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IPERTIROIDISMO SUBCLINICO



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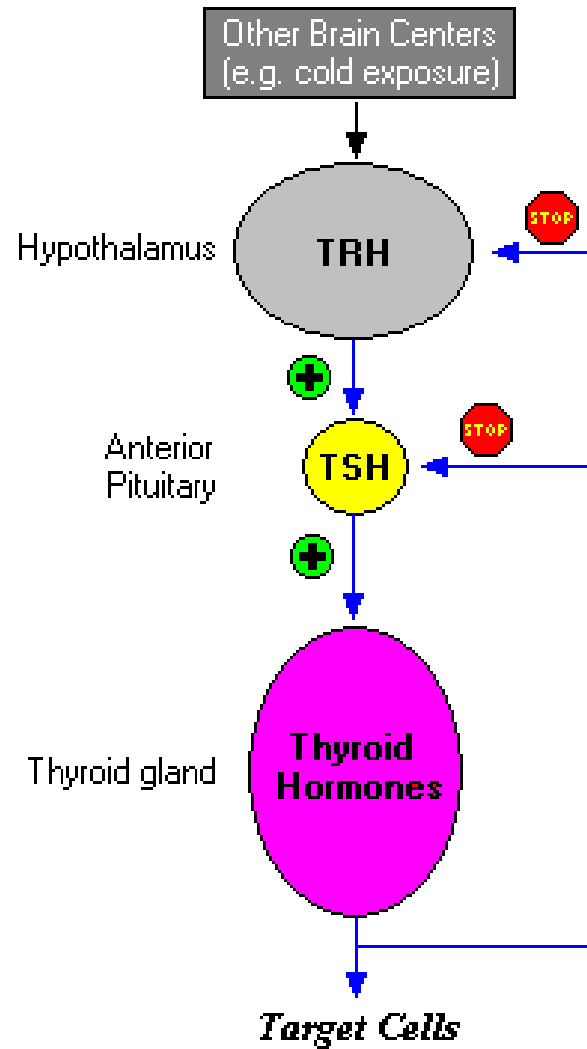
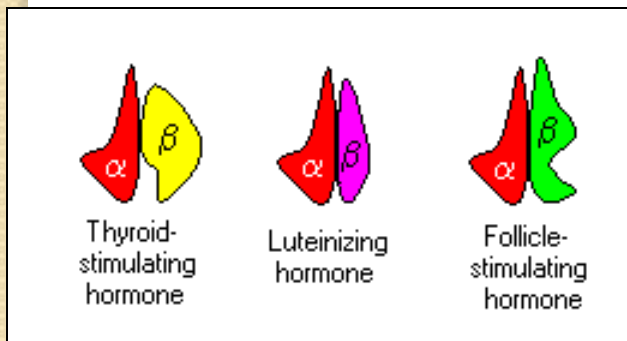
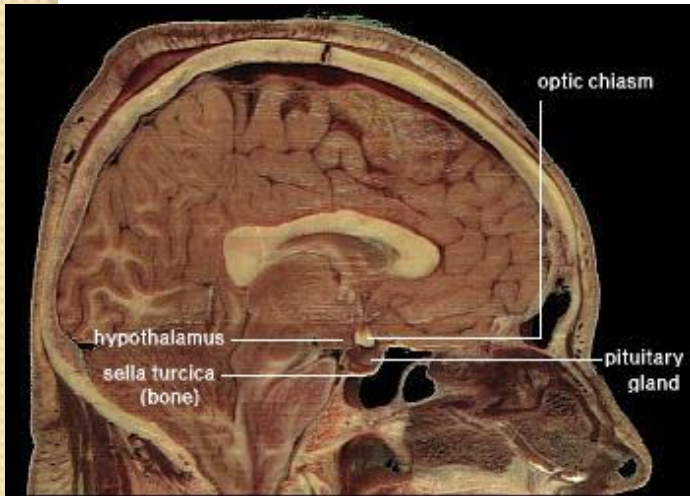
**XVIII Convegno Nazionale Geriatrico
"Dottore Angelico" - "San Raffaele Cassino"**

**L'INTEGRAZIONE OSPEDALE TERRITORIO:
Per il recupero e il mantenimento dell'autonomia**

Presidente
Luigi Di Cioccio



**CASSINO 11-12-13 Giugno
San Raffaele - Cassino**



Thyroid dysfunction in the elderly

Kristien Boelaert

Key points

- Large epidemiological studies confirm an increased prevalence of thyroid dysfunction in elderly people; subclinical or mild thyroid dysfunction is more prevalent than overt forms of thyroid hormone excess or deficiency
- Diagnosis of thyroid dysfunction is difficult in elderly individuals given its sometimes asymptomatic clinical presentation and the effects of a number of physiological changes on the biochemical evaluation of thyroid function
- Overt hyperthyroidism is associated with significantly increased risks of cardiovascular disease, osteoporosis and mortality, especially in the elderly population
- Treatment of subclinical hyperthyroidism is warranted when serum TSH concentrations are undetectable owing to important associations with cardiovascular disease and reduced BMD
- Biological end points of hyperthyroidism correlate with serum free T_4 levels; risk of atrial fibrillation and fracture susceptibility are increased with serum free T_4 concentrations at the upper limit of the reference range
- Studies on the long-term consequences of hypothyroidism on cardiovascular disease risk are inconsistent, but treatment of serum TSH concentrations >10 mIU/l with levothyroxine monotherapy is recommended in most guidelines

