

Thyroid Management

Evolving Controversy -
Science, Dogma, Opinion

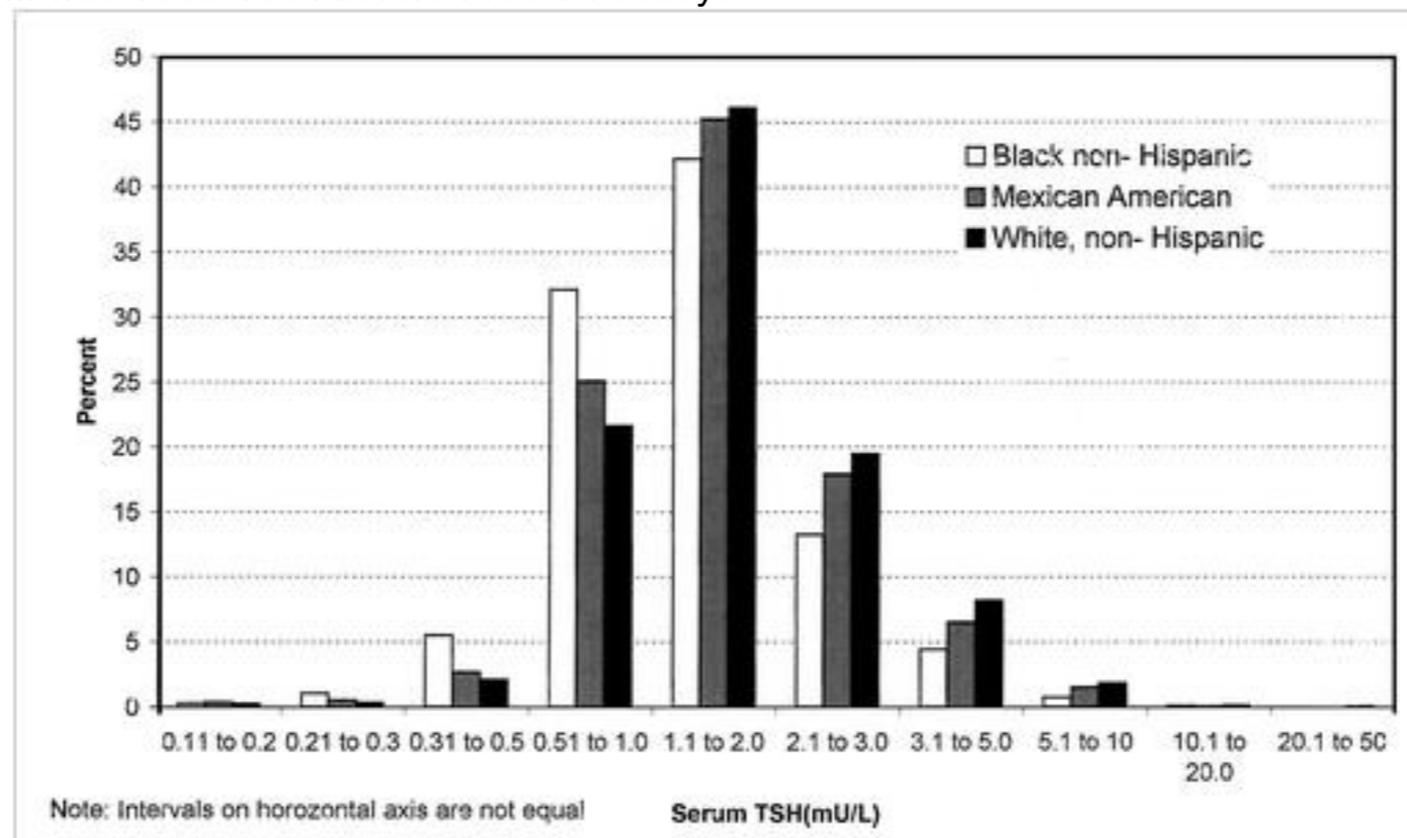
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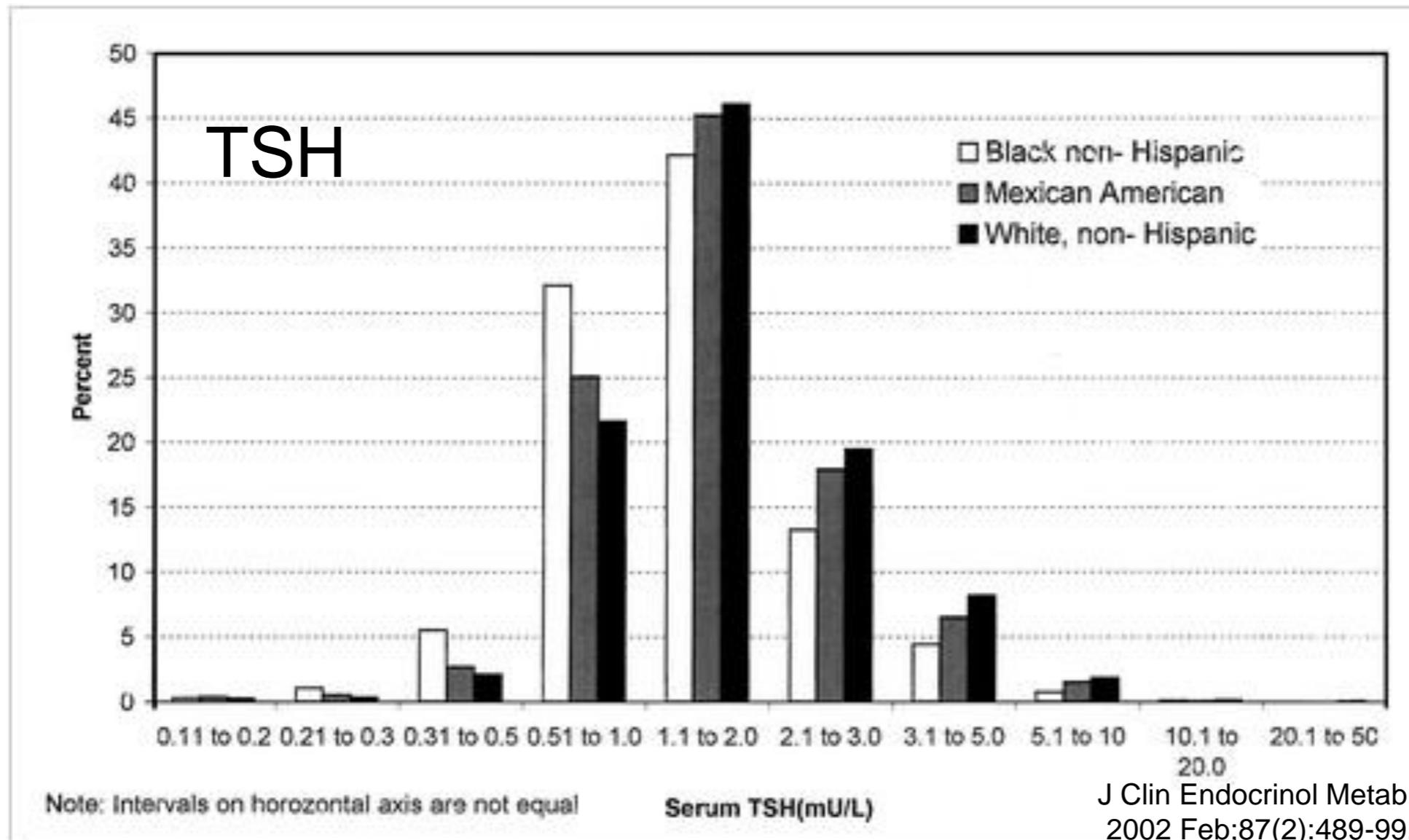
- AACE and ATA - Clinical Practice Guidelines in 2012
 - “Guidelines are neither inclusive of all proper approaches nor exclusive of others”
 - The CPCs define
 - Overt Hypothyroidism as TSH $>$ 10 with FT4 lower than ‘normal’
 - Subclinical Hypothyroidism as a TSH $>$ ‘normal’ with a normal FT4
 - Are these practical?
 - And, ... Why do we care about the TSH, FT4 et al?
 - Goal of any test is to discriminate who could benefit from Intervention
 - **What is 'Normal'?**

Normal ?

