REVIEW

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An Overview of Biotin Interference Impact on Immunoassays

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Abstract

The interference of high concentrations of biotin in patients' serum with certain immunoassays can lead to inaccurately high or low test results, which may confuse physicians and contribute to misdiagnosis and inappropriate treatment. Laboratory investigations play a crucial role in clinical decision-making by enabling physicians to manage patient outcomes effectively. Therefore, ensuring the reliability of laboratory results is of utmost importance. This paper focuses on thyroid function tests (TFTs) and the cardiac troponin test as examples of biotin interference in analytes. TFTs are essential for the routine assessment of TFT, while troponin serves as a key biomarker for heart injuries, including myocardial infarction (MI). Accurate interpretation of troponin results is critical for MI treatment strategies. Further research is needed to evaluate biotin interference in detail for other diagnostic tests. This review outlines the mechanisms by which biotin interferes with biochemical assays, highlights its impact on laboratory test accuracy, and proposes potential solutions. In conclusion, implementing precautionary measures is essential to minimize the influence of biotin interference on biochemical analytes. Different immunoassay methods, whether streptavidin-based or non-streptavidin-based, should be assessed for their susceptibility to biotin interference. Additionally, raising awareness among medical professionals and patients about this issue would aid in the early detection and management of biotin-related assay inaccuracies.

Keywords: Biotin, analytes, interference, immunoassay

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INTRODUCTION

Automated immunoassays are analytical procedures in which the quantification of an analyte relies on signal responses generated by the interaction between an antibody and an antigen.[1] These assays are widely used in routine laboratory diagnostics for hormonal profiling due to their high sensitivity, precision, and specificity.[2] However, regardless of the manufacturer, most immunoassays may be affected by interfering substances. The extent of interference varies depending on the specific type of interferent involved. Common sources of interference include icterus, hemolysis, lipemia, and biotin.[3] With exogenous biotin being a particularly significant concern. Biotin interference has been recognized as a critical issue by the United State of America (USA) Food and Drug Administration (FDA), highlighting the need for clinicians to consider the potential impact of interfering substances on laboratory test results.[3] In November 2017, the FDA issued a warning statement regarding the increasing number of clinically misleading results, raising concerns about biotin's potential influence on laboratory assays.[4] Biotin, also known as vitamin B7 or vitamin H, is a water-soluble vitamin that plays an essential role in several metabolic pathways, including carbohydrate, lipid, and protein metabolism.[5] Naturally, biotin has a molecular weight of 240 Da and is present in a wide range of foods, such as eggs, beef, fish, liver, pork, whole grains, soybeans, and green leafy vegetables. It is also available as a nutritional supplement and is used in certain medications for conditions such as diabetes, lipid disorders, biotinidase deficiency, peripheral neuropathy, and carboxylase deficiencies.[6,7] Additionally, biotin is commonly taken for cosmetic purposes, particularly to promote hair and nail growth. The recommended average daily intake of biotin is approximately 0.03 mg, a level that does not typically interfere with immunoassays, with blood concentrations ranging between 0.1 and 0.8 ng/mL.[7] However, due to its low molecular weight and strong affinity for streptavidin, biotin forms a stable bond with streptavidin in immunoassay analyzers. This binding mechanism allows for the detection of very small quantities of analytes in biological samples.[8] Biotin interference can lead to unexplained high or low test results, causing confusion among clinicians and laboratory professionals.[9] Consequently, biotin interference is emerging as a significant issue that, if left unaddressed, may result in serious clinical consequences, including potential misdiagnosis.[10] Interference typically occurs when serum biotin concentrations exceed 10 ng/mL, which is more than ten times the established upper limit of normal blood levels.[11] In this context, we have outlined the mechanisms by which biotin interferes with immunoassays, demonstrated its impact on biochemical tests, and proposed potential solutions to mitigate its effects.

