

# Thyroid

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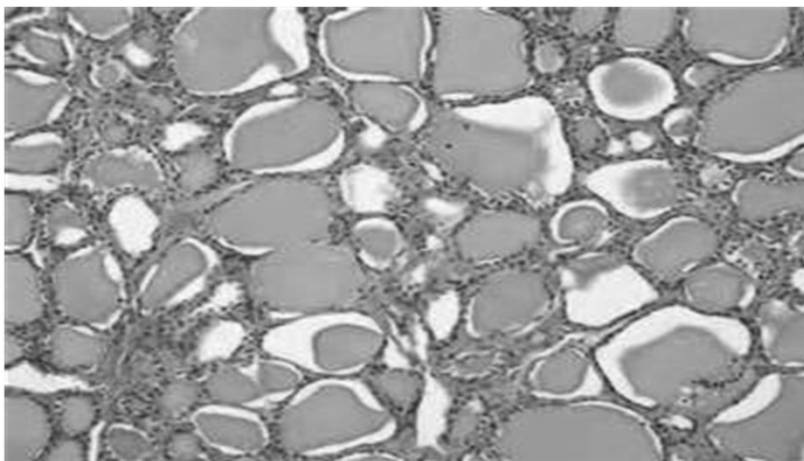
## Thyroid gland nothing else looks like it

- Cysts lined with single cells soldiers (epithelium) filled with pinkish material (colloid) that easily fills with toxins
- In between are lots of blood vessels very vascular
- Huge blood supply as runs the 'fuel' of the body
- Hormone is stored inside the follicles
- Thyroid makes thyroid hormone T3 and T4 and thyro-calcitonin or calcitonin or C cells are made by cells in spaces in between follicles

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## Thyroid



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- September 6, 1976
- **Breast Cancer Relationship to Thyroid Supplements for Hypothyroidism**
- Chandrakant C. Kapdi, MD; John N. Wolfe, MD
- Author Affiliations
- JAMA. 1976;236(10):1124-1127.  
doi:10.1001/jama.1976.03270110022020

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## Brownstein MD

- The study found a **200%** (not a 50%) increased risk of breast cancer in women who took thyroid hormone for at least 15 years as compared to women who did not take thyroid hormone.
- You read that correctly: a **200%** increase risk of breast cancer in women who took thyroid hormone as compared to women who did not take thyroid hormone.
- How could that be? The answer is simple: The increased breast risk in thyroid supplemented women is due to iodine deficiency.
- If the majority of the women were deficient in iodine, then taking thyroid hormone would be the wrong treatment.
- Thyroid supplementation increases the body's metabolic needs and therefore increases the body's need for iodine.
- If someone is iodine deficient and is prescribed thyroid hormone, thyroid supplementation will worsen the iodine-deficiency problem.

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## Rule out Iodine Deficiency

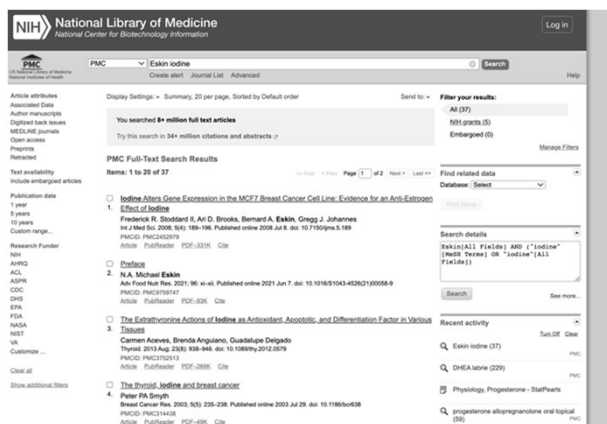
- Iodine deficiency - thyroid hormone prescription was taken as all supplemental thyroid hormones—both natural and synthetic forms— increase the body's metabolic needs for more iodine.
- Talc
- Red dye
- Gluten

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# Iodine

- Maintains normal architecture of the human breast



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## Effect of iodide-deficiency on rat mammary gland

- When rats are kept iodide-deficient, atrophy and necrosis takes place in the mammary gland and areas of dysplasia and atypia are seen.
- Administration of estradiol to iodide-deficient rats stimulates cell division in the gland and leads to the formation of alveoli.
- Continued stimulation by estradiol produces changes in the newly-formed alveolar cells. Their nucleoli are altered and show a separation of components. Ribosomes and lipid droplets increase and the cells synthesize large vacuoles containing protein.
- The secretion of great quantities of this material into areas of the tissue where regressive changes have occurred undoubtedly contributes to the formation of cysts within the gland.
- The present findings indicate that iodide-deficiency alters the structure and function of mammary gland alveolar cells and makes them highly sensitive to stimulation by estradiol.
- Effect of iodide-deficiency on rat mammary gland. Virchows Arch B Cell Pathol Incl Mol Pathol. 1979 May 31;30(2):209-20. doi: 10.1007/BF02889103. PMID: 38565.

