بسم الله الرحمن الرحيم

SUBCLINICAL HYPOTHYROIDISM: PRESPECTIVES
A HIDDEN MENACE OR MORE SMOKE BUT NO FIRE?

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Objectives , AGENDA

- Definition
- Normal TSH
- Synonyms
- Prevalence
- Causes
- Excluding SCH is a must in ??
- Manifestations; Associations
- Complications; (A hidden menace)
- Screening
- To treat or not to treat

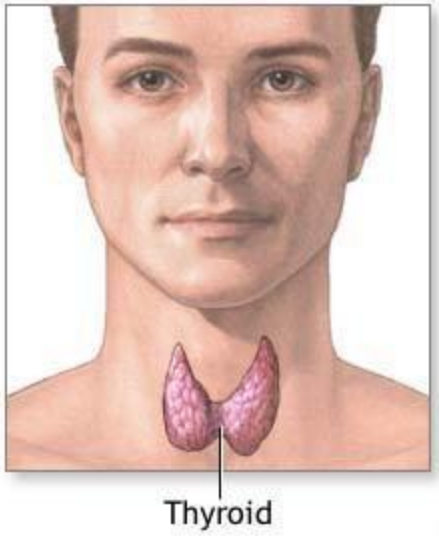
The basic concept of the function of thyroid hormones

- Up-regulate the function of other hormones e.g. growth hormone & catecholamines

