Hypothyroidism: Iodine-Induced and Why Use T3

Lewis E. Braverman, MD

Diagram of the thyroid hormone cycle, showing dietary iodine, GI absorption, plasma iodide pool, renal excretion, and the conversion of I- and tyrosine to thyroid hormones, followed by peripheral metabolism and action.
History of IDD

• Goiter in earliest art, written records
• Iodine discovered by Courtois 1811
• Coindet treated 150 goiter patients with iodine; not universally accepted due to development of sx of thyrotoxicosis
• 1896 Baumann demonstrated the presence of iodine in the thyroid
Moderate iodine deficiency (UIC 20-49 µg/L)
Mild iodine deficiency (UIC 50-99 µg/L)
Optimal iodine nutrition (UIC 100-199 µg/L)
More than adequate iodine intake (UIC 200-299 µg/L)
Risk of adverse health consequences (UIC >300 µg/L)
No data
Subnational data

Worldwide Status of Iodine Nutrition
Iodine Deficiency Disorders (IDD)

- Endemic goiter
- Cretinism
- Mental Retardation
- Hypothyroidism
- Increased infertility, miscarriage, congenital anomaly
- Increased infant mortality
**Cretinism**

- Iodine intake < 20-25 µg/day
- Mental retardation, impaired growth, and neurological abnormalities
- Susceptible brain regions: cerebral neocortex, cochlea, basal ganglia; rapid growth in 2^{nd} trimester

**Effect of I Rx on Pregnancy Rate in I Deficient Sheep**
Urinary Iodine Concentrations, Haiti 2008

n = 88


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Goitrous woman, Haiti 2008

Effects of Iodine Deficiency on IQ: A Meta-analysis

IQ 12.45 points (95% CI 8.5 – 16.5) lower in Chinese children from ID areas whose mothers were not supplemented in pregnancy

Effect of Chronic Iodide Administration on $T_4$, $T_3$ and TSH Concentrations

Effect of Daily Douche with Betadine on Serum Total Iodine Concentration
Effect of Daily Douche with Betadine on Serum TSH Concentration

![Graph showing serum TSH concentration over days 0, 1, 7, 14, and 21 after daily douche. The graph indicates a significant increase in TSH concentration on days 7, 14, and 21 compared to baseline (day 0).]

Effect of Daily Betadine Douche on Thyroid $^{123}$I Uptake

![Graph showing thyroid $^{123}$I uptake before and after daily douche. The graph indicates a significant decrease in thyroid $^{123}$I uptake after daily douche (day 14) compared to pre-douche levels.]
Effects of Iodide Loading on Thyroid Hormonogenesis: Acute Inhibition & Escape

The Acute Wolff-Chaikoff Effect
**Hypothesis**

Excess plasma iodine results in a decrease in iodide transport into the thyroid by decreasing the sodium/iodide symporter (NIS).
Experimental Design Chronic Iodide Protocol

- Control
- 0.05% NaI in Drinking Water

Days: 0, 1, 2, 3, 4, 5, 6

Thyroid: NIS, TSHr, TPO, Tg mRNAs
NIS protein

Serum: I, T4, T3, TSH

Effect of Chronic I Administration on Serum TH and TSH Concentrations

- T3 (ng/dL)
- T4 (µg/dL)
- TSH (µU/mL)

Graphs showing changes over time with p-values for statistical significance.
Effect of Chronic I Administration on NIS mRNA

Effect of Chronic I Administration on NIS Protein
Conclusion
The decrease in NIS protein following exposure to iodide excess in vivo explains the mechanism of escape from the acute Wolff-Chaikoff effect


The Wolff-Chaikoff Effect

Pramyothin et al. NEJM 2011
Iodine Induced Hypothyroidism

1. Underlying Thyroid Disease
   A. Euthyroid Graves’ Disease Previously Treated by RAI Thyroidectomy, or Antithyroid Drugs
   B. Hashimoto's Thyroiditis
   C. Euthyroid with History of SAT
   D. Euthyroid with History of Postpartum Thyroiditis
   E. Euthyroid with History of Amiodarone Induced Thyrotoxicosis
   F. Euthyroid post Hemithyroidectomy
   G. Euthyroid after Interferon-α Therapy

2. Fetus: Secondary to Transplacental Passage of Iodide

3. No Underlying Thyroid Disease
   A. Chronic Lung Disease - ? Hashimoto's
   B. Cystic Fibrosis

4. Iodide Plus Other Potential Goitrogens
   A. Lithium

Response of the Serum Thyroxine Concentration to Iodide (SKKI 5 drops daily) in Patients with Diffuse Toxic Goiter Who Had Been Rendered Euthyroid by Treatment with Radioiodine

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Effect of Chronic Iodide Administration on Serum $T_4$ and TSH Concentrations in Patients with Hashimoto's Disease: Patients Who Developed Myxedema

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Braverman L.E. et al, J Clin Endocrinol Metab. 32:315, 1971
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Serum TSH Concentrations in SAT and TX Patients During I Administration

* I discontinued in 1 patient receiving I at day 60 and 1 patient at day 90 due to clinical hypothyroidism (TSH >40)
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**Serum TSH Concentrations in PPT and Normal Control Women During SSKI Administration**

![Graph showing serum TSH concentrations](image)
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TSH Response to Iodide in Euthyroid Patients After Partial Thyroidectomy
Iodine Induced Hypothyroidism

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Effect of Iodide Administration on Serum TSH in the Fetal and Neonatal Rat

Theodoropoulous T, Braverman LE. Science 1979
Betadine Douching in Pregnancy

Fig 1: Individual cord blood thyrotropin (TSH) concentration in iodine exposed (●) and control (○) newborns. The horizontal lines represent the mean of the two groups. A significant difference, p < 0.001, was observed (Student's t test).

