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CASE REPORT

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Exploring the impact of exercise and essential amino acid plus cholecalciferol supplementation on physical fitness and body composition in multiple sclerosis: A case study

Theocharis Ispoglou[1] | **Panagiotis Ferentinos**[1] | **Konstantinos Prokopidis**[2] | **Cameron Blake**[1] | **Luke Aldrich**[1] | **Antonis Elia**[3] | **Matthew Lees**[4] | **Karen Hind**[5]

[1]Carnegie School of Sport, Leeds Beckett University, Leeds, UK

[2]Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK

[3]Division of Environmental Physiology, Royal Institute of Technology, Stockholm, Sweden

[4]Faculty of Kinesiology and Physical Education, University of Toronto, Toronto, Ontario, Canada

[5]Wolfson Research Institute for Health and Well-being, Durham, UK

Correspondence
Theocharis Ispoglou, Carnegie School of Sport, Leeds Beckett University, Headingley Campus, Fairfax Hall, Leeds LS6 3QS, UK.
Email: t.ispoglou@leedsbeckett.ac.uk

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Key Clinical Message

In MS patients, especially those frail or malnourished, combining home-based exercise twice weekly with essential amino acids and vitamin D may improve body composition, strength, and physical performance, enabling long-term functional improvements.

Abstract

Multiple sclerosis (MS) is associated with reduced bone and muscle strength and function. We aimed to investigate the effectiveness of a 24-week intervention in a 57-year-old frail female with MS. The participant completed a 2×/week exercise intervention and ingested 2×/day a supplement containing 7.5 g essential amino acids and 500 IU cholecalciferol. Body composition, 6-m gait speed (GS), handgrip strength (HGS), 30-sec arm-curl test (30ACT), 6-min walking test (6MWT), 30-sec chair-stand test (30CST), and plasma concentrations of 25-hydroxyvitamin D_3 [25(OH)D_3], insulin-like growth factor 1 (IGF-1), and amino acids were assessed at baseline, and at Weeks 12 and 24. Plasma 25(OH)D_3 increased from 23.2 to 41.3 ng/mL and IGF-1 from 131.6 to 140.7 ng/mL from baseline to post-intervention. BMI, total lean tissue mass (LTM), fat mass, bone mineral content, and the sum of 17 amino acids increased by 3.8, 1.0, 3.5, 0.2, and 19%, respectively, at Week 24. There were clinically significant increases in regional LTM (6.9% arms and 6.3% legs) and large increases in GS (67.3%), dominant HGS (31.5%), non-dominant HGS (11.8%), dominant 30ACT (100%), non-dominant 30ACT (116.7%), 6MWT (125.6%), and 30CST (44.4%). The current intervention was effective in improving components of physical fitness and body composition in a female with MS.

KEYWORDS

leucine, physical activity, protein, rehabilitation, sarcopenia

1 | INTRODUCTION

Multiple sclerosis (MS) is a chronic autoimmune disorder causing nerve sheath demyelination and symptoms such as muscle weakness, mobility decline, and lack of coordination,[1,2] generating unique health challenges and an economic burden.[3–5] Patients experience reductions in bone and skeletal muscle mass,[6] muscle strength and function,[7,8] and increased fracture risk,[9] negatively impacting quality of life.[10] Lower limb strength impairments,[8] poor balance,[11] and spasticity[12] also contribute to lower quality of life.[10] Pharmacological treatment has been the primary treatment option for patients with MS.[13]

Recent research has explored non-pharmacological treatments such as exercise, nutritional supplementation, and improved sleep quality.[14–21] Resistance exercise (RE) is particularly beneficial for MS rehabilitation as it improves muscle strength and function, mobility, quality of life,[22,23] and the immune system.[24] High-dose vitamin D supplementation raises interleukin-10 (IL-10) levels in MS patients,[19] who tend to have lower levels of IL-10, which may contribute to the development of the disease.[25] However, RE and vitamin D may not always improve physical fitness.[20,21] This could be due to unsatisfactory energy and protein intake, containing essential amino acids (EAA), which are necessary to stimulate muscle protein synthesis (MPS) and ultimately address sarcopenia,[26] a condition prevalent in MS patients.[27] EAA-based supplements enriched with L-leucine increase protein intake and optimize MPS in healthy older adults without compromising total energy intake during mealtimes[28,29] and plasma EAA concentrations are associated with muscle function in older women in the community.[30] A higher protein intake, including specific amino acids, may positively impact bone health through mechanisms such as increasing insulin-like growth factor 1 (IGF-1).[31,32] Therefore, addressing dietary protein deficiencies alongside RE may optimize musculoskeletal health and function in female MS patients. This case study evaluated the effects of a 24-week home-based intervention, including EAAs and vitamin D (cholecalciferol) supplementation, on muscle, bone, muscle strength, and function in a female patient with MS.

