Axe thyréotrope

Set point
Conséquences sur la définition des intervalles de référence

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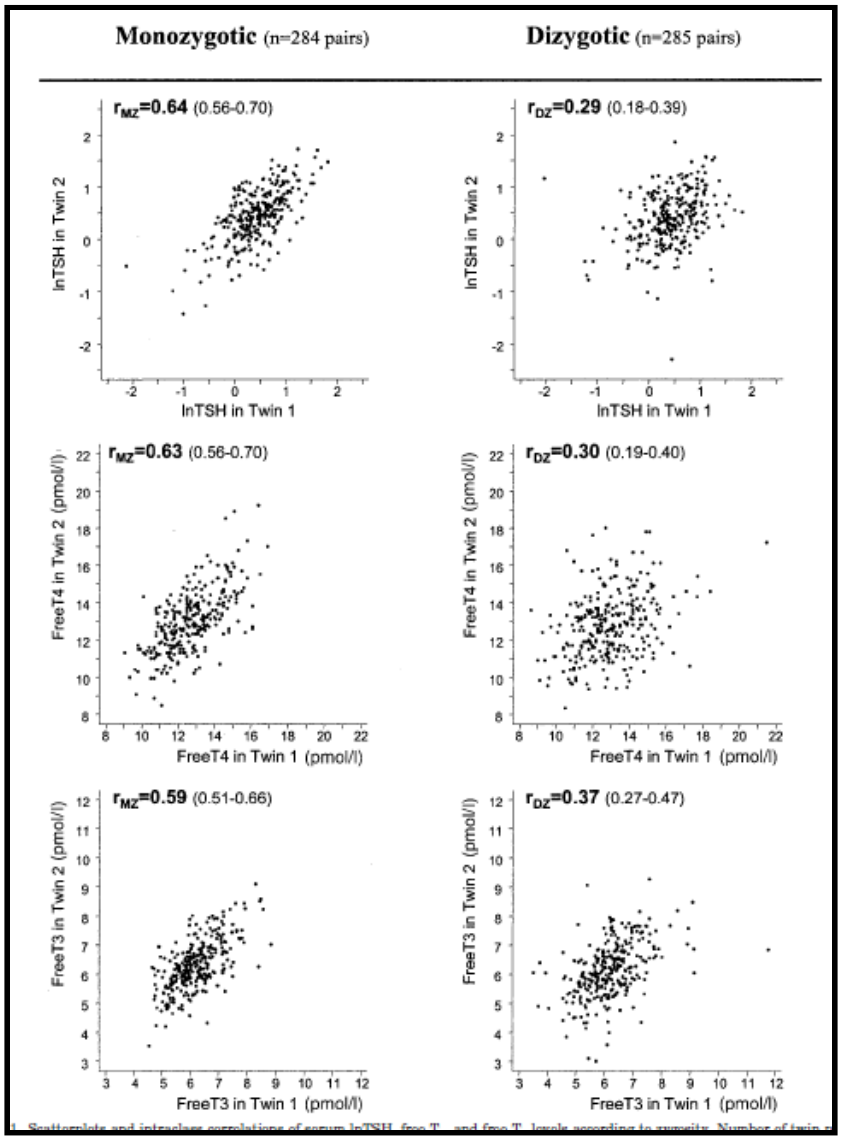
Paris , 23 juin 2012

Il existe une régulation génétique majeure gouvernant la régulation de l'axe Hypothalamo-Thyroïdien



Études chez les jumeaux

Il existe une forte corrélation intra-classe pour les HT et la TSH

Monozygotes > Dizygotes

Hansen PS et al . JCEM 2004;89:1181.

« Set Point » de l'axe thyréotrope chez le sujet sain

On peut définir
une relation log linéaire :

