Drug Testing and Analysis

Received: 5 May 2009 Revised: 4 August 2009 Accepted: 19 August 2009 Published online in Wiley Interscience: 26 October 2009

(www.drugtestinganalysis.com) DOI 10.1002/dta.58

Is human growth hormone an ergogenic aid?

Richard I. G. Holt*

Growth hormone (GH) was first isolated from the pituitary gland in the 1940s. It is believed that athletes have been abusing GH for its anabolic and lipolytic effects since the early 1980s, at least a decade before endocrinologists began to treat adults with GH deficiency. Most of our knowledge about GH abuse is anecdotal but a number of high-profile athletes have admitted using GH. Despite its widespread abuse, there is debate about whether GH is ergogenic. Indeed most scientific studies have not shown a performance enhancing effect. This review will address why this discrepancy of opinion between athletes and scientists exists and why the author believes that the scientists are wrong. Copyright © 2009 John Wiley & Sons, Ltd.

Keywords: anabolic; clinical trial; growth hormone; lipolytic; performance

Introduction

Growth hormone (GH) is a naturally occurring endogenous peptide hormone produced by the pituitary gland. It was first isolated and purified in 1945.[1] After it was shown to promote growth in hypopituitary animals, GH was introduced in the treatment of children with hypopituitarism leading to the restoration of normal growth.[2] Later studies of hypopituitary adults with appropriate replacement of thyroid, steroid and sex steroid hormones then confirmed that GH plays a pivotal role in body composition, wellbeing, physical performance and cardiovascular health in adults as well as children.[3,4] The anabolic and lipolytic actions of GH have led to its abuse by professional sportsmen and women since the 1980s in an attempt to improve their athletic performance.[5] The use of GH has been prohibited for many years and GH appears on the World Anti-Doping Agency list of banned substances.[6] Despite its apparent widespread use in professional sport, there is little scientific evidence to support its use as an ergogenic aid.[7] This review will examine the history of GH use in sport and the physiological reasons why it has attracted the attention of athletes. Finally the review will discuss the controversy between scientists and athletes and why the author believes that the scientists are wrong and the athletes are right.

History of Doping with GH

Exactly when GH was first used as a doping agent is unknown but the earliest publication to promote its use was Dan Duchaine's *Underground Steroid Handbook,* which emerged from California in 1982, by which time GH was already well established in power lifting (Figure 1).[8] Duchaine had gained substantial knowledge of the best substances and combinations to use for optimal performance and was regarded as an expert by the body-building community. His book described GH as the 'most expensive, most fashionable and least understood of the new athletic drugs' and provided an accurate description of the actions of GH. There were some fundamental errors, however, such as the recommendation and advertisement of animal GH for use in humans. It is pertinent to note that it was nearly a decade later before endocrinologists recognized the important physiological role of GH in adults.[9,10]

Ben Johnson is perhaps the most famous athlete to have taken GH. Following his disqualification from the 100 m gold medal at the 1988 Olympic Games in Seoul, when stanazolol was detected in his urine, both he and his coach Charley Francis admitted under oath at a later hearing that he had taken human GH (hGH) in addition to anabolic steroids.[11] The Seoul Olympics were not the only games to be blighted by GH, with the 1996 Atlanta Olympic Games being termed the 'Growth Hormone Games' by some athletes!

In the fall-out from the Seoul Olympic Games doping scandal, Justice Charles Dubin led an inquiry into the abuse of drugs in sports. The 900-page report concluded that despite the tight regulations surrounding its use, GH was widely available to athletes. During the hearings several athletes, including the Canadian sprinter Angella Issanjenko, admitted to using hGH.[12]

We do not know the precise extent of GH abuse amongst sportsmen and women. The lack of a reliable test for GH has certainly hindered research in this area but as it is known that testing under-reports use, even a test would not provide the full picture. We therefore need to rely heavily on anecdotal reports.[5] A few athletes, such as Lyle Alzado, an American football player, have admitted to taking GH. In a death-bed confession, he stated that 80% of American footballers have taken GH. Although initially advocated for strength disciplines, endurance athletes are also attracted to GH's lipolytic actions and reduced fat mass; in 1998 a large quantity of GH was found in a team car at the Tour de France.

Growth-hormone use may begin as early as adolescence. In a survey of two US high schools, 5% of male students admitted to having taken GH and nearly one-third knew someone who had taken GH.[13] Most GH users reported their first use between 14 and 15 years of age and had a worryingly blasé attitude and lack of knowledge of its side effects. It is possible that this study overestimated the use of GH because a large study of NCAA athletes revealed a GH use of 1%; it is possible that many of the high-school participants were taking supplements that claimed to increase GH, rather than GH itself.

