International Journal of Endocrinology Sciences
Online ISSN: 2664-9292, Print ISSN: 2664-9284
Received: 01-11-2018; Accepted: 02-12-2018; Published: 02-01-2019
www.endocrinologyjournal.net
Volume 1; Issue 1; 2019; Page No. 01-08

A basic review of endocrine diseases

Dr. Siva Rami Reddy E
Faculty of Homoeopathy, Tantia University, Sri Ganganagar, Rajasthan, India

Abstract
Endocrine diseases (basic review) are to understand very easily for graduate, post graduate and post-doctoral ayush, dental, medical etc., students. I am explaining main and important diseases in respiratory system in day to day practical life for medical students and professionals. Diseases are thyroid gland, parathyroid gland and adrenal gland.

Keywords: endocrine diseases, causes, clinical features, investigation

Introduction
We have lot of diseases to explain in Endocrine system. But only main/few diseases are reviewing for under graduate, post graduate and post-doctoral ayush, dental, medical, nursing etc., entrance and main examination purpose. Endocrine concerns the synthesis, secretion and action of hormones. There are a large number of disease of endocrine glands, but World Health Organization statistics indicate that they are a relatively rare cause of death (1-6%) some endocrine disease are common, particularly those of the thyroid gland, reproductive system and the beta cells of the pancreas.

Thyroid gland
The thyroid gland secrets predominantly thyroxine (T_4), and only a small amount of triiodothyronine (T_3); approximately 85% of T_3 is produced by monodeiodination of T_4 in other tissues such as liver, muscle and kidney. T_4 is probably not metabolically active until converted to T_3 and may be regarded as a prohormone. Thyrotrophin releasing hormone (TRH) come from hypothalamus and converted to Thyroid stimulation hormone (TSH) at glands/targets levels, /T_3, T4 at target hormones [1, 2]. There is a negative feedback of thyroid hormones on the throtrophs such that in hyperthyroidism, when plasma concentrations of T3 and T4 are raised. TSH secretion is suppressed and in hypothyroidism due to disease of the thyroid gland low T3 and T4 are associated with high circulating TSH levels. The anterior pituitary is very sensitive to minor changes in thyroid hormone levels within the normal range. Although the reference range for total T4 is 60 – 150 nmol/l, a rise or fall of 20 nmol/l in an individual in whom the levels is usually 100 nmol/l would on the one hand be associated with undetectable TSH and o the other hand with a raised TSH. The combination of normal T3 and T4 and suppressed or raised TSH is known as “sub clinical hyperthyroidism and sub clinical hypothyroidism respectively”. Excessive circulating levels of free thyroid hormones called ‘hyperthyroidism’ and decreased circulating levels of free thyroid hormones called ‘hypothyroidism’ [3, 6].

Hyperthyroidism
Hyperthyroidism is the clinical syndrome which results from exposure of the body tissues to excess circulating levels of free thyroid hormones. It is a common disorder with a prevalence of about 20/1000 females; male are affected five times less frequently. In over 90% of patients hyper thryroidism is due to Graves’ disease, multinodular goiter or an autonomously function solitary thyroid nodule (toxic adenoma) [7, 9]. It may be caused by any one of the following: (a) Graves' disease, (b) toxic multinodular goiter, (c) toxic solitary nodule ("hot" nodule), (d) ingestion of thyroid hormones (thyrotoxicosis factitia), (e) subacute thyroiditis, if) chronic thyroiditis, (g) TSH-producing pituitary adenoma, (h) trophoblastic tumors (choriocarcinoma or hydatidiform mole), (i) thyroid carcinoma, or (j) struma ovarii.

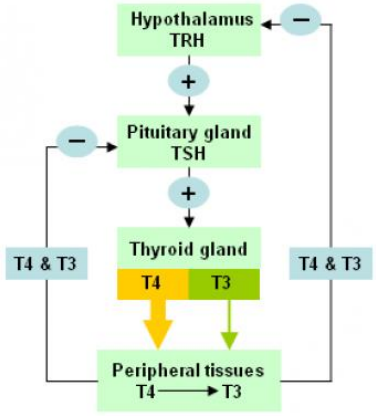


Fig 1: Background of thyroid gland

Graves’s disease
The most common cause of hyperthyroidism in iodine sufficient areas is Graves’ disease. In Sweden, the annual incidence of Graves’ disease is increasing, with 15–30 new cases per 100 000 inhabitants in the 2000. The cause of Graves’ disease is thought to be multifactorial, arising from the loss of immunotolerance and the development of autoantibodies that stimulate thyroid follicular cells by binding to the TSH receptor. Several studies have provided some evidence for a genetic predisposition to Graves’ disease. The genes involved in Graves’ disease are immune-regulatory genes and thyroid autoantigens such as the thyroglobulin and TSH-receptor genes. Given the higher prevalence of Graves’ disease in women, sex hormones and

chromosomal factors, such as the skewed inactivation of the X chromosome, are suspected to be triggers. Other factors such as infection, vitamin D and selenium deficiency, thyroid damage, and immunomodulating drugs are also suspected [10, 11].

