Herbal Medicine 3

Pathology

5.1: Endocrine System
Learning Outcomes

In today’s topic you will learn:

- Epidemiology, aetiology, pathophysiology of a range of common pathologies of the endocrine system
- Clinical signs and differential diagnosis for pathologies of the endocrine system
- Conventional treatments
- Functional and naturopathic perspectives
Hypothyroidism: epidemiology

- Affects 1% of UK population
- Women more than men (6:1)
- Subclinical hypothyroidism estimated at 6-8% (women) and 3% (men)
- Most common between ages 30 - 50
- 2.5% pregnant women develop hypothyroidism
Hypothyroidism: aetiology

- Primary Hypothyroidism (thyroid hormones, TSH) failure of thyroid gland, most common presentation; subclinical condition presents raised TSH but normal thyroid hormones
- Secondary Hypothryroidism (Thyroid hormones, TSH) failure of TSH production due to pituitary gland disease
- Common causes:
  - Autoimmune thyroiditis - atrophic form (primary atrophic thyroiditis), and goitrous form, e.g. Hashimoto's thyroiditis
  - Grave's disease (5% with thyrotoxicosis go on to develop hypothyroidism
  - Treatment of hyperthyroidism - surgical ablation, radioiodine or drug treatment
  - Severe iodine deficiency - geographical factors, rare in UK
Hypothyroidism: signs and symptoms

- Signs and symptoms are systemic due to reduced metabolic rate
- Mental and physical slowness, apathy, psychosis, constipation
- Fatigue, tiredness
- Cold intolerance
- Dry skin and hair; falling or thinning hair
- Loss of outer third of eyebrows
- Weight gain, oedema, increase in adipose tissue, puffy face
- Bradycardia
- Goitre
Hypothyroidism: tests and investigations

- T4 - most common test. T4 accounts for 80% thyroid hormone output
- Problems: T4 level can mask both TSH abnormality and T3 abnormality
- T3 (triiodothyronine)- 20% normal thyroid hormone output; T3 may be raised whilst T4 is normal. T3 is the most active hormone
- TSH (thyroid stimulating hormone): pituitary gland’s response to a drop in circulating levels of thyroid hormone, and is usually the first indication of thyroid disease
- Thyroid peroxidase antibodies: associated with Hashimoto’s thyroiditis

Reference Ranges:
- Free T4 (FT4): 10 – 24
- Total T4 (TT4): 50-160
- Thyroid Stimulating hormone (TSH): 0.4 – 4.5
- Free T3 (FT3): 4 – 8.3
Hypothyroidism: pathophysiology

- Hashimoto’s is the most common form
- Thyroid peroxidase antibodies found in serum in 90% cases
- Haplotypes HLA-DR5, HLA-B8
- Other autoimmune conditions may apply
- Enlargement of thyroid gland, firm consistency
- Thyroid follicles infiltrated by lymphocytes and plasma cells, leading to lymphoid follicle formation and increased fibrous tissue stroma
- Follicles lined with abnormal, highly eosinophilic epithelial cells (evidencing proliferation of mitochondria)
- Reduced colloid content of disrupted follicles
- Release of thyroglobulin into circulation may cause transient thyrotoxicosis
- Some cases proceed to primary atrophic thyroiditis

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Hypothyroidism: treatment

- Lifelong supplementation with synthetic levothyroxine (T4)
- Previously dessicated thyroid extract (animal source) was used
- T3 supplementation generally not used due to instability and short circulating life
- In the majority of people T4 is readily and continuously converted to T3
- TSH should be regularly monitored, since the goal of therapy is to maintain normal TSH levels
### Factors That Cause an Inability to Convert T4 to T3

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<tr>
<th>Nutrient Deficiencies</th>
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<th>Other</th>
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<tr>
<td>Chromium</td>
<td>Beta Blockers</td>
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<td>Theophylline</td>
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<td>Vitamin B12</td>
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<td>Radiation</td>
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<td>Vitamin D</td>
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<td>Stress</td>
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Sea Kelp (Ascophyllum nodosum) is an excellent dietary source of iodine. Its ability to increase glutathione peroxidase activity, an important antioxidant, prevents peroxidative damage of thyroid cells and decrease occurrence of autoimmune thyroid disease.

