Seminari del Venerdì del
Gruppo di Ricerca Geriatrica

Recenti acquisizioni in geriatria

30 dicembre 2005

L'ipotiroidismo

(subclinico)

Ignazio Di Fazio

Almost 4 decades ago, Basteine and colleagues used the term ***subclinical hypothyroidism*** to describe, for the first time, a group of clinically euthyroid individuals with circulating antithyroid antibodies, low normal plasma protein–bound iodine levels, and, using a mouse bioassay, elevated serum thyrotropin levels. Evered and colleagues subsequently described a similar group of asymptomatic individuals in whom "*conventional tests of thyroid function showed nothing abnormal . . . but they were all found to have a raised serum thyrotropin concentration.*"

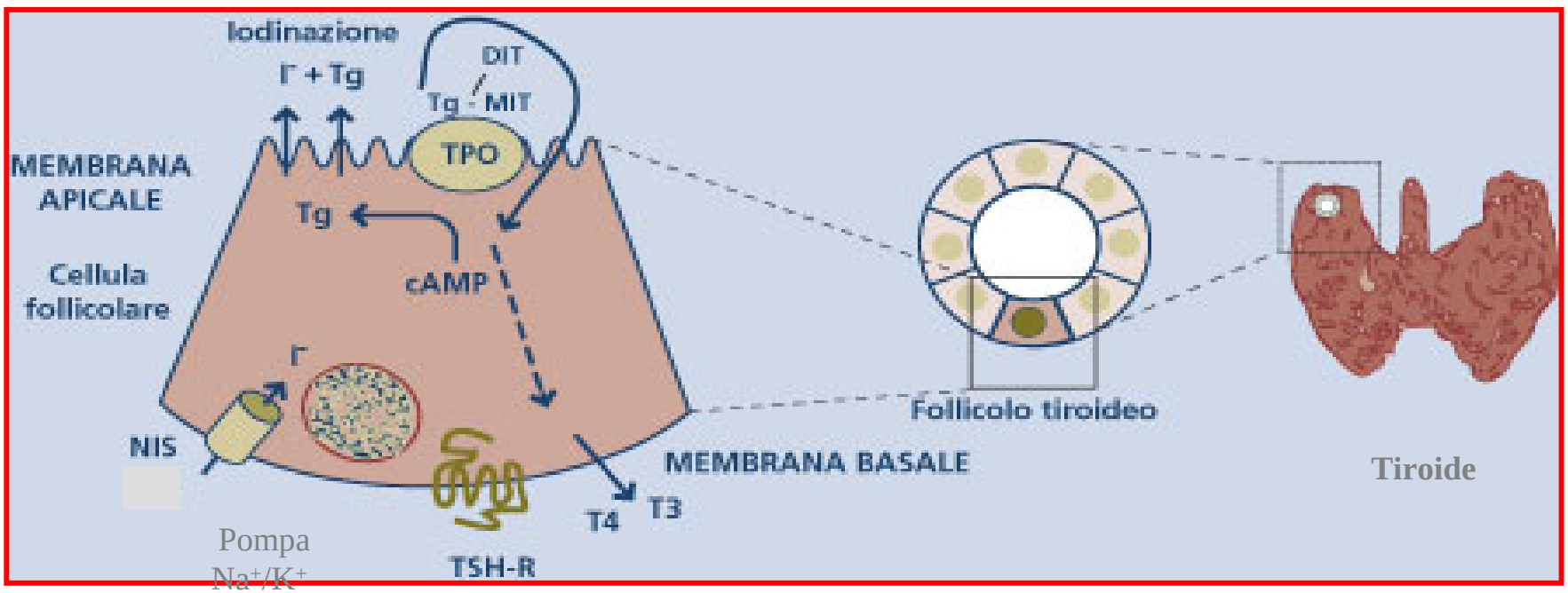
They also used subclinical hypothyroidism to describe this constellation of clinical and laboratory data. Since then, hundreds of articles have been published on this topic, but physicians are no closer to understanding whether this mild, usually asymptomatic form of hypothyroidism presents a clinical risk, requiring screening for detection and thyroid hormone treatment, or whether screening and therapy are unnecessary and possibly even counterproductive.

David S Cooper, *JAMA 2004*

Cenni di fisiologia

Biosintesi degli ormoni Tiroidei

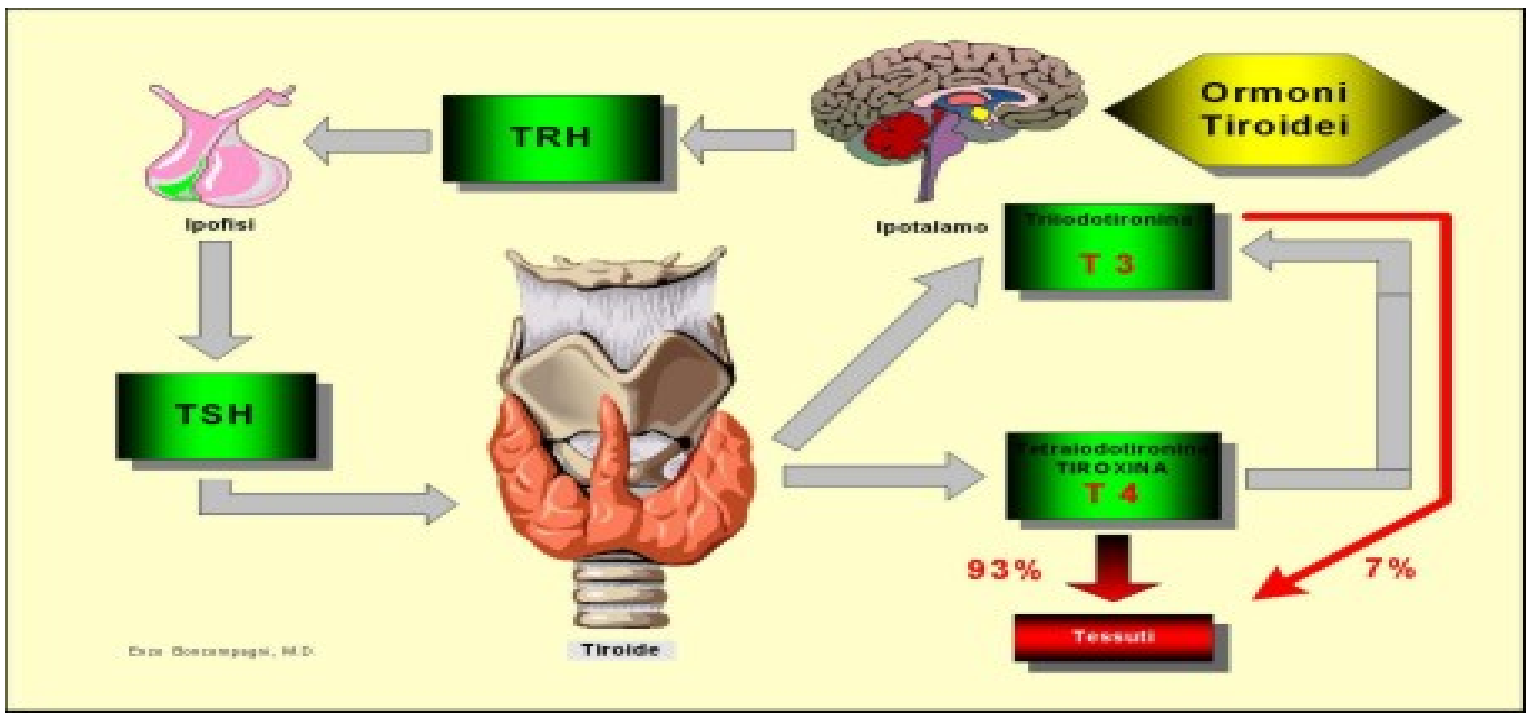
Nei Tireociti lo ione ioduro (I^-) circolante viene captato contro gradiente elettrochimico mediante la pompa dello iodio, con energia fornita da un sistema ATPasico Na^+/K^+ dipendente. La tireoglobulina (Tg), una glicoproteina presente nel lume follicolare della ghiandola, è in grado di legare I_2 ai suoi residui tirosinici per formare i due precursori inattivi, la monoiodotirosina (MIT) e la diiodotirosina (DIT). I processi di ossidazione e organificazione dello iodio avvengono sulla Tg e sono catalizzati dall'enzima perossidasi tiroidea (TPO): dalla condensazione di due molecole di DIT si forma la T4, mentre dall'unione di una molecola di DIT e una di MIT si forma la T3. Infine, in seguito alla proteolisi della Tg, si ha la liberazione di T3 e T4 e la loro secrezione in circolo.



