Endocrine Update

2022

Not Diabetes

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Learning objectives

1. Treating subclinical hypothyroidism (SCH) not associated with benefit for most
2. Hyperaldosteronism is common but not commonly diagnosed
3. Male hypogonadism is associated with sexual dysfunction, which is improved with replacement therapy

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Subclinical Hypothyroidism (SCH)

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Subclinical Hypothyroidism (SCH)

Definition

TSH levels between 4 and 10 mIU/L & normal T4 (thyroxine) levels

Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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Subclinical Hypothyroidism (SCH)

Background

- There is biological variation in TSH levels.
  - Levels may rise in response to stress and transient disease.
  - TSH levels may increase with age, and a slight increase of TSH may be normal for older people.
  - One abnormal TSH level should be followed by a repeat blood test to confirm the diagnosis.
- About 62% of TSH levels between 4 and 10 mIU/L normalize without intervention within five years

Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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Subclinical Hypothyroidism (SCH)

How common is SCH?

Really common

- It affects 4-20% of the adult population.
- It is more common in women, in older people, and those of white ethnicity.

Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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Subclinical Hypothyroidism (SCH)

What are the symptoms?

- Around 1 in 3 patients with SCH have no symptoms at all.
- The type of symptoms people link to SCH include those of overt hypothyroidism:
  - Fatigue
  - Muscle cramps/weakness
  - Cold sensitivity
  - Dry skin
  - Voice changes
  - Constipation
  - Depression/memory changes

- Many of these symptoms are not specific to hypothyroidism.
- Around 20-25% of people with normal TSH levels report 1 – 2 of these symptoms.
- The relation between symptoms and biochemical TSH levels remains unclear.

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Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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Subclinical Hypothyroidism (SCH)

What is the long-term outlook?

- The risk of progression to overt hypothyroidism is 2% to 5% a year.
- Presence of antibodies to thyroid peroxidase and higher TSH levels increase this risk.
- Observational data suggest that SCH is associated with an increased risk of coronary heart disease, heart failure, and cardiovascular mortality, particularly in those with TSH levels >10 mIU/L.
- Such associations are not found for most adults with TSH levels of 5-10 mIU/L.

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Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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USPSTF

Population	Recommendation	Grade
Nonpregnant, asymptomatic adults	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.	I

Literature scans conducted in November 2021 in the MEDLINE and PubMed databases and the Cochrane Library showed a lack of new evidence to support an updated systematic review on the topic at this time.

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Thyroid Dysfunction: Screening | USPSTF (Updated March 2015)

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Top 10 Prescription Medications in the U.S.

1. Atorvastatin
2. Lisinopril
3. Albuterol
4. Levothyroxine
5. Amlodipine
6. Gabapentin
7. Omeprazole
8. Metformin
9. Losartan
10. Hydrocodone

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www.goodrx.com (accessed Dec 12, 2021)

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SCH Guidance

Table 1 | Current guidance on thyroid hormone treatment for subclinical hypothyroidism

Organisation	Recommendation
National Institute for Health and Care Excellence (NICE) CKS guidelines, 2018[31]	• TSH >10 mIU/L: - Age <70 years, treat - Age ≥70 years, watch and wait • TSH 4-10 mIU/L: - Age <65 years with symptoms, consider trial - Age ≥65 years, watch and wait
European Thyroid Association (ETA), 2013[7]	• Age <70 years: - TSH >10 mIU/L, treat - TSH <10 mIU/L with symptoms, start trial - TSH <10 mIU/L without symptoms, observe • Age >70 years: - TSH <10 mIU/L, observe - TSH >10 mIU/L, consider treatment if clear symptoms or high cardiovascular risk
American Thyroid Association (ATA), 2012[8]	• TSH >10 mIU/L, consider treatment • TSH <10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases
UpToDate, 2018[32]	• TSH <7 mIU/L: - Age >65/70 years, observe - Age <65/70 years, treat if symptoms, observe without symptoms • TSH 7-10 mIU/L: - Age >65/70 years, treat if symptoms, observe without symptoms - Age <65 years, treat • TSH >10 mIU/L: treat

NICE Guidelines

European Thyroid Association

American Thyroid Association

UpToDate

In general, these all suggest starting replacement with SCH + symptoms

Watchful waiting with SCH + NO symptoms

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Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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#1: Reported # symptoms with SCH = Euthyroid

