Paed Endo for the General Paediatrician

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Thyroid Function Test Mini-Masterclass

An approach for General Paediatricians

Why?

- Commonest consult (after Diabetes)
- TFT accessible and commonly requested at primary care
- Often are straightforward to interpret and confirm clinical impression
- Confusion comes in when Discordant with clinical picture/ incongruent results
- We all recognise common patterns
- Some not so easy Unexpected abnormalities
- Can’t refer all…
  - Limited services
  - Cost to patient
- When to reassess and repeat VS when to treat and refer

Quick Physio 101

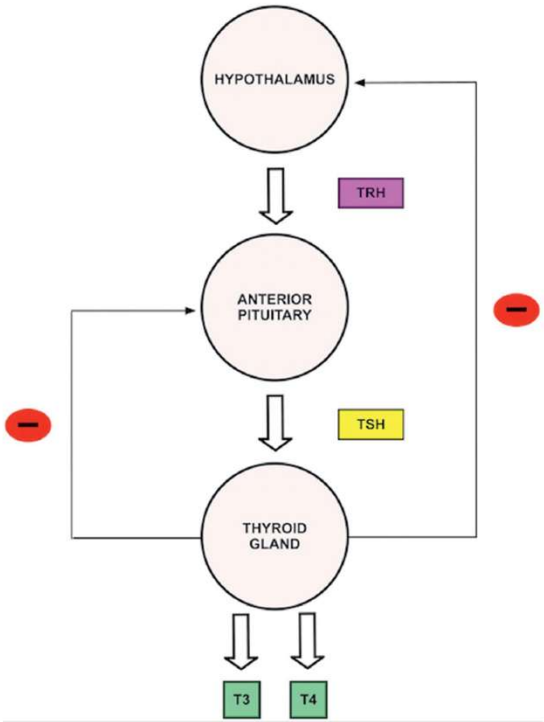


Figure 1 Hypothalamus, pituitary and thyroid gland negative feedback loop.

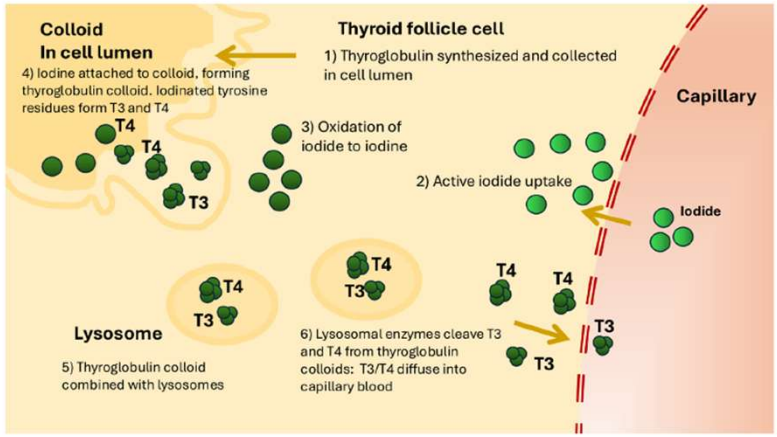


Figure 2 Thyroid hormone synthesis steps showing thyroglobulin synthesis, iodine uptake, iodination of thyroglobulin to storage and release in circulation. T3, tri-iodothyronine; T4, thyroxine.

Hardy AIA, *et al*. *Arch Dis Child Educ Pract Ed* 2024;**0**:1–6. doi:10.1136/archdischild-2024-327932

Hormone Transport and Activity

- Over 99% of T4 and T3 are bound to carrier proteins:
  - TBG (Thyroxine-Binding Globulin) is the main carrier for T4.
  - T3 binds to both TBG and albumin.
- Only free (unbound) T4 and T3 are biologically active.
- These free hormones bind to nuclear thyroid receptors in target cells to regulate gene expression.

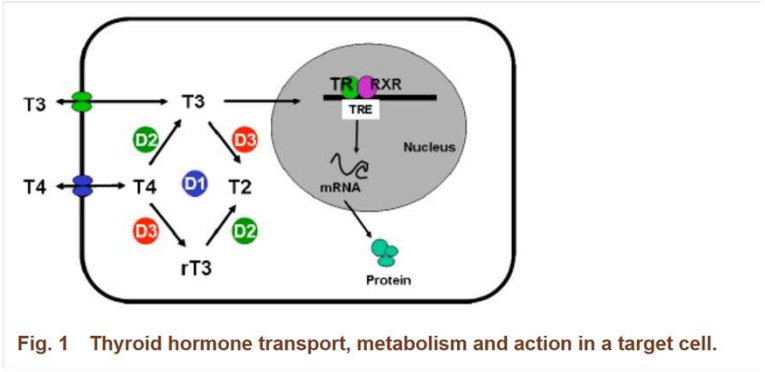


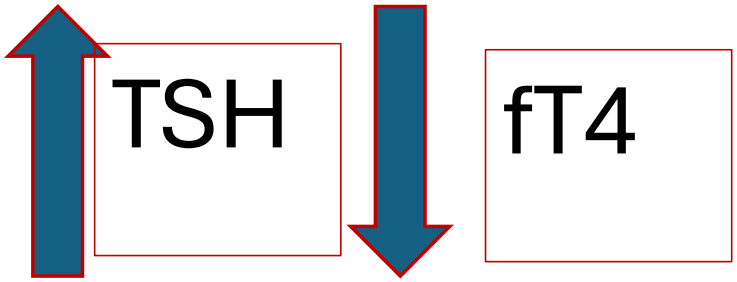
Fig. 1 Thyroid hormone transport, metabolism and action in a target cell.

