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Lifestyle intervention based on aerobic exercise and Mediterranean diet modulates IGF-1 and its binding proteins in breast cancer survivors

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Abstract

Background Obesity-related biomarkers such as insulin-like growth factor-1 (IGF-1) may help identify high-risk breast cancer survivors (BCS) who could benefit from lifestyle interventions (LIs). However, the effect of LIs on modulation of IGF-1 levels in BCS remains inconclusive.

Methods Fifty inactive BCS were randomized into a control group (CG, $n=26$) and an intervention group (IG, $n=24$). Both groups received recommendations on exercise and the Mediterranean diet; the IG additionally followed a supervised 3-month aerobic exercise program (MoviS trial, NCT04818359). Associations between baseline and LI-induced changes (Δ) in IGF-1, IGF binding protein-1 (IGFBP1) and IGFBP3 levels, along with anthropometric, metabolic, and fitness parameters, were assessed using linear and quadratic models.

Results Both groups increased physical activity (MET min/week) and Mediterranean diet adherence (MeDiet score) after the LI, while maximal oxygen uptake ($\dot{V}O_{2max}$) increased only in the IG. Reductions in BMI, fat mass, insulin levels, HOMA-IR index, total and LDL cholesterol were observed in both groups and were associated with increased IGFBP1 and decreased IGFBP3 levels. Mean IGF-1 levels remained unchanged in both groups. Baseline IGFBP1 was inversely correlated with IGF-1, LDL, BMI, fat mass, and insulin, while baseline IGFBP3 was positively correlated with IGF-1, insulin, and HOMA-IR. Baseline IGF-1 levels were negatively correlated with Δ IGF-1: participants with IGF-1 ≤ 94.7 ng/mL showed increases, whereas those with IGF-1 ≥ 173.3 ng/mL exhibited decreases post-intervention. Similar trends were found for IGFBP3 but not for IGFBP1. A three-dimensional quadratic model revealed a U-shaped relationship between baseline IGF-1, Δ IGF-1, and Δ $\dot{V}O_{2max}$: improvements in $\dot{V}O_{2max}$ were associated with IGF-1 increase in participants with low baseline IGF-1 and decrease in those with high levels. Conversely, an inverted U-shaped relationship was found between baseline IGF-1, Δ IGF-1, and Δ fat mass.

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Conclusions These findings underscore the importance of accounting for IGFBP modulation and baseline heterogeneity in IGF-1 levels when evaluating the efficacy of LIs targeting the IGF-1 system in high-risk BCS.

Trial registration ClinicalTrials.gov NCT04818359. Registration Date 26 March 2021.

Keywords IGF-1, IGF-1 binding proteins, Breast cancer survivors, Lifestyle intervention, Aerobic exercise, Mediterranean diet

Background

Breast cancer (BC) is the most commonly diagnosed cancer in women and the second most frequently occurring cancer worldwide in 2022, with 2.3 million new cases [1]. Although BC diagnoses continue to increase, advances in screening and treatment have significantly reduced the mortality recurrence rate [1]. As a result, many survivors seek information on how lifestyle factors such as physical activity and diet may influence their prognosis. Evidence has consistently shown that lifestyle interventions (LIs) can reduce symptoms, such as fatigue, and improve the overall quality of life in BC survivors (BCS) [2]. However, only a limited number of randomized controlled trials (RCTs) have evaluated the effects of LIs on cancer-related biomarkers in BCS. Consequently, the biological mechanisms linking physical activity, diet, and prognosis in BCS remain poorly understood.

One potential mechanism underlying the association between lifestyle and cancer is the insulin-like growth factor-1 (IGF-1) signaling pathway [3, 4]. The IGF-1 system comprises a ligand (IGF-1) and six IGF-1 binding proteins (IGFBPs), which regulate IGF-1 bioactivity [5]. IGFBP production is, in turn, regulated by hormones (e.g., growth hormone (GH), insulin, and glucocorticoids) as well as nutritional status. For example, GH stimulates liver IGFBP3 production to extend IGF-1's stability and ensure its physiological function [6]. Conversely, liver IGFBP1 production increases in response to catabolic conditions (e.g., starvation, hypoxia, and stress) [7] and is negatively regulated by insulin [8]. This mechanism ensures that free, bioactive IGF-1 levels increase only under anabolic conditions.

When free IGF-1 binds to its receptor (IGF-1R), it activates key oncogenic signaling pathways, including MAPK and PI3K/Akt/mTOR, which regulate cell proliferation, survival, and energy metabolism [3]. These findings imply that elevated IGF-1 levels or bioactivity can promote cell proliferation and survival, potentially contributing to carcinogenesis [3]. Notably, approximately 75% of patients with BC and 87% of those with invasive BC show IGF-1R signaling activation [9, 10]. Moreover, increased IGF-1 levels are associated with disease progression, resistance to standard therapies, and increased all-cause mortality in women with estrogen receptor (ER)-positive BC [9, 11, 12]. Unsurprisingly, targeting the IGF-1 system is one of the most investigated areas in anticancer drug development [13].

LIs, including physical activity and diet, have been proposed as non-pharmacological strategies for decreasing IGF-1 levels and bioactivity [14–21]. Indeed, LIs may influence IGF-1 signaling by lowering circulating hormone levels or modulating IGFBP expression. However, the effect of LIs on the modulation of the IGF-1 system in BCS remains inconclusive. For example, three meta-analyses reported IGF-1 reductions [14, 15, 18], whereas others found no effect on IGF-1 levels [16, 17, 20] after LIs in BCS. These meta-analyses also reported high heterogeneity (I^2) among studies. Similarly, findings regarding LI-induced changes in serum IGFBP3 and IGFBP1 levels remain inconsistent [14–18, 21].

Individual variability in baseline IGF-1 levels may partly explain the discrepancies and inconsistent findings regarding the effect of LIs on the IGF-1 system [22]. In support of this hypothesis, some studies have found an inverse relationship between baseline IGF-1 levels and LI-induced changes, as observed with exercise training [23–25] or fasting-mimicking diets [19] in healthy participants. Thus, LIs may exert stronger effects on individuals with relatively high IGF-1 baseline levels [20, 22]. Additionally, large population studies have suggested a U-shaped relationship between IGF-1 levels and age-related outcomes, including cardiovascular disease, diabetes, dementia, cancer, and all-cause mortality, where both high and low IGF-1 levels are associated with increased risk [26–29]. However, whether BCS with different baseline IGF-1 levels respond differently to the same LI remains unexplored.

