Energy flux, more so than energy balance, protein intake, or fitness level, influences insulin-like growth factor-I system responses during 7 days of increased physical activity

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Submitted 19 February 2007; accepted in final form 13 August 2007

Rarick KR, Pikosky MA, Grediagin A, Smith TJ, Glickman EL, Alemany JA, Staab JS, Young AJ, Nindl BC. Energy flux, more so than energy balance, protein intake, or fitness level, influences insulin-like growth factor-I system responses during 7 days of increased physical activity. *J Appl Physiol* 103: 1613–1621, 2007. First published August 16, 2007; doi:10.1152/japplphysiol.00179.2007.—The purpose of this study was to determine the impact of dietary factors and exercise-associated factors on the response of IGF-I and its binding proteins (IGFBPs) during a period of increased physical activity. Twenty-nine men completed a 4-day (*days 1–4*) baseline period of a controlled energy balanced diet while maintaining their normal physical activity level followed by 7 days (*days 5–11*) of a 1,000 kcal/day increase in physical activity above their normal activity levels. Two subject groups, one sedentary (Sed, mean V˙O2peak: 39 ml·kg⁻¹·min⁻¹, *n* = 7) and one fit (FIT1, mean V˙O2peak: 56 ml·kg⁻¹·min⁻¹, *n* = 8) increased energy intake to maintain energy balance throughout the 7-day intervention. In two other fit subject groups (FIT2, *n* = 7 and FIT3, *n* = 7), energy intake remained at baseline resulting in a 1,000 kcal/day exercise-induced energy deficit. Of these, FIT2 received an adequate protein diet (0.9 g/kg), and FIT3 received a high-protein diet (1.8 g/kg). For all four groups, IGF-I, IGFBP-3, and the acid labile subunit (ALS) were significantly increased by 49%, and 19% (*n* = 7 and FIT3, *n* = 7), energy intake remained at baseline resulting in a 1,000 kcal/day exercise-induced energy deficit. Of these, FIT2 received an adequate protein diet (0.9 g/kg), and FIT3 received a high-protein diet (1.8 g/kg). For all four groups, IGF-I, IGFBP-3, and the acid labile subunit (ALS) were significantly decreased by *day 11* (27 ± 4%, 10 ± 2%, and 19 ± 4%, respectively) and IGFBP-2 significantly increased by 49 ± 21% following *day 3*. IGFBP-1 significantly increased only in the two negative energy balance groups, FIT2 (38 ± 6%) and FIT3 (46 ± 8%). Differences in initial fitness level and dietary protein intake did not alter the IGF-I system response to an acute increase in physical activity. Decreases in IGF-I were observed during a moderate increase in physical activity despite maintaining energy balance, suggesting that currently unexplained exercise-associated mechanisms, such as increased energy flux, regulate IGF-I independent of energy deficit.

insulin-like growth factor binding proteins; exercise; nutritional factors

**INSULIN-LIKE GROWTH FACTOR-I (IGF-I)** can be produced both systemically in an endocrine fashion and locally in an autocrine/paracrine fashion. In terms of exercise responses, the literature has firmly established that local IGF-I expression is upregulated following exercise. However, the literature is equivocal with regard to systemic (i.e., circulating) IGF-I in that studies have shown increases (21, 25), decreases (27, 29, 33), and no changes (5, 22, 31) following both acute and chronic exercise studies. These findings are consistent with the idea that locally synthesized IGF-I plays a predominant role in body growth and has led some to question the physiological relevance of circulating IGF-I and its role in tissue remodeling. However, recent studies suggested that circulating IGF-I concentrations may be related to the development or progression of pathological conditions such as cancer (20), heart disease (17), diabetes (34), and neural disease (7). Additionally, definitive data were published illustrating the importance of circulating IGF-I in the direct regulation of bone growth and density (38).

Recently, our laboratory demonstrated that circulating IGF-I has greater prognostic utility than other conventional nutritional biomarkers when assessing weight change during metabolic strain (28). Thus the physiological significance of circulating IGF-I may reside in its ability as a biomarker to reflect changes in health and fitness profiles. However, the unclear association between exercise and circulating IGF-I emphasizes the need to further investigate the IGF-I response during periods of physical activity and altered energy states. Such information may provide greater insight with regard to the relative role of circulating vs. local IGF-I as well as the pleiotropic effects that IGF-I exerts in mediating the beneficial outcomes of exercise.

