BMJ Open Gastroenterology

Androgenic anabolic steroid-induced liver injury: two case reports assessed for causality by the updated Roussel Uclaf Causality Assessment Method (RUCAM) score and a comprehensive review of the literature

Robin Daniel Abeles ,[1,2] Matthew Foxton,[2] Shahid Khan,[1] Robert Goldin,[3] Belinda Smith,[1] Mark R Thursz,[1] Suman Verma[2]

To cite: Abeles RD, Foxton M, Khan S, *et al*. Androgenic anabolic steroid-induced liver injury: two case reports assessed for causality by the updated Roussel Uclaf Causality Assessment Method (RUCAM) score and a comprehensive review of the literature. *BMJ Open Gastro* 2020;**7**:e000549. doi:10.1136/bmjgast-2020-000549

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2020-000549).

Received 2 October 2020
Accepted 3 October 2020

[1]Divison of Surgery and Cancer, Department of Digestive Diseases, St Mary's Hospital, Imperial College London, London, UK
[2]Department of Hepatology, Chelsea and Westminster Healthcare NHS Trust, London, UK
[3]Centre for Pathology, St Mary's Hospital, Imperial College, London, UK

Correspondence to
Dr Robin Daniel Abeles;
r.abeles@imperial.ac.uk

ABSTRACT

Background Anabolic androgenic steroids (AAS) usage is widespread and increasing. AAS drug-induced liver injury (DILI) is recognised but its clinical course and management is poorly described. We report 2 cases of AAS DILI with associated renal dysfunction, managed successfully with oral corticosteroids.

Methods A comprehensive review identified 50 further cases to characterise the clinical and biochemical course. Causality grading was calculated using the updated Roussel Uclaf Causality Assessment Method (RUCAM) score. Data are presented as median values.

Results The most common AAS taken was methyldrostanolone. Patients commonly present with jaundice and pruritus but may exhibit other constitutional symptoms. Patients presented 56 days after starting, and bilirubin peaked 28 days after stopping, AAS. Causality assessment was 'unlikely' in 1 (2%), 'possible' in 31 (60%) and 'probable' in 20 (38%). Peak values were: bilirubin 705 µmol/L, alanine transaminase 125 U/L, aspartate transaminase 71 U/L, alkaline phosphatase 262 U/L, gamma-glutamyl transferase 52 U/L, international normalised ratio 1.1. Liver biopsies showed 'bland' canalicular cholestasis. 43% of patients developed kidney injury (peak creatinine 225 µmol/L). Therapies included antipruritics, ursodeoxycholic acid and corticosteroids. No patients died or required liver transplantation.

Conclusions Physicians are likely to encounter AAS DILI. Causality assessment using the updated RUCAM should be performed but defining indications and proving efficacy for therapies remains challenging.

INTRODUCTION

Anabolic androgenic steroid (AAS) use for performance enhancing and cosmetic reasons is rising with a lifetime prevalence of 3%–4% in Europe and the USA.[1]

Although the potential for cholestatic AAS drug-induced liver injury (DILI) has been recognised for many years,[2] the clinical course and optimal management of these patients remains unclear. We present two cases of AAS DILI and perform the most comprehensive literature review to date of the topic.

CASE 1

A man aged 30 years presented with a short history of jaundice and diarrhoea. He had no significant risk factors for chronic liver disease. He used Creatine supplements for performance enhancement but denied AAS use. Physical examination was unremarkable besides jaundice. His bilirubin was 181 µmol/L, alkaline phosphatase (ALP) 66 IU/L, alanine transaminase (ALT) 257 IU/L and creatinine (Cr) 97 µmol/L. Imaging ruled out biliary or vascular abnormalities. A liver screen was taken and urgent follow-up organised.

He represented with worsening lethargy and malaise 7 days later. His bilirubin had risen to 373 µmol/L but all other tests were stable. His liver screen identified undiagnosed chronic hepatitis B (HBV) with a low viral load (181 IU/mL) and a low titre of antismooth muscle antibody (1:40) but nothing else suggestive of autoimmune hepatitis. However, he was started on prednisolone 60 mg at the referring hospital with tenofovir prophylaxis against HBV 'reactivation'. On arrival to our hospital, his bilirubin had risen to 526 µmol/L, his international normalised ratio (INR) remained normal and Cr peaked at 126 µmol/L. Repeat autoimmune screen

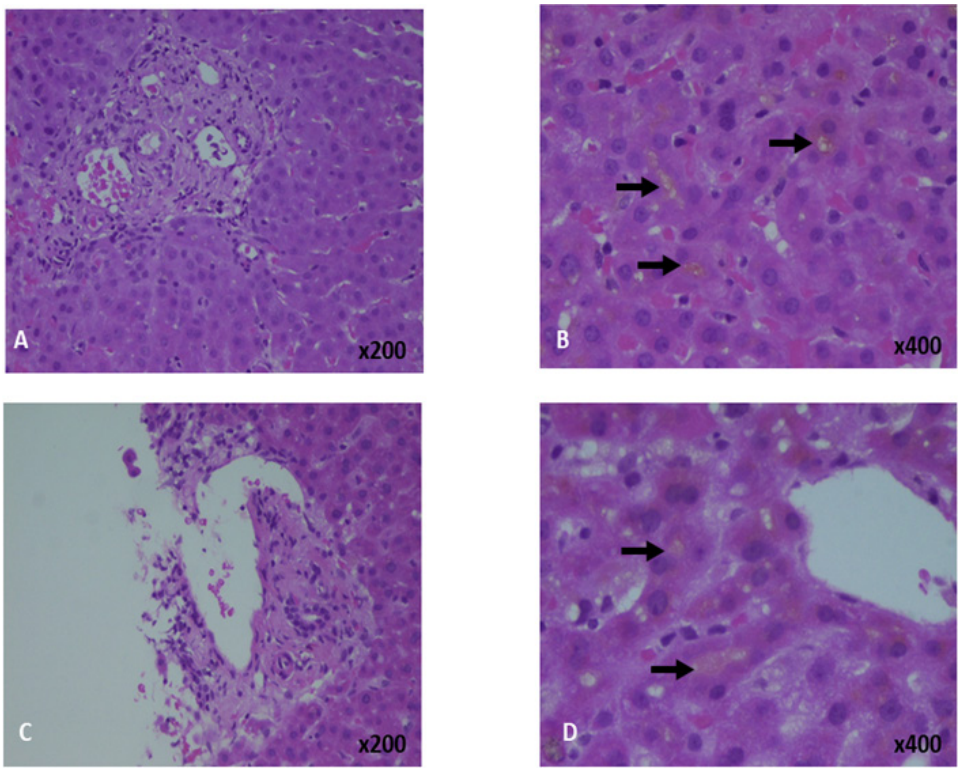

Figure 1 Liver biopsies from patient 1 (A, B) and patient 2 (C. D). The biopsies show no significant inflammation (A, C). On higher power magnification, canalicular cholestasis with bile plugs is demonstrated (arrows).

was negative and HBV DNA was fully suppressed (<20 IU/mL).

