

CASE REPORT

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Metabolic and hormonal dysfunction in asymptomatic patient using selective androgen receptor modulators: a case report

Brian Malave*

Abstract

Background Selective androgen receptor modulators (SARMs) are becoming increasingly common amongst athletes and the general population, but their side effect profile in human subjects at recreational doses is understudied.

Case presentation A 27-year-old asymptomatic male weightlifter presented for an annual physical exam and was coincidentally found to have an abnormal lipid panel, which the patient believed to be due to recreational SARMs (LGD-4033 and S-23) usage. Further work-up revealed elevated liver enzymes suggestive of hepatocellular injury and suppression of the pituitary–gonadal axis. Lipids, hepatic function, and hormones returned to baseline after cessation of SARMs.

Conclusions This is the first case report on how SARMs may impact LDL, cause hepatocellular rather than cholestatic liver injury, and alter health markers despite complete lack of symptoms. It is also the first case report on the potential negative effects of the SARM S-23.

Keywords Selective androgen receptor modulators, Hepatocellular injury, Testosterone suppression, Pituitary–gonadal inhibition, Drug-induced liver injury, Dyslipidemia

Background

Selective androgen receptor modulators (SARMs) were first developed in the late 1990s as agents that selectively target androgen receptors in muscle rather than those in other regions of the body—such as the prostate or seminal vesicles—to achieve anabolic effects of muscular strength and hypertrophy with minimal undesired androgenic effects such as prostate cancer, hair loss, or acne. Possible clinical uses include treatment of sarcopenia, osteoporosis, and cachexia; however, they are more commonly used without a prescription by weightlifters and athletes, many of whom consider SARMs a safer

alternative to anabolic steroids (Narayanan et al. 2018; Machek et al. 2020). Nonetheless, there is limited data on the safety of SARMs. This case report suggests altered lipid metabolism, hepatic dysfunction, and hormonal imbalance are possible side effects of the SARMs LGD-4033 and S-23.

Case presentation

A 27-year-old asymptomatic male weightlifter, BMI 25, presented to an ambulatory clinic for an annual physical exam. He reported eating a healthy diet and living an active lifestyle. He had no relevant family, medical, or psychosocial history. His physical exam was completely benign. A routine lipid panel revealed total cholesterol 237 mg/dL (reference range, <200 mg/dL), triglycerides 76 mg/dL (reference range, <150 mg/dL), LDL 198 mg/dL (reference range, <100 mg/dL), and HDL 24 mg/dL (reference range, \geq 40 mg/dL) (Table 1). The patient admitted to using SARMs for the past 8 weeks—4 weeks

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Table 1 Lipid panel

Test	During SARMs usage (after 7 weeks) 7/28/2022	Post-SARMs	
		8/29/2022	9/26/2022
Total cholesterol (< 200 mg)	237	176	151
Triglycerides (< 150 mg)	76	51	40
HDL (> 45 mg)	24	41	55
LDL (< 100 mg)	198	121	85
Cholesterol:HDL ratio (< 5)	9.88	4.29	2.75

Bold indicates value out of normal range

of 15 mg daily LGD-4033 (Ligandrol) followed by 4 weeks of 15 mg daily S-23. He did not report taking any other supplements or medications during the past 6 months.

A liver function test (LFT) revealed AST 75 IU/L (reference range, 10–40 IU/L), ALT IU/L 144 (reference range, 9–46 IU/L), ALP IU/L 56 (reference range, 36–130 IU/L) and total bilirubin 0.8 mg/dL (reference range, 0.2–1.2 mg/dL), indicative of hepatocellular injury (R-factor 7.3). The patient did not endorse drinking alcohol or taking any drugs. Work-up for hepatitis A, B, and C was negative. The patient did not have a history of shock, hypoxia, or heart failure within 2 weeks of onset of liver injury, and clinical presentation was not concerning for CMV, EBV, HSV, or autoimmune causes of liver injury (Table 2).

