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Keywords

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Article

The potential role of selected body composition phenotypes in the interpretation of the exercise-induced components of the insulin-like growth factor systems

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1. Introduction

Human growth hormone (hgH) is classified among anabolic hormones and has an essential role in regulating protein metabolism, hypertrophy in muscle mass, and it stimulates insulin-like growth factor-I (IGF-1) synthesis [1]. IGF-1, also called Somatomedin C, plays a key role in regulating the proliferation, differentiation, regeneration of skeletal muscles, and specific functions of many cell types [2]. The circulation of IGF-1 in skeletal muscles, which is a metabolic mediator of human growth hormone (hgH), increases during exercise, and the intensity and duration of physical activity determine the levels of circulating IGF-1 [3]. The increase in the levels of circulating IGF-1 stimulates growth in all cells, from skeletal muscle and bone to organ tissue and vessel linings [4]. However,

intrinsic and extrinsic factors, such as age, gender, genetics, nutritional status, physical activity, and stress have a crucial role in the regulation of circulating levels of IGF-1 [5]. A deficiency or excess in the levels of either hormone may result in physiological errors in metabolism due to the relationship between IGF-1 and hgH [6]. IGF-1 levels in the organism also vary depending on the muscle mass, the metabolic rate, and muscle strength [7]. The intensity of the exercise, most specifically intense exercises, has been shown to increase the circulating levels of IGF-1 [8]. Nevertheless, increased, decreased, or unaltered levels of IGF-I after resistance or endurance training complicate the dose-response relationship between IGF-1 and physical activity due to the existence of compelling evidence [9–11]. IGF-1 bioactivity is regulated in part by its six binding proteins, and each of these proteins has an essential role in regulating IGF bioavailability. Among all of these binding proteins, IGFBP-1, which is an endocrine factor that alters serum IGF bioavailability, has been proposed as the acute regulator of IGF bioavailability because of its metabolic regulation by glucoregulatory hormones [12]. It has been reported that the simple measure of total circulating IGF-I encompasses ternary, binary, and free IGF-I molecular isoforms despite the fact that only the free IGF-I isoform is bioavailable to bind tissue receptors and exert a cellular effect [13]. The results of those studies have asserted that the measures of either bioavailable or bioactive IGF-I are superior to total IGF-I since they may have utility as a more sensitive biomarker than total IGF-I for assessing physiological strain and subsequent alterations occurring in the biological matrix when assessing the health status, as well as metabolic and cardiovascular functions [14–19].

Additionally, inadequate physical activity, nutritional factors, and low and high BMI values have been shown to lead to increased health risks and IGF-I bioavailability, which may lead to increased risk of certain types of cancers [20]. Increased adiposity due to the insufficient amount of exercise may thus lead to impaired physiologic growth hormone secretion and decreased growth hormone responses to all stimuli. Accordingly, increasing physical activity may be the most effective strategy for reducing levels of bioavailable IGF since increased adiposity has been shown to lead to the impaired physiologic growth hormone secretion and decreased growth hormone responses to all stimuli [21]. Although BMI is the most frequently used method to interpret the physical activity-induced changes in body composition, this method has been criticized because BMI does not always reflect actual body adiposity and has some limitations in assessing the risk of obesity-related diseases in persons with low muscle and high body fat and in individuals with increased body fat and normal BMI [22–24]. Also, despite the interaction between the body composition and endocrine responses to the given exercise– BMI does not discriminate body fat from fat-free mass and result in variations in FFM, FFMI, NFMI, and BFM. It also does not allow a precise measure of the changes in the aforementioned components following physical activity and leads to misinterpretation of the physical activity-induced changes in the insulin-like growth factor system [25]. With this regard, it seems that body composition may be better evaluated by assessing body fat and fat-free mass [26]. Thus, the measurement of FFM, FFMI, NFFMI may have utility as a more precise method to determine the physical activity-induced changes in skeletal muscle than relying solely on BMI for assessing subsequent alterations occurring in the components of the insulin-like growth factor system which has an essential role in facilitating protein accretion and muscle hypertrophy. This study evaluated the relationship between the selected body composition interpretation methods and physical activity-induced changes in the components of the insulin-like growth factor system in physically active healthy male individuals undergoing 8 weeks of high-intensity incremental cycling training at a vigorous intensity compared with a low-intensity constant cycling training.