Regolazione della funzione Tiroidea

Sintesi e secrezione degli ormoni tiroidei sono regolati da:

- *Fattori extra-tiroidei*: Il normale funzionamento dell'attività secretoria tiroidea è regolato da una struttura in cui la secrezione ormonale dei vari organi implicati è funzionalmente integrata. Questa è l'asse "ipotalamo-ipofisi-tiroide". In condizioni fisiologiche l'ormone di rilascio della tireotropina (TRH), di origine ipotalamica, stimola la secrezione dell'ormone ipofisario tireostimolante (TSH) che, a sua volta, promuove la sintesi e la secrezione degli ormoni tiroidei.
- *Fattori intra-tiroidei:* autoregolazione dell'apporto iodico.



Effetti “regolativi” degli ormoni tiroidei

- ✓ Sul consumo di O_2 e termogenesi
- ✓ Sulla risposta ventilatoria ed ipossia ed ipercupemia
- ✓ Sulla produzione di eritropoietina
- ✓ Sul turn-over osseo (formazione – riassorbimento)
- ✓ Sui muscoli scheletrici: regola la velocità di rilassamento muscolare. *Il riflessogramma Achilleo misura i tempi di contrazione e rilassamento muscolare dopo stimolazione del tendine di Achille, ed è prolungato nella fase di rilassamento nell’ipotiroidismo.*

Thyroid function tests in the elderly

- TSH tends to decline slightly with age, but remains in normal range
- Free T_4 remains constant with age
  - There is decreased clearance of thyroxine with age
  - Decreased thyroxine secretion (60 mcg/day compared to 80 mcg/d in younger subjects)
- T_3- slight decline with age, but usually remains in normal range

EC Ridgway, 2005

L’ipotiroidismo

Hypothyroidism in the elderly and clinical features

- Prevalence in U.S. population is 5-10%.
- More common in women than men
- Common causes
  - *Autoimmune thyroiditis (Hashimoto's) is most common cause*
  - *Post-treatment of hyperthyroidism*
  - *Drug-induced: amiodarone, radiographic contrast agents, iodine-containing cough syrups, lithium*
- Often lack classic features, or are attributed to old age, e.g. dry skin, constipation, cold intolerance (seen in about 25% of cases)
- Common features in elderly- change in cognitive function, apathy, depression, CHF, carpal tunnel syndrome, arthritis, paresthesias
- Lab findings: anemia, elevated cholesterol, increased CK

EC Ridgway, 2005

Subclinical hypothyroidism

- Earliest stage of thyroid dysfunction
- Defined as elevated TSH (> 4.5 mIU/L) with normal free T4
- The most common form of thyroid dysfunction in the elderly
- The prevalence of subclinical hypothyroidism in patients older than 65 years varies from 12% to 15%
- Subclinical hypothyroidism is most often detected in older women, in whom the prevalence may be as high as 20%, 75% of those have TSH between 4.5-10mIU/l
- Progression to overt hypothyroidism is higher in elderly and patients with elevated anti-thyroid antibodies

Fatourechi V. Mayo Clin Proc 2001; Canaris GJ, Arch Intern Med 2000;
Surks MI, JAMA. 2004; Helfland M, Ann Intern Med. 2004

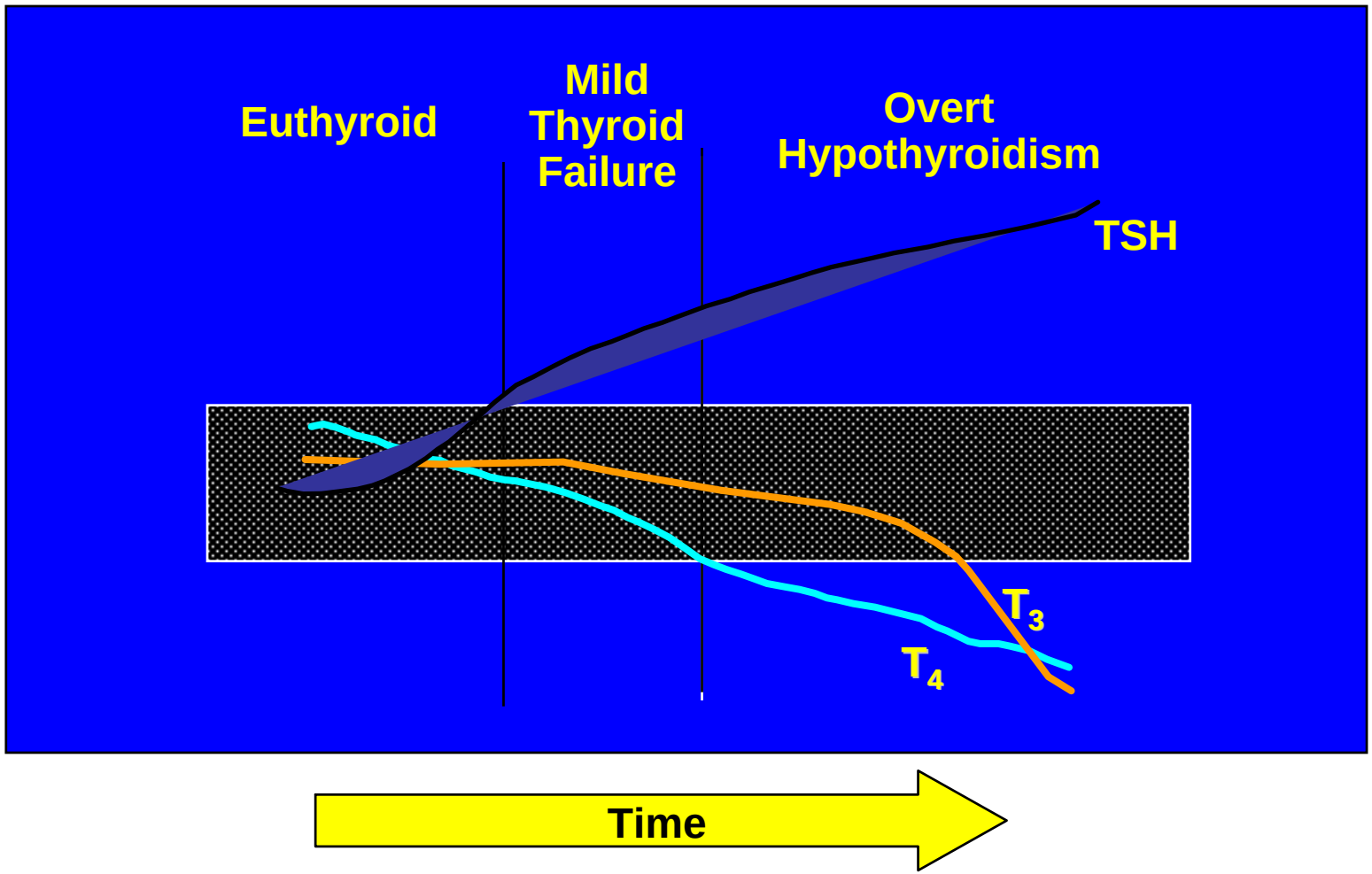
TSH as a Pharmacodynamic Marker?

- Pituitary Glycoprotein Hormone
- Controls Thyroid Gland Growth and Function
- TSH Production and Secretion Very Sensitive to Circulating Thyroid Hormones
- TSH Secretion is Pulsatile and Circadian
  - Mean Pulse Frequency = 7-13 Pulses/24 hrs
  - Mean Pulse Amplitude = 2.5 mU/L
    - Mean Daytime = 1.5-2.0 mU/L
    - Mean Nightime = 3.0-4.0 mU/L

- TSH is the most sensitive measure of Thyroid Hormone Action
- Normal Thyroid Hormone Levels are <u>not</u> accurate measures of Normal Thyroid Hormone Action
- The Toxicities of Excessive or Deficient Thyroid Hormone Levels are now defined by TSH Levels, <u>not</u> by Thyroid Hormone Levels

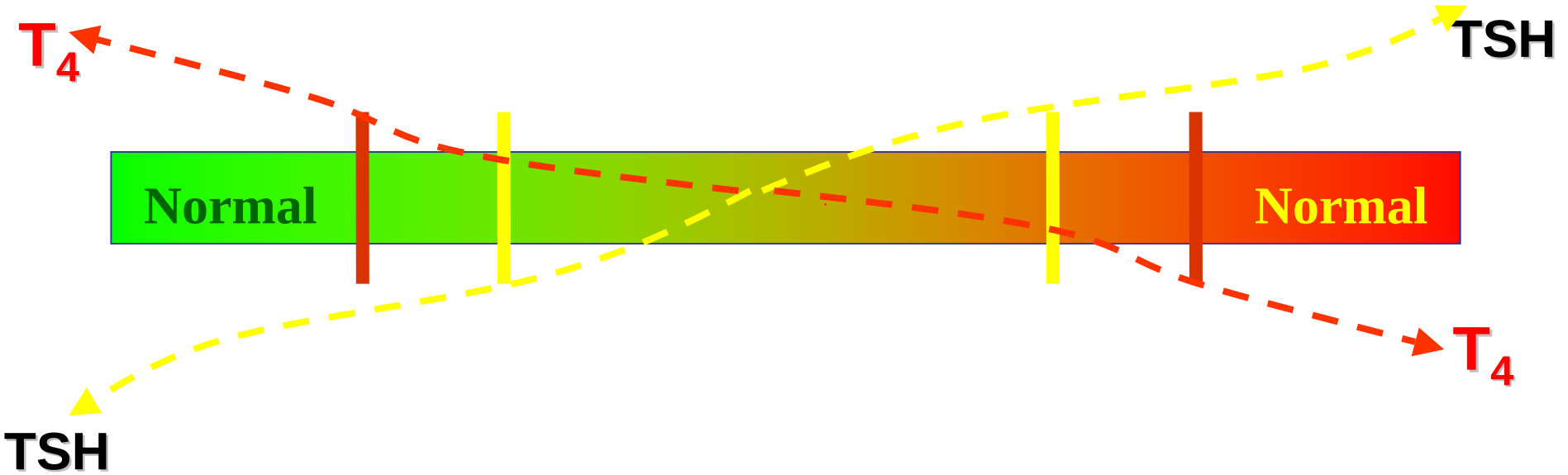
EC Ridgway, 2005

Thyroid Failure



Ayala AR, *The Endocrinologist.* 1997;7:44-50.