$\log TSH = \beta - \alpha\ FT4$

Où : sensibilité ~ α

zone de variation ± étroite autour d'une moyenne = working point

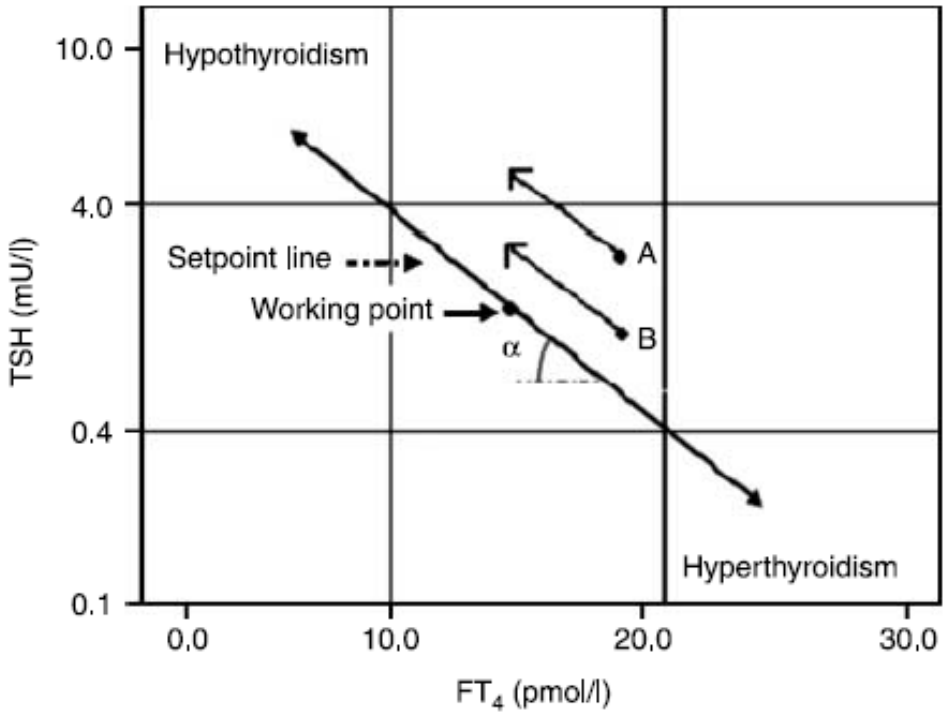
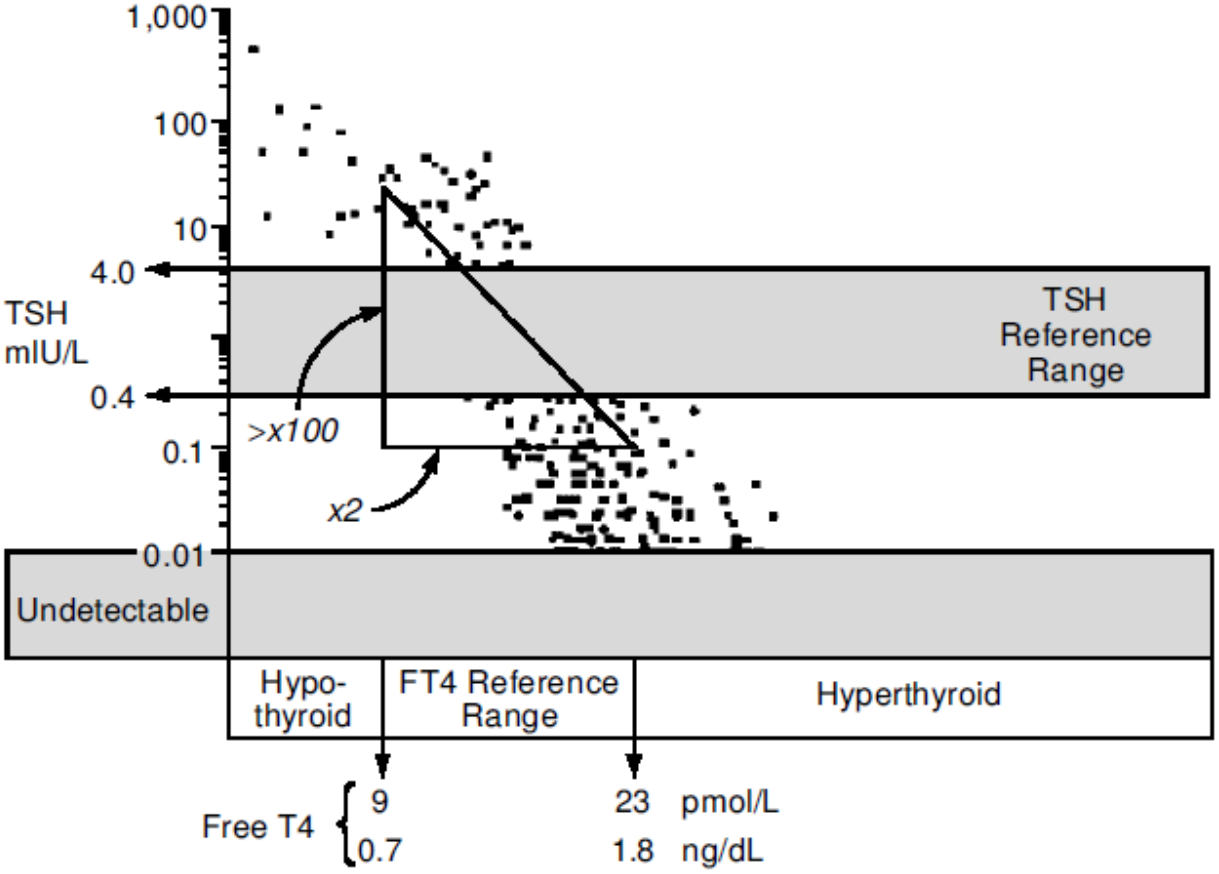
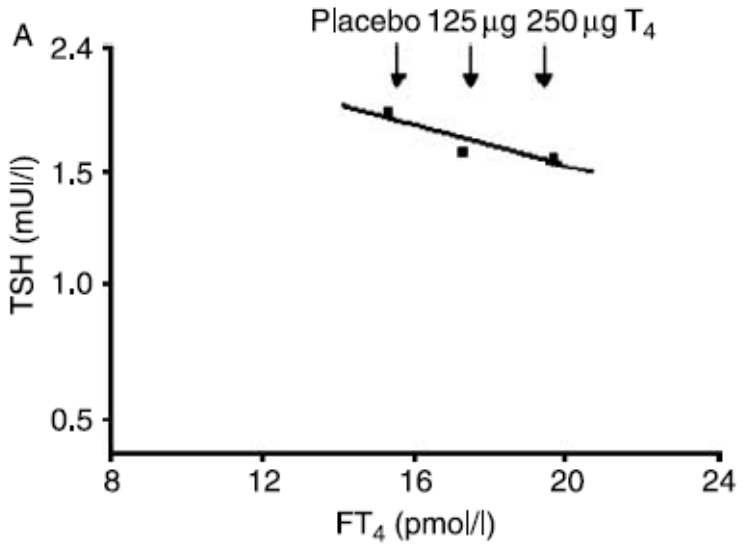


Figure 1 Log-linear relationship between serum TSH and FT_4 depicted as a straight line, representing the setpoint of the hypothalamus–pituitary–thyroid axis. The slope α indicates the sensitivity of the HPT axis for changes in FT_4. The working point at the line represents the actual thyroid state. The position of the working point of healthy euthyroid subjects varies greatly within the normal reference range (TSH 0.4–4.0 mU/l and FT_4 10–21 pmol/l).

« Set Point » de l'axe thyréotrope chez le sujet sain



Log TSH = 2.56 – 0.022 FT4, r = - 0.84, p< 0.001)
Spencer Ca et al., JCEM 1990;70:453.



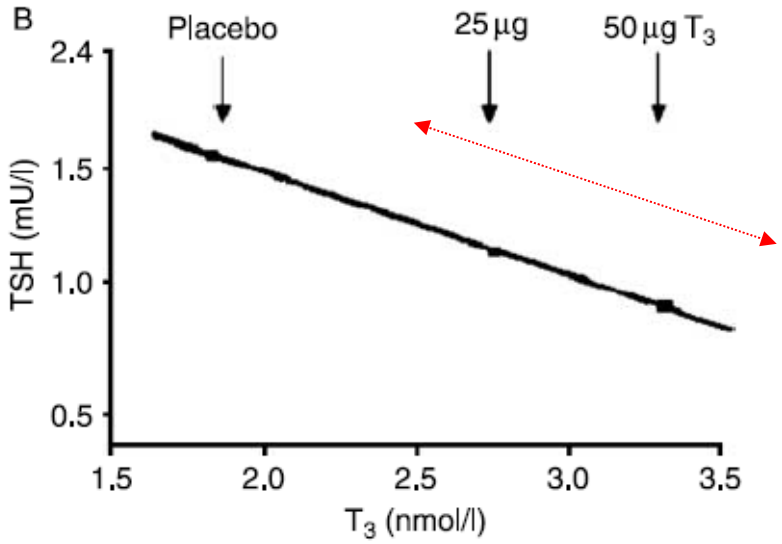


Figure 6 Log-linear relationship between TSH and FT_4/T_3 in 10 healthy subjects treated with oral T_4 (panel A) and in 11 healthy subjects treated with oral T_3 (panel B).

