The Effects of Recombinant Human Insulin-Like Growth Factor-I/Insulin-Like Growth Factor Binding Protein-3 Administration on Body Composition and Physical Fitness in Recreational Athletes

Nishan Guha, Simon P. Nevitt, Michael Francis, John A. Woodland, Dankmar Böhning, Peter H. Sönksen, and Richard I. G. Holt

Human Development and Health Academic Unit (N.G., S.P.N., M.F., J.A.W., P.H.S., R.I.G.H.), Faculty of Medicine, University of Southampton SO16 6YD, and University Hospital Southampton, National Health Service Foundation Trust SO16 6YD, and Southampton Statistical Sciences Research Institute (D.B.), University of Southampton, Southampton SO17 1BJ, United Kingdom

Context: IGF-I is thought to mediate many of the anabolic actions of GH, and there are anecdotal reports that IGF-I is misused by elite athletes. There is no published evidence regarding the effects of IGF-I administration on athletic performance.

Objective: The objective of the study was to investigate the effects of IGF-I administration on body composition and physical fitness in recreational athletes.

Design and Setting: This was a randomized, double-blind, placebo-controlled recombinant human (rh) IGF-I/rhIGF binding protein (IGFBP)-3 administration study at Southampton General Hospital (Southampton, United Kingdom).

Participants: Fifty-six recreational athletes (30 men, 26 women) participated in the study.

Intervention: Participants were randomly assigned to receive placebo, low-dose rhIGF-I/rhIGFBP-3 (30 mg/d), or high dose rhIGF-I/rhIGFBP-3 (60 mg/d) for 28 days. Body composition (assessed by dual energy x-ray absorptiometry) and cardiorespiratory fitness (assessed by incremental treadmill test) were measured before and immediately after treatment. Within-individual changes after treatment were analyzed using paired *t* tests.

Results: There were no significant changes in body fat mass or lean body mass in women or men after the administration of the rhIGF-I/rhIGFBP-3 complex. There was a significant increase in maximal oxygen consumption (VO_2 max) after treatment. When women and men and low- and high-dose treatment groups were combined, mean VO_2 max increased by approximately 7% ($P = .001$). No significant change in VO_2 max was observed in the placebo group.

Conclusions: rhIGF-I/rhIGFBP-3 administration for 28 days improves aerobic performance in recreational athletes, but there are no effects on body composition. **(*J Clin Endocrinol Metab* 100: 3126–3131, 2015)**

GH is misused by athletes for its anabolic and lipolytic properties despite it appearing on the World Anti-Doping Agency list of prohibited substances (1). For many years there was no clear evidence that GH improves athletic performance (2), but recent studies have demonstrated performance-enhancing effects of GH in athletes, particularly when combined with other anabolic agents (3, 4). IGF-I mediates many of the anabolic actions of GH

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received April 17, 2015. Accepted June 1, 2015.
First Published Online June 5, 2015

Abbreviations: BMI, body mass index; GHIS, GH insensitivity syndrome; rh, recombinant human; IGFBP-3, IGF binding protein-3; VO_2 max, maximal oxygen consumption.

(5), and there are reports that this peptide is also misused by athletes (6). It is possible that athletes will be tempted to exploit IGF-I as an alternative or additional doping agent because currently there is no internationally recognized test to detect recombinant human (rh) IGF-I misuse. Previous studies have shown that the administration of IGF-I, in combination with GH, has beneficial effects on body composition in obese postmenopausal women (7) and that rhIGF-I administration has significant effects on body composition when administered to adults with GH deficiency (8). There is no evidence, however, regarding the effects of IGF-I administration on body composition or athletic performance in healthy athletes.

We performed a randomized, double-blind, placebo-controlled study designed to detect changes in serum biomarkers in response to the administration of rhIGF-I complexed with rhIGF binding protein-3 (rhIGFBP-3) (9). A further aim of this study reported here was to determine the effects of rhIGF-I/rhIGFBP-3 administration on body composition and physical fitness in recreational athletes.

