

Thyroid Physiology Difficult Thyroid Cases A Novel Approach

Dr. Beverly Goode-Kanawati DO
Board Certified Family Practice
Board Certified Emergency Medicine

Prevalence

ref: Canaris *et al* 2000

- 24,337 Colorado residents not taking thyroid medication:
 - ~ **10 percent had unknown thyroid disease.**
 - 90% had elevated TSH levels.
 - Extrapolated to rest of US there **are in excess of 13 million *undiagnosed* cases.**
 - **Subjects taking thyroid medication**
 - **40% had abnormal TSH levels** (20% too low).
 - 92% had seen their physicians in the last year.
 - High **TSH** levels correlated with elevated lipids
-

Prevalence

□ Longitudinal study in UK estimated abnormal thyroid function in

■ 7.5% women

■ & 2.8% men.

Turnbridge et al 1977

□ Hypothyroidism much higher in older patients. **Rate in women > 60 estimated up to 24%!**

Sawin T et al 1979

Hypothyroidism: Symptoms

- Fatigue
 - Hard to get up in the morning
 - Difficulty losing weight despite reduced or stable caloric intake
 - Hair changes - loss, coarse, dry, thinning
 - Dry skin
 - Low body temperature
 - Brittle or dry nails
 - Constipation
 - Heavy or abnormal menstrual cycles (hypermenorrhea and menorrhagia)
 - Symptoms of PMS
 - Depression
 - Memory Loss
 - Decreased ability to concentrate.
 - Puffy, wrinkly skin
 - Cold hands and feet
 - Feeling cold
 - Thinning or loss of outside portion of the eyebrow
 - Low Libido
 - Muscle aches.
 - Joint pain.
 - Hoarse Voice
-

Hypothyroidism: Signs

ref: Singer PA *et al* 1995

- Peri-orbital edema
 - Delayed deep tendon reflexes
 - Pale dry skin, cool skin
 - Proximal muscle weakness
 - Bradycardia
 - Pre-tibial edema
 - Goiter
 - Hoarseness
 - Slowed speech
-

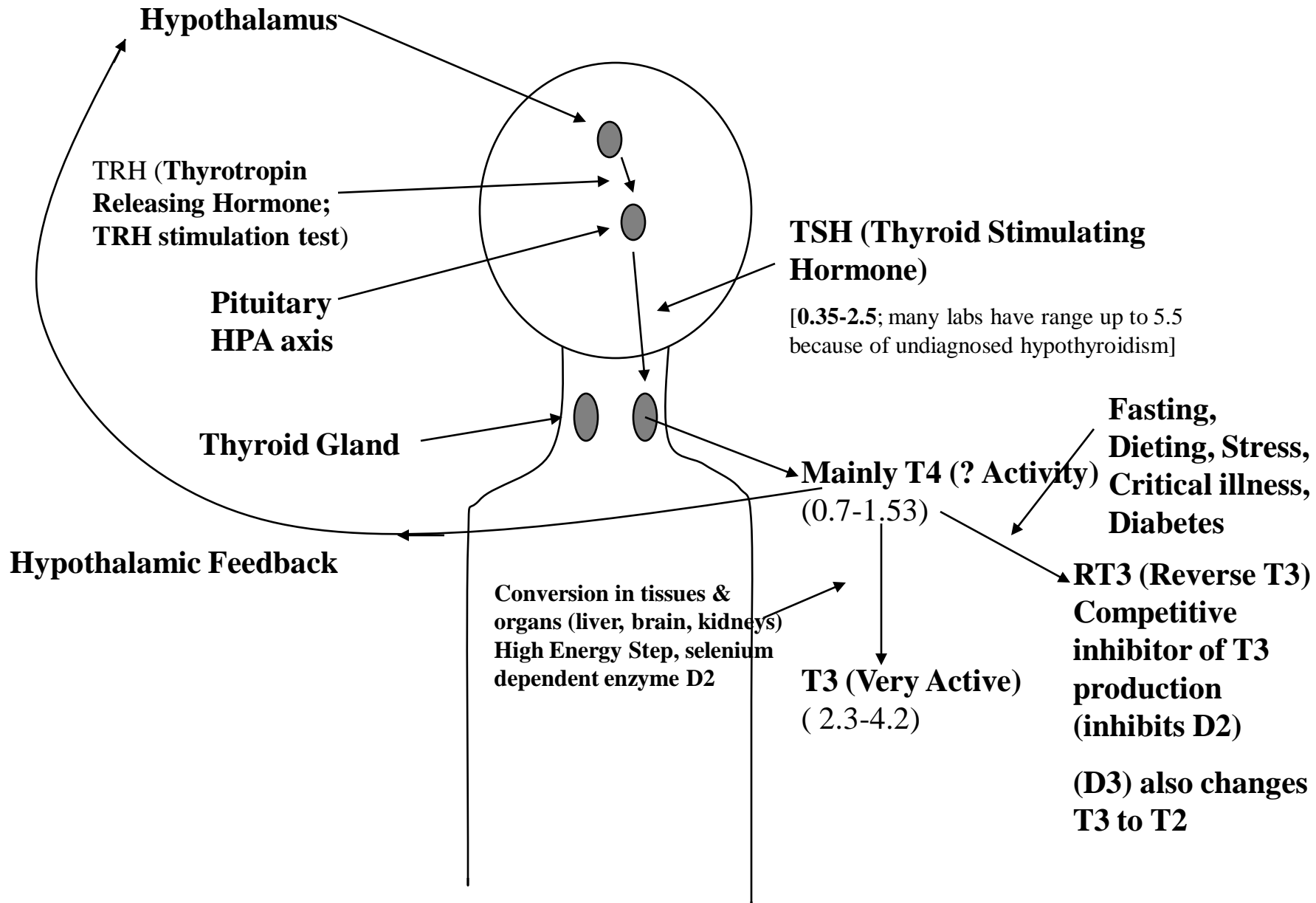
Hyperthyroidism (Grave's Disease or Thyrotoxicosis): Symptoms

- Shaky
 - Jittery
 - Rapid weight loss
 - Sweats
 - Diarrhea
 - Fatigue
 - Rapid Heart Rate
 - Palpitations
 - Nervousness
 - Exertional dyspnea
 - Heat Intolerance
 - Irritability
 - Tremor
 - Muscle weakness
 - Decreased menstrual flow
 - Sleep disturbance
 - Increased Perspiration
 - Increased frequency of bowel movements,
 - Increase or decrease in appetite
 - Noticeable enlargement of thyroid
 - Anterior neck pain
 - Photophobia
 - Eye irritation
 - Changes in visual acuity
 - Diplopia
 - Oligomenorrhea
 - amenorrhea
-

Hyperthyroidism: Signs

ref: Singer PA *et al* 1995 and Larsen *et al*, 2003

- Hyper-reflexia
 - Exophthalmos (Ophthalmopathy)
 - Tremor
 - Atrial Fibrillation
 - Congestive Heart Failure
 - Goiter
 - Tachycardia
 - Warm moist skin
 - Increased red cell mass
-