* *Correspondence to: Professor Richard I. G. Holt, IDS Building (MP887), Southampton General Hospital, Tremona Road, Southampton SO16 6YD, UK. E-mail: R. I. G. Holt@southampton.ac.uk*

Endocrinology and Metabolism Sub-Division, Developmental Origins of Health and Disease Division, School of Medicine, University of Southampton, UK

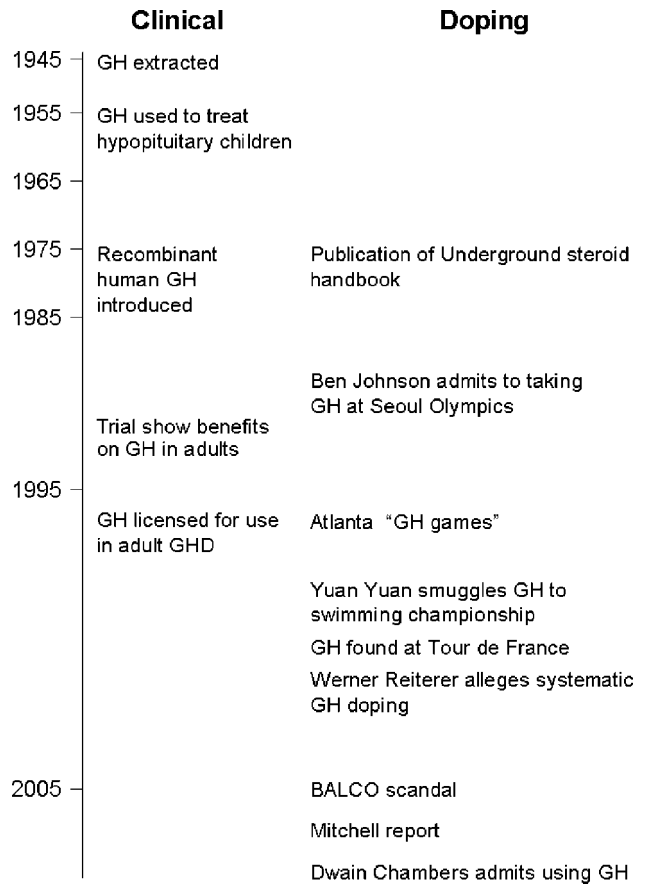

Figure 1. Time-line of GH in clinical practice and some high profile cases of abuse by professional athletes.

There are many sources of GH available to the athlete, ranging from misappropriation of GH destined for therapeutic use to targeted robberies. At the 1998 World Swimming Championships, Yuan Yuan, a Chinese swimmer, was stopped on entry into Perth with a suitcase full of GH that had been exported to China for therapeutic reasons. Six months before the Sydney Olympic Games, 1575 vials of GH were stolen from an importer's warehouse in Sydney. This is interesting in the light of the claim made by the Australian discus champion Werner Reiterer that there had been institutional and supervised use of GH prior to the Olympics. Growth hormone can be bought readily over the Internet and a recent investigation by Mathew Pinsent, ex-Olympic oarsman now working for the British Broadcasting Corporation, demonstrated that the batch he was able to purchase was pure.

Further allegations of GH abuse among other high-profile athletes appear in the controversial book *Game of Shadows,* which was written following undercover investigations by two San Francisco reporters. These include the track stars, Marion Jones and Tim Montgomery, National Football League players such as Bill Romanowski, and baseball players including Barry Bonds, Gary Sheffield and Jason Giambi.[14]

Following the raid on the Bay Area Laboratory Co-Operative (BALCO) headquarters on 3 September 2003, Victor Conte was imprisoned for four months for his role in supplying performance-enhancing drugs including GH to many high-profile American athletes including Tim Montgomery and Marion Jones and international athletes such Dwain Chambers. Tim Montgomery allegedly admitted to taking GH before a US Federal grand jury and later faced a two-year ban for doping offences while Marion Jones was later sentenced to six months' imprisonment for falsely denying administering performance-enhancing substances.[15]

These anecdotes are likely to represent the tip of the iceberg with respect to GH use. This was certainly the conclusion of Senator Mitchell's enquiry into doping in baseball in 2007, which stated that GH abuse is widespread and players had turned to GH because it is undetectable.[16]

The Actions of GH

Growth hormone has multiple metabolic and anabolic actions, which are mediated through specific GH receptors that are found on every cell of the body.[17] Growth hormone exerts most of its anabolic actions through the generation of the mitogenic polypeptide insulin-like growth factor-I.[18] The majority of circulating IGF-I is produced in the liver. As well as functioning as a hormone, IGF-I has important paracrine or autocrine actions as demonstrated by transgenic animals, in which the IGF-I gene has been selectively deleted in the liver. These animals grow normally,[19,20] albeit with the development of insulin resistance.[21,22]

Effects on Whole Body-Physiology

The physiological effects of GH are best illustrated by studies of adult GH deficiency (AGHD). In the absence of GH, lean tissue is lost and fat accumulates and waist-to-hip ratio increases correspondingly as visceral fat increases (Table 1). There is deterioration in cardiovascular health, bone mineral density, physical performance and psychological wellbeing. Exercise capacity is impaired and $VO_{2\,max}$ (aerobic capacity or the maximum ability to take in and use oxygen) is reduced.[23]

Following the administration of recombinant hGH (rhGH) to adults with GHD, the most impressive change is the normalization of body composition with an average 6 kg increase in lean body mass, mainly skeletal muscle, and a concomitant loss of fat mass.[9,10] These body composition changes are accompanied by improvements in quality of life, particularly in the area of 'increased energy' and performance enhancements.[23–25] Longer studies of GH replacement, up to 10 years, have shown that there are long-term changes in body composition and bone mineral density[26,27] and exercise performance continues to improve.[28] A recent meta-analysis of 11 randomized, placebo-controlled studies involving a total of 268 patients indicated that maximal power output, $VO_{2\,max}$ and maximum work rate all improve following GH replacement.[29]

Mechanisms to Improve Performance

Exercise requires the combustion of metabolic fuels, such as glucose for short-term high-intensity activity and free fatty acids (FFAs) for more prolonged activity, to produce kinetic energy. Oxygen delivery to muscles depends upon adequate ventilation and O_2 transport to the muscle fibres by the circulation. Thus GH may improve exercise performance through increased delivery of fuels and oxygen to exercising muscle, increased muscle strength or any combination of these factors.