- They heat up the other endocrinal functions

The Thyroid Gland is as important as heart

decreased
Thyroid hormones



increased
Thyroid hormones

Hypothyroidism

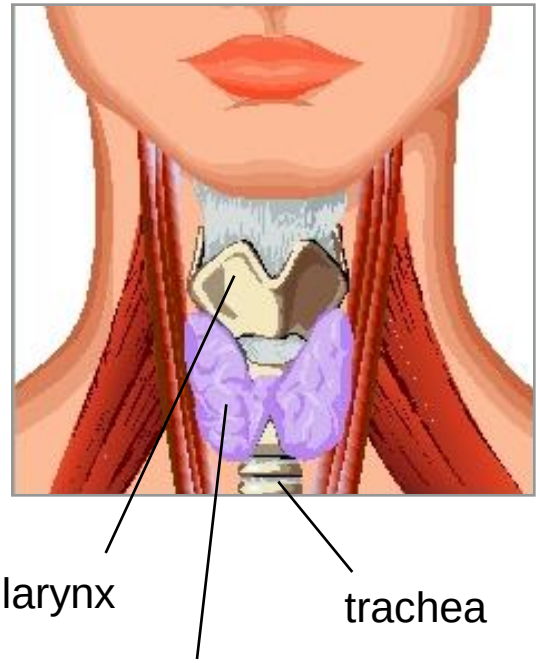
Hyperthyroidism

Hypothyroidism is much more common than Hyperthyroidism

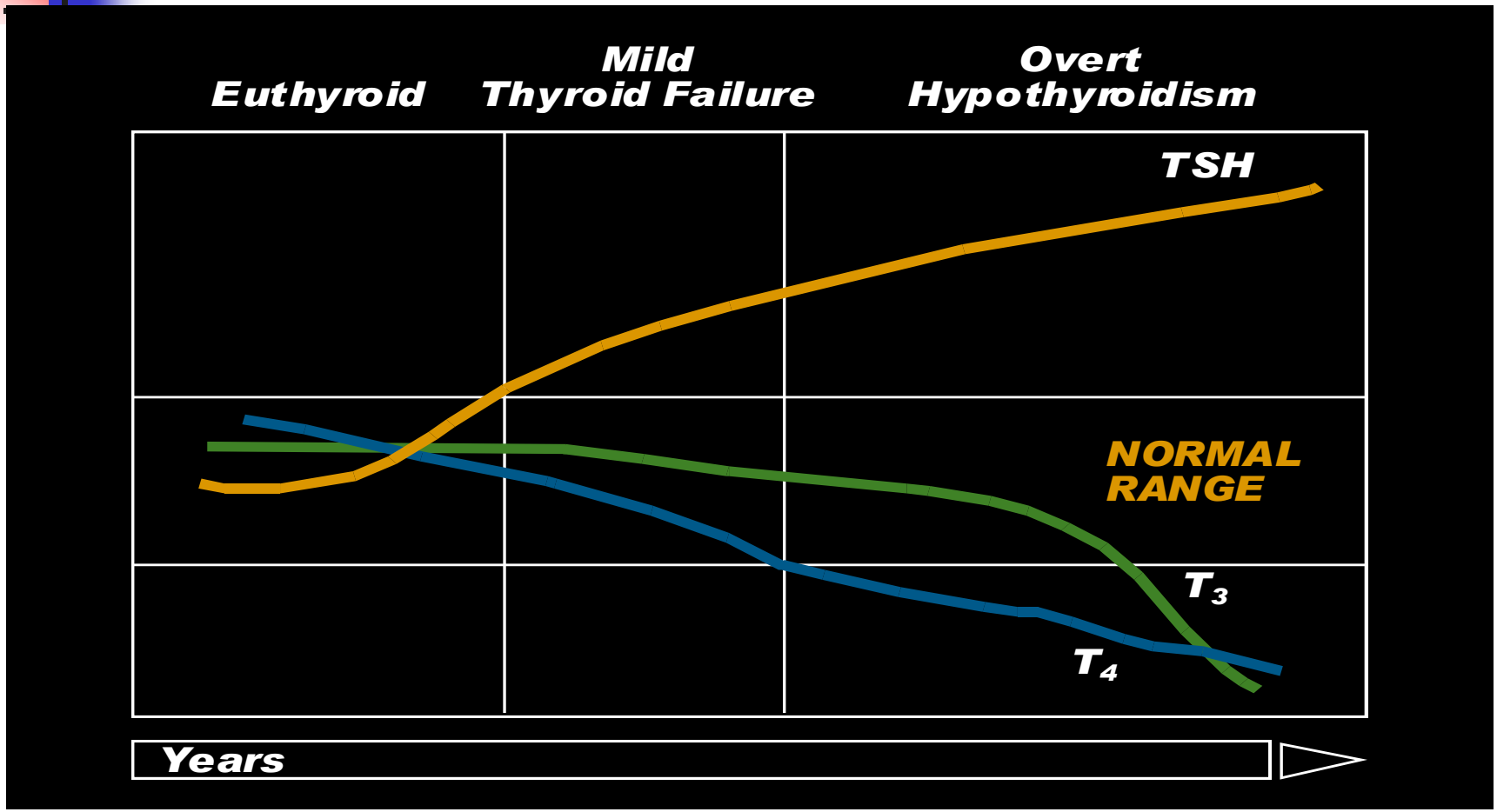
The thyroid: the “heart” of metabolism

Involvement of thyroid function in:

- Growth and development, fertility
- Energy metabolism
- Protein and carbohydrate metabolism
- Fat metabolism
- Bone metabolism
- Cardiovascular system
- Muscle function
- Brain, nervous system& psyche



Development of hypothyroidism



Adapted from Ayala AR, Wartofsky L; The Endocrinologist 1997; 7:44

Definition: SCH

Patients with elevated thyrotropin (TSH) with a normal FT4, FT3 and usually with no clinical specific S or S

(Helfand, 2004)

Normal TSH levels

- NHANES III 0.45- 4.12 mIU/ L
- NACB 0.3- 3.01 mIU/ L
- AACE 0.4- 3.0 mIU/L
- Pregnancy 1st trimester 0.02- 2.5 mIU/L
- In the old the upper limit of TSH is 7.5 mIU/L,They are normal but their pituitaries had drifted upwards from normal aging

(Marriotti et al 2005)

