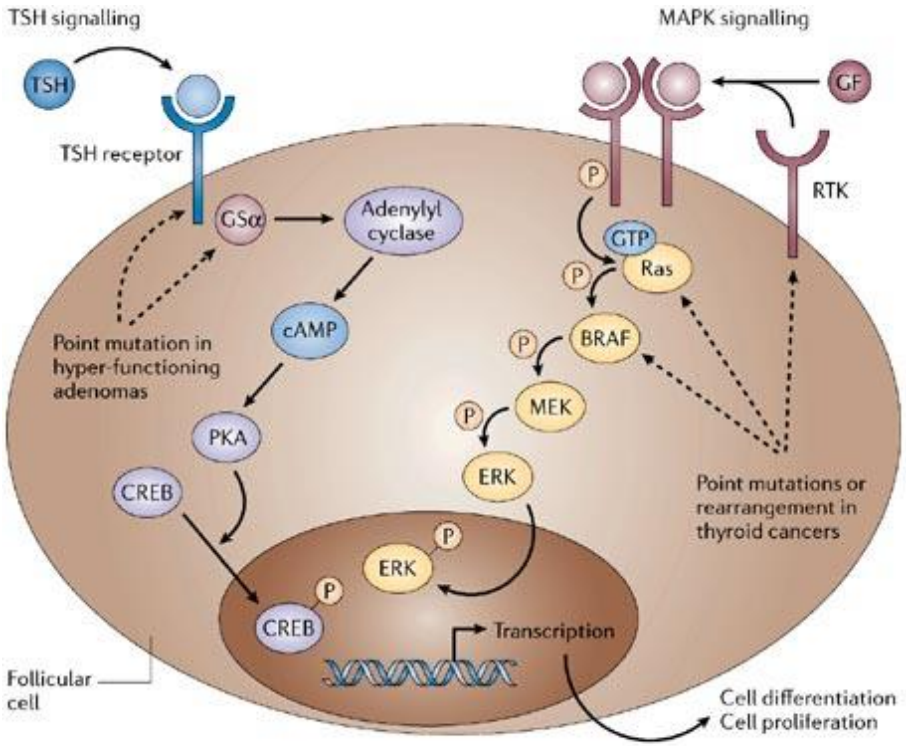

Thyroid Postgraduate Course, Diabetes & Romulo Ayuso's Memorial Lecture in Thyroid Cancer

Saturday, August 29, 2020

Thyroid Hormone Suppression in Thyroid Cancer: How Much and How Long

Juan R. Otero Martínez, MD
Endocrinologist

DISCLOSURE

- **I HAVE SERVED AS MEMBER OF SPEAKERS' BUREAUS FOR SEVERAL PHARMACEUTICAL COMPANIES.**

- **DURING THIS PRESENTATION :**
  - **I DO NOT HAVE ANY RELEVANT FINANCIAL RELATIONSHIP WITH ANY COMMERCIAL INTEREST.**

  - **I WILL NOT INCLUDE DISCUSSION OF ANY COMMERCIAL PRODUCT OR SERVICES.**

Objectives

- **Establish the differences of TSH suppression according to the extent of thyroid cancer.**
- **Describe the potential benefits and harms of using TSH-suppression thyroid hormone therapy in patients with DTC.**
- **Differentiate use of tablet versus liquid L-T4 formulations in thyroid cancer.**
- **Overview of suppression therapy in benign nodular thyroid disease.**

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- **UP TO DATE IN CLINICAL ENDOCRINOLOGY: SPED CONVENTION APRIL 2016**

- **RECURRENT PAPILLARY THYROID CARCINOMA DR. H. GHARIB FEBRUARY 2020**

Historical Note

1937 – Earliest use of thyroid hormone to treat thyroid cancer was reported by a surgeon, Sir Thomas Dunhill, at the Medical Society of London.

Described his experience with two children with recurrent thyroid cancer.

In both cases, use of “fairly large doses of thyroid” the masses resolved completely.

Historical Note

1956 – Still both patients remained alive as he reported.

But…Dunhill did not give a rationale for treating his thyroid cancer patients with thyroid hormone.

Late 1970's – TSH suppression was universally recommended for all patients with thyroid cancer, in large part of the work of Ernest Mazzaferri, who showed a significant reduction in the risk of recurrence for patients given thyroid hormone after thyroidectomy.

Historical Note

For years the party line has been: “We want TSH low so as not to stimulate the growth of cancer”.

More recently, interest have shifted to possible adverse events from the subclinical hyperthyroidism, which is associated with TSH suppression.

We have begun to tailor the degree of suppression to the extent of disease and risk of recurrence.

Evidence for TSH Suppression

- **The goal of TSH suppression is to reduce endogenous stimulation of remnant DTC cells.**
- **The rationale for this approach arose from observations that the incidence of thyroid cancer correlates with the level of serum TSH in the normal population.**

EVIDENCE FOR TSH SUPPRESSION

- **There is a meta analysis of 10 studies which concluded that suppression therapy (ST) help reduce morbility and mortality (29%) for adverse events pertaining to combined disease progression/recurrence and death.**

- **These older studies failed to differentiate thyroid hormone replacement from thyroid hormone suppression; and modern technology such as ultrasound and Tg measurement were also lacking.**

Evidence for TSH Suppression (Cont.)

- **Prospective study showed that a lesser degree of TSH suppression is an independent predictor of disease progression in patients at high risk of tumor recurrence.**

- **TSH suppression thus became standard practice based largely on the logical plausibility of its benefit, rather than demonstrable evidence of benefit.**

Evidence for TSH Suppression (Cont.)

- Other studies have investigated the optimal degree of TSH suppression and tried to identify which patients are most likely to benefit.

- A multicenter cohort study of ~3,000 patients compared TSH suppression to undetectable levels versus subnormal concentrations .
  - Benefit in overall survival was only observed in patients with tumors at highest risk of disease recurrence.
  - Patients with lowest risk DTC did not benefit from any degree of TSH suppression.

EVIDENCE FOR TSH SUPPRESSION

- **Results of studies falling under the umbrella of the National Thyroid Cancer Treatment Cooperative Study Group suggest that the most aggressive suppression therapy "was of no value in patients at low risk for recurrence but was of benefit in high risk patients".**

EVIDENCE FOR TSH SUPPRESSION

- **In more recent research analysis, following nearly 5,000 thyroid cancer patients, moderate suppression (0.1 to 4 mU/L) led to improved outcomes in patients at all stages of thyroid cancer progression as compared to TSH levels kept in the high normal range.**
- **However, any benefits disappeared after five years of follow-up.**

EVIDENCE FOR TSH SUPPRESSION

- **The benefits on TSH replacement therapy have gone back and forth, with conflictive findings about the worth of that strategy.**

MEDPAGE TODAY®

TSH Suppression: More Harm Than Good After Cancer Surgery?

This study was published as an abstract and presented at a conference. These data and conclusions should be considered to be preliminary until published in a peer-reviewed journal.

SAN JUAN -- Suppressing thyroid-stimulating hormone (TSH) after thyroidectomy for low-risk cancer increases the risk of osteoporosis in women without cutting back on cancer recurrence, researchers reported here.

In a retrospective study, women who had suppressed TSH levels had more than a three-fold increased risk of osteoporosis than those whose levels were not suppressed, Laura Wang, MD, of Memorial Sloan Kettering Cancer Center (MSKCC) in New York City, and colleagues reported at the American Thyroid Association meeting.

Therapeutic efforts should focus on avoiding harm in indolent disease," Wang said during her presentation.

After thyroidectomy for well-differentiated thyroid cancer, TSH is often suppressed because it stimulates thyroid cell proliferation, and a goal of treatment is to inhibit the growth of residual neoplastic tissue.

But there's no evidence-based consensus on the optimal TSH level that can help reduce recurrence while minimizing the risk of adverse effects, Wang said.

To assess the effects of TSH suppression on those effects -- in this study, a composite of atrial fibrillation and osteoporosis -- Wang and colleagues conducted a retrospective study of 771 patients who were treated for thyroid cancer at MSKCC from 2000 to 2006 and were followed for a median of 6.5 years.

They excluded patients with high-risk cancer, those with primary hyperparathyroidism, and those who had atrial fibrillation or osteoporosis before thyroidectomy.

