Acute Effect of Physical Exercise on Serum Insulin-Like Growth Factor-Binding Protein 2 and 3 in Healthy Men: Role of Exercise-Linked Growth Hormone Secretion

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The purpose of this study was to delineate the role of GH on serum IGF-I, IGFBP-2 and -3 responses to exercise. Hormones were evaluated in six trained male subjects before (-30, -15, 0), during (+15) and after (+30, +45, +60, +90 min) a thirty-minutes treadmill exercise (60% VO2max), both after a single administration of a somatostatin analog (i.e., octreotide, 0.1 mg sc) and after saline. The same evaluations were performed without exercise with similar treatments. The results showed that: 1) octreotide significantly inhibited the GH response to exercise, 2) exercise increased IGFBP-3 concentration (+37.4% at +90, p<0.05), whereas no modification of IGFBP-2 and of IGF-I/IGFBP-2 and IGFBP-3/IGFBP-2 ratios were observed, 3) octreotide amplified the IGFBP-3 increase after exercise (p<0.01 vs. exercise, from +30 to +60, or octreotide alone) and, without exercise, slightly increased IGFBP-3 (+15% at +75, p<0.05) and decreased IGF-I (-14.8% at +75, p<0.01). We concluded that GH has a reduced role, as a stimulating factor, in the serum acute IGFBP-3 increase after exercise and that octreotide is possibly able to directly amplify this response. Unfortunately, we can only speculate on the physiological pathways involved.

Key words: GH, IGF-I, IGFBP-2, IGFBP-3, octreotide, physical exercise.

Introduction

In recent years, the use of insulin-like growth factors (IGFs) and their binding proteins (IGFBPs) assays for studying the insulin-like growth factor system status in humans has increased [29]. The IGFBPs are a family of six high affinity car-riers (IGFBP-1 through IGFBP-6) for IGF-I and -II, found in the serum and in other extracellular fluids [2, 5]. They are not simply transport proteins as they have very complex actions: the IGFBPs modulate both the endocrine and paracrine actions of IGFs, influence their bioavailability and facilitate their storage in extracellular fluids. Furthermore, these proteins may also exert IGF-independent effects on target cells. In particular, IGFBP-3 is a glycoprotein synthesized in many tissues other than liver and it is the major form of binding protein in the human circulation as a major carrier for IGF-I and -II, whose actions may be inhibited and/or enhanced [26]. IGFBP-3 serum concentration increases after GH administration, in both GH-deficient patients and in healthy subjects [7, 21, 24], and decreases after IGF-I administration [3]. In contrast, IGFBP-2 is a non-glycosylated protein found in serum and in cerebrospinal fluid, which seems to inhibit principally IGF actions, by preventing their binding to receptors [19]. IGFBP-2 regulation is relatively undefined. GH administration has been associated with a reduction [21] or an increase in IGFBP-2 serum levels, as observed in GH-deficient subjects [24], while IGF-I administration is able to increase its serum concentration in normal subjects [34].

IGFBP production and serum concentrations are also regulated and/or influenced by hormonal pathways other than GH (insulin, sex steroid hormones, glucocorticoids, thyroid hormones, etc.), by physiological (nutritional status, puberty, aging, pregnancy) or pathological (diabetes, tumors, obesity, GH-deficiency, osteoporosis, etc.) conditions, and by physical activity [11, 20, 26].

Despite the fact that physical exercise is a powerful stimulus for GH secretion [6, 33], there are few and conflicting data about the relationship between physical activity and IGFBPs [1, 9, 10, 17, 22, 25, 28, 30]. In exercise physiology, IGFBP-2 has received less attention than other IGFBPs, while conflicting data on IGFBP-3 acute response (less than two hours after end-exercise) to a short bout of physical exercise has been reported. Furthermore, no definitive data are available on the possible influence of endogenous GH on acute IGFBP responses to exercise, even though a GH role in stimulating acute IGFBP responses to exercise has been hypothesized [25].

