Medical treatment of nodular goitre: still to be considered?

"No, it is a doubtful bargain"

Laszlo Hegedüs, MD, DMSc
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My initial attempt at outlining the talk for this symposium

Is it possible to limit the talk to 20 min?
Do we really have to reopen this debate again?
Medical (Levothyroxine, LT4?) therapy in benign nodular goitre

Some issues covered

- Understanding phenotype variation and eligibility
- Theoretical basis for using L-T4 to shrink thyroid nodules
- Current guideline recommendations
- Efficacy of L-T4 in shrinking thyroid nodules
- Potential side-effects of L-T4 therapy
- Potential effect of L-T4 in decreasing risk of papillary thyroid cancer
- Focus on available alternatives
- Conclusions
- Need of additional studies/evidence?
- Need of revising current guidelines?
The revised
ETA / AME / AACE
Thyroid Nodule Guideline

Annual meeting of the
European Thyroid Association

Lisbon
September 5th – 9th 2009

Hossein Gharib, Enrico Papini, Ralf Paschke,
Dan Duick, Roberto Valcavi, Laszlo Hegedüs, Paolo Vitti,
and the AACE/AME/ETA Task Force on Thyroid Nodules

R.P., L.H., P.V.

E.P., R.V.
AMERICAN ASSOCIATION OF
CLINICAL ENDOCRINOLOGISTS

H.G., D.D.
ITALIAN ASSOCIATION OF
CLINICAL ENDOCRINOLOGISTS
7.2.2. Levothyroxine therapy for benign nodules

• Routine levothyroxine therapy is not recommended (grade B; 1)

• Levothyroxine therapy or iodine supplementation may be considered in young patients with small nodular goiter and no evidence of functional autonomy (grade B; 1)

• .....
Key Recommendations regarding levothyroxine therapy for thyroid nodules that are negative by Fine-Needle Aspiration

- **Use of LT4 therapy may be considered** in the following (*grade C*):
  - Patients from geographic areas with iodine deficiency
  - Young patients with small thyroid nodules
  - Nodular goiters with no evidence of functional autonomy

- **Use of LT4 therapy should be avoided in most cases** and especially in the following (*grade C*):
  - Large thyroid nodules and goiters, particularly in the presence of symptoms or signs of functional autonomy
  - Clinically suspicious lesions or lesions with an inadequate cytologic sample
  - Postmenopausal women and men older than 60 years
  - Patients with osteoporosis or systemic illnesses
  - Patients with cardiovascular disease

- **Facts to remember:**
  - LT4 treatment induces a **clinically significant reduction of thyroid nodule volume in only a minority of patients** (*grade B*)
  - Long-term TSH suppression may be associated with **bone loss and arrhythmia** in elderly patients and menopausal women (*grade B*)
  - LT4 treatment should **never be fully suppressive** (TSH <0.1 µIU/mL) (*grade C*)
  - Nodule regrowth is usually observed after cessation of LT4 therapy (*grade C*)
  - If nodule size decreases, LT4 therapy should be continued long term (*grade D*)
  - If thyroid nodule grows during LT4 treatment, reaspiration and possibly surgical treatment should be considered (*grade D*)

*LT4 = levothyroxine; TSH = thyroid-stimulating hormone (thyrotropin).*
Eligibility for L-T4 therapy in nontoxic goitre

Prevalence of exclusion criteria, according to guidelines, in 745 consecutive patients

The majority have exclusion criteria

- TSH < 1.0 mIU/L
- Postmenopause
- TSH < 0.3 mIU/L *
- Volume > 100 mL
- Intrathoracic goitre
- Clinical suspicion
- Dominant thyroid cyst
- Invalid FNA
- Previous L-T4 therapy
- Elevated s-calcitonin
- Bone/Heart **

No further ex. criteria
1 additional ex. criteria
>1 additional ex. criteria

Number of patients

Eligibility for L-T4 therapy according to diagnoses in percent
Few percent are eligible!

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Eligible</th>
<th>1 ex criterion</th>
<th>2 ex criteria</th>
<th>3 ex criteria</th>
<th>4-6 ex criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>All diagnoses (n=745)</td>
<td>16</td>
<td>33</td>
<td>26</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Diffuse goiter (n=35)</td>
<td>37</td>
<td>37</td>
<td>23</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Uninodular goiter (n=320)</td>
<td>23</td>
<td>43</td>
<td>23</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Multinodular goiter (n=390)</td>
<td>9</td>
<td>24</td>
<td>28</td>
<td>21</td>
<td>18</td>
</tr>
</tbody>
</table>

