

# **Subclinical hypothyroidism (SH) – to treat or not to treat?**

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# Defintion of SH in children and adolescents

Kaplowitz et al.: J Pediatr Endocrinol 2010. Bona et al.: J Clin Res Pediatr Endocrinol 2013.  
Monzani et al.: Eur J Endocrinol 2013. Seshardi et al.: Indian J Endocr Metab 2012  
O'Grady M, Cody D.: Arch Dis Child 2011

**TSH level of 5-10mU/l with normal values of total and free T4**

- **No clinical symptoms of hypothyroidism**
  - **delayed growth and bone age**
  - **weakness, fatigue, insomnia**
  - **decreased activity and attention disorder**
  - **feeling of coolness**
  - **dry skin and hair**
  - **delayed or (rarely) premature puberty**
  - **massive menstruation bleeding**
  - **normochromic anemia**
  - **dyslipidemia**
- **Mild status with no need for treatment**

# Is TSH level >5 mU/l an appropriate criterion for diagnosis of SH in all children?

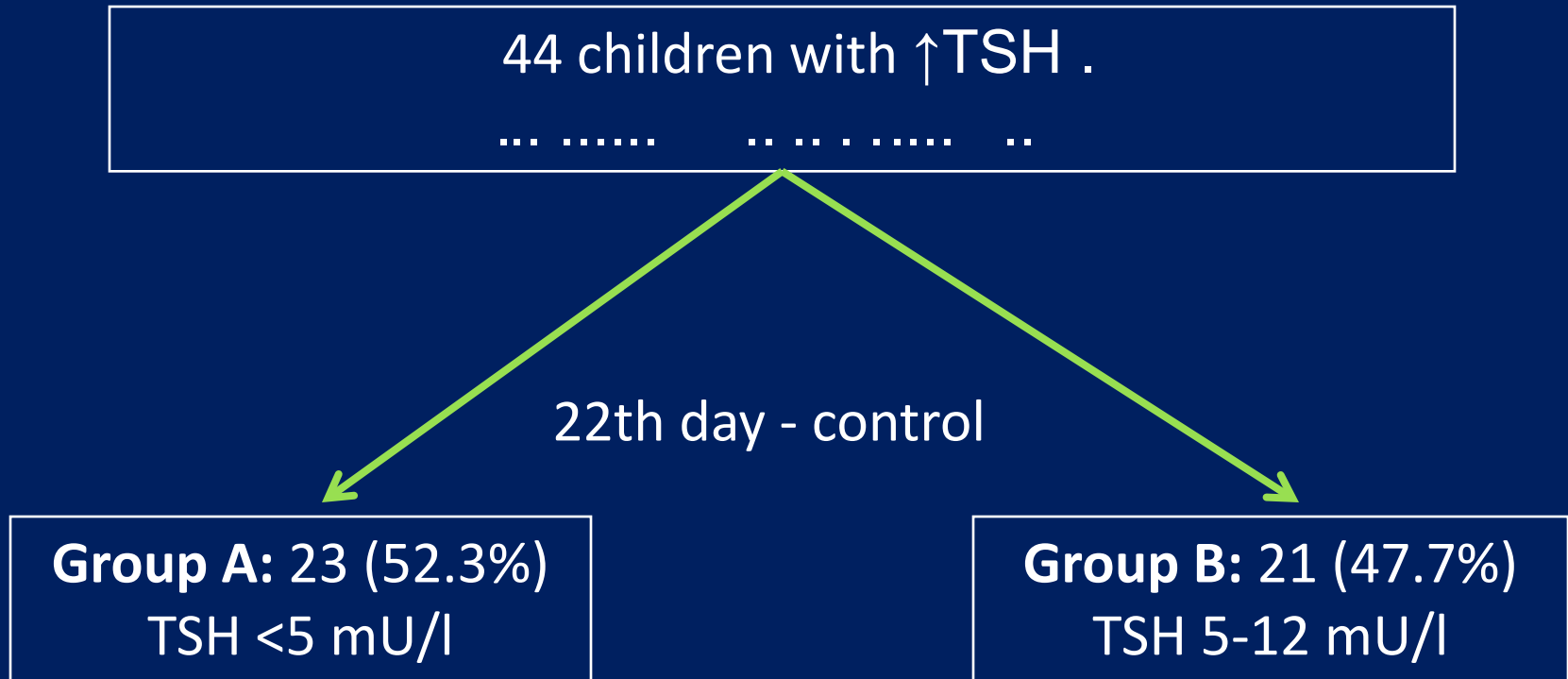
Kapelari K et al.: Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study: BMC Endocrine Disorders 2008;8:15