The disparate effects of exercise on circulating IGF-I might be attributable to effects of fitness level and/or dietary intake variations, since most studies have not adequately controlled for these coincident effects. With respect to fitness level per se, Rosendal et al. (33) reported that untrained individuals showed more extensive changes in the IGF-I system during an 11-wk physical training program than trained individuals. Variations in total energy availability regulate IGF-I and the family of insulin-like growth factor binding proteins (IGFBPs; Refs. 8, 19, 37) and may influence the circulating IGF-I responses to exercise. Smith et al. (35) demonstrated that negative energy balance induced by caloric restriction without exercise decreased IGF-I to the same extent as an equivalent exercise-induced negative energy balance. Dietary macronutrient composition also can influence the IGF-I system (15). For example, dietary protein restriction has been shown to decrease IGF-I and IGFBP-3, as well as increase IGFBP-2, even when total caloric content of the diet remains constant (36). Similarly, among subjects participating in a 6-mo strength and conditioning program, those who consumed a diet supplemented with...
additional dietary protein (2.2 g/kg) exhibited higher circulating IGF-I concentrations than subjects who consumed an isocaloric diet with a normal (1.1 g/kg) dietary protein intake (1).

While it is clearly established that circulating IGF-I declines during caloric restriction, recent work suggested that IGF-I may also decline in response to an increase in physical activity even during energy balance (26). This suggests that, rather than the overall energy balance, the IGF-I system may be responding to the energy flux of the metabolic system, defined as the absolute level of energy intake and expenditure under conditions of energy balance (4). Furthermore, it is not known whether manipulating dietary protein content of an energy-deficient diet will influence IGF-I responses to exercise. Therefore, the purpose of the current study was to further characterize the relationship between dietary factors and exercise-associated factors and their impact on the IGF-I system by strictly controlling for energy and protein intake and energy expenditure. Specifically we tested three hypotheses: 1) an increase in physical activity would significantly decrease circulating IGF-I during an energy deficit, and 2) a protein-supplemented diet would attenuate a decrease in circulating IGF-I during an energy deficit, and 3) there would be a greater decrease in circulating IGF-I in sedentary vs. fit individuals following an increase in physical activity matched with energy intake. As IGF-I binding proteins regulate IGF-I bioavailability, we also measured the circulating concentrations of IGFBP-1, -2, -3, and the ALS.

METHODS

Subjects. Twenty-nine healthy men gave informed consent to complete the study after an oral and written explanation of all study procedures and risks. All subjects were medically cleared for participation in accordance with United States Army Research Institute of Environmental Medicine guidelines for human use. The study followed the policies for protection of human subjects as prescribed in Army Regulation 70–25, and the research was conducted in adherence with the provisions of 32 CFR Part 219. As part of the initial screening, each subject’s V_{O2peak} was assessed with a continuous cycle ergometer test. The V_{O2peak} value was used to classify the subjects as fit (cut point V_{O2peak} value > 52–54 ml·kg⁻¹·min⁻¹) or sedentary (cut point V_{O2peak} value < 41–43 ml·kg⁻¹·min⁻¹). Subjects were divided into four separate experimental groups (refer to Fig. 1): one sedentary (Sed) and via random selection into three fit (FIT1, FIT2, and FIT3). Subjects were housed in the Doriot Climatic Chambers Metabolic laboratory at the Natick Soldier Systems Command in Natick, MA, for the duration of the study to ensure dietary compliance and to tightly control and measure energy expenditure.

