Micronutrient Deficiencies and the Thyroid
Interactions and public health significance

Michael Zimmermann
ETH Zurich, Switzerland
Micronutrients and the thyroid

- Multiple nutritional and environmental influences contribute to the prevalence and severity of thyroid disorders.

- Deficiencies of Se, Fe, and vitamin A can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine.
Micronutrients and the thyroid

- Multiple nutritional and environmental influences contribute to the prevalence and severity of thyroid disorders.

- Deficiencies of Se, Fe, and vitamin A can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine.
Micronutrients and the thyroid

- Multiple nutritional and environmental influences contribute to the prevalence and severity of thyroid disorders.

- Deficiencies of Se, Fe, and vitamin A can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine.
Multiple nutritional and environmental influences contribute to the prevalence and severity of thyroid disorders.

Deficiencies of Se, Fe, and vitamin A can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine.
Micronutrients and the thyroid

- Multiple nutritional and environmental influences contribute to the prevalence and severity of thyroid disorders.

- Deficiencies of Se, Fe, and vitamin A can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine.
Micronutrients and the thyroid

- Multiple nutritional and environmental influences contribute to the prevalence and severity of thyroid disorders.

- Deficiencies of Se, Fe, and vitamin A can act in concert with iodine deficiency to impair thyroid metabolism and modify the response to prophylactic iodine.
Iron and the thyroid
Iron deficiency is common in both developing and industrialized countries

- Worldwide, more than 2 billion people—mainly young women and children—are Fe-deficient.

- In developing countries, 40%–45% of school-age children are anemic, approximately 50% because of Fe deficiency.

- Women of childbearing age and pregnant women are highly vulnerable to iron deficiency anemia (IDA).

- In industrialized countries, 20-40% of pregnant women develop IDA in the 3rd trimester.
In both animal and human studies, Fe deficiency impairs thyroid metabolism

- ↓ $T_4$ and $T_3$, ↑ TSH → hypothyroidism
- ↓ hepatic 5´-deiodinase
- ↓ peripheral conversion of $T_4$ to $T_3$
- ↓ TSH response to TRH
- ↓ nuclear $T_3$ binding

Fe deficiency anemia (IDA) in rats lowers T<sub>3</sub> and T<sub>4</sub> and reduces hepatic deiodinase activity

<table>
<thead>
<tr>
<th></th>
<th>Nonanemic</th>
<th>IDA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>T&lt;sub&gt;3&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free (pM)</td>
<td>6.12 (1.46)</td>
<td>3.59 (0.40)*</td>
</tr>
<tr>
<td>Total (nM)</td>
<td>1.51 (0.12)</td>
<td>0.82 (0.20)*</td>
</tr>
<tr>
<td><strong>T&lt;sub&gt;4&lt;/sub&gt;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Free (pM)</td>
<td>15.18 (2.88)</td>
<td>8.09 (2.56)*</td>
</tr>
<tr>
<td>Total (nM)</td>
<td>122.9 (13.2)</td>
<td>63.6 (13.2)*</td>
</tr>
<tr>
<td><strong>Hepatic 5´-deiodinase activity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Km (µM)</td>
<td>36 (6)</td>
<td>28 (7)</td>
</tr>
<tr>
<td>V&lt;sub&gt;max&lt;/sub&gt; (pM l/mg/20 min)</td>
<td>1209 (302)</td>
<td>340 (132)*</td>
</tr>
</tbody>
</table>

Means (SD). * p<0.05 vs. controls.

Iron deficiency anemia in women reduces total $T_4$ and $T_3$

Mechanism?

