enophtalmous = cranial nerves
   - Pemberton sign: facial flushing + cervical veins dilatation with arm lifting = jugular vein drainage compression
   - Collateral venous circulation = jugular vein drainage compression
2. Thyroid dysfunction: signs and symptoms, with intensity proportional to the hormonal imbalance.
3. Signs suggestive for malignancy:
   - Vocal cord paralysis
   - Lateral lymphadenopathy
   - Fixation of the nodule to surrounding tissues
   - Firmness of palpation
   - Nodules> 4 cm (19.3% risk of malignancy)
   - Any nodule with rapid growth
   - Acute onset of hoarseness

When considering malignancy risk, there are suggestive events/ symptoms for neoplastic disease. **Anamnestic risk factors** suggestive for malignancy are:

- History of childhood head/neck irradiation
- Total body irradiation = bone marrow transplantation
- Family history of TC
- Family history of: Cowden's sd, MEN 2, Werner sd, familial polyposis
- Exposure to ionizing radiation in childhood/adolescence

The current **diagnostic approach** is the following:

1. Morphological evaluation = thyroid ultrasound
2. Associated imagistic evaluation = in case of compression
3. Fine needle biopsy in selected cases
4. Thyroid function evaluation

Ultrasound evaluation:

1. First line screening imaging tool
2. Selecting the nodules that need further evaluations = risk stratification
3. Guiding the FNAB
4. Monitoring lymph nodes
5. Operator-dependent
6. Evaluation in any thyroid nodule diagnose at palpation, CT, RMN or PET CT evaluation.

According to the presence of absences of the following characteristics, the thyroid nodules are evaluated as **low, intermediate or high risk**:

- Taller than wide
- Ill defined margins/infiltrative/spiculated
- Hypo echogenicity
- Micro/macro calcifications
- Absent halo
- Tortuous/Increased intranodular flow
- Sub capsular localization
- Heterogeneous pattern: inhomogeneity

The higher number of the risk characteristics, the higher the risk of malignancy.

There is always a referral to fine needle biopsy, according to the risk category:

- for diameter higher than 5-10 mm in high risk categories
- for diameter higher than 10-15 mm in intermediate risk categories
- for diameter higher than 15 – 20 mm in low risk categories

Fine needle aspiration is always UD guided, with 23-26 G needle. The cytological evaluation is reported with the current available Bethesda reporting system:

- I = nondiagnostic
- II = benign
- III = follicular lesion/unclear cytology
- IV = follicular neoplasm
- V = suspect malignant
- VI = malignant

According to FNAB, respectively the probability of malignancy, there are the following indications:

- Benign cytology — no further immediate studies
  treatment if needed
- intermediate cytology

- nonsuspicious US findings = repeat FNA 12 m
- repeated nondiagnostic FNA = OBSERVATION
- surgery in case of:
  - suspicious US findings
  - 20% increase
  - + high risk factors
- Malignant cytology = SURGERY

Currently, the limitations of FNAB are:

1. Unable to distinguish follicular cancer form adenoma
2. Expert pathologist
3. Insufficient/indeterminate in 2-16% cases
4. Practitioner skills
5. Patient acceptance

Compression evaluation

= tracheal compression = cervical anteriorposterior X Ray evaluation
= thoracic computer tomography

= **esophagus compression** = gastroscopy

= **laryngeal nerve compression** = HNO evaluation

Treatment

1. SURGICAL TREATMENT is indicated in cases with:
    a. **Malignant cytology** = total thyroidectomy
    b. **Intermediate cytology**

        = total thyroidectomy positive for a mutation/+ sonographically suspicious/+ large (> 4 cm)/+ anamnestic risk factors

        = lobectomy in absence of any increased risk factors
    c. **Benign cytology**

        = lobectomy in cases with compression symptoms/ cosmetic reasons

        = total thyroidectomy in cases with bilateral localization
    d. **functional autonomy**

        = lobectomy in toxic adenoma

        = total thyroidectomy in multinodular autonomous goiter
2. ACTIVE FOLOW-UP = ULTRASOUND + FNAB EVALUATION

    = High suspicious US =repeat FNA in 12 months

    = Growth: 2mm in 2 dimensions = repeat FNA

    = Increase in volume 50% = repeat FNA

    = Intermediate suspicious US = repeat FNA in 24 months

    = Low suspicious US=just US follow up

    = Very low suspicious US=just US follow up
3. Radioactive iodine treatment
    a. In cases of thyroid cancer
    b. In cases with functional autonomy

Summarizing, in case of autonomous nodular goiter indications of surgery or radioactive iodine treatment, as following:

SURGERY	RAIU
Younger patients	Adult patient
Children/adolescents	Nodule < 5 cm
Large nodules > 5 cm	Associated surgical risk
Compressive symptoms	No compressive symptoms

IV. PARATHYROID

IV.1. CALCIU PHOSPHATE HOMEOSTASIS

Normally, the majority of the population has 4 parathyroids, present at the top and bottom of the posterior borders of the thyroid lobes, but 0.5 - 4% of the general populations have ectopic parathyroid, up to 8-9 in total.

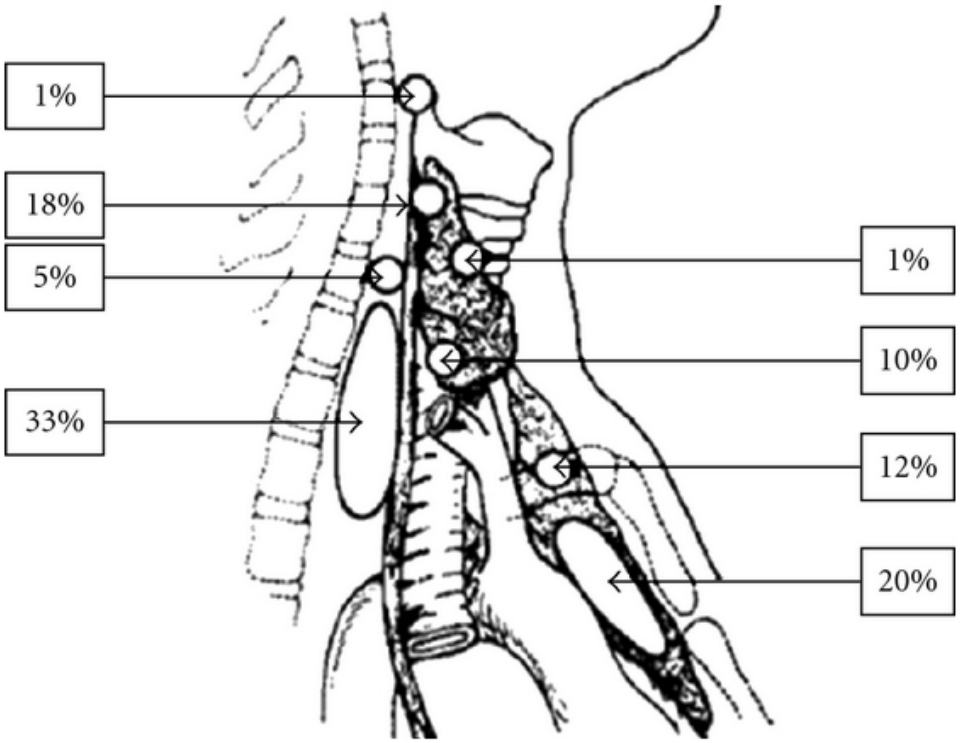


Fig. 18. Possible location of ectopic parathyroids

The superior parathyroids are most commonly located in the posterolateral aspect of the superior pole of the thyroid, at the cricothyroidal cartilage junction. They are usually found at 1 cm above the intersection of the inferior thyroid artery and the recurrent laryngeal nerve. The inferior parathyroids are more variable in location and are most commonly around the inferior thyroid poles.

The parathyroids secrete PTH, a 84 AA secreted in 6 to 7 pulses each hour. PTH is governing the calcium homeostasis.

The mean Calcium intake is around 1 gram per day. Less than 50% of the intake is absorbed at intestinal level, vitamin D dependent, with a constant intestinal loss, than can be around of 850 mg/day. The calcium in the body is organized in 2 pools or fractions:

- Readily exchangeable fraction, representing less than 1% of the total amount, a permanent balance between Ca2+ in the ECF and bone
- Stable fraction, representing 99% of the total body calcium, influenced just by bone remodeling process: formation and resorption.

The other calcium excretion mechanism is at renal level, wit up to 99% reabsorption from the total filtrated Calcium, PTH dependent, with a minimal calcium urinary loss.

Renal reabsorption is active at the following sites:

- proximal tubule = passive reabsorption
- thick ascending limbs = active PTH and Calcitonin process
- distal tubule = active PTH dependent

PTH has the following effects:

- At bone level has different effects, according to the degree of stimulation
  - PTH acute increase will induce Calcium release from the exchangeable fraction
  - Persistence of increased PTH with continuum the calcium release, from the stable deposit, by bone resorption with concomitant calcium and phosphate release.
  - Low intermittent PTH secretion will induce osteoblast activation with bine formation
  - High continuum PTH secretion will induce stimulation and recruitment of osteoclast with bone resorption
- At intestinal level will indirect stimulate calcium, favoring vitamin D activation.
- Al renal level there are:
  - Direct PTH effects
    - Stimulation of 1 alpha hydroxylase, the final vitamin D activation
    - Sustains active calcium reabsorption at the level of thick ascending limbs and distal tubule.
    - Decreases phosphate reabsorption at proximal and distal level

The effects are mediated by PTH receptor, located at renal and bone level. The receptor is highly specific for PTH, but can be influenced by PTH relate protein, produced by several malignant tumors, like squamous cell carcinoma, breast, renal, melanoma, prostate, NET; secretin; VIP; ACTH

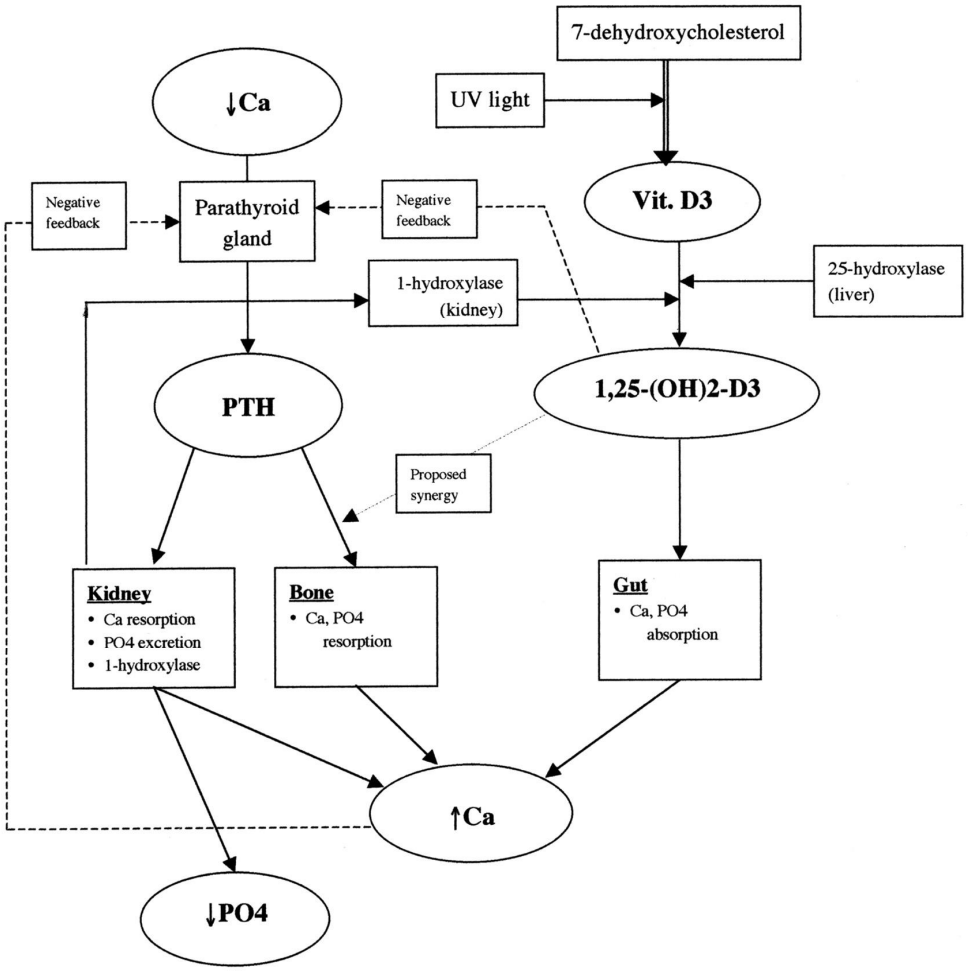


Figure 19. Calcium homeostasis

Regulation of the PTH secretion is dependent on the:

- Parathormone Calcium sensing receptor = the sensor plasmatic calcium plasmatic fluctuations.

Normally, the receptor is contracted and will restrain the PTH secretion.

Increase of Calcium will facilitate pre PTH degradation, will decrease of PTH release capacity.

Decrease of Calcium will relax the calcium sensing receptor, that will unrestraint the PTH secretion, with subsequent PTH secretion.

Calcium sensor, a G protein coupled receptor is present at the level of parathyroid chief cells, kidney tubule cells, and thyroid C cells and is responsible for the effects of calcium changes on PTH release.

Vitamin D has also to be considered in the discussion about calcium homeostasis.

There are 2 precursors for vitamin D:

- Ergocalciferol, present in different foods, worth to mention being:
    - o Enriched milk 100 UI in 240 ml
    - o Herring 680 UI in 100 gram
    - o Salmon with bone 624 UI in 100 gram
    - o Mackerel 360 UI in 100 gram
    - o Caned sardines 272 UI in 100 gram
    - o Swiss chees 44 UI in 100 gram
    - o Shiitake mushrooms 76 UI in 100 gram
- Cholecalciferol derived from a pro-vitamin D, a cholesterol derivate present in the skin, 7 dehydrocholesterol, which, under UV light will transform into cholecalciferol.
- Regardless of initial precursor, ergo- or cholecalciferol, both precursor will be activate at the liver level, to 25 hydroxy-vitamin D (1st hydroxylation in position 25), respectively at kidney level, conditioned by PTH, with the 2nd hydroxylation in position 1. At the same level, in conditions of high calcium, there will be a also a possible deactivation of vitamin D, with the2nd hydroxylation in position 24, with production of 24,25 dihydroxi-vitamin D, inactive product.

Biological effect of vitamin D are induced only by 1,25(OH)2 activated vitamin D form.

There are 2 major types of vitamin D effects:

- Classical effects
- Nonclassical effecs

The following effects considered classic, need the binding of vitamin D to its receptor, steroid class type and inducing:

1. increase calcium absorption at gut level, favored by hypocalcaemia and PTH
2. influence bone resorption and formation, with impairment in cases of vitamin D deficiency
3. facilities PTH mediated calcium reabsorption at renal level
4. normal vitamin D levels will decrease the synthesis and release of PTH al the level of parathyroid cells

Nonclassic vitamin D effects are very discussed effects currently, comprising:

- Modulating immune response: well described effects in autoimmune thyroid disease, multiple sclerosis evolution.
- Modulate reproduction influencing ovarian function, polycystic ovary appearance
- Cardiovascular function: deficiency will increase the cardiovascular and general mortality, due to secondary hyperparathyroidism
- Cell differentiation/proliferation: proved effects of vitamin D deficiency in treatment in favourable evolution of breast, colonic and prostate cancer.

Plasmatic measurement of hidroxyvitamin D level is the best method of assessment of vitamin D level in the entire body. There is still no consensus about the threshold defining vitamin D insufficient level:

Endocrine Society (2011)

– Deficiency 25 OH vitamin D < 10 ng/dL
– Insufficiency 25 OH vitamin D < 20 ng/dL
– Normal 25 OH vitamin D > 30 ng/dL

IOM (2010)

– Deficiency 25 OH vitamin D < 10 ng/dL
– Insufficiency 25 OH vitamin D < 20 ng/dL

In the presence of vitamin D insufficiency or deficiency the treatment is represented by replacement treatment with simple, inactivated precursors:

Active vitamin D preparations are reserve for cases with impaired renal activation, secondary to chronic renal disease.

- children = 2000 UI/day, 6-8 weeks
  = 50.000 UI/week 6 weeks
- adults = 6000 UI/day, 2 months
  = 50.000 UI/day, 3 times/week/1 month
  = 50.000 UI/week/ 3 months

Association of amtiepileptic medication, history of bariatric surgery, malabsorption sd or obsese adults nedd much higher supplemthal doses, up to 10.000 UI/day.

The usual 800-1200 UI/day is used only after achievement of normal values of vitamin D. Using these dosed before achievement of normal vitamin D levels, will be not enough to restore the normal levels.

Calcitonin is a 322 AA proteic hormone, produced by parafollicular C cells at thyroidal level, in any acute Calcium increase. Whenever there is a increase of Calcium, higher than 9 mg/dL will induce acute Calcitonin release, with:

- Decrease of bone resorption by altering osteoclast motility, differentiation and secretory activity,
- Increase of Calcium renal excretion, due to decrease of active renal tubular, at tick ascending limb level.
- The effects of calcitonin are limited to 1-2 days
- Calcitonin is an acute calcium regulatory hormone with no long effects

FGF 23 is a peptide produced by osteoblasts, and is responsible for maintaining the phosphate homeostasis by decreasing the activity of renal hydroxylase and phosphate resorption. FGF 23 is activated by normal levels of vitamin D and hyperphosphatemia.

All the above mentioned hormones are effective in every case of plasmatic Calcium changes, as seen in Picture 20.

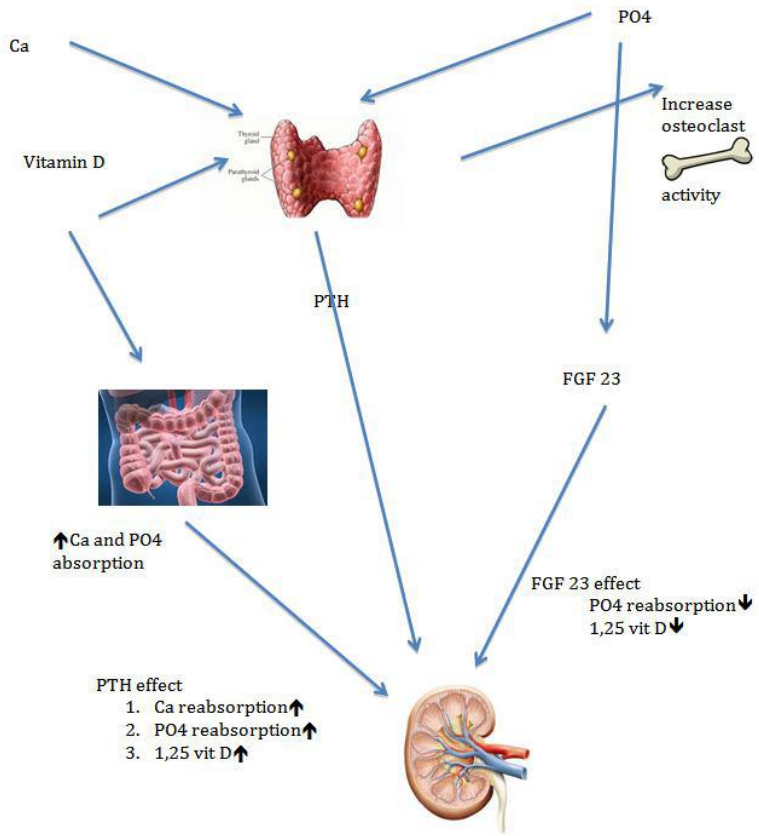


Figure 20. Calcium phosphate homeostasis

IV.2. HYPERPARATHYROIDISM

Hyperparathyroidism is considered any uncontrolled disproportionate and independent production of PTH with secondary alteration of calcium level.

There is primary form of disease due to parathyroid hyperplasia, adenoma or, rarely, carcinoma, secondary form, due to chronically altered calcium and/or phosphate level, an tertiary form of disease, the final proliferative stage of secondary form of the disease.

IV.2.1. Primary hyperparathyroidism

Etiopathogeny

A. Sporadic forms of disease

- ***Parathyroid adenoma: 85%***
  - *Muation of cellular DNA = survival/replication advantage*
    - 1p-pter 40% of adenomas
    - 6q 32% of adenomas
    - 11q 25% of adenomas
- ***Parathyroir hyperplasia: 15 %***

  - uknown cause

  - no familial clustering
- ***Parathyroid carcinoma: <1-2%***

  - CDC 73 mutation

B. Familial forms of disease:

Multiple Endocrine Neoplasia 1 = *inactivating mutation of MEN1* *11q13*

- **P**arathyroid hyperplasia95%
- **P**ituitary adenoma
- gastro**P**ancreatic tumors

MEN 2 = *RET protooncogen mutation* *10q 11.2*

- **P**arathyroid hyperplasia5-20%
- CMT
- Pheocromocytoma

MEN 4 = *CDKN1 Mutation 12p13*

- **P**arathyroid adenoma
- Pituitary adenoma
- Adrenal/renal/gonadal tumors

Hyperparathyroidism- Jaw Tumor Syndrome = *CDC 73 1q mutation*

- Parathyroid adenoma/Carcinoma
- Fibrous jaw tumor
- Wilm's tumor

Familial isolated hyperparathyroidism= MEN 1, CDC 73 CaSR mutation

- ? Subclinical form of MEN1/HPT-JT
- Unclear the isolated manifestation

Familial hypocalciuric hypercalcemia FHH= CaSR mutation

- Anomaly of the Calcium sensing receptor PTH suppression at higher Calcium levels

Neonatal sever hyperparathyroidism = CaSR 3q13 rA

- Complete loss of CASR, insuppressible PTH secretion due to complete loss of calcium sensing information

Regardless the form of hyperparathyroidism, due to insuppressible PTH levels, there will be long standing PTH induced effects in the target organs with:

- Increased bone resorption with calcium and phosphorus release in the blood
- Increased calcium uptake by intestinal mucosa
- Increased phosphate excretion at renal level
- Increased calcium reabsorption at renal level
- Increased vitamin D activation

All these effects will induce uncontrolled unsuppressible hypercalcemia with different degrees of hypophosphatemia.

The clinical picture of the disease is secondary to increased calcium levels, with organic and functional consequences, respectively bone demineralization.

The classic clinical picture, called "BONES STONES GROANS MOANS" because of typical bone, renal, digestive and mental signs, is seen in less than 1/3 of all hyperparathyroidism cases. The majority of cases are diagnosed almost asymptomatically, due to minimal bone demineralization.

Classical clinical signs:

- Renal
  - Polyuria = hypercalcemia + hypercalciuria 30%
  - Renal stone disease = hypercalciuria 45%
  - Renal colic = calcium precipitation 10%
- Gastrointestinal
  - Inapetence = due cu altered gastric secretion 30%
  - Nausea/vomiting = evolution of gastric ulcer 10%
  - Pain- evolutive of gastric ulcer 15%
  - Constipation = hypercalcemia 30%
  - Hyperacid gastric ulcer 5%
  - Acute pancreatitis = calcium precipitation 1%
- Cardiac
  - Bradicardia = hypercalcemia
  - Diastolic hypertension= increased peripheral resistance 50%
  - Short QT
  - Left ventricle hypertrophy
- Neuromuscular direct effect of hypercalciuria
  - Proximal myopathy
    15%
  - Muscular weakness
    10%
  - Fatigability 30%
- Psychological
  - Inability to focus 30%
  - Depression 30%
  - Cognition impairment 20%
- Non bone calcification in different visceral, vascular or soft parts with joint pain
- Bone demineralization will induce osteolitic lesions, with increased risk for deformations and fracture.

There are some particularities for each type of etiopathogenetic form of hyperparathyroidism:

- adult female prevalence, maximum in the 5th decade, 40% only symptomatic = PARATHYOIRD ADENOMA
- familial forms associate more sooner and more severe hypercalcemia, with equal chances in females and males, affecting all parathyroids, associating other possible pancreatic and pituitary tumors. Men 2 cases parathyroid is a less frequent disease. Men 4 cases are similar to MEN 1 but with different type of tumor locations.

In case of clinical suspicion, **the diagnostic steps** are always to following:

Clinic suspicion

1. Biologic confirmation of the suspicion
2. To determine whether there is an unifocal or multifocal lesion
3. Localization in case of unifocal lesions. Also the possibility of ectopic supranumerar glands has to be clarified before referring to the treatment.
4. Lesion evaluation presumes evaluation of all coexisting lesions, besides the parathyroid ones.
5. The last mater to discuss is whether there is a sporadic/ or a familial form. Evaluation of pears and correct treatment is imperious, in case of familial forms.

1. BIOLOGIC CONFIRMATION

Basic evaluation

Calcemia	↑
Phosphatemia	↓
Calciuria/24 hours	↑
Phosphaturia/24 de ore	↑
PTH	↑, ↑↑
25OHD	n, ↓

Completion level

Glomerular filtration rate = to exclude chronic renal disease

Calcium clearance

Vitamin D evaluation= to exclude hyperparathyroidism secondary to severe vitamin D levels

PTH related proteins = to exclude paraneoplastic hypercalcemia

TSH, FT4 = to exclude hyperthyroidism hypercalcemia

B2 mycroglobulin to exclude multiple myeloma

Differential diagnostic

TABLE XXXII. HYPERPARATHYROIDISM VERSUS PARANEOPLASTIC HYPERCALCEMIA

	PTH	**PTHrP**	**1,25OH_2D**	**Ca^{2+}**
HPTH I	↑	↓	↑	↑
malignity PTHTrP	↓	↑	↓	↑↑
malignity non PTHrP	↓	↓	↓	↑

TABLE XXXIII. PRIMARY FROM SECONDARY/TERTIARY HYPERPARATHYROIDISM

	PTH	Ca^{2+}	PO_4		**1,25 OH_2D**	**crea**	GFR
I	N, ↑	↑	↓	N,↓	↑	N	N, ↓
II	↑	↓	↑	N,↓	↓	N, ↑	< 15ml/min
III	↑↑	↑	↑	N,↓	↓	↑	< 15ml/min

TABLE XXXIV. HYPERPARATHYROIDISM HPTH/FAMILIAL HYPERCALCIURIA FHH/IDIOPATHIC HYPERCALCIURIA IH

	HPTH	**FHH**	**IH**
Calcemia	↑	↑	N
Phosphatemie	N, ↓	N, ↓	N
Calciuria	↑	↓	↑
PTH	↑	N	N
ClCa/ClCrea	↑	↓	↑

Urinary Ca < 100 mg/24 ore + Cl Ca/Cl crea < 0.01 = FHH
Urinary Ca> 4 mg/kg/24 re + Cl Ca/Cl crea > 0.02 = exclud FHH

2. TYPE OF LESION

3. LOCALIZATION OF THE LESION

4. COEEXISTING LESIONS

All these steps use imagistic diagnostic methods, with:

- Classic Radiology
  - Bone clinical picture
  - Renal clinical picture
- Ultrasound
  - Localization
  - Adenopaty /hyperplasia
- Scintigraphy
  - Localization
  - Ectopi 5 – 10 %
  - Multiple localization 10 – 20%
- CT/RMN/SPECT
  - localisation

Classic radiology evaluation identifies just consequences of the increased bone **resorption** on different bone structures:

- subperiosteal = short bines, phalangeal bines
- intracortical = cortical tunneling = long bones
- endostal = long bones
- subcondral = ligament insertion sites
- subligamentar = clavicle insertion (coracoclavicle ligament),calcaneal insertion (plantar aponevrosis)
- subtendinous
- trabecular bine resorption = salt and pepper skull
- diffuse bone demineralisation

or **osteoscelrosis =** rugger jersey vertebrae, or the typical signs, that apeears only in ling standing untreated cases,

the brown tumors (fibrocystic osteitis) = *Replacement of normal bone tissue with vascularized fibrous tissue, secondary to osteoclastic hyper activation* with expansive lithic lesions with nonsclerotic margins.

Renal calcifications, a complication of calcium precipitation, is also diagnosed by conventional X Ray evaluation.

We can have:

= nephrocalcinosis = parenchimatous calcifications or

= nephrolithiasis = pelicaliceal clacifications

Scintigraphy is based, in principle, on the different avidity to radiotracer between parathyroid and thyroid tissue, parathyroid tissue having a slower but longer concentration of the radiotracer = initial quick thyroid phase followed by postpone, tardive, parathyroid phase.

The scintigraphy allows evaluation of activity grade of parathyroid, also identifying the site of the parathyroid, and also permitting clear evaluation in cases where there are associated thyroid and parathyroid lesions.

Ultrasonography can identify thyroid and parathyroid tissue, but there is to mention that parathyroid tissue is visible on ultrasound only in cases of hyperplasia or hypertrophy. The sensitivity and specificity of the method is excellent, ectopic parathyroids, outside the region, representing the only limitation of the evaluation which is explorable by ultrasound.

Conclusind, parathyroid localization can be made my means of scintigraphy, ultrasonongarphy, or tomography or MRI, in selected cases, as sumariez in Table XXXV.

TABLE XXXV. PARATHYROID LOCALIZATION

Technique	Advantages	Sensitivity	Disadvantages
CT	Noninvasive	50-70%	Radiation ionized
MRI	Noninvasive	50-70%	Cost/availability
Ultrasound	Non irradiant noninvasive	70%	
Angiography	Golden Standard		Invasive
Venous sampling	Glandular ectopia		Invasive/extensive
Scintigraphy	Noninvasive	50%	Radiotracers

5. **SPORADIC OR FAMILIAL FORM DIAGNOSTIC**

The diagnostic of sporadic or familial form can be made accordingly to the context of the disease,

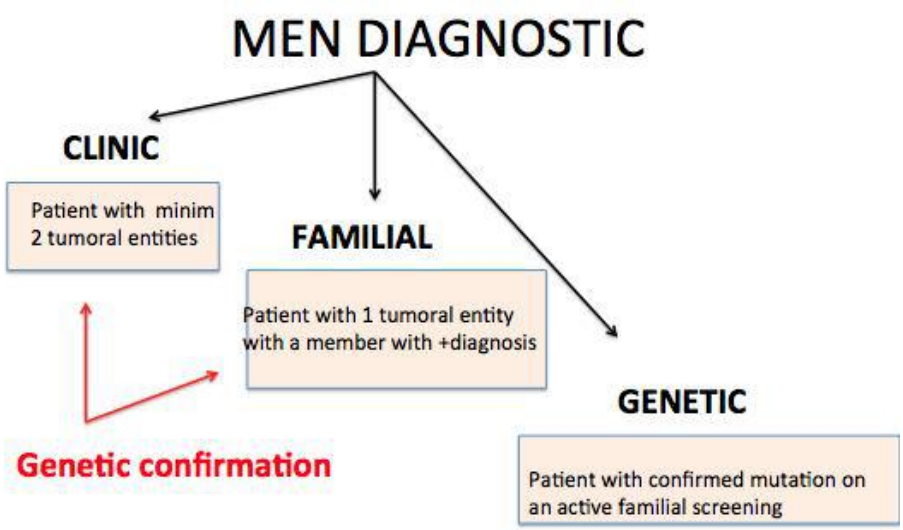


Figure 21. When do we think about genetic form of hyperparathyroidism

Differential diagnosis

The differential diagnostic has to be made with other causes of hypercalcemia. The main information that has to me remembered is that in front of a hypercalcemia, all the possible causes are serious diseases.

Almost 80% of all hypercalcemia cases are secondary to hyperparathyroidism or malignancy.

