Where do we stand with T3, Bioidenticals, and Branded Products

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Topics For Discussion • Thyroid Physiology

Evaluation of Thyroid Dosing

Subclinical Disease/ Pregnancy

Alternate Hormone Replacement Option
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• Use of T3 Therapy



Thyroid Hormone Synthesis

- Normal Gland Production includes 80% T4 and 20 % T3
- Additional Production of T3 comes from Peripheral deiodination in liver, muscle, kidney
- T4 has Lower Binding Affinity For Thyroid Receptor Than T3
- T4 May Also Be Converted to Reverse T3



T4 to T3 conversion



- Thyroid produces both T4 and T3
 - T4 is produced in significantly greater quantities compared to T3
 - Up to 80% of the T4 is converted in the body to T3
 - T3 is more biologically active than T4
- Conversion by other organs: liver, kidney, spleen and thyroid
- It is possible to have normal levels of T4 and low levels of active T3 (with low or high TSH)
- 'Free' T4 and T3 have been transported to tissues and cleaved from their protein carriers



Narrow Therapeutic Index

- Branded product vs generic options
 Cost
- Disease being managed?
- Establishment of Bioequivalence
- Reproducibility of Strength/Dose

Narrow Therapeutic Range Drugs

- "...those containing certain drug substances that are subject to therapeutic drug concentration monitoring and/or where product labeling indicates a narrow therapeutic range designation" ^{1,2}
- Unless otherwise indicated by a specific guidance, traditional limit of 80-125% is recommended
- Levothyroxine sodium is a compound with a narrow therapeutic range
- Other common NTI drugs: Warfarin, digoxin, phenytoin

1. FDA Industry Guidance: BA/BE Studies for Orally Administered Drug Products. October, 2000. 2. FDA Guidance: Levo.Sodium Tablets—*In Vivo* Pharmacokinetic and BA Studies. December, 2000.

Defining Ranges for Serum TSH

- Lab reference range
 - Defined by values in "normal" population¹
 - 0.4-5.5 mU/L
- Individual's range²
 - Much narrower than reference range
 - ±0.5 mU/L over time
- Target range³
 - Goals for thyroxine treatment of specific conditions
 - Hypothyroidism: 0.5-2.5 mU/L
 - Thyroid cancer: undetectable to 0.5 mU/L

¹ From the National Health and Nutrition Examination Survey (NHANES) III. Hollowell JG, et al. *J Clin Endocrinol Metab.* 2002;87:489-499. ²Andersen, et al. *J Clin Endocrinol Metab.* 2002;87:1068. ³Adapted from <u>www.Thyroidtoday.com</u>. Hypothyroidism Treatment Failure: Differential Diagnosis by Elliott G Levy.

Individual TSH Normal Range

- I6 caucasian men
- 24-52 yrs (median 38)
- 15 no Hx thyroid disease, goiter, or medication
- Blood samples:
 - Monthly (0900-1200)
 - Stored frozen
 - Analyzed random order in same assay run

Mean +/- 2 SD = 1.27 (0.16 - 2.39)



Participants

Anderson S, et al. J Clin Endocrinol Metab. 2002;87:1068-1072.

Individual TSH Normal Range

 Each subject's TSH range was unique
 Width of individual range ≈1/2 of group

- Widest range (# 1)
- Narrowest range (#12)



Anderson S, et al. J Clin Endocrinol Metab. 2002;87:1068-1072.

TSH Change Following 12.5 mcg Change in Levothyroxine Dose



TSH Change Following 25 mcg Change in Levothyroxine Dose (n=722)



Mild Hypothyroidism & Mild Thyrotoxicosis Definitions



Unusual Situations

Subclinical Hyperthyroidism

Subclinical Hypothyroidism

Pregnancy

Subclinical Thyroid Dysfunction Screening

• If TSH is high and FT_4 is not recorded then:

- Repeat test with FT₄
- Wait a minimum of 2 weeks and a maximum of 12 weeks
- Test high risk individuals (eg, pregnant, Hx of disease, > 60 yrs)
- Patient preferences are important in deciding management
- Further research and more definitive data are needed

Surks MI, et al. *JAMA*. 2004;291:228-238. Col NF, et al. *JAMA*. 2004;291:239-243.

Subclinical Thyroid Disease: Conclusions

- Data supporting associations of subclinical thyroid disease with symptoms or adverse clinical outcomes or benefits of treatment are few
- Consequences of subclinical thyroid disease (serum TSH 0.1-1.45 mIU/L or 4.5-10.0 mIU/L) are minimal
 - Panel recommended against routine treatment
- Insufficient evidence to support population-based screening
 - However, aggressive case finding is appropriate in
 - Pregnant women
 - Women older than 60 years
 - Others at high risk for thyroid dysfunction

Surks MI, et al. JAMA. 2004;291:228-238.