Thyroid peroxidase (TPO)

- 103 kDa enzyme at the apical membrane
- requires a heme prosthetic group likely to be ferriprotoporphyrin IX
TPO activity and expression in thyrocyte cell cultures are dependent on:

1- heme biosynthesis

2- heme insertion into TPO during ER processing allows targeting to apical pole

3- further covalent heme binding to TPO at the apical pole ($\text{H}_2\text{O}_2$ dependent)

Fayadatt et al. Endocrinology 1998;139:4277
IDA reduces heme and free protoporphyrin levels in the rat thyroid

Weanling rats given Fe-deficient diets or pair-fed with Fe sufficient diet for 5 wks

Hess et al. J Nutr 2002
Iron deficiency reduces TPO activity in rats and causes hypothyroidism

Hess et al, J Nutr 2002
Iron deficiency produces hypothyroidism in rats through impairment of TPO

<table>
<thead>
<tr>
<th>Hb (g/L)</th>
<th>n</th>
<th>T3 (ng/L)</th>
<th>T4 (mcg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;120</td>
<td>12</td>
<td>4.85±1.14</td>
<td>0.39±0.11</td>
</tr>
<tr>
<td>&lt;75</td>
<td>12</td>
<td>3.35±0.55</td>
<td>0.27±0.05</td>
</tr>
<tr>
<td>&lt;60</td>
<td>12</td>
<td>3.12±0.54</td>
<td>0.24±0.03</td>
</tr>
<tr>
<td>&lt;45</td>
<td>12</td>
<td>3.24±0.93</td>
<td>0.21±0.05</td>
</tr>
</tbody>
</table>

Hess et al. J Nutr 2002
If iron deficiency can lower TPO activity and thereby impair thyroid metabolism, does iron status influence the pathogenesis of ID in regions of coexisting deficiency?

Does iron deficiency block a child’s ability to use the iodine in iodized salt?
Coexisting deficiencies of iron and iodine are common in Africa

Goiter and IDA in African children (6-12 y)

<table>
<thead>
<tr>
<th></th>
<th>Goiter</th>
<th>IDA</th>
<th>Both</th>
</tr>
</thead>
<tbody>
<tr>
<td>Western Côte d’Ivoire (n=1014)</td>
<td>59%</td>
<td>38%</td>
<td>23%</td>
</tr>
<tr>
<td>Northern Morocco (n=775)</td>
<td>74%</td>
<td>46%</td>
<td>26%</td>
</tr>
</tbody>
</table>

Study aim

To test the effect of iodine repletion in children with goiter and iron deficiency anemia

Danane, western Côte d’Ivoire
Study design

Two groups of iodine deficient school children (n=110, 6-12 y-olds)

One group
Iron deficiency **anemia** and goiter

One group
Iron **sufficient** and goiter

Both given 200 mg oral iodized oil and followed for 30 weeks
Iron deficiency anemia impairs thyroidal response to iodized oil in African children

<table>
<thead>
<tr>
<th>Wks</th>
<th>TSH (mU/L)</th>
<th>$T_4$ (nmol/L)</th>
<th>TSH (mU/L)</th>
<th>$T_4$ (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>4.7 (0.6)</td>
<td>110 (22)</td>
<td>3.8 (0.8)</td>
<td>130 (28)</td>
</tr>
<tr>
<td>15</td>
<td>2.0 (0.6)</td>
<td>122 (24)</td>
<td>3.2 (0.6)</td>
<td>96 (17)</td>
</tr>
<tr>
<td>30</td>
<td>1.7 (0.4)</td>
<td>156 (30)</td>
<td>4.0 (0.4)</td>
<td>123 (30)</td>
</tr>
</tbody>
</table>

Iron deficiency anemia impairs thyroidal response to iodized oil in African children

<table>
<thead>
<tr>
<th>Wks</th>
<th>TSH (mU/L)</th>
<th>T4 (nmol/L)</th>
<th>TSH (mU/L)</th>
<th>T4 (nmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.7 (0.6)</td>
<td>110 (22)</td>
<td>3.8 (0.8)</td>
<td>130 (28)³</td>
</tr>
<tr>
<td>15</td>
<td>2.0 (0.6)²</td>
<td>122 (24)</td>
<td>3.2 (0.6)³</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>1.7 (0.4)²</td>
<td>156 (30)¹</td>
<td>4.0 (0.4)⁴</td>
<td>123 (30)⁴</td>
</tr>
</tbody>
</table>

Means (SD).