After these exclusions, they were left with 756 patients in the atrial fibrillation analysis. For the osteoporosis analysis, they excluded men, and analyzed a total of 537 women.

TSH suppression was defined as a median level of 0.4 mU/L or less.

Overall, they saw no differences between those with suppressed TSH and those without in terms of disease-free survival, and multivariate analyses confirmed that TSH suppression was not a predictor of recurrence.

But for their composite outcome of adverse events, they did find a significantly increased risk with suppressed TSH levels.

Wang said the TSH suppressed group developed more events of harm at twice the rate of those who were not suppressed (hazard ratio 2.1, 95% CI 1.00 to 4.3, *P*=0.05).

However, when the analysis was broken down into either outcome, there was no significantly increased risk of atrial fibrillation with TSH suppression, Wang reported.

Yet there was a major divergence in osteoporosis risk, with a significantly higher risk for those with suppressed TSH (HR 3.5, 95% CI 1.2-10.2, *P*=0.023).

And in a multivariate analysis that controlled for age, a major confounder of osteoporosis risk, TSH remained a very strong predictor of osteoporosis, Wang said (HR 4.32, 95% CI 1.45-12.85, *P*=0.009).

In order to determine an optimal TSH level, the researchers looked at risk of osteoporosis and recurrence by TSH level and found that osteoporosis risk tapered with less suppression -- particularly for levels of 0.9 to 1 mU/L -- and risk of recurrence remained about the same at these levels.

Wang concluded that there's no recurrence benefit with TSH suppression, but an increased risk of harm, particularly for osteoporosis in women, and care should be taken with regard to TSH suppression in these patients who've had thyroidectomy for low-risk disease.

Ronald Koenig, MD, PhD, of the University of Michigan in Ann Arbor, who was not involved in the study, said the findings "raise the question of whether TSH suppression is in fact necessary."

"More data are needed from a larger series of patients to inform practice guidelines, but these findings are potentially impactful since they highlight an area where revision might be indicated," Koenig told *MedPage Today*.

https://www.medpagetoday.com/

Source Reference: Wang LY, et al "TSH suppression increases the risk of osteoporosis without changing recurrence in non-high risk patients with differentiated thyroid carcinoma" *ATA* 2013; Abstract 5.

Suppressing TSH May Harm Low-Risk Thyroid-Cancer Patients - Medscape - Mar 25, 2015.

Tucker ME.

Medscape

Thyrotropin suppression does more harm than good in thyroid-cancer patients who aren't at high risk for tumor recurrence following thyroidectomy, a new study suggests.

The findings, from chart reviews of more than 700 low- and intermediate-risk differentiated–thyroid-carcinoma patients who underwent total thyroidectomy, were published in the March issue of *Thyroid* by Laura Y Wang, MD, from Memorial Sloan Kettering Cancer Center, New York, and colleagues.

Compared with low- to moderate-risk patients who had not received levothyroxine suppression of thyrotropin (TSH) following surgery, there were no differences in tumor recurrence or disease-free survival over 6.5 years among those who had received suppression.

But the risk for osteoporosis was more than threefold greater and increased further with age among women who had received thyrotropin suppression compared with those who hadn't.

"We have a one-size-fits-all approach, where we administer thyrotropin suppression to every patient with thyroid cancer after they have undergone thyroidectomy and radioactive iodine.…They are often on lifetime suppression.…We do that on purpose, to stop the growth of thyroid cancer," senior author Laura Boucai, MD, an endocrinologist at Memorial Sloan Kettering Cancer Center, told *Medscape Medical News*.

However, the recurrence rates of thyroid cancer are extremely low, and the question is "whether we truly need to give medications to these [lower-risk] patients forever to keep them at a level where they are overmedicated, when the real risk of the tumor coming back in the neck is very small," she added.

In fact, the thinking has been shifting in this direction in recent years, and the overall findings were no surprise to David S Cooper, MD, director of the thyroid clinic at Johns Hopkins University School of Medicine, Baltimore, Maryland. (continue)…

Radioiodine Treatment and Thyroid Hormone Suppression Therapy for Differentiated Thyroid Carcinoma: Adverse Effects Support the Trend toward Less Aggressive Treatment for Low-Risk Patients

Klein Hesselink EN and Links TP

European Thyroid Journal (June) 2015; 4(2): 82-92.

Abstract

Over the past decades, the incidence of differentiated thyroid carcinoma (DTC) has steadily increased, with especially a growing number of low-risk patients. Whereas DTC used to be treated rather aggressively, it is now acknowledged that aggressive treatment does not affect outcome for low-risk patients and that it can induce adverse effects. In this review an overview of the most clinically relevant adverse effects of radioiodine treatment and thyroid hormone suppression therapy (THST) is presented, and the trend toward less aggressive treatment for low-risk patients is outlined. Salivary gland dysfunction occurs in roughly 30% of patients, and is probably due to the concentration of radioiodine in the salivary glands by the sodium/iodide symporter. Beta radiation from radioiodine can result in sialoadenitis and eventually fibrosis and loss of salivary function. Furthermore, patients can experience bone marrow dysfunction following radioiodine treatment. Although this is in general subclinical and transient, patients that receive very high cumulative radioiodine doses may be at risk for more severe bone marrow dysfunction. THST can induce adverse cardiovascular effects in patients with DTC, such as diastolic and systolic dysfunction, and also adverse vascular and prothrombotic effects have been described. Finally, the effects of THST on bone formation and resorption are outlined; especially postmenopausal women with DTC on THST seem to be at risk of bone loss. In the past years, advances have been made in preventing low-risk patients from being overtreated. Improved biomarkers are still needed to further optimize risk stratification and personalize medicine.

Postoperative Thyroid-Stimulating Hormone Levels Did Not Affect Recurrence after Thyroid Lobectomy in Patients with Papillary Thyroid Cancer

Lee MC, Kim MJ, Choi HS, Cho SW, Lee GH, Park YJ and Park DJ.

Background

Thyroid-stimulating hormone (TSH) suppression is recommended for patients who undergo thyroidectomy for differentiated thyroid cancer (DTC). However, the impact of TSH suppression on clinical outcomes in low-risk DTC remains uncertain. Therefore, we investigated the effects of postoperative TSH levels on recurrence in patients with low-risk DTC after thyroid lobectomy.

Methods

Patients (*n*=1,528) who underwent thyroid lobectomy for papillary thyroid carcinoma between 2000 and 2012 were included in this study. According to the mean and dominant TSH values during the entire follow-up period or 5 years, patients were divided into four groups (<0.5, 0.5 to 1.9, 2.0 to 4.4, and ≥4.5 mIU/L). Recurrence-free survival was compared among the groups.

Results

During the 5.6 years of follow-up, 21 patients (1.4%) experienced recurrence. Mean TSH levels were within the recommended low-normal range (0.5 to 1.9 mIU/L) during the total follow-up period or 5 years in 38.1% or 36.0% of patients. The mean and dominant TSH values did not affect recurrence-free survival. Adjustment for other risk factors did not alter the results.

Conclusion

Serum TSH levels did not affect short-term recurrence in patients with low-risk DTC after thyroid lobectomy. **TSH suppression should be conducted more selectively.**

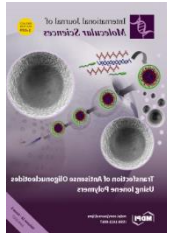
EnM Endocrinology and Metabolism

Endocrinol Metab. 2019 Jun;34(2):150-157.
Published online May 10, 2019.
https://doi.org/10.3803/EnM.2019.34.2.150


LOW RISK
HIGH RISK

TNM Classification of Thyroid Cancer, 8th edition*

TX	Primary Tumor Cannot be Assessed
T0	No evidence of primary tumor
T1	Tumor size maximum 2 cm, limited to the thyroid
T1a	Tumor size maximum 1 cm, limited to the thyroid
T1b	Tumor size >1 cm up to a maximum of 2 cm, limited to the thyroid
T2	Tumor size >2 cm up to 4 cm, limited to the thyroid
T3	Tumor size >4 cm, limited to the thyroid, or any tumor with macroscopic extrathyroidal extension (Musculus sternohyoideus, Musculus sternothyreoideus, Musculus omohyoideus)
T3a	Tumor size >4 cm, limited to the thyroid
T3b	Any tumor with macroscopic extrathyroidal extension (M. sternohyoideus, M. sternothyreoideus, M. omohyoideus)
T4a	Any tumor size with extrathyroidal extension beyond the thyroid capsule and invasion of subcutaneous soft tissue, larynx, trachea, esophagus and/or recurrent laryngeal nerve
T4b	Any tumor size with invasion of prevertebral fascia, mediastinal vessels or carotid artery
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases
N1a	Lymph node metastases unilateral in level VI or upper mediastinum
N1b	Metastases in other unilateral, bilateral or contralateral cervical lymph nodes (level I, II, III, IV and V) or retropharyngeal
M0	No distant metastases
M1	Distant metastases



