

**Dietary Supplements/Nutraceuticals
and The Thyroid
Meet The Professor
May 16, 2015
4:45-5:45 pm
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Disclosures

- **None Relevant**

Dietary Supplements and Nutraceuticals Learning Objectives

- 1. Understand the regulatory definitions of nutraceuticals and dietary supplement.
- 2. Know the specific types of commonly used nutraceuticals and dietary supplements.
- 3. Understand the clinical effects of commonly used nutraceuticals and dietary supplements.

Dietary Supplements and Nutraceuticals Outline

- **Demographics**
- Definitions
- The FDA 1994 Supplement Health and Education Act and Definitions
- Iodine, Soy Protein, Enhancers, Supplements, TRIAC, DITPA.
- Conclusions

Main Question

- **Is there a role for the use of dietary supplementation and nutraceuticals in either hypothyroid or euthyroid individuals?**

General Comments

- **Enormous topic and I have selected a few issues to discuss.
16.4 million Google responses on “thyroid and supplements”.**
- **There is a separate entire scientific literature on nutraceuticals and dietary supplements.**
- **There are many unsubstantiated claims in the lay literature.**

Use of Supplements

- A population based community survey in older adults:
- **49%** were taking at least one dietary supplement.
- **52%** had concurrent use of dietary supplements along with prescribed medications, potentially exposing them to an increased risk of adverse drug to drug interactions.

Qato et al JAMA 300: 2867, 2008.

Bernet and Chindris Expert Rev Endocrinol and Metab 2012

- An estimated **34 billion dollars** was spent in 2007 in the U.S. for alternative medical treatments, to include herbal supplements, chiropractic visits.

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Nutraceuticals

- Nutraceuticals are dietary supplements that contain a concentrated form of a presumed bioactive substance originally derived from a food, but now present in a non-food matrix, and used to enhance health in dosages exceeding those obtainable from normal foods.
- Zeisel, S.H., Science 285: 1853, 1999
- Klein, Endo Practice 17:610, 2011.

Nutraceuticals and Pharmaceuticals

- In 1994, the US government passed the **Dietary Supplement Health and Education Act** in response to the widespread use of dietary supplements by the general public.

Dietary Supplements

- According to this act, “**dietary supplements**” may be marketed as such only if the product contains a vitamin, mineral, amino acid, herb, or metabolite, constituent, extract, or combination of these ingredients that is intended to enhance the diet but is not presented for use as a traditional food product.

Dietary Supplements

- The US Food and Drug Administration (FDA) is **not required to approve** such supplements before marketing but can remove a supplement from the market if it is proved to be dangerous.
- The FDA defines a **“drug”** as a substance used for the identification, treatment, and/or prevention of disease.

The FDA 1994 Supplement Health and Education Act

- Shortcomings of this Act:
- **(1)** absence of scientifically based information regarding safety, **(2)** observed potential to cause harm, **(3)** lack of adequate scientific substantiation of clinical benefit, **(4)** quality control of manufacturing process, and **(5)** a problem must be reported for the FDA to intervene.

**Mechanick, J.I., et al.
AACE Guidelines
Endocr Pract 9: 417, 2003**

- The government mandates three possible types of claims of dietary supplement labels: **(1)** nutrient content (such as “high in calcium”); **(2)** “structure-function” or nutrition support (for example, “vitamin C prevents scurvy” or “calcium builds strong bones”), and **(3)** disease claims.

**Mechanick, J.I., et al.
AACE Guidelines
Endocr Pract 9: 417, 2003**

- The **“disease claims”** alone requires FDA authorization after a thorough scientific evaluation of relevant studies. All other products must include the following statement: “This statement has not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, mitigate, or prevent any disease.”

Nutraceuticals

- Because nutraceuticals are not considered drugs, manufacturers are permitted to make **“health claims”** pertaining to their product but **not “disease claims”**.

Blurred Lines Between Dietary Supplement/Nutraceutical and Prescription Drugs

Calcium can be considered a DS/N with a disease indication, an over-the-counter drug (calcium carbonate with or without vitamin D), or a prescription drug.

Dietary Supplements Used for Thyroid Conditions

- Myrrh: Stimulates thyroid gland.
- Lemon balm: Decreases thyroid gland secretion.
- **Linoleic acid: Increases BMR.**
- Organic iodide, Selenium.
- **TRIAC, Vitamin A, Vitamin D.**
- Vitamin E, Zinc.