2 | MATERIALS AND METHODS

2.1 | Study design and ethics approval

This study utilized a case study design. The patient completed three testing sessions separated by 12 weeks, including measures of strength, body composition, functional performance tests, and blood tests for selected physiological variables. The study adhered to the 1964 Declaration of Helsinki and received institutional ethics approval. The study was part of a larger trial registered in a Clinical Trial's Registry with the identification number ISRCTN12419961.

2.2 | Participant information

A 57-year-old female patient with MS, identified as frail and at risk of malnutrition, participated in this study. Baseline scores were 5 (symptomatic of sarcopenia) using the SARC-F[33] questionnaire, 3 (frail) using the FRAIL scale,[34] and 10 (at risk of malnutrition) using the mini-nutritional assessment questionnaire.[35] The participant's key characteristics are provided in Table 1.

2.3 | Preliminary screening and anthropometry

The participant arrived at the laboratory between 07:00 and 09:00 in a fasted, euhydrated state, with no alcohol or exercise for 24 h prior. Baseline stature, body mass, and blood pressure were recorded using standard equipment. Self-reported physical activity levels at baseline were estimated using the short-form IPAQ, which showed low activity.

2.4 | Experimental protocol

The participant completed a 24-week home-based exercise program, performing upper (hand grip, wall press, seated dumbbell curls, and seated reverse wrist curls) and lower body exercises [mini squats (assisted with a chair), calf raises, hip marching, and a one-leg stand], twice a week. The intervention promoted progressive overload and increased repetitions and sets over time. The exercise

TABLE 1 Participant characteristics.

Variable	Baseline	Week 12	Week 24
Height (cm)	157.3	157.0	156.0
Body mass (kg)	53.7	56.7	54.8
BMI (kg/m^2)	21.7	23.0	22.5
RHR (bpm)	89	82	80
SBP (mm/Hg)	121	119	119
DBP (mm/Hg)	99	91	91

Abbreviations: BMI, Body Mass Index; DBP, Diastolic Blood Pressure; RHR, Resting Heart Rate; SBP, Systolic Blood Pressure.

technique was based on NHS Choices (https://www.nhs.uk/live-well/exercise/). Rest periods of approximately 1–2 min were taken between sets. See Figure 1 for an outline of the intervention.

2.5 | Nutritional supplementation

The participant consumed 65 mL gel-based supplements (GEL) twice daily with breakfast and lunch, providing 113.6 kcal, 21.9 g of carbohydrate, 7.5 g protein in the form of EAA, and 500 IU (12.5 μg) of cholecalciferol (Vitrition UK Ltd.). The decision to supplement with EAA gel was based on suboptimal protein intakes in these meals.[26,36] Compliance was monitored by counting the number of unconsumed sachets. Table 2 shows the EAA profile of the GEL.

2.6 | Dietary intake assessment & analysis

The participant completed a 3-day self-report diet diary on three occasions (0, 10, and 22 weeks), which were analyzed using the Nutritics software (Nutritics, 2022).

2.7 | Body composition assessment

Dual energy X-ray absorptiometry (DXA) (GE Lunar iDXA, GE Healthcare) was used to assess total fat mass (TFM), lean tissue mass (LTM), bone mineral content (BMC), and total body fat percentage (TBF%), at Weeks 0, 12, and 24 as described by Lees et al[37]

2.8 | Fitness testing

The tests included a handheld grip strength test (HGS), 30s arm curl (30ACT), 30s chair-stand tests (30CST), gait speed (GS) over 6 m, and a 6-min minute walk test (6MWT). Ratings of perceived exertion (RPE) were recorded using the Borg Scale.[38] These tests informed the training exercise protocol, as previously described.[39]

2.9 | Blood sampling

Blood samples were obtained from an antecubital vein. The samples were centrifuged, stored at −80°C, and later analyzed for 25(OH)D_3 and IGF-1 using commercially available ELISA kits, and amino acid content using Liquid Chromatography Mass Spectrometry (LC–MS).

