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CASE REPORT

LGD-4033 and MK-677 use impacts body composition, circulating biomarkers, and skeletal muscle androgenic hormone and receptor content: A case report

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Abstract

LGD-4033, a selective androgen receptor modulator, and MK-677, a growth hormone secretagogue, are being used increasingly amongst recreationally active demographics. However, limited data exist describing their effects on health- and androgen-related biomarkers. The purpose of this case study was to determine changes in body composition and biomarkers during and after continued co-administration of LGD-4033 and MK-677. We also aimed to examine muscular strength and intramuscular androgen-associated biomarkers relative to non-users. A 25-year-old male ingested LGD-4033 (10 mg) and MK-677 (15 mg) daily for 5 weeks. Blood and body composition metrics were obtained pre-, on- and post-cycle. One-repetition maximum leg and bench press, in addition to intramuscular androgens and androgen receptor content, were analysed on-cycle. We observed pre- to on-cycle changes in body composition (body mass, +6.0%; total lean body mass, +3.1%; trunk lean body mass, +6.6%; appendicular lean body mass, +4.3%; total fat mass, +15.4%; trunk fat mass, +2.8%; and appendicular fat mass, +14.8%), bone (bone mineral content, -3.60%; area, -1.1%; and bone mineral density, -2.1%), serum lipid-associated biomarkers (cholesterol, +14.8%; triglycerides, +39.2%; low-density lipoprotein-cholesterol, +40.0%; and high-density lipoprotein-cholesterol, -36.4%), liver-associated biomarkers (aspartate aminotransferase, +95.8%; and alanine aminotransferase, +205.0%) and androgen-associated biomarkers (free testosterone, -85.7%; total testosterone, -62.3%; and sex hormone-binding globulin, -79.6%); however, all variables returned to pre-cycle values post-cycle, apart from total fat mass, appendicular fat mass, bone area, total cholesterol and low-density lipoprotein-cholesterol. Follicle-stimulating hormone was below clinical reference values on- (1.2 IU/L) and post-cycle (1.3 IU/L). Intramuscular androgen receptor (-44.6%), testosterone (+47.8%) and dihydrotestosterone (+34.4%), in addition to one-repetition maximum leg press and bench press (+39.2 and +32.0%, respectively),

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were different in the case subject compared with non-users. These data demonstrate that LGD-4033 and MK-677 increase several body composition parameters, whilst negatively impacting bone and several serum biomarkers. Given the sparsity of data in recreationally using demographics, further research is warranted to elucidate the acute and chronic physiological effects of these anabolic agents.

KEYWORDS

androgen receptor, ergogenic aid, growth hormone secretagogue, ibutamoren, ligandrol, muscle strength, performance-enhancing drug, selective androgen receptor modulator, testosterone

1 | INTRODUCTION

Selective androgen receptor modulators (SARMs) are a class of engineered anabolic compounds that bind differentially to the androgen receptor (AR) and alter receptor function (Christiansen et al., 2020; Machek, Cardaci et al., 2020; Solomon et al., 2019). They are posited to exert potent anabolic effects in skeletal muscle and bone (Bhasin & Jasuja, 2009; Narayanan et al., 2018), whilst lacking the undesired androgenic-related side effects (testicular atrophy, fluid retention, hypertension, gynecomastia, alopecia, decreased libido, etc.) commonly associated with anabolic androgenic steroids (Davani-Davari et al., 2019; Efimenko et al., 2021; Rahnema et al., 2014; van Amsterdam et al., 2010). This is primarily attributable to the tissue-selective nature of these compounds along with their limited ability to cross-react with other steroid receptors, aromatize to estradiol or reduce to dihydrotestosterone. For this reason, SARMs continue to be investigated in several clinical conditions, including sarcopenia, cachexia and osteoporosis, in addition to other androgen-related conditions, including urinary incontinence and prostate cancer (Bhasin & Jasuja, 2009; Kadekawa et al., 2020; Komrakova et al., 2020; Nyquist et al., 2021; Srinath & Dobs, 2014). LGD-4033 (also known as ligandrol) is a highly selective non-steroidal SARM with relatively high binding affinity that has been investigated in multiple preclinical and clinical models (Basaria et al., 2013; Fragkaki et al., 2018). Recently, however, recreational use of LGD-4033 and other SARMs has increased without evidence supporting their utility or safety (Efimenko et al., 2021; Hilkens et al., 2021; Machek, Cardaci et al., 2020; Shimko et al., 2021). Furthermore, these compounds are rarely taken in isolation or at previously studied clinical doses.