Bladderwrack (Fucus vesiculosus), another dietary source of natural iodine also demonstrates anti-estrogen properties in both human and animal studies, suggesting that it may contribute protective health to estrogen sensitive tissues. Sea Kelp and Bladderwrack both provide fucoidan a sulfated polysaccharide that has a wide variety of biological activities including antioxidant, anti-thrombotic, anti-inflammatory and anti-autoimmune effects.

Humulus lupulus (Hops), contains xanthohumol which enhances uptake of iodine into the thyroid gland by activation of sodium-iodide-symporter (NIS) proteins. Xanthohumol also decrease the expression of proinflammatory cytokines.

Coleus (Coleus forskohlii) contains forskolin which is specifically able to mimic the effect of TSH in regard to iodide uptake and organification of iodine.
Botanical Solutions: T3 & T4 Production & Secretion from thyroid cells

- Coleus (Coleus forskohlii) contains forskolin which is specifically able to mimic the effect of TSH in thyroglobulin (TG) production and promote secretion of T3 & T4.

- Bacopa monniera (Brahmi) exhibits thyroid stimulating abilities through an increase of T4 serum concentrations by 41% without any notable increase in T3 or hepatic activity.

- Ashwagandha (Withania somnifera) directly affects production of thyroid hormones. Animal studies during the late 1990s demonstrated its ability to directly act on thyroid tissue to bring about a rise in serum levels of thyroid hormones. Serum levels of thyroid hormone can also be raised in humans, so excessive dosages should be avoided.
Forskolin from Coleus Forskohlii directly increase iodothyronine deiodinase activity.

Xanthohumol from Humulus lupulus, guggulsterones from Commiphora mukul, Carnosol from Rosmarinus officinalis, and withanolides from Withania somnifera preserve iodothyronine deiodinase activity by decreasing NF-kappa activation.

Guggulsterones also directly stimulate triiodothyronine (T3) production through its action on liver enzymes, while also increasing the activity of endogenous antioxidants.
The final steps in proper thyroid function involve the coupling of membrane receptors to allow thyroid hormones to enter target cells and affect the hormone/receptor complex on target genes.

Rosemary (Rosmarinus officinalis) and Sage (Salvia officinalis) promote the function of Retinoid-X-receptors.

Humulus lupulus, Commiphora mukul, Rosmarinus officinalis, Coleus Forskohlii and Withania somnifera improve the function of Retinoid-X-receptors.
Hyperthyroidism: epidemiology

- More common in women - 10:1
- Highest prevalence in women in Caucasian populations
- 1 in 1000 women, 1 in 10,000 men
- Most common cause is Grave’s disease (60 - 86%)
- Peak onset 20 - 50 years
Hyperthyroidism: aetiology

- Family history, high iodine intake, smoking, iodine-containing medication e.g. amiodarone
- Primary hyperthyroidism (thyroid hormones, TSH): hypersecretion of thyroid hormones not secondary to raised TSH (high circulating thyroid hormones suppresses TSH)
- Secondary hyperthyroidism (thyroid hormones, TSH): overstimulation of thyroid gland caused by excessive TSH production - pituitary tumour
- Grave’s disease (exophthalmic goitre): diffusely enlarged gland stimulated to overproduce hormone by IgG autoantibody
- Toxic multinodular goitre (2nd most common cause - Plummer’s disease)
- Thyroiditis, (e.g. De Quervain’s thyroiditis): more commonly associated with hypothyroidism
- Drugs - ingestion of large doses of thyroid hormone or through iodide inducing drugs (amiodarone)
Hyperthyroidism: signs & symptoms