Agents That May Interfere With Thyroid Hormone Absorption

- Bugleweed.
- Calcium, iron, and bonemeal.

Thyroid Hormone Enhancers

- **Ashwagandha** known as an “Indian ginseng” has shown thyroid stimulatory effects leading to thyrotoxicosis in an animal study.
- *The **Coleus Forskohlii*** byproduct, forskolin, stimulates cyclic AMP production, which may play a role as a stimulant effect on thyroid hormone production by promoting sodium-iodide symporter function.

Bernet and Chindris Expert Rev Endocrinol and Metab 2012

- Guggul increases T4/T3 ratio in mice.
- **Xanthohumol increases iodine uptake and decreases T4 binding to serum proteins (Kohrle).**
- *Witheria somnifera* and *Bauhinia purpurea* increase T4/T3 secretion.
- **Bladderwrack contains iodine.**

Dietary Supplements and Nutraceuticals Outline

- **Demographics**
- **Definitions**
- **The FDA 1994 Supplement Health and Education Act**
- **Iodine, Soy Protein, Enhancers, Supplements, TRIAC, DITPA**
- **Conclusions**

What is the effect of Iodine on Thyroid Function

Nutraceuticals

- **Certain dietary supplements or nutraceuticals are purported to have the capacity to enhance thyroid function.**
- **These agents or compounds can be allocated to one of several categories: iodine containing substances, tyrosine-containing substances, and thyroid hormone extracts or analogs.**

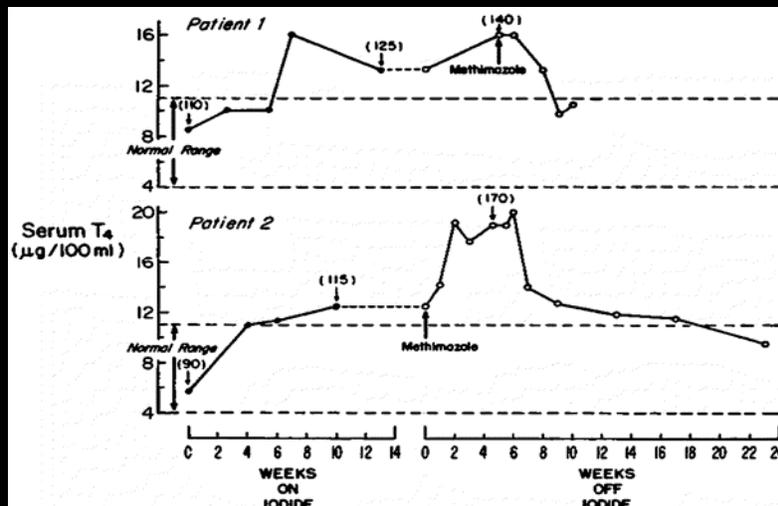
Capacity to Enhance Thyroid Function

- **Iodine containing substances (e.g., kelp) have multiple actions on the thyroid gland.**
- **Large amounts of iodine (e.g., SSKI or Lugol's solution) can be used to decrease thyroid gland T4 and T3 secretion and is used in the treatment of hyperthyroid patients.**

Kelp

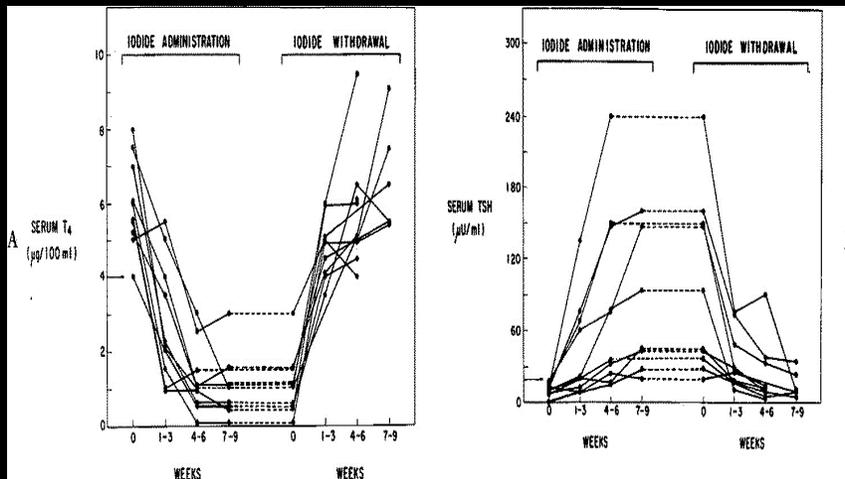
- Kelp (any of various large brown seaweeds) is classified under the order of Laminariales.
- The average iodine content in kelp-containing supplements is **1,244 $\mu\text{g}/\text{daily dose}$** , which is about **9 times** the recommended daily allowance of iodine (150 $\mu\text{g}/\text{d}$).