In some recreational settings, growth hormone secretagogues (GHSs), a class of compounds developed to stimulate the secretion of growth hormone (GH), can be co-administered with SARMs to 'maximize' anabolism (Sigalos & Pastuszak, 2018; Sinha et al., 2020). Once released into the circulation, GH stimulates the release of insulin-like growth factor 1 by the liver to induce anabolic signalling in peripheral tissues, notably skeletal muscle (Velloso, 2008). Additionally, GH can activate the GH receptor and elicit diverse downstream intracellular signalling (Carter-Su et al., 2016; Velloso, 2008). Similar to SARMs, GHSs are being investigated to treat a variety of muscle-wasting conditions (Conte et al., 2017; Murphy et al., 1998; Sigalos & Pastuszak, 2018); however, their recreational safety and utility are

not well understood. MK-677 (also known as ibutamoren) is an orally active non-peptide mimic of GH-releasing peptide, which has shown promise as an anabolic and therapeutic agent (Murphy et al., 1998; Nass et al., 2008; Svensson et al., 1998); nevertheless, currently no data exist supporting its safety and efficacy when co-administered with SARMs.

Although several investigations (Adunsky et al., 2011; Chapman et al., 1997; Dobs et al., 2013; Svensson et al., 1998; Yuan et al., 2021) and comprehensive reviews (Advani et al., 2018; Bhasin & Jasuja, 2009; Christiansen et al., 2020; Machek, Cardaci et al., 2020; Narayanan et al., 2018; Sigalos & Pastuszak, 2018; Sinha et al., 2020; Solomon et al., 2019) have illustrated SARM- and GHS-specific safety and efficacy in clinical settings, there is a paucity of literature evaluating their implications in otherwise healthy individuals. Incidentally, SARM and GHS co-administration in recreational athletes has recently grown in popularity, with the aim of enhancing aesthetics, athletic performance and muscular strength (Efimenko et al., 2021; Hilkens et al., 2021; Holt & Ho, 2019; Shimko et al., 2021). This phenomenon is of particular concern because we are unaware of any data that examine the co-administration of these compounds, either in general or at the relatively large doses commonly taken by recreational users (Van Wagoner et al., 2017).

The purpose of this case study is to report longitudinal changes in body composition and in circulating androgen- and health-related biomarkers in an individual chronically co-administering the SARM LGD-4033 and the GHS MK-677, both during and 4 weeks after the cessation of use. We also aimed to examine the muscular strength of this subject cross-sectionally, alongside skeletal muscle androgenic hormone and receptor concentrations compared with non-users.

2 | METHODS

2.1 | Subject

A resistance exercise-trained male (age, 25.3 years; height, 178 cm; and training age, 8.8 years) participated in this case report. The subject self-administered 10 mg of LGD-4033 and 15 mg of MK-677 daily for 5 weeks. Comprehensive blood analyses and body composition testing were performed before (pre-cycle), immediately after 5 weeks of continuous use (on-cycle) and 4 weeks after cessation (post-cycle)

of LGD-4033 and MK-677 use. Excision of skeletal muscle tissue and muscular strength testing were conducted cross-sectionally while the subject was on-cycle. For collection of body composition metrics and biospecimens, the subject was instructed to report to the laboratory upon waking in a rested, fasted and euhydrated state after refraining from exercise for 48 h. Methods of sample collection were approved by the Institutional Review Board for Human Subjects at Baylor University, and informed consent was obtained from the participant. All procedures in the study conformed to the ethical considerations of the *Declaration of Helsinki*.

2.2 | Body composition

Total body mass (BM; in kilograms) and height (in centimetres) were determined on a dual-beam balance scale (Detecto, Bridgeview, IL, USA). Total body water (TBW; in litres and as a percentage) was assessed via bioelectrical impedance analysis (Tanita, Tokyo, Japan). Bone mineral content (BMC; in kilograms) and density (BMD; in grams per centimetre squared), bone area (in centimetres squared), trunk/appendicular lean mass (in kilograms), trunk/appendicular fat mass (in kilograms) and visceral adipose tissue area (in centimetres squared) were determined using dual-energy X-ray absorptiometry (DEXA) (Hologic Discovery Series W, Waltham, MA, USA). A four-compartment model was used to calculate total fat mass (FM; in kilograms) and total lean body mass (LBM; in kilograms) using DEXA-derived body volume (Smith-Ryan et al., 2017; Tinsley, 2018).