- Heat intolerance and excessive sweating
- Nervousness and irritability, insomnia
- Weight loss, increased or normal appetite
- Tachycardia
- Goitre
- Exophthalmos (5% of Grave’s cases): due to infiltration of orbital tissues by fat, mucopolysaccharides and lymphocytes; can cause blindness due to compression of optic nerve
- Enlargement of fingernails (thyroid acropachy)
- Pretibial myxoedema - accumulation of mucoproteins in the deep dermis
Hyperthyroidism: pathophysiology

- IgG type immunoglobulins (thyroid stimulating immunoglobulins or TSIs) bind to TSH membrane receptors causing prolonged stimulation of thyroid (12 hours c.f. 1 hour with TSH). The autoantibody binds at a different site to the hormone-binding locus and is termed “TSH Receptor autoantibody” (TRab): 95% of Grave’s cases are TRab positive.

- Histologically the gland shows diffuse hypertrophy and hyperplasia of the acinar epithelium, reduction of stored colloid, and local accumulations of lymphocytes with lymphoid follicle formation.
Hyperthyroidism: treatment

- Thionamides (carbimazole / propylthiouracil): prevent secretion of thyroid hormones
- Beta-blockers (atenolol / propranolol): relieves some symptoms - fast heart rate, tremor, hyperactivity
- Radioactive iodine treatment (thyroid gland absorbs iodine and is killed by the radiation)
- Surgical removal of all or part of the gland; removal of affected nodules in nodular-type hyperthyroidism
Adrenal failure: epidemiology

- Primary and secondary types
- Primary: Addison’s disease (chronic adrenal insufficiency): 0.8 per 100,000 population
- 80% autoimmune basis
- Equal distribution between sexes
- Secondary more common: usually caused by suppression of HPA due to steroidal drugs
Adrenal failure (primary): aetiology

- Addison’s disease
- Surgical removal (e.g. in phaeochromocytoma)
- Trauma (especially in neonates)
- Sudden stress - Addison’s crisis precipitated by requirement for increased output from chronically failing glands
- Infections e.g. tuberculosis, histoplasmosis, cryptococcosis, cytomegalovirus, HIV
- Haemorrhage due to meningococcal septicaemia (Waterhouse Friedrichsen Syndrome)
- Infarction (antiphospholipid syndrome)
- Abrupt cessation of corticosteroid treatment (steroids cause atrophy of the adrenal cortex)
Adrenal failure (secondary): aetiology

- Hypothalamic or pituitary disease (tumour, infection, infarction, surgical destruction)
- Glucocorticoid therapy, suppresses ACTH
- Sodium valproate (anticonvulsant treatment) suppresses ACTH
- Lowered ACTH hence lowered endogenous glucocorticoids and aldosterone
Adrenal failure: signs & symptoms

- Primary: clinical features of adrenal crisis:
  - Profound hypotension and CV collapse (shock)
  - Confusion, personality change
  - Vomiting
  - Diarrhoea
  - Abdominal pain
  - Pyrexia
  - NB: adrenal crisis is a medical emergency requiring IV hydrocortisone and fluid replacement
Adrenal failure: signs & symptoms

- Secondary: common additional features
  - Pernicious anaemia
  - Vitiligo
  - Myaesthenia gravis
  - Alopecia
  - Chronic autoimmune hepatitis
  - Hypergonadotrophic hypogonadism
  - RA and Sjögren’s syndrome
Adrenal failure: pathophysiology

- (Addison’s) autoimmune destruction of adrenal cortex
- Associated with autoimmune thyroid disease and other autoimmune endocrine disease (polyglandular autoimmune disease)
- Recognised complication of AIDS
- Caseous necrosis of adrenals due to bilateral tuberculosis
- Metastatic cancers, haemochromatosis, amyloidosis
Adrenal failure (primary): pathophysiology

- Plasma ACTH↑, plasma cortisol↓
- ACTH stimulation test: ATCH administered, if cortisol levels fail to rise Addison’s is indicated
- Plasma Na+, K+ normal or↑, urea↑
- Blood glucose usually low
- Plasma renin↑, aldosterone normal or↓
Adrenal failure: treatment