Participants and Methods

Setting and participants

The study was performed at the Wellcome Trust Clinical Research Facility, Southampton General Hospital (Southampton, United Kingdom). The study received ethics approval from the Southampton and South West Hampshire Research Ethics Committee and was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines. The study was regulated by the Research and Development Office of University Hospital Southampton National Health Service Trust. The study was not defined as a Clinical Trial because the Medicines and Healthcare Products Regulatory Agency did not classify the rhIGF-I/rhIGFBP-3 complex as an Investigational Medicinal Product.

Fifty-six healthy recreational athletes (30 men, 26 women) aged between 18 and 30 years, who engaged in regular physical activity (two or more sessions per week), were recruited. Athletes were recruited by poster advertisement at the University of Southampton School of Medicine and University of Southampton sports centers. Participants were ineligible if they were competing at elite level, had a history of using performance-enhancing drugs, or if they were found to be anemic at the time of screening. Anyone with a previous history of endocrinopathy, diabetes mellitus, or neoplastic disease was excluded. Pregnant women were not allowed to participate; pregnancy tests were performed on all female volunteers prior to enrollment, and they were advised to use safe contraception for the duration of the study if sexually active. All participants provided written informed consent.

Study design

Participants were randomly assigned to receive low-dose (30 mg/d) rhIGF-I/rhIGFBP-3 complex, high-dose (60 mg/d) rhIGF-I/rhIGFBP-3 complex, or placebo. Insmed Inc provided the rhIGF-I/rhIGFBP-3 complex (mecasermin rinfabate, iPLEX, 60 mg/mL) and matching placebo. The doses used in the study were selected by Insmed Inc based on clinical trial safety data and on clinical practice. Drug vials were stored frozen at −20°C until 30 minutes prior to injection when the required dose was allowed to thaw at room temperature. The injection technique was demonstrated to each volunteer prior to the first dose. Participants self-administered the drug sc with their evening meal for 28 consecutive days. All participants were reminded by daily text message to inject the drug, and compliance was assessed by the completion of a treatment diary and by collection of empty drug vials at the end of the treatment period.

Randomization

Insmed Inc prepared the rhIGF-I/rhIGFBP-3 and provided placebo in identical packaging, labeled with the allocation number. Insmed Inc generated the random allocation sequence in blocks of varying size for men and women, and University Hospital Southampton National Health Service Trust Pharmacy staff were responsible for dispensing the study medication according to the allocation sequence. Participants and investigators were blinded to interventions at all times.

Body composition assessment

Anthropometric measurements were performed and body composition assessed before treatment (baseline) and at the end of treatment (d 28). Height was measured to the nearest half-centimeter using a wall-mounted Seca 220 stadiometer (Seca). Body weight was measured to the nearest 0.1 kg using Seca 876 electronic scales (Seca) with participants dressed in light clothing. Body composition was assessed using dual-energy X-ray absorptiometry (Hologic QDR-4500W DXA scanner) according to standardized procedures recommended by the manufacturer. Calibration was performed on the day of each scan. Participants were dressed in light clothing, and scan duration was approximately 10 minutes with radiation dose approximately 0.01 mSv. Lean body mass and body fat mass were analyzed using Hologic Discovery software (version 13.0).

Physical fitness assessment

Cardiopulmonary exercise testing was performed at the time of recruitment (to allow participants to familiarize themselves with the testing equipment and protocol), at baseline, and at the end of treatment (d 28). Participants were asked to maintain their normal exercise pattern during the treatment period. Maximal aerobic capacity was measured by incremental treadmill test on a Woodway PPS Med treadmill (Woodway) using the Bruce protocol (10). Participants were verbally encouraged to continue until exhaustion. Oxygen consumption was recorded continuously with an on-line gas analyzer (Cortex MetaLyser 3B; Cortex Biophysik GmbH). Breath-by-breath gas exchange values were averaged over 15-second intervals to estimate maximal oxygen consumption (VO_2 max), corrected for total body weight.