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## 3 mg between two new products is based on this dosage as being breast protective

- Seaweed is an important dietary component and a rich source of iodine in several chemical forms in Asian communities. Their high consumption of this element (25 times higher than in Western countries) has been associated with the low incidence of benign and cancerous breast and prostate disease in Japanese people.
- **Summary:** We review evidence showing that, in addition to being a component of the thyroid hormone, iodine can be an antioxidant as well as an antiproliferative and differentiation agent that helps to maintain the integrity of several organs with the ability to take up iodine.
- In animal and human studies, molecular iodine ( $I_2$ ) supplementation exerts a suppressive effect on the development and size of both benign and cancerous neoplasias. Investigations by several groups have demonstrated that these effects can be mediated by a variety of mechanisms and pathways, including direct actions, in which the oxidized iodine dissipates the mitochondrial membrane potential, thereby triggering mitochondrion-mediated apoptosis, and indirect effects through iodolipid formation and the activation of peroxisome proliferator-activated receptors type gamma, which, in turn, trigger apoptotic or differentiation pathways.
- **Conclusions:** We propose that the International Council for the Control of Iodine Deficient Disorders recommend that iodine intake be increased to at least 3 mg/day of  $I_2$  in specific pathologies to obtain the potential extrathyroidal benefits described in the present review.
- The extrathyronine actions of iodine as antioxidant, apoptotic, and differentiation factor in various tissues. *Thyroid*. 2013 Aug;23(8):938-46. doi: 10.1089/thy.2012.0579. PMID: 23607319; PMCID: PMC3752513.

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## Iodolactone

- Good fats + iodine
- Make iodolactones
- Has anti-tumor effects within thyroid and also outside thyroid such as BREAST.
- An iodinated derivative of arachidonic acid, 5-hydroxy-6-iodo-8,11,14-eicosatrienoic acid,  $\delta$ -lactone (6-IL) has been implicated as a possible intermediate in the autoregulation of the thyroid gland by iodine.
- In addition to antiproliferative and apoptotic effects observed in thyrocytes, this iodolipid could also exert similar actions in cells derived from extrathyroidal tissues like mammary gland, prostate, colon, or the nervous system.
- 6-iodolactone, key mediator of antitumoral properties of iodine. *Prostaglandins Other Lipid Mediat*. 2014 Aug;112:27-33. doi: 10.1016/j.prostaglandins.2014.07.001. Epub 2014 Jul 10. PMID: 25018052.

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## Iodine moves estrogen out of target tissues

- The protective effects of iodine on breast cancer have been postulated from epidemiologic evidence and described in animal models. The molecular mechanisms responsible have not been identified but laboratory evidence suggests that iodine may inhibit cancer promotion through modulation of the estrogen pathway.
- To elucidate the role of iodine in breast cancer, the effect of Lugol's iodine solution (5% I<sub>2</sub>, 10% KI) on gene expression was analyzed in the estrogen responsive MCF-7 breast cancer cell line. Microarray analysis identified 29 genes that were up-regulated and 14 genes that were down-regulated in response to iodine/iodide treatment. The altered genes included several involved in hormone metabolism as well as genes involved in the regulation of cell cycle progression, growth and differentiation.
- Quantitative RT-PCR confirmed the array data demonstrating that iodine/iodide treatment increased the mRNA levels of several genes involved in estrogen metabolism (CYP1A1, CYP1B1, and AKR1C1) while decreasing the levels of the estrogen responsive genes TFF1 and WISP2.
- This report presents the results of the first gene array profiling of the response of a breast cancer cell line to iodine treatment.
- In addition to elucidating our understanding of the effects of iodine/iodide on breast cancer, this work suggests that iodine/iodide may be useful as an adjuvant therapy in the pharmacologic manipulation of the estrogen pathway in women with breast cancer.
- Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. *Int J Med Sci.* 2008 Jul 8;5(4):189-96. doi: 10.7150/ijms.5.189. PMID: 18645607; PMCID: PMC2452979.

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## Iodine protects breast, ovary and prostate

- The high rate of breast disease in women with thyroid abnormalities (both dietary and clinical) suggests a correlation between thyroid and breast physiology. In addition, women with breast cancer have larger thyroid volumes than controls.
- Multiple studies suggest that abnormalities in iodine metabolism are the likely links. Additionally, the impact of iodine therapy for the maintenance of healthy breast tissue has been reported in both animal <sup>4-7</sup> and clinical studies <sup>8,9</sup> yet the mechanisms responsible remain unclear.
- Iodine alters gene expression in the MCF7 breast cancer cell line: evidence for an anti-estrogen effect of iodine. *Int J Med Sci.* 2008 Jul 8;5(4):189-96. doi: 10.7150/ijms.5.189. PMID: 18645607; PMCID: PMC2452979.

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- 3. Vassilopoulou-Sellin R, Palmer L, Taylor S, Cooksley CS. Incidence of breast carcinoma in women with thyroid carcinoma. *Cancer.* 1999;85:696-705. [[PubMed](#)] [[Google Scholar](#)]
- 4. Eskin BA. Dietary iodine and cancer risk. *Lancet.* 1976;2:807-808. [[PubMed](#)] [[Google Scholar](#)]
- 5. Eskin BA, Grotkowski CE, Connolly CP, Ghent WR. Different tissue responses for iodine and iodide in rat thyroid and mammary glands. *Biol Trace Elem Res.* 1995;49:9-19. [[PubMed](#)] [[Google Scholar](#)]
- 6. Funahashi H, Imai T, Tanaka Y, Tobinaga J, Wada M, Morita T, Yamada F, Tsukamura K, Oiwa M, Kikumori T et al. Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. *J Surg Oncol.* 1996;61:209-213. [[PubMed](#)] [[Google Scholar](#)]
- 7. Garcia-Solis P, Alfaro Y, Anguiano B, Delgado G, Guzman RC, Nandi S, Diaz-Munoz M, Vazquez-Martinez O, Aceves C. Inhibition of N-methyl-N-nitrosourea-induced mammary carcinogenesis by molecular iodine (I<sub>2</sub>) but not by iodide (I<sup>-</sup>) treatment: Evidence that I<sub>2</sub> prevents cancer promotion. *Mol Cell Endocrinol.* 2005;236:49-57. [[PubMed](#)] [[Google Scholar](#)]
- 8. Ghent WR, Eskin BA, Low DA, Hill LP. Iodine replacement in fibrocystic disease of the breast. *Can J Surg.* 1993;36:453-460. [[PubMed](#)] [[Google Scholar](#)]
- 9. Kessler JH. The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J.* 2004;10:328-336. [[PubMed](#)] [[Google Scholar](#)]

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## Iodine 3 mg/d took 3 months Larger breasts and larger prostates, like BPH, need more iodine.

