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Gene Doping in Sports

Mehmet Unal[1] and *Durisehvar Ozer Unal*[2]

1 Department of Sport Medicine, Istanbul University, Istanbul Medical Faculty, Istanbul, Turkey
2 Department of Molecular Biology and Genetics, Bogazici University, Istanbul, Turkey

Abstract

Gene or cell doping is defined by the World Anti-Doping Agency (WADA) as "the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance". New research in genetics and genomics will be used not only to diagnose and treat disease, but also to attempt to enhance human performance.

In recent years, gene therapy has shown progress and positive results that have highlighted the potential misuse of this technology and the debate of 'gene doping'. Gene therapies developed for the treatment of diseases such as anaemia (the gene for erythropoietin), muscular dystrophy (the gene for insulin-like growth factor-1) and peripheral vascular diseases (the gene for vascular endothelial growth factor) are potential doping methods. With progress in gene technology, many other genes with this potential will be discovered. For this reason, it is important to develop timely legal regulations and to research the field of gene doping in order to develop methods of detection.

To protect the health of athletes and to ensure equal competitive conditions, the International Olympic Committee, WADA and International Sports Federations have accepted performance-enhancing substances and methods as being doping, and have forbidden them. Nevertheless, the desire to win causes athletes to misuse these drugs and methods.

This paper reviews the current status of gene doping and candidate performance enhancement genes, and also the use of gene therapy in sports medicine and ethics of genetic enhancement.

Competition, contests and the psychology of winning and being superior to competitors have been widespread behaviours throughout the history of humankind. In addition to gaining acceptance in primitive societies, winning and being superior provides gains with regard to economical and social status in modern societies. In the course of time, these gains have caused athletes to misuse some methods and drugs.

Doping is defined as using forbidden substances or methods in order to increase physical and/or mental performance. Doping is regarded as the use of drugs and chemical substances to increase the performance in an artificial and illegal way, or the use of physiological substances in large amounts during or out of competition. Furthermore, the use of medically inappropriate substances for the treatment of illness and injuries only for the purpose of being able to participate in competition is also regarded as doping.

The prohibition of doping should be assessed in two aspects:[1-4]

1. Ethical aspect: all athletes should participate in the competitions which reward and compare the ability, strength and training of the athletes under equal conditions.

2. Medical aspect: these substances may cause severe adverse effects and in some cases even irreversible damage in the short or long term.

To protect the health of athletes and to ensure equal competitive conditions, the International Olympic Committee (IOC), World Anti-Doping Agency (WADA) and International Sports Federations have accepted performance-enhancing substances and methods as being doping, and have forbidden them. Lists of banned substances and methods are published every year.[5] The list of banned substances was updated on 17 March 2004 and will not be discussed in detail in the present article. Gene doping has been added to the latest list of prohibited methods. Furthermore, these organisations are trying to prevent misuse by regular doping controls out of competition and by controls during competition. In recent years, the genetic codes of several diseases have been decoded within the Genome Project, giving the possibility to be treated with 'gene therapy'. Parallel with the developments in the fields of genetics, molecular biology and medicine, some of these therapies will result in performance-enhancing effects. Unfortunately, this involves a possibility of misuse for athletes and has brought up the concern of 'gene doping'. The potential misuse of gene therapy as doping has inflamed the debate in a period where the ethical aspect of gene therapy itself is a discussion subject. It does not seem possible to detect gene doping with the current technology. At this point, it is important to remember that the purpose of doping controls should be to prevent doping and to protect the health of athletes with legal sanctions, rather than catching doping using athletes such as the police catch burglars.