Serum T_4 Concentrations in Two Patients with Nontoxic Goiter in Whom Iodide-Induced Thyrotoxicosis Developed.



Vagenakis AG et al. N Engl J Med 1972;287:523.

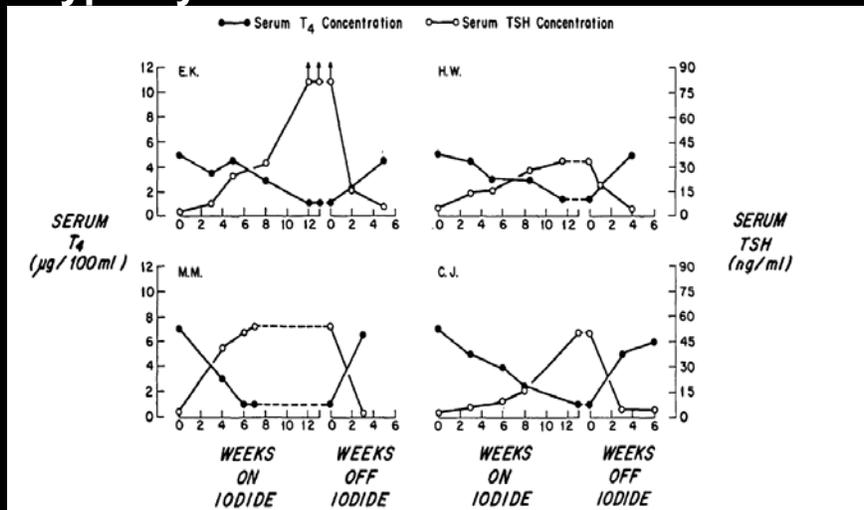
Response of the Serum Thyroxine Concentration (A) and TSH Concentration (B) to Iodide (SSKI, 5 Drops Daily) in Patients with Diffuse Toxic Goiter Who Had Been Rendered Euthyroid by Treatment with Radioiodine.



Braverman L, et al. N Engl J Med 1969;281:816.



Enhanced Susceptibility to Hypothyroidism in Hashimoto's Patients



Braverman, et al, JCEM 32: 515, 1971

Capacity to Enhance Thyroid Function

- There is little evidence that iodine supplementation in pharmacologic amounts can beneficially improve thyroid function in euthyroid individuals.
- As a result, , the AACE guidelines note that “ **No data support the role of iodine in enhancing thyroid function.**”
- Mechanick, et al., Endocr Pract 9: 417, 2003

Soy Protein

- Sathyapalan et al, JCEM 96: 1442, 2011.
- **Double-blind crossover study.**
- Received a vegetarian diet (containing 30 g soy protein and 16 mg phytoestrogen) as compared to a Western diet (containing 30 g soy protein and 2 mg phytoestrogens).
- **Three Fold increased risk of developing overt hypothyroidism (in patients who originally had subclinical hypothyroidism).**

Genostein Aglycone
Bitto et al, JCEM 95: 3067, 2010

- Genistein aglycone (Soy Phytoestrogen) positively affects postmenopausal symptoms. However, questions about its long-term safety on the thyroid gland still remain.
- Randomized, double-blind, placebo-controlled trial involving 389 osteopenic, postmenopausal women for 24 months.
- A subcohort (138 patients) continued therapy for an additional year.

Genostein Aglycone
Bitto et al, JCEM 95: 3067, 2010

- Participants received 54 mg of genistein aglycone daily (n = 71) or placebo (n = 67).
- TSH, free T₃, free T₄ and autoantibodies (thyroid peroxidase, thyroglobulin, and thyroid microsomal antigen) were assessed in **40 genostein** and **37 placebo** subjects who completed **3 years** of study.