Principle of Biotin Streptavidin Binding in Immunoassay Analyzers

Chemiluminescence immunoassay analyzers, such as the Roche Elecsys, Ortho Clinical Diagnostics VITROS, Beckman Coulter Access/DXI, and Siemens Centaur/IMMULITE/Dimension, are widely used for biochemical tests, including hormone assays, tumor markers, and therapeutic drug monitoring.[12,13] In addition to the traditional antibody-antigen system, immunoassays have incorporated other high-affinity interactions, such as the biotin-streptavidin (BAS) system, into immobilization design strategies to enhance specificity.[14] The principles of streptavidin-biotin-based immunoassays are extensively discussed in the literature. Avidins are a family of biotin-binding proteins found in both eukaryotic and prokaryotic organisms.[15] Avidin was first isolated from chicken egg whites and was named "avidin" due to its strong affinity for biotin, deriving from the combination of the words "avidity" and "biotin".[16] Streptavidin, on the other hand, was first extracted from *Streptomyces avidinii*, a bacterium known for secreting antibiotics. Both avidin and streptavidin are tetrameric proteins that share structural and functional similarities, each possessing four binding sites for biotin.[16] The additional amino acids, 12 in avidin and 8 in streptavidin, respectively, each play a crucial role in their binding strength. The BAS interaction is considered one of the most specific and stable noncovalent interactions known. Its dissociation constant (**KD**) is approximately 10^3-10^6 times lower than that of typical antigen-antibody complexes, indicating a significantly stronger interaction. For instance, the affinity constant (KD) of BAS is in the range of 10^{14}-10^{15} M^{-1}, whereas that of monoclonal antibodies typically ranges from 10^7 to 10^{11} M^{-1}. This exceptional affinity is particularly beneficial for isolating and amplifying signals, thereby enhancing the sensitivity of immunoassays for detecting extremely low analyte concentrations.[1]

The Mechanism of Biotin Interference in Immunoassay Analyzers

Excess biotin in a sample can interfere with immunoassays by preventing the target substance from binding to streptavidin-coated magnetic beads.[17] Immunoassay analyzers primarily implement two analytical approaches: the competitive assay, used for detecting small molecules, and the non-competitive (sandwich) assay, used for detecting larger molecules. The competitive immunoassay is typically applied to small hormone molecules and antibodies, including vitamin D_3, thyroxine (T4), triiodothyronine (T3), steroid hormones, thyroid-stimulating hormone (TSH) thyrotropin receptor antibody (TRAb), a-thyroid peroxidase antibody (a-TPO), and thyroglobulin antibody (a-Tg).[18] For example, in the case of T4 measurement, an excessive amount of biotin in the sample can saturate the streptavidin-binding sites, preventing streptavidin from capturing the biotinylated analyte. This leads to reduced T4-antibody complex formation on the solid phase, resulting in a falsely elevated free T4 level, a phenomenon known as pseudo-hyperthyroidism.[19] The non-competitive (sandwich) immunoassay is used for detecting larger molecules such as follicle-stimulating hormone (FSH), luteinizing hormone (LH), TSH, human chorionic gonadotropin (HCG), parathyroid hormone (PTH), Tg, and C-peptide 2.[18] In this assay, a biotinylated antibody binds to streptavidin and the analyte of interest, which is sandwiched between the biotinylated antibody and a signal antibody. The signal antibody is labeled with an enzyme or molecule to enhance signal detection. Under normal conditions, the signal intensity increases in direct proportion to the analyte concentration. However, when an excessive amount of biotin is present in the sample, it competes for streptavidin-binding sites, preventing the proper formation of the antigen-antibody complex and leading to potential assay interference.[19] See Figure 1.

Influence of Biotin Interference on Some Biochemical Tests

The specific biotin dosage that causes interference varies across different immunoassay platforms, as reported in previously published studies. Thresholds for biotin interference differ significantly among manufacturers, ranging from 2.5 to 10,000 ng/mL.[19] Individual immunoassays exhibit varying degrees of sensitivity to biotin interference. For example, one study examined the impact of biotin on biochemical parameters, including free T3, free T4, PTH, TSH, vitamin D, prolactin, LH, FSH, and C-peptide. Participants received different biotin dosages (25-300 mg), and analyte levels were compared before and after biotin elimination. Additionally, the same parameters were measured

