

# Hepatocellular Jaundice due to Hydroxycut in Monozygotic Twins

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**Liver injury associated with the use of a number of different of herbal and dietary supplements are increasingly recognized. It is though often unclear which of the sometimes multiple ingredients are responsible for the liver injury. Several case reports have been published on suspected liver injury due to Hydroxycut, which is a multi-ingredient supplement often used to induce weight loss. However, the hepatotoxic potential of Hydroxycut has though been disputed, and steatotic liver disease has also been implicated in patients who are found to have elevated liver enzymes while on Hydroxycut. We report clinically apparent liver injury with jaundice associated with the use of Hydroxycut in monozygotic twins with remarkably similar type of liver injury. Both had the genotype HLA-B 35:01 allele, a risk factor for green-tea extract induced liver injury, which is included in Hydroxycut. (J CLIN EXP HEPATOL xxxx;xxx:xxx)**

Hydroxycut is a multi-ingredient nutritional supplement marketed for “weight loss, extreme energy, and mental focus”. Hydroxycut was introduced in 2002, but in 2004, Hydroxycut products containing ephedera were withdrawn from the U.S. market due to cardiovascular risks<sup>1</sup> and then again in 2009 due to hepatotoxicity.<sup>2</sup> Other Hydroxycut products are still available and widely used, and cases of acute liver injuries have continued to be reported.<sup>3-5</sup> Although many case reports have been published, it has been disputed whether Hydroxycut causes drug-induced liver injury (DILI).<sup>6,7</sup>

We report two cases of acute hepatocellular liver injury with jaundice occurring years apart associated with the use of Hydroxycut products in previously healthy monozygotic twins without other apparent cause of hepatic injury. The second twin developed liver injury in December 2022 and during one of the outpatient visits, his twin brother told us that he had suffered from “hepatitis” in 2005, which turned out to be almost identical and also associated with the use of Hydroxycut. Teschke *et al.* have put into question reports on herbal and dietary supplements (HDSs) leading to liver injury<sup>6</sup> and also case reports on Hydroxycut.<sup>7</sup> The current case reports provide further

evidence for the likelihood of Hydroxycut-induced liver injury.

## CASE REPORTS

The first case occurred in 2005 and the second in 2022. Both twins were suspected to have DILI due to Hydroxycut products. Both patients received care at the Landspítali University Hospital in Reykjavik, Iceland.

### Case 1

A 27-year-old Caucasian male began taking Hydroxycut in 2005 and took it for two months in order to facilitate weight loss. He presented with jaundice but no abdominal pain. He had no history of liver disease and did not drink alcohol or use any prescription or illegal drugs. At presentation, his liver tests were markedly elevated with alanine aminotransferase (ALT) to aspartate aminotransferase (AST) dominance (Table 1). An ultrasound of the abdomen showed no pathological changes in the liver or biliary tree. At the first visit, the patient was instructed to discontinue the use of Hydroxycut as this was suspected to have led to the liver injury. Hepatitis serologies against hepatitis A, B, and C were negative as were immunoglobulin M antibodies to Epstein-Barr virus and cytomegalovirus, antinuclear, smooth muscle, and antimitochondrial antibodies as well as normal IgG. The follow-up a week and a month later, demonstrated improvement in liver tests (Table 1). After a month, the patient had no symptoms, and the liver tests had returned to normal.

### Case 2

A 45-year-old male took a product in 2022 called “Hydroxycut: Hardcore Next Generation” for 4 months to help

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**Abbreviations:** ALT: alanine aminotransferase; AST: to aspartate aminotransferase; DILI: rug-induced liver injury; HDS: herbal and dietary supplements; NAFLD: non-alcoholic fatty liver disease

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**Table 1 Results of Laboratory Tests and Onset and Follow-up Days 1, 7, and 56.**

	ALT (normal <45)	AST (normal <35)	ALP (normal <105)	Bilirubin (normal <25)	GGT (normal <115)
06.10.2005	3233	1503	463	227	69
12.10.2005	2214	1146	327	255	40
30.11.2005	36	29	N/A	16	23

Abbreviations: ALP, alanine aminotransferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase.

with weight loss. The patient presented with jaundice, pruritus, and fatigue. There was no medical history of liver disease, and physical examination was unremarkable. The patient's liver tests, shown in Table 2, were remarkably similar to his twin brother's tests, 17 years earlier as demonstrated in Table 1. An ultrasound scan of the abdomen showed no pathological changes in the liver or biliary tree.

