

What to do when the furnace breaks?

Addressing hypothyroidism in children

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Disclosure

- None

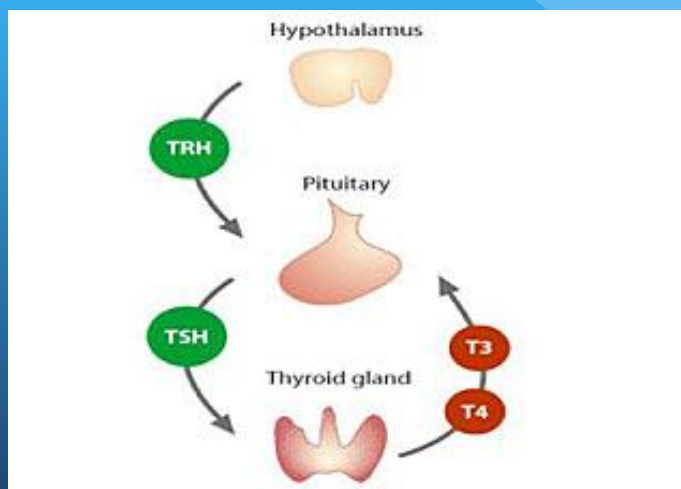
A Gland of Many Metaphors:

- “The thyroid gland is like a furnace and the pituitary gland is like a thermostat.”
- “Thyroid is like the drummer in the band, setting the pace for cellular metabolic activity, including the cells that make up your brain.
- “Thyroid hormone is like the spark plugs of the body. They ignite the fuel in the mitochondria of the cell to produce energy with which the body performs all of its functions.
- The thyroid gland, which is second in command only to the pituitary (for you Star Trek fans the thyroid is like Mr. Spock, while the pituitary would be Captain Kirk)



Objectives

- Review the function of thyroid hormone
- Discuss the presentation of hypothyroidism
- Understand laboratory work up for concerns of thyroid disease
- Know how to initiate treatment and manage hypothyroidism
- Discuss Common Clinical Conundrums



Thyroid Hormone

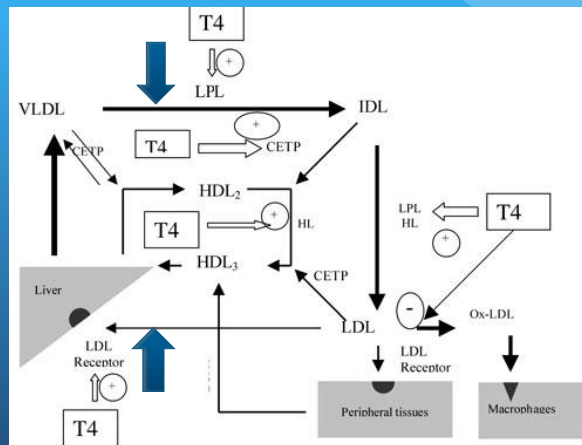
- T4 is the main hormone released from the thyroid gland
- Thyroid hormone is mainly bound in circulation to TBG, transthyretin, and albumin
 - 0.02% of T4 is unbound, 0.3% of T3 unbound
- Peripheral conversion of Free T4 (ng/dl) to Free T3 (pg/dl)
- T3 and T4 act via nuclear receptors

What does thyroid hormone do?

- CNS: Stimulates cell migration and neuronal cell maturation.
- Cardiovascular: Stimulates heart rate, contractility of the heart, cardiac output, blood flow.
- Gastrointestinal: Stimulates gastric motility.
- Lipid metabolism: Stimulates lipoprotein lipase and LDL receptors, enhances for oxidation of fatty acids.
- **Growth**: Stimulates GH synthesis, secretion, bone remodeling.
- Carbohydrate metabolism-enhances insulin-dependent entry of glucose into cells, gluconeogenesis.