In this study, we analyzed IGF-1, IGFBP1, and IGFBP3 levels in 50 BCS participating in the MoviS trial (ClinicalTrials.gov reference number: NCT04818359), an open-label RCT based on multi-component LI that combined aerobic exercise with dietary recommendations. We investigated the association between LI-induced improvements in anthropometric, metabolic, and fitness parameters, and IGF-1 system components. Moreover, using both linear and quadratic modelling, we examined the relationship between baseline IGF-1, IGFBP1, and IGFBP3 levels and the changes induced by LIs.

Methods

Study design and participants

The MoviS trial was a monocentric trial (protocol: NCT 04818359; Registration Date: 26 March 2021) conducted at the Santa Maria della Misericordia Hospital (Urbino, Italy) and the Department of Biomolecular Sciences of the University of Urbino Carlo Bo (Italy). As reported elsewhere [30], ethical approval was granted by the Human Research Ethics Committee of the University of Urbino Carlo Bo (Protocol N 21 of July 10, 2019), and written informed consent was obtained from all participants. Women were eligible for the study if they had histologically confirmed BC (stage 0-III) with no evidence of recurrent or progressive disease at recruitment; were within 12 months after surgery and at least 6 months after radiotherapy and/or chemotherapy, with or without current hormone therapy use; were aged between 30 and 70 years; non-physically active for at least 6 months (i.e., not engaged in at least 60 min/week of structured exercise during the previous 6 months); and were at risk of recurrence due to at least one of the following conditions: body mass index (BMI) ≥ 25 kg/m^2; testosterone ≥ 0.4 ng/mL; serum insulin ≥ 25 μU/mL (170 pmol/L); or metabolic syndrome.

Women were excluded if they had recurrent disease; pneumological, cardiological, neurological, or orthopedic comorbidities; or mental illnesses that prevented exercise performance [30]. Recruitment was conducted between September 2020 and August 2021 at the Santa Maria della Misericordia Hospital of Urbino (PU) in the Marche region (central Italy). In this study, we considered a subgroup of 50 participants with data available on IGF-1, IGFBP1, and IGFBP3 levels collected at T0 (baseline) and T1 (after 3-month of LIs), as shown in the CONSORT flow diagram (Supplementary material Figure S1). The inclusion/exclusion for the present study was driven by biospecimen availability and feasibility constraints, not by intervention adherence, clinical response, or biomarker values. The participants' general and medical characteristics were collected at each time point by an oncologist, while clinical-functional and biomolecular assessments were conducted by the research staff.

Lifestyle intervention

LIs began after surgery and completion of primary treatments (post-adjuvant chemotherapy or radiotherapy). As previously described [30], the participants were randomized into either the Control group (CG) (n = 26) or Intervention group (IG) (n = 24). Both groups attended a one-hour meeting consisting of a 45-minute group session and a 15-minute personalized session, during which an oncology nutritionist and an exercise oncology specialist presented and discussed the latest guidelines on physical activity and the Mediterranean diet (structured counselling session). The recommendations were based on the WCRF 2018 guidelines and the most recent nutritional and exercise guidelines for BC patients approved by the Italian Ministry of Health in 2017 and 2019 [31–33]. Additionally, all participants had the opportunity to register on the DianaWeb platform [34, 35], which provides daily nutritional advice aligned with the Mediterranean diet, while only the IG participated in the MoviS training.

The MoviS training consisted of a 3-month supervised aerobic training program with progressively increasing intensity (ranging from 40% to 70% of the Heart Rate Reserve [HRR]) and duration (from 20 to 60 min). An exercise specialist supervised two exercise sessions per week (on-site sessions), while participants independently completed one additional session per week (remote session) following the prescribed exercise intensity under remote supervision. Each participant was instructed to use a heart rate monitor (HR300, Kalenji) to verify exercise intensity in each session (on-site and remote sessions). Each participant could walk or run on a treadmill, or use a stationary bike during the on-site sessions, while the remote sessions were performed both indoors and outdoors, according to the participants' possibilities and preferences.

Anthropometrics and body composition

Anthropometric and body composition parameters were collected at T0 and T1 as follows: body height was measured using a fixed stadiometer, and body weight was measured using an electronic scale. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the body height in meters. Measurements of bioimpedance to obtain the percentage of fat mass were performed using DC430MA DC430 (Tanita Europe).

Dietary habits, physical activity level and cardiorespiratory fitness

The modified MeDiet questionnaire, consisting of a 14-item adherence screening, was used to assess adherence to the Mediterranean diet (≥ 8 points in the 14-item score indicate higher adherence) [36]. Each participant completed the questionnaire during assessments at T0 and T1. The Physical activity (PA) level was assessed using the International Physical Activity Questionnaire – Short Form (IPAQ-SF) to determine the participants' habitual PA level [37, 38]. This questionnaire contains questions on PA during the last seven days and assesses the frequency and duration of sitting, walking, moderate-intensity activities, and vigorous-intensity activities. The IPAQ-SF was completed at T0 and T1. Based on the participants' responses, total PA levels were calculated by converting questionnaire data into the metabolic

equivalent of task (MET) minutes per week (MET-min/week), and exercise intensity was associated with MET (MET = 8 for vigorous, MET = 4 for moderate, MET = 3.3 for walking), and total PA level included walking and moderate and vigorous intensity activity according to the IPAQ-SF guidelines [37, 38]. The IPAQ-SF score expressed as MET-min/week was used as a general indicator of low activity (MET < 600), moderate activity (MET ≥ 600), and high activity (MET ≥ 3000).

To evaluate the cardiorespiratory fitness, the maximal oxygen uptake (VO_{2max} [$mL \cdot min^{-1} \cdot kg^{-1}$]) was assessed using a submaximal cardiorespiratory fitness test performed at T0 and T1. A personalized test for each participant was created according to the American College of Sports Medicine (ACSM) guidelines, as described in detail by Natalucci et al. 2021 [39].

