American Association of Clinical Endocrinologists
8/4/18

Interferences with Endocrine Tests

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DISCLOSURE

Nothing to disclose
Objectives:

1. To review the causes of non-specific and analyte-specific interferences.

2. To discuss why test interferences should be suspected by the physician, not the laboratory.

3. To discuss approaches for confirming that interference is affecting a test result.
A test interference can usually only be suspected by the physician – because the hallmark of interference is discordance between the test result and the clinical presentation of the patient.

The laboratory does not typically have sufficient clinical information to suspect an interference before the test result is reported.
Physicians Should Suspect Interference with a Test Result When:

- Test Result is clinically unexpected
- Inconsistent with other clinical correlates
- Inconsistent with other biochemical tests
- Odd results in more than one method
- Significant or unexplained change from a previous test
- Patients with autoimmune or chronic diseases are more at risk
- Recent immunization, blood transfusion or monoclonal Ab therapy
- Veterinarians and those who come into contact with animals

Ismail, Clin Med 7:357, 2007
Ward, Clin Biochem 50:1206, 2017
Interferences

Non-Specific - not related to test analyte
- Heterophile (Animal) Abs
  - human anti-mouse Ab (HAMA)
  - Rheumatoid Factor (RF)
- Abnormal proteins or paraproteins
  - FT4 & FT3 (mutant albumins - FDH)
- Antibodies targeting test reagents
  - Streptavidin
  - Horse Radish Peroxidase (HRP)
  - Rhuthenium (Roche tests)
- Drugs or dietary supplements
  - High Dose Dietary Biotin

Specific - related to test analyte
- Molecular variants of test analyte
  - TSH (central hypo/hyperthyroid)
  - Tg (abnormal tumor isoforms)
- AutoAbs that bind the test analyte
  - T4Ab and/or T3Ab
  - TSHAb
  - TgAb
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Specific not related to test analyte

- Abnormal autoAbs
  - T4Ab
  - T3Ab
  - TSHAb
Heterophile Antibodies (HAb) Primarily Interfere with Tests that use Immunometric assay (IMA) methodology

IMAs use a Capture and Signal monoclonal Ab (mAb) pair selected to target different epitopes on the antigen.

- During incubation with the specimen, antigen in the serum binds both mAbs forming a bridge that links the signal to the solid support.
- After washing away unbound constituents, the signal bound to the solid support will be proportional to the serum antigen concentration.

Antigen in Serum

Signal mAb

Capture mAb

Solid Support

Chemiluminescent Signal
How Heterophile Antibodies Interfere with IMA Methodology

A. no interference

B. false high/positive (common)

C. false low/negative (rare)

Capture mAb

labeled mAb

Heterophile Ab (HAMA)

Capture mAb

labeled mAb

Ag

solid support

Ag

= antigen (test analyte)
Heterophile Ab (HAb) Interference is Test and Platform Dependent

Case: 33 yo woman with no symptoms suggesting an endocrine problem, but her sera contained HAb that caused many endocrine test abnormalities

![Graph showing test results for PRL, TSH, FSH, β-hCG, iPTH, and ACTH with different platforms: Abbott, Siemens, Beckman, Roche. The results are plotted on a logarithmic scale. The reference range is indicated by a green rectangle.](image_url)
The HAbs of Different Patients Vary in Potential for Interference

6 Hyperthyroid Sera from 6 Different Patients with HA\(b\) Measured by Different TSH IMAs on 6 Different Platforms
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Clinical Labs Use FT4 Estimate Tests, Not Direct Free T4 Measurements

1970s

- free T4 index (FT4I)
- total T4 / TBG estimate

1980s

- direct free T4 methods

1990s

- Reference Labs: equil. dialysis/ultrafiltration
- Tandem Mass Spectrometry

2017

Clinical Labs Free T4 Estimate tests

Automated FT4 immunoassays can be binding protein (albumin) dependent!

- 1-step
- 2-step
- labeled antibody

1-step labeled antibody

2-step labeled antibody
Familial Dysalbuminemic Hyperthyroxinemia (FDH)
(~1.8% prevalence in Hispanics)

FT4 pmol/L

Case 1
Case 2
Case 3
Case 4

R218H mutation

FT4 Immunoassays

DeCosimo et al AIM 107:780, 1987
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Biotin for the Masses...

START YOUR 90 DAY CHALLENGE HERE!

Let Your Inner Beauty Shine

Support the health of your hair, skin & nails

Kirkland Signature

Hair, Skin & Nails
Biotin Interference with Endocrine Tests

Biotin is an essential co-factor for fatty acid synthesis, amino acid catabolism and gluconeogenesis.