Knowledge of the relationship between the GH-IGF system (GH, IGF-I and IGF-II, IGFBPs, IGFBP proteases and IGF receptors) and physical exercise is necessary in order to clarify its
role in exercise physiology and the possible positive and/or negative effects of physical stress on such hormonal pathways. Furthermore, as hypothesized by Kicman et al. [21], the possible use of IGF-1, IGFBP-2 and -3, and their ratios in developing a method for assessing GH administration in athletes lends support to the need to study how exercise per se may modify such substances in biological fluids.

In order to evaluate the IGFBP-2 and IGFBP-3 response to acute exercise and to test the hypothesis that GH could be involved in acute IGFBP's response to exercise, we performed the present study involving two separate experiments. The aims of the first experiment (exercise trials) were both to evaluate the acute effects of a low intensity short-term physical exercise on serum IGF-1, IGFBP-2 and IGFBP-3 and to verify the hypothesized role of endogenous GH in these responses [25], by inhibiting the exercise-linked GH secretion with octreotide, a somatostatin analog [8,32]. At the end of the first experiment we made the unexpected observation that the serum IGFBP-3 response to exercise was significantly higher in octreotide-treated subjects, compared with the subjects treated with saline. For this reason, in a second experiment (rest trials) we sought to establish whether octreotide has a direct pharmacological action on the same variable at rest.

Subjects and Methods

Subjects

Six male Caucasian volunteers, regularly engaged in educational and recreational physical activity, participated in the study. The subjects had the following baseline characteristics (mean ± sd): chronological age 24.2 ± 2.3 yrs, height 175.4 ± 3.8 cm, weight 71.1 ± 5.9 kg, body mass index (BMI) 23.2 ± 1.1 kg/m² and VO₂ max 52.9 ± 2.8 ml x kg⁻¹ x min⁻¹. All the subjects were recruited from the University Institute of Motor Sciences of Rome.

The experimental protocol was approved by the local Institutional Ethical and Scientific Committee. The nature of the study was explained to each subject in detail and written informed consent was obtained.

A preliminary screening assessment was designed to detect risk factors that might contraindicate participation in the study. All the subjects were in good health and were taking no medications, amino acids or other drugs, including anabolic-doping agents. The volunteers had normal physical and sexual development. A preliminary pituitary hormonal evaluation (FSH, LH, ACTH, TSH, PRL, GH, IGF-1 and testosterone) and routine biochemical and hematological analyses were within the normal ranges in all the subjects.

Protocol

All the subjects were counselled by a nutritionist and followed a diet regimen sufficient for each individual’s needs according to the recommended dietary allowances for the Italian Population [18] (2500–2700 kcal/day: 50–55% carbohydrates, 15–20% proteins and about 30% lipids). This regimen was started two weeks before the two experimental phases (exercise trials and rest trials) and continued throughout the study. The subjects were counselled weekly and their food records reviewed in order to maintain the correct regimen throughout the study.

One week before the exercise trials, all the subjects underwent an incremental exercise test until exhaustion on a treadmill in order to evaluate individual maximal aerobic power (VO₂ max).

Exercise trials

In a first session each subject performed an acute exercise test after a single administration of saline or octreotide in a double-blind cross-over protocol. After a washout period of one week each subject performed a second identical exercise test receiving the other treatment. Each subject was therefore his own control, receiving both octreotide and saline.

The experimental sessions began for all the subjects, on both experimental days, between 08.30 a.m. and 09.00 a.m. and the environmental conditions were always identical (temperature 22–24 °C; humidity 55–60%). The subjects were requested to have breakfast (about the same kcal/kg of body weight and nutrient composition) one hour before octreotide or saline administration (in both exercise and rest trials) and then refrained from food throughout the experimental session; they drank water ad libitum.

Prior to each exercise session, a catheter was introduced into a forearm vein 30 min before starting the exercise and maintained in situ throughout the experiment. Blood collections were performed at rest, 30 and 15 minutes before (~30, ~15 min), immediately before starting the treadmill test (time 0), during exercise (~15 min), at the end of the exercise (~30 min), and during the recovery phase (~45, ~60, and ~90 min).

The subjects exercised on a motor-driven treadmill (2.5% slope) and were monitored continuously by spirometry (K2-COSMED), O₂ uptake analyzer, and ECG. After four minutes of warm-up (at 6 km/h), the treadmill was adjusted to keep VO₂ at 60% of VO₂ max (range: 57%–63% VO₂ max). This speed was then maintained for thirty minutes.