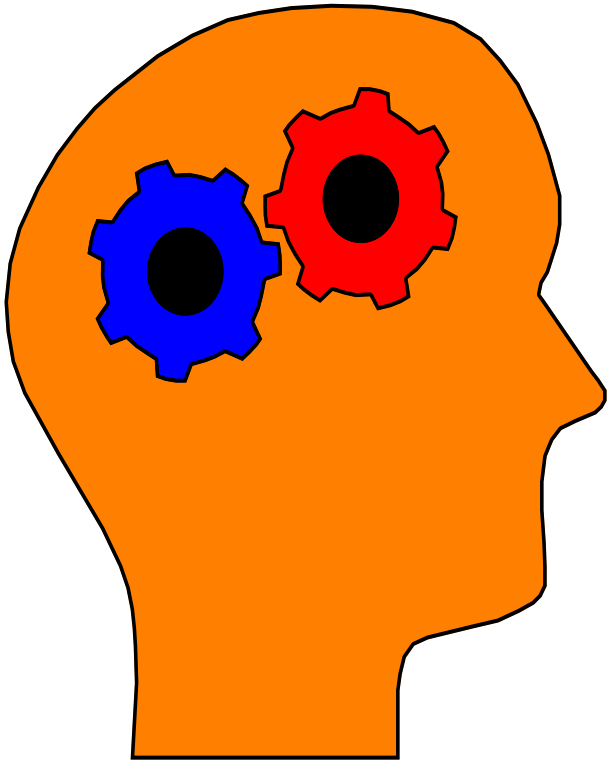
Thyroid Function in Elderly

- TSH levels tend to drop with age
- Several older patients have low FT4 with normal or minimally elevated TSH levels
- Several older patients have low TSH and normal FT4& FT3 and no evidence of thyroid dysfunction

Synonyms

- Subclinical hypothyroidism (SCH)
- Infraclinical hypothyroidism
- Biochemical hypothyroidism
- Mild tissue hypothyroidism
- Borderline hypothyroidism
- Compensatory thyrotropenimia (Sinsu Strictu) (to maintain a normal circulating thyroid hormone)
- Early hypothyroidism
- Aged drifted pituitaries

SENSITIVE TSH ASSAY- THE GREAT IRONY!



THE TSH ASSAY DETECTS INTRINSIC THYROID DISEASE MORE EFFICIENTLY THAN IT DETECTS DISEASE OF THE PITUITARY, WHERE IT IS HOUSED

Prevalence of SCH

- SCH; the most frequent thyroid disorders worldwide (Kvetny et al 2004, Razvi et al 2009)
- The most frequent endocrinopathy
- 20% of the populations esp. female and old ages
- The prevalence depends on gender and locality
- Age (in old old age> 75, the upper limit of TSH is 7.5mIU/ L)

Prevalence of SCH (cont.)

- In Egypt , goiter is endemic in Oases and south of Isna (Gholioungui 1960, Refaie 1966)
- Thyroidectomies is a common surgical insult to Egyptian thyroid frequently unnecessary
- Autoimmune disorders are not rare
- Smoking habit is very common (smoking aggravate the clinical and metabolic consequences of HT) (Muller et al 1995)
- A need for better clear awareness

Prevalence of thyroid dysfunction in elderly population (age > 35 yrs.)

Condition	Reported prevalences in adult population, %
Hypothyroidism	2
Mild (subclinical) hypothyroidism	5- 17**
Hyperthyroidism	0.2
Mild (subclinical) hyperthyroidism (TSH<0.1, normal T4,T3)	0.1- 6.0

(Adapted from Vanderpump and Tunbridge, 2000)

Causes of SCH

the same as overt hypothyroidism

- Iodine deficiency
- Autoimmune thyroiditis (Hashimoto's, de Quervian thyroiditis)
- Goiterogens (cabbage, couliflower, turnip)
- Metabolic goiter Familial; enzymatic block
- Iatrogenic thyroidectomy,I_{131}
- Drugs: antithyroid drugs Amiodarone, iodine excess, lithium, interferon
- Associated with

- autoimmune disorders; DM I, RA &Vitiligo
- IR, MS, DM II (Dessein et al 2004)