Metabolic and hormonal analyses

Blood glucose, insulin, triglycerides, HDL, LDL, and total cholesterol concentrations were determined by colorimetric assays using Beckman Coulter AU Analyzers, and the homeostasis model assessment was used to estimate insulin resistance (HOMA-IR index), as detailed in [39]. Serum concentrations of IGF-1 and IGFBP3 were measured using a solid-phase, enzyme-labeled chemiluminescent immunometric assay with the IMMULITE 2000 analyzer (Siemens Healthcare s.r.l., Italy), according to the manufacturer's protocols. The concentration of IGFBP1 was measured using Human Duo-Set enzyme-linked immunosorbent assay (ELISA) kits (R&D Systems) according to the manufacturer's instructions. The sensitivities of the assays were 20 ng/mL (IGF-1), 0.03 ng/mL (IGFBP1), and 0.1 µg/mL (IGFBP-3). The total intra- and inter-assay CVs were respectively < 3.9 and < 7.7% for IGF-1 and < 4.8 and < 7.3% for IGFBP3 across the concentrations observed in the study. The IGFBP1 Human Duo-Set ELISA had a coefficient of variation of less than 10% across the standard curve for both intra- and inter-assay precision. The technicians analyzing the serum samples were blinded to the patient allocation.

Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics. Continuous variables are expressed as mean ± standard deviations (SD) or median with interquartile range (IQR), while categorical variables are presented as absolute numbers and percentages. Between-group comparisons were performed using the chi-squared test (χ^2) or Fisher's exact test, as appropriate.

Generalized linear models for repeated measures

To evaluate the effects of the LI program on IGF-1, IGFBP1, and IGFBP3 levels as well as anthropometric, metabolic, and fitness parameters, a generalized linear model (GLM) for repeated measures was applied. This model accounted for within-subject correlations across time points (T0 vs. T1) while testing for the time effect (T0 vs. T1), group effect (intervention vs. control), and time × group interaction to assess whether responses to the intervention differed between groups. For significant effects, post-hoc tests were conducted to examine pre-to-post changes within each group, with p-values adjusted using the Bonferroni correction to control for multiple comparisons. Effect sizes were calculated using partial eta-squared (η^2) and interpreted as small ($\eta^2 = 0.01$), medium ($\eta^2 = 0.06$), or large ($\eta^2 = 0.14$).

Correlation analyses

To explore the relationships between IGF-1, IGFBP1, IGFBP3, and metabolic/anthropometric variables, a correlation matrix was computed, and a correlation plot was generated. The pairwise Spearman's rank correlation was used. Additionally, an unsupervised hierarchical clustering approach was applied to the correlation matrix to identify the clusters of highly correlated variables. Specifically, distance metric: Euclidean distance was used to quantify the similarity between variables; linkage method: Ward's minimum variance method was employed to minimize intra-cluster variance. The number of clusters was chosen by inspecting the dendrogram structure and the cophenetic correlation coefficients. The correlation matrix was conceived as an exploratory, hypothesis-generating analysis aimed at providing an overall overview of the inter-relationships among variables. Accordingly, the reported p-values were not corrected for multiple comparisons, and the findings should be interpreted as preliminary. Hierarchical clustering and correlation visualization were performed using the corrplot and hclust functions in R (packages: "corrplot", "stats").

Regression models

Linear regression analysis was conducted to examine whether T0 IGF-1 levels predicted T1 changes in the IGF-1 levels. Moreover, to determine the T0 IGF-1 levels at which no significant T1 changes in IGF-1 were observed, the 95% confidence interval (CI) for the elevation values in the linear regression analysis was calculated. The same approach was applied to IGFBP3 and IGFBP1 variables.

Quadratic modeling

Given the observed variability in IGF-1 responses, we assessed whether changes in IGF-1 (Δ IGF-1) exhibited a non-linear dependence on T0 IGF-1 and fitness/metabolic adaptations. A complete quadratic regression model was fitted to evaluate the potential U-shaped or inverted U-shaped relationship. The final model was

selected using backward stepwise elimination based on the Akaike Information Criterion (AIC).

A post-hoc power analysis was conducted to estimate the statistical power achieved with the available sample. The analysis was based on the total sample size (CG, $n = 24$; IG, $n = 26$) and an assumed large effect size (Cohen's d = 0.80). For a two-tailed independent-samples t test with $\alpha = 0.05$, the achieved power was $1-\beta = 0.796$.

Table 1 Baseline characteristics of Control group (CG) and Intervention group (IG)

	Control group (CG; *n* = 26)		Intervention group (IG; *n* = 24)		p-value
	n	%	*n*	%	
Breast cancer subtypes					0.846
Luminal A					
(ER+/PR+/HER-)	6	23	4	17	
(ER+/PR-/HER-)	0	0	1	4	
Luminal B					
(ER+/PR+/HER-)	8	31	4	17	
(ER+/PR-/HER-)	0	0	2	8	
HER2					
(ER+/PR+/HER+)	3	11	4	17	
(ER-/PR+/HER+)	2	8	0	0	
(ER-/PR-/HER+)	0	0	1	4	
TNBC	1	4	3	12	
In situ	6	23	5	21	
Stage at diagnosis					0.767
0	7	27	6	25	
I	15	58	13	54	
II	4	15	4	17	
III	0	0	1	4	
Menopausal status					0.963
Premenopausal	11	42	10	42	
Postmenopausal	15	58	14	58	
Surgery Type					0.769
Mastectomy	4	15	2	8	
Quadrantectomy	22	85	21	88	
Lumpectomy	0	0	1	4	
Treatment in addition to surgery					0.872
Only radiation	9	35	10	42	
Only chemotherapy	2	8	1	4	
Radiation and chemotherapy	9	34	9	37	
None	6	23	4	17	
Current endocrine therapy					0.786
None	10	38	10	42	
Tamoxifen	2	8	3	12	
Aromatase Inhibitor	14	54	11	46	

ER estrogen receptor, *HER* human epidermal receptor, *HER2* human epidermal growth factor receptor 2, *PR* progesterone receptor, *TNBC* triple-negative breast cancer

Differences in frequency distributions were compared by chi-squared test

A two-tailed p-value < 0.05 was considered statistically significant for all tests. All statistical analyses were conducted using the R software or SPSS (version 22; IBM Corp., Armonk, NY, USA).

