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Potential benefits of recombinant human growth hormone (rhGH) to athletes ☆

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ABSTRACT

Athletes have enjoyed almost a thirty year amnesty of rhGH abuse, which they consider has contributed to the winning of medals and the breaking of world records. Such a reprieve is almost at an end, since WADA have identified a method to detect rhGH abuse. Or have they?

The anecdotal word "on the street" is that rhGH is still undetectable and athletes believe that the benefits, at the dosages they administer, far outweigh the risks!

Scientists are aware that in a hormone deficiency condition, replacement can halt and in certain situations reverse some of the adverse effects. Growth hormone deficiency can lead to a loss of skeletal muscle mass and an increase in abdomino-visceral obesity, which is reversed on replacement with rhGH.

Since the availability of GH, athletes have been trying to extrapolate these effects from the deficiency state to the healthy corpus and increase their sporting prowess.

Past confessions from athletes, such as Ben Johnson, Kelly White, Tim Montgomery, Marion Jones and currently Dwain Chambers have demonstrated that they are prepared to tread the very fine lines that separate the "men from the boys". Rewards are so great, that anonymous surveys have identified that athletes will risk ill health, if they believe they can cheat, win and not get caught.

The question that still needs to be answered is, "does growth hormone enhance performance"?

Recent research suggests that it could. There is also a suspicion that in "cycled" low supraphysiological doses, it is no where near as harmful as WADA claim it to be.

1. Introduction

Since the isolation of human growth hormone (GH) by Li and Papkoff [1] and the synthesis of recombinant human growth hormone (rhGH) by recombinant DNA technology in the late 1970s [2], sportspersons have been trying to extrapolate the proven benefits of replacement therapy in GH deficiency (GHD) to promote athletic supremacy, in competition [3].

Physical exercise is a "knife edge" physiological state of homeostasis, which the elite athlete aspires to tip the balance in favour of anabolism.

Contemporary evidence appears to contradict the proven anabolic effect of rhGH in deficiency, in drug naïve healthy human muscle, that could improve athletic performance [4–6]. Administration of rhGH causes no further increase in muscle mass or strength, than that provided by resistance training in healthy young athletes [7–10].

Difficulties arise in targeting an appropriate dose range in such subjects, given the cardiovascular and metabolic hazards involved and the associated ethical issues.

A supraphysiological effect of rhGH on muscle in athletes is comparable with the early pathological effects of acromegaly, which can initiate a GH resistant state. In acromegaly, true muscle hypertrophy cannot be evaluated in a sporting context, since acromegaly is only identified when the pathology becomes fulminant. It is only at this stage that such patients come under the auspices and management of clinicians, with little or no knowledge or experience of its application to sport.

Despite no overt proof of performance enhancement, the use of rhGH in "sport" has increased dramatically from 6% [11] to 24% [12] over a 5 year period. The question is why?

The USA Federal investigation into the shenanigans of the Bay Area Laboratory Co-operative (BALCO) in the provision of the sublingual "designer steroid" tetrahydrogestrinone (THG) coded as

☆ Where applicable, the experiments described received approval for the investigations from an institutional human research committee here and conform with the principles of the World Medical Association's Declaration of Helsinki, 1975.

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'The Clear' which was supplied to high profile athletes [13]. The "Mitchell Report" has provided us with some of the clues [14]. The BALCO affair, attracted media attention not least because of the supply of THG but also the supply of a transdermal preparation, 'The Cream', that contained testosterone (T) and epitestosterone (E), produced specifically to evade a doping T/E ratio urinalysis.

The "Mitchell Report", released in 2007, covers the history of the use of illegal performance-enhancing substances by players in the Major League Baseball (MLB) Joint Drug Prevention and Treatment Program.

According to the report, after mandatory random testing began in 2004, rhGH became the substance of choice among players, as it is not detectable in tests. Also, it was noted that at least one player from each of the thirty MLB teams was involved in the alleged violations.

The office of the New York Attorney General has estimated that fraudulent sales of human growth hormone and other prescription drugs have amounted to 10% of New York's $3 billion in Medicaid drug expenses in 2002.

The "Mitchell Report" identified that rhGH was the substance most frequently sold to players by Kirk Radomski, a former New York mets clubhouse employee who was a significant source of illegal performance-enhancing substances until late 2005.

Also many players have purchased rhGH through "anti-aging" centres using dubious prescriptions written by physicians who have never examined, nor even met, the "customers" for whom they were writing prescriptions.

In February 2007, a government task force executed search warrants on "Signature Compounding Pharmacy", in Orlando, Florida and other businesses, including several so-called "rejuvenation centres", exposing another source of illegal performance-enhancing substances.

The Food and Drug Administration (FDA) does not approve the use of rhGH to treat an athletic injury, to become leaner, nor to improve athletic performance. Its use is a violation of federal law if it is not for an authorised purpose, even if a legitimate prescription is provided.

2. The beneficial effect of rhGH in athletes

The knowledge that multiple studies have demonstrated a decreased psychological well-being in hypopituitary patients, despite replacement with all hormones but GH [15] has been applied to the sporting arena.

The first researchers experimented on athletes using biosynthetic *N*-methionyl hGH (met-hGH), consisting of 192 amino acids, as opposed to rhGH (191 amino acids). The administration of met-hGH (2.67 mg 3 days per week) for 6 weeks in 8 well-trained exercising adults, with an age range of 22–33 years, who trained with progressive resistance exercise and maintained a high-protein diet, decreased body fat and increased lean body mass (LBM) [7].

Following the synthesis of rhGH and the benefits in GHD, early studies highlighted that an acute bolus administration in normal healthy humans in the post-absorptive state, was shown to increase net balance of forearm amino acids [16].

RhGH administration significantly increases the myosin heavy chain (MHC) 2X isoforms [17] which the authors suggested was a change into a more youthful composition, possibly induced by the rejuvenation of systemic insulin-like growth factor-I (IGF-I) levels. However, it had no effect on isokinetic quadriceps muscle strength, power, cross-sectional area (CSA), or fibre size. Resistance training (RT) and placebo, together, caused substantial increases in quadriceps isokinetic strength, power, and CSA, but these RT induced improvements were not further augmented by additional rhGH administration. In the RT and GH group, there was a significant decrease in MHC 1 and 2X isoforms, whereas MHC 2A increased. The authors suspected that RT over-rode the changes in MHC composition induced by GH administration alone.