Possible causes:

- V Vitamin= excessive use of vitamin D
- I Immobilization= will favor bone resorption with secondary calcium release
- T Thyrotoxicosis = due to bone resorption
- A Addison's disease = altered renal reabsorption
- M Milk-alkali sd.= use of excessive hydroxialuminium preparations in hyperacid peptic ulcer, with secondary alkalosis and impairment of the calcium resorption
- I Inflammatory disease = release from the leucocytes
- N Neoplasia

  hormonal: HPTHrP= paraneoplastic syndrome

  osteolitic lesions = metastatic lesion with direct calcium release from the bone

  hematologic= direct releae from the leucocytes or myelocytes
- S Sarcoidosis, granulomatous diseases
- T Thiazide, Lithium excessive use
- R Rhabdomyolysis with direct release
- A AIDS
- P Paget's disease - altered bone release

  Parenteral nutrition
  Pheocromocytoma

Treatment

I. Surgical treatment

- Is **UNIVERSAL** recommended in symptomatic forms
- Is indicated **in TARGETED** situations in asymptomatic forms:
  1. Ca^{2+} + 1.0 mg/dl upper normal value
  2. T score DXA < -2.5 (Z score < 50 years/premenopausal L1-L4/femoral neck/**distal 1/3 forearm**
  3. Vertebral fragility fracture (CT,RMN, VFA-Rx)
  4. FGR < 60 ml/min
  5. age < 50 years
- techniques:
  - Unilateral parathyroidectomy
  - Total parathyroidectomy 4/4
  - 3/4 total parathyroidectomy plus subtotal ¼ parathyroidectomy with reimplatation
  - Classic techniques
  - Minimal invasive technique– minima unilateral incision
  - Always intrasurgical PTH evaluation = minimal 50% ↓ PTH
- Advantages:
  - Cure
  - Benefits in all forms of diseases
  - Increase od BMD after surgery
  - Increases survival
  - Neurocognitive amelioration
  - Increase of QoL in 92% of cases
  - Efficiency
  - Safety procedure

- Adverse effects
    - Persistent HPTH 1-20%
    - Temporary hypocalcemia = hungry bone sd 15-20%
    - Permanent hypocalcemia = hPTH 1-2%
    - Recurrent nerve involvement 1-5%
    - Bleeding < 5%
    - Functional postsurgical hypoparathyroidism due to the suppressed healthy parathyroids, not affected by the adenoma, but which where under suppression in order to try to compensate the tumoral overproduction of PTH.
- Particularities in familial forms:
    - MEN 1 = parathyroidectomy + timectomy
    - subtotal/ total with auto transplant
    - MEN 2 = parathyroidectomy only AFTER
    - cure of pheocromocitoma
    - PHT-JT = total parathyroidectomy
    - FI HPTH = subtotal parathyroidectomy
    - FHH = strict monitoring

1. Active follow up

- **Asymptomatic form without surgical indication**
- Calcemia Annual
- DXA Annual

  Decrease in height ➔ Ct/RMN/Rx cu VFA
- FGR Annual
- Plasma creatin Annual
- Recent renal lithiasis ➔ 24 hours profile

2. Medical treatment

- Classic = hypercalcemia control
  - Hidratatation: 1st step = isotonic saline solution, Reduces calcemia with 1.6-2.4mg/dl, Insufficient in severe HCa cases
  - Diuretics: Facilitate calcium urinary excretion, Inhibits the calcium reabsorption in the ascendant portion of Henles' loop, Protects form hyper hidration, Coadministration of Furosemid
  - The medication effect dependent of the calcium load
  - Frequent electrolytic evaluation
  - Bisphosphonates
  - Calcitonin
  - Mitramycine
  - Steroids
  - IV phosphate
  - Dialysis
- Modern = CINACALCET = calcimimetic
  - Ameliorates hypophosphatemia/hyperphosphaturia
  - Decreases PTH values with around 50%
  - Ameliorates FGF 23 levels
  - Maintain BMD values
  - No significant effect of calcemia

Used in restricted sitatuations:

1. Postsurgical relapse
2. Diffuse hyperplasia forms
3. Parathyroid carcinoma

Prognostic

- **GOOD**
  - Treated HPTH I
  - Treated FI HPP
  - FHH
- **MODERATE**
  - Untreated HPTH I
  - MEN 1,2,4
- **LIMITED**
  - HPP – JT
  - Neonatal severe hypercalcemia
  - Paraneoplastic HPTH

IV.2.2. Secondary hyperparathyroidism

Etiopathogeny:

1. Renal causes
   - GFR < 15 ml/min
   - Reducing vit D activation
   - Moderate Ca ↓
   - ↓PTH Vitamin D Receptors
   - ↓ PTH calcium Receptors
   - PTH resistant to - feedback
   - Shift of the Ca-PTH regulation set point
   - Hyperphosphatemia

Mechanism:

In front of the decrease of glomerular filtration rate, there is an altered activation of vitamin D, due decrease of the number of functional nephrons, with concurrent vitamin D resistance, which will induce hypocalcemia. Also, secondary to the decrese of renal function, there is a increase in phosphatemic level, which will induce increase production of FGF 23, with extra vitamin D activation impairment.

All together will induce severe, longstanding hypocalcaemia, with secondary increase of PTH, as a compensatory mechanism, will increased bone resorption and compensatory calcium increase. Because the mechanism is chronic and ongoing, there will be no end of the over mentioned mechanism.

The phenomenon is described only in severe cases with chronic renal disease, starts in cases with filtration rate less than 30 ml/min, but is typically in stage V cases. With filtration rate < 15 ml/min.

2. Digestive causes
   - Bariatric surgery =↓ absorption
   - Celiac disease
   - Chron's disease
   - Severe vitamin D deficiency
   - ↓↓ D + ↓↓ Calcium
   - Hyperphosphatemia

IV.2.3. Tertiary hyperparathyroidism

- Terminal phase of untreated II HPTH
- Hypertrophy of PTX glands
- Autonomous, unregulated secretion

IV.3. HYPOPARATHYROIDISM

Hypoparathyroidism is represented by any situations associated with chronic parathyroid insufficiency due to surgical, autoimmune, familial or idiopathic insufficiency, with its major complication = chronic hypocalcaemia.

We can classify hypoparathyroidism as:

- ***Lezional Hypoparathyroidism***

SURGICAL
= in case od thyroidectomy with secondary parathyroid excision or ischemia

= postparathyroidectomy (4/4)

POSTRADIOACTIVE TREATEMNT with secondary parathyroid lesions

INFILTRATING DISEASE = repalecemt of healthy tissue with nonactive tissue: sarcoidosis, Wilson disease, hemochromatosis, metastasis

AUTOIMMUNE DISEASE = ant parathyroid antibodies

NEONATAL DISEASE

= isolated parathyroid agenesia

= di George sd = parathyroid + thymic agenesia

FAMILIAL DISEASE

= PTH gene mutation = inability to produce PTH

= Ca sensing receptot mutation = altered Calcium sensing mechanism with innnapropiate, to late PTH secretion in case of calcium changes

- ***Functional hypoparathyroidism***

SURGICAL
= immediately after hyperparathyroidism surgical treatment, in case of a parathyroid adenoma, when the remnant presuppressed parathyroid need time to recover

MEDICATION
= Doxorubicin, Ethanol, Magnesium deficiency, Aluminium, Cimetidine

NEONATAL
= in neonates after birth, in cases with maternal hyperparathyroidism (that will be suppress during the whole pregnancy by the hyperparathyroidism of the mother)

- ***Pesudohypoparathyroidism***

= targer organs unresponsivennes to normal PTH hormone

= hypocalcemia + hyperphosphatemia

= increased PTH

The clinical picture is sustained totally by the hypocalcaemia with neuromuscular effect, but also cardiac, ophthalmologic, dermatologic, dental and cerebral effects. According to the level of hypocalcaemia we can see latent, chronic signs, and acute signs, under special conditions: increased need, high effort, intense perspiration, reduce calcium intake.

LATENT SIGNS = appear in cases of hypocalcemie between 7.5-8.5 mg/dL., representing actually neuromuscular hyper excitability:

- **Chvostek sign**

When the facial nerve is tapped at the angle of the jaw (i.e. masseter muscle), the facial muscles on the same side of the face will contract momentarily (typically a twitch of the nose or lips) because of hypocalcemia (i.e. from hypoparathyroidism, pseudohypoparathyroidism, hypovitaminosis D) with resultant hyperexcitability of nerves. Though classically described in hypocalcemia, this sign may also be encountered in respiratory alkalosis, such as that seen in hyperventilation, which actually causes decreased serum Ca^{2+} with a normal calcium level due to a shift of Ca^{2+} from the blood to albumin which has become more negative in the alkalotic state.

- **Trousseau sign**

To elicit the sign, a blood pressure cuff is placed around the arm and inflated to a pressure greater than the systolic blood pressure and held in place for 3 minutes. This will occlude the brachial artery. In the absence of blood flow, the patient's hypocalcemia and subsequent neuromuscular irritability will induce spasm of the muscles of the hand and forearm. The wrist and metacarpophalangeal joints flex, the DIP and PIP joints extend, and the fingers adduct. The sign is also known as ***main d'accoucheur*** (French for "*hand of the obstetrician*") because it supposedly resembles the position of an obstetrician's hand in delivering a baby.

- **Provoked hyperpneea**

- **Weiss sign**

Hitting a point between the middle third and upper third of the line joining the angle of the mouth to the zygomatic process gives rise to only a contraction of the muscles of the mouth and nose.

CHRONIC SIGNS = the long term effects of incorrect treated/supplemented hypocalcemia

- Cardiac effects
  - Delayed depolarisation = ↑ QT interval
  - Alteration of excitation-contraction coupling
  - Refractory congestive heart failure
- Ophthalmologic effects
  - Subcapsular cataract – reading vision, reduced vision in bright light, halos at night
- Dermatologic effects
  - Dry skin
  - Flaky, brittle nails
- Dental effects
  - Dental aplasia/hypoplasia
  - Emanel trophic problems
  - Brown striation
  - Brittle teeth
- Cerebral effects – calcification of the basal nuclei
  - Focal seizures
  - Generalised seizures
  - Lipotimia
  - Syncope
  - Intellectual deficiency (inuntreated longstanding disease, from the childhood)

ACUTE SIGNS = acute decrease of calcium levels below 7 mg/dL.

There is an important neuromuscular hyperactivity with:

- Tonic muscular contraction = TETANY that starts at facial level and will spread, as long as the hypocalcemia is not treated:
  - Tingling parthestesias finger+ mouth
  - Carpopedal spams
  - Adduction of the thumb
  - Flexion of the metacapophalangeal joints
  - Extension of the interphalangeal joints
  - Flexion of the wrist
  - Extension and abduction of the hip
  - Flexion + extension of the toes
- GENERALISED PAINFULL INVOLUNTARY CONTACTIONS
- LARINGEAL SPAMS
- VISCERAL SPAMS (GASTRIC, PYLORIC)
- DISARTRIA
- PSYCHOLOGICLA SIGNS: ANXIETY, PANIC,
- STUPOR

Lab diagnostic

1. Calcemia ↓↓↓↓↓
2. Calciuria ↓↓↓
3. Ionised calcium ↓↓↓
4. Phosphatemia ↑↑
5. Phosphaturia ↓↓
6. PTH ↓↓↓↓

Differential diagnostic has to be made with different *other forms of hypocalcemia:*

- **Resistance to PTH**: pesudohPTH, CDK, calcitonin, bisphosphonates
- **1,25OH_2D failure**: D deficiency, hereditary type 1 rickets (renal 1α hydroxylase deficiency)
- **1,25 OH_2D resistance**: hereditary type 2 rickets
- **Acute complexation / deposition of calcium**

Acute hyperphosphatemia: crush injury, myonechrosis, tumor lysis, excessive PO4- administration (iv, oral, enteral)

Acute pancreatitis

Citrate blood transfusion

Excessive skeletal mineralisation: hungry bone sd, osteoblastic metastasis, excessive vitamin D therapy

TABLE XXXVI. DIFFERENTIAL DIAGNOSTIC OF HYPOCALCAEMIA INDUCING DISEASES

	Ca^{2+}	Urinary Ca	PO_4^-	Urinary PO_4^-	PTH	25OHD	1,25OH_2D
hPTH	↓↓	↓↓	↑	↓	↓↓↓	N, ↓	↓↓
pseudohTPT	↓↓	↓↓	↑	↓	↑↑↑	N, ↓	N, ↓
D deficiency	↓	↓	N	N		↓	↓
Type1 rickets	↓↓	↓↓	↓	N	↑↑	N	↓↓↓
Type 2 rickets	↓↓	↓↓	↓	N	↑↑	N	N

Also other causes of increased neuromuscular sensitivity had to be considered: hypomagnesaemia and respiratory alkalosis.

Treatment

The acute severe hypocalcaemia is a medical emergency due to the important neuromuscular generalized contractions

- Acute iv treatment
- 100 mg elemental Calcium PEV 10-20'

If not enough

- 100 mg/hour till the symptoms disappear
- Always associated Magnesium supplementation – 100 mEq/24 hours (because differential diagnosis is difficult because of lack of time)

After the disappearance of acute symptoms, a chronic supplemental treatment is needed in order to maintain appropriate Calcium levels, not to induce any other acute crisis:

- 1-3 g elemental calcium/day
- Multiple doses/day
- The elemental Calcium is present in different Calcium preparation in different percent, so the final amount of Calcium has to be considered according to the following values:
- Ca carbonate 40% elemental Calcium
- Ca citrate 21% elemental Calcium
- Ca lactate 13% elemental CAlcium
- Ca gluconate 9% Elemental CAlcium
- Hydroxyapatite 35% Elemental Calcium
- Combined preparation 30% elemental Calcium

The gut Ca absorption threshold is around 500 elemental Calcium/administration, so the elemental Calcium content/tablet should be maximum among this threshold, multiple daily dosis are needed.

- Hydroxyapatite = biocompatible, bone similar
- Carbonate = gastric protection
- Citrate = facilitates gastric absorption
- Phosphate = maintenance tooth quality

Natural Calcium sources can be considered, in normal situations, but in case of Hypoparathyroidism where the calcium needs are so high, the food calcium intake is minimum.

TABLE XXXVII. FOOD SOURCES OF CALCIUM

Food	Portion	Calcium content
Milk (0,1%, 1.8%, 3%)	250 ml	300 mg
Skimmed milk	250 ml	285 mg
yogurt	185 ml	295 mg
Soft cheese, mozzarella	1/1/3 cm cube	200 mg
Hard cheese	1/1/3 cm cube	245 mg
Sardines with bone	55 g	200 mg
Salmon	105 g	240 mg
Rice	250 g	300 mg
Kidney beans	250 g	170 mg
Soya	½ can	170 mg
Tofu	84 g	130 mg
Madeleine	1 piece	84 mg
Toast bread	2 slices	40 mg
Broccoli	¾ can	50 mg
Dired dates	10 pieces	150 mg
Orange 55	1 piece	50 mg
Ice cream105	125 ml	80 mg

Calcium supplementation is lifelong, except the functional forms of hypoparathyroidism, where there is a disappearance of the disease after some weeks.

- Plus Vitamin D correction

= decreased intake = normal vitamin D3 preparation

= decreased activation = 1α calcidiol preparation

= decreased general activation = calcitriol

The treatment is limited for a period of months, till the vitamin D is restored to normal, because vitamin D metabolism and function is not altered per se in Hypoparathyroidism.

- Mg deficiency correction is mandatory, for decreasing the coexisting increase in neuromuscular excitability.

Prognostic

In cases with correct supplemental therapy, under a chronic and acute situations, there is nor altered life expectancy. IF untreated, any acute crises can induce death by stupor.

CHAPTER 5. OSTEOPOROSIS

Osteoporosis is a major pathology that interests mostly the postmenopausal women without being addressed strictly to them. Old definition of osteoporosis considered osteomalacia as a different condition, namely a reduction in the amount of bone compared to the average population and age norm.

V.1. DEFINITION

The new definition of osteoporosis is fundamentally different, by taking into consideration the decrease bone strength as a result of both, the decrease in bone mineral density and bone microarchitecture deterioration, with bone fragility occurrence and secondary susceptibility to fracture .

Therefore, osteoporosis is a skeletal disease characterized by compromised bone strength, because of the alterations in the density and / or bone quality, with increased risk of subsequent fracture. From clinical point of view, the presence of fragility fractures: in distal third of the forearm (Colles fracture) or *vertebral* compression *fractures are* sufficient to define osteoporosis.

V.2. PREVALENCE

The last assess made at European level in 2013 revealed the following figures for our country: 6.2% male population over 50 years old, 20.5% of feminin population over 50 years old, with a prevalence of 4.8% in the general population. These figures fall in average range compared to the European countries, compared to a maximum value of 5.6% in Bulgaria and Belgium, respectively a minimum value of 4.2% in Slovakia.

V.3. BONE REMODELING

The bone is not an inert organ. The skeletal system permanently undergoes bone renewing process, where the osteolysis / destruction component is theoretically in balance with formation component / bone reconstruction. This balance fluctuates and in physiological or pathological situations balance can shift.

The bone compartment consists of cortical bone, which comprises 80% of the entire bone compartment, mainly represented by the shafts of long bones or trabecular bone, accounted in short bones. However, the bone surface is represented in 80% by the trabecular compartment and only 20% of the cortical.

The renewing process is also different in trabercular versus cortical compartment. Trabecular bone have a natural high turnover of about 25% / year compared to cortical bone, which has only a turnover of 5% / year. Trabecular bone is completely renewed, practically once every 4 years, compared to the cortical, which renews itself completely in 20 years.

It is more than obvious why any consistent shift in the balance of bone turnover will be seen faster at the trabecular bone compared to cortical compartment. In an ideal situation, the altered "old" bone is 100% replaced with new bone. The phenomenon is constantly, cyclical and repetitive, without stopping, carried on in several stages:

1. activation phase= the osteoclasts which are located on the bone surface are activated

2. resorption phase= the activated osteoclasts corrode the bone surface, which last for about 7-10 days.

3. resolution phase = restrainting the activated osteoclasts

4. osteoid forming phase = dependent on the osteoblasts, which form new bone matrix, then undergoes mineralization, lasting for 10-12 weeks

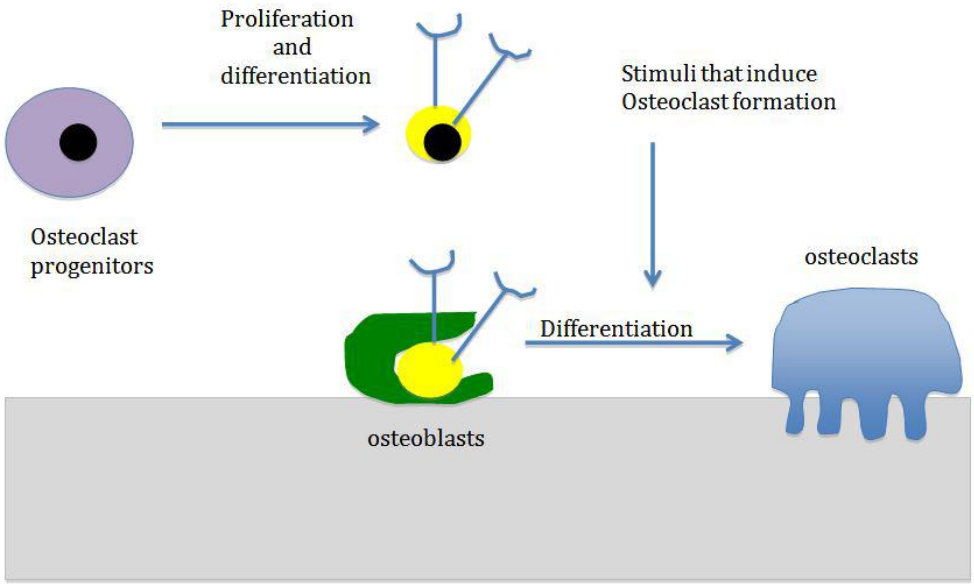


Figure 22. Bone turnover process

The local process is burdened by a number of factors:

= Locals: cytokines, Rank-Rank Ligand system, osteoprotegerin

= Systemics: vitamin D, calcitonin, and parathyroid hormone.

In the growth phase the balance is tilted, physiologically by bone formation, resulting bone growth in length and strengthening, also mineral accumulation. Theoretical the peak bone related to age is reached by the age of 20 years, but is actually different from site to site. Mentions: the peak bone age related of the trochanter bone mass is at 14.2 ± 2.0 years old, at the femoral neck is 18.5 ± 1.6 years old, respectively, the latest is in the spine at a mean age of 23 ± 1.4 years old.

The peak bone mass depends on several factors:

-genetic - Responsible for up to 60% of peak bone mass

-sex related - females, naturally, has a lower peak bone mass

-nutritional: protein intake, energy intake, calcium and vitamin D intake

-endocrine: exposure to sex steroids (puberty time installation, its length, quality of puberty), calcitriol and the growth hormone

Mechanical-factors: optimal body weight and physical activity frequency stimulates mass bone increase

Noxious factors, risk factors: smoking and early alcohol consumption or excess coffee alters peak mass bone achievement

After reaching peak bone mass, follows a plateau phase until about 25 years old, the only period in which the bone loss component is balanced by the bone formation component.

Bone loss with aging

Later, starts an involution process, which has a minimum loss rate of less than 0.1% / year, which lasts until the menopause. In men, the continuity of steroid hormones presence after age of 45-50 years makes the rate of bone loss to be minimal, until senescence period.

In women, however, immediately after menopause due to the disappearance of protective effects of ovarian steroids hormone, an accelerated process of bone loss can be observed, affecting initially the trabecular bone (the bone with the natural turnover of 25% / year) by altering both, the amount of bone (decreased bone mineralization, the degree could be seen in radiological measurements) and quality of bone (occurrence of important intertrabeculare perforations) visible in electronic microscope studies.

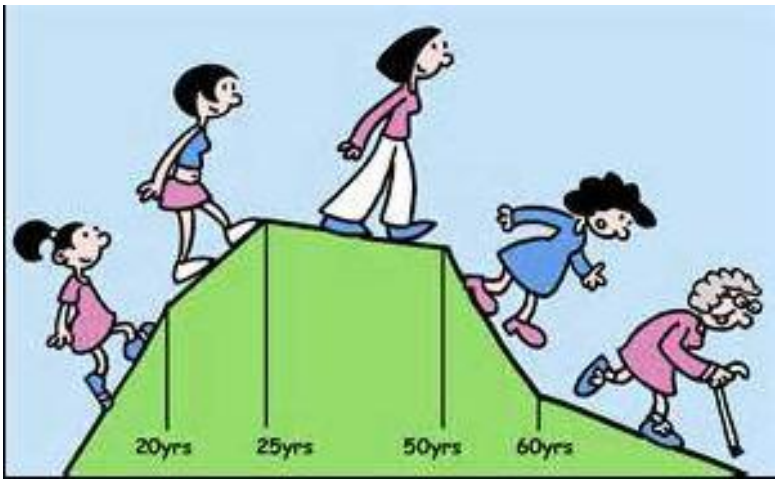


Figure 23. Bone mass evolution during life span

Thus, over the life a woman loses between 35% and 50% of the peak bone mass, reached around the age of 20-25 years.

Bone loss is accelerated in the first 5 to 8 years of menopause, the estrogen deprivation facilitating bone formation-resorption imbalance in favor to bone resorption. The first period is dominated by the alteration of trabecular bone, a sensitive, active bone, with accelerated turnover, which is why in the postmenopausal osteoporosis the spine and the distal third of forarm are predominantly interested, because their are preferentially formed from trabecular bone.

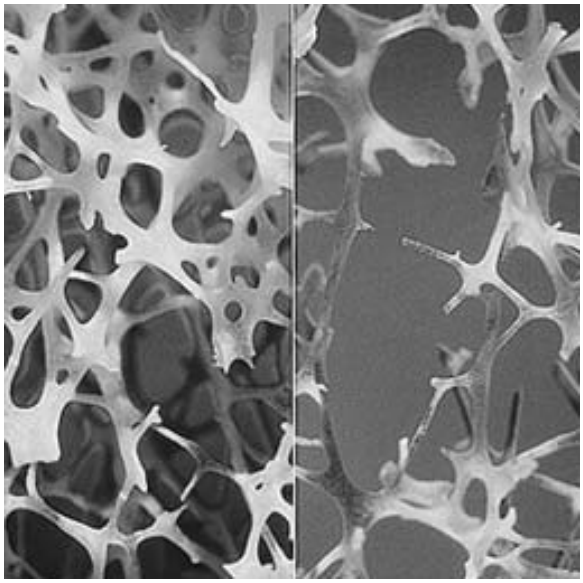


Figure 24. The alteration of trabecular bone with aging

The estrogen deprivation, a phenomenon that occurs in any of menopause, natural, surgically or drug induced, causes an increase in the number of units on the surface of bone remodeling by the disappearance of the protective effect of estrogens on bone.

In both cases the bone net balance is negative and induces bone loss.

Subsequently, a period of slow bone loss takes place, which lasts until the age of 75 years, where the decrease in osteoblast activity, with significant reduction of bone neoformation prevails as a mechanism.

The impaired bone formation mechanism interests predominantly the cortical bone, which has not been major degraded in postmenopausal but degrades in senescence. This explains why in elderly the hip fracture occurs more frequently.

In both cases the net balance is negative bone and induce bone loss.

Genetic variability, individual susceptibility, the associated risk factors, the maximum peak bone mass achieved in youth and not least the genetic stock, burden this balance.

Thus, even if in all postmenopausal women the balance is tilted to bone loss, not all women loss is as high, that not all women will develop osteoporosis. All women will have lower bone mass than the maximum personal peak bone mass, but not the same degree of bone alteration.

Theoretically, out of 10 women in menopause, 5 will develop osteopenia, 2 osteoporosis and 3 women will not have an important bone loss.

Osteoporosis prevalence study (Study PREVOSS, 2008) in Romania revealed the presence of osteoporosis in proportion of 11.5%, a severe osteoporosis in 5%, associated with a prevalent osteopenia of only 16.8%.

Related, senescence associates an increased prevalence of vitamin D deficiency, which promotes excessive alteration in bone mass. The level of parathyroid hormone increases with age as a result of both, vitamin D and that calcium deficiency, through lifestyle changes, reducing exposure to light, sedentary lifestyles, changing diets, decreased ability of the kidney to activate vitamin D, impaired ability of gastrointestinal tract to absorb calcium.

The following osteoporosis classification has a historically uses:

-type I, postmenopausal osteoporosis which appears until 70 years old, predominantly in axial trabecular bone

-type II, senile involution osteoporosis, that occurs after 70 years old, predominantly in peripheral cortical bone

-secondary = Osteoporosis caused by other than physiological factors, previously mentioned: secondary to management of glucocorticoid, secondary to chronic digestive disease, secondary to hyperparathyroidism primary, secondary hyperthyroidism, ... (endogenous or exogenous causes of hypercortisolism, malabsorption syndromes in chronic digestive diseases, increased PTH secretion, hyperthyroidism, increased prolactin secretion, etc).

Bone Quality

The bone strength is the result of two components: structure and materials composition quality. In an ideal way our bone system is a combination of strength, which ensure resistance to mechanical loads without fracture, respective flexibility that offers resistance to movement without fracture. Physical overload and overcoming deformation capacity, in both cases determine fissures to bone fractures.

Naturally, the 2 bone structures: cortical and trabecular have slightly different mechanical properties:

-the cortical bone gives strength to the detriment of flexibility

-the trabecular bone offers flexibility to the detriment of support.

Bone remodeling may change the outline of the bone and internal architecture: during the growing period it thickens structures by apposition and in periods of involution thins the structures.

Thinning structures has two consequences:

-The trabecular thickness decreases, perforations appear that interrupt the continuity in network structure of the trabecular bone, which loses elasticity, with increased risk of fragility fracture;

-Thinning of cortical bone predisposes to the appearance of intracortical porosity, which creates a pseudotrabecular structure of cortical bone, which loses its strength, with increased risk fracture through fall.

TABLBE XXXVIII. SUMMARY BONE PHYSIOLOGY

	TRABECULAR BONE	**CORTICAL BONE**
Proportion	20%	8-%
Area	80%	20%
Turnover	Increased: 25%	Slow: 5%
Renewal	4 years	20 years
Sites	short bones metaphyseal bone	Long bones Diaphyseal bone
Vulnerability	Postmenopausal	> 70 years old
Osteoporosis	Tip I axial	Tip II peripheral
Types of fractures	Distal 1/3 of forearm vertebral body	femoral neck

V. 4. SARCOPENIA

It's a whole discussion in recent years linked to a highly logical premise: bone structure is closely connected to the muscle, muscle evolution or involution causing secondary changes in bone mass. Sarcopenia is defined as a loss of muscle mass and function, secondary to aging, a natural process of involution in the physiology of the human body.

Sarcopenia cause physical disability, impaired quality of life and death. It is characterized by decreased walking speed, inability to rise from the chair, without arm support, visual alteration with subsequent risk of falls.

Impaired muscle function not only increases the risk of falls, but secondary, cause alterations in bone mass, because both bones and muscles derive from the same mesoderm structure.

There is no unaffected bone structure with atrophied muscles, the quality of muscle mass is directly affectingbone quality, independently of the degree of actives and physical exercise.

The association of bone-surrounding muscle explains the beneficial effect of sustained movement, as well as non-pharmacological intervention in the complexity of osteoporosis treatment.

The diagnosis of sarcopenia is one highly discussed and controversial.

Clinical features:

- low speed on walking = 6 meters route: beware the higher speed of 0.8m / sec
- lifting time= time required to get up from the chair, crossing a few meters, return
- prehension test= forced tighten , measured with a dynamometer
- thigh circumference <31 cm

Imaging features:

- MRI and CT is ideal - but they are expensive and represent an over evaluation diagnosis
- entire body composition analysis = bioimpedance methods
- DXA- osteodensitometry
- reduced muscle mass index > 1 standard deviation from the average young adults

The presence of this disease correlates with the osteoporosis presence and eases the complications of osteoporosis - fractures.

Communication between the bone and the muscle is based on a series of paracrine and endocrine communications, causing causing muscle synchronization with the bone, muscle being the main player of bone-muscle binomial.

V. 5. COMPLICATIONS OF OSTEOPOROSIS

We need to know that, despite DXA measurements, which we all are already used to it, the T value score is not the osteoporosis therapy target, which often is a big concern for our patients. The target of therapeutic interventions in osteoporosis is directed to fractures PREVENTION.

Even if we call these fractures, fragility fractures, all this fractures occur by falling. Sometimes the fall is mild with minimum intensity - falls from height level.

Fracture prevalence

The latest European statistics (2013), has the following data for Romania. We mention that the incidence of fractures is calculated as the number of new fractures occurred / year / 100,000 persons. Thus Romania recorded the lowest number of the femoral neck fractures in all European countries, 110 women / 100,000 women / year and 58 men / 100,000 men / year, with a prevalence in the over 50 years population of 282 women / 100,000 women / year and 110 men / men 100,000 / year. However, the annual costs arising from the treatment of this fractures are 129 million euros, in real, the antiosteopororsis medication necessary for preventing an equal number of fractures is only 7 million, representing only 5.2% of the total costs which the health system management uses for the treatment of femoral neck fractures.

Not all failures translate to fracture. Only 5-6% of falls result in fractures (1% hip fractures, 5% fractures in other sites). Often the patients deny osteoporosis and not realise the arguing risk of fractures: "I felt a few times and I did not fracture". This occurrence does not mean anything and do not give any kind of guarantee. On the contrary, a person who has fallen has increased risk of subsequent falls by repeating the trigger mechanism.

Theoretically several types of fractures are described:

1. traumatic fractures

2. pathological fractures

3. stress fractures

4. fragility fractures

Typical for steoporosis disease are the fragility fractures, which are the result of small or medium injuries, a trauma intensity which normally should not cause a fracture.

The 3 typical osteoporotic fractures: third distal forearm, vertebral body and femoral neck.

It is to discuss and remember fracture the cascade phenomenon: an osteoporotic fracture increase risk to the next fractures. Thus, after the first osteoporotic fracture, the risk of another fracture within the next year is 25% (1 in 4 women). Future risk multiplies as follows: 2.8 for an initial spinal fracture, 1.9 for a fracture of distal radius, 2.7 for a fractured humerus and 2.3 for a fractured rib.

Vertebral body fracture

It is the most common osteoporotic fracture. It is a risk marker of future fractures. This fracture occurs almost spontaneously, during the usual daily activities: c lifting shopping, bending to the floor to pick up an object, ironing crooked, lifting a suitcase, lifting the mattress of the bed, pushing some drawers / furniture or bulky luggage, hauling. 30% of vertebral fractures which are radiographic visible are clinically diagnosed.

The manifestations are divided into:

-Acute - Severe pain in the vertebral body area concerned, extremely intense, which worsens when walking or standing or bending, calms down upright or supine state, on very hard surface. The pain is very strong, not actually allowing mobilization and requires significant analgesia. The length of severe pain can extend up to a period of 4-5 weeks, with limited relief after using painkillers and muscle relaxants.

-Subacute - spine pain accentuation and functional limitation, secondary to the pain

-Chronic, secondary to axial modification with deformation changes in the spine, height loss, kyphosis or scoliosis occurrence, and dependent on the angle of fracture developing. Chronic pain, impaired motility of the spine.

-Severe deformation can associate impaired lung capacity with function alteration.

-Impaired quality life, in general by: impaired self-esteem, altered body image, dependence on painkillers, impaired sleep quality, depression, loss of independent driving, loss of social independence.

-on long term: the vertebral fractures associates increased mortality at 5 years, the risk increases with time since the last fracture, adding a summative effect to the following fractures.

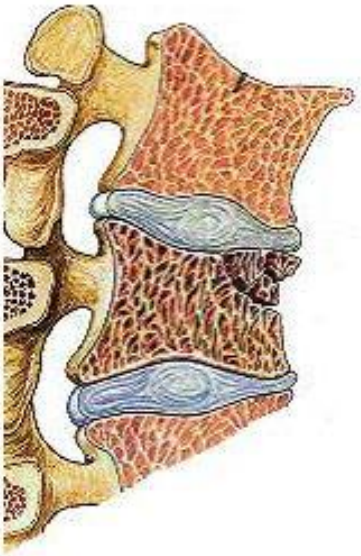


Figure 25. Vertebral body fracture

A radiological examination is recommended for vertebral fractures diagnosis in the in the following situations:

1. acute , typical pain, with a few days duration

2. chronic axial pain, unexplained

3. at least one risk factor for osteoporosis

    a. Age over > 65 years old (women) and> 70 years old (men)

    b. Height loss; 1-3 cm from the 25 years old height

    c. height loss more than 2 cm from the previous assessment

    d. ribs distance for less than 2 cm

    e. peripheral fractures (eg 1/3 distal forearm)

    f. corticosteroid therapy for more than 3 months, a prednisone dose or equivalent to more than 5 mg

The radiological assessment is the typical investigation to diagnose vertebral fracture, especially front and profile. Identifying a subsequent fracture with increased risk by classical radiology is possible only in case of a total spine length decrease more than 4 cm, decrease that occurs only after several vertebral compression fractures.