Conversion of T4 to T3

- ❑ **Selenium dependent enzyme** Larsen *et al* 2003 p341
- ❑ **High energy step**
 - Diabetes and insulin resistance results in: T4 normal, T3 diminished, reverse T3 elevated Bagni N 1982,
 - hypothyroidism causes decrease response to insulin, Cettour-Rose P. *et al* 2005
- ❑ Conversion of T4 to Reverse T3 is D3 dependent (and T3 to T2)
- ❑ **RT3 acts as competitive inhibitor of T3 production**
 - inhibits D2 – enzyme that converts T4 to T3 Simone S *et al* 2005

Corticosteroid Release Impairs Thyroid Production:

REF: Larsen *et. al.* 2003

❑ **Fasting, Critical illness**

- worse on exogenous corticosteroids
- Decreased Free T3, normal TSH, & increased RT3

❑ Glucocorticoid admin suppresses TSH

❑ thyroid function diminished in hypo-adrenalism.

❑ Reactive hypoglycemia: Pt may not meet strict criteria, but c/o shaky, cold hands & feet, headache or irritable if missing or delayed meal... *form fruste* and clinically significant

❑ Food Allergy

❑ Life Stress index: Holmes & Rahe; Glaser & Glaser

Environmental Chemicals Impair Thyroid Function

- **Environmental chemicals – a number of environmental pollutants described as “endocrine disruptors” have a negative affect on thyroid function and hormones.**
 - **Examples include:** Bogazzi F *et al* 2003, Ishihara A *et al* 2003, Yamauchi K *et al* 2003, Ishihara A *et al* Jan 2003, Kitamura S *et al* 2002
 - polychlorinated biphenyls (PCB)
 - Diethylstilbestrol ioxynil
 - Malathion
 - 4-nonylphenol
 - bisphenol A
 - n-butylbenzyl phthalate
 - 2,6-Dichloro-4-nonylphenol
 - 3,3',5-trichlorobisphenol A
 - tetrabromobisphenol A (TBBPA)
 - tetrachlorobisphenol A (TCBPA)
-

Medications that Impair Thyroid

ref: Carella C *et al* 200;1 May, Carella C *et al* 2002 Jun; Rotondi M *et al* 1998; Surks MI, Sievert R 1995; Gracious BL *et al* 2004; Vainionpaa LK *et al* 2006, Steinhoff BJ 2006, Cansu A *et al* 2006, Correll CU, Carlson, HE 2006, Gracious BL *et al* 2004, Caksen H *et al* 2003, Isojarvi JI *et al* 2001, Isojarvi JI *et al* 1992; Gaskill CL *et al* 2000; Sherman SI 2003 March

- Interferon
 - Interferon B (for MS)
 - Ribavarin
 - Amiodarone
 - Lithium
 - Phenytoin, carbamazepine, valproate
Phenobarbital
 - Bexarotene (Rx for cutaneous T-cell
lymphoma)
-

Food & Drugs Interfering with Thyroid Absorption

Surks MI, Sievert R 1995; Messina M, Redmond G 2006

- Colestipol
 - Cholestyramine
 - Aluminum hydroxide
 - Ferrous Sulfate
 - Sucralfate
 - Soy foods (when taken at the same time)
-

Autoimmune Thyroiditis (AT)

- ❑ **Iodine deficiency** most common cause for hypothyroidism worldwide. Vanderpump MP *et al* 2002
 - ❑ **AT is the major cause of Hypothyroidism & hyperthyroidism in iodine sufficient areas**
 - ❑ **Cause:** Bagchni N *et al* 1995
 - **Oxidative damage** (antioxidant deficit) to thyroid components, thyroid enzymes, receptor sites *etc.*
 - 1 study high dose iodine in susceptible & normal chickens caused damage to all of their thyroid glands but AT only occurred in obese chicken strain.
 - When pretreated with antioxidant no injury occurred & therefore neither group developed AT.
-

Thyroid Disease: laboratory tests

□ **Baseline:**

Free T3, Free T4, TSH [free hormone is what is available to the cell for use]

□ **Thyroid antibodies:**

Hashimoto's Antibodies: Thyroid Peroxidase Antibody, Anti-Thyroglobulin Antibody

Graves (Thyrotoxicosis): Thyroid Stimulating Immunoglobulins (thyrotropin receptor stimulating antibodies), Thyrotropin receptor (blocking) antibodies

Why test for antibodies?

Weetman AP, Fornightly review: Hypothyroidism: screening and subclinical disease. BMJ 1997;314:1175 (19 April)

- ❑ The risk of developing **frank hypothyroidism is increased when there are thyroid antibodies present** or sub-clinical hypothyroidism.
 - ❑ Especially in **females over 40 years of age with non-specific symptoms**
 - ❑ **TSH levels >2 mU/l are associated with a higher risk of hypothyroidism in the future.**
 - ❑ “The simplest explanation is that thyroid disease is so common that **many people predisposed to thyroid failure are included in a laboratory's reference population**, which raises the question whether thyroxin replacement is adequate in patients with thyroid stimulating hormone levels above 2mU/l.”
(the reference range alluded to here is .5-4.5 mU/l)
-

Why test antibodies? (cont): Dayan CM, Daniels

GH 1996; Vanderpump MP *et al*, 1995 Rosenthal MJ *et al*, 1987

- The presence of thyroid antibodies indicates autoimmune thyroid disease correlating with lymphocytic infiltration.
 - Microsomal antibody titers are predictive of hypothyroidism in the future.
-

Why test for antibodies? (cont)

Weetman AP. Postpartum thyroiditis and insulin-dependent diabetes mellitus: an important association. J Clin Endocrinol Metab 1994;79:7-9.; Weetman AP et al 1997; Giani C et al 1996

- ❑ **DM II insulin dependent women are “3 times more likely to develop postpartum thyroid dysfunction..”**
 - ❑ **Patients with breast cancer are 3 times more likely to have thyroid antibodies** and would benefit from screening for thyroid dysfunction.
 - ❑ Women who have **thyroid antibodies are more likely to suffer from post-partum depression**
-

Why test antibodies? (cont)

Harris B et al

1992; Weetman AP, 1997; Weetman AP 1997

- Definite reasons for screening:
 - Type I DM
 - Antepartum
 - Hx of post-partum thyroiditis
 - unexplained infertility
 - women over 40 with non-specific complaints
 - refractory depression
 - bipolar affective disorder with rapid cycling
 - Turner's syndrome
 - Down's syndrome
 - Autoimmune Addison's disease

- Secondary Reasons for screening:
 - Breast cancer
 - dementia,
 - Fam Hx of autoimmune thyroid disease
 - Pregnancy
 - postpartum thyroiditis
 - Obesity
 - idiopathic edema
-