L-T4 therapy is associated with overt or subclinical hyperthyroidism in many, which leads to increased morbidity and mortality. Hyperthyroidism is associated with excess mortality; a meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>RR (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osman et al.</td>
<td>2.17 (1.11, 4.23)</td>
<td>3.30</td>
</tr>
<tr>
<td>Goldman et al.</td>
<td>1.40 (1.28, 1.53)</td>
<td>15.77</td>
</tr>
<tr>
<td>Franklyn et al.</td>
<td>1.13 (1.09, 1.17)</td>
<td>16.80</td>
</tr>
<tr>
<td>Hall et al.</td>
<td>1.47 (1.42, 1.52)</td>
<td>16.83</td>
</tr>
<tr>
<td>Flynn et al.</td>
<td>1.05 (0.94, 1.17)</td>
<td>15.26</td>
</tr>
<tr>
<td>Nyrienda et al.</td>
<td>1.04 (0.94, 1.15)</td>
<td>15.51</td>
</tr>
<tr>
<td>Metso et al.</td>
<td>1.07 (1.01, 1.13)</td>
<td>16.53</td>
</tr>
<tr>
<td><strong>Overall</strong> (I-squared = 96.9%, p = 0.000)</td>
<td><strong>1.21 (1.05, 1.38)</strong></td>
<td><strong>100.00</strong></td>
</tr>
</tbody>
</table>

random effects analysis

Brandt et al., EJE 2011
Hyperthyroidism and excess mortality, also when treated. Population-based Danish register-study

Kaplain-Meier survival curve in singletons

A: Background population

Brandt et al. JCE&M, 2012
Hyperthyroidism (treated) and mortality

Waterfall plot showing the difference in survival time between cases and controls in disease discordant and death concordant twin pairs.

- Twins pairs where the case died first
- Twins pairs where the control died first

$p<0.05$, difference in observation-time 391 days (excess mortality >1 yr)

Modified from Brandt et al. JCE&M 2012
Judging the value of L-T4 therapy for benign nodular goitre lies in the eye of the beholder

- Poor efficacy of LT4-therapy
- Potential side-effects of LT4-therapy
- No consensus of prophylactic LT4-therapy as anti-neoplastic therapy
- If efficacious, only in relatively small solid nodules in euthyroid patients
- These are generally asymptomatic
- Ample alternatives with better efficacy in this situation
  - Percutaneous ethanol injection therapy
  - Laser ablation
  - Radiofrequency ablation
- If multinodular, better efficacy with radioiodine
Italian multicenter study *(Laser versus observation)* in around 200 benign solid solitary nodules

**Volume changes (ml) at 12 months**

\[ \Delta \text{ volume (ml): T0 vs T6 and T12} \]

Borrowed, with kind appreciation, from E. Papini et al.
Volume Changes (ml)

- T0: 7,5 ml
- T6: 1,3 ml

- T0: 6,9 ml
- T6: 7,1 ml

P < 0.0001
Multinodular nontoxic goiter reduction: radioiodine versus L-T4
Lack of efficacy of L-T4

Wesche et al. JCEM 2001
Augmenting the effect of 131-I in multinodular goitre.
Effect of 0.3 mg rhTSH on mean goitre volume reduction in benign nontoxic multinodular goitre. Double-blind randomized study

* p=0.04, between groups
** p=0.01, between groups
*** p=0.002, between groups

+35% reduction compared to placebo

Nielsen et al., Arch Intern Med, 2006
Medical (Levothyroxine, LT4?) therapy in benign nodular goitre
Some issues covered

- Understanding phenotype variation and eligibility (Covered. Few eligible)
- Theoretical basis for using L-T4 to shrink thyroid nodules (Covered)
- Current guideline recommendations (Covered. Discouraged)
- Efficacy of L-T4 in shrinking thyroid nodules (Covered. Efficacy poor)
- Potential side-effects of L-T4 therapy (Covered. Considerable)
- Potential effect of L-T4 in decreasing risk of papillary thyroid cancer (Hypothesis?)
- Much better treatment options available
- Conclusions
- Need of additional studies/evidence? (To be debated)
- Need of revising current guidelines? (Already decided)
Judging the value of L-T4 therapy for benign nodular goitre lies in the eye of the beholder

Further conclusions

• If efficacious, only in relatively small solid nodules in euthyroid patients
• These are generally asymptomatic
• Ample alternatives with better efficacy in this situation
  - Percutaneous ethanol injection therapy
  - Laser ablation
  - Radiofrequency ablation
Judging the value of L-T4 therapy for benign nodular goitre lies in the eye of the beholder

Without L-T4 therapy?

With L-T4 therapy?

Or, mirage in Pisa (Fata Morgana)?
In my view, balancing efficacy versus side-effects of LT4-therapy in nodular nontoxic goitre makes this a poor bargain