Roti et al. The Endocrinologist 1997

Excessive Iodine Exposure During Late Pregnancy and Thyroid Dysfunction

ZhongNa S, et al. JCEM 2012
Congenital Hypothyroidism From Excess Prenatal Maternal Iodine Ingestion

All mothers were taking Iodoral (12.5 mg iodine) daily during pregnancy

Connelly et al. J Pediatrics 2012

TSH: >100 419 217
Dietary Iodine Ingestion and Breastmilk Iodine

Leung et al. *Thyroid* 2012 (in press)
Iodine Excess from Korean Seaweed Soup

- 10 brands of seaweed soup from China & Korea available in the U.S. were selected for testing
- Mean iodine content of blended seaweed soup:
  \[ 1705 \, \mu g/250 \, mL \]

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Maternal Intake of Seaweed Soup and Infant Thyroid Function

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Rhee et al. Thyroid 2011

Nihiyama et al. Thyroid 2004
Overt Hypothyroidism in a Breastfed Infant (Seaweed Soup)

Infant TSH was >100 mIU/L


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Iodine-Induced Hypothyroidism in 3 Boston Neonates

- All infants had a normal newborn Massachusetts TSH screen

- **Baby #1**:  
  - Cardiac cath on day 3 of life  
  - Filter bloodspot iodine 0.020 µg (normal <0.01)  
  - Spot urine iodine 835 µg/L (normal 150-220)  
  - TSH 175 mIU/L on day 25

- **Baby #2**:  
  - Two cardiac caths on days 2 and 3 of life  
  - Serum iodine 888 µg/L (normal 40-92)  
  - Filter bloodspot iodine 0.085 (normal <0.01)  
  - Spot urine iodine 2,664 µg/L (normal 150-220)  
  - TSH 43 mIU/L on day 13

- **Baby #3**:  
  - Cardiac cath on day 17 of life  
  - Spot urine iodine 13,827 µg/L (normal 150-220)  
  - TSH 30 mIU/L on day 31

Thaker V, et al, *Endo Society 2013*
Deiodinases

T4

D2, D1

D3, (D1)

T3

D1: Liver, Kidney (Circulating T3)
D2: Brain, Pituitary (Brain T3)

T2

D1, D2

rT3

T4 to T3 Conversion

Braverman, Ingbar, Sterling  JCI 1971
T4 to T3 Conversion

Braverman, Ingbar, Sterling *JCI* 1971

T4+T3 vs. T4 alone

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study duration</th>
<th>Objective benefit</th>
<th>Subjective benefit</th>
<th>Patient preference for the combined levothyroxine and liothyronine period?</th>
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<tbody>
<tr>
<td>Bovbjerg (32,33)</td>
<td>33</td>
<td>5 weeks</td>
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<td>Walsh (34)</td>
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<td>Clyde (36)</td>
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<td>Siegmann (37)</td>
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<td>Saxavurus (38)</td>
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<td>Apelhof (39)</td>
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<td>Ercolani-Monaco (40)</td>
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<td>Rodrigues (41)</td>
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<td>Regalbaut (42)</td>
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<td>Schwik (43)</td>
<td>29</td>
<td>5 weeks</td>
<td>No</td>
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<td>NA</td>
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*Table 1: Randomized Controlled Trials of Combination Levothyroxine and Liothyronine Therapy in Hypothyroid Patients.*

Abbreviation: NA, not applicable.

*Patient preference for the combined levothyroxine and liothyronine treatment. NA indicates the patients were not asked about their preference.*

McDermott M. *Endo Pract* 2012
Sulfation and Desulfation of T3

\[ T3 \xrightarrow{\text{S}} T3S \xrightarrow{\text{-S}} T2 \]

Phase I - Thyroidectomized patients: mean serum concentrations of T3S levels (ng/dl) levels in the four groups in 48 hours.

Phase I - Healthy volunteers: Mean serum concentrations of T3S levels (ng/dl) (in 3 groups and placebo).

Mean serum T3S in TX patients and healthy volunteers.
Mean serum TT3 in TX patients and healthy volunteers

Phase I - Thyroidectomized patients: mean serum concentrations of TT3 (ng/dl) levels in the four groups in 48 hours

Phase I - Healthy Volunteers: mean serum concentrations of TT3 (ng/dl) levels in the four groups in 96 hours

Correlation between T3S dose, T3S AUC and TT3 AUC

Phase I - Thyroidectomized patients: T3S dose (µg/kg body weight) correlation with the T3S AUC (n=27)

Phase I - Thyroidectomized patients: T3S dose (µg/kg body weight) correlation with the TT3AUC (n=27)
## Principal Collaborators: 1960-2013

<table>
<thead>
<tr>
<th>Name</th>
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<tr>
<td>Sidney Ingbar MD</td>
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<td>Sam Pino BS</td>
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<td>Apostolos Vagenakis MD</td>
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<td>Fred Azizi MD</td>
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<td>Ello Roti MD</td>
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<td>Elsie Allen MD</td>
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<td>Sharon Alex BS</td>
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<td>Shih-Lieh Fang PhD</td>
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<td>Walter Reinhardt MD</td>
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<td>Theodore Theodoropoulos MD</td>
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<td>Marjorie Safran MD</td>
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<td>Rajata Rajatanavin MD</td>
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<td>Jennifer Lawrence MD</td>
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<td>Michael Appel PhD</td>
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