2.3 | Muscular strength testing

To determine muscular strength, the subject performed one-repetition maximum (1RM) tests for barbell bench press and 45°-angled leg press (Nebula Fitness Equipment, Scottsdale, AZ, USA) as previously described by researchers in our laboratory (Cardaci et al., 2020) and in accordance with the National Strength and Conditioning Association (NSCA) guidelines (Haff & Triplett, 2015). The subject refrained from exercise for 48 h before testing. The 1RM was recorded as the maximum weight that the participant was able to lift for one repetition for each exercise. A goniometer was used to establish 90° of knee flexion on the leg press, and a marker placed corresponding to that depth was used to enforce the full range of motion on each repetition.

2.4 | Venipuncture and blood analyses

Antecubital venous blood samples were taken into 10 ml vacutainer tubes using a 21-gauge phlebotomy needle. Comprehensive blood analyses (complete blood count, metabolic, lipid, and androgen-associated markers) were analysed by a Clinical Laboratory Improvement Amendments-certified laboratory. Blood data were collected pre-cycle, on-cycle and post-cycle. All pre-cycle blood analyses were provided retrospectively. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) were not assessed pre-cycle;

New Findings

- **What is the main observation in this case?**

Co-administration of LGD-4033 and MK-677 increased body mass, lean mass and fat mass, while negatively impacting bone, serum lipids, liver enzymes, testosterone (total and free) and, probably, follicle-stimulating hormone.

- **What insights does it reveal?**

Our cross-sectional data imply that these compounds might alter intramuscular androgenic hormone and receptor concentrations along with promoting muscular strength, when compared with previously published data from trained males.

however, these hormones were assessed on- and post-cycle to infer potential decrements in upstream hypothalamic-pituitary-gonadal activity (Machek, Cardaci et al., 2020).

2.5 | Skeletal muscle biopsy and tissue processing

A single muscle sample was obtained in a fasted and rested state via percutaneous muscle biopsies (total ~30 mg) from the middle portion of the vastus lateralis muscle of the dominant leg (midpoint between the patella and greater trochanter) at a depth between 1 and 2 cm using a 14-gauge TRU-CORE 1 automatic biopsy instrument (Angiotech, Medical Device Technologies, Gainesville, FL, USA) after subcutaneous administration of local anaesthetic (1 ml of 1% lignocaine/xylocaine) as previously performed by our laboratory (Cardaci et al., 2021; Hwang et al., 2020; Machek, Hwang et al., 2020; Wilburn, Machek, Cardaci, Hwang et al., 2020, 2020). After removal, adipose tissue was trimmed from the muscle specimens and they were immediately frozen and stored at -80°C for later analysis. The muscle sample was weighed and homogenized using a commercial tissue extraction reagent (Invitrogen Corporation, Camarillo, CA, USA). Total muscle protein was isolated and supplemented with a protease inhibitor cocktail (Sigma Chemical Company, St. Louis, MO, USA) with broad specificity for the inhibition of serine, cysteine and metalloproteases. Total muscle protein content was analysed in duplicate and determined spectrophotometrically at a wavelength of 750 nm (Bio-Rad, Hercules, CA, USA) using bovine serum albumin as the standard.

2.6 | Intramuscular androgenic hormone and receptor analyses

Intramuscular total AR, testosterone and dihydrotestosterone concentrations were assessed using commercially available enzyme-linked immunosorbent assay (ELISA) kits (MyBioSource, San Diego, CA, USA; Eagle Biosciences, Nashua, NH, USA). The specificities