In the Past, thyroxine toxicity defined by clinical presentation T4 and TSH levels



Graves'
Thyroid Storm

Overt Hypothyroidism
Myxedema Coma

Currently, Thyroxine Toxicity Defined Only By TSH Level

Subclinical Hyperthyroidism

Bone Loss
Fractures
Myocardial Dysfunction
Cardiac Arrhythmias
Death

Subclinical Hypothyroidism

Increased Lipids
Abnormal Vascular Function
Atherosclerosis, MI
Death
Thyroid Cancer

Screening
& trattamento farmacologico

Recommendations of Eight Organizations Regarding Screening of Asymptomatic Adults for Thyroid Dysfunction

TABLE 1. RECOMMENDATIONS OF EIGHT ORGANIZATIONS REGARDING SCREENING OF ASYMPTOMATIC ADULTS FOR THYROID DYSFUNCTION.

ORGANIZATION	SCREENING RECOMMENDATIONS
American Thyroid Association[5]	Women and men >35 yr of age should be screened every 5 yr
American Association of Clinical Endocrinologists[6]	Older patients, especially women, should be screened
College of American Pathologists[7]	Women ≥50 yr of age should be screened "if they seek medical care"; all geriatric patients should be screened on admission to the hospital and at least every 5 yr
American Academy of Family Physicians[8]	Patients ≥60 yr of age should be screened
American College of Obstetrics and Gynecology[9]	Women in "high-risk groups" (those with autoimmune disease or a strong family history of thyroid disease) should be screened starting at 19 yr of age
American College of Physicians[10]	Women >50 yr of age with an incidental finding suggestive of symptomatic thyroid disease should be evaluated
U.S. Preventive Services Task Force[11]	Insufficient evidence for or against screening
Royal College of Physicians[12]	Screening of the healthy adult population unjustified

Cooper *NEJM*, 2001

The NEW ENGLAND JOURNAL of MEDICINE

Current Controversies in Endocrinology: Screening of Asymptomatic Elderly for Subclinical Hypothyroidism

Nina J. Karlin, MD, Nancy Weintraub, MD, and Inder J. Chopra, MD, MACP

(J Am Med Dir Assoc 2004; 5: 333–336)

Several issues concerning treatment of subclinical hypothyroidism remain unresolved.

Most agree that a trial of levothyroxine **treatment should be considered in symptomatic patients with positive antithyroid antibodies, high LDL cholesterol, goiter, or repeated serum TSH levels greater than 10 mIU/L.**

More longitudinal studies are needed to fully comprehend the consequences of untreated subclinical hypothyroidism on symptoms, atherosclerosis, and overall quality of life, and **how levothyroxine treatment influences these parameters.**

Screening for Subclinical Thyroid Dysfunction in Nonpregnant Adults: A Summary of the Evidence for the U.S. Preventive Services Task Force

Mark Helfand, MD, MPH

Ann Intern Med. 2004;140:128-141.

An elevated TSH level—even a mildly elevated one—is a risk factor for later development of overt hypothyroidism.

Early treatment would prevent this progression, but the balance of benefits and harms is unclear.

Other potential harms of subclinical thyroid dysfunction are not well established.

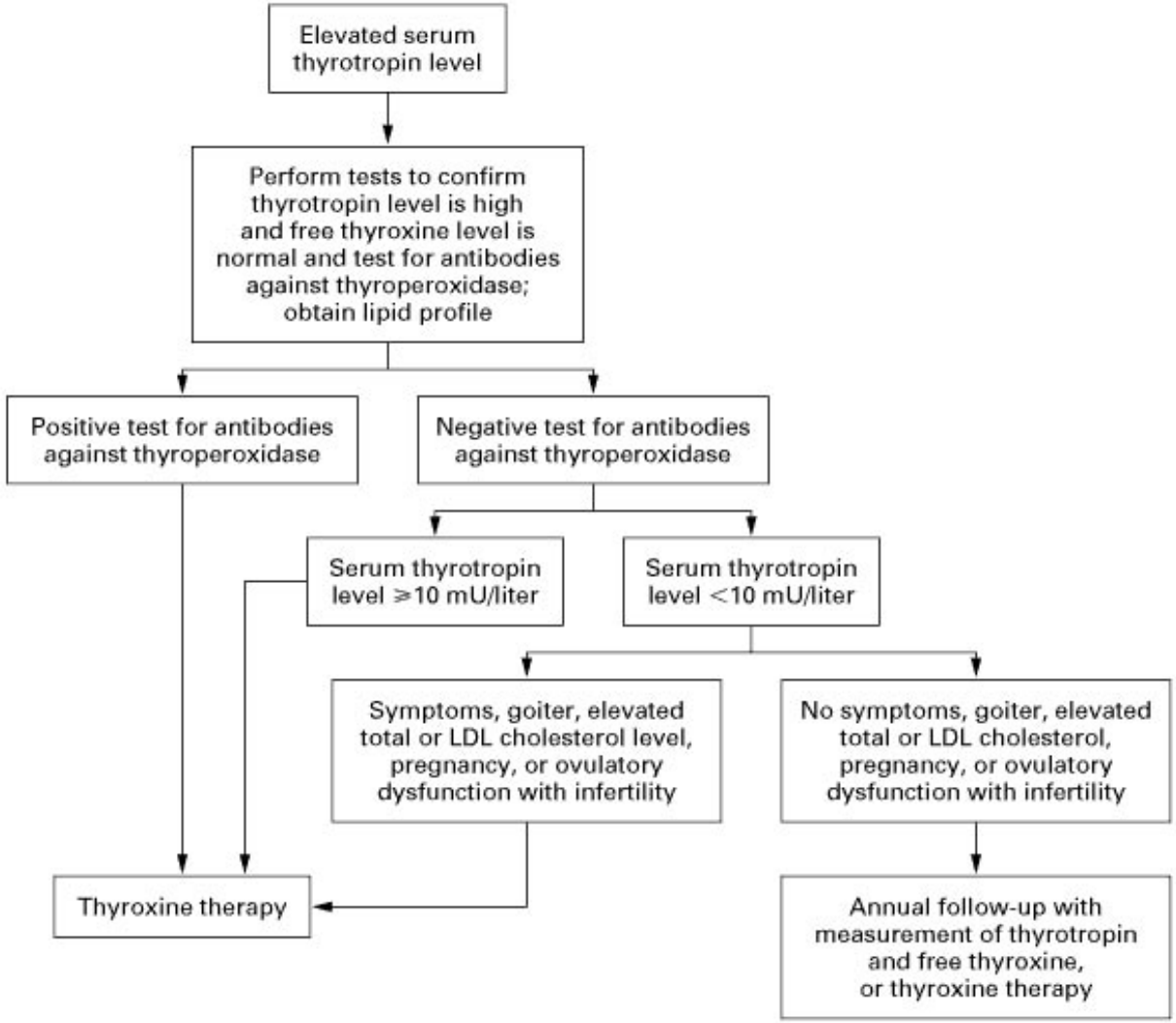
Data on **osteoporosis**, **fracture**, **hyperlipidemia**, and **atherosclerotic** disease are **inconsistent**, and most data come from patients who take L-thyroxine or have clinically evident thyroid disease.

Not surprisingly, experts give conflicting advice about the treatment of subclinical hypothyroidism.

Good evidence shows that **L-thyroxine reduces symptoms** (but not lipid levels) in patients who have a markedly elevated TSH level (**>10** mU/L) following surgery or radioiodine treatment.

The main gap in the evidence is the **lack of convincing data from controlled trials** that early treatment reduces lipid levels, symptoms, or the risk for cardiovascular disease in patients with mild thyroid dysfunction detected by screening.