We are living inThe Era of Hips & Waists

Types of thyroiditis

- Acute (suppurative, thyroid abscess) infectious causes
- Subacute (granulomatous, de Quervians) possibly post-viral
- Postpartum (painless) autoimmune (anti-TPO antibodies) same pattern as subacute
- Silent (painless) autoimmune
- Drug-induced; amiodarone, lithium, alpha-interferon
- Traumatic, rare (palpation, radiation) seat belt injury, choking injury
- Hashimotos (chronic lymphocytic) autoimmune anti-TPO
- Riedels (fibrous) rare sclerosing disease

Symptoms and Signs of SCH

By definition no evident or manifest S or S

However

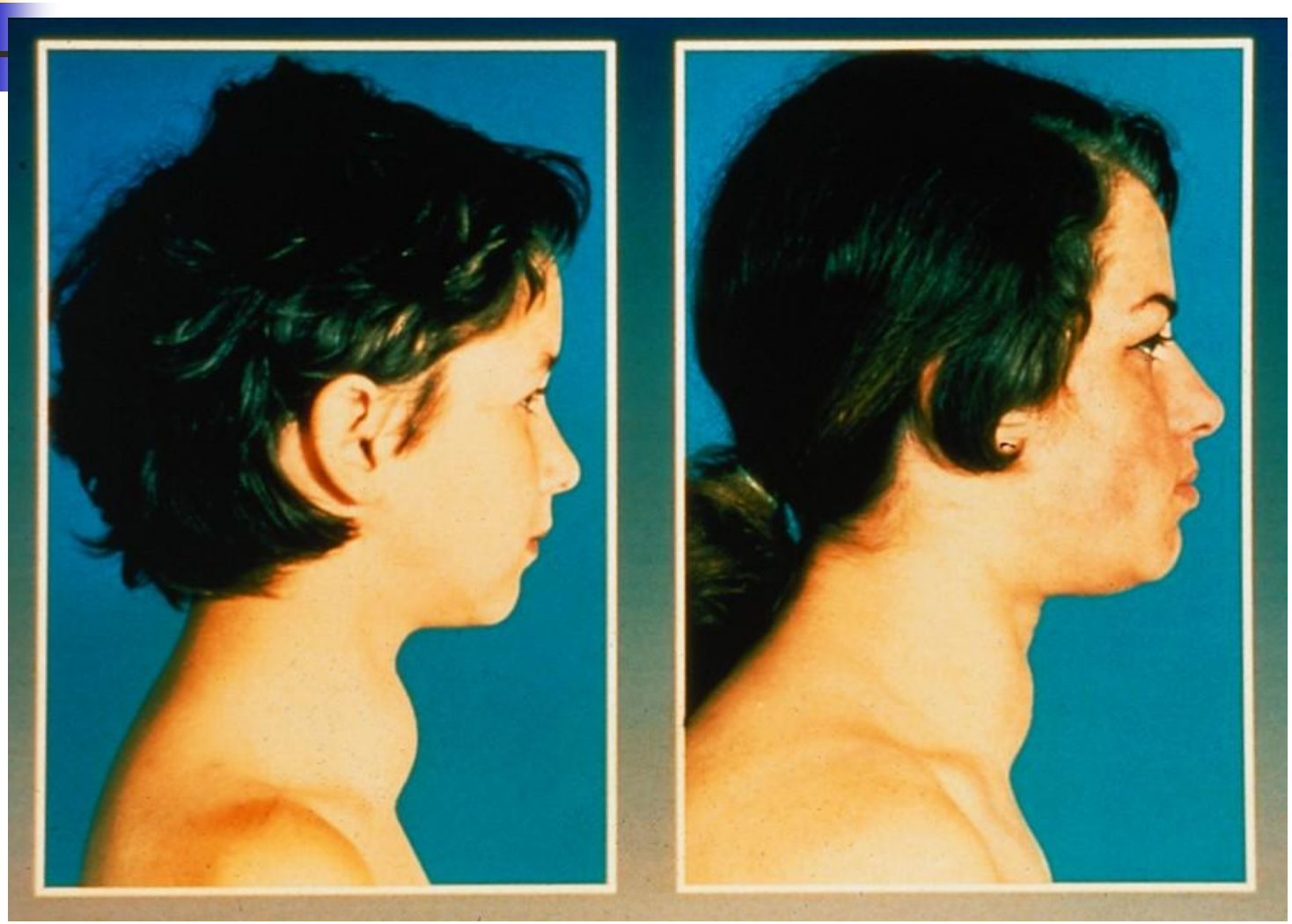
- Because there are thyroid hormone receptors in virtually every tissue of the body (Wartofsky et al 2006)
- Because thyroid gland is the heart of metabolism (CHO, fat, protein)
- Because thyroid hormones heat up other hormones (GH, catecholamines)