1. Gene Doping

The definition of 'gene doping' is the non-therapeutic use of genes, genetic elements and/or cells that have the capacity to enhance athletic performance. It is the use of 'gene therapy', normally used for the treatment of diseases, for enhancing sport performance and obtaining superiority over competitors. As can be seen from the definition of gene doping, the primary concern is the abuse of genetics and the use of gene therapy by healthy athletes in order to increase performance.[6-10]

Scherling[9] from the Copenhagen Muscle Research Centre in Denmark has expressed that gene doping is the biggest threat in athletics. Gene doping contains the insertion of artificial genes in patients. The artificial gene produces an appropriate RNA, which synthesises protein. The purpose of gene therapy in the form of inserting artificial genes in patients are:

- to kill or weaken cancer cells;
- to enable the body itself to produce drugs that are administered today;
- to replace defect genes with healthy copies.[9,11,12]

The biggest problem in gene therapy today is the lack of control over the expression of the artificial gene. The gene is inserted for treatment but it is not yet clear if the artificial gene will have other effects than expected. In 1999, an 18-year-old patient was treated with gene therapy for a rare liver disorder. Although the patient's condition was not life-threatening at the beginning of the treatment, the patient died after a short time from multiple organ failure. This case attracted attention to the unknown risks of this new developing field.[13]

Dr Don Catlin et al.[13] expresses "If history is any indication, less-than-scrupulous athletes and coaches will be interested in these new types of drugs, despite significant health risks".

Although gene therapies are developed for the treatment of diseases, it is very likely that gene therapy can increase performance if used by healthy athletes. Some examples of this can be seen in the following sections. Presently, numerous genes are being studied with regard to gene therapy. These genes will find an application area when their effects on different treatments have been shown. Many of these gene therapies will contain the potential for gene doping.

2. How is the Artificial Gene Introduced?

The artificial gene is introduced by:[9,14,15]

- direct injection of DNA into the muscle;
- insertion of genetically modified cells;
- introduction utilising a virus.

Gene doping is not merely gene manipulation, but also includes indirect genetic technologies, such as biosynthetic drugs (drugs for increasing oxygen). Genetic performance-enhancement technologies

should consist of the full range of possible applications. Blood oxygenation is a fundamental factor in optimising muscular activity. Increasing oxygen transport to tissues is associated with improvement in athletic performance. The methods and drugs used by athletes to enhance oxygen delivery are: blood transfusion; endogenous stimulation of red blood cell production using erythropoietins (EPOs); EPO gene therapy; and allosteric effectors of haemoglobin. The identification of new drugs for the treatment of anaemia have been used for doping purposes.[16]

2.1 The Gene for Erythropoietin

Erythropoietin is a hormone that is 90% secreted by the kidneys and 10% by the liver and other organs. When its amount increases in the blood, it stimulates the erythropoiesis and causes an increase of erythrocytes in the blood, which in turn increases haemoglobin and haematocrit levels. Blood oxygenation is a fundamental factor in optimising muscular activity. Increasing oxygen transport to tissue is associated with improvement in athletic performance. The aerobic capacity is increased and exhaustion is delayed. The effects of the EPO gene are systemic.[17]

In 1997, viruses carrying EPO was delivered to the cells of mice and monkeys at the Laboratory of Genetics, University of Chicago. Increases of 81% were seen in the haemoglobin and haematocrit levels.[13] In 1998, Zhou et al. showed in a study that haematocrit levels of monkeys increased by 75% when viruses containing EPO were delivered.[18]

2.2 The Insulin-Like Growth Factor-1 Gene

It is found that the insulin-like growth factor-1 gene (IGF-1), also called muscle growth factor, causes muscle hypertrophy and increased power for patients with degenerative muscle diseases such as muscular dystrophy. It affects locally. Muscle hypertrophy and increased power is observed at the muscle directly treated.

In a study from 1998, Barton-Davis et al. showed a significant increase in the power and size of the muscles of mice injected with a virus carrying a gene for IGF-1.[19] Similar studies are continuing in England and at the University of Pennsylvania. This therapy could be adapted to strengthen one specific muscle in an athlete.