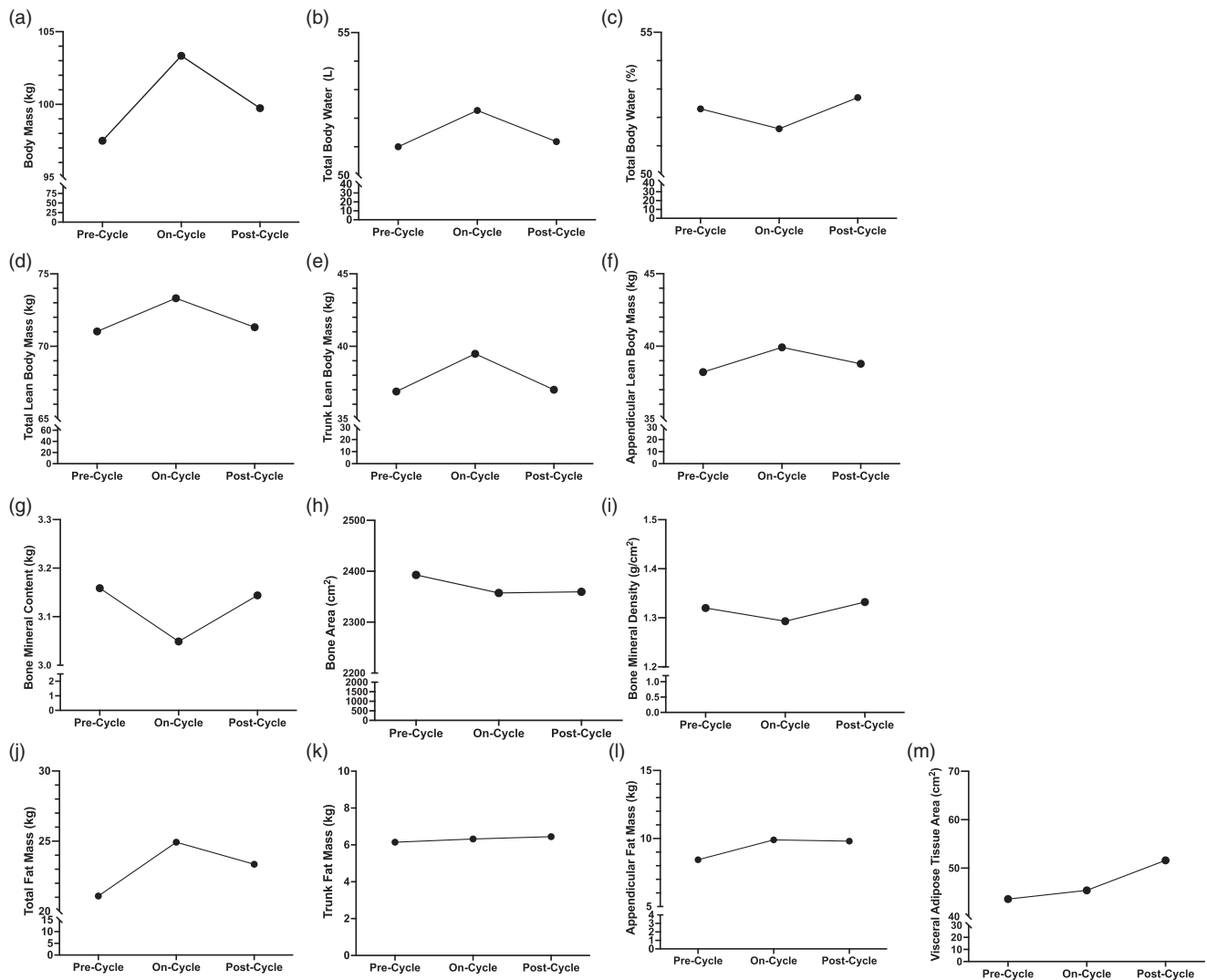


FIGURE 1 Anthropometric and body composition-associated parameters pre-, on- and post-cycle following co-administered LGD-4033 and MK-677.

of total AR, testosterone and DHT ELISA kits were all 100%, with the sensitivity estimated to be 0.1 ng/ml, 0.018 pg/ml and 6 pg/ml, respectively. The sample was analysed in duplicate, and absorbances were determined at a wavelength of 450 nm using a microplate reader (iMark, Bio-Rad, Hercules, CA, USA) against known standard curves. Final concentrations were expressed relative to total protein concentration.