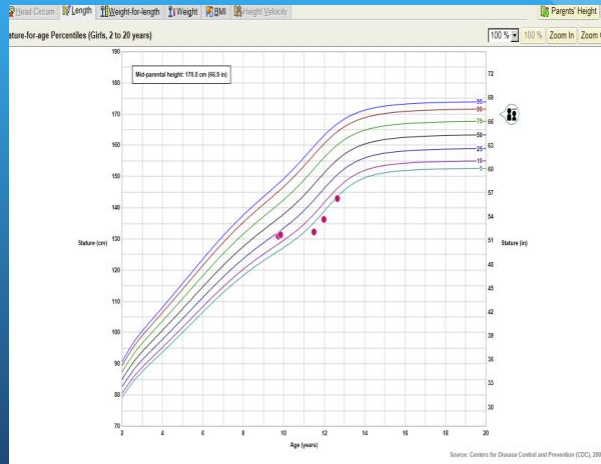
What are signs/symptoms of low thyroid?

- CNS: impact development in first 3 years of life; sluggishness, sleepiness, decline in school performance
- Cardiovascular: bradycardia
- Gastrointestinal: constipation
- Lipid metabolism: increased LDL and TG



<http://www.hormones.gr/images/dyn/liberop.jpg>

Growth attenuation



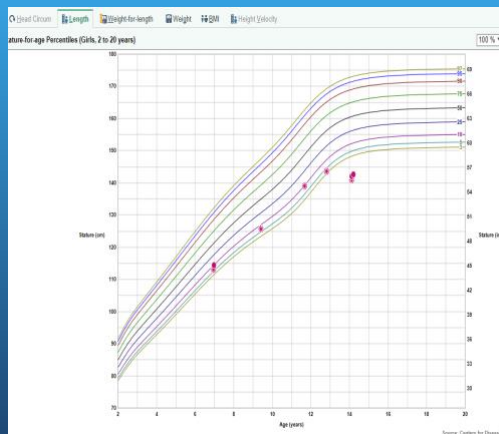
- Dry skin, sallow skin
- Cold intolerance
- Tired
- On exam:
 - Goiter: present 40% of time
 - Delayed deep tendon reflexes

Van Wyk Grumbach Syndrome

- Precocious puberty with breast development/menarche in girls or testicular enlargement in boys.
- Key difference: **Growth attenuation** NOT acceleration.
- Mechanism: not well understood. ? Shared alpha subunit of TSH, LH, and FSH?
- 4 case reports: TSH > 100 mIU/ml, LH 1-2 mIU/ml, Estradiol > 100 pg/ml, ovaries noted for cysts. Started therapy, puberty regressed.

Precocious Puberty: An Unusual Presentation of Hypothyroidism, *International Journal of Pediatrics*, Volume 1, Issue 2, December 2013, Page 51-54

14 year female presents with poor growth and right hip pain which started in the groin region, and now along the outside of her hip. On exam, she has well as some limited degree of abduction on that side



TSH= > 100 mIU/ml
Free T4= <0.4 ng/dl
TPO= 245 IU/ml (< 9)



<http://www.raymondliumd.com/images/SCFE%20illustrated%20and%20cropped.jpg>

Hypothyroidism and slipped capital femoral epiphysis (SCFE)

- SCFE—commonly presents during adolescents and associated with obesity.
- Has been associated with severe hypothyroidism, but exact mechanism unclear
- Recommended thyroid function screening in patients with SCFE and atypical presentation:
 - presenting at <10 or >16 years of age
 - Bilateral SCFE
 - Associated with poor growth

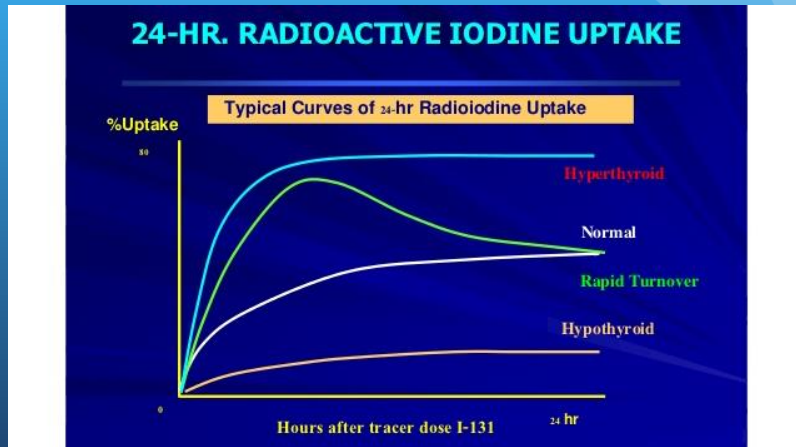
Moyer J, et al J Pediatr Endocrinol Metab. 2016;29:427-434.