Purpose: To define the spectrum of symptoms in adults with SCH

Patients: 8903 adults, $\bar{x}$ age 50 who 1) Consulted physicians for mild to moderate sx OR 2) Were diagnosed after routine screening

Design: Blood samples & questionnaire* | 376 with SCH compared to 7619 euthyroid controls

Primary outcome: Difference in reported symptoms between those with SCH and those euthyroid

Results:
- Reported # of symptoms in each group was 2
- TSH had no impact on symptoms score
- Co-morbidity had the highest impact on symptom reporting (e.g., higher BMI assoc with dyspnea)

*13 hypothyroidism associated sxs: tiredness, dry skin, mood lability, constipation, palpitations, restlessness, shortness of breath, wheezing, globus sensation, difficulty swallowing, hair loss, dizziness/vertigo, and anterior neck pain

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Does Subclinical Hypothyroidism Add Any Symptoms? Evidence from a Danish Population-Based Study. Am J Med. 2021 Sep;134(9):1115-1126.e3.

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#1: Reported # symptoms with SCH = Euthyroid

Conclusion: People with SCH do not experience thyroid disease-related symptoms more often than euthyroid subjects.

In subclinical hypothyroidism, clinicians should focus on concomitant diseases rather than expecting symptomatic relief following levothyroxine substitution.

*13 hypothyroidism associated sxs: tiredness, dry skin, mood lability, constipation, palpitations, restlessness, shortness of breath, wheezing, globus sensation, difficulty swallowing, hair loss, dizziness/vertigo, and anterior neck pain

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Does Subclinical Hypothyroidism Add Any Symptoms? Evidence from a Danish Population-Based Study. Am J Med. 2021 Sep;134(9):1115-1125.e1.

Cohort study

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#2: SCH not assoc with cognitive function

Purpose: To assess associations of baseline thyroid dysfunction with cognitive function and dementia.

Patients: Analysis of 23 cohorts including 74,565 participants with cognitive function and/or dementia measurements and TSH measurement; 57.5% ♀; Median age: 57 – 93; Median follow-up: 1.7 – 15.3 years

Design: Based on TSH levels: 5 classifications of thyroid function: 1) Overt hyperthyroidism 2) Subclinical hyperthyroidism 3) Euthyroid 4) Subclinical hypothyroidism 5) Overt hypothyroidism

Primary outcome: Global cognitive function (MMSE)
Secondary outcomes: Executive function, Memory/Dementia
Results:

- 89.3% | Euthyroid
- 00.8% | Overt hyperthyroidism
- 03.4% | Subclinical hyperthyroidism
- 05.6% | Subclinical hypothyroidism
- 00.9% | Overt hyperthyroidism

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Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. JAMA Intern Med. 2021 Nov 1;181(11):1440-1450.

Cohort study

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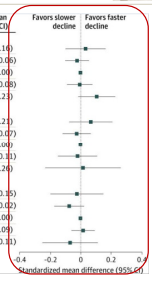
#2: SCH not assoc with cognitive function

Cognitive function by thyroid status	No. of studies	No. of participants	I^2, %	Standardized mean difference (95% CI)
Global cognition				
Overt hyperthyroidism	13	240	5.02	0.03 (-0.10 to 0.16)
Subclinical hyperthyroidism	13	894	24.50	-0.02 (-0.10 to 0.06)
Euthyroidism	13	18752	Reference	0.00 (-0.00 to 0.00)
Subclinical hypothyroidism	13	1651	47.81	-0.00 (-0.09 to 0.08)
Overt hypothyroidism	13	242	0	0.11 (-0.01 to 0.23)
Executive function				
Overt hyperthyroidism	6	177	0	0.07 (-0.07 to 0.21)
Subclinical hyperthyroidism	7	416	0	-0.02 (-0.12 to 0.07)
Euthyroidism	7	12 368	Reference	0.00 (-0.00 to 0.00)
Subclinical hypothyroidism	7	1156	69.48	-0.02 (-0.15 to 0.11)
Overt hyperthyroidism	7	137	0	0.02 (-0.23 to 0.26)
Memory				
Overt hyperthyroidism	5	122	0	-0.02 (-0.20 to 0.15)
Subclinical hyperthyroidism	6	372	0	-0.07 (-0.17 to 0.02)
Euthyroidism	6	9397	Reference	0.00 (-0.00 to 0.00)
Subclinical hypothyroidism	6	643	0	0.02 (-0.06 to 0.09)
Overt hyperthyroidism	6	109	0	-0.07 (-0.25 to 0.11)