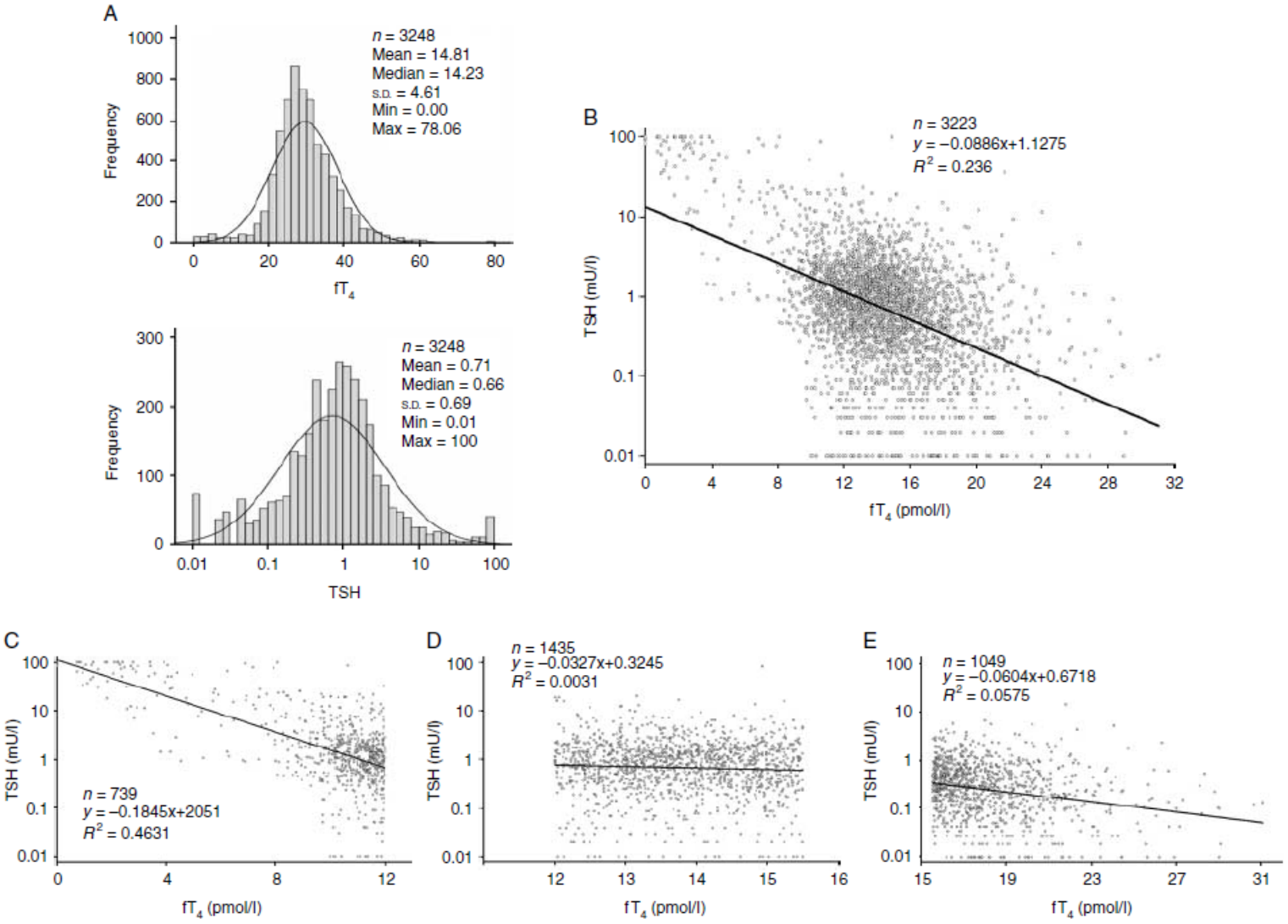
Effet de la charge en HT

En T4 [A]

En T3 [B]

Un individu évolue, de façon réversible, sur sa ligne de sensibilité

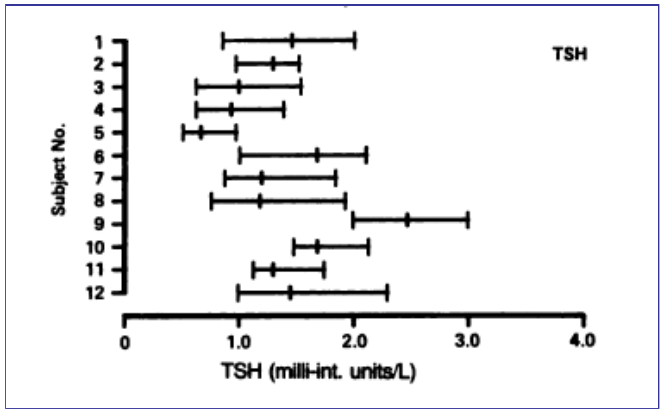
La vérité à l'épreuve du temps…..

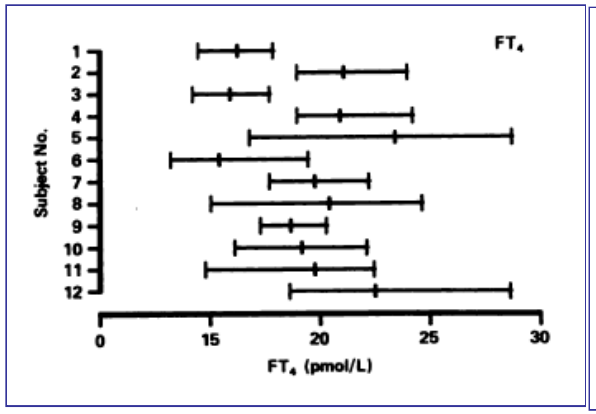


Hoermann R et al. Eur J Endcorinol 2010;162:1123.

Variabilité Individuelle et Normes de Population

Intra-and Interindividual Biological Variation of Five Analytes Used in Assessing Thyroid Function : Implications for Necessary Standards of Performance and the Interpretation of Results
Browning MC et al. Clin Chem 1986.





