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Biotin blood test

As a library, NLM provides access to scientific literature. Inclusion in an NLM database does not imply endorsement of, or agreement with, the contents by NLM or the National Institutes of Health. Learn more: PMC Disclaimer | PMC Copyright Notice . 2019 Aug 23;11(8):e5470. doi: 10.7759/cureus.5470 A 67-year-old female with a past medical history of multiple endocrine issues presented for follow-up subsequent to abnormal routine blood testing results. These included low thyroid stimulating hormone (TSH), low parathyroid hormone (PTH), and mildly elevated calcium levels. The presence of hypercalcemia and accompanying low PTH raised the concern for malignancy, while the depressed TSH indicated hyperthyroidism. Review of the patient’s medications revealed daily supplementation with 5 mg of vitamin B7 (biotin). The biotin was discontinued after suspecting the supplement was interfering with the patient's lab values. The labs were repeated one month later. The results showed normalized TSH, PTH, and calcium levels. The increasingly wide-spread use of biotin supplementation and the use of biotin as a component in many of the most common clinical assays has led to a trend of lab errors due to biotin interference. While some physicians are aware of the possibility of skewed results, steps need to be taken to prevent misdiagnosis. This includes ensuring that information about this issue is more widely disseminated, accurately accounting for a patient’s supplement use, reconciling proper clinical correlation with lab results, and promptly reporting when biotin is determined to be the cause of otherwise unexplained lab errors. Keywords: biotin-streptavidin immunoassay, biotin, vitamin b7, lab errors, endocrinology Biotin-associated interference is being increasingly recognized as a cause of abnormal lab results. Biotin is widely marketed and used for the promotion of hair, skin, and nail growth. Biotin-streptavidin binding kinetics make it ideal for use in a multitude of molecular tests and immunoassays. Depending on the specific design of the assay, high plasma concentrations of biotin can lead to falsely decreased or increased results of the molecule in question [1]. There have been recent reports published indicating instances of interference with assays for free thyroxine (T4), total T4, free triiodothyronine (T3), total T3, thyroid stimulating hormone (TSH), parathyroid hormone (PTH), testosterone, estradiol, -human chorionic gonadotropin (β-hCG), ferritin, troponin, and various cancer markers [2-4]. While the Food and Drug Administration (FDA) has released a safety statement concerning the possibility of biotin interference, many patients may still be unknowingly consuming high enough levels to cause an interaction with common, but critically important lab tests [5,6]. Despite the relatively recent attention being paid to these interactions, many physicians may still be unaware of the potential for biotin interference resulting in incorrect diagnoses and treatment, unnecessary work-ups, and significant emotional stress to the patient as the result of false positive or negative lab work. A 67-year-old female with a past medical history of syndrome of inappropriate antidiuretic hormone (SIADH) and primary hyperparathyroidism status post partial parathyroidectomy presented for follow-up subsequent to abnormal routine blood testing results. These included low TSH, low PTH, and mildly elevated calcium levels. The presence of hypercalcemia (10.6 mg/dL) and accompanying low PTH (4.3 pg/mL) raised the concern for malignancy, while the depressed TSH (.24 mIU/L) indicated hyperthyroidism. Due to her previous endocrine issues, the patient was sent for further evaluation by endocrinology. Review of the patient’s medications revealed she was taking calcium, fenofibrate, sertraline, vitamin D3, ranitidine, as well as daily supplementation with 5 mg of biotin. Upon this discovery, the biotin was discontinued while the other medications were taken as prescribed. Her labs were repeated one month later, including a 24-hour urine calcium and creatinine level. These results showed a normalized TSH (3.3 mIU/L), PTH (21 pg/mL), and calcium (10.0 mg/dL), as shown in Table 1. PTH: Parathyroid hormone; TSH: Thyroid stimulating hormone. Labs (Reference Range) At Presentation One Month Follow-up PTH (15-65 pg/mL) 4.3 pg/ml 21 pg/ml TSH (.465-4.683 mIU/L) 0.24 mIU/ml 3.30 mIU/ml Calcium (6.8-10.5 mg/dL) 10.6 mg/dL 10 mg/dL Calcium 24-hour urine (42-353 mg/24 hours) N/A 250 mg/24 hours Ionized Calcium (4.57-5.43 mg/dL) N/A 5.25 mg/dL Biotin is a water-soluble B vitamin naturally occurring in many foods, especially dairy products. It is required for various carboxylation reactions, acting as a co-enzyme in gluconeogenesis, lipogenesis, and fatty-acid synthesis [7]. It is widely marketed for its