

# ADVANCES IN HEPATOLOGY

Current Developments in the Treatment of Hepatitis and Hepatobiliary Disease

Section Editor: Eugene R. Schiff, MD

## Supplement-Induced Liver Injury



Victor J. Navarro, MD  
Professor of Medicine  
Sidney Kimmel Medical College  
Division of Hepatology  
Einstein Healthcare Network  
Philadelphia, Pennsylvania

### G&H How common is supplement-induced liver injury in the United States?

**VN** That is a difficult question to answer because the true number of people who sustain liver injury is not known. Not all people with liver injury go to a doctor, and among those who do go, not all are ill enough to be identified by the doctor. Many times, the doctor might not even ask the proper questions to determine whether a patient has been taking supplements. Therefore, it is unclear how often supplement-induced liver injury actually occurs. What is known is that more than half of US adults use some type of supplement and that the use of supplements is likely on the rise, based upon the number of supplements being sold and the amount of money being spent on them. Doctors have also recently been noting that, in their experiences, more and more patients are presenting with liver disease or injury from supplements. Thus, we can make the assumption that liver injury from supplements is becoming more common.

### G&H Which supplements seem to be associated with liver injury?

**VN** Right now, the supplements most likely to cause liver injury are thought to be those that improve one's physical performance, endurance, and appearance. An example is bodybuilding supplements, which are most commonly used by young men. The other most likely cause of supplement-induced liver injury involves over-the-counter weight-loss supplements. There are currently numerous supplements that fit this category; there is no one particular supplement that is especially injurious.

We are trying to understand whether there is one particular ingredient of these supplements that might be causing injury, but not even that much is known. It is suspected that there might be several injurious ingredients that are more likely to be present in, for example, weight-loss supplements. One such ingredient may be green tea extract, which refers to an extract of the plant, not the green tea that people drink. In very high doses, it is possible that green tea extract may cause liver injury. In addition, it has been suspected that bodybuilding and performance-enhancing supplements may be tainted or may contain anabolic steroids, many of which are illegal and should not be present in those products.

### G&H Are any traditional herbal medicines associated with liver injury?

**VN** There might be. It is challenging to answer this question because liver injury is fairly rare and traditional herbal medicines are often dispensed from herbal practitioners without a label; thus, it is not clear what is actually contained in these products. My colleagues and I are currently in the process of conducting research examining what is included in common herbal products to determine what might be the cause of liver injury, but we do not know yet.

### G&H What are the possible mechanisms behind supplement-induced liver injury?

**VN** Liver injury is probably an idiosyncratic (ie, unpredictable) phenomenon. It might have something to do with the dose that people take; people may be taking too

high of a dose because there is no governmental or research control on what exact dose should be taken. It might be the way that people take these supplements. For example, if people take certain types of supplements when they are fasting, there might be an increased chance of causing injury. It might be that there is a genetic predisposition to liver damage from some supplements. Patients who experience liver injury from appearance- or performance-enhancing supplements tend to be young men who almost always present in the same way (with very severe jaundice and itching) and who all improve several months after discontinuation of the supplement. The pattern is so consistent that there has been some speculation that there might be a genetic predisposition for this type of liver injury. However, if there is, it has not yet been found.

### **G&H** How can liver injury be diagnosed?

**VN** The first step is that providers have to understand that the possibility of liver injury exists, and that is usually because the patient presents with jaundice or has elevated liver injury test results and does not feel well. Whenever a patient presents with suspected liver injury or damage, it is important to obtain a careful history and find out whether he or she has been taking any supplements. Next, providers have to make sure that the patient's symptoms are not caused by anything other than supplements. There are many causes of liver injury, such as viruses, gallstones, and alcohol, so providers have to exclude all of these causes when examining patients. By excluding other causes in a patient with a history of supplement use, providers can make a diagnosis of medication- or supplement-induced liver injury with greater confidence. A liver biopsy is not necessary to make the diagnosis, although it can reveal the severity of the injury.

### **G&H** How should these patients be managed?

**VN** There is no specific treatment for liver injury caused by supplements except to stop the injurious supplement and watch the patient.

It is also important to keep in mind that some forms of supplement-induced injury can look just like treatable causes of liver disease, and vice versa. A good example is autoimmune liver disease, in which the immune system, for reasons that are unclear, causes inflammation in the liver. Another possibility is that medications can trigger the immune system to cause injury in the liver. These patients can be treated with corticosteroids, which can help attenuate the degree of liver disease.

### **G&H** Is it always necessary to completely stop use of the injurious supplement?

**VN** If there is suspicion that a supplement is causing the injury, then use of that supplement should be completely stopped and should not be restarted because it is not exactly known why people develop liver injury. If the injury is actually triggered by an immune reaction, for example, then even a smaller exposure can cause a more severe reaction.

### **G&H** Can injury to the liver usually be reversed?

**VN** Most people do recover; it is very rare that a person who develops severe liver injury does not get better. In particular, liver injury from appearance- and performance-enhancing supplements is almost always, if not always, recoverable. People do not die from this type of liver injury, although there may be a very prolonged period of illness with jaundice, itching (a common symptom of liver injury), and missing work.