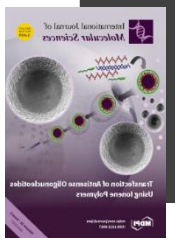
Differentiated Thyroid Cancer-Treatment: State of the Art.
Schmidbauer B, Menhart K, Hellwig D and Grosse J Int J Mol Sci (June) 2017; 18(6): 1292.
Published online 2017 Jun 17. doi: 10.3390/ijms18061292
PMCID: PMC5486113
PMID: 28629126

Common risk-stratification of DTC based on the TNM classification

high-risk group: pT3, pT4, each N1, all M1;

low-risk group: pT1b, pT2, cN0/pN0, cM0;

very low risk-group: pT1a, cN0/pN0, cM0.



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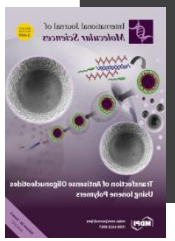
The American Thyroid Association defines in their current guideline a stratification based on the risk of structural disease recurrence:



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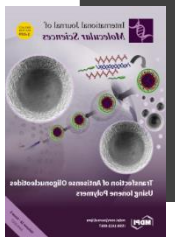
high-risk group: gross extrathyroidal extension, incomplete tumor resection, distant metastases, or lymph node >3 cm;

intermediate-risk: aggressive histology, minor extrathyroidal extension, vascular invasion, or >5 involved lymph nodes (0.2–3 cm);

low-risk: intrathyroidal DTC, ≤5 lymph nodes micrometastases (<0.2 cm).

New Molecular and Genetic Biomarkers



Differentiated Thyroid Cancer-Treatment: State of the Art.
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In the last few years new molecular and genetic biomarkers, such as:

- **BRAF (V600E),**
- **phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit α (PIK3CA),**
- **tumor protein p53 (TP53),**
- **RAC-α serine/threonine-protein kinase 1 (AKT1) and**
- **telomerase reverse transcriptase (TERT)**

became more important for the management of diagnosis, therapy and observing of DTC.

Next slide shows the impact of the two well-evaluated molecular markers BRAF and TERT. Some of these alterations might be interesting molecular targets for new therapies.

Mutations of BRAF and TERTp in follicular-derived thyroid carcinoma and clinicopathological impact

Mutation	Histology	Clinicopathological Associations
BRAF	papillary thyroid carcinoma (PTC)	recurrence, multifocality, extrathyreoidal extension, lymph nodes metastasis, advanced stage, absence of capsule, vascular invasion, more aggressive histological subtype
BRAF	micro PTC	multifocality, extrathyreoidal extension, advanced stage, lymph node metastasis
BRAF	thyroid carcinoma derived from follicular cells	no association
TERT	papillary thyroid carcinoma	more advanced stage by tall cell variant, higher tumor size, vascular invasion, older age, poor outcome, lymph node and distant metastasis
TERT	thyroid carcinoma derived from follicular cells	more aggressive histologic variants, concomitant presence of mutated RAS/BRAF, age > 45, higher tumor size, vascular invasion, persistent or recurrent disease, lymph node metastasis

Postoperative Risk Stratification

Low Risk	Intermediate Risk	High Risk
• No metastases	• Microscopic invasion of tumor into soft tissue outside the thyroid	• Extra-thyroidal invasion
• Complete surgical resection	• Cervical lymph node metastasis	• Incomplete surgical resection
• No local invasion	• High-risk histology (e.g. poorly differentiated elements) or angioinvasion	• Distant metastases
• Low-risk histology		

ETA (2014) and ATA (2015) Guidelines

Initial Approach

- If risk is so low that RRA is not indicated, then TSH suppression is not required at all.
- Maintain TSH in the low-normal range at less than 2mU/l (expert opinion)
- Encapsulated follicular variant of PTC, recently classified as a condition of low malignant potential, would automatically be categorized in this low risk group.

- **All other patients are initially assumed to be at higher risk and should have TSH suppression to less than 0.1 mU/l after TT and RRA.**

- **The need for long-term TSH suppression should then be decided based on the dynamic risk stratification after stimulated Tg measurement at 9-12 months.**

Dynamic Risk Stratification: Response to Initial Therapy of Differentiated Thyroid Cancer

EXCELLENT RESPONSE	INDETERMINATE RESPONSE	POOR RESPONSE
• Suppressed and stimulated Tg < 1 lg/l • Neck US (or other imaging) without evidence of disease	• Suppressed Tg < 1 lg/l and stimulated Tg ≥1 and <10 lg/l, • OR Neck US (or other imaging) with nonspecific changes or stable sub-centimeter lymph nodes	• Suppressed Tg ≥1 lg/l or stimulated Tg ≥ 10 lg/l • Rising Tg values • Persistent or newly identified disease on cross-sectional or nuclear medicine imaging

DYNAMIC RISK STRATIFICATION

- **Patients with a stimulated thyroglobulin of less than 0.1 µg/l and neck ultrasound that is negative for recurrence no longer require TSH suppression but should have the TSH concentration maintained at less than 0.2 mU/l.**

- **Patients whose dynamic risk stratification indicates an incomplete response to initial treatment should continue to have their TSH concentration suppressed to below 0.1 mU/l indefinitely.**

DYNAMIC RISK STRATIFICATION

- **Patients who fall into an intermediate category with suppressed thyroglobulin less than 1 µg/l and stimulated thyroglobulin of between 1 and 10 µg/l or with non-specific changes on imaging should have TSH suppression to the intermediate level of suppression to between 0.1 and 0.5 mU/l for at least 5-10 years, at which point the requirement can be re-assessed.**

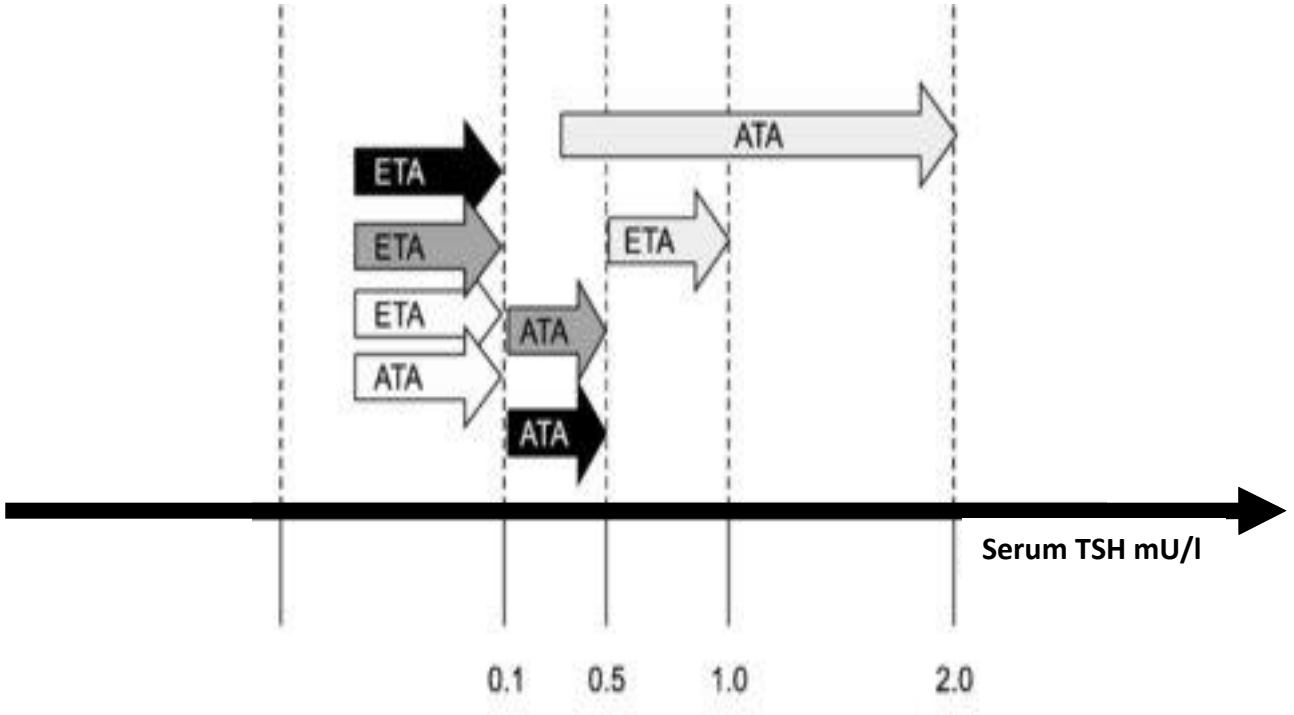
- **Monitoring of serial unstimulated thyroglobulin levels is a key component of regular follow-up of these patients.**