3 | RESULTS

3.1 | Body composition

There was an increase from pre- to on-cycle in BM (+6.0%; Figure 1a), total LBM (+3.1%; Figure 1d), trunk LBM (+6.6%; Figure 1e), appendicular LBM (+4.3%; Figure 1f), total FM (+15.4%; Figure 1j), trunk FM (+2.8%; Figure 1k), appendicular FM (+14.8%; Figure 1l) and TBW (+2.5%; Figure 1b). A decrease from on- to

post-cycle was observed in BM (−5.7%; Figure 1a), total LBM (−2.8%; Figure 1d), trunk LBM (−6.7%; Figure 1e), appendicular LBM (−2.9%; Figure 1f) and TBW (−2.1%; Figure 1b), while trunk FM increased further (+1.9%; Figure 1k) and total FM (−6.7%; Figure 1j) and appendicular FM (−1.0%; Figure 1l) decreased, albeit not to pre-cycle levels. The BMC (−3.6%; Figure 1g), bone area (−1.1%; Figure 1h) and BMD (−2.1%; Figure 1i) decreased from pre- to on-cycle. From on- to post-cycle, BMC (+3.02%; Figure 1g) and BMD (+2.9%; Figure 1i) returned to near pre-cycle values, whereas bone area (+0.1%; Figure 1h) did not. Visceral adipose tissue area increased from pre- to on-cycle (+4.0%; Figure 1m) and increased further from on- to post-cycle (+13.6%; Figure 1m).

3.2 | Blood biomarkers

Increases were observed from pre- to on-cycle in total cholesterol (+14.8%; Table 1), triglycerides (+39.2%; Table 1) and low-density

TABLE 1 Pre-, on- and post-cycle comparison of comprehensive analysis of serum biomarker values

Marker	Units	Reference range	Pre-cycle	On-cycle	Post-cycle
White blood cells	$\times 10^3/\mu\text{l}$	3.6–9.9	5.3	5.8	4.7
Red blood cells	$\times 10^6/\mu\text{l}$	4.32–5.71	5.33	5.06	5.24
Hemoglobin	g/dl	13–16.6	15.4	14.9	14.9
Haematocrit	%	40–49	47.9	44.4	46.1
Platelet count	$\times 10^3/\mu\text{l}$	158–384	167	234	157 ^a
Mean corpuscular volume	fl	76–98	90	87.7	88
Mean corpuscular haemoglobin	pg	26.7–33.2	28.9	29.4	28.4
Mean corpuscular haemoglobin concentration	g/dl	32.3–36.1	32.2 ^a	33.6	32.3
Red cell distribution width	%	12–14.8	13.4	13.1	12.3
Neutrophils	%	38–73	50.2	46.3	48
Lymphocytes	%	17–48	30.7	37.4	38.8
Monocytes	%	6.0–13.0	17 ^b	13.4 ^b	11.1
Eosinophils	%	1.0–8.0	1.3	2.4	1.5
Basophils	%	0–1	0.6	0.5	0.6
Fasting glucose	mg/dl	70–100	100	98	95
Blood urea nitrogen	mg/dl	9–25	15	17	24
Creatinine	mg/dl	0.67–1.17	1.14	1.05	1.26 ^b
Sodium	mmol/L	136–145	140	138	139
Potassium	mmol/L	3.5–5.1	4.5	5.0	4.1
Chloride	mmol/L	100–109	101	99 ^a	101
Carbon dioxide	mmol/L	21–32	28	27	28
Calcium	mg/dl	8.5–10.1	9.0	9.3	9.2
Total protein	g/dl	6.7–8.4	6.6 ^a	6.7	6.9
Albumin	g/dl	3.4–5.0	4.6	4.2	4.4
Globulin	g/dl	1.9–3.7	2.0	2.5	2.5
Total bilirubin	mg/dl	0.20–1.0	0.4	0.3	0.5
Alkaline phosphatase	U/L	45–117	55	41 ^a	58
Aspartate aminotransferase	U/L	0–35	24	47 ^b	25
Alanine aminotransferase	U/L	7–56	20	61 ^b	29
Glomerular filtration rate, calculated	ml/min/1.73 m ²	>60	89	98	79
Total cholesterol	mg/dl	<200	155	178	177
Total triglyceride	mg/dl	<150	51	71	73
High-density lipoprotein-cholesterol	mg/dl	>39	55	35 ^a	50
Low-density lipoprotein-cholesterol	mg/dl	<100	90	126 ^b	111 ^b
Total testosterone	ng/dl	250–827	639	241 ^a	659
Free testosterone	pg/ml	30.6–152.0	148	85.7	148.1
Sex hormone-binding globulin	nmol/L	14.55–94.64	29.9	6.1 ^a	31.9
Follicle-stimulating hormone	IU/L	1.5–12.4	Not assessed	1.2 ^a	1.3 ^a
Luteinizing hormone	IU/L	1.2–8.6	Not assessed	4.6	5.4

^aLower than standard clinical reference range.^bHigher than standard clinical reference range.