2200 children aged (years)	TSH (mU/l)			FT4 (pmol/l)		
	2.5	median	97.5 ↓	2.5 ↑	median	97.5
0-1/12	0.7	3.5	18	8.5	26	30.5
1/12-1.0	1.1	3.8	8.2	9.2	15.5	25.3
1-5	0.8	2.7	6.3	10.5	15.7	22.4
6-10	0.8	2.3	<u>5.4</u>	10.6	15.9	20.9
11-14	0.7	2.1	4.6	10.4	15.2	21.4
15-18	0.5	1.7	4.3	10.6	15.2	22.6

# Natural course of SH in children with neonatal hyperthyrotropinemia

- „false positive” result of neonatal screening
  - transient or constant hyperthyrotropinemia in later age?

# Natural course of SH in children of healthy mothers



# Natural course of SH

2<sup>nd</sup>- 3<sup>rd</sup> year of life  
(N=44)



**Group 1: 16 (36.4%)**  
TSH <4 mU/l  
(11A+5B)

**Group 2: 28 (63.6%)**  
TSH 4-10 mU/l  
(12A+16B)



Normal

5<sup>th</sup> year of life

9/28 (32%)  
Norm. TSH

19/28 (68%)  
↑TSH

Normal

8<sup>th</sup> year of life

Normal

14/19 (74%).  
↑TSH

Increased TSH values persisted until late childhood

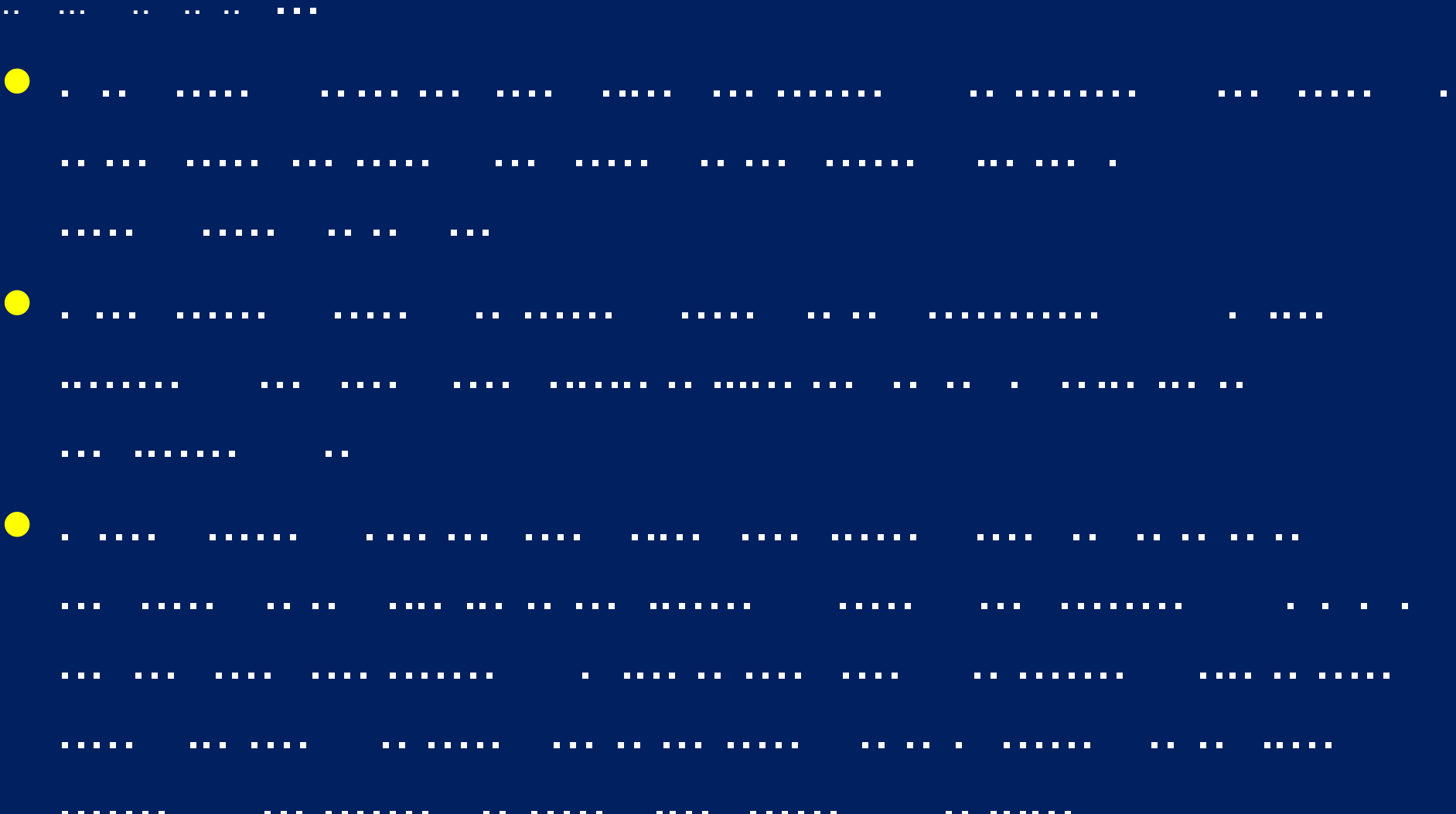
in 14 (32%) of 44 children with transient neonatal hyperthyrotropinemia

*Leonardi et al., JCEM  
2009*

# **Structural and genetic disorders in 44 children with neonatal hyperthyrotropinemia**

- **Abnormal thyroid ultrasound (19; 43%)**
  - **Hypoplasia of thyroid lobe (13)**
  - **General thyroid hypoplasia (3)**
  - **Small goiter (3)**
- **Mutation/polymorphism TPO (4)**