SCH may be associated with many S&S for the expert thyroidologist&physician

Individual& conditions in whom SCH has to be suspected

- Previous thyroid insults (**scar**, goiterogens, drugs)
- Goiter
- Autoimmune disorders (DM I)
- Type II DM, IRS
- Unexplained symptoms

Two young women with goiter

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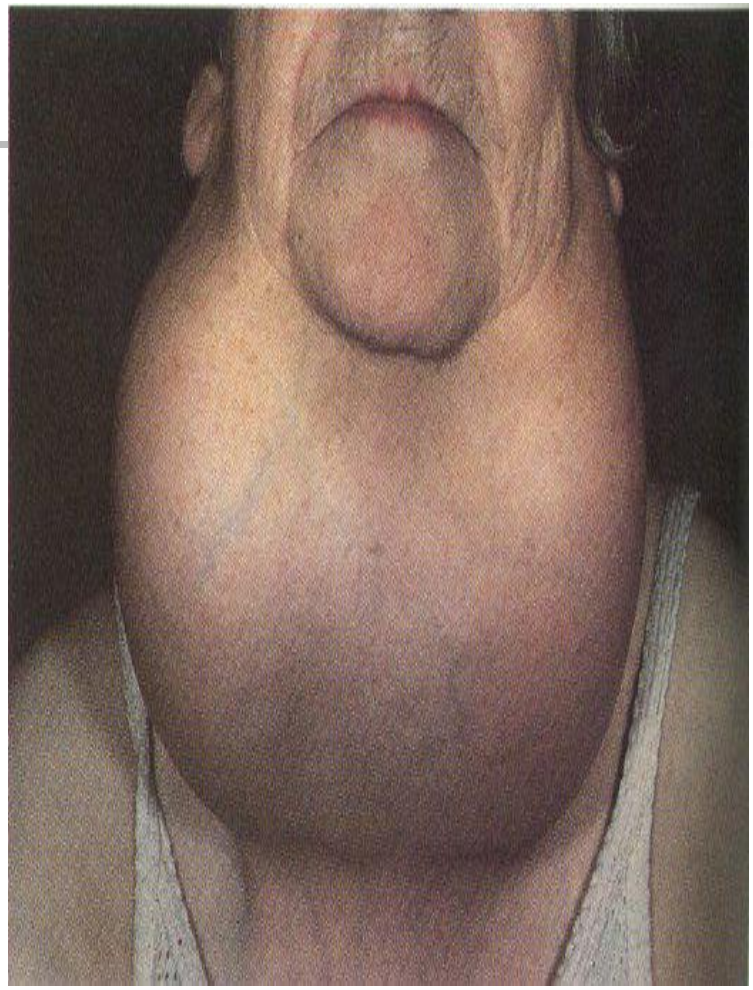


Unexplained symptoms

- Fatigability
- Undue tiredness
- Poor quality of life (measured by Psychological General Wellbeing Index PGWI)
- Depression& cognitive impairment esp. in elderly (Hogervorst et al 2008)
- **Weight gain** with poor response to ttt
- Obesity resistance to life style modification
- Dry skin
- Carotinodermia
- Cold intolerance
- Constipation

"Why do you call it a thyroid 'problem' when it's giving me an excuse for the 20 pounds I gained this year???"