Table 1. Clinical features of GH deficiency and effect of GH replacement

	Effect of GH deficiency	Effect of GH replacement
Body composition	Increased body fat	Decreased fat mass
	Increased waist: hip ratio (WHR)	Decreased WHR
	Increased visceral fat mass	Decreased visceral fat
	Decreased lean body mass	Increased lean body mass
	Decreased bone mineral density	Increased bone mineral density
Physical performance	Decreased muscle mass	Increased muscle mass
	Decreased muscle strength	Increased muscle strength
	Decreased maximal exercise performance	Increased maximal exercise performance
	Decreased maximum oxygen uptake	Increased VO_2 max, maximum power output, maximum heart rate and anaerobic threshold
	Decreased maximum heart rate	Increased red cell mass
Psychological wellbeing	Decreased ability to cope with daily life	Increased energy levels
	Increased level of perceived health problems	Increased ability to participate in physical activities without tiring
	Decreased physical and mental energy	Increased emotional reaction and social isolation scores
	Decreased concentration skills	Increased perceived quality of life
	Decreased initiative	Increased self-esteem
	Increased social isolation	Decreased sleep requirement
	Decreased self-esteem	
	Decreased sex life	
	Increased sleep requirement	
Cardiovascular system	Increased prevalence of cardiovascular events	Increased left ventricular mass
	Increased hypertension	Increased stroke volume
	Decreased left ventricular mass	Increased cardiac output and resting heart rate
	Decreased fibre shortening	Decreased diastolic blood pressure

Effects on Intermediate Metabolism

Glucose homeostasis

In healthy subjects and adults with GHD, GH increases fasting hepatic glucose output, by increasing hepatic gluconeogenesis and glycogenolysis, and decreases peripheral glucose utilization through the inhibition of glycogen synthesis and glucose oxidation.[30–34]

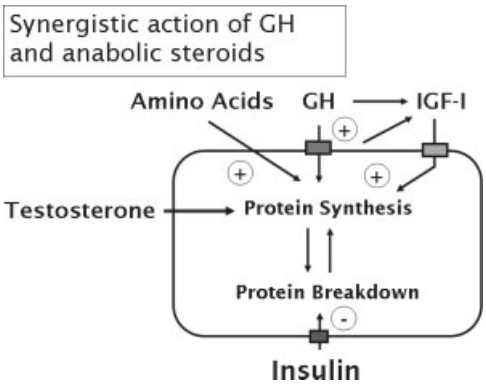

Figure 2. The synergistic action between insulin, IGF-I and GH in regulating protein synthesis. Without insulin, GH loses much (if not all) of its anabolic action. Growth hormone and IGF-I stimulate protein synthesis directly, whereas insulin is anabolic through inhibiting protein breakdown. The anabolic action of both GH and IGF-I appears to be mediated through induction of amino acid transporters in the cell membrane. It is not yet clear how much of the action of IGF-I is through locally generated IGF-I ('autocrine' and 'paracrine') or through circulating IGF-I that is largely derived from the liver.

Although this acute effect on glucose homeostasis would appear to be disadvantageous for performance, it should be remembered that long-standing AGHD is associated with insulin resistance and that any acute assessment of glucose homeostasis does not take into account changes in IGF-I which also affect insulin sensitivity by stimulating peripheral glucose uptake, glycolysis and glycogen synthesis.[35]

Lipolysis

Growth hormone directly stimulates lipolysis through activation of adenylyl cyclase followed by activation of cAMP-dependent protein kinase and hormone-sensitive lipase and indirectly by increasing the sensitivity of adipocytes to other lipolytic factors such as catecholamines.[36] Consequently GH administration to humans, either by continuous infusion or by a bolus injection, leads to increased fasting free fatty acid (FFA) concentrations with the peak effect around 2 to 3 hours after the injection.[37] In young, healthy subjects the nocturnal or exercise-induced peak of GH precedes a peak of FFAs by 2 hours.[38] During times of fasting or energy restriction, the lipolytic effect of GH is enhanced, while the effect is suppressed by co-administration of food or glucose.[39]

The action of GH of lipolysis during exercise may be particularly important. Studies of lipolysis and fatty acid turnover in GHD subjects have shown that following the discontinuation of GH, there was reduced lipolysis and fatty acid release into the circulation, which was more marked during exhaustive exercise.[40] There is also preliminary evidence that GH replacement increases whole-body fat oxidation during exercise. These studies suggest that GH has a crucial role in the delivery of free fatty acids to exercising muscle.

