Awareness of biotin: A growing problem in clinical practice☆

Cuidado con la biotina: un problema creciente en la práctica clínica

Vitamin B_7, H or biotin is a water-soluble B-group vitamin that acts as a cofactor for essential carboxylase enzymes in different metabolic pathways (acetyl-CoA carboxylase, pyruvate carboxylase, propionyl-CoA carboxylase, and methylcrotonyl-CoA carboxylase) of the tricarboxylic acid cycle, gluconeogenesis, and leucine metabolism. Considered an essential nutrient, it is present in small amounts in many plant and animal foods, thereby facilitating its recommended daily intake. Vitamin B_7 is also present in many pharmaceutical products (multivitamins), and has become popular as a beauty supplement for the skin, nail growth, seborrheic dermatitis and alopecia. It is available as an over-the-counter parapharmaceutical product.

There are marketed supplements for the treatment of demyelinating diseases (multiple sclerosis [MS] and adrenomyeloneuropathy)[1–3] since, when administered at high doses (300 mg/day), biotin plays an essential role in the direct stimulation of soluble guanylate cyclase, as well as of the antiinflammatory and neuroprotective effect of cyclic guanosine monophosphate (cGMP) upon the cerebral microvasculature.[1,4,5] Thus, biotin therapy is a promising treatment for MS,[1,4,5] the high prevalence of which (33 cases per 100,000 inhabitants)[1] is of growing concern. This use of biotin has resulted in a rise in the number of cases of laboratory interference,[2,3] as pointed out by the United States Food and Drug Administration (Safety communication of November 2017), affecting different laboratory tests such as troponin T testing (a reduction to below percentile 99), with the associated risk of potentially erroneous diagnoses.[1,6]

In addition to its biological function, biotin possesses special physicochemical characteristics, such as its capacity to recognize and specifically bind to streptavidin, which has led to its incorporation into the design of immunoassays.[7–9] The intake of high doses of biotin may interfere with the results of immunoassays that include the biotin-streptavidin system among its components.[1] Interference may be either positive or negative, depending on the assay design. Thus, non-competitive or sandwich immunoassays (such as those used for determining TSH) are usually affected, yielding falsely lowered results, while in competitive immunoassays (the measurement of FT4, FT3 and TSHR-Ab) excess biotin competes with the biotinylated analog for the streptavidin binding sites, yielding falsely elevated results.[1,7]

Although biotin interference with the results of some immunoassays was known about, its incidence was very low, since treatments involving high doses of biotin were limited to patients with congenital metabolic defects (biotinidase or carboxylase deficiency[4,5]).

We present an illustrative case of a misdiagnosis of hyperthyroidism in a patient with MS receiving supplemental multivitamin treatment with high-dose biotin.

A 57-year-old woman presented with a history of relapsing-remitting MS and primary autoimmune hypothyroidism subjected to replacement therapy and endocrinological follow-up, with adequate control (normal TSH). The most recent controls showed contradictory values consistent with secondary hyperthyroidism: TSH 3.70 μU/ml (0.30–5.0), FT4 2.07 ng/dl (0.93–1.78) and anti-TPO antibodies 44.5 IU/ml (0–34), in the absence of clinical signs of hyperthyroidism and with normal physical examination findings. Further thyroid testing was thus decided upon, with the following results: TSH 1.50 μU/ml and FT4 2.10 ng/dl, with TSHR-Ab < 1 U/l.

In view of the clinical-biochemical discordance, the patient was questioned again, and she confirmed that she was receiving treatment with biotin megadoses of 300 mg/day (10,000 times the recommended daily dose) because of the potential neuroprotective effects of biotin, which exerted a stabilizing effect upon MS progression that improved the patient symptoms and quality of life.[1,4,5]

The above situation corresponded to the TSH and FT4 results obtained with reagents from Roche Diagnostics® on the E170 modular analytical platform (electrochemoluminescence) with streptavidin and biotinylated / ruthenylated antibodies. For this reason we decided to repeat the thyroid study with an alternative immunoassay (chemiluminescent immunoassay with paramagnetic particles) from Abbott Diagnostics® (Architect i4000SR), which uses acridinium ester as a reaction marker. The results obtained, FT4 1.4 ng/dl (0.8–2.0) and TSH 2.8 μU/ml (0.5–4.0), ruled out hyperthyroidism, and confirmed the existence of laboratory interference.