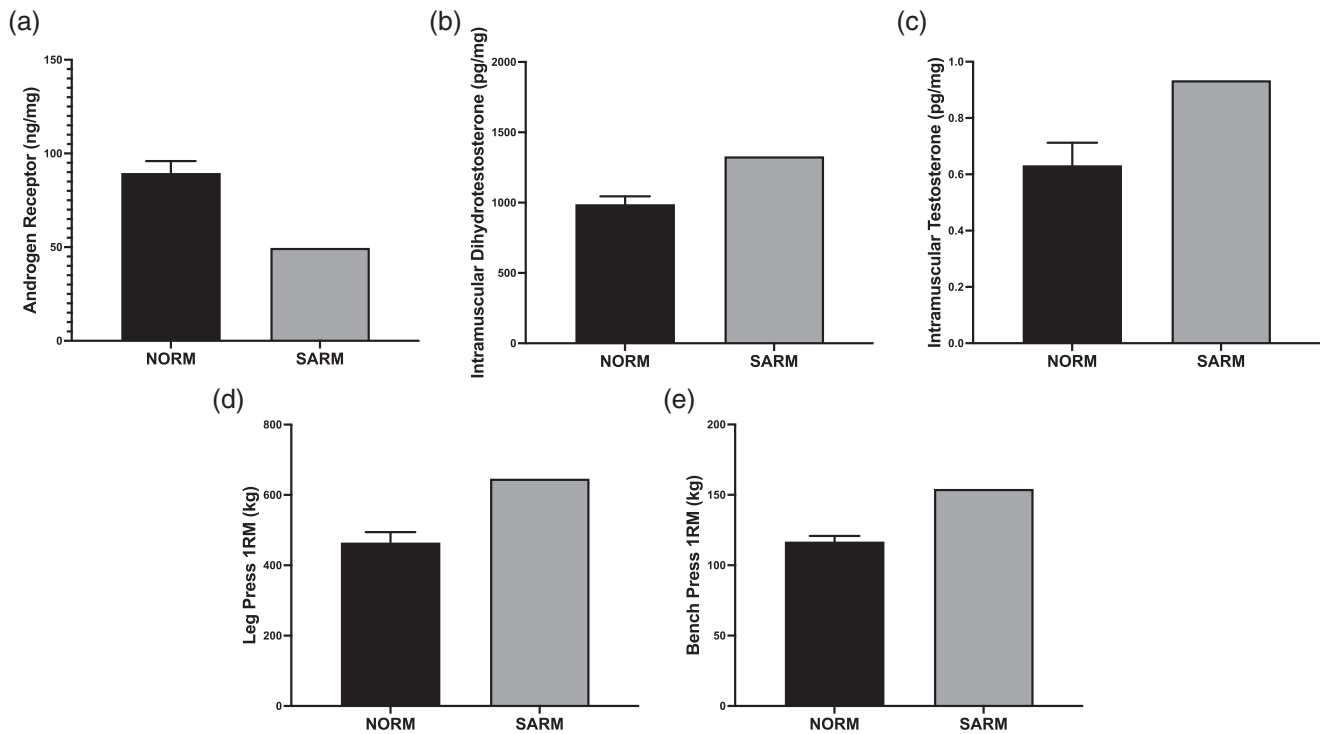


FIGURE 2 Cross-sectional comparison between the case subject and a previously described healthy, recreationally trained male population with regard to intramuscular androgen targets and to leg and bench press strength metrics (Cardaci et al., 2020). Abbreviations: 1RM, one-repetition maximum; NORM, values from the literature; SARM, values from the present subject. The 'NORM' values are shown as the mean (\pm SEM).

lipoprotein-cholesterol (above reference value; +40.0%; Table 1) and remained elevated post-cycle. High-density lipoprotein-cholesterol decreased from pre- to on-cycle (below reference value; -36.4%; Table 1) and returned to near baseline values post-cycle. Aspartate aminotransferase (+95.8%; Table 1) and alanine aminotransferase displayed an increase from pre- to on-cycle (+95.8 and +205.0%, respectively; both above reference value; Table 1), which subsequently returned to near baseline post-cycle. A decrease in total testosterone (below reference value; -62.3%; Table 1), free testosterone (-85.7%; Table 1) and sex hormone-binding globulin (SHBG; below reference value; -79.6%; Table 1) from pre- to on-cycle was observed, and all returned to near baseline values post-cycle. Follicle-stimulating hormone was below reference values on- (1.2 IU/L; Table 1) and post-cycle (1.3 IU/L; Table 1), while LH was within the reference range. All other metabolic, immune and haematological markers assessed did not change notably over time (Table 1).

