Acute Hepatitis Associated with “Thermogenic Fat Burner” Weight-Loss Supplementation

Marko Popovic MD(C), Maxime Billick MD, CM, Matthew R. Robinson MD, CM, FRCPC

About the Authors:

Marko Popovic is with the Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada

Maxime Billick is with the Department of Medicine, University of Toronto, Toronto, Ontario, Canada

Matthew Robinson is with the Division of General Internal Medicine, University of Toronto, Toronto, Ontario, Canada

Correspondence to Dr. Matthew R. Robinson: matthew.robinson@uhn.ca

Submitted: February 18, 2018. Accepted: March 26, 2018. Published: November 9, 2018. DOI: 10.22374/cjgim.v13i4.273

Abstract

Thermogenic fat burner treatments are used to increase an individual's basal metabolic rate, thus mimicking exercise and inducing weight loss. In rare circumstances, these supplements are associated with hepatotoxicity. We describe the case of a 21-year-old male who presented with painless jaundice and a weight loss of 25% of body weight following 8 weeks of thermogenic fat burner supplementation. Laboratory investigations revealed a severe transaminase and bilirubin elevation (AST/ALT > 2000 IU/L, total bilirubin = 148 µmol/L). An otherwise extensive workup, including a liver biopsy, did not identify a precise cause. Two weeks after discharge, his condition stabilized with a significant improvement in his laboratory abnormalities. In this report, we discuss the likely ingredients that contributed to the patient's condition, including *Garcinia cambogia* and green tea leaf extract, and review similar cases documented in the literature.

Case Report

In September 2017, a 21-year-old male presented to his local emergency department in Toronto, Canada with a one-day history of painless jaundice, dark urine, dizziness, and nausea. In May 2017, the patient began increasing his exercise frequency to 5 days per week and improving his diet to lose weight. Additionally, he consumed the following oral supplements for an 8-week course of appetite suppression: Evlution Nutrition Lean Mode Stimulant-Free Weight Loss Supplement™ (3 capsules every 12 hours) (Table 1A) and Evlution Nutrition Trans4orm Thermogenic Fat Burner™ (2 capsules every 12 hours) (Table 1B).

In 8 weeks, he lost approximately ¼ of his body weight (initial weight: 200 lbs, final weight: 150 lbs). At presentation, he had stopped supplementation use for 4 weeks as he achieved his weight-loss goals. His social history was also significant for alcohol use of approximately 10–20 drinks per week during this time, predominantly occurring at social gatherings. Two weeks after supplement discontinuation, he began producing consistent dark urine despite 3–4 litres of water intake daily, which was

Table 1A. Ingredient List - Evlution Nutrition Lean Mode Stimulant-Free Weight-Loss Supplement™

Frequency of use: 3 capsules every 12 hours (ingredients per 3 capsules)	
<i>Garcinia cambogia</i>	500mg [60% hydroxycitric acid (HCA)]
Green coffee bean extract	500 mg
Conjugated linoleic acid	500 mg
Acetyl-L-carnitine	500 mg
Green tea leaf extract	250 mg
Additional ingredients: gelatin, magnesium stearate, silica	

followed by episodes of nausea, vomiting, and headache several days later. Throughout this period, his functional status was unchanged and he did not experience any concurrent illness.

On examination, his vital signs were stable, and his abdomen was non-tender and without organomegaly. Examination was otherwise notable for jaundice with scleral icterus. He was

Table 1B. Ingredient List – Evlution Nutrition Trans4orm Thermogenic Fat Burner™

Frequency of use: 2 capsules every 12 hours (ingredients per 2 capsules)	
Green tea leaf extract	500 mg
Bitter orange peel powder	400 mg
L-tyrosine	175 mg
Choline bitartrate	150 mg
Alpha-glycerolphosphorylcholine powder	25 mg
BioPerine (black pepper fruit extract)	5 mg
Niacin	15 mg
Vitamin B6	2 mg
Vitamin B12	6 µg
Chromium picolinate	120 µg
Other ingredients: gelatin, natural caffeine (from coffee bean), silicon dioxide, folic acid	

managed conservatively and admitted to the General Internal Medicine service for workup of his acute hepatitis.