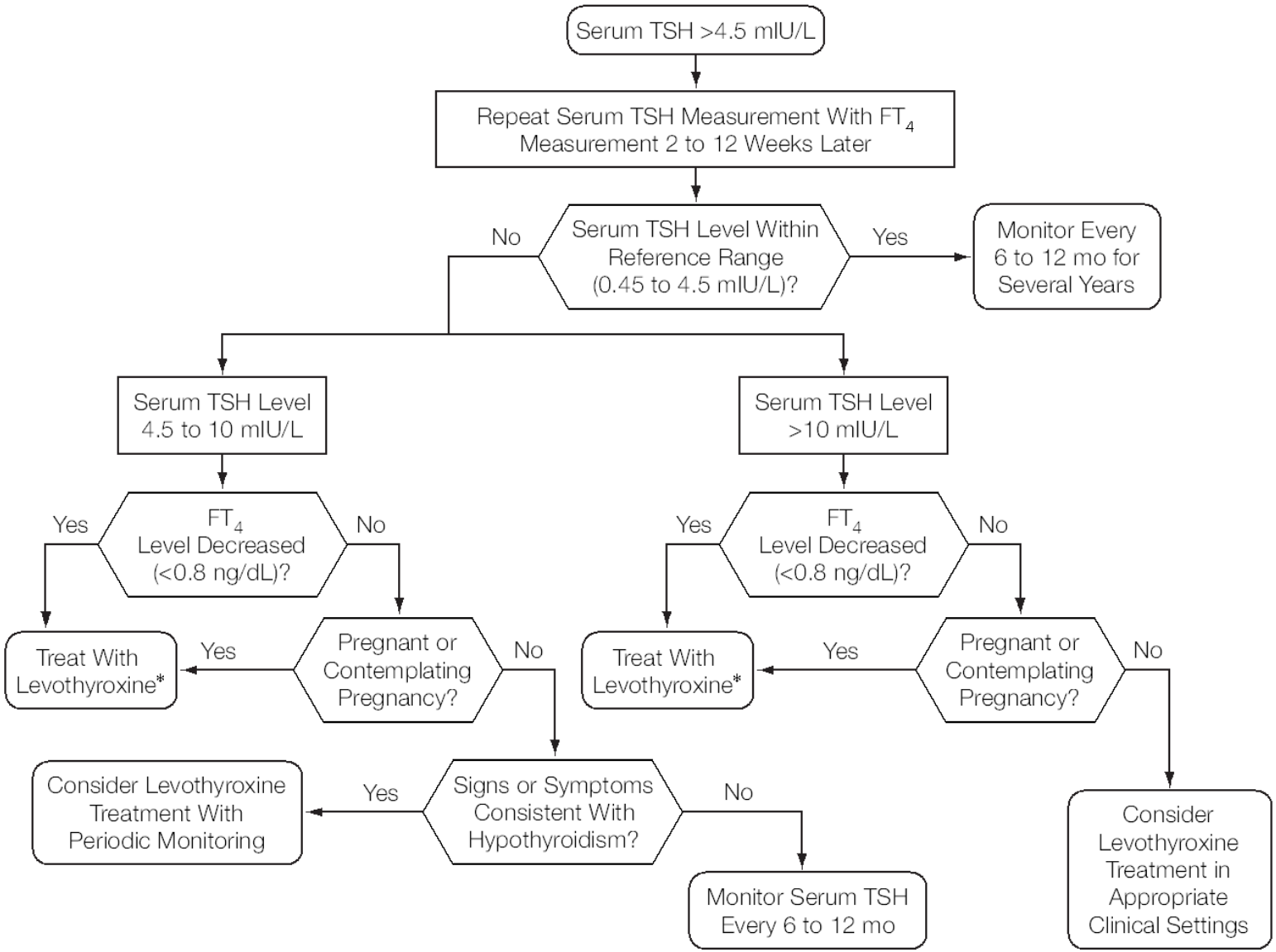
An Algorithm for the Management of Subclinical Hypothyroidism



Cooper *NEJM*, 2001

The NEW ENGLAND JOURNAL of MEDICINE

Figure 1. Suggested Approach to Diagnosis and Management of Subclinical Hypothyroidism



NF Col, *JAMA* 2004

Subclinical Thyroid Disease

Scientific Review and Guidelines for Diagnosis and Management

Table 1. Quality of Evidence on the Strength of Association and Risks/Benefits of Treatment of Subclinical Hypothyroidism

	Strength of Association		Benefits of Treatment	
Clinical Condition	Serum TSH 4.5-10 mIU/L	Serum TSH >10 mIU/L	Serum TSH 4.5-10 mIU/L	Serum TSH >10 mIU/L
Progression to overt hypothyroidism	Good	Good	*	*
Adverse cardiac end points	Insufficient	Insufficient	No evidence	No evidence
Elevations in serum total and LDL cholesterol	Insufficient	Fair	Insufficient	Insufficient
Cardiac dysfunction	†	Insufficient	Insufficient	Insufficient
Systemic hypothyroid symptoms	None	Insufficient	Insufficient	Insufficient
Neuropsychiatric symptoms	None	Insufficient	Insufficient	Insufficient

Abbreviations: LDL, low-density lipoprotein; TSH, thyroid-stimulating hormone.
*Thyroid hormone therapy normalizes serum TSH at any TSH concentration. Overt hypothyroidism occurs earlier in untreated patients with serum TSH >10 mIU/L than in those with serum TSH between 4.5 and 10 mIU/L.
†Data did not distinguish between serum TSH concentrations between 4.5 and 10 mIU/L and >10 mIU/L.

MI Surks et al, *JAMA* 2004

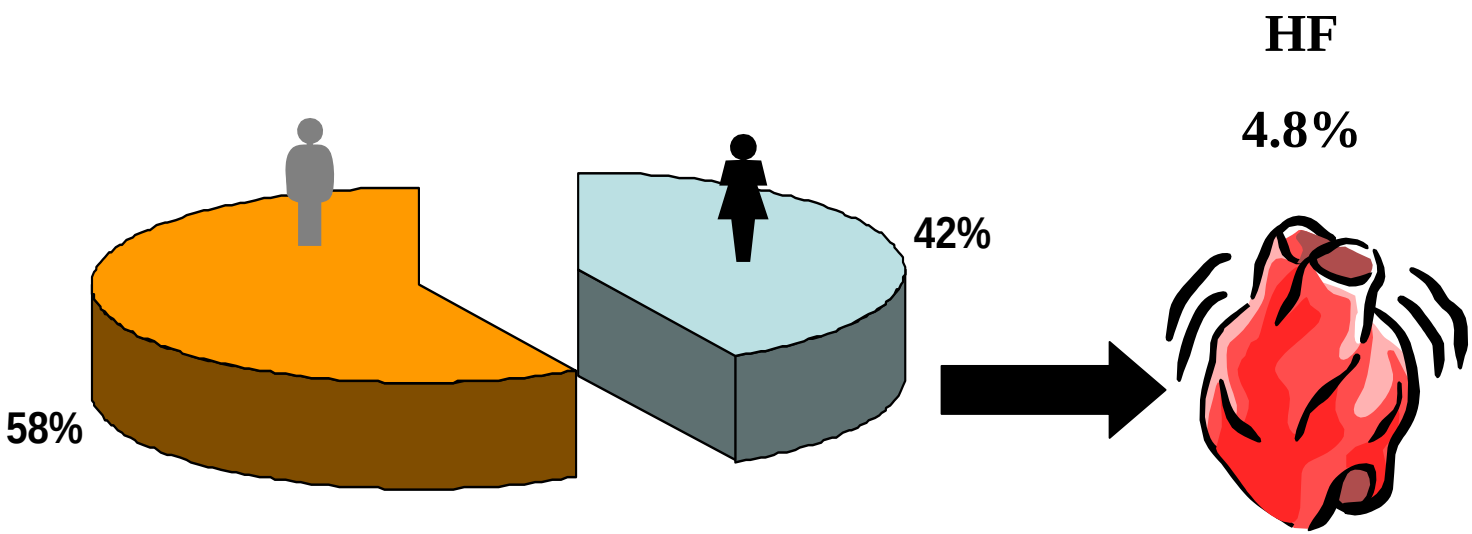
Ipotiroidismo subclinico & malattie cardiovascolari

- To date, **longitudinal community-based studies** of the relationship between the serum TSH level at the time of study entry and the incidence of CVD during the follow-up period have been **mostly negative**.
- In the largest and longest study to date, ***2.779*** randomly selected men and women 18 years or older from the **Whickham area** in England were carefully examined and then followed up for **20 years**. **No association** was noted between the presence of autoimmune thyroid disease at study entry and subsequent death from ischemic heart disease.
- Similarly, in the **Birmingham study** of a community-based cohort of ***1.191*** men and women 60 years or older, **no association** existed between an elevated serum TSH level on study entry and death from circulatory disease during the **10-year** follow-up period.
- The **Nagasaki** study of ***2.550*** men and women 40 years or older showed **no association** between SH and incident ischemic heart disease during a 6-year follow-up.
- Finally, in the **Leiden** study of all persons in the population aged **85 years**, an elevated serum TSH level at entry was associated, remarkably, with a **decreased risk of death from cardiovascular disease** during the **4-year follow-up** period.