3.3 | Muscular strength and intramuscular androgenic hormone and receptor content

In comparison to our previously published data in resistance-trained non-users (Cardaci et al., 2020), intramuscular AR content was less (-44.6%; Figure 2a), whereas intramuscular testosterone (Figure 2c) and dihydrotestosterone (Figure 2b) were greater (+47.8 and +34.4%, respectively) in the case subject. Moreover, 1RM leg press (Figure 2d)

and bench press (Figure 2e) were notably greater (+39.2 and +32.0%, respectively) in the user compared with these previously published data in non-users.

4 | DISCUSSION

In this case report, we document the pattern of change in body composition along with health- and androgen-related biomarkers in a resistance-trained male self-administering 10 mg of LGD-4033 and 15 mg of MK-677 daily for 5 weeks. Additionally, these data are the first to cross-sectionally report the intramuscular androgenic hormone and receptor concentrations of an individual while ingesting these compounds. Our data consequently indicate that LGD-4033 and MK-677 co-administration increased body mass, lean body mass and fat mass while negatively impacting BMD, in addition to serum lipids, liver enzymes, testosterone (total and free) and, likely, FSH. Importantly, we also report minimal LGD-4033 and MK-677 co-administration-mediated impacts on renal and haematological markers. Moreover, the present cross-sectional data imply that these anabolic agents ostensibly alter intramuscular androgen hormone and receptor concentrations, along with promoting greater relative lower and upper body strength compared to previously published data on trained males (Cardaci et al., 2020).

Although our data suggest that these compounds may increase body mass, muscle mass and muscular strength akin to anabolic-androgenic

steroids (Andrews et al., 2018; Varanoske et al., 2022, 2020), the negative effects on FM, bone, circulating blood lipids, liver enzymes and androgen-related markers should be strongly considered as important contraindications (Albano et al., 2021; Andrews et al., 2018; Machek, Cardaci et al., 2020; Varanoske et al., 2020). Specifically, the observed BMC, bone area and BMD decrements might potentially be attributable to an LGD-4033-mediated decrease in circulating testosterone as an aromatizable substrate for estradiol conversion (Machek, Cardaci et al., 2020). Although several alternative SARM compounds demonstrate enhanced bone-associated parameters amidst impaired hypothalamic-pituitary-gonadal axis activity, the chronically high dose taken by the present case subject might have physiologically superseded any potential positive BMD augmentations (Furuya et al., 2012; Gao et al., 2005; Kearbey et al., 2007; Yin et al., 2003). Furthermore, although a majority of the assessed serum biomarkers in the present investigation returned to baseline post-cycle, FSH and low-density lipoprotein-cholesterol remained outside clinical reference ranges. These persistent alterations might suggest that pharmacological interventions are warranted as post-cycle strategies to rescue hormonal and lipid homeostasis. Interestingly, fat mass also remained elevated 4 weeks post-cycle, whereas lean body mass returned to baseline. These data ultimately suggest a potentially expedited return to an individual's skeletal muscle mass baseline relative to adipose tissue after cessation of compound administration.

We also document a substantial reduction in serum total and free testosterone along with SHBG after 5 weeks of continued LGD-4033 and MK-677 use, demonstrating notable androgenic activity. Although we also corroborate Basaria et al. (2013), amongst other SARM-focused investigations (Chen et al., 2005; Clark et al., 2017; Miller et al., 2011; Neil et al., 2018), by demonstrating an LGD-4033-mediated reduction in serum total and free testosterone and concomitant SHBG, the present case study also presents a possibly novel impact of LGD-4033 and MK-677 use on intramuscular androgens and AR content. Although data are limited on this phenomenon, we cautiously hypothesize that this might be a consequence of previously suggested 'unique' and/or 'incomplete' interactions or competitive binding between non-steroidal SARMS and the AR (Bhasin & Jasuja, 2009; Furuya et al., 2013; Machek, Cardaci et al., 2020; Ponnusamy et al., 2017). Ostensibly, these interactions might alter intracellular androgenic hormone influx or AR transcriptional/translational activity.

