Updates in Thyroid Disease

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Thyroid Outline

- Background
- Hypothyroidism
- Hyperthyroidism
- Thyroid nodules
- Thyroid Cancer
- Conclusions
- Resources/References

Thyroid

- Produces the hormone thyroxine (T4)
  - Four iodine atoms
- Triiodothyronine (T3)
  - Three iodine atoms
- Various enzymes convert between T3 and T4
- Most of T3 is made by other tissues converting T4
Goiter

- Definition: enlargement of the thyroid gland
- Can occur with EITHER hypo or hyperthyroidism
- Can be secondary a a benign “Multinodular goiter”–multiple thyroid nodules
- Iodine deficiency

[Diagram of thyroid gland and the structures labeled]

[Chemical structures of L-thyroxine (T4) and Liothyronine (T3)]

[Website link: http://www.abc.net.au/health/library/stories/2005/06/16/1831822.htm]
Hypothyroidism

• According to the American Thyroid Association, 2-3% of Americans have hypothyroidism
Risk factors

• Family history
• Radiation exposure to the neck
• Down’s syndrome or Turner’s syndrome
• Having other autoimmune diseases like rheumatoid arthritis, Addison’s disease (adrenal insufficiency), celiac disease, Type 1 diabetes

Symptoms

• Less energy
  □ More fatigue, trouble awakening in the morning, need for more sleep, and tendency to fall asleep during the day
  □ Feeling cold when other people feel warm

□ Less sweating
□ Drier, itchier skin
□ Drier, coarser, more brittle hair
Symptoms

- Hair loss
- Loss of appetite
- Mild weight gain (5-20 pounds) and difficulty losing weight

Symptoms

- New or worsening problems with memory, slower thinking
- New snoring
- Muscle cramps and joint aches
- New feeling of pins and needles in the hands and feet (paresthesia)

Symptoms

- New or worsening constipation
- Puffiness around the face (especially the eyes), hands, ankles, and feet because of fluid build-up
- Carpal tunnel syndrome
Symptoms

- Heavier and/or more frequent menstrual periods, worse cramps, worse premenstrual symptoms, milky discharge from the breasts
- Feeling irritable
- New or worsening depression
- New or worsening hoarse voice

Symptoms

- New or worsening hearing loss
- Goiter (swelling in the front of the neck, caused by enlargement of the thyroid)
- Slowing of heart rate
- Higher cholesterol levels
- Growth delay in children

Causes

- Autoimmune – Hashimoto’s disease
- Surgical Removal
- Radiation/Radioactive iodine ablation
- Inherited from birth (congenital)
- Medications
- Iodine deficiency or excess
- Pituitary diseases
**Autoimmune**

- The immune system normally protects the body against bacterial and viral "invaders."
- In autoimmune diseases ("auto" means "self"), the immune system attacks a normal part of the body.
- In autoimmune hypothyroidism, the immune system accidentally attacks cells in the thyroid. This causes the cells to become inflamed and damaged, interfering with their ability to make thyroid hormone.
- When enough thyroid cells have been destroyed, too few are left to meet the body's need for thyroid hormone.

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**Autoimmune**

- Autoimmune thyroid disease is more common in women than men.
- It can start at any age, but becomes more common as people get older.
- In women, it often begins during pregnancy, after delivery, or around menopause.

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**Autoimmune**

- Autoimmune hypothyroidism can begin suddenly, but in most people it develops slowly over years.
- The most common form of autoimmune hypothyroidism is called Hashimoto’s disease. This can sometimes cause the thyroid to shrink over time.
Thyroid blood tests

- TSH: Thyroid stimulating hormone
  - Produced by the pituitary
  - High TSH and low Free T4: primary hypothyroidism
  - Low TSH and high Free T4: primary hyperthyroidism
  - Low Free T4 and inappropriate TSH (low or normal): central hypothyroidism
  - High TSH, high thyroxine: pituitary adenoma

TSH (mU/L)
Thyroid Stimulating Hormone

- Normal: 0.4 – 4
- Hyperthyroidism: 0 – 0.4
- Borderline (subclinical hypothyroidism)
  - 4 - 10
- Overt hypothyroidism
  - TSH > 10

Thyroxine (T4)

- Free thyroxine (FT4)
- Inverse relationship with TSH
- The lower the TSH, usually the higher the FT4 (Free T4)
- The Free T4 parallels T3
Thyroid blood tests, cont.

