Case – Biotin supplements interfering with prostate-specific antigen assays

A cautionary tale

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INTRODUCTION

Prostate-specific antigen (PSA) holds major significance in the detection and monitoring of patients with prostate cancer. In patients with already diagnosed prostate cancer, rapidly increasing PSA levels may signify potential disease progression requiring prompt intervention.

Measurement of PSA levels is usually done through enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay, which require antibodies binding to the PSA-antigen. Many different factors may interfere/affect these assays, which is why calibration and quality control must be done routinely to guarantee accurate and reproducible results. Comparability between different test methods might show differences, especially if there is an underlying factor interfering with the signal.[1]

Biotin is a vitamin (B7) that is often taken as an over-the-counter dietary supplement. Unfortunately, this supplement has a strong affinity for streptavidin, which is used in some immunoassay techniques, and can lead to erroneous results in important lab values, such as PSA.[2] This case report describes a case of biotin interference leading to discordant PSA results between two different manufacturer's instruments, leading to treatment delays.

CASE REPORT

A 78-year-old man with metastatic prostate cancer presented in March 2023 with increasing PSA levels. He was initially diagnosed with prostate cancer in June 2014, for which he underwent radical prostatectomy for a pT3b N0 (0/4 lymph nodes involved) adenocarcinoma, Gleason score 7 (4+3), with extensive perineural invasion and negative margins. His PSA at presentation was 9 µg/L. In August 2015, he developed metastatic disease involving the pelvic and periaortic lymph nodes, ribs, manubrium, and left ischial tuberosity. He was started on abiraterone 1000 mg orally daily with 5 mg prednisone and disease control was achieved from 2015–2020.

In 2020, his PSA increased to 6.0 µg/L and a computed tomography (CT) scan confirmed oligoprogression in the manubrium. He was switched from prednisone to dexamethasone and his manubrium lesion was treated with stereotactic body radiotherapy (SBRT), which resulted in PSA response down to 3.9 µg/L by August 2020 and nadir of 0.049 µg/L in April 2021. His PSA eventually rose again to 1.9 µg/L in December 2022 and 3.9 µg/L in February 2023. A prostate-specific membrane antigen-positron emission tomography (PSMA-PET) scan showed multiple pathologic lymph nodes in the right lower cervical region and level 2/3 right axilla and a lesion in the right scapula. These were treated with radiation in February 2023.

Unfortunately, outpatient bloodwork in June of 2023 using the Abbott PSA assay showed progressively increasing PSA levels of 7.8 µg/L, with further increase to 10.9 µg/L in August. He was restaged with CT and bone scans in July 2023, which found progressive disease in the left ribs, iliac crest, thoracic spine, and left skull. The patient was offered and accepted chemotherapy with docetaxel but wanted to delay treatment start for a few weeks to attend to personal matters. PSA was repeated at the cancer center upon his return on October 4, using the Ortho Vitros PSA assay. This yielded a result of 6.02 µg/L, which was lower than expected based on the trending upwards PSA values observed with the Abbott assay. The patient was not keen to start chemotherapy, and the decision was made to monitor closely for further rapid increases/changes in PSA concentrations. For convenience, the patient opted to use an outpatient laboratory (using the Abbott assay) to monitor PSA levels.

KEY MESSAGES

- Biotin supplements can interfere with PSA immunoassays, leading to unreliable values.
- Caution should be taken about interpreting PSA values on patients taking biotin supplements.

A repeat PSA test was performed with the Abbott PSA assay on October 31 and the level was 20.9 µg/L. To confirm the number, the patient had PSA tested in the hospital laboratory a week later and the Ortho assay reported a value of 9.4 µg/L. This was an unusual finding, as Ortho PSA concentrations are typically higher than Abbott PSA concentrations when tested on the same samples.[3]

To investigate this discrepancy more thoroughly, the hospital laboratory performed interference testing for the Ortho PSA assay first by performing serial dilution and human anti-mouse antibody (HAMA) testing. The HAMA test was negative; however, the serial dilution did not yield linear results, suggesting the presence of an interference. Given that biotin is used in the Ortho Vitros PSA assay design (and not Abbott's), the hospital's laboratory treated the patient's serum with streptavidin magnetic beads to bind biotin prior to retesting on the Ortho Vitros PSA assay, and the result was significantly higher after treatment (16.7 µg/L vs. 9.4 µg/L before treatment).

After a review of the discrepant results (Figure 1) and the interference testing identifying the presence of biotin in the sample, the patient's medications were reviewed again and he disclosed that he was taking biotin 500 mcg daily. The patient agreed to stop taking biotin completely, and after two weeks, the patient's PSA was 20.9 µg/L with the Ortho Vitros PSA assay, congruent with the increasing PSA levels observed with the Abbott PSA assay. The patient was promptly reconsented and started chemotherapy with docetaxel. He has permanently abstained from using biotin in the future and all PSA values will be measured with the hospital's laboratory Ortho Vitros PSA assay to help maintain consistency in future results.