1. p < 0.01 vs. baseline;
2. p < 0.001 vs. baseline;
3. p < 0.01 between groups;
4. p < 0.001 between groups.

No improvement in thyroid function.

Goiter reduction is greater in the iron sufficient group after iodine treatment.

<table>
<thead>
<tr>
<th>Thyroid size</th>
<th>Group 1 goiter and nonanemic</th>
<th>Group 2 goiter and anemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.5</td>
<td>8.1</td>
</tr>
<tr>
<td>After iodine</td>
<td>4.6</td>
<td>6.3</td>
</tr>
<tr>
<td>% change from baseline</td>
<td>-45.5</td>
<td>-21.8</td>
</tr>
</tbody>
</table>
Goiter rate after 200 mg oral iodine

- Nonanemic (Group 1)
- Iron deficiency anemia (Group 2)

$P < 0.0001$ between groups.

Correlation: baseline Hb and change in thyroid volume

Hemoglobin (g/dl)

% change TVol

$R^2 = 0.606$
Anemia impairs response to iodine...

...and iron treatment restores it

Dual fortification of salt with iodine and iron

Combat anemia and improve iodine efficacy in salt

But adding iron to salt is a challenge because of color changes

new Fe compound: **micronized ferric pyrophosphate**

- white color, nonreactive yet well absorbed
Study Design

Moroccan schoolchildren (n=377) randomized by HH to two groups

Iodized salt

vs.

Salt fortified with iodine and FePP

Salt given to 212 households (2 kg / month) for one school year

Rif Mountains of northern Morocco
Severe endemic goiter in north Morocco debilitates generations

10 yr-old girl

Her grandmother
Salt dual fortified with iodine+Fe improves T4 compared to iodine alone

<table>
<thead>
<tr>
<th>Wks</th>
<th>Iodized Salt</th>
<th>Iodine+Fe Salt</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>UI (µg/L)</td>
<td>T₄ (nmol/L)</td>
</tr>
<tr>
<td>Baseline</td>
<td>18 (0-127)</td>
<td>82.1±17.3</td>
</tr>
<tr>
<td>40</td>
<td>182 (14-474)</td>
<td>85.3±12.7</td>
</tr>
</tbody>
</table>

Means (SD). ¹P<0.02 between groups.

Hypothyroxinemia

Prevalence of HypoT4 (%)

Baseline 10 wks 20 wks 40 wks

Iodine+Fe salt
Iodized salt

### Changes in thyroid volume iodized salt vs. iodine+Fe salt

<table>
<thead>
<tr>
<th>Thyroid vol (ml)</th>
<th>Iodine</th>
<th>Iodine+Fe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.9±3.4</td>
<td>9.1±3.7</td>
</tr>
<tr>
<td>9 months</td>
<td>7.3±2.4</td>
<td>5.7±2.1</td>
</tr>
<tr>
<td>%change from baseline</td>
<td>-18.0±6.6</td>
<td>-37.8±9.1</td>
</tr>
</tbody>
</table>

Means±SD. ¹ P < 0.01 between groups

*Zimmermann et al. Am J Clin Nutr 2003*
Goiter

Iron & iodine salt
Iodized salt

Prevalence of Goiter (%)

Baseline 10 wks 20 wks 40 wks

Conclusions

Iron deficiency anemia in children impairs response to iodized oil and salt

Mechanism: impairment of Fe-dependent TPO

Adding iron to iodized salt not only combats anemia but also increases iodine efficacy
Iron deficiency and thyroid status during pregnancy

- Pregnant women are highly vulnerable to iron deficiency anemia (IDA) because their increased iron needs are rarely met by dietary sources.

- In industrialized countries, the prevalences of anemia and iron deficiency during pregnancy range from 6 to 28% and 24 to 44%, respectively.