2. Materials and Methods

2.1. Subjects

Thirty healthy male participants with at least 3 years of sports history voluntarily participated in this study (age: 21.33 ±1.24 years, height: 177.80 ±5.97 cm, weight: 73.99 ±7.66 kg, lean mass: 64.64 ±7.34 kg, percentage of body fat: 13.17 ±5.00 %), respectively. A randomized controlled trial with a parallel groups study design was used including vigorous and moderate intensity training groups and a control group in order to investigate the changes in serum biomarker responses induced by trainings with different intensities. The inclusion criteria applied in the research were healthy, physically active (e.g. at least 3 times in a week) male participants aged between 18 and 30 years old, who were not suffering from any kind of acute or chronic disease that would limit their ability to participate in the study; refusal to give informed consent, failure to adhere to pre-test requirements, evidence of altered training/fitness were the exclusion criteria from the study. All training interventions were conducted three times per week throughout eight weeks with one-day interval. The participants gave written informed consent prior to participating in the study approved by the Institutional Review Board in accordance with the ethical standards of the Helsinki Declaration.

2.2. The Assessment of Anthropometric Parameters

The anthropometric parameters were determined using Bioelectrical impedance analysis (Tanita 418-MA Japan). The participants' heights were measured by means of a stadiometer in the standing position (Holtain Ltd. U.K.). All participants were instructed to maintain their usual food intake, hydration, and physical activity and training sessions were started 1–2 days after baseline tests at individual training intensity based upon each participants' baseline maximum oxygen consumption parameters. BMI was calculated by dividing body weight by the square of height (kg/m^2). Body fat was calculated based on a simple equation, and the results were expressed in kilogram units [kg].

$$\text{Body fat} = \text{weight [kg]} * (\text{body fat [\%]} / 100)$$

Fat free mass (FFM) was estimated using the following method, and the results were also expressed in kilograms [kg].

$$\text{Fat free mass} = \text{weight [kg]} * (1 - (\text{body fat [\%]}/ 100)$$

Fat free mass index (FFMI) allows distinguishing between fat gain and muscle gain following an exercise. The increase in the fat mass results in a decreased FFMI while and increased FFMI shows the gain in muscle mass. The formula shown below was used to calculate FFMI. The results were expressed in kilograms per square meter [kg/m^2].

$$\text{FFMI} = \text{fat free mass [kg]}/ (\text{height [m]})^2.$$

Normalized fat-free mass index (NFMI) was also calculated since the participant's height may affect FFMI. To better isolate muscle, a normalized FFMI formula was usedm, and the results were expressed in kilograms per square meter [kg/m^2].

$$\text{NFFMI} = \text{FFMI [kg/m}^2\text{]} + 6.1 * (1.8 - \text{height [m]}).$$

2.3. The Assessment of Cardiovascular Components Used to Determine Individual Training Intensity

Maximum oxygen consumption (VO_{2max}) and time to exhaustion were measured in a preliminary test session using Ergoline Ergoselect 100/200 cycle ergometer over a one-week interval to determine training intensity both for vigorous (120% of maximum oxygen consumption) and moderate (65% of maximum oxygen consumption) training groups. In the first visit, a progressive cycle ergometer test was used to determine maximum oxygen consumption and maximum individual fatigue intolerance point. Participants started to pedal at 50 Watt and were asked to pedal between 95–100 rpm. Each stage consisted of 2

minutes, and the load was increased by 50 Watt with the completion of every stage until a plateau in VO_2 despite an increase in cycling intensity, a respiratory exchange ratio (RER) above 1.1, 90% of the predicted maximal HR. If the stage of 2 min could not be completed, the load of the previous stage was recorded. The load that VO_{2max} elicit was recorded to determine individual training intensity used during vigorous and moderate trainings. Throughout the test, the Borg scale was used in assessment of the perceived exertion during exercise.

In the following session, participants were tested at their individual fatigue intolerance point at a constant load until volitional exhaustion. Following 10-min warm-up period at 60% of maximum fatigue intolerance point, the load was immediately increased (in less than 20 s) up to maximum individual training intensity, and the participants were encouraged to pedal at a constant speed of 100 rpm to their volitional exhaustion. O_2 was measured breath by breath (CareFusion MasterScreen CPX, Germany) and subsequently averaged over 15-second intervals. Before each test, the automated gas analyzer was calibrated according to the manufacturer's recommendations. The heart rate was also monitored and recorded throughout the test sessions using 12-lead ECG. Individual training intensity was determined using baseline fatigue intolerance point parameters.