Thyroid dysfunction in the elderly

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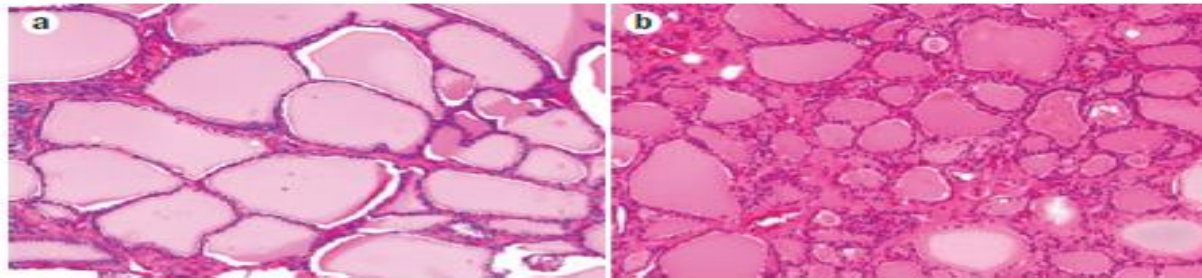


Figure 1 | Photomicrographs of haematoxylin and eosin stained sections of normal thyroid tissue in a 17-year-old (a) and a 58-year-old woman (b) at identical magnification (original magnification $\times 10$). The follicles are generally of smaller size with a reduced amount of colloid as well as a slight fibrous interstitial expansion in the older individual. These images are representative; considerable variation within the range of normality exists when comparing the histological appearances of thyroid tissue in different individuals, which depends on age, male or female sex, nutritional and hormonal status. Permission obtained from A. Warfield, University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK.

Table 1 | Diagnostic tests of nonthyroidal illness vs subclinical hyperthyroidism

Laboratory tests	Nonthyroidal illness*	Subclinical hyperthyroidism†
TSH	Normal or low or undetectable	Undetectable or low
Total T ₄	Normal or low	Normal to high normal
Free T ₄	Normal or low	Normal to high normal
Total T ₃	Low	Normal to high normal
Free T ₃	Low	Normal to high normal
Reverse T ₃	High	Normal

*Treatment of underlying condition. No thyroid-specific treatment required. †Consider radioactive iodine or antithyroid drug therapy if persistent. Abbreviation: vs., versus.

Epidemiologia delle patologie da iperfunzione tiroidea

Ipertiroidismo conclamato:

0.1-2 % della
popolazione generale

Il 60-80% dei pz ipertiroidi ha il
Morbo di Basedow

Incidenza/anno (donne):
0.5/1000

Picco di età: 40-60 anni

Ipertiroidismo subclinico:

0.3-4 % della popolazione
generale

Rapporto F/M = 10/1

Tale patologia si incrementa
coll'aumentare dell'età

Iper-tiroidismo subclinico

- Caratteristiche atomiche

Aumento-diminuzione volume (secondo vari studi)

- Eccessiva somministrazione di iodio a pazienti con M. di Basedow eutiroidei, specialmente in quelli in remissione dopo un trattamento farmacologico con antitiroidei
- Hormonal change

Change secret. TSH or TRH

Levels TSH down and Free T3= with increase reverse T3 and T4=

- Somministrazione o assunzione di iodio in pazienti con patologia tiroidea latente, specie nelle aree di deficit iodico lieve-moderato; Iodio per uso cosmetico, improprio, alternativo, ecc.

Ipertiroidismo subclinico nell'anziano

- Valori normali TSH 0.1-0.3
- Alcune persone anziane con bassi valori di T4 hanno valori inappropriatamente normali di TSH. La discrepanza riflette un più basso set-point della inibizione della secrezione di TSH mediata dall'ormone tiroideo, probabilmente dovuta all'incremento della conversione ipofisaria di T4 a T3.
- Spesso presente effetto di farmaci steroidi, β -bloccanti, antidepressivi, ecc.

L'ipertiroidismo subclinico

- La combinazione di livelli soppressi di TSH (<0.1 mU/L) e normali di iodotironine FT4 ed FT3 definisce il quadro biochimico dell'ipertiroidismo subclinico
- La sintomatologia è assente o minima
- D.D. con altre condizioni non ipertiroidiche

Segni e Sintomi Chiari dell'ipertiroidismo

Nervosismo/Tremori

Disturbi mentali, irritabilità

Difficoltà nel dormire

Occhi sporgenti
(esoftalmo)/Sguardo
Fisso/alterazione della visione

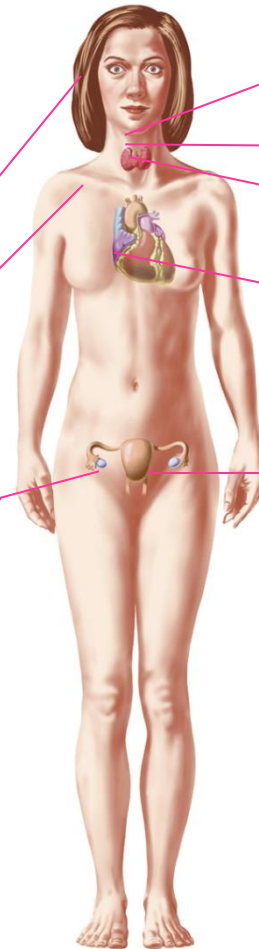
Tiroide aumentata di volume
(gozzo)