Statistical analyses

We based sample size calculations on predicted responses in serum biomarkers to exogenous IGF-I administration. Power calculations were not performed for body composition or physical fitness outcomes because there were no pilot data on which

to perform the necessary calculations. Differences in baseline characteristics between treatment groups were assessed using an ANOVA. Data from participants in low- and high-dose treatment groups were analyzed separately and combined. Within-individual changes between baseline and day 28 were assessed using paired *t* tests. Between-group comparisons were performed using unpaired *t* tests. The relationship between change in VO_2 max and baseline body mass index (BMI) was assessed using linear regression. Because body composition and physical fitness data were skewed and their distribution was normalized by log transformation, all analyses were performed on log-transformed data. The value of $P < .05$ was considered statistically significant. Statistical analyses were performed using SPSS version 19 (SPSS Inc) and SAS version 8 (SAS Institute Inc).

Results

Six of the 62 participants screened were not randomly assigned to treatment because of personal reasons. Dual-energy x-ray absorptiometry scans were not available for five participants because of scheduling and technical difficulties with the equipment. Posttreatment (d 28) physical fitness tests were not possible for three participants because of technical difficulties with the equipment. The analysis therefore included 51 participants for body composition measurements and 53 participants for physical fitness assessment. Compliance with treatment was greater than 99%. Table 1 shows the baseline characteristics of the groups. The 30 male participants comprised 29 white Europeans and one Asian. The 26 female participants comprised 20 white Europeans, two Asians, one African, and three of mixed race. In men, there were significant differences at baseline between treatment groups in mean weight and lean body mass. There were no significant differences at baseline between treatment groups in men or women in age, height, BMI, fat mass or VO_2 max.

Adverse events

No participant discontinued the study because of adverse effects related to the study medication. Participants in all treatment groups (nine in the high dose group, 12 in the low dose group, and nine in the placebo group) reported local erythema and pain at the site of sc injections; it is likely that this was a reaction to the solvent used to dissolve the drug and placebo. These symptoms were mild and resolved completely after stopping treatment. Three participants in the high-dose rhIGF-I/rhIGFBP-3 group reported increased appetite during treatment, but no participant experienced symptomatic hypoglycemia during the study.

Table 1. Baseline Characteristics and Changes in Body Composition and Physical Fitness After 28 Days of rhIGF-I/rhIGFBP-3 Treatment in 56 Recreational Athletes