Initial investigations revealed an aspartate aminotransferase (AST) of 2179 IU/L, an alanine aminotransferase (ALT) of 3016 IU/L, an alkaline phosphatase (ALP) of 260 IU/L, and a total bilirubin of 148 µmol/L. His complete blood count, extended electrolyte profile, creatinine, blood sugar, lipase, and albumin were all within normal limits. Serology for hepatitis A, B, C; cytomegalovirus, Epstein-Barr virus, and human immunodeficiency virus testing; drug and toxin screen; autoimmune hepatitis screen and Wilson's disease testing were all negative. Ferritin was elevated (4026 µg/L), presumably due to an inflammatory process. Of note, his transferrin saturation was elevated at 0.96 with a normal transferrin. Due to the elevated transferrin saturation, genetic testing for hemochromatosis was conducted, yielding a negative result. An initial ultrasound and computed tomography scan both showed nonspecific thickening of the gallbladder, likely secondary to hepatitis. A liver biopsy performed showed an immune-mediated hepatitis with confluent necrosis in zone 3 and moderate hepatocanalicular cholestasis.

Given the exclusion of other causes, the most likely etiological insult was prolonged hepatotoxic drug exposure from weight-loss supplementation, likely potentiated by significant alcohol intake. Throughout his hospitalization, the patient remained asymptomatic except for mild pruritus, with stable vital signs and continued significant jaundice and scleral icterus. He was seen in clinic 2 weeks after discharge and had resolving liver enzymes and bilirubin (AST=742 IU/L, ALT=1446 IU/L,

ALP=172 IU/L, total bilirubin=98 µmol/L). Based on suspicion of the association between the patient's clinical status and his weight-loss supplementation, adverse event reports were filed with Health Canada and the United States Food and Drug Administration (FDA).

Discussion

Dietary supplementation is exceedingly popular in North America. One survey in the United States showed that approximately 15.2% of all adults (men: 9.7%, women: 20.6%) had ever used a weight-loss supplement and 8.7% of adults reported use within the past year.¹ Many herbal weight-loss supplements have been associated with hepatotoxicity, even though they are often marketed as 'natural.'² Thermogenic fat burner treatments are commonly taken to increase the individual's basal metabolic rate in an attempt to mimic exercise and induce weight loss.³ In the case of the patient above, both *Garcinia cambogia* and green tea leaf extract found in his thermogenic weight-loss supplements have been found to cause hepatotoxicity.⁴⁻⁶

Garcinia is a plant traditionally used in Asia as a condiment and to make meals more filling.⁷ Its active ingredient, hydroxycitric acid (HCA), is believed to suppress appetite by inhibition of lipogenesis via the inhibition of ATP citrate lyase.⁸ Hepatotoxicity associated with the consumption of *Garcinia cambogia* is rare but has been previously documented.⁴ The Council for International Organizations of Medical Sciences (CIOMS) scale is used to predict whether liver failure may be due to a given medication or supplement. Our patient received a score of 9 for his supplement consumption, thus indicating a highly probable etiology for hepatotoxicity, for which *Garcinia cambogia* is a likely contributory agent.⁹