Results

The baseline characteristics of BCS enrolled in this study are shown in Table 1. The average age at T0 was 51.0 years (± 6.4) for the CG and 52.5 years (± 7.2) for the IG. The BC subtypes, stage at diagnosis, menopausal status, surgery type, treatment in addition to surgery, and current endocrine therapy were not significantly different between the groups (Table 1).

Effects of LI on body composition, cardiorespiratory fitness, metabolic profile, MeDiet score and physical activity level

There was a significant interaction between group and time for VO_{2max}, total PA level, and MeDiet scores, which increased more in the IG than in the CG (Table 2). No significant group × time interaction was found for BMI, fat mass, or metabolic variables. However, the main effect of time was a reduction in BMI, fat mass, insulin, HOMA-IR index, and total and LDL cholesterol in both groups at T1. The main effect of group showed that total cholesterol and total PA level were higher in the IG than in the CG.

Effects of lifestyle intervention on IGF-1, IGFBP1, and IGFBP3 levels

There was no significant interaction between group and time on IGF-1, IGFBP1, or IGFBP3 levels (Table 3). However, the main effect of time was an increase in IGFBP1 and a reduction in IGFBP3 levels at the end of the study.

Correlation between IGF-1, IGFBP1 and IGFBP3 levels with variables measured at T0 and with changes (Δ) between T0 and T1

The correlations between IGF-1, IGFBP1, and IGFBP3 levels and body composition, VO_{2max}, and metabolic variables at T0 are shown in Fig. 1. IGF-1 levels at T0 were negatively correlated with IGFBP1 (r = -0.33; $p = 0.046$) and positively correlated with IGFBP3 ($r = 0.40$; $p = 0.002$). IGFBP1 levels were negatively correlated with LDL levels (r = -0.40; $p = 0.007$), BMI (r = -0.52; $p < 0.0001$), fat mass (r = -0.54; $p < 0.0001$), and insulin levels (r = -0.41; $p = 0.041$). IGFBP3 levels were positively correlated with insulin levels ($r = 0.33$; $p = 0.008$) and HOMA-IR index ($r = 0.29$; $p = 0.011$). Hierarchical cluster analysis showed that the variables could be categorized into three clusters (highlighted boxes in Fig. 1). As expected, BMI, fat mass, and metabolic variables shared the same cluster (bottom-right box in Fig. 1). IGF-1 and IGFBP3 levels belonged to the same median cluster and were positively correlated.

Table 2 Comparison between T0 and T1 of anthropometric and body composition, cardiorespiratory fitness, metabolic profile, MeDiet score and PA level

	Control group (CG; $n = 26$)			Intervention group (IG; $n = 24$)			$p\ (n^2_p)$	$p\ (n^2_p)$	$p\ (n^2_p)$
	T0	T1	Δ%	T0	T1	Δ%	Time	Group	T×G
BMI (Kg/m^2)	24.7 ± 4.7	24.0 ± 4.4	-2.8	26.1 ± 5.2	25.3 ± 5.0	-3.1	**< 0.001** (0.351)	0.400 (0.015)	0.665 (0.004)
Fat mass (%)	30.4 ± 6.4	29.3 ± 6.2	-3.6	31.9 ± 7.6	30.1 ± 7.1	-5.6	**< 0.001** (0.362)	0.541 (0.008)	0.225 (0.033)
VO_2max (mL·min^{-1}·kg^{-1})	31.8 ± 4.1	31.1 ± 4.2	-2.2	31.3 ± 4.9	33.2 ± 4.6	+6.1	0.073 (0.068)	0.711 (0.003)	**0.002** (0.187)
Glucose (mg/dL)	95.2 ± 10.2	94.3 ± 6.6	-0.9	97.1 ± 9.6	97.1 ± 10.3	0.0	0.663 (0.004)	0.484 (0.011)	0.944 (0.000)
Insulin (μU/mL)	6.2 ± 2.5	5.7 ± 2.1	-7.1	7.0 ± 5.21	6.1 ± 4.8	-11.9	**0.018** (0.116)	0.606 (0.006)	0.445 (0.013)
HOMA-IR index	1.5 ± 0.7	1.3 ± 0.5	-10.0	1.7 ± 1.4	1.5 ± 1.3	-12.3	**0.019** (0.114)	0.579 (0.007)	0.591 (0.006)
Triglycerides (mg/dL)	81.6 ± 28.9	75.5 ± 34.3	-7.5	99.5 ± 78.5	93.2 ± 79.8	-6.3	0.112 (0.054)	0.144 (0.046)	0.352 (0.019)
Total Cholesterol (mg/dL)	204.0 ± 31.4	196.9 ± 35.4	-3.5	237.1 ± 44.5	214.8 ± 34.0	-9.4	**< 0.001** (0.216)	**0.043** (0.086)	0.072 (0.068)
HDL (mg/dL)	61.0 ± 13.4	62.3 ± 13.7	+2.1	62.9 ± 12.0	64.3 ± 12.9	+2.2	0.062 (0.074)	0.811 (0.001)	0.826 (0.001)
LDL (mg/dL)	122.8 ± 23.9	118.5 ± 26.4	-3.5	145.0 ± 31.4	129.3 ± 25.3	-10.8	**< 0.001** (0.216)	0.071 (0.069)	0.059 (0.075)
MeDiet score	7.1 ± 1.3	7.3 ± 2.1	+2.9	6.8 ± 2.2	8.2 ± 2.0	+27.9	**0.003** (0.181)	0.611 (0.006)	**0.033** (0.099)
PA level (MET-min/week)	485.4 ± 325.6	530.4 ± 320.4	+35	510.9 ± 304.6	972.3 ± 321.5	+152.4	**< 0.001** (0.376)	**0.005** (0.162)	**< 0.001** (0.290)

T0 baseline, *T1* after 3-month of lifestyle intervention, n^2_p partial eta squared, *Δ%* percentage changes over time, *BMI* body mass index, *VO_2max* maximal oxygen uptake, *HOMA* homeostasis model assessment, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *MeDiet score* adherence to Mediterranean diet (Mediet Score DianaWeB), *PA level* Physical activity level