	Women				Men			
	Placebo (n = 8)	Low-Dose IGF-I (n = 9)	High-Dose IGF-I (n = 9)	Combined IGF-I Group (n = 18)	Placebo (n = 10)	Low-Dose IGF-I (n = 10)	High-Dose IGF-I (n = 10)	Combined IGF-I Group (n = 20)
Mean age (SD), y	21.9 (2.2)	21.7 (3.4)	21.4 (1.7)	21.6 (2.6)	22.0 (2.8)	21.9 (2.7)	23.2 (2.7)	22.6 (2.7)
Mean height (SD), cm	167.5 (7.7)	165.2 (2.3)	169.0 (6.6)	167.1 (5.2)	185.0 (5.8)	179.3 (10.2)	181.3 (6.2)	180.3 (8.3)
Weight, kg								
Mean (SD), baseline	61.7 (7.0)	60.2 (4.9)	60.5 (7.4)	60.3 (6.1)	92.4 (16.2)	76.9 (12.0)[a]	80.7 (12.9)[a]	78.8 (12.3)[a]
Mean (SD), day 28	62.2 (6.3)	60.0 (5.5)	60.4 (7.1)	60.2 (6.2)	92.3 (16.2)	77.3 (12.8)	80.8 (13.2)	79.0 (12.8)
Mean change (SD), day 28 minus baseline	0.5 (1.0)	−0.2 (1.1)	−0.1 (1.1)	−0.1 (1.1)	−0.1 (1.5)	0.4 (0.9)	0.1 (1.9)	0.2 (1.5)
BMI, kg/m^2								
Mean (SD), baseline	22.0 (1.6)	22.0 (1.8)	21.2 (2.4)	21.6 (2.1)	27.0 (4.3)	23.8 (2.5)	24.6 (3.9)	24.2 (3.2)
Mean (SD), day 28	22.2 (1.6)	21.8 (2.2)	21.1 (2.4)	21.5 (2.3)	26.9 (4.4)	23.8 (2.7)	24.6 (3.8)	24.2 (3.2)
Mean change (SD), day 28 minus baseline	0.2 (0.3)	−0.2 (0.5)	−0.1 (0.4)	−0.1 (0.4)	−0.1 (0.6)	0 (0.3)	0 (0.6)	0 (0.5)
Fat mass, kg[b]								
Mean (SD), baseline	17.8 (6.0)	16.5 (5.0)	16.5 (3.8)	16.5 (4.3)	17.2 (10.4)	12.3 (4.1)	15.6 (8.0)	13.7 (6.0)
Mean (SD), day 28	17.8 (6.0)	16.3 (5.4)	16.0 (3.9)	16.1 (4.5)	17.1 (9.9)	12.5 (3.8)	15.5 (7.7)	13.7 (5.7)
Mean change (SD), day 28 minus baseline	0 (0.7)	−0.2 (1.3)	−0.5 (1.8)	−0.4 (1.6)	−0.1 (0.9)	0.2 (1.0)	−0.1 (1.2)	0 (1.1)
Lean body mass, kg[b]								
Mean (SD), baseline	42.0 (2.9)	40.4 (3.2)	40.7 (4.2)	40.6 (3.6)	69.6 (6.4)	60.2 (7.9)[a]	63.7 (7.0)[a]	61.6 (7.5)[a]
Mean (SD), day 28	42.8 (4.1)	40.4 (3.3)	41.1 (5.2)	40.7 (4.2)	69.9 (7.3)	60.5 (8.8)	63.7 (7.7)	61.8 (8.3)
Mean change (SD), day 28 minus baseline	0.8 (1.5)	0 (1.4)	0.4 (2.0)	0.1 (1.7)	0.3 (1.6)	0.3 (1.3)	0 (1.5)	0.2 (1.4)
VO_2 max, ml/min/kg[c]								
Mean (SD), baseline	47.0 (7.5)	48.1 (8.8)	46.2 (5.6)	47.2 (7.2)	48.0 (8.3)	51.9 (12.3)	48.0 (10.6)	50.0 (11.3)
Mean (SD), day 28	49.4 (10.3)	52.0 (5.5)	50.8 (7.3)	51.4 (6.3)[d]	49.8 (6.3)	54.0 (11.3)	51.9 (9.2)	53.0 (10.1)[d]
Mean change (SD), day 28 minus baseline	2.4 (5.3)	3.9 (5.9)	4.6 (7.4)	4.2 (6.5)	1.8 (8.2)	2.1 (5.5)	3.9 (7.5)	3.0 (6.5)

Data from low- and high-dose treatment groups were analyzed separately and combined.

[a] Significant difference at baseline ($P < .05$) compared with the placebo group.

[b] Data from two women (both in the placebo group) and three men (all in the high dose IGF-I group) were excluded because of scheduling difficulties.

[c] Data from one woman (in the placebo group) and two men (both in the placebo group) were excluded because of technical difficulties with the equipment.

[d] Significant difference ($P < .05$) compared with baseline.