Hashitoxicosis

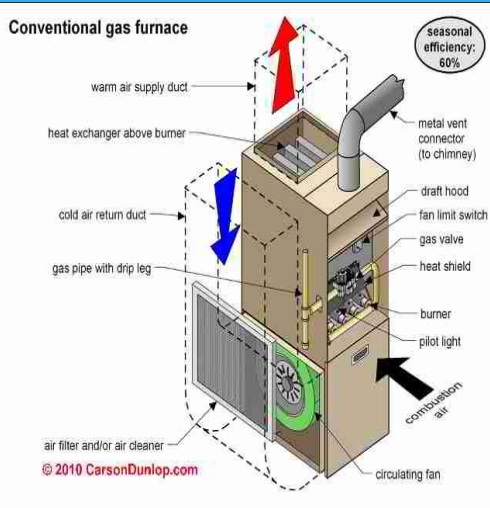
- Transient phase of hyperthyroidism associated with inflammatory destruction of the thyroid gland and “leakage” of thyroid hormone from the gland
- Suppressed TSH, increased Free T4 (Free T3). Positive thyroid peroxidase and thyroglobulin antibodies. Negative Graves markers
- Followed by state of euthyroid or **HYPOTHYROIDISM**
- Ultrasound-less vascularity as seen in Graves

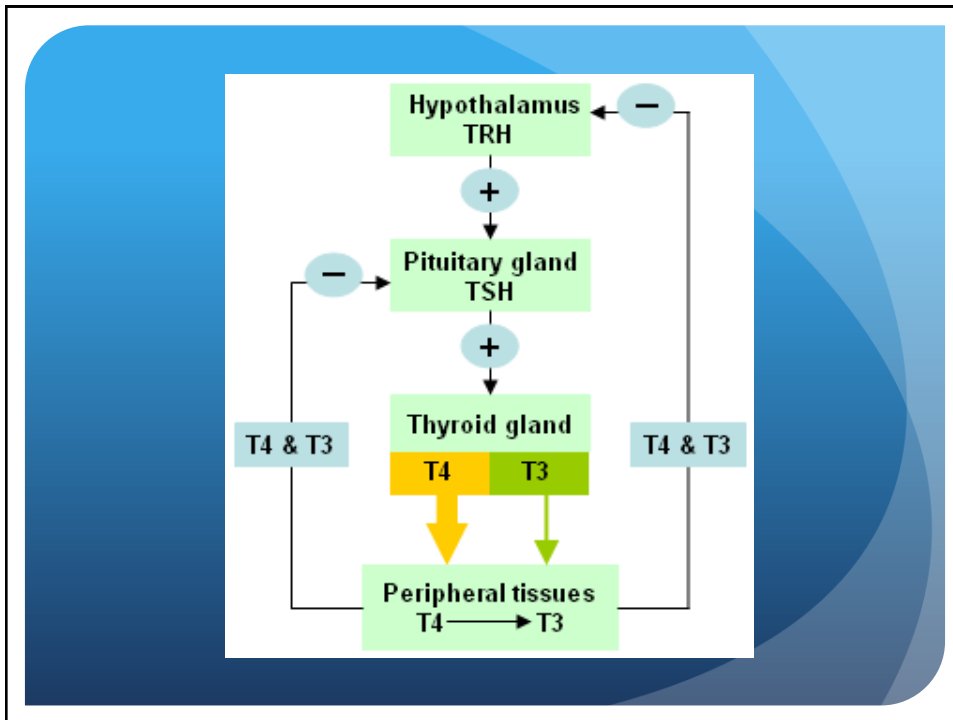
A. J. Unnikrishnan “Hashitoxicosis: A Mini Review”
Thyroid Research and Practice; 2013

