

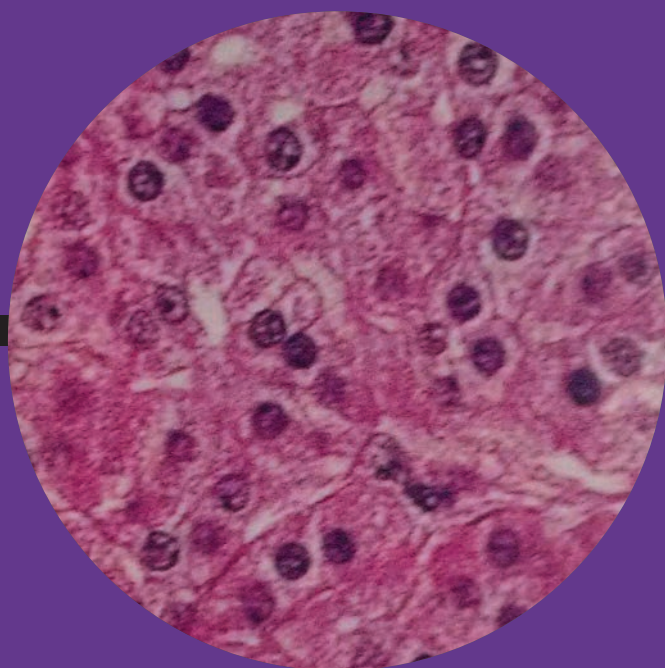


2013 / Vol 17 / Supplement 1 (ESICON 2013, Bhopal)

Indian Journal of Endocrinology and Metabolism

Official Publication of The Endocrine Society of India

www.ijem.in



Detecting growth hormone misuse in athletes

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ABSTRACT

Athletes have been misusing growth hormone (GH) for its anabolic and metabolic effects since the early 1980s, at least a decade before endocrinologists began to treat adults with GH deficiency. Although there is an ongoing debate about whether GH is performance enhancing, recent studies suggest that GH improves strength and sprint capacity, particularly when combined with anabolic steroids. The detection of GH misuse is challenging because it is an endogenous hormone. Two approaches have been developed to detect GH misuse; the first is based on the measurement of pituitary GH isoforms and the ratio of 22-kDa isoform to total GH. The second is based on the measurement of insulin like growth factor-I (IGF-I) and N-terminal propeptide of type III procollagen (P-III-NP) which increase in a dose-dependent manner in response to GH administration. Both methodologies have been approved by the World Anti-Doping Agency (WADA) and have led to the detection of a number of athletes misusing GH.

Key words: Athletes, clinical trial, discriminant function, growth hormone, IGF-I, misuse, performance, P-III-NP

INTRODUCTION

Growth hormone (GH) is secreted by the anterior pituitary gland and plays an important role in maintaining body composition, well-being, physical performance, and cardiovascular health in adults as well as children.^[1,2] These features have led to its misuse by professional sportsmen and women who wish to improve their athletic performance.^[3] GH use was prohibited by the International Olympic Committee (IOC) in 1989 and it appears on the current World Anti-Doping Agency (WADA) list of prohibited substances.^[4] The true prevalence of GH misuse is unknown because of the secrecy that surrounds its misuse but there are sufficient high profile cases to suggest that the scale of misuse warrants the concern of WADA. It is unclear when GH was first used to enhance performance but “The Underground Steroid Handbook” was the earliest publication to describe the potential beneficial effects of

GH,^[5] at least 10 years before clinical endocrinologists started treating adults with GH deficiency.^[6,7]

This review will examine whether GH is performance enhancing properties and will discuss the challenges involved in the detection of exogenous GH administration and the work undertaken to develop a robust test to detect its misuse.

WHY ATHLETES MISUSE GH?

Exercise depends on an adequate supply of nutrients and oxygen to the muscle fibers. Glucose for short-term high-intensity activity and free fatty acids (FFAs) for more prolonged activity are combusted to release kinetic energy. GH has a number of effects on protein anabolism and intermediate metabolism that may improve exercise performance through increased fuel and oxygen delivery to exercising muscle, increased muscle strength or any combination of these factors.^[8] In addition, it may improve cardiovascular function^[9,10] and thermoregulation.^[11]

The potent physiological actions of GH have been demonstrated through a series of randomized controlled trials of GH replacement in people with GH deficiency. Prior to treatment, adults with GH deficiency lose lean tissue while accumulating fat, in particular visceral fat.^[12,13]