DYNAMIC RISK STRATIFICATION

- **With regard to historical patients who never received dynamic risk stratification, the BTA guidelines suggest they should be suppressed to below 0.1 mU/l for 5-10 years after the need for continuing TSH suppression should be reevaluated.**

- **In no instance is suppression to TSH to less than 0.1 mU/l recommended, given the increased risk of osteoporosis and cardiovascular harm and the doubtful benefit for DTC long-term outcomes and mortality.**

Differences Among Consensus Guidelines of the ATA and ETA for L-T4 Therapy in Patients with Differentiated Thyroid Cancer

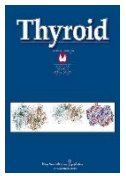


High risk (initial therapy): ATA and ETA: Serum TSH <0.1 mU/l

High risk disease free (follow-up): ATA: Serum TSH 0.1-0.5 mU/l for 5-10 years; ETA: Serum TSH <0.1 mU/l for 3*-5 years

Low risk (initial therapy): ATA: Serum TSH 0.1-0.5 mU/l; ETA: Serum TSH ,0.1 mU/l

Low risk disease free (follow-up): ATA: Serum TSH 0.3-2 mU/l; ETA: Serum TSH 0.5-1 mU/l



Benefits of Thyrotropin Suppression Versus the Risks of Adverse Effects in Differentiated Thyroid Cancer
Biondi B and Cooper DS. Thyroid 2010; 20(2): 135-146.
Published Online:12 Feb 2010 https://doi.org/10.1089/thy.2009.0311

ETA=European thyroid Association; ATA=American Thyroid Association; TSH=Thyrotroptin

L-T4 Therapy in DTC: A Balance Between Cancer Aggressiveness and the Risk of Adverse Effects

- **The key question for clinicians is which patients require total suppression of serum TSH levels, given the risk of recurrent or metastatic DTC, and how do advanced age and comorbidities influence the degree of TSH suppression?**

Risk Assessment for Thyrotropin Suppression in Differentiated Thyroid Cancer at Initial Evaluation

Low risk from tumor recurrence or death

- No local or distant metastases
- Complete surgery
- No locoregional or vascular invasion
- No aggressive histology (e.g., tall cell, insular, columnar cell carcinoma)
- No uptake outside the thyroid bed on initial posttreatment scan

Low risk from TSH suppression

- Young and middle-aged patients
- Asymptomatic patients
- No cardiovascular disease
- No alterations of cardiac rhythm
- No symptoms of adrenergic overactivity
- No cardiovascular risk factors
- No comorbidities
- Premenopausal women
- Normal BMD*
- No risk factors for osteoporosis

*BMD, bone mineral density.

Risk Assessment for Thyrotropin Suppression in Differentiated Thyroid Cancer at Initial Evaluation (Cont.)

Intermediate risk from tumor recurrence or death

- Microscopic invasion into the perithyroidal soft tissues
- Aggressive histology
- Vascular invasion

Intermediate risk from TSH suppression

- Elderly subjects
- Hypertension
- Symptoms and signs of adrenergic overactivity
- Cigarette smoking
- Cardiovascular risk factors and diabetes
- Perimenopausal women
- Osteopenia
- Risk factors for osteoporosis

Risk Assessment for Thyrotropin Suppression in Differentiated Thyroid Cancer at Initial Evaluation (Cont.)

High Risk From Tumor Recurrence or Death

- Increased age (>45-50 years)
- Increased size (>4 cm)
- Macroscopic tumor invasion
- Incomplete tumor resection
- Distant metastases
- Radioiodine uptake outside the thyroid bed after a posttreatment radioiodine scan performed after ablation of remnant thyroid

High Risk From TSH Suppression

- Clinical heart disease
- Very elderly
- Postmenopausal
- Comorbidities

Suggested Initial Thyrotropin Targets in Thyroid Cancer Patients According to Risk Assessment

		Risk of cancer recurrence and progression		
		High	*Intermediate*	*Low*
Risk from T_4 therapy	*High*	<0.1 mU/L[a]	<0.1 mU/L[a]	0.5–1 mU/L
	Intermediate	<0.1 mU/L[b]	<0.1 mU/L[b]	0.5–1 mU/L
	Low	<0.1 mU/L	<0.1 mU/L	0.1–0.5 mU/L

[a]With high risk from L-T4: consider cardiovascular drugs, calcium, vitamin D, and antiresorptive drugs.
[b]With intermediate risk from L-T4 and high or intermediate risk of tumor progression: consider β-adrenergic blocking drugs, calcium, and vitamin D.
L-T4, levothyroxine.

Suggested Thyrotropin Targets in Thyroid Cancer Patients According to Risk Assessment during Follow-up

		Risk of cancer recurrence and progression		
		High	*Intermediate*	*Low*
Risk from T_4 therapy	*High*	<0.1 mU/L persistent or metastatic disease; 0.1–0.5 mU/L if disease free for 5–10 years[a]	0.5–1 mU/L if disease free for 5–10 years, then 1–2 mU/L	1–2 mU/L
	Intermediate	<0.1 mU/L persistent or metastatic disease[b]; 0.1–0.5 mU/L if disease free for 5–10 years	0.1–0.5 mU/L if disease free for 5–10 years, then 1–2 mU/L	1–2 mU/L
	Low	<0.1 mU/L persistent or metastatic disease[c]; 0.1–0.5 mU/L if disease free for 5–10 years	0.1–0.5 mU/L if disease free for 5–10 years, then 0.3–2 mU/L	0.3–2 mU/L

[a]With high risk from L-T4 with persistent/metastatic disease: TSH suppression should be adapted to the clinical situation.
[b]With intermediate risk from L-T4 with persistent/metastatic disease: consider cardiovascular drugs, calcium, and vitamin D.
[c]With low risk from L-T4 with persistent/metastatic disease: periodic cardiovascular and BMD assessment.

In Children: What Are the Goals and Potential Risks of TSH Suppression Therapy?

DTCs in children are well-differentiated tumors that may respond to TSH stimulation with increased growth and Tg production.

For that reason, TSH suppression has been an important cornerstone of treatment, especially for high-risk groups.

However, there are no data in children with which to compare the outcomes, risks, and benefits of various TSH suppression strategies.

In Children: What Are the Goals and Potential Risks of TSH Suppression Therapy? (Cont.)

Some experts recommend initial TSH suppression to < 0.1 mIU/L followed by relaxation to 0.5 mIU/L following remission of DTC.

Recognizing the paucity of data regarding TSH suppression in children with DTC, the panel has concluded that the initial TSH goal should be tied to ATA Pediatric Risk level and current disease status.

In children without evidence of disease, the TSH can be normalized to the low-normal range after an appropriate period of surveillance.

In Children: What Are the Goals and Potential Risks of TSH Suppression Therapy? (Cont.)

