

(www.drugtestinganalysis.com) DOI 10.1002/dta.95

Growth hormone: barriers to the implementation of human growth hormone testing in sport



In this issue Journals Editor Paul Trevorrow hosts DTA's Editor in Chief, Professor Mario Thevis and Dr Gary Green, Guest Editor of this special issue dedicated to the implications of human growth hormone (hGH) use and testing in sports. The following interview is a fully citable transcript from the Podcast published by *Drug Testing and Analysis* available at <http://specandsepnw.libsyn.com/>

Publicity over human growth hormone has lead a lot of scientists who are not traditionally in the drug testing field to apply some of their technologies to this problem

Why is there so much interest amongst athletes for hGH?

It appears that for hundreds of years people have been looking for a "fountain of youth" drug. hGH is the latest in a long line of substances that fits the bill. We have seen the proliferation of anti-aging clinics across the United States (and probably over the world), if you search for 'Buy Human Growth Hormone' on the internet you will obtain hundreds if not thousands of web-sites willing to sell these substances.

There has been a lot of hype about hGH, it certainly seems to be very difficult to regulate and according to Dr Perl's Perspective article^[1] selling growth hormone is more lucrative than selling cocaine! It has become a very lucrative industry and I have personally reviewed hundreds of patient files from doctors illegally prescribing the drug. It is a bleak picture to see so many physicians prescribing hGH mainly for profit with very little motivation in terms of helping patients.

It is hoped that by bringing this issue to light through journal articles and through the media that increased pressure can bring these illegal operations to be shut down or better regulated. Unfortunately, it is the public that are at most risk from the adverse effects of the illegal prescription of hGH.

Does hGH increase athletic performance when given alone?

Athletes will frequently take substances in combination with other drugs or in very high doses and it is not ethical to perform placebo controlled research at the doses that athletes use. As a result we are left with anecdotal reports and interviews with athletes regarding its use. It does seem that athletes think that it works. We have reports of athletes using it alone and in combination with anabolic steroids.



We also have the proliferation in the US of anti-aging clinics that prescribe hGH for "Performance Enhancement". In those clinics (the ones I have reviewed) they give hGH in combination with low doses of anabolic steroids. The doctors who make these prescriptions seem to think that there is a synergistic effect and theoretically that does have some validity.

In terms of any well controlled double blind studies, they have been equivocal. There may be some slight increase in performance but one of the challenges is that the effect in the sporting arena is very different from a controlled study. For example in the Olympic Games the difference between 1st place and 10th place can be tenths of seconds. To measure a difference on that scale in the lab is very difficult where as for an athlete; finishing 1st or 10th is a big difference. At this point we do not know whether hGH works or not but athletes seems to think that it does.

What are the regulations regarding hGH both from a sports organization standpoint and a legal standing?

Most sports organization prohibit the use of hGH and this predates any kind of adequate testing. It has been banned by many sports organizations for many years. From a legal standpoint, hGH is a prescription drug (at least in the US) and it occupies a very unique place in US drug regulations. It is one of the few drugs that cannot be given for off label indication. There are a very narrow number of diagnoses that you can prescribe hGH for, such as HIV, wasting states, obviously hGH deficiency (in pediatrics and in adults) as well as other rare diseases such as Prader-Willi Syndrome or Turner Syndrome. This has not prevented a number of anti-aging clinics from prescribing hGH although their prescription habits are probably very illegal. The fact that hGH has relatively narrow prescribing patterns has not stopped a proliferation on the black market. If you search for hGH on the internet you will not have any trouble finding hundreds of sites illegally selling human growth hormone.

Are there any non-analytical methods of deterring hGH use?

One of the ways several athletes have been adjudicated for hGH has been through the legal side. Several athletes have been

caught trafficking hGH, either receiving it, or selling it. This is known as a “non analytic positive” where someone has been suspended from play, not as a result of a drug test but as a result the determination that they had been using it based on legal documents or arrest records. This has been another avenue of deterring hGH use without necessitating a drug test.

Why is testing so difficult for hGH?

The problem is that recombinant human growth hormone is very similar to the hGH that everybody makes naturally. hGH is made by the anterior pituitary in a cyclical manner throughout the day. It increases with certain activities like exercise and stress. The recombinant form of hGH is very similar. In addition there is a very small amount of hGH that goes in to the urine and trying to find one small protein from the hundreds of proteins in urine is like trying to find a needle in a haystack. That has created a big problem in terms of urine testing.