2.4. Collection of Blood Samples

During baseline and follow-up test sessions, 5 ml of fasting blood sample was drawn from the brachial vein 15 min before (pre-), 15–30–min after (post-) and 24 h after the interventions (24h-post) between 08:00 a.m.–12:00 p.m. The participants were seated after the interventions for 15 min until the first blood samples were collected. Blood samples were stored at –80°C and analyzed after completing the study. Serum IGF-1 and IGFBP-1 samples were collected using Elabscience kits (IGF-1: Detection Range: 1.56~100 ng/ml; Sensitivity: 0.94ng/ml; IGFBP-1: Detection Range: 0.16~10ng/ml; Sensitivity: 0.10 ng/ml) and analyzed using Enzyme-linked Immunosorbent Assay (ELISA)-method according to the manufacturer's instructions (R&D Systems, Minneapolis, USA), and the proportion of IGF-1 to IGFBP-1 was used to measure bioavailability of IGF-1 [27]. No nutritional supplements were allowed during the study period. All participants were also instructed to maintain the usual nutrition throughout the study period. Blood samples were also taken prior to time to exhaustion tests both at baseline and 2 minutes after the intervention to determine blood lactate concentrations. Blood samples were collected from earlobe using Lactate Pro 2 handheld analyzer (LT-1730, Arkray Inc, Kyoto, Japan).

2.5. Isokinetic Strength Measurements

Prior to the assessment of isokinetic strength parameters of dominant and non-dominant legs, the participants were seated in the upright position with the hips flexed at an angle of 90°. Each participant performed dynamometer trials over a series of 10 sub-maximal repetitions both during knee flexion (concentric) and extension (concentric) at 180°/sec followed by 5 maximal bilateral knee extension repetitions, from 90o of flexion to full extension (0°), at an angular velocity of 60°/sec and 180°/sec at a maximal effort. The dominant leg was chosen as the leg used to kick a ball. Gravity correction was made prior to all test sessions.

2.6. Statistical Analysis

Using the Shapiro Wilk-W test study, the normality of distribution was calculated, followed by a two-way mixed ANOVA with repeated measurements to analyze the results obtained for subgroups before and after treatment (groups vs. pre/post-treatment). The Wilcoxon paired test, the Mann-Whitney U non-paired test and the Kruskal-Wallis test with Bonferroni correction for non-paired data were conducted to evaluate the results obtained for all groups before and after treatment. Using the coefficient of Pearson product moment correlation, correlations were tested. All outcomes have been described as the mean ±SD.

The level of statistical significance, for all comparisons, was set at $p < 0.05$ and $p < 0.001$. GraphPad Software The GraphPad Prism 6 was used for graphical expression.

3. Results

There were no significant differences between groups concerning body composition phenotypes, VO_{2max}, and neuromuscular components before the treatment period (Table 1). The percentage fat mass significantly decreased in moderate and vigorous training groups ($p < 0.05$). VO_{2max} parameters significantly increased following both moderate and vigorous training regimen compared to baseline measurements (Table 1). No statistically significant differences occurred with regard to knee extension and flexion parameters following 8 weeks of training.

Table 1. Comparison of mean values of anthropometric and physiological variables and their significance using Wilcoxon Signed-Rank Test for Paired samples.

Variable	Control (n = 6)		Moderate (n = 12)		Vigorous (n = 12)	
	Before	After	Before	After	Before	After
Body weight, kg	75.27±7.25	75.17±7.12	70.97±9.11	71.67±9.14	75.76±6.59	75.18±5.80
Percent fat mass, %	14.60±5.54	14.65±5.55	10.98±4.68	9.89±4.58*	13.89±5.31	12.37±5.20*
VO_{2max}, ml/kg.min^{-1}	47.68±5.77	48.26±3.15	43.64±3.62	54.13±2.65**	48.40±5.02	56.71±4.20**
DNE, Nm	274.67±6.5	268.50±27.7	250.50±28.8	239.83±28.57	282.75±53.32	290.67±45.32
NDKE, Nm	239.67±13.4	237.83±36.8	241.08±22.2	243.42±34.4	255.08±33.70	258.50±39.15
DNF, Nm	147.17±15.5	143.67±21.6	149.83±14.1	145.43±26.2	167.83±32.11	170.50±32.18
NDKF, Nm	123.83±11.9	121.17±10.5	132.58±22.8	133.50±17.8	163.42±31.00	166.58±25.30
Body weight, kg	75.27±7.25	75.17±7.12	70.97±9.11	71.67±9.14	75.76±6.59	75.18±5.80