Table 1

Causes	Frequency (%)
Graves' disease	76
Multinodular goiter	14
Autonomously functioning solitary thyroid nodule	5
Thyroiditis	3
Iodide induced e.g.drugs etc.,	1
Extra thyroidal source of thyroid hormone excess	0.2
TSH induced	0.2
Follicular carcinoma + metastases	0.1

Pathogenesis

Graves' disease is an autoimmune disorder caused by antibodies that bind to and stimulate the TSH receptor (TSHR), often called thyrotropin receptor antibodies (TRAb) or thyroid stimulating immunoglobulin (TSI) (Fig. 2). These oligoclonal IgG antibodies act as TSH agonists. They are specific for the disorder and are found in 80% to 100% of untreated patients. TSH receptor antibodies can have different grades of functional activity determined by the differences in conformational molecular binding that induces structural changes in the TSH receptor. Those that bind to the ectodomain, or extracellular portion of the TSHR, with high affinity are stimulating in nature, whereas antibodies that recognize various other epitopes are less stimulatory, neutral, or even blocking. Multiple antibodies may be present in an individual patient and the degree of thyroid stimulation is determined by the bioactivity and relative concentration of the different antibodies. More recently, it has been suggested that the extracellular A-subunit of the TSH receptor is the predominant immunogen in Graves' disease. Timers of the subunit, either shed from a trimeric holoreceptor or components that have undergone multimerization to form trimers, are responsible for pathologic antibody formation. Evidence comes from studies showing that immunization with purified TSHR-A subunit produced only nonfunctioning antibodies. Mouse models of Graves' disease have been successfully established by immunization with recombinant adenovirus vectors expressing the A-subunits of the TSHR. TSHR-stimulating antibodies activate the TSHR, resulting in binding of Gs/Gq proteins that trigger cyclic AMP (cAMP) and inositol trisphosphate (IP3)-mediated pathways. This promotes thyroid growth, increased vascularity, iodide uptake, and increased thyroid hormone production and release [12, 15]. Different mechanisms have been proposed to explain the development of autoimmunity in Graves' disease and include the following:

Failure of activated T cells to undergo anergy, deletion, and apoptosis:

The development of self-tolerance occurs by a process of elimination of self-reacting T cells during the process of maturation in the thymus and peripheral immune system. There is a combination of both positive and negative selection and T-cells reactive to endogenous peptides are triggered to undergo apoptosis. When selfreactive T-cells escape deletion, such as those recognizing thyroid antigens [TSH receptor, thyroid peroxidase (TPO), thyroglobulin], an autoimmune process is initiated.

Bystander activation of thyroidal T-cells

This refers to activation of thyroid specific T cells in susceptible individuals indirectly as a result of inflammation [via cytokines, such as interferon (IFN)-γ] produced by nonthyroid specific bystander immune cells which could have arisen from an infection and infiltrated the thyroid gland. This phenomenon of T-cell activation has been demonstrated in animal models of thyroiditis.

Expression of major histocompatibility complex (MHC) Class II molecules by the thyroid cells:

Thyroid cells in general do not express MHC molecules, which are essential for the presentation of antigens to immune cells. Epithelial cells from patients with autoimmune thyroid disease over express MHC/human leucocyte antigen (HLA) class II molecule which leads to an augmented presentation of thyroid antigens and activation of thyroid specific T-cells. MHC molecule expression can be induced by cytokines and interferon's produced in the thyroid gland from an infection or trauma

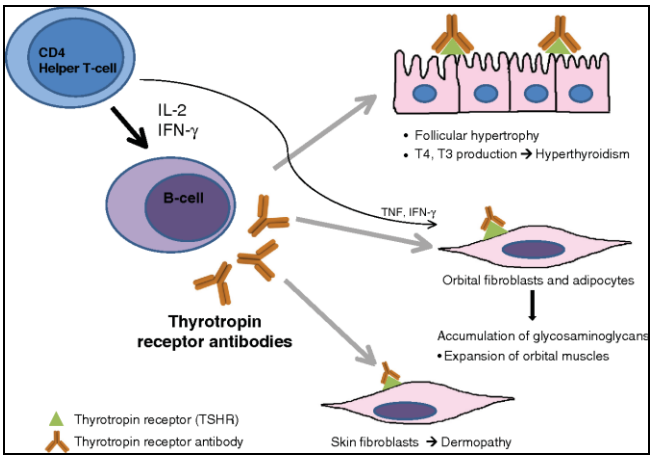


Fig 2: Pathogenesis of Graves' disease

Clinical features

Hyperthyroidism usually develops insidiously and most patients have had symptoms for at least six months before presentation. Almost every system is affected and the clinical feature are goiter (diffuse + bruit, nodular), weight loss despite normal or increased appetite, hyperdefaecation, diarrhoea, steatorrhoea, anorexia, vomiting, sinus tachycardia, atrial fibrillation, increase pulse pressure, angina, cardiomyopathy, cardiac failure, dyspnoea, asthma, tremor, muscle weakness, proximal myopathy,periodic paralysis, increased sweating, alopecia, pigmentation, vitiligo, pretibial myxoedema, amenorrhoea, infertility, spontaneous abortion, loss of libido, impotence, diplopia, loss of visual acuity, heat intolerance, fatigue, gynaecomastia, thirst, osteoporosis.

Graves' ophthalmopathy:

The cardinal feature is accumulation of hydrophilic glycosaminoglycans in the orbital muscles and the connective tissue, which causes swelling and edema. Glycosaminoglycans are produced by the stimulation of orbital fibroblasts and adipocytes by cytokines from activated T-cells that infiltrate the orbit. TSHR and insulin-like growth factor 1 (IGF-1) receptors (IGF-1R) are expressed by orbital fibroblasts in higher quantities in individuals with thyroid-associated ophthalmopathy than in

healthy individuals. In vitro, stimulation of orbital fibroblasts with TSH and IGF-1 cause a synergistic increase in glyscosaminoglycan production. Stimulation of the receptor by TRAbs activates an inflammatory response and cytokine production; though it is still not known if the TSHR in the orbital tissues acts as the primary antigen that initiates the autoimmune response. A role of stimulatory IGF-1R autoantibodies has also been proposed but is still questionable. A recent study by Krieger *et al*. showed no evidence of IGF-1R stimulating antibodies in patients with Graves' ophthalmopathy, but demonstrated immunoglobulins that bind to TSHR and then result in a cross talk with the IGF-1R leading to its activation. The presentation of Graves' ophthalmopathy can range from being a very mild disease to potentially eyesight threatening severe disease that could be irreversible. Symptoms include eyelid retraction, edema, proptosis, a pressure-like sensation at the back of the eyes, dry eyes, foreign body or gritty sensation in the eyes, tearing, photophobia, optic neuropathy, and corneal ulceration [16].

