Hepatotoxicity Associated with Anabolic Androgenic Steroids Present in Over-The-Counter Supplements: a Case Series

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Abstract

With the aim of improving their physical performance, athletes and non-athletes have been using anabolic-androgenic steroids (AAS). Over the past several decades, there has been an increase in the prevalence of AAS use without adequate supervision or monitoring. We present three cases of AAS-related liver injury with the intention to discuss the use of nutritional supplements as a growing public health concern. Our three patients were able to obtain these "food supplements" containing AAS from health shops. We have shown with high level of evidence that the AAS were the cause of acute liver injury in these patients. All other causes of liver disease were excluded by laboratory evaluation and liver imaging. They all had a similar clinical picture with rapid development of fatigue, jaundice and pruritus. The first patient was on statin for his hyperlipidemia, but the clinical picture was not compatible with statin induced hepatotoxicity. He was on a stable dose and did not have a rise in liver tests with rechallenge. The third patient did consume alcohol in binges but the biopsy was not consistent with alcohol-induced injury. The liver biopsy in all three patients was suggestive of AAS-induced hepatotoxicity. (1) Finally, all three patients were young and relatively healthy and the liver panel results normalized gradually after cessation of the AAS. The aminotransferases in particular normalized according to their half-life after discontinuation of the insulting agent. Synthetic AAS that are not classified as controlled substances continue to fall outside the Food and Drug Administration (FDA) jurisdiction. They are still available in over-the-counter supplements and are a cause for serious hepatotoxicity in the United States. Stricter control of their use outside the medical necessity should be applied and healthcare providers should be aware of their potential harm.

Background and Aims

With the aim of improving their physical performance, athletes and non-athletes have been using anabolic-androgenic steroids (AAS). Over the past several decades, there has been an increase in the prevalence of AAS use without adequate supervision or monitoring. This manuscript describes 3 cases of AAS-related liver injury with the intention to discuss the use of nutritional supplements as a growing public health concern.

Methods

In the present article we present 3 young men who sustained a liver injury after consumption of anabolic androgenic steroids.

Results

As demonstrated by the cases in this report, synthetic AAS caused a remarkable cholestatic hepatotoxicity. Despite a relatively uneventful recovery, their clinical courses were associated with considerable morbidity.

Conclusion

Synthetic AAS that are not classified as controlled substances continue to fall outside the Food and Drug Administration (FDA) jurisdiction. They are still available in over-the-counter supplements and are a cause for serious hepatotoxicity in the United States. Stricter control of their use outside the medical necessity should be applied and healthcare providers should recognize the significance of the problem.

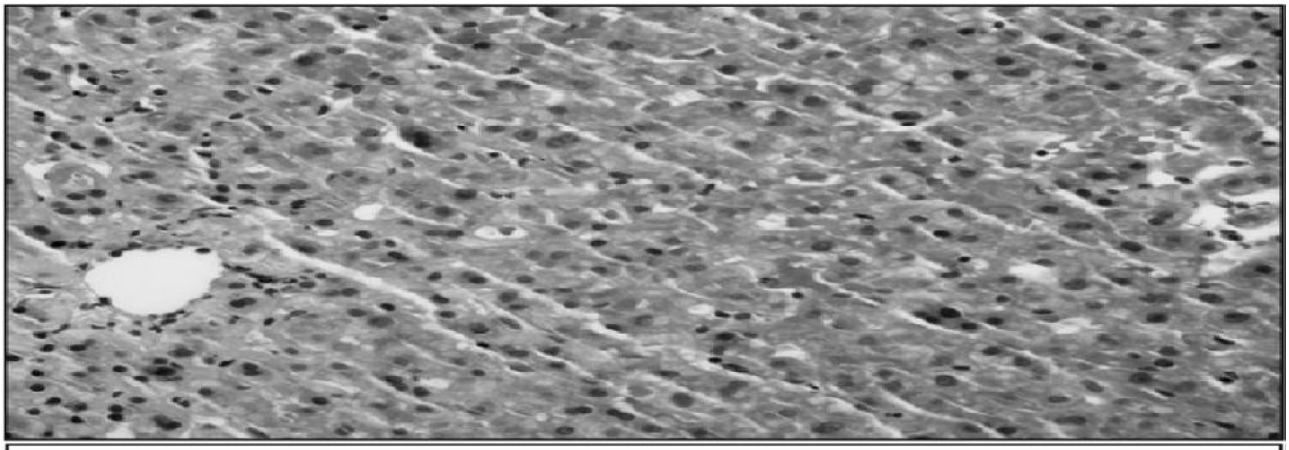


Figure 2A: H&E stain shows bile pigments in zone 3 hepatocytes and bile plug in canalicular space (acute cholestasis). In addition to acute cholestasis, congestion in sinusoid is noted.