Protein metabolism

Protein synthesis and degradation are each regulated by multiple hormonal and nutritional factors, and protein turnover in individual tissues and the whole body is in a state of constant flux. Growth hormone and IGF-I, together with insulin, have synergistic anabolic effects on protein metabolism (Figure 2).[41]

In healthy humans, the acute administration of GH modestly stimulates muscle and whole-body protein synthesis and leads to nitrogen retention, as shown by decreased urinary excretion rates of urea, creatinine and ammonium.[42] The increase in protein synthesis occurs partly as a result of a local action of GH and partly through the generation of IGF-I, which inhibits whole-body protein breakdown and stimulates protein synthesis.[43]

Adults with GHD have reduced skeletal muscle mass and isometric muscle strength[25,44–46] while some studies suggest that there is also reduced isokinetic strength.[44,45] Following the long-term replacement of GH, muscle strength is normalized.[25,45]

In addition to the anabolic effect on skeletal muscle, GH has profound effects on bone metabolism. GH deficiency is associated with osteopaenia, which is reversed by GH replacement.[47] In addition to a direct anabolic effect on bone, GH and IGF-I may also increase intestinal calcium absorption and serum 1,25 OH_2 vitamin D concentrations.[48,49]. It has been reported that several athletes have admitted to taking GH in order to maintain bone strength and reduce the risk of stress fractures.[41]

Cardiovascular Effects

Most studies have shown that GHD adults have reduced left ventricular mass and ejection fraction. A recent meta-analysis of placebo-controlled trials of GH replacement in adults with GHD demonstrated a significant improvement in left ventricular posterior wall thickness and stroke volume.[50] GH replacement in adult GHD also increases left ventricular ejection fraction during exercise, which is necessary to provide adequate blood supply to exercising muscle.[51]

Thermoregulation

It is believed that GH has a role in the maintenance of body temperature during exercise. Body temperature is a regulator of GH secretion during exercise and impaired thermoregulation has been observed during heat exposure and exercise in untreated GHD adults.[52,53]

Effect of Growth Hormone in Healthy Adults

While it is clear that GH has significant beneficial effects in AGHD, it does not necessarily follow that the administration of supra-physiological doses of GH will lead to a performance advantage in healthy adults. Indeed acromegaly, which is usually caused by the over-secretion of GH by a pituitary adenoma, provides evidence of the opposite. Acromegaly is not associated with athletic prowess but is characterized by marked abnormalities in protein and carbohydrate metabolism[54,55] and is usually associated with muscle weakness rather than excessive strength.[56] Protein remodelling in longstanding acromegaly is abnormal in most organ systems, including skeletal muscle,[57] resulting in tissue disorganization and functional impairment and in some cases cardiomyopathy.

This argument has been used by some scientists against a performance benefit for GH. It needs to be appreciated, however, that acromegaly often remains undiagnosed for many years and the clinical presentation at diagnosis may not reflect earlier stages of the disease. By the time of diagnosis there has usually been prolonged, massive GH excess, which is often accompanied by deficiencies of other pituitary hormones, such as ACTH.

As is seen in many biological systems, the response to GH may follow a 'Starling's curve', where increasing GH leads to an improved performance until a point where this starts to decline. Consequently prolonged acromegaly may tell us little about the effects of lesser GH excess earlier in the natural history of the illness. Often patients will give a history of increased strength in the first few years of their condition if questioned carefully. The case history of an elite rower who competed during the early stages of his acromegaly is illuminating in this regard. Not only was he one of the strongest crew but he could also tolerate harder training sessions than his colleagues and recovered more quickly afterwards.[58] Although only a clinical anecdote, it illustrates that the timing and degree of GH excess are important for its physiological and pathological effect.

Effect of GH in the Elderly

Growth hormone secretion falls by around 14% per decade during adulthood.[59] As such, more than 30% of elderly people have circulating IGF-I levels below the normal range in young adults. This age-related decline in GH, together with a similar fall in testosterone secretion, may contribute to the detrimental aspects of ageing and has led to an interest in providing GH replacement to older individuals.[60]

Although several intervention trials have shown that either GH or testosterone individually can have anabolic effects in older adults, this has not always translated into functional improvements.[61] One of the first randomized controlled studies to demonstrate a performance benefit in healthy elderly adults was undertaken by Giannoulis and colleagues.[62] In this study, lean body mass increased with GH but exercise capacity was only improved when GH was combined with testosterone.

Effect of GH in Healthy Young Adults

The effects in elderly adults cannot necessarily be extrapolated to young adults because of the major differences in GH secretion between young and old. In addition to the overall fall in GH secretion, described above, the GH response to exercise is diminished in the elderly.[63]

Most studies in normal young healthy subjects have failed to demonstrate an appreciable acute effect of physiological GH secretion in response to exercise. In one exercise study, neither glucose oxidation nor fat oxidation was influenced by exercise induced GH secretion. Furthermore when GH secretion was suppressed by the somatostatin analogue, octreotide, there was no effect on glucose, glycerol or free fatty acids during 30 minutes of exercise at 70% of VO_2 max and 90 minutes of recovery.[64]

By contrast, administration of supraphysiological doses of GH to normal young subjects increases resting insulin secretion, lipolysis, fatty acid availability and fat oxidation, and reduces glucose uptake into skeletal muscle.[39,65] During moderate- to high-intensity exercise, plasma levels of glucose, glycerol, FFA and lactate were all greater following the prior administration of a single dose (7.5 IU (2.5 mg)) of recombinant human GH.[66]