Diet and activity intervention. Refer to Table 1. Baseline period (days 1–4): for the 4-day baseline period, all subjects were given a controlled diet that replicated their normal energy intake and they also maintained their normal physical activity level. Throughout the study, dietary protein intake was held constant at 0.9 g protein·kg body wt⁻¹·day⁻¹ (Sed, FIT1, FIT2) or 1.8 g protein·kg body wt⁻¹·day⁻¹ (FIT3). To determine normal energy intake and activity, each subject kept a 3-day diet and activity record the week preceding the study. All subjects were interviewed to ensure the accuracy of the 3-day records. During the interview, each subject was asked to describe in detail (type, duration, and intensity) their typical weekly exercise habits and to quantify their exercise training history for the 6 mo leading up to the study. Energy intake and expenditure values were compared and used collectively to determine each subject’s energy requirements and activity prescription during the 4-day baseline period to maintain energy balance. The actual total daily energy expenditure (TDEE) for each subject was verified using indirect calorimetry during each activity (as described below) on day 1 of the 4-day baseline period to ensure that energy balance was maintained. The type, intensity, and duration of all activities (normal daily and physical) throughout the baseline period were tightly controlled by dividing each 24-h period into prescribed 15-min blocks at a specific metabolic equivalent (MET) level to duplicate the subjects’ normal daily caloric expendi-

![Fig. 1. Experimental design displaying the subject inclusion criteria, the intervention description for the 4 experimental groups, and the comparisons and research questions being investigated.](http://jap.physiology.org/DownloadedFrom/)
tecture and simulate their normal activity level. Exercise/caloric inter-
vention period (days 5–11): during days 5–11, subjects increased their
daily energy expenditure by 1,000 kcal/day by performing additional
exercise at 50–65% of their \( V_{O2peak} \). For subject comfort and to
reduce injuries, exercise was divided among different modes (bike,
treadmill, elliptical) and performed in 15-min bouts spaced throughout
the day. As during the baseline period, the type, intensity, and
duration of all activities (normal daily and physical) throughout the
intervention period were tightly controlled by dividing each 24 h
period into prescribed 15-min blocks at a specific MET level. On
the first day of the 7-day exercise intervention (day 5), Sed and FIT1
increased their energy expenditure and caloric intake (the groups were
in energy balance), while FIT2 and FIT3 increased energy expenditure
but did not increase caloric intake (the groups were in an energy
deficit). For days 6–8, subjects replicated the activity of day 5. On
day 9, energy expenditure was again verified and duration was
adjusted to obtain the desired expenditure. Days 10–11 replicated the
activity of day 9. On day 12, fasting blood samples were obtained
in the morning, after which there was no further activity.

Description of TDEE verification. TDEE was measured on baseline
period day 1 and on exercise intervention period days 5 and 9. While
still in bed, each subject was awoken enough to attach a noseclip
and a two-way rebreathing valve to collect samples of expired air
and calculate \( V_{O2} \) and \( V_{CO2} \) (Parvo Medics, Sandy, UT) to determine
resting metabolic rate. The measured resting metabolic rate was used
to estimate the energy expended while the subjects slept (EE\(_{sleep}\)).
During each different exercise session throughout the day, once steady
state was reached (~5 min), the subjects’ expired air was collected for
10 min using the same computer-based metabolic system. The energy
expenditure from each exercise session was used to determine the
total energy cost of all physical activities (EE\(_{physical\ activity}\)). The same
procedure was used to determine the energy cost of non-exercise
activities [i.e., watching TV, playing video games, reading (EE\(_{other}\)]).
TDEE was determined by adding the total energy cost of all
activity and exercise sessions to the estimated energy expenditure
of sleep (EE\(_{total}\) = EE\(_{sleep}\) + EE\(_{physical\ activity}\) + EE\(_{other}\)). For the
purpose of this study we are considering our subjects to be in a
state of increased energy flux when they have an increase in TDEE,
resulting from increased physical activity, matched with an in-
crease in energy intake to maintain energy balance. This working
definition of energy flux has previously been published in the
literature (4, 6, 13).

Study diet. Three to five days prior to starting the baseline period,
subjects were asked to consume a diet that contained the same amount
of protein as the study diet to help habituate hepatic enzymes to
a specific protein level. Subjects were instructed by dietitians on how to
do this during the prescreening evaluation of their 3-day diet record.
The controlled diet consumed throughout the experimental phase of
the study, when the subjects were residing in the metabolic laboratory,
consisted of whole foods and liquid supplements provided to each
subject in individually prescribed amounts. All meals were prepared
in the USARIEM metabolic kitchen by a registered dietitian. Throughout
the study, the protein content of the diet was held constant
at 0.9 (Sed, FIT1, and FIT2) or 1.8 (FIT3) g/kg body wt \(^{-1}\) day\(^{-1}\).
Total energy content was adjusted by adding or subtracting fat- and
carbohydrate-containing foods so that the caloric ratio of these nutri-
ents in the diet remained ~1:2, respectively. The dietary composition
of the total daily energy intake was ~8 to 12.6% protein, 32–37% fat,
and 55% carbohydrate and contained at least 80% of the recom-
dined daily allowance for vitamins and minerals. Meals were served
according to a fixed schedule, but water and sugar-free noncaffeinated
drinks were taken ad libitum.

