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GENE DOPING: BIOMEDICAL AND LAWS ASPECTS OF GENETIC MODIFICATION OF ATHLETES

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Abstract

The desire to increase their own physical performances in order to obtain better results in sports led athletes to seek alternative methods to train hard. In the time, the results obtained in genetics have been used in the field of sport, creating a new form of doping: "gene doping". The athletes may be able to use gene therapy to re-engineer their bodies for better performances. In the sport, leading authorities predict that the genetic engineering of athletes will be widespread by the 2004 Olympics. This new type of doping can be dangerous and detrimental to health as with it, gene transfer vectors may be produced in non-controlled laboratories. It is really difficult to identify athletes who have resorted to gene doping because many of the muscle based gene technologies are unlikely to be detected by urine or blood tests. Various options have been advanced to detect the use of genes for the purpose of doping but they turn out to be too invasive and not easily achievable. Athletes are not fully aware of the physical problems associated with the use of gene doping and they and their supporting staff will be educated on this subject in order to prevent the use.

***Keywords**: gene doping, gene therapy, anti doping*

Introduction

Drug abuse is one of the biggest problems in sports. It involves the repeated and excessive use of chemical substances to realize a certain effect [1]. It can also be referred to as substance abuse or doping [2]. Doping has ancient origins. Probably would have the same age of sport as from the moment when the man began to practice physical activity in competition with other men, he sought to improve own performance by taking mixtures of various types of plant origin [2]. In fact, it seems that the term doping is derived from an ancient African dialect "doop" as meaning a mixture or a potion. The willingness to compromise the performance involved, as victims, even the animals [3].

Doping exists not only in professional sport but also affects amateur athletes who are making increasing use of performance-enhancing drugs. Doping is thus increasingly a matter that concerns the whole society [4-5].

Doping poses a threat to sport worldwide. It undermines the principle of open and fair competition [3]. It is a factor that discourages the practice of sport in general and puts the professional under unreasonable pressure. It seriously affects the image of the industry and represents a serious threat to individual health [5].

In the course of time, doping has shown a great ability to discover and always use new substances and appropriated the new scientific discoveries [5].

During the last 2 decades, progress in deciphering the human gene map as well as the discovery of specific defective genes encoding particular proteins in some serious human diseases have resulted in attempts to treat sick patients with gene therapy. There has been large attenction on human recombinant proteins which were gene-engineered and produced in vitro (*insulin, insulin-like growth factor-1, erythropoietin, growth hormone*). These substances and methods also became improper tools for dishonest athletes [6].

In fact, a new frontier reached by the doping is the use of genes [7]. It is, in essence, to use the results obtained in the medical field regarding the use of genes for therapeutic purposes and to use them for purposes far less noble. In this regard, it is said that gene doping is an outgrowth of genetic therapy. Unfortunately, the increase in discoveries of new substances and new methods of doping is not associated with an equally increased awareness of the many health risks with taking the above substances or the subjection to these methods [8-9].

At the present, one of the prime candidates for gene doping is myostatin. Fedoruk and Rupert examined the possibility of using myostatin inhibitors to enhance performance exploring the possibility of using gene manipulation [10] .

Numerous groups have initiated a flurry of efforts to merge two of the most exciting and promising technologies in biomedicine, gene therapy and RNA interference (RNAi) [11]. Gene doping in sport, a potential new form of misuse of gene transfer technology [6]. To counter the phenomenon in question, you need information campaigns and awareness to athletes of all ages [8-9].

A brief history of doping

For a long time the man has tried to improve in artificial way his own physical performances [3]. The reasons of these attempts are various and they are changed in the time. Surely one of the first reasons have been the necessity to get best results in the hunting. Today, instead, the athletes modify artificially his own performances for purposes of profit. In fact, best performances mean, great earnings [12].

Already in the early 1900s it was realized that the use of substances to increase their physical performance, not only falsified the results of competitive sport but it was also very dangerous for the health [2,8].

In 1928 the International Association of Athletics Federations became the first International Sport Federation (IF) to ban the use of stimulating substances. Only after the death of a cyclist at the Olympic Games in Rome in 1960 urged the relevant authorities to introduce the first anti-doping test.