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10.4103/2230-8210.119494

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Skeletal muscle mass and strength^[14-16] is reduced with a consequent impairment of physical performance, exercise capacity, and VO_2 max (aerobic capacity or the maximum ability to take in and use oxygen).^[17] Following treatment with recombinant human GH (rhGH), body composition normalizes^[6,7] and physical performance improves.^[18]

It does not necessarily follow, however, that the administration of supraphysiological GH doses will lead to further performance advantage in healthy adults. Indeed the opposite is suggested by acromegaly, which is characterized by marked abnormalities in protein and carbohydrate metabolism,^[19,20] muscle weakness rather than excessive strength,^[21] and cardiomyopathy.^[22] A systematic review of 44 articles describing 27 studies reported that although GH administration was associated with increase in lean body mass and decrease in fat mass, it did not improve a number of measures of performance.^[23]

Most recently trials have begun to show a performance benefit for GH. The first was undertaken in abstinent anabolic steroid users and demonstrated significant improvements in strength, peak power output, and VO_2 max as well as the expected changes in body composition.^[24] It is possible that the prior use of steroids may have rendered the athletes particularly sensitive to the anabolic actions of GH. A further randomized, placebo-controlled trial of 6-weeks' treatment with rhGH demonstrated a short-lived improvement in sprint capacity in both men and women with GH and a synergistic effect with testosterone in men.^[25]

POTENTIAL ADVERSE EFFECTS OF GH MISUSE

The side effects associated with GH administration in GH deficiency are well-documented and may affect any athlete receiving GH;^[26] however, as anecdotal evidence suggests that many athletes are taking much higher doses than those used therapeutically, it is possible that features of acromegaly may become apparent with prolonged use. Additional long-term effects may include fluid retention, which may lead to ankle swelling, hypertension, headache, diabetes, and cardiomyopathy. There is also a potential for increased risk of certain cancers; including colorectal, thyroid, breast, and prostate cancer.^[27] Cadaveric GH, with its attendant risk of the prion-induced Creutzfeldt-Jakob disease, is still available in the black market.^[28]

CHALLENGES IN THE DETECTION OF GH MISUSE

Detecting the misuse of exogenous GH poses a formidable challenge for several reasons.^[3] rhGH has an identical amino

acid sequence to the native 22-kDa isoform of the hormone, while cadaveric GH is indistinguishable from endogenous GH. It has a short half-life (<20 min) and is secreted in a pulsatile manner leading to widely varying circulating GH concentration throughout the day. Exercise and stress are potent stimulators of GH secretion^[29,30] and so high GH concentrations in the post-competition setting would be expected.

DEVELOPMENT OF A TEST TO DETECT GH MISUSE

Two different yet complementary approaches have been investigated to detect GH misuse; the first, pioneered by Christian Strasburger, Martin Bidlingmaier and Zida Wu in Germany, is based on the detection of different pituitary GH isoforms, while the second, which was developed by the GH-2000 and GH-2004 teams, utilizes the measurement of GH-sensitive markers.

THE ISOFORM METHOD

Endogenous pituitary GH occurs in multiple isoforms of which 70% is in the form of a 22 kDa polypeptide.^[31] By contrast, rhGH comprises solely the 22-kDa isoform. When rhGH is administered, endogenous pituitary secretion is downregulated through negative feedback and the concentration of non-22-kDa isoforms is suppressed. The isoform method relies on the measurement of the ratio of 22 kDa GH to total GH.^[32]

The proportions of GH isoforms are unaffected by age, sex, sporting discipline, and pathological states,^[33,34] but exercise causes a transient relative increase in the 22-kDa isoform, thereby reducing the sensitivity of the test if samples are taken immediately after competition.^[35,36] This method was introduced prior to the 2004 Athens Olympic Games and subsequently improved when the assays used for the method were commercialized.^[37]

After testing over 1,000 samples, the first adverse analytical finding came in February 2010 when the British Rugby League player, Terry Newton, tested positive.^[38] Since then, several other positive tests have been reported including the announcement in September 2010 from the Canadian Center for Ethics in Sport that Matt Socholotuk, a University of Waterloo football player, had tested positive for GH use on 31 March 2010.^[39] The following year, Colorado Sky Sox first baseman Mike Jacobs became the first baseball player to test positive for GH and was subsequently suspended for 50 games by Minor League Baseball.^[40]

In 2011, Andrus Veerpalu, an Estonian Olympic gold medal winning skier, tested positive for GH. However, he

pleaded his innocence and challenged the laboratory finding in the Court of Arbitration for Sport who subsequently acquitted Veerpalu on 25 March 2013 as the court was not convinced that the threshold for considering an adverse analytical finding was sufficiently reliable to uphold the doping conviction; nevertheless, the court stated “that there are many factors in this case which tend to indicate that the Athlete did in fact himself administer exogenous hGH”.^[41]

The Achilles’ heel of the isoform method is its short window of detection.^[42] Recombinant GH, even when injected subcutaneously, is cleared rapidly and GH is frequently undetectable in a blood sample taken the morning after an injection,^[43] while spontaneous GH secretion returns to normal within 48 h of the last dose of rhGH.^[44] Consequently, any athlete who ceases GH several days prior to a competition will not be detected. As such, the optimal use of this method is likely to be in unannounced ‘out of competition’ testing, as happened in the case of Terry Newton. A further disadvantage of this method is that it will not detect the use of cadaveric GH or GH secretagogues as these do not alter the isoform profile.