promotional effects on hair, skin, and nail growth, and is commonly sold as part of a multivitamin pill, or as a stand-alone supplement. The current recommended dose of biotin for adults is 30 ug/day according to the Office of Dietary Supplements at the National Institute of Health, and the Food and Nutrition Board at the National Academy of Sciences, Engineering, and Medicine [7,8]. However, as seen with this patient, it is commonly found in supplements at levels from 5 mg up to 20 mg; a several hundred-fold increase [4-5]. While the amount of biotin naturally received through dietary means is not enough to interfere with clinical tests, the levels found in these supplements can generate significant errors. A wide variety of laboratory tests rely on biotin as a component of the assay. These include endocrine and autoimmune tests, as well as those for malignancy and heart damage markers. In 2017, Holmes et al. reviewed the manufacturer's instructions for 374 methods performed by eight of the most popular immunoassay analyzers in the United States and found that 59% relied on biotin-based methods [4]. Biotin itself was initially discovered in 1927, but its role as a vitamin was not firmly established till several decades later [9]. Streptavidin is a glycoprotein whose name is derived from the bacteria in which it is found, Streptomyces avidinii, and the protein avidin, which is found in egg-whites. Streptavidin and avidin share an extremely powerful and specific ligand binding affinity for biotin [10]. Biotin is small and thus able to bind to a wide variety of molecules without altering their chemical properties. This property of biotin, along with streptavidin’s powerful and specific binding capabilities, makes it an excellent target for capture in laboratory assays [11]. Biotin mainly interferes with two types of clinical assays. The first is called a sandwich assay. Although the design of these assays as used by some companies makes them relatively immune to biotin interference, many are still susceptible. The sandwich assay is commonly used to determine levels of TSH, β-hCG, PTH, insulin, ferritin, pro b-type natriuretic peptide, prostate-specific antigen, and others [11]. These assays work by using two antibodies, both of which bind to the substance of interest, or in clinical chemistry terms, the analyte. The Fc region of one antibody is attached to the assay plate, while biotin is attached to the Fc portion of the other antibody in a process called biotinylation. Beads coated with streptavidin then bind the biotinylated antibodies, which can be used to create a fluorescent signal for detection [11]. When biotin is present in high concentrations from a sample obtained from a patient, it can saturate enough streptavidin on these beads to significantly limit their ability to bind the biotinylated antibodies. In this manner, high plasma levels of biotin in blood samples can lead to falsely lower analyte levels in assays that use a sandwich mechanism [4,11]. The mechanism of biotin interference in this type of assay can be seen in Figure 1. The other type of assay in which biotin interference can play a significant role is called a competitive assay. This type of assay is typically used to measure levels of small steroids and other molecules, including free T4, total T4, free T3, total T3, cortisol, and 25-hydroxyvitamin D (calcifediol) [11]. In a competitive assay, biotinylated antibodies bind the analyte. The biotinylated antibody then binds streptavidin on the surface of the plate. However, the analyte must compete with another molecule in the assay which is structurally similar to the analyte, but contains a label that can be detected [11]. If the analyte is present in high concentration, fewer antibodies will be bound to the labeled competitor, resulting in a weaker signal. Conversely, if the analyte is present in low concentrations, the antibodies will bind more labeled competitors, and the signal will be stronger. Therefore, if biotin is highly concentrated in the patient sample, it will bind more streptavidin on plate, leading to less binding of antibody (regardless of attachment to analyte or labeled competitor), a weaker signal, and falsely elevated results [4,11]. The mechanism of biotin interference in this type of assay can be seen in Figure 2. Concurrent to its increased popularity as a supplement, biotin is also increasingly being used as an alternative treatment for certain diseases. When administered at doses of 300 mg/day, one clinical trial showed clinical improvement in 13 out of 103 patients with multiple sclerosis, versus none in the placebo control arm [12]. More modest levels of biotin supplementation have been shown to significantly reduce fasting glucose levels in patients with type 2 diabetes mellitus, as well as triglyceride levels in those with and without type 2 diabetes mellitus [13-15]. However, some of