Healy et al. [18] identified that rhGH administered for 4 weeks rhGH in a dose of 0.067 mg kg^{-1} day^{-1}, to 6 males, exerted an anabolic effect both at rest and during exercise in endurance-trained athletes. Plasma levels of glycerol and free fatty acids (FFA) and glycerol rate of appearance (Ra) at rest, during and after exercise increased. Glucose Ra and glucose rate of disappearance (Rd) were greater after exercise, and resting energy expenditure and fat oxidation were greater under resting conditions.

Irving et al. [19] administered an acute bolus rhGH infusion of 0.01 mg kg^{-1} to 9 males, with a mean age of 24 years, a mean body fat of 17.7% and a mean maximal oxygen uptake ($\dot{V}O_2$max, a measure of endurance performance) of 37.9 ml kg^{-1} min^{-1}, who completed six, 30-min randomly assigned Monark cycle ergometer exercise trials at a power output midway between the lactate threshold and $\dot{V}O_2$max consumption. There were no condition effects for total work, caloric expenditure, heart rate response, the blood lactate response, or ratings of perceived exertion response (RPE). However, there was a lower $\dot{V}O_2$max without a drop-off in power output. This could not be explained but the authors suggested that rhGH administration could improve exercise economy. This may have been as a consequence of production of FFA by GHs lipolytic effect, providing the substrates for the maintenance of energy metabolism.

Ehrnborg et al. [6] administered 4 weeks rhGH in a dose of 0.033 mg kg^{-1} day^{-1} and a dose of 0.067 mg kg^{-1} day^{-1} to a cohort of physically active individuals of both genders, with a mean age of 26 years. Despite no increase in strength being observed, IGF-I increased by 134% (baseline vs. 1 month), body weight increased by 2.7%, LBM increased by 5.3% and body fat decreased by 6.6%.

Plasma levels of glycerol and free fatty acids increased at rest and during exercise during rhGH administration, 0.067 mg kg^{-1} day^{-1}, for 4 weeks, in six trained male athletes. The resultant effect was an increase in both resting energy expenditure and fat oxidation, along with an increase in glucose production and uptake after exercise [20].

The results of these studies support the hypothesis of performance enhancement, but are not entirely conclusive.

2.1. Failures to demonstrate a benefit in athletes

According to Yarasheki et al. (1992) rhGH administration, 0.04 mg kg^{-1} day^{-1}, for 12 weeks, did not enhance muscle anabolism associated with heavy-resistance exercise in seven male, aged 21–34 years, with a mean weight of 70.6 kg [8].

In their study of 7 healthy male weight lifters, (mean age of 23 years) Yarasheki et al. (1993) reported that the fractional rate of skeletal muscle protein synthesis and the whole body rate of protein breakdown did not increase during a constant intravenous infusion of [^{13}C] leucine at the end of 14 days of rhGH administration. This was using a dosage of 0.04 mg kg^{-1} day^{-1} [9].

Similarly, the administration of rhGH in 8 healthy males, with a mean age of 23 years and a mean body fat of 10.1%, in a dose of 0.03 mg kg^{-1} day^{-1}, for a period of 6 weeks, had no effect on maximal strength during concentric contraction of the biceps and quadriceps muscles [10].

Wallace et al. [4] demonstrated that there was no improvement in performance characteristics of 8 healthy athletes, (mean age of 27 years) as measured by cycle ergometry and $\dot{V}O_2$max assessment, following rhGH administration, 0.05 mg kg^{-1} day^{-1}, for 7 days.

A single rhGH dose (2.5 mg) in seven highly trained males, with a mean age of 26 years and a mean $\dot{V}O_2$max of 65 ml min^{-1} kg^{-1}, who performed 90 min of bicycling 4 h after taking the rhGH, prevented two subjects from completing the exercise protocol. It increased plasma lactate and glycerol as well as serum non-

esterified fatty acids (NEFA) and this appeared to compromise exercise performance. $\dot{V}O_2$max remained unaltered until exhaustion, whilst plasma glucose was higher (9%) during exercise. This would suggest that any benefits of exercise in terms of increased glucose tolerance appeared to be negated by rhGH [21].

Berggren et al. [5] administered rhGH for 4 weeks, 0.033 mg kg^{-1} day^{-1} and 0.067 mg kg^{-1} day^{-1}, to a cohort of physically active individuals of both genders, with a mean age of 26 years, without an alteration in power or $\dot{V}O_2$.

Despite large dosages being administered to these athletes, the evidence suggests that for relatively young drug naïve individuals, performance enhancement is not viable by the use of rhGH alone.

3. The effects of different dosages of rhGH

Despite supraphysiological dosages of rhGH being administered to drug naïve athletes, approximating acromegalic levels of GH, no performance enhancement has been identified by the scientific community. It is possible that the cohort sizes used by researchers, to date, have been too low to achieve the results that are still anecdotally claimed to be as a result of self-administration. Professional bodybuilders and power lifters are believed to administer dosages of the hormone, up to 0.066 mg kg^{-1} day^{-1} [22]. However, effects of rhGH have also been studied at greater than physiological dosages, and although these may well have been below the dosages abused by bodybuilders, they have still resulted in serum concentrations of IGF-I that are at least twice normal [9,23]. There have been significant physiological effects such as increased lipolysis, altered carbohydrate metabolism, activation of the renin–angiotensin system, and water retention. Another explanation for the lack of evidence of increased strength in apparently healthy individuals is that rhGH has been reported to have anabolic effects on bone and collagen metabolism [24] and the collagenous components of skeletal muscle and connective tissue elements of skin may also show up as new LBM. A small increase in visceral protein and collagen equates to an increased positive nitrogen balance, but such an effect on connective tissue would not necessarily make the muscle generate greater strength or power. It may enhance resistance to injury or faster repair, which would be very advantageous to competitive athletes.

WADA suggest that excess rhGH may compromise health and therefore performance [25]. However, contrary to scientific opinion [22] it is unlikely that competitive Olympic athletes are using the high dosages that have been used in research to detect rhGH (personal communications).

A letter sent to the Times newspaper [26], by the main culprit in the BALCO affair, Victor Conte, has identified the doping regime of the former banned athlete, Dwain Chambers, who tested positive for THG in 2003. Conte served a reduced sentence of 4 months in 2005, after co-operating with the US federal authorities, for the illegal distribution of steroids and has admitted to giving Chambers "the full enchilada" of drugs, of seven banned substances, including rhGH. The letter from Conte [27], provided at Chambers behest, to co-operate with the UK authorities, in an attempt to re-establish his athletic career, identifies that Chambers took rhGH 3 times per week in a dose of 4.5 IU per week. He was cycling the rhGH, 3 weeks on, 1 week off. This is a relatively small dose, but in combination with the other doping agents, he believed it would have a synergistic effect [27].