LM Crapo *Arch Intern Med*; 165, Nov. 28 2005

Le dimensioni del problema:
Ipotiroidismo e Cardiopatia

- Prevalenza nell'adulto: 6 – 8 casi su 1000 (> F, età avanzata, area a carenza iodica)
- In Italia: su 1.047 pazienti (42% Maschi e 58% Femmine, età media 69,7 ± 10 anni), nel 4,8% HF è associato a IPOTIROIDISMO.



RICA. Registro Insufficienza Cardiaca Cronica in Italia 2004

Subclinical Hypothyroidism and Atherosclerosis
The Rotterdam Study

Random sample = 1.149 females

Age = 69 ± 7.5 yrs

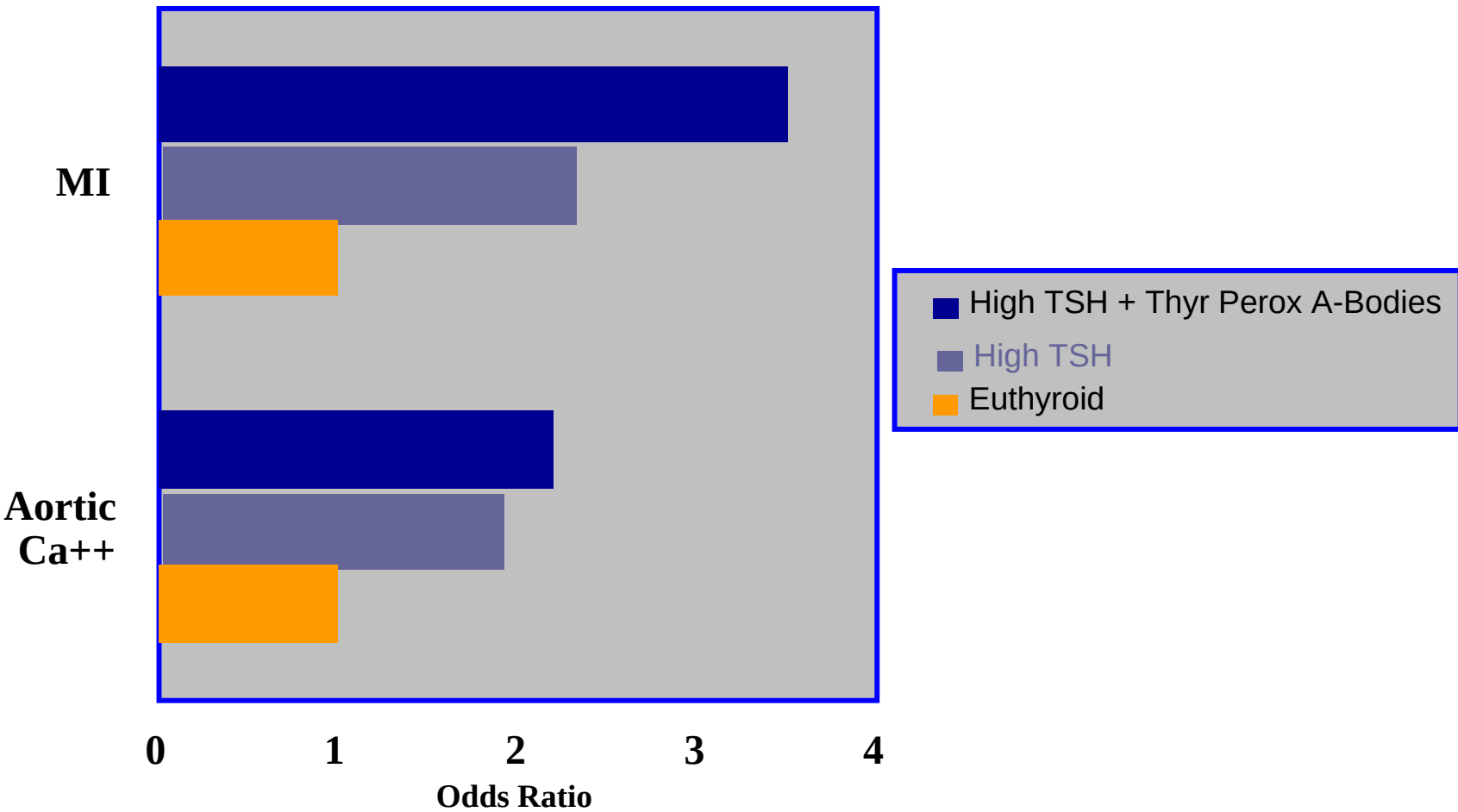
TSH Elevated = 10.8% (>4 uU/ml)

End Points = Aortic Atherosclerosis (aortic calcification)
Myocardial Infarction (MI)

Methods = Cross-sectional

Hak AE et al *Annals Int Med* 132:270, 2000

Subclinical Hypothyroidism and Atherosclerosis
The Rotterdam Study



**Adjusted for age, BP, BMI, smoking, lipids*

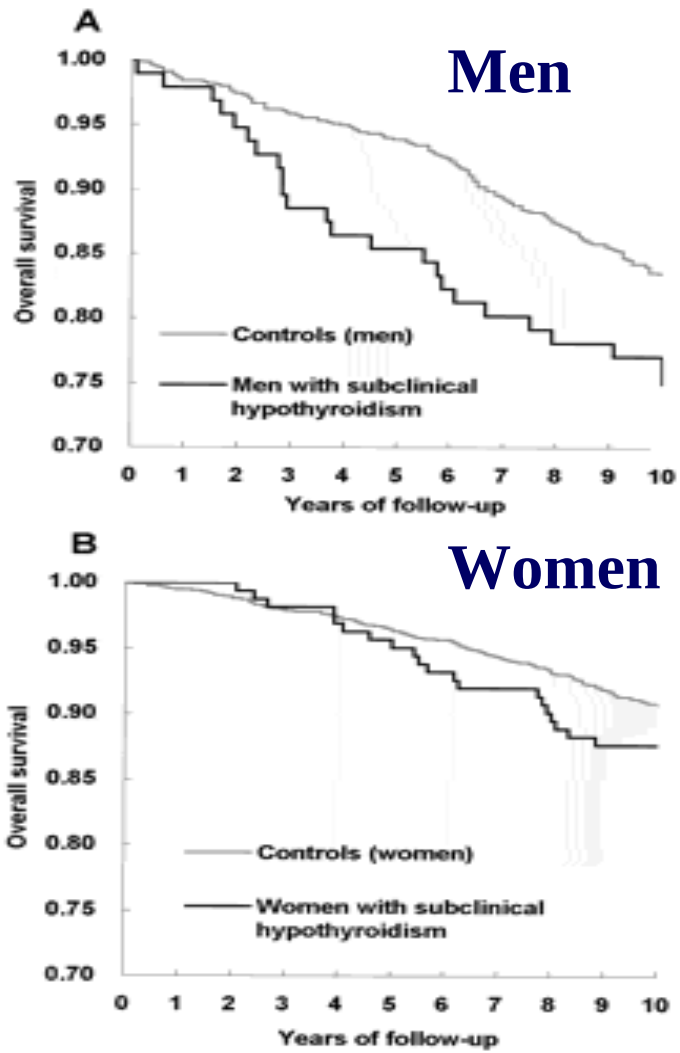
Hak AE et al *Annals Int Med,* 2000

"Minimally" Elevated TSH
CV Disease + Mortality

Japanese Study

- **2550 subjects**
- **10.2% TSH > 5**
- **240/257 (96%) TSH 5-10**

- **In patients with TSH 5-10:**
  - Overall OR 2.7
  - Men OR 4.5
  - Women OR 1.7
  - INDEPENDENT OF CVD Risk Factor



p<0.05

NS

Imaizumi et al. *JCEM*. 2004.