2.3 The Gene for Myostatin

An increase in muscle size and power is observed in cases lacking a myostatin gene. In a study in 1999, Lee and McPherron observed an increase in hypertrophy and power in the muscles of mice when the myostatin gene was removed.[20]

2.4 The Vascular Endothelial Growth Factor Gene

Another possible gene therapy could be vascular endothelial growth factor (VEGF). It has been shown that this gene increases production of new blood vessels in the case of peripheral arterial diseases. In 1998, Baumgartner et al.[21] showed that the production of new vessels in an organism increased when a virus carrying a gene for VEGF was delivered. An increase in the production of new blood vessels means increased blood flow to the heart, liver, muscles, lungs and others, which delays exhaustion. This gene therapy technique employs the common cold virus to deliver the VEGF gene to cells so even detecting the virus would not prove an athlete had been cheating.

2.5 The Gene for Leptin

Leptin is an important hormone with regard to the feeling of hunger and toughness. Weight loss is observed when the gene stimulating leptin is injected to obese mice. In 1997, Murphy et al. showed that obese mice injected with a virus carrying a gene for leptin lost weight.[22]

Rankinen et al. studied the human gene map for performance and health-related fitness phenotypes. They found that the map includes 90 gene entries, plus two on the X chromosome. These candidate gene studies need the more detailed exploration of DNA variation in exons, splicing, sequences and promotor regions.[23]

3. Possibility of Detecting Gene Doping

Cheats will avoid detection by injecting themselves with copies of genes naturally present in the body, such as those encoding growth factors or testosterone.[9] There are many methods available to

detect blood doping and EPO abuse,[24,25] but possible suspicious results come from major plasma volume changes. Detection of blood doping in sports have failed because of the need for new analytical methods in the doping laboratory. Further progress in analytical research is necessary. Haemoglobin and haematocrit values change during the competition season and according to the type of exercise. Subject-specific haematological changes can be determined sequentially to define reference ranges. The haematological passport should be used within a global strategy.[26] One possibility would be to inject the gene for EPO, an introduced gene would be identical to natural EPO.

According to Larry Bowers, the lead toxicology and testing expert with the US Anti-Doping Agency, there would be no way to test for this type of doping with current technologies.[13] The authors of the cover story of the September 2000 issue of *Scientific American* conclude their assessment by saying "All intents and purposes, gene doping will be undetectable. Examining sudden improvements in performance may be an indication of illicit behaviour, but it is not a scientifically reliable test for it".[27]

4. Risks of Gene Doping

The aspect of gene therapy that causes the most concern is the known and unknown health risks. It is not possible to know the results of using gene therapy for healthy people. It is very likely that it would bring a lot of health problems.

Artificially increasing EPO levels in healthy people will increase the amount of red blood cells and therefore viscosity, which in turn will increase the risk of heart attack and paralysis. As the blood thickens, it will become difficult for the body to successfully pump blood to all tissues of the body, causing clots wherever vessels cannot compensate for this increased density. It is possible that unknown EPO users also use blood thinning drugs, which can lead to other health problems.

Furthermore, being able to increase EPO production does not mean being able to decrease the production when needed. Athletes using synthetic EPO hormones are facing similar risks, but the hormone is metabolised in the system and the proportion of red blood cells therefore returns to normal levels, whereas injection of the gene for EPO can mean continuous production of red blood cells.[28]

The use of a gene for IGF-1 or removal of the gene for myostatin causes differentiation in the muscle. The muscles would likely become disproportionately strong and pulling on surrounding tendons and bones that might cause tears or fractures.[19]

Integration of viral vectors into the host genome carries the risk of insertional mutagenesis. Abnormal regulation of cell growth, toxicity from chronic over-expression of the growth factor and cytokines, and malignancy are all theoretically possible dangers. Scientists emphasise that it is not the few detectable risks that are the most dangerous aspects of gene therapy, but the risks that are totally unknown.[29]

5. World Anti-Doping Agency Warning

The IOC and WADA concur that if there is a new drug out there, some athletes and coaches are going to abuse it. As the use of anabolic steroids, testosterone and peptide hormone have shown, unscrupulous athletes and coaches will likely be tempted to get their hands on the latest performance-enhancing drugs.