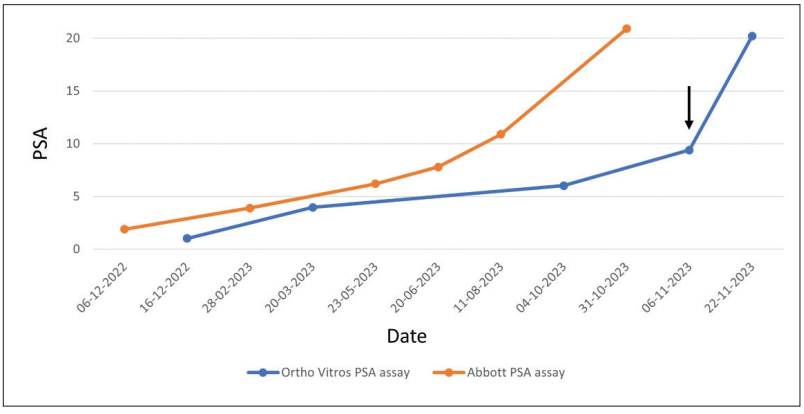

Figure 1. Difference in prostate-specific antigen (PSA) levels obtained using the Ortho Vitros PSA assay and Abbott PSA assay on a patient taking over the counter biotin supplementation. Arrow indicates when the patient stopped taking the biotin supplements.

DISCUSSION

Many diagnostic companies have sandwich immunoassays that use biotin-laden antibodies specific to PSA that attach to a streptavidin coat or bead. When patients take supplementary biotin, the streptavidin in the assay may become saturated with the existing biotin in the serum and will not bind the biotin-laden antibodies that have attached to the PSA molecule, thus resulting in a lower concentration of PSA.[4] The Ortho Vitros PSA assay uses this streptavidin-biotin-based immunoassay design, however, the Abbott PSA assay does not use this mechanism and thus is able to provide more accurate PSA results for patients taking biotin.[5,6]

Once the patient stopped taking the supplement, the values of the hospital's laboratory (Ortho Vitros) and outpatient laboratory (Abbott) PSA assays converged. Although it is unclear the minimal dose required for biotin to interfere with these assays, a dose of 10 mg daily has been shown to cause significant interference in multiple different assays, such as TSH, T4, troponins, and PSA.[7]

In this case, our patient was taking a daily supplement of 500 mcg, which is significantly lower than the documented biotin levels required to cause an interference; however, the amount of biotin ingested is not the only variable to consider when assessing biotin interference, as other factors, such as age, metabolism, and chronicity of the supplements, likely affects the overall levels of biotin in the blood.[8]

The time required to clear the biotin is also unclear but it is estimated that a 600 mcg biotin dose has a 1.8-hour half-life;[6] given that the patient had been using these supplements for years, we estimated that the wait time required to help clear the biotin interference was approximately two weeks, and sufficient for this patient, as evident from the convergence of values between the Ortho Vitros and Abbott PSA assays.

Although relatively rare, there are many causes of biotin deficiency, which include inborn errors of

metabolism, parenteral nutrition without replacement, severe malnutrition, prolonged use of broad-spectrum antibiotics, use of anti-epileptics, and inflammatory bowel disease.[7] Given that our patient does not fit any of these conditions, stopping the supplement is unlikely to affect his overall outcome. The use of vitamins and dietary supplements have increased over the last decade;[9] however, there are challenges to providing products with clear definitions, proof of efficacy, regulation, and appropriate use of these products.[10] Although products with biotin seem harmless, there are definitely unintended consequences from consuming these products when interpreting laboratory tests that use biotin-streptavidin in their assay design.

CONCLUSIONS

This case represents a cautionary tale about an over-the-counter supplement that may seem innocuous but may result in real-life consequences for the patient. In this case, the hospital's laboratory PSA assay was erroneously resulting in lower PSA values, leading to delays in chemotherapy and confusion for the patient. Medication evaluation and reconciliation is routinely done by the medical oncology team and the pharmacy team to help avoid any drug-drug interactions and rarely involves asking about over-the-counter medications or supplements. In this case, however, the use of biotin was not seen as interfering with the treatment at hand and thus was not flagged. More consideration should be taken to interpret PSA results for patients taking biotin supplements and where the PSA assay uses a biotin-streptavidin design.

COMPETING INTERESTS: Dr. Kavsak has participated in advisory boards for laboratory tests related to cardiovascular disease for Quidel, Roche Diagnostics, and Siemens Healthcare Diagnostics; has been a speaker on laboratory tests related to cardiovascular disease for Abbott Diagnostics, Siemens Healthcare Diagnostics, and Thermo Fisher Scientific; has received study grants for laboratory tests related to cardiovascular disease from Abbott Diagnostics, Ortho Clinical Diagnostics, Roche Diagnostics, and Siemens Healthcare Diagnostics; and participated in a clinical trial of female sex specific cutoffs for cardiac troponin (CODE-MI trial) supported by the Canadian Institutes for Health Research. Dr. Hotte has participated in advisory board for AAA-Novartis, Astellas, Bayer, Janssen, and Pfizer; has received grants, grants-in-aid, and honoraria from Astellas, Bayer, BMS, and Janssen; has participated in clinical trials supported by AAA/Novartis, Astellas, BMS, CCTG, Eisai, Merck, Pfizer, SeaGen, and SignalChem (with funds to institution; uncompensated personally); and hold an uncompensated leadership position (Chair, GU Disease Site Group) with the Canadian Cancer Trials Group (CCTG). Dr. Dodbiba does not report any competing personal or financial interests related to this work.

This paper has been peer reviewed.

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