- A randomized, double-blind, placebo-controlled, multicenter clinical trial was conducted with 111 otherwise healthy euthyroid women with a history of breast pain.
- Patients had to document moderate or severe breast pain by recording a score > or =5 on a visual analog scale (VAS) of pain for > or =6 days per cycle and had to present with fibrosis involving at least 25% of both breast surfaces. Subjects could not be effectively treated with more conservative measures such as local heat or nonprescription analgesics.
- There was not a statistically significant difference in the dropout rate for patients on placebo (11.8%), 1.5 mg/day (31.3%), 3.0 mg/day (18.4%), or 6.0 mg/day (25%) of molecular iodine for 6 months.
- Physicians assessed breast pain, tenderness, and nodularity each cycle; patients assessed breast pain and tenderness with the Lewin breast pain scale at 3-month intervals and with a VAS at each cycle.
- A statistically significant improvement ( $p < 0.01$ ) associated with dose was observed in the Lewin overall pain scale for all treated groups compared to placebo.
- Reductions in all three physician assessments were observed in patients after 5 months of therapy in the 3.0 mg/day (7/28; 25%) and 6.0 mg/day (15/27; 18.5%) treatment groups, but not the 1.5 mg/day or placebo group.
- Patients recorded statistically significant decreases in pain by month 3 in the 3.0 and 6.0 mg/day treatment groups, but not the 1.5 mg/day or placebo group; more than 50% of the 6.0 mg/day treatment group recorded a clinically significant reduction in overall pain.
- All doses were associated with an acceptable safety profile.
- No dose-related increase in any adverse event was observed.
- The effect of supraphysiologic levels of iodine on patients with cyclic mastalgia. *Breast J.* 2004 Jul-Aug;10(4):328-36. doi: 10.1111/j.1075-122X.2004.21341.x. PMID: 15239792.

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## Eskin 1976

- Dietary iodine and cancer risk. Lancet. 1976 Oct 9;2(7989):807-8. doi: 10.1016/s0140-6736(76)90646-2. PMID: 61482.

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## Is iodine a gatekeeper of the integrity of the mammary gland? Iodolactones

- Iodine is natural anti-proliferative element in breast tissue.
- This paper reviews evidence showing iodine as an antioxidant and antiproliferative agent contributing to the integrity of normal mammary gland. Seaweed is an important dietary component in Asian communities and a rich source of iodine in several chemical forms. The high consumption of this element (25 times more than in Occident) has been associated with the low incidence of benign and cancer breast disease in Japanese women.
- In animal and human studies, molecular iodine (I<sub>2</sub>) supplementation exerts a suppressive effect on the development and size of both benign and cancer neoplasias. This effect is accompanied by a significant reduction in cellular lipoperoxidation. Iodine, in addition to its incorporation into thyroid hormones, is bound into antiproliferative iodolipids in the thyroid called iodolactones, which may also play a role in the proliferative control of mammary gland.
- We propose that an I<sub>2</sub> supplement should be considered as an adjuvant in breast cancer therapy.
- Is iodine a gatekeeper of the integrity of the mammary gland? J Mammary Gland Biol Neoplasia. 2005 Apr;10(2):189-96. doi: 10.1007/s10911-005-5401-5. PMID: 16025225.
- Instituto de Neurobiología, Universidad Nacional Autónoma de México, Juriquilla.

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## Iodine

- Dietary iodine deficiency and breast cancer mortality: an ecological study. Serra Majem LL, Tresserras R, Canela J, Salleras L. Int J Epidemiol. 1988 Sep;17(3):686-7. doi: 10.1093/ije/17.3.686. PMID: 3209348 No abstract available.
- The thyroid, iodine and breast cancer. Smyth PP. Breast Cancer Res. 2003;5(5):235-8. doi: 10.1186/bcr638. Epub 2003 Jul 29. PMID: 12927031 **Free PMC article**. Review.
- Letter: Dietary iodine and risk of breast, endometrial, and ovarian cancer. Edington GM. Lancet. 1976 Jun 26;1(7974):1413-4. doi: 10.1016/s0140-6736(76)93066-x. PMID: 59054 No abstract available.