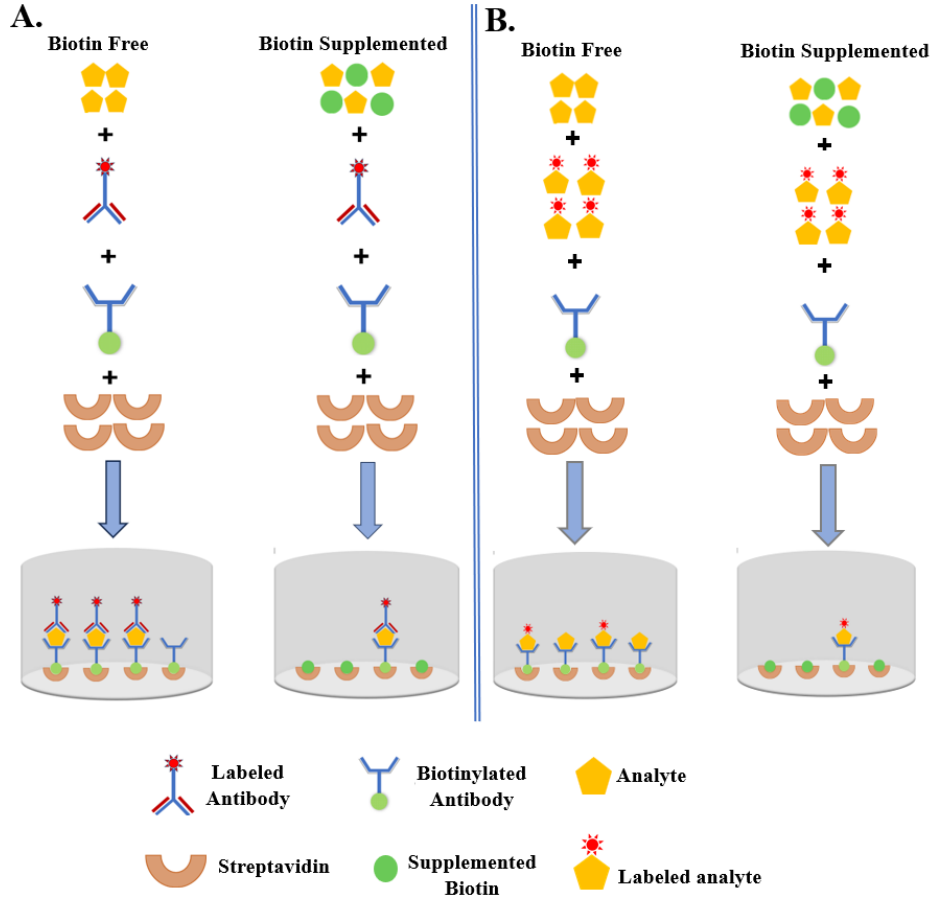

Figure 1. Shows biotin interference mechanism: (A) non-competitive (sandwich) immunoassay; (B) competitive immunoassays.

using an alternative assay without using the BAS technique to confirm the findings. The study revealed that most results were abnormal in participants taking more than 100 mg/day of biotin, with the degree of abnormality proportional to serum biotin concentration. Furthermore, analyte levels that exceeded normal reference ranges returned to normal after biotin elimination, confirming that biotin was the primary cause of the interference.[13] Biotin is primarily excreted through the kidneys; therefore, its concentration in urine may also interfere with certain analytes. For instance, one study reported that in patients undergoing urine HCG testing, biotin supplementation should be considered if repeated testing using an immunoassay device yields invalid results.[20] The following sections will discuss thyroid function tests (TFTs) and cardiac troponin (cTn) assays as examples of biotin interference in clinical analytes. TFTs are essential parameters for assessing TF, while troponin is a key biomarker for cardiac injury, including myocardial infarction (MI). Accurate interpretation of troponin levels is crucial for MI management. Further studies are needed to evaluate biotin interference in other tests, including natriuretic peptides, prostate-specific antigen, alpha-fetoprotein, vitamin B12, and so on.