On repeat questioning he admitted to taking methyldrostanolone, starting 6 weeks, and finishing 2 weeks, prior to presentation.

Intravenous N-acetyl cysteine (NAC) was given, stopping 48 hours later along with prednisolone. His bilirubin dropped to 486 µmol/L but rose again to 633 µmol/L. Other peak values included ALT 257 IU/L, aspartate transaminase (AST) 143 IU/L, ALP 123 IU/L, gamma-glutamyl transferase (GGT) 31 IU/L and INR 1.1. As his liver biochemistry had worsened, he proceeded to liver biopsy to ensure no alternative pathology was present. The biopsy showed fibrous expansion of the portal tracts, reactive ductular changes with only mild-to-moderate inflammation without plasma cells or eosinophils but marked canalicular cholestasis (figure 1A,B).

AAS DILI was suspected with an R score of 11.7, consistent with hepatocellular pattern. The updated Roussel Uclaf Causality Assessment Method (RUCAM) score was 4 consistent with 'possible' causality.[3]

Prednisolone 40 mg was restarted with a temporally related drop in bilirubin and Cr and he was discharged 4 days later. Liver function tests resolved (ALT 61 IU/L, ALP 56 IU/L, bilirubin 9 µmol/L) over 2 months as the steroids were tapered down and stopped (figure 2A).

CASE 2

A man aged 36 years presented with non-specific abdominal pains followed by 5 days of jaundice and pruritus. He had no risk factors for chronic liver disease. He admitted to using Creatine and 'Winter Cherry' (Ashwagandha) for 2 months, stopping 1 month prior to presentation, for performance enhancement. On further questioning, he then admitted to also having taken methyldrostanolone.

He was jaundiced with excoriations but no peripheral stigmata of chronic liver disease. His bilirubin was 140 µmol/L, ALT 460 IU/L, ALP 219 IU/L, GGT 25 IU/L, Cr 94 µmol/L and INR 1.0. His liver screen was unremarkable. Imaging excluded biliary or vascular pathology. He was started on chlorphenamine and ursodeoxycholic acid (UDCA) for pruritus. Despite 5 days of intravenous NAC, his bilirubin rose to 428 µmol/L. A liver biopsy was performed due to this rise to exclude alternative pathology. The biopsy showed mild focal lymphocytic infiltration with marked canalicular and intrahepatocyte cholestasis (figure 1C,D).

Possible AAS DILI was diagnosed with an R score of 6.3 (hepatocellular) and a RUCAM score of 4.[3] Despite increasing the UDCA and changing to hyroxyzine, his bilirubin rose to 750 µmol/L and Cr to 151 µmol/L. He was given empirical antibiotics and intravenous fluids in case of covert infection but despite a transient improvement, the bilirubin rose again peaking at 768 µmol/L associated with a Cr of 166 µmol/L. Prednisolone 40 mg was started with an improvement in bilirubin and Cr over the next 7 days. The prednisolone was weaned rapidly to 25 mg but the bilirubin plateaued at ~400 µmol/L. Prednisolone was increased to 40 mg, associated with a further improvement in bilirubin and normalisation of Cr. The

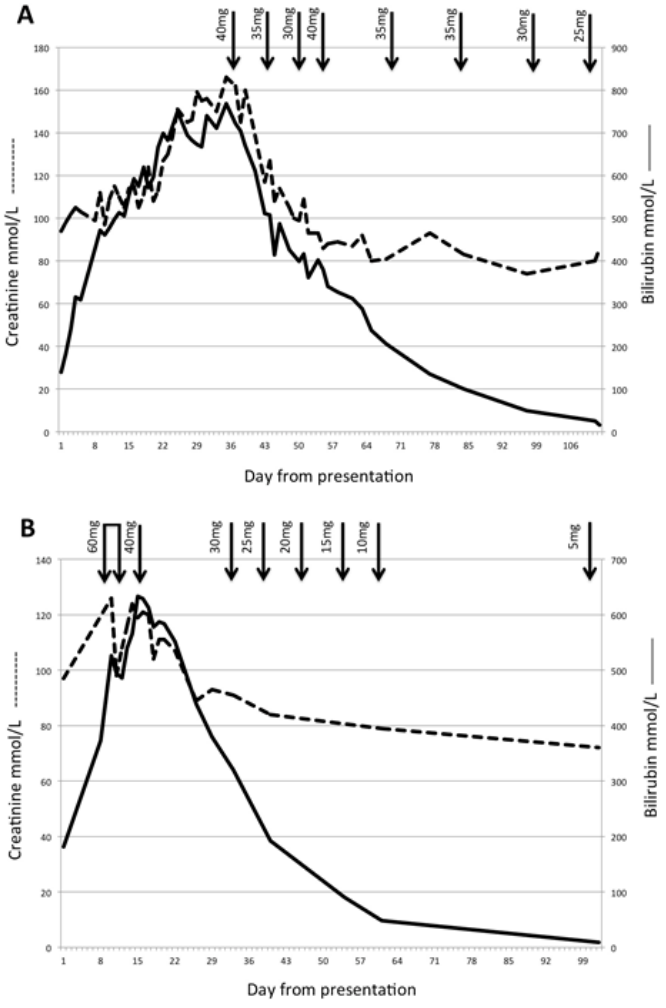

Figure 2 Changes in bilirubin (µmol/L, solid line) and creatinine (µmol/L, dashed line) from day of presentation in patient 1 (A) and patient 2 (B). Arrows indicate dose of prednisolone.

patient was discharged 3 days later and his prednisolone was weaned slowly (figure 2B). The bilirubin, ALT and ALP normalised over the next 2.5 months (bilirubin 16 µmol/L, ALT 73 IU/mL, ALP 123 IU/L).

REVIEW OF THE PUBLISHED LITERATURE

Methods

A PubMed search using the terms 'anabolic steroid liver' returned 966 titles. Titles and abstracts were screened for cholestatic AAS DILI. Non-English or non full-text articles were excluded. Included manuscripts' references were also screened for relevance. Thirty manuscripts were included in the final analysis.

The largest published single series (Spanish-South American registry) comprised 25 patients,[4 5] however, only summary statistics were provided so individual cases could not be included but serve as a comparison group. All data are presented as median and IQR.