Further laboratory data revealed free testosterone 48.7 pg/mL (reference range 35–155 pg/mL), total testosterone 145 ng/dL (reference range, 250–1100 ng/dL), LH 1.3 mIU/mL (reference range, 1.5–9.3 mIU/mL), and FSH 1.2 mIU/mL (reference range, 1.6–8.0 mIU/mL). His baseline values prior to SARMs usage were all within normal limits (Table 3).

Repeat labs at 3 weeks after cessation of SARMs showed return of his total cholesterol, HDL, LDL, testosterone, LH, and FSH to normal values, and down-trending AST and ALT. Repeat labs at 2 months after cessation showed resolution of his LFTs to baseline (Tables 1, 2 and 3).

Discussion

SARMs were developed as a safer alternative to anabolic steroids, with improved tissue selectivity intended to minimize negative side effects. However, the results presented here suggest that SARMs may have several negative effects on a patient’s overall health, even in the absence of symptoms.

Lipids

This patient had an elevated LDL and cardiac risk (total cholesterol/HDL) ratio of 9.9 after SARMs usage, putting him at increased risk for coronary artery disease (ratio > 5). His cardiac risk ratio was reduced to 4.29 after 3 weeks of SARMs cessation, and 2.75 at 2 months cessation. He did not report taking lipid-lowering medications at any point.

Table 2 Liver function tests

Test	Pre-SARMs	Last day SARMs usage 8/05/2022	Post-SARMs	
	8/12/2020		8/29/2022	9/26/2022
AST	26 (0–39 U/L)	75 (10–40 U/L)	54 (10–40 U/L)	29 (10–40 U/L)
ALT	30 (0–55 U/L)	144 (9–46 U/L)	120 (9–46 U/L)	28 (9–46 U/L)
ALP	73 (40–130 U/L)	56 (36–130 U/L)	51 (36–130 U/L)	60 (36–130 U/L)
Bilirubin, total	0.6 (0.2–1.3 mg/dL)	0.8 (0.2–1.2 mg/dL)	0.7 (0.2–1.2 mg/dL)	0.5 (0.2–1.2 mg/dL)

Bold indicates value out of normal range

Table 3 Hormones

Test (range)	Pre-SARMs			Last day SARMs usage 8/5/2022	Post-SARMs	
	7/24/2020	8/12/2020	9/1/2020		8/29/2020	9/26/2022
Testosterone, free (33–155 pg/mL)	–	–	104	48.7	105	87.2
Testosterone, total (250–1100 ng/dL)	438	367	486	145	341	445
Luteinizing hormone (LH; 1.5–9.3 mIU/mL)	3.1	–	–	1.3	2	1.9
Follicular-stimulating hormone (FSH; 1.6–8.0 mIU/mL)	1.5	1.4	–	1.2	1.7	1.7