Indications for stopping the test were muscular pain, fatigue, heart rate (HR) derangement, and severe ECG abnormalities. HR was determined from the ECG before drug or saline administration, before and during the exercise, and in the recovery phase.

Before the start of each exercise test, immediately after the second basal blood collection (~15 min), each subject received either a) 1 ml of vehicle saline solution subcutaneously (sc) in the shoulder (ex-saline trial) or b) 0.1 mg of a somatostatin-analog (octreotide-Sandostatin-R, Sandoz Pharma) sc in the shoulder (ex-octreotide trial).

Octreotide is an 8 amino acid synthetic peptide analog engineered to overcome the limitation of native somatostatin. Octreotide has greater pharmacological activity than the native molecule, it is highly selective for the inhibition of basal and stimulated GH secretion, and has a much longer duration of action (an elimination half-life of 113 minutes compared with two to three minutes for somatostatin). Peak serum concentra-
tion occurs within 30 minutes after subcutaneous administration [16].

Rest trials

In order to evaluate the possible direct effects of octreotide on hormonal parameters, we performed two experimental trials, with a two week wash-out period between trials. The same subjects received either 1.0 ml sc injection of saline (rest-saline trial) or 0.1 mg sc injection of octreotide (rest-octreotide trial) at rest in a randomized double-blind protocol. The experimental sessions began for all the subjects, on both experimental days, between 08.30 a.m. and 09.00 a.m. and the environmental conditions were always identical (temperature 20–22°C; humidity 60–65%). Prior to each rest trial a catheter was introduced into a forearm vein thirty minutes before octreotide or saline administration and maintained in situ. Blood collections were performed before (−30, −15 min), immediately before octreotide or saline injection (time 0), and every 15 minutes until +75 minutes (+15, +30, +45, +60, +75 min) and at +105 minutes.

In all trials the catheter was flushed with physiological saline to avoid blood clotting after taking each blood sample. Following blood sample collection the serum was separated, frozen and stored at –70°C until it was assayed. All the samples were analysed for GH and IGF-I, IGFBP-2 and IGFBP-3.

Blood collections for immediate lactate and hematocrit analysis were performed in exercise trials at the same blood collection intervals.

Hormonal assays

Hormonal determinations were carried out in duplicate in a single assay for each experiment (exercise and rest trials). GH, IGF-I, and IGFBP-3 were determined by immunoradiometric assays. IGFBP-2 was measured by radioimmunoassay kits. All hormone assay kits were purchased from DSL (Webster, Texas, USA). The intra- and inter-assay coefficients of variation (CV) were for GH 4.1% and 8.7%, for IGF-I 4.9% and 5.1%, for IGFBP-3 3.0% and 1.0%, for IGFBP-2 8.6% and 9.2%, respectively. The sensitivity for GH was 0.01 μg/l, for IGF-I was 2 μg/l, for IGFBP-3 was 0.5 μg/l, for IGFBP-2 was 0.5 μg/l. The reference ranges from DSL (Webster, Texas, USA) reported for men (20–30 yr) were as follows: GH, 0.5–3.83 μg/l; IGF-I, 169–628 μg/l; IGFBP-3, 2250–7380 μg/l; IGFBP-2, 131–963 μg/l.

Serum lactate and hematocrit assay

Duplicate determination of blood lactate was performed using capillary blood from a pre-warmed fingertip. Blood lactate concentration was analysed using an enzymatic method (YSI lactate analyzer model 23L). The lactate intra- and inter-assay coefficients of variation were 3.0% and 3.7%, respectively, and the sensitivity was 0.6 mmol/l. A capillary tube sample of blood was spun at 3000 rpm for 3 minutes, and the hematocrit was determined in conventional fashion. Percent changes in plasma volume were also estimated using hematocrit equation [31].

Statistical analysis

The hormonal data are expressed as mean ± sd. Areas under curves (AUCs) were calculated by trapezoidal integration.