Uptake to define Hashitoxicosis

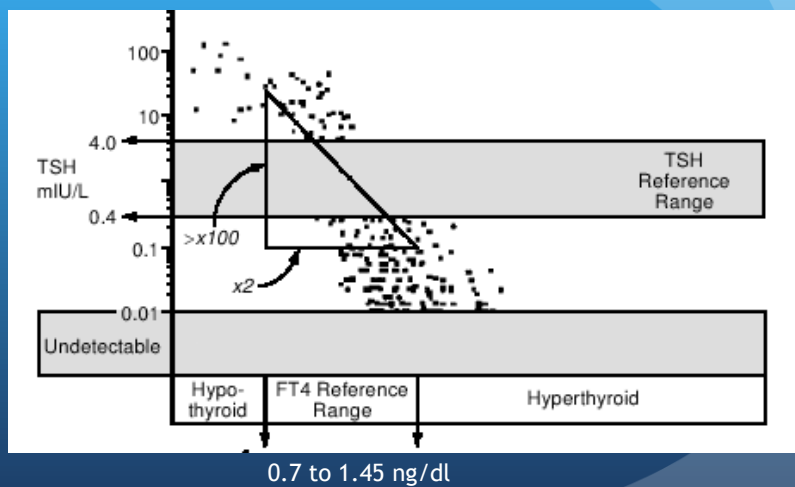


Diagnosis of hypothyroidism





Thyroid Assays: TSH, Free T4



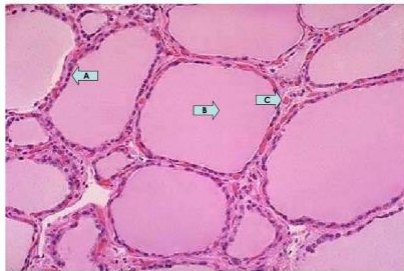
Etiology of Acquired Hypothyroidism

- Hashimoto's Thyroiditis:
 - Antiperoxidase antibody (TPO Ab) 85-90% positive
 - Antithyroglobulin antibody (Tg Ab) 30-50% positive
- Ultrasound-not necessary unless concern of nodule (asymmetry on exam). Common findings include diffuse enlargement

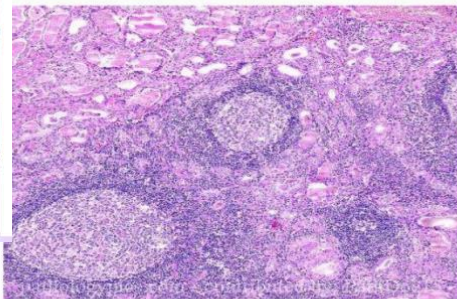
Lymphocytic infiltration

<https://image.slidesharecdn.com/cpc-4-3-1-end-thyroid-pathlec-view-100707014056-phpapp02/95/pathology-of-thyroid-endocrine-disorders-25-728.jpg?cb=1278467411>

Normal Thyroid



Hashimoto's thyroiditis



A lymphocytic infiltration with prominent follicles with germinal centers

https://www.google.com/search?q=lymphocytic+infiltration+of+thyroid+gland&client=firefox-b-1-ab&source=lnms&tbm=isch&sa=X&ved=0ahUKEwiI80O5v9rYAhVOwWMKHZDsAXQQ_AUICigB&biw=1440&bih=713#imgrc=gxJ7xthqobqABM

What if antibodies are positive, but thyroid levels are normal?

- Prevalence of positive antibodies:
 - NHANES 3 : **6.3%** of adolescents positive TG ab and **4.8%** positive TPO.
- Natural history:
 - 105 children with positive abs, but normal TSH. After **5 years**, 65% euthyroid, and **only 26% developed TSH 2 fold** above reference range.