Blood collection. Fasting blood samples were collected in the
morning on days 3, 5, 6, 11, and 12 by venipuncture. The blood
samples were immediately delivered to the lab, allowed to clot at
room temperature and then centrifuged. The serum was then aliquoted
and stored at \(-80^\circ\)C until assays were performed.

Body composition. Body weight was measured at baseline and on
day 11 of the intervention using a calibrated electronic battery-
powered scale accurate to 0.1 kg. Body composition was determined
by whole body dual energy X-ray absorptiometry (DEXA). Total
body estimates of percent fat and non-bone lean tissue were deter-
mined using manufacturer-described procedures and supplied algo-
rithms (Lunar, Madison, WI). DEXA measurements were done at
baseline and on day 11 of the intervention.

IGF-I system assays. Total IGF-I, IGFBP-1, and IGFBP-3 concen-
trations were determined by two-site immunoradiometric assays
(IRMA). IGFBP-2 was measured using a RIA. Total ALS was
measured by ELISA. All immunoassays were products of Diagnostic
System Laboratories (Webster, TX). IRMA and RIA were performed
on a Cobra gamma counter (Packard Instruments, Downers Grove,
IL). ELISA were performed using a 96-well plate reader and micro-
plate absorbance reader (Molecular probe, Molecular Probes, Eugene,
OR). The analyses were divided into three groups:
Sed vs. FIT1, FIT1 vs. FIT2, and FIT2 vs. FIT3. This allowed us to
independently investigate the effects of fitness level, energy balance,
and protein intake while controlling for the other variables.

Table 1. Timeline of study for all four groups

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 8</th>
<th>Day 9</th>
<th>Day 10</th>
<th>Day 11</th>
<th>Day 12</th>
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<td>8</td>
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<td>10</td>
<td>11</td>
<td>12</td>
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<td>Exercise/ Caloric Intervention</td>
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<td>Controlled diet</td>
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<td>Normal daily activity</td>
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<td>Additional 1,000 kcal exercise</td>
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<td>X</td>
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<tr>
<td>Fasting blood draw</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
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</table>

X denotes what day(s) intervention was performed. TDEE, total daily energy expenditure.

### Statistical analysis
The analyses were divided into three groups: Sed vs. FIT1, FIT1 vs. FIT2, and FIT2 vs. FIT3. This allowed us to
independently investigate the effects of fitness level, energy balance,
and protein intake while controlling for the other variables.

All results are reported as means (SD). A repeated-measures
ANOVA (Statistica, StatSoft, Tulsa, OK) was used to compare the
IGF-I system concentrations between and within groups on
days 3, 5, 6, 11, and 12. A \( P \) value of \( P < 0.05 \) was accepted as
indicating significant differences.
RESULTS

Body composition. Table 2 displays the body composition changes for the study. Sed and FIT1 did not experience any significant changes in body weight, lean body mass (LBM), or fat mass. FIT2 and FIT3 showed significant decreases in body weight (3.5 and 3.2%, respectively), LBM (2.5 and 2.0%, respectively), and fat mass (11 and 13.5%, respectively).

Energy balance. Table 3 displays the caloric intake and expenditure data for the study. During the baseline period (days 1–4), all subjects were in energy balance and maintained their normal daily intake and expenditure as calculated from their individual diet and activity records. For the 7-day exercise intervention period (days 5–11), all subjects increased their daily energy expenditure by ~1,000 kcal/day. Energy intake was increased to match expenditure or remained unchanged depending on the intervention group.