Table 3 Comparison between T0 and T1 of IGF-1, IGFBP1 and IGFBP3 levels

	Control group (CG; $n = 26$)			Intervention group (IG; $n = 24$)			$p\ (n^2_p)$	$p\ (n^2_p)$	$p\ (n^2_p)$
	T0	T1	Δ%	T0	T1	Δ%	Time	Group	T×G
IGF-1 (ng/mL)	154.3 ± 57.1	152.3 ± 51.8	-1.3	137.2 ± 41.6	138.9 ± 34.0	+1.2	0.847 (0.001)	0.274 (0.026)	0.746 (0.002)
IGFBP1 (ng/mL)	31.1 ± 23.9	38.0 ± 28.0	+22.2	28.5 ± 28.9	43.8 ± 41.6	+53.7	**0.001** (0.208)	0.850 (0.001)	0.206 (0.036)
IGFBP3 (μg/mL)	6.0 ± 1.2	5.8 ± 1.1	-4.3	5.8 ± 0.9	5.3 ± 0.7	-8.3	**0.001** (0.202)	0.146 (0.045)	0.285 (0.025)

T0 baseline, *T1* after 3-month of lifestyle intervention, *IGF-1* Insulin-like Growth Factor-1, *IGFBP1* IGF-1 Binding Protein 1, *IGFBP3* IGF-1 Binding Protein 3

The top-left cluster contained IGFBP1, $VO_{2max,}$ and HDL levels, which showed a positive correlation.

Subsequently, we tested the hypothesis that IGF-1, IGFBP1, and IGFBP3 levels change depending on their T0 values (Fig. 2) [19, 22–25]. There was a negative correlation between T0 IGF-1 level and Δ IGF-1 ($r = -0.32$; $p = 0.026$). We then calculated the 95% CI for the elevation values in the linear regression to define the T0 IGF-1 values associated with non-significant Δ IGF-1 (i.e., ordinate equals zero). The CI for IGF-1 ranges from 94.7 ng/mL to 173.3 ng/mL, with a mean of 137.5 ng/mL. This indicated that participants with T0 IGF-1 values within this range exhibited no significant Δ IGF-1 following LI. In contrast, IGF-1 levels increased in participants with T0 values below 94.7 ng/mL and decreased in those with T0 values above 173.3 ng/mL. Similar results were obtained for IGFBP3 ($r = -0.42$; $p = 0.002$; CI for the elevation values 2.5 μg/mL to 5.4 μg/mL; mean = 4.7 μg/mL). IGFBP-1 values showed marked asymmetry in distribution, and no relationship was found between T0 IGFBP1 values and Δ IGFBP1 ($r = -0.13$; $p = 0.366$).

The correlation between Δ IGF-1, Δ IGFBP1, Δ IGFBP3, Δ BMI, Δ fat mass, Δ VO_{2max}, Δ insulin, Δ HOMA-IR index, Δ LDL, Δ PA level, and Δ MeDiet score was also analyzed (Fig. 3). Δ fat mass was positively correlated with Δ IGF-1 ($r = 0.35$; $p = 0.02$) and negatively correlated with Δ IGFBP1 ($r = -0.33$; $p = 0.02$) (Fig. 3A); Δ insulin was negatively correlated with Δ IGFBP1 ($r = -0.35$; $p = 0.01$) and positively correlated with Δ IGFBP3 ($r = 0.42$; $p = 0.002$) (Fig. 3B); and, Δ IGFBP1 was