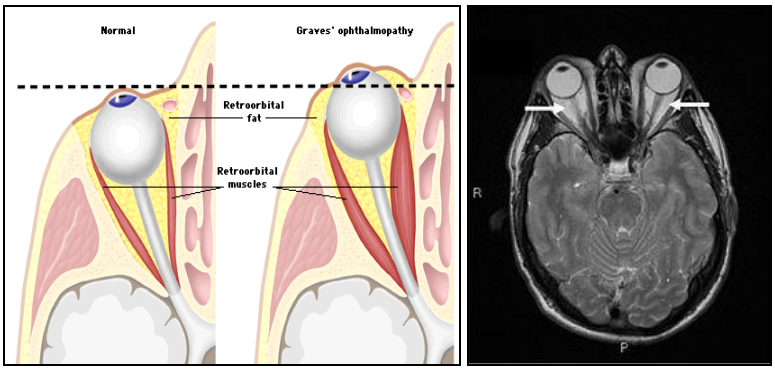


Fig 3: Different between normal graves opthalmopathy and CT image

Diagnosis

Serum TSH should be measured first, because it has the highest sensitivity and specificity in the diagnosis of thyroid disorders. If low, serum free T_4 or free T_4 index, and free or total T_3 concentrations should be measured to distinguish between subclinical hyperthyroidism. It also identifies disorders with increased thyroid hormone concentrations and normal or only slightly raised TSH concentrations, as in patients with TSH-secreting pituitary adenomas or peripheral resistance to thyroid hormone. A thyroid radioactive iodine uptake test in patients with Graves' disease would show diffusely increased uptake. However, radioactive iodine uptake would be normal or high with an asymmetrical and irregular pattern in toxic multinodular goitre, and a localised and focal pattern in toxic adenoma, with suppressed uptake in the remaining thyroid tissue. Radioactive iodine uptake in patients with thyrotoxicosis from extrathyroidal sources of thyroid hormone or from release of preformed thyroid hormones, as in silent or painful thyroiditis, will be very low. Thyroid ultrasound and thyroid radioactive iodine uptake have similar sensitivity for the diagnosis of Graves' disease (95·2% and 97·4%, respectively). Advantages of ultrasound are absence of exposure to ionising radiation, and higher accuracy in the detection of thyroid nodules and lower cost than with radioactive iodine uptake [17].

Management

It can be manage with anti-thyroid drugs and constitute homoeopathic medications.

Parathyroid gland

The parathyroid glands are unique organs responsible for maintaining the critical function of calcium homeostasis. There are commonly four parathyroid glands that weigh approximately 40 grams each and are generally located posterior and inferior to the thyroid in the neck. These organs secrete parathyroid hormone (PTH), which controls calcium regulation. Secretion of PTH is modulated not only by serum calcium but also phosphorus and vitamin D through negative and positive feedback loops. In the bone, PTH binds to PTH type 1 receptors (PTH1R) to assist with calcium resorption. In the kidney, PTH acts to increase renal calcium, decrease phosphate reabsorption, and activate metabolism of vitamin D. In the intestine, PTH transcriptionally upregulates 1 alpha hydroxylase, leading to increased production of 1,25-dihydroxyvitamin D, which in turn enhances calcium and phosphorus reabsorption. These actions of PTH on the bones, kidneys, and intestines are a careful orchestration of interrelated processes driven by feedback loops. Subsequently, excessive or insufficient secretion of PTH can lead to disruption of these loops and, in turn, alterations in calcium homeostasis. Both the direct action of PTH on the heart and alterations of calcium homeostasis (e.g., hypercalcemia or hypocalcemia) comprise the two primary mechanisms by which diseases of the parathyroid affect the cardiovascular system. In recent years, clinical and molecular research has bolstered awareness of several cardiovascular complications that are associated with parathyroid disorders—namely, hypertension, arrhythmias, heart failure, and calcific disease of vessels and valves [18, 20].

Primary Hyperparathyroidism

One of the more common disorders of the parathyroid glands is primary hyperparathyroidism (PHPT), an overproduction of PTH that subsequently leads to hypercalcemia. This is most commonly due to a solitary parathyroid adenoma, but about 15% of cases can be caused by diffuse hyperplasia of the glands.5 While the typical complications and symptoms of PHPT are well known (e.g., nephrolithiasis, osteoporosis, constipation, and weakness), cardiovascular complications are increasingly gaining recognition. Indeed, patients with symptomatic PHPT have increased mortality due to myocardial infarction, stroke, and other cardiovascular causes, and they also have increased all-cause mortality.