TSH and Free T4 Relationship

- Each person has a genetically determined TSH–Free T4 set point
- The relationship is negatively log-linear:
  - A small drop in free T4 causes a large rise in TSH.
  - Example: A 50% drop in free T4 can cause a 100-fold increase in TSH.

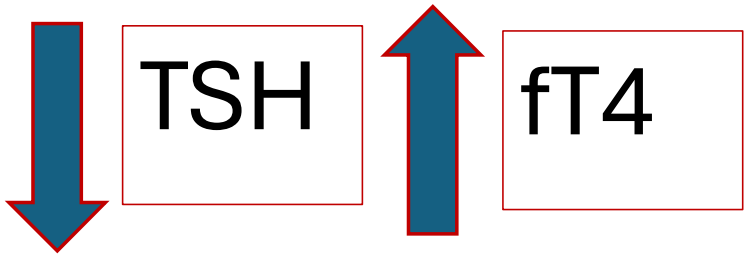
- population reference ranges for TH are relatively broad – in contrast to the narrow individual variations of serum TH seen in normal subjects

Hypothyroidism- Clinical



CLINICAL MANIFESTATIONS		
Infants (often asymptomatic)		**Children & Adolescents**
Early signs: • Prolonged jaundice • Pallor • Large anterior fontanelle • Hypotonia • Edema • Hypothermia	**Late signs:** • Poor feeding • Poor growth • Umbilical hernia • Developmental delay • Macroglossia • Lethargy	• ***Short stature*** • Delayed bone age • Puberty delay • Menstrual irregularity • Goiter • Fatigue • Constipation • Dry Skin

Hyperthyroidism - Clinical



Foetal Presentation:
- Transplacental transfer of maternal TSIs
- Intrauterine growth restriction
- foetal hydrops
- intrauterine death
- craniosynostosis

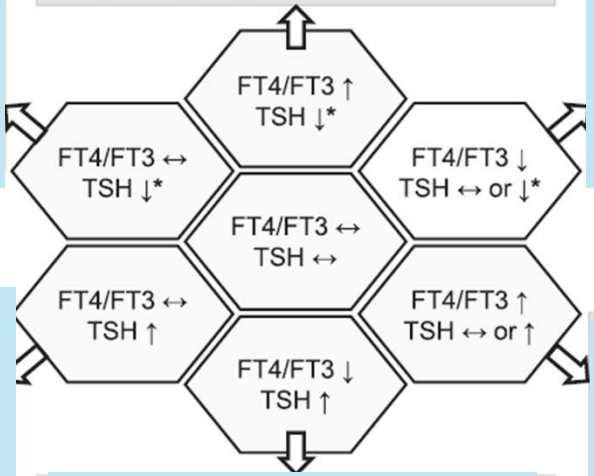
Postnatal (Children and Adolescents):
- Mimic anxiety, ADHD, exercise-induced asthma, or arrhythmias
- Restlessness
- warm moist skin
- fine tremor
- proximal muscle weakness
- Goitre (with bruit)
- Graves ophthalmopathy
- Accelerated growth & advanced bone age,
- Delayed puberty

But what happens when its not that straightforward...

Primary Hyperthyroidism

Subclinical Hyperthyroidism

Secondary/Central Hypothyroidism



Subclinical Hypothyroidism

Central Hyperthyroidism (TSHoma) Or TH resistance

Drugs
NTI
Assay
Familial protein abn

Primary Hypothyroidism

Fig. 2. Different patterns of thyroid function tests and their causes. **Key**: ATDs, antithyroid drugs; FDH, familial dysalbuminaemic hyperthyroxinaemia; FT4, free thyroxine; FT3, free triiodothyronine; NTI, non-thyroidal illness; TKIs, tyrosine kinase inhibitors; TSH, thyroid-stimulating hormone/thyrotropin [*signifies that TSH may be either fully suppressed (for example as seen in classical primary hyperthyroidism) or partially suppressed (i.e. measurable, but below the lower limit of normal)]. Reproduced with permission from: Koulouri O, Gurnell M. How to interpret thyroid function tests. *Clin Med* 2013; 13:282–6. Copyright © 2013 Royal College of Physicians.

Thoughtful Thyroid Testing

- Only test if concerned about HPT axis
  - Testing is often prompted by vague symptoms (e.g., fatigue, obesity) or parental concern.
  - Over-testing can lead to incidental findings, unnecessary anxiety, and costly referrals.
- Minor abnormalities are common and often clinically insignificant
- What do you expect to find? Hypo or Hyper?

When considering a TFT

- Reference range – not considering age, gender, ethnicity, iodine status, BMI
- Circadian rhythm
- Medications can affect
  - Compete with protein binding sites
  - Affect hepatic clearance
  - Interfere with assay
  - LT4 absorption in those on therapy
- Family history of thyroid issues/ carrier protein abnormalities

Which test?