Genistein Aglycone
Bitto et al, JCEM 95: 3067, 2010

- **Results:** Genistein administration over 3 yr **did not affect** serum thyroid hormones or autoantibodies.
- **Conclusion:** These data suggest that **genistein aglycone intake does not significantly increase** the risk of clinical or subclinical hypothyroidism at the dose of 54 mg/d.

Is Selenium Administration Useful in Thyroid Disorders?

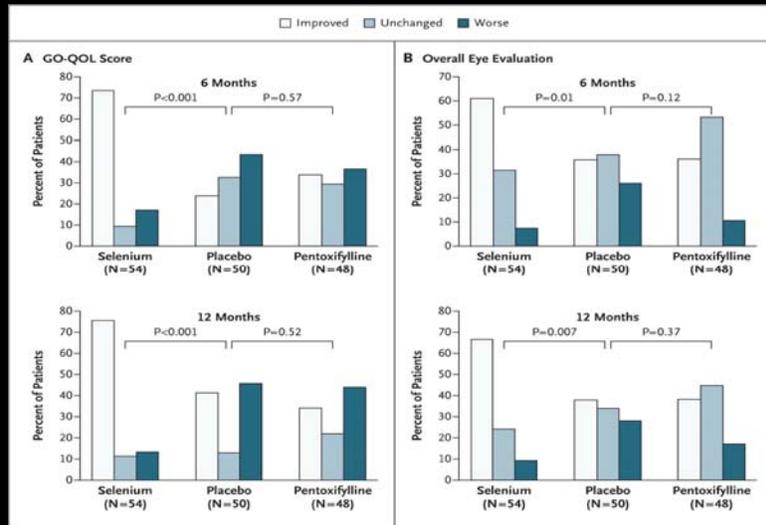
Selenium and Graves' Ophthalmopathy
Marcocci C et al. N Engl J Med 2011;364:1920-1931

- Randomized, double-blind, placebo-controlled trial to determine the effect of selenium in 159 patients with mild Graves' orbitopathy.
- Sodium selenite (**100 µg twice daily**), pentoxifylline (**600 mg twice daily**), or placebo (**twice daily**) orally for **6 months** then followed for **6 months** after treatment was withdrawn.

Selenium and Graves' Ophthalmopathy
Marcocci C et al. N Engl J Med 2011;364:1920-1931

- At the 6-month evaluation, treatment with selenium, but not with pentoxifylline or placebo, was associated with **improved quality of life** ($P < 0.001$), **less eye involvement** ($P = 0.01$) and **decreased progression** of Graves' orbitopathy ($P = 0.01$).
- No adverse events were evident with selenium.

Selenium Therapy and Graves' Ophthalmopathy



Marcocci C et al. N Engl J Med 2011;364:1920-1931.

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Selenium and Graves' Ophthalmopathy Marcocci C et al. N Engl J Med 2011;364:1920-1931