Patient 1: 36 year-old white male with history of hyperlipidemia on a statin for one year, presented to Saint Louis University hepatology clinic in July 2010 with 7- to 8-week history of fatigue and pruritus followed by anorexia, weight loss of 22 lbs, dark-colored urine, and jaundice. He denied any abdominal pain, vomiting or change in mental status. His current medications included pravastatin 10 mg once daily and a multivitamin. In addition he admitted to using a muscle supplement "*Muscle Fortress Methyl V-Test*" on a daily basis since May 2010. One of the major ingredients of this supplement is the anabolic steroid 17-α methyl testosterone. He denied any prior liver disease, family history of liver disease, recent travel, alcohol, acetaminophen, or illicit drug consumption. Physical examination revealed significant jaundice and scleral icterus. However, there was no evidence of fluid overload or hepatic encephalopathy. Initial work up revealed a picture of cholestatic hepatitis with a total bilirubin level of 7.5mg/dl, alanine aminotransferase level of 815 U/L (5 –45 U/L), an aspartate aminotransferase level of 233 U/L (12–50 U/L), an alkaline phosphatase level of 114 U/L (33–133 U/L), a serum albumin level of 3.4 g/dL (3.4–5.5 g/dL), and an international normalized ratio of 1.1. His kidney function was mildly impaired with a creatinine level of 1.3. Serologic tests excluded infection with hepatitis A, B, C, Epstein-Barr Virus (EBV), and Cytomegalo Virus (CMV) viruses. Human immunodeficiency virus (HIV) and markers for autoimmune hepatitis (ANA, F-Actin) and primary biliary cirrhosis (AMA) were negative. Imaging including an ultrasound, and magnetic resonance imaging with magnetic resonance cholangiopancreatography revealed mild hepatomegaly without any intrahepatic or extrahepatic biliary dilation. Liver biopsy showed acute cholestasis with focal mild sinusoidal dilation suggesting that anabolic steroid might be the causative agent.

The patient was started on cholestyramine and diphenhydramine for symptom control. His kidney function normalized, the aminotransferases normalized according to their half-lives, the total bilirubin level peaked at 35.7 mg/dl, his jaundice and pruritus gradually resolved over a 10-week period. Figure1 demonstrates graphically the course of cholestasis. He was referred for evaluation for liver transplantation, but listing was deferred after his clinical improvement. His statin was then resumed and was well tolerated.