Biotin Interference in Thyroid Function Test

TFT, including TSH, free T3, and free T4, along with thyroid antibodies, is a frontline parameter in the routine assessment of TF. Several studies have indicated that consuming 10 mg of biotin daily may interfere with the measurement of T4, T3, and TSH, leading to inaccurate results that could result in the misdiagnosis of hyperthyroidism or hypothyroidism.[21,22] For example, when TSH is measured using a sandwich assay technique, an excessive amount of biotin in the sample can cause signal suppression. This occurs because biotin saturation of streptavidin-binding sites reduces the attachment of immune complexes to the solid phase, leading to an artificially decreased TSH level.[23] In contrast, T3 and T4 are measured using competitive binding assays, where both endogenous and labeled analytes compete for antibody-binding sites. Higher biotin concentrations can result in falsely elevated T3 and T4 levels because biotin inhibits the binding of both the labeled analyte and the endogenous analyte to the streptavidin-coated solid phase. During the washing step, unbound antibodies are removed, eliminating any signal representing the endogenous analyte concentration. As a result, the serum concentration of the endogenous analyte becomes inversely proportional to signal intensity, leading to an artificially elevated T3 and T4 measurement.[24] Several experimental studies have evaluated biotin interference with thyroid hormone measurements across different immunoassay platforms. For instance, a study conducted by Odhaib et al.[2] examined the correlation between thyroid test results and biotin dosage using the Snibe Maglumi 800 and Roche Cobas e411 immunoassay systems. The study found that participants who ingested 20 mg or more of biotin showed altered thyroid test results. Some of the TFT findings from this study are presented in Table 1.

Table 1. Shows the results of certain thyroid parameters during and after discontinuing biotin intake (patients took ≤20 mg of biotin as prescribed)

Analyte	Unit	Result with biotin intake	Result after biotin stopped (48 hrs)	Reference range
TSH	µIU/mL	0.05	1.44	0.27-4.2
		0.04	1.11	
		<0.05	6.34	
FT4	ng/dL	2.93	1.08	0.9-1.7
		3.23	2.30	
		5.03	1.42	
FT3	pg/mL	6.09	2.31	1.21-4.18
		/	2.24	
		12.11	2.15	
Anti-TPO	IU/mL	6.33	/	0-34
		3.22	/	
		8.77	/	
TRAb	mIU/mL	4.74	/	<2
		0.68	/	
		9.3	3.32	

/: Not given. TSH: Thyroid-stimulating hormone, FT4: Free thyroxine, FT3: Free triiodothyronine, Anti-TPO: Antithyroid peroxidase, TRAb: Thyrotropin receptor antibody.

Although some parameter values in Table 1 were not provided, the findings clearly demonstrate the interference of biotin with thyroid analytes. This interference was eliminated once biotin intake was discontinued. However, in the case of TPO and TSH TRAb, a longer period of biotin withdrawal may be required before levels return to the normal range.[2] Similarly, a study, conducted by James et al.[25], measured TSH, free T4, and free T3 in a patient taking a high dose of biotin (10,000 µg) as a prescription supplement. The initial thyroid profile results were as follows: TSH=0.03 mIU/L; free T4>8.0 ng/dL; and free T3>30.0 pg/mL. However, after discontinuing biotin for five days, the results normalized to TSH=1.66 µg/dL, free T4=0.86 ng/dL, and free T3=2.9 pg/mL. The normal reference ranges for these parameters are TSH (0.4-4.0 µg/dL), free T4 (0.9-1.7 ng/dL), and free T3 (2.3-4.1 pg/mL). This provides further evidence of biotin interference in immunoassay analyzers and the potential misinterpretation of TFT results. Furthermore, a study by Li et al.[26] evaluated biotin interference using both immunoassay methods: sandwich assays for TSH, and competitive assays for free T4 (FT4), and free T3 (FT3). Various biotin concentrations (31.25-1000 ng/mL) were introduced into serum samples, and analytes were measured using the Roche Cobas 8000 e602 system. The study found that serum biotin concentrations were positively correlated with interference levels in some assays. At a biotin concentration of 250 ng/mL, the TSH level (1.65 µIU/mL) was reduced by 12.42%, while FT4, and FT3 levels were falsely elevated. Additionally, an artificial increase in TRAb titers has been reported.[27] Another study investigated biotin interference in TFTs using the Beckman UniCel DxI 800 and Roche Cobas e602 analyzers. The study found that biotin interference was present in some, but not all, thyroid parameters. Notably, interference was more pronounced in the Beckman UniCel DxI 800 system, compared to the Roche Cobas e602. For example, FT3, FT4, and total T3 levels were significantly higher in the Beckman DxI 800 system, whereas anti-TSHR, anti-TPO, and anti-Tg levels were more affected in the Roche Cobas e602 system. However, total T4 levels remained unaffected at biotin doses of up to 5 mg in the Roche Cobas e602 analyzer.[28] These findings underscore the importance of considering biotin-induced interference when monitoring TF, particularly in asymptomatic patients.