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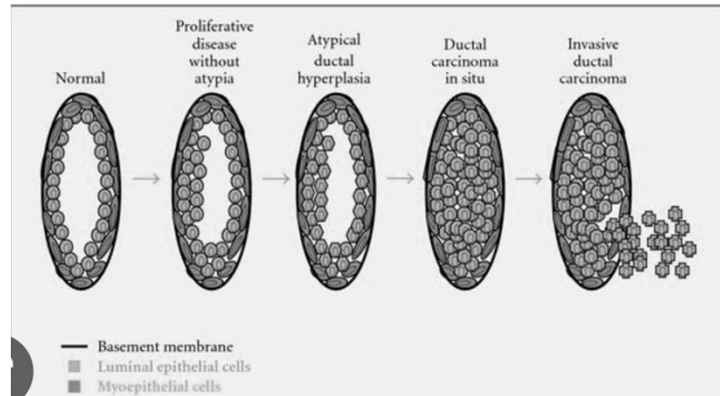
## Iodine – Autoimmune Thyroid

- **Conclusions: out of almost 800 patients**
- According our study results, patients with primary BC present a greater incidence of autoimmunity disorders, especially when diagnosed in the pre-menopausal setting.
- However, further prospective studies are required to definitively prove causality.
- LDN and also Hormone Balance & Protect Acts like a Natural LDN
- Association between benign thyroid disease and breast cancer: a single center experience. BMC Endocr Disord. 2019 Oct 17;19(1):104. doi: 10.1186/s12902-019-0426-8. PMID: 31623603; PMCID: PMC6798360.

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## Continuum

- Continuum
- Normal > fibrocystic > hyperplasia > cancer
- What reduces risk: iodine, euthyroid, progesterone, clear receptors of EDCs



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## Case Report MD Anderson Cancer PREVENTION Center

- 36 yo nullparous
- Dx 32 lobular hyperplasia
- Recommended 5 yrs of tamoxifen
- 3<sup>rd</sup> year SERM raloxifene
- Started to bleed
- Endometrial stripe slightly enlarged
- Recommended hysterectomy stat
- Gave iodine, new products, vaginal first pass progesterone,
- Post vaginal US normal within 6 weeks and able to avoid hysterectomy

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## Newest Thinking

- If high risk of cancer, then treat like you have cancer prophylactically to avoid cancer
- When in reality often need iodine, progesterone and get receptors to be working more optimally.

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## Department of Surgery, Queen's University, Hotel Dieu Hospital, Kingston, Ont.

- **Objective:** To determine the response of patients with fibrocystic breast disease to iodine replacement therapy.
- **Design:** Review of three clinical studies beginning in 1975: an uncontrolled study with sodium iodide and protein-bound iodide; a prospective, control, crossover study from iodide to molecular iodine; and a prospective, control, double-blind study with molecular iodine.
- **Setting:** University affiliated breast-treatment clinics.
- **Patients:** Study 1: 233 volunteers received sodium iodide for 2 years and 588 received protein-bound iodide for 5 years. Study 2: the treatment of 145 patients from study 1 treated with protein-bound iodide for several months who still had symptoms was switched to molecular iodine 0.08 mg/kg; 108 volunteers were treated initially with molecular iodine. Study 3: 23 patients received molecular iodine, 0.07 to 0.09 mg/kg body weight; 33 received an aqueous mixture of brown vegetable dye and quinine. The numbers in study 2 increased over the review period so that 1365 volunteers were being treated with molecular iodine by 1989.
- **Interventions:** All patients in study 3 had pre- and post-treatment mammography and measurement of serum triiodothyronine, thyroxine and thyroid-stimulating hormone levels.
- **Main outcome measures:** Subjective evaluation--freedom from pain--and objective evaluation--resolution of fibrosis.
- Average dose: 3-5 mg of iodine/d.
- **Results:** Study 1: 70% of subjects treated with sodium iodide had clinical improvement in their breast disease, but the rate of side effects was high; 40% of patients treated with protein-bound iodide had clinical improvement. Study 2: 74% of patients in the crossover series had clinical improvement, and objective improvement was noted in 72% of those who received molecular iodine initially. Study 3: in the treatment group 65% had subjective and objective improvement; in the control group there was a subjective placebo effect in 33% and an objective deterioration of 3%.
- **Conclusions:** The fibrocystic breast reacts differently to sodium iodide, protein-bound iodide and molecular iodine. Molecular iodine is nonthyrotropic and was the most beneficial.
- All thyroid function tests remained in normal safe ranges.
- Iodine replacement in fibrocystic disease of the breast. Can J Surg. 1993 Oct;36(5):453-60. PMID: 8221402.

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## Iodine + P

- Concerning the suppressive effect of inorganic iodine on the growth of 7,12-dimethyl-benz(a)anthracene (DMBA)-induced breast tumor in female Sprague-Dawley (SD) rats, we previously reported that although iodine itself had a suppressive effect on the tumor growth, its effect was not as strong as that of MPA (medroxy-progesterone acetate).
- Iodine and progesterone – suppressive on bc proliferation.
- However, the combined medication of iodine at a low concentration + MPA showed a stronger effect than MPA alone.
- The purpose of the present study is to elucidate this mechanism of action by determining the uptake of the administered iodine into breast tumor tissue. Breast tumors were induced with DMBA in female SD rats, and these animals were treated with MPA + inorganic iodine at various concentrations for 4 weeks to determine tumor growth and tumor iodine content. In the comparison of tissue iodine content in growth-suppressive tumors with that in nonsuppressive tumors, the former showed a much higher iodine content.
- This suggests that direct uptake of inorganic iodine by breast tumors led to the suppression of tumor growth
- Suppressive effect of iodine on DMBA-induced breast tumor growth in the rat. *J Surg Oncol.* 1996 Mar;61(3):209-13. doi: 10.1002/(SICI)1096-9098(199603)61:3<209::AID-JSO9>3.0.CO;2-F. PMID: 8637209.