Secondary hyperparathyroidism

Secondary hyperparathyroidism (SHPT) is seen early in

chronic kidney disease (CKD) and is almost always present in ESRD. While the exact sequence of events leading to SHPT is not definitively established, it is generally thought to be driven early on by disturbances in renal phosphate handling and by the more recently discovered bone-derived fibroblast growth factor 23. In fact, even small decreases in calcium levels caused by these processes are enough to stimulate the parathyroid to secrete PTH. Secondary hyperparathyroidism is an important contributor to cardiovascular mortality in ESRD and CKD, especially in more advanced stages. Indeed, in ESRD patients, the 5-year mortality is as high as 50%, with CVD as the leading cause of death, and is not explained solely by traditional risk factors such as age, diabetes, and smoking.

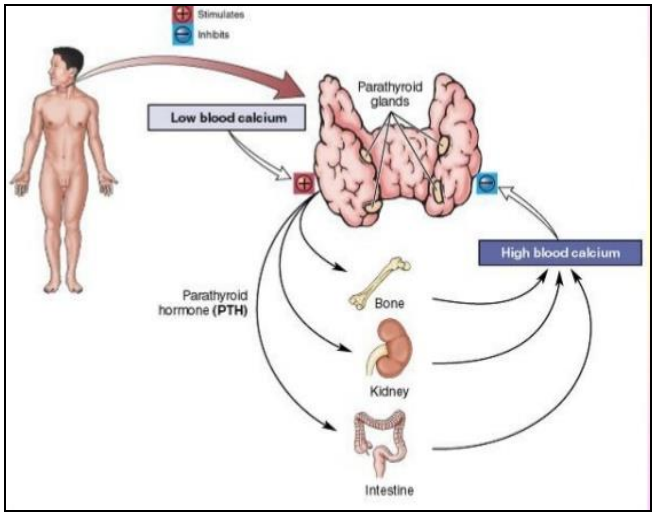


Fig 4: Parathyroid gland

Excess PTH (as seen in primary and secondary hyperparathyroidism) is associated with a higher incidence of hypertension, left ventricular hypertrophy, heart failure, cardiac arrhythmias, and valvular calcific disease, which may contribute to higher cardiac morbidity and mortality.

Hypoparathyroidism

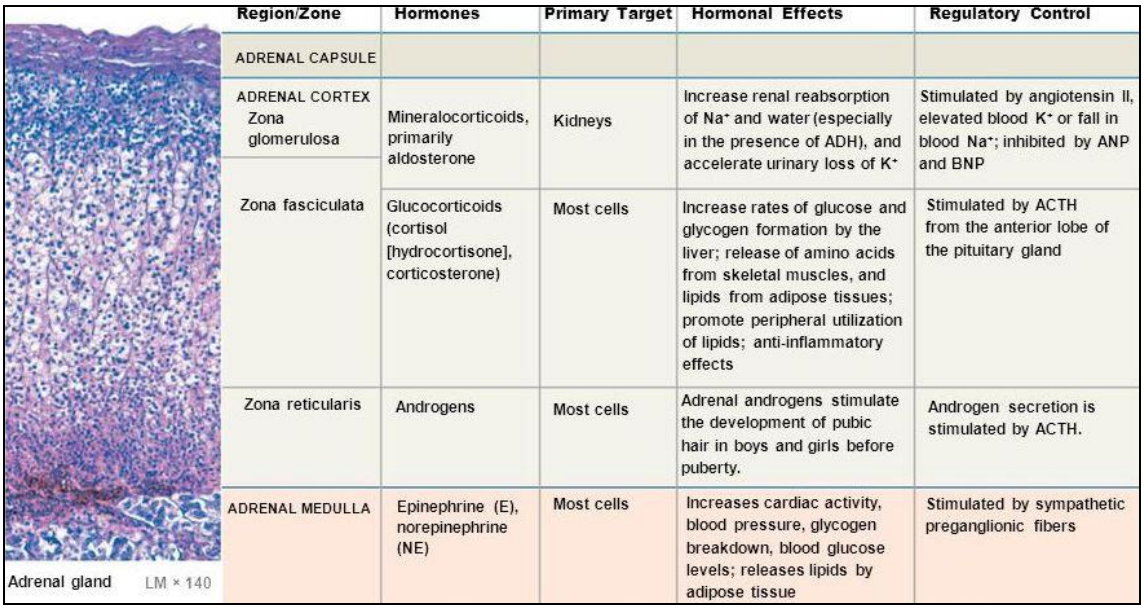
Hypoparathyroidism is an uncommon condition characterized by absent or low PTH levels, hypocalcemia, and hyperphosphatemia. The etiology of hypoparathyroidism is broad and can be congenital or acquired. For example, DiGeorge syndrome, which is due to a chromosomal deletion at 22q11.2, is characterized by parathyroid hypoplasia in addition to cardiac defects, thymic hypoplasia, neurocognitive problems, and renal and skeletal abnormalities, among others. The cardiac effects from hypoparathyroidism stem from the resulting hypocalcemia. For example, hypocalcemia causes QT prolongation, which can predispose patients to potentially life threatening arrhythmias. Additionally, dilated cardiomyopathy from chronic hypocalcemia is a well-known but uncommon complication. Decreased PTH states (as seen in congenital and acquired disorders of the parathyroid glands) are associated with cardiac arrhythmias and dilated cardiomyopathy [21, 23].

Management

The most common treatment is to remove the enlarged gland (or glands). This surgery cures the problem 95 percent of the time. Instead of surgery, some people with mild or no symptoms of primary hyperparathyroidism may decide to try hormone replacement therapy or medication options.

Adrenal gland

Adrenal gland is divided in to 3 zones. Those are zona glomerulosa, zonae fasciculate and reticulans in cortex region. Zona glomerulosa will release aldosterone (angiotension II), zonae fasciculate release cortisol (ACTH) and zona reticulans release adrenal androgens (ACTH principal stimuli). Do to sympathetic nervous system will release adrenaline, nor adrenaline in medulla region [24, 26].