In the first experiment (exercise trials), for each hormone and treatment, AUCs were calculated from pre-exercise values (from −30 to 0 min: ex-basal-AUCs), from exercise values (from 0 to +30 min: ex-AUCs) and from post-exercise values (from +30 to +90 min: post-ex-AUCs). In addition, we calculated for ex-AUCs and post-ex-AUCs the percentage of variation (Δ%) with respect to their ex-basal-AUCs. The Δ% was also calculated for each point time values compared to its 0-time value. For each hormone, differences in AUC values due to exercise and octreotide treatment were evaluated using 2 trials (saline and octreotide trials) by 3 time periods (pre-, ex-, post-time periods) repeated measure ANOVA with post-hoc comparison as appropriate. Then, an analysis of time protocol values were performed using 2 trials (saline and octreotide trials) by 8 time periods (−30, −15, 0, +15, +30, +45, +60, +90 time points) repeated measure ANOVA with post-hoc comparison as appropriate.

In the second experiment (rest trials), for each hormone and treatment, we calculated the percentage of variation (Δ%) of each point time value after octreotide or saline compared to its basal value (B), considered as the mean of the three pre-test values (−30, −15 and 0 samples). In addition, AUCs were calculated from all point time values before octreotide or saline administration (rest-basal-AUCs, from −30 to 0 min) and after (rest-test-AUCs, from 0 to +105 min). In order to evaluate the effect of octreotide or saline administration also in the exercise trials, equivalent areas were calculated from the octreotide or saline administration point time to the end-recovery (from −15 to +90 min: ex-test-AUCs). The AUCs calculated from values after octreotide or saline administration (test-AUCs) were compared among all four trials (octreotide-rest, saline-rest, octreotide-ex, saline-ex) using the repeated measure ANOVA with post-hoc comparison as appropriate. Furthermore, an analysis for each protocol time was performed using 2 trials (saline and octreotide trials) by 8 time periods (−15, 0, +15, +30, +45, +60, +75, +105 time points) repeated measure ANOVA with post-hoc comparison as appropriate. In both trials the IGF-I/IGFBP-2 and IGFBP-3 ratio were also calculated and statistical evaluations were performed as appropriate. We set α = 0.05 and power (1-β) = 0.75. Power was determined estimating omega squared and then using the Pearson-Hartley charts.

Results

All the subjects completed all of the experimental sessions. None showed side effects during or after any exercise or rest trial. During the ex-octreotide trial the heart rate at +15 minutes, end-exercise, and 3 minutes of the recovery (130±7, 141±8 and 94±7 beats/min, respectively) was significantly lower than in the ex-saline trial (142±8, 153±9 and 105±9 beats/min, respectively; p < 0.05). In the two exercise trials the pre-exercise (0) serum lactate levels were similar in both trials (ex-saline trial: 0.8 ± 0.1 mmol/l and ex-octreotide trial: 0.7 ± 0.1 mmol/l). During exercise lactate increased significantly to the same level in both trials with maximal values at +15 and +30 min (ex-saline trial: 2.1 ± 0.2 mmol/l and ex-octreo-
tide trial: 2.2 ± 0.2 mmol/l; p < 0.01 vs. basal values in both trials) and decreased at pre-exercise levels 15 min after exercise. No differences in serum lactate concentration were found between exercise trials, during exercise or recovery. In the two exercise trials hematocrit and plasma volume did not change during and after exercise and no differences were found between trials.

**Exercise trials (saline/octreotide)**

In both ex-saline and ex-octreotide trials, the ex-basal-AUCs and absolute serum concentrations of all evaluated hormones (GH, IGF-I, IGFBP-2 and IGFBP-3) were in the normal ranges and no differences were found between pre-exercise values before and after saline or octreotide administration or between trials.

**GH (Fig. 1)**

When subjects received saline the mean ex-basal-GH AUC (7.7 ± 5.0 µg/l/30') showed a significant increase during (158.3 ± 78.0 µg/l/30'; p < 0.01) and after exercise (180.0 ± 86.0 µg/l/30'; p < 0.05). The mean absolute serum GH concentration rose significantly during and after exercise, reaching the maximum value at the end of exercise (p < 0.001) and remaining significantly higher than pre-exercise values until one hour after exercise (p < 0.05).