the results from these data are conflicting. Biotin also plays an important role in the treatment of several inherited metabolic disorders. In fact, one of the earlier reports warning about biotin interference in lab tests came from a 2016 report by Kummer et al. [3]. In this report, the authors describe the development of lab results indistinguishable from Graves' disease (i.e., excessively elevated free T3 and T4, low thyrotropin, and elevated levels of anti-thyrotropin receptor antibodies) in six children receiving high dose biotin in the setting of inherited metabolic disorders. Due to biotin’s under-recognition as a potential confounder of lab tests, three of these children received methimazole for treatment of their apparent hyperthyroidism (two of them for over a year) before the culprit was found [3]. This report highlights the difficulties in distinguishing abnormal lab results from biotin-induced errors, and the very high level of clinical suspicion needed in order to avoid potentially harmful intervention. Many patients may be unaware of the presence of biotin in their multivitamins or prenatal vitamins, and as a result, it may go unreported to their primary care providers [1]. It is important to note that high levels of biotin supplementation strictly interfere with in vitro lab tests. At the supplement levels being discussed, it would not generally cause toxicity and would not lead to disruption of endocrine, metabolic, or other pathways. In other words, the patient’s abnormal blood results would not be reflected in the patient, who is likely to be asymptomatic. It is therefore important to maintain a high index of suspicion and ask about biotin supplementation levels when an otherwise asymptomatic patient presents with abnormal results. When clinical suspicion of biotin interference is high, it has been suggested that a patient waits at least several days before repeating the abnormal tests [1,5,11]. Given the relatively recent attention being paid to these interactions, many physicians may still be unaware of the potential for biotin interference, resulting in incorrect diagnoses and treatment, unnecessary work-ups, and significant emotional stress, as seen with this patient. The 2017 safety report released by the FDA has alerted the public and health care workers about the possibility of biotin interference, but many patients may still be unknowingly consuming high enough levels to cause an interaction with common, but critically important lab tests [5-6]. The FDA currently recommends that health care providers consider biotin interference as a possible source of error if a lab test result does not match a patient’s clinical presentation, and that if it is determined that biotin is the cause of the error, that this be reported to the lab test manufacturer, as well as the FDA through MedWatch, the FDA Safety Information and Adverse Event Reporting program [6]. Biotin supplementation remains an under-recognized cause of abnormal lab results. It has been shown to skew a wide variety of laboratory tests including troponin, thyroid, parathyroid, and electrolyte assays, as well as many others. These lab errors can cause emotional strain on the patient, lead to costly and unnecessary work-ups, and potentially harmful and unnecessary interventions. A high degree of suspicion is required on the part of the clinician in order to catch and correctly attribute these lab errors to biotin over-supplementation. This requires not only that healthcare providers be knowledgeable about this interaction, but also that they can account for all of the ingredients in reported supplements. When biotin interference is identified as the source of error, this information should be reported to the lab test manufacturer and the FDA. 1.Biotin interference in diagnostic tests. Chun KY. Clin Chem. 2017;63:619–620. doi: 10.1373/clinchem.2016.267286. 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InChI=1S/C10H16N2O3S/c13-8(14)4-2-1-3-7-9-6(5-16-7)11-10(15)12-9/h6-7,9H,1-5H2,(H,13,14)(H2,11,12,15)/t6-,7-,9-/m0/s1InChIKeyInChIKey=YBJHBAHKTGYVGT-ZKWXMUAHSA-NSMILESC(CCCC(O)=O)[C@H]1[C@@]2([C@@](NC(=O)N2)(CS1)[H])[H]Canonical SMILESO=C1NC2CSC(CCCCC(=O)O)C2N1Other Names for this Substance1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, (3aS,4S,6aR)-Biotin1H-Thieno[3,4-d]imidazole-4-pentanoic acid, hexahydro-2-oxo-, [3aS-(3aα,4β,6aα)]-(3aS,4S,6aR)-Hexahydro-2-oxo-1H-thieno[3,4-d]imidazole-4-pentanoic acidBioepidermDeleted or Replaced CAS Registry Numbers3672-05-7, 15720-24-8, 22879-79-4, 58073-87-3 Dietary supplementation with biotin is increasingly recognized as a patient safety risk, as it might lead to incorrect results for various common laboratory tests. Biotin (also known as vitamin H, vitamin B7, and coenzyme R) is a water-soluble vitamin that acts as an enzyme cofactor in fatty acid biosynthesis, the citric acid cycle, and metabolism of