2.10 | LC–MS sample and standard preparation

Plasma samples were deproteinized by adding 1 mL of a 50:50 methanol: acetonitrile v/v solution containing 0.5% formic acid to 250 μL of plasma, using a dilution factor of 5. The resulting solution was vortexed for 30 s, then centrifuged and filtered before being stored in suitable glass vials. A labeled intermediate standard was

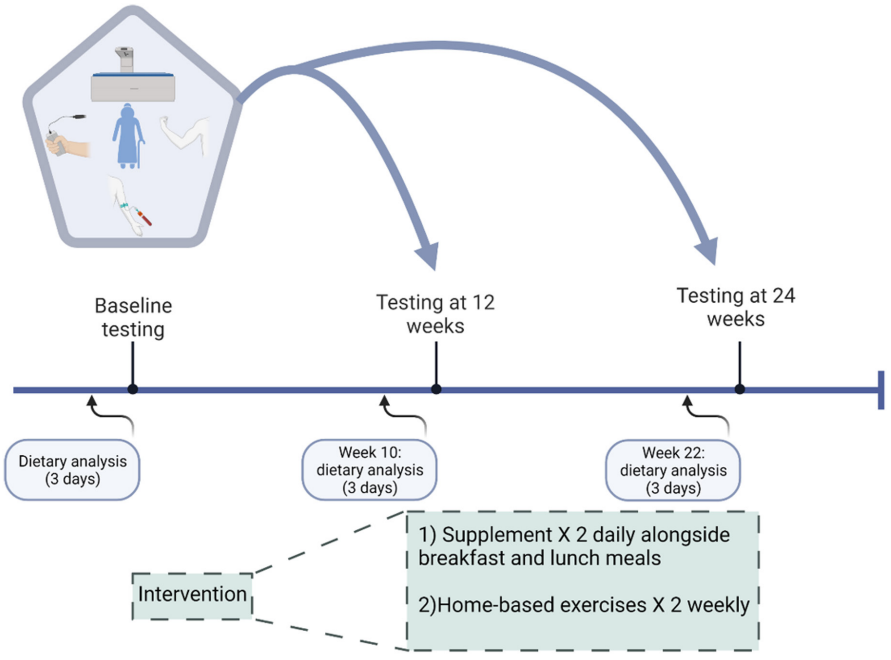

FIGURE 1 Outline of intervention, tests, and testing procedures.

TABLE 2 Essential Amino Acid (EAA) profile in 65 mL (7.5 g EAA) GEL supplement.

Amino Acid	mg/finished product
L-Leucine	3000
L-Lysine Hydrochloride	900
L-Valine	900
L-Isoleucine	830
L-Threonine	830
DL-Phenylalanine	530
L-Histidine Hydrochloride	380
DL-Methionine	150

added to ensure accurate quantification, while unlabelled standards were used to identify target analytes and optimize the chromatography and mass spectrometer acquisition parameters. Quality control samples were used to measure recovery and ensure correct method application.

2.11 | LC–MS method and analysis

An ultra-high-pressure liquid chromatography (UHPLC) analytical apparatus, the Nexera X2 module (Shimadzu Corporation Europa GmbH) with two pumps, an autosampler, column oven, and column switching valve were used. Chromatographic separation of compounds occurred using a Raptor Polar X column (Restek). Mass spectrometric detection was carried out by the LCMS-8045 triple quadrupole instrument. The analysis was carried out in positive MRM mode with a single transition for each compound. Mobile phases used were as follows: A—water, 0.5% formic acid; B—9:1 Acetonitrile:Water v/v, 20 Mm Ammonium Formate, formic acid (pH 3.0). A gradient elution was used according to a previously verified method (Restek, 2021): Gradient (%B) 0 min—88%; 3.5 min—88%; 8 min—30%; 8.01 min—88%; 10 min—88%; flow rate 0.5 mL/min; column over temperature 30°C. Samples and standards injected at 5 μL injection volume and performed by an autosampler.

2.12 | Statistical analysis

Lab-Solutions Insight and Microsoft Excel were used for data handling and quantification. Results are presented as absolute values or means (±SD) of 3 days, when appropriate. Least significance change (LSC) was estimated by multiplying 2.77 with %CV precision errors for GE Lunar iDXA.[40,41] Figure 1 was created with BioRender.Com.