Profile assessment allows morphometric measurements of vertebral spine, which facilitate the classification of these fractures, respectively identify them early, long before determining a height loss of the entire body.

Vertebral fractures can be cuneiform, biconcave, or total flattened (collapsed). Naming the type of deformation is a descriptive concern and does not influence the severity of deformity. The severity of the fracture is defined by the degree of vertebral colaps or bone destruction. The vertebral body height is measured on the anterior, medial and posterior line, a fracture being considered any decrease of at least 25% of vertebral body height.

Any vertebral fracture will have a type and severity.

The presence of a vertebral fracture (clinical or morphometric diagnosed) represents an indication for therapy. The assessment of vertebral fractures is essential for pro-active attitude, antiosteoporotic treatment and prophylaxis for next fractures.

Fracture of distal third forearm

The incidence of this fracture is difficult to assess because it is often a fracture that does not require hospitalization, some women do not even appeal to plaster casts.

This type of fragility fracture predominantly occurs in young women, through a typical fall down mechanism: keeping the protective mechanisms (defense mechanisms), during fall with a reflex , the women put their hand in front of the body, so the hand be the first contact with the ground, to protect the other essential structure: femoral nech/vertebral spine / arm / femur.

Figure 26. Falling on one hand

Due to typical symptoms, it is often diagnosed clinically (pain, deformity, crackles, shortness of the superior segment) and confirmed by radiology imaging.

Complications are on the short term: pain, disability, temporary difficulty in usual movements (difficulty during daily dressing, toilet, daily activities), with the possibility of complications on medium term= degenerative arthritis or on

long term = regional pain Syndrome, secondary to somatic reflex dystrophy, complications found in those situations in which orthopedic treatment was not performed in the acute phase.

Even if the forearm fractures are not an uncommon, noisy event, they should be considered a marker of subsequent vertebral and femoral fractures, doubling their risk. This applies regardless of the age at which the fracture occurs (even at 42-45 years old).

Femoral neck fractures

The femoral neck fracture is the most feared complication of osteoporosis due to morbidity and mortality associated with it.

The fall that causes femoral neck fracture is on one side, passive, it is characteristic to older people, who have lost the defense reflex and do not put their arms in front of the body, as a defense mechanism when they fall, they don't fall forward, they fall passively sideways or on their back, the hip coming into direct contact with the ground.

Trauma itself is relatively small, mostly at the same height level: sitting down beside the chair, slipping, tripping, less than 20% being in the context of fainting.

Figure 27. Lateral falling mechanism

The latest statistics on the epidemiology of osteoporosis in Romania shown that the vertebral fracture incidence increases with age:

TABLE XXXIX. FRACTURE RISK IN ROMANIAN POPULATION – WOMEN AND MEN

Age group	Hip	Vertebral Spine	Forearm	Others
Women				
50-54	17	44	108	112
55-59	34	94	260	298
60-64	60	105	225	230
65-69	115	168	280	394
70-74	228	321	409	646
75-79	407	396	397	856
80-84	667	419	417	1133
85+	1048	493	447	1761

Age group	Hip	Vertebral Spine	Forearm	Others
Men				
50-54	50	129	36	223
55-59	70	121	106	648
60-64	94	225	177	924
65-69	124	194	186	797
70-74	186	283	119	954
75-79	274	316	78	732
80-84	410	285	80	1091
85+	587	394	108	1701

Despite prosthetic treatment and decreased mortality to effective only 5% to next year, with changing historical standards, the femoral neck fracture by falling down remains associated with a increase mortality in general due to the prolonged immobilization in bed, pulmonary embolism, or death. So, the occurrence of a femoral neck fracture decreases the survival expectation by 12-20%. The main predictors of death after fracture neck femoral are: male gender, older age, decreased muscle strength of the quadriceps, subsequent fractures, sedentary, hypoanabolic syndrome, smoking, factors that are independent of other possible comorbidities.

The vast majority of fractures are identified clinically, through radiology imaging confirmed and solved surgically.

Over half of people who have had a femoral neck fracture are partially or totally incapacitated after event, most often being institutionalized, only 20% being with complete autonomy. Complications, mortality and extreme costs justify the concerns about primary prevention and not necessarily secondary. Finally, our entire activity has as an end point preventing this major and feared complication of osteoporosis.

V. 6. SPECIAL FORMS

- Corticosteroid-induced osteoporosis

Corticotherapy is part of standard treatment for many diseases.

What we often forget are the details related with the administration versus bone compartment:

1. exposure to a supraphysiologic doses of glucocorticoids cause accelerated bone loss, especially in the first year of corticotherapy with at least 7.5 mg doses of prednisone / day

2. to sustain an osteoporosis diagnosis, T-scores in DXA evaluation after corticotherapy may be -1.8

3. therapy with calcium and vitamin D should be done in any situation with chronic use of glucocorticoids

4. the use of more than 3 weeks of 5 mg prednisone or equivalent, increases the risk of subsequent osteoporotic fractures

5. fragility fractures are very common, occurring in 30-50% of patients receiving glucocorticoids

6. fracture risk decreases substantially with glucocorticoid treatment cessation

7. the mineral bone density value is not a good predictor of fracture risk, because it's value increase even in T score of 0.0

Etiopatiogenia mechanisms:

- Direct inhibition of new bone formation by inhibiting the activity of osteoblasts and collagen type I synthesis, decreasing IGF1, osteocalcin and alkaline phosphatase;

-Decreases intestinal calcium absorption

-Increases urinary calcium excretion

- Decreases levels of osteoprotegerin

-Hypotalamus- pituitary -gonadal axis inhibition, with secondary hypogonadism

The accelerated process of bone loss, triggered by chronic use of corticosteroids can be stopped only by therapy cessation.

This side effects can be managed /diminishing by simultaneous use of additional calcium, vitamin D and sex steroids, if it is necessary, during the corticotherapy.

- **Osteoporosis associated with endocrine disorders**

The most common endocrine disorders that cause secondary osteoporosis are hyperthyroidism, hyperparathyroidism, and hypogonadism and type I diabetes.

Hyperthyroidism - is the most common endocrine pathology associated with increased fracture risk, whether or not we have associated hypercalcemia. Florid untreated hyperthyroidism cause accelerated bone loss by hypercatabolic state, consistent with accelerated turnover in the whole body= essence of hyperthyroidism.

Decreased bone mineral density is reversible with the resolution of hyperthyroidism. Untreated hyperthyroidism involves increased risk of fracture.

Thyroid hormone replacement treatment has no adverse effects on bone. High-dose treatment, replacement suppressive dose used in thyroid cancers, theoretical has resorption effect, but basically alters in small measure the bone mineral density.

Hypogonadism

Regardless of the pathogenesis, secondary (central, low FSH, LH decrease level of sexual steroids) - through injuries at hypothalamus and pituitary level: tumors, surgery interventions, tumoral stroke, pituitary ischemia, central autoimmune diseases, hemochromatosis, genetic disorders, anorexia nervosa, either primary (high LH, FSH, decreased level of sexual steroids) - through gonadal injury: genetic disease (Turner syndrome, Klinefelter syndrome, with variants) the prolonged deficiency of sexual steroids alter the bone density.

Depending on the age onset of the hygonadism the bone alteration are different. The disease with Pre pubertal onset, especially those unrecognized and untreated with hormone replacement alters the achievement of peak bone mass. In these cases, the evaluation at a young age, reveals a significantly low bone mineral density than the average population of young adults, generating elevated Z scores. Diseases onset in adulthood has accelerated bone loss records, with low values of bone density compared to the average population of the same age.

In the first instance replacement therapy with sex steroids (testosterone or estro-progestatives) must be done quickly, to recover bone mass and accelerate the new bone formation. In the second situation osteoporosis therapy it is necessary, the hormone replacement therapy being just an option. Supplementation with calcium and vitamin D in appropriate doses is required.

Primary hyperparathyroidism

- is a rarely diagnosed condition, although in the literature is described as the second most frequent condition, after thyroid pathology. In 90% of cases , it is caused by a single parathyroid adenoma and only in 10% of cases, due to a diffuse parathyroid hyperplasia .

Theoretically the clinical features are meaningful and simple: frequent kidney stones, with multiple infection in the upper urinary tract, frequent renal colic, repetitive, multiple fractures after variable trauma intensity, accelerated bone demineralization, predominantly the cortical compartment, increased serum calcium with decreased serum phosphorus and increased urinary excretion of calcium and phosphorus. However, most cases are not diagnosed clinically, but rather at random reveal of repeated increased calcium level in the boold.

The key message is: CHECK any random hypercalcemia found! The high level of serum calcium are rarely due to the therapy with overdoses of calcium preparations, but is never secondary due to alimentation cause. The discreet elevated PTH levels can suggest a hyperparathyroidism. Certainly the mild and the subclinical forms of the disease are not diagnosed. The only effective treatment of primary hyperparathyroidism is the surgical cure, the practice of parathyroidectomy, with spectacular increases of bone mineral after the procedure. These spectacular increases of bone density stay up to 10 years after surgery. The vitamin D deficiency, which associates slight increase PTH, does not determine hypercalcemia. Secondary and tertiary hyperparathyroidism cause a specific bine disease , which is not covered by any form of osteoporosis.

Type I diabetes associates minimal changes in mineral bone density. The type II diabetes associates an increase in bone density, due to increased weight and hyperinsulinemia, but also an increase in risk fracture, bone quality being affected by secondary glycosylation products effect. Important bone loss is associated with Cushing syndrome, but reversible after surgical treatment of disease. Other endocrine disorders that affects the bone density and increase the risk fracture, are acting through indirect mechanisms related to sex steroids alteration or changes in calcium homeostasis.

- **Gastrointestinal Disorders**

A number of gastrointestinal diseases alters gastric absorption of calcium and vitamin D. Some liver disease alters hepatic activation of vitamin D. As a result of these mechanisms accelerated bone loss occurs through the following cascade of events:

- Decrease absorption of calcium and vitamin D
- Hypocalcemia brief

- Mobilization of the regulating hormone: PTH
- transient hyperparathyroidism
- Mobilizing calcium from bone
- secondary hyperparathyroidism
- Cortical bone bone demineralization
- Restore serum calcium level

Celiac disease, jejunum ileal bypass, chronic liver disease, pancreatic insufficiency, gastrectomy may disturb the bone mass. Bariatric interventions cause low bone mass, but it is difficult to assess the bone mass, given that the osteodensitometry in obese persons are difficult to achieve due to excess fat tissue

Pay attention to the correct evaluation of these cases. Often, chronic deficiency of vitamin D and calcium cause osteomalacia and not osteoporosis, the introduction of antiresorptive medication being incorrect.

- **Medications that cause bone loss**

Before labeling a bone demineralization, even in a postmenopausal woman, must not forget the asseasment of associated consumption of drugs that affects mineral bone density; corticosteroids (chronic corticotherapy), medroxyprogesteron acetate, anticonvulsants, heparin, cyclosporine, aromatase agonists and thiazolidinediones

- **Osteoporosis in young people**

When we talk about osteoporosis in young two aspects are commented:

1. true osteoporosis:

It is a diagnosis of exclusion of other disorders that can cause diminished bone mass. It is always difficult to make a differential diagnosis between osteoporosis and osteomalacia in young adults.

Osteogenesis imperfecta is an autosomal recessive syndrome characterized by brittle bones with a history of recurrent fractures, with secondary skeletal deformities. The clinical picture is suggestive, with short stature, long bones deformed, blue sclera, imperfect and incomplete dentition, impaired hearing acuity, scoliosis, ligamentous laxity.

2. False of osteoporosis =wrong diagnosis

We often see in young adults DXA measurements being determined. The result, if is not performed by a skilled person, can show a T score of less than 2.5 and can be mislabeled as osteoporosis.

The diagnosis of osteoporosis in young people and children, requires the presence of a Z score less than -2. T score values are completely uninteresting to young people. WHO criteria for definition of osteoporosis (T-score less than of -2.5) are exclusive to postmenopausal women and the elderly. Never the osteoporosis diagnosis,in young people, can be based only on osteodensitometry exam. Clinical suspicion is required to support an osteoporosis diagnosis assesment in young people: significant decrease in height, hypoanabolic syndrome, chronic use of resorptive medication. A decreased T score in a young person, do not mean osteoporosis but a mistake in DXA interpretation.

- ***Osteoporosis in men***

The mechanism of bone demineralisation in men is similar to that of women. Low bone mineral density is obtained due to diminished peak bone mass or due to an accelerated process of bone loss. Accelerated bone loss is less pronounced in men than women, totaling a maximum of 15 to 20% of peak bone mass, in years to come after 30 years (until the age of 80 years). The main link is not represented by androgen deprivation, a phenomenon that is partial and incomplete in men, but secondary to hyperparathyroidism, which is characteristic elderly. Risk factors for fragility fractures are the same: excessive smoking, excessive consumption of alcoholic, family history of femoral neck fracture, chronic use of corticosteroids. The particularity in the prevalence of osteoporosis in men is 50% due to secondary forms of osteoporosis, compared with women where less than 20% are due to secondary forms of osteoporosis: hypogonadism, alcoholism, gastrectomy, gastrointestinal disorders.

The osteoporosis diagnosis is the same, with a T-score less than -2.5, by comparing the values of bone mineral density in young men, with those of Z score, in cases of young men or teenagers.

V. 7. DIAGNOSIS

The diagnosis of osteoporosis is primarily an imaging diagnosis, which shows a considerable decrease in mineral bone density, related to the average adult population between 20-30 years old

The clinical diagnosis

1. positive history of fragility fracture (fractures occurred after a fall from same level height with minimal trauma)
2. osteoporosis has no direct symptoms
3. the symptoms are secondary complications and fractures, which we should remember that are not diagnosed in two thirds of cases. The clinical features are the following:
4. significant decrease in height,
5. a decrease of more than 2 cm from a recent measurement,
6. chronic pain
7. distal third forearm , femoral neck or spine deformations

Risk factors identification:

1. low weight, habitus hypoanabolic
2. Advanced age
3. Late menarch or delayed onset of puberty
4. Early menopause age
5. Menopause duration
6. Smoking in general
7. Chronic acohol consumption
8. History of fragility fracture
9. Inflammatory or chronic digestive disease

Fracture risk factors for fractures !!!!! are not the same risk factors for low bone mass

1. diminished bone density
2. old age
3. personal history of fracture
4. Family history of osteoporosis or fragility fracture (any first degree relative not just the mother)
5. active smoking
6. low-weight
7. History of falls
8. sarcopenia
9. dementia
10. cortocosteroids therapy

Imaging diagnosis

There are several techniques for measuring mineral bone density.

The measurements of central skeleton, represented by lumbar spine and femoral neck can be assessed by DXA (dual X-ray absorptiometry) or quantitative computed tomography (QCT). the Peripheral skeleton includes distal forearm, radius, distal phalanges, tibia and calcaneus. It can be assessed through peripheral DXA or QCT, but also by absorptiometry single X-ray absorptiometry radiogrametrie or Digital Radiographic.

The gold standard in measuring mineral bone density is the DXA assessment. The method allows:

1. osteoporosis diagnosis - WHO valid criteria for postmenopausal osteoporosis

- normal T-score> -1
- osteopenia -1 <score T <-2.5
- osteoporosis T score> -2.5
- severe osteoporosis T> -2.5 plus fragility fracture

DXA is performed at 2 sites, the lumbar spine and femoral neck from the non dominant limb. Distal forearm is not routinely used, it's representing an alternative for measuring when one of tje mentioned sites are impossible to measure- morbid obesity, bilateral femoral prosthesis, hyperparathyroidism.

The lumbar spine vertebrae evaluation standard include the assessment of L1-L4 , eliminating from the final analysis of 1 or 2 vertebrae (in case of artifact, or an other modifying pathological, vertebral compression). Assessment can not be done on a single vertebra.

Femoral Evaluation - it is consider the T score value from the femoral neck or from total hip which is smaller

DXA interpretation *to other categories than postmenopausal women:*

1. in premenopausal women: lombar spine + femoral neck assessment; osteoporosis is diagnosed when one Z score value <-2.0 plus clinical criteria.

2. in children: DXA spine and whole body reveal positive diagnosis in case of Z score <-2.0 plus history of fractures: in the lower limbs, the upper extremities or vertebral compression.

3. in men: Z score <-2.0 in men under age 50 plus clinical criteria, in men over 50 years. T-score <-2.5

The limitations of the method are strictly linked to local imaging: use recent assessments with contrast agents (<72 hours), very heavy weight (exceeding capacity of DXA table - known value for each machine), prosthetic orthopedic lumbar and / or femoral neck, recent scans with bone tracer. Also, in people over 65 years old with osteoarthritis associated pathology, it influences the

results through the presence of osteosclerosis foci by giving the apparent increase bone density (false best). Aortic atherosclerotic plaques also can generate image plus.

Contraindications are limited to pregnancy, recent use of contrast agents or radioactive isotopes.

The assessment with other mentioned techniques can evaluate fragility fracture risk, but can not be used in osteoporosis diagnosis after the WHO definition or to monitoring response to treatment or spontaneous evolution along years.

The classical radiology asseassment can not be used to sustain osteoporosis diagnosis. Even if radiology imaging are revealing some aspect of demineralised bone, this assessment is purely indicative and has no diagnostic value.

X-rays are used exclusively for classical complications of osteoporosis : acute fracture diagnosis, evolution, framing vertebral fractures.

X-rays also can make differential diagnosis between classical osteoporosis, osteomalacia and fractures on pathological bone(bone metastases, multiple myeloma)

Lab diagnosis

The laboratory diagnosis has limited importance in assessing bone mineral density. It is especially useful in evaluating the potential secondary causes of osteoporosis.

Turnover bone markers are rarely used in everyday medical practice.

The markers for bone formation or bone resorption are determined because their are giving information on the process of bone remodeling, in the absence of the osteoporosis diagnosis. These markers are used to emphasize an active process, not diagnostic threshold values. Are used predominantly in research, their assessment beeing necessery in identify the degree of bone turnover inhibition, respectively for the safety assessment of recombinant PTH therapy.

The bone markers are the following:

- bone formation: alkaline phosphatase (bone origin), osteocalcin and N terminal procollagen propeptides
- bone resorption: C-telopeptide, N-telopeptide (serum and urinary dosages), deoxypyridinoline

Application:

1. Assessment of risk fracture = women who are "faster losing bone" have much higher risk of fracture than other categories: increased values of telopeptide C or N or serum crosslaps suggest a fast bone mode

2. Monitoring treatment with anti osteoporosis agents = determination of resorption markers can only be made after a few months.their measuring allow the identification of the patients who respond to treatment, in contrast to DXA measurements in which case sometimes requires two years until efficacy can be evaluated.

Risk fracture evaluation (assessment)

The relative risk assesses the impact of association / coexistence of multiple risk factors for the possibility of a fracture.

There are many predictive factors related with risk fracture, but recently a quantified and standardized model was developed, adapted to the peculiarities of social-demographic pattern of each country: the FRAX was developed and validated in 2008 and based on validated data. for Romania since 2011.

The free site access: https://www.shef.ac.uk/**FRAX**/

After accessing site by selecting country: Europa and then country: Romania, the dialogue page will appear like follow:

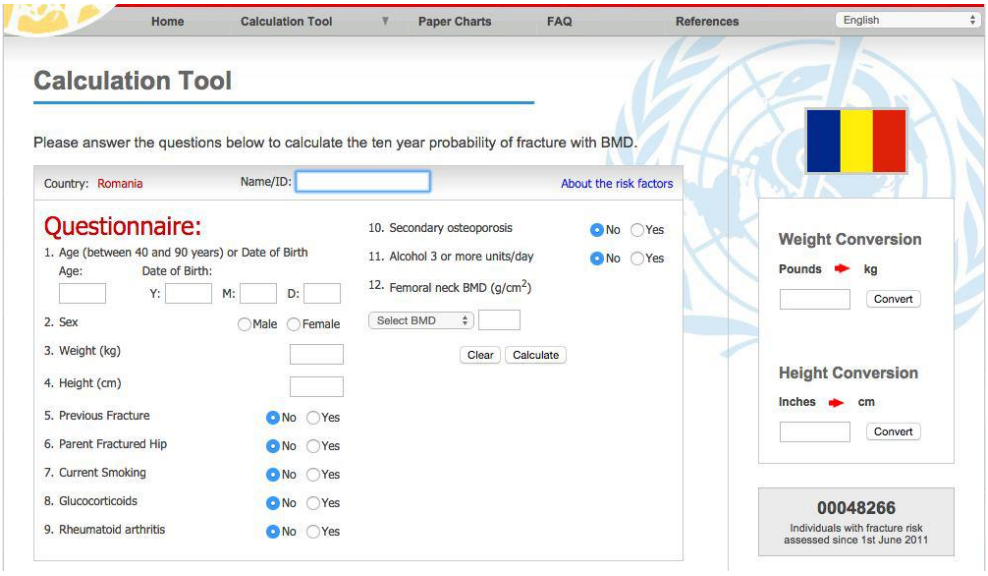


Figure 28. FRAX window – Romania data base

This window allows selecting risk factors that are considered important in FRAX model and introduce the DXA results. Without the DXA results the FRAX assessment can not be possible. Frax assessment represents a risk predictor model for risk fracture to 10 years, which includes personal and family risk factors, as well the momentary reasult of frax measurement.

As it can be seen, the quantified fracturerisk by the FRAX model are the following: age, body mass index, a personal history of fracture, family history of hip fracture, smoking, current use or personal antecedent of corticotherapy, rheumatoid arthritis, Chronic consumption of alcohol, secondary causes of osteoporosis and the bone mineral density value - in g / cm^2 - when using certain devices DXA - General Electric, Hologic, Nordal, DMS <MediClin or T score value if other appliances are used.

It is considered an osteoporosis equivalent or indication for anti osteoporosis agents administration a FRAX index value for the spine above 20% and / or for the hip of more than 3%.

FRAX advantages:

1. Easy to use
2. quantitative estimate the risk fracture
3. the probability for vertebral and nonvertebral fracture is useful from the clinic point of view than predicting clinical fracture risk relative (presence of a fragility fracture doubles the risk for subsequent farcturi)
4. is a method that evaluate the cost / benefit ratio of a drug interventions, especially when it comes to expensive drugs.

FRAX disadvantages:

1. certain risk factors for fracture are not included in the model: the fall risk, rate of bone loss, bone turnover, other medications that cause bone loss, family history for other osteoporotic fractures then femoral neck
2. Secondary osteopororsis are underestimated (selecting secondary osteoporosis category not change the FRAX value)
3. It is compulsory BMD measurement of femoral neck
4. The Number of prevalent fracture is not quantifiable - no the difference between 1 or 4 fragility fracture
5. it applies only to patients who never used anti osteoporosis agents
6. The model is limited to women in the age range of 40-90 years old.

Differential diagnosis

Routine osteodensitometry DXA measurements may reveal low T scores, typical for osteoporosis, in its absence. Osteomalacia, osteogenesis imperfecta, osteitis fibcrochistica of chronic kidney disease, multiple myeloma, mastocytosis are independent inflammatory diseases, disorders of bone marrow, no OSTEOPOROSIS. Each requiring a different medical approach, not treatment for osteoporosis

Marrow disease

Multiple myeloma is one of the conditions that must be considered in front of any event with multiple fractures. It shouldn/t be the last condition to be considered, but first. In front of a case with multiple fractures, the first step is to exclude this disease and then to label osteoporotic fractures as secondary. A specific medication si used, chemotherapy, corticosteroid therapy, radiotherapy, the disease evolution not be influenced at all by anti osteoporosis medication.

Systemic mastocytosis is a rare disorder characterized by mast cell proliferationin to the skin, bone marrow, spleen, liver and lymph nodes. Bone involvement requires the presence of osteoslerosis regions alternating with osteomalacia.

V.8. TREATMENT

The treatment goal is not "treating T score" as many of our patients are tempted to believe it. The goal of treatment with anti osteoporotic agents:

- decrease the risk of fracture by:
    - stabilizing and increase the bone mineral density
    - maintaining or improving the bone quality
    - preventing falls

-management fractures:
    - pain relief
    - stabilizing fracture
    - anatomic path recovery
    - management comorbidities
    - functionality recovery

Nonpharmacologic Measures

Despite the general tendency to deny the impact of lifestyle changes on many conditions, sufficient protein intake, coffee consumption control, quitting smoking, limiting alcohol consumption significantly improves the risk fracture. In general, the exercises, controlled exposure to sunlight, eliminating risk factors for fracture in the household, reduce fracture risk.

Diet measurements

There is a not general consensus of daily doses of calcium requirement but the general recommendations (2011) are:

Daily calcium dose recommendation (DDR)

Categories	DDR (mg)
Children	800
teenagers	1300
Pregnancy/lactation	1300
premenopausal	1000
postmenopausal	1500
men < 70 ani	1000
men> 70 ani	1200

This daily dose is not the additional required dose of calcium but the total dietary reference intake from food and supplemented, if it is necessary with calcium preparations.

When it is evaluate the dietary intake of calcium should be considered all the factors that influence calcium requirement:

- excessive consumption of coffee increases urinary calcium excretion

- excessive protein consumption favors excretion of calcium

- high fiber diet does not significantly influence calcium balance

- associated calcium and salt consumption promotes kidney stones

The minimum threshold required daily for calcium is 400 mg / daily.

In the table are described the food sources containing significantly calcium amounts:

Dietary calcium source:

food	portion	Calcium containing per portion
Milk (0.8%; 1.5%; 3%)	250 ml	300 mg
Buttermilk	250 ml	285 mg
Yogurt	185 ml	295 mg
Curd cheese, mozzarella	Cube 1/1/3 cm	200 mg
Hard cheese	Cube 1/1/3 cm	245 mg
Ice cream	125 ml	80 mg
Sardines with sauce	55 g	200 mg
Salmon	105 g	240 mg
Rice	250 g	300 mg
Beans	½ mug	170 mg
Soy	½ mug	170 mg
Tofu	84 g	130 mg
Whole bread	2 slice	40 mg
Broccoli	¾ mug	50 mg
Dry figs		
Orange	1 fruit	50 mg

Exercises

Movements (physical effort) has direct and indirect benefits and effects on bone compartment.

- muscle tone increases bone mineral density by 1-2%

- exercises allows to maintain agility, decreasing fall risk

- practice motion is a part of healthy lifestyle standard

- the lower limb muscle mass tone absorbs much of the energy developed by falling down on hip, decreasing the risk of femoral neck fracture.

- physical activity is the primary means to prevent senile dementia.

Multidimensional intervention in the treatment of osteoporosis is essential for controlling the fall risk:

-Isometric physical exercise

-30 minutes daily walking

-correct visual anomalies

-reducing the intake of drugs that increase risk of falls: benzodiazepines, hypnotics, antidepressants, overdosed antihypertensive with hypotension or significant fluctuations in blood pressure.

MEDICATION

Supplements

Calcium administration

The market abounds with numerous calcium preparations. Before administrating calcium supplements, it is recommended to evaluate the dietary calcium intake, of each patient, using the previous table. The standard recommended dose are not always needed.

To choose the correct preparation for each patient it is absolute necessary to known some aspects:

- calcium carbonate is preferred in patients with gastric hyperacidity, , gastro esophageal reflux, peptic ulcer. The absorption rate = 36%

-calcium citrate is preferred in elderly population with an acidity, but with precaution in those with hyperacidity. The absorption rate = 29-33%

- calcium lactate = neutral. The absorption rate = 22%

- calcium gluconate= neutral. The absorption rate = 19%

- calcium chloride= neutral. The absorption rate = 17%

- calcium coral = no effect on bone. The lowest absorption rate of all preparations = 15%

- hydroxyapatite= calcium bio compatibility which gives bone mimetic effect

The combined supplements are preferable because they allow a greater digestive absorption rate.

Vitamin D management

The evaluation of the vitamin D status is essential in determining the therapeutic conduct to all cases with bone demineralization, not just in cases of osteoporosis.

The Vitamin D deficiency definition by IOM (Institute of Medicine) is the evidence of a lower value than 20 ng / ml, respectively the evidence of a deficit, values less than 10 ng / mL. The American Society of Endocrinology defines safety bone threshold 30 ng / ml, deficit below 20 ng / ml, respectively severe deficit at levels below 10 ng / ml.

The Vitamin D deficiency (<30 ng / ml) is becoming a global phenomenon, a public health problem, due to the increased prevalence, up to 77%, in the general adult population, independent of gender. Vitamin D is essential for developing and maintaining skeletal health. Many studies published in the last decade sustain the idea that the suboptimal vitamin D is associated with impaired quality of bone. A sufficient vitamin D prevents calcium extraction from bone structure to compensate the insufficient intake, reduces bone remodeling, has protective effect on bone, reduce fragility fractures with subsequent bone fracture.

Age is often associated with vitamin D deficiency due to:
- sun exposure decrease
- frequently use of protective sun cream factors
- diminishing hepatic activation
- diminishing Renal activation
- dietary mistakes

Recent data showed a high prevalence of extreme vitamin D deficit in the Romanian population.

We have to remember that there is a difference between the recommended maintenance dose of vitamin D and the necessary dose for supplementation / correction of vitamin D deficiency.

The inactivate vitamin D preparations, whether they are ergocalciferol (D2) and cholecalciferol (D3) or combined preparations (D2 to D3) are used in the same quantities, as recommended below.

TABLE XLI. DIETARY SOURCES OF VITAMIN D

Food	**Portion**	**Amount of vitamin D**
Vitamin enriched milk	240 ml	100 UI
Vitamin enriched orange juice	240 ml	100 UI
Vitamin enriched cereals	4 spoons	80 UI
Pickled herring	100 g	680 UI
Smoked salmon with bones !!!	100 g	624 UI
Pickled mackerel	100 g	360 UI
Conserved Sardines	100 g	272 UI
Hard cheese	100 g	44 UI
Raw shiitake mushrooms	100 g	76 UI
Multivitamins	1 cp	200-400 UI

Considering the above, please think about quantities and foods that are recommended to have a sufficient intake of vitamin D from food only.

The recommend daily doses of vitamin D are (IOM 2010):

- 0-12 months 400 UI
- 1-70years old 600 UI
- > 70years old 800 UI

If anti osteopororsis agents are used, especially in the case of antiresorptive it is strongly recommended for a higher maintenance doses of about 1000-1200 IU dose/day. Treatment with anti osteoporotic without vitamin D supplementation decreases the desired effect.

Calcium and vitamin D administrationn is essential simultaneous with some category of drugs like the anti osteoporosis agents Their absence from the treatment management has the fallow certain effects:

- Decrease effectiveness of light anti resorption agents: estrogen and medium agents like : bisphosphonates
- hypocalcemia as a side effect associated with strong antiresorptives like parenteral bisphosphonates and denosumab
-hypocalcemia as a severe side effect in case of bone-forming injectable drugs administration: PTH

Major anti Osteoporotic Drugs

The therapy target is to prevent fragility fractures, therefore all drugs on the market have / had to demonstrate their efficiency in fracture prevention.

Monitoring DXA is used in everyday medical practice, it is considered a surrogate marker of fracture risk reduction.

On the market are multiple classes of anti osteoporotic drugs:
1. the antiresorptive class = estrogen, selective estrogen receptor modulators, bisphosphonates, calcitonin, Denosumab, Odanacatib
2. the anabolic class= PTH, Abaloparatid, antibodies antisclerostina
3. dual drug = strontium ranelate

Estrogens
Only oral or systemic administerd estrogen influence the rate of bine demineralization, the needed time to treat beeign around 10 years.

- Side effects = minimal
- Precaution and contrainidications: Breast cancer, cancer of the endometrium, trombembolism history, and severe hepatic pathology, the presence of cardiovascular disease at the time of medication, epilepsy.
- The maximum length of administration = 5 years (a duration that is ineffective for bone quality improvement)

Estrogen receptor modulators with the class representative = raloxifene, bazedoxifene

- Oral, daily
- Skeletal-effect: Inhibits the markers of bone resorption. Lowers the risk of fragility fractures at vertebral level only, unproven effect on hip or nonvertebral fractures.
- Extraskeletal effect: inhibits endometrial proliferation, lower the risk of breast cancer
- Side effects: no influence on climax symptoms, even exacerbates the neurovegetative syndrome, cause muscle cramps and contractions, increases the risk of thromboembolic events, increase the risk of fatal stroke,
- Contrainidications and precautions: Women on fertility age, history of venous thromboembolic events (active or history), including deep vein thrombosis, pulmonary embolism and retinal vein thrombosis, hepatic dysfunction including cholestasis., severe renal dysfunction, unknown etiology of uterine bleeding, endometrial cancer suspicious.
- The length of administration = an usage limit is not exactly appreciate, most studies recommends not exceed 5-6 years

Bisphosphonates

1. Are the most recommended anti soteoporotic agents
2. The class representative are:
    a. alendronic acid– oral, weekly administration,
    b. Ibandronic acid –oral , monthly administration or once in 3 months intravenously
    c. risendronic acid – oral, twice on month administration
    d. zolendronic acid –annually administration , intravenously
    e. acid pamindronic- once in 3 month administration

    -Mecanism Action: regardless of the type of preparation or administration way, the entire class of bisphosphonates cause the osteoclasts apoptosis, filling space left after remodeling

    -effect is greater in the trabecular compartment (which is as we know 5 times more active than the compartment cortical). The result is an increase in bone mineral density, markers of bone resorption and decrease after a few years of use the risk fracture. The effect on bone mineral density lasts up to 6 years.