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## Iodine and Hashimoto's

- **Aim:** The effect of an iodine prophylaxis on the induction of Hashimoto's thyroiditis as well as the influence of various therapeutic approaches on the course of antithyroglobulin (TgAb) and antiperoxidase (TPOAb) antibodies in manifest diseases are evaluated.
- **Method:** A collective of 375 euthyroid subjects without relevant goiter received daily doses of 200 micrograms iodide, weekly doses of 1.53 milligrams iodide, or no medication. A second group of 377 patients suffering from Hashimoto's thyroiditis was treated with a non-suppressive hormone medication, a suppressive hormone administration, a combination of a non-suppressive hormone therapy with low dose iodide (50-150 micrograms/day), mere iodide in doses of 200 micrograms/day, or received no therapy. The mean observation period in these two groups was 860 and 848 days, respectively.
- **Results:** There was no significant increase of the antibody levels in the subgroup with 200 micrograms iodide/day and in the non-treated subjects of the first collective.
- However, the group that received 1.53 milligrams iodide/week presented a distinct increase of the TgAb as well as the TPOAb, and the incidence of Hashimoto's thyroiditis was 4-fold higher than in the two other subgroups.
- The patients of the second collective revealed a significant decrease of the TgAb in the subgroups treated with up to 200 micrograms iodide/day, while the reduction of the TPOAb depended on the thyrotropin level and was most significant in the suppressed group ( $p < 0.0001$ ).
- **Conclusion:** To lower the incidence of autoimmune thyroid diseases in predisposed subjects, a daily iodine supplementation seems to be superior to high-dose weekly administrations. A hormone therapy combined with a daily, low-dose iodine medication is able to reduce the TgAb and the TPOAb levels even in patients with Hashimoto's thyroiditis.
- [Effect of iodine and thyroid hormones in the induction and therapy of Hashimoto's thyroiditis]. *Nuklearmedizin.* 1999;38(5):144-9. German. PMID: 10488481.

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## Type of Underactive Thyroid

- Overt
- Subclinical
- If worse on iodine therapy and get hyperthyroid r/o autogenous not nodule.
- Very rare for iodine to increase or decrease thyroid function
- But never say never about anything.

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## Blood values for thyroid are “lacking”

- [www.medscape.com](http://www.medscape.com)
- **Preconception TSH and Pregnancy Outcomes**
- **A Population-Based Cohort Study in 184 611 Women**
- **They even recommended a trial of thyroid replacement in infertile women with “normal labs”**
- **It’s all starting to change but slowly.**

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## Subclinical

- Normal hormone levels
- Symptoms of low thyroid
- No treatment deemed necessary
- Less than optimal thyroid function (low production of T4, poor conversion of T4 to T3, poor cell uptake of T3, dysfunctional thyroid receptors excess of cortisol, insufficiency of iodine)
- Poor methylators as methylation depends on Thyroid hormone – conversion of riboflavin to MTHFR is impaired.
- Medscape

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## Lots of Studies

- Subclinical hypothyroidism linked to significant symptoms
- Aggressive heart disease
- Severe mood disorders
- Cognitive issues! (Dr. Gaby's psychiatric patient)
- Increased risk for morbidity and mortality
- More appropriate term: Mild Thyroid Failure not demonstrated by typical labs (MTF) or SCHAT – subclinical hypothyroidism

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## Mildest deficiency

- But can have far reaching issues
- Increased heart disease risk
- Higher inflammation hs CRP
- Higher total cholesterol
- Higher bad cholesterol LDL c and

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## If not treated:

- Higher risk of faster CAD 2.2 fold higher
- 1.5 fold higher death from it
- Treatment is warranted despite normal TSH and T4

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## First step

- Is often looking at the minerals needed: iodine, selenium, zinc, magnesium and B vitamins
- As well as addressing any ADRENAL issues first
- Three musketeers adrenal, thyroid, progesterone

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## Thyroid > < Progesterone

- Low thyroid, low P
- Thyroid hormone stimulates progesterone release from human luteal cells by generating a proteinaceous factor. J Endocrinol. 1998 Sep;158(3):319-25. doi: 10.1677/joe.0.1580319. PMID: 9846161.
- Thyroid hormone induces the synthesis of a putative protein in the rat granulosa cell which stimulates progesterone release. J Endocrinol. 1996 Aug;150(2):309-18. doi: 10.1677/joe.0.1500309. PMID: 8869597.

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## Prog helps convert T4 to T3

- Recent literature lacks studies on the effects of progesterone withdrawal on peripheral conversion of thyroxin (T4) into triiodothyronine (T3) by iodothyronine deiodinase 2 (D2) in different body tissues.
- The present study aimed to assess the possible relation of progesterone to T4, T3, and D2 in ovariectomized rats. Thirty female Wistar rats were included into a sham-operated control group and an ovariectomized group. Four months following the surgical procedures, measurements of estradiol, progesterone, free T4, free T3, and thyroid-stimulating hormone (TSH) were done. Also, estradiol/progesterone and T4/T3 ratios were calculated. Tissue homogenates from the kidney, liver, brain, thyroid, mandible, and femur were used to assess expression of D2 mRNA. The estradiol/progesterone ratio showed a significant increase in ovariectomized rats. T4 showed a significant increase in contrast to T3 which showed a highly significant decrease following ovariectomy. The T4/T3 ratio was significantly increased in ovariectomized rats. In addition, D2 expression was significantly attenuated in all tissue homogenates of the ovariectomized group. The present work showed a significant positive correlation between T4 and T3 in the sham-operated control rats, which was abolished in ovariectomized rats. A negative significant correlation between progesterone and T4 was revealed in ovariectomized rats. There was also a significant positive correlation between progesterone and D2 expression in the ovariectomized group.
- The results of the present study hypothesize that progesterone withdrawal may underlie the decrement in D2 expression, with consequent reduction in the peripheral conversion of T4 into T3 leading to a hypothyroid state.
- An evidence for the transcriptional regulation of iodothyronine deiodinase 2 by progesterone in ovariectomized rats. *J Physiol Biochem.* 2014 Jun;70(2):331-9. doi: 10.1007/s13105-013-0307-y. Epub 2013 Dec 23. PMID: 24362948.