The strategy that has been used for the detection of hGH is what is known as the isoform test. There are several different types of isoforms that are naturally produced. The recombinant form has the 22 kDa isoform. The testing strategy is to measure the ratio of the 22 kDa isoform to the 20 kDa to determine if someone has used recombinant hGH. Again, urine testing is very difficult given the paucity of hGH in the urine and so what regulators have turned to is a blood test which has a better chance of positive detection. A challenge with implementing the blood test is that athletes have been conditioned to accepting urine testing as a part of sports with blood testing low to be accepted by many sports organizations.

In addition to direct detection with the isoform test, what other strategies could be employed?

Other researchers have attempted to determine indirect methods of hGH use. For example the isoform method that we mentioned is a direct test; it shows that the 22 kDa form is in the persons system and that is evidence of hGH use. Another strategy is instead of trying to detect the actual drug, test to see if there is evidence of use by the end product. For instance, when you take hGH many other substances become elevated such as IGF-1 and Procollagen III. If we can determine that these biomarkers are elevated then this would provide indirect evidence of exogenous hGH use. The advantage of this strategy would be that in addition to detecting recombinant hGH it would also detect pituitary hGH used from other sources, it could also detect the use of IGF-1 and other compounds that modulate hGH use. The problem with this method is that it is an indirect test where as drug testing has traditionally tried to obtain a fingerprint or direct evidence of the banned substance being used, the indirect method has the benefit of being able to detect many more substances.

Is the goal of drug testing zero use of hGH?

The goal is to make it as difficult as possible for someone to abuse these types of performance enhancing drugs. More importantly, to protect the athletes who are trying to compete cleanly, make them feel that there is somewhat of a level playing field and that we can deter drug use to make a fair competition. Ultimately, even though it is the few athletes that get caught using performance enhancing drugs that make the headlines, it has to be remembered that the majority of athletes compete cleanly, do play by the rules, and do respect their sport. It is those athletes that we really want to protect.

What is the current status the hGH isoform test?

Serum testing (using blood for the detection of recombinant hGH) has been used at the 2004 Athens games, the 2006 Turin games and the 2008 Beijing Olympics. It has been used at those

Olympiads and there have been no positive tests reported. Until you have a positive test it is very difficult to assess the effectiveness of the assay and there are several reasons as to why there have been no positives. One reason may be that the test is not effective. Another reason may be that the window of detection is too narrow. With the isoform test you can only detect hGH use for about 24 hours after administration. During the Olympic Games athletes know the period in which they are likely to be tested so it is possible that they stop using hGH outside of this window of detection. Again the major limitations of this approach are that firstly, it has to be a blood test and second, the window of detection is very narrow in comparison to the effectiveness window. In other words the effects of hGH would last much longer than the narrow 24 hour detection window afforded by the test.

In comparison to the status of the isoform test, what is the status of the IGF-1 indirect marker approach?

The advantage of the biomarker approach is that it affords a much larger window of detection. The longer the period of detection the greater the deterrence effect because it forces athletes who want to cheat to take the substance much further out from competition. It would also allow for better out-of-competition testing. In addition, there has been some research taken in adopting the biomarker test not just in serum but in urine, again this may allow for a wider window of detection and allow for easier non-invasive testing.

How do you see the future for hGH tests?

One of the nice things about the field of drug testing is that we are constantly having new innovations. On one hand, the people that want to cheat are jumping ahead in terms of technology and on the other, we have improvements in the scientific community. The publicity over hGH has lead a lot of scientists who are not traditionally in the drug testing field to apply some of their technologies to this problem. One example in this issue of *Drug Testing and Analysis* is from Dr. Liotta and his group who present a paper in which they attempt to apply nanotechnology to the problem^[2].

Through the use of nanotechnology this group has addressed the problem by selectively isolating the hGH and then subjecting it to analysis. Another example is the newly formed Partnership for Clean Competition which is a consortium of professional sports organizations whose grant funding has started to attract different approaches to the problem of hGH detection as well as other problems in the arena of drug testing. We are hoping that attention to these issues will bring even more scientists to the forefront with alternative technologies able to address some of the limitations we have discussed in this interview.

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