Radetti et al. "J Pediatr 2006; 149:827

- 10 year old female with fatigue and positive family history for hypothyroidism

date	6/11/2016	7/11/2016	10/7/2016	11/23/2016	5/7/2017	12/28/2017
TSH (uIU/ml)	5.15	3.26	3.63	4.11	6.46	2.46
TPO (<9 IU/ml)		249				

Adult Studies

- The prevalence of positive TPOAb in a randomly selected subgroup of adults over 40 years of age with no history of thyroid disease:
 - **Females** (n= 582) was 13.9%
 - Males (n=360) was 2.8%

European Journal of Endocrinology (2000) 143 639±647

Other: Etiologies of Acquired hypothyroidism

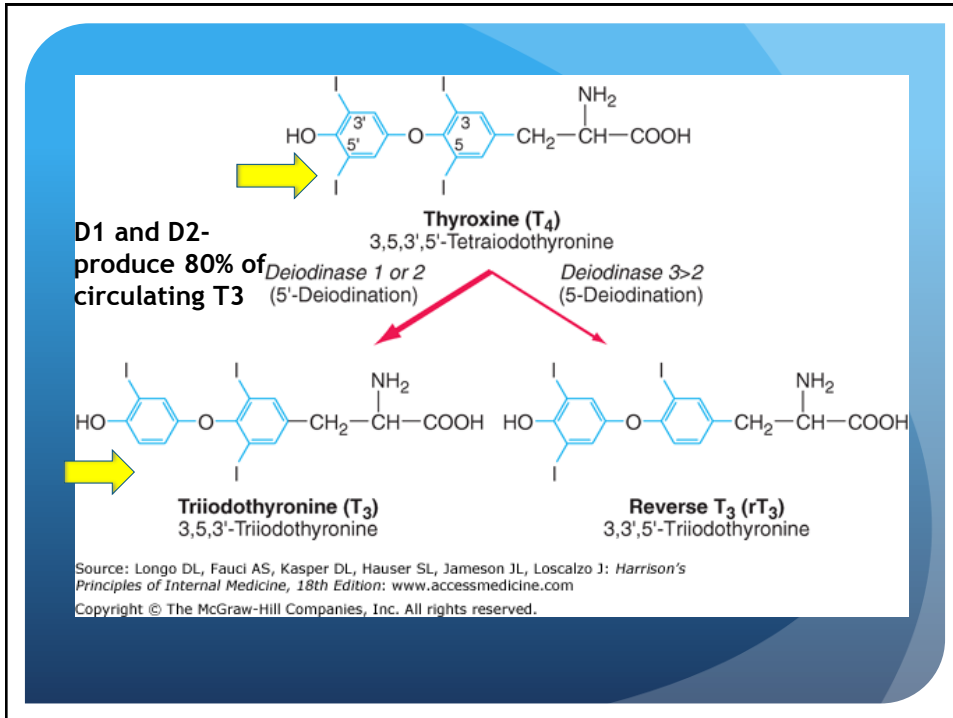
- Subacute granulomatous thyroiditis
- Iodine deficiency-rare in North America (iodonized salt)
- Medications: Anticonvulsants, lithium, amiodorone
- Thyroid injury-radiation, chemotherapy, surgery
- Central hypothyroidism—**LOW TSH** with Low Free T4

Treatment for hypothyroidism

- Levothyroxine (T4): L-Thyroxine, T4
- Brand names: Synthroid, Levoxyl, levothyroid

How supplied





Brand vs Generic

- Various bioavailability that is not consistent from brand to brand to generic (potency can vary 95% to 105%)
- Joint position statement (AACE, ES, ATA) -2004
 - Concerns about the sensitivity of the FDA's methodology for determining levothyroxine bioequivalence
 - Levothyroxine formulation should not be switched. If a switch occurs, thyroid-stimulating hormone laboratory values should be monitored
- American Association of Clinical Endocrinologists, The Endocrine Society, American Thyroid Association. AACE, TES, and ATA Joint Position Statement on the Use and Interchangeability of Thyroxine Products. American Association of Clinical Endocrinologists website, December 8, 2004. www.aace.com/pub/pdf/guidelines/AACE-TES-ATA-ThyroxineProducts.pdf.