- **Mutation/polymorphism TSH-R (12)**

# Structural and genetic disorders in 44 children with neonatal hyperthyrotropinemia







# Mothers with autoimmune thyroiditis (+ antiTPO antibodies)

- control check out of the newborn between 2<sup>nd</sup> and 4<sup>th</sup> week of life
- in 1/3 of the newborns mild hyperthyrotropinemia
- In most cases self remission within 1<sup>st</sup> month of life
- only in ca. 2% of newborns transient treatment with LT4 was needed

# Reasons for estimating TSH levels

- Justified
  - . Neonatal screening
  - . Presence of goiter
  - . Symptom complex suggesting thyroid dysfunction
  - . Autoimmune disease
  - . Genetic syndromes (Turner, Down)
- In practice...
  - . Routine control evaluation
  - . Obesity
  - . Family history of thyroid diseases
  - . Disorders of maturation and growth
  - . Chronic fatigue, attention disorder
  - . Dryness of skin and hair

# Does SH have a similar clinical presentation in every situation independent of etiology?

- Hashimoto thyroiditis
- Developmental disorders of thyroid
- Mutation of TSH receptor
- Blocks of thyroid synthesis – double oxidase 2, phosphodiesterase 8B, TPO
- Post operation/ irradiation of thyroid
- Antiepileptic drugs, iodine deficiency
- Status post acute illness
- Obesity
- Trisomy 21
- Idiopathic SH