THE GH-2000 MARKER METHOD

The GH-2000 marker method measures two serum proteins, insulin-like growth factor-I (IGF-I) and N-terminal propeptide of type III procollagen (P-III-NP), both of which increase in a dose-dependent manner in response to GH administration and therefore act as “markers” of GH administration. This method was first conceived by Peter Sönksen who established the large multicenter GH-2000 project, with funding from the European Union under their BIOMED 2 initiative, the International Olympic Committee and GH manufacturers Novo Nordisk and Pharmacia. Initially, 25 potential markers of GH action were considered;^[45,46] but IGF-I and P-III-NP were chosen for the GH-2000 test because these provided the best discrimination between individuals receiving GH or placebo during a 28-day randomized controlled GH administration trial.^[47] Both IGF-I and P-III-NP have little diurnal or day-to-day variation, low intraindividual variation^[48] and only change minimally in response to exercise.^[45,46] The markers are used in conjunction with the use of gender specific equations, “discriminant functions”, to improve the sensitivity and specificity of the test compared with single-marker analysis [Table 1].^[47] The markers decline with age as endogenous GH secretion declines and a factor relating to the inverse of age is also included in the formulae.^[49]

Although the principle of the method was approved at an IOC workshop in Rome in March 1999,^[50] further work has been needed to ensure that a number of confounding

Table 1: GH-2000 discriminant function equations

Male score

$$-6.586 + 2.905 \cdot \log(\text{P-III-NP}) + 2.100 \cdot \log(\text{IGF-I}) - 101.737 / \text{age}$$

Female score

$$-8.459 + 2.454 \cdot \log(\text{P-III-NP}) + 2.195 \cdot \log(\text{IGF-I}) - 73.666 / \text{age}$$

GH: Growth hormone, P-III-NP: N-terminal propeptide of type III procollagen, IGF: Insulin-like growth factor, Log: Natural logarithm

factors including ethnicity,^[51,52] injury,^[53] sporting discipline,^[49,54] exercise,^[45,46,55] and body habitus^[49,54] would not invalidate the test. The test has subsequently been validated in independent laboratories in Germany^[56] and Australia.^[57]

Although IGF-I and P-III-NP are more stable than GH, the markers still exhibit a wide interindividual variability that could mean that those with lower baseline marker concentrations are potentially harder to catch. Within individuals, however, there is much less variability which raises the possibility of the use of a biological “athlete passport” or “profiling” to improve the test sensitivity.^[48]

The test was introduced at the London Olympic and Paralympic games which led to the disqualification of Nikolay Marfin and Vadim Rakitin, two Russian powerlifters, who admitted to misusing GH after an adverse analytical finding.^[58]

CONCLUSION

It is widely believed that athletes are misusing GH for its anabolic and metabolic effects. Recent studies suggest that GH has a modest performance benefit in amateur athletes, particularly when combined with anabolic steroids. Over the last decade, there have been major advances in methodologies to detect GH and this should mean that athletes will no longer be able to take GH with impunity.

ACKNOWLEDGEMENTS

The author is the co-principal investigator of the GH-2004 project which is funded by the World Anti-Doping Agency, United States Anti-Doping Agency, and Partnership for Clean Competition. I would like to acknowledge the rest of the GH-2004 team and support from UK Anti-Doping. I would like to thank all the athletes, both amateur and professional, who volunteered to take part in the GH-2000 and GH-2004 studies. I thank the nurses of the Wellcome Trust Clinical Research Facility and medical students at the University of Southampton for their assistance in recruitment and follow-up of the GH-2004 subjects. The GH-2004 team is indebted to the GH-2000 team who left us a legacy of invaluable samples.

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Cite this article as: Holt RI. Detecting growth hormone misuse in athletes. *Indian J Endocr Metab* 2013;17:S18-22.

Source of Support: World Anti-Doping Agency, United States Anti-Doping Agency, and Partnership for Clean Competition, **Conflict of Interest:** None declared.