IGF-I system responses: impact of energy balance on IGF-I (FIT1 vs. FIT2). No interaction or group effects were demonstrated. We observed similar changes in IGF-I, IGFBP-1–2–3, and ALS for both FIT1 (maintained energy balance) and FIT2 (energy deficit of 1,000 kcal/day) in response to the 7-day increase in physical activity (see Fig. 2). IGF-I was similar across days 3–6, but decreased significantly by days 11 and 12. IGFBP-1 exhibited no significant differences. IGFBP-2 was increased on day 5 and remained elevated throughout the study. IGFBP-3 and ALS decreased on days 6 and 11, respectively, and remained lower throughout the study.

Impact of dietary protein intake on IGF-I (FIT2 vs. FIT3). No interaction or group effects were demonstrated. We observed similar changes in IGF-I, IGFBP-1–2–3, and ALS for both FIT2 (adequate protein diet, 0.9 g/kg) and FIT3 (high-protein diet, 1.8 g/kg) in response to the 7-day increase in physical activity (see Fig. 3). IGF-I was similar across days 3–6, but decreased significantly by days 11 and 12. IGFBP-1 increased at day 6 and remained elevated. IGFBP-2 increased on day 5 and showed an additional increase by day 11. IGFBP-3 and ALS decreased by days 11 and 12, respectively.

Impact of fitness level on IGF-I (Sed vs. FIT1). No interaction effects were demonstrated, however, a main group effect was demonstrated for IGFBP-1 (P = 0.01) and IGFBP-2 (P = 0.02). We observed similar changes in IGF-I, IGFBP-1–2–3, and ALS for both Sed (V̇O2peak: 39 ml·kg⁻¹·min⁻¹) and FIT1 (V̇O2peak: 56 ml·kg⁻¹·min⁻¹) in response to the 7-day increase in physical activity (see Fig. 4). IGF-I decreased at day 6 and was significantly lower throughout the remainder of the study. IGFBP-1 exhibited no significant differences. IGFBP-2 was increased on days 5 and continued to increase thereafter. IGFBP-3 and ALS decreased by days 6 and continued to decrease thereafter.

DISCUSSION

The purpose of this study was to further characterize the relationship between diet and exercise and their influence on the IGF-I system by isolating the singular effects of variations in energy balance, dietary protein intake, and fitness level on circulating concentrations of IGF-I and IGF binding proteins. Studying circulating IGF-I remains important due to its utility as a biomarker reflecting health and fitness status as well as to the fact that the relationship between systemic and local IGF-I remains obscure. Because of the effect of nutritional intake on the IGF-I system, we tightly controlled the daily caloric intake and total energy expenditure for each individual subject during the 11-day study period. Our data clearly demonstrate that alterations in the circulating IGF-I system occur with increased daily physical activity over a 7-day period. The IGF-I system changes observed during the 7 days of increased activity were similar despite: 1) differences in energy balance, 2) differences in dietary protein intake, and 3) differences in fitness level. As the increase in physical activity was the common factor inherent to the observed IGF-I alterations, our data suggest that the

Table 2. Anthropometric data

<table>
<thead>
<tr>
<th></th>
<th>Weight, kg</th>
<th>LBM, kg</th>
<th>Fat mass, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>Sed</td>
<td>74.4 (7.3)</td>
<td>73.6 (7.2)</td>
<td>59.3 (4.6)</td>
</tr>
<tr>
<td>FIT1</td>
<td>73.4 (7.4)</td>
<td>72.5 (8.1)</td>
<td>62.1 (5.0)</td>
</tr>
<tr>
<td>FIT2</td>
<td>73.3 (7.2)</td>
<td>70.9 (7.4)*</td>
<td>63.3 (5.2)</td>
</tr>
<tr>
<td>FIT3</td>
<td>85.7 (9.1)</td>
<td>83.0 (9.1)*</td>
<td>73.1 (7.5)</td>
</tr>
</tbody>
</table>

Values are mean (SD). LBM, lean body mass; Sed, sedentary groups; FIT, fit groups. * Denotes significant decrease from the Pre value (P < 0.05).