Thyroid dysfunction not associated with:

- Global cognitive function
- Executive function
- Memory or dementia risk

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Association of Thyroid Dysfunction With Cognitive Function: An Individual Participant Data Analysis. JAMA Intern Med. 2021 Nov 1;181(11):1440-1450.

Cohort study

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#3: Older patients with SCH, T4 provides no benefit

Purpose: To determine whether levothyroxine was associated with clinical benefits in older persons with SCH.

Patients: DBRCT 737 adults x̄ age 74.4 (53.7% ♀) with TSH 6.40 at baseline and normal T4. Levothyroxine vs placebo (both dose adjusted) | 1 year follow up

Primary outcomes: Hypothyroid symptoms score (range 0 -100) & Thyroid related QOL & Tiredness score (range 0 - 100) Minimum clinically important difference 9 points
Secondary outcomes: Executive function, Memory, Dementia

Results:

- TSH after 1 year:
  - 5.48 in placebo group
  - 3.63 in l-thyroxine group (median dose 50 mcg/d)

Δ TSH = 1.85

- Δ Hypothyroid symptoms score = 0
- Δ Tiredness score = 0.4
- No beneficial effect of executive fnt, memory, dementia

Conclusion: Levothyroxine provided no apparent benefits in older persons with subclinical hypothyroidism.

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Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med 2017; 376:2534-2544

RCT

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#4: Patients > 80 with SCH, T4 provides no benefit

Purpose: Measure the effect of levothyroxine rx for SCH on thyroid-related quality of life in adults ≥ 80

Patients: 251 adults, x̄ age 85 (45% ♀) | x̄ TSH 6.40 at baseline with normal T4

- 112 participants received l-thyroxine & 139 received placebo
- Levothyroxine vs placebo (both dose adjusted) | 1 year follow up

Primary outcomes: Hypothyroid symptoms score (range 0 -100) & Thyroid related QOL & Tiredness score (range 0 - 100) Minimum clinically important difference 9 points
Secondary outcomes: Executive function, Memory, Dementia

Between group Δ's | all nonsignificant

Results:

- TSH after 1 year:
  - 5.49 placebo group
  - 3.69 l-thyroxine group (median dose 50 mcg/d)

- Hypothyroid symptoms score = 1.3
- Δ Tiredness score = -0.1
- ADL score = 0.09
- Cognitive fnt = 1.24

Conclusion: These findings do not support routine use of levothyroxine for treatment of subclinical hypothyroidism in adults aged 80 years and older.

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Association Between Levothyroxine Treatment and Thyroid-Related Symptoms Among Adults Aged 80 Years and Older With Subclinical Hypothyroidism. JAMA. 2019 Nov 26;322(20):1977-1986.

RCT

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#5: Patients with SCH, T4 provides no benefit

Purpose: To conduct a meta-analysis of the association of thyroid hormone therapy with quality of life and thyroid-related symptoms in adults with subclinical hypothyroidism.

Patients: 21 publications (2192 randomized adults) | Rx duration 3 – 18 months

Primary outcomes: General QOL and thyroid-related symptoms

Results:

- TSH after Rx:
  - 0.5 – 3.7 mIU/L l-thyroxine group
  - 4.6 – 14.7 mIU/L in the placebo group

SMD Δ Hypothyroid symptoms score = 0.01
SMD Δ QOL score = -0.11

Conclusion: Among nonpregnant adults with subclinical hypothyroidism, the use of thyroid hormone therapy was not associated with improvements in general quality of life or thyroid-related symptoms.

SMD = Standard Mean Difference

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Association of Thyroid Hormone Therapy With Quality of Life and Thyroid-Related Symptoms in Patients With Subclinical Hypothyroidism. A Systematic Review and Meta-analysis. JAMA. 2019;320(13):1349-1359.