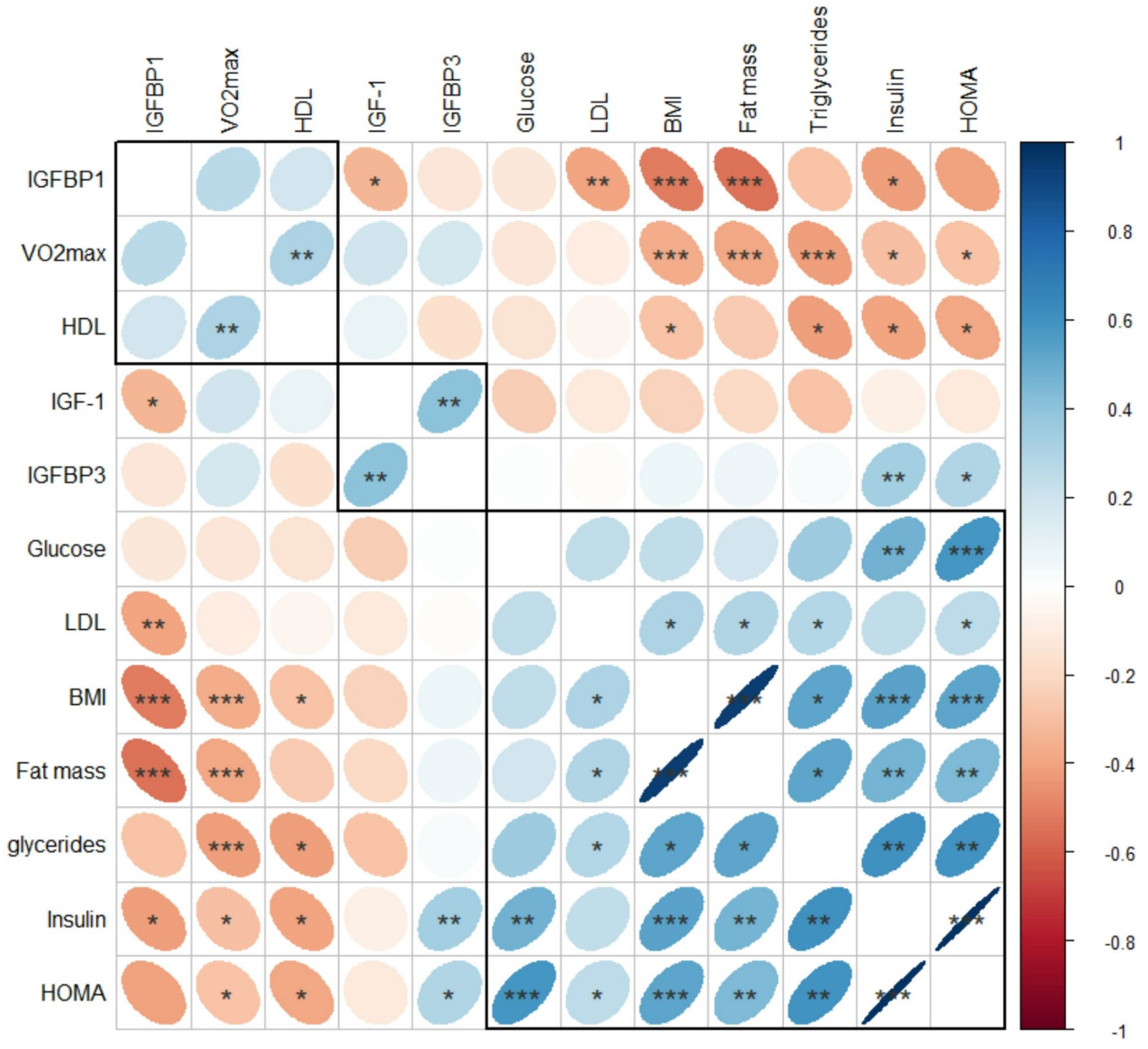

Fig. 1 Correlation plot of IGF-1, IGFBP1 and IGFBP3 levels and body composition, $\dot{V}O_{2max}$, and metabolic variables measured at T0. The highlight boxes indicate highly correlated variables. Spearman rank correlation, *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

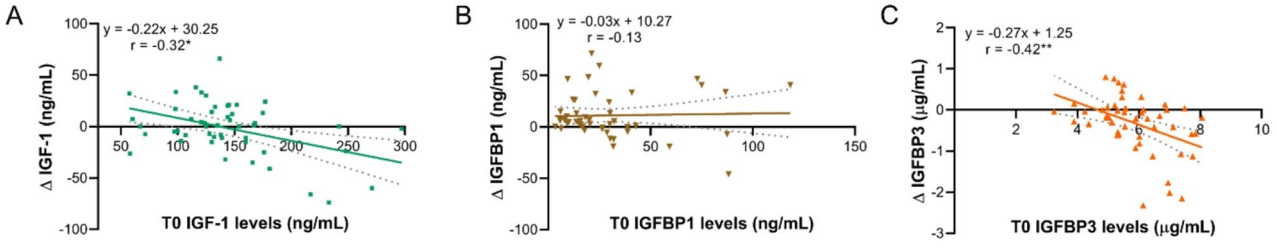

Fig. 2 Correlations between: **A** T0 IGF-1 levels and Δ IGF-1; **B** T0 IGFBP1 levels and Δ IGFBP1; **C** T0 IGFBP3 levels and Δ IGFBP3. Spearman rank correlation, * $p < 0.05$; ** $p < 0.01$

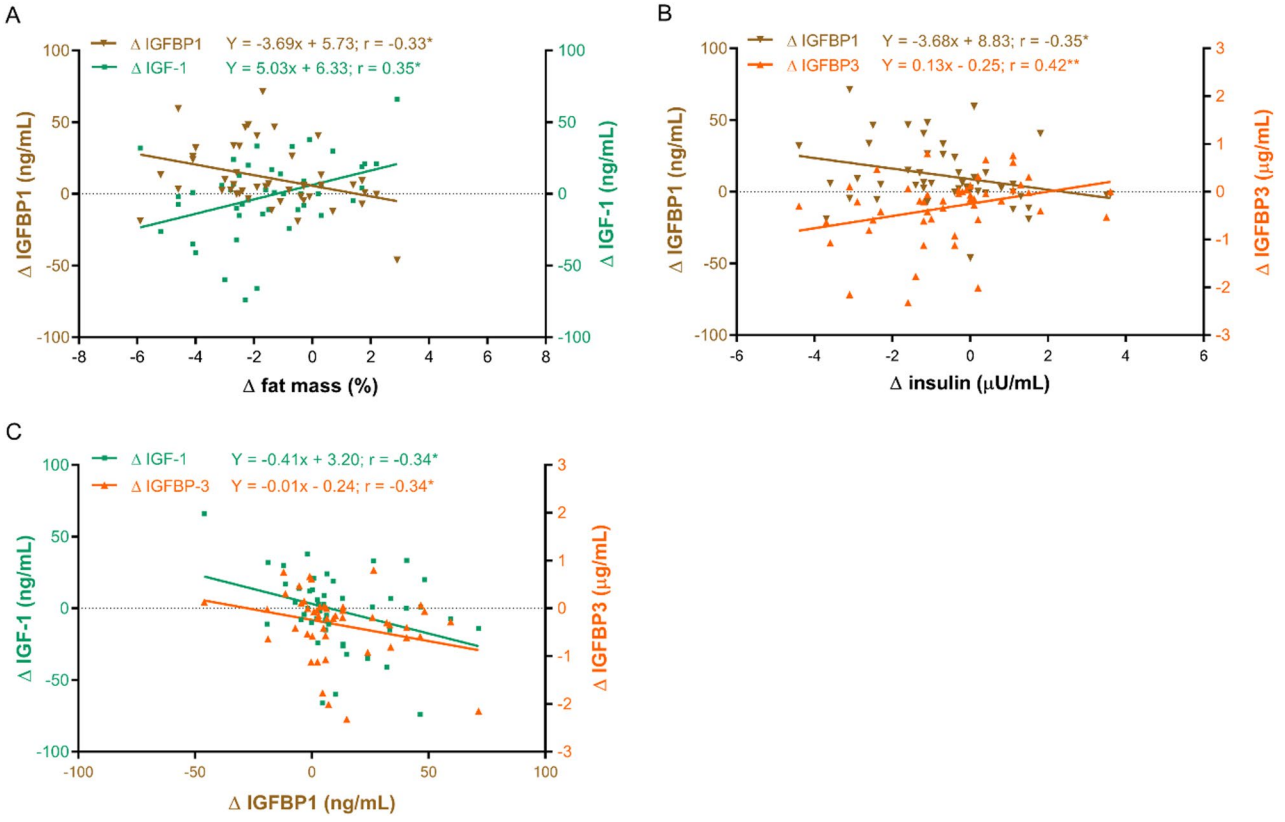

Fig. 3 Correlations between: **A** Δ fat mass, IGFBP1 and IGF-1; **B** Δ insulin, IGFBP1 and IGFBP3; **C** Δ IGFBP1, IGF-1 and IGFBP3. Spearman rank correlation, * $p < 0.05$; ** $p < 0.01$