- NHANES III - 17,353 patients > age 12 yrs
 - 13,344 were defined as 'disease-free'
 - Excluded those who self-reported thyroid issues, had a goiter or were taking thyroid Rx
 - Excluded those who were pregnant, taking androgens or estrogens, or had high T Abys
 - 'Reference' ranges for 'Normal' - the 2.5 and 97.5 %iles
 - Mean TSH = 1.5 with a Reference Range = 0.39 - 4.1
 - The TSH = 4.1 UNL is a Grade A recommendation in the CPGs
 - Mean Total T4 = 8.7 with a Reference Range = 4.5 - 13.2
 - NHANES III was 1988-1994 before Free T4 assays



Normal ?



- 95% of Pts without evidence of thyroid disease have TSH < 2.5
- Hence, some argue that the ULN for TSH should be 2.5

When to Test

- TSH Circadian Rhythm
 - TSH levels Highest very early a.m., Lowest late afternoon
 - May vary by up to 30 - 40% and this pattern is maintained even in those on Rx
 - Serial TSHs - same pt, same time of day?
 - Up to 40% variation
 - Hence, 'variations of TSH within 'normal' of up to 40% do not necessarily reflect a change in thyroid status'
J Clin Endocrinol Metab.1986;62:960-964
 - TSH may be low during acute illness and may be high transiently (up to 20) during recovery from a non-thyroid illness
Arch Intern Med. 1981;141:873-875.

Testing T4

- Free T4 testing is preferred in almost all settings over a Total T4
 - Most students are never taught use of older Total T4 x T3RU = FTI
 - Many conditions alter Thyroid Binding Globulin TBG that alter the Total T4
 - e.g., Estrogen / BCPs raise TBG, elevating Total T4, while the Free T4 is stable
- FT4 levels after a steady dose of T4 in athyreotic patients
 - Half-Life of T4 in blood may be about a week
 - FT4 levels may transiently be 15 - 20% higher in the hours after a dose
 - FT3 levels remain steady after a T4 dose
 - TSH levels remain steady - timing of T4 dose has little impact on TSH test

Testing T3

More Variability

- Caveats about Free vs Total Testing are the same
 - But, the T3 and FT3 assays are not as precise as some expect
 - Half-Life of T3 in blood may vary from <1 day to perhaps 3 days
 - Free T3 level may rise 40% during 4 hours after a T3 dose
 - TSH may be suppressed for 5 hours after a dose of T3
- Hence, if using T3 or T3/T4 Rx, Test in the a.m., before taking the Rx
- FT3 or TT3 levels useful for Hyperthyroid, but less reliable for Dx of Low
 - Conversion of T4 into T3 is well-preserved
 - Patients may be hypothyroid and still have normal FT3
 - T3 may also Lower in Chronic illness - decreased T4 to T3 conversion

When to Treat

- Combination of SSx and labs - we are all different
 - A pt with TSH = 15 may come in feeling fine
- Some studies have shown beneficial CV effects with treatment of those with TSH 2.5 - 4.5
 - But there are no outcome studies in this group
 - Except, target Upper TSH for Pregnancy:
 - 1st Trimester = 2.5 - or planning pregnancy (Grade B rec)
 - 2nd Trimester = 3.0
 - 3rd Trimester = 3.5