Region/Zone	Hormones	Primary Target	Hormonal Effects	Regulatory Control
ADRENAL CAPSULE				
ADRENAL CORTEX Zona glomerulosa	Mineralocorticoids, primarily aldosterone	Kidneys	Increase renal reabsorption of Na^+ and water (especially in the presence of ADH), and accelerate urinary loss of K^+	Stimulated by angiotensin II, elevated blood K^+ or fall in blood Na^+; inhibited by ANP and BNP
Zona fasciculata	Glucocorticoids (cortisol [hydrocortisone], corticosterone)	Most cells	Increase rates of glucose and glycogen formation by the liver; release of amino acids from skeletal muscles, and lipids from adipose tissues; promote peripheral utilization of lipids; anti-inflammatory effects	Stimulated by ACTH from the anterior lobe of the pituitary gland
Zona reticularis	Androgens	Most cells	Adrenal androgens stimulate the development of pubic hair in boys and girls before puberty.	Androgen secretion is stimulated by ACTH.
ADRENAL MEDULLA	Epinephrine (E), norepinephrine (NE)	Most cells	Increases cardiac activity, blood pressure, glycogen breakdown, blood glucose levels; releases lipids by adipose tissue	Stimulated by sympathetic preganglionic fibers

Fig 5: Adrenal Hormones

Principal function of adrenal hormones glucocorticoids: carbohydrate metabolism regulation, increase protein catabolism, immunomodulation, cardiovascular regulation. In mineralocorticoids

Are sodium retention, potassium excretion. In catecholamines are increase heart rate, modulate vascular tone (vasoconstriction by noradrenaline and vasodilation by adrenaline), antagonize insulin action[27].

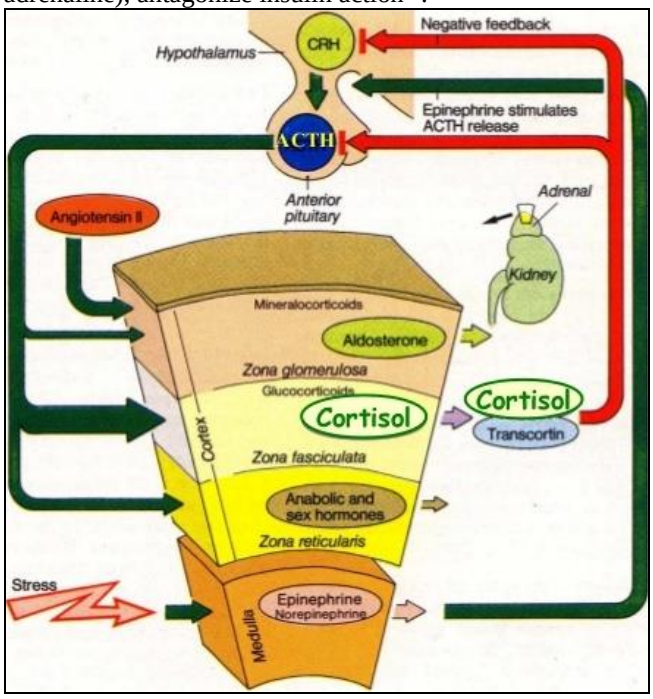


Fig 6: Regulation of adrenal gland secretion

Hyperfunction of the adrenal gland

Excess glucocorticoid caused formed Cushing's syndrome.

Cushing's syndrome

Cause of cushing syndrome are classified as a ACTH dependent: Pituitary dependent bilateral adrenal hyperplasia (i.e. cushing disease), ectopic ACTH syndrome (bronchial carcinoid, small cell lung carcinoma, pancreatic carcinoma), iatrogenic (ACTH therapy) (or) ushing's syndrome, a potentially lethal disorder characterized by endogenous hypercortisolism, may be difficult to recognize, especially when it is mild and the presenting features are common in the general population. However, there is a need to identify the condition at an early stage, as it tends to progress, accruing additional morbidity and increasing mortality rates. Once a clinical suspicion is raised, screening tests involve timed measurement of urine, serum or salivary cortisol at baseline or after administration of dexamethasone, 1 mg. Each test has caveats, so that the choice of tests must be individualized for each patient. Once the diagnosis is established, and the cause is determined, surgical resection of abnormal tumor/tissue is the optimal treatment. When this cannot be achieved, medical treatment (or bilateral adrenalectomy) must be used to normalize cortisol production [28, 30].

Non ACTH depend are iatrogenic (chronic glucocorticoid therapy e.g. for asthma), adrenal adenoma, adrenal carcinoma.

Pseudo cushings syndrome, i.e. cortisol excess as part of another illness are alcohol excess, major depressive illness, primary obesity (mild biochemical features, some clinical overlap).

Clinical features

Weight loss, menstrual irregularity, hirsutism, psychiatric, backache, muscle weakness, central obesity, plethora, moon face, hypertension, bruising, striae, muscle weakness presented.