American Thyroid Association Pediatric Thyroid Cancer Risk Levels and Postoperative Management in Children with Papillary Thyroid Carcinoma

ATA pediatric risk level[a]	Definition	Initial postoperative staging[b]	TSH goal[c]	Surveillance of patients with no evidence of disease[d]
Low	Disease grossly confined to the thyroid with N0/Nx disease or patients with incidental N1a disease (microscopic metastasis to a small number of central neck lymph nodes)	Tg^{e}	0.5–1.0 mIU/L	US at 6 months postoperatively and then annually x 5 years Tg^{e} on LT_4 every 3–6 months for 2 years and then annually
Intermediate	Extensive N1a or minimal N1b disease	TSH-stimulated Tg^{e} and diagnostic ^{123}I scan in most patients (see Fig. 2)	0.1–0.5 mIU/L	US at 6 months postoperatively, every 6–12 months for 5 years, and then less frequently Tg^{e} on LT_4 every 3–6 months for 3 years and then annually Consider TSH-stimulated Tg^{e} – diagnostic ^{123}I scan in 1–2 years in patients treated with ^{131}I
High	Regionally extensive disease (extensive N1b) or locally invasive disease (T4 tumors), with or without distant metastasis	TSH-stimulated Tge and diagnostic 123I scan in all patients (see Fig. 2)	< 0.1 mIU/L	US at 6 months postoperatively, every 6–12 months for 5 years, and then less frequently Tg^{e} on LT_4 every 3–6 months for 3 years and then annually TSH-stimulated Tg^{e} – diagnostic ^{123}I scan in 1–2 years in patients treated with ^{131}I

a ''Risk'' is defined as the likelihood of having persistent cervical disease and/or distant metastases after initial total thyroidectomy – lymph node dissection by a high volume thyroid surgeon and is not the risk for mortality, which is extremely low in the pediatric population. See Section C7 for further discussion. b Initial postoperative staging that is done within 12 weeks after surgery. c These are initial targets for TSH suppression and should be adapted to the patient's known or suspected disease status; in ATA Pediatric Intermediate- and High-risk patients who have no evidence of disease after 3–5 years of follow-up, the TSH can be allowed to rise to the low normal range. d Postoperative surveillance implies studies done at 6 months after the initial surgery and beyond in patients who are believed to be disease free; the intensity of follow-up and extent of diagnostic studies are determined by initial postoperative staging, current disease status, and whether or not 131I was given; may not necessarily apply to patients with known or suspected residual disease (see Fig. 3) or FTC. e Assumes a negative TgAb (see Section D2); in TgAb-positive patients, consideration can be given (except in patients with T4 or M1 disease) to deferred postoperative staging to allow time for TgAb clearance. ATA, American Thyroid Association; LT4, levothyroxine; TgAb, thyroglobulin antibody; US, ultrasound

Adverse Effects of Exogenous SHyper

In young and middle-aged patients

- Patients affected by DCT treated with doses of L-T4 leading to undetectable serum TSH levels may have symptoms and signs of thyroid hormone excess and resultant poor compliance with L-T4 treatment.
- TSH-suppressive doses of L-T4 can impair quality of life as measured by psychological, social, and physical items, particularly when the serum TSH is undetectable.

Adverse Effects of Exogenous SHyper

In young and middle-aged patients (Cont.)

- Some important cardiovascular risk factors (increased heart rate, increased left ventricular mass, increased mean arterial pressure, and diastolic dysfunction) can develop in young and middle-aged individuals receiving long-term TSH suppression with L-T4.

- These alterations may be of clinical importance, because the same cardiovascular risk factors associated with long-term TSH suppression may predict an increased risk for cardiac mortality and future cardiovascular events in the general population.

Adverse Effects of Exogenous SHyper

In older patients

- The adverse effects of SHyper are closely related to the patient's age.
- Elderly patients have a higher risk of developing adverse effects of TSH suppression, although they can be less symptomatic than younger persons in the presence of thyroid hormone excess.
- Atrial fibrillation (AF) may be the first manifestation of overt hyperthyroidism or SHyper in elderly patients.

Adverse Effects of Exogenous SHyper

In older patients (Cont.)

- Two prospective studies reported an increased risk of AF in elderly subjects affected by endogenous or exogenous SHyper compared with euthyroid subjects over a 10- and a 13-year follow-up, respectively.
- A higher risk of AF has also been associated even with minimal TSH serum suppression (between 0.1 and 0.4 mU/L) in elderly subjects.
- AF is an important risk factor for cardiovascular morbidity and mortality in thyrotoxic patients and in the general population.

- **An increased T3 concentration during L-T4 therapy is indicative of overt iatrogenic hyperthyroidism, and the combination of serum total or free T3 and serum TSH may be the best parameters for monitoring TSH-suppression therapy in patients with DTC.**

Bone Mineral Density and Fracture Risk in Exogenous SHyper

Data on the potential role of TSH on bone remodeling are conflicting.

Two recent reviews assessed the effects of TSH suppressive therapy on bone mineral density (BMD) in patients with DTC.

The studies were stratified according to sex and menopausal status and the results suggested that TSH suppression did not affect BMD in men or in premenopausal women, whereas postmenopausal patients were at risk of bone loss.

Bone Mineral Density and Fracture Risk in Exogenous Shyper (Cont.)

In general, it appears that TSH suppression induced by L-T4 therapy accelerates bone turnover, but only in postmenopausal women.

However, the degree of serum TSH suppression required to avid this effect is unknown.

Several studies have evaluated whether SHyper increases the risk of fractures.

Women with a history of thyroid cancer appeared to have their first fracture earlier ($p<0.01$) than women without thyroid disease.

Bone Mineral Density and Fracture Risk in Exogenous Shyper (Cont.)

Bauer et al, prospectively evaluated fracture risk in 686 women older than 65 years with low serum TSH due to both exogenous and endogenous SHyper.

After adjustment for age, history of hyperthyroidism, and use of estrogen and thyroid hormone, women with serum TSH level of ≤0.1 mU/L had a threefold increased risk of hip fracture and a fourfold increased risk of vertebral fracture compared with women with normal serum TSH levels.

Women receiving L-T4 doses to maintain serum TSH in the range of 0.1-0.5 mU/L also have an increased risk of fractures.

Bone Mineral Density and Fracture Risk in Exogenous Shyper (Cont.)

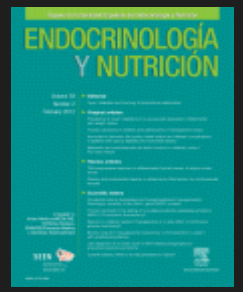
A suppressed serum TSH (≤0.03 mU/L) was associated with a doubled risk of osteoporotic fracture in postmenopausal women (mean age: 60.3 years) in a recent population-based study of all patients taking LT4 therapy.

Patients with a serum TSH below the reference range, but not fully suppressed (0.04-0.4 mU/L), had no increased risk of fracture.

However, data on FT4 levels or T3 levels were not reported in these studies.