**IGF-I (Fig. 1)**

In the ex-saline trial, no modifications in the IGF-I absolute values (serum concentrations and AUCs) were observed, even though the IGF-I AUC showed a small but significant mean percentage increase after exercise (Δ%) of +13.7 ± 2.9% (p < 0.05). In the octreotide-treated subjects the IGF-I AUCs and absolute IGF-I plasma levels did not change. When the mean percentage modifications of the post-ex-IGF-I AUCs were compared between trials, a significantly higher value in ex-saline trial (p < 0.05) was observed.

**IGFBP-2 (Fig. 2)**

In both the ex-saline trial and ex-octreotide trial, no changes in IGFBP-2 (AUCs and absolute serum levels) were found, even though in the ex-octreotide trial a significant IGFBP-2 percentage maximum fall was observed at the end-recovery (−11.3 ± 8.6%; p < 0.01). However, for IGFBP-2 AUC the degree of power was < 0.75, while for all the other evaluated hormones it was > 0.75. This probably reflects a high inter-individual variability for IGFBP-2.

![Fig. 1](image1.png) **Fig. 1** GH and IGF-I (mean ± sd) responses to 30 min acute exercise on a treadmill at 60% of VO₂max in moderately trained male subjects (n = 6) after saline or somatostatin analog (i.e., octreotide, ST) administration. a: p < 0.05, b: p < 0.01, c: p < 0.001 saline vs. ST; *: p < 0.05. **: p < 0.01. ***: p < 0.001 vs. 0-time value.

![Fig. 2](image2.png) **Fig. 2** IGFBP-2 and IGFBP-2 AUCs (mean ± sd) responses to 30 min acute exercise on a treadmill at 60% of VO₂max in moderately trained male subjects (n = 6) after saline or somatostatin analog (i.e., octreotide, ST) administration. a: p < 0.05 saline vs. ST.

In the ex-octreotide trial, the GH AUC showed only a slight significant increase during exercise (62.9 ± 33.7 µg/l/30'; p < 0.05), while the post-ex GH AUC (20.3 ± 23.6 µg/l/30') did not show modifications compared to the ex-basal-GH AUC (5.1 ± 4.1 µg/l/30'). As expected, the ex-GH AUC and the post-ex-GH AUC were significantly lower than in the ex-saline trial (p < 0.01 and p < 0.05, respectively). This is probably due to the fact that in ex-octreotide trial serum GH concentrations rose slightly only during exercise and quickly returned to pre-exercise levels.

The comparison between trials showed a significant difference in serum IGFBP-2 Δ% values at the end of the recovery period (p < 0.05); IGFBP-2 increased in the ex-saline trial (+3.6%) and decreased in the ex-octreotide trial (−11.3%).

**IGFBP-3 (Fig. 3)**

In the ex-saline trial, a significant increase in post-ex-IGFBP-3 absolute values was observed at the end-recovery (+ 37.4 ± 31.2%; p < 0.05). In the ex-octreotide trial, a significant increase was observed of post-ex-IGFBP-3 AUC (+ 34.4 ± 11.9%;
p < 0.01) and absolute end-exercise (p < 0.01) and half-recovery (p < 0.05) IGFBP-3 serum levels. In particular, there was a significant mean percentage increase of the absolute post-exercise IGFBP-3 levels, from end-exercise (+50.6 ± 12.1%; p < 0.01) to thirty minutes of recovery (+37.2 ± 28.2%; p < 0.05). The comparison between trials showed significantly higher values of post-exercise IGFBP-3 AUC (p < 0.01) and absolute IGFBP-3 serum levels (from end-exercise to thirty minutes of the recovery period, p < 0.01 and p < 0.05, respectively) in octreotide-treated subjects.

**IGF-I/IGFBP-2 and IGFBP-3/IGFBP-2 ratios (Fig. 4)**

No changes in the IGF-I/IGFBP-2 ratio were observed. The IGFBP-3/IGFBP-2 ratio increased significantly at the end of exercise (p < 0.01) and at the end of the recovery period (p < 0.05) only in the ex-octreotide trial. In this trial the IGFBP-3/IGFBP-2 ratio maximum increase was observed at the end of exercise (+53.6%), and it was significantly higher than the corresponding point of the ex-saline trial (p < 0.05).

**Rest trials (saline/octreotide) (Table 1)**

In both the rest-saline trial and rest-octreotide trial, the pre-test basal AUCs and absolute serum concentrations of all evaluated hormones were within the normal range and no differences were found between trials.