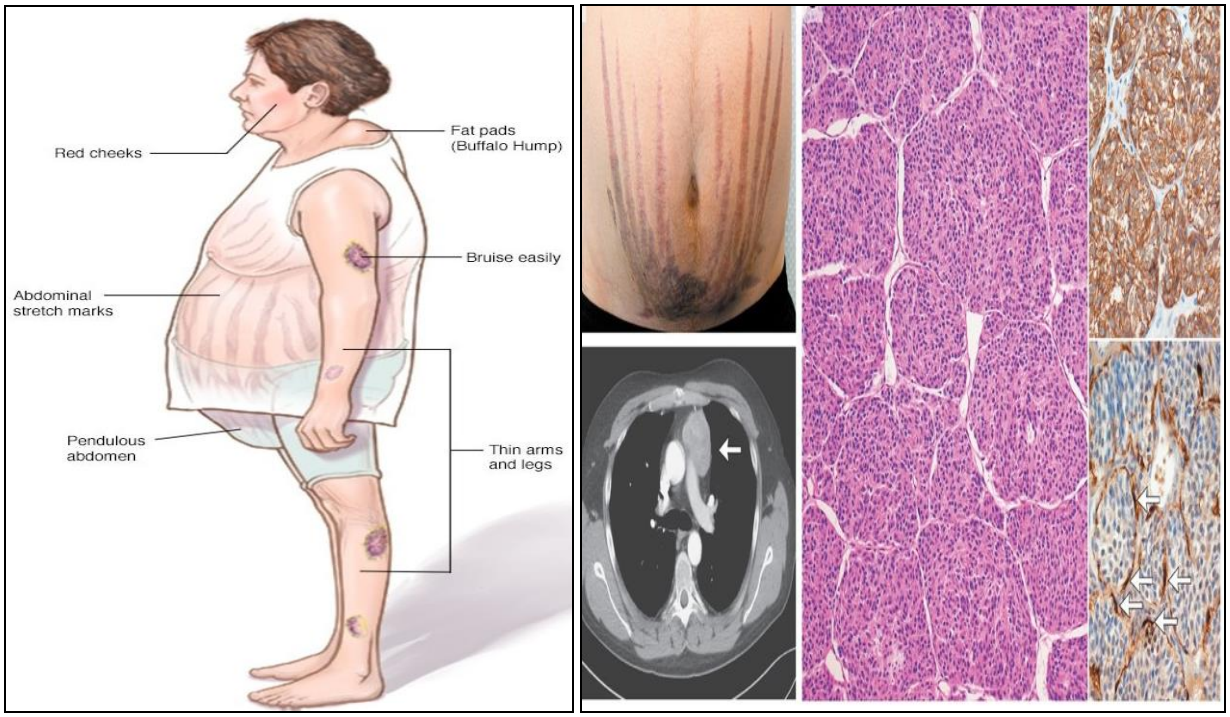


Fig 7: Cushing syndrome

Investigations

A clinical practice guideline from the Endocrine Society recommends use of at least two of three different screening tests: 24-hour urine free cortisol (UFC) excretion, late

night/bedtime salivary cortisol levels and the 1 mg overnight dexamethasone suppression test (DST; or alternatively the 2 mg 2-day DST). The screening tests all reflect different physiologic abnormalities in Cushing's syndrome: high integrated daily cortisol production (UFC), loss of bedtime salivary or serum cortisol nadir, and impaired response to glucocorticoid negative feedback. Thus, they are complimentary, and the use of more than one test is extremely helpful, as the results generally should corroborate each other. Other tests have not been widely validated for this use (e.g., 0.5 mg DST, fractional overnight UFC), or are not widely available (24-hour 17-hydroxycorticosteroid excretion), and are not recommended. The result of each cortisol screening test (saliva, serum, urine) is considered normal if it falls within the normal reference range; cortisol values 8 hours after administration of 1 mg dexamethasone at 2,300 to 2,400 hours should normally be <1.8 µg/dL (50 nmol/L). Because of this, prescribers of a screening test must know about certain characteristics of the cortisol assay used to measure the result, to avoid misinterpretation.

Management

This ie essential, as untreated Cushing's syndrome has a 50% – 60% five year mortality. Most patients are prepared for surgery with medical therapy for a few weeks.

Hypofunction of the adrenal gland:

Addison's disease

This is a rare condition with an estimated incidence in the developed world of eight cases per million populations. However, adrenal insufficiency is a well-recognized complication in patients with AIDS and may result from a variety of causes including tuberculosis, fungal and cytomegalovirus infections. Classically, hyperpigmentation is associated with the disease, and intraoral pigmentation is perceived as the initial sign and develops earlier than the dermatological pigmentation. The symptoms of the disease usually progress slowly and an event of illness or accident can make the condition worse and may lead to a life threatening crisis. In this case, several oral as well as systemic manifestation of the Addison's disease was encountered [31].

Aetiology: Whereas primary adrenal insufficiency last century was most commonly due to tuberculosis, autoimmune disease currently accounts for most of the cases presenting outside of the newborn period. The various etiologies of Addison's disease can be grouped into three categories: 1) adrenal dysgenesis; 2) adrenal destruction; and 3) impaired steroidogenesis. Congenital adrenal hypoplasia (AHC), mutations of steroidogenic factor-1 (SF-1), and ACTH unresponsiveness can all lead to adrenal dysgenesis/hypoplasia, albeit the latter usually results in isolated deficiency of glucocorticoids. Autoimmune polyglandular syndrome (APS), adrenoleukodystrophy (ALD), adrenal hemorrhage, adrenal metastases, infections, and amyloidoses can all lead to destruction of adrenal gland. Congenital adrenal hyperplasia (CAH), mitochondrial disorders, the Smith-Lemli-Opitz syndrome (SMOS), an enzyme deficiency in cholesterol metabolism, can all lead to impaired steroidogenesis. At birth, adrenal hemorrhage from anoxia/sepsis is most common, adrenal insufficiency from CAH usually presents in neonates, and in older children it often occurs as part of an autoimmune poly glandular syndrome or APS. In boys, adrenoleukodystrophy, DAX-1-related disorders are increasingly recognized, whereas adults have increasing incidences of infectious and metastatic adrenal failures.