- **TSH recommended as first-line screening tool**
- Additional tests
  - free T4 Use selectively and interpret with caution
  - Free T3 expensive and adds little diagnostic value
  - antibodies should be reserved for specific indications (2nd line)
  - Thyroid “panel” AVOID
- TSH should be measured in the **morning** and at the **same lab** for consistency.
- Total T4 and T3 are affected by changes in binding proteins (e.g., TBG).

TSH assay interference

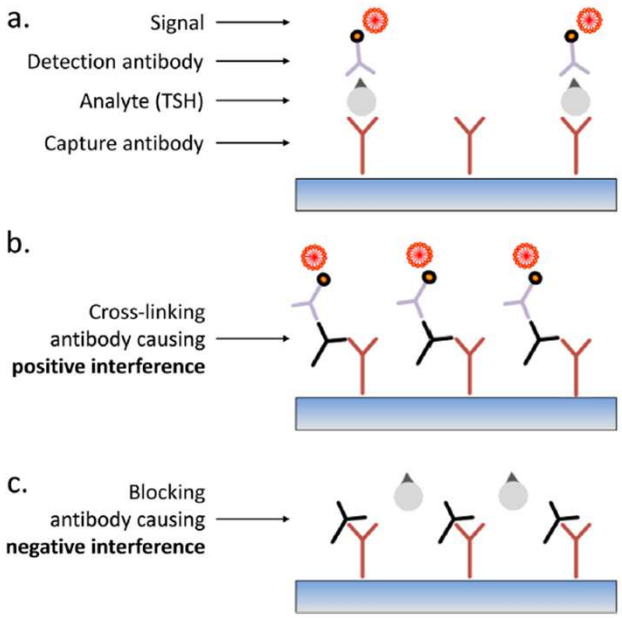


Fig. 4. Schematic representation of an immunoradiometric assay for measurement of serum TSH. **a.** TSH is bound by both capture (immobilised) and detection (labelled) antibodies. **b.** The presence of a human anti-animal (HAA) or heterophilic antibody that is capable of cross-linking the capture and detection antibodies even in the absence of analyte (TSH), results in positive assay interference. **c.** In contrast, an HAA or heterophilic antibody that binds either the capture or detection antibody to prevent crosslinking (even in the presence of TSH) results in negative assay interference.

Confirmatory fT4

- **Free T4** is the **biologically active** form of thyroxine and is responsible for regulating metabolism and feedback inhibition on TSH.
- It is useful in:
  - **Confirming overt hypothyroidism** (elevated TSH + low free T4).
  - **Identifying central hypothyroidism** (low free T4 + low or inappropriately normal TSH).
  - **Assessing hyperthyroidism** (low TSH + elevated free T4).
- **Free T4** has largely replaced **total T4** in clinical practice due to fewer issues with protein binding.

fT4 Assay interference

- the assay must detect very low concentrations of ‘free’ hormone relative to a vast excess of protein-bound analyte (>99.5%)
- Isolated low or high free T4 values with normal TSH are often **false positives**.
- the presence of factors in serum which affect the equilibrium between T4 and its binding proteins will confound hormone measurement.
  - Heparin
  - Antibodies
- Variant thyroid hormone binding proteins (e.g. albumin in familial dysalbuminaemic hyperthyroxinaemia (FDH) with altered affinity for T4

Challenges in Interpreting Thyroid Function Tests

- Overuse and misuse of testing
- Medication and supplements
- Circadian rhythm
- Non-thyroidal illness
- Assay limitations
- Individual setpoints

Recommendation: In minor derangements with no clear pattern:

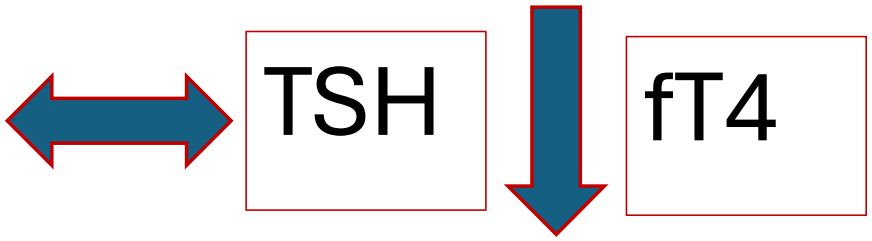
- Reappraise
- Repeat
- Review
- Refer

Puzzles!!!

Puzzle # 1

- An 18 month old girl
- admitted for severe wasting, moderate stunting,
- sparse hair and angular stomatitis
- admitted for nutritional rehabilitation.
- A Thyroid function test has been ordered by the intern with her other initial bloods
    - TSH 8.8 mU/L (RI 1.2–9.7),
    - fT4 10 pmol/L (RI 12.0–22.0).