Unexplained symptoms (cont.)

- Infertility (male& female)
- Menstrual irregularity
- Galactorrhea

In pregnancy:

- Abortion
- PIH
- Pre eclampsia
- Growth restriction
- Poor neuropsych development& fetal survival
- ↓ IQs

Unexplained signs

- HTN
- Dyslipidemia
- Rapid progression of D. nephropathy& CVD in type II DM (Chen et al 2007)
- Premature atherosclerosis
- ↓ Ankle brachial index
- ↑ cIMT(Aortic AS with normal lipogram, Rotterdam study)
- ECG evidence of CAD (↑ QTc- ↑ QT dispertion)
- Ischaemic changes

Late Ahmad Abd El Aziz Ismaael& Late Gholuongui 1965

Potential Risks of SCH (The Hidden Menace)

- Progression to overt HT(50% of persons within few years)
- Dyslipidemia
- CV complications
- Neurological and neuropsychatric effect
- Depression (the only curable depression)
- Suicidal tendency

Dyslipidemia:

SCH lasting > 6-12 months is associated with an

- Atherogenic lipid- profile& hypercoagulable state
- Hypercholestrolemia
- Hypertriglyceridemia
- Post prandial lipemia

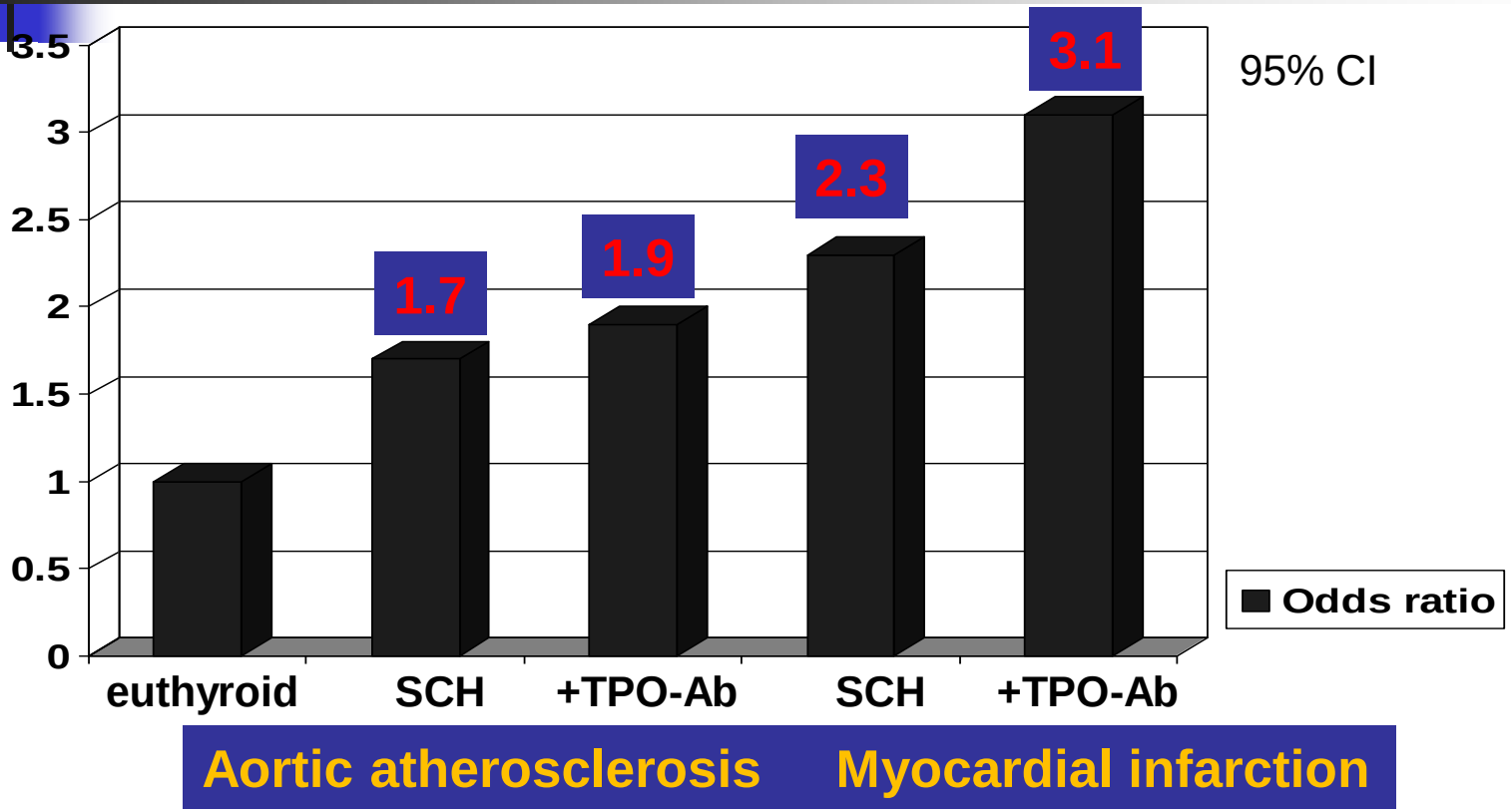
  Oral lipid tolerance test: PP lipemia (↑TG > 80%) is7 fold more in mild SCH (Tanaci et al 2006)
- ↑ LDL-cl
- Slight ↓ HDL-cl
- TTT of SCH by LT4 reduces statin induced myopathy
- Consider LT4 before statin ttt in SCH