The R value, updated RUCAM score and the causality grading was calculated for each case.[3]

Results

Fifty-two patients (50 male, median age 29 (IQR 25–41)) were included (online supplemental table 1). Besides the earliest cases,[6 7] AAS were taken for performance enhancement. The most common AAS, either alone or in combination was methyldrostanolone (methasterone). Jaundice and pruritus were the most common presenting symptoms, accompanied by constitutional symptoms such as lethargy, gastrointestinal symptoms or weight loss. Median time to presentation was 56 days (IQR 42–72). At presentation Bilirubin was 314 µmol/L (IQR 174–590), ALT 125 IU/L (IQR 85–233), AST 71 IU/L (IQR 58–112) and ALP 190 IU/L (IQR 123–287). Bilirubin peaked 28 days (IQR 14–35) after stopping AAS at 705 µmol/L (IQR 549–872). Peak ALT was 125 IU/L (IQR 85–233), AST 71 IU/L (IQR 58–112), ALP 262 IU/L (IQR 183–372), GGT 52 IU/L (IQR 29–67) and INR 1.1 (IQR 1–1.3). The time to resolution from peak bilirubin was 90 days (IQR 75–120). One patient developed encephalopathy and two developed INR ≥1.5.

The median R value was 2 (0.8–4.3) with 10 (19%) having 'hepatocellular' and 42 (81%) 'mixed or cholestatic' liver injury. The median updated RUCAM score was 5 (4–6) with causality assessments of 'unlikely' in 1 (2%), 'possible' in 31 (60%), 'probable' in 20 (38%). In 13 (25%) cases, concomitant bodybuilding supplements were recorded, 2 along with Ashwagahanda.

Liver biopsies predominantly showed marked canalicular and intrahepatocyte cholestasis with only mild or moderate inflammation. Twenty-two patients (43%) developed acute kidney injury (AKI) with a peak Cr of 225 µmol/L (IQR 174–406). Two patients received renal replacement therapy,[8] one peritoneal dialysis[7] and three molecular adsorbent recirculating system (MARS).[9] Besides lower ALT values and higher incidences of renal dysfunction, these results are similar to those seen in the Spanish-South American series[5] (online supplemental table 2).

'Standard medical therapy' or no therapeutic details were given for 24 patients.[9–18] Seventeen patients received antipruritic therapy, predominantly antihistamines and rifampicin, colestyramine, naltrexone and phenobarbital. Twelve patients received UDCA alone, 3 received corticosteroids alone (Abeles RDA)[19 20] and 12 received corticosteroids and UDCA (3 due to 'failure' of UDCA (Abeles RDA)),[19 21] 6 patients received MARS[9 16 22] and 1 received plasmapheresis.[23]

DISCUSSION

Most DILIs resolve with cessation of the causative agent. Registry data, representing the most severe forms of DILI, show mortality/liver transplant rates of 4%–10%.[24–26] Within the US-DILIN group, dietary supplements were the primary implicating agent in 16% of those patients but the proportion due to AAS is not given.[27] From 1963 to 2014, UK MHRA data recorded 4/61 fatal liver deaths

from AAS DILI (2 related to jaundice, 1 liver failure and 1 from cirrhosis).[28]

Hy's law predicts a 10% mortality in DILI if the transaminases are 3× upper limit of normal (ULN) and the bilirubin (excluding unconjugated hyperbilirubinaemia) is >2×ULN without initial elevated ALP.[29] When validated in registry data studies,[25 26 30 31] Hy's law shows a high sensitivity but low specificity and so is used as a signal of serious hepatotoxicity in drug development rather than a clinical predictor of severe outcome. In this series, when able to calculate, 50% (17/34) fulfilled Hy's law yet there were no deaths nor transplantations nor were there any in the Spanish-South American series.[5] These data reassure the physician that the prognosis for AAS DILI is excellent.

The RUCAM scale (and its update) is validated and specifically designed for DILI with scores given for defined key elements to provide a causality grading assessment and has been widely used for over 25 years. It is intended to be used prospectively, raising methodological challenges when applied to historical case series with incomplete data, as in the presented work. Liver injury assessment, demonstrating ALT of at least 5× ULN and/or hepatic ALP of at least 2× ULN, is a prerequisite. Within the data available for this series, 30 (58%) fulfilled this prerequisite, rising to 35 (67%) if peak values were used instead of admission ones. This raises the possibility that despite publication, some of these cases may have been misclassified as AAS-induced DILI.

Liver biopsy is not required for diagnosis of DILI,[3] but is often performed due to diagnostic uncertainty, especially when therapies are being considered or in the face of worsening biochemistry despite cessation of the implicating drug, as in the two cases presented. Although safe, liver biopsy carries established risks. These data, demonstrating that peak bilirubin is seen 28 days after presentation, reassure the physician that biopsy can usually be avoided. Biopsies from patients with hepatocellular injury, as defined by the R score, often have a 'bland' cholestatic pattern histologically, this is likely due to timing due to the evolution of a cholestatic phase after the initial hepatocellular phase. The recommendation for causality assessment is that the R value should be calculated at the first time point that qualifies as being indicative of DILI.[3]

Another challenge for causality assessment for AAS is that many patients use concomitant bodybuilding supplements, stopping concurrently, as was the case for both our presented cases. To distinguish between them, RUCAM assessment should be performed for each potential agent, thereby reducing the 'concomitant drug/herb' score for both agents. Hepatotoxicity is labelled on AAS leading to a higher score than supplements, so are usually favoured as the culprit agent.

Although a new diagnosis of HBV was found in case 1, this was not felt to be clinically related to his acute presentation so did not lose a point within the 'alternative causes' for liver disease RUCAM domain. There are conflicting data as to whether HBV affects the risk of DILI with antituberculosis medications,[32 33] but pre-existing chronic liver disease was not shown to affect risk within the DILIN prospective study.[24]

The use of therapies such as steroids, UDCA or dialysis devices may mask the natural course of ALT or ALP in the dechallenge phase and therefore, if given, score the patient zero in the 'course after cessation of drug' RUCAM component.[3] Thirty-one (60%) cases received at least one form of therapy over the dechallange phase. However, this resulted in only three patients being 'classified down' from 'probable' to 'possible' and one from 'possible' to 'unlikely'. The presented 'case 2' was treated with UDCA with the resultant RUCAM score 3 points lower (4 vs 7) than it might have been, moving from a causality assessment of 'probable' to 'possible'. In practice, the physician may have to sacrifice a degree of diagnostic rigour when faced with a decision whether to commence treatment for a patient.

