Medical treatment of nodular goiter: still to be considered?

Yes, may be of use

Salvatore M. Corsello
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Nodular thyroid disease: a common clinical problem

- at autopsy or by US
- by palpation

Mazzaferri NEJM 1993
Nodular thyroid disease: a common clinical problem

• In iodine-sufficient areas the prevalence of palpable thyroid nodules ranges between 3-7% of the population

• In mild to moderate iodine-deficient areas (i.e.: Italy) the prevalence is higher (~10%)
The widespread use of ultrasonography (US) has resulted in a dramatic increase in the prevalence of clinically inapparent thyroid nodules. Prevalence is similar to that reported in autopsy data in patients with no history of thyroid disease. Thyroid US can detect thyroid nodules in 19%-76% of randomly selected individuals.

Mortensen JCEM 1955
Ezzat Arch Intern Med 1994
Tan Ann Intern Med 1997
Hegedus NEJM 2004
Levothyroxine therapy in nodular thyroid disease

To treat or not to treat?
If to treat...why?
• Even if the pathogenesis of such growth is poorly understood, TSH is considered an important stimulating factor of nodular growth.

• Suppression of TSH secretion might be expected to result in a decrease in nodule size or at least prevent any further enlargement.

Suppressive therapy is expected to be ineffective in patients in whom serum TSH concentrations are already subnormal due to autonomous thyroid hormone production.
LT4 suppressive therapy in nodular thyroid disease

Benign nodules can spontaneously grow to more than 15% of their initial size:

- 30% within one year
- 90% at five years

*if these nodules are not treated*

Evidence suggest that LT4 therapy, in doses suppressing serum TSH to subnormal levels:

- may decrease nodule size
- may prevent the appearance of new nodules in regions of the world with borderline / low iodine intake

Alexander EK Ann Intern Med 2003
Zelmanovitz JCEM 1998
Wemeau JCEM 2002
Castro JCEM 2002
Data in iodine-sufficient populations are less compelling, suggesting that only about 17–25% of thyroid nodules shrink more than 50% with LT4 suppression of serum TSH.

**ATA guidelines (2009)**
Routine suppression therapy of benign thyroid nodules in iodine sufficient populations is not recommended

**AACE / AME / ETA guidelines (2010)**
Routine LT4 treatment in patients with nodular thyroid disease is not recommended. LT4 therapy or iodine supplementation may be considered in:
- Young patients who live in iodine-deficient geographic areas and have small thyroid nodules;
- Young patients who live in iodine-deficient geographic areas and have nodular goiters and no evidence of functional autonomy.
Management of the nontoxic multinodular goiter:
a North American survey

**Index case**: 42-yr-old woman with an irregular, nontender, bilaterally enlarged thyroid of 50–80 g and no clinical suspicion of malignancy or thyroid dysfunction.

- **56.4%** would advocate the use of LT4 therapy
- **76%** would reach a slightly suppressed serum TSH level (0.1 – 0.3 mcU/ml)
- **42%** would use a long-term LT4 therapy
Index case: 42-yr-old woman with an irregular, nontender, bilaterally enlarged thyroid of 50–80 g and no clinical suspicion of malignancy or thyroid dysfunction.

- 51.6% would advocate the use of LT4 therapy
- 32.3% would reach a slightly suppressed serum TSH level (0.1 – 0.3 mcUI/ml)
- 50% would use a long-term LT4 therapy

Management of the nontoxic multinodular goiter: a European survey

Index case: 42-yr-old woman with an irregular, nontender, bilaterally enlarged thyroid of 50–80 g and no clinical suspicion of malignancy or thyroid dysfunction.

- 51.6% would advocate the use of LT4 therapy
- 32.3% would reach a slightly suppressed serum TSH level (0.1 – 0.3 mcUI/ml)
- 50% would use a long-term LT4 therapy

Bonnéma Clin Endocrinol 2000
Management of the solitary thyroid nodule: a European survey

**Index case:** 42-yr-old woman with a solitary 2 x 3 cm thyroid nodule and no clinical suspicion of malignancy

- **40%** would advocate the use of LT4 therapy
- **43%** would reach a slightly suppressed serum TSH level (0.1 – 0.3 mcU/l/ml)
- **62%** would use a long-term LT4 therapy
Efficacy of TSH suppressive therapy in reducing thyroid nodule

Relative changes in thyroid volume in patients with nontoxic goiter treated with placebo, LT4 + carbimazole and LT4 alone for 9 months, and than followed for other 9 months.