# Autoimmune thyroiditis in children and adolescents (Hashimoto disease)

Hashimoto disease is a dynamic process:

*Radetti et al. J Pediatr 2006:* hypothyroidism is developing within 5 years in 35.2% of euthyroid patients with prevalent autoantibodies

*Demirbilek et al., Clin Endocrinol (Oxf). 2009:* after stopping of treatment with  $LT_4$ , normalisation of hormone levels is observed in 30.5 % of patients with hypothyroidism

*Wasniewska et al. Horm Res in Paediatr 2012 :* at establishing diagnosis 52% of children remain euthyroid, 41.5% in SH, 6.5% in hyperthyroidism. Dysfunctions are more prevalent in younger children

# SH in Turner syndrome

- Increased prevalence of anti TPO antibodies
- Need for performing TSH and  $fT_4$  evaluation from 4<sup>th</sup> year of age in all patients
- In the course of time there is a progress toward hypothyroidism requiring  $LT_4$  substitution in 25% of patients

# SH in Down syndrome

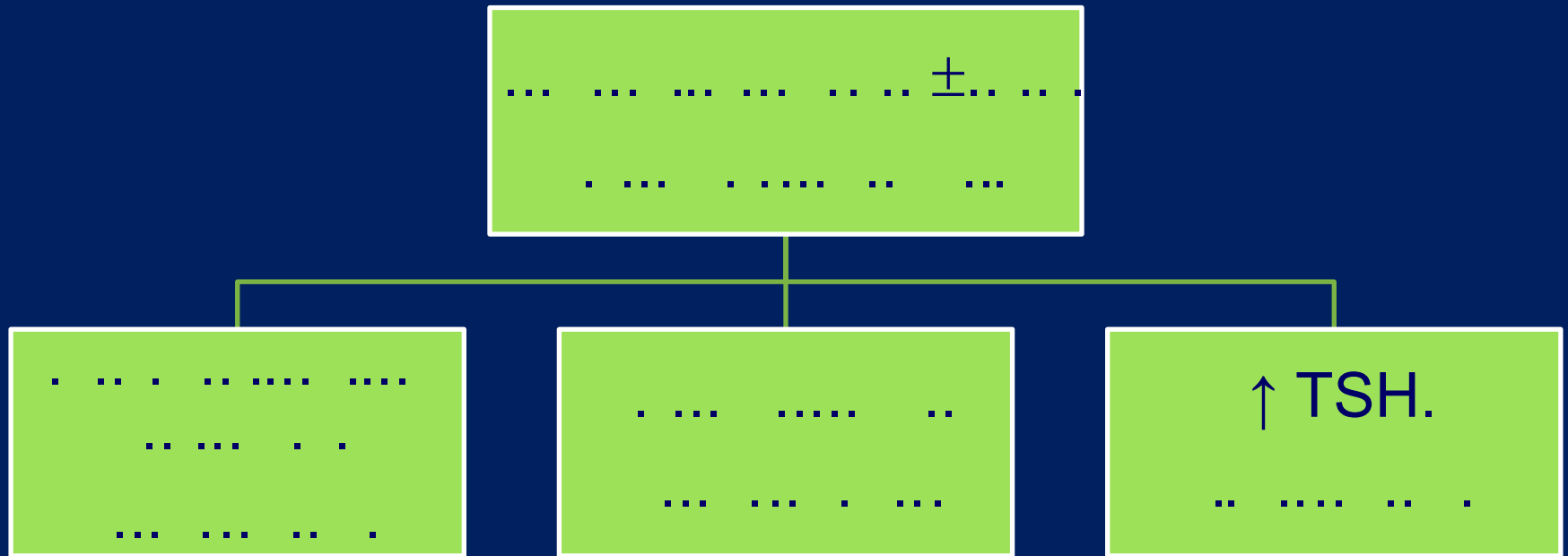
- 53 children with Down syndrome aged  $2.4 \pm 1.1$  years
- TSH 4.2-23.9mU/l
- SH regressed spontaneously in 73.6%
- Prognostic factors for remission were lack both of goiter and antibodies
- Progression to overt hypothyroidism was observed in 35.7% children with prevalent antibodies
- Thyroid dysfunction in children with Down syndrome is significantly more frequent than in healthy children, however very often it is a transient process