While research is limited in humans, previous authors have highlighted the potential deleterious effects of LGD-4033 and MK-677 use in humans for non-clinical contexts (Basaria et al., 2013; Flores et al., 2020; Koller et al., 2021; Machek, Cardaci et al., 2020; Nass et al., 2008). Similar to our present findings, increases in lean body mass (Basaria et al., 2013), elevated liver enzymes (Basaria et al., 2013; Flores et al., 2020; Koller et al., 2021) and liver injury (Barbara et al., 2020; Flores et al., 2020; Koller et al., 2021), along with suppression of free and total testosterone, FSH, SHBG, high-density lipoprotein-cholesterol and triglycerides have all been documented with LGD-4033 use, demonstrating clear evidence of the androgenic activity of LGD-4033 (Basaria et al., 2013; Koller et al., 2021). Furthermore,

previous data suggest that LGD-4033 (amidst the large propensity of existing SARM compounds) appears to increase skeletal muscle mass without commensurate improvements in muscular strength and function. Conversely, our cross-sectional data imply that LGD-4033 might support increases in muscle mass and strength, albeit this might be attributable to our subject co-administering MK-677 or consuming a relatively larger (10-fold higher) LGD-4033 dose than those previously administered in humans (Basaria et al., 2013). Furthermore, differences in training age between the case subject and previously published resistance-trained non-users (Cardaci et al., 2020) might explain, in part, the observed differences in muscular strength.

In the absence of LGD-4033, MK-677 has been shown to increase body mass, fat mass, muscle mass, bone mineral density, total body water, appetite and to improve physical function (Adunsky et al., 2011; Nass et al., 2008; Svensson et al., 1998), primarily posited to be by increasing circulating GH and insulin-like growth factor 1 (Chapman et al., 1997). Although previous investigations have described MK-677-mediated decreases in serum low-density lipoprotein-cholesterol, equivocal alterations in androgenic hormones and elevated blood glucose, the present findings illustrate broad decrements in serum lipids, suppressed androgenic targets and negligible changes in glucose (Chapman et al., 1997; Murphy et al., 1998; Nass et al., 2008; Sinha et al., 2020). Consequently, the discrepancy in the differential effects of MK-677 on the aforementioned parameters is likely to be attributable to co-administration with LGD-4033. It also remains possible that the elevations in both TBW and fat mass were mediated by MK-677, but it is ultimately difficult to parse out the impacts of each individual compound in the present study.

5 | CONCLUSION

Recreational SARM and GHS use has grown as a popular method to enhance aesthetics, muscular strength and/or athletic performance, despite a lack of empirical support to substantiate their utility or safety in non-clinical demographics (Efimenko et al., 2021; Machek, Cardaci et al., 2020). Furthermore, SARMS are rarely taken at previously studied clinical doses and are commonly co-administered with other pharmacological agents. Although this case report suggests that LGD-4033 and MK-677 harness significant anabolic properties and are likely to increase skeletal muscle mass and strength, our data also highlight a plethora of deleterious impacts on circulating metabolic, lipid and androgen-related markers. SARMS and GHS therein might erroneously be used as safer alternatives to anabolic-androgenic steroids and should be considered more thoughtfully for their contraindications (Albano et al., 2021; Machek, Cardaci et al., 2020). Additionally, these are the first data to document intramuscular androgenic hormone and receptor content, and may be important to elucidate the anabolic and deleterious effects of these compounds in humans further. Future investigations are tasked with evaluating the long-term effects of these and similar co-administered compounds on the physiology of recreational users, in addition to how any deleterious side effects can be optimally ameliorated.

AUTHOR CONTRIBUTIONS

Thomas D. Cardaci and Darryn S. Willoughby conceived and designed the study. Thomas D. Cardaci, Steven B. Macheck, Dylan T. Wilburn, Jeffery L. Heleson, Dillon R. Harris, Harry P. Cintineo, and Darryn S. Willoughby performed the data collection. Thomas D. Cardaci, Steven B. Macheck, and Darryn S. Willoughby analyzed the data. Thomas D. Cardaci, Steven B. Macheck, and Darryn S. Willoughby interpreted the data. Thomas D. Cardaci, Steven B. Macheck, and Darryn S. Willoughby drafted the manuscript. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

CONFLICT OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

Data are available upon request from the corresponding author.

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