A hidden menace?

- ↑IHD (but only in subjects younger than 65) (Salman Ragvi et al 2008)
- Rotterdam Study (Hak et al 2000), higher prevalence of AS, MI, after adjustment of age, BP, BMI, smoking (Imazumi et al 2004)
- In SCH cardiac structure & function remain normal at rest, but impaired ventricular function during exercise
- SCH might increase the risk of transient AF after CABG (Park et al 2009)
- Evidence of peripheral ischeamia, CAD& carotid atherosclerosis in SCH in young& old age groups (W.Refaie et al 2010)

Subclinical hypothyroidism (SCH): a cardiovascular risk factor

(increased TSH>4, normal fT4)



Hak AE et al. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in 1149 elderly women: the Rotterdam Study. Ann Intern Med 2000;132(4):270-8

A hidden menace? (cont.)

- SCH can worsen many risk factors for CVD including HTN, ↑LDL cl and abnormal endothelial function
- SCH influences ventricular repolarization
- (higher QT dispersion, prolonged QTc interval and autonomic modulation of the heart) (Owecki et al 2006)
- Acceleration of D. nephropathy (Chen et al 2007)

More smoke but no fire

- In the Wickham survey in England for 20 years, there was no relationship between SCH and the incidence of IHD& mortality (Vanderpump et al 1996)
- Meta analysis no undue harm (Rodondi et al 2006, Salman Razvi et al 2009)
- Based on observational and interventional studies- some arguments on the benefits of euthyroidism restoration only in patients with TSH superior to 10 mu/ L (Schlienger et al 2006)

SCH and Pregnancy

- SCH ttt is mandatory & pre conceptional assessment is a must to avoid
- Pre eclampsia
- PIH
- Poor neuropsychological development and survival of the fetus
- Goiter and hypothyroidism(fetal)
- Poor IQ
- 50% increase in the dose of T4 during 1st trimester
- Screening for SCH in pregnancy and post partum and post menopausal female with CAD regardless of age (Mayer et al 2006)

To TTT or Not to TTT

- A compensatory hyperthyrotropinemia. Sensu Strictu
- Aged pituitary

- The 4 trends in ttt:

1- TTT all

2- No ttt whatsoever

3- TTT when there is certain situation

4- Individual ttt (case by case)

To TTT or Not to TTT (cont.)