Berghout Lancet 1990
Efficacy of TSH suppressive therapy in reducing thyroid nodule

**LT4 group**
- Responders (30/64) 47%
- Partially responders (17/64) 27%
- Non responders (17/64) 26%

**Placebo group**
- Responders (10/59) 17%
- Partially responders (8/59) 14%
- Non responders (41/59) 69%

Wemeau JCEM 2002
Efficacy of TSH suppressive therapy in reducing thyroid nodule: meta-analysis

Cumulative meta-analysis concerning the capacity of LT4 suppressive therapy to **decrease** a STN volume to less than 50% of its baseline value.

Cumulative meta-analysis concerning the capacity of LT4 suppressive therapy to **arrest** the expansion of a STN volume to less than 50% of its baseline value.

Zelmanovitz JCEM 1998
Efficacy of TSH suppressive therapy in reducing thyroid nodule

Long-Term Changes in Nodular Goiter: A 5-Year Prospective Randomized Trial of Levothyroxine Suppressive Therapy for Benign Cold Thyroid Nodules

Nodule volume changes in the L-T4 treatment group and in the control group (median and range).

Nodule volume changes in the treatment group: differences between patients with TSH levels greater than 0.1 mU/L and patients with TSH levels less than 0.1 mU/L.

Thyroid volume changes in the L-T4 treatment group and in the control group.
Efficacy of TSH suppressive therapy in reducing thyroid nodule

The characteristics that seem to predict a greater response to TSH suppressive therapy are:

• “Small”, solid nodules
• “Recent” nodules
• Nodules with degenerative changes on biopsy/ultrasound
• Nodule with abundant colloid on biopsy/ultrasound
• Nodules without hyperplastic or fibrotic changes on biopsy/ultrasound
Efficacy of TSH suppressive therapy + iodine in reducing thyroid nodule

**Reduction of Thyroid Nodule Volume by Levothyroxine and Iodine Alone and in Combination: A Randomized, Placebo-Controlled Trial**

M. Grussendorf, C. Reiners, R. Paschke, and K. Wegscheider, on behalf of the LISA investigators

*J Clin Endocrinol Metab, September 2011, 96(9):2786–2795*

**Total nodal volume**

**Thyroid volume**
Levothyroxine therapy in preventing nodular recurrence after hemithyroidectomy: A retrospective study

M. Alba¹, D. Fintini², R.M. Lovicu¹, R.M. Paraoliva¹, G. Papi³, C.A. Rota¹, A. Pontecorvi¹, and S.M. Corsello¹  J. Endocrinol. Invest. 32: 330-334, 2009

In patients who have undergone hemithyroidectomy for benign monolobar nodular disease, LT4 therapy may prevent nodular recurrence.

TSH suppression may not be required for prevention of recurrence
Thyroid nodules and cancer risk

• Clinically overt thyroid cancer accounts for 1% of all new malignancies in the United States (0.4% of all cancer deaths)

• Thyroid cancer can occur in 5-15% of thyroid nodules

Factors potentially associated to thyroid cancer risk:

✓ Age (< 20 or > 70)
✓ Male gender
✓ Solitary vs multiple nodularity (?)
✓ Large (4 cm) or rapidly growing nodules (especially during thyroid hormone therapy)
✓ Neck irradiation
✓ Family history (familiar nonmedullary thyroid carcinoma: ~ 5% of cases)

Yu Thyroid 2010
Frates JCEM 2006
Rago EJE 2010
Hegedus Endocr Rev 2003
Nosè Endocr Pathol 2010

TSH ?
TSH and cancer risk

- Well-differentiated thyroid cancers express TSH receptors
- Although oncogenes and other growth factors are involved in thyroid cancer growth and development, TSH can act as a cancer stimulus.
- This hypothesis is supported by:
  - improved survival in thyroid cancer patients treated with suppressive doses of levothyroxine
  - cases of tumor growth post-T4 withdrawal or recombinant TSH

Shi Clin Endocrinol 1993
Derwahl JCEM 1998
Jonklaas Thyroid 2006
Braga JCEM 2001
“In the last few years, it has been reported that in patients with nodular thyroid diseases, the risk of thyroid malignancy increases with increasing concentrations of serum TSH, and even within normal ranges, higher TSH values are associated with a higher frequency and more advanced stage of thyroid cancer.”
TSH values and cancer risk