As all data derive from uncontrolled case reports, ascertaining the efficacy of therapies in AAS DILI is challenging. Despite the likely publication bias favouring intervention, most reported cases of AAS DILI resolve spontaneously with no specific therapy. Although Wree *et al* found that, compared with historical controls, corticosteroid-UDCA combination resulted in a quicker reduction in bilirubin in DILI, subgroup analysis for AAS DILI was not significant.[34] Several patients in this series progressed to second-line therapy (corticosteroids, MARS or plasmapheresis) due to lack of response of UDCA.

For our cases, a temporal relationship was seen between starting corticosteroids (or escalating after a rapid wean for patient 2) and a reduction in serum bilirubin (figure 2A,B) with no significant side effects or adrenal suppression.

The role of NAC in non-paracetamol DILI is unclear. In some cases, labelled 'non-paracetamol ALF', paracetamol may be the underlying aetiology.[35] The risks of NAC are few and it may benefit in improving transplant-free survival in DILI with deranged clotting.[36] A short trial of NAC is therefore reasonable but should be stopped quickly if there is no response.

MARS or plasmapheresis effects an expected biochemical and clinical response[14 16 22] but is not widely available, has a high resource utilisation and is associated with its own risks.

AKI commonly complicates AAS DILI. In this series, eight patients underwent renal biopsy; two had acute tubular necrosis,[17 18] one had IgA nephropathy[37] and five had bile acid nephropathy.[9] In keeping with these histological findings, peak bilirubin correlates with peak Cr and a level of ~440 µmol/L predicts the development of AKI.[5] For our patients, Cr mirrored the bilirubin once the bilirubin rose above ~440 µmol/L (figure 2A,B).

Lastly, our cases illustrate the importance of careful history-taking. Both patients initially denied taking AAS only admitting so on subsequent questioning. Reasons that patients may not report AAS use include

embarrassment or fear of the legal implications. Under UK law, AAS are classified as class C drugs that can only be prescribed. They are, however, legal to import in person for personal use but not using postal or courier services. Under US law, AAS fall under schedule III where a medical certificate is required even for possession. Of additional concern, some AAS preparations, including 'Megavol' taken by patient 1, claim to have the benefit of liver protection by including NAC and milk thistle within the formulation!

In conclusion, AAS use is widespread and rising and all physicians are likely to encounter patients with AAS DILI. The updated RUCAM score and causality assessment should be calculated on all patients where DILI is suspected, although conclusively identifying AAS as the culprit agent can be challenging due to the frequent concurrent consumption of body building supplements and the clinical desire to give treatment. Thankfully, the prognosis is excellent and that, although there is a paucity of high-quality data to guide management, it is reasonable to consider antihistamines or UDCA in symptomatic patients or corticosteroids in those with extreme elevations of bilirubin associated with elevated Cr.

Twitter Suman Verma @hepatologysuman

Contributors RDA, BS and SV conceived of the presented idea. RG reviewed, reported and prepared the histology. RDA wrote the manuscript with comments and editing from MF, SK, BS, RG, MRT and SV.

Funding RDA was funded at the time by an Imperial College London, Wellcome funded Clinical Lectureship. The Division of Integrative Systems Medicine and Digestive Disease receives financial support from the National Institute of Health Research (NIHR) Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. De-identified patient data.

ORCID iD

Robin Daniel Abeles http://orcid.org/0000-0002-1527-4456

REFERENCES

1 Sagoe D, Molde H, Andreassen CS, *et al*. The global epidemiology of anabolic-androgenic steroid use: a meta-analysis and meta-regression analysis. *Ann Epidemiol* 2014;24:383–98.
2 DeLorimier AA, Gordan GS, LoWE RC, *et al*. Methyltestosterone, related steroids, and liver function. *Arch Intern Med* 1965;116:289–94.
3 Danan G, Teschke R. RUCAM in drug and herb induced liver injury: the update. *Int J Mol Sci* 2015;17:14.
4 Medina-Caliz I, Garcia-Cortes M, Gonzalez-Jimenez A, *et al*. Herbal and dietary supplement-induced liver injuries in the Spanish DILI registry. *Clin Gastroenterol Hepatol*2018.
5 Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, *et al*. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. *Aliment Pharmacol Ther* 2015;41:116–25.
6 Slater SD, Davidson JF, Patrick RS. Jaundice induced by stanozolol hypersensitivity. *Postgrad Med J* 1976;52:229–32.
7 Evely RS, Triger DR, Milnes JP, *et al*. Severe cholestasis associated with stanozolol. *Br Med J* 1987;294:612–3.
8 Tabatabaee SM, Elahi R, Savaj S. Bile cast nephropathy due to cholestatic jaundice after using stanozolol in 2 amateur bodybuilders. *Iran J Kidney Dis* 2015;9:331–4.
9 Diaz FC, Saez-Gonzalez E, Benlloch S, *et al*. Albumin dialysis with Mars for the treatment of anabolic steroid-induced cholestasis. *Ann Hepatol* 2016;15:939–43.
10 Brazeau MJ, Castaneda JL, Huitron SS, *et al*. A case report of supplement-induced hepatitis in an active duty service member. *Mil Med* 2015;180:e844–6.
11 Cabb E, Baltar S, Powers DW, *et al*. The diagnosis and manifestations of liver injury secondary to off-label androgenic anabolic steroid use. *Case Rep Gastroenterol* 2016;10:499–505.
12 El Sherrif Y, Potts JR, Howard MR, *et al*. Hepatotoxicity from anabolic androgenic steroids marketed as dietary supplements: contribution from *ATP8B1/ABCB11* mutations? *Liver Int* 2013;33:1266–70.
13 Shah NL, Zacharias I, Khettry U, *et al*. Methasteron-associated cholestatic liver injury: clinicopathologic findings in 5 cases. *Clin Gastroenterol Hepatol* 2008;6:255–8.
14 Singh V, Rudraraju M, Carey EJ, *et al*. Severe hepatotoxicity caused by a methasteron-containing performance-enhancing supplement. *J Clin Gastroenterol* 2009;43:287.
15 Magee CD, Witte S, Kwok RM, *et al*. Mission compromised? drug-induced liver injury from prohormone supplements containing anabolic-androgenic steroids in two deployed U.S. service members. *Mil Med* 2016;181:e1169–71.
16 Eapen J, Ayoola R, Subramanian RM. 'The efficacy of extracorporeal liver support with molecular adsorbent recirculating system in severe drug-induced liver injury'. *Oxf Med Case Reports* 2018;2018.
17 Rosenfeld GA, Chang A, Poulin M, *et al*. Cholestatic jaundice, acute kidney injury and acute pancreatitis secondary to the recreational use of methandrostenolone: a case report. *J Med Case Rep* 2011;5:138.
18 Yoshida EM, Karim MA, Shaikh JF, *et al*. At what price, glory? severe cholestasis and acute renal failure in an athlete abusing stanozolol. *CMAJ* 1994;151:791–3.
19 Krishnan PV, Feng Z-Z, Gordon SC. Prolonged intrahepatic cholestasis and renal failure secondary to anabolic androgenic steroid-enriched dietary supplements. *J Clin Gastroenterol* 2009;43:672–5.
20 El Khoury C, Sabbouh T, Farhat H, *et al*. Severe cholestasis and bile cast nephropathy induced by anabolic steroids successfully treated with plasma exchange. *Case Rep Med* 2017;2017:1–4.
21 Stępień PM, Reczko K, Wieczorek A, *et al*. Severe intrahepatic cholestasis and liver failure after stanozolol usage – and review of the literature. *Clin Exp Hepatol* 2015;1:30–3.
22 Anand JS, Chodorowski Z, Hajduk A, *et al*. Cholestasis induced by parabolan successfully treated with the molecular adsorbent recirculating system. *Asaio J* 2006;52:117–8.
23 Flores A, Nustas R, Nguyen H-L, *et al*. Severe cholestasis and bile acid nephropathy from anabolic steroids successfully treated with plasmapheresis. *ACG Case Rep J* 2016;3:133–5.
24 Chalasani N, Bonkovsky HL, Fontana R, *et al*. Features and outcomes of 899 patients with drug-induced liver injury: the DILIN prospective study. *Gastroenterology* 2015;148:1340–52.
25 Robles-Diaz M, Lucena MI, Kaplowitz N, *et al*. Use of Hy's law and a new composite algorithm to predict acute liver failure in patients with drug-induced liver injury. *Gastroenterology* 2014;147:109–18.
26 Björnsson E, Olsson R. Outcome and prognostic markers in severe drug-induced liver disease. *Hepatology* 2005;42:481–9.
27 Fontana RJ, Hayashi PH, Gu J, *et al*. Idiosyncratic drug-induced liver injury is associated with substantial morbidity and mortality within 6 months from onset. *Gastroenterology* 2014;147:96–108.
28 Neuberger J. Editorial: showing due DILI-gence--the lessons from anabolic steroids. *Aliment Pharmacol Ther* 2015;41:321–3.