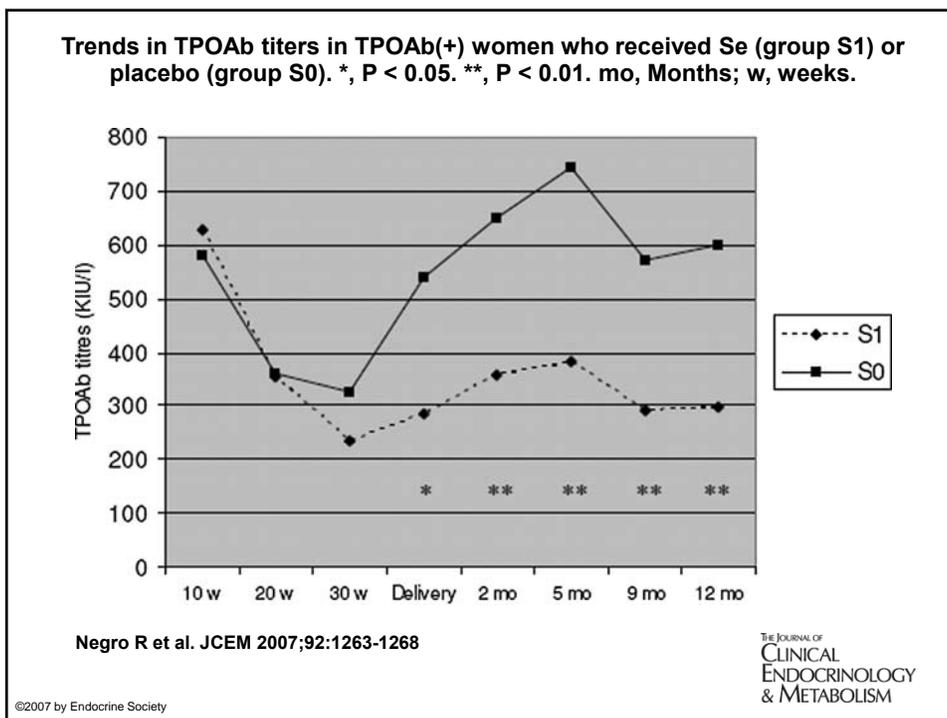
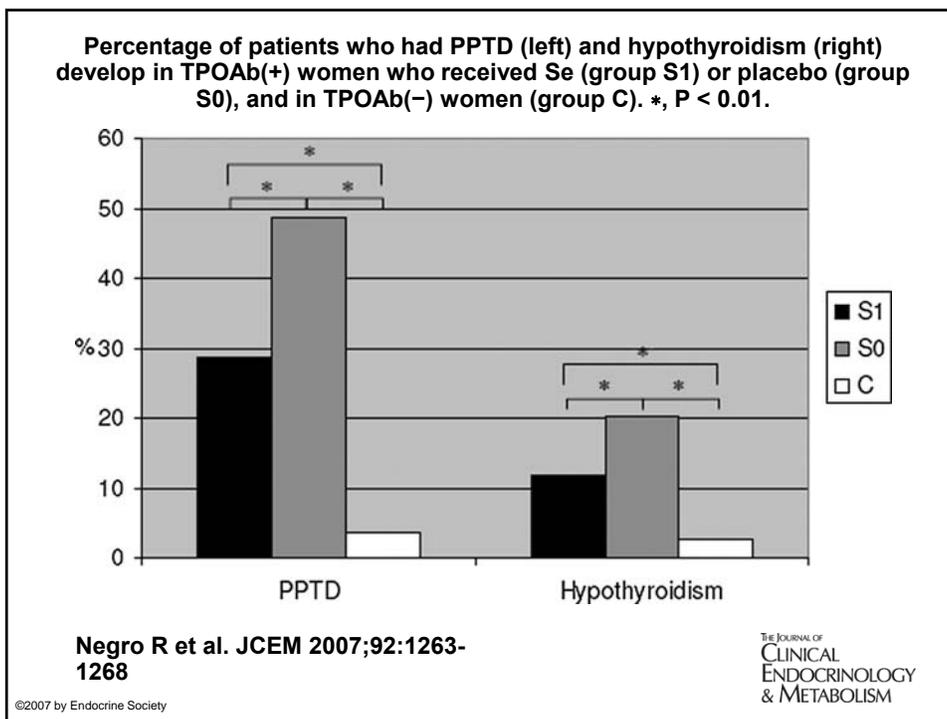
- Conclusion
- Selenium administration significantly improved quality of life, reduced ocular involvement, and slowed progression of the disease in patients with mild Graves' orbitopathy.

The Influence of Selenium Supplementation on Postpartum Thyroid Status in Pregnant Women with Thyroid Peroxidase Autoantibodies
Negro et al, JCEM 92: 1263, 2007

- During pregnancy and the postpartum period, 77 TPOAb(+) women received selenomethionine **200 µg/d** (group S1), 74 TPOAb(+) women received **placebo** (group S0), and 81 TPOAb(-) age-matched **non pregnant women** were the control group (group C).

The Influence of Selenium Supplementation on Postpartum Thyroid Status in Pregnant Women with Thyroid Peroxidase Autoantibodies
Negro et al, JCEM 92: 1263, 2007

- PPTD and hypothyroidism were significantly less frequent in group S1 compared with S0 (**28.6 vs. 48.6%**, $P < 0.01$; and **11.7 vs. 20.3%**, **respectively**, $P < 0.01$).
- Selenium supplementation during pregnancy and in the postpartum period reduced thyroid inflammatory activity and the incidence of hypothyroidism.