Drug tests were first introduced at the Olympic Winter Games in Grenoble and at the Olympic Games in Mexico in 1968 [13].

It felt a strong need to create an independent organization that would be able to represent a reference point for sports authorities and governmental and that had as its primary objective to defeat the doping [13-14].

The World Anti-Doping Agency (WADA) was an international organization, that is established on November 10, 1999 with the aim to promote, coordinate, and monitor the fight against doping in sport in all its forms. In fact, in 2004, the aforementioned organization has harmonized the rules and regulations governing anti-doping across all sports and all countries for the first time through the issuance of a Code [12] which defines the doping as the "nontherapeutic use of cells, genes, genetic elements, or modulation of gene expression, having the capacity to enhance performance" (World Anti-Doping Agency, 2008].

In accordance with the WADA Code doping is the presence of a prohibited substance or its metabolites or markers' banned; the use or the attempted use of a prohibited substances or a prohibited method ; the refusing or the failing, without compelling justification, to submit to sample collection (Table 1, Table 2); the violation of applicable requirements regarding athlete availability for out-of-competition testing; the tampering or the attempting to tamper with any part of doping control ; the possession of prohibited substances and prohibited methods; the trafficking or the attempted trafficking in any prohibited substance or prohibited methods; the administration or the attempted administration to any athlete of any prohibited methods or prohibited substances, or the assisting, the encouraging, the aiding, the abetting, the covering up or any other type of complicity involving an anti-doping rule violation or any attempted anti-doping rule violation [13].

Gene for sports doping

Genetic is the science of heredity and variation in living organisms [8]. It investigates gene function, genome structure, chromatin organization, recombination rate, mutation processes and evolutionary

Table 1. *The WADA Prohibited List for 2013*

Substances and methods prohibited at all times (in- and out-of-competition)*
S1. Anabolic agents
S2. Peptide hormones, growth factors and related substances
S3. Beta-2 agonists
S4. Hormone antagonists and modulators
S5. Diuretics and other masking agents
M1. Enhancement of oxygen transfer
M2. Chemical and physical manipulation
M3. Gene doping
Substances and methods prohibited in competition
In addition to the categories S1 to S5 and M1 to M3 defined above, the following categories are prohibited in competition:
S6. Stimulants
S7. Narcotics
S8. Cannabinoids
S9. Glucocorticosteroids
Substances prohibited in particular sports
P1. Alcohol
P2. Beta-blockers

Table 2. *Prohibited List and reason of use*

INCREASE OF MUSCLE MASS	S1	S2	S3		
INCREASE OF ENDURANCE AND EFFORT	S2	S3	S6	M1	
INCREASE OF REACTIVITY AND AGGRESSION	S6	S7	S8	S9	P1
MASKING AGENTS	S4	S5			

history, to provide a coherent understanding of the human genome and its complex relationship with human biology, physiology and disease [10-12]. The human genome represents the whole genetic information of each individual. These information's reside on the chromosomes (23 pairs), which are present in each nucleus of all the cells that make up the organs. The chromosomes contain DNA (*DeoxyriboNucleic Acid*) which is a double helix composed of four bases. The genetic information is determined by the sequence of these bases in a chain of nucleotides. This sequence determines the order of amino acids to create a specific protein chain, such as enzymes or structural proteins. The sequence information that is necessary to obtain one specific polypeptide chain is called a gene [15,16].

The insertion of copies of a gene into living cells in order to induce synthesis of the gene's product: the desired gene may be microinjected directly into the cell or it may be inserted into the core of a virus by gene splicing and the virus allowed to infect the cell for replication of the gene in the cell's DNA.

siRNA plays many roles, but its most notable is in the RNA interference (RNAi) pathway, where it interferes with the expression of specific genes with complementary nucleotide sequence. siRNA also acts in RNAi-related pathways, e.g., as an antiviral mechanism or in shaping the chromatin structure of a genome.