- Thryoglobulin: (Tg)
  - Protein only made by thyroid gland
  - Used as a cancer marker after surgery for thyroid cancer
- TPO antibodies (Thyroperoxidase)
  - Positive in Hashimoto’s disease or hyperthyroidism
  - Not needed to make the diagnosis of hypothyroidism

Subclinical Hypothyroidism

- TSH slightly high 4-10, but normal FT4
- ATA (American Thyroid Association) does not treat until TSH rises to above 10

Hypothyroidism Treatment

- Levothyroxine (generic)
Taking levothyroxine

- Levothyroxine (generic)
- Synthroid, Levoxyl (name brand)
- Take in am on empty stomach 30 min before food
- Separate multivitamins, Calcium/Iron supplements by 4 hours

T3 and T4

- The American Thyroid Association does not recommend treatment with T3 and T4 combinations
  - Armour Thyroid (T3 +T4)
    - Porcine derived (PIG)
    - dessicated

Gender Differences

- Carlé A et al.
- Gender differences in symptoms of hypothyroidism: a population-based DanThyr study
- Clin Endocrinol (Oxf). April 2, 2015
Gender Differences

• Denmark
• Included patients who had just been diagnosed with hypothyroidism while they were participating in a DanThyr study
  – Designed to study iodine intake and thyroid disease in that country.
• 147 patients participated

• All participants (patients and normal volunteers) completed a questionnaire regarding hypothyroid symptoms present in the last 12 months.
• also included questions about neck symptoms such as trouble swallowing due to an enlarged thyroid (goiter).
• In total, 140 patients and 560 normal volunteers were included and 16% of them were men.

• In the group of the hypothyroid patients, 94.9% of women and 91.3% of men reported at least one symptom
• most common symptoms were fatigue (80.6%), dry skin (62.1%) and difficulty breathing (51.4%)
• In the normal volunteers, 73.7% of women and 51.1% of men also reported at least one hypothyroid symptom.
  – In this group, the following symptoms were much more significantly present in women than men: fatigue, difficulty breathing, dry skin, mood changes, palpitations, constipation and the sensation of “something in the throat”.
• When the data from all participants was analyzed together (males and females, patients and controls), it was seen that the presence of symptoms was indicative of hypothyroidism.
• The data also showed that men with two to three hypothyroid symptoms were likely to have hypothyroidism, but women reporting two to three symptoms were likely to have normal thyroid levels.

• In this study, the presence of hypothyroid symptoms did not differ significantly between men and women with hypothyroidism.
• However, it was also shown that normal women were significantly more likely than normal men to report hypothyroid symptoms.

• Therefore, the presence or absence of symptoms is more reliable in diagnosing hypothyroidism in men than in women.
• Another implication of this study is that since so many patients who do not have hypothyroidism report symptoms consistent with such, complaints of persistent symptoms even after the treatment of hypothyroidism would be very common especially in female patients.
Screening

- Screening recommendations from major groups have been conflicting.
  - The American Academy of Family Physicians (AAFP) recommends periodic assessment of thyroid function in older women.
  - The American College of Physicians (ACP) suggests that office screening of women older than 50 years may be indicated.
- The American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE) recommend measurement of TSH in any individual at risk for hypothyroidism:
  - e.g., personal history of type 1 diabetes or other autoimmune disease, family history of thyroid disease, history of neck radiation to the thyroid, history of thyroid surgery.
  - Consideration of measurement of TSH in patients over the age of 60 years.
- The United States Preventive Services Task Force found insufficient evidence to assess the benefits and harms of screening.