Brand vs Generic

- Study looking at generic (n=27) vs brand (n=35) in young children with congenital hypothyroidism and found no difference in TSH variation or dose adjustment. *Lominick et al J Clin Endocrinol Metab 98: 653-658, 2013*
- Cost difference:
 - Brand, 90 day supply: \$54
 - Generic at Walmart 90 day: \$10
- What to do:
 - Council patients on staying on same form of thyroid replacement. If change in pharmacy-need labs rechecked
 - Special populations: infants, pregnant women, post thyroid cancer

Dosing of levothyroxine

Age	L4 dose (ug/kg)
0-3 mo	10-15
3-6 mo	8-10
6-12 mo	6-8
1-3 yrs	4-6
3-10 yr	3-4
10-15 yr	2-4
> 15 yr	2-3
Adult	1.6

Pediatric Practice Endocrinology
2014

Follow up

- Thyroid hormone has long half life (5-7 days)
- Retest thyroid tests 6-8 weeks after dose adjustment
- Goal of therapy-TSH in normal range, Free T4 in upper third of reference range for age
- Administer 30-60 minutes prior to food “most important to administer the same way every day”
- If change in manufacturers, notify provider to re check labs sooner

Pediatric Practice Endocrinology, Chapter 4 Thyroid
Kappy, Allen, and Geffner, 2014

What can impact dosing

- Noncompliance
 - Supervision
 - Filling prescriptions?
 - Pill box
- Food/Medications
 - Soy
 - Calcium
 - Iron
 - Medications—phenytoin, Carbamazepine, rifampin

- 8 yr male with type 1 DM (dx age 4 years) s/p thyroidectomy for papillary thyroid cancer. Wt: 36 kg
- Labs every 3 months:

Thyroidectomy



TSH (uIU/ml)	160	126	58	33	18	0.4
DOSE (mcg)	62.5	125	150	200	200	200

TTG IGA > 300

Counseling patients with Hashimoto's Thyroiditis

- Prognosis: very good. Depending on severity, may be lifelong.
- Reproduction: for women, important to have levels followed prior to conception and during the pregnancy. Thyroid needs can increase by an average of 47%
- Other autoimmune diseases: (**Autoimmune polyglandular syndrome APS**):
 - 1-Mucocutaneous candidiasis, hypoparathyroidism, adrenal insufficiency, hypothyroidism
 - 2-Adrenal insufficiency, hypothyroidism, celiac, hypoparathyroidism, autoimmune hepatitis.

Special populations

Down Syndrome and Thyroid

- Hashimotos Thyroiditis-rate of 13-34%
- Graves disease-6.5%
- Mechanism-dysregulation of immune system-defect in inhibitory activity. May be due to insufficient expression of AIRE gene, located on Chromosome 21.
- Commonly subclinical hypothyroidism

Down Syndrome and Thyroid

- AAP Guidelines-Health Supervision for Children with Down Syndrome (2011)
- Repeat TSH at 6 and 12 months of age
- Then repeat **annually throughout life**

Turner Syndrome and Thyroid

- Hashimotos Thyroiditis-prevalence rate of 10-20%
- Graves disease 1.7-3%
- Mechanism for increased autoimmune thyroid disease: ? Haploinsufficiency of genes in X chromosome that play role in autoimmune disease

Turner Syndrome and Thyroid

- AAP Guidelines “Health Supervision for Children with Turner Syndrome” Pediatrics, 2003
- Check thyroid functions tests at diagnosis and then annually.

Type 1 Diabetes and Thyroid

- Thyroid disease most common associated autoimmune disease with type 1 DM
- 17-30% of patients with type 1 DM will develop thyroid disease
- American Diabetes Guidelines 2018- Measure TSH at diagnosis and then every 1-2 years
- Check thyroid antibodies-if TSH is abnormal or goiter.

Common Clinical Conundrums

What to do about a goiter?