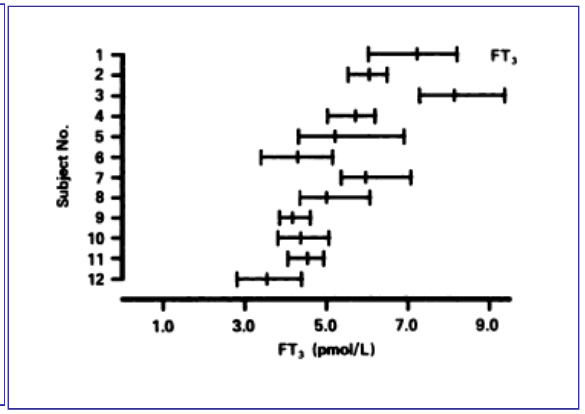


Table 4. Ratios of Intra- to Interindividual Variance, Including and Excluding Analytical Variance

Analyte	$\sqrt{(V_I + V_A)/V_G}$	$\sqrt{V_I/V_G}$
TT_4	0.66	0.50
FT_4	0.92	0.78
TT_3	0.67	0.51
FT_4	0.49	0.34
TSH	0.56	0.50

Thus, in an **in an individual patient**, **results outside the usual biological variation of that individual will not be recognized by the naive application of conventional population- based reference ranges**

Removing the analytical variance emphasizes **the insensitivity of population based reference ranges to changes in individuals**

Varaibilité intra-individuelle des hormones de l'axe Thyréotrope

TABLE 4. INTRA-INDIVIDUAL AND INTER-INDIVIDUAL VARIABILITY IN SERUM THYROID TESTS

Serum Analyte	*Time span*	*%CV**	*%CV***
TT4 /FT4	1 week	3.5	10.8
	6 weeks	5.3	13.0
	1 year	9.2	17.1
TT3 /FT3	1 week	8.7	18.0
	6 weeks	5.6	14.8
	1 year	12.0	16.8
Thyrotropin (TSH)	1 week	19.3	19.7
	6 weeks	20.6	53.3
	1 year	22.4	37.8
Thyroglobulin (Tg)	1 week	4.4	12.6
	6 weeks	8.7	66.6
	4 months	14.0	35.0
		*intra-individual	**inter-individual

1) TSH varie de façon exponentielle pour garantir une TT4 / FT4 stable
   la TSH est la moins stable des Hormones de l'axe
2) Une variation individuelle significative peut parafitement rester
   dans les normes de population

Varaibilité intra-indiviuelle et intervalle de référence

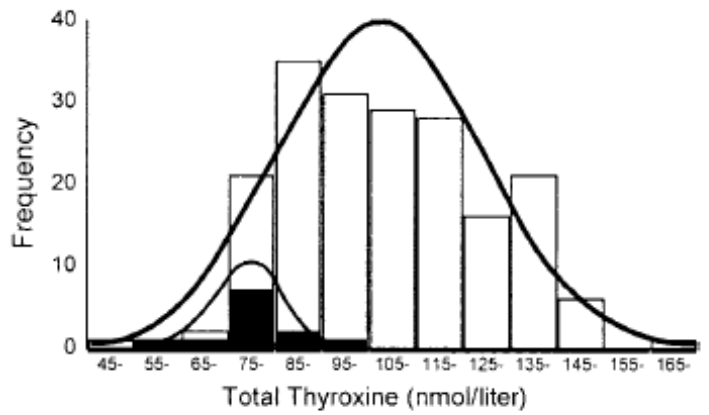


FIG. 2. The distribution of 12 monthly measurements of total T_4 in 15 healthy men (□) and in one individual, number 11 (■). The distribution in one individual is about half the width of the distribution in the group.

TABLE 2. Number of tests required to describe the homeostatic set point in an individual

	Precision of set point		
	5%	10%	25%
TSH	85	25	5
TT_3	25	5	1
TT_4	25	5	1
FT_I	25	5	1

Calculated from: $n = (Z \times CV_{analytical}^2 + CV_{intraindividual}^2)^{1/2}/D)^2$ where: D is percent closeness to the homeostatic set point, Z is the number of standard deviations required for a confidence interval (*i.e.* 1.96 for 95%), n is the number of specimens.

Intervalle de référence d'une population = {histoire des sets points des sujets de référence}

Fluctuations individuelles << Fluctuations de la population de référence

Andersen S et al. Biological variation is important for interpretation of thyroid function tests. THYROID, 2003;13(11) : 1069

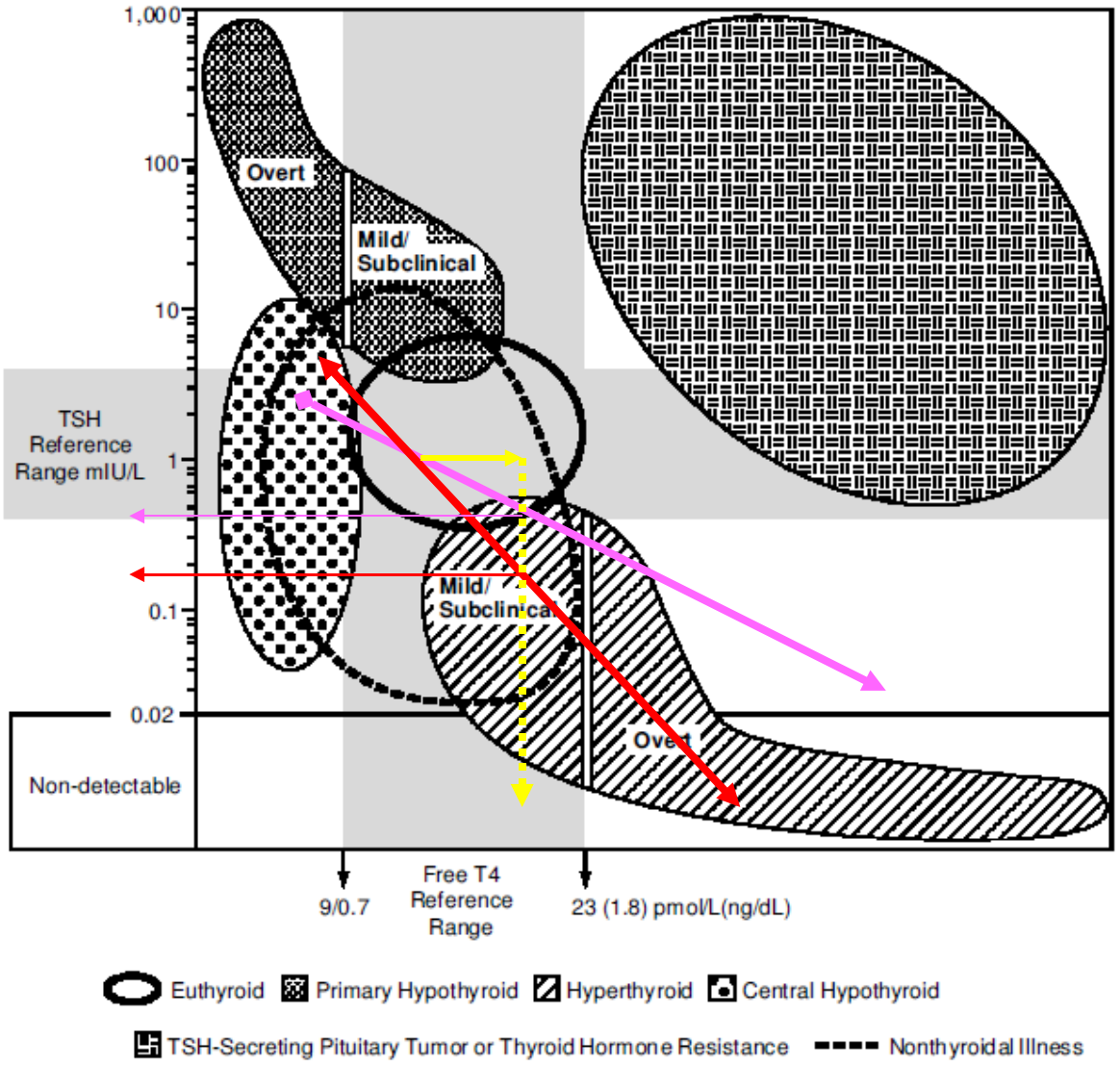
Guideline 8. Guidelines for Interpreting Thyroid Test Results