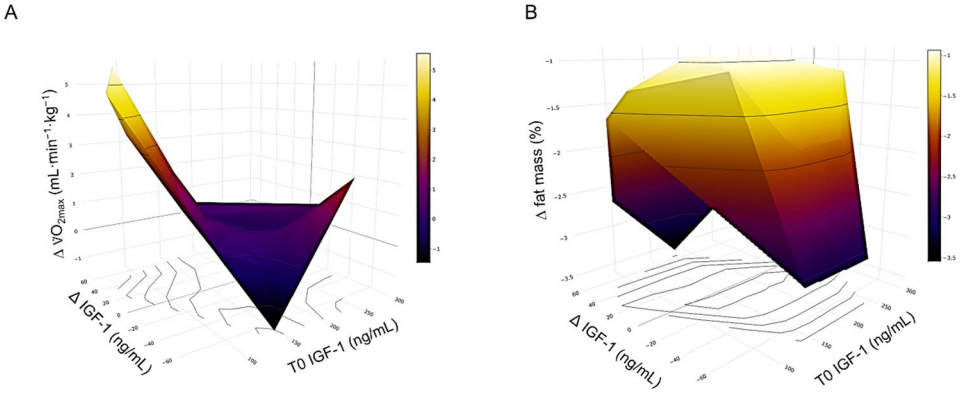

Fig. 4 Three-dimensional quadratic relationship between T0 IGF-1 levels, Δ IGF-1, and **A** Δ VO_{2max} and **B** Δ fat mass

negatively correlated with Δ IGF-1 (r = -0.34; $p = 0.02$) and Δ IGFBP3 (r = -0.34; $p = 0.02$) (Fig. 3C).

Subsequently, we analyzed the three-dimensional quadratic relationship between T0 IGF-1 levels, Δ IGF-1, and Δ VO_{2max} (Fig. 4A) or Δ fat mass (Fig. 4B). This analysis tested the non-linear dependence of Δ IGF-1 versus T0 IGF-1 levels, considering also LI-induced VO_{2max} or fat mass variation. Δ VO_{2max} was chosen because it mainly depends on PA levels, whereas Δ fat mass mostly depends on variations in dietary habits. The relationship between T0 IGF-1 levels, Δ IGF-1, and Δ VO_{2max} followed a U-shaped pattern; participants with T0 IGF-1 levels above the 82nd percentile, corresponding to the upper limit of the 95% CI for the elevation level, exhibited a decrease in IGF-1 levels when VO_{2max} improved. Conversely, in patients with T0 IGF-1 levels below the 12th percentile, corresponding to the lower limit of 95% CI, an increase in VO_{2max} was associated with an increase in IGF-1 levels. The relationship between T0 IGF-1 levels and Δ IGF-1 and Δ fat mass displayed an inverted U-shaped pattern: participants with T0 IGF-1 levels above the 82nd percentile showed a reduction in

IGF-1 levels when fat mass decreased, whereas those with T0 IGF-1 levels below the 12th percentile showed an increase in IGF-1 levels in response to fat mass reduction.

Discussion

This study demonstrated that a LI program based on exercise and Mediterranean diet recommendations (MoviS trial, protocol: NCT 04818359) increased IGFBP1 levels, decreased IGFBP3 levels, and modulated IGF-1 levels in BCS, depending on its baseline values. The BCS participants in the MoviS trial showed improvements in anthropometric and body composition values (BMI and fat mass percentage), physical activity level (PA level), adherence to the Mediterranean diet (MeDiet score), and metabolic markers (insulin, HOMA-IR index, total and LDL cholesterol) in both CG and IG. The magnitude of improvement was greater in the IG, particularly for the VO_{2max}, total PA, and MeDiet scores, likely due to the more structured and supervised aerobic exercise training provided in this group.

With regard to the IGF-1 system, although mean serum IGF-1 levels remained stable after LI, significant changes in IGFBPs were observed in both the CG and IG. Specifically, IGFBP1 levels increased, whereas IGFBP3 levels decreased following the 3-month LI program, suggesting that LI modulated IGF-1 bioavailability indirectly through IGFBPs regulation. Baseline analyses showed that IGFBP1 levels was negatively correlated with IGF-1, LDL, BMI, fat mass, and insulin levels. This is consistent with previous findings indicating that liver IGFBP1 expression and secretion decreases under anabolic conditions, leading to increased IGF-1 bioactivity [7, 8]. Thus, the reductions in fat mass and insulin observed at the end of LI may have directly contributed to increased IGFBP1 levels. Notably, IGFBP-1 is unique among IGFBPs in its rapid response to metabolic and hormonal variations [40, 41], allowing it to regulate IGF-1 bioactivity in response to fasting and insulin fluctuations. Conversely, IGFBP3 was positively correlated with IGF-1, insulin, and HOMA-IR levels at baseline, and with LI-induced changes in insulin levels. These opposing trends between IGFBP1 and IGFBP3 underscore the complex regulation of IGFBPs in response to lifestyle changes and highlight the importance of measuring IGFBPs when assessing the impact of interventions on the IGF-1 system.

Another key finding of this study was that changes in IGF-1 and IGFBP3 levels were dependent on their baseline levels. Specifically, participants with higher baseline IGF-1 levels (> 173 ng/mL) exhibited a reduction in IGF-1 levels after LI, whereas those with low baseline IGF-1 levels (< 95 ng/mL) showed an increase. A similar pattern was observed for IGFBP3.

The high inter-individual variation in circulating IGF-1 levels, attributable to genetics, age, nutritional status, and health-related factors, complicates the prediction modelling of IGF-1 responses to LI. Furthermore, the absence of a clinically defined threshold for IGF-1 levels further challenges the ability to predict the effects of LI on IGF-1 levels. To address this complexity, we tested for the presence of a non-linear relationship between LI-induced changes in IGF-1 levels and anthropometric, VO_{2max} and metabolic variations, accounting for baseline IGF-1 levels.