Irregolarità mestruali/
Dismenorrea

Aumento della motilità
intestinale

Caldo, mani umide

*Aborto spontaneo nel primo
trimestre
Vomito eccessivo in gravidanza*



Raucedine/
abbassamento del tono
della voce

Persistente secchezza o mal di
gola
Difficoltà a deglutire

Palpitazioni/tachicardia

Ridotta fertilità

Perdita di peso o guadagno

Intolleranza al caldo

Aumento della
sudorazione

**Paralisi
improvvisa**

Storia familiare di malattia tiroidea e
diabete

Ipertirodismo subclinico

- La disponibilità del metodo di dosaggio immunometrico del TSH sensibile ha consentito l'identificazione di valori ridotti di TSH ($<0,5$ mU/L) con frazioni tiroidee normali.
- Prevalenza: 0.7-12.4 % (variabilità dipende dalla definizione di bassi valori di TSH)
- Progressione all'ipertirodismo infrequente (4% dei soggetti)
- Transitorio - permanente

Panel 1: Classification of subclinical hyperthyroidism and other low serum TSH states

Causes of persistent subclinical hyperthyroidism

Exogenous

- Iatrogenic (intentional or unintentional)

Endogenous

- Toxic multinodular goitre
- Solitary toxic nodule (solitary autonomous nodule)
- Graves' disease

Causes of transient subclinical hyperthyroidism

- Treatment of overt hyperthyroidism with antithyroid drugs or radioiodine
- Evolution of various forms of thyroiditis, including subacute thyroiditis (also called viral or DeQuervain's), silent thyroiditis (also called painless thyroiditis; typically develops in the postpartum period), and occasionally type 2 amiodarone-induced thyrotoxicosis (amiodarone-induced thyroiditis)

Causes of low serum TSH concentrations that are not subclinical hyperthyroidism*

- Low serum TSH at end of the first trimester of pregnancy²⁵
- Low serum TSH seen in severe non-thyroidal illness and with treatment with high-dose glucocorticoids or dopamine
- Low serum TSH seen in some elderly individuals without apparent thyroid disease²⁵
- Low serum TSH seen in some black individuals as a consequence of racial differences in the distribution of TSH concentrations in the general population⁹
- Low serum TSH seen in some smokers²⁶
- Serum TSH below the reference range but at a normal concentration for that individual because the reference range only encompasses 95.0–97.5% of the general population

TSH=thyroid-stimulating hormone. *TSH usually >0.1 mIU/L.

Ipertirodismo subclinico

- *Esogeno:*

- pt che assumono tiroxina (terapia soppressiva del gozzo, follow up k tiroideo)
- interferenze (iodio)

- *Endogeno:*

- adenoma pretossico, gozzo multinodulare pretossico
- Tiroidite autoimmune
- Iperemesi gravidica
- Terapia con tireostatici in corso di Basedow

Ipertiroidismo subclinico- diagnosi differenziale

- Tumori ipofisari o ipotalamici (bassi valori di TSH si associano a ipotiroidismo)
- Malattie non tiroidee (pz in terapia intensiva o che assumono corticosteroidi di sintesi)
- Terapia con tireostatici per ipertiroidismo clinico
- Errore di laboratorio



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Natural history, diagnosis and management of subclinical thyroid dysfunction

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Keywords:

subclinical thyroid dysfunction
subclinical hyperthyroidism (exogenous and endogenous)
subclinical hypothyroidism
thyrotropin
L-thyroxine
replacement therapy
thyroid cancer
thyroid autonomy
thyrotropin suppression
prevalence
progression
cardiovascular risk
heart
bone
osteoporosis
symptoms
elderly
anti-thyroid drugs
radioiodine

Subclinical thyroid dysfunction (STD) represents a condition of slight thyroid hormone excess or deficiency, which may be associated with important adverse effects.

This review will focus on the natural history, diagnosis and management of subclinical thyroid dysfunction.

Since STD is only detected as a thyroid stimulating hormone (TSH) abnormality, it is essential to exclude transient causes of abnormal serum TSH before treating this disorder.

Treatment of subclinical hyperthyroidism (SHyper) is recommended in elderly patients with undetectable serum TSH for the increased risk of atrial fibrillation, osteoporosis and bone fractures and for the higher risk of progression to overt disease.

Treatment of subclinical hypothyroidism should be considered in patients with serum TSH above 10 mU/L for the increased risk of progression to overt hypothyroidism and the increased risk of coronary heart disease and heart failure events, which have been documented in patients with TSH increase above 10 mU/L.

About 75% of patients with STD have mild dysfunction. The mild form of STD (low but detectable serum TSH in SHyper and mild increased serum TSH between 5 and 9 mU/L in SHypo) is associated with a minor risk of disease progression to overt dysfunction. The best treatment for STD remains controversial. Treatment of the mild form of STD should be considered after evaluating the patients' age, the adverse risk factors, the potential beneficial effects of treating this disorder and any underlying co-morbidities. Mild SHypo should be treated in infertile and pregnant women.