Note: Pre- and post-training parameters for all groups (values are mean ± SD). Asterisk (*) – a significant change from pre- to post-training within same group ($p < 0.05$). Asterisks (**) – a significant change from pre-to post-training within same group ($p < 0.001$). BMI: body mass index, VO_{2max}: maximum oxygen consumption, DNE: dominant limb knee extension, NDKE: non-dominant limb knee extension, DNF: dominant limb knee flexion, NDKF: non-dominant limb knee flexion.

However, bioavailable IGF significantly increased in all groups compared to baseline measurements (control: $Z = –3.94$, $p = 0.000$; vigorous: $Z = –4.62$, $p = 0.000$; moderate: $Z = –3.49$, $p = 0.000$).

Table 2. Body composition and IGF-I system levels before and after training (n = 30).

Variable	Minimum		Maximum		Mean (SD)	
	Before	After	Before	After	Before	After
Body mass index, kg/m²	18.26	18.16	28.37	28.09	23.35 (2.50)	23.25 (2.22)*
Fat-free mass, kg	49.71	49.82	73.85	74.13	64.50 (5.11)	64.28 (5.23)
Fat-free mass index, kg/m²	16.85	17.26	22.76	23.24	20.41 (1.46)	20.34 (1.53)
Normalized fat-free mass index, kg/m²	16.69	16.79	22.76	24.03	20.55 (1.61)	20.48 (1.69)
Bioavailable IGF-I pre 15 min, ng.mL^{-1}	1.05	1.17	15.93	29.11	3.95 (3.18)	8.92 (4.73)***
Bioavailable IGF-I post 30 min, ng.mL^{-1}	0.81	0.24	9.62	21.01	3.99 (1.77)	9.41 (3.71)***
Bioavailable IGF-I post 24 h, ng.mL^{-1}	1.44	0.81	13.90	16.67	5.88 (3.00)	8.63 (3.00)***
Body mass index, kg/m²	18.26	18.16	28.37	28.09	23.35 (2.50)	23.25 (2.22)*

Note: Pre- and post-training parameters for all groups (values are mean ± SD). Asterisk (*) – a significant change from pre- to post-training within all groups ($p < 0.05$). Asterisks (**) – a significant change from pre-to post-training within all groups ($p < 0.000$).

There were no statistically significant correlations between bioavailable IGF, body composition phenotypes and neuromuscular components. However, the partitioning of BMI into FFM, FFMI, and NFFMI were found to be statistically significantly correlated both with the changes in the bioavailable IGF system and neuromuscular components (Figures 1a, 1b, 1c). Bioavailable IGF was not correlated with BMI following 8 weeks of exercise ($r = –.267$, $p = 0.154$). However, negative significant correlations were found between bioavailable IGF and fat-free mass ($r = –.472$, $p = 0.008$), fat-free mass index ($r = –.425$, $p = 0.019$), and normalized fat-free mass index ($r = –.379$, $p = 0.039$).