Natural History for the Progression of Subclinical Hypothyroidism

• Over 10-year follow-up:

(n=82 women)

- > 34% progressed to overt hypothyroidism
- > 57% remained subclinically hypothyroid
- > 9% euthyroid

Greatest predictors of overt disease

- Initial TSH level
- Presence of anti-thyroid antibodies

Huber, et al. J Clin Endocr Metab. 2002.

Subclinical Hypothyroidism Progression to Overt Disease

 258 healthy elderly followed x 4 yrs
 13.2% had subclinical hypothyroidism based on normal T₄ and elevated TSH

4 yrs later : 33% overtly hypothyroid 80% of those with (+) Ab's

Rosenthal, et al. JAMA. 1987;258:209.

Should We Be Using T3?

Treatment – different formulations

Generic name	Composition	Brand names	
Levothyroxine	T4	Synthroid	
		Levoxyl	
		Euthyrox	
		Levothroid	
		Unithroid	
Liothyronine	Т3	Cytomel	
Liotrix	4:1 mixture T4 and T3	Thyrolar	
Thyroid USP	Thyroid extract	Armour thyroid	
	of pork or beef	S-P-T	
		Thyrar	
		Thyroid strong	

Combined T₄/T₃ Therapy Summary of Studies

	Bunevicius	Bunevicius	Walsh	Sawka	Clyde
	NEJM	JIN	JCEM	JCEM	JAMA
N	33	11	110	40	44
Thyroiditis	48%	100%	85%	100%	67%
Duration	5 wks	5 wks	10 Wks	15 wks	16 wks
T3 Dose	12.5	12.5	10	25	15
TSH T4/T3 vs T4	0.5 vs 0.8	0.7 vs 0.8	3.1 vs 1.5	1.8 vs 1.7	2.0 vs 2.1
Cognitive	Improved	Same	Same	Same	Same
Mood	Improved	Same	Same		Same
SHBG Cholesterol	Higher Same		Lower Higher		Same Same

Bunevicius. N Engl J Med. 1999 Feb 11;340(6):424-9. Bunevicius. Int J Neuropsychopharmacol. 2000 Jun;3(2):167-174. Walsh et al. J Clin Endocrinol Metab. 2003 Oct;88(10):4543-50. Sawka et al. J Clin Endocrinol Metab. 2003 Oct;88(10):4551-5. Clyde. JAMA. 2003 Dec 10;290(22):2952-8.

$T_4/T_3 \ Combination \ Therapy$

◎ N=23 (20F, 3M) 23-69 yo

- 21 After-sx/radioiodine; 2 autoimmune thyroiditis
- Two 12-week periods
- No washout
- \odot Run-in 4 weeks with T_4
- \circ 1st period: 100-175 mcg T₄
- \odot 2nd period: 5% of T₄ substituted with T₃

$T_4/T_3 \ Combination \ Therapy$

 In replacement therapy using LT₄ plus T₃ compared with LT₄ monotherapy
 Cognitive performance and mood do not improve
 Combination therapy is not superior to monotherapy

Siegmund W, et al. Clin Endocrinol. 2004;60:750-757.

 Serum TSH and FT4 measured in 14 non-autoimmune hypothyroid (NTD) subjects

	T ₄	T ₄ /T ₃
Mood scores		
Beck Depression Inventory	6.1 <u>+</u> 6.9	3.7 <u>+</u> 3.8
State-Trait-Anxiety Inventory	32.7 <u>+</u> 6.3	32.0 <u>+</u> 6.6
Cognitive Performance		
Memory (Digit Symbol Test)	55.4 <u>+</u> 11.6	55.5 <u>+</u> 10.3
Working (Digit Span Test)	11.9 <u>+</u> 2.1	12.3 <u>+</u> 1

While not statistically significant, this small study shows that cognitive performance and mood do not improve with combination therapy

Siegmund W, et al. Clin Endocrinol. 2004;60:750-757.

- N=28 subjects with overt hypothyroidism
- Randomized double-blind crossover
- Patients euthyroid on 100 mcg LT4
- 3 8-week periods
 - Maintained on 100 mcg
 - Switched to 75 mcg LT4 and 5 mcg T3
 - 14:1 proportion of endogenous production
 - 87.5 mcg LT4 with 7.5 mcg add-on T3

Escobar-Morreale, HF. Annals of Int Med. 2005;142:412-424.

- Combination tx resulted in:
 - \forall FT4
 - slightly increased TSH in standard combination
 - slightly ψ TSH in the add-on T3 combination
 - unchanged FT3
 - no difference in primary or secondary outcomes

Escobar-Morreale, HF. Annals of Int Med. 2005;142:412-424.