- **Q. What does this TFT indicate?**



Non-thyroidal illness

Differential of Central/ secondary hypothyroidism

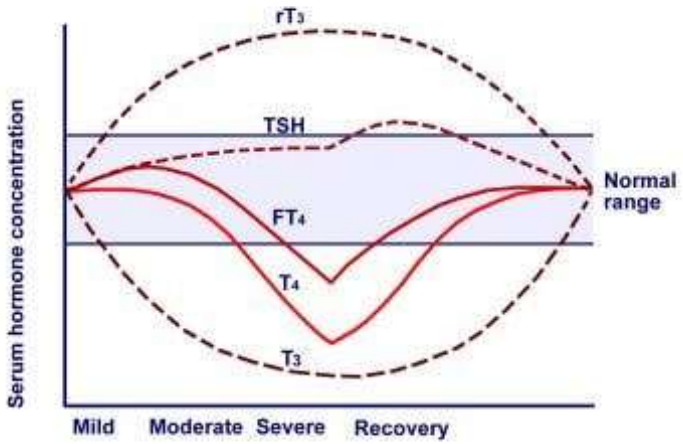
observed in subjects with

- poor nutrition/starvation,
- sepsis,
- burns,
- malignancy,
- post-surgery, and with
- chronic liver and renal disease
- acute, major psychiatric illness,

REAPPRAISE
REPEAT
REVIEW
REFER

Non-Thyroidal Illness (Sick Euthyroid Syndrome)

- absence of an intrinsic abnormality of HPT function
- considered a secondary adaptive change. beneficial vs maladaptive response debated, but
- No current evidence for T4 therapy in most
- Changes in TH (especially T3) and TSH may be seen as early as 24 h after the onset of NTI
- Many patterns:
  - raised T4 with non-suppressed TSH observed, but usually resolves spontaneously within a short time frame (<2weeks); in others,
  - TSH elevated or suppressed but normal T4 or T3

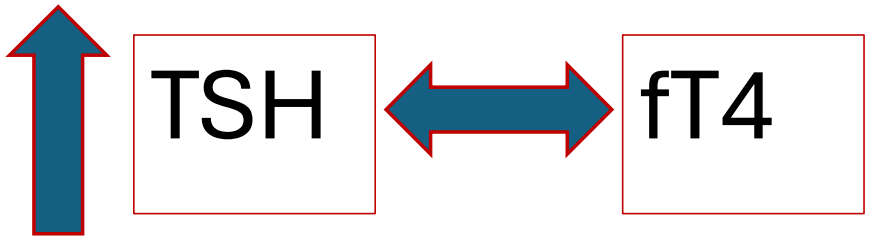


Puzzle # 2

- The parents of a 9-year-old boy are concerned about his behaviour.
- He has no goitre, and there are no clinical features to suggest hypothyroidism or hyperthyroidism.
- His weight has been increasing since age 5 years and is now on the 99.6th centile. His height remains on the 50th centile and he is prepubertal.

- TSH 7 mU/L (RI 0.6–4.8),
- fT4 17.8 pmol/L (RI 12.5–21.5)
- anti-TPO antibodies negative.

- **Does a marginally high TSH with normal fT4 suggest hypothyroidism?**
- **Is a high TSH the cause or effect of excess weight gain?**

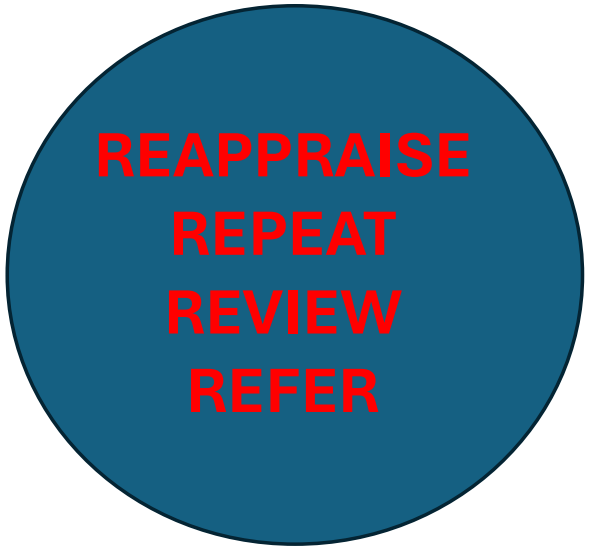


- subclinical hypothyroidism, compensated hypothyroidism and isolated hyperthyrotropinaemia
- Prevalence <3%
- In the absence of typical features of hypothyroidism, goitre and markers of autoimmunity such as thyroid peroxidase antibodies,
- current evidence suggests that problems with cognitive function, linear growth or bone maturation are unlikely.
- In this case, behaviour changes are also unlikely with minor thyroid dysfunction.
- Mildly elevated TSH levels may spontaneously normalise and no treatment is required in up to 75% of CYP.
- Reassure
- rarely it may evolve to overt hypothyroidism in association with
  - thyroid peroxidase antibodies and
  - chromosomal defects
  - autoimmune conditions (e.g., coeliac disease, type 1 diabetes, Addison's disease)
- A repeat TFT in 3 months in asymptomatic patients older than 3 years with TSH<10 mU/L.