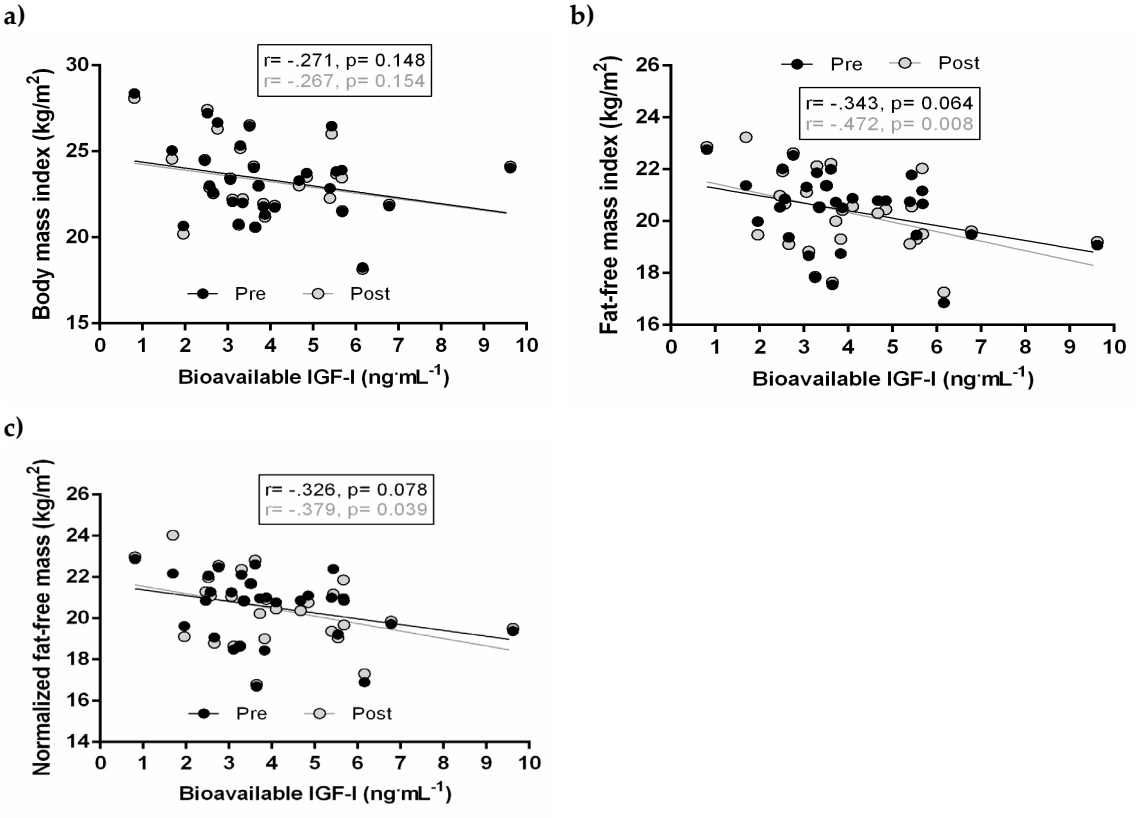

Fig. 1. Interactions between bioavailable IGF and (a) body mass index, (b) fat-free mass index, (c) normalized fat-free mass index

Similarly, BMI adjusted knee extension ($r = –.284$, $p = 0.129$) and flexion ($r = –.282$, $p = 0.131$) parameters were not significantly correlated with bioavailable IGF following either training modality (Figures 2a and 2b).

However, when both knee extension and flexion moment were adjusted with FFMI ($r = –.515$, $p = 0.004$; $r = –.554$, $p = 0.001$), and NFFMI ($r = –.492$, $p = 0.006$; $r = –.543$, $p = 0.002$), muscular strength characteristics were negatively significantly correlated with bioavailable IGF, respectively (Figure 2c, 2d, 2e, 2f).