3 | RESULTS

3.1 | Energy and macronutrient intake

The compliance with the nutritional regime was 100%. Energy and relative protein intake averaged 1703 (±348.2), 1360 (±101.9) and 1364 (±141.3) kcal/d and 1.04 (±0.3), 1.32 (±0.1) and 1.26 (±0.1) g/kg/d^{-1} at baseline, Weeks 10 and 22, respectively. Table 3 provides additional details of the participant's diet.

3.2 | Body composition

LTM and FM measurements showed a greater percentage change in the initial 12 weeks and remained elevated at Week 24 compared to baseline. BMI slightly increased, whereas TBF% and BMC remained relatively unchanged. See Table 4 for details on body composition.

3.3 | Fitness testing and Ratings of Perceived Exertion (RPE)

Fitness tests showed significant improvement over the 24-week intervention period, with a reduction in RPE in most tests (Table 5). The 6MWT showed the greatest improvement at Week 24, with a distance covered over 100% longer than the baseline, and a large decrease in RPE.

3.4 | Blood variables

Circulating [25(OH)D_3] increased significantly from baseline (23.2 ng/mL) to 24 weeks (41.3 ng/mL), with a percentage change of 78%. IGF-1 showed a smaller increase (6.9%) over the same period (baseline = 131.6 ng/mL; 24 weeks = 140.7 ng/mL). The plasma concentration of 17 amino acids increased by 10.3% and 19.1% at Weeks 12 and 24, respectively, compared to baseline (see Table 6).

4 | DISCUSSION

In this 24-week case study, a home-based intervention consisting of RE twice a week and EAA and vitamin D-enriched nutritional supplements twice daily improved body composition, muscle strength, physical performance, plasma amino acid profile, 25(OH)D_3 concentration, and IGF-1 in a 57-year-old female patient with

TABLE 3 Nutritional intakes across the intervention.

Outcomes	Baseline (no gels) M (±SD)	Week 10 (plus 2 gels daily) M (±SD)	Week 22 (plus 2 gels daily) M (±SD)
Target Energy Intake (kcal)	1358	1504	1579
Carbohydrate (g/kg/d^{-1})	4.3 (±0.5)	3.6 (±0.1)	4.2 (±0.7)
Fat (g/kg/d^{-1})	1.04 (±0.3)	0.49 (±0.1)	0.36 (±0.1)
Fiber (g)	22 (±7.4)	12.7 (±0.9)	19.7 (±4.5)
Non-starch polysaccharides (NSP) (g)	18 (±5.7)	9.2 (±0.1)	14.5 (±2.5)
Saturated fat (g)	25 (±16.9)	10.6 (±5.9)	3.9 (±0.6)
Monounsaturated fat (g)	6 (±4.7)	1.1 (±1.4)	4.1 (±0.8)
Polyunsaturated fat (g)	1.8 (±0.6)	1.2 (±0.8)	1.7 (±0.3)

TABLE 4 Body composition outcomes including mean changes and mean percentage (%) changes.

Body composition outcomes (in brackets LSC when appropriate)	Absolute values			Changes and % changes			
	Baseline	12 weeks	24 weeks	Change (0–12 weeks)	Change (%) (0–12 weeks)	Change (0–24 weeks)	Change (%) (0–24 weeks)
Body mass (kg)	53.7	56.7	54.8	3.0	5.6	1.1	2.0
BMI (kg/m^2)	21.7	23.0	22.5	1.3	6.0	0.8	3.8
LTM (kg) (1.39% CV)	30.4	32.0	30.7	1.5	5.0	0.3	1.0
FM (2.27% CV)	21.0	22.5	21.7	1.5	7.2	0.7	3.5
BMC (1.7% CV)	1.6	1.6	1.6	0.0	−1.9	0.0	0.2
% total body fat (2.4% CV)	39.6	40.1	40.2	0.6	1.5	0.6	1.5
Arms LTM (kg) (4.3% CV)	2.8	3.1	3.0	0.3	10.2	0.2	6.9
Arms FM (kg) (5.4% CV)	2.0	2.2	2.0	0.3	14.6	0.0	0.2
Legs LTM (kg) (3.2% CV)	9.4	10.3	10.0	0.9	9.8	0.6	6.3
Legs FM (kg) (3.7% CV)	8.0	8.3	8.6	0.3	3.7	0.5	6.4
Trunk LTM (kg) (2.7% CV)	15.8	16.1	15.3	0.3	1.7	−0.5	−3.4
Trunk FM (kg) (5.2% CV)	10.3	11.2	10.5	0.9	8.9	0.2	2.0

Note: Value highlighted in green when % change exceeded LSC at week 24.