Minimally Elevated TSH and Lipids

- **45 Subclinical Hypo Patients**

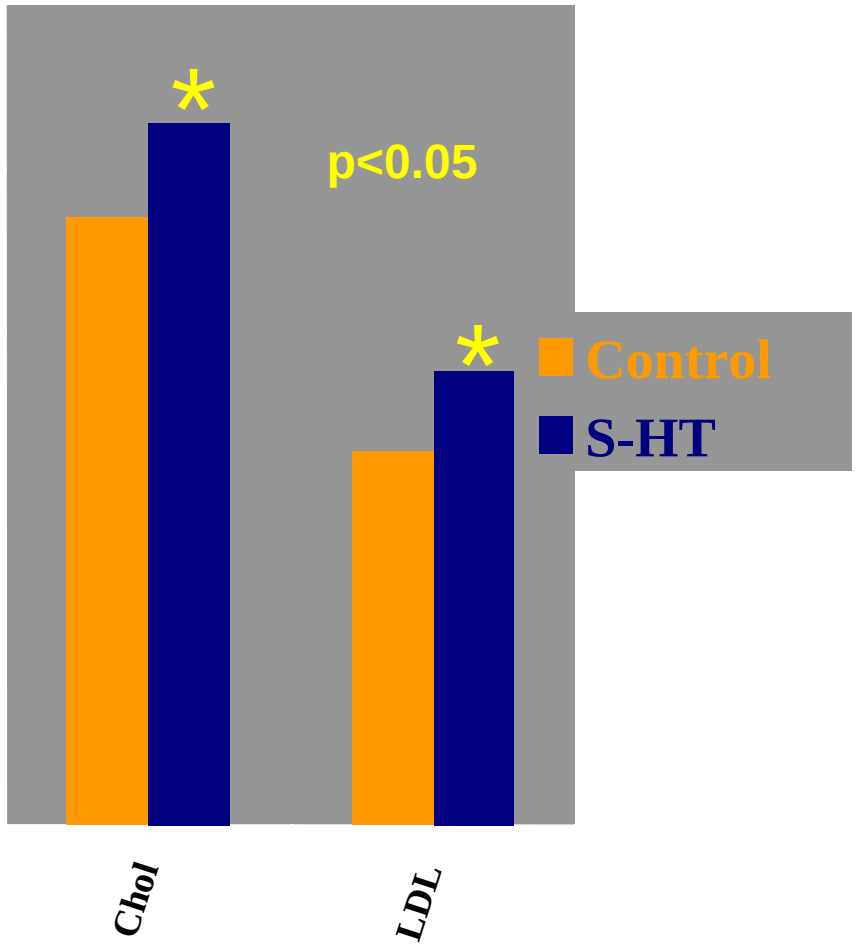
  TSH = 6.3 uU/ml

- **32 matched controls**

  TSH = 1.2

  (gender, age, BMI)

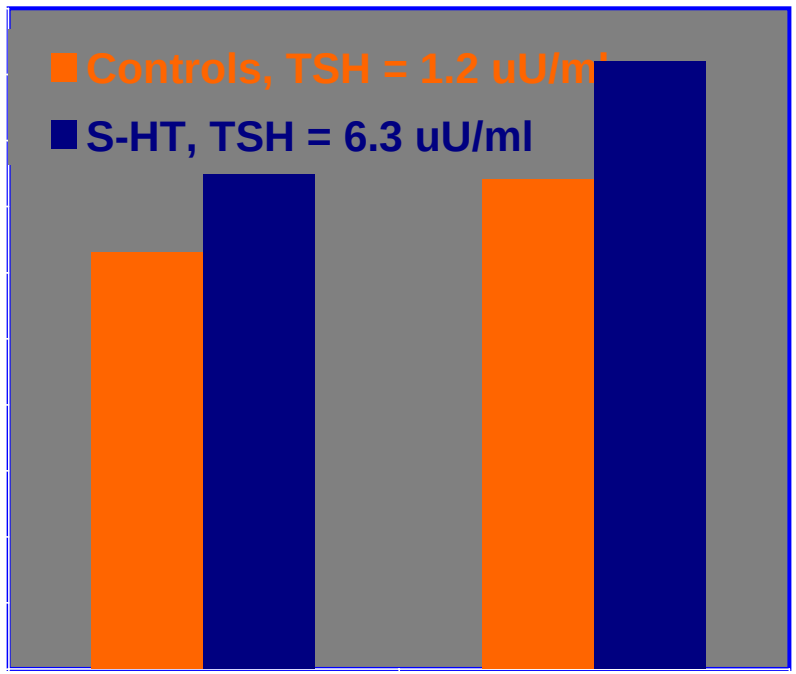
- **No obesity, smokers, DM.**
- **Blinded RCT**



Monzani F JCEM, 2004

Sub-Clinical Hypothyroidism and Increased Carotid Artery Intimal Media Thickness

- **45 SubClinical Hypothyroid Patients**
  - 78% with TSH <10
- **32 matched euthyroid controls (gender, age, BMI)**
- **No obesity, smokers, DM.**
- **Double Blind RCT**



Carotid Artery IMT by US as a marker of early atherosclerosis

Monzani F JCEM, 2004

Effects of Subclinical Thyroid Dysfunction on the Heart

Bernadette Biondi, MD; Emiliano A. Palmieri, MD; Gaetano Lombardi, MD; and Serafino Fazio, MD

Background: Mounting evidence indicates that subclinical thyroid dysfunction has important clinical effects and prognostic implications, supporting the view that it is not a compensated biochemical change sensu strictu.

Purpose: To review clinical information on the effects of subclinical thyroid dysfunction on the heart.

Data Sources: English-language articles identified from files and a MEDLINE search (1970–September 2001), references of relevant articles, textbooks, and meeting abstracts.

Study Selection: Reports on the effects of subclinical hypothyroidism and subclinical hyperthyroidism on the cardiovascular system in humans.

Data Extraction: Data on cardiac structure and performance, arrhythmias, and risk for coronary artery disease were independently assessed by all authors and summarized.

Data Synthesis: Subclinical hypothyroidism is associated with impaired left ventricular diastolic function at rest, systolic dysfunction on effort, and enhanced risk for atherosclerosis and myocardial infarction. Subclinical hyperthyroidism is associated with increased heart rate, atrial arrhythmias, increased left ventricular mass with marginal concentric remodeling, impaired ventricular relaxation, reduced exercise performance, and increased risk for cardiovascular death. All abnormalities were reversed by restoration of euthyroidism (subclinical hypothyroidism) or were blunted by β-blockade and tailoring of the L-thyroxine dose (subclinical hyperthyroidism).

Conclusion: The heart responds to the minimal but persistent changes in circulating thyroid hormone levels typical of subclinical thyroid dysfunction. Thus, the condition is not a compensated biochemical change sensu strictu, and timely treatment should be considered in an attempt to avoid adverse cardiovascular effects.

Ann Intern Med. 2002;137:904-914. www.annals.org

For author affiliations, see end of text.

ORIGINAL INVESTIGATION

Subclinical Thyroid Dysfunction as a Risk Factor for Cardiovascular Disease

John P. Walsh, MBBS, PhD; Alexandra P. Bremner, PhD; Max K. Bulsara, MSc; Peter O'Leary, PhD; Peter J. Leedman, MBBS, PhD; Peter Feddema, BSc; Valdo Michelangeli, PhD

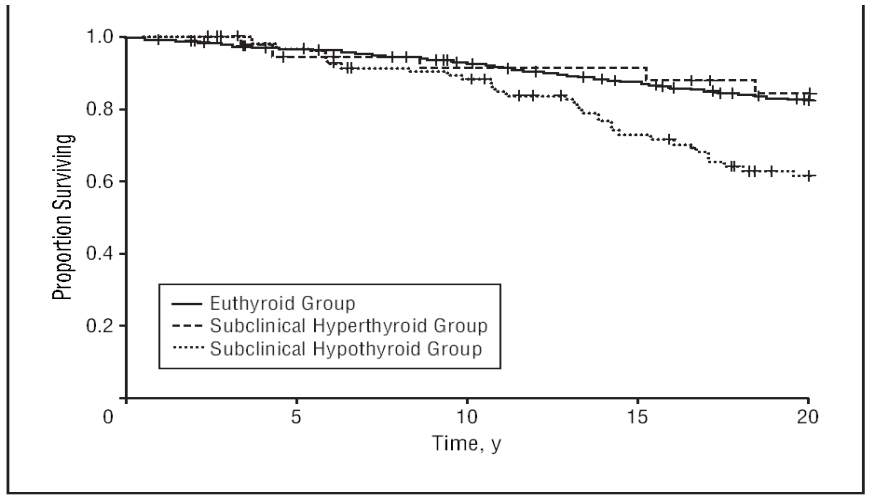


Figure. Kaplan-Meier plots for survival free of coronary heart disease events (fatal or nonfatal) in subjects without coronary heart disease at baseline.

Table 4. Hazard Ratios for Coronary Heart Disease Events (Fatal and Nonfatal) in the Longitudinal Analysis of Subjects Free of Coronary Heart Disease at Baseline*

Variable	Subclinical Hyperthyroid Group (n = 37)	Euthyroid Group (n = 1752)	Subclinical Hypothyroid Group (n = 101)	Subclinical Hypothyroid Group: Thyrotropin ≤10.0 mIU/L (n = 77)	Subclinical Hypothyroid Group: Thyrotropin >10.0 mIU/L (n = 24)
Coronary heart disease events					
Observed	5	229	33	23	10
Expected	6.0	245.0	14.7	10.8	3.8
Hazard ratio (95% confidence interval)					
Age and sex adjusted	1.0 (0.4-2.5)	1.0	1.7 (1.2-2.4)	1.5 (1.0-2.3)	2.2 (1.2-4.2)
P value	.79	. . .	<.01	.06	.01
Further adjusted†	1.3 (0.6-3.3)	1.0	1.8 (1.2-2.7)	1.6 (1.0-2.6)	2.6 (1.3-5.3)
P value	.51	. . .	<.01	.04	<.01

Arch Intern Med. 2005;165:2467-2472

2.108 patients (>50 years old)

Cross-sectional analysis,
S-HT (n=119) had a significantly **higher prevalence of CHD** than euthyroid (n=1906) (OR 1.8).