Longer term administration of GH (0.2 U/kg.day) also affects intermediate metabolism. Healthy subjects, who had received four weeks of recombinant human GH, had increased lipolysis and FFA at rest, during and after submaximal exercise.[67] Although GH did

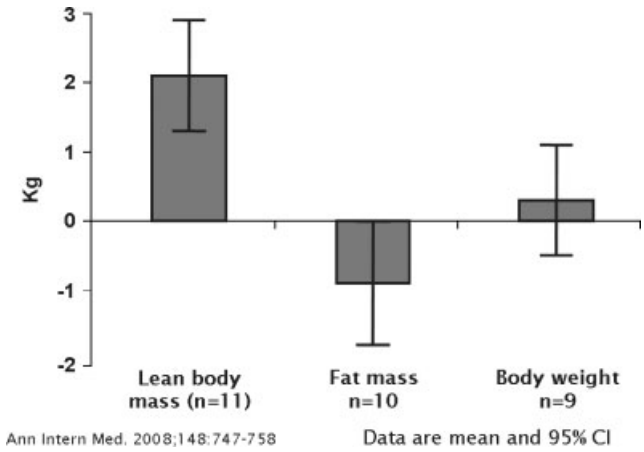

Figure 3. Change in body composition in up to 11 clinical trials in healthy adults. Data are mean ±95% confidence intervals. N refers to the number of trials included in the meta-analysis. Data are from *Ann. Intern. Med.* **2008**; ***148***-(10): 747–758.[69]

not influence glucose turnover at rest there was an increased rate of glucose production and uptake during and following exercise.

In addition to the effect on glucose and lipid metabolism, supraphysiological GH administration to young healthy adults may also affect protein metabolism. Some studies have identified increases in whole-body protein turnover and muscle protein synthesis but the results have varied between studies of athletic and non-athletic subjects and are dependent on whether the studies were conducted at rest or during exercise.[68]

Overall it appears that GH administration increases lean body mass in young normal or trained subjects, although to what extent this reflects total body water increased rather than muscle protein is not fully known. These studies, however, have not shown that the changes in intermediate metabolism and body composition translate into performance benefits. A recent systematic review of 44 articles describing 27 study samples addressed this question.[69] Three-hundred-and-three participants, aged 27 ± 3 years and with body mass index of 24 ± 2 kg/m^2 were included. As assessed by VO_2 max, they were physically fit and received 36 ± 21 μg/kg of growth hormone per day. These doses are similar to doses used to treat GH deficiency in clinical adult endocrinology practice but are thought to be lower than the doses used by athletes.[70] Although the review confirmed that GH increases lean body mass and decreases fat mass (Figure 3), it failed to find any change in respiratory quotient, VO_2 max, bicycling speed, power output, energy expenditure or strength.

The first study to demonstrate a performance benefit for GH in young adults was a single-blind study of six days' rhGH administration in a cohort of ex-anabolic steroid abusers.[71] Subjects were only included if they had been abstinent from any drug use for 12 weeks, as confirmed by a urinalysis drug screen performed at a World Anti-Doping Agency accredited laboratory. As well as body composition changes, strength and peak power output significantly increased. It is important to consider why this study succeeded in demonstrating a change in VO_2 max and power output, where others have not. Unlike previous studies, the investigators controlled for historical and current training regimens and the men were familiar with the training before and during the study, having undertaken previous work with the group. It is also important that the study used a model of steroid-withdrawn athletes who may be in a metabolic state that makes them particularly sensitive to the anabolic actions of GH. Finally there is no doubt about compliance as all injections were supervised.

Why the Athletes are One Step Ahead of the Scientists

Most scientists regard randomized controlled trials (RCT) as the gold standard for determining cause and effect. These trials try to eliminate bias and other confounding factors by randomly allocating different treatments (in this case GH) to subjects to ensure that any confounders are equally distributed between treatment groups. Ideally RCTs include a placebo arm where one group of individuals receives an inactive agent and the participants and investigators should be blinded to the intervention.

This approach may be appropriate for clinical interventions where the results of the trial need to be extrapolated to a wider group of patients but it may not be the best way of determining whether GH has a performance benefit in elite athletes. Most RCTs are designed to have the power to examine differences of 20–30% as this constitutes a clinically meaningful outcome. By contrast, the winning margins in sport are considerably smaller where a performance benefit of less than 1% may determine whether an individual wins a gold medal or not. As an example, the winning margin in the Coxless fours at 2004 Olympic Games in Athens was 0.08 s or 0.02% of the race time. As such most clinical trials will not have the power to detect such small differences.