odd-numbered fatty acids and branched-chain amino acids. It has additional roles in gluconeogenesis and gene expression. In the diet, biotin is bound to proteins found in organ meats, such as liver, kidney, and pancreas, as well as in eggs, yeast, and milk. Cereal grains, fruits, most vegetables, and muscle meat are poor sources of biotin. In Western populations, dietary biotin intake is estimated to be 35 to 70 µg daily, a level in line with the recommended dietary allowance. Most multivitamin pills contain about 30 µg of biotin. High-dose supplementation (doses greater than 1 mg/d) plays a role in therapy for several diseases, including biotinidase deficiency, mitochondrial metabolic disorders, and multiple sclerosis.1 Doses up to 10 mg a day are frequently encountered in nutritional supplements taken to improve hair, skin, and nail health. The problem is that many common blood tests employ a biotin-streptavidin reaction as part of the test procedure. While the amount of usual dietary biotin intake is not expected to be high enough to affect these tests, biotin supplementation at doses greater than 1 mg per day can cause either falsely low or falsely high test results, depending on the analyte and platform used for testing. Biotin interference is particularly dangerous for patients in emergency situations who do not know they are taking high doses of biotin or when the treating physician does not know the patient is taking high doses. A literature search revealed an increasing number of published cases, most describing the problem of biotin interference in thyroid function tests.2 High-dose biotin can produce a dangerous combination of positive and negative interference among the thyroid tests (free thyroxine, free triiodothyronine, thyroid-stimulating hormone, and thyroid-stimulating hormone receptor antibodies) and paint a picture of Graves disease in patients who have either no clinical symptoms or unrelated symptoms. Without good clinical observations, this could lead to unnecessary procedures and treatments. Interference of high-dose biotin with thyroid tests is particularly troubling for patients with multiple sclerosis, as large doses of this vitamin are emerging as a new treatment.3 Interference with parathyroid hormone, follicle-stimulating hormone, luteinizing hormone, sex-hormone binding globulin, estradiol, progesterone, testosterone, cortisol, folate, vitamin B12, and ferritin testing has also been reported.2 The list of affected immunoassays varies for each analytic platform, and for a given test the manufacturer-supplied product information must be consulted to determine if biotin is an interferent. For some platforms, the list is extensive and includes the aforementioned tests, as well as those for cardiac function, β–human chorionic gonadotropin, and cancer biomarkers.4 In many of these immunoassays, biotin was an established interferent, but at doses thought to be rarely encountered in the general population. While manufacturers are aware of the increasing use of high-dose biotin and its potential effects on patient care, they have not, to date, suggested any concrete solutions beyond having patients abstain from this vitamin. Solutions proposed by local clinical laboratories include diluting the specimen with a validated assay diluent, running specimens on a different platform known to be unaffected by biotin, and using streptavidin-agarose beads to remove the biotin before the sample is run on the affected analyzer.5 All of these solutions will increase the costs associated with testing and highlight the potential financial implications of high-dose biotin on the health care system. Interference of high-dose biotin on immunoassays in the clinical laboratory is an emerging issue. Many questions have not been addressed. What is the prevalence of high-dose biotin in a given patient population? What are the pharmacokinetics of high-dose biotin? How effective is the use of streptavidin-agarose beads to remove biotin interference? For many laboratories, the current solution is basic: It is recommended that patients abstain from taking biotin for at least 48 hours before specimen collection. The most effective approach, however, is an extensive communication campaign to educate physicians and patients. 1.Tourbah A, Lebrun-Frenay C, Edan G, Clanet M, Papeix C, Vukusic S, et al. MD1003 (high-dose biotin) for the treatment of progressive multiple sclerosis: a randomised, double-blind, placebo-controlled study. Mult Scler. 2016;22(13):1719–31. doi: 10.1177/1352458516667568. Epub 2016 Sep 1. [DOI] [PMC free article] [PubMed] [Google Scholar] 2.Elston MS, Sehgal S, Du Toit S, Yarndley T, Conaglen JV. Factitious Graves’ disease due to biotin immunoassay interference—a case and review of the literature. J Clin Endocrinol Metab. 2016;101(9):3251–5. doi: 10.1210/jc.2016-1971. 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