Q. Is a high TSH the cause or effect of excess weight gain?

- Obesity is positively associated with marginally high TSH levels, which normalise when weight is lost.
  - no causal relationship has been found
  - Leptin-mediated production of TRH and TSH
  - reduced peripheral deiodinase activity have been proposed but not proven

Subclinical Hypothyroidism



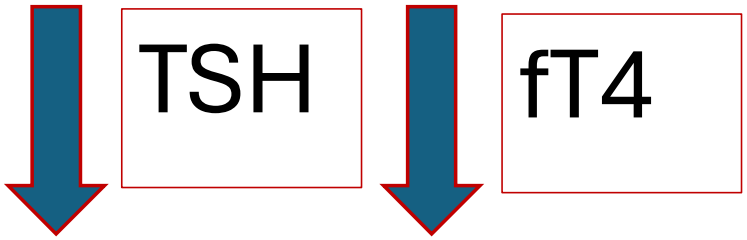
- **Elevated TSH (>10 mIU/mL)**:
  - Suggests overt hypothyroidism
  - Confirm with free T4, consider thyroid antibodies
  - Treatment often needed (levothyroxine)
  - Refer
- **Mildly elevated TSH (4.5–10 mIU/mL)**:
  - avoid diagnosing subclinical hypothyroidism based on a single test.
  - Possible transient elevation or subclinical hypothyroidism
  - Causes: Hashimoto's, Obesity, Down/Turner syndrome, medications
  - Recheck in 6–8 weeks,
  - consider antibodies if persistent
  - Treat if symptomatic, goitre present, or TSH >10

Puzzle # 3

- A 1-month-old female
- reviewed for prolonged jaundice.
- She is breast-fed and is thriving well.

- TSH 1.56 mU/L (RI 1.0–6.8)
- fT4 5.5 pmol/L (RI 14.0–22.0)

- **Q. What is the most likely diagnosis? How will you manage this patient?**



- The fT4 is low in the absence of a TSH response
- pituitary gland is failing to respond to lack of feedback.
- central hypothyroidism
- Refer to paediatric endocrinology team
  - hypothalamic/pituitary hormone deficiencies
  - Treatment
  - Refer for continues care
- Brain MRI is recommended to identify abnormalities of the pituitary gland and optic nerves.
- central adrenal insufficiency due to abnormalities in the hypothalamic-pituitary-adrenal axis:

glucocorticoid replacement must precede LT4 replacement to avoid the precipitation of an adrenal crisis.

Puzzle # 4

- A 5-year-old boy was diagnosed to have congenital hypothyroidism with no gland on thyroid scanning.
- His levothyroxine dose had been increased to 100 mcg/day.

- (TSH) 20 mU/L (RI 0.7–5.9).
- (fT4) 18.2 pmol/L ((RI) 12.3–22.8)

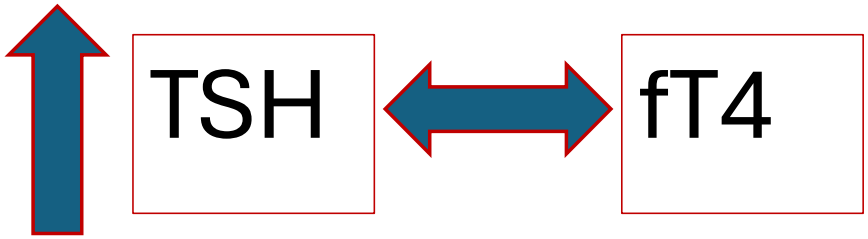
What is the next most important step?

a. Increase the medication dosage to levothyroxine 125mcg/day.

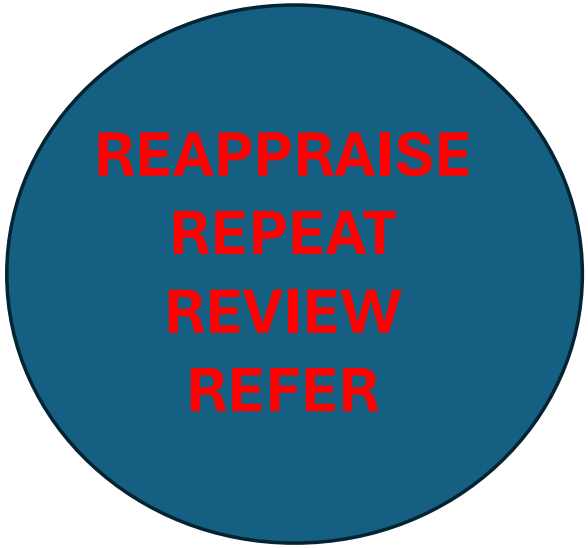
b. Explore dose, when and how levothyroxine taken.

c. Refer to a paediatric endocrinologist.

d. Switch daily to weekly levothyroxine under supervision.



- Answer: b
- Non-adherence is likely; if levothyroxine (LT4) is taken a few days before clinic, free thyroxine (fT4) may be normal but thyroid stimulating hormone (TSH) remains high.
- A referral to a paediatric endocrinologist is not immediately required but may be considered if non-adherence continues.
- Ensure TH taken correctly
  - same time daily
  - Empty stomach
  - No Fibre, espresso
  - Soy, calcium, iron, AlOH at time of dose
  - PPI's / achlorhydria
  - Coeliac disease, lactose intolerance



Primary Hypothyroidism

- Diagnosis: High TSH low T4
- Causes: congenital or acquired
- Can test Anti TPO if suspect acquired
- Treatment:
  - <3 mo - 10-15mcg/kg
  - 3-6 mo – 8-10mcg
  - 6mo-12yr – 120mcg/m^2
  - Adult 50-200mcg dly (titrate)
- Monitoring: keep TSH <2mIU with normal fT4
- Issues: non-adherence vs TH malabsorption

Drug interference

- Biotin Supplementation
  - High-dose biotin (100–300 mg/day) interferes with biotin-based immunoassays, causing falsely low TSH and falsely high free T4/T3.
  - This can mimic hyperthyroidism and lead to misdiagnosis (e.g., factitious Graves' disease).
  - Discontinue biotin at least 48 hours before testing.
- Several medications alter TSH or thyroid hormone levels:
  - Antiepileptics (valproate, carbamazepine, phenytoin): increase hormone clearance → subclinical hypothyroidism.
  - Amiodarone, lithium, TKIs: interfere with hormone production/secretion.
  - Glucocorticoids, beta-blockers: affect peripheral metabolism.
  - Dopamine, octreotide, ipilimumab: suppress TSH secretion.