A further problem with clinical trials is that they are designed to test one or at most two interventions. Growth hormone is frequently used by athletes in combination with insulin and anabolic steroids in varying concentrations during differing training and dietary regimens. It is impossible to control for all these variables within a single trial and therefore it seems likely that the athletes using the 'n = 1' design are in a better position to address the question whether GH is performance enhancing. This approach was certainly used effectively by coaches from the former German Democratic Republic.[72] The importance of synergism between different agents has been alluded to in the previous section where it is notable that the only study to demonstrate a performance benefit for GH was in a group of abstinent steroid users.[71]

Clinical trials are rightly highly regulated and a prime concern is to ensure the safety of the participants and as a result relatively low doses of GH have been used. Long-term safety appears to concern athletes less and anecdotal reports suggest that the doses are up to tenfold higher than those used in clinical trials.[70] While the lower doses used in clinical studies may affect the power of the study to detect a benefit for GH, the higher dose may place the athletes at risk of diabetes, hypertension, cardiomyopathy and possibly cancer.[5]

These issues question the suitability of the RCT to determine the effect of GH on performance in elite athletes and lead to the conclusion that the athletes are probably right, although a definitive answer to this question may never be found, not least because of the ethical considerations. Consequently it is likely that the debate will continue; it is salient, however, to reflect on the similar arguments about anabolic steroids that occurred over 20 years ago. Several articles and reviews were written at that time commenting on the lack of scientific proof for the benefit of anabolic steroids.[73,74] At the same time, East German coaches using the n = 1 approach demonstrated the marked performance benefits with anabolic steroids.[72] The effectiveness of steroids is

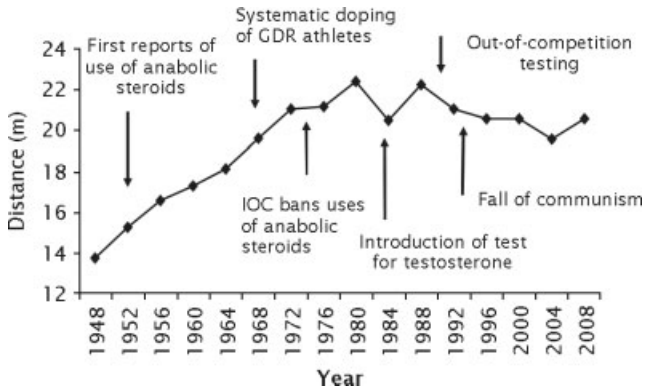

Figure 4. Winning distance of the women's Olympic shotput with relevant information about the abuse of anabolic steroids by athletes.

further demonstrated by the Olympic record for the women's shot-put that was set in 1980 (Figure 4). By contrast, the winning throw in Beijing would not have made the final in 1980. Subsequently the performance benefit of steroids has been proven but the athletes arrived at that conclusion first!

Conclusion

It is widely believed that athletes are abusing GH for its anabolic and lipolytic effects. There is little convincing scientific evidence that GH provides a performance benefit but it should be remembered that absence of evidence is not evidence of absence.

Acknowledgements

The author is the principal investigator of the GH-2004 study, the aim of which is to develop a test to detect GH abuse in sport. The GH-2000 study is funded by the World Anti-Doping Agency and US Anti-Doping Agency.