- Glucocorticoicoid replacement
- Mineralocorticoid replacement
- Monitor BP - check for postural hypotension
- Normalise NA & K (Fludrocortisone)
- Steroid card & MedicAlert bracelet
- Importance of regular administration of hormone
Cushing’s Syndrome: epidemiology

- Range from 0.7 - 2.4 per million, but now thought to be more prevalent due to subtlety of some symptoms
- In obese type 2 diabetics the incidence is between 2% and 5%, especially where hypertension and poor blood glucose control is present
- Two divisions:
  - ACTH-dependent disease: excessive ACTH from the pituitary (Cushing's disease), ectopic ACTH-producing tumours or excess ACTH administration (80-85%)
  - Non-ACTH-dependent: adrenal adenomas, adrenal carcinomas, excess glucocorticoid administration (15-20%)
Cushing’s Syndrome: aetiology

- Corticotropin-dependent causes account for about 80-85% of cases:
  - 80% are due to pituitary adenomas (Cushing's disease). The remaining 20% are due to ectopic corticotropin syndrome, which is usually due to small-cell carcinoma of the lung and bronchial carcinoid tumours, but may occur with almost any endocrine tumour, e.g. phaeochromocytoma, pancreatic neuroendocrine tumours, medullary thyroid cancer, gut carcinoids.

- Corticotropin-independent Cushing's syndrome:
  - Is most often due to a unilateral tumour: adrenal adenoma in 60% and adrenal carcinoma in 40% of cases. Very rare adrenal causes of Cushing's syndrome are corticotropin-dependent macronodular adrenal hyperplasia, primary pigmented nodular adrenal disease and McCune-Albright syndrome.
Cushing’s Syndrome: presentation

- Truncal obesity, supraclavicular fat pads, buffalo hump, weight gain
- Facial fullness, moon face
- Proximal muscle wasting and weakness
- Diabetes or glucose intolerance
- Gonadal dysfunction
- Hypertension
- Skin: skin atrophy, purple striae, easy bruising, hirsutism, acne; pigmentation occurs with ACTH-dependent causes
- Psychological problems: depression, cognitive dysfunction, and emotional lability
- Osteopenia or osteoporosis
Cushing’s Syndrome: presentation

- Oedema
- Women may complain of irregular menses
- Thirst, polydipsia, polyuria
- Impaired immune function: increased infections, difficulty with wound healing
- Child: growth retardation
- Patients with an ACTH-producing pituitary tumour may develop headaches, visual problems, and galactorrhoea
- Destruction of the anterior pituitary may cause hypothyroidism and amenorrhoea
Cushing’s Syndrome: pathophysiology

- General: prolonged inappropriate elevation of free cortisol levels
- ACTH dependent: primary hypersecretion of ATCH (Cushing’s disease):
  - Bilateral adrenal hyperplasia secondary to excessive secretion of ATCH by a corticotroph adenoma of pituitary gland
  - Production of ectopic ACTH or CRH by non-endocrine neoplasm, e.g. small cell lung cancer, carcinoid tumours: patient rarely survives long enough to develop physical features of Cushing’s syndrome
- Non-ACTH dependent:
  - Iatrogenic steroid therapy (most common cause)
  - Adrenal cortical adenoma - also common as an incidental finding in up to 30% of all autopsies: tumour is typically 2-5cm in diametre, yellow due to lipids esp. cholesterol, from which hormones are synthesised; most are non-active, with only a small percentage causing Cushing’s
  - Adrenal cortical carcinoma - affects cortisol and sex hormones, patients have clinical features of Cushing’s and androgenic effects; local invasion and metastatic spread common
Cushing’s Syndrome: treatment

- Cortisol lowering or inhibiting drugs
- Surgery: pituitary or adrenal - bilateral adrenectomy for toxic levels of cortisol
- Radiation - pituitary tumours
Diabetes Mellitus: epidemiology