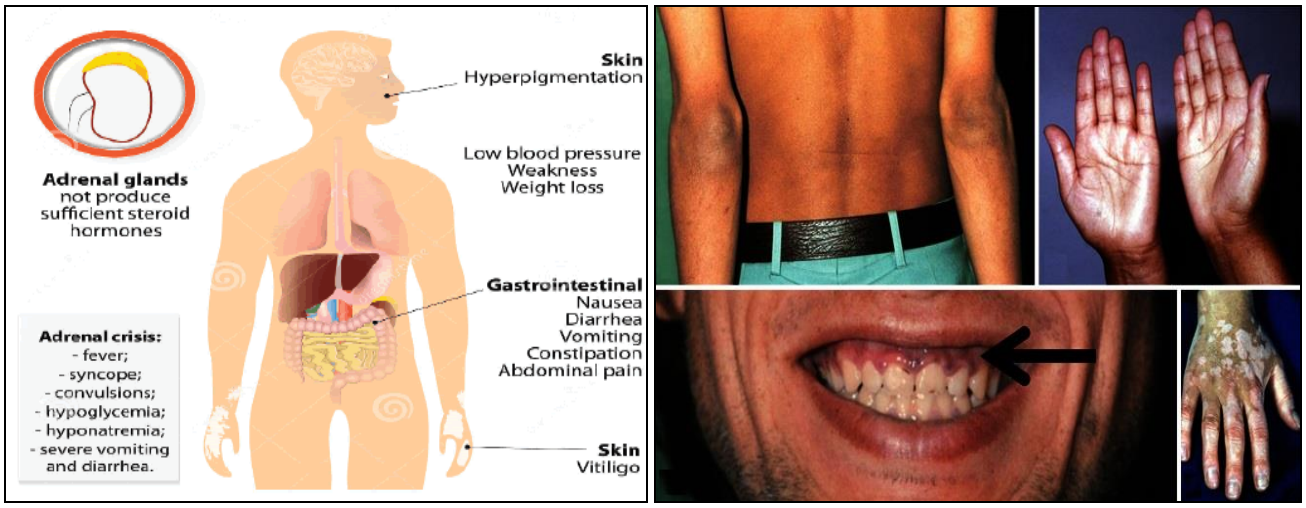


Fig 8: Addison's disease

Clinical features

Glucocorticoid insufficiencies are weight loss, malaise, anorexia, nausea, vomiting, gastrointestinal like diarrhoea or constipation, postural hypotension, hypoglycaemia. Mineralocorticoid insufficiency is hypotension. Increased ACTH secretion are pigmentation occurs over sun exposed areas, pressure areas e.g. elbows, knees, palmar creases, knuckles, mucous membranes, conjunctivae, recent scars. Losses of adrenal androgen are decrease in body hair, especially in female. In chronic presentation symptoms are chronic fatigue syndrome or depression and it is the pigmentation that commonly raises suspicion. The blood pressure may be normal with the patient lying down. Postural hypotension (i.e. a fall in systolic pressure of at least 20 mm Hg) is almost invariably present. Vitiligo is present in 10 -20% [32].

Investigation

A morning serum cortisol level higher than 500 nmol/L (18 g/dL) usually excludes Addison disease, while a level below

165 nmol/L (6 g/dL) is suggestive of adrenal insufficiency. However, most patients will need a short synacthen test for confirmation or exclusion of Addison disease. This involves injecting 250 g of synacthen (tetracosactrin; synthetic analogue of adrenocorticotrophic hormone (ACTH]) intramuscularly or intravenously. Blood samples for serum cortisol are taken at 0, 30, and 60 minutes. An increase in serum cortisol level 30 or 60 minutes after the synacthen injection to above 500 nmol/L (18 g/dL) is considered a normal response, although the threshold cortisol level may vary according to local laboratory reference ranges. If the cortisol response to synacthen is inadequate, plasma ACTH level should be measured. A raised plasma ACTH level confirms the diagnosis of Addison disease, whereas patients with secondary adrenal insufficiency due to pituitary or hypothalamic disorders have a low or inappropriately normal plasma ACTH level. Plasma renin activity is elevated in Addison disease and is sometimes a useful investigation to distinguish between Addison disease and secondary adrenal insufficiency [33].

Management

Patients with Addison's disease always need glucocorticoid replacement therapy and usually, but no always, mineralocorticoid. If the Addison's disease results from tuberculosis then this will need to be treated appropriately.