- In developing countries, the majority of women are anemic in the second half of pregnancy.
Iron deficiency and thyroid status during pregnancy

- Requirements for thyroid hormone during pregnancy sharply increase to maintain maternal euthyroidism and transfer thyroid hormone to the fetus.
- To support this, the iodine requirement in pregnancy increases from 150 to 250 µg/d.
- Thus, maternal thyroid function is particularly vulnerable in regions of marginal iodine intake.
- Even mild maternal thyroid dysfunction may impair neurodevelopment in the offspring.
Iron deficiency and thyroid status during pregnancy

- **Study objective**: to investigate if maternal iron status is a determinant of TSH and/or TT4 concentrations during pregnancy in an area of borderline iodine deficiency
Study design

- Representative national sample of Swiss pregnant women (n=365) in the 2nd and 3rd trimester

- TSH, TT4, hemoglobin, serum ferritin (SF), transferrin receptor (TfR) and urinary iodine (UI) were measured

- Body iron stores were calculated and stepwise regressions done to look for associations
## Results

<table>
<thead>
<tr>
<th></th>
<th>2nd trimester</th>
<th>3rd trimester</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>164</td>
<td>201</td>
<td>365</td>
</tr>
<tr>
<td>Body iron stores (mg/kg body weight)</td>
<td>4.4 (-5.31-10.91)</td>
<td>2.13 (-8.34-9.52)</td>
<td>2.84 (-8.34-10.91)</td>
</tr>
<tr>
<td>Serum total thyroxine (nmol/L)</td>
<td>154 ± 31</td>
<td>134 ± 32³</td>
<td>142 ± 33</td>
</tr>
<tr>
<td>Serum TSH (mU/L)²</td>
<td>1.5 (0.5-4.6)</td>
<td>1.9 (0.5-5.5)</td>
<td>1.7 (0.5-5.5)</td>
</tr>
<tr>
<td>No. [%] &gt;4.0 mU/L</td>
<td>1 [.06]</td>
<td>11 [6]</td>
<td>12 [3]</td>
</tr>
<tr>
<td>Urinary iodine (µg/L)²</td>
<td>143 (30-317)</td>
<td>138 (38-433)</td>
<td>139 (30-433)</td>
</tr>
<tr>
<td>No. [%] &lt; 150 µg/L</td>
<td>85 [52]</td>
<td>131 [65]</td>
<td>216 [59]</td>
</tr>
</tbody>
</table>

Zimmermann et al, JCEM 2007
Results

- RR of TT4 <100 nmol/L in women with negative body iron stores was 7.8 (95% CI: 4.1; 14.9)

- Of 12 women with TSH >4.0 mU/L, 10 of them had negative body iron stores

- SF, TfR and body iron stores were highly significant predictors of TSH and T4 (all p<0.0001)

Zimmermann et al, JCEM 2007
Iron deficiency predicts higher maternal TSH

\[ y = -2.6291x + 7.7984 \]

\[ R^2 = 0.4124 \]

Zimmermann et al, JCEM 2007
Iron deficiency predicts lower maternal T4

\[ y = 0.0818x - 9.02 \]

\[ R^2 = 0.4672 \]

Zimmermann et al, JCEM 2007
Poor maternal iron status predicts both higher TSH and lower TT4 concentrations during pregnancy in an area of borderline iodine deficiency.

Argues for early detection and treatment of iron deficiency in pregnancy, not only to combat anemia, but also to avoid its potential adverse effects on maternal thyroid function and fetal development.
Vitamin A and the thyroid
Vitamin A deficiency

- VA is essential for the functioning of the immune system and the eye
  - VA deficiency (VAD) affects >100 million children
  - VAD causes blindness and is responsible for as many as 1 in 4 child deaths in deficient regions

- VA and iodine deficiencies often coexist in children in developing countries
  - e.g. rural areas of West and North Africa, 32-57% of children suffer from both VAD and goiter
In animals, VA status has a major impact on thyroid metabolism.