- Biotin intake of 0.02-0.15 mg/day (in multi-vitamins) is adequate for adults.
- Clinical Use: High dose Biotin Rx. (>10 mg/d) is used to Rx. multiple sclerosis.
- OTC Use: 5 -10 mg/d (125x normal) is typical in hair, skin and nail supplements.
- ~8% Mayo outpatients (77% female, median age 62) used biotin (0.5-20 mg/d).
- Most patients do not list biotin in the EMR medication list!
- Biotin >5 mg/d can cause falsely low or high endocrine test results - the magnitude & direction of interference depending on test and analytic platform.
- The manufacturer recommendation to wait >8hr after last dose before testing is insufficient for high doses. Note: any renal impairment slows biotin clearance.
Case: 44 yo female patient who appeared euthyroid > 2 years after RAI treatment for Graves’ hyperthyroidism, but then developed discordant thyroid tests.

**Biotin Interference is both Analyte and Method Dependent**

<table>
<thead>
<tr>
<th>Date</th>
<th>TSH</th>
<th>FT4</th>
<th>Ref. Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/31/16</td>
<td>3.1</td>
<td>1.4</td>
<td>0.3 - 4.5 mIU/L</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.8 - 1.8 ng/dL</td>
</tr>
<tr>
<td>9/20/16</td>
<td>0.5</td>
<td>6.8</td>
<td>0.05 - 0.83 ng/mL</td>
</tr>
</tbody>
</table>

**TSH**

- **Beckman platform:**
  - 5/31/16: 3.1 mIU/L
  - 9/20/16: 0.5 mIU/L

**FT4**

- **Beckman platform:**
  - 5/31/16: 1.4 ng/dL
  - 9/20/16: 6.8 ng/dL

**FT3**

- **Beckman platform:**
  - 5/31/16: 220 pg/mL
  - 9/20/16: 0.05 - 0.83 ng/mL

**Biotin Interference**

- Analyte and method dependent
- Kwok Path 44:278, 2012
- Elston JCEM 101, 3251, 2016
Direction of Biotin Interference (falsely high or falsely low test result) depends on the Methodology (IMA vs IA), the Test Analyte and the Biotin Dose.

**Noncompetitive (IMA)** (used for large analytes)

- Trop T
- TSH
- LH
- FSH
- SHBG
- PRL

**Competitive Immunoassay (IA)** (used for autoAbs and small analytes)

- TgAb
- TPOAb
- TSHab
- FT4
- FT3
- Cort
- T
- DHEAS
- E2
- Prog

Legend:
- Low dose biotin
- Medium dose biotin
- High dose biotin

Trambas et al. Ann Clin Biochem 1/2017
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1. TSH is a heterogeneous glycoprotein hormone
2. Circulates as a mixture of different glycoisoforms
3. Not all TSH glycoisoforms are bioactive
4. Hypothalamic TRH influences TSH molecular glycosylation, molecular conformation, metabolic clearance and bioactivity
Central Hypo. - TSH isoforms with impaired biologic activity are secreted and detected by TSH IMAs

TSHomas - TSH isoforms with enhanced biologic activity are secreted and detected by TSH IMAs

Persani et al JCEM 85:3631-5, 2000
Persani et al JCEM 78:1034, 1994
Even with **Intact H-P Axis** TSH Heterogeneity Causes Between-Method Variability

**IFCC study: Different TSH methods**

*All method mean*

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Tg in Sera, Especially Tumor-Derived Tg, is Heterogeneous – causing Serum Tg to Differ 2-Fold when measured by Different Methods!

UK NEQAS QC program

Method:
Mean serum Tg (ng/mL) ± 2sd

A

B

C

D
It is Critical to Monitor Tg Concentrations Using the Same Method!

Long-Term Serum Tg Monitoring (TSH stable <1.0 mIU/L)

expected Tg level from normal remnant without RAI Rx. if disease-free

below assay functional sensitivity

thyroidectomy

1Angell et al Thyroid 24:1127,2014
In the Absence of TgAb

Constant (non-elevated) TSH maintained

No Thyroid Injury

The Tg Trend used as Tumor-Marker

Can only monitor the Tg trend using same method!

Changes in Tumor Mass

Efficiency of that individual’s tumor to secrete Tg

Baudin et al JCEM 88;1107, 2003
Tuttle et al EMCNA 37:419, 2008
Thyroglobulin Doubling-Time (Tg-DT) (TSH < 0.1 mIU/L) has Prognostic Value

From: Miyauchi et al Thyroid 21:707, 2011

- **Tg-DT = < 1 yr**
- **Tg-DT = 1-3 yrs**
- **Tg-DT = ≥ 3 yrs**
- **Tg-DT = -21.6 yrs**

Survival (%)

Time (years)

Thyroglobulin (ng/mL)

Tg-DT <1
Tg-DT 1-3
Tg-DT ≥ 3
Tg-DT not detect.
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Case - Thyroid Hormone Autoantibodies causing Interference