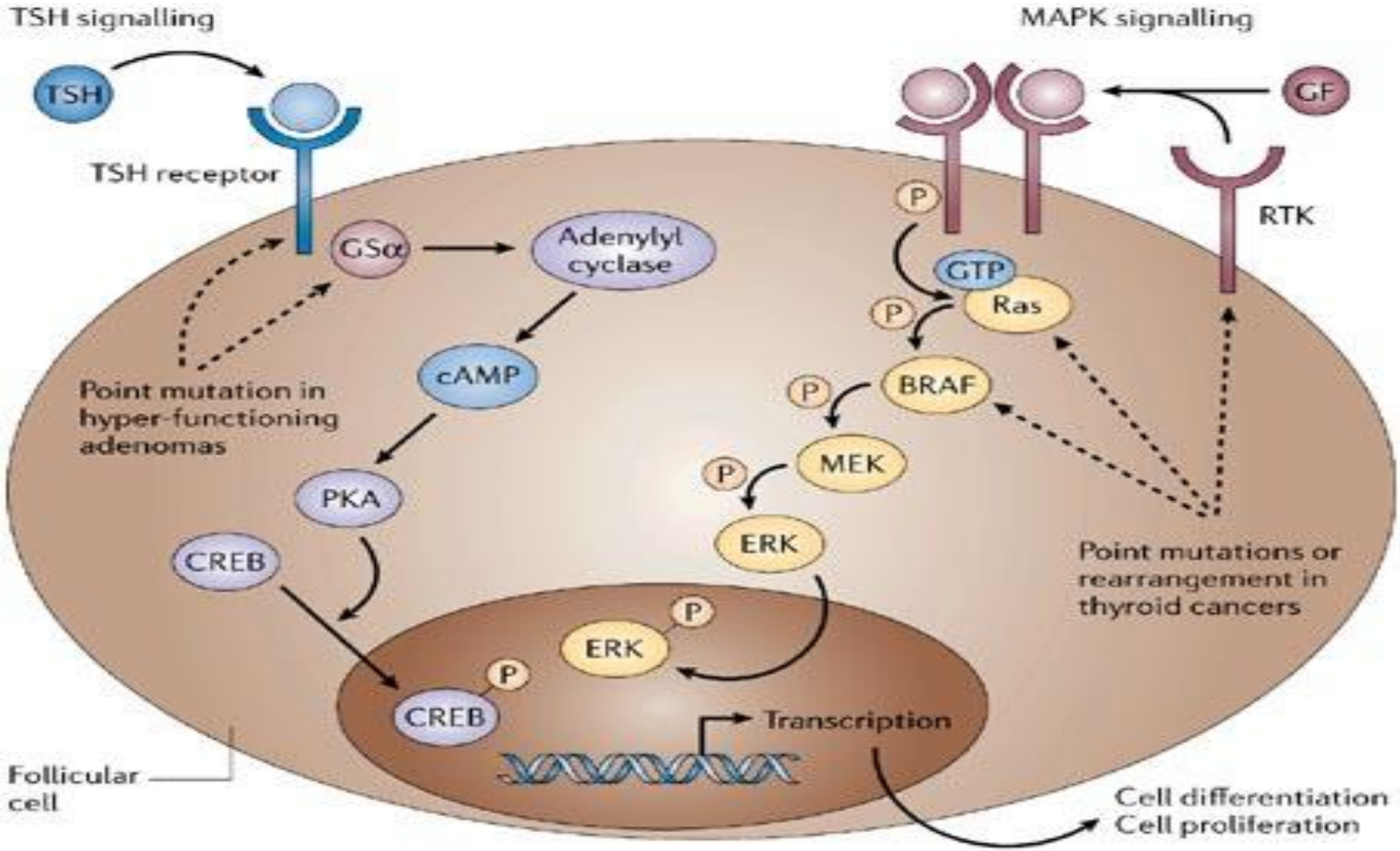
A new paradigm in thyroid hormone action

ENDOCRINOLOGIA Y NUTRICION



Endocrinología y Nutrición (February 2012): 59(2); 125-130.

- Integrin known as $\alpha_v\beta_3$ have a specific site that acts as an TH receptor.
- TH nongenomic actions has been confirmed to be due to the interaction with their surface receptor in integrin $\alpha_v\beta_3$.
- Integrin activation by THs could be responsible for the angiogenesis promoter action of THs.
- **T4- $\alpha_v\beta_3$ complex** acted by activating the signaling pathway dependent upon MAPK.



MAPK and Impact on Thyroid Cancer

There is evidence to suggest that the pathophysiological mechanism in which THs play a stimulatory role in cancer progression is the activation of the MAPK signaling pathway.

This is a key pathway in cell differentiation and proliferation which has been shown to be determinant in the development of PTC.

MAPK and Impact on Thyroid Cancer (Cont.)

All of these data have led to the impact of ST in the treatment scheme for DTC and suggested a potential new, unknown adverse effect of ST:

- **The possibility that ST is related to either DTC evolution or to the occurrence of a 2nd tumor.**

With the few experimental data available it has been postulated that in some patients ST may have a stimulating action on residual tumor growth, even in the absence of TSH.

- **Doses of L-T4 that reduce circulating TSH to 0.4 mμ/L are able to induce maximun suppression of serum Tg, suggesting that increasing the degree of TSH suppression may not further decrease tumor function.**

- **TSH suppression does not inhibit TSH-independent tumor growth in advanced and metastatic thyroid cancer.**

Case Presentation

64 years old woman with celiac disease, autoimmune thyroiditis and CAD.

Diagnosed with multifocal PTC follicular variant post thyroidectomy and lymphadenectomy.

RRA performed.

Undetectable Tg but persistent TgAb positivity.

Case Presentation (Cont.)

TSH suppressed with L-T4 tablet 3 µ/kg/day (225 µg/day) but not tolerated due to angina and PVC's despite β-blocking therapy. Later angioplasty was required.

L-T4 dose tapered to 2.4 µg/kg/day (190 µg/day).

Follow-up neck ultrasound showed a single lymph node 12x7 mm suspect for local relapse.

TSH inhibition became more pressing but L-T4 increase was delayed in view of unstable cardiac condition.

L-T4 dosage was frequently modified in response to wide TSH fluctuations being TSH=12.7 the most recent value reported.

Case Presentation (Cont.)
Biochemical Tests and L-T4 doses

Date	Weight, kg	L-T4 dose	TSH, mIU/l (nv 0.28–4.3)	Tg, µg/l	Anti-Tg antibodies, IU/ml (nv <60)
		Tablet			
05/03/2008	75	225 µg/day 3 µg/kg/day	0.04	<0.2	-
18/12/2008	76	193 µg/day 2.5 µg/kg/day	0.01–0.02	<0.2	166–357
28/05/2009	77	190 µg/day 2.4 µg/kg/day	0.02–0.34	<0.2	174–219
23/09/2011	80	185 µg/day 2.3 µg/kg/day	0.3–2.3	<0.2	110–190
21/03/2014	81	170 µg/day 2.1 µg/kg/day	0.17–5.7	<0.2	<60
23/01/2015	84	165 µg/day 2 µg/kg/day	4.5–12.4	<0.2	<60
		Liquid solution			
03/07/2015	84	175 µg/day 2.1 µg/kg/day	0.05	<0.2	<60

Which factors should you take in consideration to achieve TSH suppression target?

a. Compliance

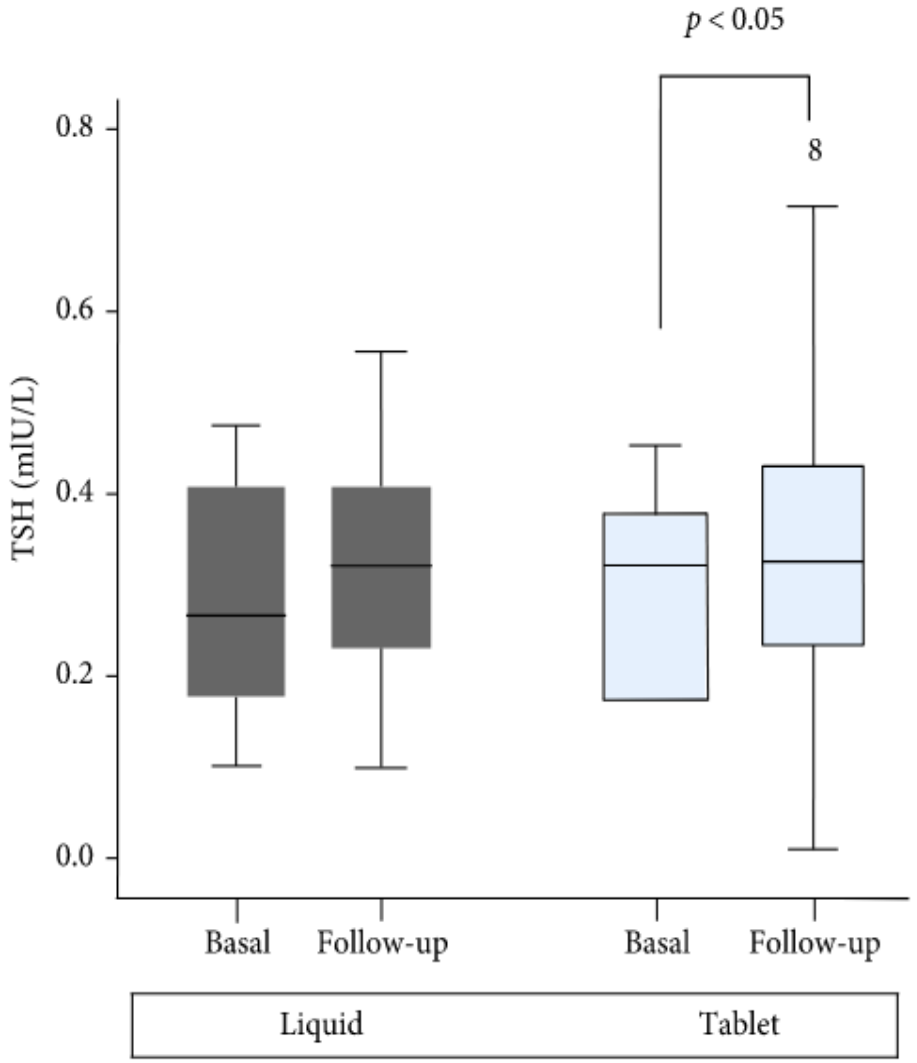
b. Reasonable gluten-free diet

c. L-T4 formulation

d. All of the above

Why L-T4 formulation ?