Hepatitis serologies against hepatitis A, B, C, and E were negative as were immunoglobulin M antibodies to Epstein-Barr virus and cytomegalovirus, antinuclear, smooth muscle, and antimitochondrial antibodies and no peripheral eosinophilia. At the first visit, the patient was instructed to stop taking the Hydroxycut product. After a month from presentation, the jaundice had resolved, and liver tests normalized completely within two months (Table 2).

The type of liver injury in both twins was hepatocellular with an initial R value of 16.3 in case 1 and 17.7 in case 2.

Due to recent reports on a strong risk association between HLA-B 35:01 allele with liver injury due to HDS containing green-tea extract, this was tested in both twins. They were both positive for that HLA allele. The frequency of HLA-B35:01 is only found in 1.87% of the general population of Iceland according to data from deCODE genetics, [www.decode.com](http://www.decode.com).

## DISCUSSION

Multiple case reports have been published on the suspected association between acute liver injury and the use of different Hydroxycut products.<sup>3-5</sup> However, Teschke *et al.*

analyzed the case reports in the literature in 2013 and 2018.<sup>6,7</sup> They concluded that in these cases of liver injury in patients using HDS for weight loss, non-alcoholic fatty liver disease (NAFLD) was overlooked as NAFLD might be the main cause of liver damage. However, in contrast with NAFLD, which is a chronic asymptomatic liver injury with usually low ALT and AST, the liver injury associated with Hydroxycut has been reported to be of acute nature, with aminotransferase levels most often above 1000 U/L,<sup>3-5</sup> which is in line with the two current case reports.

Both of the cases in the current report had a very similar type of liver injury and were in agreement with most previously reported cases with hepatocellular type of injury with levels of aminotransferases over 1000 U/L, with jaundice.<sup>3-5</sup> Neither of the patients had a history of chronic liver disease or recent exposure to prescription drugs or other HDSs. Serological investigations and hepatobiliary imaging were normal. It is difficult to confirm that a specific drug/dietary supplement is the cause of DILI as there is currently no biomarker to establish the diagnosis of DILI. However, in both of these cases the Hydroxycut product was the most likely cause of liver injury, with a very clear positive dechallenge. It is interesting to note that the patients are identical twins and had remarkably similar biochemical pattern of liver tests after taking a Hydroxycut product, both containing green-tea extract with 2-4 months to onset of liver injury.

The mechanism of how Hydroxycut products might cause liver injury is not known, but it is probably due to the green-tea extract included in the Hydroxycut products (8). Green-tea extract has recently been identified as a well-documented cause of liver injury.<sup>9</sup>

**Table 2 Results of Laboratory Tests and Onset and Follow-up days 1, 4, 7, 12, 33, and 68.**

	ALT (normal <70)	AST (normal <35)	ALP (normal <105)	Bilirubin (normal <25)	GGT (normal <115)
09.12.2022	2733	1492	227	264	74
12.12.2022	2635	1304	241	261	57
15.12.2022	1766	803	174	133	53
20.12.2022	1077	381	138	75	60
10.01.2023	84	45	97	27	43
14.02.2023	39	26	89	10	36

Abbreviations: ALP, alanine aminotransferase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transpeptidase.

Hydroxycut has been associated with at least 50 instances of clinically apparent acute liver injury and has a likelihood score B of causing DILI.<sup>8</sup> Both twins underwent genetic testing, and both had the HLA-B 35:01 allele. A study from the DILI network found this allele to be a strong risk factor for DILI due to green-tea extract.<sup>9</sup> The HLA-B 35:01 allele has also been recently suggested to be a potential biomarker for herbal-induced liver injury in general according to a study from China.<sup>10</sup>

The current case reports further cement the suspicion that Hydroxycut and more specifically green-tea extract are causes of DILI. The patients are monozygotic twins, both had the HLA-B 35:01 allele developing hepatocellular jaundice, which suggests that the Hydroxycut products were the cause of liver injury. This report also highlights the importance of awareness of DILI due to HDSs. Physicians should be aware of any HDS that their patient is taking and warn them of the possible side effects, especially those with known liver disease, as the adverse reaction might be more severe.

### CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Sigurdur S. Sigurdarson MS: data collection, initial draft, approval of the last version of the manuscript, Mar Kristjansson MD: data collection, revision of the article, approval of the last version of the manuscript, Einar S. Bjornsson MD PhD: study design, revision and approval of the last version of the manuscript.

### CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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### DATA AVAILABILITY STATEMENT

All relevant data are included in the article.

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