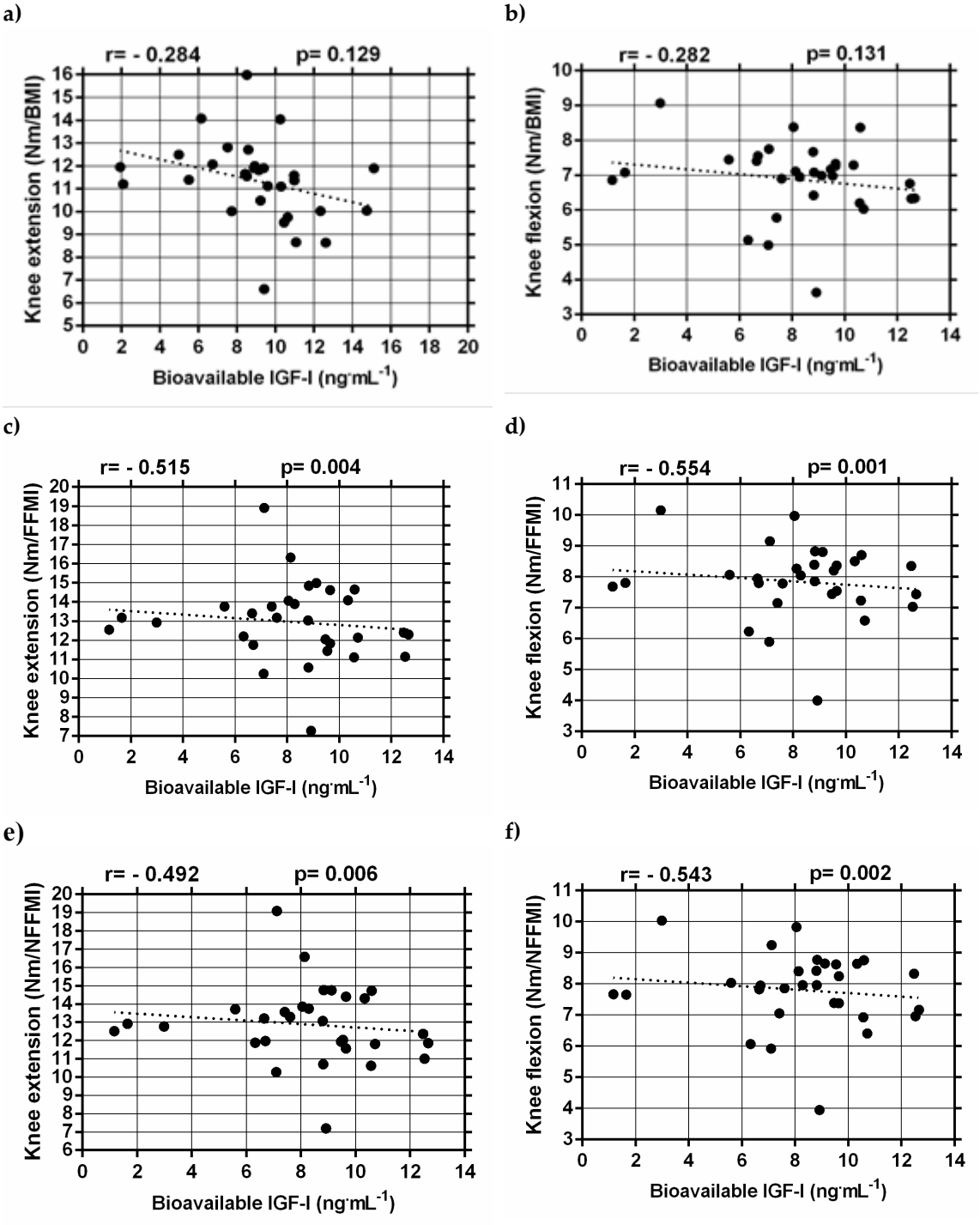

Fig. 2. Relationships between bioavailable IGF and knee extensor and flexor muscle strength corrected for body composition phenotypes.

Additionally, for relative bioavailable IGF changes, FFM ($r = 0.41$, $r^2 = 0.17$, $p = 0.024$), the FFMI ($r = 0.43$, $r^2 = 0.18$, $p = 0.019$), and NFFMI ($r = 0.38$, $r^2 = 0.14$, $p = 0.039$) percentage change explained nearly three times the variance as the BMI percentage change ($r = 0.27$, $r^2 = 0.07$, $p = 0.154$).

4. Discussion

This study evaluated the training-induced adaptations of components of the insulin-like growth factor system and their interaction with the changes in BMI, FFM, FFMI, and NFFMI in healthy male participants undergoing 8 weeks of high-intensity incremental

cycling training at vigorous intensity and low-intensity constant cycling training. The main findings in this study were that (1) bioavailable IGF-1 did not decrease following short-term moderate and vigorous cycling training, (2) increases in bioavailable IGF-I showed an increased anticatabolic effect following exercise and it had a greater association with FFM, FFMI, and NFFMI than observed for BMI, (3) for relative bioavailable IGF changes, FFM, FFMI, and NFFMI percent change explained nearly three times the variance as the BMI percentage change.

Studies to date have shown that modifications in IGF bioavailability have been proposed as a mechanism linking obesity and cancer risk while increased concentrations were associated with higher BMI [28]. On the other hand, an increase in total IGF-I and a decrease in IGFBP-1, which is typically considered inhibitory to IGF-I bioactivity, has shown to be indicative of potentiated bioavailability/bioactivity [29]. Also, an elevated ratio IGF-1/IGFBP-1 have shown to be associated with low levels of bioavailable IGF-1 and a catabolic state [30].