Meta-analysis

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#6: Depressive Sx not affected by l-thyroxine Rx

Purpose: To assess the effect of levothyroxine on the development of depressive symptoms in older adults with SCH

Patients: 472 adults , $\bar{x}$ age 74.5 (56% ♀) | , $\bar{x}$ baseline TSH 6.57 | 211 randomized to l-thyroxine and 216 to placebo | Rx duration 10 months

Primary outcomes: Scores on the Geriatric Depression Scale (GDS-15)
Minimally clinically important difference = 2

Results:
- TSH after Rx:
  - 3.83 mIU/L l-thyroxine group
  - 5.91 mIU/L in the placebo group

Baseline GDS-15 scores
- 1.26 l-thyroxine group
- 0.96 placebo group

12-month GDS-15 scores
- 1.39 l-thyroxine group
- 1.07 placebo group

No difference when adjusted by:
- Age
- GDS-15 score of ≥ 2
- TSH levels

Conclusion: These results do not provide evidence in favor of levothyroxine therapy in older persons with subclinical hypothyroidism to reduce the risk of developing depressive symptoms.

RCT

Levothyroxine Therapy on the Development of Depressive Symptoms in Older Adults With Subclinical Hypothyroidism: An Ancillary Study of a Randomized Clinical Trial. JAMA Netw Open. 2021 Feb 1;4(2):e2036545

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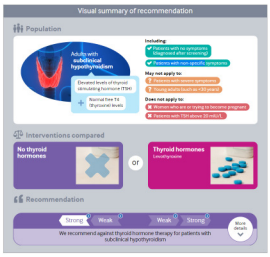
#7: BMJ Guideline



For adults with SCH, thyroid hormones consistently demonstrate no clinically relevant benefits for quality of life or thyroid related symptoms, including depressive symptoms, fatigue, and body mass index (moderate to high quality evidence).

Thyroid hormones may have little or no effect on cardiovascular events or mortality (low quality evidence), but harms were measured in only one trial with few events at two years' follow-up.

The panel concluded that almost all adults with SCH would not benefit from treatment with thyroid hormones.**

** It does not apply to women who are trying to become pregnant or patients with TSH >20 mIU/L. It may not apply to patients with severe symptoms or young adults (such as those ≤30 years old).

Bekkering Et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ 2019;365:l2006

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Aldosterone

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Primary Aldosteronism

Primary aldosteronism, (AKA Conn syndrome), = pathological conditions associated with an aldosterone secretion …. that is relatively autonomous from renin--angiotensin system activity

Primary aldosteronism is widely recognized as the most common form of secondary hypertension

Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. Journal of Hypertension: October 2018 - Volume 36 - Issue 10 - p 1914–1928

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Renin–angiotensin–aldosterone system | **Normal Physiology**

Low renal perfusion
↓
Renin release from kidneys
↓
Angiotensin I
↓
Angiotensin II
↓
Aldosterone secretion
↓
Salt and water retention
↓
Increases renal perfusion

Negative feedback

Normal circumstances, when

Plasma aldosterone is low
Plasma renin is low

The aldosterone to renin ratio is low

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Renin–angiotensin–aldosterone system | **Abnormal**

Low renal perfusion
↓
Renin release from kidneys
↓
Angiotensin I
↓
Angiotensin II
↓
Aldosterone secretion
↓
Salt and water retention
↓
Increases renal perfusion

- feedback

Aldosterone continues to be released, independent of renin

Hyperaldosteroneism

Plasma aldosterone is high
Plasma renin is low

The aldosterone to renin ratio is high

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#8: Primary hyperaldosteronism is common

Purpose: To characterize the prevalence of nonsuppressible renin-independent aldosterone production, as well as biochemically overt primary aldosteronism, in relation to blood pressure.

Design & primary outcome: Cross-sectional study of participants with normotension (n = 289), stage 1 hypertension (n = 115), stage 2 hypertension (n = 203), and resistant hypertension (n = 408) all completing tests for hyperaldosteronism.

Results: 11.3 to 22.0% had biochemically overt primary aldosteronism.

Conclusion: The prevalence of primary aldosteronism is high and largely unrecognized.

Greater severity of increased aldosterone associated with higher blood pressures

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The Unrecognized Prevalence of Primary Aldosteronism. A Cross-sectional Study. Ann Intern Med. 2020 Oct 20;173(9):681-685.