Do Dietary Supplements Contain T4/T3?

T4/T3 Content of Health Supplements Kang et al, Thyroid 23: 1233, 2013

- Evaluated the thyroid hormone content of ten popular, commercially available health supplements marketed for “thyroid support.”
- Used HPLC to separate and identify the chemical components of each supplement, the researchers measured the levels of the thyroid hormones T3 and T4.

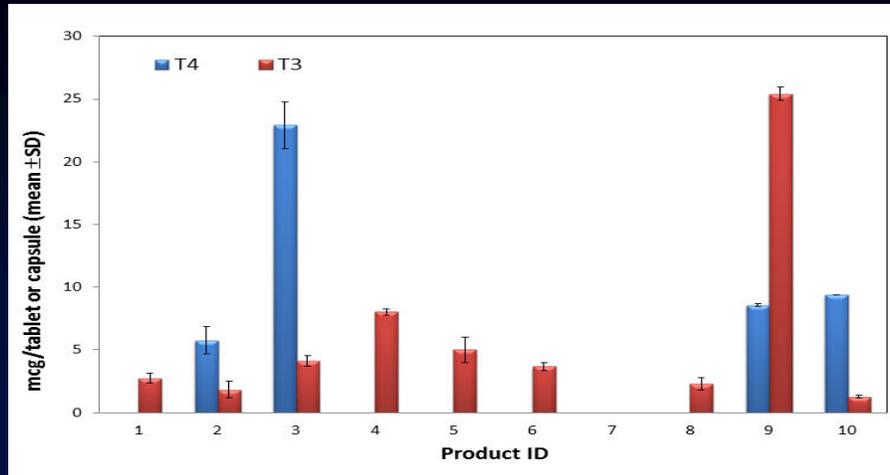
T4/T3 Content of Health Supplements Kang et al, Thyroid 23: 1233, 2013

- **9 of 10** supplements contained a detectable amount of T3 (**1.3-25.4 micrograms/tablet**).
- **Five** of the supplements, if taken in the recommended dose, would deliver greater than **10 mcg/day of T3**.
- This amount equals about **50%** of the total amount of T3 produced by the body in one day.

T4/T3 Content of Health Supplements Kang et al, Thyroid 23:1233, 2013

- **Four** of the 10 supplements would deliver **8.5-91.6 mcg/day** of T4 at the recommended dose.
- The dose of T4 prescribed to treat hypothyroidism in an average-sized adult ranges between 50-125 mcg/day.
- **Only 1 out of the 10** supplements had **no** detectable levels of T4 or T3.

Measured Thyroxine and Thyronine in OTC Thyroid Supplements



T4/T3 Content of Health Supplements
Kang et al, Thyroid 23: 1233, 2015.

Bernet and Chindris Expert Rev Endocrinol and Metab 2012

- Ohye et al reported 12 cases of thyrotoxicosis from OTC use of dietary supplements.
- **Administration to volunteers raised serum T4.**
- Ohye et al, Arch Int Med 165: 831, 05.

Do Health Supplements Contain Triac?

Capacity to Enhance Thyroid Function

- The use of various thyroid hormone analogues to enhance thyroid function is a very controversial area.
- **TRIAC (3,5,3'-triiodothyroacetic acid)** is a metabolite of levothyroxine that has significant metabolic action. It can bind to the T3 receptor and can decrease TSH secretion.

Capacity to Enhance Thyroid Function

- Although **TRIAC** has effects similar to thyroid hormone (in selected circumstances), there is a lack of evidence it is beneficial when administered to euthyroid individuals.