    -administration:
3. **An adiministration over 5 years lenght it is not justified**
4. side effects:
    a. Gastric intolerance , dyspepsia, stomach ache, nausea
    b. flu like effect - chills, malaise, myalgia, symptoms which last for 12-14 hours maximum, a side effect mostly seen after intravenously administration

c. Hypocalcemia, especially seen in parenteral preparations
d. Eye effect
e. Renal dysfunction: glomerulosclerosis segment (pamindronic acid), tubular dysfunction (zoledronic acid)
f. Jaw osteonecrosis -rarely side effect, more associated with injectable doses (after antiresorptive doses, given in bone metastases tumor, rarely after osteoporotic doses)
g. atypical fractures- subtrochanteric fractures -in case of trickle use

Contraindications and precautions:

h. digestive ulcer , gastritis, gastroesophageal reflux for the drugs with oral path
i. Creatinine Clearance > 35 ml / min
j. Incorrect diagnosis of osteoporosis: ostemalacia, osteogenesis imperfecta, hyperparathyroidism

After 5 years of therapy it is strongly recommend the drug cessation for 1 year - named the drug holiday.

Calcitonin

- is a antiresorptive biological agent
- induces a minimal increase in bone mineral density and discreet decrease in markers of bone resorption
- has a strong analgesic effect
- is preferred to be administrated on an extreme short period of time, for exclusively analgesic benefit , not as case an antiosteoporotic agent
- is not part of the usual's medications used in osteoporosis treatment algorithms

Denosumab

- It is a human antibody, monoclonal type Ig2 that binds with high affinity to human RANKL, which normally activates the osteoclasts precursors. As an specific effect determine the specific binding and strong inhibition of osteoclastic inhibitors with important bone resorption.
- Denosumab is at the moment the only representative of this class of drugs
- subcutaneously every 6 months
- special features: the treatment cessation cause a rebound phenomenon, with a discrete decrease in bone mineral density, accelerating for a short period of bone resorption
- side effects:
    - Hypocalcemia, muscle cramps and fasciculations (given the lack of insufficient additional vitamin D)
    - lombar pain, extreme limbs pain, musculoskeletal pain, cystitis and hypercholesterolemia
    - Constipation , flatulence

- Infection in the upper respiratory tract (5%)
- cutaneous rush

- Contraindications and precautions: hypersensitivity on the compound, undiagnosed hypocalcemia

Odanacatib

Odanacatib is a cathepsin K inhibitor that provides bone formation with decreasing bone resorption, not only increasing bone mineral density and strength; is still under study.

PTH = Teriparatide

- PTH is an anabolic hormone. The teriparatide is the 1-34 portion of the natural parathyroid hormone,that during intermittent administration causes acceleration of bone formation (increase the number of osteoblasts, inhibits osteoblasts apoptosis and the production of sclerostin), rebuilds bone geometry, increases bone volume by periosteal apposition, thickens cortical bone, increase the number and the trabecular thickness.
- Daily subcutaneous administration
- The length of the therapy = 2 years
- Bone-effect: increase bone mineral density, decreases the rate of vertebral and nonvertebral fracture by 65% (2 years) and on peripheral with 53% (2 years). The effect on the hip is seen after more than 2 years of treatment.
- It targets elderly with severe osteoporosis and multiple fragility fractures.
- is not a first line medication, being recommended as line 2 or 3 therapy
- However best effects are observed in naïve patients (who no personal history of antiosteoporitic medication). The administration of the teriparatide after a bisphosphonate needs a longer relapse period until a consistent increase in bone mineral density can be noticed, especially in the femoral neck.

Indications:

1. women with severe osteoporosis: T score <-3 and at least one fragility fracture
2. postmenopasaul women, with T score <-2.5 + unresponsive to treatment with bisphosphonates: fragility fracture under therapy, about 8% decreased bone mineral density in the last 5 years
3. postmenopausal women with osteoporosis and side effects / proven intolerance to bisphosphonates
4. osteoporosis increased risk fracture : T-score> /2.5, with a minimal increased FRAX score or minimum 3 risk factors
5. secondary osteoporosis after corticotherapy

Contraindication and precautions:
- hypersensitive to the active substance
- pregnancy and lactation
- pre existing hypercalcemia
- impaired renal function
- disturbance in bone metabolism (Including hyperparathyroidism and Paget's disease) other than primary osteoporosis or glucocorticoid-induced osteoporosis
- Unexplained elevations of alkaline phosphatase
- previously skeletal radiotherapy or implant radiation beam
- malignancies or bone metastases should be excluded from teriparatide therapy

k. Side effects
l. Anemia
m. Hypercholesterolemia
n. Depression
o. Dizziness , headache , sciatic pain, syncope
p. Palpitations
q. Muscle cramps
r. Hypocalcemia in case of inefficient calcium supplemental

Strontium ranelate

- It Is a special preparation with dual mechanism : stimulates bone formation and inhibits the bone resorption
- it is daily administrated, orally
- Skeletal-effect: increase bone mineral density, decrease the risk of vertebral fracture by 49% (1 year of treatment), with 19% decrese in risk of nonvertebral fractures (minimum 1 year) and 36% decrease of the femoral neck fractures risk (minimum 2 years)
- side effects:
  - gastric intolerance
  - facilitates thromboembolic mechanisms
  -Contraindications and precautions:
  - personal history of Thromboembolic antecedents or thrombophilia
  - Important untreated coronary disease
  - personal history of myocardial infarction
  - untreated high blood pressure
  - ischemic or hemorrhagic vascular stroke

TABLE XLVII THERAPY MANAGEMENT - THE AGENTS RESPONSE ON DIFFERENT BONE SITES

Medication	**spine**	**Femur**
Estrogen	✓✓	✓
Alendronic acid	✓✓✓	✓✓
Risendronic acid	✓✓✓	✓✓
Ibandronic acid	✓✓✓	✓✓
Zolendronic acid	✓✓✓	✓✓
Calcitonin	-	-
Raloxifene	✓	±✓
Bazodoxifen	✓	±✓
Strontium ranelate	✓✓✓✓	✓✓✓
Denosumab	✓✓✓	✓✓
Teriparatide	✓✓✓✓	✓
PTH 1-84	✓✓✓✓	✓

Treatment follow up- rules:

1. it is required that DXA monitoring should be done on the same DXA device, because of the device feature of LSC value (least significant change);
2. the value of the bone demineralization progression it is calculate considering the variation in g / cm2 and percentage not by assessing T score value;
3. increase in bone mineral density on the spine and femoral neck, but maintaining a T-score <-2.5 = continue treatment with the same preparation
4. increase in bone mineral density at the femoral neck and spine, but with a T-score> -2.5 =maintenance treatment with vitamin D and calcium
5. strictly increase in bone mineral density on the spine vertebral = increase without an effective increase in the mineral density of the vertebral body, the arthrosis component - revaluation prescribed medication
6. increase bone mineral density at the spine with decreased mineral density at the femoral neck = change antiosteoporotic type of drug

VI. ADRENAL

VI.1. ADRENAL HORMONES PHYSIOLOGY

Adrenals are 2 small glands, located above the kidneys, 3-5 cm long, 1.5-2.5 gram weight. They consist of outer cortex, with mesodermal origin, representing 90% of the adrenal glands, sustaining the steroidal secretion of glucocorticoids, mineralocorticoids and sexual steroids, respectively inner medulla, originated from the neural crest, sustaining the catecholamine secretion.

The secretion capacity is dependent of the architectural particularities, enzymatic machinery present in different adrenal regions, respectively blood supply: from the outer cortex toward the central area, radially, sinusoid system. These elements are different at the level of the 3 cortical adrenal layers:

- Zona glomerulosa, the most outer layer, abundant in smooth endoplasmic reticulum, the unique source of mineralocorticoid secretion, due the unique presence of P450 Aldosterone synthetase.
- Zona fasiculata, the medium cortical layer, abundant In lipid droplets, which produces glucocorticoids, respectively androgens, due to the presence of 17 alpha hydroxylase and P450 aromatase.
- Zona reticulata, the most inner layer of the adrenal cortex, which develops only 3 years postnatal, sustaining glucocorticoids and androgens synthesis.

The steroidogenesis starts always with cholesterol (plasma membrane cholesterol or cytoplasmic pool of cholesterol), the unique source of all steroids, the first synthesis step being always the transformation of cholesterol in pregnenolone, induced by Steroid Acute Regulatory enzyme, STAR, under the direct stimulation of ACTH.

ACTH stimulates the cholesterol release from the intracellular cholesterol esters., controlling the synthesis and secretion of Glucocorticoids and androgens. Under normal conditions, ACT does not influence the mineralocorticoid secretion, which is under the renin –angiotensin system control. Only in cases of tumoral ACTH overproduction, there is also an increase of the mineralocorticoid production.

Adrenal medulla could be considered a sympathetic nervous system ganglion., containing large chromaffin cells, neuronal cell with catecholamine secreting proprieties. Adrenal medulla is responsible for the secretion of 80% of the circulating epinephrine respectively 15-20% of norepinephrine secretion.

VI.1.1. Glucocorticoids

Glucocorticoid secretion:

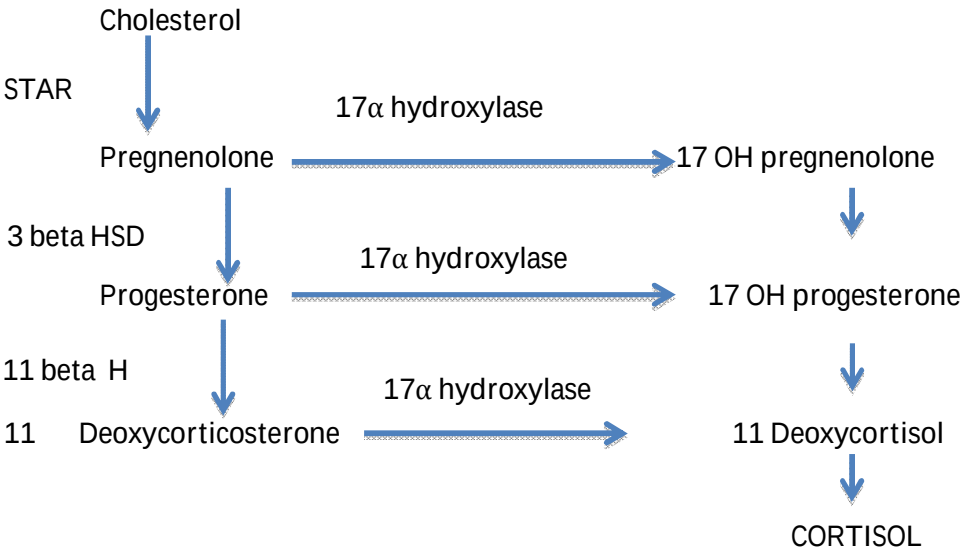


Figure 25. The glucocorticosteroid secretion line schema

Glucocorticoids secretion is present only at the level of fasciculate and reticulate zones, due to the unique expression of 17 alpha hydroxylase enzyme, the key step in glucocorticoid synthesis.
Glucocorticoid control:

- Basal circadian rhythm of ACTH will induce a cortisol circadian rhythm, with the maximum secretion peak around 04.00-06.00 AM, and the nadir around 07.00 PM. This secretion type ensures high levels of cortisol during morning, throughout the day, with decrease in the afternoon, and recovery period during night.
- The circadian rhythm is present in all diseases, even in Addison disease, and is overwritten only in tumoral glucocorticoids productions.
- Any type of stress: physical, emotional, chemical, surgery, trauma, pain, low temperatures, will induce CRH activation, with secondary ACTH release with subsequent increase of cortisol secretion.
- After adequate increase, peripheral hormonal levels control central structures by the feedback control loops:
    - Long feedback from adrenal to pituitary
    - Long feedback from adrenal to hypothalamus
    - Short feedback loop from pituitary to hypothalamus

Cortisol, the main representative of the glucocorticoids, is a lipophilic hormone, that circulates in conjugated formulations: sulphate, glucoronide, bound to carrier proteins: Cortisol Binding Globulin (CBG) being the main carrier protein. CBG is produces at the hepatic level, being influence by different diseases, as all carrier proteins described before:

↑ CBG	↓ CBG
hyperestrogenic states	CBG deficiency
HYPERThyroidism	
hypothyroidism	
Diabetes	liver disease
hematologic disorders	nephrotic sd.

CBG can be saturated by plasmatic cortisol levels higher than 25 mcg/100 mL. Under normal conditions only 10% of the general cortisol circulates free, being responsible for the biological affects. IN cases of increased cortisol production, the fraction of free cortisol will increase significantly, due to the saturability of the CBG, not described in other hormonal carrier proteins.

The biological effect need the coupling of cortisol to its receptors, intracellular receptors, all cells having glucocorticoid receptors.

The main biological effects of cortisol are:

1. METABOLISM:
   - Glucose homeostasis
     - Increases gluconeogenesis
     - increases plasma glucose levels
     - decreases glucose utilisation
     - increases hepatic glycogen synthesis
     - permissive effects of glucagon and catecholamine effects
   - Proteic homeostasis
     - Degrades muscle protein and increases nitrogen excretion
     - Decreases amino acid utilization
     - Increases proteolysis
   - Lipid homeostasis
     - Redistributes fat
     - Increases fat mobilization

2. Hemodynamic
   - Maintains vascular integrity and reactivity = vascular reactivity
   - Maintains responsiveness to catecholamine pressor effects
   - Maintains fluid volume

3. Immune function
    - Increases antiinflammatory cytokine production
    - Decreases proinflammatory cytokine production
    - Decreases inflammation
    - Inhibition of prostaglandin and leukotriene
    - Inhibition of bradykinin and serotonin
    - Decreases circulating eosinophil, basophil and lymphocytes
    - Alteration od cell mediated immunity
    - Increases neutrophil, platelet and red blood cell counts

4. Bone cartilage: decreases IGF1 effect
5. Antiproliferative effects of fibroblasts and keratocytes
6. Normal secretion is mandatory for the milk secretion
7. Influence surfactant production at pulmonary alveoli level
8. Modulates the ADH release, according to the volume balance of the system
9. Favors the kidney filtration rate
10. Affect thyroid hormone interactions by favorinf peripheral conversion of FT3 and T4, inceraeing the thyroid hormone metabolism.
11. Stimulates the appetite
12. CNS
    - Suppression of REM sleep phase
    - Influence the hippocampal glutamate receptors, conditioning the memories
    - Increases the intraocular pressure

VI.1.2. Andrenal androgens

Androgens continue the steroid line, starting from the over mentioned intermediate hormones. The androgen secretion is present not only at the adrenal level, but also at the levels of gonads, following the same secretion steps. The gonads do have only the enzymes needed for androgen synthesis.

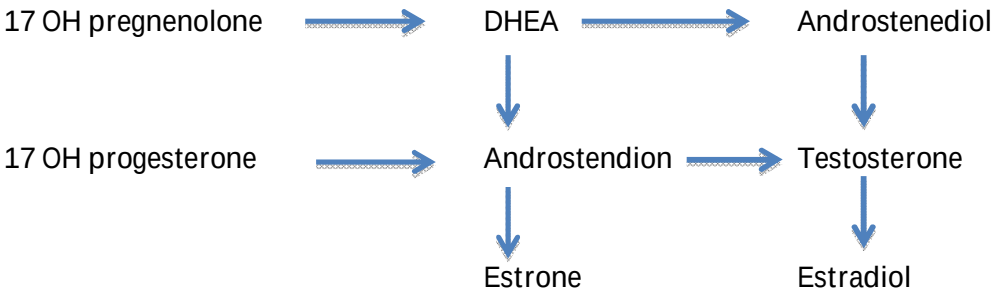


Figure 26. Adrenal androgens secretion schema

Androgens effects differ in male versus women, because of the different signification from the general androgen level in both genders: in women, adrenal androgens represent 50% of the total androgens in the adult women body. Here they are responsible for:

- general feeling of well being
- influence arousal
- maintains libido
- facilitates bone growth process
- maintains muscle mass and bone mass
- induces the formation and maintenance of axillary and pubic hair

Deficiency will induce loss of axillary and/or pubic hair with hypoactive desire disorder.

In men, the effects are incomplete understood and less important, because the adrenal androgens represent up to 5% of the total androgens in the male adult. The described effects are the same as in female, with less impact in case of deficiency. Interestingly enough, the deficiency will induce increase risk of cardiovascular disease.

Regulation

The androgen production is under the control of ACTH, all conditions inducing cortisol secretion will also induce androgen secretion.

There is to mentioned a special negative feedback, seen only in hyper secretion cases, when high plasmatic levels of adrenal androgens will inhibited, the gonadostat. The same cross negative feedback is seen in any case with increased glucocorticoid production.

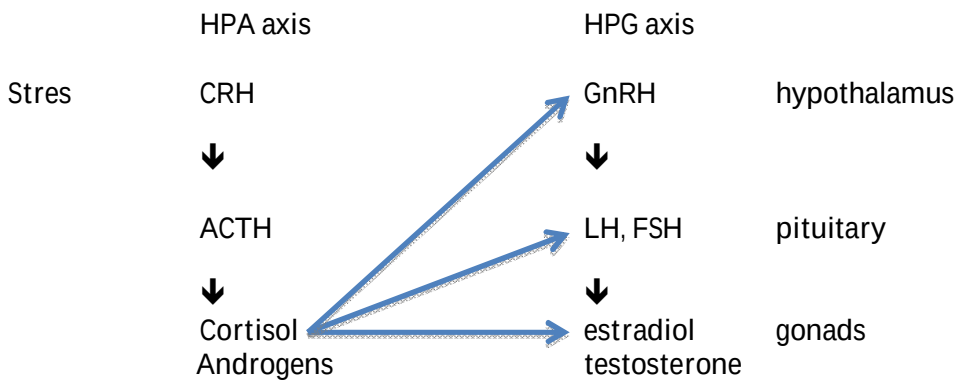


Figure 27. Cross feedback of adrenal steroids on gonads

Axis evaluation of lie glucocorticoid line evaluates:

BASAL ASSAYS

1. ACTH basal = an unique plasmatic evaluation of ACTH is not reliable indicator of pituitary function because of the short half-life time, and also because a normal ACTH value can induce a false negative result and cannot be used, as TSH or FSH, to the screening evaluation assay in the adrenal function. Also a normal ACTH level does not mean normal pituitary function and does not evaluate the response to stress, essential for the survival.

2. Combined evaluation of ACTH + cortisol can make a difference between central versus peripheral diseases:

	Central disease	Peripheral disease
Insufficiency	↓ACTH + ↓cortisol	↑ACTH+ ↓cortisol
Hyper secretion	↑ACTH + ↑cortisol	↓ACTH + ↑cortisol

3. plasmatic cortisol evaluation has to consider:
    1. the episodic cortisol secretion
    2. CBG dependent evaluation = consider diseases that significantly alter CBG
    3. Circadian rhythm –different normal values during the day. Always the exact hour of sampling must me known
    4. Reactive increase in any stress situation - not every high cortisol level means tumoral hyper secretion
    5. No evaluation of the functional adrenal reserve, just evaluation of the moment of blood sample
    6. Always integrate the value with the clinical picture and situation

4. Midnight salivary cortisol is a measurement not affected by CGB/protein changes, being the ELECTION method for screening for TUMORAL HYPERPRODUCTION

5. Free plasma cortisol can be also use, unaffected by carrier proteins levels, but still influence by the HPA axis.

6. Urinary free cortisol = 24 hours urine can difference between tumoral and reactive increase in cortisol, but the use of the evaluation decreased after the appearance of salivary cortisol evaluation. Normaly, less then 1% of the secreted cosritsol in excreted in the urine. IN case of hypersecretion, when te binding capacity f CBG is exceeded, plasma cortisol increases, with proportional increase of the urinary cortisol. The test id useful in cases of tumoral hyper secretion, but cannot be used in cases of insufficiencies, because of lack of sensibility.

7. 17- Hydroxycorticosteroids = largely of historical interest and should not be at present used.

FUNCTIONAL ASSAYS always need to be used, in case of a suspicion of adrenal dysfunction.

I. ***Stimulatory testes*** have to be used in case of any suspicion of insufficiency:

PITUITARY FUNCTIONAL RESERVE – evaluates the capacity of ACTH to increase, in case of high needs. The reserve should be tested in cases of suspected ACTH insufficiency. Different stimulation mechanisms can be used:

= hypoglycemia (Insulin induced)
=Metyrapone (cortisol biosynthesis inhibition)
=CRH

In case of normal ACTH function and reserve there will be an ACTH increase and also a cortisol increase
In case of insufficiency there will be no ACTH increase with no adrenal response:

- Metyrapone test = blocks cortisol synthesis, ↑ ACTH, ↑11 DOC
  normal: ACTH > 100 pg/mL 11 DOC > 7 ng/dL
  I insufficiency: ↑ACTH no DOC increase
  II insufficiency no ACTH no DOC increase

- Hypoglicemia test = ↑CRH, ↑ACTH, ↑cortisol
  normal ACTH > 100 pg/mL cortisol > 20 mcg/dL
  I insufficiency ACTH > 100 pg/mL no cortisol increase
  II insufficiency No ACTH increase no cortisol increase
  III insufficiency No ACTH increase no cortisol increase

ADRENAL FUNCTIONAL RESERVE evaluates the capacity of cortisol to increase, in case of high needs, secondary to the ACTH physiological release.

The test is very simple, and uses ACTH with direct measurement of cortisol:

- Rapid ACTH test – iv/im 250 mcg rACT
  basal cortisol, 30' stimulated cortisol > 20 mcg/dL
  ↓↓↓ I/ II insufficiency
- Low dose ACTH – not for clinical routine

II. ***Inhibitory testes*** need to be used to confirm the tumoral hyper secretion. Dexamethasone, an artificial glucocorticoid, with high potency of suppression of adrenal axis . Different inhibition schema are used:

- midnight inhibition: 1 mg DXM 23.00, with measuring the morning plasmatic cortisol, that should decrease below 1.8 mcg/dL

  In presence of any tumoral excess there will be no significant decrease of cortisol. This is the screening test I case of suspected Cushing.

- high dose inhibition: 8 mg DXM 23.00, with measuring the morning plasmatic cortisol, that should decrease at least with 50%.

  Adrenal tumors will not respond to this inhibition, but pituitary ACTH production can respond to this inhibition.

- 2 days inhibition: need the use of 4 doses a day, 2 following days of 2 mg DXM with measuring te plasmatic cortisol in the following morning. The same 50% decrease is expected in plasmatic cortisol. Cushing Sd will show a lesser inhibition, but ectopic sd will show no inhibition al all.

TABLE XLVIII. INHIBITORY TESTS IN DIFFERENT HYPER SECRETING SYNDROMES

Disease	ACTH	Plasmatic Cortisol	Midnight DXM	High dose DXM	2 days DXM
Cushing disease	↑	↑	Negative	Positive	-/+
Cushing sd	↓	↑	Negative	-/+	Positive
Ectopic ACTH	↑↑	↑↑	Negative	Negative	Negative
Ectopic CRH	↑↑	↑↑	Negative	Negative	Negative
iatrogenic	↓	↓	0	0	0

Androgen evaluation:
Basal adrenal androgens evaluation should be the following:

- IN WOMEN
  - 17 Oh progesterone = the precursor of all androgens is increased in tumoral hyper secretion, adrenogenital syndrome, but also in polycystic ovarian syndrome, because the ovarian steroid synthesis chain is the same as in the adrenal cortex
  - DHEAS = is important mainly in insufficiency syndromes
  - Androstendion = is showing both adrenal and ovarian steroids
  - Urinary products: 24 hour urine sampling: 17 cetosteroids should not be used because of the very low sensitivity and specificity.

- IN MALES
  - 17 OH progesterone is evaluated in suspicion of adrenogenital syndrome
  - other adrenal androgens are not currently evaluated

VI.1.3. Mineralocroticoids

Mineralocorticoid secretion is present at he level of zona glomerulosa, the place where there is 17 hydroxilase line but there is Aldosterone synthetase, which will induce the following synthesis from the pregnenolone, progesterone line to the mineralocorticoid hormones: 11 Deoxycorticosterone, corticosterone and aldosterone.

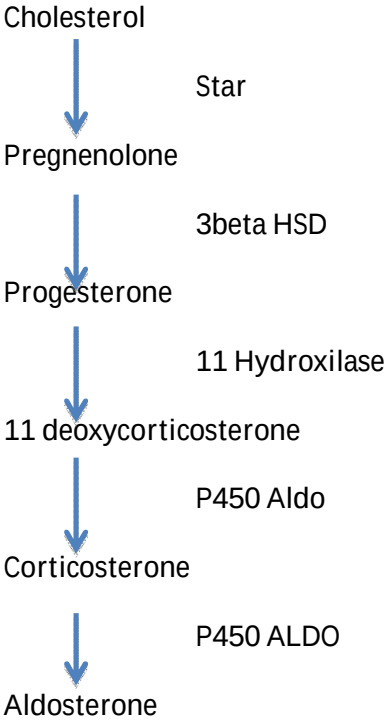


Figure 28. Mineralocorticoid secretion schemas

Aldosterone, because of its lipophilic structure, circulates bound to albumin and CBG (50-70%) respectively 30-50% circulate free.

11 Deoxycorticosterone, corticosterone and Aldosterone are part of the renin angiotensin system, that preserves the fluid and Natrium balance in the body. In any case of decreased circulatory volume:

1. Vomiting
2. Diarrhoea
3. Intense/prolonged sweating
4. Other causes of salt and water loss

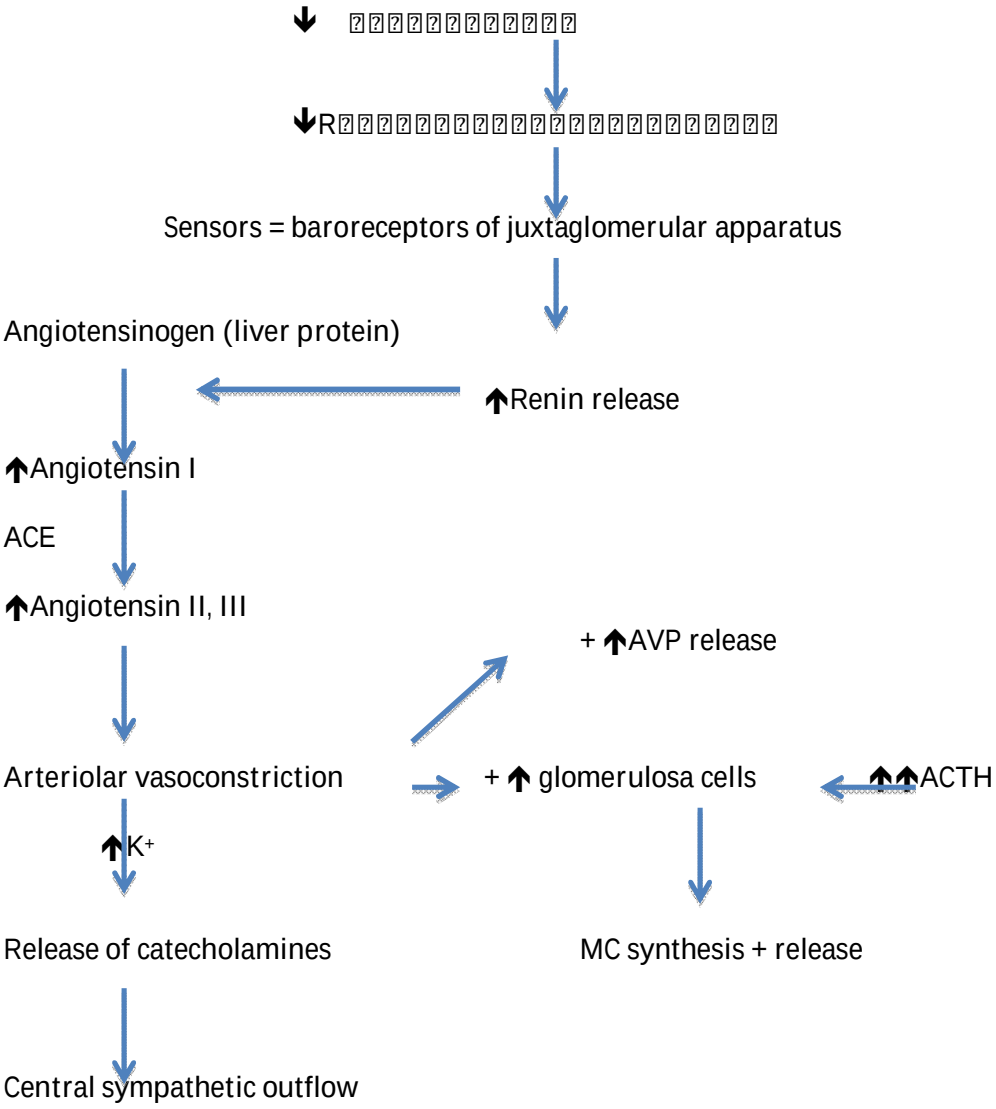


Fig 29. Mineralocorticoid secretion control

Mineralocorticoids effects are dependent of the MC effect of cell membrane receptors, similar to glucocorticoids receptors, but there is an active inactivation of glucocorticoids at the renal sites.

There is also an additional control mechanism of Aldosterone synthesis, with stimulation is any condition associated with increased kalemia, such in strenuous exercise or high food intake, with increase of Aldosterone release form the secretory vesicles, with secondary increase of kalium excretion, not only at renal level, but also excretion in feces, saliva and sweat, till the restoration of normal kalium levels.

= classic effect: renal cortical collecting duct induces:

- **open Na^+ channels on the luminal membrane = Na^+ reabsorption**
- **↑luminal electronegativity = tubular K secretion**
- **Na-K ATP $_{aza}$ on the basolateral membrane = Na export, K uptake**
- **Water reabsorption in following the Natrium influx, at the luminal level** (we do not have a free water reabsorption as described in the AVP renal effect).

= nonclassic effect:

- Expression of collagen genes
- Activation of tissue growth factors: TGFβ 2, PAI 1
- ↑Genes mediating inflammation

These effects are responsible for microangiopathic changes, necrosis and fibrosis, which are present in all situations with increased MC level, even in unbalanced cases, not necessary in tumoral increased cases. These changes are present at the heart, vessels and kidney levels.

Mineralocorticoid evaluation:
BASAL ASSAYS

1. Natrium and Kalium balance
2. Plasmatic Aldosterone level
3. Renin plasmatic activity
4. Paired plasmatic Aldosterone + plasmatic renin activity can be used without

interrupting antihypertensive medication, without posture stimulation (standing up).

The use of Angiotensin Conversion Enzyme or Angiotensin II receptor blockers can induce a false increase of plasmatic renin activity .

- ✓ ↑PAC > 15 ng/dL
- ✓ ↓ PRA < 1.0 ng/mL/h, independent of medication
- ✓ plasmatic aldosterone concentration (PAC)/plasma renin activity > 20
- ✓ sensitivity of 80% and specificity of 75%

FUNCTIONAL ASSAYS

The functional tests are used only in cases of suspicion of tumoral secretion. There are no dynamic tests in cases of insufficiency suspicion.

- Oral sodium load test
  - High sodium intake: total 5000 mg in 3 days
  - In days 3: 24 H urine: Aldosterone, sodium, creatin
  - > 200 mEq sodium
  - ALD > 12 mcg/24 h = consistent for HyperALDO
- Intravenous saline infusion test
  - 2 liter NAcl0.9% Iv pump 4 hours
  - Measure PAC: normal PAC < 5 ng/dL
    HyperAldo > 10 ng/dL
    intermediate 5=10 ng/dL I HTA

VI.1.4. Adrenal medulla

The catecholamine synthesis is based on the ingested tyrosine and also from synthetized phenylalanine. Both substances are concentrated at neuronal/cromaffin cell structures.

The dietary sources of tyrosine are: spirulin, dried fish (cod), game, veal, goose, duck, canned fish, caviar, cocoa, protein powder (soy based), liver, cuttlefish, bratwurst, oat bran, wheat bran, rice bran and dried herbs.