Medication/Class	Effect on TSH	Effect on T3	Effect on T4	Mechanism of Action
Biotin (high dose)	↓ (falsely low)	↑ (falsely high)	↑ (falsely high)	Interferes with immunoassays; mimics hyperthyroidism
Valproate	↑	↓	↓	Reduces synthesis and metabolism of thyroid hormones
Carbamazepine	↑	↓	↓	Induces hepatic enzymes; increases hormone clearance
Phenytoin	↓	↓	↓	Displaces T4 from binding proteins
Amiodarone	↑ or ↓	↑ or ↓	↑ or ↓	High iodine content; affects hormone synthesis
Lithium	↑	↓	↓	Inhibits thyroid hormone release
Glucocorticoids	↓	↓	↓	Suppresses TSH secretion and peripheral conversion
Dopamine	↓	↓	↓	Inhibits TSH secretion at pituitary level
Beta-blockers (e.g., propranolol)	No significant effect	↓	No significant effect	Inhibits peripheral conversion of T4 to T3
Tyrosine kinase inhibitors (TKIs)	↑	↓	↓	Interferes with hormone synthesis and metabolism
Octreotide	↓	↓	↓	Suppresses pituitary TSH secretion
Ipilimumab	↓ or ↑	↓ or ↑	↓ or ↑	Can induce thyroiditis or hypophysitis

Puzzle # 5

- A 4-year-old girl with Down's syndrome has the following TFT on her annual screen:

  - TSH 8.5 mU/L (RI 0.7–5.9).
  - fT4 17.8 pmol/L (RI 12.3–22.8),

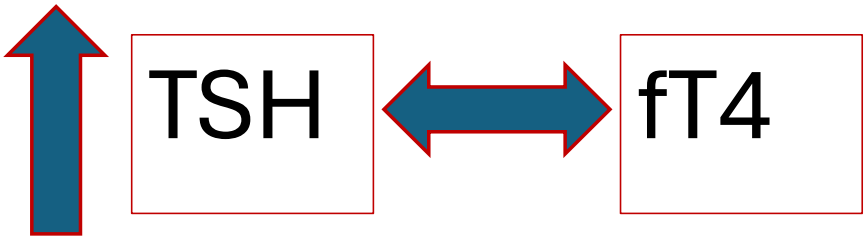
- **What is the most important next step?**

  a. Commence levothyroxine as the TSH is high.

  b. Accept these results as normal values.

  c. Repeat the TFT the next day.

  d. Repeat the TFT in 3 months



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- Answer d
- Abnormal TFT and mildly raised TSH common in T21
- Assess symptoms, signs, linear growth, development
- Anti-TPO antibodies may indicate autoimmune hypothyroidism.
- fT4 is in the upper part of the normal interval - LT4 replacement not necessary.
- raised anti-TPO antibodies may lower the threshold at which to treat with LT4.
- immediate TFT not useful as
  - changes usually take several weeks (thyroxine has a half-life of 6 days).
- A repeat TFT in 3 months
  - may show normalisation of TSH.
  - may climb upward and fT4 may reduce – Replace LT4

Trisomy 21

- Thyroid abnormalities common:
  - nonautoimmune subclinical hypothyroidism most common
  - elevated TSH and normal FT4(Prevalence 25-60%)
  - Postulated that it is a reframing of HPT axis activity resulting in an asymptomatic upward shift of median TSH values
- Recommended screening
  - 3 monthly in 1st year,
  - 6 monthly until age 3 and
  - annually after
- Lack of syndrome specific reference ranges results in overestimation of occurrence of hypothyroidism in T21
- Meyerovich et al. reported a normal TSH reference range for healthy patients with DS to be 1.5–8.9 μIU/mL.