29 Zimmerman HJ, Disease D-IL. *Hepatotoxicity, the adverse effects of drugs and other chemicals on the liver*. 1 edn. New York: Appleton-Century-Crofts, 1978: 351–3.
30 Andrade RJ, Lucena MI, Fernández MC, *et al*. Drug-induced liver injury: an analysis of 461 incidences submitted to the Spanish registry over a 10-year period. *Gastroenterology* 2005;129:512–21.
31 Lo Re V, Haynes K, Forde KA, *et al*. Risk of acute liver failure in patients with drug-induced liver injury: evaluation of Hy's law and a new prognostic model. *Clin Gastroenterol Hepatol* 2015;13:2360–8.
32 Kim WS, Lee SS, Lee CM, *et al*. Hepatitis C and not hepatitis B virus is a risk factor for anti-tuberculosis drug induced liver injury. *BMC Infect Dis* 2016;16:50.
33 Wang N-T, Huang Y-S, Lin M-H, *et al*. Chronic hepatitis B infection and risk of antituberculosis drug-induced liver injury: systematic review and meta-analysis. *J Chin Med Assoc* 2016;79:368–74.
34 Wree A, Dechêne A, Herzer K, *et al*. Steroid and ursodesoxycholic acid combination therapy in severe drug-induced liver injury. *Digestion* 2011;84:54–9.
35 Davern TJ, James LP, Hinson JA, *et al*. Measurement of serum acetaminophen-protein adducts in patients with acute liver failure. *Gastroenterology* 2006;130:687–94.
36 Hu J, Zhang Q, Ren X, *et al*. Efficacy and safety of acetylcysteine in "non-acetaminophen" acute liver failure: A meta-analysis of prospective clinical trials. *Clin Res Hepatol Gastroenterol* 2015;39:594–9.
37 Jasiurkowski B, Raj J, Wisinger D, *et al*. Cholestatic jaundice and IgA nephropathy induced by OTC muscle building agent superdrol. *Am J Gastroenterol* 2006;101:2659–62.

Supplemental Table 1: Clinical and biochemical data for all included cases

	Case no.	Country	Age	Sex	AAS taken	Clinical presentation	Time from starting AAS to presentation (days)	Time from stopping AAS to peak Bili (Days)	R Value	Pattern of liver injury	Updated RUCAM score & Causality grading	Peak Bili (umol/L)	peak ALT (IU/L)	Peak ALP (IU/L)	Peak Cr (umol/L)	Time to resolution from peak Bili (days)	Primary therapy	Other therapies
Slater SD, 1976[1]	1	UK	62	M	Stanozol	Jaundice and pruritis, weight loss	210		0.92	cholestatic or mixed	6-Probable	156	51			105	Nil	
Everly RS, 1987[2]	2	UK	65	F	Stanozol	Jaundice and pruritis	120		1.48	cholestatic or mixed	6-Probable	660	140	284	404	135	Nil	
Everly RS, 1987[2]	3	UK	62	F	Stanozol	Jaundice and pruritis	150		0.31	cholestatic or mixed	6-Probable	732		534	133	135	Nil	
Everly RS, 1987[2]	4	UK	65	M	Stanozol	Jaundice and pruritis	40		0.58	cholestatic or mixed	7-Probable	798		360	1021	135	Nil	
Awaii HI, 2014[3]	5	US	18	M	Beastrodol 40mg	jaundice, vomiting, difficulty concentrating	14	28	7.31	Hepatocellular	6-Probable	658	229	218		90	UDCA	Colestyramine, Rifampicin
Brazeau MJ, 2015[4]	6	US	26	M	Mutant Plexx, Methylstenbolone, Epistan, Halodrol, 13-ethyl-3-methoxy-gona-2,5(10)-diene-17-one (Max LMG).	Jaundice and pruritis	120	14	5.58	Hepatocellular	3-Possible	84	223			90	nil	
Cabb E, 2016[5]	7	US	45	M	Oxandrolone 50mg OD and testoterone inj weekly	Jaundice and pruritis	104	25	1.85	cholestatic or mixed	3-Possible	109	162	286			nil	
Diaz FC, 2016[6]	8	Spain	29	M	Epithiostanol	Jaundice and pruritis	30	30	4.30	cholestatic or mixed	6-8Probable	1060	169	248	177	120	MARS	Standard medical therapy
Diaz FC, 2016[6]	9	Spain	20	M	Epithiostanol	Jaundice and pruritis	33	30	5.43	Hepatocellular	6-Probable	968	344	292	203	120	MARS	Standard medical therapy
Diaz FC, 2016[6]	10	Spain	23	M	Epithiostanol	Jaundice and pruritis	31	30	1.36	cholestatic or mixed	6-Probable	860	109	248		120	MARS	Standard medical therapy
Diaz FC, 2016[6]	11	Spain	26	M	Epithiostanol	Jaundice and pruritis	30	30	2.59	cholestatic or mixed	6-Probable	694	300	347	124	120	MARS	Standard medical therapy
Ding NS, 2013[7]	12	Australia	46	M	Stanozol 40mg, Methandrostenal-one 40mg	Jaundice and pruritis	210		1.27	cholestatic or mixed	3-Possible	302	125	295		49	UDCA	
Eapen J, 2018[8]	13	US	26	M	methyl-1-etiochoenolol-epietiocholanolo-ne	Jaundice and pruritis		14	2.65	cholestatic or mixed	4-Possible	616	106			60	MARS	Standard medical therapy
El Sherrif Y, 2013[9]	14	UK	25	M	Methyldrostanol-one	jaundice, lethargy anorexia	49	42	4.53	cholestatic or mixed	4-Possible	614	207	137		105	nil	
El Sherrif Y, 2013[9]	15	UK	45	M	Methyldrostanol-one	Jaundice and pruritis abdo pain	56	63	1.76	cholestatic or mixed	5-Possible	229	152	259	173		nil	
Elsharkawy AM, 2012[10]	16	UK	32	M	Methandrosteno-lone 5mg	Jaundice, nausea and vomitting	60	4	0.87	cholestatic or mixed	6-Probable	800	76	262		90	UDCA	Chlorphenamin and Colestyramine
Elsharkawy AM, 2012[10]	17	UK	16	M	Methandrostenol-one 10mg TDS	Jaundice, pruritis, abdo pain, nausea	27	7	2.31	cholestatic or mixed	6-Probable	635	156	203		120	UDCA	colestyramine, Rifampicin, naltrexone
Jasiurkowski B, 2006[11]	18	US	23	M	Methasterone (Superdrol) 10mg then 20mg	Jaundice, pruritis, abdo pain, nausea and vomitting	74	28	1.25	cholestatic or mixed	6-Probable	718	93	280	301	75	UDCA 1.2g	Hydroxyzine