There remains controversy in the literature regarding whether HCA induces hepatotoxicity. The most significant case was described in 2016, when Corey et al. published a case report of a 52-year-old female with acute liver failure requiring liver transplantation, presumably attributable to use of twice daily 1000 mg *Garcinia cambogia* extract (USA Nutra Labs) containing 60% HCA per serving.⁴ In 2008, Dara et al. reported a case series and literature review on hepatotoxicity from *Garcinia*-containing Hydroxycut (Inova Health Sciences).¹⁰ One case described a 40-year-old female who experienced 3 days of epigastric abdominal pain, diarrhea, nausea, vomiting, and anorexia secondary to acute hepatocellular hepatitis. She was taking 6 pills of Hydroxycut daily for one week prior to presentation. She recovered with supportive care, and was discharged without complications on day 3 of her admission. In the second, a 33-year-old female presented with one month of jaundice. Previously, she had taken Hydroxycut for 2 weeks, which was discontinued upon the onset of symptoms. Similar to our 21-year-old male patient, her acute hepatitis was

immune-mediated with an elevation in anti-nuclear antibody and anti-smooth muscle antibody. At the time, this represented the first described case of an immune-mediated hepatitis from Hydroxycut, which is typically associated with a hepatocellular pattern of liver injury. Her symptoms and condition eventually resolved without sequelae.

In 2010, Sharma et al. reported the first case of Hydroxycut hepatotoxicity in Hawai'i.¹¹ They described the case of a 19-year-old male presenting with a 2-day history of fever, myalgias, scleral icterus, and an erythematous rash over the lower extremities presumed secondary to acute cholangitis with hyperbilirubinemia. One week previously he began using Hydroxycut. He was admitted and received broad-spectrum antibiotics; however, no infectious etiology could be determined. He was discharged after 17 days in hospital, with a gradual recovery of laboratory abnormalities and normalization by 14 weeks after onset. In their literature review, the authors note that even though certain Hydroxycut preparations have been withdrawn from the market by the manufacturer, similar products exist that may lead to adverse events.

Following the recall of Hydroxycut by its manufacturer, Fong et al. in 2010 described a case series which sought to characterize the clinical presentation of drug-induced liver injury.¹² Typical symptoms included jaundice, fatigue, nausea, vomiting, and abdominal pain. Most cases of hepatitis were associated with a hepatocellular pattern. All patients were admitted to hospital, and 3 of 8 required liver transplantation. One patient on the FDA MedWatch database died secondary to acute liver failure.^{5,12} When all 17 cases were considered, 8 were definitely related to Hydroxycut ingestion, while 5 were highly likely, 2 were probable, and 2 were possibly related.

In contrast, Chuah et al. performed a review of clinical toxicities of Hydroxycut in 2012.¹³ They reviewed multiple cases in which HCA was suspected to cause hepatotoxicity and determined that adverse reactions were associated with polyherbal or multicomponent products. In addition, many of the products contained HCA in negligible amounts or occasionally not at all. They stressed that it was not possible to establish causality based on association, as it was not known which ingredients in the products were responsible for the adverse liver effects. Based on the findings of 17 clinical studies and 873 subjects, they concluded that the level for no observed adverse effects in HCA is up to 2800 mg/day. This is a higher threshold than what was reported to be consumed by our patient.

It is important to acknowledge that our patient had a total exposure of 8 weeks to supplementation, during which time he did not develop symptoms. It is possible that he may have had subclinical laboratory abnormalities during this time. Nonetheless, our literature review of previous cases shows that it is

uncommon for symptoms to appear 2 weeks after supplementation discontinuation, as was the case in our patient.^{4,10-12}

While HCA was strongly suspected to be associated with hepatotoxicity in our patient, the impact of other ingredients should not be discounted. Green tea leaves are the only other ingredient labelled in his supplements that have been associated with hepatotoxicity. Green tea leaves are taken as supplements for their presumed health benefits, including promotion of weight loss, due to intrinsic antioxidant activity.⁶ The leaves are composed of catechins, including epigallocatechin-3-gallate, which have been implicated as causes of liver damage via mitochondrial toxicity and reactive oxygen species generation within hepatocytes.⁶ A systematic review noted the potential of green tea extract to cause hepatotoxicity.⁶ In short, green tea extract may have contributed to hepatocyte injury and thus hepatitis; however, there is stronger evidence supporting the association of acute hepatitis with *Garcinia cambogia*, as illustrated above.