**GH, IGFBP-2 and IGF-I/IGFBP-2 ratio**

No changes of the AUCs and absolute values were observed after octreotide or saline administration.

**IGF-I**

In the rest-octreotide trial, a significant reduction of the serum IGF-I concentration was observed at 75 and 105 minutes after drug administration (Δ% = −14.8 ± 6.1%, p < 0.01 and −10.8 ± 6.1%, p < 0.05, respectively). The comparison of the serum IGF-I Δ% between rest trials showed significantly lower values at the same time points in the rest-octreotide trial (p < 0.01).

**IGFBP-3**

In the rest-octreotide trial a significant increase of absolute IGFBP-3 serum levels 75 min after drug administration (+15.4 ± 3%; p < 0.05) was observed, while no differences were observed between trials.

**IGFBP-3/IGFBP-2 ratio**

In the rest-octreotide trial a significant increase of the IGFBP-3/IGFBP-2 ratio was observed 75 and 105 minutes after octreotide administration (+19.2 ± 10.3% and + 17.3 ± 20.2%, respectively; p < 0.05). The statistical evaluation between trials showed a significantly higher value of this ratio at + 75 minutes of the rest-octreotide trial (p < 0.01).

**Discussion**

In the present study we evaluated both 1) the acute serum IGFBP-2 and -3 responses to a short-term physical exercise and 2) the role of endogenous GH in these responses using octreotide, which significantly reduced the exercise-dependent GH increase. Furthermore, 3) an analysis of possible direct action of octreotide on the evaluated parameters at rest was also performed. In exercise trials we did not find any modification of plasma volume, whereas, as already observed [8], the heart
Table 1  Time values refer to hormonal point time values of rest trials with saline or somatostatin analog (octreotide) treatment. For rest trials, Rest-basal-AUC values are area under curve of basal values and Rest-test-AUC are area under curve of test values (after saline or octreotide administration). In italics are reported data for Ex-test-AUC (exercise trials: area under curve of values after saline or octreotide administration)

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<td>B</td>
<td>0.4 ± 0.5</td>
<td>295 ± 78</td>
<td>4977 ± 302</td>
<td>635 ± 80</td>
<td>0.43 ± 0.10</td>
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<td>+ 15 min</td>
<td>0.2 ± 0.3</td>
<td>295 ± 73</td>
<td>4922 ± 455</td>
<td>649 ± 116</td>
<td>0.44 ± 0.10</td>
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<td>+ 30 min</td>
<td>0.3 ± 0.4</td>
<td>317 ± 72</td>
<td>4663 ± 291</td>
<td>663 ± 109</td>
<td>0.46 ± 0.11</td>
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<td>+ 45 min</td>
<td>0.2 ± 0.2</td>
<td>310 ± 76</td>
<td>5203 ± 914</td>
<td>699 ± 128</td>
<td>0.45 ± 0.10</td>
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<td>+ 60 min</td>
<td>0.4 ± 0.4</td>
<td>284 ± 66</td>
<td>5024 ± 653</td>
<td>649 ± 87</td>
<td>0.42 ± 0.10</td>
<td>8.18 ± 1.48</td>
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<td>+ 75 min</td>
<td>0.6 ± 0.7</td>
<td>303 ± 77</td>
<td>5290 ± 488</td>
<td>644 ± 87</td>
<td>0.44 ± 0.10</td>
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<td>+ 105 min</td>
<td>0.5 ± 0.6</td>
<td>303 ± 79</td>
<td>5173 ± 573</td>
<td>663 ± 97</td>
<td>0.44 ± 0.09</td>
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<td>B</td>
<td>0.1 ± 0.1</td>
<td>319 ± 66</td>
<td>5026 ± 412</td>
<td>662 ± 86</td>
<td>0.47 ± 0.09</td>
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<td>+ 15 min</td>
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<td>5117 ± 380</td>
<td>626 ± 64</td>
<td>0.47 ± 0.08</td>
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<td>+ 30 min</td>
<td>0.1 ± 0.1</td>
<td>337 ± 66</td>
<td>4729 ± 325</td>
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<td>0.47 ± 0.08</td>
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<td>4408 ± 488</td>
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<td>290 ± 67</td>
<td>5062 ± 569</td>
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<td>+ 75 min</td>
<td>0.3 ± 0.5</td>
<td>271 ± 55b</td>
<td>5778 ± 483a</td>
<td>638 ± 64</td>
<td>0.41 ± 0.10</td>
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<td>0.2 ± 0.2</td>
<td>284 ± 61b</td>
<td>5508 ± 937</td>
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<td>0.44 ± 0.10</td>
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<td>Rest-basal-AUC</td>
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<td>148491 ± 5734</td>
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<td>170166 ± 22538</td>
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<td>Rest-basal-AUC</td>
<td>5 ± 4</td>
<td>9352 ± 1854</td>
<td>152136 ± 11771</td>
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<tr>
<td>Rest-test-AUC</td>
<td>6 ± 7</td>
<td>9110 ± 1836</td>
<td>154107 ± 13607</td>
<td>19340 ± 1343</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ex-test-AUC</td>
<td>30 ± 24e</td>
<td>11546 ± 3013</td>
<td>208880 ± 33240</td>
<td>22367 ± 3777</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as the mean ± sd. a P < 0.05 versus time B within saline or octreotide treatment. b P < 0.05 versus the correspondent time point of saline treatment. c P < 0.05 versus rest trials. d P < 0.01 versus rest trials