Capacity to Enhance Thyroid Function

- At low doses, TRIAC can inhibit pituitary secretion of TSH and has been used as a treatment for selective pituitary resistance and thyrotropin-dependent hyperthyroidism.
- Beck-Peccoz et al, JCI 6: 217, 1983

Capacity to Enhance Thyroid Function

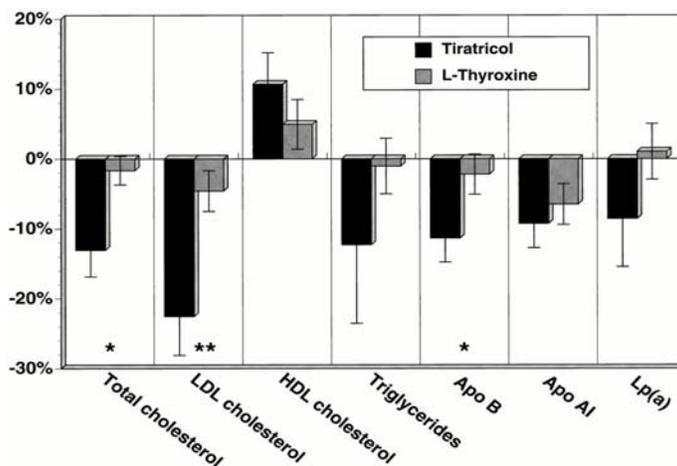
- At higher doses, however, significant metabolic stimulation, symptoms of hyperthyroidism, and overt thyrotoxicosis can occur.
- Bauer BA, Mayo Clin Proc 77: 587, 2002

TRIAC

Sherman et al studied 24 athyreotic patients randomized to treatment, titrated to suppress thyrotropin to less than 0.1 mU/L, with levothyroxine (1.9 µg/kg daily) or TRIAC (24 µg/kg twice a day).

Sherman et al, JCEM 82: 2153, 1999

Lipoprotein responses to treatment regimens, expressed as the percent change (mean ± sem) in the parameter during treatment with study drug compared with the baseline value. *, P < 0.05, **, P < 0.01.

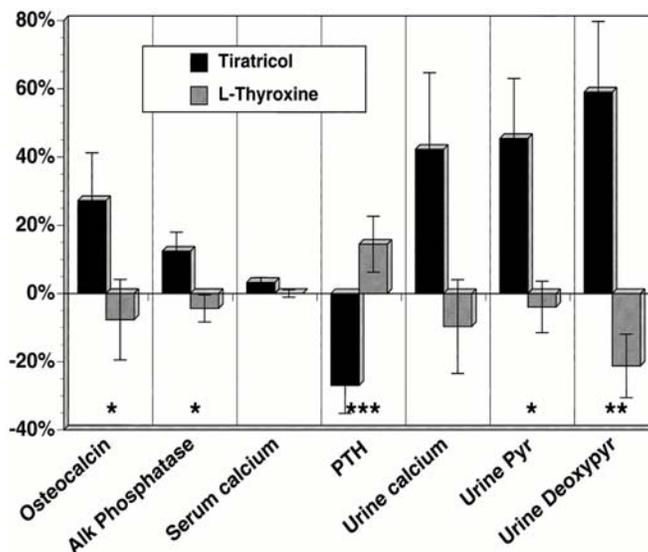


Sherman S I et al. JCEM 1997;82:2153-2158

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Skeletal responses to treatment regimens, expressed as the percent change (mean ± sem) in the parameter during treatment with study drug compared with the baseline value. *, P < 0.05, **, P < 0.01, ***, P < 0.005.



Sherman S I et al. JCEM 1997;82:2153-2158

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TRIAC

After 2 months **similar effects** of TRIAC and T3 were noted on cardiovascular function, resting metabolic rate, body weight, urinary urea nitrogen excretion, and the thyrotoxicosis symptom score in both groups.

TRIAC

TRIAC treated patients, however, had augmented hepatic and skeletal effects in comparison with the levothyroxine-treated patients . A pituitary-specific effect of TRIAC was **not observed**.

Sherman et al, JCEM 82: 2153, 1999

TRIAC

- The FDA banned several TRIAC containing products, but others are still available to the public.
- AACE **does not** recommend the use of any desiccated thyroid product or thyroid analogue as a “regulator” or “enhancer” of thyroid function.
- Mechanick, et al., Endocr Pract 9: 417, 2003