Thyroid and Depression

- hypothyroidism and depression
 - Clear association
 - Very subtle signs in laboratory testing and symptoms can be dramatically affected by even small amounts of thyroid hormone.
 - **Patients with depression have double to triple the levels of antithyroid antibodies compared to the general population.**
 - Therefore patients with depression are more likely to have autoimmune thyroid disease and should be monitored carefully.
 - Further there are lower concentrations of a transthyretin (“cerebral carrier of T4 protein”) in the CSF of depressive patients. The lowest levels correlating with more severe depression. The lack of this protein ultimately produces a deficit of T3. (Sintzel F., et al. 2004).
-

Thyroid and Depression (cont)

Brouwer JP et al. 2005; Gitlin M, et al., 2004; Corruble E. et al., 2004

- ❑ TSH levels have been shown to be slightly higher in patients with major depression.
 - ❑ In **patients treated for depression** with anti-depressant medications (SSRI's):
 - those with **lower TSH had greater improvement in depressive symptoms**
 - ❑ When TSH is in the upper range of normal (top 25 percent of the range):
 - depressed patients have a poorer response to antidepressant medications, especially SSRIs
 - **This may also be a sign that they will do better with TCAs**
-

Thyroid and Depression (cont) Cole DP., et al., 2002

- The **lower thyroid and higher TSH levels:**
 - **are associated with slower response to antidepressant medications in patients with bipolar depression**
 - They did more poorly when their thyroid levels were not above the middle of the reference range and the TSH on the lower end of the reference range
-

Thyroid and Depression (cont) Cole, DP

et al., 2002; Sintzel F., et al. 2004

- ❑ **Up to 75% of people with bipolar depression type I may have thyroid problems causing a poorer response to antidepressant medications**
 - ❑ In animal models with hypothyroidism the synthesis of serotonin is decreased and **supplying T3 increases levels of serotonin**
-

Thyroid and Depression (cont) Sintzel F., et

al. 2004

- Some specialists recommend a trial of T3 in people who do not respond to anti-depressant medications.
 - **Recommend trial dosage of 25-50mcg/D for 3 weeks**
 - **I Recommend: start low, go slow!**
 - **3 mcg of T3, titrate to patient & laboratory response**
-

Thyroid and Depression (cont) Jackson IM,

et al., 1998

- Hypothyroidism can cause depression.
 - This type of depression typically responds to T4 therapy.
 - Some experts recommend:
 - depressed patients with sub-clinical hypothyroidism or thyroid antibodies (autoimmune thyroiditis) should be given a trial of thyroid hormone.
 - **In at least 25 % of cases the use of T3 treatment will be helpful.**
 - Further, there may be unusual imbalances in thyroid testing such as mild elevation of thyroxine and positive thyroid stim test and a lack of the normal rise in TSH at night.
 - **Higher cortisone levels affect the brain which leads to decreased production of TSH**
-

Thyroid and Depression (cont): Joffe RT

et al, 1992; Langer G et al 1986

- When patients have both depression and sub-clinical hypothyroidism:
 - as defined as having elevated TSH and normal circulating levels of T4 and T3
 - more often have a panic disorder along with the depression
 - as well as a poorer response to the use of antidepressant medications
 - In patients with psychiatric diagnoses such as **schizophrenia, major depression, minor depression and bipolar disorders**
 - **A blunted TRH stimulation test (less than 5 microU/ml) was clinically predictive of greater likelihood to relapse and poorer response to antidepressants and neuroleptic drugs.**
-

Thyroid and Depression (cont): Loosen PT

et al., 1985

- A review study of over 50 reports
 - with over 1000 patients with depression
 - They summarize: “ **The finding of diminished TSH response to exogenously administered TRH (positive TRH stimulation test), in a significant proportion of depressed patients has now been established as one of the most reproducible findings in biological psychiatry in approximately 25% of patients with major depression.**”
-

Cardiovascular Disease, Cholesterol and Thyroid

Brindels et al 1999; Erem, 2006; Muller et al, 2001; Danzi S., Klein, 2004;

- There is a well established association between thyroid disease and cardiovascular disease.
 - Cholesterol levels are higher in patients with
 - Sub-clinical Hypothyroidism, and
 - Hyperthyroidism
 - Some patients with hypothyroidism have an **increase in certain clotting factors** leading to vascular obstruction.
 - This may be part of the explanation for the increased levels of coronary artery disease in these patients.
 - **Low T3 alone** without other indicators of hypothyroidism has been **associated with cardiac disease** states.
-

Cardiovascular Disease and Thyroid

(cont)

Flynn, et al, 2006; Kung AW et al 1995; Siu CW et al 2007;

- ❑ In **hypothyroid** patients there is an **increased risk of myocardial infarction**.
 - ❑ In **hyperthyroid** patients an **increased risk of arrhythmias** (particularly atrial fibrillation).
 - ❑ **CHF especially with atrial fibrillation can be a presenting symptom of hyperthyroidism.**
 - Systolic dysfunction improved significantly in 3 months after treatment for most of the patients.
 - However 1/3 had persistent dilated cardiomyopathy.
 - ❑ Patients with **Sub-clinical Hypothyroidism and even asymptomatic lymphocytic thyroiditis** are known have **increased risk of coronary artery disease.**
 - Typically, elevated total cholesterol, triglycerides, LDL, lipoprotein a
 - and a low HDL.
-

Thyroid and Cardiovascular Disease

(cont)

Biondi B, Klein I, 2004; Danzi S, Klein I 2003

- Other parameters of accelerated cardiovascular disease have been discovered in hypothyroidism.
 - Such as **increased arterial stiffness, homocysteine, C-reactive protein, endothelial dysfunction, and abnormal coagulation.**
 - These changes are generally reversible with thyroid replacement.
 - Hypertension and thyroid:
 - hyperthyroidism changes include: increased cardiac output, contractility, tachycardia, widened pulse pressure, decreased systemic vascular resistance, and increased basal metabolic rate.
 - hypothyroidism changes include: decreased cardiac output, narrow pulse pressure, increased systemic vascular resistance, and decreased metabolic rate
-

T3 versus T4

- **T4** is a combination of tyrosine with 4 iodine molecules.
 - **T3** is formed by de-iodinization of the T4 to a compound consisting of tyrosine and 3 Iodine molecules.
 - **T3** is the truly active form of thyroid. This is due to its much greater binding affinity for receptor sites, 5-10 times as much.
-

T4 and T3 Equivalency

- A recent NIH study states 1:3 – in other words T3 is 3 times as potent as T4 (Celi FS et al. 2009)
 - Because it is important to avoid the use of too much T3 especially in the elderly, -- it is wiser to use a ratio of 1:5 in your calculations
-

Converting T4 to a combination of T4 and T3

- ❑ May continue Synthroid and do one of the following:
 - ❑ Can leave the Synthroid at the same dosage and add small amount of T3.
 - ❑ Or can reduce the dosage of Synthroid and add a larger amount of T3.
 - ❑ Remember T3 is the equivalent of 4-5 times the amount of T4.
-