19 year old man complaining of fatigue (x 12 months) but appeared clinically euthyroid. His family history of hypothyroidism prompted the ordering of thyroid tests:

<table>
<thead>
<tr>
<th>Laboratory:</th>
<th>new specimen</th>
<th>reference ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>FT4</td>
<td>4.7 <em>(repeat 5.2</em>)</td>
<td>0.8 - 1.9 ng/dL</td>
</tr>
<tr>
<td>FT3</td>
<td>5.2 <em>(repeat 4.1</em>)</td>
<td>1.6 - 4.2 pg/mL</td>
</tr>
<tr>
<td>TSH</td>
<td>0.9 (repeat 1.3)</td>
<td>0.3 - 5.5 mIU/L</td>
</tr>
</tbody>
</table>

Possibilities: Technical interference (HAb or T3Ab + T4Ab) - most likely
Central hyperthyroidism (TSHoma) - rare
Thyroid hormone resistance (THR)

Investigations:
- FT4 and FT3 tests using other manufacturers methods - variable
- Test for HAb/HAMA (Scantibodies blocker tube) - negative
- Test for Thyroid Hormone autoantibodies (PEG precipitation) - positive

Loh et al Endo Pract 20:134, 2014
Case - TSHAb (macro TSH) causing Interference

- 23 y/o old college student who had a thyroid evaluation following complaints of fatigue. The thyroid gland appeared normal to palpation and the patient denied taking any prescription or OTC drugs or vitamins.

Laboratory tests:

<table>
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<tr>
<th>Test</th>
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<tbody>
<tr>
<td>Total T4</td>
<td>7.5</td>
<td>4.5 - 12.5 μg/dL</td>
</tr>
<tr>
<td>Total T3</td>
<td>125</td>
<td>80 - 180 ng/dL</td>
</tr>
<tr>
<td>FT4</td>
<td>1.6</td>
<td>0.9 - 1.9 ng/dL</td>
</tr>
<tr>
<td>TSH (assay #1)</td>
<td>25/43</td>
<td>0.3 - 5.5 mIU/L</td>
</tr>
<tr>
<td>TSH (assay #2)</td>
<td>0.52</td>
<td>0.3 - 4.2 mIU/L</td>
</tr>
<tr>
<td>TSH (assay #3)</td>
<td>14</td>
<td>0.3 - 3.0 mIU/L</td>
</tr>
<tr>
<td>TSH (assay #4)</td>
<td>61</td>
<td>0.3 - 4.0 mIU/L</td>
</tr>
<tr>
<td>TSH-alpha subunit</td>
<td>&lt; 0.2</td>
<td>&lt; 1.0 ng/mL</td>
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- Discordance between clinical status and between different methods suggested an interference. HAb were negative. Gel Chromatography of the serum showed a high molecular weight TSH-TSHAb complex – “macro TSH”.

Estimates of prevalence = 0.8 - 1.6% Hattori et al Thyroid 27:138, 2017.
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TgAb prevalence in patients with differentiated thyroid cancer is more than two-fold higher than the general population.

- **NHANES III**: n = 17,353
  - General Population: 12%
  - Currently TgAb+: 23%
  - Hx. of TgAb+ became TgAb-neg.: 13%
  - Never had TgAb: 36%

NHANES III* (Spencer et al., COEDO 5:394, 2014)
Laboratories currently reflex Tg specimens to different methodologies based on the specimen’s TgAb status (+/-)

Maximize clinical sensitivity

Minimize TgAb Interferences

reflex Tg testing

? TgAb present in serum

NO

75%

YES

25%

Tg-Ria or Tg-MS

Resistant to Interferences

Inferior sensitivity to $^{2G}\text{Tg-IMA}$

Most prone to Interferences

Highest Functional Sensitivity

$^{2G}\text{Tg·IMA}$
<table>
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<th>Tg assay Classes</th>
<th>Principle</th>
<th>TOT</th>
<th>Strengths /Limitations</th>
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</table>
| Immunometric Assay (IMA)         | Noncompetitive format uses monoclonal Abs (MAbs) | hours (can be automated) | • FS* = 0.10 to 0.9 ng/mL^2  
• Prone to interferences by:  
  - TgAb (false-low/UD values)  
  - HAb^ (HAMA) false-high values  
• Uses MAbs-may lack specificity to detect abnormal tumor Tg isoforms |
| Radioimmunoassay (RIA)           | Competitive format uses polyclonal Abs (PAbs)   | ~ 6 days (difficult to automate) | • FS* = 0.5 to 2.0 ng/mL^2  
• Resistant to TgAb interference  
• No HAb^ (HAMA) interference  
• PAbs – broader epitope specificity for detecting abnormal tumor Tgs |
| Liquid Chromatography -         |                                                |                       |                                                                                      |
| Tandem Mass Spec. LC-MS/MS       |                                                |                       |                                                                                      |
| (2009 - present)                |                                                |                       |                                                                                      |