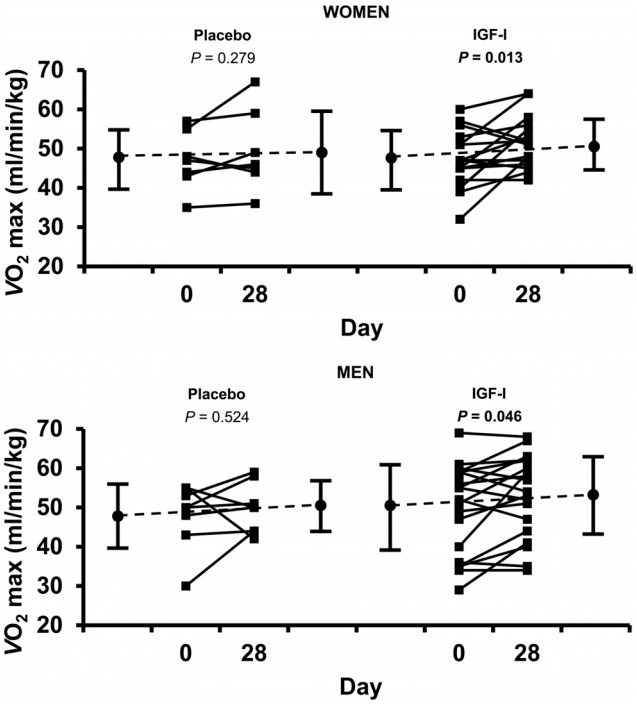

Figure 1. The effects of rhIGF-I/rhIGFBP-3 administration on physical fitness in 26 female and 30 male recreational athletes. Individual data points are shown (squares and solid lines) along with mean ± SD (circles and dashed lines). Intraindividual changes were assessed using paired *t* tests, after logarithmic transformation of the data. IGF-I indicates rhIGF-I/rhIGFBP-3 administration (low and high dose groups combined). Data from one woman (placebo group) and two men (both placebo group) were excluded because of technical difficulties with the equipment.

Effects of treatment on body composition

There were no significant changes in fat mass or lean body mass in women or men after administration of either rhIGF-I/rhIGFBP-3 complex or placebo (Table 1).

Effects of treatment on physical fitness

rhIGF-I/rhIGFBP-3 administration significantly increased VO_2 max (Figure 1 and Table 1). At baseline, there was no significant difference in mean VO_2 max between women and men (47.1 ± 7.1 mL/min·kg vs. 49.9 ± 10.5 mL/min·kg; $P = .394$). There was also no significant difference at baseline between the low- and high-dose treatment groups (50.1 ± 10.7 mL/min·kg vs 47.2 ± 8.4 mL/min·kg; $P = .432$). The within-individual changes were therefore assessed before and after combining the data from women and men and from low- and high-dose treatment groups. There was an approximately 7% increase in mean VO_2 max in athletes treated with rhIGF-I/rhIGFBP-3 ($P = .001$). When the treatment groups were assessed separately, there was a 6% increase in mean VO_2 max within the low-dose group ($P = .033$) and 9% increase within the high-dose group ($P = .020$), but there was no significant difference in the relative increase between the low- and high-dose groups ($P = .617$). When women and men were assessed separately, there was an approximately 9% increase in mean VO_2 max within the female rhIGF-I/rhIGFBP-3 group ($P = .013$) and a 6% increase within the male rhIGF-I/rhIGFBP-3 group ($P = .046$). There was no significant difference in the relative increase between women and men ($P = .599$). No significant change in VO_2 max was observed within the placebo group ($P = .279$ in women, $P = .524$ in men). Men in the placebo group were significantly heavier than in the rhIGF-I/rhIGFBP-3 treatment group (Table 1), but there was no significant relationship between change in VO_2 max and baseline BMI ($r = 0.195$, $P = .162$).

Discussion

This study demonstrates the effects of rhIGF-I/rhIGFBP-3 administration on body composition and physical fitness in 56 recreational athletes. It is the first study to demonstrate an improvement in aerobic performance in young, healthy participants after administration of rhIGF-I/rhIGFBP-3, although there were no significant effects on body composition.