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#9: Testing for primary hyperaldosteronism not common

Purpose: To evaluate testing rates for primary aldosteronism and evidence-based hypertension management in patients with treatment-resistant hypertension.

Design & primary outcome: Retrospective cohort study of veterans (N = 269,010) with apparent treatment resistant HTN and the rates of testing the plasma aldosterone-renin ratio & the rates of using mineralocorticoid receptor antagonist (MRA) therapy (e.g., spironolactone)

Results: 1.6% were tested (higher rates with nephrologists & endocrinologists vs primary care physicians) & testing associated with 4x higher rate of MRA therapy and better BP control over time

Conclusion: Testing for primary aldosteronism is rare in treatment resistant HTN

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Testing for Primary Aldosteronism and Mineralocorticoid Receptor Antagonist Use Among U.S. Veterans. A Retrospective Cohort Study. Ann Intern Med. 2021 Mar;174(3):358-357

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#10: Primary Aldosteronism | Testing rare with low K

Purpose: To evaluate testing rates for primary aldosteronism amongst 26,533 Canadian adults with hypertension plus potassium <3.5 mEq/L from 2009 to 2015 with follow-up through 2017

Design & primary outcome: Retrospective cohort study | % of patients tested with an aldosterone-to-renin ratio

Results:
- 1.6% overall were tested
- 4.8% if hypokalemia noted ≥5 times
- 3.9% if severe hypokalemia (< 3.0 mEq/L)
- 1% in older adults on ≥ 4 antihypertensive meds
- Rates of screening 39 – 52% higher among endocrinologists, nephrologists and cardiologists

Conclusion: Testing for primary aldosteronism is rare in patients with HTN & hypokalemia

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Screening Rates for Primary Aldosteronism Among Individuals With Hypertension Plus Hypokalemia: A Population-Based Retrospective Cohort Study. Hypertension. 2022 Jan;79(1):178-186.

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#11: Primary Aldosteronism | When to screen

Subgroup	Recommendation to screen for primary aldosteronism	Comment
Therapy-resistant hypertension/grade 3 hypertension	Yes	Prevalence of PA increases with the severity of hypertension [5,6,31,32]
Hypertension at young age (<40 years old)	Probably, may require lower cut-offs	No data to confirm high prevalence/benefit in young patients with hypertension [33,34]
Hypokalemia	Yes	PA prevalence in patients affected by hypertension and serum K^+ <3.7 mmol/l is 28.1% and rises up to 88.5% in patients with spontaneous hypokalemia of less than 2.5 mmol/l [35]
Adrenal incidentaloma	Yes	Prevalence of PA in patients with adrenal incidentaloma is 1.6 to 4.33% [36,37]*
Family history of PA/early stroke	Yes	Only in young, first-degree relatives with hypertension
Obstructive sleep apnea, obesity	No	The vast majority of patients with PA are tested for blood pressure levels grade at least 2 or hypokalemia [38]
Atrial fibrillation	Yes	If unexplained by structural heart disease and other conditions like hyperthyroidism [39]
Grade 2 hypertension	Yes	Especially if treatment response is poor; prevalence of PA increases with the severity of hypertension [5,6,31]
Grade 1 hypertension	Doubtful	Balance between costs and benefits should be considered

PA, primary aldosteronism.
*It must be acknowledged that the prevalence is calculated including also patients not affected by arterial hypertension and it is expected to double if considering only patients affected by arterial hypertension.

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Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. Journal of Hypertension. October 2020. Volume 38 (10). p 1919–1928

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#11: Primary Aldosteronism | How to screen

Measurement of plasma renin activity (PRA) and aldosterone concentration and calculation of the aldosterone to renin ratio (ARR) are the mainstay of PA screening work-up

- AM blood collection after patients have been out of bed for > 2 hours & seated for 5–15 minutes.
- Patients should have unrestricted dietary salt intake before testing and should be potassium-replete
- Not be taking drugs affecting the ARR (e.g., spironolactone, triamterene, amiloride, potassium-wasting diuretics) for > 4 weeks*

- Suspect Primary Aldosteronism:
  - PRA < 1 ng/mL/hr & Plasma aldosterone concentration (PAC) > 10 ng/dL
  - PAC (ng/dL) / PRA (ng/mL/h) > 20