Zhiqing Huang et al showed, about Real-time quantitative PCR, that the level of MKK4 expression was efficiently reduced by MKK4-specific siRNA. Western blot assays showed that knockdown of MKK4 attenuated the myostatin-induced downregulation of MyoD and myogenin expression [17].

Gene doping is defined, for the first time in the 2003, in the IOC List of Prohibited Substances and Methods, as the "Gene or cell doping is defined as the non-therapeutic use of genes, genetic elements and /or cells that have the capacity to enhance athletic performance" [13,16].

The goals of gene doping include the injection of novel genes of the modulation of existing genes too; however, the gene doper introduces the gene products for the enhancement of physiologic parameters expedient to the athlete's competitive tasks, rather than the treatment of a medical illness [16-18].

Now, in the 2013 WADA Prohibited List, gene doping, is "the transfer of polymers or nucleic acid analogues" and "the use of normal or genetically modified cells"[14].

The discovery of the complete human genome with approximately 30.000 different genes leads to new possibilities for diagnosis and prevention of a wide variety of diseases. In addition, this knowledge may be used for the design of a new therapeutics use, including gene therapy, based on the DNA sequence informations [18]. Gene therapy may be defined as the transfer of genetic material to human cells for the treatment or prevention of a disease or disorders. Its principle is based on the delivery to a cell, of a therapeutic gene which may compensate an absent or abnormal gene [9]. This material can be encapsulated into a virus, such as adenovirus or retrovirus, or into a lipid, such as a liposome. The viruses are crippled so that they are no longer pathogenic. The encapsulated genetic material is mostly referred to as a vector and is introduced into the body by direct injection into the target organ or administered by aerosol for lung delivery [12,18]. Also, it is possible to isolate cells from a patient and treat these cells with the vector in the laboratory and then re-implant these into the patient. Gene therapy is currently an experimental therapy and its use is strictly regulated [16,19].

Unfortunately these new important discoveries for the human health are been used in distorted way by the athletes. In fact the athletes may be able to use gene therapy to re-engineer their bodies for better performances. They know that any physiologic process involved in producing a motor action or assisting the implementation of a motor movement could be a candidate for gene doping [8].

There are obvious candidates for the aspiring gene cheat (Table 3) and Gene doping have gene and system targets (Table 4).

Growth hormone (*GH*) has a multitude of effects on the body associated with growth. It has a well-documented stimulatory effect on carbohydrate and fatty acid metabolism, and a possible anabolic effect on muscle proteins [18].

Doessing and Kjaer (2005) also suggest a role for GH as an anabolic agent in connective tissue in human skeletal muscle and tendon [16]. Recombinant GH is already being used as a doping agent in sports. Insulin-like growth factor 1 is a protein that stimulates cellular proliferation, somatic growth and differentiation [18].

Table 3. *Genes for sports doping and physiologic response*

Gene/Product	System/ target tissue	Gene product properties	Physiologic response	Sport
ACE	Skeletal muscles	Peptidyl dipeptidase	ACE-I seems to correlate with enduranceACE-D involved in sprint and powers	Endurance
ACTN2,3	Muscular system	Actin-binding proteins related to dystrophin	Involved in fast twitch muscles	Endurance and sprint
Endorphins, Enkephalins	Central and peripheral nervous systems	Widely active peptides	Pain modulation. Increases risk of overuse of musculoskeletal and cardiovascular system.Increase stress and pressure on heart	Endurance
EPO	Hematopoietic system	Glycoprotein hormone	Increases RBC mass and oxygen delivery	Endurance
HGH	Endocrine and muscular system	191–amino acid protein	Increases muscle size, power, and recovery	Entrengh
HIF	Hematologic and immune systems	Multisubunit protein	Regulates transcription at hypoxiaresponse element	Enduranceaerobic
IGF-1	Endocrine/metabolic/ skeletal muscle	70–amino acid protein	Increases muscle size, power, and recovery	Entrengh
Interleukin-15	Skeletal muscle	cytokine with strong antitumor properties	Myoblast proliferation and muscle-specific myosin heavy chain (MCH) expression	Strength
Myostatin.	Muscular system	2-subunit protein	A negative muscle mass regulator. Demage of tendons ligament and bone	Entrengh
PPAR-δ	Skeletal muscle and adipose tissue	Nuclear hormone receptor protein	Promotes fat metabolism and increases number of slow twitch fibers	Speed and endurance
VEGF	Vascular endothelium and angiogenesis	Glycosylated disulfide-bondedhomodimers	Induces development of new blood vessels	Endurance