Hyperthyroidism

- TSH < 0.45
- Subclinical: TSH < 0.45 but normal FT4
- Causes:
  - Thyroiditis
  - Graves’ disease
  - Toxic nodule
  - Toxic multinodular goiter
Hyperthyroidism symptoms

- Tachycardia
- Palpitations
- Atrial fibrillation
- Sweats
- Tremor
- Diarrhea
- Heat intolerance
- Anxiety
- Insomnia

Thyroiditis

- Secondary to meds
- Pregnancy
- Virus
- Other

Graves’ disease

- Autoimmune
- The body attacks the thyroid gland
- Former President George H. W. Bush
- Comedian Rodney Dangerfield
Thyroid uptake and scan

- Imaging test to determine the cause of hyperthyroidism
- Uptake: percentage
- Scan: picture

Thyroid Uptake and Scan

Graves’ Disease

- Increased uptake
- Homogenous (uniform) scan
Graves’ Eye Disease

Hyperthyroidism treatment

• Antithyroidal medications:
  – Methimazole – start 15-20 mg daily
  – PTU (propylthiouracil)

• Beta blockers – heart receptor blockers
  – Propranolol 40 mg po qid prn symptoms
Methimazole Rare Side Effects

• Rash
• Joint pains
• Liver problems
• Low blood counts (agranulocytosis)

Radioactive iodine ablation (I-131)

• Permanent destruction of thyroid
  – Swallow capsule
• Requires permanent thyroid hormone replacement therapy (levothyroxine)
• Used for Graves’ disease, toxic multinodular goiter, solitary toxic nodule, thyroid cancer

Thyroid nodules
Thyroid nodules

- Very common
- Usually found incidentally on imaging
- 50% of adults over age 50
- Some stay same size, shrink, or grow

Thyroid nodules

- 5-15% chance of cancer
- Usually found incidentally
  - During other imaging
    - Carotid Ultrasound
    - CT scan of neck
- Some have higher risk of malignancy
  - PET scan -33%
- Usually asymptomatic

Thyroid nodules

- Increased risk of cancer:
  - Family history
  - Radiation exposure to the neck (lymphoma treatment)
  - Rapid growth
  - Compressive symptoms
Nodule Characteristics

• Size
• Echogenicity (how dark/dense)
• Roundness
• Blood flow/vascularity
• Calcifications
• Cystic component

Size

• Solid nodules
  – hypoechoic— 1 cm cutoff
  – Isoechoic or hyperechoic—1 – 1.5 cm
• Mixed solid/cystic nodules – 2 cm
• Pure cyst – does not need to be biopsied

Thyroid nodule follow up

• Repeat thyroid ultrasound 6-18 months after biopsy
• Risk of false negative (5-15%)
  – Chance of missing a cancer with a negative biopsy

Significant Growth Warranting Repeat Biopsy

• More than 50% change in volume
• Or
• 20% increase in at least 2 dimensions with a minimal increase of 2 mm in a solid nodule

• Durante C et al
• The natural history of benign thyroid nodules
• JAMA 2015;313:926-35
• The goals of this multicenter Italian study were to determine how often and how quickly benign nodules grow and to determine whether cancer was diagnosed in nodules that grew during a 5-year period of observation.

• All nodules that had ultrasound features suspicious for malignancy or were solid and larger than 10 mm were biopsied. Suspicious features included hypoechogenicity, microcalcifications, irregular margins, taller-than-wide shape, and intranodular vascularity.
• When a patient had multiple suspicious nodules, only the largest nodule was biopsied.
• The size of each nodule was measured in three dimensions.

• Each patient had annual ultrasound examination and thyroid function tests.
• When a nodule was found to be suspicious during the follow-up, a repeat biopsy was performed
• At the 5-year follow-up, most nodules >1 cm underwent repeat biopsy
• A total of 992 patients were studied, with a total of 1567 nodules.
• The average age was 52 years, 82% were women, and about half had a family history of thyroid nodules.
• In 579 patients, 630 nodules (40% of the total) were classified as benign based on biopsy.
• Data representing 5 years of follow-up were available for 875 patients.
• Shorter follow-up occurred in 117 patients; 71 were lost to follow-up, 4 died of unrelated causes, and 42 had thyroidectomy for nodule growth or suspected thyroid cancer.

• In 69% of the patients, the nodule size remained stable during follow-up. In 18.5%, one or more nodules shrunk. Significant growth of the nodule occurred in 15.4% of patients.
• Overall, 174 of the 1567 original nodules increased in size, with an average change in the largest diameter of more than 4.9 mm.

