CLINICAL VIGNETTE

Liver Toxicity Due to Nutritional Supplements

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A 34-year old morbidly obese female, originally from South Africa presented with 10 days of diffuse crampy abdominal pain radiating to her right upper quadrant and right shoulder. She also reported nausea, vomiting, non-bloody watery diarrhea, subjective fever with no chills. The patient thought she had "food poisoning" which she managed at home with supportive measures of fluids and bland food for 1 week. Her diarrhea improved in the following days but abdominal pain persisted. She developed pruritus involving her upper body, thighs and hands and was told by her friend that her eyes turned yellow which prompted the medical evaluation.

She denied recent travel or sick contact, eating new or raw food, alcohol use or intravenous drug use or new sexual contacts. She also denied new medications but acknowledged taking multiple supplements given to her by her naturopathic doctor for alternative treatment of cervical dysplasia. She sought the help of a naturopathic doctor to avoid a LEEP procedure for cervical dysplasia. She started taking herbs and vitamin supplements approximately 3 months prior to presentation. The supplements include berberine, slippery elm, Vitamin A 10,000 units, turmeric, and Vitamin D injections.

On examination, her vital signs included: BP 128/89, pulse 86, T 36.7C, RR 16. She was alert and oriented with fluent speech. Her exam was significant for icteric sclerae and moderate tenderness in the right upper quadrant of her abdomen without hepatosplenomegaly. No skin rash or asterixis.

Laboratory results showed: AST 425, ALT 445, Total bilirubin 11, alkaline phosphatase 388, albumin 3.9. PT/INR/APTT 11.2/1.1/32, Hepatitis A Total positive, IgM negative, HBsAb positive, HBsAg negative, HBcAb negative, HCV Ab negative, Hep E Ab negative, HIV negative, CMV PCR negative, EBV PCR negative, Tylenol <10, Urine tox negative, Iron 98, TIBC 448, Ceruloplasmin 33, ANA negative, smooth muscle Ab negative, mitochondrial Ab negative, liver kidney microsome Ab IgG negative, vibrio stool culture negative, Vit A 0.2.

Abdominal ultrasound showed cholelithiasis with no evidence of acute cholecystitis, and mild heterogeneity of liver echotexture. MRCP showed diffuse periductal enhancement and cholelithiasis, without biliary dilatation.

Hospital course and outpatient course:

The patient was evaluated and treated in the Intensive Care Unit. Hepatology consult was obtained and medications and supplements were discontinued including berberine, slippery elm, turmeric, Vitamin A and Vitamin D. HCTZ-Triamterene was also discontinued because jaundice was listed as a potential side effect. Ursodiol was started for pruritis. Supportive measures with hydration continued and liver enzymes and bilirubin improved slightly in the following days prior to discharge. Three months later, the patient's liver enzymes, alkaline phosphatase and bilirubin all returned to normal. She will consult a general surgeon for cholecystectomy as the presence of gallstones may have contributed to this hospitalization. It was concluded that the interactions between the numerous dietary supplements in the presence of pre-existing fatty liver and gallstones contributed to liver failure in this patient.

Discussion

These are challenges in advising patients who take dietary supplements. It is estimated that more than 50% of American adults use at least 1 dietary supplement to maintain or promote their health.[1-4] American consumers spent $26.7 billion on dietary supplements in 2009.[5] The increasing popularity of herbs and dietary supplements is attributed to many factors but started after the passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994. This significantly changed the way in which herbs, vitamins and supplements are marketed and regulated. Under this Act, supplements are not approved by the FDA and manufacturers are not required to demonstrate product safety or effectiveness before marketing and selling products to the general population. The FDA can only ban a product after documenting that the product is harmful.

The rising popularity of supplements can also be attributed to effective marketing emphasizing "natural" method of healing, easy accessibility from the internet or local drugstore, cost effectiveness and expectation to improve or prevent a number of conditions "naturally". Despite their popularity, physicians and patients often have limited knowledge on the supplement's potential risks and benefits. In this case report, several factors contributed to the challenge in properly identifying and advising a patient taking multiple dietary supplements that had potential for individual or cumulative dangerous supplement-drug interaction.