Abbreviations: BMC, bone mineral content; BMI, Body mass index; FM, fat mass; LSC, least significant change; LTM, Lean tissue mass.

MS. These findings suggest that exercise and nutritional interventions may improve the physical capacity of individuals with MS.

The 6-month intervention resulted in notable enhancements in performance tests, particularly in the 6MWT, which displayed a 125.6% increase at Week 24 compared to baseline. The performance tests also exhibited decreased RPE scores, indicating favorable physiological changes, with the most significant reduction observed after the 6MWT, an indirect measure of aerobic fitness.[42] Despite the 6MWT results not reaching the normal range (498–604 m),[43] we can infer that true physiological changes in cardiovascular fitness occurred, as RPE and heart rate are highly related,[44] even though we did not calculate the heart rate walking speed index.[45] The participant's ACT scores, which were initially below normal,[43] improved by Week 24, while hand grip strength was within the normal range at baseline.[46] The right arm HGS improved more than the left arm HGS at Weeks 12 and 24. The participant's performance in the 30s CST, initially below the expected range, achieved scores within the range only at Week 24. Gait speed, initially identified as sarcopenic (0.8 m/s) at baseline, improved throughout the intervention.[47] Body composition exhibited clinically significant increases[40,41] in regional LTM (arms and legs) and FM, mainly due to increased FM in the legs. At 3 months, the body mass increased but slightly decreased after mid-testing, possibly due to the fear of weight gain. Dietary intakes at Weeks 10 and 22 suggest a slight caloric deficit, which may explain some changes in body composition.

TABLE 5 Performance outcomes (absolute values, changes and percentage changes) as well as the corresponding ratings of perceived exertion (RPE) values at baseline, weeks 12 and 24.

Performance outcome measures	Absolute values including corresponding RPE if applicable in adjacent cell						0–12 weeks changes and corresponding RPE if applicable in adjacent cell			0–24 weeks changes and corresponding RPE if applicable in adjacent cell			
	Baseline	RPE	Week 12	RPE	Week 24	RPE	Change (0–12 weeks)	RPE	Change (%) (0–12 weeks)	RPE (%)	Change (0–24 weeks)	RPE	Change (%) (0–24 weeks)	RPE (%)
Left Arm 30s arm curl test (repetitions)	6	17	8	15	13	14	2.0	−2.0	33.3	−11.8	7.0	−3.0	116.7	−17.6
Right Arm 30s arm curl test (repetitions)	7	15	9	13	14	12	2.0	−2.0	28.6	−13.3	7.0	−3.0	100	−20
Left Arm HGS (kg) max	22.0	N/A	24.6	N/A	23.1	N/A	2.6	N/A	11.8	N/A	1.1	N/A	5.0	N/A
Right Arm HGS (kg) max	19.7	N/A	28.0	N/A	25.9	N/A	8.3	N/A	42.1	N/A	6.2	N/A	31.5	N/A
30s Chair Stand test (repetitions)	9	12	8	11	13	12	−1.0	−1.0	−11.1	−8.3	4.0	0.0	44.4	0.0
6-minute walk test (m)	180	19	234	16	406	15	54.0	−3.0	30.0	−15.8	226.0	−4.0	125.6	−21.1
Gait speed over 6 m (m/s)	0.8	N/A	0.9	N/A	1.4	N/A	0.1	N/A	8.3	N/A	0.5	N/A	67.3	N/A

Abbreviations: HGS, Hand grip strength; N/A, not applicable.