VAD in rats increases serum TSH and circulating T3, and increases thyroid size – central hyperthyroidism

(Morley et al 1978)

High dose oral VA decreases TSH and circulating T3 (↓75%) – central hypothyroidism

Mechanism?

(Morley et al 1970)
TSH

Thyroid hormone

Promoter region of pituitary TSHβ gene
Thyroid hormone

Promoter region of pituitary TSHβ gene

retinoic acid (vitamin A)

Thyroid hormone
VAS modulates thyroid hormone feedback of TSH secretion (Haugen et al 1997; Wolf 2002)

Both the T3-activated thyroid receptor and the VA-activated retinoid X receptor suppress transcription of the TSHβ gene by occupying half-sites on the promoter DNA.

Transcription of TSH β mRNA

Promoter region of pituitary TSHβ gene
VAS modulates thyroid hormone feedback of TSH secretion (Haugen et al. 1997; Wolf 2002)

High dose Vitamin A  
Thyroid hormone

Retinoic acid  
9-cis-Retinoic acid  
T3

RAR  
RXR  
TR

RARE  
RXRE  
TRE

Promoter region of pituitary TSHβ gene

Transcription of TSH β mRNA
VAS modulates thyroid hormone feedback of TSH secretion (Haugen et al 1997; Wolf 2002)

Vitamin A  
Retinoic acid → RAR  

Thyroid hormone  
9-cis-Retinoic acid → RXR  
T3 → TR

Transcription of TSH β mRNA  

↑ TSH  
↑ thyroid hormone, ↑ thyroid size

Promoter region of pituitary TSHβ gene
Weanling rats \((n=56)\) fed diets deficient in:
- vitamin A
- iodine
- or VA and iodine
for 30 days in a pair-fed design

Combined VA and iodine deficiencies increase TSH stimulation of the thyroid, thyroid size and goiter.

\textit{Biebinger et al. Thyroid 2006}
Combined VA and iodine deficiencies increase expression of pituitary TSHβ mRNA

**FIG. 1.** Pituitary thyrotropin β mRNA concentrations in weanling rats fed diets deficient in vitamin A (VAD group), iodine (ID group), vitamin A and iodine (VAD + ID group), or sufficient in both vitamin A and iodine (control) for 30 days. a: Significantly different from control group ($p < 0.05$; ANOVA, post-hoc test: Bonferroni). b: Significantly different between ID and VAD + ID group ($p < 0.01$; ANOVA, post-hoc test: Bonferroni).
VA treatment reduces TSHβ mRNA expression and TSH hyperstimulation in combined VA and iodine deficiency

Weanling rats (n=96) fed diets deficient in VA and iodine for 30 d. Then repleted with iodine and/or vitamin A for 10 d

Biebinger et al, J Nutr 2006
Chemotherapy with bexarotene, a synthetic retinoid, produced profound clinical hypothyroidism... through binding to the pituitary RXR and suppression of TSH secretion.
In areas of iodine deficiency, could a child's **vitamin A status** influence his/her risk for goiter and hypothyroidism?
## Cross sectional study of school children ($n = 298$) with severe ID and poor VA status

### Number of children with low T4, goiter by VA status

<table>
<thead>
<tr>
<th>VA status</th>
<th>T4 &lt;65 pmol/L</th>
<th>T4 ≥65 pmol/L</th>
<th>Goiter Present</th>
<th>Goiter Absent</th>
</tr>
</thead>
<tbody>
<tr>
<td>VA deficient (SR &lt;0.70 µmol/L)</td>
<td>0</td>
<td>50</td>
<td>49</td>
<td>1</td>
</tr>
<tr>
<td>Low VA status (SR ≥0.70 µmol/L and &lt;1.05 µmol/L)</td>
<td>7</td>
<td>142</td>
<td>141</td>
<td>8</td>
</tr>
<tr>
<td>VA sufficient (SR ≥1.05 µmol/L)</td>
<td>38</td>
<td>61</td>
<td>75</td>
<td>24</td>
</tr>
</tbody>
</table>