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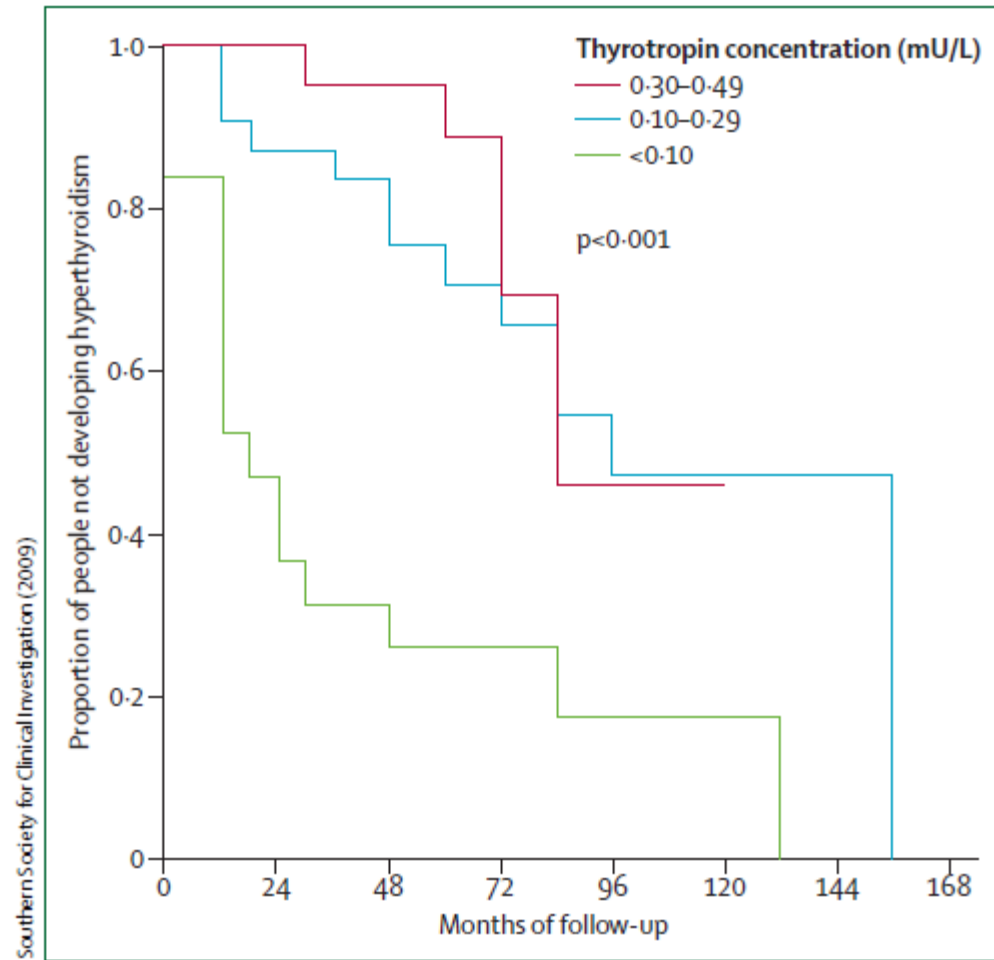


Figure 2: Kaplan-Meier curves for time of follow-up without development of overt hyperthyroidism in patients with subclinical hyperthyroidism according to TSH concentrations

Adapted from Díez and Iglesias,¹⁹ by permission.