Forms of Available T3

- ❑ T3 can be made into a longer acting preparation by compounding pharmacists.
 - ❑ This also allows you to adjust the dosage by very small amounts.
 - ❑ Some patients are very sensitive to very small changes or additions of thyroid hormone.
-

Armour thyroid

- Armour (brand name)
 - has been found to be consistent dose to dose.
 - There have been issues of inconsistent strength with generic desiccated thyroid
 - In this same study 2 out of 4 generic T4 preparations were abnormally high. (Rees-Jones RW et al 1980, Gaby AR, 2004)
 - Armour thyroid: 60mg =1 grain= T4 38mcg, T3 9mcg
 - Comes in 15mg, 30mg, 60mg and up so dosage may be appropriately titrated.
-

Other forms of Desiccated Thyroid

- ❑ Naturethroid – similar to Armour thyroid
 - ❑ Milligram dosing slightly different
 - ❑ Armour thyroid 60mg = Naturethroid 65mg – both contain 38mcg of T4 and 9mcg of T3
-

Conversion from Synthroid to Armour Thyroid

- ❑ Consider 1 mcg of T3 = 5mcg of T4
 - ❑ Example: Synthroid 100mcg
 - ❑ Armour 60mg = 38mcg T4
 - ❑ Take the T3 9mcg X 5 =45
 - ❑ Total of 38 plus 45 = 83mcg
 - ❑ Adding another 15mg of Armour would add another 9.5mcg of T4 and 2.25mcg of T3
 - ❑ Multiply 2.25 X 5 = 11.25 plus the 9.5= 20.75
 - ❑ 83+20.75= 103.75
 - ❑ So you would give this patient 60mg plus 15mg to start.
-

Conversion from Desiccated Thyroid to separate T4 and T3 Preparations

- ❑ Remember: for every 60mg of Armour thyroid or 65mg of Naturethroid – you have 38mcg of T4 and 9 mcg of T3
 - ❑ In this case you could give Levothyroxine 25mcg 1 ½ tablets per day (37.5mcg) and Triiodothyronine T3 5mcg at 2 per day
 - ❑ If you do not want to give as much T3, only 5mcg instead of 10 --- you would take 5mcg and multiply by 5 and add this to the T4 (37.5 plus 25 = 62.5 – in this case you could give 2 ½ 25mcg tabs per day or round down to 50mcg per day
-

Adding T3 to a T4 Preparation

- Patient is on 100mcg of T4 preparation
 - you wish to change some the thyroid to the T3 form and add 5mcg of T3
 - Subtract 25mcg (5 times 5) from 100mcg
 - So this patient would be on 75mcg of T4 and 5mcg of T3
-

Case History 1

- ❑ 46 year old female
 - ❑ Social Hx: physician/high stress
 - ❑ VS = BP 110/68 P 64, T 97.8, Ht 5'10", Wt 127 lbs
 - ❑ Allergies: Rye flour hives
 - ❑ Medications: Levoxyl 112mcg 5 days per week and Levoxyl 125mcg 2 days per week
 - ❑ Hx: Diagnosed 3 years previously with Graves and treated with radioactive iodine. Has had many dosage adjustments, being treated by endocrinologist
-

Case History 1 (cont)

Complaints:

- Hyper-menorrhoea and a period that lasted 3 months, heavy with clots,
 - Weight fluctuates up and down 5-6 pounds
 - Fatigue
 - Feeling cold
 - Weight gain despite reduced caloric intake
-

Case History 1 (cont)

- ❑ Labs from 6 months prior Free T4 .96, TSH .14
 - ❑ Requested change to Armour thyroid: Armour thyroid 30mg - 3 in the AM and 2 in the afternoon
 - ❑ Second visit:
 - ❑ VS = BP 100/60, P 68, T 97.7, Ht 5'10", Wt 118 lbs
 - ❑ ROS = Feeling much better on Armour thyroid, good energy, getting more done, all symptoms much improved or resolved
 - ❑ Lab results =
 - T Chol 193, FreeT4 1.04, TSH .016, Free T3 3.5 (AM cortisol normal)
 - Thyroid peroxidase 72 (0-34) , TSI 107 (less than 130 nl)
 - Thyrotropin receptor antibody 2.1 (greater than 1.5 positive)
 - Homocysteine 12.9
-

Case History 1 (cont)

- 7 Months later:
 - T Chol 183, HDL 89, LDL 88
 - Thyroid peroxidase enzyme 46
 - Thyrotropin receptor antibody 1.3
 - Free T4 .99, TSH .024, Free T3 3.1
-

Case History 1 (cont)

- ❑ 2 years later:
 - ❑ VS = BP 111/69, P 64, T 97.4, Ht 5'10", Wt 127 lbs
 - ❑ Taking thyroid in the AM: Free T3 4.5, Free T4 1.03, TSH .005,
 - ❑ 2 weeks later blood drawn in AM without taking thyroid that AM:
 - Free T3 2.4, Free T4 1.02, TSH .010
 - Homocysteine 6.0
 - ❑ New test added Vitamin D 25 hydroxy 12.7
 - ❑ RX: Armour thyroid 150mg Mondays and Thursdays and 120mg the rest of the days
-

Case History 2

- ❑ 45 year old female
 - ❑ VS = BP 154/97, P 86, T 97.8, Ht 5'4 ¾", Wt 167 lbs
 - ❑ Allergies: Augmentin
 - ❑ Medications: Synthroid 200mcg, Loestrin 1/20
 - ❑ Hx: Diagnosed with hypothyroidism – her physician had her taking almost 300mcg – she had been taking a soy shake when this was discontinued her dosage was reduced to 200mcg
 - ❑ About age 30 had ½ thyroid removed due to pre-cancerous nodules, had been on 150mcg for 12 years the last 2-3 years her need has fluctuated
-

Case History 2 (cont)

Complaints:

- migraine,
 - allergic rhinitis,
 - depression,
 - sinus headaches,
 - MVP with occasional palpitations, occasional rapid heart rate
 - weight gain,
 - fatigue,
 - weakness,
 - hair loss,
 - loss of outer portion of eyebrow,
 - Hyper-menorrhea
-

Case History 2 (cont)

- PE: unremarkable
 - Lab from year before: Free T4 2.2
TSH .52
 - Changed patient to Armour thyroid
120mg in the AM and 30mg in the
afternoon
-

Case History 2 (cont)

- ❑ Pt returned 11 months later:
 - ❑ VS = BP 140/86, P 80, T 96.5, Ht 5'4 3/4", Wt 157 lbs (loss of 10 pounds)
 - ❑ Reports most all symptoms resolved on Armour thyroid!
 - ❑ Labs: Free T4 1.01, Free T3 3.1, TSH 2.228
 - ❑ Note patients symptoms are improved, with a higher TSH and lower Free T4 with about the same amount of total thyroid hormone. 95mcg of T4 and 22.5 of T3 (total equivalency using multiplier of 5 is 112.5 plus 95= 207mcg)
-