*FS. Functional sensitivity = 20% between-run CV over 6-12 months.  
^HAb (HAMA) = Heterophile (often Human Anti-Mouse) Antibodies
Tg-IMA Methodology is More Prone to TgAb Interference than Tg-RIA

42 Euthyroid TgAb+ controls with:
- Intact thyroid glands
- TSH between 0.3 and 3.0 mIU/L

reference range for TgAb-negative controls

Serum Tg ng/mL

functional sensitivity estimates

Spencer & LoPresti, NCPERM 4:223, 2008
TgAb Effects on Tg measurements is evident in Patients who undergo a Change in their TgAb Status

Patient A

Patient B

TgAb Effects on Tg measurements is evident in Patients who undergo a Change in their TgAb Status
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| Immunomeric Assay (IMA) (1990 - present) | Noncompetitive format uses monoclonal Abs (MAbs) | hours (can be automated) | • FS* = 0.10 to 0.9 ng/mL²  
• Prone to interference by:  
  - TgAb (false-low/UD values)  
  - HAMA^ (false-high values)  
• MAbs – may lack specificity to detect abnormal tumor Tg isoforms |
| Use: TgAb- sera                       |                                               |                |                                                                                                                                                                                                                       |
| Radioimmunoassay (RIA) (1973 - present) | Competitive format uses polyclonal Abs (PAbs)  | ~ 6 days (difficult to automate) | • FS* = 0.5 to 2.0 ng/mL²  
• Resistant to TgAb interference  
• No HAb (HAMA)^ interference  
• PAbs - broad epitope specificity to detect abnormal tumor Tgs |
| Use: TgAb+ sera                       |                                               |                |                                                                                                                                                                                                                       |
| Liquid Chromatography - Tandem Mass Spec. LC-MS/MS (2009 - present) | Extensive preanalytical specimen preparation: ± immunoaffinity concn. reduction, alkylation & trypsin digestion before immunoaffinity concn. of target peptides | ? 1-2 day (difficult to automate) | • FS* range ~ 0.5 ng/mL²  
• No HAb (HAMA)^ interference  
• Claims TgAb does not interfere are not supported by reports that 40% TgAb+ patients with structural Dz have no Tg detected by LC-MS/MS. |
| Labs promoting their use for: TgAb+ sera |                                               |                |                                                                                                                                                                                                                       |

*FS = Functional sensitivity
CV = Coefficient of Variation
HAMA = Heterophile Antibodies
Dz = Disease
Tg = Thyroglobulin
TgAb = Thyroglobulin Antibody
When TgAb is Present:

Serum Tg may be unreliable (by any method!)

ATA Guideline #63(C7) suggests:

For patients with TgAb detected, the TREND in the TgAb levels may be monitored as a “surrogate” tumor marker test.

Haugen et al Thyroid 26, 1:2016
Guidelines recognize the value of monitoring the TgAb trend as the 1° (surrogate) tumor-marker, while monitoring the Tg trend as a 2° tumor-marker (because in-vitro and/or in-vivo TgAb interferences potentially influence all Tg methodologies to some extent).

Critical to Use the Same TgAb Method!

Spencer JCEM 96:3615, 2011; Verburg Thyroid 23, 1211, 2013
Spencer Curr Opin Endocrinol Diabetes Obes 21:394, 2014 Haugen Thyroid 26:1, 2016
TgAb Methods Differ in Sens. and Spec. because of Patient-Specific TgAb Heterogeneity

1. Different methods report different numeric values (can differ 100-fold!)
2. MCO cutoffs for “positive TgAb” set too high (for AITD not TgAb interference of Tg)
3. Optimal cutoff for TgAb “positivity” is the assay’s functional sensitivity not the MCO
4. Method insensitivity: Sera TgAb+ by one method may be “negative” by another.

Manufacturer Cut-Offs (MCO) are set to detect thyroid autoimmunity & are too high to detect TgAb interference with Tg measurement
Laboratory Investigations for Interference Suspected by Physician:

- Check for a possible preanalytical problem:
  - inadequate centrifugation
  - hemolysis, lipemia, icterus
  - specimen mislabeling/patient identity problem
  - carry-over from the previous spec with very high analyte
  - high-dose hook effect

- Repeat the test - using a different manufacturers platform
- Repeat the test in a Heterophile Ab blocker tube (Scantibodies)
- Precipitate macro-complexes (IgG) with 25% PEG 2000
- Perform serial dilutions for suspected (+) or (-) interference
- Selectively remove immunoglobulins
- Perform column chromatography
More information on is available in two webinars available on USC laboratory website:

www.thyroidlab.com/updates