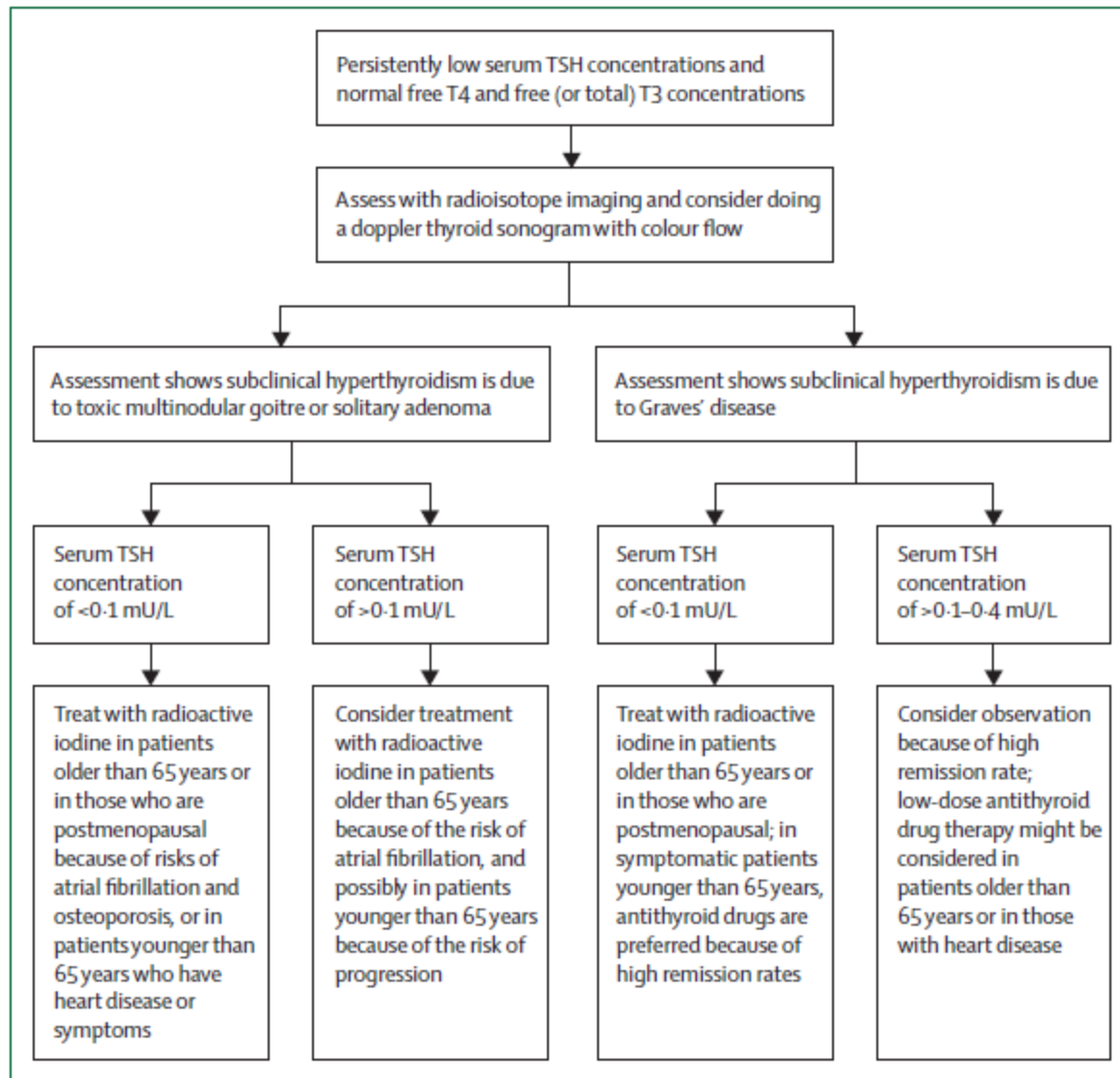


Figure 4: Algorithm for assessment and treatment of subclinical hyperthyroidism

This figure shows the algorithm outlined in panel 2. TSH=thyroid-stimulating hormone. T4=thyroxine. T3=tri-iodothyronine.

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Thyroid Status, Cardiovascular Risk, and Mortality in Older Adults: The Cardiovascular Health Study

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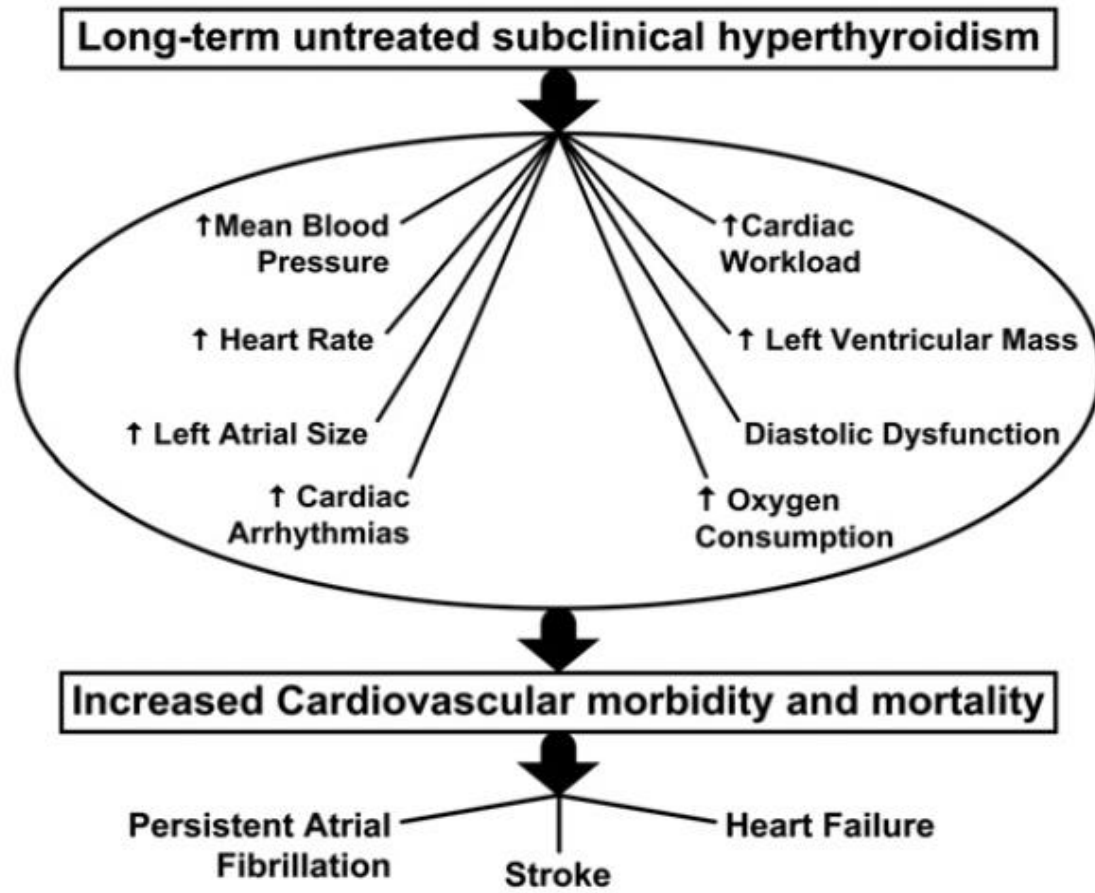
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Abstract

Context—Previous studies have suggested that subclinical abnormalities in TSH levels are associated with detrimental effects on the cardiovascular system.



Cardiovascular risk in patients with long-term untreated subclinical hyperthyroidism.

Thyroid dysfunction in the elderly

Kristien Boelaert

Table 2 | Meta-analyses on the cardiovascular effects of subclinical hyperthyroidism

Study	Relative risk of CHD (95% CI)	Number of included studies	Relative risk of CV mortality (95% CI)	Number of included studies	Relative risk of all-cause mortality (95% CI)	Number of included studies
Singh et al. ¹¹³	1.207 (0.780–1.870)	2	1.351 (0.949–1.923)	2	NA	NA
Volzke et al. ¹¹⁴	NA	NA	0.95 (0.52–1.74)	2	1.08 (0.72–1.62)	1
Ochs et al. ¹¹⁵	1.21 (0.88–1.68)	6	1.19 (0.81–1.76)	5	1.12 (0.89–1.42)	5
Haentjens et al. ¹¹⁶	NA	NA	NA	NA	1.41 (1.12–1.79)	7
Yang et al. ¹¹⁷	1.19 (1.10–1.28)	17	1.52 (1.08–1.23)	17	1.25 (1.00–1.55)	17
Collet et al. ¹¹⁸	1.21 (0.99–1.46)	6	1.29 (1.02–1.62)	10	1.24 (1.06–1.46)	10

Abbreviations: CHD, coronary heart disease; CV, cardiovascular; NA, not applicable.