- For diagnostic testing (case-finding) thyroid test results are typically reported together with a "normal" reference interval that reflects between-person variability.
- The "normal" reference interval does not indicate the magnitude of difference between test results that constitutes a clinically significant change in an individual patient.

Analytical variability together with between-person and within-person estimates of biological variability suggests that the magnitude of difference in thyroid test values that would be clinically significant when monitoring a patient's response to therapy are:

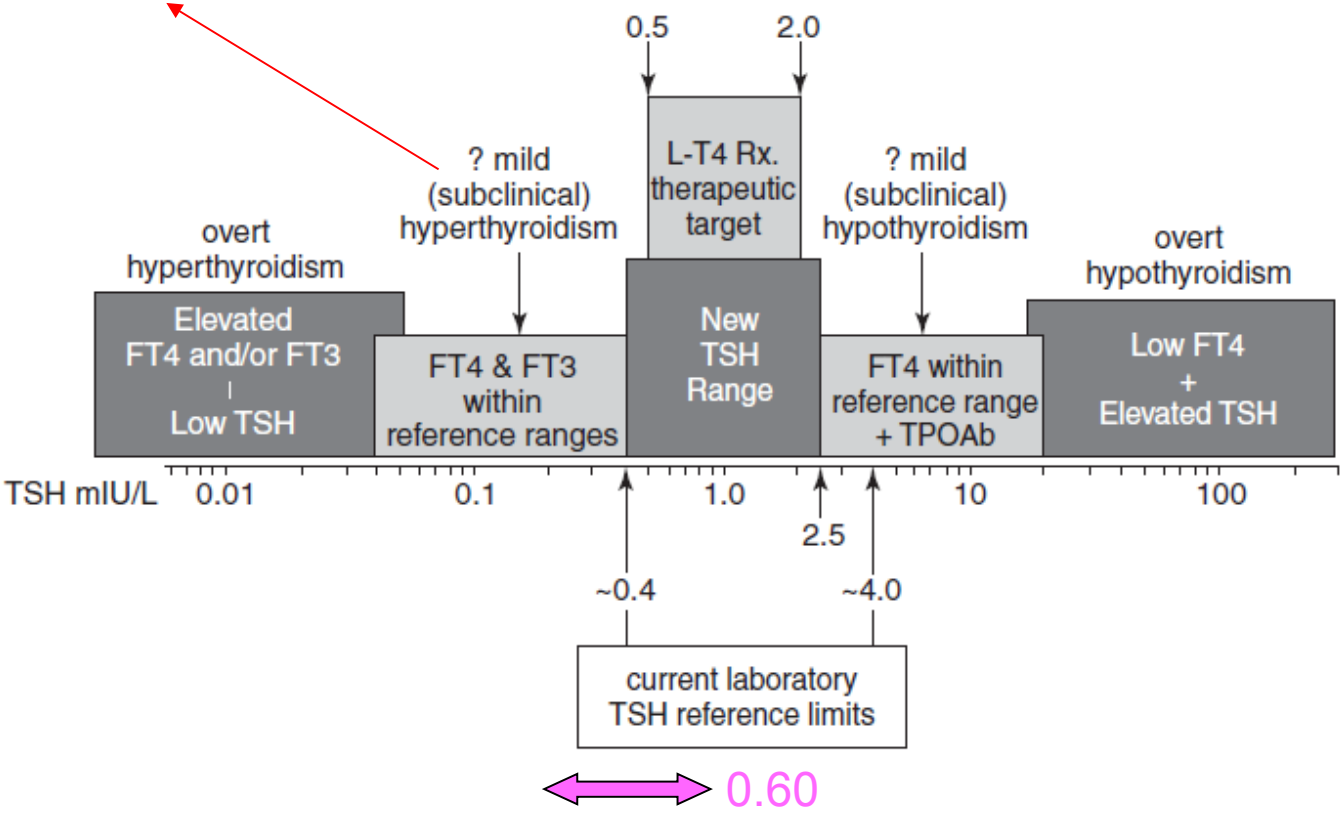
TT4=	**28 (2.2) nmol/L (μg/dL)**
FT4=	**6 (0.5) pmol/L (ng/dL)**
TT3=	**0.55 (35) nmol/L (ng/dL)**
FT3=	**1.5 (0.1) pmol/L (ng/dL)**
TSH=	**0.75 mIU/L**
Tg=	**1.5 μg/L (ng/mL)**