Table 3. Average caloric intake and expenditure

<table>
<thead>
<tr>
<th></th>
<th>Days 1–4</th>
<th>Days 5–11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intake</td>
<td>Expenditure</td>
</tr>
<tr>
<td>Sed</td>
<td>2,861 (351)</td>
<td>3,538 (758)</td>
</tr>
<tr>
<td>FIT1</td>
<td>3,538 (758)</td>
<td>3,558 (734)</td>
</tr>
<tr>
<td>FIT2</td>
<td>3,470 (375)</td>
<td>3,491 (398)</td>
</tr>
<tr>
<td>FIT3</td>
<td>3,919 (953)</td>
<td>3,932 (942)</td>
</tr>
</tbody>
</table>

Values are mean (SD) in kcal. Days 1–4 was the baseline period. The intervention occurred on days 5–11, with activity being increased 1,000 kcal/day for all groups. For the intervention period, groups Sed and FIT1 were given extra calories to account for the increased activity while groups FIT2 and FIT3 were not given extra calories, resulting in a caloric deficit. Superscripts denote that value is significantly different from specified group (SED, 1FIT1, 2FIT2, 3FIT3); *significantly different from the intake value (P < 0.05).
The circulating IGF-I system is influenced by yet unidentified exercise-associated mechanisms that are stimulated during periods of increased energy flux (periods of increased energy intake and expenditure under conditions of energy balance) and not necessarily solely dependent on an energy deficit.

Impact of energy balance on IGF-I (FIT1 vs. FIT2). Surprisingly, this study observed a ~30% decline in circulating IGF-I over a 7-day period of increased physical activity, which was a similar response regardless of whether subjects were in an energy balance or in a 1,000 kcal/day energy deficit. The belief that energy restriction is the principal regulator causing IGF-I decrements during a negative energy balance has been supported by numerous studies (11, 12, 16, 18, 26, 29, 35, 36). For example, Smith et al. (35) previously demonstrated similar IGF-I declines during an energy deficit whether the deficit was created by exercise or caloric restriction and concluded that the IGF-I decline was mainly the result of a mismatch between energy intake/expenditure. Our data challenge this well-established concept by reporting a decline in IGF-I during a 7-day period of energy balance (FIT1 group). In essence, we demonstrated that the well-known IGF-I decline normally observed during a catabolic, negative energy balance can also be observed with increased physical activity while maintaining energy balance.

The current study contributes to a growing body of evidence that the “normal” response pattern of IGF-I during short-term, acute physical activity is that of a reduction. Declines in IGF-I have also been demonstrated in exercise training studies ranging from 5 to 12 wk in such diverse populations as male and female adolescents (9, 10) and end-stage renal disease patients (30). Although these previous training studies did not control energy intake and expenditure to the extent implemented in the current study, the subjects in those studies did maintain body mass and/or increase muscle thigh volume, indicating that the subjects trained in an overall state of energy balance. In addition, we are confident that the results observed for the current study are the effects from the 7-day intervention and not the effect from the last bout of exercise, as we previously demonstrated no changes in 12-h circulating total IGF-I concentrations after an acute bout of exercise (31).

Of further interest are the findings from Nemet et al. (26) who examined IGF-I responses during 7 day of strenuous exercise in two groups that were either underfed or overfed. In this study, the daily exercise-associated energy expenditure for both the overfed and underfed groups was similar to the current study (~1,000 kcal/day). The overfed group had a positive energy balance of 393 kcal/day, a 1% increase in body mass and did not experience any change in IGF-I, whereas the underfed group had a negative energy balance of 2,052 kcal/day, a 1.5% decrease in body mass, and reported a similar IGF-I decline as observed in the current study (~30%). Nemet

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**Fig. 2.** Graphs A-E display the mean concentrations of insulin-like growth factor (IGF)-I, IGF binding protein (IGFBP)-1, IGFBP-2, IGFBP-3, and the acid labile subunit (ALS), respectively, for 1 and 2 groups of fit subjects (FIT1 and FIT2) over the 7-day intervention. The FIT1 (caloric balance) vs. FIT2 (caloric deficit) comparison addressed the question of energy balance on IGF-I system responses. Graphs F-J combine the mean concentrations of both groups to show the observed time effect of the 7-day intervention on the IGF-I system. The dotted line divides the graphs into the baseline period [days 1–4 (D1-D4)] and the intervention period (D5-D11). Mean concentrations with different superscripts are significantly different (P < 0.05).
et al. (26) suggested that exercise prevented the overfed group from demonstrating an increase in IGF-I and with the use of regression analyses, further illustrated that under conditions of energy balance, exercise may induce declines in IGF-I concentrations.