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Clinical Research Article

Thyroid Function Tests in Children and Adolescents With Trisomy 21: Definition of Syndrome-Specific Reference Ranges

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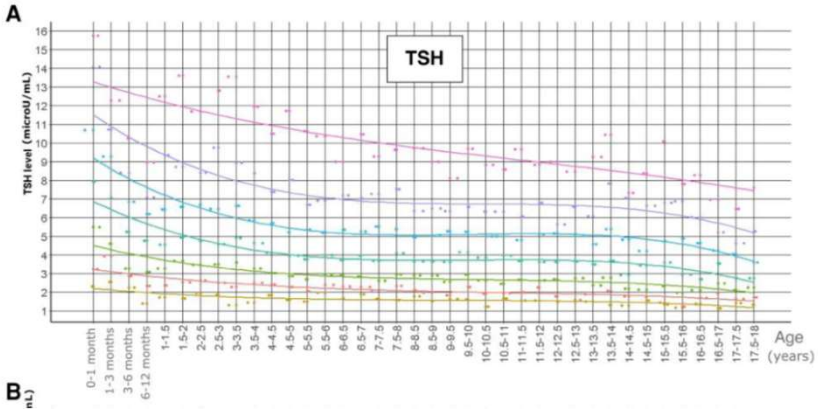


- 548 children with DS vs healthy controls,
  - same centre, same lab,
- Significant intraindividual variability of TSH values over time
- Downward median trend over time (same as healthy controls)
- A single abnormal TSH value- poor statistical accuracy in predicting future onset of overt hypothyroidism
- Identified 75th centile of syndrome specific TSH normogram to predict increased risk for developing overt hypothyroidism (neg predictive value 90-94%)
- a longitudinal integrated assessment of the course of TSH levels over time may result in a more accurate prediction of the evolution into hypothyroidism
- https://b4-uni25-5627493duksfy852qr80fewbsn3986g43jkgkzie8.shinyapps.io/Percentile-Thyroid-ChildrenTrisomy21/
- Hopefully will translate into amended guidelines and an easy to use tool/table

Comparison of TSH values in T21 vs controls

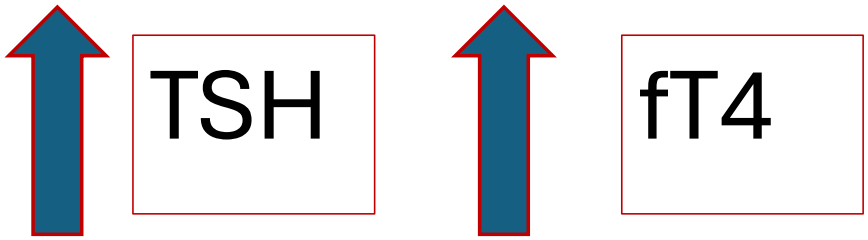
Table 3. Comparison of TSH values among patients with Down syndrome vs healthy controls

	Healthy controls	DS patients				Healthy controls	DS patients	
Age class (years)	Threshold: 97.5th centile (microU/mL)	*N* of TSH over the threshold	*N* of TSH measures	Proportion of TSH over the threshold (%)	*P* value[a]	TSH 50th centile (microU/mL)	TSH 50th centile (microU/mL)	*P* value[b]
0-1	6.75	69	233	29.6	<.0001	3.24	5.30	<.0001
1-6	6.07	460	1815	25.3	<.0001	2.7	4.38	<.0001
6-11	5.34	254	1111	22.9	<.0001	2.41	3.87	<.0001
11-18	5.09	123	589	20.9	<.0001	2.25	3.41	<.0001

Comparison between the TSH levels recorded in our study population with those reported and published for non-trisomic patients.
Over the age classes assessed, from 20.9% (11-18 years) to 29.6% (0-1 year) of all TSH values in DS patients were greater than the 97.5th centile for non-syndromic patients, with this distribution being statistically remarkably significant ($P < .0001$ at any timepoint).
Accordingly, median TSH levels recorded for every age class of patients with DS were statistically greater than the median value reported for healthy controls ($P < .0001$ at any timepoint).
Abbreviations: DS, Down syndrome; TSH, thyrotropin (thyroid-stimulating hormone).
[a]One-sample test on proportion: DS patients vs reference threshold in healthy controls.
[b]One-sample test on median: DS patients vs reference median in healthy controls.

Puzzle # 6

- 4 year old boy with global developmental delay, impaired hearing and speech delay. He is noted to be underweight, tachycardic and sweaty at his clinic visit.
    - TSH 10 (1.2-6.5)
    - fT4 35 (12-18.5)
- What clinical pattern is this
- What biochemical pattern?
- Diagnosis?



- Hyperthyroidism
- Central vs Resistance
- TSHoma (1/ 1 000 000 population) vs Resistance to thyroid hormone 1 in 50 000 births)
- Clinically thyrotoxic (arrhythmias) and goitre
- Thyroid hormone receptor B mutations