4. Beneficial effects of rhGH in GH resistant states

When rhGH is given in conjunction with the corticosteroid, prednisone, it counteracts the protein catabolic effects of prednisone in healthy volunteers and results in increased whole body protein synthesis rates, with no effect on proteolysis [28].

The infusion of rhGH over 24 h causes a net glutamine release from skeletal muscle into the circulation and increased glutamine synthetase messenger ribonucleic acid (mRNA) levels. This could compensate for reduced glutamine precursor availability, post-trauma, in hyper-catabolic trauma patients, which can account for its anti-catabolic effects [29].

The use of acipimox (an anti-lipolytic) with rhGH administration in a fasting state, eliminated the ability of GH to restrict fasting protein loss, indicating that stimulation of lipolysis by GH is its principle protein-conserving mechanism, resulting in muscle protein breakdown increasing by 50% [30].

5. Recent studies in simulated catabolic states in sport

With the knowledge that physical exercise may result in catabolism, if optimum conditions are not adhered to and despite the knowledge that sportspersons may be abusing very high dosages of rhGH, studies have been conducted in a simulated catabolic state in apparently healthy sportspersons.

A cohort of 24 abstinent androgenic-anabolic steroid (AAS) using males administering 0.019 mg kg^{-1} day^{-1} rhGH, a comparatively small supraphysiological dose, were compared with a cohort of 24 abstinent AAS using controls. They were randomly divided, using a single blind procedure into two groups: (1) control group (C) with a mean age of 32 years and (2) rhGH using group (GH) with a mean age of 32 years. The time period of AAS abstinence of 12 weeks, was considered an adequate period for elimination of any anabolic effects of AAS use. Abstinence was confirmed on urinalysis by a WADA accredited laboratory. Suspected catabolism was confirmed by measurement of IGF-I (Fig. 1). Baseline IGF-I levels were well below 200 ng ml^{-1}.

5.1. Effect on psychological profile

This was assessed using the Hospital Anxiety and Depression Scale (HADS) questionnaire, developed by Zigmond and Snaith

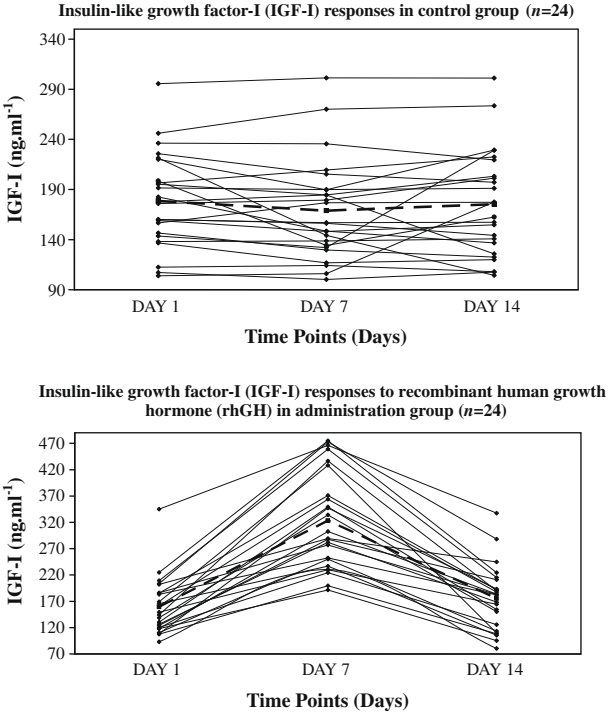

Fig. 1. Individual subject responses for insulin-like growth factor-I (IGF-I) between control group and rhGH administration group.

Table 1
Hospital anxiety and depression scale questionnaire scores.

Aggregate score	Interpretation
0–7	Normal
8–10	Mild
11–14	Moderate
15–21	Severe

[31] for use with physically ill patients. The questionnaire consists of 14 questions: seven questions are related to anxiety and seven questions are related to depression. Each item is rated from a score of 0–3, depending on the severity of the problem described in each question, giving a maximum subscale score of 21 for anxiety and depression, respectively (Table 1).

5.2. Effect on HADS (Table 2)

The daily administration of rhGH for 6 days, significantly decreased anxiety and depressive symptoms, which remained suppressed one week following cessation [32]. RhGH treatment of GHD, is known to increase vasoactive intestinal polypeptide and the dopamine metabolite, homovanillic acid, and also elevates β-endorphin levels in the cerebrospinal fluid [33]. RhGH replacement in GHD has been shown to improve emotional control and well-being, accompanied by lower scores on anxiety in adult males with distorted, underestimated body size, low self-esteem and depression [34]. A large proportion of GHD adults complain of low energy levels, emotional lability and mental fatigue and have an impaired quality of life, and psychiatric morbidity, which improves after as short a period as one months rhGH treatment [35].

5.3. Effect on serum analytes associated with psychological profile (Table 3)

An elevated PRL has been associated with a diminished central fatigue [36] and consequently the elevated PRL could be one factor accounting for the elevated mood of the rhGH recipients. Blunted GH and prolactin (PRL) release, abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis and hypercortisolaemia, have all been demonstrated in depression [37]. Various forms of stress and exercise are known to stimulate the HPA axis and release GH and PRL in an intensity-dependent fashion [38]. Lowering cortisol enhances GH response to GH releasing hormone in healthy subjects [39].

Excess cortisol secretion down-regulates serotonin (5-hydroxytryptamine [5-HT]) neurotransmission which leads to clinical depression in vulnerable individuals [40] and to dysfunction in the 5-HT1A receptor activity [41]. The regulation of the release of PRL also involves the monoamine neurotransmitter systems that have been implicated in the pathophysiology of depression.

Lower serotonin function has been reported in humans with higher levels of impulsive and novelty seeking behaviour. It is possible that lower serotonin turnover in the brain may render a subject more susceptible to any serotonin-lowering insult.

In non-depressed humans, L-tryptophan, a serotonin precursor, produces an increase in plasma PRL concentrations. PRL responses to L-tryptophan are reported to be blunted in depressed patients [42].

Table 2
Hospital anxiety depression scale (HADS) Subject scores. Questionnaire analysis for control (C) group vs. growth hormone (GH) group.