# **Hyperthyrotropinemia in non treated 427 patients with Down syndrome in the life span of 6<sup>th</sup> month and 64<sup>th</sup> year of life**

- **Patients with Down syndrome and with SH with advanced age present increase of TSH levels with concomitant increase in fT<sub>4</sub> concentration**
- **This phenomenon is probably due to syndrome per se and not due to Hashimoto disease**
- **Treatment with levothyroxine should be started (with normal fT<sub>4</sub> level ) only if TSH exceeds 9mU/l**



# 2 - year, prospective evaluation of SH course in children and adolescents

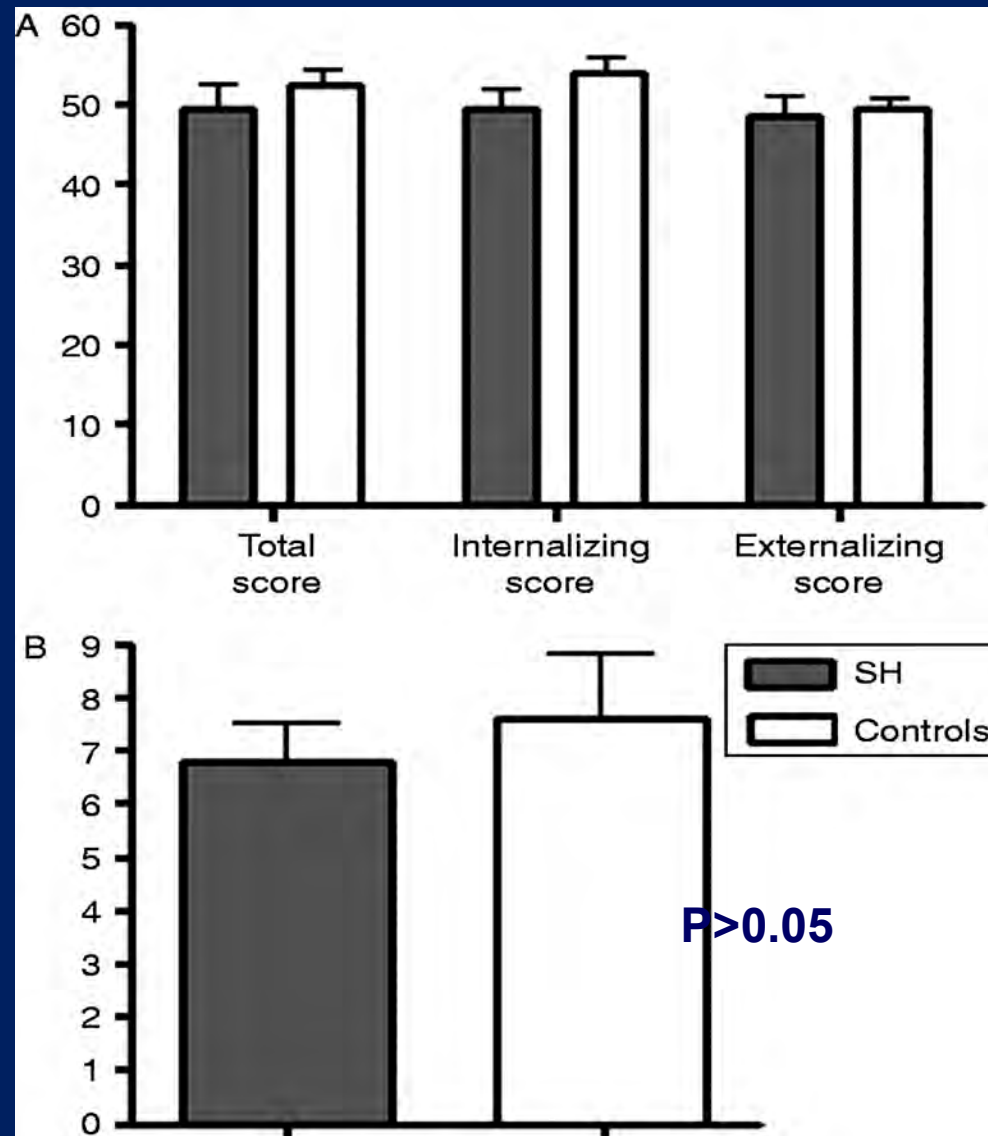


*16 children – after 6-12 months*  
*22 children – after 12-24 months*

## **2 - year, prospective evaluation of the SH course in children and adolescents**

- **In majority of children natural course of idiopathic SH did not show progressive mode; gradual normalisation of TSH or persistence of mild hyperthyrotropinemia were observed**
- **Changes of TSH concentration were not accompanied by changes of fT4 levels**
- **Neither changes in general physical status nor in auxological parameters (length, mass) in the natural course were observed**