The steps in catecholamine synthesis are:

1. Thyrosine ➔ Dopa rate limited step of catecholamine synthesis
   ? Axonal nerve terminal
2. Dopa ➔ Dopamine
   all tissues: kidney, brain, vas deferens
3. Dopamine ➔ Norepinephrine secretory vesicles
   93% nonadrenal sympathetic nerve cells
   7% adrenal medulla
4. Norepinephrine➔ Epinephrine – *major source* of circulating Epinephrine

Conversion = dependent on PNMT, cortisol dependent enzyme

5. Storage = intracellular = cytoplasm vesicles (dynamic equilibrium)
6. Secretion coupled with release
7. Secretory vesicles: catecholamine: ATP = 4+1 + neuropeptides, Ca, ACTH, VIP, chromograninm enkephalins
8. Membrane cell de polarisation .... Catecholamine release

The adrenal medulla is responsible for the secretion of up to 90% of circulating Epinephrine and only -10% of Norepinephrine, in response to any increased body need:

- Exercise
- Angina pectoris
- Myocardial infarction
- Hemorhhage
- Anesthesia
- Surgery
- Hypoglicemia
- Asphyxia
- Hypoxia (Nadr)

All catecholamine have very short half life time, around 2 minutes. 50% of the total circulating catecholamine circulate also bound to albumins, They are metabolized by the liver, and are excreted as metabolites:

- **Vanillylmandelic acid** (VMA) = Adr, Nadr metabolite
- **Homovanillic acid** (HVA)= Dopamine metabolite

The effects of catecholamine are diffuse, because of the large distribution of specific receptors:

- Alpha1 receptors more sensitive to Norepinephrine
- Alpha 2 receptors more sensitive to Norepinephrine
- Beta 1 receptors equal sensitivity to norepinephrine and epinephrine
- Beta 2 receptor more sensitive to epinephrine
- Beta 3 receptors more sensitive to norepinephrine

TABLE XLIX. DIFFERENT CATECHOLAMINE EFFECTS DEPENDENT ON THE MAIN RECEPTOR

	α1 adrenergic	α2 adrenergic	β1 Adrenergic	β2 Adrenergic
Vascular muscle	Vasoconstriction ↑BP	Vasoconstriction ↑BP		Vasodilation ↓ BP
Cardiac			↑Contraction force/rate	
Intestine	↑Sphincter tone Muscle relax		↑Sphincter tone ↓Motility	↑Motility
Pancreas cells		↓glucagon, insulin release		↑glucagon, insulin release
Prostate	↑Contraction, ejaculation			
Bladder	Detrusor contraction			Detrusor relaxation
Kidney			↑Renin secretion	T4→ T3
Uterus	↑ pregnant uterus contraction			↓nonpregnant uterus contraction
Skin	Pilomotor contraction			
Muscle				↑contraction ↑glycogenolysis
Adipose cell		↓Lipolysis		↑Lipolysis
Calorigenesis			↑calorigenesis	

VI.2. GLUCOCORTICOID HYPERSECRETION = CUSHING PATHOLOGY

VI.2.1. Etiopathogeny

The excess of glucocorticoids can be seen in one the following situations:

- Chronic glucocorticoid therapy = iatrogenic Cushing
- Spontaneous = endogenous hyper secretion due to
  - Ectopic CRH hyper secretion
  - Ectopic ACTH hyper secretion
  - Pituitary tumor- ACTH producing
  - Adrenal hyper secretion
    - Adrenal tumors: adenoma and carcinoma
    - Adrenal hyperplasia

Another classification of possible causes of hyperlucocorticoids is in respect to ACTH dependency:

- ACTH dependent disease:
  - Pituitary adenoma – ACTH producing
  - Nonpituitary neoplasm – ectopic CRH or ACTH secretion
- ACTH independent disease:
  - Iatrogenic use: synthetic glucocorticoids, megestrol acetat
  - Adrenal tumors (adenoma, carcinoma)
  - Nodular adrenal hyperplasia:
    1. Primary pigmented nodular adrenal hyperplasia
    2. Massive macronodular adrenonodular hyperplasia
    3. Food dependent (GIP mediated)

Regardless the cause of glucocorticoids excess, the sign and symptoms are similar, mainly dependent on the effects of glucocorticoid excess on systems:

- Obesity
  - Most common
  - Central: face, neck, trunk, abdomen, extremities sparing
  - MOON FACE = 75%
  - BUFFALO HUMP 65%
  - At least hat redistribution from the periphery to the abdomen
- Skin changes
  - Thinning = transparent appearance
  - Facial pltehrora
  - Bruisability = 40%

- Striae = 50% (unusual in young patients) = ed, purple, depressed wide (0.5-2 cm)
- Slowly healing
- Acne (GC and androgen excess)
- Fungal infections: tinea versicoloc
- Hirsutism
- 80% females = adrenal androgens!!!
- Facial
- Abdomen, breasts, chest, upper thighs
- Virilism = exception !!! Carcinoma

- Hypertension
  - Classic = 75% cases
  - Difficult/resistant to treatment
  - Increase morbidity/mortality in Cushing
- Gonadal dysfunction
  - Inhibition of FSH+LH
  - Amenorrhea 75%, infertility
  - Decrease libido/sexual function
- SNC
  - Emotional lability, irritability
  - Depression, anxiety, poor concentration, poor memory
  - Sleep disorders 0 insomnia/morning awakening
  - Psychotic disorders: delusion, hallucinations, paranoia
  - Loss of brain volume … Partially reversible after treatment
- Muscle = weakness, muscle loss
  - Typical proximal: scapular/pelvic arch atrophy: specific pain and altered function, seen in cases of staris climbing, coming up frona chair, helding the arms above the head.
- Bone – demineralisation due to altered bone turnover
  - Growth delay … Children = anatgonst effct on IGF1
  - Bone loss… Adults = increased osteoclast acitivty
  - Fragility fractures = altered bone structure and resitance
  - Compression spine fracture 20% of cases
  - Avascular femoral/humeral head necrosis = typical complication of severe glucocorticoida effects
- Renal calculi – because of hypercalciuria –described in up to 15% of cases
- Thirst + polyuria
- Metabolism
  - Hyperglicemia/ AGT/DM
  - Increased hyperglycaemic tendency
  - Increased DM complications
  - Increased protein destruction: skin, muscles and bone
  - Fat accumulation, increased dyslipidemia prevalence

- **Typical signs**

CUSHING DISEASE = ACTH secreting pituitary adenoma

Mechanism of hypersecretion:

1. ACTH hypersecretion + bilateral adrenal HT + hypercortisolism
2. Absent circadian periodicity of ACTH and cortisol
3. Absent responsiveness to stress
4. Abnormal feedback to glucocorticoids
5. Subnormal responsiveness of GH, TSH, LH+FSH to stimulation
6. Androgen excess

= GCS hyper secretion + androgens hype secretion= bilateral adrenal cortex hyperplasia: reticularis and fasciculata zone: Cortisol + androgen excess

Clinical aspects:

- The most frequent cause of Cushing 80%
- More frequent in females with a ratio of 8:1
- Max 20-40 years, but with a general range from childhood u to 70 years of age
- Mostly pituitary adenoma are diagnosed as microadenoma (50%<5 mm, 90% < 1 cm) because of the suggestive clinical signs that allow a precocious diagnostic)
- Diffuse corticotroph cell hyperplasia: very rare
- As all secreting adenomas, the 4 typical syndromes can be described:

Somatic syndrome = morphological sd = typical Cushing signs
Tumoral syndrome = functional sd = compression signs
Hormonal syndrome = endocrine sd = other pituitary insufficiencies due to mechanical/chemical effect
Metabolic syndrome = hyperglicemia

CUSHING SYNDROME = ADRENAL TUMOR

Mechanism:

1. Unilateral CORTIZOL secretion
2. Associated adrenal involution contralateral gland + uninvolved isolateral gland
3. Central suppression of CRH + ACTH
4. !! due to the functional suppression of the healthy, nontumoral tissue, after surgery, the functional insufficiency remains, up to several weeks.

- Adrenal adenomas induce due to an unique G Protein mutation proliferation only of 1 type of secreting cells mainly glucocorticoid secreting cells. The tumors can be encapsulated, with different sizes, up to 6 cm large and 70 gram weight. The clinical picture is typical, with insidious onset.

- Adrenal carcinomas are secondary to hyperplasia of multiple cells with multiple secreting steroids, with different glucocorticoids and/or androgens. Typically the tumors are big, with weight exceeding 100 gram, up to 1 kg. They have increased vascularization, capsule invasion and aggressive and rapid progression. Due to these facts the clinical picture is represented by hyper secretion of glucocorticoids and also androgens, with quick and rapid changing/evolving clinical signs.

ECTOPIC CUSHING

Mechanism:

1. Tumoral, non-adrenal and non-pituitary secretion, due to a paraneoplastic mechanism, of similar ACTH or CRH molecules
2. Typical tumors with CRH/ACTH secreting potential are:
   - Ectopic CRH

   Lung small cell carcinoma
   - Ectopic ACTH

   Lung carcinoid tumors
   Small cell lung carcinoma
   Neuroendocrine tumors
   Thymus, gut, ovary, pancreatic islet cell tumors, MCT

From the clinical point of view, in a known case with a typical pulmonary cancer, aggressive features appear, mainly hyperglycemia, with severe hypertension, due to associated mineralocorticoid hyper secretion

IATROGENIC CUSHING

1. can appear after glucocorticoid use, as corticotherapy (not as supplemental therapy) for at least 3 weeks, of 7.5 mg Prednisone or equivalents.
2. synthetic glucocorticoids have enhanced proprieties, for the immumodulator/antiproliferative or antialergic effect, but these benefic effects coma with also increased negative glucocorticoid effects, such as:
   - Bone demineralisation
   - Glaucoma
   - Posterior subcapsular cataract
   - Intracranial hypertension
   - Aseptic femoral/humeral necrosis
   - Pancreatitis
   - Myopathy
   - Psychogenic/psychotic changes
   - Growth impairment in children
   - Alteration of pre-existing diseases: DM, HT, GU/DU, psychiatric diseases

3. the iatrogenic effect is dependent on the glucocorticoid potency of the medication, the dose and also the treatment duration.
4. rapid onset of typical clinical features: obesity, round face, skin changes.
5. as in Cushing syndrome, because of the increase exposure to glucocorticoids, there is a functional suppression of the healthy adrenal tissue, functional suppression that can last up to 2 years after glucocorticoid treatment.

TABLE XLIX. SYNTHETIC GLUCOCORTICOIDS

Steroid	GC activity	MC activity	HhCSR axis suppression
Cortisol	1	1	1
Prednisone	4	0.75	4
Hydrocortisone	1	1	1
Corticosterone	0.8	0.8	0.8
Prednisone	4	0.75	4
Prednisolone	4	0.75	4
Metilprednisolone	5	0.5	5
Dexamethasone	25	-	17
Triamcinolone	5	-	4
Aldosterone	0.1	400	-
Fludrocortisone	10	125	10

VI.2.2. Diagnostic

In case of clinical suspicion of glucocorticoid excess, the following diagnostic steps have to be done:

1. Hyper secretion – screening tests
2. Abnormal feedback = inhibition tests
3. Localisation of primary disease = imaging techniques
4. Additional evaluation

SCREENING TESTS

- ACTH + cortisol central ≠ secondary ≠ ectopic

- plasmatic cortisol always increased,
  exception corticotherapy where , but still not
  any increase cortisol level means glucocorticoid
  excess

There are different situations where cortisol levels are high, without having a tumor: obesity, stress, rapid weight gain, and emotional stress.

- Midnight salivary cortisol – screening method = always increased (exception iatrogenic Cushing)
- Free plasma cortisol – always increased in any tumoral GCS hyper production

TABLE L. ACTH + CORTISOL LEVELS IN DIFFERENT GLUCOCORTICOID EXCESS SYNDROMES

Disease	ACTH	Plasmatic Cortisol
Cushing disease	↑	↑
Cushind sd	↓	↑
Ectopic ACTH	↑↑	↑↑
Ectopic CRH	↑↑	↑↑
Corticotherapy	↓	↓

DEMONSTRATING THE LACK OF NORMAL INHIBITION - inhibition tests
- 1st test is the midnight 1 mg Dexamethasone = that will exclude all the nontumoral increases of glucocorticoids
- 2nd test = high midnight inhibition test: no inhibition in Cushing syndrome and in ectopic Cushing, , possible normal response or partial inhibition in Cushing disease (to the still normal HPA function),
- 3rd test = 2 day inhibition test: no inhibition in Cushing syndrome and ectopic Cushing, normal inhibition or partial inhibition in Cushing disease.

TABLE LI. CONFIRMATION TESTS OF DIFFERENT CUSHING'S

Disease	ACTH	Plasmatic Cortisol	1 mg Midnight	8 mg midnight	2 days
Cushing disease	↑	↑	Negative	Positive	-/+
Cushing syndrome	↓	↑	Negative	-/+	-
Ectopic ACTH	↑↑	↑↑	Negative	Negative	Negative
Ectopic CRH	↑↑	↑↑	Negative	Negative	Negative
Cortico therapy	↓	↓	0	0	0

LOCALISATION TESTS
Once there is a conformation of important cortisol secretion, with no response to normal inhibition, the localization of the tumoral process is the definitive step in the diagnostic. Possible location are: adrenal, pituitary or ectopic, tumoral no glucocorticoid lesions.

- ***Pituitary evaluation*** – as in previous discussed chapters, the 1st diagnostic evaluation, with the best sensitivity and specificity, especially in this situation where are expecting a microadenoma, *is MRI with contrast agent*.
- There is important to consider that 1 positive MRI is not sufficient for a diagnostic (always must be preceded by biochemical suspicion and confirmation), because up to 10% of the general population have some changes visible at MRI evaluation.

- *Inferior pertrosal sinus sampling* = is a rare used evaluation, only in cases with normal pituitary MRI with clear suspicion of central disease.
- In case of clinical and chemical suspicion, if the pituitary MRI and abdominal Tomography are negative consider the evaluation of ectopic tumors.
- ***Adrenal evaluation*** – is possible with different evaluations:
    - *Computer tomography:* is the 1st imagistic screening toll in adrenal pathology. The density below 10 Hounsfield Units is typically for adenoma, higher than 10 Hounsfield Units is typically for carcinoma. Also higher washout is suggestive for benign lesions, respectively lower washout rate, with increased concentration are suggestive for carcinoma.
    - *MRI*: evaluates typical the carcinomas, as big, bright signal in T2 weighted images
    - *PET CT* increases sensitivity in special cases: tumoral diseases with secondary metastatic lesions/ paraneoplastic disease
    - *Scintigraphy with iodocholesterol (marked cholesterol that is preferential uptake in the overactive adrenal tissue_* = morphofunctional evaluation that evaluates the activity degree at adrenal level: unilateral hyperactivity = adrenal adenoma/ bilateral increased activity = ACTH dependent Cushing
- ***Ectopic evaluation*** = ***Chest CT, chest MRI***

ADITIONAL EVALUATION

- Blood count:
    - ↑Hb, Ht,
    - ↑N, ↓Eo, ↓Ba,↓ lymphocites
- Hyperglycaemia, AGT, DM
- Dyslipidemia: ↑Cholesterol, ↑Tg
- Ionogram: normal, posible: ↑Na^+ ↓ K, ↑Ca^{2+}
- ↑PO_4^- + alkalosis = ectopic ACTH
- Pituitary evaluation
- TSH + FT4
- FSH/LH + E2, progesterone
- IFG1 + GH
- Visual field
- free H_2O Clearance, U+ P Osm, ADH
- DEXA
- Conventional X ray = bone complications

VI.2.3. Differential diagnostic

- GCS forms
- Pseudo Cushing
  - Depression
  - Obesity with rapid weight gain
  - Chronic alcoholism
  - Bulimia nervosa
- Adrenogenital Sd
- Adiposogenital sd = Obesity + hypogonadism
- Gonadal steroid producing tumors

VI.2.4. Treatment

CUSHING DISEASE
1st line = surgical treatment = *Selective transphenoidal surgery*
85% = success in microadenomas +25% in MACROadenoma

Hemihypophysectomy (after venous sampling)
In cases with no clear tumoral image on MRI but clear biochemical diagnostic
50 % success
!!! Transient adrenocortical insufficiency 12-18 months (microadenoma)
!!! Remnant disease (Macroadenoma/extrasellar extension)
!!! Transient DI 10%

Bilateral total adrenalectomy old, abandoned technique, because of the remnant pituitary adenoma, which can increase, favoured by glucocorticoid insufficiency= Nelson Sd.

2nd line = Radiotherapy
In persistent/recurrent forms of diseases.

- *Conventional radiotherapy: remission of 55-70% in 1-3 years*
- *Gamma knife:* remission in 65-75% in1 years

Complications of radiotherapy are:
1. Late loss of pituitary function
2. Possible visual defects: optic chiasm damage
3. Cranial nerves damage

3rd line therapy = Medication
- Medication that inhibit adrenal cortisol secretion
- No effective treatment for ACTH secretion
- TEMPORARY .... Severe Hypercortisolism....presusrgical preparation

- **Ketoconazole** = inhibits P450scc, P450 c11 = 600-1200 mg/zi
- Hepatoxicity
- **Metyrapone** = inhibits P450scc
- Indirect ATCH increase, gastrointestinal side effects
- **Mitotane** = adrenolitic = adrenal atrophy
- Effective in 80% only under treatment – weeks/months
- !!! Severe nausea, vomitibg, diarrhea, somnolence, skin rash
- **Somatostatin analoques**

Follow up rules:

- *short term*
  - Remnant disease
  - Antero + postero-pituitary evaluation
  - Transient DI evaluation and treatment
- *long term*
  - Disease relapse
  - Anteropituitary function (in cases with associated radiotherapy)

CUSHING SYNDROME

1st line surgical treatment = unilateral adrenalectomy
Minim invasive laparoscopic approaches are proffered.
Transient postoperative adrenal functional insufficiency appear 1000% and have to be treated.
In carcinoma cases – unsatisfactory results, but the surgery is used for local decompression (in case of big tumors) and partial decrease steroid secretion.

2nd line = medical treatment: several medication are used:
= MITOTANE = 6-12 g/day induces adrenal destruction, with 70% steroid secretion reduction and a 35% reduce tumor size.
= Ketokonazole + Metyrapone are used to reduce steroid secretion, but have liited effects due to associated liver toxicity.

3rd line = RADIOTHERAPY / CHEMOTHERAPY are NOT USEFULL.

Follow up rules:

- *short term*
  - Remnant disease
  - Contralateral SR function: !!! Functional suppression for 12-18 months
- *long term*
  - Disease relapse
  - Contralateral SR function
  - ? Supplemental therapy

ECTOPIC CUSHING

- Possible in carcinoid tumors, pheocromocytoma, thymus carcinoids
- Difficult in metastatic diseases

1. Control MC effect: Spironolactone, Potassium replacement
2. Medication: bock steroid production: KETOKONAZOLE
3. Bilateral adrenalectomy in uncontrolled cases

Prognostic

- Any untreated form of Cushing = fatal because of metabolic and cardiovascular complications
- Cushing disease – aged matched SMR if correct treated
- Relapse if incomplete treatment in case of:
    - Adrenal adenoma = excellent (if treated)
    - Adrenal carcinoma = poor
    - Ectopic ACTH = poor

VI.3. HYPERALDOSTERONISMUS

Hyperaldosteronismus is considered any situation inducing exaggerate Aldosterone secretion, with alteration of secretion patterns and control mechanisms.

VI.3.1. Etiopathogeny

There are 2 form of Hyperaldosteronismus:
= primary form of the disease, because of primary alteration of glomerular zone activity due to

- Adenoma = 35% of cases
- Carcinoma = 1% of cases
- Bilateral idiopatic hyperplasia = 65% of cases
- Familial HyperALdo (FHA)
    - Type I = GC remediable 1%
      Autosomal dominant inheritance type, with variables degrees of hyperladosteronism, hincreased hybrid steroids, suppression with exogenous GC
    - Type II = GC irremediable 2%
      Familial occurrence of bilateral/unilateral adrenal hyperplasia
    - Type III = K channels mutation
      Altered aldosterone synthesis due to altered Kalium receptivity due to the receptor mutation (left shifting of the threshold kalium-aldosteron point)

= secondary form of disease, where is an altered secretion of ALOD due to constant stimulation of the regulation loop in case of:

- Increased renin production
  - renin producing tumors
  - long term oral estrogens administration: oral contraceptive, hormonal replacement treatment
  - renal artery stenosis
- any cause that constantly decreases blood pressure or natremia
  - congestive heart failure
  - dehydration
  - liver failure/cirrhosis
- iatrogenic
  - long term use of diuretics
  - high doses of Fluodrocortisone

VI.3.2. Clinical picture of primary Hyperaldosteronismus

Classical clinical picture, with complete biological picture is present in up to 0.5% of the hypertensive patients. If we consider the subclinical, non hypokalemic cases, the percent increased dramatically, comprising up to 5 to 10% of all hypertensive patients.

The disease is more frequent in females, with a maximum in the 3rd to 6th decade, rare in children, if present is suggesting a genetic syndrome.

The typical symptoms are related to the 2 major complications of Hyperaldosteronismus:

1. Hypertension is moderate to severe in the vast majority of cases, resistant to treatment, with rapid onset of the complications due to the résistance to treatment but also due to the nonclassic, microangiopathic changes:
   - Cardiac failure
   - Hemiparesis (stroke)
   - Carotid bruits
   - Proteinuria, CKD
   - Headache, seizure
   - Retinal changes

There is to mention that, due to hypernatremia there are NO EDEMA in hyperaldosteronismus, as seen in other forms of congestive heart failure.

2. hypokalemia signs are related to alteration of neuromuscular function with:

- Muscle weakness
- Fatigue
- Temporary paralysis
- Cramping
- Headaches
- Tingling
- Muscle spasms
- Palpitations
- Abdominal dystension/ileus

Even if the association of symptoms is clear, the diagnostic made only from the clinical point of view means late diagnostic with a lot of missed cases.

Currently there is a different approach with active screening in face of any following situations:

1. any hypertensive patient with random hypokalemia
2. moderate + severe hypokalemia under potassium wasting diuretics
3. refractory hypertension – no response with 3 drugs
4. any hypertension treated with 4 drugs
5. any hypertensive with a detected adrenal incidentaloma
6. any hypertension with young age onset

VI.3.3. The positive diagnostic has the following stepts:

- clinical/contextual suspicion
- screening for hyperladosteronism
- confirmation of hyperaldosteronism
- location of hypersecretion

- ***Screening for hyperladosteronism***

Ionogram : ↑ *Natriemia n,* ↓ *Kalemia*
↓ *Natriuria* ↑ *Kaliuria > 30 mEq/day*

Plasmatic aldosterone levels which are increased usually > 15 ng/dl

Decreased plasmatic renin activity < 1.0 ng/ml/hour

Increased Plasmatic Aldosterone to Renin Activity ration PAC/ARP > 20

Combined evaluation of Aldosterone and renin allows the measurement under antihypertensive medication, without stopping the medication, difficult procedure especially in severe, refractory hypertensive patients. The only exception is represented by mineralocorticoid receptor antagonist, Spironolactone and Eplerenone, which have to be stopped 6 weeks prior the assays. Angiotensin conversion enzyme inhibitors and Angiotensin II receptor blockers can induce false positive elevated plasmatic renin activity, but the impact, when looking to Aldosterone- renin ratio is very small. High values of this ration, at least over 20, are highly sensitive (80%) and specific (75%) in diagnosing primary hyperaldosteronism, both in clinical and especially in subclinical form of the disease.

- **Confirmation of hyperaldosteronism**

Demonstrating the lack of suppressibility of the aldosterone synthesis makes the dynamic test. Normal, Aldosterone increases Natrium reuptake, Natrium normalization inducing cessation of Aldosterone secretion. Sodium load tests are used to demonstrate the presence or the absence of suppressibility. 2 different sodium load tests are used:

1. Oral sodium load test
   - High sodium intake: total 5000 mg in 3 days
   - In days 3: 24 H urine: Aldosterone, sodium, creatin
   - > 200 mEq sodium
   - ALD ? 12 mcg/24 h = consistent for HyperALDO
2. Intravenous saline infusion test
   - 2 liter NAcl0.9% Iv pump 4 hours
   - Measure PAC: normal PAC < 5 ng/dL
     HyperAldo > 10 ng/dL
     intermediate 5=10 ng/dL I HTA

- **Localization test**

As in Cushing syndrome, 1st line imaging evaluation, in case of a hyperaldosteronism suspicion is represented by CT with contrast enhancement with evaluation of:

- low density tumor, with increased washout of the contrast agent, in case of an adenoma
- higher density tumor, with delayed washout, in case of a carcinoma
- unilateral or bilateral adrenal cortex hyperplasia

IN unclear cases or in the presence of a carcinoma suspicion, MRI evaluation can follow.

There is no use of scintigraphy in the diagnostic of hyperladosteronism, because there is no active radiotracer that is characteristic for mineralocorticoid secretion line, as it is for the glucocorticoid secretion line.

In unclear cases, where the clinical, biochemical and functional diagnostic are highly suggestive for hyperaldosteronism, but there is no clear imagine suggestive for a tumor or a diffuse hyperplasia, bilateral adrenal venous sampling is used. This method there is a catheterization of both adrenal veins, with separate blood sampling from both sides, with measurement of the major steroids aldosterone, cortisol, androgens. There is always a side with overactive secretion, with suppressed or decreased contralateral secretion.

VI.3.4. Treatment

The treatment goals are the control of hypertension and to normalize Aldosterone levels.

1st line treatment is represented by surgery, with approaches dependent on the form of the disease:

- unilateral laparoscopic adrenalectomy in case of an adenoma
- unilateral laparoscopic adrenalectomy in case of unilateral hyperplasia
- bilateral approaches are NOT USED

The efficacy of the treatment is monitored by measuring:
= Plasmatic Aldosterone levels = 2 -3 days after the surgery
= K levels monitoring for 4 weeks
= in case of unilateral form of disease, regardless tumor or hyperplasia, a temporary functional hypoAldosteronism is expected, due the suppressed levels of renin, which will be temporarily be treatment with Aldosterone supplemental therapy, the synthetic Fludrocortison.
The hyperaldosteronism hypertensive component – resolves in 1-3 months, but hypertension per se does not necessarily disappear, especially in long standing cases, where microangiopathic vascular changes are irreversible, and maintain the hypertension. In this cases there is only a decrease of the severity of the disease with the decrease of needed drugs for treatment.

2nd line treatment is represented by medication. Mineralocorticoid receptor blockade agents are uses, such as:
Spironolactone
12.5 – 25 .... 400 mg/day
= TARGET high normal **K levels**
= normalisation of blood pressure in 4 to 8 weeks

Eplerenone
25 – 50 mg/day
= TARGET high normal **K levels**
= normalisation of blood pressure in 4 to 8 weeks
Mediation is used preoperatively, or in cases with bilateral hyperplasia, cases where surgery is not recommended.

Possible side effects are represented by hypervolemia when the association with thiazide diuretics is indicated.

Always congruent general methods, used in all cases with hypertension are used:

- Sodium restricted diet (<100 mEq/day)
- Normal body weight, with body weight reduction, in case of overweight patients
- Tobacco avoidance
- Regular aerobic exercise

VI.4. ADRENAL INSUFFICIENCY

As in all peripheral gland insufficiencies, adrenal insufficiency can be classified as:

1. PRIMARY INSUFFICIENCY – altered adrenal function, due to d=various causes, with no response to the physiological stimuli (ACTH, volume depletion, hypotension, stress and Renin) with gradual decrease of **glucocorticoid + mineralocorticoid + androgen** secretion.
2. SECONDARY INSUFFICIENY – any kind of alteration of ACTH production, with subsequent adrenal inactivation, with lack of **glucocorticoid + androgen** secretion
3. TERTIARY INSUFFICIENCY – any kind of hypothalamic CRH production alteration, with circadian rhythm loss and no response capacity of ACTH, and secondary of **glucocorticoids and androgens**.

VI.4.1. Primary insufficiency

Causes:

- Autoimmune adrenal disease, with adrenal atrophy due to action of anti adrenal antibodies (21 hydroxilase antibodies)
  The disease can be isolated or part of the autoimmune polyendocrine (APS) syndrome 1 or 2.
  APS type 1 comprise:
  - Addison's disease
  - Hypoparathyroidism
  - Delayed or slow sexual development
  - Vitamin B12 malabsorption/deficiency (pernicious anemia)
  - Candidiasis (chronic yeast infection)
  - Hepatitis

APS type 2 comprise:

- Addison's disease
- Autoimmune thyroid disease
- Delayed or slow sexual development
- Type I diabetes
- Vitiligo
- Celiac disease

Schmidt disease – association of autoimmune thyroid and adrenal diseases

- Chronic infections, typical end stage tuberculosis disease, CItomegalovirus infections, HIV infection or fungal disease (histoplasmosis, coccidiodomycosis).
- Infiltrative disease – amyloidosis/hemochromatosis
- Bilateral metastasis present in 50% of adrenal metastatic disease, secondary in lung, breast, gastrointestinal and renal cancers.
- Genetic
  Adrenoleukodistrophy is a rare genetic disorder, X linked, characterized by the breakdown loss of myelin and adrenal progressive dysfunction, due to inability of alter the very long chain fatty acids. The concentration of unsaturated wry long cj=chain fatty acids, especially 26 carbon chains are significantly elevated in the plasma of the patients. Not all tissues are affected at the same time in all patients., some being asymptomatic for very log periods of time, some having walking and balance problems, some have adrenal insufficiency and other have the cerebral demyelinating form of disease.

  There is a fatty accumulation in the neurons, with altered mitochondrial function and secondary myeloneuropathy.

  In the adrenal cells there is am accumulation of VLFCA esterified to cholesterol, toxic substamces for the adrenal cortex with secondary apoptotic cell death.

  Familial glucocorticoird deficiency = alteration of adrenal sensitivity to ACTH< with lack of adrenal hormonal synthesis, due to a mutation of the ACTH receptor.

  AAA = glucocorticoid insufficiency + alacrima + achalasia
- Bilateral adrenal hemorrhagia is a rare form of the insufficiency, seen in anticoagulant treated patients, with of without preexisting coagulopathies.

- Iatrogenic disease:
  Permanent insufficiency in base of bilateral adrenal removal
  Chronic use of adrenolytic medication: Ketokonazol, Metyrapone, aminogluthetimide, Triostane, Mitotane, Etomidate.
  Functional, auto limited insufficiency, n case of unilateral adrenal removal in a Cushing disease, because of the suppression

Etiopathogeny
= impaired cortical adrenal activity, low/very low glucocorticoids level
= activation of long feedback loop
= increase in CRH and ACTH production
= no final adrenal response
= Continuum central stimulation with no adrenal response
= clinical signs and symptoms are present after 90% loss of the adrenal functional capacity. Always there is a gradual onset with a slow evolution, with initial loss of adrenal functional capacity (capacity to respond to stress or any situation that imposes increased needs) followed by decrease of function, even under normal circumstances.

Mineralocorticoid insufficiency appears along the evolution of the disease.

Clinical picture

Chronic picture – is seen after years of alteration of the adrenal secretion capacity. It is comprised by:

Weakness, fatigue, anorexia, weight loss *100%*
Malaise, fatigue accentuated during the day, increased in any difficult day
Weight decrease, 15-20 k, because of the appetite loss due to glucocorticoid loss

Hyperpigmentation is seen in the vast majority of primary forms of disease, as an effect of 92% cases. The sign is due to ACTH hyper secretion, paired with Melanocortin secretion, responsible for hyperpigmentation. It is almost generalised, more prone at the levels of:
- gums, palmar crest
- pressure zone like elbows
- nail beds, nipples,
- perianal, perivaginal, buccal mucosa

Hypotension, in 88% of cases, due to decrease of peripheral vascular resistance but also due to decrease of stroke volume

GI disturbances are frequent, in about 50% of cases, even in chronic situations: nausea, vomiting, diarheea

Salt carving is a rare syndrome, present in severe associated mineralocorticoid deficiency, seen in 19%

Postural symptoms are even less present, also mineralocorticoid deficient induced.
Loss of adrenal androgens is responsible for

Axillary/pubic hair loss seen only in women with longstanding disease
Increase in cardiovascular morbidity and mortality, seen in men
Alteration of libido and arousal, seen especially in women.
The clinical signs of androgen loss in males are scares, because of the testicular testosterone secretion which represents up to 95% of the androgenic level in the system.

Whenever there is a situation with increased need compare with basal need or there is an risk of developing acute symptoms, due to the inability of the adrenal to adjust glucocorticoid synthesis an release, according to the increased needs.