rate after exercise was significantly lower in octreotide-treated subjects.

IGFBPs and IGF-I responses to physical exercise

Our results showed a significant exercise-linked increase of serum IGFBP-3 levels at the end-recovery. This result partially supports data from other experiments on the acute IGFBP-3 response to short duration exercise [25,28]. In fact, Schwarz et al. [28] observed, in subjects with lower mean VO₂max and basal serum IGFBP-3 levels compared with our volunteers, an earlier IGFBP-3 increase (end-exercise) and a lower IGFBP-3 maximal response after acute exercise. The discrepancies between different experimental studies are probably due to the many factors influencing acute IGFBPs responses to exercise (i.e., gender, age, training status, type, duration and intensity of exercise, nutrition, hormonal status, etc.). For example, plasma IGFBP-3 increased immediately after a short-term exercise on a cycle-ergometer, both at low and high intensity [28], while no acute effects on plasma IGFBP-3 concentration were observed immediately after a marathon run [22] or after a long distance Nordic ski race [25].

From our data, it is difficult to establish whether the observed acute serum IGFBP-3 increase after exercise in the saline trial is the consequence of an increased synthesis and/or secretion, of a reduced removal from circulation and/or of an exercise-dependent shift in blood volume from regions with high IGFBP-3 concentration (i.e., the liver) to the peripheral circulation. Excluding the synthesis of new IGFBP-3 molecules, which would require a longer period, an increased output of pre-existing IGFBP-3 from the liver may also be hypothesized.

In both the ex-saline and ex-octreotide trials no changes in IGFBP-2 were found, whereas the comparison between exercise trials showed a significant difference in serum IGFBP-2 Δ%: increased in the ex-saline trial and decreased in the ex-octreotide trial. A positive relationship between physical activity and serum IGFBP-2 was observed in adolescents after training [10]. These results seem in contrast with the observed inverse relationship between IGFBP-2 and GH status under certain ex-
Experimental conditions, however, there are few and conflicting data on this topic [21,24].

In our experiment we observed a significant percentage of increase of IGF-I AUC after exercise. The discrepancy with a similar experiment, where no modifications of the absolute post-ex IGF-I AUC were reported, is probably only apparent, particularly because this previous study did not report the percentage of increase of IGF-I AUC [8]. Furthermore, controversial results in the analysis of IGF-I responses to exercise may result from the high variability of basal IGF-I concentrations in humans and from the variability of individual IGF-I responses to acute exercises. When observed, it is possible that any IGF-I increase during and immediately after exercise may be related to rapid non-classic GH actions and/or to other factors (i.e., adipose and/or muscular cell disruption, IGFBP modifications, other exercise-related hormones, etc.) and not to de novo synthesis [4]. In fact, if there is an exercise-GH-dependent IGF-I synthesis, it should be possible to observe it only some hours after the end of an acute exercise or over a longer period of training, when the physical activity is able to amplify the pulsatile release of GH [33].