# Psychological and behavioural evaluation of children with persistent SH vs. control group



# Evaluation of psycho-emotional development in children with thyroid dysfunction (NHANES III study)

- In examination of 1 327 children aged 13-16 years, SH was diagnosed in 1.7%
- *Wide Range Achievement + Wechsler Intelligence Scale* tests were performed in all 1 327 children
- In children with SH better spatial imagination and reading ability were detected as compared to children with normal thyroid function

# SH and obesity

- . ↑ TSH in 12-17% obese children
- Positive correlation between TSH/fT<sub>3</sub> and BMI z-score (*compensatory mechanism*)
- Lack of correlation between TSH and lipid values
- . Reduction of body mass → trend to decrease of TSH and fT<sub>3</sub>

*Grandone et al. Eur J Endocrinol 2009*

*Reinehr et al. JCEM 2006*

*Wolters et al. Eur J Endocrinol 2013*

# Obesity and thyroid function.

- **↑TSH, ↑vN fT3, N fT4,**

- **Goiter**

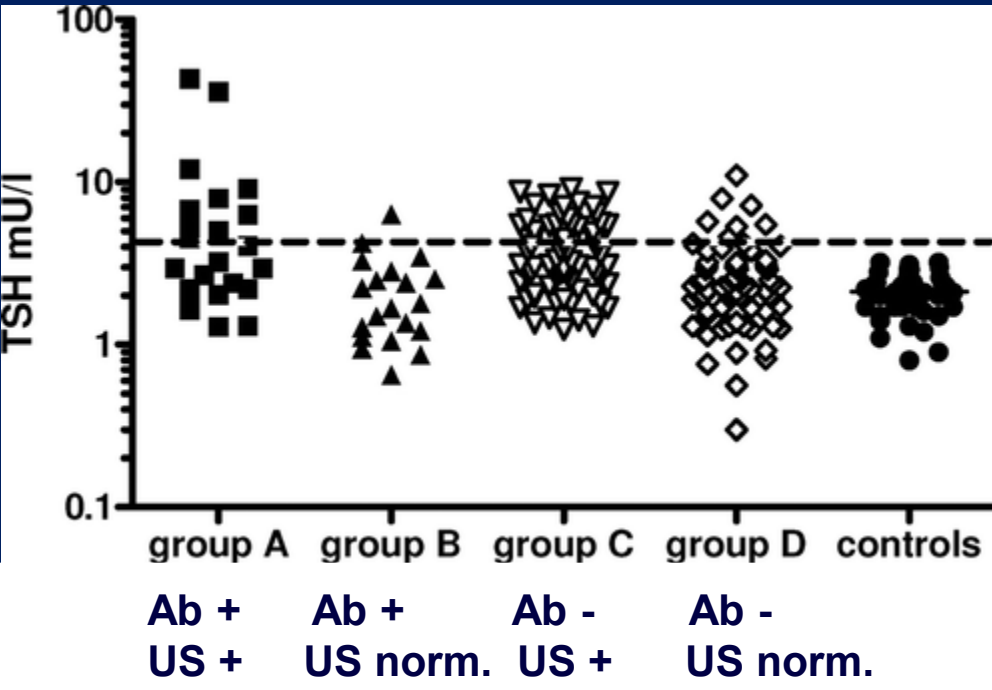
- . Disturbances in the hypothalamic-pituitary axis (leptin, NY, MSH $\alpha$ , agouti protein-TRH)
- . Resistance to thyroid hormone (pituitary)
- . Adaptation process to increase energy expenditure ( $\uparrow$  5 'deiodinase -  $\uparrow$  FT3)