Variables	Control group			GH group		
				(PRE-GH)	(on-GH)	(POST-GH)
Day	1	7	14	1	7	14
Depression	3.3 ± 2.8	3.0 ± 2.8	3.0 ± 2.8	4.5 ± 4.7	1.5 ± 2.5[a,c]	2.5 ± 3.0[a,b]
Anxiety	5.5 ± 1.8	5.3 ± 2.1	5.3 ± 2.5	6.8 ± 4.5	3.6 ± 3.5[a,c]	4.1 ± 3.1[a]

Figures are presented as means ± standard deviations (SD).
[a] $P < 0.017$ = significantly different to PRE-GH.
[b] $P < 0.017$ = significantly different to on-GH.
[c] $P < 0.05$ = significantly different to C.

Table 3
Serum analytes associated with psychological profile.

Variables	Control group (C)			Administration group			Reference range
				(PRE-GH)	(on-GH)	(POST-GH)	
Day	1	7	14	1	7	14	
Creatinine (umol L^{-1})	95.9 ± 17	92.3 ± 13	95.6 ± 15	103.3 ± 25	91 ± 12[a,b]	106 ± 24	(50–100)
Total protein (g L^{-1})	76.5 ± 10	78.6 ± 7	76.4 ± 8	75.7 ± 5	71.8 ± 4[a,b,c]	75.7 ± 5	(58–80)
Albumen (g L^{-1})	44.1 ± 6	45.8 ± 4	45 ± 6	44.4 ± 4	41.7 ± 4[a,b,c]	44.1 ± 5	(38–50)
CRP (mg L^{-1})	1.35 ± 1.9	1.38 ± 2.1	1.44 ± 2.1	1.77 ± 2.1	1.26 ± 1.5[a,b]	1.78 ± 2.0	(<3)
fT_4 (pmol L^{-1})	15.6 ± 1.9	15.3 ± 1.8	15.9 ± 1.7	15.3 ± 2.0	14 ± 1.6[a,b,c]	15.1 ± 1.5	(9.6–26.5)
PRL (μ L^{-1})	175 ± 102	142 ± 55	159 ± 108	205 ± 110	196 ± 95[c]	170 ± 101	(50–560)
Cortisol (nmol L^{-1})	389 ± 162	378 ± 125	404 ± 146	402 ± 133	381 ± 138	389 ± 149	(140–690)

Serum analyte responses for control (C) group vs. growth hormone (GH) group.
Figures are presented as means ± standard deviations (SD).
CRP = hsC-reactive protein; fT_4 = free thyroxine; PRL = prolactin; PSA.
Total protein, albumin and fT_4 significantly decreased in GH compared with C ($P < 0.05$) and significantly decreased within GH ($P < 0.017$).
Prolactin (PRL) significantly increased in GH compared with C ($P < 0.05$).
Creatinine significantly decreased within GH ($P < 0.017$).
Within the GH group, CRP, was significantly decreased on rhGH administration ($P < 0.017$).
[a] $P < 0.017$ = significantly different to PRE-GH.
[b] $P < 0.017$ = significantly different to POST-GH.
[c] $P < 0.05$ = significantly different to C.

Table 4
Subject demographics.

Variables	Control group (C)			Administration group		
				(PRE-GH)	(on-GH)	(POST-GH)
Day	1	7	14	1	7	14
BM (kg)	84 ± 10.2	84 ± 10.1	83.3 ± 10.1	85.8 ± 11.6	86.4 ± 11.7[a]	85.2 ± 11.5[a,b]
BMI (kg m^{-2})	26.3 ± 4.4	26.3 ± 4.3	26.2 ± 4.3	27.5 ± 3.0	27.7 ± 3.1[a]	27.3 ± 3.0[a,b]
Hydrostaticbody fat%	20.4 ± 3.8	20.1 ± 3.7	20.0 ± 3.9	20.2 ± 6.2	19.2 ± 6.3[a]	19.2 ± 6.0[a]
FFMI (kg m^{-2})	20.9 ± 3.3	20.9 ± 3.3	20.9 ± 3.3	21.9 ± 1.9[b]	22.3 ± 1.9	22.0 ± 1.9[b]
RT (years)	12.2 ± 3.6	12.2 ± 3.6	12.2 ± 3.6	12.2 ± 3.6	12.2 ± 3.6	12.2 ± 3.6
WT (no. week^{-1})	4.4 ± 1.1	4.4 ± 1.1	4.4 ± 1.1	4.4 ± 1.1	4.4 ± 1.1	4.4 ± 1.1
TT (min)	47 ± 15	47 ± 15	47 ± 15	47 ± 15	47 ± 15	47 ± 15
Energy intake (kJ day^{-1})	18,050 ± 4100	18,100 ± 2020	18,175 ± 3100	17,900 ± 3020	18,450 ± 3900	18,100 ± 2020
Protein intake (g day^{-1})	205 ± 60	195 ± 55	213 ± 45	207 ± 35	217 ± 65	210 ± 50

Training and drug using history for control (C) group vs. growth hormone (GH) group. Figures are presented as means ± standard deviations (SD).
BM = body mass; BMI = body mass index; FFMI = fat free mass index; RT = resistance training; WT = weight training; TT = training time.
BM (kg) and BMI (kg m^{-2}) significantly increased within GH ($P < 0.017$) and significantly decreased on cessation ($P < 0.017$).
Body fat (%) significantly decreased within GH ($P < 0.017$) and remained significantly decreased on cessation ($P < 0.017$).
Fat free mass index (FFMI) increased significantly within GH and decreased significantly on cessation ($P < 0.017$).
[a] $P < 0.017$ = significantly different to PRE-GH.
[b] $P < 0.017$ = significantly different to on-GH.

Higher levels of depressive symptoms have been associated with higher levels of the inflammatory cytokine C-reactive protein (CRP) [43]. Physical activity, which stimulates GH production, is consistently associated with lower CRP levels [44].

The self-administration of rhGH by the intelligent athlete, may prevent any chinks in the psychological armour, in preparation for stressful combat and so improve psychological performance pre-contest and provide an edge over competitors.