We have shown that, within the group treated with rhIGF-I/rhIGFBP-3, there was a statistically significant increase in VO_2 max. It has been suggested previously that small increments in VO_2 max can have an important influence on the outcome of aerobic endurance events (11). VO_2 max can be improved by physical training, and it has been shown that major factors determining the level of improvement in aerobic fitness include the volume, intensity, and frequency of training as well as the initial level of fitness (12). Highly trained athletes might seek alternative means of improving VO_2 max when no further improvements can be attained through training alone, and the effects of IGF-I may therefore be attractive to this population.

The mechanisms of VO_2 max improvement have not been investigated in this study. Oxygen consumption during exercise is dependent on many factors including efficient inspiration by the respiratory system, transport of oxygen in the circulation to skeletal muscles, and effective aerobic metabolism by skeletal muscle fibers. It is possible that effects on the cardiovascular system contributed to the improved aerobic performance. It has been shown previously that iv administration of rhIGF-I caused an increase in cardiac output, heart rate, and stroke volume in healthy volunteers (13). Furthermore, it has been proposed that IGF-I has a role in regulating vascular tone through alterations in nitric oxide synthesis (14), and changes in im blood flow could have contributed to the effects on aerobic fitness. These cardiovascular variables

were not assessed in this study. Another potential explanation for the improvement is that IGF-I treatment increases respiratory muscle strength as has been shown in a previous rhGH administration study in abstinent anabolic steroid users, in which both maximal oxygen uptake and mean inspiratory pressure were increased after rhGH treatment (4). It has also been shown previously that serum IGF-I concentrations are positively correlated with hemoglobin concentrations (15). An increase in hemoglobin might explain improved aerobic performance after IGF-I treatment through enhanced oxygen delivery to exercising skeletal muscle. Hemoglobin concentrations were not measured in our participants, so it was not possible to determine the contribution of this factor to the improvement observed in this study. Future studies into the effects of IGF-I on athletic performance should include evaluation of effects on the cardiovascular, respiratory, and hematological systems.

The significance of the observed improvement in VO_2 max to elite athletic performance is unclear; we do not know whether an elite athlete would benefit in the same way as the recreational athletes in this study. To put these results in the context of elite aerobic performance, a 9% improvement in aerobic performance in women translates into approximately 75 seconds gained over the course of an elite women's 5000-m race (the current world record time for women in this event is 14:11.15 min). Race performance, however, relies on several factors in addition to VO_2 max such as glycogen depletion, lactic acid accumulation, and biomechanical factors. Furthermore, the effects of IGF-I on skeletal muscle strength in athletes were not examined in this study; future studies should investigate the effects of IGF-I administration on variables such as maximal strength, explosive power, and sprint capacity, as have been investigated in previous rhGH administration studies (3). If significant improvements in these aspects of physical performance are demonstrated, it would suggest potential benefits of IGF-I administration to athletes in power sports such as sprinting and weight-lifting.

The effects of rhIGF-I/rhIGFBP-3 administration on physical fitness were not accompanied by significant changes in fat mass or lean body mass in this study. Previous IGF-I administration studies have yielded conflicting results in terms of effects on body composition, depending on the population studied. One study investigated the effects of rhGH and rhIGF-I administration in a group of 33 obese postmenopausal women who were undertaking a diet and exercise program over 12 weeks. The administration of rhGH alone and rhGH combined with rhIGF-I resulted in an increase in fat-free mass in these women, whereas the administration of rhIGF-I alone had no effect on fat-free mass (7). Furthermore, substantial changes in body composition were observed when rhIGF-I was administered to adults with GH deficiency (8) and to adults with GH insensitivity syndrome (GHIS; a condition caused by mutations in the gene for the GH receptor) (16). In both of these studies, rhIGF-I administration was associated with increased lean body mass and decreased adiposity, and the findings in the latter study were attributed to the stimulatory effects of rhIGF-I on lipolysis and lipid oxidation in adults with GHIS. When rhIGF-I was administered to a group of 16 healthy postmenopausal women for 1 year, however, there were no changes in lean body mass or adipose tissue after treatment (17), similar to the results of our current study. It is possible that the positive effects of IGF-I administration on body composition in patients with GHIS reflects the severe nature of their IGF-I deficiency (18), whereas the healthy recreational athletes in the current study with normal endogenous IGF-I production are less likely to respond.