References

[1] C. H. Li, H. M. Evans, M. E. Simpson, *J. Biol. Chem.* **1945**, *159*, 353.
[2] M. S. Raben, *N. Engl. J. Med.* **1962**, *266*, 82.
[3] R. C. Cuneo, F. Salomon, G. A. McGauley, P. H. Sonksen, *Clin. Endocrinol.* **1992**, *37*(5), 387.
[4] P. V. Carroll, E. R. Christ, P. H. Sonksen, *Trends Endocrinol. Metab.* **2000**, *11*(6), 231.
[5] R. I. Holt, P. H. Sonksen, *Br. J. Pharmacol.* **2008**, *154*(3), 542.
[6] World Anti-Doping Agency, The World Anti-Doping Code – The 2008 Prohibited List International Standard, http://www.wada-ama.org/rtecontent/document/2008_List_En.pdf. **2008**, accessed 4 August 2009.
[7] M. J. Rennie, *Br. J. Sports Med.*, **2003**, *37*(2), 100.
[8] D. Duchaine, *Underground Steroid Handbook,* HLR Technical Books: Venice CA, **1982**.
[9] J. O. Jorgensen, S. A. Pedersen, L. Thuesen, J. Jorgensen, T. Ingemann-Hansen, N. E. Skakkebaek, J. S. Christiansen, *Lancet* **1989**, *1*(8649), 1221.
[10] F. Salomon, R. C. Cuneo, R. Hesp, P. H. Sonksen, *N. Engl. J. Med.* **1989**, *321*(26), 1797.
[11] D. Mackay, How HGH cheats hit the end of the line, *Guardian,* Wednesday 28 July 2004.
[12] C. J. Dubin, *Commision of Inquiry into the Use of Drugs and Banned Practices Intended to Increase Athletic Performance,* Canadian Publishing Center: Ottawa, **1990**.
[13] V. I. Rickert, C. Pawlak-Morello, V. Sheppard, M. S. Jay, *Clin. Pediatr.* **1992**, *31*(12), 723.
[14] M. Fainaru-Wada, L. Williams, *Game of Shadows: Barry Bonds, Balco, and the Steroids Scandal That Rocked Professional Sports,* Gotham Books: New York, **2006**.
[15] M. Fainaru-Wada, L. Williams, Sprinter admitted use of BALCO 'magic potion' November testimony to federal grand jury contradicts record-holder's public denials, *San Francisco Chronicle,* Thursday 24 June 2004.
[16] 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, http://files.mlb.com/mitchrpt.pdf, accessed 4 August 2009.
[17] R. I. G. Holt, *CME Bull. Endocrinol. and Diabetes* **2004**, *5*(1), 11.
[18] D. Le Roith, C. Bondy, S. Yakar, J. L. Liu, A. Butler, *Endocr. Rev.* **2001**, *22*(1), 53.
[19] K. Sjogren, J. L. Liu, K. Blad, S. Skrtic, O. Vidal, V. Wallenius, D. LeRoith, J. Tornell, O. G. Isaksson, J. O. Jansson, C. Ohlsson, *Proc. Natl. Acad. Sci. USA* **1999**, *96*(12), 7088.
[20] S. Yakar, J. L. Liu, B. Stannard, A. Butler, D. Accili, B. Sauer, D. LeRoith, *Proc. Natl. Acad. Sci. USA* **1999**, *96*(13), 7324.
[21] K. Sjogren, K. Wallenius, J. L. Liu, Y. M. Bohlooly, G. Pacini, L. Svensson, J. Tornell, O. G. Isaksson, B. Ahren, J. O. Jansson, C. Ohlsson, *Diabetes* **2001**, *50*(7), 1539.
[22] S. Yakar, J. L. Liu, A. M. Fernandez, Y. Wu, A. V. Schally, J. Frystyk, S. D. Chernausek, W. Mejia, D. LeRoith, *Diabetes* **2001**, *50*(5), 1110.
[23] R. C. Cuneo, F. Salomon, C. M. Wiles, R. Hesp, P. H. Sonksen, *J. Appl. Physiol.* **1991**, *70*(2), 695.
[24] G. A. McGauley, R. C. Cuneo, F. Salomon, P. H. Sonksen, *Horm. Res.* **1990**, *33*(Suppl 4), 52.
[25] R. C. Cuneo, F. Salomon, C. M. Wiles, R. Hesp, P. H. Sonksen, *J. Appl. Physiol.* **1991**, *70*(2), 688.
[26] G. Gotherstrom, B. A. Bengtsson, I. Bosaeus, G. Johannsson, J. A. Svensson, *J. Clin. Endocrinol. Metab.* **2007**, *92*(4), 1442.
[27] G. Gotherstrom, B. A. Bengtsson, I. Bosaeus, G. Johannsson, J. Svensson, *Eur. J. Endocrinol.* **2007**, *156*(1), 55.
[28] J. O. Jorgensen, L. Thuesen, J. Muller, P. Ovesen, N. E. Skakkebaek, J. S. Christiansen, *Eur. J. Endocrinol.* **1994**, *130*(3), 224.
[29] W. M. Widdowson, J. Gibney, *J. Clin. Endocrinol. Metab.* **2008**, *93*(11), 4413.
[30] J. F. Bak, N. Moller, O. Schmitz, *Am. J. Physiol.* **1991**, *260*(5 Pt 1), 736.
[31] J. Fowelin, S. Attvall, H. von Schenck, U. Smith, I. Lager, *Diabetologia* **1991**, *34*(7), 500.
[32] J. Fowelin, S. Attvall, I. Lager, B. A. Bengtsson, *Metab. Clin. Expt.* **1993**, *42*(11), 1443.
[33] J. Fowelin, S. Attvall, H. von Schenck, U. Smith, I. Lager, *Diabet. Med.* **1995**, *12*(11), 990.
[34] W. V. Tamborlane, R. S. Sherwin, V. Koivisto, R. Hendler, M. Genel, P. Felig, *Diabetes* **1979**, *28*(8), 785.
[35] F. Salomon, R. C. Cuneo, A. M. Umpleby, P. H. Sonksen, *Clin. Sci.* **1994**, *87*(2), 201.
[36] R. G. Yip, H. M. Goodman, *Endocrinol.* **1999**, *140*(3), 1219.
[37] T. K. Hansen, *Growth Horm. IGF Res.* **2002**, *12*(5), 342.
[38] N. Moller, J. O. Jorgensen, J. Moller, L. Orskov, P. Ovesen, O. Schmitz, J. S. Christiansen, H. Orskov, *Metab. Clin. Expt.* **1995**, *44*(10 Suppl 4), 33.
[39] N. Moller, J. Gjedsted, L. Gormsen, J. Fuglsang, C. Djurhuus, *Growth Horm. IGF Res.* **2003**, *13*(Suppl A), S18–S21.
[40] J. Gibney, M. L. Healy, M. Stolinski, S. B. Bowes, C. Pentecost, L. Breen, C. McMillan, D. L. Russell-Jones, P. H. Sonksen, A. M. Umpleby, *J. Clin. Endocrinol. Metab.* **2003**, *88*(4), 1792.
[41] P. H. Sonksen, *J. Endocrinol.* **2001**, *170*(1), 13.
[42] D. A. Fryburg, R. A. Gelfand, E. J. Barrett, *Am. J. Physiol.* **1991**, *260*(3 Pt 1), 499.
[43] D. A. Fryburg, *Am. J. Physiol.* **1994**, *267*(2 Pt 1), 331.
[44] Y. J. Janssen, J. Doornbos, F. Roelfsema, *J. Clin. Endocrinol. Metab.* **1999**, *84*(1), 279.
[45] G. Johannsson, G. Grimby, K. S. Sunnerhagen, B. A. Bengtsson, *J. Clin. Endocrinol. Metab.* **1997**, *82*(9), 2877.
[46] O. M. Rutherford, S. A. Beshyah, J. Schott, Y. Watkins, D. G. Johnston, *Clin. Sci.* **1995**, *88*(1), 67.
[47] J. M. Gomez, N. Gomez, J. Fiter, J. Soler, *Horm. Metab. Res.* **2000**, *32*(2), 66.
[48] B. Lund, P. C. Eskildsen, A. W. Norman, O. H. Sorensen, *Acta Endocrinol.* **1981**, *96*(4), 444.