5.4. Effect on anthropometry (Table 4)

A study by Graham et al. [45] showed that LBM increased and body fat decreased significantly, 24 abstinent AAS using weight lifters (mean age of 32 years) who administered 0.019 mg kg^{-1} day^{-1} of rhGH. Body fat remained decreased one week following cessation. However, there was no significant change in fat distribution. GH increases lipolysis, with a direct effect on the adipocyte, and lipid oxidation by increasing substrate availability. IGF-I does not mediate the effects of growth hormone on lipolysis as there are no functional type-1 IGF-I receptors in adipocytes [46]. There were no differences between protein and kilocaloric intakes which could have biased the IGF-I and body composition responses. The rapid significant weight gain may also have been the result of a direct effect of rhGH on serum sodium (Table 3) and water, thereby increasing LBM most probably by activation of the renin–angiotensin system, enhanced aldosterone secretion, inhibition of atrial natriuretic peptide (ANP) and by a direct action on renal tubules [47,48].

Effects on respiratory function and endurance performance (Table 5 and Fig. 2).

Forced expiratory volume in 1 second/forced expiratory vital capacity ratio (FEV_1/FVC), maximum expiratory pressure (MEP), maximum inspiratory pressure (MIP) and $\dot{V}O_2$max all increased on rhGH administration [49]. MEP, MIP and $\dot{V}O_2$max remained in an elevated state one week following cessation.

Endurance exercise responses are presented in Table 5 and individual responses for $\dot{V}O_2$max are presented in Fig. 2.

There are no GH receptors present in the lung, but the expression of IGF-I and IGF receptors and IGF binding proteins in human lungs suggests that IGF-I has a role, possibly GH-induced, in the growth and development of human lungs [50].

RhGH increases lipid oxidation, decreasing protein oxidation and increasing protein synthesis [28] and may have led to increased protein synthesis in respiratory skeletal musculature, accounting for the significant increase in MEP and MIP.

Myostatin is a cytokine implicated in differentiated skeletal muscle growth and is a member of the TGFß super-family that has gained attention due to its remarkable expression profile and dramatic actions. Myostatin mRNA expression is inhibited by rhGH with significantly increased lean body mass being translated into increased aerobic performance, determined by $\dot{V}O_2$max [51]. The increase in FEV_1/FVC ratio suggests an enhanced lung capacity.

Table 5
Respiratory muscle function.

Variables	Control group (C)			Administration group		
				(PRE-GH)	(on-GH)	(POST-GH)
Day	1	7	14	1	7	14
FEV_1/FVC (%)	83 ± 6	82 ± 5	82 ± 5	84 ± 7	85 ± 6[b]	85 ± 6
MIP (cm H_2O)	122 ± 21	129 ± 28	126 ± 28	131 ± 30	144 ± 24[a,b]	146 ± 31[a,b]
MEP (cm H_2O)	155 ± 32	157 ± 32	156 ± 32	165 ± 36	179 ± 35[a,b]	178 ± 34[a,b]
$\dot{V}O_2$ peak (ml kg^{-1} min^{-1})	44.8 ± 7.9	45.4 ± 8.3	44.6 ± 8.3	41.8 ± 9.8	45.4 ± 9.9[a]	45.1 ± 8.2[a]

Spirometric, inspiratory and expiratory muscle function and peak oxygen uptake ($\dot{V}O_2$peak) responses for control (C) group vs. growth hormone (GH) group.
Figures are presented as means ± standard deviations (SD).
FEV_1 = forced expiratory volume in 1 s.
FEVC = forced expiratory vital capacity.
MIP = maximum inspiratory pressure; MEP = maximum expiratory pressure.
FEV_1/FVC, MEP and MIP ratio significantly increased compared with the C group ($P < 0.05$).
Within the GH group MEP and MIP increased on rhGH administration and on cessation (all $P < 0.017$).
[a] $P < 0.017$ = significantly different to PRE-GH1.
[b] $P < 0.05$ = significantly different to C.

5.5. Effects on power (Fig. 3)

Maximum power output (PPO) and mean power output (MPO) increased on rhGH administration and there was no difference in fatigue index (FI) between groups. PPO remained in an increased state one week following cessation [45].

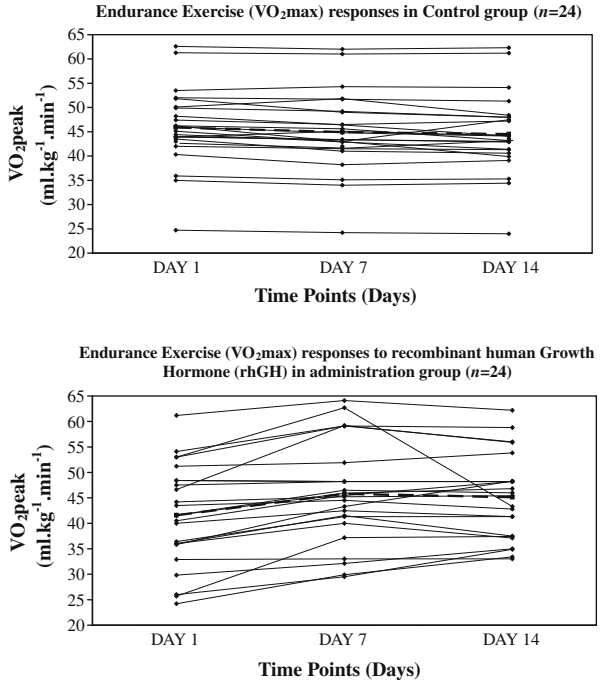

Fig. 2. Individual subject responses for endurance exercise (VO_2max) between control group and rhGH administration group.

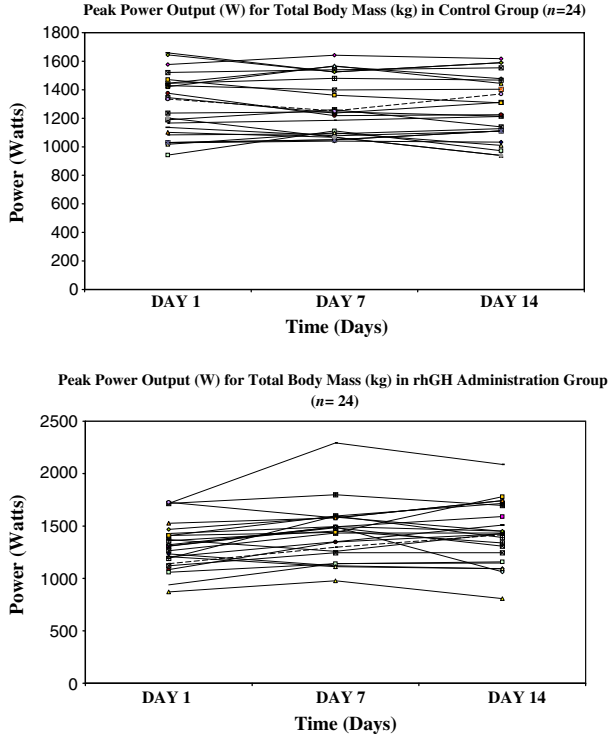

Fig. 3. Individual subject responses for peak power output (W) for total body mass (kg) between control group and rhGH administration group.