However, clinicians should be particularly cautious when managing the subset of patients who have severe jaundice (ie, high bilirubin levels) as well as very elevated liver injury test results, indicating the presence of a large amount of inflammation in the liver. The combination of high bilirubin levels and liver injury test results induced by medications, which may also be true for supplement-induced liver injury, may indicate that the patients are at risk for becoming very sick, even to the point of needing a liver transplant or dying from the liver injury.

### **G&H** How does supplement-induced liver injury compare with medication-induced liver injury?

**VN** Probably the most important difference is that the outcome of supplement-induced liver injury can be more severe than medication-induced liver injury. In our research, my colleagues and I have found that patients who had supplement-induced liver injury were more likely to need liver transplantation than patients who had liver injury from medications.

### **G&H** Are there any regulations surrounding herbal and dietary supplements?

**VN** The regulatory framework for herbal and dietary supplements is the Dietary Supplement Health and Education Act, which was written in 1994 and has undergone several amendments since then. In essence, the law states that a manufacturer does not need to prove that the product it is selling is safe in animals or humans. However, although safety does not have to be proven, the manufacturer must say that the supplement is safe. Also, the manufacturer is restricted in the claims that it can make; it is not allowed to say that a supplement can cure or treat disease.

In addition, if a manufacturer becomes aware of a severe reaction to its supplement, the manufacturer is supposed to report it. The manufacturer is also supposed to truthfully portray on the supplement's label what is actually included in the product. However, there have been many examples in which it is clear that what was in the product was not on the label, and vice versa. Thus, these regulations are imperfect. They are not designed to prove the safety of the products in humans, and in many circumstances, most of these products have never been tested in humans. Therefore, it is unclear whether the supplements even have the capacity to cause injury of the liver or other organs, for that matter.

### G&H Are there any databases of liver injury induced by supplements?

**VN** My colleagues and I are currently compiling a research database through the Drug-Induced Liver Injury Network (DILIN). There are also databases that are maintained by the government, for example the Office of Dietary Supplements, which has an extensive database of supplements and some toxicities. However, I believe that the DILIN is the only database that focuses on banking cases of liver injury from supplements. The DILIN has shown us that there is an increase of liver injury cases among its study group and that the proportion of these cases that are caused by supplements is also increasing. We suspect that the majority of cases are occurring because of either appearance- and performance-enhancing supplements or weight-loss supplements, and it appears that their use is becoming more prevalent.

### G&H Do you have any advice for doctors managing patients who are interested in taking supplements or who may have liver injury?

**VN** Doctors should always ask patients during office visits whether they are taking, or thinking of taking, supplements and, if they are, should state the importance of not exceeding the dosage listed on the label. It is unclear whether the label actually has any rationale behind it for dosing, but exceeding the dose makes no sense and might put the patient in harm's way.

In addition, doctors should keep in mind that most vitamins and minerals or multivitamins are safe when

used as directed. However, once manufacturers start adding multitudes of ingredients and then bringing in natural products such as herbs (perhaps in high concentrations, which in and of itself is difficult to judge because of the lack of standards for appropriate concentrations of herbals in a supplement), the product may become unsafe. Also, it is important that providers remember that dietary supplements are intended to supplement the diet. That means that there should be some deficiency that the supplements are treating or improving. However, most supplements, particularly performance-enhancing and weight-loss supplements, do not follow this guideline. It is important that providers keep in mind that supplements are not required to be tested for safety in humans. The public has the perception that all supplements are safe, and the vast majority are; it is the rare patient who becomes ill.

### G&H What are the next steps in research in this area?

**VN** My colleagues and I are trying to develop a better understanding of the actual culprits of liver injury. We are collecting products that we think cause injury to patients and are digging deep into the products to analyze them chemically and determine whether there are common patterns or types of ingredients that might be the actual causes of liver injury.

*Dr Navarro has no relevant conflicts of interest to disclose.*

### Suggested Reading

Chalasani N, Bonkovsky HL, Fontana R, et al; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology*. 2015;148(7):1340-1352.e7.

Chalasani NP, Hayashi PH, Bonkovsky HL, Navarro VJ, Lee WM, Fontana RJ; Practice Parameters Committee of the American College of Gastroenterology. ACG Clinical Guideline: the diagnosis and management of idiosyncratic drug-induced liver injury. *Am J Gastroenterol*. 2014;109(7):950-966; quiz 967.

Navarro VJ, Barnhart H, Bonkovsky HL, et al. Liver injury from herbals and dietary supplements in the U.S. Drug-Induced Liver Injury Network. *Hepatology*. 2014;60(4):1399-1408.

Navarro VJ, Khan I, Björnsson E, Seeff LB, Serrano J, Hoofnagle JH. Liver injury from herbal and dietary supplements. *Hepatology*. 2017;65(1):363-373.

Zheng EX, Navarro VJ. Liver injury from herbal, dietary, and weight loss supplements: a review. *J Clin Transl Hepatol*. 2015;3(2):93-98.