Treatment with T4

- Generic vs Brand Debate
 - Thyroxine has a Narrow Therapeutic Range
 - Multiple doses at about 10% increments
 - CPC: “because of uncertainty about the sensitivity of current bio-equivalence assessment procedures to assure true inter-changability among the tablets, current recommendations encourage the use of a consistent L-thyroxine preparation for individual patients to minimize variability from refill to refill”
 - For a generic to be bio-equivalent, the FDA requires that 90% of the time, the amount absorbed be within 80% and 125 % of the reference Rx.

http://www.fda.gov/ohrms/dockets/ac/03/briefing/3926B2_03_King%20Pharmaceutical-Backgrounder.pdf

<u>Labeled Dose (mcg.)</u>	<u>80% x Dose (mcg.)</u>	<u>125% x Dose (mcg.)</u>
25.0	20.0	31.3
50.0	40.0	62.5
75.0	60.0	93.8
88.0	70.4	110.0
100.0	80.0	125.0
112.0	89.6	140.0
125.0	100.0	156.3
137.0	109.6	171.3
150.0	120.0	187.5
175.0	140.0	218.8
200.0	160.0	250.0
300.0	240.0	375.0

- Within a specific generic producer, consistency is good
- However, if a patient bounces from generic to generic, there may be significant changes in dose received

Treatment: T4 vs T4 with T3

Daily Controversy

- T4 alone has been the standard for 30 yrs
- T4 is converted into T3 by a De-iodinase
- Some may indeed have a De-Iodinase Deficiency
- More than a generation of providers have been taught 'Do not RxT3, only T4', but the Pendulum may be swinging

'Natural Thyroid'?

- Usually panned by teaching institutions
 - But, increasingly popular
- Most have T4 and T3 in a Weight Ratio of about 4:1
 - However, T3 is more potent per mcg than T4
- Some variation with Porcine (Armour) vs Bovine (Naturethroid and Westhroid), but generally interchangeable
- Latest CPC still advises T4 only, but down-graded this recommendation from Grade A to Grade B because of increasing evidence that many patients feel better with combination Rx - - HRC is taking Armour
- These Rx's are dosed in mg or grains (1 grain = 65 mg) vs T4 and T3 which are in mcg (confuses some puts)
- Some split their daily dose BID because of the T3 effects
 - But as already noted, the T3 half-life varies widely.

Biotin

- Popular for hair, nails skin
 - Inst of Medicine recommends daily of 30 mcg – as in Centrum
 - Many patients are taking 10 mg / day
- Most immunoassays use Biotin-streptavidin to anchor or capture assay antibodies
 - With competitive immunoassays, this yields falsely High T3, T3, Cortisol results
 - But, the effect of Biotin varies from lab to lab
 - Some may have a falsely low TSH
 - Stopping Biotin even for one day – water soluble, cleared quickly.
 - Case: Clinically Euthyroid on T4: TSH = 1.5, Free T4 = 2.4 (0.7-1.8)

F Y I

Table 10
Agents and Conditions Having an Impact on
L-thyroxine Therapy and Interpretation of Thyroid Tests

10.1. Interference with absorption

Bile acid sequestrants (cholestyramine, colestipol, colesevelam)
 Sucralfate
 Cation exchange resins (Kayexelate)
 Oral bisphosphonates
 Proton pump inhibitors
 Raloxifene^a
 Multivitamins (containing ferrous sulfate or calcium carbonate)
 Ferrous sulfate
 Phosphate binders (sevelamer, aluminum hydroxide)
 Calcium salts (carbonate, citrate, acetate)
 Chromium picolinate
 Charcoal

Orlistat^b
 Ciprofloxacin
 H₂ receptor antagonists^a
 Malabsorption syndromes

- Celiac disease
- Jejunioileal bypass surgery
- Cirrhosis (biliary)
- Achlorhydria

 Diet

- Ingestion with a meal
- Grapefruit juice^a
- Espresso coffee
- High fiber diet
- Soybean formula (infants)
- Soy