Bold indicates value out of normal range

Table 4 Drug-induced liver injury secondary to SARMs

References	Patient age/ sex	SARM	Duration	Presenting symptoms	Initial/peak bilirubin	Initial ALT/ AST/ALP	Peak ALP	Initial/ peak R-factor*	Type of liver injury	RUCAM (or DILIN) score	Management
Flores et al. (2020) (2 case reports)	1. 24 years M 2. 49 years M	1. LGD-4033 2. RAD-140	1. 9 weeks 2. 4 weeks	Jaundice, nau- sea, lethargy, weight loss	1. 6.78/6.78 2. 17/20.2	1. 589/175/197 2. 200/111/111	1. 289 2. 327	1. 8.2/1.6 2. 5.0/0.5	1. Mixed/chole- static 2. Mixed/chole- static**	1. 7 2. 6	SARM cessation, supportive care
Barbara et al. (2020)	32 years M	LGD-4033	2 weeks	Jaundice, fatigue, pruritis, weight loss	35/38.2	229/91/88	525	-/-	Mixed/choles- tatic**	-	SARM cessation, supportive care
Barbara et al. (2020)	52 years M	RAD-140/LGD- 4033	7 weeks	Jaundice, RUQ pain, pruritis, diarrhea	34.5/34.5	46/36/529	529	0.2/0.2	Cholestatic**	-	SARM cessation, supportive care
Bedi et al. (2021)	"Early 40s" years M	MK-2866	8 weeks	Jaundice, weight loss, lethargy, diar- rhea	19.9/43	112/69/268	>400	0.8/-	Cholestatic**	-	SARM cessation, supportive care
Akhtar et al. (2021)		RAD-140/LGD- 4033/MK-2866	24 weeks	Jaundice, abdominal pain, pruritis	6.9/34	115/61/173	434	-/-	Cholestatic	-	SARM cessation, supportive care
Koller et al. (2021) (2 case reports)	1. 19 years M 2. 28- years M	1. LGD-4033 2. LGD-4033/ MK-2866	1. 4 weeks 2. 12 weeks	1. Jaundice 2. Jaundice, nausea, fatigue	1. 238/238 2. 401/401	1. 132/-/92.4 2. 144/-/92.4	1. 92.4 2. 131	1. 3.9/3.9 2. 3.9/2.0	1. Mixed** 2. Mixed/chole- static**	1. 6 2. -	SARM cessation, supportive care
Khan et al. (2022)	29 years M	Unspecified	4 weeks	Jaundice, icterus, pruritis, fatigue	16.9/22.6	165/79/213	305	-/-	Cholestatic**	(DILIN causality 1; severity 3 +)	SARM cessation, supportive care
Leung et al. (2022)	24 years M	RADO-140	5 weeks	Jaundice, icterus, abdominal pain, pruritis	1.2/38.5	313/182/103	251	4.4/1.2	Mixed/choles- tatic**	(DILIN causality 1; severity 2)	SARM cessation, supportive care
Lee et al. (2022)	23 years M	LGD-4033/RAD- 140/YK-11	12 weeks	Jaundice, icterus, pruritis, loss of appetite	29.2/36.37	148/88/151	290	0.8/-	Cholestatic	6	SARM cessation, supportive care
Present case, 2022	27 years M	LGD-4033/S-23	8 weeks	None	0.8/0.8	144/75/56	73	7.3/7.3	Hepatocellular	6	SARM cessation, supportive care

SARM, Selective Androgen Receptor Modulator; ALP, alkaline phosphatase; ALT, alanine transaminase; AST, aspartate aminotransferase; RUQ, right upper quadrant
LGD-4033 (Ligandrol), MK-2866 (Ostarine or Enobosarm), RAD-140 (Testolone); RUCAM, Roussel Uclaf Causality Assessment Method

*Peak R-factor refers to R-factor when patient's ALP was the highest during the hospital course. Not all R-factors were reported and could not be calculated if reference ranges for laboratory normal values were not provided

**Liver biopsy confirmed diagnosis

A variety of SARMs—including LGD-4033—have been demonstrated to lower HDL levels in subjects, likely secondary to a SARM-mediated increase in hepatic lipase (Machek et al. 2020; Guo et al. 2022). However, no literature to date has suggested that SARMs increase LDL or total cholesterol levels. Although this patient did not have a baseline lipid panel prior to starting SARMs, his lipid panel improvement after cessation—despite no change to his diet or exercise regimen—suggests that SARMs likely raised his LDL and total cholesterol levels. More research should be done on the relationship between SARMs and LDL.

Hepatic function

The patient's Roussel Uclaf Causality Assessment Method (RUCAM) score was 6, making his recent SARMs usage a likely cause of his liver injury (Danan and Teschke 2019). His liver function test values are indicative of a hepatocellular rather than cholestatic pattern ($R\text{-factor} > 5$ [$R = (\text{ALT}/\text{ULN ALT}) / (\text{ALP}/\text{ULN ALP})$]). In the past two years, there have been several case reports of symptomatic patients taking SARMs who were found to have a cholestatic or mixed pattern of hepatic injury (Flores et al. 2020; Barbara et al. 2020, 2020; Bedi et al. 2021; Akhtar et al. 2021; Koller et al. 2021; Khan et al. 2022; Leung et al. 2022; Lee et al. 2022) (Table 4). However, no other case report indicates a purely hepatocellular cause of injury, or hepatic injury in an asymptomatic patient.