Analytical discordance between a prior diagnosis of Hashimoto thyroiditis and biochemical hyperthyroidism has been seen in recent studies, pointing to biotin as a triggering factor. It is important to assess the possibility of interference with biotin, particularly when the results show no clinical correlation. In the context of possible interference, the laboratory test results should be obtained or verified using techniques that are not affected by the presence of biotin. Although such situations are considered to be exceptional, the number of reported cases is increasing, and clinicians must be made aware of the existence of frequent and relevant interference due to biotin use through dietary supplements, as well as of the need to contrast the results against the clinical data before starting unnecessary interventions or treatments.

The recommended daily dose of biotin in adults is 30 μg/day, and supplementing is advised in deficiency states and during pregnancy. However, people receiving supplemental biotin therapy have a much higher intake (≥ 40 mg/day). Biotin, even in large doses, causes no toxicity. It is necessary to define the waiting time required before performing sampling and determination,[1] the recommended minimum period being 8 h for biotin treatments of >5 mg/day.[1] For concentrations of 100–300 mg, recent studies indicate a half-life ranging from 7.8–18.8 h.[3] Therefore, considering the half-life of biotin, 5 half-lives are required to reduce biotin levels to below the analytical tolerance of TSH, FT4, FT3 and antithyroid antibodies (though the

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Table 1 Effect of biotin upon thyroid function tests using different laboratory test platforms.

Platforms	Roche[a] (sandwich)	Roche[a] (competitive)	Beckman Coulter[b]	Beckman Coulter[b]	Vitros[c]	Abbott[d] DiaSorin[e]	Other affected platforms[f]
Tests	TSH	FT4, FT3, anti-TPO, anti-Tg, TSHR-Ab and Tg	Tg	FT4 and FT3	TSH	None	Some assays
Result	False negatives	False positives	False negatives	False positives	False negatives	No interference	Variable

Source: Trambas et al.[1]
Anti-Tg: thyroglobulin antibodies; Anti-TPO: thyroid peroxidase antibodies; Tg: thyroglobulin; TSH: thyroid stimulating hormone; TSHR-Ab: TSH receptor antibodies; FT4: free thyroxine; FT3: free triiodothyronine.
Biotin-streptavidin technology is widely used in multiple platforms susceptible to interference.
[a] Roche: most immunoassays (sandwich and competitive) are affected. Sandwich (negative bias): TSH, LH, FSH, prolactin, SHBG, PTH, ACTH, insulin, C-peptide, pro-BNP, troponin T, total and free PSA, β-hCG, AFP, CEA, CA19.9 and CA15.3. Competitive (positive bias): folic acid, vitamin B_{12}, cortisol, testosterone, estradiol, DHEA-S, FT4, FT3 and Tg. Digoxin and thyroid antibodies (anti-TPO, anti-Tg and anti-TSHR) are extremely susceptible.
[b] Beckman Coulter: TSH not affected.
[c] Vitros (Ortho Clinical Diagnostics): FT4 and FT3 not affected, since streptavidin is not used.
[d] Abbott (Architect): does not use biotin-streptavidin technology.
[e] DiaSorin (Liaison XL): does not use biotin-streptavidin technology.
[f] Other affected platforms: Immunodiagnostic Systems iSYS and Siemens (ADVIA Centaur, Immulite, Dimension Vista LOCI): ultra troponin I, for which Siemens recently issued a warning note about biotin interference (false positive readings).

latter may require longer periods of time).[1] Less sensitive tests require a lower number of half-lives to fall within the tolerance of the test as compared to highly sensitive tests. Recently, the American Thyroid Association has recommended the discontinuation of biotin therapy for at least two days before thyroid function assessment,[10] as a way to prevent a false diagnosis of hyperthyroidism, with a longer period[1] (7 days[4]) being required to reverse TSHR-Ab positivity to normal values. Since biotin elimination is almost exclusively through the kidneys, situations of renal failure result in a significant accumulation of biotin and metabolites.

Although tumor markers are less susceptible, biotin may simulate favorable responses to therapy and mask disease recurrence. Special mention should be made of thyroglobulin, which may be decreased ≥10% in patients with differentiated thyroid cancer[1] (Table 1).

Clinical laboratories should assess the type of analytical platform and adopt adequate measures to assess and respond to this growing threat. There is a need both for additional studies and for analytical innovation in order to prevent the potential consequences of biotin interference.

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