Typical precipitation factors are:

- **Surgery**
- **Diarrhoea**
- **Fever**
- **Trauma**
- **Infections**
- **Birth**

Acute signs are:

- Severe hypotension ..... Shock , because of adrenal + mineralocorticoid deficiency
- Fever
- Dehydration, volume depletion, polyuria because of adrenal + mineralocorticoid deficiency
- Nausea, vomiting, anorexia ... worsen volume depletion
- Weakness, apathy, depressed mentation
- Tendency to hypoglycemia..... hypoglycemia
- Hyponatremia, Hyperkalemia, because of adrenal + mineralocorticoid deficiency
- lymphocytosis
- !!! If untreated SHOCK, COMA, DEATH

Specific signs and symptoms are present in different pathogenies:

- history of tuberculosis infection
- association of acute signs + abdominal signs in cases of acute bilateral adrenal hemorhagy:
  abdominal/flank/back pain
  abdominal/flank tenderness
  abdominal distension
  abdominal rigidity
  chest pain
  rebound tenderness
- associated neurological signs
- previous severe fungus infection
- associated granulomatous lesions

Diagnostic steps:
Standard evaluation

- basal plasmatic cortisol levels

!!! a normal morning value does not mean a normal functioning pituitary

- combined ACTH + plasmatic cortisol level
  ↑ ACTH + n, ↓ cortisol = primary insufficiency
- ↓Aldosterone level + low with ↑ plasmatic renin levels
- ↓ DHEAS, DHEA, androstenedion

Additional tests

- Blood count: ↓Neutrophiles , ↑Eo, ↑Ba, ↑lymphocyte
- Anemia: normochromic, normocytic
- Azotemia, ↑creatinine, ↑BUN = volume depletion
- Hypoglycaemia
- Hyponatremia, hyperkalemia = MC insufficiency
- EKG: low voltage, vertical QRS axis, nonspecific ST-T changes

Confirmation tests = stimulatory tests

- *Rapid ACTH test – iv/im 250 mcg rACT*
  - basal cortisol, 30' stimulated cortisol > 20 mcg/dL
  - ↓↓↓ I/ II insufficiency
- Low dose ACTH – not for clinical routine
- *Metyrapone test = blocks cortisol synthesis, ↑ ACTH, ↑11 DOC*
  - normal: ACTH > 100 pg/mL 11 DOC > 7 ng/dL
  - I insufficiency: ↑ACTH no DOC increase
  - II insufficiency no ACTH no DOC

- *Hypoglicemia test = ↑CRH, ↑ACTH, ↑cortisol*
    - o normal ACTH > 100 pg/mL cortisol > 20 mcg/dL

    I insufficiency ACTH > 100 pg/mL no cortisol increase
    II insufficiency No ACTH increase no cortisol increase
    III insufficiency No ACTH increase no cortisol increase

- *CRH test =, ↑ACTH, ↑cortisol*
    - o normal ACTH > 100 pg/mL cortisol > 20 mcg/dL

    I insufficiency ACTH > 100 pg/mL no cortisol increase
    II insufficiency No ACTH increase no cortisol increase
    III insufficiency ACTH > 100 pg/mL cortisol > 20 mcg/dL

Etiopathogenic diagnostic

- *Adrenal antibodies titers* **=** 21hydroxilase antibodies – confirm autoimmune disease
- Measurement of long chain fatty acid = adrenoleukodystrophia
- Ophaltomogical evaluation = AAA syndrome
- Sputum tests/skin tests/pulmonary X ray
- Evaluation of fungal infections
- Evaluation of HIV infection
- Abdominal CT
  = calcification = tubercolosis/haemorrhage
  = enlargement = infiltration, infections, CMV, malignant infiltration

Treatment

❖ Acute insufficiency

Glucocorticoid acute replacement
- HHC – 100 mg iv, immediately

1st day … than 100 mg every 6 hours = 400 mg

2nd day …. 50 mg every 6 hours – 200 mg

Maintenance 3-4 days = chronic supplemental dose
!!! Under important doses of HHC - no associated MC replacement needed

General and supportive measures
- Correct volume depletion – glucose/saline solution
- Evaluate + precipitating factors
- Correction of hypoglycemia

1. Immediate diagnosis and treatment of hypoglycemia is essential. Children with seizures or prolonged recurrent episodes of hypoglycemia are more likely to experience brain damage.
2. When the cause of hypoglycemia is unknown, start an intravenous line and collect 5-10 mL of blood in a heparinized tube.
3. When hypoglycemia is suspected, start treatment without waiting for the results of the blood or plasma glucose tests.
4. In neonates, administer intravenous (IV) 10% dextrose at 2.5 mL/kg as a rapid IV bolus followed by a continuous IV infusion of 3-5 mL/kg/h (5-8 mg glucose per kg/min).
5. In children, administer 50% dextrose diluted to 25% in water at an initial dose of 1 mL/kg IV followed by an IV infusion of 10% dextrose at 2-3 mL/kg/h (3-5 mg glucose per kg/min).
6. If any difficulty in establishing IV access occurs, intramuscularly administer glucagon at 0.03 mg/kg (not to exceed 1 mg). Glucagon therapy has a transient effect and must be followed by an intravenous dextrose infusion as above.

❖ Chronic insufficiency

- Glucocorticoid chronic replacement 2/3 morning+1/3 noon
  Standard dose = 12-16 mg/m^2/24 h

Hydrocortisone	15-25 mg/day
Cortisone acetate	20-30 mg/day
Prednisolone	5-7.5 mg/day

- Overtreatment may result in poor linear growth, hypertension, edema, euphoria, insomnia, headache, steroid-induced acne, hyperglycemia, Cushing syndrome, peptic ulcers, and cataract formation.
- Intercurrent illness or stress necessitates a readjustment of glucocorticoid dosage. For minor stress, such as a fever or upper respiratory tract infection, double or triple the glucocorticoid dosage until the illness has resolved. If the patient is ill with vomiting or diarrhea and cannot tolerate oral fluids and medication, hospitalization may be necessary. In individuals with severe stress, such as surgery or serious illness, the daily requirement for parenteral hydrocortisone is 40-100 mg/m^2/24h (approximately 3-10 times the maintenance dose) in 3-4 divided doses.
- With a major decline in the clinical condition of the patient (eg, development of hypotension, fever, decreasing mental status, acute intercurrent illness), promptly initiate treatment for possible adrenal crisis even before the diagnosis is confirmed.

- The treatment of an adrenal crisis includes fluid, dextrose, and glucocorticoid replacement in order to restore fluid volume and prevent hypoglycemia and death. Adequately treat any precipitating event such as an infection.
- Fluids administered (eg, 0.9% NaCl with 5% dextrose) should be administered at 1.5-2 times the maintenance rate (2250-3000 mL/m^2/d). If the patient presents in shock, administer 0.9% NaCl (10-20 mL/kg) during the first hour of treatment. In addition, cortisol as a soluble ester (21-hemisuccinate or 21-phosphate) must be administered as an immediate IV bolus and every 6 hours (25 mg for infants; 50 mg for small children; 100-150 mg for larger children or adolescents).
- Once the clinical condition improves, gradually taper down the steroid dosage by one third every day until the patient is back to maintenance dose.

- Mineralocorticoid chronic 1morning dose
  Fludrocortison 0.05-0.2 mg/day

- Androgen chronic 1morning dose
  DHEA 30-60 mg/day

Treatments follow-up

GCS

- Normalisation of appetite, sense of well being
- Decrease of hyperpigmentation
- Weight evaluation
- NO direct lab assay … ? Plasma cortisol daily curves

MC

- BP evaluation
- Na, K evaluation normal range
- PRA < 5 ng/mL/h adequate replacement

VI.4.2. Secondary/tertiary insufficiency

Because ACTH is controlling only adrenal androgens and glucocorticoids, the clinical picture is not so severe like in primary insufficiency, but stil, if untreated, also secondary insufficiency can be fatal.

Causes: all know causes of pituitary insufficiency:

- Secreting/nonsecreting tumors with pituitary compression
- Irradiation (more probable after conventional radiotherapy compared with radiosurgery)
- Posttraumatic
- Postsurgical, more frequent after craniotomy compared with transphenoidal approach
- Postischemic = typical in heavy birth giving associated with untreated important blood loss.

  During the pregnancy the pituitary is hyperplasic, in order to sustain the increased body hormonal needs especially from respect of PRL secretion. Because of this hyperplasia, the vulnerability of the pituitary to ischemia is very high. Classically, the ACTH producing cells are very resilient to trauma, the classical insufficiency order is: GH, FSH + LH, TSH, ACTH and PRL.
- Posthemorrhagic = the natural evolution of some pituitary tumors can undergo a spontaneous process of involution, with tumor apoplexy, that can comprise not only the tumor but also the surrounding healthy tissue. This complication is mostly severe, with bad outcome for the patients but if sustained hemodynamic, the period after the acute apoplexy associates different degrees of pituitary insufficiency.

Etiopathogeny

= ACTH insufficiency appears gradually

= there is first a subclinical form of disease sub suboptimal ACTH increase under stress situations

= than there is a chronic phase of the disease with typical signs and symptoms.

= due to lack of ACTH there is no activation of the steroid secretion tree in the adrenal, with altered transformation of cholesterol in pregnenolone, under the STaR enzyme.

= the long loop negative feedback is active, but there is no pituitary response to it

Clinical picture is similar to that of primary inssuficency with the following differences:

The diagnostic can be made in condition of suggestive clinical symptoms, or, in presence of a predisposing factors, active adrenal screening should be done.

No hyperpigmentation of the skin (no melanocortin secretion, no POMC secretion ability)

Less severe hypothermia with hyperkalemia, due to preserved mineralocorticoid secretion.

Less severe postural symptoms

Less severe dehydration

Associate pituitary sign and symptoms, which always have to be organized in

1. Tumoral sd..... Other hypersecretions
2. Hormonal sd... Associated hyposecretions
3. Functional sd.... Compression
4. Metabolic ... .hypoglycaemia

Standard evaluation

- basal plasmatic cortisol levels

  !!! a normal morning value does not mean a normal functioning pituitary

- combined ACTH + plasmatic cortisol level

  ↑ ACTH + n, ↓ cortisol = primary insufficiency

- ↓Aldosterone level + low with ↑ plasmatic renin levels
- ↓ DHEAS, DHEA, androstenedion

Additional tests

- Blood count: ↓Neutrophiles , ↑Eo, ↑Ba, ↑lymphocyte
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- Hypoglycaemia
- Hyponatremia, hyperkalemia = MC insufficiency
- EKG: low voltage, vertical QRS axis, nonspecific ST-T changes
- Abdominal CT
  = calcification + tubercolosis/haemorrhage
  = enlargement: infiltration, infections, CMV, malignant infiltration
- Ophthalmic examination = suggestive for AAA syndrome

Confirmation tests = stimulatory tests

- *Rapid ACTH test – iv/im 250 mcg rACT*
  - basal cortisol, 30' stimulated cortisol > 20 mcg/dL
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- Low dose ACTH – not for clinical routine
- *Metyrapone test = blocks cortisol synthesis, ↑ ACTH, ↑11 DOC*
  - normal: ACTH > 100 pg/mL 11 DOC > 7 ng/dL
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  - II insufficiency no ACTH no DOC
- *Hypoglicemia test = ↑CRH, ↑ACTH, ↑cortisol*
  - normal ACTH > 100 pg/mL cortisol > 20 mcg/dL
  - I insufficiency ACTH > 100 pg/mL no cortisol increase

  II insufficiency No ACTH increase no cortisol increase
  III insufficiency No ACTH increase no cortisol increase

Specific tests

- Complete pituitary evaluation
- Check for other liner insufficiencies
- Check for possible hyper secretion

Treatment

Same rules are valid as in primary insufficiency, with the mention that there is no need for mineralocorticoid replacement.
There is to mention that in case of a combined pituitary insufficiency, ACTH line has to be treated first, before TSH. If thyroid line is addressed first, there is an increase of the metabolism, of remnant glucocorticoid with increased catabolism.

Treatments follow-up

- Normalisation of appetite, sense of well being
- Decrease of hyperpigmentation
- Weight evaluation
- NO direct lab assay … ? Plasma cortisol daily curves

No to forget active treatment for other secreting remnant tumors: Somatostatin analoques/Dopameinergic agents/Pegvisomant.

Prognostic of disease:

- Without treatment = FATAL in maximum 2 years
- Survival independent of the underlying cause
- Bilateral haemorrhage often recognised only at autopsy

VI.5. CONGENITAL ADRENAL HYPERPLASIA

This pathology comprises a sum of diseases, all characterized by adrenal enzymatic insufficiency, with alteration of the normal secretion pattern. The clinical picture is dependent on which enzyme is inactive.

The most common defects are: 21 hydroxylase deficiency, 17 hydroxylase deficiency and 11 hydroxylase deficiency, but all enzymes can de altered.

VI.5.1. 21 Hidroxylase deficiency

Mechanism - due to the altered action of 21 hydroxylase, there is insufficient secretion of cortisol, which will activate the feedback mechanism, with increased ACTH production, with subsequent cholesterol activation to pregnenolone, but with excessive secretion on the only active arm, the androgen synthesis.

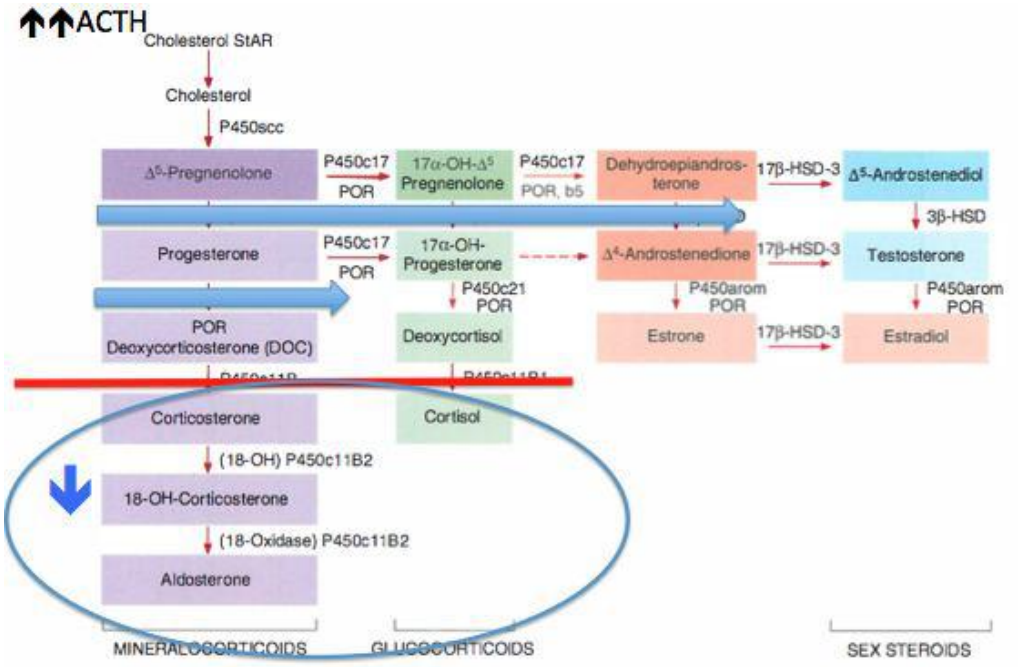

Figure 29 . 21 Hidroxylase deficiency etiopathogenic mechanism

There are 2 major clinical forms:

- Classic form

  + CGS deficiency = 20%

    Shock
    Hypoglycaemia

    The degree of glucocorticoid insufficiency s proportional with the enzymatic defect

  + MC deficiency = 80%

    Hyponatremia, HyperK

  +Excess of androgens

    Ambiguous genitalia F
    Cryptorchid M

- Non classical form

  Isolated androgens excess

  1:27 Ashkenazi Jews
  1: 50 Hispanics
  1: 333 Italy
  1:1000 Caucasians
  Normal at birth
  Minimal virilisation around puberty
  Hirsutism, slight clitoridian enlargement, premature adrenarche

The degree of androgen excess can induce different clinical signs and changes:

- In females

  Virilisation of OGE
  Normal OGI
  Acne, seborrhoea
  Hirsutism
  Heterosexual precocious puberty = opposite sex pubertal characteristics
  Small final stature

- In males

  Normal OGE
  Normal OGI
  Severe acne, seborrhoea
  Isosexual precocious puberty = same sex pubertal characteristics
  Small final stature

Diagnostic

1. Increased precursors: 17 Oh progesterone
   at birth- umbilical cord : 100-200 ng/dL
   - basal > 200 ng/dL (typical > 500 ng/dL)
   - rapid ACTH stimulation > 1000 ng/dL

2. Decreased following hormones
   cortisol ↓ negative rapid ACTH test
   Aldosterone ↓
   Aldosterone/Renin = ↓

Treatment

Classic form = acute administration
HHC 50 mg/m^{2}cs
normal saline solution
Fludrocortisone 0.05-0.1 mg
= long term treatment
Hydrocortisone 10-15 mg/m^2/day
Fludrocortisone 0.05-0.2 mg/day
Follow up = 17 OH progesteron < 400, normal TT, androstenedion

Surgical treatment = correction of virilising changes in girls

- Clitoridian reduction .....age 1 year (0-4)
- Clitoridectomy (13%) .....age 1.5 year (0.4-3)
- Vaginoplasty .....age 2.5 year (0.1-18)
- Vaginal dilatation .....age 12.7 year (0.2-18)

Psychological support

- 71% psychosexual problems
  - Gender role behavior shift in direction of masculinization
  - Extreme degree if gender change in mid-adult
  - Gender changed patients attracted exclusively to F

Nonclassic form = chronic androgen suppression
Small dose of DXM = suppress the androgen overproduction
!!! Cortisol levels evaluation

VI.5.2. 17 Hidroxylase deficiency

Mechanism - due to the altered action of 1 hydroxylase, there is insufficient secretion of cortisol, which will activate the feedback mechanism, with increased ACTH production, with subsequent cholesterol activation to pregnenolone, but with excessive secretion on the only active arm, the androgen synthesis.. The difference compared with 21 hydroxilase, is that DOC is oversecreted, due to ths coninuos stimulatory mechanism, and DOC is the st mineralocorticoid in the secretory chain.

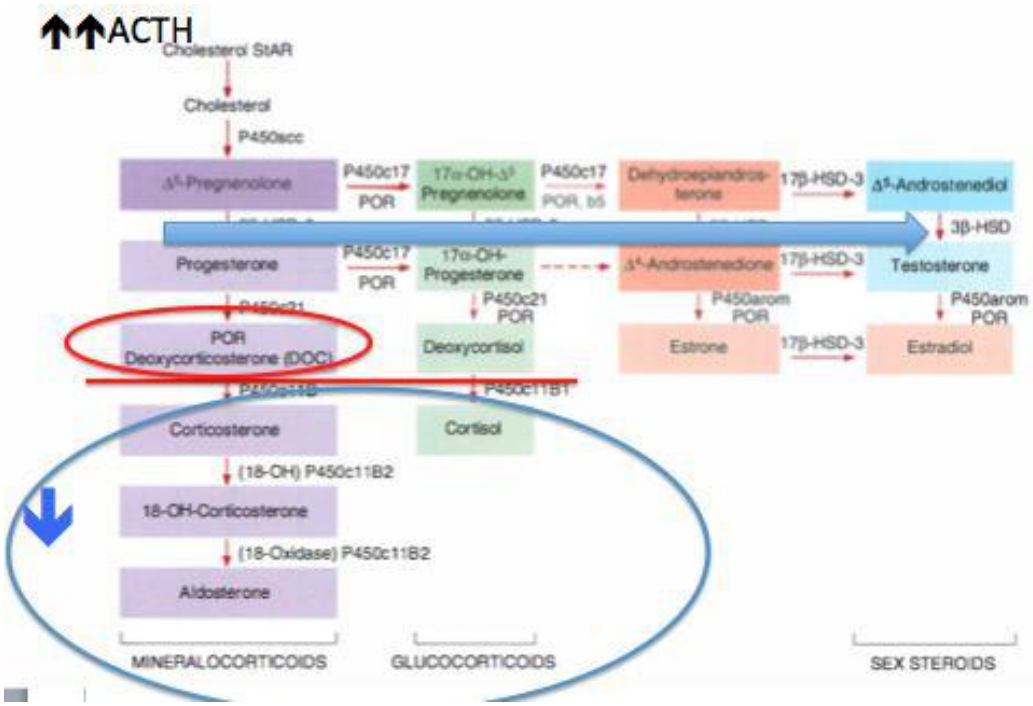

Figure 30. 11 Hydroxylase deficiency etiopathogenic mechanism

Clinical picture associates:

- **Excess androgens signs**
  - In females

    Virilisation of OGE
    Normal OGI
    Acne, seborrhoea
    Hirsutism
    Heterosexual precocious puberty
    Small final stature

- In males

  Normal OGE
  Normal OGI
  Severe acne, seborrhoea
  Isosexual precocious puberty = same sex pubertal characteristics
  Small final stature

- **DOC, 11 DOC excess = MC = Hypertension: hypernatremia, Hypokalemia, ↓ Renin**
- **cortisol insufficiency = degree ≈degree of enzymatic defect**

Diagnostic

1. ↑BP, hyper Na, hypoK
2. ↓cortisol, no response to ACTH rapid test
3. ↑ ACTH
4. Androgens: DHEA, androstendion
5. Suppression test : NO decrease of androgens, decrease of ACTH

Treatment

- GCS supplemental therapy
- Androgen suppression
- BP control
  - potassium sparing diuretics
  - Ca Chanel Blockers

VI.5.3. 17 hydroxylase deficiency

Mechanism - due to the altered action of 17 hydroxylase, there is insufficient secretion of cortisol, which will activate the feedback mechanism, with increased ACTH production, with subsequent cholesterol activation to pregnenolone, but with excessive secretion on the only active arm, the mineralocorticoid line synthesis.

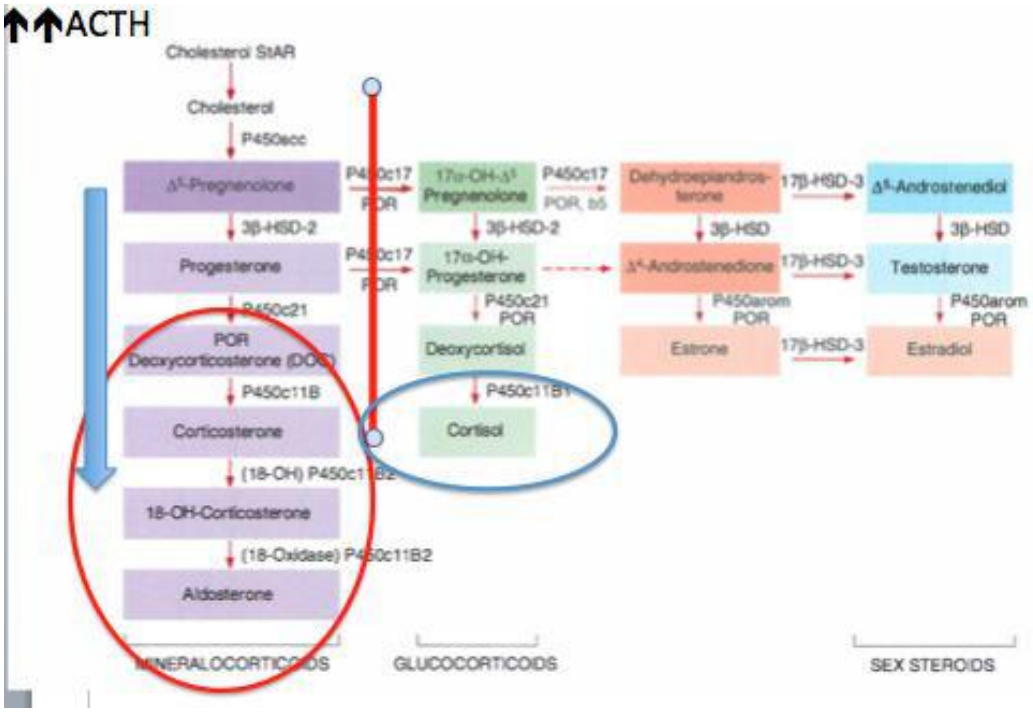

Figure 31. 17 Hydroxylase deficiency etipopathogenetic mechanism

Clinical picture associates symptoms of:
+ glucocorticoid insufficiency
+ mineralocorticoid excess = hypertension, hypernatremia, hypokalemia
+ androgen deficiency

- In females

  Normal OGE
  Delayed puberty
  High final stature

- In males

  Ambiguous genitalia/sexual infantilism
  Delayed puberty
  High final stature

Treatment

1. glucocorticoid replacement therapy
2. androgen supplemental therapy in males during puberty

VI.6. CATECHOLAMINE EXCESS

Tumoral catecholamine excess appearance under cromaffin cell hypertrophy: medular adrenal tumor (feocromocytoma) or nervous ganglionar tumor (paraganglioma).

Pheocrmocytoma

- Yearly incidence = 2-8 cases/1 mil persons
- Pheo = chromaffin cell tumors .... 90% of all
- Unilateral 90% — 65% right — paroxysmal hypertension
  35% left — sustained hypertension
- Bilateral 10% — familial disease
  10% RULE — 10% bilateral, 10% malignant 10% extradrenal
- Synthesis up to 27 the normal adrenal production rate
- ↑↑↑ quantities > storage capacity = diffuse out of the tumor in the circulation
- Preferential secretion of Norepinephrine ≠ normal adrenal
- !!! No correlation between secretion/tumor sizes!!!!
- Usually there is not a isolated hyper secretion of catecholamine, but combined with several possible cosecretory substances:
  - *ACTH*
  - *Adrenomodullin*
  - *FNA*
  - *Beta endorphin*
  - *Calbidin*
  - *Calcitonin*
  - *Cholecystokinin*
  - *Chromogranin A*
  - *Cytokines*
  - *Epo*
  - *GhRH*
  - *IL – 6*
  - *GH*
  - *Neurotensin*
  - *PTH RP*
  - *Renin*
  - *Serotonin*
  - *Sotatostatin*
  - *VIP*
  - *NSE*

The majority of cases are isolated forms of disease, but 10% of cases are bilateral localization in familial forms. The familial form of disease, with pheocormocitoma along the other endocrine lesions are:

1. MEN 2 A: pheocromocitoma + hyperparathyroidism + medular thyroid carcinoma
2. MEN 2 B:Pheocromocitoma + medular thyroid carcinoma + mucosla neurinoma
3. Von Hippel Lindau disease: VHL : pheocormocitoma ± hemangioblastoma ± small cell renal carcinoma
4. Von Rechklinghausen neurofibromatosis: s
   skin: cafeaulait, neurofibromas, neural gliomas
   Endocrine: Pheo, HPTH, SST carcinoma
5. Familial paraganglioma: isolated, familial paraganglioma
6. Carney triad:

Myxomas: heart, breast, skin
Spotty skin pigmentation
Endocrine: Acth independent Cushing, FTC, CSR carcinoma, GH adenoma, Sertolli cell cc

7. Beck Wiedemann sd.
8. Prolyl hydroxylase D2 gene mutation

Clinical picture is typically represented by paroxysms, according to the nonsystematic catecholamine secretory release:

- Hypertension sustained/paroxystic 90%
- Headaches 80%
- Diaphoresis 70%
- Sweating 65%
- Palpitations 60%
- Tremor 40%
- Abdominal/chest pain 35%
- Pallor 30%
- Nausea/vomiting 30%
- Fever 28%
- Fatigue 25%
- Flushing 18%
- Dyspnoea 15%
- Diarrhoea = hypermetabolic state 6%

The paroxysms are typical induced by specific triggers. There is an individual pattern of hyper secretion symptoms that increase, over time, in severity and frequency. There is also to notice that the crises are not universal present and there are around up to 30% of patients who do not exhibit paroxysms.

Specific triggers of the paroxysms are described:

- Thyramine containing foods, that will enhance MOA synthesis and will favor catecholamine release/effect:
  - Meats
  - Aged cheese
  - Fish
  - Beer
  - Wine
  - Chocolate
  - Bananas
- Specific drugs
  - MAO inhibitors
  - Radiocontrast Iodine
  - Tryciclic antidepresants
  - Sympathycomimetics
  - Glucagon
  - Chemotherapy
  - Prednosine
  - ACTH
  - Opiates
  - Methyldopa
  - Metoclopramide
  - Nicotine
  - Cocaine
- Specific activities (squeeze effect)
  - Bending
  - Rolling in the bed
  - Exertion
- Abdominal palpation
- Micturition

Because making the diagnostic only when clinical suggestive is not early enough and also not sensitive enough, there is a process of active screening in any case of:

1. Young hypertensive
2. Hypertension with
   - Weight loss
   - Typical symptoms
   - Seizures
   - Orthostatic hypotension
   - Unexplained shock
   - Cardiomiopathy
   - Familial sd: MEN 2,neurofibromatosis, ...
3. Marked lability of the BP
4. Family history of Pheocromocitoma
5. Shock/severe TA associated with: anaesthesia, delivery, surgery
6. Adrenal mass
7. Mass in the area of paraganglia

In case of clinical suspicion the following diagnostic steps are needed:

Standard evaluation

- *Plasma fractionated free metanephrines*

The most sensitive test 97%, specificity of 87%
! Age, sex reference range
90% circulating metanephrine + 50% normetanephrine = adrenal origin
Only 3% - free ↑↑↑↑ continuous tumor hypersecretion = metabolites leak out permanently from the cell
FALSE POSITIVE: smoking, local anaesthetics, IMAO, coffee.
Patient: fasting, resting supine

- *24 Hour urine fractionated metanephrines*

! Suggestive for diagnostic = al least 3 times higher

- *Plasma fractionated catecholamines*

False positive: sympathetic activation

- *Urine fractiones catecholamines/dopamines*

A single voiding urine specimen following the paroxysm

Additional tests

- Chromogranina A
  Co secreted with the catecholamine
  Circadian rhythm !! 08.00-11.00 AM evaluation
  ↑↑ in secreting/nonsecreting tumors
  False positive: liver disease, inflammatory bowel disease, hepatocellular carcinoma, prostate cancer, pituitary tumors, PAR, stress.
- Evaluation of hypertension complications
- Urinary VMA (low sensitivity of 63%), ARP (no help)

Confirmation tests = stimulatory tests

- *Clonidine suppression test*
  Basal free plasma metanephrines
  IV 0.3 mg/kgc
  After 3 hours: free plasma metanephrines: ↓↓ 40% , < 112 pg/mL

Localization tests

- After biochemical diagnostic = localisation is needed
- CT
- MRI bright in T2 weighted images (hypervascularisation)
  ≠ malignancies, adenomas, hemorrhage
  Metaiodbenzylguanidine scanning
  MIBG = actively transported in the medulla cells (NADR transporter system)
- PET
  ^{18}F- Deoxyglucose = standard evaluation
  ^{18}F- Fluorodopamine = highly suggestive for Pheo
  ^{18}F- DOPa = metastatic Pheo
- Octreoscan = metatstatic Pheo
- US = adrenal tumor visualisation

Differential diagnosis

- Cardiac arrhythmias
- Clonidine withdrawal
- Coronary vasospasm
- Encephalitis
- Essential hypertension
- Hypertensive crisis + stroke/surgery/acute pulmonary edema
- Hypoglycaemia
- Hypogonadal hot flushes
- Lead poisoning
- Mastocytosis
- Migraine and cluster headache
- Renovascular hypertension
- Sleep apnoea
- Thyrotoxicosis
- Toxaemia of pregnancy

Treatment

Medical management
TARGET = Normalize blood pressure and decrease the effects of hypertension

1. Alpha adrenergic blockers: Doxazosin, Prazosin
2. Calcium channel blockers: Nicardipine, Nifedipine
3. ACEI: in combination with other
4. Beta blockers: after HTA treatment, nonselective agents
5. Metyrosine: (↓ thyrosin hydrolaze) = preoperative
6. Octreotid (SST analoques long acting) – uncontrolled Pheo

Lifestyle - !!!! Vigorous exercise/thyramine containing foods

Surgical management

- Laparoscopy
- Needle scope adrenalectomy
- Adrenal cortex sparing surgery
- Open laparotomy

!!! Increased catechol values/ / / 10 days after surgery

In case of malignant pheocromocytoma (10% of all cases) the following treatment options are recommended:

- Surgery
- Chemotherapy: Sunitinib, Cyclophosphamide, vincristine, decarbazine
- Bisphosphonates
- Radiation therapy
- Arterial embolization/radiofrequency ablation
- I MIBG

Treatment follow up steps are:

- Catecholamine should normalize 2 weeks after perfect surgery
- Cromogranin A – useful tumor marker
- Evaluation yearly, at least for 5 years
- Intensive lifestyle changes
- Aggressive cardiovascular treatment

Prognostic

- *Mortality < 3 % in treated cases*
- *Benign treated Pheocromocytoma.... 96% survival in 5 years*
- *Malignant pheocromocytoma .... 50% survival in 5 years*

VII. GONADS

VII.1. OVARIES

The ovary is peritoneal located para uterine, usually in the depression on the pelvic sidewalls between the ureter and external iliac vein, being suspended in by association of three ligaments:

- The suspensory (infundibulopelvic) ligament attaches to the cranial pole of the ovary and extends to the pelvic brim, containing the ovarian vessels, lymphatics, and nerves
- The mesovarium connects the anterior portion of the ovary to the posterior leaf of the broad ligament
- The utero-ovarian ligament attaches to the inferior pole of the ovary and extends to the uterus

The average adult ovary is 2.5 -5 cm X 2.5 cm X 1 cm in size and weighs 3 to 8 g.

From the periphery to the center the following layers are present:

- tunica albuginea
- simple cuboid epithelium = germinal epithelium
- cortex
- medulla

The ovarian artery enters the ovarian hilum and branches into spiral arteries chat enter the medulla and extend to the ovarian cortex. The medulla contains only vessels and no secretory cells. The ovarian cortex, situated at the periphery of the glans, is containing all the secretory cells, structured in follicles in different stages of development and stroma, with anatomic and functional interrelations. Each follicle contains in the middle a germinal cell (gametes) surrounded by follicular cells. The theca cells differentiate from interfollicular stroma in response to proteins secreted from growing follicles, being the main source of the androgen secretion in the ovaries.