Longitudinal analysis (20 y.)
S-HT (n=101), **21 cardiovascular deaths** observed (HR, 1.5)
and **33 coronary heart disease** (HR, 1.7).

The increased risk of coronary heart disease events remained significant after further adjustment for standard cardiovascular risk factors. **Subclinical hypothyroidism may be an independent risk factor for coronary heart disease.**

ORIGINAL INVESTIGATION

Subclinical Hypothyroidism and the Risk of Heart Failure, Other Cardiovascular Events, and Death

Nicolas Rodondi, MD, MAS; Anne B. Newman, MD, MPH; Eric Vittinghoff, PhD; Nathalie de Rekeneire, MD; Suzanne Satterfield, MD; Tamara B. Harris, MS, MD; Douglas C. Bauer, MD

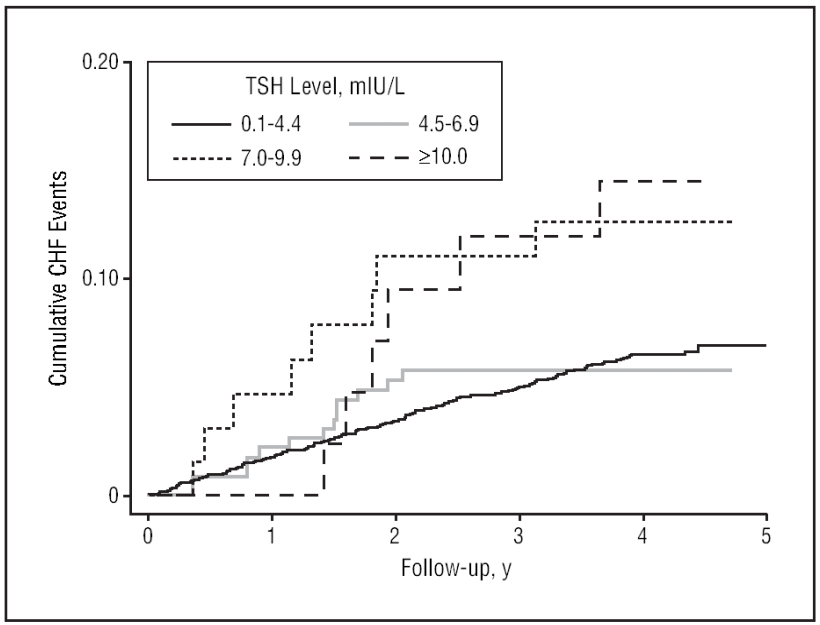


Figure. Cumulative congestive heart failure (CHF) events in older subjects according to thyrotropin (TSH) levels. The rate of CHF events increased with higher TSH levels (P=.03 for trend). Participants with a TSH level of 7.0 mIU/L or greater had a higher rate of CHF events compared with euthyroid participants (P=.006); this was not the case for those with a TSH level between 4.5 and 6.9 mIU/L.

3.075 patients, aged 70 to 79 at enrollment, follow-up 4 years.

Subclinical hypothyroidism was present in 12.4% of the participants.

CHF events occurred more frequently among those with a TSH level of **>7.0** mIU/L, but not among those with TSH levels between 4.5 and 6.9 mIU/L.

In multivariate analyses, the **risk of CHF** was higher among those with high TSH levels (TSH of 7.0-9.9 mIU/L: **HR, 2.58** and TSH of 10.0 mIU/L HR, **3.26**).

Subclinical hypothyroidism is associated with an increased risk of CHF among older adults with a TSH level of 7.0 mIU/L or greater, but **not with other cardiovascular events and mortality**.

Arch Intern Med. 2005;165:2460-2466

Ipotiroidismo subclinico & stato mentale

- Several intervention trials have suggested that S-HT is associated with **memory deficits** in younger individuals that are **reversible** to some extent with thyroid hormone therapy.
- Cross-sectional studies of **geriatric populations** have **not shown differences** in **cognitive function** between euthyroid individuals and those with mild hypothyroidism.
- In cross-sectional studies focusing on **depression** in geriatric populations, some found **a possible relationship** between depression and **elevated TSH** levels, while others did not.

Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment

Bono G, Fancellu R, Blandini F, Santoro G, Mauri M. Cognitive and affective status in mild hypothyroidism and interactions with L-thyroxine treatment.
Acta Neurol Scand 2004: 110: 59–66. © Blackwell Munksgaard 2004.

Objectives – While clinical hypothyroidism is associated with frank neuropsychological and affective alterations and is considered one of the causes of reversible dementia, the occurrence of these alterations and their treatment in mild hypothyroidism (MH) remains a controversial issue. Our aim was therefore to evaluate cognitive and psychological functions in a selected population of recently-diagnosed MH patients with minor subjective symptoms. *Materials and methods* – Thirty-six MH women (mean age 51.9 ± 13.5 years) were observed after a careful assessment had excluded subjects with neurological, psychiatric and/or somatic disorders, or confounding conditions. The subjects were evaluated for thyroid function and tested with an extensive battery of neuropsychological tests and psychological rating scales, in basal conditions and after 6 months of L-thyroxine treatment. *Results* – Baseline neuropsychological performance was within the normal range, while an age-dependent reduction was found in attentive function. After L-thyroxine treatment, an increase in serum fT4 was detected in parallel with thyroid stimulating hormone (TSH) reduction. Verbal fluency and depression scores showed a slight improvement. A positive correlation was found between TSH reduction and improved mood scores. *Conclusion* – From the analysis of the results, treatment of asymptomatic MH would seem advisable in order to re-set hormonal levels and, particularly in older subjects, to protect the brain against the potential risk of cognitive and affective dysfunctions.

G. Bono[1], R. Fancellu[1], F. Blandini[2], G. Santoro[3], M. Mauri[1]

[1]Unit of Neurology, Ospedale di Circolo, University of Insubria, Varese, Italy; [2]IRCCS C. Mondino Institute of Neurology, Pavia, Italy; [3]Department of Internal Medicine, Ospedale di Circolo, University of Insubria, Varese, Italy

Key words: depression; L-thyroxine; neuropsychological functions; reversible dementia; subclinical hypothyroidism; thyroid hormones; TSH

Giorgio Bono, Unit of Neurology, Ospedale di Circolo, University of Insubria, 57 Viale Borri, 21100 Varese, Italy
Tel.: +39-0332-278427
Fax: +39-0332-261440
e-mail: neurova@tin.it

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Ipotiroidismo subclinico & stato funzionale

Thyroid Status, Disability and Cognitive Function, and Survival in Old Age

Jacobijn Gussekloo, MD, PhD
Eric van Exel, MD, PhD
Anton J. M. de Craen, PhD
Arend E. Meinders, MD, PhD
Marijke Frölich, PhD
Rudi G. J. Westendorp, MD, PhD

Context Despite the equivocal outcomes of randomized controlled trials, general clinical opinion favors screening and treatment of elderly individuals with subclinical thyroid disorders.

Objectives To determine whether subclinical thyroid dysfunction should be treated in old age and the long-term impact of thyroid dysfunction on performance and survival in old age.

Design, Setting, and Participants A prospective, observational, population-based follow-up study within the Leiden 85-Plus Study of 87% of a 2-year birth cohort (1912-1914) in the municipality of Leiden, the Netherlands. A total of 599 participants were followed up from age 85 years through age 89 years (mean [SD] follow-up, 3.7 [1.4] years).

Main Outcome Measures Complete thyroid status at baseline; disability in daily life, depressive symptoms, cognitive function, and mortality from age 85 years through 89 years.

Results Plasma levels of thyrotropin and free thyroxine were not associated with disability in daily life, depressive symptoms, and cognitive impairment at baseline or during follow-up. Increasing levels of thyrotropin were associated with a lower mortality rate that remained after adjustments were made for baseline disability and health status. The hazard ratio (HR) for mortality per SD increase of 2.71 mIU/L of thyrotropin was 0.77 (95% confidence interval [CI], 0.63-0.94; $P=.009$). The HR for mortality per SD increase of 0.21 ng/dL (2.67 pmol/L) of free thyroxine increased 1.16-fold (95% CI, 1.04-1.30; $P=.009$).

Conclusions In the general population of the oldest old, elderly individuals with abnormally high levels of thyrotropin do not experience adverse effects and may have a prolonged life span. However, evidence for not treating elderly individuals can only come from a well-designed, randomized placebo-controlled clinical trial.