In contrast to the decline in circulating IGF-I over 7 days of exercise observed in the current study and reported by Nemet et al. (26), Ormsbee et al. (32) reported no changes in circulating IGF-I during 5 days of physical activity (500 kcal/day) in energy balance, negative energy (approximately −500 kcal/day), or positive energy balance (≈500 kcal/day). Taken together, the collective findings to date suggest that circulating IGF-I declines during both large increases in energy flux (level of high energy intake and high expenditure under conditions of energy balance) as well as during a negative energy balance.

**Impact of dietary protein intake on IGF-I (FIT2 vs. FIT3).**

Our results demonstrate that increasing dietary protein intake (1.8 g/kg body wt) did not attenuate the decline in circulating IGF-I concentrations compared with a normal dietary protein intake (0.9 g/kg body wt) in fit individuals subjected to a 1,000 kcal/day exercise-induced energy deficit over a 7-day period. Previous research has shown an increase in circulating IGF-I following prolonged strength and conditioning training with protein supplementation compared with carbohydrate supplementation (1). Cross-sectional analysis has also shown a positive association between dietary protein intake and circulating IGF-I concentrations (14). It is possible that the acute increase in activity resulting in an exercise-induced negative energy balance in our subjects could not be corrected by increasing dietary protein intake without a concomitant increase in caloric intake. Isley et al. (15) demonstrated the existence of a threshold of energy intake that is necessary to return circulating IGF-I concentrations to prefasting concentrations and suggested that overall energy intake may be of greater importance than the macronutrient content of the diet. Our results provide additional support to this idea by suggesting that when adequate energy is not available (i.e., during a 7-day period of an exercise-induced caloric deficit), similar decreases in IGF-I concentrations are observed with both adequate (0.9 g/kg body wt) and high (1.8 g/kg body wt) dietary protein intake. When adequate energy is available, a positive correlation has been shown between protein intake and IGF-I (16). Therefore it is possible that increasing dietary protein intake could have modulated IGF-I concentrations if our subjects had been in energy balance.

Our data also suggest that macronutrient content of the diet may not be as important as total energy availability in maintaining lean body mass during periods of increased physical activity. It was suggested that increasing dietary protein intake while decreasing total energy intake with or without exercise can result in decreases in body weight while sparing lean body

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**Fig. 3.** Graphs A-E display the mean concentrations of IGF-I, IGFBP-1, IGFBP-2, IGFBP-3, and the ALS, respectively, for FIT2 and FIT3 over the 7-day intervention. The FIT2 (0.9 k/kg protein) vs. FIT3 (1.8 g/kg protein) comparison addressed the question of dietary protein intake on IGF-I system responses. Graphs F-J combine the mean concentrations of both groups to show the observed time effect of the 7-day intervention on the IGF-I system. The dashed line divides the graphs into the baseline period (D1–D4) and the intervention period (D5–D11). Mean concentrations with different superscripts are significantly different ($P < 0.05$).
mass (24). In the current study, we demonstrated that increasing dietary protein intake, 0.9 (FIT2) vs. 1.8 g/kg body wt (FIT3), did not conserve lean body mass when normal daily activity was increased to induce an energy deficit. Layman et al. (23) showed that overweight females on a high-protein diet tended to lose less lean mass than those on a normal protein, high-carbohydrate diet; however, lean mass was still lost, except in subjects that exercised in addition to increasing protein intake. The discrepancy in these findings is most likely due to the fact that our subjects experienced a relatively greater daily energy deficit due to a greater exercise stress.

**Impact of fitness level on IGF-I (Sed vs. FIT1).** Both the Sed and FIT1 groups experienced similar declines in IGF-I during the 7-day period of increased energy flux. Also observed was a significant increase for IGFBP-2 and a decrease for IGFBP-3 and ALS, but no alterations for IGFBP-1. The magnitudes of these changes were similar for both the sedentary and fit subjects. Our results suggest that initial fitness level does not alter the circulating IGF-I response to an acute increase in 7 days of physical activity. These findings are in contrast to Manetta et al. (25), who demonstrated a differential response of IGF-I in trained vs. sedentary subjects to a single bout of endurance exercise. Furthermore, Rosendal et al. (33) showed a differential effect of an 11-wk strength and conditioning program on the circulating IGF-I system when comparing untrained vs. trained individuals. They demonstrated that only the untrained group experienced a significant perturbation in total and free IGF-I, IGFBP-2, and IGFBP-3 proteolysis that persisted throughout the entire 11 wk and suggested that untrained vs. well-trained individuals have a lower threshold of physiological stress that is needed to impact the IGF-I system. However, they noted that at the start of the training, IGF-I decreased in both untrained and well-trained subjects. It is likely that the increase in metabolic activity, rate of energy flux, associated with an acute increase in exercise results in an alteration in the IGF-I system regardless of training status.