We demonstrated that a non-linear model better explained the association between baseline IGF-1 levels and changes in VO_{2max}, fat mass, and IGF-1 levels, revealing a U-shaped relationship. Specifically, the LI-induced improvement in VO_{2max} was associated with increased IGF-1 levels in participants with low baseline values (i.e., below the 12th percentile) and with a reduction in those with high baseline values (i.e., above the 82nd percentile). Along this line, an inverted U-shaped relationship emerged between baseline IGF-1 levels and changes in IGF-1 and fat mass, where a reduction in fat mass was associated with an increase in IGF-1 in participants with low baseline values and a decrease in those with high baseline values. In contrast, BCS participants who did not improve VO_{2max} or fat mass, as well as those with mid-range baseline IGF-1 levels (between the 12th and 82nd percentiles), exhibited minimal changes in IGF-1 levels.

These findings align with prior research suggesting a U-shaped relationship between IGF-1 levels and disease risks, including cardiovascular disease, diabetes, and overall mortality, in which both low and high IGF-1 levels are associated with adverse health outcomes [26–29]. Similarly, a recent meta-analysis involving 30,876 participants suggested that low-to mid-range IGF-1 levels (120–160 ng/ml) might represent an optimal range indicative of health [27]. Additionally, a large study of 945 older adults in the U.S. found that individuals with stable IGF-1 levels over a 11.3-year follow-up showed lower mortality compared to those with fluctuating IGF-1 levels [42]. In this study, we demonstrated that the modulation of systemic IGF-1 levels after the LI program occurred only in participants with low or high basal values, helping to normalize IGF-1 levels to a potentially physiological range. This highlights the importance of considering baseline IGF-1 levels to accurately model and predict the effects of LI on the IGF-1 system.

The findings of this study have several important implications for the design of future RCTs and other studies that assess the effects of LI on the IGF-1 system. First, our results indicate that lifestyle-based interventions markedly affect IGFBP levels, with opposing responses observed for IGFBP1 and IGFBP3. Given that approximately 99% of circulating IGF-1 is bound to IGFBPs [5], ignoring the effects of LI on IGFBPs may yield misleading

conclusions regarding IGF-1 system modulation through diet and exercise.

Second, in high-risk populations such as BCS, IGF-1 should not be viewed solely as a pro-tumoral factor, but also as a potential health marker [43, 44]. Indeed, while high IGF-1 is causally associated with an increased cancer risk in BCS, low IGF-1 levels might indicate poor general health due to cancer therapies, reduced lean mass, and inadequate nutritional intake [22, 45–47]. This observation emphasizes the need for personalized approaches when designing interventions aimed at modulating the IGF-1 system. In this scenario, monitoring circulating IGF-1 levels might allow us to identify at-risk individuals, namely those with relatively low or high IGF-1 levels and those with high IGF-1 fluctuation, who are most likely to benefit from a LI. Rather than focusing on a global increase or decrease in IGF-1 levels, the modulation of IGF-1 in response to LIs should be viewed as an adaptive response aimed at maintaining homeostasis.

This study had several limitations. First, the MoviS paricipants were non-physically active and had at least one hormonal risk factor or metabolic syndrome, which may limit the generalizability to other, healthier BCS groups. In addition, the present analyses were conducted on a randomly selected subset of MoviS participants with available paired blood samples, which may not fully represent the entire MoviS cohort or the broader BCS population. Second, since both CG and IG participants showed improvements in Mediterranean diet adherence, physical activity level, anthropometric and body composition measurements, and metabolic markers, we could not clearly distinguish the independent effects of the Mediterranean diet and aerobic exercise on the IGF-1 system. The structured counselling session about lifestyle recommendations provided to all MoviS participants may explain the lack of significant differences between the CG and IG. Third, the LI duration was only 3 months, and thus we cannot draw conclusions regarding longer-term effects on the IGF-1 system. Finally, since only IGFBP3 and IGFBP1 levels were measured, we cannot exclude the possibility that other IGFBPs that potentially affect IGF-1 bioactivity may have been modulated by LI. In this regard, further efforts should be directed toward the development of high-throughput assays to directly measure IGF-1 bioactivity [48].

Conclusions

In conclusion, our study shows that LI-induced changes are strongly associated with the IGF-1 system, particularly through alterations in IGFBP1 and IGFBP3 levels. Furthermore, the apparent stability of circulating IGF-1 levels pre- and post-intervention was due to the divergent modulation observed in BCS participants with relatively low or high baseline IGF-1 levels. Given its affordability, robustness, and consistency, IGF-1 may serve as a valuable biomarker for identifying high-risk individuals, namely those with relatively low or high IGF-1 levels or with high IGF-1 variability over time, for inclusion in LI programs. Future research should focus on exploring the dynamic interactions between IGF-1, its binding proteins, and lifestyle factors, and examine long-term IGF-1 trajectory changes and their implications for health and disease outcomes.

Abbreviations

ACSM	American College of Sports Medicine
BC	Breast cancer
BCS	Breast cancer survivors
BMI	Body mass index
CG	Control group
ELISA	Enzyme-linked immunosorbent assay
ER	Estrogen receptor
GH	Growth hormone
HOMA-IR	Homeostatic model assessment for insulin resistance
HRR	Heart rate reserve
I^2	High heterogeneity meta-analyses
IG	Intervention group
IGF-1	Insulin-like growth factor-1
IGFBP1	Insulin-like growth factor-1 binding protein 1
IGFBP3	Insulin-like growth factor-1 binding protein 3
IPAQ-SF	International physical activity questionnaire – short form
LI	Lifestyle intervention
MeDiet	Mediterranean diet
MET	Metabolic equivalent of task
MoviS	Movement and health beyond care study
PA	Physical activity
$\dot{V}O_{2max}$	Maximal oxygen uptake
WCRF	World cancer research fund

Supplementary Information

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Supplementary Material 1.

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Author contributions

GA, DS, MDS, RE and EB conceived the study; VN, MI, CFM and FL supervised exercise intervention and performed fitness evaluations and analyses; AV, MI, EB and RE assessed dietary habits; LV, RS, GB and SB performed blood sample collection and analyses; MF, VC and RE performed clinical parameters evaluation; DS and MBLR performed data collection and statistical analysis; EB and RE supervision and acquisition of funding. GA, DS and MDS drafted the manuscript. All authors revised the article and approved the submitted version.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Ethical approval was granted by the Human Research Ethics Committee of the University of Urbino Carlo Bo (Protocol N 21 of July 10, 2019), and written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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