Serum Thyrotropin Concentration as a Novel Predictor of Malignancy in Thyroid Nodules Investigated by Fine-Needle Aspiration


The Journal of Clinical Endocrinology & Metabolism 91(11):4295–4301
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* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$, compared with TSH less than 0.4 µU/ml.
Higher Serum Thyroid Stimulating Hormone Level in Thyroid Nodule Patients Is Associated with Greater Risks of Differentiated Thyroid Cancer and Advanced Tumor Stage

Megan Rist Haymart, Daniel John Repplinger, Glen E. Leverson, Diane F. Elson, Rebecca S. Sippel, Juan Carlos Jaume, and Herbert Chen

*(J Clin Endocrinol Metab 93: 809–814, 2008)*

### TSH and cancer stage

<table>
<thead>
<tr>
<th>TNM stage</th>
<th>No. of patients</th>
<th>Mean TSH</th>
<th>P value</th>
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<tbody>
<tr>
<td>I and II</td>
<td>204</td>
<td>2.1 ± 0.24</td>
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<tr>
<td>III and IV</td>
<td>35</td>
<td>4.9 ± 1.59</td>
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</table>
Lower levels of TSH are associated with a lower risk of papillary thyroid cancer in patients with thyroid nodular disease: thyroid autonomy may play a protective role

E Fiore, T Rago, M A Provenzale, M Scutari, C Ugolini¹, F Basolo¹, G Di Coscio², P Berti³, L Grasso, R Elisei, A Pinchera and P Vitti

Endocrine-Related Cancer (2009) 16 1251–1260

<table>
<thead>
<tr>
<th>TSH (μU/ml)</th>
<th>OR</th>
<th>95% CI</th>
<th>P value a</th>
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<tbody>
<tr>
<td>0.40–0.59</td>
<td>0.80</td>
<td>0.51–1.27</td>
<td>0.18</td>
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<tr>
<td>0.60–0.89</td>
<td>2.01</td>
<td>1.46–2.77</td>
<td>&lt;0.0001</td>
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<tr>
<td>0.90–1.59</td>
<td>2.66</td>
<td>1.98–3.58</td>
<td>&lt;0.0001</td>
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<tr>
<td>1.60–3.40</td>
<td>4.29</td>
<td>3.17–5.08</td>
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<td>&gt;3.40</td>
<td>3.50</td>
<td>2.10–5.83</td>
<td>0.0011</td>
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</table>
Levothyroxine therapy in nodular thyroid disease: for many, but not all!

- Not to treat
  - Voluminous MG
  - Functional autonomy
  - Patients older than 60 years
  - Comorbidities (osteoporosis, cardiovascular and/or systemic disease)

- To treat
  - Low iodine intake
  - Young patients
  - Nodules < 3 cm, without functional autonomy
Levothyroxine therapy & heart damage: YES, BUT…

- Abnormalities of heart morphology associated with impaired exercise performance occur as a consequence of long term therapy with fixed TSH-suppressive doses of LT4.
- These abnormalities improve or disappear after careful tailoring of TSH-suppressive therapy.

Individual tailoring of the TSH-suppressive LT4 dose was in all cases associated with normalization of all echocardiographic and ergometabolic parameters.

**Oxygen consumption**  
Mercurso JCEM 2000

**Anaerobic threshold**
Levothyroxine therapy & bone damage: YES, BUT…

• No change in the mean bone mineral density of women after 1 yr of l-T4 therapy for benign solitary thyroid nodules (mean TSH < 0.3 mIU/liter).

  Zelmanovitz, JCEM, 1998

• A significantly increased risk for new hip and vertebral fractures was shown in women older than 65 yr of age who had low TSH levels, but not in those with LT4 therapy.

  Bauer, Ann Intern Med, 2001

• LT4-suppressive therapy is associated with bone loss in post-menopausal women. Anyway, this can be easily prevented by adding dietary calcium supplementation (1’000 mg/die).

  Kung JCEM 1996
Several studies show goiter recurrence few months after LT4 discontinuation.

*TSH suppressive therapy is generally supposed to be of indefinite duration*

**YES, BUT…**

- Patients in clinical studies sometimes undergo LT4 therapy for a short period of time (months).
- Studies generally include only young patients.
- Increasing age is accompanied by reduction of several stimuli to thyroid nodule growth: **BMI; GH; IGF1; estrogens**
Levothyroxine therapy in nodular thyroid disease

Yes, may be of use
Thank you!