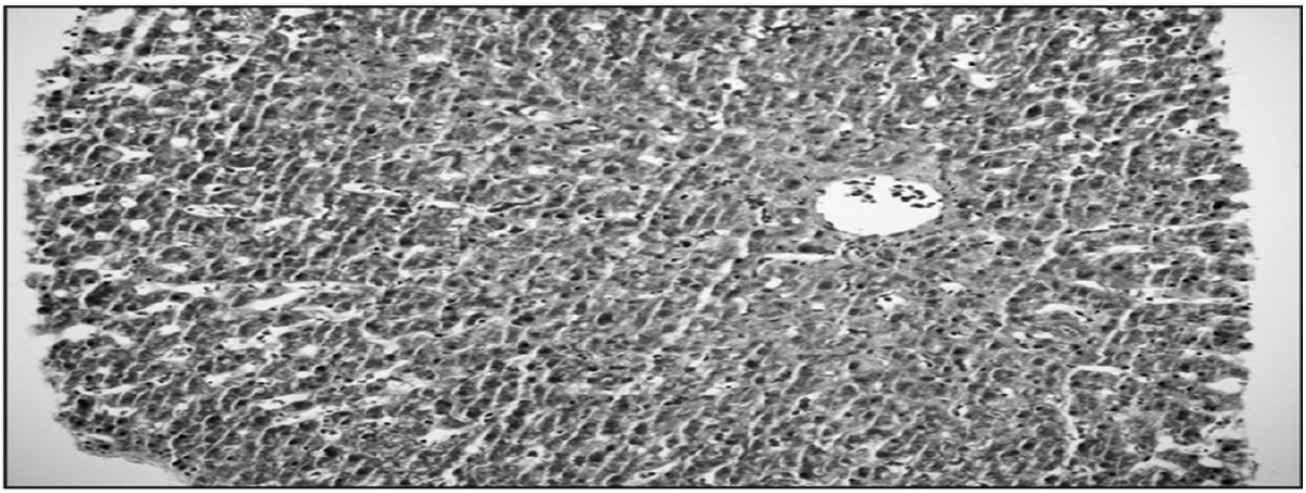
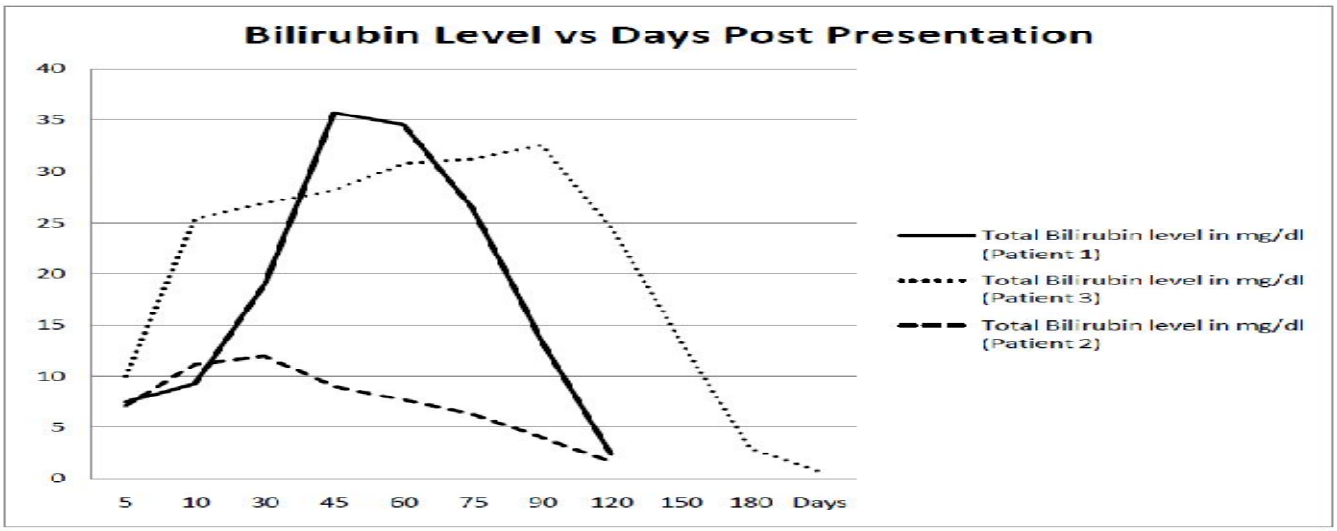


Figure 2B: Trichrome stain shows sinusoidal dilation with perisinusoidal fibrosis.

Patient 2: A 21 year-old male athlete without significant past medical and surgical history was evaluated in the outpatient hepatology clinic in November 2009 because of worsening abdominal pain and malaise. His symptoms were associated with nausea and vomiting for 6 weeks, followed by intense pruritus, insomnia, and jaundice. He has been taking an oral weight lifting supplement "*Ultra Mass Stack*" by Advanced Performance Supplement that contained anabolic steroids. He has no significant personal or family history of liver diseases. He denied any alcohol intake or illicit drug use. Physical examination revealed profound jaundice with mild hepatomegaly. Initial work up disclosed a picture of cholestatic hepatitis with a total bilirubin level of 11.3, alanine aminotransferase level of 211 U/L, an aspartate aminotransferase level of 69 U/L, an alkaline phosphatase level of 116 U/L, a serum albumin level of 3.7 g/dL, and an international normalized ratio of 1.0. Serologic tests excluded the possibility of a viral hepatitis and HIV. Markers for autoimmune hepatitis and primary biliary cirrhosis were negative. An ultrasonography confirmed hepatomegaly and showed no biliary dilation. A percutaneous liver biopsy showed acute cholestasis, sinusoidal dilation and focal congestion with delicate focal perisinusoidal fibrosis consistent with anabolic steroid related liver injury. (Figure 2B) Because of the intense and painful pruritus, he was initially hospitalized and treated supportively for few days. Upon discharge, he was initiated on hydroxyzine and ursodeoxycholic acid and his symptoms gradually improved. After 12-14 weeks he became completely asymptomatic and his liver chemistries normalized.



Patient 3: A previously healthy 42-year-old white male sought medical attention in December 2009 after a 2-week history of worsening jaundice. His jaundice was associated with anorexia, malaise, and increasing pruritus.