Similarly to the adrenal, ovarian epithelial cells produce different hormones according to the enzymatic apparatus present in each type of cells: The theca cells produce androgens only, because of lack of aromatase, and the granulosa cells produce estrogens, in the follicular phase, respectively progesterone in the luteal phase, because they contain aromatase but tack in CYP17 The other stromal cells that contribute to androgen production can be divided into two populations of cells: the secondary interstitial cells (derived from theca) and the hilum cells, involved in androgen production.

The steroidogenesis stars, as expected, from cholesterol, following the same steps as in the adrenal, but need the combined activity of theca and granulosa cells.

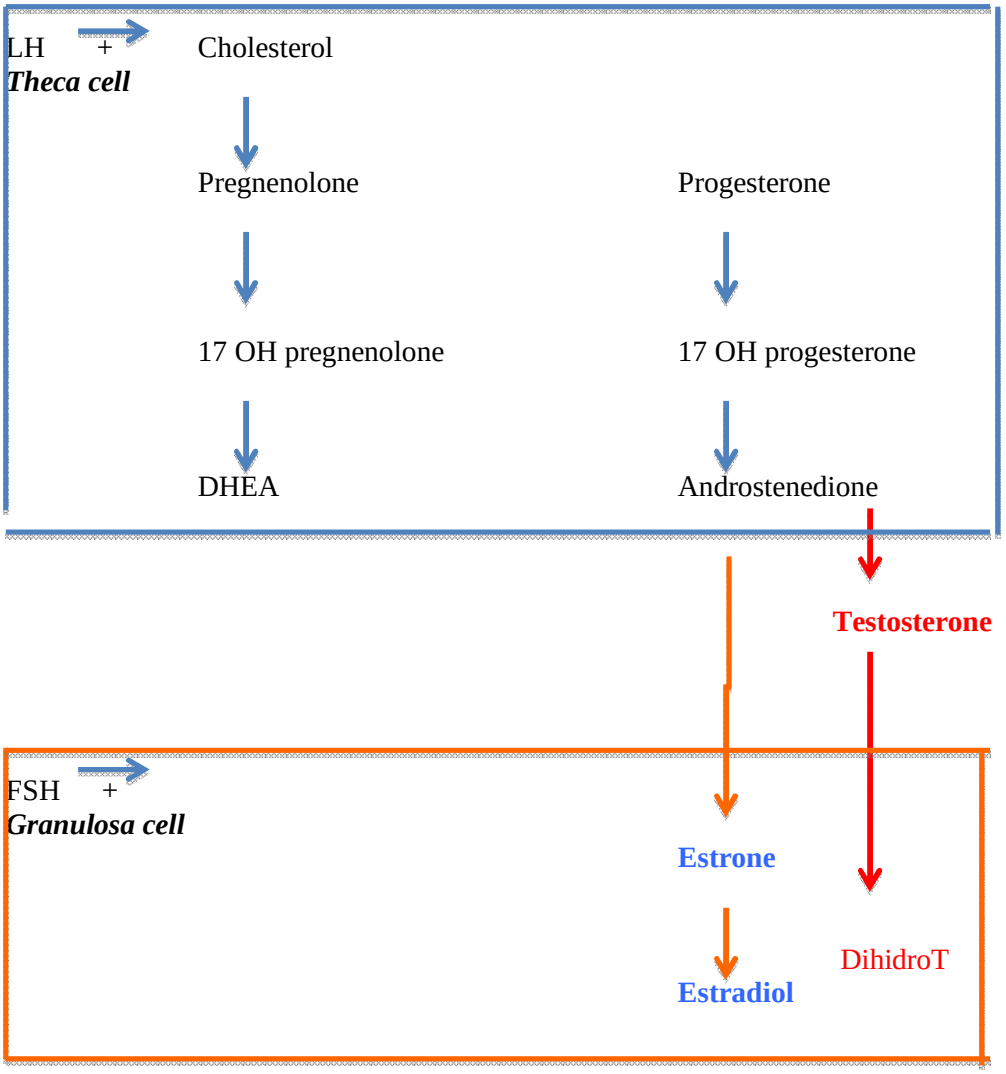

Figure 32. Ovarian steroidogenesis

The morphologic follicular unit, consisting of theca cells and granulosa cells, is also a functional hormonal unit capable responsible for estrogen production (two-cell theory). Produced hormones are:

= androgens: In total, ovaries are responsible for the 2/3 of testosterone:1/3 direct secretion and 1/3 indirect secretion (from peripheral conversion of androstendion). The DHEAS produced by the ovaries represent only 5% of the total body production.

= estrogens; 95% of the estradiol is produced by the ovary, 50% of the estrone is produced by the ovaries (the rest from peripheral conversion).

TABLE LI. SEX STEROIDS IN FEMALE SYSTEM

Hormone	Ovaries	Adrenal	Peripheral conversion
Estradiol	95	<1	<5
Estrone	>50	<1	<50
Testosterone	33%	33%	33%
Androstendion	50	50	-
DHEAS	<5	>90	-

The functionality of the ovaries is seen just in cases of mature functional pituitary ovarian unit, respectively between puberty and menopause.

The hormones circulate free in small percent, the majority being couple to sex different proteins: Sex Hormone Binding Globuline (38%), albumin (60%) and approximately 2% is unbound. Estradiol may be directly conjugated (16a-hydroxylared or 2-hydroxylated) or is metabolized to estrone prior to conjugation. The remaining estrogens are weakly bound to proteins. Progesterone is metabolized into many imermediates prior to conjugation. Pregnanediol glucuronide is the major metabolite observed in the urine.

VII.2. TESTES

Adult testes are an ellipsoid stricture, with a mean volume of 18.6 ± 4.8 ml, with mean dimensions of 5x3x2 cm. The location changes during life: in preconception they are situated in the abdomen, the descendens of testes in the scrotum begins in the last months of intrauterine life, testosterone dependent. At birth the vast majority of males have the testes in the scrotum. The scrotum is an active protective envelope, that contains but also preserves the local temperature lower compared with the body temperature, needed for a normal spermatogenesis.

Starting form periphery several layers are seen: visceral tunica vaginalis, tunica aluginea and tunica vasculosa , all comprising the testicular capsule. Tunica albuginea has fibrotic extensions into the testicular capsule.

The testis contain 3 major types of cells, all present in the wall of seminiferous tubules, comprise in the bulk of the testes:

- Leydig cells – steroid producing cells, staring from cholesterol,
- Sertolli cells – interstitial cells that
    - mechanically sustain the wall of the tubules and also produce Antimullerian hormone responsible for male sexual differentiation

    - provide an environment essential for germ cell differentiation
    - movement of the germ cells from the base of the tubule toward the lumen
    - phagocytosis of the altered cells/residual bodies
- Germinal cells = present at the basal membrane of the tubules, that sustain during the whole life span, the gametogenesis. The process is standard, starting from
    - the spermatogonia, that permanent proliferate indefinitely, like stem cells, al the level of basal membrane,
    - primary spermatocytes
    - secondary spermatocytes
    - spermatids
    - spermatozoa

Through meiotic division, the spermatids are formed; they contain a haploid number of chromosomes. The interval from the beginning of spermatogenesis to release of mature spermatozoa into the tubular lumen is approximately 64 days. The spermatozoa are delivered at the luminal end of the seminiferous tubule and are released into de stream. At this point, spermatozoa are fully genetically equipped, by inactive from the functional point of view.

The seminiferous tubules convert in an anastomotic network of ducts, called rete testis, that convert to epididymis, that confer on the gametes the capacity for fertilizing an ovum. The epididymis serves as a reservoir for sperm. Spermatozoa stored in the epididymis enter the vas deferens. Adjacent seminal vesicles bring fluid with plasma fructose, which provides nourishment to the spermatozoa. The ejaculatory ducts terminate in the prostatic urethra. There additional fluid (20% of total volume) is added by the prostate.

Steroidogenesis is the most simple steroidogenesis in the system, being performed starting from cholesterol, at the level of Leydig cells, cells equipped just with the enzymes able to synthetase sexual steroids. The conversion of testosterone, the main steroid product of the males, responsible for 95% of the entire testosterone in the body, to the most active form, dihydrotestosterone is present at the peripheral level, by 5 alpha reductase 1 present mainly in the skin, and 2 present at the urogenital tract.

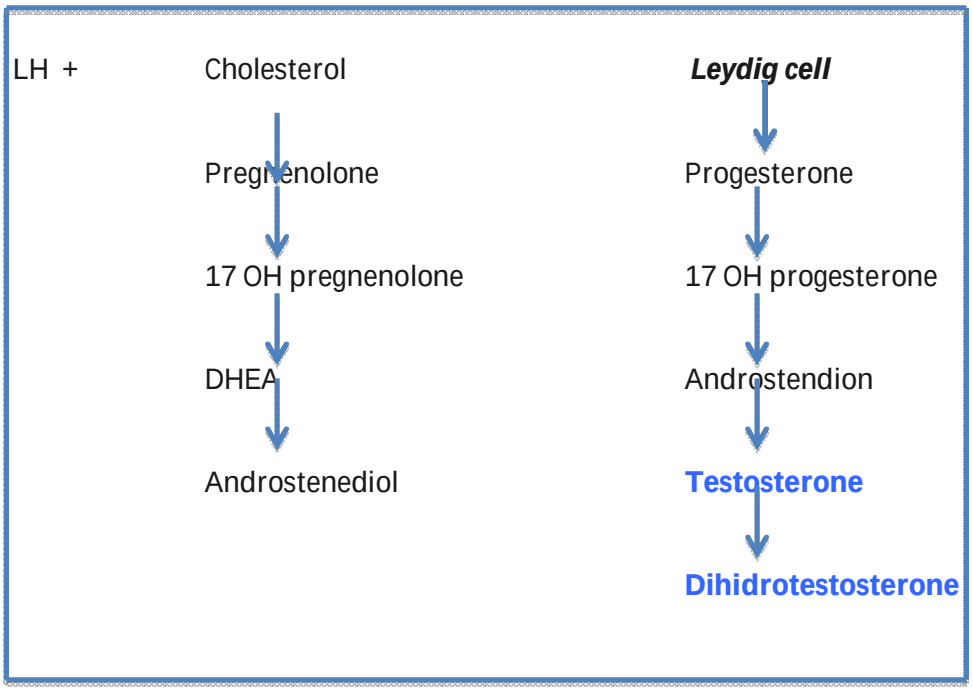

Figure 33.

TABLE LII. SEX STEROIDS IN THE MALE SYSTEM

Hormone	**Testes**	**Adrenal**	**Peripheral conversion**
Testosterone	95	<1	<5
Dihydrotestosterone	< 20	<1	80
Estradiol	< 20	<1	80
Estrone	<2	<1	98
DHEAS	<10	90	-

The hormones circulate free in small percent, the majority being couple to sex different proteins: Sex Hormone Binding Globuline (44%), albumin (54%) and approximately 1-2% is unbound.

The functionality of the testes is seen just in cases of mature functional pituitary testicular unit, respectively between puberty and death.

VII.3. GONADOSTAT

Although the gonadostat is present at the moment of birth, there is a physiological inhibition of the system, up to the puberty, an interval free of sexual steroid hormones, needed for the correct somatic and cognitive development. Puberty means not only finalization of the phenotypic sexualisation, but also gaining the full procreation capacity.

After spontaneous disinhibition, by the time of puberty onset, around 8-9 years in girls and 9-10 years in boys, there is a continuous GnRH hypothalamic production (arcuate nucleus) responsible for gonadotropin release, according to the frequency and amplitude of GnRH secretion:

- low frequency = preferential FSH secretion
- high frequency = preferential LH secretion

VII.3.1. MALE SYSTEM

FSH = is conditioning the spermatogenesis, phenomenon present in the walls of the seminiferous tubules, stimulating:

- Sertolli cell stimulation
- Testicular growth
- Gametogenesis
- Facilitates cell replication

LH = is sustaining the androgen production, required for somatic, sexual and reproductive purposes:

- Leydig cell stimulation
- Testicular steroid genesis
- Very high intra testicular (intraluminal) testosterone levels

Once started, the secretion is continuous, without any daily/monthly variation.

Testosterone secreted at the level of Leydig cells is released in the general blood stream. It acts of intracellular steroid receptors, direct of after activation to dihydrotestosterone (activation by 5 alpha reductase) or after metabolization= aromatization in 17-beta estradiol.

The secretion chain is similar to the adrenal steroidogenesis, but gonads lack of aldosterone synthetase and 11 hydroxylase, so the secretion goes only in direction sexual steroid secretion.

Summarizing, testosterone effects are the following:

TABLE LIII. ANDROGEN EFFECTS IN MALES

Testosterone	**Dihydrotestosterone (5 α reductase activity)**	**17 β Estradiol (aromatase activity)**
Embryonic development of wolffian duct derivate structure	Embryonic development of prostate	Bone growth
Pubertal growth of larynx/deepening of voice	Masculinization of external genitalia in fetal life	Osteoporosis prevention
Anabolic effects on muscle	Testes descent in fetal life	Feed back regulation of GnRH
Anabolic effects o erythropoiesis	Pubertal growth of external genitalia	Growth cartilage closure
Anabolic effect on bone: periostal bone apposition, protein synthesis,	Development of pubic/axillary hair	
Inhibition of breast development	Development of facial/body hair	Favoring breast development
Libido stimulation	Male pattern balding in adulthood	
Erection facilitation Nocturnal erection induction		
Metabolic effect: ↓Lipid uptake Stimulate lipolysis ↓Adipocyte precursor cells ↑Metabolic rate ↑Lipid oxidation ↑Glucose disposal		

Regulation:

- Peripheral testosterone levels act, by the long negative feedback loop on the pituitary, regulating LH levels.
- Sertolli cells produce Inhibine, acting by the same long negative feedback loop on FSH level, controlling spermatogenesis.

There is to mention, that even if spermatogenesis and Hormonogenesis are produced by different cells, there spermatogenesis is not active only in case of a normal local testosterone level, meaning altered Leydig cell production will influence gametogenesis process.

Testosterone is sustaining the male phenotypic pattern:

- During fetal life – masculinization of external genitalia, masculinization if internal genitalia + involution of he female internal ducts, secondary to Antimullerian hormone, produced by intact Sertolii cells
- During puberty – growth spurt, facial hair, body hair, further masculinization and growth of the sexual organs
- During life - sustained the masculinization aspects

The male system, once activated during puberty, will be active during the entire life span of the male, with small gradual decrease, in the senescence.

VII.3.2. FEMALE SYSTEM

In females, the mechanism is more complex, due to the different menstrual cycle phases:

Follicular phases = a succession of well organized events:

- Monthly recruitment of some primordial follicles (present in the normal ovary at birth), random phenomenon, nit depended on gonadotrophs effect
- Once recruited, the follicular growth is stimulated and sustained by FSH
- Under FSH stimulation, the follicles growth following some stages:
    - primary follicle = the 1st stage of follicular growth
        - oocyte begins to grow
        - zone pellucida is formed
        - granulosa cells change from squamous to cuboidal
    - secondary follicle
        - maximal oocyte growth
        - proliferation of granulossa cells
        - acquisition of theca cells

- tertiary follicle – early antral phase
  - antrum formation in the follicular cavity
  - antral fluid = steroids
  - appearance of LH receptors on the thecal cells
  - differentiation of granulosa cells, FSH dependent
- Antral follicle
- Preovulatory follicle
- Once there is a preovulatory follicle, in parallel with the increased intrafollicular estrogen level, there is a high secretion of Inhibine, responsible for the involution of all other mature/in different growth stages follicles, in order to prevent multiple pregnancies because of multiple ovulations.
- Steroidogenesis is made in the secretory cells present in the wall of the follicles (theca cells) that will produce by the same steroid secretion chain, starting with cholesterol, testosterone, that will be finally transformed in estradiol, at the levels of granullosa cells (present just in antral and preovulatory development stages)

Ovulation occurs when one of the growing follicles has sufficient high estrogen levels in order to induce the typical positive feedback on LH levels. The increase in LH will induce the ovulation = the intra-abdominal rupture of the follicle with the release of oocyte, that will be captured by the fallopian tube.

Luteal phase

- The rupture ovulatory follicle will form the future luteal corpus, granullosa cells with transform form predominant estradiol secretion to preferential progesterone secretion. Progesterone secretion will induce specific endometrial changes needed for a possible implantation.
- The secreted Inhibine will induce more central FSH and LH inhibition. After 7 to 10 days, if there is not active embryonic beta HCG secretion (similar to LH), there is no central sustained of the luteal body, with involution and decrease of progesterone and estradiol secretion.
- The decrease of the hormones in needed for appearance of withdrawal menstrual bleeding.
- When Inhibine level is small enough, due to the physiological involution of luteal body, there FSH production will star to increase, with subsequent follicular growth and beginning of a new cycle.
- If fertilization is obtained, the luteal body will continue to function and to produce progesterone, because the embryonic structure sustains itself, by producing beta HCG. Beta HCG will sustain luteal body, that will continue to produce important amount of progesterone, that will sustain the embryonic development and growth. This phenomenon is present up to week 8 to 12, till placenta is correctly formed and will continue the progesterone secretion.

Estradiol is the major representative of estrogens, along with estrone and estriol. They act of intracellular receptors, with different effects, according the the activated receptor:

- *α receptor – classic receptor*

UTERUS = induces endometrial proliferation
= sensitizes uterine muscle to Oxt effect (↑ Oxt rec)
= ↑ production of watery cervical mucus
OVARY = potent mitotic effect on granullosa cells
BREAST = growth + differentiation of ductal epithelium
= mitotic activity of ductal cylindrical cells
= Growth of connective tissue

- *β receptor – nonclassic receptor*

LIVER = metabolic modulation
= ↑lipoprotein receptor, ↓total Chol,↓ LDLC, ↑HDLC
= coagulation + fibrinolysis: ↓fibrinogen, ↓antithrombin III, ↓PAI 1,
= ↑ globuline: TBG, CBG, SHBG
CNS = neuro-protective
Bone = anti-resorptive: ↑bone maturation, ↓bone turnover

- *Nongenomic effects*

= Inhibits endothelial cells apoptosis
= Promotes angiogenic activity of endothelial cells
= short term vasodilatation
= Vascular smooth muscle tone ↑NO, Prostacyclin
= activation of growth factor: osteoblast, endothelial cells, neurons, human breast cancer cells

Progesterone effects are:
FERTILITY
= Stimulates the release of mature oocytes
= Stimulation of uterine growth
= Facilitate implantation
= Maintains pregnancy

- stimulation of uterine growth
- differentiation of myometrium
- inhibition of myometrium contractility

= Down regulate E2 receptor at endometrial level

BREAST = Stimulates breast cell proliferation

GENERAL = Increases body temperature

The female system is functional, starting the puberty, with monthly cyclic function until the physiological or premature cessation, due to the loss of ovarian reserve.

VII.4. SYSTEM EVALUATION

VII.4.1. Female system

The gonadostat can be evaluated by means of:

- clinical evaluation: signs and symptoms of hypoestrogenemia/signs and symptoms of hypernadrogenia: tegmental and pilar hypernadrogenia

- functional evaluation has consider always all the compartments:
  - peripheral function
  - pituitary function
  - dynamic evaluation always in cases of suspected insufficiency with different stimulatory tests
  - additional evaluation of thyroid and/or adrenal function

Ovarian compartment evaluation

- estradiol and total testosterone assay – performed in day 2-3 of the menstrual cycle
- estradiol and progesterone – performed 7 days before the estimated day of menses begin, to evaluate the peak luteal phase
- mid cycle evaluation of ovulation is not made by measurement of plasmatic estradiol
- AntiMullerian hormone = evaluates the ovarian follicular reserve and is predictive for the response to stimulatory treatments, in cases with infertility
- Inhibin B reflects the volume of granulosa cells within the ovary, serving as an indicator of the size of the growing cohort of follicles (ovarian reserve).
- Inhibine A has less importance

Pituitary compartment evaluation

- plasmatic LH, FSH , PRL measurement
- FSH in day 3 – evaluates the follicular activity
  - > 10 UI/L = suboptimal response capacity
  - > 20 UI/L – altered follicular proliferation activity
  - > 40 UI/L = ovarian insufficiency
- LH – LH plasmatic peak precedes ovulation by 12-18 hours, but the plasmatic measurements are difficult to be make, in ovulation needs to be identified. Therefore urinary LH measurement, is used as ovulation indicator, because serial measurements are easy to be done.

Always central and peripheral compartment need to be evaluated together.

TABLE LIV. EVALUATION OF CENTRAL VERSUS PERIPHERAL INSUFFICIENCY

	E2	Progesterone	TT	LH	FSH
Ovarian insufficiency	↓	↓	N, ↓	↑	↑
Central insufficiency	↓	↓	□□□ ↓	↓	↓
PCOS	N	↓	↑	↑	N

Dynamic performed tests are stimulatory tests only:

- LHRH stimulatory test- administration of 1 mcg LhRH (iv) with LH and FSH measurement before LhRH administration, 20' and 60'.
  Normally there is a 3 fold increase of LH and 10 fold increase in FSH
  The response is normal in peripheral insufficiency
  The response is blunted in partial pituitary insufficiency
  The response is absent in total pituitary insufficiency and hypothalamic insufficiency.

➢ Morphological evaluation

The most used evaluation is represented by ultrasound assessment. Performed trans vaginal or trans abdominal (with lower sensitivity and specificity – used only in virgo intacta patients).
Ultrasound evaluation is suggestive for:

- follicular activity
- evaluation of ovulation
- evaluation of luteal body presence = suggestive for prevalent ovulation
- indirect information regarding ovarian function are delivered by the endometrial thickness:
  Imaging the endometrium on days 5-10 of a woman's cycle reduces the variability in endometrial thickness
  < 1 mm – atrophy- estradiol deficiency
  1-6 mm – normal depth in premenopausal women
  > 15 mm - hyperplasia – relative/absolute hypersecretion = the top value of normal endometrial thickness in premenopausal women
  > 6 mm – hyperplasia in postmenopausal women

The appearance can be non-specific and cannot reliably allow differentiation between hyperplasia and carcinoma [5]. Usually, there is a homogeneous increase in endometrial thickness, but endometrial hyperplasia may also cause asymmetric/focal thickening with surface irregularity, an appearance that is suspicious for carcinoma.

Computer tomography and MRI evaluation are needed only in cases with suspected tumors, endometriosis, important cysts. These evaluation are not performed on regular basis for routine diagnostic algorithm of the morphological evaluation of the ovaries.

- Genetic evaluation: karyotype evaluation is needed in all cases of amenorrhea, infertility or altered puberty.

VII.4.2. Male system evaluation

- Clinical evaluation:
  - Prepubertal deficiency: poor secondary sexual development, eunuchoid skeletal proportion, pitched voice, spares axillary and pubic hair, sparse facial hair, lack of upper abdominal and chest hair. The closure of epiphyseal plates is delayed, so the growth is linear, without growth spurt, but continuous and longer than in normal children, with a final height higher than the mean population.
  - Postpubertal deficiency: has less clinical signs, with significant symptoms

- Genital evaluation:
  - Signs of preconceptional hypogonadism: epispadias, hypospadias
  - Penis length – in flaccid state
  - Testicular volume is evaluated by comparison with the ellipsoids with Prader orchidometer
  - Varicocele/hydrocele = are important just in cases of infertility

- Functional evaluation has consider always all the compartments:
  - peripheral function:
    A. Semen analysis: at least 3 sequential analysis should be made. It is indicated just in cases with infertility of cases with hypo-gonadism, for a complete testicular performance evaluation.
    B. Hormonal evaluation:
  - Testicular function: Total testosterone, Free Testosterone, SHBG, hCG
    In order to calculate free testosterone total testosterone and SHBG can be measured and calculation of free testosterone is available on www.issaam.ch
    hCG is needed in cases of tumoral testicular lessions

- pituitary function: LH, FSH, PRL

- dynamic evaluation always in cases of suspected insufficiency with different stimulatory tests:
  LHRH stimulatory test- administration of 1 mcg LhRH (iv) with LH and FSH measurement before LhRH administration, 20' and 60'.
    Normally = 3-5 fold increase of LH and 10-15 fold increase in FSH
  The response is normal in peripheral insufficiency
  The response is blunted in partial pituitary insufficiency
  The response is absent in total pituitary insufficiency and hypothalamic insufficiency

- Additional evaluation of thyroid and/or adrenal function

- Biopsy:
  Testicular biopsy is indicated in patients with oligo/ azoospermia and normal hormonal profile, to evaluate the germinative proliferation capacity of the system.

- Genetic evaluation: systemic karyotype evaluation is recommended in cases of infertility or altered puberty.

- Morphological evaluation: testicular ultrasound – evaluation of tumoral lesions. Always ultrasound has to complete with tomography or MRI evaluation.

VII.5. PUBERTY

Puberty has to be considered a phase in the continuous evolution of the hypothalamic hypophysis gonadal function, which stares in the intrauterine life, continues during puberty with achievement of the final somatic and reproductive stage, which will be maintained during the adult life.

Staring the postnatal period, the gonadostat, both in males and females is inactivated, due to the oversensitive negative feedback, by which small quantities of sexual steroids will inhibit the pituitary, associated with a supra neural suppression of the GnRH producing neurons.

Puberty means the self-activation on the axis due to the decrease of the sensitivity of the feedback mechanism, and also du the spontaneous activation of the pulsatile GnRh secretion.

The end effect of puberty is represented by adult appearance, sexual maturity and complete fertility.

Puberty is preceded by:

1. adrenarche – adrenal sexual steroids synthesis activation, around 6 years of age, 2 years before puberty onset
2. decrease of gonadostat inhibition – 1 year before puberty onset
3. gradual increase of the interactions between hypothalamus = pituitary = gonads

There is a physiological onset means the self activation of the intrinsic oscillatory functioning mechanism of the neurons from the arcuate nucleus.

VII.5.1. Puberty in females

The general accepted limits are between 8 to 13 years of age, with a normal time span of around 4.5 years, after the activation.

Definitions
Telarche - breast budding
Pubarche – pubic hair appearance
Menarche – first menstrual cycle

The limits of the normal puberty are listed in Table LII.

TABLE LV. PUBERTY AGE LIMITS

Telarche/pubarche at 7 years Telarche/pubarche at 8 years	6,7% 14,7%
Menarche at 11 years at 12 years	13,4% 35,2%
Mean telarche age Telarche limits	9,96 years 8 – 12 years
Mean adrenarche age Adrenarche limits	10,51 years 9-12 years
Mean menarche age Menarche limits	12,88 years 12-14 years

The somatic changes during puberty are classified acording to the Tanner stages as following:

- Telarche

STAGE 1 – preadolescent = small mamelonar elevation
STAGE 2 – the sign of the 1st moon = small elevation of the breast and areola
STAGE 3 – more significant increase in the entire breast
STAGE 4 – the 2nd moon sign = on the increased breast extragrowth of the areola
STAGE 5 – adult type breast

Pathogeny = ovarian estrogen secretion is responsible for the first sign of breast goring process, estrogen and progesterone are responsible for te end stage growing continuation.

- **Even in breast budding is the 1st clinical puberty sign in girls, the height spurt is considered the 1st effective sign of puberty.**
- Pubarche
  STAGE 1 – preadolescent = velar hair (soft, blond, short)
  STAGE 2 – small black, long, corse terminal hair, along the margins of labia major
  STAGE 3 – terminal hair with increased aria growth to the pubic junction
  STAGE 4 – terminal hair in entire pubic region
  STAGE 5 – terminal hair in the pubic region and also on the inner hip region

Pathogeny = secretion of the adrenal sexual steroids

In the majority of cases there is a concordance between pubarche and telarche, but they have always to be considered separately because of different underlying mechanisms.

Other somatic changes seen are:

- External genitalia
  - Increase and protrusion of labia major
  - Increase of the vaginal mucosa, cornification of the cells
  - Leucorrhea
  - Decrease of vaginal pH, due to estrogen presence anf bacterial millieu changes
  - Deposition of adipose tissue at prepubic level
  - Increase of clitoridian dimension
- Internal genitalia
  - Increase of the dimension of the uterus from 2-3 cm to 5-8 cm, with subsequent volume increase 3-15 ml
  - Ovarian increase up to 15 ml
  - Follicular activity – physiological multichistic ultrasound appearance

- Body proportion: **head-pelvis/pelvis-heel**
  - Newly born 1,7
  - 1 year of age 1,4
  - 10 years 1
  - puberty 0,92

- Body composition:
  - Bone mass ↑

- Muscle mass ↑
- Adipouse mass ↑: hips, tights proportionate to estrogen levels
- Water mass ↓

➢ **CNS:**
  - Decresse of brain plasticity (ex: decrease of foreign languanges learning capacity)
  - EEG changes: decrease of amplitude and frequency of delta waves
  - Decrease of deep sleep up to 50%;
  - Behavior: abstract thinking, evaluation ability, introspection, personal inedittiy, complete sexual orientation, autonomy

Along to the somatic changes and growth, puberty means achievment of the total fertility, due to the activation of the gonadostat.

VII.5.2. Puberty in males

The general accepted limits are between 9 to 14 years of age, with a normal time span of around 4.5 – 5 years, after the activation.

Definitions
Gonadarche - testicular growing
Pubarche – pubic hair appearance

The somatic changes during puberty are classified acording to the Tanner stages as following:

➢ Gonadarche

STAGE 1 – preadolescent = no visible signs of development
STAGE 2 – testicular and scrotal growth (4-6 ml)
STAGE 3 – more significant increase on the testes (8-10 ml) and the scrotum with penile increase, in length
STAGE 4 – penile increased in diameter with further testicular growth (14-16 ml)
STAGE 5 – adult type aspect (> 18 ml)
Pathogeny = secretion of the testicular steroids

➢ Pubarche
STAGE 1 – preadolescent = velar hair (soft, blond, short)
STAGE 2 – small black,long, corse terminal hair, at the base of the penis
STAGE 3 – terminal hair with increased aria growth to the pubic junction
STAGE 4 – terminal hair in entire pubic region
STAGE 5 –erminal hair in the pubic region and also abdominal wall

Pathogeny = ovarian estrogen secretion is responsable for the fisrt sign of breast goring procces, estrogen and progesteron are responsable for te end stage growing continuation.

In the majority of cases there is a concordance between pubarche and telarche, but they habve always to be considered separatelly becuase of different underlying mechanisms.

- Fertility
- 11 years – 1st signs of spermatogenesis
- 11-15 years - sperm is present in the early morning urine
- 15-17 years - normospermia
- skin
  - thickenng of the skin
  - oily skin
  - deepenig of the voice, due to irreversible cartilague changes
  - body hair – without beeing considered a major secondary characteristic
  - facial hair - without beeing considered a major secondary characteristic

- Bone
  - The total height spur = 30-35 cm
  - The lenght of the growth process is more important than the menarche age, take of moment or growth speed
  - The peak bone mass is achieved after the puberty

- Body proportion: **head-pelvis/pelvis-heel**
  - Newly born 1,7
  - 1 year of age 1,4
  - 10 years 1
  - puberty 0,92

- Body composition:
  - Bone mass ↑
  - Muscle mass ↑
  - Adipouse mass ↓
  - Water mass ↓

- **CNS:**
  - Decrease of brain plasticity (ex: decrease of foreign languages learning capacity)
  - EEG changes: decrease of amplitude and frequency of delta waves
  - Decrease of deep sleep up to 50%;
  - Behavior: abstract thinking, evaluation ability, introspection, personal identity, complete sexual orientation, autonomy

Along to the somatic changes and growth, puberty means achievement of the total fertility, due to the activation of the gonadostat.

The complete pubertal evolution, in both sexes, can be organized as seen in Table LIII.

TABLE LVI. SOMATIC CHANGES IN PUBERTY, BOTH IN FEMALES AND MALES

Boys	**Mean age**	**Girls**
	8-10	Uterus growth
	10-11	Telarche (B2)/pubarche (P2)
Gonadache (G2)	11-12	Height spurt
Acne		Sesamoid bone
Prostate growth		Acne
		Breast budding (B3)
		Growth of internal/external genitalia
		Mature vaginal epithelium
Pubarche (P2)	12-13	Breast increase (B3)
Height spurt		Breast areola (B4)
Sesamoid bone		Full axillary hair (AH1)
Accelerated growth of testis/penis	13-14	Menarche
Full axillary hair (AH1)	14-15	Regulated menstrual cycle
P4		B4/5
Voice change		P5
Facial hair		Fertility
P5	15-16	Closing of growth cartilages
Adult spermatozoa		
Closing of growth cartilages	> 17	

- Socio sexual behavior
- 10-14 years = early adolescence: physical changes insecurity sexual curiosity & exploration
- 15-18 years = middle adolescence: more monogamous focused, growing maturity & responsibility
- > 18 years = late adolescence = more mature social / sexual skills

VII.6. SYSTEM INVOLUTION

After the onset of the gonadostat, during puberty, both in males and females, the hypothalamic hypophysis gonadal axis functions during the whole adult life, both in males and females.

VII.6.1. Menopause

Is the natural phenomenon of ovarian function cessation, in all situations when the ovarian follicular deposits are gone. The female gametogenesis is limited, conditioned by the number of primordial follicles, present, at birth, in the female newborn body. There is no possibility of influencing/prolonging or replication of the follicular reserve.