- Global: 285 million in 2010, expected 438 million by 2030
- India, China, USA, Russia, Brazil
- 6 x more common in those of South Asian descent; 3 x more common in those of African/Afrocarribean origin (in UK)
- UK: 2.6 million in 2009; expected 4 million by 2025
- 145,000 dx in 2008: 400 per day, 17 per hour, 3 every ten minutes
- UK-wide approx 1 in 20 (dx or non-dx)
- Undiagnosed number could run to a further 500,000
- UK - highest in England (5.1%), lowest in Scotland (3.9%)
- 10% type 1; 90% type 2 (UK figures)
- Slightly higher in men than women; incidence rises with age
- Increasingly seen in younger people
Diabetes Mellitus: aetiology

- Type I: NIDDM
  - Most likely cause is antibody-mediated destruction of β-cell population of islets of Langerhans
  - Patients in this category have similar genetic predisposing features to those with other autoimmune conditions

- Type II: IDDM
  - Also present genetic factors, familial tendency with up to 90% concordance rate in identical twins: however, no HLA associations, therefore aetiology considered to be polygenic
  - Insulin resistance due to impairment of function of insulin receptors on target cell surfaces, associated with obesity, sedentary lifestyle and poor diet
  - Relative insulin deficiency - reduced secretion compared with amounts required, probably due to ageing of islet cells
**Diabetes Mellitus: diagnostics**

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<tr>
<th>Diagnosis</th>
<th>Fasting Sample</th>
<th>2 hours after 75g glucose load</th>
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<tbody>
<tr>
<td>Normal</td>
<td>$&lt;5.6 \text{ mmol/L}$</td>
<td>$&lt;7.8 \text{ mmol/L}$</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>$5.6 - 6.9 \text{ mmol/L}$</td>
<td>$7.8 - 11 \text{ mmol/L}$</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>$\geq 7.0 \text{ mmol/L}$</td>
<td>$\geq 11.1 \text{ mmol/L}$</td>
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Diabetes Mellitus: complications

- Hypoglycaemia: complication of over-treatment with insulin
- Diabetic ketoacidosis (DKA): common in type I due to increased breakdown of triglycerides, increased production of ketone bodies, ketoacidosis and unconsciousness
- Hyperosmolar non-ketotic state: more common in type II: raised plasma glucose, plasma osmolarity, cerebral dehydration, coma
- Lactic acidosis: increased concentrations of lactic acid (end product of glycolysis, causes coma
- Chronic: micro- and macrovascular angiopathy; accelerated atherosclerosis (macrovascular damage); diabetic nephropathy; diabetic retinopathy; peripheral neuropathy (microvascular damage); increased susceptibility to infection
Diabetes Mellitus: treatment

- **Lifestyle modification**
- **Metformin**: inhibits glucose release from liver, increases insulin responsiveness; treatment of choice for obese patients
- **Sulphonylureas** (e.g. Gliclazide): increases insulin production from pancreas; used for non-obese patients, intolerance of metformin or adjunct to metformin if glucose not controlled. Risk of hypoglycaemia through overproduction of insulin
- **Thiazolidinediones** (TZDs): render cells more sensitive to insulin. Risk of peripheral oedema and CV compromise
- **Insulin**
Pathological Effects of Steroid Treatment

- Osteoporosis
- Weight gain
- Increased susceptibility to infection
- Hypertension
- Diabetes (Hyperglycaemia)
- Skin problems
- Muscle weakness
- Mood and behaviour changes
- Cataracts
- Duodenal and stomach ulcers
References and Indicative Reading


http://www.medicinenet.com/hypothyroidism/page5.htm
http://www.patient.co.uk/doctor/Adrenal-Insufficiency-and-Addison's-Disease.htm
http://www.patient.co.uk/doctor/Cushing's-Syndrome.htm
http://www.patient.co.uk/health/Steroid-Tablets.htm