- Retrospective study, N=939, ages 5-17 years who presented with goiter
- 37% had thyroid dysfunction
- 63% (n=592) had a simple goiter
 - 2 year follow up, 88% remained simple goiter
- “The pathogenesis of euthyroid simple goiter remains unclear. The histologic findings are of enlarged thyroid follicles filled with abundant colloid, with no evidence of inflammation, infection, or neoplasm.”

Kim et al, J Pediatr 2016;170:253-9.

What to do about a goiter?

- Check thyroid function tests along with TPO and TG antibodies
- If negative abs and normal thyroid function tests- reasonable to repeat in 6-12 months
- Serial exams, if increasing in size or concerns of asymmetry, then obtain ultrasound to look for nodules

What about screening siblings?

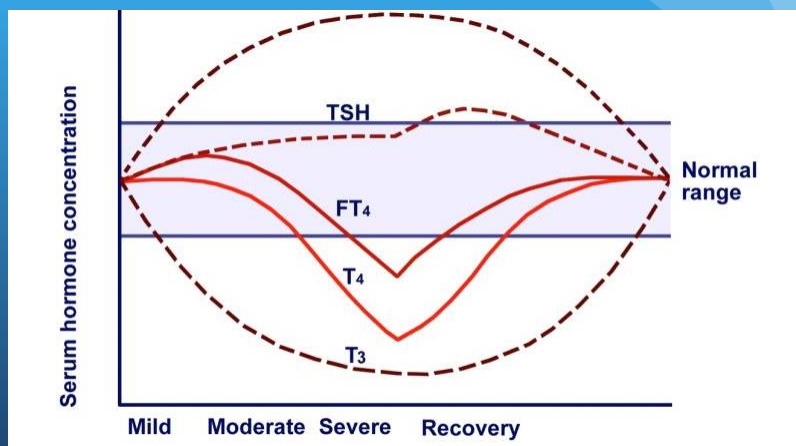
- Study in India, evaluated first degree relatives of adults with Hashimotos thyroiditis
- 38% positive for thyroid antibodies
- 16% positive for Hashimotos thyroiditis (elevated TSH with abs)
 - Parents > Siblings > Offspring (9.6%).
- Increase with age and more prevalent in females.

[Bothra N, et al. Clin Endocrinol. 2017;doi:10.1111/cen.13323.](https://doi.org/10.1111/cen.13323)

What to do with compensated (subclinical) hypothyroidism?

- Defined by slightly elevated TSH with normal Free T4
- Effects 2 % in pediatric population
- Only few progress to overt hypothyroidism
- Risks: goiter, positive antibodies, rising TSH
- Treatment when TSH > 10 mIU/ml or large goiter, or associated condition (T1DM) or signs/symptoms of low thyroid

Sick euthyroidism



What about an elevated TSH and obesity?

- Study looking at increased TSH in pediatric obese patients vs lean.
- SH defined as TSH of 4.4-10 mIU/ml
 - Obese (N=1796) : 10.4% with SH
 - Lean (N=1210): 6.4% with SH
- Overall, TSH levels statistically higher in the obese vs lean

Dahl et al, J Clin Res Pediatr Endocrinol 2017;9 (1) 8-16

Should we treat elevated TSH in the obese patient?

- 246 obese pediatric patients in 1 year obesity intervention study vs 71 nonobese controls
- Baseline: Obese children had statistically higher TSH and Free T3 levels vs nonobese.
- 17% of obese cohort had a TSH > 3.55 mIU/ml
- 20% (N=49) demonstrated weight loss at 1 year
 - Both TSH and Free T3 lowered in those with weight loss vs not in those without weight loss

Conclusion: Not necessary to treat moderately elevated TSH levels in obese patients

Reinehr et al. J Clin Endocrinol Metab 2006; 91: 3088

<https://www.uwhealth.org/healthfacts>

Hypothyroidism in Children

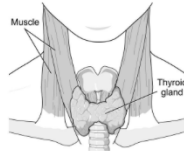
Your child has been diagnosed with hypothyroidism. This occurs when the thyroid gland, one of the body's endocrine glands, does not make enough thyroid hormone. Thyroid hormone affects your child's weight gain, controls body temperature, helps control the heartbeat, and is one of the controls of the body's growth and the brain's development. This handout will answer some questions you may have about the condition and how it is treated.