Effetto dell'ipertiroidismo subclinico sul cuore

- > frequenza cardiaca (studi Holter)
- > prevalenza ed incidenza di FA, soprattutto dopo i 60 anni
- Non c'è consenso sull'effetto funzione ventricolare sn a riposo. Tutti gli studi hanno evidenziato un aumento della massa vn sn, con tendenza al rimodellamento concentrico. Condizione non classificabile ancora come IVS
- Riscontro di alterato rilassamento vn, ridotta performance all'esercizio, ecc.-
- Effetto negativo dell' ipertrofia miocardica sulla funzione diastolica stessa
- Significato prognostico dell'aumento della massa vn sinistra non chiaro (no studi epidemiologici)

IPERTIROIDISMO SUB-CLINICO

- **Cuore:**
- >frequenza, >frequenza di b. atriali prematuri
- Possibile induzione di tachicardia nodale atrioventricolare da rientro
- >contrattilità cardiaca
- Ipertrofia vn sn e settale (proporzionale alla durata dell'ipertiroidismo subclinico)
- Disfunzione diastolica
- Peggioramento dell'angina o dell'insufficienza cardiaca congestizia
- Ridotta tolleranza all'esercizio

Review Article

A Clinical Review of the Association of Thyroid Stimulating Hormone and Cognitive Impairment

Sylvia Annerbo¹ and Johan Lökk^{1,2}

In this focused review, we have performed an examination between low serum TSH and cognitive impairment in older people. In general, taking into account the largest and most powerfully designed studies, there is a strong body of evidence supporting the association between SH and cognitive impairment.

The scarce number of publications on these topics indicates the need of more research especially regarding longitudinal and interventional studies, thus hopefully robustly enabling confirmation or rejection of causality between TSH abnormalities and dementia.

TABLE 1: Longitudinal population-based studies. Relationship between subclinical hyperthyroidism (SH) and cognitive decline.

Author	Study size (n)	Mean age	Followup (years)	Participants thyroid status	Thyroid function (normal range)	Outcomes
Vadiveloo et al., 2011 [25]	12,115	66.5 ± 15.9	5.6 (median)	SH and euthyroid	TSH (0.4–4.0 mU/L) FT4 (10–25 pmol/L) FT3 (0.9–2.6 nmol/L)	Positive association SH and dementia
de Jong et al., 2009 [26]	615	77.5	5	SH and euthyroid	TSH (0.4–4.3 mU/L) FT4 (0.85–1.94 ng/L)	Positive association FT4 and dementia/AD
Tan et al., 2008 [27]	1,864	71	12.7	SH and euthyroid	TSH (0.5–5.0 mU/L)	Positive association Lowest and highest tertile TSH and AD
Yeap et al., 2012 [28]	3,401	76.8	5.9	Euthyroid only	TSH (0.4–4.3 mU/L) FT4 (10–23 pmol/L)	Positive association FT4 and dementia
Forti et al., 2012 [29]	660	73.3 ± 6.0	3.8 ± 0.7	Euthyroid and subclinical hypothyroidism	TSH (0.45–4.5 mU/L) FT4 (10.3–25.7 pmol/L)	No association TSH and MCI/AD Positive association High TSH and VAD
S. Annerbo et al., 2009 [30]	200	81.0 ± 4.6	6.7	All thyroid status (mean TSH 1.76 ± 1.03)	TSH (0.2–4.0 mU/L) TT4	No association TSH and AD

TABLE 2: Cross-sectional studies. Relationship between subclinical hyperthyroidism (SH) and cognitive decline.

Author	Study size (<i>n</i>)	Mean age	Participants thyroid status	Thyroid function (normal range)	Outcomes
Bensenor et al., [31] 2010	1119	<i>D</i> = 78.5 ND = 71.9	SH and euthyroid	TSH (0.4–4.0 mU/L) FT4 (0.77–2.19 ng/L)	Positive association SH and dementia especially vascular dementia
Ceresini et al., [32] 2009	916	>65	SH and euthyroid	TSH (0.46–4.68 mU/L) FT4 (0.77–2.19 ng/L)	SH group had significantly lower MMSE compared to the euthyroid group
Zhang et al., [33] 2012	40	67.08	All thyroid status	TSH (0.3–5.0 mU/L) TT4 (58.1–140.6 nmol/L) TT3 (0.92–2.97 nmol/L)	Lower TSH in euthyroid AD patients with agitation and irritability symptoms
de Jongh et al., [34] 2011	1219 (34 SH)	75.5	Euthyroid, SH, and subclinical hypothyroidism	TSH (0.3–4.5 mU/L) FT4, FT3	No association SH and impaired global cognitive function
Quinlan et al., [35] 2010	69	60.9–66.8	All thyroid status	TSH, FT4, TT4, TT3 (1.4–1.6 nmol/L)	Higher TT3 was associated with more cognitive impairment in MCI group

Iper-tiroidismo subclinico

- Osso e metabolismo minerale:
 - ↓ BMD
 - ↓ ↑ osteocalcina sierica
- Altri organi e funzioni:
 - < ore di sonno
 - > enzimi epatici
 - > CPK
 - < qualità della vita (Short-Form score)
(nervosismo, cardiopalmo, tremori, sudorazione).