Case History 3

- ❑ 36 year old female
 - ❑ VS = BP 116/76, P 78m T 98.6, Ht 5'2", Wt 169 lbs
 - ❑ Medications: Zoloft 50mg daily, Ativan .5mg
 - ❑ Depression history per patient:
 - Has had problems for many years first "nervous breakdown" in 1995.
 - October 2004 had severe depression was given Cogentin then higher doses of Zoloft felt much better on this for 5 weeks
 - then severe depression recurred in December 2004 and she was hospitalized.
 - Tried a several different antidepressants. Now feels very depressed, not suicidal but does not want to do anything and stays home most of the time. Not able to take Zoloft, feels more depressed with it now.
-

Case History 3 (cont)

- History of Hashimoto's thyroiditis:
 - when took Armour thyroid did ok on 15mg but not feel much better,
 - then tried 30mg felt prickly sensation and stomach rush,
 - when took Levothyroid 12.5mcg did not feel anything
 - when took 25mcg was able to have BM but then felt more lethargic.
 - Other complaints:
 - Constipation
 - Abnormal weight gain
 - Cold hands and feet
 - Eczema
 - Arthralgias
 - Fatigue
 - Cephalgia
-

Case History 3 (cont)

- Long acting T3 3mcg prescribed to take
 - daily for one week
 - then increase two per day as tolerated
 - Initial Labs:
 - Lipids: T Chol 267 TG 349, HDL 49, LDL 148, VLDL 70,
 - HbA1C 5.3
 - Homocysteine 8.5
 - Thyroid: Free T4 1.09, TSH 3.166, Free T3 2.6
 - TPO antibodies: 4518, Antithyroglobulin Ab 380, Thyroid stimulating immunoglobulin 103
-

Case History 3 (cont)

Next visit:

- Symptoms much improved with T3.
 - Headaches gone
 - depression much better
 - now wants to get out and go and do things
 - daily BM
 - joint pain gone
 - Taking some supplements and made some diet changes.
-

Case History 3 (cont)

- One month later, labs, on 5mcg LA T3 =
 - Free T4 1.01
 - TSH 2.463
 - T3 2.6

 - 2 months later, labs:
 - Free T4 .98,
 - TSH 3.196,
 - Free T3 2.9
 - Thyroid stimulating immunoglobulins 85, Thyroid peroxidase 1845, Antithyroglobulin 121
-

Diet and Nutrient Recommendations

- ❑ Limit soy to:
 - 2 servings per day
 - take at a different time than the thyroid medication.
 - ❑ Avoid sugars and foods containing chemicals (preservatives, dyes, high pesticide content) and refined ingredients.
 - ❑ High quality multivitamin from a health food store.
 - ❑ Selenium 150-300mcg per day (as seleno-methione)
 - ❑ Vitamin C 1000mg 1-2 per day
 - ❑ Vitamin E 400IU per day.
 - ❑ Omega 3 fish oils 2 per day.
 - ❑ Calcium and Magnesium (preferably combined with trace minerals)
-

Selenium

Rayman MP 2000

Selenium is a trace mineral, best known as a component of glutathione (antioxidant) and enzyme for thyroid production.

Selenium is needed for:

- Proper Immune Function
- Proper thyroid function: remember a selenium dependent enzyme is required to convert T4 to T3**
- Key nutrient in counteracting the development of virulence in HIV (see other studies regarding other viruses)
- Required for sperm motility
- May reduce risk of miscarriage
- Deficiency associated with cardiovascular disease, altered mood states
- Elevated selenium intake associated with reduced cancer risk

Selenium and Immune System

- Study where subjects **with adequate selenium status** were given 200mcg per day had a marked effect on the immune system:
 - The data indicated that the supplementation regimen resulted in 118% increase in cytotoxic lymphocyte-mediated tumor cytotoxicity and
 - 82.3% increase in natural killer cell activity as compared to baseline values Kiremidjian-Schumacher L *et al* 1994
- Selenium and other anti-oxidant deficiencies contribute to the host acquisition of more serious infections including serious viral infections and contributes to the formation of more virulent strains.

Beck MA. *et al* 2004 Beck MA *et al* 2003 Beck MA *et al* May15, 2003 Gomez RM *et al* 2002 Gomez RM *et al* 2001

Selenium Deficiency

- ❑ Case reports of children with selenium deficiency showing signs of hypothyroidism with high TSH and a positive TRH test completely reversed by selenium repletion after four weeks. Pizzulli A. Ranjbar A, 2000
 - ❑ Keshan disease in children, cardiomyopathy directly related to selenium deficiency Levander OA *et al* 1981
-

Selenium

- ❑ **Decreased selenium** levels were found in patients with **acute MI**. Kok FJ *et al* 1989
 - ❑ Decrease serum selenium leads to decreased HDL and reduced glutathione peroxidase levels. **Repleting selenium may reduce risk of coronary disease.**
Luoma PV *et al* 1984
 - ❑ Adequate selenium **may help protect against cancers** by enhancing antioxidant protection through glutathione and by “inhibition of enzymes converting carcinogens to their ultimate forms in the cell” they recommend an intake of 150-300mcg per day as adequate protection without toxicity. Hocman G, 1988
-

Selenium Need

- ❑ Established adequate intake: 50-200mcg per day (1980 by US Food and Nutrition Board) calculated on animal studies alone.
 - ❑ Further research revealed the daily healthy adult need to be about 1mcg/kg/day (so for 150lb person need is about 70mcg per day)
Olander OA, Morris VC, 1984
 - ❑ **More recent studies suggest the daily need is closer to 80-100mcg per day** (using glutathione peroxidase content in platelets rather than serum) Rayman MP 2000
 - ❑ **SAFETY: Doses up to 750mcg per day are without side effects or toxicity.** Angstwurm MW.
Gaertner R 2006
-

Selenium Deficiency in General Special Populations

- ❑ **Average intake study** in population done in 1981 showed **45% of those diets did not provide 70mcg per day** Welsh SO *et al* 1981
 - ❑ Average intake of **pregnant and lactating women** showed **42% consumed less than 70mcg per day**
Levander OA, *et al* 1981, Levander OA *et al* 1987
 - ❑ **Vegetarians and those eating diets low in animal protein** (phenylketonuric and hyperphenylalaniemic patients) would be at higher risk of selenium deficiency
Marit ME *et al* 2000
 - ❑ Patients taking **Proton pump inhibitors** -specifically omeprazole (Losec and Prilosec) - blocked mineral absorption. Epstein M *et al* 2006, Hamdan II 2001
 - ❑ Probable decrease absorption of minerals **hypochlorhydria or achlorhydria** Carter RE 2nd 1992, Champagne *et al* 1989
-

Selenium Absorption

BIOAVAILABILITY

Selenomethionine is the more bioavailable form of selenium (found in animal protein) (“... total intake of selenium may be less important nutritionally than its availability..”) Thomson, CD et al 1982)

Selenium Values in Food

3 ounces of Cooked Meat and Poultry and Fish

	µg Se
Beef (top sirloin, lean)	27.9
Beef liver (pan fried)	48.5
Pork loin lean roasted	29.8
Chicken breast roasted	23.5
Turkey breast roasted	27.2
Cod	32

Other Foods:

Brazil nuts, dried, unblanched, 1 ounce	544
Whole egg, one medium	14
Oatmeal instant one cup	12
White and brown rice	10
Whole wheat breast one slice	10
White bread enriched one slice	4

Taken from: Beef Facts: Selenium: Dietary Sources and Bioavailability, National Cattlemen's Beef Association
And: Dietary Supplement Fact Sheet: Selenium, Office of Dietary Supplements, NIH Clinical Center, NIH

Thyroid Physiology Difficult Thyroid Cases A Novel Approach

Questions?