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## Prog upregulates free t3 genes

- Thyroid cancer and thyroid nodules are more prevalent in women than men, so female sex hormones may have an etiological role in these conditions. There are no data about direct effects of progesterone on thyroid cells, so the aim of the present study was to evaluate progesterone effects in the sodium-iodide symporter *NIS*, thyroglobulin *TG*, thyroperoxidase *TPO*, and *KI-67* genes expression, in normal thyroid follicular cells, derived from human tissue. *NIS*, *TG*, *TPO*, and *KI-67* mRNA expression increased significantly after TSH 20  $\mu$ UI/mL, respectively: 2.08 times,  $P < 0.0001$ ; 2.39 times,  $P = 0.01$ ; 1.58 times,  $P = 0.0003$ ; and 1.87 times,  $P < 0.0001$ .
- In thyroid cells treated with 20  $\mu$ UI/mL TSH plus 10 nM progesterone, RNA expression of *NIS*, *TG*, and *KI-67* genes increased, respectively: 1.78 times,  $P < 0.0001$ ; 1.75 times,  $P = 0.037$ ; and 1.95 times,  $P < 0.0001$ , and *TPO* mRNA expression also increased, though not significantly (1.77 times,  $P = 0.069$ ).
- These effects were abolished by mifepristone, an antagonist of progesterone receptor, suggesting that genes involved in thyroid cell function and proliferation are upregulated by progesterone.
- This work provides evidence that progesterone has a direct effect on free T3 thyroid cells, upregulating genes involved in thyroid function and growth.
- Progesterone Upregulates Gene Expression in Normal Human Thyroid Follicular Cells. *Int J Endocrinol.* 2015;2015:864852. doi: 10.1155/2015/864852. Epub 2015 May 21. PMID: 26089899; PMCID: PMC4454767.

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## Vitamin D helps convert T4 to T3

- **Objective:** This study aimed to assess the effect of vitamin D3 administration to diabetic rats on thyroid profile and deiodinase 2 (D2).
- **Methods:** Thirty male Wistar rats were included into three groups; control, streptozotocin-induced diabetic and diabetic supplemented with vitamin D3 groups. Ten weeks later, serum levels of free T4, free T3 and TSH were measured. Tissue homogenates from liver, kidney, muscle, femur bone, heart and brain were obtained and assessed for D2 mRNA.
- **Results:** Diabetic rats demonstrated significant increase in free T4 and significant decrease in free T3. These changes were ameliorated by vitamin D3 administration. D2 mRNA was significantly reduced in all tissue homogenates obtained from diabetic rats, while vitamin D3 treatment significantly enhanced D2 in liver and brain homogenates.
- **Conclusion:** Diabetes mellitus inhibited peripheral conversion of T4 into T3 secondary to reduction in D2 expression. Vitamin D3 greatly corrected the alterations in thyroid profile and D2 expression.
- **Keywords:** Deiodinase 2; diabetes mellitus; thyroid hormones; vitamin D3.
- Effect of vitamin D3 on thyroid function and de-iodinase 2 expression in diabetic rats. Arch Physiol Biochem. 2015;121(5):206-9. doi: 10.3109/13813455.2015.1107101. Epub 2015 Nov 24. PMID: 26599099.

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## Hypothyroid

- Look at D levels
- Free T3 levels
- And consider PR in both genders.

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## Hormone Cross-Talk – before BHRT in perimenopause, fix thyroid and adrenal and possibly start with progesterone therapy

- Accumulating evidence has shown that thyroid hormones (THs) are vital for female reproductive system homeostasis. THs regulate the reproductive functions through thyroid hormone receptors (THRs)-mediated genomic- and integrin-receptor-associated nongenomic mechanisms, depending on TH ligand status and DNA level, as well as transcription and extra-nuclear signaling transduction activities. These processes involve the binding of THs to intracellular THRs and steroid hormone receptors or membrane receptors and the recruitment of hormone-response elements.
- In addition, THs and other reproductive hormones can activate common signaling pathways due to their structural similarity and shared DNA consensus sequences among thyroid, peptide, and protein hormones and their receptors, thus constituting a complex and reciprocal interaction network.
- Moreover, THs not only indirectly affect the synthesis, secretion, and action of reproductive hormones, but are also regulated by these hormones at the same time. This crosstalk may be one of the pivotal factors regulating female reproductive behavior and hormone-related diseases, including tumors. Elucidating the interaction mechanism among the aforementioned hormones will contribute to apprehending the etiology of female reproductive diseases, shedding new light on the treatment of gynecological disorders.
- A New Perspective on Thyroid Hormones: Crosstalk with Reproductive Hormones in Females. *Int J Mol Sci.* 2022 Feb 28;23(5):2708. doi: 10.3390/ijms23052708. PMID: 35269847; PMCID: PMC8911152.