WADA states that the best way to prevent gene doping is a combination of regulation, education and research. For this purpose, WADA organised a conference in March 2002. Scientists, athletes, technicians, policy makers and legal experts related to the field were invited to form a consensus. Richard W. Pound, chairman of WADA, expressed that "Gene therapy has enormous potential to revolutionise medicine's approach to curing disease and improving the quality of life. Unfortunately, this same technology, like many others, can be abused to enhance athletic performance".[3]

Ted Friedmann, University of California San Diego, Center for Molecular Genetics, said "We must underscore that the work on genetic therapies should be considered research, promising for the future betterment of mankind but still unpredictable and of unproven safety… The time is right, however, for the sport and science communities to be working out how to prevent the possible misuse of these methods in the future".[8,13]

According to the Swedish exercise physiologist Bengt Satlin, the anti-doping struggle will have to face gene doping tests in a couple of years. Don Catlin, UCLA Olympic Analytical Laboratory, expressed that drug-testing agencies always try to keep up with new methods to enhance athletic performance, and that there will always be people searching for new doping methods. Catlin thinks that gene doping may become one of those new methods.[13]

General warnings from international antidoping agencies on gene doping are as follows:

- gene transfer technology, which is still at the investigational stage, is nevertheless already beginning to demonstrate clinical efficacy;
- gene therapy contains potential for misuse with regard to enhancement of athletic performance;
- in order to prevent misuse, collective efforts of relevant institutions and people is necessary;
- ethical regulations should be respected;
- legal framework with regard to gene therapy should be built up.

Sport-specific warnings from international antidoping agencies on gene doping are as follows:

- athletes have the right to benefit from gene therapy;
- gene therapy used for enhancement of performance should be prohibited;
- WADA should have sanctions for gene doping;
- relevant institutions and people should research and develop methods to prevent abuse;
- financial support should be assured for research in the field.

Although gene transfer technologies have been developed for treatment of diseases, these therapies have performance-enhancing effects when used by healthy athletes. This involves a possibility of misuse for athletes who want to enhance their performance in artificial ways. Like other members of the society, athletes should have the right to benefit from gene therapy for treatment of diseases and in case of other medical conditions; however, gene therapy contains many risks regarding sport ethics and the health of athletes. Use of non-therapeutic gene transfer technologies only for enhancement of performance should be prohibited like doping is for the generation of today. The purpose of international anti-doping agencies should be remembered; namely to provide the opportunity for athletes to compete in an ethical and healthy way.

Genetics plays an important role in determining characteristics desired for success in a given sport. Authorities must work on education of the public to encourage personal ethical reflection on the appropriate uses and limits of genetic enhancement technologies.[30] Governments and other organisations related to sports and gene therapy should begin to work on appropriate policies regarding the use of gene therapy. They must develop regulations for genetic manipulation and use of genetic enhancement technologies. They should also compare the risks and benefits of genetic enhancement and the impact of these technologies on social values.

6. Conclusions

Scientists around the world are searching for ways to use the information gained from the Human Genome Project. Gene therapies are designed to alter damaged or diseased genes and athletes will some day try to abuse these therapies to enhance their performance. Use of non-therapeutic gene transfer technologies solely for enhancement of performance contains many risks regarding the health of athletes. There would be no way to test gene doping with current technologies. Governments and sports organisations should begin to work appropriate policies regarding the use of gene therapies by healthy athletes in order to increase their performance.

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Correspondence and offprints: Dr *Mehmet Unal*, Department of Sport Medicine, Istanbul University, Istanbul Medical Faculty, 34390 Istanbul, Turkey.
E-mail: mhmt_unal@yahoo.com