Dr. Beverly Goode-Kanawati DO
Board Certified Family Practice
Board Certified Emergency Medicine
Phone 919-844-4552
drbgoode@bellsouth.net

What pets do when we're at work!









References Lipids and CV Disease in Thyroid Disorders

- Bindels, Alexander J. G. H., Westendorp, Rudi G.J., Frolich, Marijke; Seidell, Jacob C. Blokstra, Anneke, Smelt, Augustinus H. M, The prevalence of subclinical hypothyroidism at different total plasma cholesterol levels in middle aged men and women: a need for case-finding? *Clinical Endocrinology*. 50(2):217-220, February 1999.
 - Biondi B. Klein I. Hypothyroidism as a risk factor for cardiovascular disease. [Review] [162 refs] [Journal Article. Review] *Endocrine*. 24(1):1-13, 2004 Jun.
 - Danzi S. Klein I. Thyroid hormone and the cardiovascular system. [Review] [110 refs] [Journal Article. Review] *Minerva Endocrinologica*. 29(3):139-50, 2004 Sep.
 - Danzi S. Klein I. Thyroid hormone and blood pressure regulation. [Review] [81 refs] [Journal Article. Review] *Current Hypertension Reports*. 5(6):513-20, 2003 Dec.
 - Erem, Cihangir Blood coagulation, fibrinolytic activity and lipid profile in subclinical thyroid disease: subclinical hyperthyroidism increases plasma factor X activity. *Clinical Endocrinology*. 64(3):323-329, March 2006.
-

References Cardiovascular Disease and Thyroid

- Flynn, R W.V. : MacDonald, TM.; Jung, RT.; Morris, AD.; Leese, GP. Mortality and Vascular Outcomes in Patients Treated for Thyroid Dysfunction. Journal of Clinical Endocrinology & Metabolism. 91(6):2159-2164, June 2006
 - Kung AW. Pang RW. Janus ED. Elevated serum lipoprotein(a) in subclinical hypothyroidism.[see comment]. [Journal Article] Clinical Endocrinology. 43(4):445-9, 1995 Oct.
 - Kung AW. Pang RW. Lauder I. Lam KS. Janus ED. Changes in serum lipoprotein(a) and lipids during treatment of hyperthyroidism. [Journal Article] Clinical Chemistry. 41(2):226-31, 1995 Feb.
 - Polikar R. Burger AG. Scherrer U. Nicod P. The thyroid and the heart. [Review] [97 refs] [Journal Article. Review] Circulation. 87(5):1435-41, 1993 May.
 - Muller, B, Tsakiris, DA, Roth CB, Gugliemetti, M. Staub, J.J., Marbet, GA, Haemostatic profile in hypothyroidism as potential risk factor for vascular or thrombotic disease. European Journal of Clinical Investigation. 31(2):131-137, February 2001.
-

References Cardiovascular Disease and Thyroid

- Siu CW. Yeung CY. Lau CP. Kung AW. Tse HF. Incidence, clinical characteristics and outcome of congestive heart failure as the initial presentation in patients with primary hyperthyroidism. [Journal Article] Heart. 93(4):483-7, 2007 Apr.
 - Tan KC. Shiu SW. Kung AW. Effect of thyroid dysfunction on high-density lipoprotein subfraction metabolism: roles of hepatic lipase and cholesteryl ester transfer protein. [Journal Article] Journal of Clinical Endocrinology & Metabolism. 83(8):2921-4, 1998 Aug.
 - Tan KC. Shiu SW. Kung AW. Plasma cholesteryl ester transfer protein activity in hyper- and hypothyroidism. [Journal Article. Research Support, Non-U.S. Gov't] Journal of Clinical Endocrinology & Metabolism. 83(1):140-3, 1998 Jan.
-

References Thyroid and Depression

- Brouwer JP. Appelhof BC. Hoogendijk WJ. Huyser J. Endert E. Zuketto C. Schene AH. Tijssen JG. Van Dyck R. Wiersinga WM. Fliers E. Thyroid and adrenal axis in major depression: a controlled study in outpatients. [Journal Article] *European Journal of Endocrinology*. 152(2):185-91, 2005 Feb.
 - Cole DP. Thase ME. Mallinger AG. Soares JC. Luther JF. Kupfer DJ. Frank E. Slower treatment response in bipolar depression predicted by lower pretreatment thyroid function. [Journal Article] *American Journal of Psychiatry*. 159(1):116-21, 2002 Jan.
 - Corruble E. Berlin I. Lemoine A. Hardy P. Should major depression with 'high normal' thyroid-stimulating hormone be treated preferentially with tricyclics?. [Clinical Trial. Journal Article. Randomized Controlled Trial] *Neuropsychobiology*. 50(2):144-6, 2004.
 - Dayan CM, Daniels GH. Chronic autoimmune thyroiditis. *N Engl J Med* 1996;335:99-107.
 - Extein I. Pottash AL. Gold MS. The thyrotropin-releasing hormone test in the diagnosis of unipolar depression. [Journal Article] *Psychiatry Research*. 5(3):311-6, 1981 Dec.
 - Gaby AR. "Sub-laboratory" Hypothyroidism and the Empirical use of Armour Thyroid. [Review], *Alternative Medicine Review*, 9 (2), 2004
 - Gitlin M. Altshuler LL. Frye MA. Suri R. Huynh EL. Fairbanks L. Bauer M. Korenman S. Peripheral thyroid hormones and response to selective serotonin reuptake inhibitors. [Clinical Trial. Journal Article] *Journal of Psychiatry & Neuroscience*. 29(5):383-6, 2004 Sep.
-