DITPA

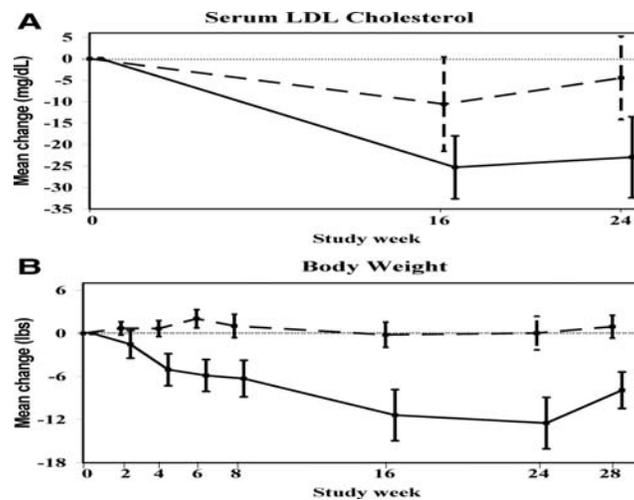
3,5 Diiodothyropropionic Acid

- Goldman, et al, Circulation 119: 3093, 2009.
- DITPA (3,5-Diiodothyropropionic Acid), a thyroid hormone analog to treat heart failure: phase II trial veterans affairs cooperative study.

DITPA 3,5 Diiodothyropropionic Acid

- **CONCLUSIONS:**
- DITPA improved some hemodynamic and metabolic parameters, but there was **no evidence** for symptomatic benefit in congestive heart failure.

Changes ($\pm 95\%$ confidence intervals) in serum LDL cholesterol concentration (A) and body weight (B) in patients treated with DITPA (solid lines) and placebo (dashed lines) for 24 wk.



Ladenson P W et al. JCEM 2010;95:1349-1354

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Dietary Supplements and Nutraceuticals Outline

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- Conclusions

Conclusions

- Iodine: May cause hyper or hypothyroidism.
- **Soy Protein: May exacerbate subclinical hypothyroidism.**
- Enhancers, Supplements: No known beneficial effect.
- **TRIAC, DITPA: Selected thyroid hormone analogues may have biologic activity.**

Main Question

- Is there a role for the use of dietary supplementation and nutraceuticals in either hypothyroid or euthyroid individuals? **NO.**
- **Selenium may be beneficial in patients with postpartum thyroiditis and Graves' ophthalmopathy.**

Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association

- The majority of dietary supplements fail to meet a level of scientific substantiation deemed necessary for the treatment of disease. The authors do not recommend the use of these or any unproven therapies.
- There are no data supporting its(TRIAC) use in lieu of synthetic T4 in the treatment of hypothyroidism.

Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association

- There are no preclinical or clinical studies demonstrating any thyromimetic properties of any of these Dietary Supplements/Nutraceuticals.
- There are simply not enough outcome data to suggest a role at the present time for routine selenium use to prevent or treat hypothyroidism in any population.

Clinical Practice Guidelines for Hypothyroidism in Adults: Co-sponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association

- Physicians should specifically engage patients regarding all forms of Dietary Supplements or Nutraceuticals, specifically those marketed as "thyroid support", and consider the possibility that any DS/N could be adulterated with T4 or T3.
- Garber et al., Thyroid 22: 1200, 2012
Endocrine Practice 18: 988, 2012.

**Guidelines for the Treatment of
Hypothyroidism
American Thyroid Association Guidelines**

- Jonklaas, Bianco, Bauer, Burman, Cappola, Celi, Cooper, Kim, Peeters, Rosenthal, Sawka
- Thyroid 24: 1670, 2014.

**Guidelines for the Treatment of
Hypothyroidism
American Thyroid Association Guidelines**

Is there a role for the use of dietary supplementation, nutraceuticals, and over-the-counter products in either hypothyroid or euthyroid individuals?

**Guidelines for the Treatment of
Hypothyroidism
American Thyroid Association Guidelines**

- **Strong recommendation against nutraceuticals is provided despite low-quality evidence, because there are potential risks but few proven benefits.**

**Guidelines for the Treatment of
Hypothyroidism
American Thyroid Association Guidelines**

- **We recommend against the use of dietary supplements, nutraceuticals, or other over-the-counter products either in euthyroid individuals or as a means of treating hypothyroidism.**
- We particularly caution against the use of pharmacologic
- doses of iodine because of the risk of

**Guidelines for the Treatment of
Hypothyroidism
American Thyroid Association Guidelines**

- We particularly caution against the use of pharmacologic doses of iodine because of the risk of thyrotoxicosis and hypothyroidism in those with intact thyroid glands susceptible to becoming further dysregulated because of underlying thyroid pathology.
- Strong recommendation. Low-quality evidence.