Beyond hepatotoxic supplementation, alcohol likely contributed to our patient's condition. A landmark article by Cohen and Kaplan showed that in 98% of patients with alcoholic liver disease, the increase in ALT was less than 6–7 times the upper end of normal (i.e., ALT increase of 240–280).¹⁴ As a result, the observed increase in transaminases was likely not attributable to alcohol alone; however, it may have been a contributory factor. Prior reports discussed above do not specifically comment on the use of alcohol as a potential contributory factor to the hepatotoxicity that was observed.^{3-5,13}

In summary, we present the case of a 21-year-old male with acute hepatitis likely due to weight-loss supplementation containing HCA and green tea leaf extract. Significant alcohol use was likely a contributing factor, but was unlikely to account for the majority of his clinical presentation. Healthcare professionals are encouraged to be aware of these associations and to always conduct a thorough history of complementary and alternative medicines when evaluating patients with acute hepatitis.

Financial Support

None.

Acknowledgements

None.

Conflicts of Interest

None.

Consent

The authors have obtained patient consent for participation in this study.

Contributors

All of the authors wrote and revised the article, gave final approval of the version to be published and agreed to act as guarantors of the work.

References

1. Blanck HM, Serdula MK, Gillespie C, et al. Use of nonprescription dietary supplements for weight loss is common among Americans. *J Am Diet Assoc* 2007;107:441–7.
2. Corey RL, Rakela J. Complementary and alternative medicine: risks and special considerations in pretransplant and post-transplant patients. *Nutr Clin Pract* 2014;29:322–31.
3. Krishna YR, Mittal Y, Grewal P, et al. Acute liver failure caused by ‘fat burners’ and dietary supplements: a case report and literature review. *Can J Gastroenterol* 2011;25(3):157–60.
4. Corey R, Werner KT, Singer A, et al. Acute liver failure associated with *Garcinia cambogia* use. *Ann Hepatol* 2016;15(1):123–6.
5. Stevens T, Qadri A, Zein NN. Two patients with acute liver injury associated with use of the herbal weight-loss supplement hydroxycut. *Ann Intern Med* 2005;142:477–8.
6. National Institute of Diabetes and Digestive and Kidney Diseases. Green Tea (*Camellia Sinensis*). National Library of Medicine; United States; 2017.
7. Sergio W. A natural food, the Malabar Tamarind, may be effective in the treatment of obesity. *Med Hypotheses* 1988;27(1):39–40.
8. Sullivan AC, Singh M, Srere PA, Glusker JP. Reactivity and inhibitor potential of hydroxycitrate isomers with citrate synthase, citrate lyase, and ATP citrate lyase. *J Biol Chem* 1977;252(21):7583–90.
9. Danan G, Benichou C. Causality assessment of adverse reactions to drugs-I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. *J Clin Epidemiol* 1993;46:1323–30.
10. Dara L, Hewett J, Lim JK. Hydroxycut hepatotoxicity: a case series and review of liver toxicity from herbal weight loss supplements. *World J Gastroenterol* 2008;14(45):6999–7004.
11. Sharma T, Wong L, Tsai N, Wong RD. Hydroxycut® (herbal weight loss supplement) induced hepatotoxicity: a case report and review of literature. *Hawai’i Med J* 2010;69:188–90.
12. Fong TL, Klontz KC, Canas-Coto A, et al. Hepatotoxicity due to Hydroxycut®: a case series. *Am J Gastroenterol* 2010;105(7):1561–6.
13. Chuah LO, Yeap SK, Ho WY, Beh BK, Alitheen NB. In vitro and in vivo toxicity of *Garcinia* or hydroxycitric acid: a review. *Evid Based Complement Alternat Med* 2012;2012:197920.
14. Cohen JA, Kaplan MM. The SGOT/SGPT ratio – an indicator of alcoholic liver disease. *Dig Dis Sci* 1979;24(11):835–8.