Meta-analyses have demonstrated significant improvements in "timed up and go" testing,[48] short and long walk tests,[49] and walking speed in MS patients[50] following RE, which corroborates our findings. The inclusion of a sufficient per-meal EAA dose may have contributed to enhanced LTM and muscle strength.[51,52] Our data suggest an increase in daily protein intake from approximately 1 g/kg/d^{-1} to 1.3 g/kg/d^{-1}, with noticeable elevations in plasma NEAA (+18.3%) and EAA (+20.6%) at the conclusion of the 24-week intervention, attributable to the 2xEAA gel supplementation. This finding is consistent with earlier studies that proposed a relationship between plasma amino acids and muscle function in older women.[30] The total sum of plasma amino acids in the participant increased, shifting away from the potential development of sarcopenia.[30] The rise in alanine, arginine, glutamic acid, lysine, and IGF-1 supports the intervention's potential to improve bone health.[31,32] However, larger studies are required to verify the role of amino acids in muscle protection.

Despite its inclusion in our intervention, the effectiveness of vitamin D supplementation remains unclear. While some studies suggest a positive effect of vitamin D and RE on strength,[53] recent trials have yielded inconsistent results.[20,21] Previous research has shown no changes in HGS and MS functional composite scores with weekly administration of vitamin D (20,000 IU) alone. High doses of vitamin D (50,000 IU every 5 days for 3 months) may promote anti-inflammatory properties by raising IL-10 levels,[19,54,55] but the impact of lower doses, such as 20,000 IU/week, is controversial. Some studies report an inadequacy in suppressing markers of systemic inflammation,[56] while others show increased TGF-β levels.[57] Daily supplementation of 1000 IU cholecalciferol led to an increased 25(OH)D_3 concentration in our case, likely due to the combined effect of supplementation and sunlight exposure from March to August.

5 | CONCLUSIONS

In conclusion, this 6-month case study involving a female with MS demonstrated the positive impact of incorporating resistance exercise and nutritional supplementation on body composition, muscle strength, and physical performance. However, because this was a case study, it precludes the generalization of outcomes, and further identical interventions with larger MS populations are needed to confirm their effectiveness. Despite this limitation, the intervention appears to be a safe and effective strategy for improving the physical capacity of individuals with MS.

TABLE 6 Plasma Amino Acids Concentration. Essential amino acids (EAAs); non-essential amino acids (NEAAs).

Amino Acids (μmol/mL)	Baseline	Week 12	Week 24	% increase Week 12-baseline	% increase Week 24-baseline
Alanine	237.6	275.0	301.3	15.8	26.8
Arginine	69.6	80.2	84.4	15.2	21.2
Asparagine	59.9	60.8	64.2	1.5	7.2
Aspartic Acid	4.2	5.5	5.1	30.6	20.4
Glutamic Acid	95.3	93.6	128.0	−1.8	34.2
Glutamine	506.0	595.8	583.7	17.7	15.3
Histidine*	40.9	44.8	49.1	9.7	20.1
Isoleucine*	34.1	34.2	36.8	0.5	8.1
Leucine*	69.2	58.3	65.5	−15.6	−5.4
Lysine*	148.8	148.1	186.6	−0.5	25.4
Methionine*	17.8	20.2	19.7	13.2	10.5
Phenylalanine*	41.9	47.2	48.8	12.7	16.5
Proline	89.7	95.5	95.1	6.4	6.0
Serine	87.6	95.1	100.3	8.5	14.4
Threonine*	71.8	100.4	127.5	39.7	77.5
Tyrosine	40.1	38.7	46.2	−3.4	15.2
Valine*	146.0	148.8	154.2	1.9	5.6
Sum of EAAs	570.5	602.1	688.2	5.5	20.6
Sum of NEAAs	1190.0	1340.2	1408.2	12.6	18.3

Note: An asterisk (*) indicates essential amino acids (EAAs).

AUTHOR CONTRIBUTIONS

Theocharis Ispoglou: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; resources; software; supervision; visualization; writing – original draft; writing – review and editing. **Panagiotis Ferentinos:** Data curation; formal analysis; project administration; writing – review and editing. **Konstantinos Prokopidis:** Data curation; visualization; writing – review and editing. **Cameron Blake:** Data curation; formal analysis; software; writing – original draft. **Luke Aldrich:** Data curation; formal analysis; methodology; software; writing – review and editing. **Antonis Elia:** Data curation; formal analysis; methodology; software; writing – review and editing. **Matthew Lees:** Data curation; formal analysis; methodology; software; writing – review and editing. **Karen Hind:** Conceptualization; funding acquisition; investigation; methodology; project administration; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

No conflict of interest has been reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Theocharis Ispoglou https://orcid.org/0000-0002-7608-6512

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