**IGF binding protein responses.** Our results suggest that 7 days of increasing normal daily activity by 1,000 kcal/day not only decreases circulating concentrations of IGF-I but can also impact the bioavailability of IGF-I by altering the concentrations of regulatory binding proteins such as IGFBP-1 (increased), and -2 (increased), -3 (decreased), and -ALS (decreased). The increase that we observed in IGFBP-1 was only significant in the two groups that were in a 1,000 kcal/day exercise-induced caloric deficit and this increase likely contributes to the maintenance of glucose homeostasis. Nutritional status is considered a major regulator of IGF binding proteins (3). Caloric restriction has been shown to increase concentrations of IGFBP-1 and -2 and to decrease IGFBP-3 and ALS (2, 8, 29). IGFBP-1 is affected by acute dietary manipulations, whereas IGFBP-2 and -3 are thought to be impacted only after

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**Fig. 4.** Graphs A-E display the mean concentrations of IGF-I, IGFBP-1, IGFBP-2, IGFBP-3, and the ALS, respectively, for sedentary (Sed) and FIT1 over the 7-day intervention. The Sed (low fitness) vs. FIT1 (high fitness) comparison addressed the question of fitness level on IGF-I system responses. Graphs F-J combine the mean concentrations of both groups to show the observed time effect of the 7-day intervention on the IGF-I system. The dashed line divides the graphs into the baseline period (D1–D4) and the intervention period (D5–D11). Mean concentrations with different superscripts are significantly different ($P < 0.05$).
a more chronic dietary restriction (37). Our current data support evidence that similar alterations in IGF binding proteins can also occur during a period of increased daily exercise when energy balance is maintained.

Significance/conclusion. Circulating IGF-I has been reported to be influenced by many factors. The utility of circulating IGF-I resides in its apparent ability to serve as a biomarker reflecting metabolic and health status. Understanding the relative roles of these influencing factors and the precise significance of circulating IGF-I, particularly with regard to exercise responses, remain important topics in the field of applied endocrinology. Having a greater understanding of the temporal response pattern of circulating IGF-I within the context of various physical activity and diet behaviors should allow us to delineate between acute “stress” responses and more chronic “adaptation” responses. Whereas the bulk of the exercise-IGF-I literature has either been focused on acute (i.e., 1 exercise session) or longer-term training adaptations (>8 wk), this study provides data on the short-term (7 days) responses.

The salient findings from this study were that 7 days of increased physical activity resulted in declines in circulating IGF-I and that these response patterns were not altered by fitness level, dietary protein intake, or energy balance. The fact that IGF-I declined even during a 7-day period of energy balance (FIT1 group) challenges the well-established notion that a negative energy balance is the principal regulator of declines in IGF-I and suggest to us that currently unexplained exercise-associated mechanisms, perhaps involved with increased energy flux, influence IGF-I concentrations independent of an energy deficit. Furthermore, except in cancer, a low level of IGF-I usually predicts a negative health outcome. Therefore, the observation of an activity-induced reduction of circulating IGF-I in the current study does not necessarily correspond with the beneficial effects of physical activity. This finding does raise questions concerning the significance of circulating IGF-I and perhaps indicates that there is not a tight association between IGF-I alterations induced by a short period of increased activity and longer term adaptations. Future efforts will need to resolve the mechanisms underlying the changes observed in circulating IGF-I and their relationship to local changes at the cell/tissue level. Counterintuitively to the known anabolic role that IGF-I plays, we postulate that a reduction in circulating IGF-I is the normal, adaptive response during 7 days of increased physical activity.

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REFERENCES