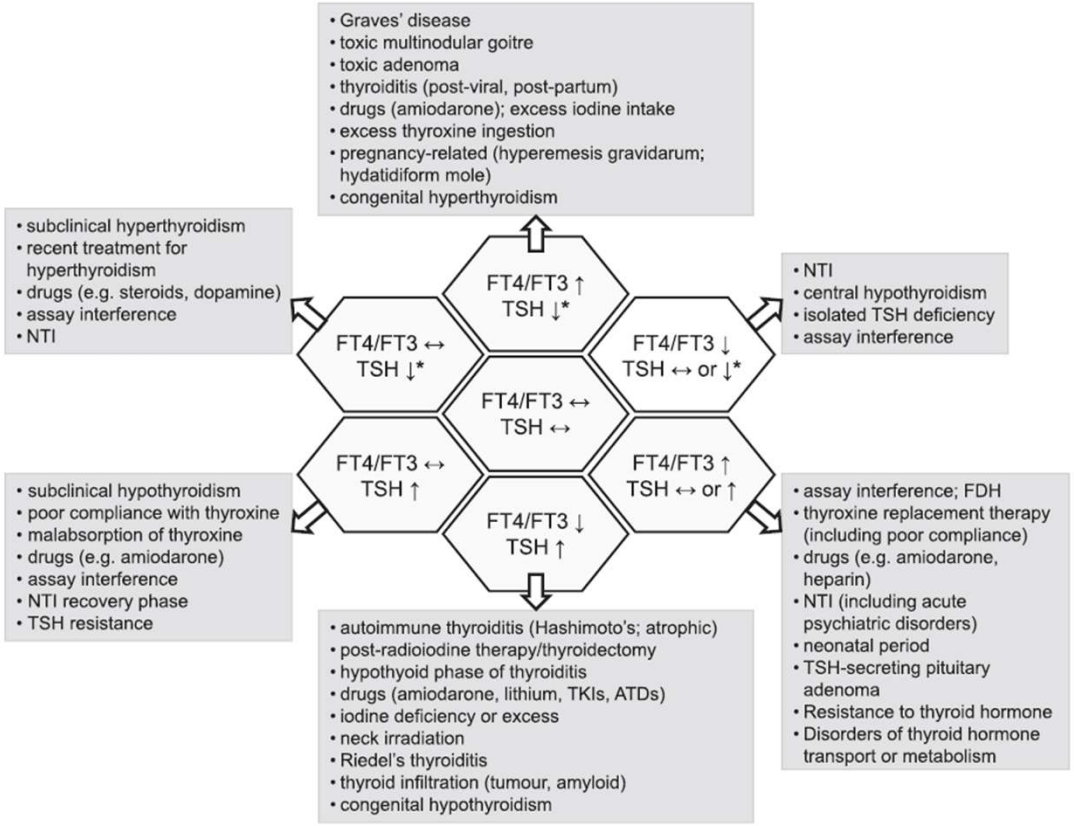
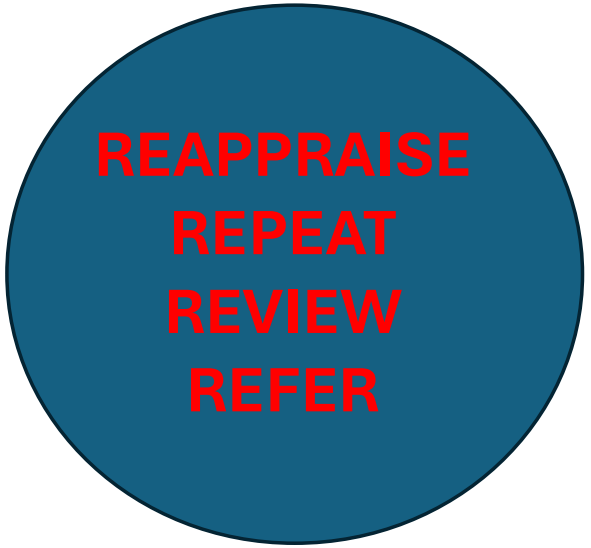


Fig. 2. Different patterns of thyroid function tests and their causes. **Key**: ATDs, antithyroid drugs; FDH, familial dysalbuminaemic hyperthyroxinaemia; FT4, free thyroxine; FT3, free triiodothyronine; NTI, non-thyroidal illness; TKIs, tyrosine kinase inhibitors; TSH, thyroid-stimulating hormone/thyrotropin [*signifies that TSH may be either fully suppressed (for example as seen in classical primary hyperthyroidism) or partially suppressed (i.e. measurable, but below the lower limit of normal)]. Reproduced with permission from: Koulouri O, Gurnell M. How to interpret thyroid function tests. *Clin Med* 2013; 13:282–6.

Questions?

Take home message

- Do I need to test?
- Is now a good time to test?
- What pattern am I expecting to find
- Have I explored:
  - History
  - Drugs
  - Current illness
  - Potential assay concerns
- And when the result is
  - discordant or
  - incongruent



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Low TSH in Pediatrics: Causes & Interpretation

- **TSH 0.1–0.4 mIU/mL (Mild Suppression)**
- **Possible Causes**:
  - Subclinical hyperthyroidism (normal free T4 and T3).
  - Transient suppression.
  - Early autoimmune hyperthyroidism.
  - Autonomously functioning thyroid nodule.
  - Multinodular goitre.
  - Thyroiditis.
  - Exogenous thyroid hormone ingestion.
- **Interpretation**:
  - Repeat TSH in 1–2 weeks with free T4 and total T3.
  - Consider thyroid antibodies (TSI, TRAb) if autoimmune disease suspected.
  - Monitor for symptoms: weight loss, tachycardia, irritability, tremors.
- **Management**:
  - Observe every 3–6 months if asymptomatic.
  - Refer if persistent or symptomatic.

Subclinical hyperthyroidism Normal TSH High FT4

- Uncommon <1% (NHANES and TEARS epidemiological cohorts
  - Progression to overt hyperthyroidism in <1% and over 5-7 years
  - Spontaneous normalising in 37.6%
- Causes:
  - Ingestion of thyroid hormone
  - Autoimmune hyperthyroidism
  - Autonomously function thyroid nodule
  - Thyroiditis
- Decision to treat not always clear
- Observe, Repeat, review, refer if symptomatic or persistent /worsening