Interference of Biotin in Cardiac Troponin

cTn I (cTnI) and cTn T (cTnT) are widely recognized as the gold-standard biomarkers for diagnosing acute MI (AMI).[29] Troponin is among the clinical laboratory tests most susceptible to biotin interference[30], which can lead to falsely elevated or decreased results. For instance, sandwich immunoassays are commonly used to detect cTns, utilizing two antibodies: a biotinylated capture antibody and a detection antibody coupled to a target molecule to form cTn-antibody complexes. These complexes bind to immobilized streptavidin. In cTn assays based on this method, excess biotin can saturate streptavidin, preventing the binding of cTn-antibody complexes and leading to a falsely decreased cTn concentration. This interference can result in missed AMI diagnoses due to falsely reduced troponin levels.[31] Previous studies have reported falsely decreased troponin levels in patients taking high-dose biotin supplements. For example, one study observed that at a biotin concentration of 250 ng/mL, the measured high-sensitivity cTn T (hs-cTnT) level of 54.14 ng/L decreased by 13.77 ng/L.[25] However, evaluations of the fifth-generation troponin T assay indicated no interference at biotin concentrations up to 20 µg/L.[32] A study assessing biotin interference (>20.0 ng/mL) in the TnT Gen 5 assay (known as "Elecsys Troponin T-high sensitivity" outside the USA) concluded that the likelihood of false-negative AMI diagnoses due to biotin interference was very low.[33] Similarly, a cohort study by Mumma et al.[34] demonstrated that no biotin interference was detected at concentrations below 20.0 ng/mL in the Elecsys Troponin T-Gen 5 assay. Additionally,Nguyen et al.[35] investigated the risk of biotin interference in samples tested for hs-cTnT. Biotin concentrations in patient samples ranged from 0.02 ng/mL to 11.38 ng/mL. The study concluded that the risk of biotin interference in hs-cTnT results was minimal due to the low circulating biotin levels (<20 ng/mL). Furthermore, a study by Vroemen et al.[36] assessed biotin interference in hs-cTnT immunoassays in an acute cardiac unit using Roche Diagnostics analyzers. After removing biotin with streptavidin-coated magnetic microparticles, no significant difference was observed in the measured hs-cTnT levels when comparing values before and

after biotin removal [11.8 (5.6-24.2) ng/L vs. 11.8 (5.6-24.1) ng/L]. These findings suggest that the impact of biotin interference on troponin assays is assay-dependent. Therefore, clinicians should consider assay-specific variations when interpreting troponin results in patients taking biotin supplements.