## Obesity and thyroid function

Thomas Reinehr Molecular and Cellular

Endocr 2010.

# SH and obesity



TSH in group A i C > group B i D  
Ultrasound picture with reduced echogenicity may present as an early marker of thyroid dysfunction  
Ab – antibody; US - ultrasound

Ultrasound picture in obese may mimic autoimmune thyroiditis



inflammation → cytokine production in adipose tissue

→ Increased vascular permeability

→ Inhibition of Na-I symporter and iodine reuptake by thyroid (↑ TSH)

# **The influence of L-thyroxine administration on the treatment results in obese children with SH**

- **30 obese children with SH treated for  $\pm 24$  months with L-thyroxine and diet vs. 33 obese euthyroid children treated with diet**
- **BMI difference between both groups after 24 months statistically insignificant**
- **3 months after stopping treatment with L-thyroxine 53% children had persisted symptoms of SH**
- **No child presented progression to overt hypothyroidism**



# SH and obesity

- **Hyperthyrotropinemia is rather a consequence than the cause for obesity**
- **↑ TSH in obesity has no correlation with metabolic parameters**
- **When idiopathic, with no prevalent antibodies, it should not be treated with LT4**

# SH

- **Should TSH be monitored ?**

*If yes, for how long?*

- **Should the treatment with  $LT_4$  be started immediately?**

*What is the influence of treatment on general psychosomatic development of the child?*

# **Is TSH level >10 mU/l a reliable indication for LT4 substitution in children and adolescents?**

Surks ML et al.: Subclinical thyroid disease. Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-238

- **There is no perspective, randomized and controlled trial in children regarding indications to LT4 treatment; the value of TSH>10 mU/l was arbitrary accepted from adult population.**
- **In adult population it was documented that TSH level >10 mU/l correlates with increased total cholesterol and LDL fraction values, and, probably with heart dysfunction and general and neuropsychiatric symptoms.**

**However beneficial effect of LT4 treatment on the above mentioned disorders was not documented.**

# Lack of explicit guidelines of LT4 treatment in children and adolescents with SH

Kaplowitz et al.: J Pediatr Endocrinol 2010. Bona et al.: J Clin Res Pediatr Endocrinol 2013.  
 Monzani et al.: Eur J Endocrinol 2013. Seshardi et al.: Indian J Endocrinol Metab 2012  
 O'Grady M, Cody D.: Arch Dis Child 2011

	Kaplowitz 2010	O'Grady 2011	Seshardi 2012	Monzani 2013	Bona 2013
TSH>10 mU/l	+	+	+	+	+
TSH 5-10 in idiopathic SH					
goiter			+	+	+
Subjective or objective symptoms of hypothyroidism			+		+
↑TPOAb and/or TgAb				+	+
Thyroid hypoplasia in infants		+			+
Concomittant chronic diseases: diabetes; celiac disease; short stature; trisomy 21; Turner syndrome					+
After radioiodine treatment		+			

# Lack of consensus regarding treatment with LT4 in patients with SH and trisomy 21

	UK 2001	Ireland 2009	US 2011	Canada 2011	Australia 2006
TSH>10 mU/l	+	+	+	+	+
TSH 5-10 in idiopathic SH					
Consider treatment if ↑TPOAb and/or TgAb	+	+	No consensus		

# Treatment decision with LT4 should be based on FT4 level instead on TSH – normal FT4 level in non treated idiopathic SH is not correlated with worsened somatic and intellectual outcome in children and adolescents

Cerbone M et al.: Linear growth and intellectual outcome in children with long-term idiopathic subclinical hypothyroidism. Eur J Endocrinol 2011;164:591-597.