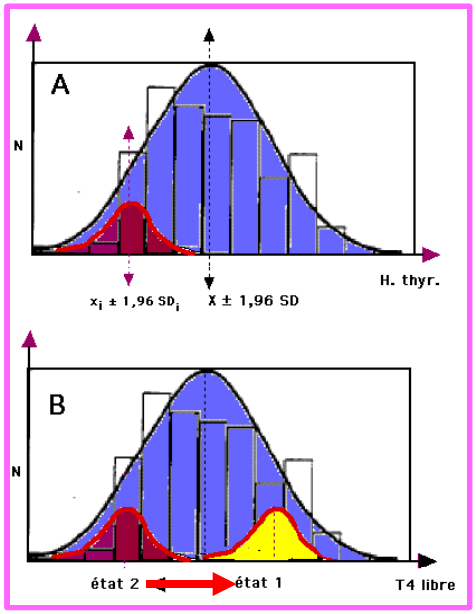
Variation secrétoire et couple TSH, FT4 : morbidité et biologie hormonale



Optimal Thyrotropin Level: Normal Ranges and Reference Intervals Are Not Equivalent

L'AVC « subclinique » des biologistes hormonaux…





Zone à risque morbide prouvée →

Quels tests permettent d'avancer ?

Dickey et al Thyroid 2005; 15(9):1035

TSH « Normale » et densité minérale osseuse

The association between serum thyroid-stimulating hormone in its reference range and bone status in postmenopausal American women

Martha Savaria Morris, Bone 2007

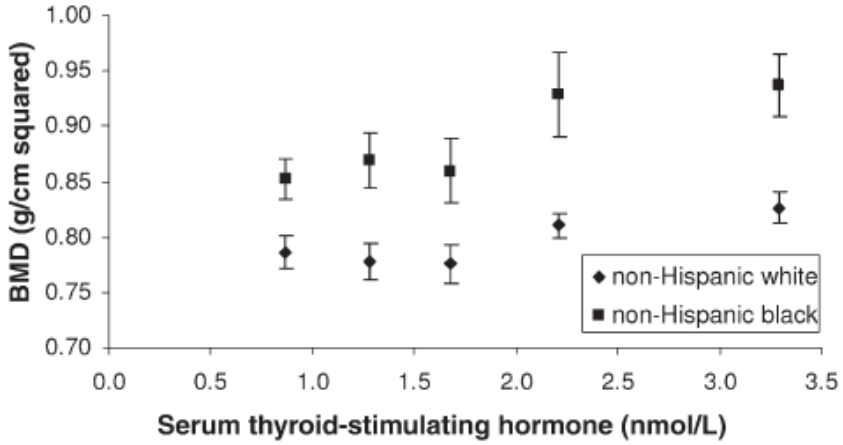


Fig. 1. Least-square mean (95% CI) total hip bone mineral density (BMD) in relation to increasing serum thyroid-stimulating hormone among 118 non-Hispanic black and 332 non-Hispanic white healthy, postmenopausal women aged ≥35 years who were members of the morning subsample of the third U.S. National Health and Nutrition Examination Survey. Means are controlled for age, body mass index calculated as weight in kg/(height in meters)^2, serum T_4, estrogen-replacement therapy, smoking status, and physical activity level.

…the odds ratios (95% CI) relating TSH between 0.39 and 1.8 mIU/L (the median of the reference range) versus TSH between 1.8 and 4.5 to osteoporosis and osteopenia were 3.4 (95%CI, 1.3–9.2) and 2.2 (1.2–3.8), respectively.

Furthermore, BMD increased significantly as TSH increased over its reference range.

These results may reflect the existence of clinically significant thyroid hyperfunction in women with serum TSH in the reference range.

TSH “Normale” et Hypersecrétion génétique non autoimmune

1994 : N Eng J Med (Sawin) :	⇑ ACFA x 3,1 (TSH < 0,1 mU/L)
	⇑ ACFA x 5.2 (TSH < 0,4 mU/L)
1999 : J Int Med (Tenerz):	⇑ fréquence ACFA : 28% versus 10%
2001 : Am Heart J (Auer) :	⇑ ACFA à 12.7 % si 0.03 < TSH < 0,4
2001 : Lancet (Parle) :	⇑ mortalité cardio-vasculaire à 5 ans (TSH < 0,6)
2007 : Arch Int Med (Gammage)	⇑ ACFA avec la FT4, dans la zone N
2007 : J Clin Endocrinol Metab (Cappola)	⇑ ACFA (x 2,18) si TSH < 0,44 mU/L
2007 : J Clin Endocrinol Metab (Metso)	⇑ mortalité cérébrovasculaire > ^{131}I [RR 1.12]
2008 : Eur J Endocrinol (Haentjens)	⇑ mortalité relative (41%) [TSH : 0,3 à 0,6 mU/L]
2011 : Eur J Endocrinol (Brandt)	⇑ mortalité globale / hyperthyroïdie (20 %)