• New nodules were found in 93 patients (9.4%).
• Multiple nodules, nodule volume, younger age, and male sex were associated with nodule growth, whereas age >60 years was associated with a lower growth rate.
• Repeat biopsy was performed in 365 cases, with confirmation of the original diagnosis in 99%.
Implications

• This study shows that benign thyroid nodules usually remain stable, as 85% of asymptomatic benign thyroid nodules did not change in size during 5 years of follow-up.

• Only 15% of nodules grew significantly during a 5-year follow-up and a new finding of thyroid cancer was rare.
• Less than 1% of patients had features of a thyroid cancer during careful follow-up.
• Of the 7 cancers identified, 2 were in nodules that were not present in the initial evaluation.
• The data show that benign nodules may grow, but only a small proportion are diagnosed as cancers during follow-up.

Thyroid cancer
More Thyroid Cancer?

- Brito JP et al.
  - The impact of subclinical disease and mechanism of detection on the rise in thyroid cancer incidence: a population-based study in Olmsted County, Minnesota during 1935 through 2012.
  - Thyroid. 2015 Sep;25(9):999-1007

- This study used information from the Rochester Epidemiology Project, a database of medical records of patients between 1935-2012 living in Olmsted County, Minnesota.
- During the study period from 1935-2012, there were 476 cases of thyroid cancer.
- Only 64% had come to attention because of symptoms in the neck or if a physician felt a lump in the neck.
- The remaining 32% were discovered because of other tests done, including radiologic imaging studies, in patients who had no local neck symptoms.

- The frequency of new thyroid cancer cases increased steadily from 1935 until 1970, when the number of new thyroid cancer patients in each year remained stable until 1990.
- However, the frequency of new cases again increased between 1990-2012.
- While the frequency of new thyroid cancers found because of symptoms or a neck lump remained stable throughout the nearly 80 years, the thyroid cancers identified by imaging studies were the ones which steadily increased.
• Furthermore, those cancers which were less aggressive tended to be the ones which were becoming more common.
• Overall, despite the increased rate of diagnosing thyroid cancer, only 2.3% of patients died from their thyroid cancer.
• This figure has been stable when comparing between those with the disease during the 1930s vs. those in the 2000s.

Implications of Study

• The reasons for why thyroid cancer has been increasing in recent decades are controversial.
• The investigators suggest that the increasing common use of radiologic imaging studies done for other reasons, which detected thyroid cancers that were more likely to be without symptoms in this study, is one of the major reasons.
• Since the rate of death from thyroid cancer has remained completely stable despite this, one can question whether finding occult thyroid cancers necessarily impacts a person’s health.
• Others have also suggested that thyroid autoimmunity, iodine nutrition, environmental exposures, genetic factors, variable access to medical care, treatment patterns, and obesity may also be important reasons that explain why thyroid cancer has become more common.
• More research is needed to better understand the complexities related to the rising trend of thyroid cancer observed in recent decades.
Sofia Vergara – Modern Family Actress

Film Critic – Roger Ebert
Papillary thyroid cancer

Types of Thyroid Cancer

• Papillary (80%)
• Follicular
• Medullary
• Anaplastic
Thyroid cancer stats

• The American Cancer Society’s estimates for thyroid cancer in the United States for 2014 are:
  – About 62,980 new cases of thyroid cancer (47,790 in women, and 15,190 in men)
  – About 1,890 deaths from thyroid cancer (1,060 women and 830 men)

Thyroid cancer treatment

• Surgery
  – Lobectomy
  – Total thyroidectomy
• Surgery risks:
  – Bleeding
  – Infection
  – Vocal cord injury
  – Parathyroid gland injury (control calcium levels)

• Radioactive iodine ablation (RAI)
  – Iodine 131
  – Capsule or liquid
  – Post-exposure precautions
• Radiation (External Beam)
• Chemotherapy
• Thyroid hormone suppression (levothyroxine treatment)
Thyroid Cancer

- 97.8% survive 5 years
- 2004-2010 data
  - The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute

Conclusions

- Hypothyroid symptoms common in women without hypothyroidism
- Subclinical hypothyroidism does not need treatment until TSH > 10
- Hyperthyroidism – Thyroid uptake and scan
- Thyroid cancer incidence rising

References

- American Thyroid Association
  - Thyroid.org
- Thyroid cancer survivors
  - Thyca.org
- American Cancer Society
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