He initially attributed this to eating at an outside restaurant. He consumes alcohol about once or twice a week-typically 4-6 beers per outing. However, he stopped all alcoholic beverages completely over the last two weeks. He has never been jaundiced before and he denies any family history of liver disease. His only medications are over-the-counter supplements including a multivitamin and a protein and muscle building supplement containing anabolic steroid. The latter was added by his gym coach as a pre-work out supplement 3 weeks prior to the initiation of his symptoms. The review of system is also positive for insomnia from the pruritus and indigestion. He voluntarily quit taking this supplement 2 days prior to his initial evaluation. Physical examination was significant for severe scleral icterus. The liver edge was not palpable and there were no stigmata of chronic liver disease. He had a flat affect without any focal neurological signs. His complete blood count (CBC) and basic metabolic panel were within normal limits. His liver panel was as follows: alkaline phosphatase level, 112 U/L; aspartate aminotransferase level, 77 U/L;alanine aminotransferase level, 237 U/L; and bilirubin level, 10.0 mg/dL. The international normalized ratio was normal. A detailed work-up to rule out other possible causes of liver disease was initiated. Viral serologies were negative. Iron studies, serum copper levels, and ceruloplasmin levels were within the normal range. Antibody screen including antinuclear antibody, antimitochondrial antibody, antismooth-muscle antibody, and anti–liver-kidney microsomal antibody-1 were also negative. Abdominal imaging revealed a liver of normal echogenicity without any lesions, intra or extra hepatic biliary dilation. Liver biopsy was subsequently performed and illustrated a marked acute cholestasis with minimal inflammation and some sinusoidal dilation which were highly suggestive of drug toxicity.

He was treated conservatively and symptomatically with questran, hydroxyzine, ursodeoxycholic acid, analgesics and topical creams for his painful pruritus. His total bilirubin level peaked at 32.5, and then it gradually decreased over a period of 12 weeks. (Figure 1)

Discussion

The clinical spectrum of hepatic injury derived from AAS is wide. Because the use of these substances is without medical supervision, most of the clinical experience comes from single case reports.

A particularly dangerous class of anabolic steroids is the synthetic steroids, which are found over the counter. They are made specifically for athletes and have no approved medical use. They have not been tested or approved by the Food and Drug Administration (FDA) and represent a health threat in particular to athletes.

Our three patients were able to obtain these "food supplements" containing anabolic steroids from health shops and there is a high level of evidence that they were the cause of acute liver injury in these patients. All other causes of liver disease were excluded by laboratory evaluation and liver imaging. They all had a similar clinical picture with rapid development of fatigue, jaundice and pruritus. The first patient was on statin for his hyperlipidemia, but the clinical picture was not compatible with statin induced hepatotoxicity. He was on a stable dose and did not have a rise in liver tests with rechallenge. The third patient did consume alcohol in binges but the biopsy was not consistent with alcohol-induced injury. The liver biopsy in all three patients was suggestive of AAS-induced hepatotoxicity. (1) Finally, all three patients were young and relatively healthy and the liver panel results normalized gradually after cessation of the AAS. The aminotransferases in particular normalized according to their half-life after discontinuation of the insulting agent. It should be emphasized that pre-existing liver disease or simultaneous use of other medications may increase the hepatotoxicity associated with AAS. (2) Hepatic toxicity related to AAS often is reversible, at least partially, as has been reported in several case reports, and in some series (3,4,5); however, progression to critical hepatic insufficiency is also possible. (6) Reported patterns of liver injury include peliosishepatis (blood-filled cysts in the liver), hepatic adenoma, hepatocellular carcinoma, hepatocellular injury, and even hepatocellular necrosis. (7) A recent study has demonstrated that AAS use could also be a risk factor for toxicant-associated fatty liver disease (TAFLD). (8)In addition to their hepatotoxic effects, AAS can adversely affect other organs including atherosclerosis (9), nephrotoxicity, and suppression of the endogenous testicular function and growth. (10) The life-time prevalence of AAS use is at least 3% in young men world-wide. The lifetime prevalence among US college students is 20 in every 1000 college men and about 2 in every 1000 college women. (11) Natural AAS are considered schedule III drugs according to federal law. Schedule III drugs are those that have mild abuse potential, and have been approved for medical use. Federal law states that it is unlawful for anyone to manufacture or distribute a controlled substance.

In the Controlled Substances Act, anabolic steroids are defined to be any drug or hormonal substance chemically and pharmacologically related to testosterone that promotes muscle growth. Synthetic steroids that are not classified as controlled substances continue to fall outside FDA jurisdiction. (12) Because of this loop hole, AAS are still available online and in health shops and are being marketed as dietary supplements. AAS dependence is a valid diagnostic entity, and a growing public health problem. (13) Lifetime AAS use was significantly associated with other risky health behavior including excessive alcohol consumption and illicit drug use. (14) Synthetic AAS as demonstrated by the cases in this report can cause serious hepatic injury. We recommend that the federal government should close the loop holes in the regulation of these substances. Until this happens, it is critical for all health care providers to recognize the growing importance of the problem, and to have a high index of suspicion for AAS hepatotoxicity, particularly in young men who present with unexplained jaundice, pruritus, and cholestatic liver chemistries.

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