[49] S. Burstein, I. W. Chen, R. C. Tsang, *J. Clin. Endocrinol. Metab.* **1983**, *56*(6), 1246.
[50] P. Maison, P. Chanson, *Circulation* **2003**, *108*(21), 2648.
[51] A. Colao, P. Marzullo, C. Di Somma, G. Lombardi, *Clin. Endocrinol.* **2001**, *54*(2), 137.
[52] A. Wheldon, R. L. Savine, P. H. Sonksen, R. I. Holt, *Growth Horm. IGF Res.* **2006**, *16*(2), 125.
[53] A. Juul, N. Hjortskov, L. T. Jepsen, B. Nielsen, J. Halkjaer-Kristensen, N. Vahl, J. O. Jorgensen, J. S. Christiansen, N. E. Skakkebaek, *J. Clin. Endocrinol. Metab.* **1995**, *80*(11), 3335.
[54] A. Colao, R. Baldelli, P. Marzullo, E. Ferretti, D. Ferone, P. Gargiulo, M. Petretta, G. Tamburrano, G. Lombardi, A. Liuzzi, *J. Clin. Endocrinol. Metab.* **2000**, *85*(1), 193.
[55] S. Ezzat, M. J. Forster, P. Berchtold, D. A. Redelmeier, V. Boerlin, A. G. Harris, *Medicine (Baltimore)* **1994**, *73*(5), 233.
[56] T. L. McNab, *Endocr. Pract.* **2005**, *11*(1), 18.
[57] M. Nagulesparen, R. Trickey, M. J. Davies, J. S. Jenkins, *Br. Med. J.* **1976**, *2*(6041), 914.
[58] R. Sharp, *Growth Horm. IGF Res.* **2009**, *19*(4), 291.
[59] A. A. Toogood, *Horm. Res.* **2003**, *60*(Suppl 1), 105.
[60] R. Savine, P. Sonksen, *Horm. Res.* **2000**, *53*(Suppl 3), 37.
[61] H. Liu, D. M. Bravata, I. Olkin, S. Nayak, B. Roberts, A. M. Garber, A. R. Hoffman, *Ann. Intern. Med.* **2007**, *146*(2), 104.
[62] M. G. Giannoulis, P. H. Sonksen, M. Umpleby, L. Breen, C. Pentecost, M. Whyte, C. V. McMillan, C. Bradley, F. C. Martin *J. Clin. Endocrinol. Metab.* **2006**, *91*(2), 477.
[63] R. I. Holt, E. Webb, C. Pentecost, P. H. Sonksen, *J. Clin. Endocrinol. Metab.* **2001**, *86*(12), 5715.
[64] R. J. Chalmers, S. R. Bloom, G. Duncan, R. H. Johnson, W. R. Sulaiman, *Clin. Endocrinol.* **1979**, *10*(5), 451.
[65] K. C. Copeland, K. S. Nair, *J. Clin. Endocrinol. Metab.* **1994**, *78*(5), 1040.
[66] K. H. Lange, B. Larsson, A. Flyvbjerg, R. Dall, M. Bennekou, M. H. Rasmussen, H. Ørskov, M. Kjaer, *J. Clin. Endocrinol. Metab.* **2002**, *87*(11), 4966.
[67] M. L. Healy, J. Gibney, C. Pentecost, P. Croos, D. L. Russell-Jones, P. H. Sonksen, A. M. Umpleby, *J. Clin. Endocrinol. Metab.* **2006**, *91*(1), 320.
[68] M. W. Widdowson, M. L. Healy, P. H. Sonksen, J. Gibney, *Growth Horm. IGF Res.* **2009**, *19*(4), 308.
[69] H. Liu, D. M. Bravata, I. Olkin, A. Friedlander, V. Liu, B. Roberts, E. Bendavid, O. Saynina, S. R. Salpeter, A. M. Garber, A. R. Hoffman, *Ann. Intern. Med.* **2008**, *148*(10), 747.
[70] M. Saugy, N. Robinson, C. Saudan, N. Baume, L. Avois, P. Mangin, *Br. J. Sports Med.* **2006**, (40 Suppl 1), i35–i39.
[71] M. R. Graham, J. S. Baker, P. Evans, A. Kicman, D. Cowan, D. Hullin, N. Thomas, B. Davies, *Horm. Res.* **2008**, *69*(6), 343.
[72] W. W. Franke, B. Berendonk, *Clin. Chem.* **1997**, *43*(7), 1262.
[73] E. C. Percy, *Can. Med. Assoc. J.* **1977**, *117*(6), 601.
[74] H. A. Haupt, G. D. Rovere, *Am. J. Sports Med.* **1984**, *12*(6), 469.