Many patients express strong preference to use "natural" alternatives in place of pharmacological drugs or conventional procedures. Herbs and vitamins are assumed by many patients to be milder and safer than pharmacological drugs because they

are "natural". For some patients, the use of dietary supplements represent an effort to take control of their health. In some cultures, herbs and "traditional" medicine are an important part of daily life, passed down for generations. Some patients turn to supplements after failure from conventional medicine, while others use them as a quick "fix" cure to a problem. This cure can be obtained without a physician visit, lifestyle changes or unpleasant procedures.[6] In this case, the patient underwent colposcopy for cervical dysplasia but required additional LEEP procedure which the patient declined. Instead patient avoided what she perceived as a painful and possibly traumatic procedure and sought help from a naturopathic doctor who prescribed a combination of berberine, slippery elm, Vitamin A, Vitamin D, and probiotics as alternative treatment. Vitamin A is a relatively safe vitamin when taken in safe doses. Most multivitamins contain less than 50,000 IU Vitamin A per capsule and this rarely leads to liver toxicity. However, if taken daily in the amount of 50,000 units or greater, it could lead to hypervitaminoses A. Hypervitaminoses A consists of mild elevation of liver enzymes, cholestatic hepatitis, non-cirrhotic portal hypertension, progressive fibrosis and cirrhosis. However, individual tolerability may vary and pre-existing steatosis, chronic alcohol consumption, concurrent use of other potentially hepatotoxic agents and young age may predispose individuals to develop liver toxicity from otherwise safe herbs and supplements. In addition to Vitamin A, the use of slippery elm, Vitamin D and berberine have each been implicated to cause liver toxicity.[6]

Many patients do not disclose their alternative medicine use to their health care providers. Although more than half of Americans use dietary supplements, a study showed that patients did not disclose their complementary and alternative medicine (CAM) use to their physicians for a variety of reasons. The primary reason given for nondisclosure was their primary physicians simply did not ask. The second most common reason was the belief that their primary physicians did not need to know their use of alternative medicine. Other reasons include physician disinterest, anticipation of a negative response from their physician and assumption that their physicians lacked knowledge regarding alternative medicine.[7] The highest rate of disclosure was seen in patients who had a consistent patient-doctor relationship.

Despite varying patient and physician attitudes towards dietary supplements, studies suggest most physicians have an open attitude toward alternative therapies but have limited ability to discuss alternative medicine issues due to an inadequate knowledge base.[8] Many physicians believe they lack the training to respond to their patients' questions regarding dietary supplements. In a recent survey in which more than 80% of respondents were general practice physicians, 76% said they were "poorly informed" about herbal medicines.[8,9] Physicians need better education about supplement safety, efficacy and regulation and be able to discuss them openly with their patients.

Important steps to assist in promoting open discussion regarding alternative medicines.

1. Inquire about supplement use. Many patients may not volunteer information regarding their supplement use but are often willing to engage in a conversation about it when asked by their physicians. Physicians should encourage disclosure from their patients by asking directly and withholding judgment. It is important for physicians to be open regarding their level of understanding and express willingness to learn about specific vitamins, herbs and other supplements. Physicians need better education about supplement safety, efficacy and regulation and discuss them openly with their patients. By applying these measures, patients can make more informed decisions and possibly enhance or strengthen physician-patient relationship.

2. Discuss dietary supplement regulations. It is important to inform patients that under DSHEA, supplements do not require FDA approval before production or distribution. Dietary supplements are assumed to be safe unless proven otherwise. This is in marked contrast to regulation of drugs which requires extensive safety and efficacy data and FDA approval before making it available to the public.

3. Evaluate safety and efficacy of supplements. Despite increasing demand in the use of dietary supplements, many studies have failed to show evidence supporting their efficacy. When physicians encounter unfamiliar medication, herb or supplement, there are resources available to assist in providing needed information regarding safety and efficacy such as the National Institute of Health Center for Complementary and Alternative Medicine, Natural Medicines Comprehensive Database, Memorial Sloan Kettering Cancer Center Integrative Medicine and the Cochrane Library. The NIH Center of Complementary and Alternative Medicine has a database of 100,000 citations from traditional studies.[1] Other sites that contain meta-analyses can be found at the Cochrane Collaboration and NIH CCAM. APPENDIX A provides reliable informational resources for primary care physicians and other health care providers.