*Zimmermann et al. JCEM 2004*

### Children with VAD or low VA

<table>
<thead>
<tr>
<th>Condition</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>hypothyroidism</td>
<td>0.06</td>
<td>0.03, 0.14</td>
</tr>
<tr>
<td>goiter</td>
<td>6.51</td>
<td>2.94, 14.41</td>
</tr>
</tbody>
</table>
Conclusions

- VAD in ID-affected children increases risk for goiter but decreases risk for hypothyroidism

- probable mechanism
  - VAD $\rightarrow$ ↓ activation of pituitary retinoid receptor
  - ↑ transcription of the TSHβ gene
  - ↑ TSH secretion
    - increases thyroid size
    - maintains circulating thyroid hormone protecting against hypothyroidism

Zimmermann et al. JCEM 2004
Conclusions

- Blanket high dose VA treatment (up to 200,000 IU/dose) is often given to children and young women in VA deficient areas.

- In an area of IDD, could high dose VA, by decreasing TSH stimulation of the goitrous thyroid, impair its ability to maintain euthyroidism in the face of marginal iodine supply?
Study design

- South African school children \((n = 410)\) with iodine and VA deficiencies
- RCT, double-blind 2x2 intervention trial
- Four groups
  - Iodine treatment \((200 \text{ mg iodine as iodized oil})\)
  - VA treatment \((200,000 \text{ IU as retinyl palmitate})\)
  - Both iodine and VA
  - Placebo capsule
- Followed for 6 months
Vitamin A repletion reduces TSH in VA- and iodine deficient children

By ANOVA, **p<0.01, *p<0.05

Zimmermann et al, AJCN 2007
Vitamin A repletion reduces thyroid size and goiter in VA- and iodine deficient children

By ANOVA, **p<0.02, *p<0.05

Zimmermann et al, AJCN 2007
High dose VA given alone does not reduce TT4 in VA- and iodine deficient children

Zimmermann et al, AJCN 2007
Conclusions

- VA treatment alone reduces TSH hyperstimulation in IDD/affected areas and may enhance the response to iodine, **reducing risk for goiter and its sequelae**

- These findings are likely mediated through the **pituitary retinoid receptor** and **TSHβ gene expression**
The future

- UNICEF/WHO have described the global iodized salt initiative as "probably the most effective public health nutrition program ever."

- However, 1/3rd of children worldwide (over 250 million) remain iodine deficient and goitrous.

- Reaching this remaining third will require strategies that also correct other micronutrient deficiencies that affect the response to iodized salt (Se, vitamin A, iron).
The future

- Micronutrient interactions at the molecular level
  - within the pituitary genome for vitamin A
  - within the thyrocyte membrane for iron

may have far-reaching affects on public health
of children and pregnant women

- Argues strongly for combined approaches to correct these common deficiencies
## Coworkers

<table>
<thead>
<tr>
<th>HNL, ETHZ</th>
<th>INSP, Côte d’Ivoire</th>
<th>MOH, Morocco</th>
</tr>
</thead>
<tbody>
<tr>
<td>R Hurrell</td>
<td>P Adou</td>
<td>N Chaouki</td>
</tr>
<tr>
<td>C Zeder</td>
<td>JB Gbato</td>
<td>A Dib</td>
</tr>
<tr>
<td>S Hess</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Wegmüller</td>
<td></td>
<td></td>
</tr>
<tr>
<td>R Biebinger</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kinderspital Zürich</th>
<th>MRC, South Africa</th>
</tr>
</thead>
<tbody>
<tr>
<td>T Toressani</td>
<td>P Jooste</td>
</tr>
<tr>
<td>L Molinari</td>
<td>X Mbhenyane</td>
</tr>
</tbody>
</table>

## Supported by

- Swiss National Science Foundation
- Thrasher Research Fund
- Nestlé Foundation, WHO
- ETH Zürich