* Drugs with minimal effect on plasma aldosterone levels: alpha-adrenergic blockers, verapamil

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#11: Primary Aldosteronism | How to screen

If a patient screens positive:
- Commonly will be sending the patient to endocrinology or nephrology
- Confirmatory testing usually required (oral sodium loading test)
- If positive -> adrenal CT scanning & renal vein sampling

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Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. Journal of Hypertension. October 2020. Volume 38 (10). p 1919–1928

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#11: Primary Aldosteronism | How to screen

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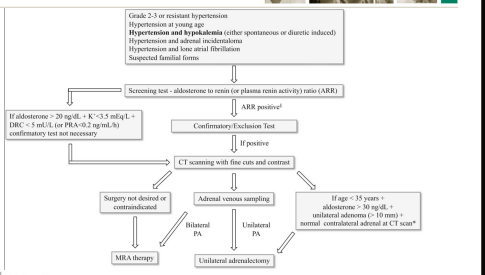

Genetics, prevalence, screening and confirmation of primary aldosteronism: a position statement and consensus of the Working Group on Endocrine Hypertension of The European Society of Hypertension. Journal of Hypertension. October 2020, Volume 38 (10), p. 1919–1928

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Testosterone

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Dx low testosterone | Total T < 300 ng/dL | 2 separate occasions | Early morning (fasting)

Low testosterone identified | Measure LH

- If T is low and LH is low or normal, measure prolactin and obtain an MRI
- If PRL = persistently high -> evaluate for endocrine disorders (prolactinoma)

Dx testosterone deficiency

- Low total T AND symptoms &/or signs

Male hypogonadism diagnosis is based upon the presence of signs and symptoms of male hypogonadism and unequivocally low serum total testosterone concentrations between 8 and 10 AM on at least two occasions

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Symptoms | Patient reported sx assoc with low T such as:

- Reduced energy or endurance | diminished work and/or physical performance | fatigue
- Depression | irritability
- Reduced motivation | poor concentration | impaired memory
- Reduced sex drive | changes in erectile function | infertility
- Visual field changes (bitemporal hemianopsia)
- Anosmia (↓ smell)

Which of these symptoms (if any) have been associated with hypogonadism in well-designed studies?

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#12: Off-label T Rx = common

Purpose: To systematically review all available evidence on marketing and TRT in the USA to July 2017.

Results:

Prevalence of hypogonadism depends on how total T is measured

- Based upon a single serum T < 300 | 76.8%
- Based upon 2 serum T < 300 | 18.3%
- Based upon serum T measured & sx & measurement between 5:00 and 10:00 AM | 5.6%

Appropriate dx of hypogonadism

Trends in T prescriptions

- ↑ 1.8 – 4X over 2 decades

Among men prescribed T

- Up to 26.6% did not have a serum T evaluation
- 19.5% did not have a documented T < 300 ng/dL
- Up to 40% did not have PSA or hematocrit testing

Conclusion: Many patients are prescribed testosterone without an appropriate diagnosis of hypogonadism, which may be related to the marketing efforts for off-label prescribing.

Marketing and Testosterone Treatment in the USA: A Systematic Review. Eur Urol Focus. 2017 Oct;3(4-5):395-401.

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#13: Adult-onset low T assoc with sexual dysfunction

Purpose: To characterize clinical symptoms of low testosterone in a general population of middle aged and elderly men

Patients: Survey of 3369 randomly selected adult men ($\bar{x}$ age = 59.7; $\bar{x}$ T = 475 ng/dL)

Methods: Correlation of symptoms (general, sexual, physical, psychosocial) with testosterone levels (total and free) in symptomatic vs non-symptomatic groups

Results:

- Only 3 sexual symptoms (poor morning erection, low sexual desire, erectile dysfunction) were associated with decreased testosterone levels

Conclusion: Late-onset hypogonadism can be defined by the presence of at least three sexual symptoms associated with a total testosterone level of < 317 ng/dL & a free testosterone of < 64 pg per milliliter

Identification of late-onset hypogonadism in middle-aged and elderly men. N Engl J Med. 2010 Jul 8;363(2):123-35.