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## T4 + T3 - Department of Medicine, Washington Hospital Center, Georgetown University, Washington,

- GTA Forte II
- SR T3
- **Purpose of review:** Because of the longstanding controversy regarding whether hypothyroid patients can be optimally replaced by treatment with levothyroxine (L-T4) alone, numerous studies have addressed potential benefits of combined therapy of triiodothyronine (T3) with L-T4. Results of these studies have failed to support a potential benefit of combined therapy. A strong argument for the addition of L-T3 to L-T4 monotherapy has been lacking until recent genetic studies indicated a rationale for such therapy among a small fraction of the hypothyroid patient population.
- **Recent findings:** Interest in this issue has focused on the importance of the deiodinases in maintaining the euthyroid state and the role of genetic polymorphisms in the deiodinase genes that would affect thyroid hormone concentrations in both blood and tissues. One such polymorphism in the D2 gene, Thr92Ala, is associated with reduced T4 to T3 activation in skeletal muscle and thyroid, linked to obesity and alterations in thyroid-pituitary feedback, and in responses to thyroid hormone treatment.
- **Summary:** Although our professional organizations continue to recommend L-T4 alone for the treatment of hypothyroidism, the possibility of a D2 gene polymorphism should be considered in patients on L-T4 monotherapy who continue to complain of fatigue in spite of dosage achieving low normal serum thyroid stimulating hormone levels. A suggestive clue to the presence of this polymorphism could be a higher than normal free T4/free T3 ratio. Clinicians could consider adding T3 as a therapeutic trial in selected patients. Future well controlled clinical trials will be required to more fully resolve the controversy.
- Combination L-T3 and L-T4 therapy for hypothyroidism. *Curr Opin Endocrinol Diabetes Obes.* 2013 Oct;20(5):460-6. doi: 10.1097/01.med.0000432611.03732.49. PMID: 23974776.

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## In-depth sound thyroid testing

- TSH is not most sensitive and misses a lot of cases.
- Some growing suggestion that the receptors on the pituitary for thyroid are completely divergent from the rest of the human body.
- Total T4, Total T3, free T3, reverse T3, TPO and TBG, serum iodine, TSH.
- Symptoms rule!
- Achille's heel reflex – photomotogram,
- Also tests lead issues/
- **Br J Ind Med. 1993 Mar; 50(3): 229–233. Latency of the Achilles tendon reflex for detection of reduced functions of the peripheral nervous system in workers exposed to lead.**

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## Achilles Heel

- The tap to half relaxation time of tendon achilles reflex was measured in thirty control subjects, forty-five thyrotoxic and sixty hypothyroid patients.
- The half relaxation time in the control males and females was 279.33 +/- 76.39 msec and 320.00 +/- 52.37 msec. respectively.
- In thyrotoxic males and females the half relaxation time was 256.67 +/- 31.62 msec (P less than 0.01) and 252.50 +/- 47.68 msec (P less than 0.01) respectively. Amongst the hypothyroid male and female patients the half relaxation time was 405.0 +/- 35.56 msec (P less than 0.01) and 422.5 +/- 115.36 (P less than 0.01) respectively. As all these values were statistically significant, we consider the photomotographic measurement of ankle reflex as an important aid to the diagnosis of thyroid hormone imbalances.
- Thyroflex - <https://thyroflex.com/index.php/thyroflex/>
- Ankle reflex photomotogram in thyroid dysfunctions. J Assoc Physicians India. 1990 Mar;38(3):201-3. PMID: 2391297.
- West J Med. 1977 Aug; 127(2): 177. **Photomotogram (Achilles Reflex Test)**
- Annals of Internal Medicine August 1, 1964 **The Achilles Reflex in Thyroid Disorders**
- A Critical Evaluation

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## Achilles Reflex

- **Photomotogram** (achilles reflex test). [No authors listed] West J Med. 1977 Aug;127(2):177. PMID: 18748025 Free PMC article. No abstract available.
- 2
- [Functional exploration of the thyroid in pregnancy by means of the **photomotogram**]. Zucchelli GP, Brunori De Luca I. Riv Ostet Ginecol. 1965 Sep;20(9):593-603. PMID: 5858944 Italian. No abstract available.
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- Ankle reflex **photomotogram** in thyroid dysfunctions. Khurana AK, Sinha RS, Ghorai BK, Bihari N. J Assoc Physicians India. 1990 Mar;38(3):201-3. PMID: 2391297
- 4
- [The behavior of the Achilles reflex, as studied in the **photomotogram**, in the picture of functional symptomatology of the thyroid gland. Contribution to its use in mass investigations]. Zoli A, Brat A, Giardina A, Cotrozzi G. Riv Crit Clin Med. 1965 Jun;65(3):356-76. PMID: 5880433 Italian. No abstract available.

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## Conversion issues

- T4 may not convert to T3
- Due to: dieting, stress, selenium, iron, zinc deficiencies
- Insufficient zinc/selenium
- Insufficient progesterone (in both genders)
- Drugs: amiodarone, beta blockers including some glaucoma meds and dilantin

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# May not need treatment forever

- If get to the thyroid before completely damaged
- Fix adrenals
- Reboot receptor
- **Make sure sex steroids are optimal**
- It can recover its function; it is not true that once on thyroid medication, always on thyroid medication
- Thyroid glandulars!
- Selenium keeps thyroid functioning better
- Selenium and rubidium changes in subjects with pathologically altered thyroid. Biol Trace Elem Res. 1992 Jan-Mar;32:253-8. doi: 10.1007/BF02784608. PMID: 1375062.