The values obtained for power outputs during the high intensity cycle ergometry test suggested that the decrease in% body fat and increased weight and LBM, must have contributed to an increased efficiency in force velocity relationships, which in turn would have led to the increased PPO. The findings also indicated that the GH group were able to produce higher PPO and maintain their performance for longer as indicated by the MPO without an observable alteration in fatigue. The increased stimulation of energy expenditure consequential to the conversion of T_4 to T_3, following rhGH administration, may have contributed to the increase in PPO [52].

5.6. Effects on strength (Figs. 4 and 5)

Strength (bench press and squat) increased on rhGH administration and remained in an elevated state one week following cessation [45]. The increase in strength demonstrated the effects of the hormone, improving nitrogen balance and protein anabolism and was comparable to the effects in debilitating catabolic conditions [53,54]. It would seem plausible to assume that the hormone would have the same effect on skeletal muscle, in this AAS abstinent cohort. Subjects were considered to be in a catabolic phase, depicted by the significant lowering of creatinine, total protein and albumin, suggesting these substrates were being used for anabolism, stimulated by rhGH.

Administration of rhGH in such subjects could have had a suppressive effect on myostatin and increased skeletal contractile muscle synthesis [55]. The effects of AAS are known to result in larger type I, IIA, IIAB and IIC muscle fibre areas and it is possible that previous use of AAS had increased the number of myonuclei per muscle fibre to an extent that a 12-week washout programme was an insufficient time interval for return of the proportion of central nuclei to baseline [56]. This 'latent catabolism' may have been ameliorated by the combination of 'rhGH' administration and 'AAS pre-conditioning' and account for the significant increase in strength. Such a condition would be dissimilar to GHD and may explain why drug-free athletes cannot achieve the same strength increases. Such findings are of relevance because they reflect the

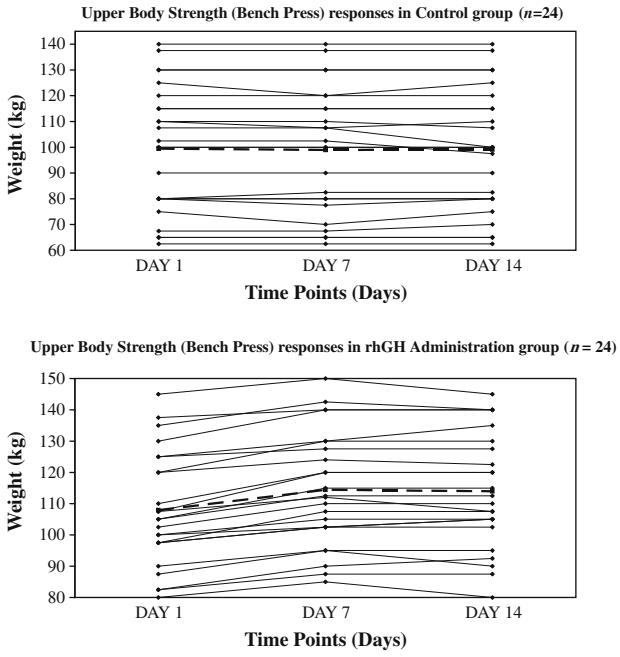

Fig. 4. Individual subject responses for upper body strength (bench press) between control group and administration group.

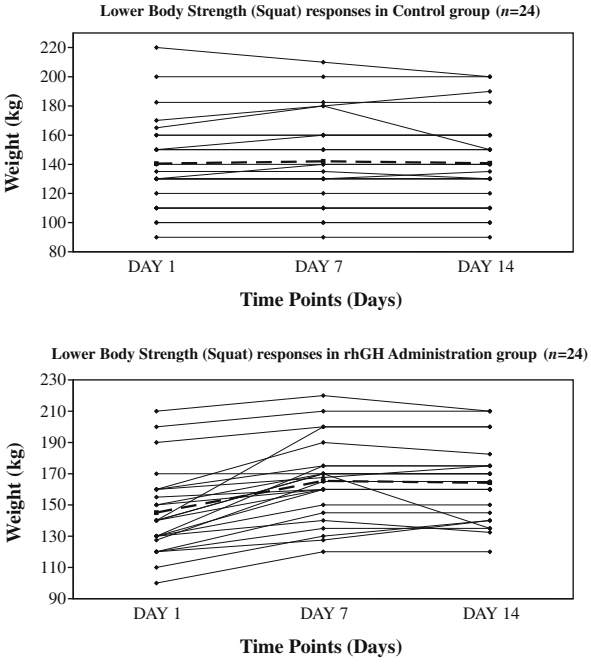

Fig. 5. Individual subject responses for lower body strength (squat) between control group and administration group.

situation whereby athletes may switch from using AAS to the use of rhGH to circumvent a dope test.

6. What makes rhGH the anabolic agent to abuse?

The major actions of GH are that it is a very potent anabolic agent, promoting protein synthesis and simultaneous lipolysis. These benefits are commonly acknowledged in sport.

It probably stimulates protein synthesis through mobilisation of amino acid transporters in a similar manner to insulin and glucose transporters [57].

In the optimum nutritional and training environment, rhGH may enhance constructive skeletal muscle development, to a supraphysiological status. This is a genuine belief by athletes who have sampled the forbidden fruit (personal communications)!

Repetitive strain injuries can lead to stress fractures, tendonitis and possible tendon rupture. RhGH may prevent such injuries by the elevation of collagen and bone markers (osteocalcin, procollagen type III [P-III-P], type I collagen telopeptide [ICT] and C-terminal propeptide of type I collagen [PICP]) [58]. Correspondingly if injuries are present rhGH may enhance the healing process.

RhGH is available through the black market and the internet in adequate quantities, is relatively safe and currently undetectable [22].

A method of cycling the drug, one week on, one week off, can have significant effects on performance whilst thwarting the current detection techniques of the authorities [45].

In summary, for the unethical athlete the rewards of victory are colossal and the benefit of taking rhGH can be considerable, "the difference between gold or failure".