Role of GH in the IGF-I and IGFBP-3 responses to physical exercise

The present findings did not confirm the role of GH as a stimulating factor for the observed acute IGFBP-3 increase after exercise in our experimental conditions. In fact, independently of the possible direct action of octreotide on serum IGFBP-3 concentration (see "Direct action of octreotide on IGFBP-3"), it is of interest that in the exercise-octreotide trial the reduced GH response to exercise was associated with a faster and a significantly greater IGFBP-3 response than exercise- or octreotide-only alone.

In order to explain the amplification of the IGFBP-3 response to exercise observed in octreotide-treated subjects, it could be also hypothesized that GH exerts an "inhibitory action" on stress-related IGFBP-3 increase or that other hormonal responses to exercise enhance the IGFBP-3 response to octreotide or vice versa. Speculatively, the possible presence of an inhibitory GH action on stress-related serum IGFBP-3 concentration might be useful to maintain a higher level of free-IGF-I in the tissue milieu during and immediately after exercise.

Furthermore, our data did not allow us to define exactly the role of GH in the acute IGF-I response to exercise trial. In fact, the significant IGF-I reduction observed in the rest-octreotide trial, probably due to a direct non GH-dependent effect of octreotide [14], was a confusing factor. The possible mechanisms involved in suppressive non GH-dependent action of octreotide on serum IGF-I levels may include effects on local IGF-I production, via specific tissue receptors for octreotide, and/or the octreotide-dependent changes in the IGFBP's serum and/or tissue concentrations.

Direct action of octreotide on IGFBP-3

This study described the stimulating effect of octreotide on serum IGFBP-3 both after exercise and in the rest-octreotide trial (Table 1). These actions might be the expression of a direct non GH-dependent pharmacological effect of octreotide. In addition, we still had to understand if the direct octreotide-dependent pathways involved in the IGFBP-3 increase are the same in the two experimental conditions (exercise and rest trials).

The literature provides some experimental data on the direct octreotide induction of IGFBP3s in men [12,27]. In acromegalic patients, chronic octreotide administration results in a decrease of both IGF-I and IGFBP-3 because it decreases GH hypersecretion. In healthy subjects, different mechanisms should be considered in order to explain the observed stimulating action of octreotide on serum IGFBP-3: (a) octreotide was able to acutely stimulate liver IGFBP-1 and IGFBP-3 mRNA expression in rats [15]; b) the serum IGFBP-3 might increase as consequence of an octreotide-mediated inhibition of tissue peptidase activity [23] and/or for an inhibition of a putative hormonal regulator(s) [16]; (c) an octreotide-dependent reduction of splanchnic blood flow could be responsible for a redistribution of serum IGFBP-3 in the general circulation.

In conclusion, we showed that acute physical exercise is able to acutely stimulate serum IGFBP-3 and IGF-I concentrations and that GH has a reduced role, as a stimulating factor, particularly in the observed IGFBP-3 response. Our evaluation of the IGF-I/IGFBP-2 and IGFBP-3/IGFBP-2 ratios should be useful in order to know how these parameters are influenced by acute physical activity. The observed reduced influence of physical exercise on these ratios, if further confirmed after different types of exercise and/or competition, would lend support to the use of these parameters more than absolute hormone concentrations in monitoring GH administration as doping in athletes [21]. Considering all the possible direct actions of octreotide on the IGF system, the present experimental model could remain of use in exercise physiology in particular in the evaluation GH-dependent parameters not directly influenced by octreotide.

The exact role of the IGFs and IGFBP3s in the physiological adaptation to physical exercise is not known. The direct and indirect biological functions of the IGFs and IGFBP3s have been reviewed elsewhere [19,26], in particular the actions of the IGF system on skeletal muscles [13]. In the future it would be useful to evaluate the role of the GH-IGF system in athletic activity also studying the modifications of GH biological activity and of the free-IGFs and IGFBP pathways at the cellular level (autocrine and paracrine actions) in the different tissues milieu during and after different types of exercise. In fact, the exercise-associated changes in circulating hormones may not accurately reflect all the changes that occur in the exercising tissues themselves.

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