Liver damage from SARMs is thought to be idiosyncratic, with immune cells attacking the subject's own hepatocytes, cholangiocytes, or both. This is supported by liver biopsies of patients with SARMs-mediated drug-induced liver injury (DILI) that demonstrated lymphocytic infiltrate (Flores et al. 2020; Barbara et al. 2020; ; Bedi et al. 2021; Koller et al. 2021; Khan et al. 2022; Leung et al. 2022; Barbara et al. 2020). The rarity of cases of SARMs-induced DILI relative to extent of misuse and lack of association between dosage or length of use with severity of liver injury also suggests an idiosyncratic response (Danan and Teschke 2019; Flores et al. 2020).

It should be noted that while liver biopsies have been performed in other case reports of SARMs-mediated DILI, this was usually done for a patient with worsening symptoms or liver function enzymes, in which case additional diagnostic evidence was beneficial (Flores et al. 2020; Barbara et al. 2020; ; Bedi et al. 2021; Koller et al. 2021; Khan et al. 2022; Leung et al. 2022; Barbara et al. 2020). The patient in this case report was completely asymptomatic and his liver function enzymes improved with cessation of SARMs, so a liver biopsy was not performed. His clinical history, serologic, and radiographic evaluations were negative for other etiologies, so biopsy

results would have been of minimal benefit in determining prognosis or guiding further management.

Hormonal suppression

This patient's labs suggest that SARMs suppress the pituitary–gonadal axis. Clinical trials have shown that SARMs—including both LGD-4033 and S-23—suppress testosterone, LH, and FSH when given for as little as 2 weeks (Machek et al. 2020; Neil et al. 2018; Clark et al. 2017; Jones et al. 2009; Gao et al. 2005; Yin et al. 2003; Miller et al. 2011; Basaria et al. 2013). It is concerning that most of these studies utilized doses much lower than what this patient was taking, ranging from 0.01 to 3 g/day, compared to this patient's 15 g/day. The suppression appears to be temporary, with subjects' blood markers returning to normal within 1 to 3 months, as did this patient's. One can assume that longer cycles of SARMs usage or higher doses might lead to longer recovery times, although this has not been validated in the literature.

Shortcomings

One drawback to this study is that the patient's SARMs were not sent for testing of purity or contamination. A 2017 JAMA study found that of 44 products sold as SARMs online, only 52% contained SARMs, with 39% containing another unapproved drug (Wagoner et al. 2017). This patient's SARMs were purchased from a company that provides third-party testing for purity, however, which adds some layer of validity. Another drawback is that since this patient took two different SARMs, it is difficult to determine how much of his results are due to LGD-4033, S-23, or both.

Conclusions

In conclusion, this case documents the likely negative effects of SARMs on lipid metabolism, liver function, and hormone balance. This is the first case report of SARM's effects on LDL, hepatocellular rather than cholestatic liver injury, and altered health markers in an asymptomatic individual. This is also the first case report on the possible side effects of the SARM S-23 on human subjects.

Abbreviations

SARMs	Selective androgen receptor modulators
BMI	Body mass index
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
LFT	Liver function test
ALT	Alanine transaminase
AST	Aspartate aminotransferase
ALP	Alkaline phosphatase
LH	Luteinizing hormone
FSH	Follicular stimulating hormone

RUCAM Roussel Uclaf Causality Assessment Method
 DILI Drug-induced liver injury
 ULN Upper limit of normal

Acknowledgements

Thank you to Pamela Bagely for her assistance with the research process, from literature review strategies to citation-specific questions.

Author contributions

BM is sole author. The author read and approved the final manuscript.

Funding

No funding was obtained for this study.

Availability of data and materials

The datasets generated and/or analyzed during current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests

The authors declare no competing interests.

Received: 16 December 2022 Accepted: 22 January 2023

Published online: 30 January 2023

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