Abbrevation: ACE, angiotensin-converting enzyme; ACTN3, actinin binding protein 3; EPO, erythropoetin; HGH, human growth factor; HIF, hypoxia inducible factor; IGF-I, insulin-like growth factor; PPAR-delta, peroxisome proliferators-activated receptor (delta); VEGF, vascular endothelial growth factor. (Gaffney, Parisotto, 2007)

Table 4. *System and organ targets and physiologic response. ACE, angiotensin converting enzyme; ACTN, actinin binding proteins; EPO, erythropoetin; HGH, human growth hormone; HIF, hypoxia inducible factor; IGF-I, insulin-like growth factor; PPAR-delta, peroxisome proliferator activated receptor; VEGF, vascular endothelial growth factor*

System/organ targets	Physiologic response and gene
Central and peripheral nervous systems	Modulate pain using endorphin releasing genes
Skeletal muscle	Increase either fast twitch or slow twitch fibers with ACE, ACTN3, HGH, PPAR-delta for either endurance or explosiveness. Increase size and power, by injecting IGF-1, Myostatin genes
Joints	Induce super lubricants with IGF-1
Cardiovascular and Hematopoietic system	Increase vascularity with VEGF. Increases RBC mass and oxygen supply using EPO and HIF genes
Vascular endothelium	Induces development of new blood vessels

Risks of gene doping

Gene doping can be dangerous and detrimental to health (Table 5). The main concerns stem from the fact that currently is not yet certain of the long-term effects of the use of genes [16]. In addition there is a risk that the modification of the body through the use of gene therapy may also have an impact on future generations [19,20].

Table 5. *Genetic doping and some health damages that may be relate to both the vector used and the encoded transgene*

Genetic doping and some health damages
Cancer
Virus infection
Autoimmunization
Hearth attack and Stroke
Muscle or tendons and ligaments rupture

In particular, one of the main problems is linked to the carrier of genetic transfer that for purposes of doping can be produced in laboratories not controlled and the DNA, which can be easily and cheaply produced with materials available from legal suppliers, could be contaminated with chemicals and other impurities from the production and purification process [20-21]. Moreover, the introduction in the body of the athlete of contaminated DNA can cause the onset of virus also infectious. Healthy people who unnaturally boost their *Erythropoietin* (EPO) levels increase their chances of stroke and heart attack because adding red blood cells makes the blood thicker [20]. As it gets thicker, it becomes more difficult for the body to pump it successfully to all tissues of the body, causing clots wherever vessels cannot compensate for this increased density. Whereas the athletes using synthetic EPO today face similar risks, after a few weeks the risk subsides as EPO is cleared from the body and red blood cell production returns to normal levels. But if EPO would be delivered by gene therapy, the level and duration of *EPO* production is less controllable. The hematocrit would be less manageable and could continue almost indefinitely giving rise to pathological EPO levels [20-23].

About legal consequences the WADA's Code and generally the anti-doping community, gene doping, like doping in any form, undermines principles of fair play in sport and most importantly, involves major health risks to athletes who partake in gene doping. Since the realisation of the threat of gene doping to sport in 2001, the anti-doping community and scientists from different disciplines concerned with potential misuse of gene therapy technologies for performance improvement have focused extensive efforts on developing robust methods for gene doping detection which could be used by the World Anti-Doping Agency to monitor athletes and would meet the requirements of a legally defensible test [22].