	36 children aged 4-18 lat with idiopathic SH	3 years of observation	p	Control group 36 healthy children	p
TSH (0.3-4.2 mU/l)	6.4	6.4	NS	2.6	<0.0001
FT4 (9-26 pmol/l)	18	18	NS	16.7	NS
height (SDS)	-0.7 ± 0.2	-0.8 ± 0.2	NS	-0.6 ± 0.2	NS
WK/WCH	-0.92 ± 0.03	-0.97 ± 0.03	NS	-0.96 ± 0.6	NS
IQ	-	99.7 ± 1.9	-	101.6 ± 2.4	NS

# Treatment with LT4 reduces thyroid size in Hashimoto thyroiditis independent of thyroid function

Svensson et al.: Levothyroxine treatment reduces thyroid size in children and adolescents with chronic autoimmune thyroiditis. J Clin Endocrinol Metab. 2006;91:1729-1734.

	90 Children with Hashimoto thyroiditis aged 6-18 years	Thyroid size difference after 3-year treatment with LT4 (SDS)	p
Goiter in SH	29	-1.4	<0.001
Goiter (>2 SDS) in overt hypothyroidism	9	-1.8	<0.002
Goiter in euthyroidism	23	-0.4	<0.001
Patients without goiter	29	-0.6	<0.005

## **Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review**

Alice Monzani, Flavia Prodam, Anna Rapa, Stefania Moia, Valentina Agarla, Simonetta Bellone and Gianni Bona

- **SH seems to be transient disease with low risk of progression to overt hypothyroidism**
- **The presence of goiter, increasing both of anti TPO, anti TG titers and TSH levels are the risks of disease progression**
- **There is no enough evidence to confirm beneficial effect of L-thyroxine treatment on children's growth and thyroid size**



**Natural history of subclinical hypothyroidism in children and adolescents and potential effects of replacement therapy: a review**

Alice Monzani, Flavia Prodam, Anna Rapa, Stefania Moia, Valentina Agarla, Simonetta Bellone and Gianni Bona

- **Treatment with LT4 is not justified in children with SH and TSH levels between 5 – 10 mU/l when there is no goiter and no antibodies detected**
- **Further randomized, double blind, clinical trials are warranted to fully evaluate possible influence of treatment with LT4 on growth, thyroid volume, neurocognitive functions and circulatory system**

# Suggested guidelines regarding SH monitoring

- TSH levels of 5-10 mU/l – periodic control – repeat TSH evaluation in 8-12 weeks together with  $fT_4$  and possibly with antiTPO. If results are normal - no subsequent control required
- If  $\uparrow$ TSH, as above – repeat TSH and  $fT_4$  in 6-12 months
- Repeat TSH and  $fT_4$  levels in every 6 months during 2-year period. If  $\uparrow$  TSH persists as above with other parameters negative – stop control in 3 years
- Perform check out if the patient is pregnant or has clinical symptoms of hypothyroidism

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# Suggested management in SH

- TSH >10 mU/l (repeated evaluations) – indicated treatment with LT<sub>4</sub>
- TSH 5-10 mU/l; goiter, autoantibodies present and/or *symptoms of hypothyroidism* – consider LT<sub>4</sub> treatment

*Arrigo et al., J Endocrinol Invest 2008*

*Kaplowitz PB, Int J Pediatr Endocrinol. 2010*

*Karmisholt et al. Europ J Endocrinol 2011*

**Thank you**