	Euthyroid	Combination Therapy	Add-on Therapy
TSH	1.95 <u>+</u> 1.44	2.56 <u>+</u> 1.65	1.09 <u>+</u> 1.33
Fatigue	6.7 <u>+</u> 5.4	6.6 <u>+</u> 5.3	7.3 <u>+</u> 5.0
Depression	12.4 <u>+</u> 5.3	13.2 <u>+</u> 4.9	13.1 <u>+</u> 5.3
Digital Span	12.4 <u>+</u> 5.3	13.2 <u>+</u> 4.9	13.1 <u>+</u> 5.3
QOL (SF-36 general health)	60.9 <u>+</u> 17.1	62.2 <u>+</u> 17.5	61.8 <u>+</u> 17.3

Escobar-Morreale, HF. Annals of Int Med. 2005;142:412-424.





Which Thyroid Tests Should You Request?

- Thyroid Stimulating Hormone (TSH)
- Free Thyroxine (Free T4)
- Free Triiodothyronine (Free T3)
- Thyroid Peroxidase Antibodies (TPO) (for hypothyroidism symptoms)
- Thyroglobulin Antibodies (Tg)
- Thyroid Stimulating Immunoglobulins (TSI) (for hyperthyroidism symptoms)
- Reverse T3
- Thyroid Ultrasound (for goiter or enlargement)
- NOTE: Get Ferritin tested (esp. if you have hair loss), Vitamin D, for weight loss challenges, Leptin and Fasting Glucose, and 24-hour saliva cortisol for adrenals

www.Facebook.com/ThuroidSupport

Oppenheimer, Braverman, Ladenson....

 "In Practice Most Serious Problems Arise from Flawed Human Behaviors NOT Improper Drug Formulation"

Desiccated Natural Thyroid

- Desiccated thyroid is a drug prepared from dried porcine (pig) thyroid
- Desiccated thyroid was the only thyroid drug available in the early 1900s, until levothyroxine was introduced in the 1950s
- Natural thyroid fell out of favor as the synthetic product was touted as more modern and stable
- Since the 1990s, desiccated thyroid has enjoyed a resurgence, primarily with older doctors and holistically-oriented physicians who claim that it resolves symptoms better than synthetics in some patients
- Several brands of desiccated thyroid are available by prescription, including Nature-Throid and Armour Thyroid



Sea Kelp

VITAMIN WORLD

get healthy

250

TABLETS

150 mcg of Natural Source Iodine

Supports Thyroid Health*

Vigetarian Dietary Supplement

HEALTH BENEFITS OF KELP

Nutrients* Dietary Fiber 5% Carbohydrate 3% Protein 3% Minerals* Copper 7% Potassium 5% Phosphorus 3%

Vitamins* Vitamin K 82% Folate 45% Riboflavin 9%

Helps prevent breast cancer Stimulates red blood cell production

Organic

www.organicfacts.net

Helps to regulate hormonal function throughout body Helps boost protein content in body

Helps to maintain acid-base balance in body

Prevents onset of osteoporosis or other bone mineral deficiencies

Protects from effects of radiation poisoning which may cause cancer

Caution: People with pre-existing heart conditions or high cholesterol to avoid consumption of kelp

*% Daily Value per 100g. For e.g. 100g of kelp provides 82% of daily requirement of vitamin K.

Jod-Basedow phenomenon (Historical)

- Definition- <u>Hyperthyroidism induced by excess lodine.</u>
- Coindet (French physician) in 1821 published his cases about Hyperthyroidism.
- In the English speaking world this became known as Graves' disease (1835), and in the German speaking world as von Basedow's disease (1840).
- Coindet's cases of hyperthyroidism were actually lodine-induced, hence it came to be known as the lodine-Basedow phenom.
- Jod is German for Iodine, hence the Jod-Basedow phenom!
- Coindet was deprived of credit for not only describing Hyperthyroidism, but also the variant of hyperthyroidism caused by excess lodine
- The credit was given to Dr "Jod" who never existed!

Wolff-Chaikoff effect

The Wolff-Chaikoff effect is a reduction in thyroid hormone levels caused by ingestion of a large amount of iodine.

It is generally seen only in patients with either autoimmune thyroid disease (eg. Graves disease) or with patients with severe hyperthyroidism

It is an autoregulatory phenomenon that inhibits organification (oxidation of iodide) in the thyroid gland, the formation of thyroid hormones inside the thyroid follicle, and the release of thyroid hormones into the bloodstream.

The Wolff-Chaikoff effect can be used as a treatment principle against hyperthyroidism (especially thyroid storm) by infusion of a large amount of iodine to suppress the thyroid gland.

Rx controversies:

"As of 2012 there are no controlled trials supporting the preferred use of desiccated thyroid hormone over synthetic L-thyroxine in the treatment of hypothyroidism or any other thyroid disease."

American Thyroid Association

 Garber, Jellrey R., et al. "Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association." Endocrine Practice 18.6 (2012): 988-1028.