However, as opposed to those findings, the results of the current study revealed no statistically significant correlations between BMI and bioavailable IGF following either training modality (Figure 1a). Despite the significant decreases in the percentage of body fat and BMI following moderate and vigorous trainings, no interaction was observed between BMI and the changes in bioavailable IGF. On the other hand, the partitioning of BMI into FFM, FFMI, and NFFMI rather than relying on sole measures of BMI were negatively significantly correlated with bioavailable IGF (Figures 1b, 1c, 1d). Our results showed that fifty-three percent of recruits gained FFM following 8 weeks of cycling training. BMI increased in 43.3% of the participants, while FFMI and NFFMI increased in 56.7% of the participants. Furthermore, the overall increase in the mean value for bioavailable IGF-I was inversely correlated with the increases in FFM and its indexes rather than BMI. In accordance with that, another study also reported a stronger association between bioavailable IGF-I and activity-induced variations in FFM than did total IGF-I with changes in FFM. They suggested that the utility of bioavailable IGF-I as a biomarker tracking changes in FFM may be generalized to a wide variety of circumstances when altered metabolic conditions lead to body composition changes [31]. Another study reported that fat-free mass may take up approximately 75–90% of body weight in normal adults [32]. Thus, it may be more reasonable to disregard BMI to assess fat-free mass since it largely reflects total body weight rather than fat body weight. These results suggest that the use of BMI may offer inconsistent and inaccurate information on a subject's body composition due to its major limitation in distinguishing between fat-free mass and fat body mass.

From the standpoint of a non-linear relationship between BMI and IGF, bioavailable IGF has been shown to increase as a result of resistance training-induced increases in IGF-1 levels which may also be contributing to the significant strength gain [33], whereas another study reported that IGF-1 is associated with higher levels of aerobic fitness and muscular endurance, but not with muscle strength or fat-free mass and subsequent anabolism for muscle hypertrophy [34]. The results of the current study showed that the changes in strength parameters following either training modality were insignificant whereas VO2max significantly increased following either training modality (Table 1). Despite the importance of IGF-I in normal muscle growth and anabolism, the results of the current study revealed no statistically significant correlations between muscle strength performance and bioavailable IGF following either training modality. However, when muscular strength indices were adjusted with FFM, FFMI, and NFFMI, the changes in muscular strength performance were negatively significantly correlated with bioavailable IGF (Figures 2b, 2c, 2d). Our results showed that fifty-three percent of recruits gained FFM during cycling training. BMI increased in 43.3% of the participants, while FFMI and NFFMI increased in 56.7% of participants. These results reveal that, since height and fat-free mass are taken into account to calculate FFMI, it reduces the bias associated with % body fat when calculating these indices. Additionally, FFMI and NFFMI seem to be better indicators when the relative contribution of skeletal muscle performance needs to be measured

quantitatively in order to exclude a false diagnosis of excess body fat based on single BMI measurements. These results suggest that when only BMI is used as a single criterion, the divergent relationships between the indices of muscular performance, body composition, and IGF responses to the given exercise cannot be distinguished. Additionally, the use of FFMI and NFFMI as opposed to BMI seems to provide more precise information since they may quantify the physical activity-induced changes in lean mass on the basis of total fat-free mass rather than total body weight. Moreover, due to the fact that increased adiposity might have the potential to underestimate the increase in connective tissue, the use of BMI may also underestimate the decrease in skeletal muscle and result in improper classification among the subjects. From a different standpoint, FFMI and NFFMI may also offer information with regard to the metabolic disturbances related to high fat mass which may also lead to a loss in muscle mass. With this regard, the variations in bioavailable IGF may be better evaluated using the methods based on a measure of skeletal muscle mass normalized for height, such as FFMI and NFFMI, in combination with fat mass rather than utilizing BMI as the phenotypic expression of adiposity which has considerable limitations in delineating fat mass from the fat-free mass.

5. Conclusions

The obtained results revealed that increased bioavailable IGF-I suggests an increased anticatabolic effect and inverse interaction with body composition phenotypes following exercise. The partitioning of BMI into FFM, FFMI, and NFFMI rather than relying on sole measures of BMI seem to offer more precise results in the assessment of the interactions between the body composition, neuromuscular performance adjusted with body composition phenotypes, and training-induced changes in insulin-like growth factor system. With this in mind, it could be speculated that neither moderate nor vigorous cycling exercise without additional strength training or nutritional program would affect serum IGF-1 biomarkers or reduce IGF bioavailability. Further research needs to be warranted considering the participants' nutritional status. In addition to the dose-response relationship between exercise and serum biomarker responses, a training regimen should also be designed using different nutritional programs to decrease IGF bioavailability.

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