Definitions
Premenopause = any female after 40 years of age;
Menopause = permanent cessation of menses;
Perimenopause = period between menses irregularities and 1 year after the last menses;
Postmenopause = starts 1 year after the last menstrual bleeding;
Transition period = transition form the normal ovarian function to ovarian insufficiency;
Mean transition age = 46 years
Mean transition length = 5 years
Beginning of the premenopause = 39 - 51 years of age

The age of menopause is influenced by several factors, the major determinant being ovarian functional reserve. Earlier menopause is favored by:

- low socioeconomic status
- smoking
- low educational status

Later menopause status is induced by:

- chronic alcohol consumption
- long use of oral contraceptives
- increased number of pregnancies

Classification:

- natural menopause, regardless age. If onset is before the age of 45, the used term is premature ovarian failure.
- iatrogenic menopause
    - surgery - ovarectomy regardless uterine status
    - radiotherapy – applied in the region for uterine/ovarian/bladder/colonic/bine cancer
    - chemotherapy – almost all treatment regimen, especially if females are very young
    - medication - Antiestrogens (aromatase inhibitors)/ GhRh analogues

Signs and symptoms

- transition period

  Transition period is dominated by the hyperestrogenemia (relative due to normal estrogen secretion but lower progestin secretion, due to anovulation, or absolute hyper secretion, due to exacerbated follicular maturation)
- Anovulatory menstrual cycles, with polimenorrhea (frequent bleeding), hypomenorrhea, menorrhagia or metrorrhagia.
- Endometrial hyperplasia and hypertrophy
- Mastodynia, risk of breast proliferation overt malignant breast proliferation

- menopause period

Menopause period is governed by all symptoms related to estrogen deprivations. The symptoms can be grouped in:
Short term symptoms = vasomotor symptoms – hot flushes are considered the landmarks symptoms:

- incidence 10% of premenopausal women, 85% of menopausal women, at least in the first 2 years of menopause, but can last for decades in 25% of women
- risk factors: smoking, overweight, sudden estrogen deprivation, heat, stress, emotions, night period
- differential diagnostic = hyper catabolic status: leukemia, carcinoids, overt hyperthyroidism
- is induced by changes of basal body temperature, concordant to hypothalamic pulses, followed by a adaptive, reflex vasodilation.

Other symptoms: headache, nervousness, emotional lability, weight gain.

Medium term symptoms = degenerative/atrophic signs are:

- vaginal and urethral atrophy due to estrogen deprivation, alteration of cellular integrity, decrease of vascularization, alteration of the vaginal flora, with decrease of Doderlein bacillus, with alteration of biological balance, cellular dehydration, decreased lubrication capacity.
  Symptoms: pain, burning, local infections, lower urinary tract symptoms, nicturia, alguria, hematuria, urinary incontinence.
- general skin dehydration
- dehydrated/brittle nails
- dehydrated hair
- emotional sensitivity: nervousness, anxiety, emotional lability, altered sleep and insomnia, tiredness, fatigability.
- General body changes: increase in total body fat, decrease of gluteal muscle, decrease of breast tonus, increase in volume due to fat transformation
- Decrease of basal metabolic rate
- decrease of muscle mass and force

Long term effects = involution

- Cognition = alteration of cognition and memory is typical for older women. Literature data suggest the benefic effects of estrogen's on this phenomenon. The incidence of Alzheimers' disease decreases with around 40% after a mean treatment period of at least 5 years, with significant disease incidence reduction, in case of use for a period longer than 10 years. Still there is no consensus regarding the possible benefits of treatment of the clear risk, in case of treatment longer than 10 years of age.
- Cardiovascular system = the benefit effects of estrogen of cardiovascular system are well known. Still, these benefic, mainly antioxidativ and vasodilator, respectively protective effect, are present only in the presence of sustained estrogen presence. After a withdrawal period, the same hormones can induce negative effects. Also there is a difference between primary prophylaxis and secondary prophylaxis, for cardiovascular disease. Use of estrogen supplemental therapy in cases with prevalent cardiovascular disease, was the major problem in cases with adverse effects of estrogen treatment in the well know WHY studies.
- Bone = estrogens deprivation can induce increased bine turnover, wth subsequent bone demineralization, alteration of bone structure, resistance with increased fracture risk.

Diagnostic

1. *Clinical – combination of signs and symptoms*
2. Hormonal assays: high FSH and LH with low estradiol + progesterone. Exclusion of other causes of amenorrhea
3. Ultrasound: lack of ovarian follicular activity, small endometrial depth

Specific evaluation during transition period

- History of dysfunctional hemorrhage
- Clinical exam, vaginal evaluation
- Transvaginal ultrasound: only endometrium higher than 5 mm should be referred to biopsy
- Additional evaluation, in cases with difficult control of dysfunctional hemorrhage: colposcopy, cervical biopsy, bioptic endometrial evaluation, hysteroscopy
- Breast ultrasound and mammography

Specific evaluation during menopause

- annually: gynecological evaluation, PAP smear
- DXA evaluation
- mammography
- lab exams: lipidogram, hepatic evaluation

Treatment options

Currently, hormonal replacement therapy both among patients and some medical doctors is influenced by a lot of negative attitudes. The major professional societies in the field have established new rules for this treatment.
Treatment options:

1. hormonal supplemental therapy
2. estrogens mimetic agents
3. selective estrogens receptor modulators
4. nonhormonal options
5. androgens

1. HORMONAL SUPPLEMENTHAL THERAPY

✓ **GENERAL APPLIED RULES**

- supplemental treatment has to start as soon as possible after the onset of menopause no more than 1-1.5 years after the onset of menopause
- the safety length of treatment is considered up to 5 years, longer treatment period are evaluated individualized for each case apart
- in the presence of uterus, always estroprogestins association is needed:
- in cases with hysterectomy estrogen only treatment can be used
- I the transition period, treatment use starts in cases with significant FSH increase, higher than 20 UI/L
- Use estrogen doses do decrease with age
- Therapeutic regimen: COMBINED = 21 days of estrogens + 10 days of progesterone or CONTINUOS = daily administration of fixe dose of estrogens + progestin

✓ **INDICATIONS**

- Neurovegetative symptoms
- Symptoms induce by genital moderate to severe atrophy in the context of menopause
- Osteoporosis prophylaxis just in cases with severe risk

✓ **CONTRAINDICATIONS**

- Prevalent breast cancer;
- Suspicion of any malignancy, estrogen dependent
- Any undiagnosed vaginal bleeding
- Unevaluated endometrial hyperplasia
- Pulmonary thromboembolism
- Profound venous thrombosis
- Arterial thromboembolic disease
- Untreated hypertension
- Active hepatic disease
- Prevalent Stroke
- know sensitivity to any preparation
- porfiria cutanea tarda

✓ **CONDITIONS WHICH NEED SUPERVISION**

- Leiomyoma (uterine fibroids) or endometriosis
- Risk factors for thromboembolic disorders (see below)
- Risk factors for oestrogen dependent tumours, e.g. 1st degree heredity for breast cancer
- Hypertension
- Liver disorders (e.g. liver adenoma)
- Diabetes mellitus with or without vascular involvement

- Cholelithiasis
- Migraine or (severe) headache
- Systemic lupus erythematosus
- A history of endometrial hyperplasia (see below)
- Epilepsy
- Asthma
- Otosclerosis

✓ **IMMEDIAT WITHDRAWAL OF THE MEDICATION**
- Jaundice or deterioration in liver function
- Significant increase in blood pressure
- New onset of migraine-type headache

✓ **Used preparation**

Estrogens have to be administered in the minimal efficient dose, considering the age of the patients. Different preparation can be used.

- conjugated estrogens	0,3-0,625 mg
- micronized estradiol	0,5-1 mg
- transdermic estradiol	14-100 mcg
- etinilestradiol	0,01-0,02 mg
- estriol	

- Administration route

1. orally
   - The most frequent use route
   - Affected by the 1st hepatic passage: increased globulin production: SHBG, CGB, TBG, angiotensinogen, coagulation factors
   - Unstable final plasmatic concentration
   - Not recommended in cases with hypertriglyceridemia, colelithiasis risk

2. transdermal
   - Efficient just for treatment of neurovegetative sd.
   - Inefficient for prophylaxis of bone demineralization
   - Metabolism does not imply the 1st hepatic barrier
   - No effect on procoagulatory molecules
   - Can induce just local effects

3. vaginal
   - Ideal just for local symptoms, such as vaginal atrophy
   - Partial effect on neurovegetative symptoms
   - The effects are dependent on the used dose
   - No effect on osteoporosis prophylaxis

Progestin's are recommended just in female with present endometrium, regardless the onset of menopause. All types of progestin have protective effects on endometrium.
The most used progestin are listed below, with different dosage, dependent on the administration regimen:

	Cyclic	*Continuos*
- Medroxiprogesteron acetat	5 mg	2,5 mg
- matural progesterone	200 mg	100 mg
- Noretindron	0,5 mg	0,35 mg
- Levonorgestrel	0,075 mg	

- Administration route

1. orally

2. vaginal

The differ just in respect to weight gain and compliance

- Possible adverse effects
    - Bloating, hydric retention, sleep disturbances, general well being changes, mood changes
    - Proliferative breast effects = enhancing the malignant cell transformation, estrogen dependent.

✓ **SUPPLEMENTHAL TREATMENT POSSIBLE RISKS**

- Are favored by: use of longer than 5 years, estrogen only treatment in patients with intact uterus, suspicion of estrogen depended malignancy, secondary cardiovascular prevention (not primary prevention)
- Currently, breast cancer risk is not considered as a direct effect of estrogen supplemental therapy, since, the mean development toe for a breast cancer is 7 to 8 years, and the maximum supplemental treatment is offered for 5 years. Still, supplemental treatment can accelerate a previous present cancer, this is why periodic imagistic evaluation has to be made before and along the treatment.
- Thrombosis risk is described in case of estrogen use. The effect is described just for oral route, due to the metabolization at liver site, this is why the current recommendations for long run treatment is the use on NON oral route, vaginal or transdermal. Which are both free of effect on coagulation molecules.
- Weight gain is seen just in overdosing cases
- Persistence of neurovegetative symptoms is seen in underdosed cases

2. ESTROGEN MIMETIC AGENTS

This family has a sole representative, Tibolone, a unique molecule, with estrogens, progestin and also androgen mimetic effects at different sites:

- bone = estrogen mimetic effect
- breast = no effect/ inhibition of cellular proliferation, stimulation of apoptosis
- endometrium = progestin mimetic effect
- cardiovascular system = no effect
- CNS = androgen mimetic effect

Indication, contraindications and cautions are the same as for the supplemental therapy.

✓ UNDESIRABLE EFFECTS

- Edema
- Lower abdominal pain, abdominal discomfort
- Acne, abnormal hair growth
- Vaginal discharge, endometrial thickening, postmenopausal hemorrhage
- Breast tenderness, Breast discomfort, nipple pain
- Vaginal candidiasis, mycosis, vaginal discharge, vulvovaginitis
- Weight increase

3. ESTROGEN RECEPTOR MODULATORS

The estrogen receptor modulators are mainly use as antiosteoportic drugs. They have different effects at different sites: estrogen like effects on bone with neutral effects on breast and endometrium. The immediate menopause symptoms, such as hot flushes, are not influenced by these agents, the utility in menopause being scares. The antiosteoporotic effects is small, but the breast protection is demonstrated by large studies.

4. NONHORMONAL TREATMENT

There are different of label recommendations of medications and intervention that can decrease the intensity of neurovegetative syndrome, in postmenopausal women. Without being so efficient as hormonal methods, they can ameliorate the clinical picture of this patients:

- ***Ambient changes***: decrease of ambient temperature
- ***Relaxation techniques***
- ***Antidepressant*:** Venlafaxin, Aproxetin, Fluoxetin = 60-65% decrease

!! AE: nausea, dry mouth, insomnia, fatigalibity, sexual dysfunction, gastrointestinal symptoms

- ***Clonidine*****:** central alphaadrenergic agonist = can decrease up to 50% the sympotms, if adminsiterde orally 0,1 mg/day
- ***Gabapentin*****:** GABA analoque – cand reduce vasomotor symptoms up to 45% in doses of 900 mg/day
- ***Fitoestrogenis*** : preparations derived from Soy, can reduce the symptoms up to 30%; the effects disappear after several weeks of use.
- ***Actaea racemosa*** (Cimicifuga racemosa = Black cohosh, orally 40 mg/day equals the effects of 0,6 mg conjugated estrogens;
- ***Vitamina E*** 2x400 UI/day induces a modest decrease of heats by 1 event/day

5. ANDROGEN SUPPLEMENTHAL TREATMENT

The androgen deficiency in females is characteristic for surgical menopause, being also present in some women with natural menopause. Physiological, small amounts of testosterone are produce even in menopause, by the ovarian thecal cells. Adrenal steroids (DHEAS, DHEA, androstendion) are converted, in the periphery also in small amounts of androgens, responsible for the general well being sense, sexual inters, arousal, muscle mas and mood.

Androgen deficiency in women can be suspected in the presence of the following symptoms:

- Loss of libido, decrease of sexual motivation, decrease of excitability, alteration of sexual phantasies and satisfaction
- Head ache, fatigability, decreased vitality, loss of concentration capacity, decrease of muscle mass

Positive diagnostic can be only, in the presence of symptoms, only and low testosterone levels, compared with premenopausal women.

Treatment can be made, only after supplementation of the estrogen line, using testosterone preparation, preferably transdermic preparation, in 1/10 of the standard male dose (off label use) or using transdermal testosterone preparation for women.

The same contraindication, caution and periodical evaluation, as in estrogen replacement treatment are used.

If supplemental therapy is used, periodical evaluation is mandatory:

- Annual breast evaluation by mammography, after 10 days of estrogen/androgen withdrawal
- Annual gynecological evaluation with measurement of endometrial thickness
- Metabolic evaluation: lipids
- Bone mineral density evaluation

If any adverse effect appear or any contraindications appear, the immediate supplemental therapy withdrawal is indicated.

VII.6.2. Late onset hypogonadism

There is biological phenomenon that can be considered similar with the menopause, in females. The major difference is made be the infinite capacity of the spermatozoa line to regenerate, with theoretically endless spermatogenesis coupled with endless Leydig cell activity.

But, still there is a progressive, slow decrease in the steroidogenesis capacity in males, starting 40 years of age, in a rate of around 1%/years. The phenomenon is not universal, is not seen in all males, and is favored by some life style habits, unfavorable to testosterone production.

Life style habits that favors partial hypogonadism:

- chronic alcohol consumption
- weight excess
- metabolic syndrome
- diabetes mellitus
- sedentary life

Etiopathogeny of late onset hypogonadism due to metabolic alteration.

Classification

- physiological involution = late onset hypogonadism, partial hypogonadism
- iatrogenic = overt hypogonadism due to
    - Regional radiotherapy
    - Surgery = bilateral orchiectomy
    - Chemotherapy = the vast majority of the treatment regimen can induce alteration of spermatogenesis
    - Long term medication- Kalium sparing diuretics, anti androgens, GhRH analogues

Clinical signs and symptoms of late onset hypogonadism are differed compared with typical signs and symptoms of overt hypogonadism.

Signs and symptoms of overt late onset hypogonadism:
There are normal signs of testosterone impregnation- normal secondary sexual characteristics, normal size genital, normal aspect/length of the penis, with normal tegmental testosterone impregnation signs, normal voice and normal height and body composition.

The signs are subtle with:

- reduced sexual desire and sexual activity
- reduced nocturnal erections
- hot flushes
- changes in mood, fatigue and ager
- sleep disturbances
- metabolic syndrome

Long standing, untreated LOH will influnec the body composition with more frequent

- visceral obesity
- lower bone mass with increased risk of fragility bone fracture
- insulin resistance and type 2 diabetes mellitus
- sarcopenia
- diminished cognitive function

Diagnostic

In the presence of significant symptoms, in order to make a positive diagnostic the following are needed:

- 2 measurement of total testosterone that has to be decreased < 10 nM/L are needed
- Alternative: measurement of SHBG level + total testosterone level and calculation of free testosterone by the free calculator www.
- Additional evaluations:
  a. LH – normal or decreased in late onset hypogonadism due to the alteration of gonadostat, induced by obesity and insulin resistance
  b. LH – increased in overt hypogonadism due to surgical, chemical or radiological castration
  c. Additional evaluations are needed to exclude secondary causes of hypogonadism: TSH, FT4, PRL, creatin, renal filtration rate.

Active screening has to be done in diseases where partial testosterone deficiency is common:

1. obesity
2. metabolic syndrome
3. end stage renal disease
4. moderate to chronic obstructive lung disease
5. sarcopenia
6. type 2 diabetes mellitus

TREATEMENT OPTIONS

Theoretically life style changes, such as exercise on regular basis, weight loss, diet, active sexual life, can increase the endogenous production of testosterone. Because the changes need to be significant, the proportion of males which can auto regulate the endogenous testosterone is very small.

HORMONAL SUPPLEMENTHAL THERAPY

✓ GENERAL APPLIED RULES

- Supplemental treatment has to start as soon as possible after the onset of menopause no more than 1-1.5 years after the onset of menopause

✓ **INDICATIONS**

- Multiple clinical symptoms following unsuccessful treatment of obesity and comorbidities
- Type 2 diabetes mellitus with hypogonadism
- Clear low testosterone levels

✓ **CONTRAINDICATIONS**

- Prevalent breast cancer
- Prostate cancer
- Severe chronic cardiac failure NYHA class IV
- Haematocrit > 0.54%
- Male infertility plus active desire to have children
- Severe sleep apnea
- Severe lower urinary tract due to benign prostatic hyperplasia

✓ **CONDITIONS WHICH NEED SUPERVISION**

- Dyslipidemia
- Benign prostatic hyperplasia
- Sleep apnea
- Ht levels in the upper normal range values
- Infertility with uclear procreative

✓ **IMMEDIAT WITHDRAWAL OF THE MEDICATION**

- Jaundice or deterioration in liver function

✓ **Used preparation**

Testosterone preparation have to be administered in the minimal efficient dose, considering the age of the patients. Different preparation can be used.

- testosterone cypionate and enanthate are administered intramuscular, every 2-3 week, due to the short acting proprieties, with unstable plasmatic levels.
- testosterone undecanoate is administered intramuscular, every 3 months, because of long standing activity with stable plasmatic levels, but with long wash out period.
- bioidentical testosterone is used as skin patches or gel, with transdermal application, with daily application, with stable plasmatic level and very short wash out period.
- sublingual and buccal testosterone provide physiological testosterone plasmatic level with daily administration, very short washout period.
- subdermal depots are implanted every 5-7 months offers an compliant variant with stable plasmatic levels, but with long wash out period.

✓ **SUPPLEMENTHAL TREATMENT POSSIBLE RISKS**

- Association of testosterone therapy and male cancer risk is not demonstrated, but a preexisting breast cancer can be favored in progression by the use of exogenous steroid hormones
- Prostate growth is favored by testosterone, however, there is no clear indication that testosterone therapy does increase the risk of prostate cancer per se.
- Cardiovascular disease: testosterone therapy has benefic actions on some of the cardiovascular risk factors. Caution should be used in patients with severe preexisting cardiovascular pathology.
- There is no consistent evidence that testosterone therapy can aggravate a preexisting obstructive sleep apnea, but till clear evidence appears, caution should be used.
- Venous tromobebolism is an issue only in the presence of underlying thrombophilia.
- Increase in Hematocrit is described, so periodical evaluation ins needed and, if hemoconcentration appears, cessation of treatment is recommended.

If supplemental therapy is used, periodical evaluation is mandatory:

- Treatment efficacy should be monitored by assessing total testosterone levels every 3 months in the 1st year of treatment, and the annauly
- Haematocrit and haemoglobin monitoring – at the start and every 3 moths during therapy, in the1st year of treatment, than every annually
- PSA should be monitored every 3 months during the 1st year of treatment;. An increase higher than 1 ng/mL in 3 months or a total value higher than 4 ng/mL
- Bone density is monitored early only in old patients
- Major cardiovascular events have to be monitered
- If any adverse effect appears or any contraindications appear, the immediate supplemental therapy withdrawal is indicated.

VII.7. HORMONAL CONTRACEPTIVE METHODS

Contraception

All contraceptive methods block at least 1 of the factors involved in procreation process:

FEMALE FACTORS:

- Ovulation factor
- Tubal factor
- Uterine factor
- Cervical factor

MALE FACTORS:

- Gametogenesis
- Sperm activation
- Sperm transportation
- Sperm ejaculation

Contraceptive methods:

For FEMALES

- **Natural methods**
  - Abstinence
  - Withdrawal
  - Combined
- **Barrier methods**
  - Diaphragm, Calotte, Sponge
  - Female condoms
- **Hormonal methods**
- **Mechanical methods**
  - IUD
- **Surgical methods**

For MALES

Barrier methods
- Male condoms

Hormonal methods

Surgical methods

TABLE LVII. FAILURE RATE – THEORETICAL VERSUS REAL LIFE VALUES

Method	**% minimum expected pregnancies**	**% registered pregnancies**
No protection	85	85
COC	0.1	7.6
Progestin only	0.5	3.0
Implant progestin	0.005	0.2

Injectable progestin	0.3	0.3
IUD – cupru	0.6	0.8
IUS – progestativ	0.1	0.1
Female sterilization	0.2	0.4
Male sterilization	0.1	0.15
No protection	85	85
Periodical abstinence		20.5
Calendar	9.0	20.0
Ovulation	3.0	17.0
temperature	2.0	22.0
Postovulation tests	1.0	18.1
Retreat	4.0	23.6
Diafragm (mutiparous)	20.0	40.0
Diafragm (nuliparous)	9.0	20.0
Spermicide	6.0	25.7
Both	6.0	12.1

The current hormonal used methods are:

- Combined contraceptives- estroprogestins
  - Oral
  - Patches
  - Vaginal ring
  - Emergency
  - Long acting
- Progestin only contraceptives
  - Oral
  - Emergency
  - Long acting
  - Intrauterine system
- Male contraception
  - Androgens

VII.7.1. Combined contraceptives:

Mechanism of action:

1. the exogenous etinyl estradiol will inhibit the hypothalamic GrH pulsatory release
2. the exogenous synthetic estrogens will inhibit LH and FSH release
3. the lack of LH and FSH synthesis and secretion will inhibit follicular growth and secondary ovulation
    a. estradiol inhibits FSH = no follicular growth
    b. progestin inhibit preovulatory LH surge = no ovulation
4. there are no sigs of estrogen deprivation because of the synthetic estrogen in the pill
5. progesterone component will favor also local changes that will impair the nidation/implantation process:
   = cervical mucus changes – less permeable
   = endometrial changes – low proliferation

There are several generations of oral combined contraceptives:

Almost all have etinyl estradiol as synthetic estrogen, and differ according to the used progestin component. There are only 2 preparation using estradiol valerate, an estrogen more similar with the natural estradiol, used in adult women.

They are all micro dose preparation 50 mcg EE:

1st GENERATION	**> 50 mcg EE**		
2nd GENERATION	**20-35 mcg EE +**	**levonorgestrel**	
	norgestimate	**CILEST**	
	CPA	**DIANE, MELLEVA**	
3rd GENERATION	**20-35 mcg EE +**	**gestodene**	**FEMODEN STODETTE**
		desogestrel	**MARVELON, MERCILON**
4th GENERATION	**20-30 mcg EE +**	**drospirenon**	**YASMINE, YAZ**
		dienogest	**JANINE**
	E valerat		**QLAIRA,**
	nomegestrol acetat		**CYCLOPROGYNOVA**

Progestins can be group in different families, with importat different effects:

- **Estrane family**: 1st generation
  - Norethindrome acetate — *progestational effect*
  - Ethynodiol diacetate — *adrenergic effect*
- **Gonane family**: 2nd + 3rd generation
  - Levonorgestrel, Norgestrel — *androgenic effect*
  - Desogestrel — *no androgenic effect*, *high progestational selectivity*
  - *!!! Prothrombotic*
  - Norgestimate — *low antiadrigenic effect*
- 4th generation Drospirenon**e** — *antiandrogenic + anti MC*

Different therapeutic regimen are used:

Conventional regimen: 21 days + 7 days pause
24 days + 4 days pause

Modern regimen: 26 days + 2 days pause
= length of menses
= no increase cumulative doze
= better follicular maturation inhibition
= more stabile endometrium

Long term regimen: 6 months + 2 weeks pause

- Indicated in
  =Endometriosis
  =Catamenial epilepsy
  =Premenstrual migraine
  =Comfort
  =Endometrium stability

The adverse effects and also the contraindication of oral contraceptives are because of the supraphysiological effects of estrogens and progesterone:

- Effects on coagulation
  - High estradiol doses induce ↑↑ factor V, VII,X, fibrinogen
  - 20 mcg EE — NO effect
  - 30 mcg EE — slight procoagulant effect
  - !!! Association with smoking ± increase age (>35 mg) increases risk
  - presence of thrombophilic mutations increases risk exponentially
  - both venous thrombosis are arterial thrombosis can appear, under special circumstances:

VTE

- ↑ risk x2 during consumption
- Maximum in the 1st year of use
- Favoured by overweight
- Smoking ↑ risk
- Estrogen dependent
- Risk ↓ duration after treatment withdrawal

But, if we talk about increase venous thrombosis risk, the risk in general female population should also be discussed:

TABLE LVII. VENOUS THROMBOEMBOLISM RISK IN GENERAL FEMALE POPULATION

Population	Relativ risk	Incidence
Young women	1	5-10/10.000/year
Pregnant women	12	60-120
COC > 35 mcg EE	6-10	30-100
COC < 30 mcg EE	2	10-20
+ Leydig mutation	6-8	30-80
+ Leydig mutation + COC	10 – 15	50-100
Leydig mutation homozygote	80	400-800

Arterial thrombosis:

- Only in case of association with smoking + hypertension
- Dose dependent (!!! > 35 mcg)
- Favored by increase age
- Smoking = additive effect
- Ideally pre treatment screening

- Breast pain and tenderness
- Nausea
- Increase in weight .. possible steroid side effect
- Facial hyperpigmentation
- ↑ Ferritin, thrombin
- ↑Vitamin A, ↓vitamin B, ↓vitamin C, ↓folic acid
- .. Depression
- cell proliferation = sensitive cells: endometrial cells/brest cells

1. Endometrial cc PROTECTION 50% ↓ > 1 year
2. Ovarian cc PROTECTION 40% ↓ > 3 years
3. Colorectal cc PROTECTION 40% ↓
4. Uterine col cc ↑RISK X1.5 (5 years) X 2 (10 years)
5. Hepatocellular cc TEORETICAL RISK
6. Breast cc
   recent/current use ↑ *20%*
   length of use *safety period = 15 years*
   metastatic disease ↓*RISK*
   no extra risk increase in positive familial history

CONTRAINDICATIONS:

I. ABSOLUTE
   a. Thromboembolic disease
   b. Severe alteration of hepatic function
   c. Migraine
   d. DM with vascular impairment
   e. Breast cancer
   f. Undiagnosed vaginal bleeding
   g. Pregnancy
   h. Smoker> 35 years of age
   i. Severe hypertriglyceridemia
   j. Uncontrolled hypertension

II. RELATIVE
   a. Migraine without aura
   b. Treated hypertension
   c. Uterine myoma
   d. Hyperglycemia
   e. History of gestational diabetes
   f. Programmed surgery
   g. Epilepsy
   h. Gal bladder diseases
   i. SLE
   j. Smoking
   k. Hepatic disease
   l. Dyslipidemia
   m. Breast feeding

In order to avoid this complications following pretreatment evaluations are compensatory:
Identifying potential risk categories

- ✓ TGP, TGO, creatin, ANCA, lupus cells
- ✓ Breast ultrasound
- ✓ Gynaecological exam
- ✓ TV ultrasound
- ✓ coagulopathy profile

The following uses are listed:

1. Contraceptive use
2. Non contraceptive use:
    a. Control of menstrual cycle
    b. Catamenial headache = continues use
    c. Ovarian cancer protection
    d. Supplemental therapy – precocious ovarian insufficiency, iatrogenic insufficiency, ovarian digenesis
    e. Dysmenorrhea
    f. Functional ovarian cyst
    g. PCOS
    h. Hyperandrogenia: acne, hirsutism
    i. Mittelschmerz

Alternative administration roots:

- ➢ transdermal = no effect on coagulation mechanism
  = no 1st hepatic passage
  = higher compliance
  = apply once a week, 3 weeks/months
- ➢ intravaginal = no effect on coagulation mechanism
  = no 1st hepatic passage
  = higher compliance
  = apply once a months, maintaining 3 weeks + 1 week pause
- ➢ injectable = im, monthly =Cycloproverra/Lunelle/Feminema
  = 5 mg Estradiol cypionate + 25 mg MPA
  = No endometrial instability like in progestin only preparation
  = !! Inhibits lactation
  = Better compliance
  = !!!1 monthly administration
  = 1st hepatic passage effect

- oral emergency intercourse/accident = In the first 13 hours after unprotected sexual
  = Yuzpe regimen = 2 cp 50 mcg EE + 250 mcg levonorgestrel, repeated after 12 hours
  = 3 + 2 pills
  = Effective immediately up to 72 hours
  = Ovulation inhibition!!!!

RULES OF TREATMENT

1. Check for contraindications
2. 1st use = always from day 1
3. Than normal cyclic administration depending on the administration route
4. If 1 pill is forgotten, administer it as soon as possible, with continuation of the normal administration rhythm.
5. If 2 consecutive days the pills are forgotten, administer them as soon as possible, continue the normal administration + use of a back up method for the next 7 days

VII.7.2. Progestin only preparation

Mechanism of action:

1. Endometrial involution only in condition of continuous administration
2. Dense cervical mucus 2-4 hours
3. Cervical impermeability 22 hours
4. Alteration of tubal movements
5. Inhibition of LH preovulatory surge:
   a. No present on oral preparations (exception Desogestrel)
   b. Permanent and stable in injectable preparation
   c. Temporary effect in implants (only the first 2 years)

There are no effects on metabolism, no effects on coagulation process without any vascular or thrombotic side effects, but the administration has to be continuous in order to have an endometrial-sustained involution, in order to make nidation/implantation impossible.

Current indications of progestin only oral contraceptives are:

- Contraception needed, no possible estrogen administration
- Lactating women
- Smokers older than age 35
- Contraindication to estrogen administration
- Young girls with altered menstrual cycle pattern

Possible adverse effects are relative to the progestin content:

- Irregular menses = spotting, breakthrough bleeding, amenorrhea, shortened cycles (due to in endometrial instability because of lack of estrogen co administration and decreased endometrial healing process)
- Duration – up to 1 year
- Headache, breast tenderness, dizziness
- Abdominal pain, anxiety, weight gain

Injectable preparations:

- Depot medroxyprogesterone
- 104 mg sc 3 months
- 150 mg im 3 months
- Very effective
- Specific indications
  - ✓ Minimum interval between pregnancies of > 1 year
  - ✓ Efficient method independent of coital activity
  - ✓ Adverse effects to estrogen
  - ✓ Breast feeding
  - ✓ Seizures

Implants

- Etonogestrel IMPLANON/NEXPLANON
- Extremely effective
- Long acting 3 yeas
- Possible adverse effects:
  - o Bleeding irregularities,
  - o Infrequent bleeding (33.6%),
  - o Amenorrhea (22.2%),
  - o Prolonged bleeding (17.7%)
  - o Frequent bleeding (6,7%)
  - o Weight gain (2.3%),
  - o Emotional liability (2.3%),
  - o Headache (1.6%),
  - o Acne (1.3%),
  - o Depression (1.0%)
- Special indications
  - ✓ Minimum interval between pregnancies of > 3 year
  - ✓ Efficient method independent of coital activity
  - ✓ Adverse effects to estrogen
  - ✓ Decreased compliance to frequent administration
  - ✓ Anaemia

Emergency preparations

- 1st day after administration
- Classically = as seldom as possible
- Currently WHO – contraceptive method (up to x4 times/months)
- PREVENTION OF OVULATION
- OVULATION DELAY
- no influence on nidation
- no abortive effect!!!

CONTRAINDICATIONS

I. ABSOLUTE
   a. Known/suspected breast cancer
II. RELATIVE (benefits are smaller than theoretical/proven risks)
   a. Bariatric surgery
   b. Ischemic heart disease/stroke
   c. SLE
   d. Migraine with aura
   e. Severe cirrhosis
   f. Malignant liver tumor
   g. Antiretroviral medication
   h. Rifampicin/Rifabutin therapy

Progesterone receptor modulators

- Mifepristone = 600 mg
- Ulipristal acetate = 30 mg

- Mechanism
  - Inhibits follicular ovarian maturation/growth
  - Delays/decreases endometrial maturation
  - Delays menstruation
  - Temporary ovulation delay

Male hormonal methods are still on research stage, without any active preparation on the marked. The following preparation could be used for a hormonal contraception in males:

1. Androgens only
2. Progestin with androgen replacement
3. GnRH antagonist + androgen replacement

Curently there is no licensed preparation for male contraception.

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