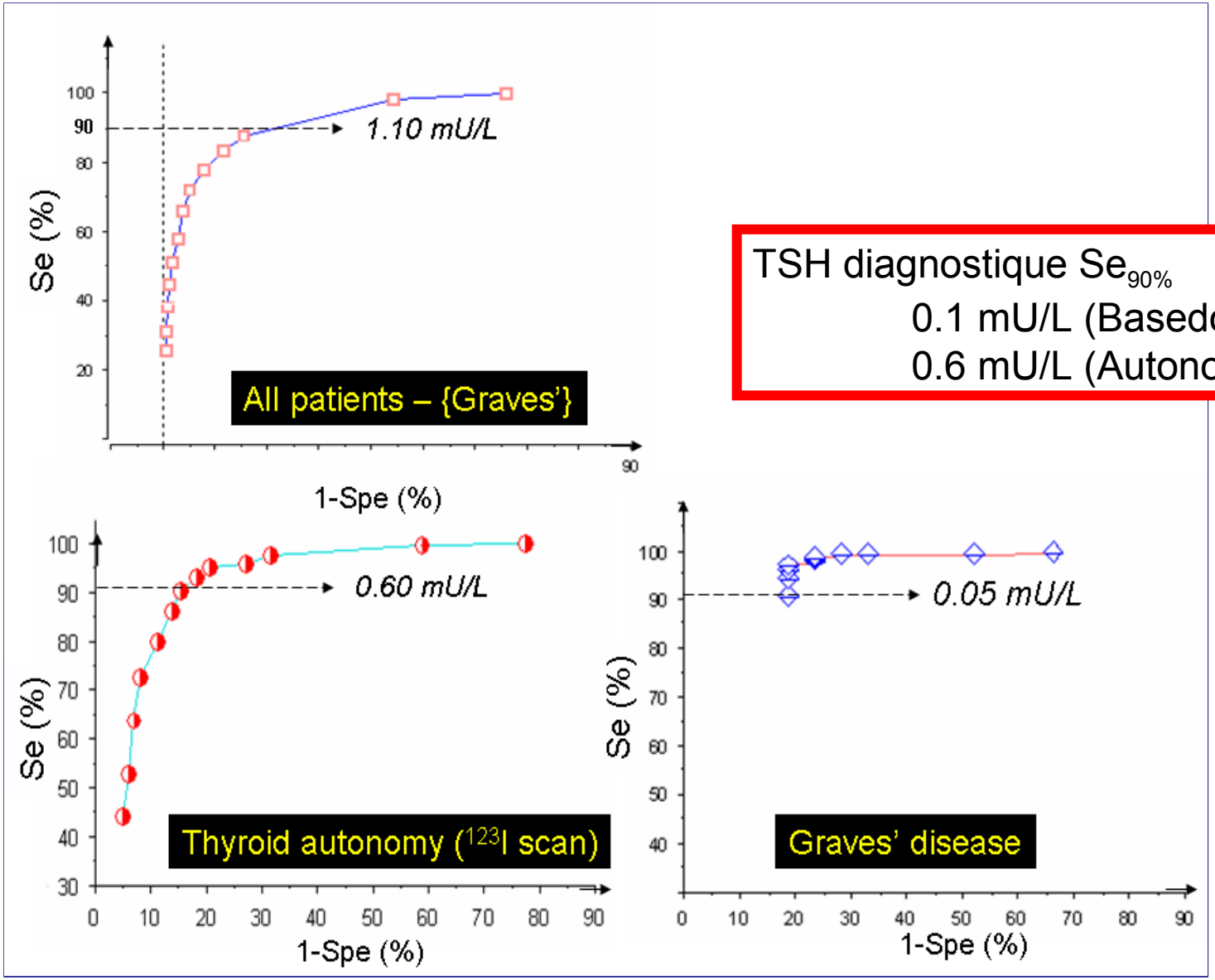
1. Les syndromes d’autonomisation sont responsables d’un abaissement chronique et modéré de la TSH
2. L’abaissement de la TSH est un facteur de risque d’ACFA permanente et de surmortalité
3. L'ACFA est un risque indépendant d’accident vasculaire cérébral, d’angor et d’insuffisance cardiaque avec un RR de décès x 2

Population > 65 ans & TSH < 0,1 : 45000 ACFA et 6500 AVC [CTD : 440 DC/ an)

Population générale avec SA ?

2 études d’intervention par ^{131}I : PIRATHES et COCHIN (n = 268)

Biologie hormonale thyroïdienne et impact morbide



TSH diagnostique $Se_{90\%}$

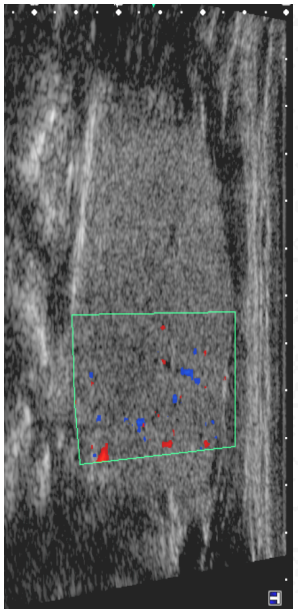
0.1 mU/L (Basedow)

0.6 mU/L (Autonomie)

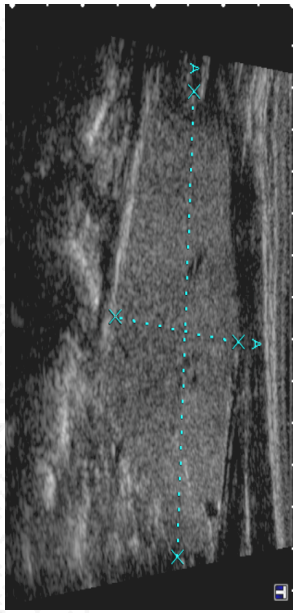
Guideline 27. Clinical Utility of TSH Assays (Functional Sensitivity < 0.02 mIU/L)

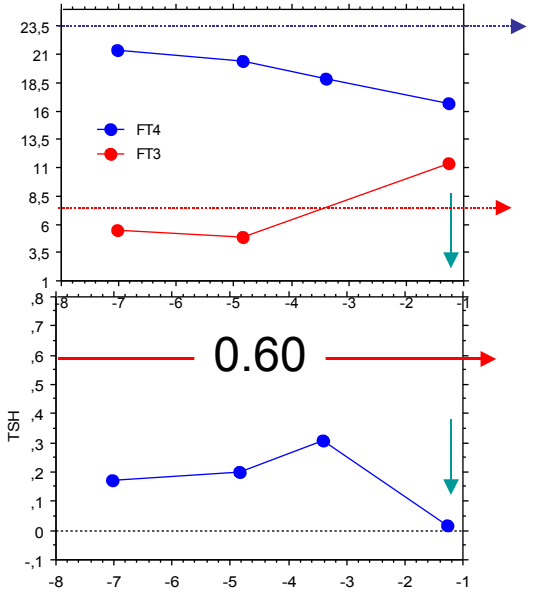
- ☐ Serum TSH measurement is the most diagnostically sensitive test for detecting mild (subclinical), as well as overt, primary hypo- or hyperthyroidism in ambulatory patients.
- ☐ The majority (>95%) of healthy euthyroid subjects have a serum TSH concentration below 2.5 mIU/L. Ambulatory patients with a serum TSH above 2.5 mIU/L when confirmed by a repeat TSH measurement made after 3-4 weeks, may be in the early stages of thyroid failure, especially if TPOAb is detected.
- ☐ A serum TSH measurement is the therapeutic endpoint for titrating the L-T4 replacement dose for primary hypothyroidism (see Guideline 23) and for monitoring L-T4 suppression therapy for differentiated thyroid carcinoma (see Guideline 24).
- ☐ Serum TSH measurements are more reliable than FT4 in hospitalized patients with non-thyroidal illness not receiving dopamine. Serum TSH should be used in conjunction with T4 (TT4 or FT4) testing for hospitalized patients (Guidelines 6 and 26).
- ☐ TSH cannot be used to diagnose central hypothyroidism because current TSH assays measure biologically inactive TSH isoforms.
- ☐ Central hypothyroidism is characterized by an inappropriately normal or slightly elevated serum TSH level and a blunted (<2-fold rise/ ≤4.0 mIU/L increment) TRH response.
- ☐ When the serum FT4 is low and yet the serum TSH is only minimally elevated (<10 mIU/L), a diagnosis of central hypothyroidism should be considered.
- ☐ Serum TSH measurements are an important pre-natal and first trimester screening test to detect mild (subclinical) hypothyroidism in the mother (see Guideline 4).
- ☐ A low TSH in the setting of a multinodular goiter suggests the presence of mild (subclinical) hyperthyroidism due to thyroid autonomy.
- ☐ A serum TSH measurement is required for confirming that an elevated thyroid hormone level is due to hyperthyroidism and not a thyroid hormone binding protein abnormality (such as FDH).
- ☐ A serum TSH measurement is the primary test for detecting amiodarone – induced thyroid dysfunction (see Guideline 5).