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#14: TRT assoc with slight improvement in sexual function

Purpose: A systematic review and meta-analysis of RCTs to determine the effects of TRT on patient important outcomes and adverse events in hypogonadal men.

Patients + Methods: Four RCTs (including 1779 patients; all with morning testosterone < 300 ng/dL + ≥ 1 sx or sign of hypogonadism) on at least 12 weeks of TRT vs placebo at low risk of bias.

Results:
- TRT vs placebo
  - Sexual desire and/or libido = SMD 0.17
  - Erectile dysfunction = SMD 0.16
  - Sexual satisfaction = SMD 0.16
  - Mood and/or energy = no difference

Results:
- TRT vs placebo
  - Erythrocytosis RR 8.14
  - LUTS = no difference

Conclusion: In hypogonadal men, TRT improves sexual desire, erectile function and sexual satisfaction; however, it increases the risk of erythrocytosis.

LUTS = lower urinary tract symptoms
SMD = standard mean difference

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The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. J Clin Endocrinol & Metabol Volume 103, Issue 5, May 2018, Pages 1745–1754

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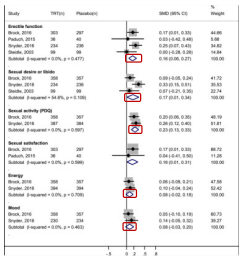
#14: TRT assoc with slight improvement in sexual function

Slight Positive Effect
- Erective function
- Sexual desire or libido
- Sexual activity

No Effect
- Energy
- Mood



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The Efficacy and Adverse Events of Testosterone Replacement Therapy in Hypogonadal Men: A Systematic Review and Meta-Analysis of Randomized, Placebo-Controlled Trials. J Clin Endocrinol & Metabol Volume 103, Issue 5, May 2018, Pages 1745–1754

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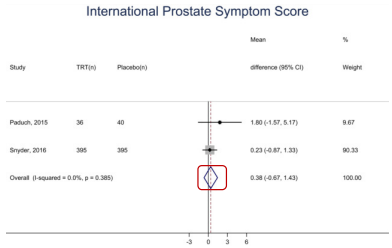
#14: TRT assoc with slight improvement in sexual function



No ADE
- Prostate sx

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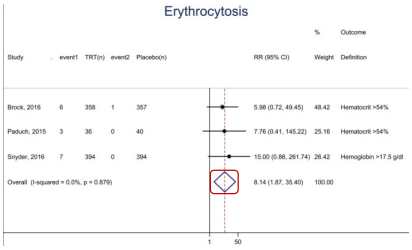

ADE
- Erythrocytosis

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#15: Testosterone Rx for age-related low T | ACP Guideline

Recommendation 1a: Discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function (conditional recommendation; low-certainty evidence).

Recommendation 1b: Reevaluate symptoms within 12 months … discontinue testosterone … if no improvement in sexual function (conditional recommendation; low-certainty evidence).

Recommendation 1c: Consider intramuscular rather than transdermal formulations … costs are considerably lower for the intramuscular formulation and clinical effectiveness and harms are similar.

Recommendation 2: Do not initiate testosterone treatment in men with age related low testosterone to improve energy, vitality, physical function, or cognition (conditional recommendation. low-certainty evidence).

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Testosterone Treatment in Adult Men With Age-Related Low Testosterone: A Clinical Guideline From the American College of Physicians. Ann Intern Med. 2020 Jan 21;172(2):126-133.

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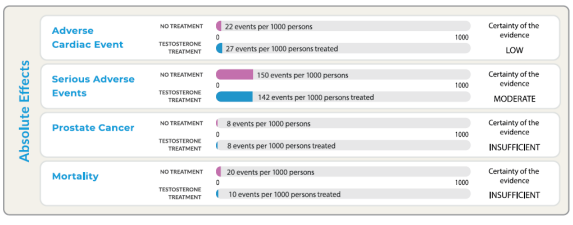
#13: Testosterone Rx for age-related low T | ACP Guideline



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Bottom-Lines

- There is no discernable benefit of treating subclinical hypothyroidism in most adults
- Hyperaldosteronism is common; looking for it is not common
- Symptomatically, low T is associated with sexual dysfunction & not associated with energy, mood
- T replacement associated with improved sexual function at the cost of a higher risk of erythrocytosis

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END

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