Kafrouni MI, 2007[12]	19	US	40	M	Methasterone (Superdrol) 20mg	Jaundice pruritis and weight loss	110	42	2.17	cholestatic or mixed	4-Possible	855	301	416			Prednisolone 40mg - 1 week, UDCA for pruritis	
Kafrouni MI, 2007[12]	20	US	31	M	Methasterone (Superdrol) and Halodrol	Jaundice, weakness and flu like Sx, Pruritis and weight loss	56	35	0.47	cholestatic or mixed	6-Probable	747	59	375		105	UDCA	colestyramine, hydroxyzine, rifampicin
Anand JS, 2006[13]	21	Poland	21	M	Trenbolone	Jaundice and pruritis	49		3.18	cholestatic or mixed	5-Possible	1120	106			60	UDCA but then MARS	Topical steroids, phenobarbital
Krishnan PV, 2009[14]	22	US	21	M	Methasterone (Superdrol)	Jaundice, pruritis, nauseas and anorexia		21	3.07	cholestatic or mixed	5-Possible	665	256			90	Prednisolone 40mg	
Krishnan PV, 2009[14]	23	US	30	M	Dehydroepiandrosterone	Jaundice and pruritis	35		5.77	Hepatocellular	3-Possible	137	200			90		Hydroxyzine and colestyramine
Krishnan PV, 2009[14]	24	US	38	M	17a-methyl-etioallocho-lan-2-ene-17b-01	Jaundice, pruritis lethargy, nausea and weight loss	98	53	2.84	cholestatic or mixed	3-Possible	920	467		212	75	UDCA then Prednisolone 40mg added 3 weeks later for 'unremitting jaundice'	Hydroxyzine
Magee CD, 2016[15]	25	US	29	M	Methasterone, Stenbolone, desoxymethyltest-osterone	Jaundice and fatigue	70	10	3.33	cholestatic or mixed	6-Probable	340	112	101		56		
Hymel BM, 2013[16]	26	US	26	M	Mastabol (17 beta-Hydroxy-2alpha-methyl-5alpha-androstan-3- one propionate)	Jaundice, pruritis weight loss	41		0.80	cholestatic or mixed	6-Probable	404	117	441				Phenobarbitol
NASR J, 2009[17]	27	US	42	M	Methasterone (Superdrol)	Jaundice, pruritis weight loss	84		0.83	cholestatic or mixed	5-Possible	705	98	353	318	120	UDCA 1.2g	Hydorxyzine, naltrexone
Rosenfeld GA, 2011[18]	28	Canada	50	M	Methandrosteno-lone 10mg BD 3 weeks, TDS 5 weeks	Jaundice , abdo pain, weight loss	56	6	1.09	cholestatic or mixed	5-Possible	937	64	206	299			Standard medical therapy
Yoshida EM, 1994[19]	29	Canada	26	M	Stanazol 125mg im twice weekly	Jaundice, nausea and vomitting, malaise	56	28	0.72	cholestatic or mixed	4-Possible	876		369	418	150		Standard medical therapy
Shah NL, 2008[20]	30	US	33	M	Methasterone	Jaundice, pruritis, loss of appetite, amalaise		39	0.23	cholestatic or mixed	3-Possible	790	102	474	203	120	nil	
Shah NL, 2008[20]	31	US	28	M	Methasterone	Jaundice, pruritis lethargy abdo pain	120	30	1.62	cholestatic or mixed	7-Probable	872	99	217	407	60	nil	
Shah NL, 2008[20]	32	US	25	M	Methasterone	Jaundice, pruritis, lethargy, abdo pain, diarrhoea	42	30	1.72	cholestatic or mixed	5-Possible	599	289	182		60	nil	
[2] Shah NL, 2008[20]	33	US	20	M	Methasterone	Jaundice pruritis, malaise, anorexia constipation	42	32	4.27	cholestatic or mixed	6-Probable	547	554	184		60	nil	