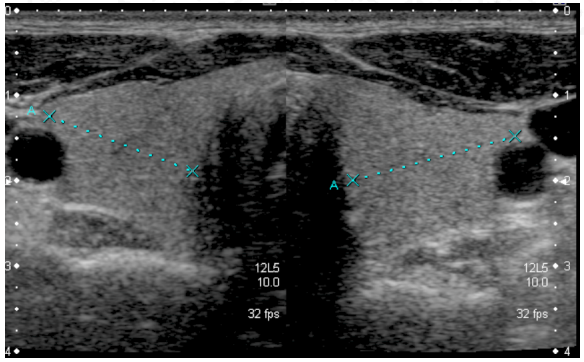
Guidelines Comittee. Nat Acad Clin Biochem. Thyroid 2003;13:3 - 126



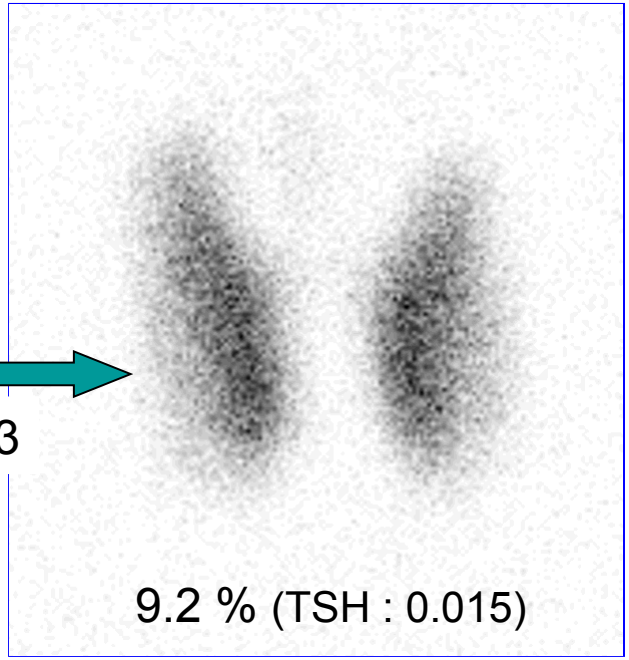
13.1 % (TSH:0.20 mU/L)







IT3



9.2 % (TSH : 0.015)

DISA

FIX0 = FIXaut (9.2) + FIXtsh (3.9)

TSH comme facteur prédicif de passage à la toxicité ?

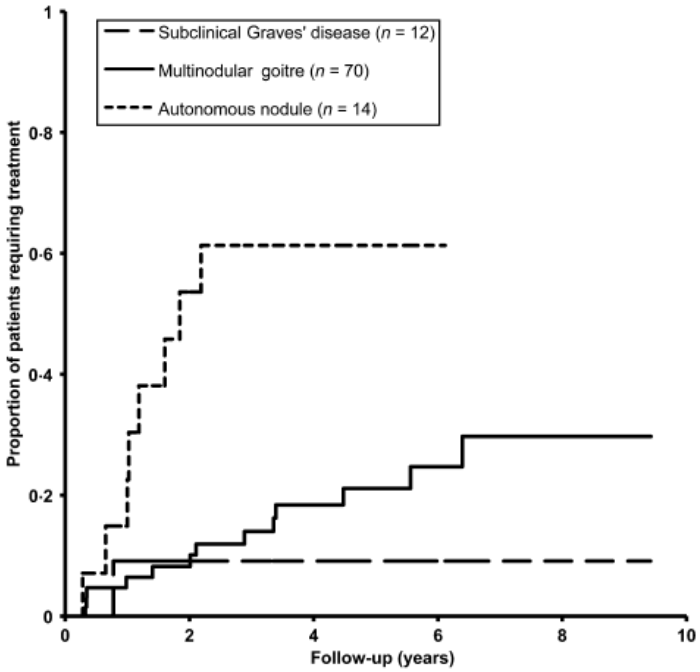


Fig. 1 Kaplan–Meier curves for proportion of patients with subclinical thyrotoxicosis who developed overt thyrotoxicosis during follow-up according to initial scintiscan classification.

Underlying thyroid pathology determined by scintigraphy was the only independent predictor of outcome (P = <0.003).

Table 2. Proportion of individuals developing overt thyrotoxicosis over time according to scintiscan category

	sGD (n = 12)	MNG (n = 70)	AN (n = 14)
1 year	0·09	0·06	0·15
2 years	0·09	0·08	0·54
3 years	0·09	0·14	0·61
5 years	0·09	0·21	0·61

sGD, subclinical Graves' disease; MNG, multinodular goitre; AN, autonomous nodule.

Aspect scintigraphique (UFA)

Hyperthyroïdie :

8% à 1 an

26% à 5 ans

62 % de traitement

Extension aux hypersecrétions non freinables
(syndromes d'autonomisation)

Subclinical thyrotoxicosis in an outpatient population – predictors of outcome. Clin Endocrinol 2011;74, 257–261
Belinda Jet al.

Conclusion

- Normes individuelles et relativement étroites, notamment sur la FT4
- La TSH doit être répétée, notamment dans les zones frontières
- Les normes biologiques (transformées log TSH) n'évaluent que très imparfaitement le risque morbide
- Les termes d'hyper et d'hypo subclinique sont inappropriés

- L'exemple des hypersecrétions autonomes
  - Scintigraphie moléculaire quantifiée : meilleur test diagnostic et prédictif d'hypersecrétion chez un sujet particulier
    - logTSH = b – a FT4
    - FIX ^{123}I = b + a TSH