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Subclinical Thyroid Dysfunction and Incident Hip Fracture in Older Adults

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Incidence Rates of Hip Fractures and HR Estimates of Hip Fracture Associated With Subclinical Thyroid Function Status in Men and Women: Cardiovascular Health Study

	Men			Women		
	Subclinical Hyperthyroidism	Euthyroidism	Subclinical Hypothyroidism	Subclinical Hyperthyroidism	Euthyroidism	Subclinical Hypothyroidism
All men (N = 1372)						
No. at risk	29	1159	184	142	1694	359
No. (%) of events	4 (13.8)	58 (5.0)	18 (9.8)	17 (12.0)	198 (11.7)	36 (10.0)
Incidence per 1000 person-years (95% CI)	13.65 (5.32–34.56)	4.96 (3.84–6.40)	10.27 (6.50–16.17)	10.90 (6.82–17.39)	10.18 (8.86–11.69)	8.93 (6.46–12.34)
HR (95% CI)						
Age-adjusted	3.07 (1.11–8.46)	1 [Reference]	1.86 (1.09–3.16)	1.06 (0.65–1.74)	1 [Reference]	0.87 (0.61–1.24)
Multivariable model 1 ^a	2.57 (0.79–8.38)	1 [Reference]	2.03 (1.13–3.66)	0.96 (0.52–1.78)	1 [Reference]	0.74 (0.48–1.13)
Multivariable model 2 ^b	3.27 (0.99–11.30)	1 [Reference]	2.31 (1.25–4.27)	1.36 (0.66–2.81)	1 [Reference]	0.87 (0.55–1.36)
Participants not taking thyroid-altering medication at baseline (n = 1287) ^c						
No. at risk	16	1096	175	34	1543	321
No. (%) of events	3 (18.8)	55 (5.0)	16 (9.1)	4 (11.8)	184 (11.9)	30 (9.3)
Incidence per 1000 person-years (95% CI)	21.09 (7.02–60.17)	4.94 (3.80–6.42)	9.66 (5.96–15.64)	11.12 (4.33–28.25)	10.36 (8.97–11.95)	8.20 (5.75–11.68)
HR (95% CI)						
Age-adjusted	4.95 (1.54–15.86)	1 [Reference]	1.73 (0.99–3.03)	0.98 (0.36–2.64)	1 [Reference]	0.79 (0.54–1.16)
Multivariable model 1 ^a	4.56 (1.06–19.64)	1 [Reference]	1.84 (0.98–3.43)	1.70 (0.54–5.38)	1 [Reference]	0.70 (0.45–1.10)
Multivariable model 2 ^b	4.91 (1.13–21.27)	1 [Reference]	2.45 (1.27–4.73)	2.42 (0.84–6.31)	1 [Reference]	0.87 (0.54–1.41)

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Adjusted for age, race, self-reported health status, frailty status, smoking, alcohol use, height, weight, and calcium supplementation.

^b Adjusted for multivariable model 1 covariates plus time-varying covariates for use during follow-up of antiosteoporosis medication (for men: 13 of 1327 noncases [1.0%] and 1 of 81 cases [1.2%]) and



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Conclusions—Older men with subclinical hyperthyroidism or hypothyroidism are at increased risk for hip fracture. Whether treatment of the subclinical syndrome reduces this risk is unknown.



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Subclinical Thyroid Dysfunction and the Risk for Fractures:

A Systematic Review and Meta-analysis

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Abstract

Background—Data on the association between subclinical thyroid dysfunction and fractures conflict.

Purpose—To assess the risk for hip and nonspine fractures associated with subclinical thyroid dysfunction among prospective cohorts.

Data Sources—Search of MEDLINE and EMBASE (1946 to 16 March 2014) and reference lists of retrieved articles without language restriction.

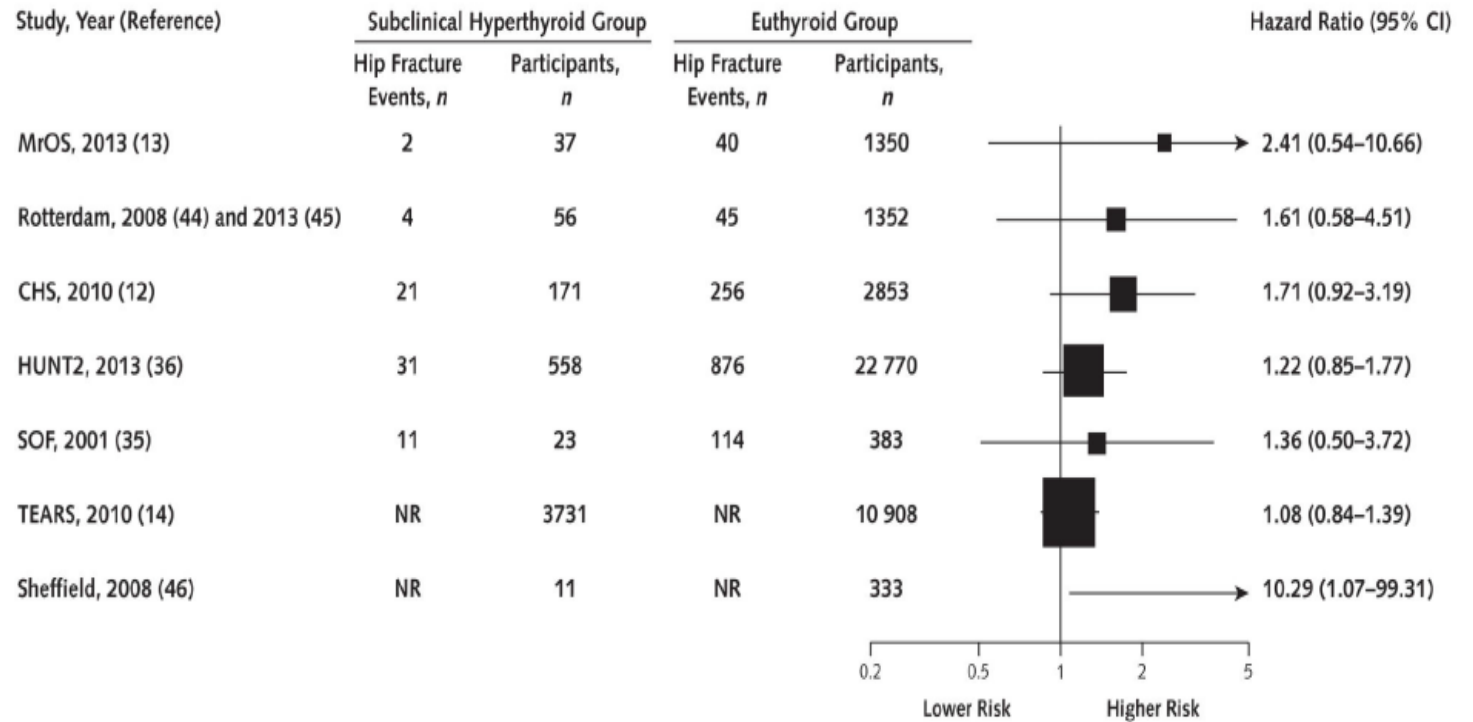
Study Selection—Two physicians screened and identified prospective cohorts that measured thyroid function and followed participants to assess fracture outcomes.