References Thyroid and Depression

- Jackson IM. The thyroid axis and depression. [Review] [55 refs] [Journal Article. Review. Review, Tutorial] *Thyroid*. 8(10):951-6, 1998 Oct.
 - Joffe RT. Levitt AJ. Major depression and subclinical (grade 2) hypothyroidism. [Journal Article] *Psychoneuroendocrinology*. 17(2-3):215-21, 1992 May-Jul.
 - Langer G. Koinig G. Hatzinger R. Schonbeck G. Resch F. Aschauer H. Keshavan MS. Sieghart W. Response of thyrotropin to thyrotropin-releasing hormone as predictor of treatment outcome. Prediction of recovery and relapse in treatment with **antidepressants** and neuroleptics. [Journal Article] *Archives of General Psychiatry*. 43(9):861-8, 1986 Sep.
 - Loosen PT. The TRH-induced **TSH** response in psychiatric patients: a possible neuroendocrine marker. [Review] [266 refs] [Journal Article. Review] *Psychoneuroendocrinology*. 10(3):237-60, 1985.
 - Sintzel F. Mallaret M. Bougerol T. [Potentializing of tricyclics and serotoninergics by thyroid hormones in resistant depressive disorders]. [Review] [47 refs] [French] [Journal Article. Review] *Encephale*. 30(3):267-75, 2004 May-Jun.
 - Sokolov ST. Levitt AJ. Joffe RT. Thyroid hormone levels before unsuccessful **antidepressant** therapy are associated with later response to T3 augmentation. [Journal Article] *Psychiatry Research*. 69(2-3):203-6, 1997 Mar 24.
-

References

- Angstwurm MW. Gaertner R. Practicalities of selenium supplementation in critically ill patients. *Current Opinion in Clinical Nutrition & Metabolic Care*. 9(3):233-8, 2006 May.
- Bagni N. Brown TR. Sundick RS. Thyroid injury is an initial event in the induction of autoimmune thyroiditis by iodine in obese strain chickens. *Endocrinology*. 136(11):5054-60, 1995 Nov.
- Bagchi N. Thyroid function in a diabetic population. *Special Topics in Endocrinology & Metabolism*. 3:45-55, 1982.
- Beck MA. Handy J. Levander OA. Host nutritional status: the neglected virulence factor. [Review] [39 refs] [Journal Article. Review] *Trends in Microbiology*. 12(9):417-23, 2004 Sep.
- Beck MA. Levander OA. Handy J. Selenium deficiency and viral infection. [Review] [28 refs] [Journal Article. Review] *Journal of Nutrition*. 133(5 Suppl 1):1463S-7S, 2003

References

- Beck MA. Williams-Toone D. Levander OA. Coxsackievirus B3-resistant mice become susceptible in Se/vitamin E deficiency. *Free Radical Biology & Medicine*. 34(10):1263-70, 2003 May 15.
 - Bogazzi F. Raggi F. Ultimieri F. Russo D. Campomori A. McKinney JD. Pinchera A. Bartalena L. Martino E. Effects of a mixture of polychlorinated biphenyls (Aroclor 1254) on the transcriptional activity of thyroid hormone receptor. *Journal of Endocrinological Investigation*. 26(10):972-8, 2003 Oct.
 - Caksen H. Dulger H. Cesur Y. Atas B. Tuncer O. Odabas D. Evaluation of thyroid and parathyroid functions in children receiving long-term carbamazepine therapy. *International Journal of Neuroscience*. 113(9):1213-7, 2003 Sep.
 - Canaris GJ, Manowitz NR, Mayor G, Ridgway EC: The Colorado thyroid disease prevalence study. *Arch Intern Med* 160:526-534, 2000
-

References

- Cansu, Ali ; Serdaroglu, Ayse ; Camurdan, Orhun ; Hrfanoglu, Tugba ; Bideci, Aysun ; Gucuyener, Kvlcm The Evaluation of Thyroid Functions, Thyroid Antibodies, and Thyroid Volumes in Children with Epilepsy during Short-Term Administration of Oxcarbazepine and Valproate. *Epilepsia*. 47(11):1855-1859, November 2006.
 - Carella C. Mazziotti G. Morisco F. Manganella G. Rotondi M. Tuccillo C. Sorvillo F. Caporaso N. Amato G. Long-term outcome of interferon-alpha-induced thyroid autoimmunity and prognostic influence of thyroid autoantibody pattern at the end of treatment. *Journal of Clinical Endocrinology & Metabolism*. 86(5):1925-9, 2001 May.
 - Carella C. Mazziotti G. Morisco F. Rotondi M. Cioffi M. Tuccillo C. Sorvillo F. Caporaso N. Amato G. The addition of ribavirin to interferon-alpha therapy in patients with hepatitis C virus-related chronic hepatitis does not modify the thyroid autoantibody pattern but increases the risk of developing hypothyroidism. *European Journal of Endocrinology*. 146(6):743-9, 2002 Jun.
-

References

- Cater RE 2nd. The clinical importance of hypochlorhydria (a consequence of chronic Helicobacter infection): its possible etiological role in mineral and amino acid malabsorption, depression, and other syndrome. Medical Hypothesis. 39(4):375-83,1992 Dec
 - Celi,FS et al. The pharmacodynamic equivalence of levothyroxine and liothyronine. A randomized, double blind, cross-over study in thyroidectomized patients. Clin Endocrinol (Oxf). (2009)
 - Champagne ET Low gastric hydrochloric acid secretion and mineral bioavailability. Advances in Experimental Medicine & Biology. 249:173-84, 1989
 - Correll, CU; Carlson, HE. Endocrine and Metabolic Adverse Effects of Psychotropic Medications in Children and Adolescents. Journal of the American Academy of Child & Adolescent Psychiatry. 45(7):771-791, July 2006.
-

References

- Epstein M McGrath S Law F Proton-pump inhibitors and hypomagnesemic hypoparathyroidism. *New England Journal of Medicine*. 355(17):1834-6, 2006 Oct 26.
 - Gaby AR, Sub-laboratory Hypothyroidism and Empirical use of Armour Thyroid, *Alternative Medicine Review*, 2004;Vol9:2:157-179.
 - Gaskill CL. Burton SA. Gelens HC. Ihle SL. Miller JB. Shaw DH. Brimacombe MB. Cribb AE. Changes in serum thyroxine and thyroid-stimulating hormone concentrations in epileptic dogs receiving phenobarbital for one year. *Journal of Veterinary Pharmacology & Therapeutics*. 23(4):243-9, 2000 Aug.
 - Giani C, Fierabracci P, Bonacci R, Giglotti A, Compani D, De Negri F, et al. Relationship between breast cancer and thyroid disease: relevance of autoimmune thyroid disorders in breast malignancy. *J Clin Endocrinol Metab* 1996;81:990-4
-

References

- Gomez RM. Berria MI. Levander OA. Host selenium status selectively influences susceptibility to experimental viral myocarditis. [Journal Article. Research Support, Non-U.S. Gov't] Biological Trace Element Research. 80(1):23-31, 2001 Apr.
 - Gomez RM. Solana ME. Levander OA. Host selenium deficiency increases the severity of chronic inflammatory myopathy in Trypanosoma cruzi-inoculated mice. [Journal Article] Journal of Parasitology. 88(3):541-7, 2002 Jun.
 - Gracious BL. Findling RL. Seman C. Youngstrom EA. Demeter CA. Calabrese JR. Elevated thyrotropin in bipolar youths prescribed both lithium and divalproex sodium. Journal of the American Academy of Child & Adolescent Psychiatry. 43(2):215-20, 2004 Feb.
-