References

1. Adams AC, Astapova I, Fisher FM, Badman MK, Kurgansky KE, Flier JS. *et al*. Thyroid hormone regulates hepatic expression of fibroblast growth factor 21 in a PPARalpha-dependent manner. J Biol Chem. 2010; 285:14078-14082.
2. Araki O, Ying H, Zhu XG, Willingham MC, Cheng SY. Distinct dysregulation of lipid metabolism by unliganded thyroid hormone receptor isoforms. Mol Endocrinol. 2009; 23:308-315.
3. Arrojo EDR, Bianco AC. Type 2 deiodinase at the crossroads of thyroid hormone action. Int J Biochem Cell Biol. 2011; 43:1432-1441.
4. Astapova I, Hollenberg AN. The *in vivo* role of nuclear receptor corepressors in thyroid hormone action. Biochim Biophys Acta. 2013; 1830:3876-3881.
5. Baxter JD, Webb P. Thyroid hormone mimetics: potential applications in atherosclerosis, obesity and type 2 diabetes. Nature Rev Drug Discov. 2009; 8:308-320.
6. Bergh JJ, Lin HY, Lansing L, Mohamed SN, Davis FB, Mousa S, Davis PJ. Integrin alphaVbeta3 contains a cell surface receptor site for thyroid hormone that is linked to activation of mitogen activated protein kinase and induction of angiogenesis. Endocrinology. 2005; 146:2864-2871.
7. Hedberg CW, Fishbein DB, Janssen RS. An outbreak of thyrotoxicosis caused by the consumption of bovine thyroid gland in ground beef. N Engl J Med. 1987; 316:993-98.
8. Cooper DS, Biondi B. Subclinical thyroid disease. Lancet. 2012; 379:1142-54.
9. Nyström HF, Jansson S, Berg G. Incidence rate and clinical features of hyperthyroidism in a long-term iodine sufficient area of Sweden (Gothenburg) 2003-2005. Clin Endocrinol (Oxf). 2013; 78:768-76.
10. Abraham P, Avenell A, Park CM, Watson WA, Bevan JS. A systematic review of drug therapy for Graves' hyperthyroidism. Eur J Endocrinol. 2005; 153:489-498.
11. Abraham-Nordling M. Graves' disease: A long-term quality-of-life follow up of patients randomized to treatment with antithyroid drugs, radioiodine, or surgery. Thyroid. 2005; 15:1279-1286.
12. Allannic H, Fauchet R, Orgiazzi B, Madec AM, Genetet B, Lorcy Y. *et al*. Antithyroid drugs and Graves' disease: A prospective randomized evaluation of the efficacy of treatment duration. J Clin Endocrinol Metab. 1990; 70:675-679.
13. Amodio F, Di Martino S, Esposito S, Iorio S, Hierholzer J, Rea G *et al*. Role of flowmetric analysis and of color-Doppler ultrasonography with contrast media in the different phases and follow-up of Graves' disease. Radiol Med. 2001; 102:233-237.
14. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E. *et al*. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 1998; 338:73-78.
15. Brent GA. Graves' disease. N Engl J Med. 2008; 358:2544-2554.
16. Jacobsen R, Lundsgaard C, Lorenzen J, Toubro S, Perrild H, Krog-Mikkelsen I. *et al*. Subnormal energy expenditure: A putative casual factor in the weight gain induced by treatment of hyperthyroidism. Diabetes Obes Metab. 2006; 8:220-227.
17. Kubota S, Amino N, Matsumoto Y, Ikeda N, Morita S, Kudo T. *et al*. Serial changes in liver function tests in patients with thyrotoxicosis induced by Graves' disease and painless thyroiditis. Thyroid. 2008; 18:283-28.
18. Shoback D, Sellmeyer D, Bikle DD. Metabolic bone disease. : Gardner DG, Shoback D, Greenspan's basic & clinical endocrinology. 9th ed. New York, NY: The McGraw-Hill Companies, 2011, p 227-284.
19. Pyram R, Mahajan G, Gliwa A. Primary hyperparathyroidism: Skeletal and non-skeletal effects, diagnosis and management. Maturitas. 2011. November. 2008; 70(3):246-55.
20. Schlüter KD. PTH and PTHrP: Similar Structures but Different Functions. News Physiol Sci. 1999; 14:243-9.
21. Brown J, de Boer IH, Robinson-Cohen C. Aldosterone, parathyroid hormone, and the use of renin-angiotensin-aldosterone system inhibitors: the multi-ethnic study of atherosclerosis. J Clin Endocrinol Metab. 2015; 100(2):490-9.
22. Kiernan TJ, O'Flynn AM, McDermott JH, Kearney P. Primary hyperparathyroidism and the cardiovascular system. Int J Cardiol. 2006; 113(3):E89-92.
23. Silver J, Naveh-Many T. FGF-23 and secondary hyperparathyroidism in chronic kidney disease. Nat Rev Nephrol. 2013; 9(11):641-9.
24. Iacobellis G, Petramala L, Cotesta D. Adipokines and cardiometabolic profile in primary hyperaldosteronism. Journal of Clinical Endocrinology and Metabolism. 2010; 95(5):2391-2398. doi: 10.1210/jc.2009-2204.
25. Rossi GP, Sticchi D, Giuliani L. Adiponectin receptor expression in the human adrenal cortex and aldosterone-producing adenomas. International Journal of Molecular Medicine. 2006; 17(6):975-980.
26. Maniero C, Fassina A, Seccia TM. Mild hyperparathyroidism: a novel surgically correctable feature of primary aldosteronism. Journal of

Hypertension. 2012; 30(2):390-395.
27. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM. *et al*. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2008; 93:1526-1540.
28. Nieman LK, Biller BM, Findling JW, Murad MH, Newell-Price J, Savage MO. *et al*. Treatment of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015; 100:2807-2831.
29. eltzer K, Pengpid S, James C. The globalization of whitening: prevalence of skin lighteners (or bleachers) use and its social correlates among university students in 26 countries. Int J Dermatol. 2016; 55:165-172.
30. Baid SK, Rubino D, Sinaii N, Ramsey S, Frank A, Nieman LK. *et al*. Specificity of screening tests for Cushing's syndrome in an overweight and obese population. J Clin Endocrinol Metab. 2009; 94:3857-3864.
31. Grossman AB. Thomas Addison and his disease. Grand Rounds. 2004; 4:L8-9.
32. Hiatt JR, Hiatt N. The conquest of Addison's disease. Am J Surg. 1997; 174:280-3.
33. Stewart PM, Krone NP. The adrenal cortex. In: Kronenburg HM, Melmed S, Polonsky KS, Reed Larson P, editors. Williams Textbook of Endocrinology. 12th ed. Philadelphia PA: Saunders Elsevier, 2011, pp. 515-20.