Glossary of Terms

- **Gland** – A special group of cells in the body that sends out a hormone.
- **Hormone** – A chemical messenger sent out from a gland into the bloodstream where it can carry its message to other cells in the body.
- **Euthyroid** – "Eut" means "normal." Euthyroid means the thyroid gland is working normally.
- **Hypothyroid** – "Hypo" means "too little, not enough." Hypothyroid means the thyroid gland is not making enough thyroid hormone.
- **Hyperthyroid** – "Hyper" means "too much." Hyperthyroid means the thyroid gland is making more thyroid hormone than the body needs.

The Thyroid Gland

The thyroid is a butterfly-shaped gland in the center front of the neck. A healthy thyroid sends out hormones, called triiodothyronine (T3) and thyroxine (T4). When the thyroid gland gets a message from the brain that the body needs these two hormones, the thyroid gland sends them into the bloodstream. The blood then carries thyroid hormone everywhere in the body.



If the thyroid gland slows down or stops making enough thyroid hormone, the symptoms may include:

- Swelling in the front of the neck.
- Intolerance to cold, feel cold all the time.
- Feel tired or sleepy during the day.
- Constipation.
- Poor growth.
- Rough or brittle hair.
- Mild weight gain due to puffiness in face, hands, and feet

Hypothyroidism does not cause obesity.

Treatment

Hypothyroidism is treated with a thyroid hormone pill. The thyroid hormone pill doctors often give is called Synthroid or levothyroxine sodium. It is important to take this pill at the same time every day as part of your daily routine so you don't forget to take it. Each person or family should find the right routine that works for them. Be careful not to give this pill at the same time with calcium or iron.

The child that is still growing will need different doses of thyroid hormone as the child gets bigger. The doctor may do a blood test before or after clinic visits to make sure the dose is correct. The doctor may make changes in the dose of the pill based on your child's lab results.

The symptoms of hypothyroidism will go away with treatment. It is still very important to keep taking the thyroid pills. Without the pills, the symptoms will return.

Signs of too little thyroid hormone

- Sleepiness
- Constipation
- Feeling cold all the time
- Decreased appetite in babies
- Weight gain
- Rough, coarse hair

Signs of too much thyroid hormone

- Jittery, unable to sit still
- Crabby
- Weight loss
- Feel warm all the time
- Diarrhea
- Insomnia, trouble sleeping

Clinic Visits

The doctor or nurse will check thyroid function in several ways during clinic visits.

- **Palpation** – the doctor will feel the thyroid for any changes in size or if one side is bigger than the other.
- **Reflexes** – The doctor will tap the knee, ankle, and elbow with a rubber hammer to see if it twitches. If the thyroid hormone is low (hypo), the reflexes may be slow. If the thyroid hormone is high (hyper), the reflexes may be fast.

- **Heart rate** – The heart rate may be slower with hypothyroidism. With hyperthyroidism, the heart rate may be faster.
- **Blood pressure** – Blood pressure may be low with hypothyroidism. Blood pressure may be high with hyperthyroidism.
- **Skin and hair** – Skin and hair may be dry and rough with hypothyroidism. In hyperthyroidism, skin and hair may be moist and oily.
- **Height and weight** – With hypothyroidism your child may not grow at the proper rate. With hyperthyroidism, your child may grow at the proper rate and may also lose weight. Your child will be weighed and measured during clinic visits to see if your child's body is growing as it should.

Pediatric Endocrinology
(608) 263-6420

After hours, this number is answered by the paging operator. Ask for the endocrinologist on call. Leave your name and phone number with the area code. The doctor will call you back.

If you live out of the area, call
1-800-323-8942.

<https://www.youtube.com/watch?v=WbpzAVSurlQ>



Thyroid Problems in Children



<https://thehealthyhousewives.files.wordpress.com/2013/01/cartoon.png>