JAMA. 2004;292:2591-2599 www.jama.com

THYROID DYSFUNCTION IN ELderly individuals often occurs unnoticed. Hence, screening for both hypothyroidism and hyperthyroidism has been recommended, especially in old age.[1,2] Apart from finding individuals with previously unrecognized overt hypothyroidism and hyperthyroidism, screening will also reveal persons with subclinical thyroid dysfunction. These individuals have abnormal plasma levels of thyrotropin combined with normal plasma levels of free thyroxine.

Subclinical thyroid dysfunction has been associated with various negative clinical outcomes and an increased risk of overt thyroid dysfunction. Two recent literature reviews of subclinical thy-

Table 2. Baseline Characteristics for Clinical Strata of Thyroid Function*

	Abnormally Low Thyrotropin†			Abnormally High Thyrotropin§		
	Overt Hyperthyroidism	Subclinical Hyperthroidism	Normal Level of Thyrotropin‡	Subclinical Hypothyroidism	Overt Hypothyroidism	*P* Value for Trend‖
No. of participants	2	17	472	30	37	
Body mass index	21.5 (2.3)	25.6 (5.1)	27.1 (4.5)	27.7 (3.8)	28.3 (4.8)	.02
Total cholesterol, mmol/L	5.6 (0.7)	5.4 (1.5)	5.7 (1.1)	6.4 (1.3)	5.8 (1.0)	.04
Triglycerides, mmol/L	1.3 (0.5)	1.7 (1.1)	1.5 (0.7)	1.9 (1.1)	1.9 (1.2)	.004
C-reactive protein, mg/L	4.8 (2.0)	5.4 (2.6)	4.8 (2.9)	7.4 (2.6)	4.4 (7.9)	.77

SI conversion factors: To convert total cholesterol, divide by 0.0259; triglycerides, divide by 0.0113.
*Data are presented as mean (SD) except for C-reactive protein, which is geometric mean (SD).
†Defined as below 0.3 mIU/L.
‡Defined as 0.3 to 4.8 mIU/L.
§Defined as above 4.8 mIU/L.
‖Differences in mean baseline characteristics were analyzed with analysis of variance test for linearity.

At the start of the follow-up period, individuals who had elevated serum thyrotropin levels at baseline had comparable activity, cognitive function, and depressive feelings compared with individuals with normal thyroid function. Thus, there was no evidence that overt or subclinical hypothyroidism affected elderly individuals' performance status or mood.

After 3 years, none of the individuals with subclinical hypothyroidism had progressed to overt hypothyroidism.

During the annual follow-up examination, those participants with increased serum thyrotropin levels actually had a similar or less rapid decline in specific disability measures compared with individuals with normal thyroid function.

In this prospective observational study of a population-based cohort of individuals aged 85 years, no consistent associations were found between thyroid status and ADLs, depressive symptoms, and cognitive performance, neither in the cross-sectional nor in the prospective analyses.

Gusselkoo, 2004

In summary, it appears that neither subclinical hypothyroidism nor overt hypothyroidism is a cause of decline in performance, altered cognition or mood, or long-term survival in the oldest old.

Cooper, 2004

Ipotiroidismo subclinico & outcome funzionale

Table 1. Demographic characteristics, mental and functional status on admission

		Normal thyroid function (n=1.073)	***S-HT (n=71)***	***p***
		Mean ± S.D.		
Demographic	***Age** (years)*	78.1±7.3	76.4±7.4	.000
	Female (%)	73.3	66.2	.000
Mental & Functional Status	***MMSE***	22.0±6.1	21.5±5.7	n.s.
	GDS	5.8±3.6	6.1±3.7	n.s.
	BARTHEL INDEX (last week)	62.6±28.7	57.3±30.6	n.s.

Table 2. Comorbidity, nutritional status and biomarkers of inflammation

		Normal thyroid function (n=1.073)	S-HT (n=71)	p
		Mean ± S.D.		
Comorbidity	***Burden od Diseases***	10.3±4.2	11.8±3.6	.005
	Drugs *(number on adm.)*	5.5±2.8	6.1±2.6	.002
Nutritional status & Inflammatory burden	***BMI (Kg/m²)***	26.6±5.9	27.9±4.9	n.s.
	Total cholesterol (mg/dl)	179.6±44.4	186.2±42.9	n.s.
	Albumin (g/l)	3.5±.4	3.4±.4	n.s.
	ESR (mm/h)	28.6±24.5	27.3±21.4	n.s.
	C-RP (U/dl)	2.1±5.1	2.1±4.5	n.s.

Tabella 3. Functional Outcome

	Normal thyroid function	S-HT	p
	(n=1.073)	(n=71)	
Balance and gait (Tinetti score)			
		Mean ± S.D.	
On admission	14.0±8.9	12.6±9.4	n.s.
On discharge	19.2±7.9	16.4±8.7	.005
Change admission to discharge	5.2±5.5	3.8±4.1	.005

Table 4. Determinants of Functional Recovery

Dependent variable
Delta-Tinetti

Adjusted R^2= .37 p<.005

Variables	B	95% C.I.	Sig.
Subclinical hypothyroidism	-2.2	- (3.3 – 1)	.001
Age	-.07	- (11 – .03)	.000
MMSE	.13	(.06 – .20)	.000
Depressive symptoms	-.11	- (.20 – .03)	.001
Tinetti score (on admission)	-.39	- (.4 – 36)	.000
Stroke	-.51	- (.3 – 13)	.000

Values were computed in multiple linear regression model adjusted for following diseases (heart diseases, diabetes and atrial fibrillation), and potential predictors as total cholesterol, albumin and c-reactive protein.

Presentazione “subclinica” & outcome

L’esempio del diabete

Impaired fasting glucose concentration in non diabetic patients with ischemic heart disease: a marker for a worse prognosis

EZ Fisman, M Motro, A Tenebaum, V Boyko, L Mandelzweig, S Behar

American Heart Journal, 2001

- 11.853 subject (>45 years) with documented CHD
- 3 groups:
  - non diabetic,
  - **IFG** (glucose 110-125mg/dl),
  - undiagnosed diabetic patients
- Follow-up: from 6 to 9 years
- **IFG**: consistent predictor of increased all cause (HR 1.4) and ischemic heart disease mortality (HR 1.3)

ARTICLE

Impaired Fasting Glucose and Cardiovascular Outcomes in Postmenopausal Women with Coronary Artery Disease

Alka M. Kanaya, MD; David Herrington, MD, MHS; Eric Vittinghoff, PhD; Feng Lin, MS; Vera Bittner, MD, MSPH; Jane A. Cauley, DrPH; Stephen Hulley, MD; and Elizabeth Barrett-Connor, MD

Ann Intern Med. 2005;142:813-820.

Commento (1)

- I nostri dati dimostrano che nei pazienti con ipotiroidismo sub-clinico è maggiore il rischio di scarso recupero funzionale dopo un periodo di riabilitazione motoria.
- Tale rischio è indipendente dalla comorbilità.
- In apparente contraddizione con i nostri dati, Gussekloo e collaboratori hanno recentemente dimostrato l'assenza di un legame tra S-HT e outcome quali stato funzionale, stato cognitivo e sintomi depressivi, a distanza di quattro anni.

Commento (2)

- Dal nostro punto di vista, l'effetto clinico dell'S-HT sullo stato funzionale potrebbe evidenziarsi in corso di aumentata richiesta energetica, come avviene nel breve periodo della riabilitazione motoria. Nel lungo periodo, invece, la relazione esistente tra tiroide e stato funzionale, potrebbe essere mascherata dall'instaurarsi di un nuovo equilibrio funzionale.
- L'S-HT influenzerebbe l'outcome funzionale, attraverso un ridotto "rate metabolico", la cui importanza appare critica durante la fase di riabilitazione.

Conclusioni

- L’S-HT è molto probabilmente associato ad eventi cardiovascolari, probabilmente mediati dalle alterazioni del metabolismo lipidico.
- Sono insufficienti i dati della letteratura relativamente all’ associazione tra S-HT e funzioni cognitive, tono dell’umore, perdita dell’autosufficienza e sopravvivenza.
- Il livello di TSH sierico sembra comunque essere alla base delle alterazioni fisiopatologiche tipiche dell’ipotiroidismo (sia overt che subclinico)
- Le evidenze esistenti, sembrano accreditare la necessità di effettuare screening della funzione tiroidea nei pazienti anziani asintomatici
- Ad oggi non esistono sufficienti evidenze riguardo all’efficacia del trattamento dell’ipotiroismo subclinico, *ma potrebbe essere ragionevole il trattamento nei pazienti anziani con patologia cardiovascolare*?
- I nostri dati, in linea con le evidenze relative al ruolo del IFG rispetto all’outcome cardiovascolare, aprono delle prospettive nel rapporto tra malattie a presentazione “subclinica” ed outcome nell’anziano
- Lo scarso recupero funzionale nei pazienti anziani potrebbe rappresentare un ”sintomo geriatrico” dell’S-HT che non dovrebbe quindi essere considerato solo una diagnosi di laboratorio.

*The **young man** knows the rules, but the **old man** knows the exceptions.*

Oliver Wendell Holmes