TSH values at first check-up (i.e., 8–12 months after ^{131}I remnant ablation) and at follow-up (i.e., after 12 months from first check-up) in patients taking tablets and/or liquid L-T4 formulation.



TSH Variability of Patients Affected by Differentiated Thyroid Cancer Treated with Levothyroxine Liquid Solution or Tablet Form
Cappelli C, Pirola I, Gandossi E, Casella C, Lombardi D, Agosti B, Marini F, Delbarba A, and Castellano M.
Volume 2017. Article ID 7053959 (5 pages) https://doi.org/10.1155/2017/7053959

LT4-OS

- **Have higher absorption rate than L-T4 tablets and therefore a shorter Tmax (1.94 vs. 2.42 hours)**

- **Causes less variability in TSH in comparison to LT4 tablets, specially when factors interfering with L-T4 absorption were presented as:**
  - **Concurrent use of PPI, calcium/iron supplements**
  - **Coffee**
  - **Coexisting celiac disease**
  - **Enteral tube feeding**
  - **Bariatric surgery**

LT4-OS

- **Patients switching from tablets to liquid formulation may need a decrease in dose.**

CONCLUSIONS

- **Achieving a balance between therapeutic goals and the side effects of L-T4 is a thorny issue, specially when comorbidities are present.**

- **The oral solution is a valuable tool in complex cases where strict control of therapeutic goals is crucial.**

CLINICAL PEARL

Thyrotropin Suppression by Metformin
Vigersky RA, Filmore-Nassar A and Glass AR
J Clin Endocrinol Metab (January) 2006; 91 (1): 225–227
https://doi.org/10.1210/jc.2005-1210

Patient 4 is a 75-yr-old woman treated with L-T4 175 mcg daily for many years after hypothyroidism developed after a thyroidectomy for papillary thyroid cancer 50 yr previously.

She also has hypertension and osteoarthritis.

Her other medications were aspirin, calcium, verapamil, hydrochlorothiazide, gabapentin, lisinopril, and furosemide.

After diagnosis of type 2 diabetes mellitus in 1998, treatment with insulin was initiated, resulting in moderate control (A1c 7.6%).

CLINICAL PEARL (Cont.)

Thyrotropin Suppression by Metformin
Vigersky RA, Filmore-Nassar A and Glass AR
J Clin Endocrinol Metab (January) 2006; 91 (1): 225–227
https://doi.org/10.1210/jc.2005-1210

Addition of metformin XR (500 mg daily) in February 2003, did not improve glycemic control (A1c 8.5% after 3 months) but was associated with a fall in serum TSH from 1.91 to 0.39 IU/ml over 3 months.

Five and 14 wk after discontinuation of metformin, serum TSH increased to 0.54 and 1.17 IU/ml, respectively.

The patient's weight did not change while on metformin.

TSH responses of patients 1– 4 to the administration of metformin

Patient	Age (yr)/gender	Underlying disease	Dose of L-T4 (μg)	Duration of DM (yr)	Met (mg/d)	Baseline fT4 (pmol/l)	Post-Met fT4 (pmol/l)	Baseline TSH (μU/ml)	Post-Met TSH (μU/ml)
Normal						10.3–30.6	10.3–30.6	0.43– 4.7	0.43– 4.7
1	58/M	Graves' disease treated with I-131	150	N/A	1500	15.3–23.9 (n=5)	13.4	1.19 –1.90 (n=5)	0.11
			150		1500	13.2	18.0	1.4	0.11
2	67/F	Hashimoto's	224	14	500	N.D.	N.D.	0.64	0.31
			224		1000	N.D.	29.6	0.31	0.17
			200		1000	29.6	18.7	0.17	0.21
3	66/M	Thyroidectomy for MNG	125	5	1000	N.D.	1.65a	1.3	0.36
			107		1000	1.65α	1.06α	0.36	0.14
4	**75/F**	**Thyroidectomy for PTC**	**175**	**5**	**500**	**N.D.**	**35.6**	**1.91**	**0.39**
			175		**0**	**35.6**	**24.7**	**0.39**	**1.17**

Metformin and low levels of thyroid-stimulating hormone in patients with type 2 diabetes mellitus

Fournier JP, Yin H, Yu OHY, and Azoulay L.

CMAJ October 21, 2014 186 (15) 1138-1145
DOI: https://doi.org/10.1503/cmaj.140688

Background: Small cross-sectional studies have suggested that metformin, a first-line oral hypoglycemic agent, may lower thyroid-stimulating hormone (TSH) levels. **Our objective was to determine whether the use of metformin monotherapy, when compared with sulfonylurea monotherapy, is associated with an increased risk of low TSH levels (< 0.4 mIU/L) in patients with type 2 diabetes mellitus.**

Methods: Using the Clinical Practice Research Datalink, we identified patients who began receiving metformin or sulfonylurea monotherapy between Jan. 1, 1988, and Dec. 31, 2012. We assembled 2 subcohorts of patients with treated hypothyroidism or euthyroidism, and followed them until Mar. 31, 2013. We used Cox proportional hazards models to evaluate the association of low TSH levels with metformin monotherapy, compared with sulfonylurea monotherapy, in each subcohort.

Results: A total of 5689 patients with treated hypothyroidism and 59 937 euthyroid patients were included in the subcohorts. Among patients with treated hypothyroidism, 495 events of low TSH levels were observed during follow-up (incidence rate 119.7/1000 person-years). In the euthyroid group, 322 events of low TSH levels were observed (incidence rate 4.5/1000 person-years). Compared with sulfonylurea monotherapy, metformin monotherapy was associated with a 55% increased risk of low TSH levels in patients with treated hypothyroidism (incidence rate 79.5/1000 person-years v. 125.2/1000 person-years, adjusted hazard ratio [HR] 1.55, 95% confidence interval [CI] 1.09–2.20), with the highest risk in the 90–180 days after initiation (adjusted HR 2.30, 95% CI 1.00–5.29). No association was observed in euthyroid patients (adjusted HR 0.97, 95% CI 0.69–1.36).

Interpretation: **In this longitudinal population-based study, metformin use was associated with an increased incidence of low TSH levels in patients with treated hypothyroidism, but not in euthyroid patients. The clinical consequences of this need further investigation.**

TSH-Lowering Effect of Metformin in Type 2 Diabetic Patients

Differences between euthyroid, untreated hypothyroid, and euthyroid on L-T4 therapy patients

Cappelli C, Rotondi M, Pirola I, Agosti B, Gandossi E, Valentini U, De Martino E, Cimino, Chiovato L, Agabiti-Rosei E, and Castellano M.

Diabetes Care (September) 2009; 32(9): 1589-1590

OBJECTIVE To assess the interplay between metformin treatment and thyroid function in type 2 diabetic patients.
RESEARCH DESIGN AND METHODS The acute and long-term effects of metformin on thyroid axis hormones were assessed in diabetic patients with primary hypothyroidism who were either untreated or treated with levothyroxine (L-T4), as well as in diabetic patients with normal thyroid function.
RESULTS No acute changes were found in 11 patients with treated hypothyroidism. After 1 year of metformin administration, a significant thyrotropin (TSH) decrease ($P < 0.001$) was observed in diabetic subjects with hypothyroidism who were either treated ($n = 29$; from 2.37 ± 1.17 to 1.41 ± 1.21 mIU/l) or untreated ($n = 18$; 4.5 ± 0.37 vs. 2.93 ± 1.48) with L-T4, but not in 54 euthyroid subjects. No significant change in free T4 (FT4) was observed in any group.
CONCLUSIONS Metformin administration influences TSH without change of FT4 in patients with type 2 diabetes and concomitant hypothyroidism.