Some Techniques to Mitigate Biotin Interference

The sensitivity of an assay to biotin interference largely depends on the assay design, particularly when using the BAS system. Immunoassays that apply preformed principles are less susceptible to biotin interference, typically exhibiting a bias of less than 10%, which is considered acceptable.[37] In preformed assays, streptavidin-coated beads are pre-conjugated with a biotinylated antibody during the manufacturing process, forming a stable complex before the patient sample is introduced into the assay. Due to the strong BAS interaction, the biotinylated bond is not easily broken, ensuring that excess serum biotin does not interfere with the binding of the capture antibody or antigen to its target analyte. Siemens platforms rely on preformed assays in their immunoassay machines.[38] In contrast, immunoassay platforms that depend on non-preformed assay designs are more susceptible to biotin interference. This is because the formation of the biotinylated antibody complex occurs after the addition of the patient sample, exposing the antibody complex to excess biotin present in the sample. Elevated serum biotin levels can competitively bind to the streptavidin-coated beads, potentially inhibiting the binding of the biotinylated capture antibody or antigen to its target analyte, leading to false results.[39] Some researchers propose substituting the BAS complex with other immune complexes. For example, the fluorescein isothiocyanate (FITC)-anti-FITC technique utilizes the interaction between an FITC label and an anti-FITC antibody for immobilization and analyte detection. Although this approach is similar to the BAS complex, FITC exhibits a lower affinity and reduced nonspecific binding compared to BAS interactions.[1] With growing awareness of biotin interference, immunoassay manufacturers are working to eliminate this issue in their platforms. For instance, Roche has introduced a high-sensitivity troponin T/TSH test kit designed to resist biotin interference at concentrations up to 1.2×10^6 pg/mL, which may improve immunoassay reliability.[40] Due to variations in signal detection methodologies, different analytical platforms exhibit varying degrees of sensitivity to biotin interference. The Abbott Architect system, which does not rely on the BAS capture principle for analyte detection, is a suitable option for patient testing regardless of biotin withdrawal. In contrast, the Roche Cobas e602 system is advised after the biotin supplementation discontinuation at doses of 5-10 mg/day for a minimum of 24 hours, while the Beckman UniCel DxI 800 platform requires a cessation period of at least 48 hours to minimize potential interference.[28] Acridinium ester immunoassays that utilize the BAS design are unaffected by biotin up to 1200 ng/mL and have been reassessed for risk of biotin interference up to a level of 3500 ng/mL.[41] Serial dilution, testing on a different platform, or stopping biotin supplementation (Roche Diagnostics, which recommends discontinuing biotin for at least 8 hours) is a possible option to avoid interference. Patients with renal impairment may require more than 48 hours for biotin clearance, as biotin is primarily excreted through the kidneys, and retesting after clearance is recommended.[42] Direct biotin measurement is also recommended for confirmation when assessing interference.[7] However, these methods have limitations, including time consumption, potential dilution errors, and the need for reference laboratory testing. To date, there is no conclusive approach to completely eliminate biotin interference; therefore, laboratories may apply one of the aforementioned techniques to confirm suspected biotin interference.

CONCLUSION

Biotin interference in certain immunoassays can lead to inaccurate results, potentially causing misdiagnosis and inappropriate therapy. Therefore, precautionary measures are essential to minimize the impact of biotin on biological analytes during analysis. To fully understand the extent of biotin interference, several factors must be considered, including biotin concentration, immunoassay principles, analyte type, and the dosage at which interference occurs. These factors highlight the need for a prompt and precise analytical method to assess biotin interference, particularly when immunoassay results do not align with clinical findings. Although there is an urgent need for a rapid analytical procedure to accurately measure biotin interference, the complete replacement of current immunoassay analyzers may take several years. In the meantime, patients are advised to discontinue biotin supplementation before undergoing certain laboratory tests, for at least 48 hours or even longer, depending on the specific test, dosage, and frequency of biotin intake to prevent misinterpretation of results.

MAIN POINTS

- Patients should discontinue the use of biotin supplements 1 to 2 days before laboratory tests for low doses and 3 to 7 days for high doses.
- Laboratories must determine the minimum biotin concentration that could result in clinically significant interference in their assays.
- The patient's medical history and supplement consumption should be thoroughly documented prior to conducting the tests.
- In emergencies or for unconscious patients, it is preferable to use methods with lower biotin interference for troponin testing.
- Clinicians must establish a correlation between clinical findings and laboratory results for patients who are reported to be taking biotin in doses over 5 mg.

Footnotes

Authorship Contributions

Concept: A.M., A.A., Design: N.S.A., A.A., A.O., Data Collection and/or Processing: S.A., O.M., Analysis and/or Interpretation: N.H., Y.H., A.A.B., A.S.A., Literature Search: A.A.Y., E.M., S.A., Writing: A.A.Y., E.M., S.A.

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