Shah NL, 2008[20]	34	US	21	M	Methasterone	Jaundice, abdo pain, weight loss, anorexia, malaise	42	28	2.29	cholestatic or mixed	5-Possible		58	170		105	nil	
Sanchez-Osorio M, 2008[21]	35	Spain	29	M	Mesterolone, testosterone udecanoate, nandrolone, oxymethoone, stanazol, testosterone	Jaundice, pruritis, abdo pain, weight loss	105	5	1.02	cholestatic or mixed	8-Probable	581	54	694		150	UDCA	
Singh V, 2009[22]	36	US	51	M	Methasterone (Superdrol) dehydroepiandros-terone,	Jaundice	42	35	29.01	Hepatocellular	4-Possible	872	172	106		150	UDCA	Colestyramine, UDCA, Hydroxyzine, Plasmaphoresis
Singh V, 2009[22]	37	US	25	M	Methasterone (Superdrol) 2 pills per day for 2 months, Aminovol, ergomax	Jaundice and pruritis	60	28	6.38	Hepatocellular	5-Possible	923	236	111		60	nil	Zolpidem, doxepin, Colestyramine, Rifampicin
Singh V, 2009[22]	38	US	33	M	Methasterone (Superdrol)10mg TDS for 3 weeks	Jaundice and pruritis	35	14	1.73	cholestatic or mixed	6-Probable		69			120	nil	
Stepien PM, 2009[23]	39	Poland	19	M	Stanazol 50mg im alt days	Jaundice, pruritis, malaise	60	21	2.45	cholestatic or mixed	6-Probable		135	77	141	135	initially UDCA and LOLA then due to failure hydrocor-tisone.	
Wree A, 2011[24]	40	Germany	46	M	?				0.00	cholestatic or mixed	4-Possible	547	66	403			UDCA 750 and Pred 50mg 3d	
Wree A, 2011[24]	41	Germany	22	M	?				0.00	cholestatic or mixed	4-Possible	410	52				UDCA 1500, Pred 1g 3d	
Wree A, 2011[24]	42	Germany	22	M	?				0.00	cholestatic or mixed	4-Possible	650	67				UDCA 1500, Pred 1g 3d	
Wree A, 2011[24]	43	Germany	24	M	?				0.00	cholestatic or mixed	4-Possible	1163	53				UDCA 750, Pred 250mg 3d	
Wree A, 2011[24]	44	Germany	26	M	?				0.00	cholestatic or mixed	4-Possible	1180	59				UDCA 750, Pred 250mg 3d	
Flores A, 2016[25]	45	US	31	M	Promagnon and Epitiostanoll	Pruritis, jaundice, AKI mild confusion			0.00	cholestatic or mixed	3-Possible	906						Hydroxyzine, Colestyramine, UDCA, sertraline, naloxone
El Khoury, 2017[26]	46	Lebanon	35	M	Stanazol, Trenbolone, testosteroine proprionate	Jaundice, Pruritis, Abdo pain and vomiting			8.28	Hepatocellular	3-Possible	549	450	329			UDCA	Hydroxyzine
Luciano RL, 2014[27]	47	US	41	M	Nandrolone, Testosterone, methandrostenol-one	Jaudice, Pruritis, malaise, weight loss		52	6.68	Hepatocellular	2-Unlikley	819	267				UDCA	Hydroxyzine, Colestyramine
Tabatabaee SM, 2015[28]	48	Iran	30	M	Stanazol	Jaundice, nausea, malaise		0	0.19	cholestatic or mixed	4-Possible	821	33	535			nil specified	Haemodialysis
Tabatabaee SM, 2015[28]	49	Iran	43	M	Stanazol	Jaundice		36	0.29	cholestatic or mixed	4-Possible	992	66	690				Haemodialysis

Viella AL, 2013[29]	50	US	50	M	Incredible Bulk and Spartan 45(α- methyl-etioallocholan-2-ene-17β-ol 15 mg, 2α,3α-epithio- 17α-methyletioallocho-lanol 10 mg, and Bulgarian Tribulus Terrestris extract 300 mg; Spartan 45 : 4-chloro-17α-methyl-androst-4-ene-3,17β-diol 15 mg, 2α, METHASTERONE 17α-dimethyl-17β-hydroxy-5α-androstan-3-one 15 mg, and 13-ethyl-3-methoxy-gona-2,5(10)-diene-17-one)	Jaundice, diarrhoea	60	9	2.34	cholestatic or mixed	4-Possible	535	125	180		105	Prednisolone short course then UDCA added	Colestyramine, Hydroxyzine
Abeles RD	51	UK	30	M	Superdrol	Jaundice, malaise, diarrhoea	42	21	11.68	Hepatocellular	4-Possible	633	257	123	122	90	Prednisolone 60mg then 40mg	
Abeles RD	52	UK	39	M	Methandienone (Xyenobol Dianabol10mg)	Jaundice, abdo pain pruritis malaise	56	53	6.30	Hepatocellular	4-Possible	768	460	603	166	76	NAC intitally for 5 days, no response, UDCA 750 no response. Pred 40mg started respnse but loss then regained	Antihistamines
Summary stats	**N**	**Region**	**Age**	**Sex**	**AAS taken**	**Clinical presentation**	**Time from starting AAS to presentation (days)**	**Time from stopping AAS to peak Bili (Days)**	**R Value**	**Pattern of liver injury**	**Updated RUCAM score & Causality grading**	**Peak Bili (umol/L)**	**peak ALT (IU/L)**	**Peak ALP (IU/L)**	**Peak Cr umol/L**	**Time to resolution from peak Bili (days)**	**Primary therapy**	**Other therapies**
Median	52 cases	North America 23 (44%) Europe 25 (48%) Mid east 3 (6%) Australia 1 (2%)	29	Male 50 (96%)			56	28	2.0	Hepatocellular 10 (19%) cholestatic or mixed 42 (81%)	Median 5.0 Unlikely 1 (2%) Possible 31 (60%) Probable 20 (38%)	705	125	190	203	90		
25th Percentile			24				41.5	14	0.8		4.0	549	71	123	167	75		
75th percentile			38				72	35	4.3		6.0	872	234	287	300	120		

AAS Andorgenic Anabolic Steroid, Bili Bilirubin, ALT Alanine Amino-Transferase, ALP Alkaline Phosphatase, Cr Creatinine, UDCA Ursodeoxycholic Acid, MARS Molecular Adsorbent Recirculating System, LOLA L-Ornithine L-Aspartate, NAC N-Acetyl Cisteine.