The need for reevaluation of thyroid function in these patients within 6–12 months after starting metformin is indicated.

Metformin is a widely used drug for the treatment of type 2 diabetes (1,2). It is commonly regarded as a safe drug in that no clinically relevant pharmacologic interactions have been described when it is prescribed together with the most commonly used drugs, with the exceptions of folate and B12 vitamin (3,4,5).

Recently it has been reported that metformin is able to interfere with thyroid hormone profile, as shown by a decrease in the serum levels of thyrotropin (TSH) to subnormal levels in hypothyroid patients in stable levothyroxine (L-T4) treatment (6,7). However, no data are available for untreated hypothyroid patients or for euthyroid diabetic patients.

Given that both metformin treatment and hypothyroidism are frequent occurrences in diabetic patients (8), we aimed to further characterize the interplay between metformin and circulating thyroid function parameters by evaluating thyroid hormone axes in different categories of patients who were started on metformin because of a first diagnosis of diabetes

Possible Mechanisms (speculative)

May have changed the affinity and/or number of TH receptors.

Increased the dopaminergic tone.

Induced constituent activation of the TSH receptor.

These hypothesis would require that metformin be able to cross the blood brain barrier. This has not been studied.

If the effect of metformin is central and not peripheral, it could be used as an adjunct for the treatment of patients with thyroid cancer because it appears to suppress TSH without causing biochemical hyperthyroxinemia or clinical hyperthyroidism.

Take Home Message for Endocrinologists

The bottom line is that one sized thyroid hormone therapy and TSH target ranges does not fit all differentiated thyroid cancer patients.

The TSH target should be based on the severity of the disease and most importantly, the response to therapy weighted against the individual's risk factors for taking excess thyroid hormone therapy.

Take Home Message for PCP

Thyroid cancer patients can have different TSH targets than patients who do not have cancer but are taking thyroid hormone therapy.

Should not adjust thyroid therapy in a patient with DTC unless they are familiar with the guidelines from ATA.

If unsure, work with the patient endocrinologist to adjust TH therapy.

Goals of Follow-up?

Evolving Management Approach

1960-2000

Seek and destroy residual/recurrent thyroid cancer

Surgery/RAI/EBRT/Systemic Therapy to Improve Clinical Outcomes

2001-2020

Identify clinical significant residual/recurrent disease

Observe clinically insignificant disease.

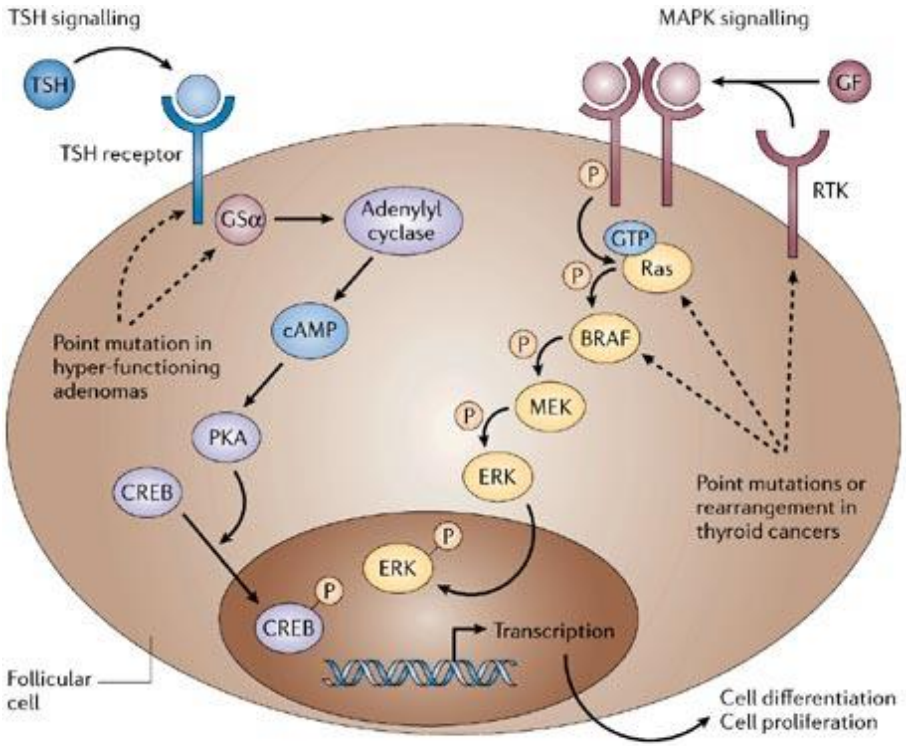
Treat clinically significant disease.

In the future,

1. **TSH suppression may be achieved with thyroid hormone analogs that suppress pituitary TSH secretion, with less effect on the cardiovascular system and the skeleton.**

2. **Another possibility is the development of retinoids or other compounds that specifically decrease pituitary TSH secretion.**

3. **Finally, an integrated genetic and morphological approach to the pathological diagnosis of DTC may help to identify those patients with DTC who are at high risk of recurrence and who will most benefit from TSH suppression, and those patients who are at low risk and who do not require it.**



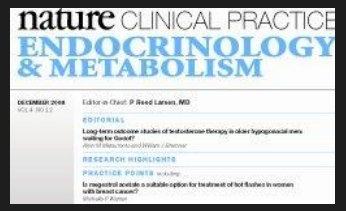
Thyroid Postgraduate Course, Diabetes & Romulo Ayuso's Memorial Lecture in Thyroid Cancer

Saturday, August 29, 2020

THANK YOU!!

Nonsurgical Approaches to the Management of Thyroid Nodules

- Thyroid-hormone-suppressive therapy with levothyroxine was preferred by over 40% of clinicians for treatment of solitary thyroid nodules.
- Over 50% of clinicians considered TSH suppression to be the treatment of choice for multinodular goiters.
- The latter finding is surprising, since there is very little published evidence of the efficacy of this approach, and its use is not recommended in any of the currently accepted treatment guidelines.



Nat Clin Pract Endocrinol Metab 2006; 2(7): 384-394.

Nonsurgical Approaches to the Management of Thyroid Nodules (Cont.)

- A meta-analysis of six randomized, controlled clinical trials demonstrated a significant benefit with levothyroxine treatment in one study;[39] whereas, in another, the results of treatment were clearly negative.[36] On the average, the effects of levothyroxine failed to reach statistical significance.

Nat Clin Pract Endocrinol Metab 2006; 2(7): 384-394.

Nonsurgical Approaches to the Management of Thyroid Nodules (Cont.)

- A subset of benign thyroid nodules do respond to thyroid-hormone-suppressive therapy.
- Other nodule characteristics associated with responsiveness to levothyroxine therapy are:
  - a recent diagnosis
  - relatively small volumes (<10 ml, <2.5 ml, or <1.5 ml)
  - and an abundance of colloid in FNAs.
- Of note, thyroid nodules rapidly return to their pretreatment size after discontinuation of therapy. This observation, obviously, implies the necessity for long-term administration of levothyroxine.

Nat Clin Pract Endocrinol Metab 2006; 2(7): 384-394.

Nonsurgical Approaches to the Management of Thyroid Nodules (Cont.)

- Its use is inappropriate in certain groups of patients, such as those over 60 years of age.
- Benign thyroid nodules in this age-group are generally characterized by very slow growth, or no growth at all.
- Elderly patients and postmenopausal women in particular are also at increased risk for the potential adverse effects of hormone suppression

Nat Clin Pract Endocrinol Metab 2006; 2(7): 384-394.

Pre/Post Test

IN A PATIENT WITH DTC AND ASSESSING THE POSSIBILITY OF TSH SUPPRESSION THERAPY, ALL OF THESE ARE CORRECT EXCEPT FOR?__

a. The initial approach in low risk DTC is that TSH suppression is not required at all.

b. Encapsulated follicular variant of PTC is categorized as a low risk group.

c. TSH <0.1 is recommended to both, high risk initial therapy and high risk disease-free (follow-up).

d. The need for long term TSH suppression should be decided based on the dynamic risk stratification.

e. Low risk disease-free follow-up, TSH up to 2 could be recommended.

ANSWER: c