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Hyperthyroidism and nutritional supplements Watch out!

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Biotin is a B vitamin, which acts as a coenzyme in several carboxylation reactions. From a nutritional viewpoint, 30 µg/day are considered sufficient to meet tissue requirements.
Biotin is also an essential component of many *in vitro* immunoassays, due to two characteristics: 1) its ability to establish strong covalent bonds with molecules of different size, including many hormones 2) its high affinity for streptavidine (several orders of magnitude higher than the one between apten and antibody) leading to a bond extremely resilient to dissociation. The interaction biotin-streptavidin is at the base of a multitude of hormonal assays commonly used in many laboratories worldwide.
While physiologic concentrations of biotin do not usually lead to interference with immune assays, higher concentrations may determine both false positive and false negative responses. The use of biotin as a nutritional supplement is gaining momentum, as it has been claimed that it may reinforce the growth of hair and nails, aid in better glycemic control and improve peripheral neuropathies. Nutritional supplements commercially available contain pharmacological amounts of biotin, hovering around 5000-10000 µg. Very recently, it has been stated that daily mega-doses of over 100 000 µg may control symptoms in multiple sclerosis (MS) and other neurological conditions.
A recent report from Harvard, published in *Thyroid*, describes a patient with MS referred for an endocrine consult due to biochemical tests suggestive of Graves' disease (raised FT4 and FT3, suppressed TSH, raised Ab anti TSH receptor). A review of the patient's medication history, prompted by the absence of accompanying clinical features, led to the detection of a very high consume of biotin as a treatment for MS. Since the lab used a *sandwich* method for the TSH and competitive methods for hormones and antibodies (all based on the reaction between biotin and streptavidine) it was possible to recognize the artifact. A brief suspension of therapy with biotin allowed the total normalization of the lab results.
An increasing number of reports in several medical journals has confirmed to what extent such interference may affect clinical practice. In august 2016, for example, Trambas et al have reported in the *New England Journal of Medicine* that in patients with MS, the ingestion of 300 mg of biotin before blood sampling could cause falsely high results for FT4, FT3, testosterone, estradiol, progesterone, DHEAS and vitamin B12, and falsely low results for TSH, PSA, PTH, LH et FSH. Kummer et al have highlighted that biotin is also used in patients with alopecia, onicorexis, dermatitis, diabetes mellitus and depression, and that «mega-tablets» may be easily acquired on line without prescription. The table summarizes the potential extension of the problem. **Many immune assays provide results highly inaccurate if used less than two days after the ingestion of biotin (seven days for thyroid receptor antibodies).**
Over the last few months, several articles have expanded the list of exams prone to interference, while others have proposed ways to deal with this problem. Journals like *Journal of Clinical Endocrinology and Metabolism, Clinical Chemistry, Thyroid, Clinical Chemistry and Laboratory Medicine,* and scientific societies like the *Endocrine Society* and the *College of American Pathologists* alerted their members, in 2016, about the ability of biotin to interfere with some lab methods employed to measure hormones, and suggested potential solutions where feasible. Technical interventions, like pre-absorption of all samples with streptavidine, are currently limited by cost and practical issues. A laboratory in San Paulo, Brazil, warns all patients, before sampling the blood for exams at risk of being affected, of the need to halt biotin supplements during the preceding 48 hours, and adds a note in the report further confirming the risk of interference if this advice has not been heeded. In countries like Italy where lab units tend to be more and more centralized, this approach would prove impractical due the sheer number of tests executed daily. In areas like the Emilia Romagna region of Italy, where almost all the requests for lab tests are computerized, it may perhaps be simpler and more effective to recognize these patients at the time the sample is accepted.

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Assays prone to biotin interference					
Hormones	ACTH AMH Androstenedione Cortisol C-peptide DHEA-sulphate Estradiol Estriol GH FSH/LH HbA1c hCG IGF-1 IGF-BP3 Inhibin A Insulin PAPP-A PIGF Progesterone Prolactin SHBG Testosterone	**Thyroid**	Ab anti-Tg Ab anti-TPO TRAb Calcitonin T3/FT3 T4/FT4 TBG Thyroglobulin TSH	**Oncology**	ACE Alpha-fetoprotein ß-microglobulin BR 27.29 Ca125 Ca15-3 Ca19-9 Ca72-4 Cyfra 21-1 HE4 HER-2/neu Gastrin NSE PAP proGRP PSA S100 sFIT-1 TPS
		Bone metabolism	Ab anti-CCP ßcross-laps Osteocalcin PTH P1NP Pirilinks-D Vitamin D		
		Hepatic fibrosis	Hyaluronic acid PIIINP TIMP-1	**Cardiology**	BNP CK-MB D-dimer Myoglobin NT-proBNP Troponin I/T
		Anemia	Erythropoietin Ferritin Folic acid Vitamin B12		
Infectious diseases	Ab anti-HAV Ab anti-HBc (and IgM) Ab anti-HBe Ab anti-HBs Ab anti-HCV 2 Ab anti-HIV ½ Clostridium Difficilis (toxin) CMV IgG/IgM HBeAg HBsAg Helicobacter Pylori IgG Herpes I/II IgG HIV Ag p24 HIV Ag HIV combo HSV-1/2 IgG Rubella IgG/IgM Syphilis Toxo avidity Toxo IgG/IgM			**Sepsis/ inflammation**	C1-inhibitor C3/C4 IgA/IgE/IgG/IgM IL6/IL8/IL10 LBP PCR Prealbumin Procalcitonin TNF-alpha Transferrin
Drugs	Carbamazepine Cyclosporine Digoxin/digitossin Gentamicin Lignocaine Lithium Micophenolate Phenobarbital Phenytoin Procainamide Sirolimus Tacrolimus Teophylline Tobramycin Vancomycin Valproate			**Toxicology**	6-acetyl-morphine Acetaminophene Amphetamine Barbiturates Benzodiazepine Caffein Cannabinoids (THC) Cocaine (metabolites) Ecstasy Methadone (metabolites) Metaqualon Methotrexate Opioids Phencyclidine Propoxyphene Salicylate Tricyclics

Interacting with the institution charged with organizing lab services across the region and the local IT department, an alert may be issued directly to the clinician requesting the TSH for a patient who assumes high doses of biotin, adding the suggestion to **discontinue the intake two days before the sampling**. Importantly, since biotin interferes with several but not all lab methods, the lab should add to the result of the assay the method used, essential information if the clinician is to correctly interpret the recommendations of the literature.
Ultimately, the only feasible solution is that the clinician be aware of the problem, expand the drug history to cover the possible intake of biotin, and communicate with the lab when the results do not match the clinical scenario.

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