- Early ttt is advised not only to prevent progression to overt HT, but also to improve abnormal cardiac autonomic function and ventricular repolarization

  (Galettu et al 2006)

- Prudent (wise and careful, gradual building up the dosage of LT4 is mandatory)

To TTT or Not to TTT (cont)

- Start with a dose 0.2 U/Kg& ↑ every 2-4 weeks and check TSH/ 2 months, but no full replacement
- For special cases combination with T3 (active hormone)
- Discussion of therapy (team work endocrinologist, cardiologist, Psychatrist and neurologist)
- Avoid over dosage, because , they are more liable to develop AF
- Consider ttt for 3 months
- Individualize therapy for each patient

SCH

before

after ttt

An early case of myxedema treated with dessicated thyroid gland (usually from cow or pig)

Screening recommendations

(American Thyroid Association)

- Screening for mild thyroid failure by TSH

  - Beginning at age 35 years and every 5 years
  - Women (especially if infertile, pregnant, postpartum& postmenopausal)
  - The elderly (especially those with functional, physical or cognitive impairment)
  - Patients with a family history or personal past medical history of thyroid disorders or treatment

Ayala AR, Wartofsky L.e case for more aggressive screening and treatment of mild thyroid failure. Cleveland Clin J Med 2002;69(4):313-20

Screening recommendations (cont.)

- Patients with DM, cardiovascular dysfunction, hypercholesterolemia& other endocrinopathy
- Vitiligo
- Leukotrichia (premature gray hair)
- Pernicious anemia
- Patients with signs of underlying mild thyroid failure such as unexplained bradycardia, depression, or sleep apnea
- Chronic medications; lithium, amiodarone, expectorants with potassium iodide& interferon

Laboratory tests that may impose the need for screening

(1) Hypercholesterolemia
(2) Hyponatremia
(3) Anemia
(4) Increased CPK, LDH
(5) Hyperprolactinemia
(6) Elevated CEA

- Screening of all newborns for hypothyroidism has already been a widely accepted practice which in many countries is mandated by law

- What about Egypt?

Why should we screen for thyroid dysfunction?

- Because it has been shown by decision analysis that screening with THS testing is at least, as cost-effective as screening strategies for other common diseases e.g. DM, dyslipidemia, breast cancer
- This is more favorable in population older than 35 years, particularly in women US Preventive Services Task Force

Take home message

- The following four questions have to be solved (Werssel et al 2003)
- Q1: Does elevated TSH always develop overt HT?
- Q2: Do patients with SCH always develop overt HT?
- Q3: Are SCH symptomatic?
- Q4: Does ttt with LT4 cure these symptoms? If they exist?

Answer 1:

Does elevated TSH always develop overt HT?

Elevated TSH with normal FT4, ***can***, but does not necessarily mean thyroid failure (It is a mild form of thyroid failure)

Answer 2:

Do patients with SCH always develop overt HT?

- Yes if :
- S TSH > 10 mu/ L
- Positive TPO Ab, Thyroglobulin Ab,TSH receptors Ab
- Pregnancy, infertility
- Other risk factors for atherosclerosis& goiter etc. dyslipidaemia

(Corssmit& Wiersinga 2003)

Answer 3:

Are SCH symptomatic?

Typical thyroid specific symptoms (Wayne scoring, Zulewski) are not

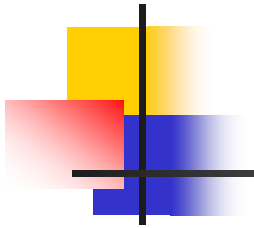
CV, neuropsychatric& altered risk factors for atherosclerosis are present

Answer 4:

Does ttt with LT4 cure these symptoms?
If they exist?

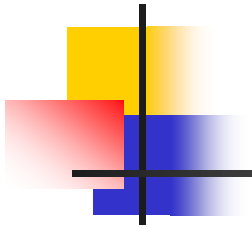
Some of the symptoms esp. Fatigability, undue tiredness& CV seem to be treatable by LT4 together with

improvement of quality of life



Diagnose the common and ttt the curable

(Late Mohammad Ibrahim 1970)



Thank you