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# Sustain Any Hormone



+

+

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## Can use this for any hormone

kidneys (great with cytozyme KD)

Adrenals (great with cytozyme AD)

Heart (great with cytozyme H)

Hypothalamus (great with cytozyme HT)

Great with glucose balance

Eyes

Etc.

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## T3 is the active hormone

- T3 binds to thyroid receptor much greater than T4
- Decrease T3 conversion is always accompanied by increased conversion to reverse T3

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## Reverse T3

- RT3 - Reverse T3 – why does body make it?
- Proper levels of reverse T3 are needed for the brain for proper function and connectivity if too low or too high
- Helps with differentiation of astrocytes
- Activates cytoskeleton in brain

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## TBG

- Thyroid function is blocked
- If excessively bound to thyroid binding globulin
- Increased in ER alpha dominance, pregnancy, taking oral birth control pills, oral estrogen pills, thyroid replacement therapy, chronic sleep disturbances

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## Elevated Antibodies

- Gluten, lectins, heavy metals, leaky gut
- Toxins that damage the gut lining +/- receptors
- Many EDCs attack 5-deiodinase enzyme
- That is why taking Receptor Detox helps keep thyroid healthy.

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## Thyroid Receptor Health

- Too low of cortisol damages thyroid receptor response (cortisol rules receptor density, elevator analogy)
- Sometimes need a bit of hydrocortisone to up-regulate thyroid receptor
- But Cytozyme-AD acts best; try first
- EDCs inhibit thyroid binding to thyroid receptor

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## Thyroid/Adrenal Best Buds

- Too low cortisol = too little thyroid receptors
- Too high cortisol – tissue resistance to signals of thyroid
- Just right C means just right T

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## Thyroid Symptoms:

- Thinning outer 1/3<sup>rd</sup> eyebrows
- Thinning hair
- Cold hands and feet!
- Low body temp
- Dark circles/puffy eyes
- Dry skin
- Slow transit time, history of constipation
- Scalloped tongue (mild, moderate, severe)
- Achilles reflex time (photomotogram, thyroflex)

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## Thyroid Symptoms cont.

- Wake up tired
- Lack of energy but improves as day continues
- Weight gain, especially lower torso
- Memory loss
- Anxiety
- Insomnia
- Mood issues
- Elevated blood fats no matter how you eat
- Adrenal – energy crashes, thyroid tired much of the time

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## Thyroid a healthy body makes daily

- T4 (thyroxine): 100 mcg/day
- T3 (triiodothyronine): 30 mcg/day
- 20% produced by thyroid gland
- 80% by conversion of T4
- T3 4 times more potent than T4
- Reverse T3: 1% activity of active T3

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## Synthroid not identical to your own thyroid hormone

- Acacia, confectioner's sugar (contains corn starch), lactose monohydrate, magnesium stearate, povidone, and talc
- And then below this you'll see some of the color additives, which include FD&C Yellow No. 6 (in 25 mcg tablets), FD&C Red No. 40 and FD&C Blue No. 2 (in 75 mcg strength), etc.
- And gluten. Not necessary to put on the label.
- Gluten can cross-react with corn and is grandfathered in a cheap adhesive.

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## Cytomel

- **Cytomel** (liothyronine sodium). This is a brand of synthetic T3. The inactive ingredients consist of calcium sulfate, gelatin, starch, stearic acid, sucrose and talc.
- Giving T3 compounded and SR is best as it acts fast and can "hit" the heart and make it beat out of rhythm. SR is much kinder on the heart especially an older heart.

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## Armour

- This is a form of natural thyroid hormone that is derived from porcine thyroid glands.
- It consists of both T3 and T4, and many people do better when taking natural thyroid hormone when compared to synthetic thyroid hormone.
- However, some people react to the ingredients of Armour.
- The inactive ingredients include calcium stearate, dextrose, microcrystalline cellulose, sodium starch glycolate and opadry white.
- Also the FDA made many formulations change and not working as well as it once did.

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## Nature-Throid.

- is another form of natural thyroid hormone that is derived from porcine thyroid glands, and therefore also consists of both T3 and T4.
- The inactive ingredients include colloidal silicon dioxide, dicalcium phosphate, lactose monohydrate, magnesium stearate, microcrystalline cellulose, croscarmellose sodium, stearic acid, Opadry II

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## Tirosint


- Most medications used to treat hypothyroidism are tablets. In addition to levothyroxine, they contain a variety of excipients (inert ingredients) such as wheat starch (gluten), lactose, sugars, dyes and talc. These can sometimes cause irritation or make it harder for your body to absorb your thyroid medicine. The unique formulation of Tirosint helps to avoid these problems.

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## Common Excipients

- Modified wheat starch (gluten)
- Lactose monohydrate
- Dyes
- Confectioners' sugar (contains corn starch)
- Microcrystalline cellulose
- Butylated hydroxyanisole (BHA)
- Talc
- Croscarmellose sodium
- Calcium phosphate dibasic
- Colloidal silicon dioxide
- Mannitol
- Crospovidone
- Magnesium stearate
- Acacia
- Sucrose
- Povidone
- Sodium lauryl sulfate

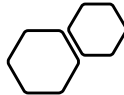
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Thyroid support: 2 of each BID

- [Brain Res Bull.](#) 2001 May 15;55(2):309-12.
- The distribution patterns of trace elements in the brain and erythrocytes in a rat experimental model of iodine deficiency.**

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Whenever you want "sustained" healthy signaling



Sex steroids, vitamin D, T, adrenals, thyroid  
And even for those on prednisone, hydrocortisone  
And other medications that work better at sustained  
Levels throughout the day.



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