References

[1] C.H. Li, H. Papkoff, Preparation and properties of growth hormone from human and monkey pituitary glands, Science 124 (1956) 1293–1294.
[2] D.V. Goeddel, H.L. Heyneker, T. Hozumi, R. Arentzen, et al., Direct expression in *Escherichia coli* of a DNA sequence coding for human growth hormone, Nature 281 (1979) 544–548.
[3] F. Salomon, R.C. Cuneo, R. Hesp, P.H. Sonksen, The effects of treatment with recombinant human growth hormone on body composition and metabolism in adults with growth hormone deficiency, New Engl. J. Med. 321 (1989) 1797–1803.
[4] J.D. Wallace, R.C. Cuneo, R. Baxter, et al., Responses of the growth hormone (GH) and insulin-like growth factor axis to exercise, GH administration and GH withdrawal in trained adult males: a potential test for GH abuse in sport, J. Clin. Endocrinol. Metab. 84 (1999) 3591–3601.
[5] A. Berggren, C. Ehrnborg, T. Rosen, et al., Short-term administration of supraphysiological recombinant human growth hormone (GH) does not increase maximum endurance exercise capacity in healthy, active young men and women with normal GH-insulin-like growth factor I axes, J. Clin. Endocrinol. Metab. 90 (2005) 3268–3273.
[6] C. Ehrnborg, L. Ellegard, I. Bosaeus, B.A. Bengtsson, T. Rosen, Supraphysiological growth hormone: less fat, more extracellular fluid but uncertain effects on muscles in healthy, active young adults, Clin. Endocrinol. (Oxf.) 62 (2005) 449–457.
[7] D.M. Crist, G.T. Peake, P.A. Egan, D.L. Waters, Body composition response to exogenous GH during training in highly conditioned adults, J. Appl. Physiol. 65 (1988) 579–584.
[8] K.E. Yarasheki, J.A. Campbell, K. Smith, Effect of growth hormone and resistance exercise on muscle growth and strength in young men, Am. J. Physiol. 262 (1992) 261–267.
[9] K.E. Yarasheki, J.J. Zachwieja, T.J. Angelopoulos, Short-term growth hormone treatment does not increase muscle protein synthesis in experienced weight lifters, J. Appl. Physiol. 74 (1993) 3073–3076.
[10] R. Deyssig, H. Frisch, W.F. Blum, T. Waldhor, Effect of growth hormone treatment on hormonal parameters, body composition and strength in athletes, Acta Endocrinol. (Copenh.) 128 (1993) 313–318.
[11] F.M. Grace, J.S. Baker, B. Davies, Anabolic androgenic steroid (AAS) use in recreational gym users – a regional sample of the mid-glamorgan area, J. Subst. Use 12 (2001) 145–153.
[12] J.S. Baker, M.R. Graham, B. Davies, "Steroid" and prescription medicine abuse in the health and fitness community; a regional study, Eur. J. Int. Med. 17 (2006) 479–484.
[13] D.H. Catlin, M.H. Sekera, B.D. Ahrens, et al., Tetrahydrogestrinone: discovery, synthesis, and detection in urine, Rapid Commun. Mass Spectrom. 18 (2004) 1245–1249.
[14] G.J. Mitchell, Report to the Commissioner of Baseball of an Independent Investigation into the Illegal Use of Steroids and Other Performance Enhancing Substances by Players in Major League Baseball, DLA Piper US LLP, December 13, 2007, pp. 1–409.
[15] B. Stabler, J.R. Turner, S.S. Girdler, et al., Reactivity to stress and psychological adjustment in adults with pituitary insufficiency, Clin. Endocrinol. 6 (1992) 467–473.
[16] D.A. Fryburg, R.A. Gelfand, E.J. Barrett, Growth hormone acutely stimulates forearm muscle protein synthesis in normal humans, Am. J. Physiol. 260 (1991) 499–504.
[17] K.H. Lange, B. Larsson, A. Flyvberg, et al., Acute growth hormone administration causes exaggerated increases in plasma lactate and glycerol during moderate to high intensity bicycling in trained young men, J. Clin. Endocrinol. Metab. 87 (2002) 4966–4975.
[18] M.L. Healy, J. Gibney, D.L. Russell-Jones, et al., High dose growth hormone exerts an anabolic effect at rest and during exercise in endurance-trained athletes, J. Clin. Endocrinol. Metab. 11 (2003) 5221–5226.
[19] B.A. Irving, J.T. Patrie, S.M. Anderson, et al., The effects of time following acute growth hormone administration on metabolic and power output measures during acute exercise, J. Clin. Endocrinol. Metab. 89 (2004) 4298–4305.
[20] M.L. Healy, J. Gibney, C. Pentecost, et al., Effects of high-dose growth hormone on glucose and glycerol metabolism at rest and during exercise in endurance-trained athletes, J. Clin. Endocrinol. Metab. 91 (2006) 320–327.
[21] K.H. Lange, J.L. Andersen, N. Beyer, et al., GH admin changes myosin heavy chain isoforms in skeletal muscle but does not augment muscle strength or hypertrophy, either alone or combined with resistance exercise training in healthy elderly men, J. Clin. Endocrinol. Metab. 87 (2002) 513–523.
[22] J.K. Powrie, E.E. Bassett, T. Rosen, et al., Detection of growth hormone abuse in sport. On behalf of the GH-2000 project study group, Growth Horm. IGF Res. 17 (2007) 220–226.
[23] K.E. Yarasheki, J.J. Zachwieja, J.A. Campbell, D.M. Bier, Effect of growth hormone and resistance exercise on muscle growth and strength in older men, Am. J. Physiol. 268 (1995) 268–276.
[24] C.A. Lisset, S.M. Shalet, Effects of growth hormone on bone and muscle, Growth Horm. IGF Res. 10 (2000) 95–101.
[25] <http://www.wada-ama.org>.
[26] <http://www.timesonline.co.uk/tol/sport/more_sport/athletics/article3942201.ece>.
[27] <http://news.bbc.co.uk/sport1/hi/olympics/athletics/7403158.stm>.
[28] F.F. Horber, M.W. Haymond, Human growth hormone prevents the protein catabolic side effects of prednisone in humans, J. Clin. Invest. 86 (1990) 265–272.
[29] G. Biolo, F. Iscra, F. Bosutti, et al., Growth hormone decreases muscle glutamine production and stimulates protein synthesis in hypercatabolic patients, Am. J. Physiol. Endocrinol. Metab. 279 (2000) 323–332.
[30] H. Nørrelund, K.S. Nair, S. Nielsen, et al., The decisive role of free fatty acids for protein conservation during fasting in humans with and without growth hormone, J. Clin. Endocrinol. Metab. 88 (2003) 4371–4378.
[31] A.S. Zigmond, R.P. Snaith, The hospital anxiety and depression scale, Acta Psychiatr. Scand. 67 (1983) 361–370.

