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Perspective

Biotin Effects on Thyroid Function Test

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Perspective

Thyroid Function Tests (TFT) are the most common immunoassay tests ordered in the endocrine laboratory [1,2]. Analytical interferences are the bane of all immunoassay systems [3]. Many automated immunoassay analyzers employ biotin in their system to label the antigen, e.g. Free Thyroxine (fT4) or Thyroid Stimulating Hormone (TSH) and antibody e.g. TSH Receptor Antibodies (TRAb). Biotin's affinity for streptavidin enables the biotinylated antigen/antibody complexes to bind very tightly to streptavidin with very high specificity and low non-specific binding [4]. The biotinylated antibody (e.g. TRAb) or biotinylated antigen (e.g. TSH, fT4) is then captured onto a streptavidin-coated solid phase (coated tube or microparticles). The resultant interaction generates a signal that is quantified and translated into the analyte concentration depending on the assay format. In a competitive assay, a low signal represents a low analyte concentration but the low signal indicates a high analyte concentration in a sandwich (non-competitive) assay protocol.

Biotin has recently come to the fore as a new immunoassay interferent [5]. A peculiar interference in streptavidin-biotin systems due to biotin was first reported in 1996 on the Boehringer ES 700 immunoassay system [6]. The ES system which employed streptavidin coated tubes and biotinylated antibodies generated discrepant cord blood TSH and fT4 results in a baby given biotin. Boehringer's immunoassay system was subsequently acquired by Roche. In the Roche system TSH is a non-competitive immunoassay while fT4, fT3, and TRAb employ a competitive format. It is the resultant combination of false TFT (low TSH, high fT4, high fT3, high TRAb) [7]. That may mislead the unsuspecting to conclude that they are dealing with a hyperthyroid patient.

In adults, the recommended daily dose of biotin is 30ug [8]. Megadoses of biotin (10-15g/day) are also administered to patients with inborn error of metabolism such as Biotin-Thiamine-Responsive Basal Ganglia Disease (BTBGD) or biotin cycle defects (biotinidase deficiency and multiple carboxylase deficiency) [9]. These high doses of biotin spuriously affect TFT results [7]. The biotin effect on TFT began after patients with Multiple Sclerosis (MS) reported improvement with high doses of biotin [10]. This encouraging effect prompted a neurologist to prescribe 300mg of biotin to a 63-year old woman with multiple sclerosis of 15 years standing. She was subsequently referred for assessment of possible hyperthyroidism. She was asymptomatic and clinically euthyroid. Her pre-biotin thyroid tests were normal. Interference was suspected and confirmed with repeat TFT testing on another non-biotin analytical platform [11]. Another patient with MS was misdiagnosed as Graves' disease after high dose biotin treatment [12]. Besides biotin other antibodies and components can interfere with the Roche immunoassay system [13-16]. It is thus important for the ordering doctor to be alert and the laboratory scientist to be aware about their assay methodology [5,7,17].

A recent comprehensive review on this biotin-immunoassay effect is available and well worth consulting [18]. Almost all analytes (hormones, vitamins, tumor markers, viral markers) on streptavidin-biotin immunoassay systems will be affected by high-dose biotin consumption [18,19]. Peak serum biotin levels are attained by 2 hours after biotin ingestion. Should we be concerned that there is a silent epidemic of false hyperthyroid TFTs waiting to descend on those using biotin-immunoassay platforms? Our reaction should be based on clear vision and thinking. The biotin TFT effect is a matter of biotin dose. The Roche package insert warns of biotin interference in patients treated with more than 5 mg biotin per day. Most adult over-the-counter multivitamin supplements contain less than 30-300ug biotin per tablet. Consuming both 30 and 300ug of biotin daily did not cause any immunoassay interference for the Roche system (data not shown). With some difficulty we found a 3 mg preparation (Biotin Forte) in a high-end health food store touted for hair and nail health. One of us took this biotin tablet daily for 1 week. Blood was drawn before starting biotin (Pre-biotin) and 2 hours after taking biotin on Day 7. The TFT results are shown in (Table 1). Minor differences are noted between the pre- and post-biotin TFT results; certainly well within their reference change value.

To simulate a 5 mg biotin intake, serum was spiked with biotin to give a final biotin concentration of 15.6ng/mL [20]. The Roche immunoassays were minimally affected (<5% analytical bias) except for TSH and troponin (10% negative bias) and slightly over 10% positive bias in some other analytes (Tg-Ab, TPO-Ab, TRAb); still less than their assay variation. Higher dose biotin supplements (up to 10 mg) are available for purchase over the internet. When 6 healthy volunteers ingested 10 mg biotin daily for a week [21], the biotin-immunoassay results impacted (5/8 of the competitive assays and 4/15 of the sandwich assays) included TSH, total T3, fT3, total T4, fT4, PTH, prolactin, NTproBNP, 25-hydroxy vitamin D, PSA and ferritin.

Patients with rare inborn errors of metabolism and the few MS patients on biotin therapy are known entities followed-up at specialist centers. Thus laboratories need to notify their neurologists of which immunoassays may be prone to biotin interference. MS is a disease of temperate latitudes such as USA, Europe, Australia and New Zealand. Hence in our usual clinical practice, the issue of biotin induced assay interference is likely to be minor.

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Table 1: Effect of 3 mg biotin daily on Roche Thyroid Test Results.

ANALYTE	Pre-Biotin	Post-Biotin	Difference (Pre-Post Biotin)	Agrees with Predicted Biotin Effect
Sandwich Assay TSH mU/L	1.4	1.2	0.2 (14.3%)	Yes
Competitive Assay				
fT4 pmol/L	15.3	15.6	- 0.3 (2.0%)	Yes
fT3 pmol/L	4.1	3.9	0.2 (4.9%)	No
TRAb mU/L	0.4	0.9	- 0.5 (125%)	Yes

When TFT results are at variance with the clinical circumstance antibody interferences, assay artifact and less common entities (e.g. thyroid hormone resistance, pituitary TSH-secreting adenoma) are considered. A detailed history (including supplements) will shed light on biotin interference. This interference can be confirmed by re-testing samples on biotin-free automated immunoassays, after discontinuing biotin intake or biotin neutralization [21,22]. However, it is the attending doctor that realizes that the TFT result may be spurious. Close communication between the bench and bedside plus heightened awareness of this biotin effect will avert any diagnostic and therapeutic mishap.

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