This study has some limitations. First, the study involved recreational rather than elite athletes because it is not possible to administer substances that are prohibited in sports to elite athletes. The baseline physical fitness levels and body composition of an elite athlete population would be different from the athletes in the current study, and we do not know whether rhIGF-I/rhIGFBP-3 administration would have the same effect on an elite athlete as on a recreational athlete. Second, athletes may be misusing rhIGF-I alone or rhIGF-I in combination with rhGH, rather than the rhIGF-I/rhIGFBP-3 complex used in this study, and the effects on body composition and physical fitness may differ in those scenarios. The rhIGF-I/rhIGFBP-3 complex (mecasermin rinfabate) was administered in this study because of its longer serum half-life and lower risk of side effects such as hypoglycemia, compared with rhIGF-I alone (19). The drug is a recombinant protein complex of rhIGF-I and rhIGFBP-3, combined noncovalently in equimolar proportions. This forms a ternary complex with endogenous acid-labile subunit and maintains rhIGF-I in a bound form in the circulation. There are no confirmed cases of elite athletes obtaining and misusing rhIGF-I/rhIGFBP-3, but it would seem an attractive anabolic agent with a lower risk of side effects, compared with either rhIGF-I alone or insulin. Third, we do not know the doses of IGF-I that are being misused by elite athletes or the typical duration of treatment. It is likely that the drug would be taken for a longer period than the 28 days used in this study, and it is possible that the prolonged administration could lead to more marked changes in body composition as well as physical fitness.

In conclusion, this study demonstrates that 28 days of rhIGF-I/rhIGFBP-3 administration improves aerobic fit-

ness but has no effect on body fat or lean body mass in recreational athletes. The significance of this improvement in elite athletes requires further investigation, as do the mechanisms underlying the benefits on aerobic performance. The results of this study support the inclusion of IGF-I on the World Anti-Doping Agency list of prohibited substances and highlight the need to develop methods for detecting IGF-I misuse.

Acknowledgments

We thank all the volunteers for their participation in the study. We thank the nurses of the Wellcome Trust Clinical Research Facility at Southampton General Hospital for their assistance with the study visits. We also thank the University of Southampton Faculty of Medicine and sports societies for allowing us to approach potential participants. We thank Insmed Inc for providing the rhIGF-I/rhIGFBP-3 complex and placebo and for organizing the randomization for the study. We also thank the University Hospital Southampton National Health Service Trust Pharmacy staff for their assistance with dispensing the study medication. We also thank Osquel Barroso (World Anti-Doping Agency) for his comments on the manuscript.

Address all correspondence and requests for reprints to: Professor Richard I. G. Holt, The Institute of Developmental Sciences (IDS Building), MP887, Southampton General Hospital, Tremona Road, Southampton SO16 6YD, United Kingdom. E-mail: r.i.g.holt@southampton.ac.uk.

This work was supported by the World Anti-Doping Agency Grant 05B3RH.

Disclosure Summary: The authors have nothing to disclose.