[32] M.R. Graham, B. Davies, D. Hullin, A. Kicman, D. Cowan, J.S. Baker, Recombinant human growth hormone in abstinent androgenic-anabolic steroid use: psychological, endocrine, and trophic factor effects, Curr. Neurovasc. Res. 4 (2007) 9–18.
[33] J.O. Johansson, G. Larson, M. Andersson, et al., Treatment of growth hormone-deficient adults with recombinant human growth hormone increases the concentration of growth hormone in the cerebrospinal fluid and affects neurotransmitters, Neuroendocrinology 61 (1995) 57–66.
[34] G. Riva, E. Molinari, Body image and social attitude in growth-hormone-deficient adults, Percept. Motor Skill. 80 (1995) 1083–1088.
[35] T. Mahajan, A. Crown, S. Checkley, A. Farmer, S. Lightman, Atypical depression in growth hormone deficient adults, and the beneficial effects of growth hormone treatment on depression and quality of life, Eur. J. Endocrinol. 151 (2004) 325–332.
[36] C.L. Bethea, F.K. Pau, S. Fox, Et al. Sensitivity to stress-induced reproductive dysfunction linked to activity of the serotonin system, Obstet. Gynecol. Surv. 7 (2005) 448–450.
[37] E.J. Sachar, A.G. Frantz, N. Altman, J. Sassin, Growth hormone and prolactin in unipolar and bipolar depressed patients: responses to hypoglycaemia and L-dopa, Am. J. Psychiatr. 130 (1973) 1362–1367.
[38] A. Luger, P.A. Deuster, P.W. Gold, D.L. Loriaux, G.P. Chrousos, Hormonal responses to the stress of exercise, Adv. Exp. Med. Biol. 245 (1988) 273–280.
[39] T.G. Dinan, Glucocorticoids and the genesis of depressive illness. A psychobiological model, Brit. J. Psychiatr. 164 (1994) 365–371.
[40] J.F.W. Deakin, F.G. Graeff, 5HT and mechanisms of defence, J. Psychopharmacol. 5 (1991) 305–315.
[41] W. Pitchot, C. Herrera, M. Ansseau, HPA axis dysfunction in major depression: relationship to 5-HT(1A) receptor activity, Neuropsychobiology 44 (2001) 74–77.
[42] L.H. Price, D.S. Charney, P.L. Delgado, G.R. Heninger, Serotonin function and depression: neuroendocrine and mood responses to intravenous L-tryptophan in depressed patients and healthy comparison subjects, Am. J. Psychiatr. 148 (1991) 1518–1525.
[43] M. Elovainio, L. Keltikangas-Jarvinen, L. Pulkki-Raback, et al., Cardiovascular risk in young Finns study. Depressive symptoms and C-reactive protein: the cardiovascular risk in young Finns study, Psychol. Med. 36 (2006) 797–805.
[44] E.P. Plaisance, P.W. Grandjean, Physical activity and high-sensitivity C-reactive protein, Sports Med. 36 (2006) 443–458.
[45] M.R. Graham, J.S. Baker, P. Evans, et al., Physical effects of short term rhGH administration in abstinent steroid dependency, Horm. Res. 69 (2008) 343–354.
[46] M. DiGirolamo, S. Eden, G. Enberg, et al., Specific binding of human growth hormone but not insulin-like growth factors by human adipocytes, Fed. Eur. Biochem. Soc. 205 (1986) 15–19.
[47] J. Moller, J.O.L. Jorgensen, N. Moller, et al., Expansion of extracellular volume and suppression of atrial natriuretic peptide after growth hormone administration in normal man. Metabolic effects of growth hormone in humans, J. Clin. Endocrinol. Metab. 72 (1991) 768–772.
[48] D.M. Hoffman, I. Crampton, C. Sernia, Short term growth hormone (GH) treatment of GH deficient adults increases body sodium and extracellular water, but not blood pressure, J. Clin. Endocrinol. Metab. 81 (1996) 1123–1128.
[49] M.R. Graham, J.S. Baker, P. Evans, et al., Short-term recombinant human growth hormone administration improves respiratory function in abstinent anabolic-androgenic steroid users, Growth Horm. IGF Res. 17 (2007) 328–335.
[50] A.D. Stiles, A.J. D'Ercole, The insulin-like growth factors and the lung, Am. J. Respir. Cell Mol. Biol. 2 (1990) 93–100.
[51] W. Liu, S.G. Thomas, S.L. Asa, et al., Myostatin is a skeletal muscle target of growth hormone anabolic action, J. Clin. Endocrinol. Metab. 8 (2003) 5490–5496.
[52] J. Moller, J.O. Jorgensen, N. Moller, J.S. Christiansen, J. Weeke, Effects of growth hormone administration on fuel oxidation and thyroid function in normal man, Metabolism 41 (1992) 728–731.
[53] J.G. Esposito, S.G. Thomas, L. Kingdon, S. Ezzat, Anabolic growth hormone action improves submaximal measures of physical performance in patients with HIV-associated wasting, Am. J. Physiol. Endocrinol. Metab. 289 (2005) 494–503.
[54] G.X. Chen, C.M. Han, Influence of rhGH on the prognosis of patients with severe burns a prospective multi-center clinical trial, Zhonghua Shao Shang Za Zhi 21 (2005) 347–349.
[55] B. Langley, M. Thomas, A. Bishop, M. Sharma, S. Gilmour, R. Kambadur, Myostatin inhibits myoblast differentiation by down-regulating MyoD expression, J. Biol. Chem. 277 (2002) 49831–49840.
[56] A. Eriksson, F. Kadi, C. Malm, L.E. Thornell, Skeletal muscle morphology in power-lifters with and without anabolic steroids, Histochem. Cell Biol. 124 (2005) 167–175.
[57] P.H. Sonksen, Insulin, growth hormone and sport, J. Endocrinol. 170 (2001) 13–25.
[58] J.D. Wallace, R.C. Cuneo, P.A. Lundberg, et al., Responses of markers of bone and collagen turnover to exercise, growth hormone (GH) administration and GH withdrawal in trained adult males, J. Clin. Endocrinol. Metab. 85 (2000) 124–133.