References

- Hamdan II. In vitro study of the interaction between omeprazole and the metal ions Zn(II), Cu(II), and Co(II). *Pharmazie*: 56(11):877-81,2001 Nov
 - Harris B, Othman S, Davies JA, Heppner GJ, Richards CJ, Newcombe RG, et al. Association between postpartum thyroid dysfunction and thyroid antibodies and depression. *BMJ* 1992;305:152-6
 - Hocman G, Chemoprevention of cancer:selenium. *Int J Biochem*. 1988;20(2):123-132
 - Ishihara A. Nishiyama N. Sugiyama S. Yamauchi K. The effect of endocrine disrupting chemicals on thyroid hormone binding to Japanese quail transthyretin and thyroid hormone receptor. *General & Comparative Endocrinology*. 134(1):36-43, 2003 Oct 15.
-

References

- ❑ Ishihara A. Sawatsubashi S. Yamauchi K. Endocrine disrupting chemicals: interference of thyroid hormone binding to transthyretins and to thyroid hormone receptors. *Molecular & Cellular Endocrinology*. 199(1-2):105-17, 2003 Jan 31.
 - ❑ Isojarvi JI. Pakarinen AJ. Myllyla VV. Thyroid function with antiepileptic drugs. *Epilepsia*. 33(1):142-8, 1992 Jan-
 - ❑ Isojarvi JI. Turkka J. Pakarinen AJ. Kotila M. Rattya J. Myllyla VV. Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. *Epilepsia*. 42(7):930-4, 2001 Jul.
 - ❑ Kitamura S. Jinno N. Ohta S. Kuroki H. Fujimoto N. Thyroid hormonal activity of the flame retardants tetrabromobisphenol A and tetrachlorobisphenol A. *Biochemical & Biophysical Research Communications*. 293(1):554-9, 2002 Apr 26.
 - ❑ Kok FJ, Hofman A, Witteman JC, de Bruijn AM, Kruyssen DH, de Bruin M, Valkenburg HA. Decreased selenium levels in acute myocardial infarction. *JAMA* 1989 Feb 24;261(8):1161-4
-

References

- ❑ Larsen et al, Williams Textbook of Endocrinology, 10th Edition, USA, Saunders, 2001. 351-2, 341
- ❑ Luoma PV Sotaniemi EA Korpela H Kumpulainen J, Serum selenium, glutathione peroxidase activity and high density lipoprotein cholesterol—effect of selenium supplementation. Res Commun Chem Pathol Pharmacol. 1984 Dec;46(3):469-72.
- ❑ Messina M. Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. Thyroid. 16(3):249-58, 2006 Mar.
- ❑ Pizzuli A Ranjbar A. Selenium deficiency and hypothyroidism; a new etiology in the differential diagnosis of hypothyroidism in children. Biological Trace Element Research. 77(3):199-208, 2000 Dec.
- ❑ Rayman MP The importance of selenium to human health. Lancet 2000;356:233-241
- ❑ Rees-Jones RW, Rolla AR Larsen PR Hormonal content of thyroid replacement preparations. JAMA 1980;243:549-550

References

- Rosenthal MJ. Hunt WC. Garry PJ. Goodwin JS. Thyroid failure in the elderly. Microsomal antibodies as discriminant for therapy. JAMA. 258(2):209-13, 1987 Jul
 - Rotondi M. Oliviero A. Profice P. Mone CM. Biondi B. Del Buono A. Mazziotti G. Sinisi AM. Bellastella A. Carella C. Occurrence of thyroid autoimmunity and dysfunction throughout a nine-month follow-up in patients undergoing interferon-beta therapy for multiple sclerosis. Journal of Endocrinological Investigation. 21(11):748-52, 1998 Dec.
 - Sawin T, Chopra D, Azizi F, Mannix JE, Bacharach P. The aging thyroid: increased prevalence of serum thyrotropin levels in the elderly. JAMA. 1979;242:247-250.
 - Sherman SI. Etiology, diagnosis, and treatment recommendations for central hypothyroidism associated with bexarotene therapy for cutaneous T-cell lymphoma. Clinical Lymphoma. 3(4):249-52, 2003 Mar.
 - Singer PA, Cooper DS, Levy EG, et al. Treatment guidelines for patients with hyperthyroidism and hypothyroidism. JAMA 1995;273:808-12.
-

References

- Simone Sampaolo, Angel Campos-Barros, Gherardo Mazziotti, Sergio Carlomagno, Vincenzo Sannino, Giovanni Amato, Carlo Carella, and Giuseppe Di Iorio. Increased Cerebrospinal Fluid Levels of 3,3',5'-Triiodothyronine in Patients with Alzheimer's Disease. *J. Clin. Endocrinol. Metab.*, Jan 2005; 90: 198 - 202.
 - Steinhoff, Bernhard J. MD. Optimizing therapy of seizures in patients with endocrine disorders. *Neurology*. Optimizing Therapy of Seizures in Specific Clinical Situations. 67(12) Suppl 4:S23-S27, December 26, 2006.
 - Surks MI, Sievert R. Drugs and thyroid function. *New England Journal of Medicine*. 333(25):1688-94, 1995 Dec 21.
 - Turnbridge WMG, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Wickham survey. *Clin Endocrinol (Oxf)*. 1977;7:481-493.
-

References

- Vanderpump MP, Tunbridge WM. Epidemiology and prevention of clinical and subclinical hypothyroidism. *Thyroid*. Oct 2002; 12 (10):839-47
 - Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, Grimley Evans J, Hasan DM, Rodgers H, Tunbridge F et al. The incidence of thyroid disorders in the community: a twenty year follow-up of the Whickham Survey. *Clin Endocrinol* 1995;43:55-68.
 - Vainionpaa LK. Mikkonen K. Rattya J. Knip M. Pakarinen AJ. Myllyla VV. Isojarvi JI. Thyroid function in girls with epilepsy with carbamazepine, oxcarbazepine, or valproate monotherapy and after withdrawal of medication. *Epilepsia*. 45(3):197-203, 2004 Mar.
-

References

- Weetman AP. Postpartum thyroiditis and insulin-dependent diabetes mellitus: an important association. *J Clin Endocrinol Metab* 1994;79:7-9.)
 - Weetman AP, Fornightly review: Hypothyroidism: screening and subclinical disease. *BMJ* 1997;314:1175 (19 April)
 - Yamauchi K. Ishihara A. Fukazawa H. Terao Y. Competitive interactions of chlorinated phenol compounds with 3,3',5-triiodothyronine binding to transthyretin: detection of possible thyroid-disrupting chemicals in environmental waste water. *Toxicology & Applied Pharmacology*. 187(2):110-7, 2003 Mar 1.
-