R Value calculated (ALT/ULN ALT)/(ALP/ULN ALP), if no ALP available then assumed to be 1. RUCAM Roussel Uclaf Causality Assessment Method

1. Slater SD, Davidson JF, Patrick RS. Jaundice induced by stanozolol hypersensitivity. Postgrad Med J 1976;52:229-32.
2. Evely RS, Triger DR, Milnes JP, Low-Beer TS, Williams R. Severe cholestasis associated with stanozolol. Br Med J (Clin Res Ed) 1987;294:612-3.
3. Awai HI, Yu EL, Ellis LS, Schwimmer JB. Liver toxicity of anabolic androgenic steroid use in an adolescent with nonalcoholic fatty liver disease. J Pediatr Gastroenterol Nutr 2014;59:e32-3.
4. Brazeau MJ, Castaneda JL, Huitron SS, Wang J. A Case Report of Supplement-Induced Hepatitis in an Active Duty Service Member. Mil Med 2015;180:e844-6.
5. Cabb E, Baltar S, Powers DW, Mohan K, Martinez A, Pitts E. The Diagnosis and Manifestations of Liver Injury Secondary to Off-Label Androgenic Anabolic Steroid Use. Case Rep Gastroenterol 2016;10:499-505.
6. Diaz FC, Saez-Gonzalez E, Benlloch S, et al. Albumin dialysis with MARS for the treatment of anabolic steroid-induced cholestasis. Ann Hepatol 2016;15:939-43.
7. Ding NS, De Cruz P, Lim L, Thompson A, Desmond P. Androgenic-anabolic steroid drug-induced liver injury. Intern Med J 2013;43:215-6.
8. Eapen J, Ayoola R, Subramanian RM. 'The efficacy of extracorporeal liver support with molecular adsorbent recirculating system in severe drug-induced liver injury'. Oxf Med Case Reports 2018;2018:omx077.
9. El Sherrif Y, Potts JR, Howard MR, et al. Hepatotoxicity from anabolic androgenic steroids marketed as dietary supplements: contribution from ATP8B1/ABCB11 mutations? Liver Int 2013;33:1266-70.
10. Elsharkawy AM, McPherson S, Masson S, Burt AD, Dawson RT, Hudson M. Cholestasis secondary to anabolic steroid use in young men. BMJ 2012;344:e468.
11. Jasiurkowski B, Raj J, Wisinger D, Carlson R, Zou L, Nadir A. Cholestatic jaundice and IgA nephropathy induced by OTC muscle building agent superdrol. Am J Gastroenterol 2006;101:2659-62.
12. Kafrouni MI, Anders RA, Verma S. Hepatotoxicity associated with dietary supplements containing anabolic steroids. Clin Gastroenterol Hepatol 2007;5:809-12.
13. Anand JS, Chodorowski Z, Hajduk A, Waldman W. Cholestasis induced by parabolan successfully treated with the molecular adsorbent recirculating system. ASAIO J 2006;52:117-8.
14. Krishnan PV, Feng ZZ, Gordon SC. Prolonged intrahepatic cholestasis and renal failure secondary to anabolic androgenic steroid-enriched dietary supplements. J Clin Gastroenterol 2009;43:672-5.
15. Magee CD, Witte S, Kwok RM, Deuster PA. Mission Compromised? Drug-Induced Liver Injury From Prohormone Supplements Containing Anabolic-Androgenic Steroids in Two Deployed U.S. Service Members. Mil Med 2016;181:e1169-71.

16. Hymel BM, Victor DW, Alvarez L, Shores NJ, Balart LA. Mastabol induced acute cholestasis: A case report. World J Hepatol 2013;5:133-6.
17. Nasr J, Ahmad J. Severe cholestasis and renal failure associated with the use of the designer steroid Superdrol (methasteron): a case report and literature review. Dig Dis Sci 2009;54:1144-6.
18. Rosenfeld GA, Chang A, Poulin M, Kwan P, Yoshida E. Cholestatic jaundice, acute kidney injury and acute pancreatitis secondary to the recreational use of methandrostenolone: a case report. J Med Case Rep 2011;5:138.
19. Yoshida EM, Karim MA, Shaikh JF, Soos JG, Erb SR. At what price, glory? Severe cholestasis and acute renal failure in an athlete abusing stanozolol. CMAJ 1994;151:791-3.
20. Shah NL, Zacharias I, Khettry U, Afdhal N, Gordon FD. Methasteron-associated cholestatic liver injury: clinicopathologic findings in 5 cases. Clin Gastroenterol Hepatol 2008;6:255-8.
21. Sanchez-Osorio M, Duarte-Rojo A, Martinez-Benitez B, Torre A, Uribe M. Anabolic-androgenic steroids and liver injury. Liver Int 2008;28:278-82.
22. Singh V, Rudraraju M, Carey EJ, et al. Severe hepatotoxicity caused by a methasteron-containing performance-enhancing supplement. J Clin Gastroenterol 2009;43:287.
23. Stepien PM, Reczko K, Wieczorek A, et al. Severe intrahepatic cholestasis and liver failure after stanozolol usage - case report and review of the literature. Clin Exp Hepatol 2015;1:30-3.
24. Wree A, Dechene A, Herzer K, et al. Steroid and ursodesoxycholic Acid combination therapy in severe drug-induced liver injury. Digestion 2011;84:54-9.
25. Flores A, Nustas R, Nguyen HL, Rahimi RS. Severe Cholestasis and Bile Acid Nephropathy From Anabolic Steroids Successfully Treated With Plasmapheresis. ACG Case Rep J 2016;3:133-5.
26. El Khoury C, Sabbouh T, Farhat H, Ferzli A. Severe Cholestasis and Bile Cast Nephropathy Induced by Anabolic Steroids Successfully Treated with Plasma Exchange. Case Rep Med 2017;2017:4296474.
27. Luciano RL, Castano E, Moeckel G, Perazella MA. Bile acid nephropathy in a bodybuilder abusing an anabolic androgenic steroid. Am J Kidney Dis 2014;64:473-6.
28. Tabatabaee SM, Elahi R, Savaj S. Bile cast nephropathy due to cholestatic jaundice after using stanozolol in 2 amateur bodybuilders. Iran J Kidney Dis 2015;9:331-4.
29. Vilella AL, Limsuwat C, Williams DR, Seifert CF. Cholestatic jaundice as a result of combination designer supplement ingestion. Ann Pharmacother 2013;47:e33.

Supplemental Table 2: Comparison of current series and the Spanish/South-American series of Robles-Diaz *et al.*

	Current series (Abeles RD)	Robles-Diaz [1]
Number of cases	52	25
Age	29	31
Male	50 (96%)	25 (100%)
Days from starting AAS to presentation	56	49
Bilirubin umol/L	314	241
ALT IU/L	125	784
ALP IU/L	190	191
Renal dysfunction	22 (43%)	6 (24%)

AAS Androgenic Anabolic Steroid, ALT Alanine transferase, ALP Alkaline Phosphatase

1. Robles-Diaz M, Gonzalez-Jimenez A, Medina-Caliz I, et al. Distinct phenotype of hepatotoxicity associated with illicit use of anabolic androgenic steroids. Aliment Pharmacol Ther 2015;41:116-25.