APPENDIX A- Additional Information

U.S. Food and Drug Administration - Information about the regulation of dietary supplements by the FDA can be found at www.fda.gov/Food/DietarySupplements/ default.htm. Adverse effects occurring with the use of dietary supplements should be reported to the FDA's MedWatch program, which collects and monitors this information (1-800-332-1088 or www.fda.gov/Safety/MedWatch).

National Center for Complementary and Alternative Medicine - The NCCAM Clearinghouse provides information on the center and CAM therapies, including free publications and free federal database searches of the scientific and medical literature. The NCCAM (www.nccam.nih.gov) can be reached at vog.hin.maccn@ofni or by telephone at 1-866-464-3615.

National Institutes of Health, Office of Dietary Supplements - The Office of Dietary Supplements (ODS) evaluates scientific information, supports research, shares data, and educates the public about dietary supplements. The resources offered include publications and international bibliographic information from databases about dietary supplements. The office can be reached at www.ods.od.nih.gov or by phone at (301) 435-2920.

The U.S. Pharmacopoeia - The USP is a nongovernmental public standards-setting author-ity for prescription, over-the-counter, and other health care products that are manufactured and sold in the U.S. The U.S. Pharmacopeia–National Formulary (USP–NF) describes quality standards for dietary supplements. The USP also offers a voluntary supplement-testing program as well as a listing of quality-tested supplements. More information is available at www.usp.org.

Herbal Companion to the *AHFS–DI* (American Hospital Formulary Service–Drug Information) - *AHFS–DI* is a publication from the ASHP that includes monographs on uses, indications, dosage ranges, cautions, interactions, regulatory status, and references regarding herbal supplements. This science-based information was collected from more than 3,000 sources and has been reviewed by an advisory board of physicians, scientists, and other medical professionals who are recognized as experts in herbal therapies. More information can be found at www.ashp.org/import/news/ pressreleases/ pressrelease.aspx?id=107.

The Review of Natural Products: Facts and Comparisons - This comprehensive publication includes more than 350 peer-reviewed, evidence-based monographs. This reference provides detailed information about natural products, including their botany, history, chemistry, pharmacology, medicinal uses, toxicology, drug interactions, and patient information. More information can be found at www.factsandcomparisons.com/ review-of-natural-products-bound.aspx.

PDR for Herbal Medicines (Physician's Desk Reference for Herbal Medicines) - This compendium of general and clinical knowledge of herbal medicine, published by Thomson Reuters, provides evidence-based identification, safety, efficacy, and therapeutics information cross-referenced to therapeutic category, indication, side effects, and drug interactions.

Natural Medicine Comprehensive Database - This comprehensive database (www.naturaldatabase.com) includes evidence-based information on herbs, vitamins, minerals, and other dietary supplements regarding their interactions, uses, safety, efficacy, special populations, and ingredients.

American Botanical Council - This nonprofit organization is dedicated to promoting the effective and safe use of medicinal plants and phytomedicines. The council publishes the journal *HerbalGram*, offers literature reviews, and provides access to continuing education materials on dietary supplements, including the *German Commission E Monographs*. These monographs describe more than 300 herbal products that have been evaluated by members of a German regulatory agency, including physicians, pharmacists, scientists, and toxicologists, by using case, clinical, and field studies as well as other scientific literature. More information can be found at www.herbalgram.org.

Natural Standard, The Authority on Integrative Medicine - An international research collaboration, Natural Standard collects and synthesizes data on CAM therapies and dietary supplements. This information is incorporated into fully referenced evidence-based monographs that have undergone a blinded editorial and peer-review process. Natural Standard also publishes reference books, research reports, and monthly newsletters that can be accessed at www.naturalstandard.com.

Journal of Natural Products - This publication focuses on the chemistry and biochemistry of naturally occurring compounds and the biology of the living systems from which they are derived. The journal (http://pubs.acs.org/journal/jnprdf) is co-published monthly by the American Chemical Society and the American Society of Pharmacognosy.

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Submitted April 2, 2017
Last Revised March 20, 2018