References

1. **World Anti-Doping Agency.** The World Anti-Doping Code: the 2014 prohibited list international standard. 2014. http://www.wada-ama.org/en/World-Anti-Doping-Program/Sports-and-Anti-Doping-Organizations/International-Standards/Prohibited-List/. Accessed June 10, 2014.
2. **Liu H, Bravata DM, Olkin I, et al.** Systematic review: the effects of growth hormone on athletic performance. *Ann Intern Med*. 2008; 148:747–758.
3. **Meinhardt U, Nelson AE, Hansen JL, et al.** The effects of growth hormone on body composition and physical performance in recreational athletes: a randomized trial. *Ann Intern Med*. 2010;152: 568–577.
4. **Graham MR, Baker JS, Evans P, et al.** Short-term recombinant human growth hormone administration improves respiratory function in abstinent anabolic-androgenic steroid users. *Growth Horm IGF Res*. 2007;17:328–335.
5. **Le Roith D, Bondy C, Yakar S, Liu JL, Butler A.** The somatomedin hypothesis: 2001. *Endocr Rev*. 2001;22:53–74.
6. **Australian Crime Commission.** Organised crime and drugs in sport. 2013. http://www.crimecommission.gov.au/sites/default/files/organised-crime-and-drugs-in-sports-feb2013.pdf. Accessed May 15, 2015.
7. **Thompson JL, Butterfield GE, Gylfadottir UK, et al.** Effects of human growth hormone, insulin-like growth factor I, and diet and exercise on body composition of obese postmenopausal women. *J Clin Endocrinol Metab*. 1998;83:1477–1484.
8. **Mauras N, O'Brien KO, Welch S, et al.** Insulin-like growth factor I and growth hormone (GH) treatment in GH-deficient humans: differential effects on protein, glucose, lipid, and calcium metabolism. *J Clin Endocrinol Metab*. 2000;85:1686–1694.
9. **Guha N, Erotokritou-Mulligan I, Bartlett C, et al.** Biochemical markers of insulin-like growth factor-I misuse in athletes: the response of serum IGF-I, procollagen type III amino-terminal propeptide, and the GH-2000 score to the administration of rhIGF-I/rhIGF binding protein-3 complex. *J Clin Endocrinol Metab*. 2014;99: 2259–2268.
10. **Bruce RA, Kusumi F, Hosmer D.** Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. *Am Heart J*. 1973;85:546–562.
11. **Shephard RJ.** Is the measurement of maximal oxygen intake passe? *Br J Sports Med*. 2009;43:83–85.
12. **Mujika I.** The influence of training characteristics and tapering on the adaptation in highly trained individuals: a review. *Int J Sports Med*. 1998;19:439–446.
13. **Russell-Jones DL, Bates AT, Umpleby AM, et al.** A comparison of the effects of IGF-I and insulin on glucose metabolism, fat metabolism and the cardiovascular system in normal human volunteers. *Eur J Clin Invest*. 1995;25:403–411.
14. **Schini-Kerth VB.** Dual effects of insulin-like growth factor-I on the constitutive and inducible nitric oxide (NO) synthase-dependent formation of NO in vascular cells. *J Endocrinol Invest*. 1999;22: 82–88.
15. **Kong AP, Choi KC, Wong GW, et al.** Serum concentrations of insulin-like growth factor-I, insulin-like growth factor binding protein-3 and cardiovascular risk factors in adolescents. *Ann Clin Biochem*. 2011;48:263–269.
16. **Mauras N, Martinez V, Rini A, Guevara-Aguirre J.** Recombinant human insulin-like growth factor I has significant anabolic effects in adults with growth hormone receptor deficiency: studies on protein, glucose, and lipid metabolism. *J Clin Endocrinol Metab*. 2000;85: 3036–3042.
17. **Friedlander AL, Butterfield GE, Moynihan S, et al.** One year of insulin-like growth factor I treatment does not affect bone density, body composition, or psychological measures in postmenopausal women. *J Clin Endocrinol Metab*. 2001;86:1496–1503.
18. **Mauras N, Haymond MW.** Are the metabolic effects of GH and IGF-I separable? *Growth Horm IGF Res*. 2005;15:19–27.
19. **Williams RM, McDonald A, O'Savage M, Dunger DB.** Mecasermin rinfabate: rhIGF-I/rhIGFBP-3 complex: iPLEX. *Exp Opin Drug Metab Toxicol*. 2008;4:311–324.