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What are the clinical and research implications of these findings? Recent guidelines recommend treatment of subclinical hyperthyroidism in all persons older than 65 years (63), and our findings of a possibly increased fracture risk associated with subclinical hyperthyroidism are consistent with these guidelines, although there are no studies in which treatment resulted in a reduced fracture risk. Given the high prevalence of both osteoporosis and subclinical thyroid dysfunction in our aging populations, our findings may have public health implications. However, because this is a meta-analysis of observational studies, we cannot rule out that our findings are due to reasons other than subclinical thyroid dysfunction. A meta-analysis of individual-participant data that does not have potential aggregation bias could provide more insight through uniform TSH cutoff levels, standardized adjustment for potential confounding factors, and a thorough analysis of subgroups. To prove causality, large randomized, controlled trials are necessary to assess the efficacy of normalizing TSH levels in subclinical thyroid dysfunction associated with fracture risk (64). For subclinical hyperthyroidism, its low prevalence and the requirement for long follow-up make such trials a challenge. But for subclinical hypothyroidism, the ongoing TRUST (Thyroid Hormone Replacement for Subclinical Hypothyroidism) trial (ClinicalTrials.gov: NCT01660126) will clarify this issue (65).

In summary, our systematic review indicates that subclinical hyperthyroidism might be associated with an increased risk for hip and nonspine fractures, but additional large, high-quality studies are needed.





Conclusioni

Segni e Sintomi Chiari dell'ipertiroidismo ?

Nervosismo/Tremori

Disturbi mentali, irritabilità

Difficoltà nel dormire

Occhi sporgenti (esoftalmo)/Sguardo Fisso/alterazione della visione

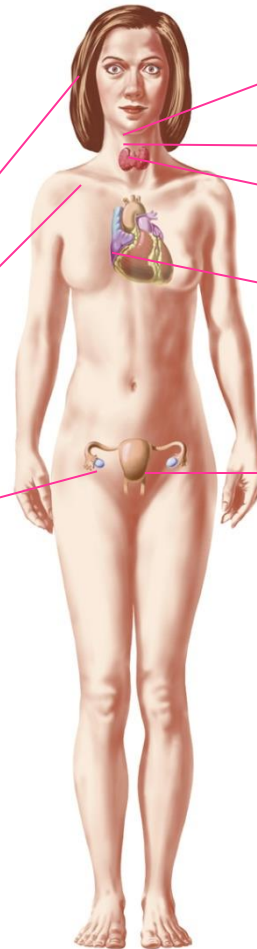
Tiroide aumentata di volume (gozzo)

Irregolarità mestruali/
Dismenorrea

Aumento della motilità intestinale

Caldo, mani umide

Aborto spontaneo nel primo trimestre
Vomito eccessivo in gravidanza



Raucedine/
abbassamento del tono della voce

Persistente secchezza o mal di gola
Difficoltà a deglutire

Palpitazioni/tachicardia

Ridotta fertilità

Perdita di peso o guadagno

Intolleranza al caldo

Aumento della sudorazione

Paralisi improvvisa

Storia familiare di malattia tiroidea e diabete

Ipertiroidismo subclinico nell'anziano

- Ipertiroidismo *APATICO*
- No sintomi da iperattività
- Sintomi cardiopolmonari (tachicardia, FA, dispnea, edema), anoressia, perdita di peso, stipsi, disturbi dell'umore, ecc.



TAKE HOME MESSAGE

Practice points

- Subclinical thyroid dysfunction is a frequent disorder and may progress to overt disease
- Exo and Endo SHyper may be responsible for an increased cardiovascular risk, especially in presence of undetectable serum TSH
- Elderly patients with SHyper have an increased risk of atrial fibrillation, particularly in presence of an underlying heart disease
- Elderly patients with exogenous and endogenous subclinical hyperthyroidism have an increased risk of bone fracture

• **Increased risk for Cognitive Impairment**







La cattedrale di Cosenza, monumento in stile gotico cistercense, al suo interno la tomba di Isabella d'Aragona.



Grazie per l'attenzione!



Louis-Ferdinand Celine, Il dottor Semmelweis, Adelphi, 1993