Detection of gene doping

Currently, if it is rather easy to resort to the use of genes for the purposes of doping, the same cannot be said with regard to the identification of athletes who have made use of the aforementioned genes [22-25]. Unfortunately, in fact, not enough routine tests to which are subjected the athletes. The detection of associated chemicals or viral particles may be of use but this would involve tissue sampling [10,24]. It will be unlikely that athletes can be forced to give consent to this procedure given the invasive nature of the biopsies necessary to submit [24]. Furthermore many forms of genetic doping do not require the direct injection of genes in the desired target organ. The DNA which is used for gene transfer of the gene is of human origin, and therefore not different from that of the person applying gene doping [21,25]. The gene doping will in most instances result in the production of a human protein chain, which by itself is identical to the persons own proteins. Only the blood level of the protein may be indicative for doping abuse [26]. In the case of Epotype treatment, this might be detectable, because of the resulting increase in hemoglobin and hematocrit. However, genes may be turned on and off by taking specific medicines [19]. In the course of time have been proposed alternatives to the aforementioned biopsy such as: 1) the use of a microchip that could monitor thousands of genes; 2) the monitoring of the protein fingerprint: hundreds of biological proteins chain could produce the above mentioned protein of biochemistry of the athletes and a suspicious alterations of such an individualized fingerprint could be a signals of the recourse to the gene doping; 3) to label the transgene product with a genetic "bar code" [16]. Unfortunately, the criticism that has been issued to the latter alternative is that they do not solve the problem of invasive tests to find out recourse to the use of genes for non-therapeutic purposes.

Conclusions

The human race has celebrated its athletes since the ancient time. The yearning for success by athletes has caused the search for best results at any cost, legal or illegal [21]. The sports, in fact, world breaks down into two opposite sides: the proponents of loyalty and the promoters of doping [4]. There is a constant struggle in which from time to time doping throws a trump card on the table. It is very difficult to answer in a time and effective way to the new challenges posed by doping. It, in fact, succeeds in appropriating of the new scientific discoveries and to use them for its own purposes[22].

The WADA has been founded with the principal aim to fight against the doping and it has the pur-

pose to guarantee that the athletes can participate in a doping-free sport. Doping, in fact, damages the spirit and the values of the sport such as health, fairness, honestly, respect for laws and rules and equality [9].

Gene Doping is defined, for the first time in the 2003, in the IOC List of Prohibited Substances and Methods, as the "Gene or cell doping is defined as the non-therapeutic use of genes, genetic elements and /or cells that have the capacity to enhance athletic performance"[12].

Now, in the 2013 WADA Prohibited List, gene doping, is "the transfer of polymers or nucleic acid analogues" and "the use of normal or genetically modified cells" [14].

The discoveries of gene therapy, have generated new opportunities for cheating in sports [9]. Gene doping is a manifestation of it and is developing rapidly. The problems to defeat this new doping method are many and are mainly ethical and economic: tests are becoming more expensive and likely to be too invasive. A road most economically advantageous tender may consist of awareness campaigns and information since the younger athletes [23-26]. It also needs to educate coaches about the serious risks to the health of their athletes (cancer, virus infection, autoimmunization, heart attack and stroke, damage of skeletal muscle, rapture of tendons and ligaments) [18]. In fact, unfortunately, the health risks associated with the use of the genes for the purpose of doping is not yet well known by athletes and their coaching staff [21,23]. It is necessary that the WADA develops written, interactive and in different languages educational materials pertaining to the risks of gene doping so that the athletes can increase their awareness and knowledge about this method of doping [24-25].

Also, research needs to be coordinated in order to investigate the development of methods to detect gene doping. The pharmaceutical industry should preferably subscribe to a code in which they state that they will not produce or sell genetic products for other than therapeutic use, banning gene doping [24-26].

Unfortunately in the present social and sports context, doping is still little known, especially among the younger age. This lack of knowledge could be remedied by governative and sports institutions. Gene doping needs more scientific investigations. In addition to economic problems, is also associated with ethical problems because the tests that should undergo athletes are currently too invasive. In Italy, the obligation to undergo this type of test would run counter to the articles 13 and 32 of the Italian Constitution, which enshrine that *"Personal liberty is inviolable. Not is allowed any form of detention, inspection or personal search or any other restriction of personal liberty except by a reasoned judicial authority and only in the cases and manner provided by law "* and *" The Republic safeguards health as a fundamental right of 'individual and collective interest, and guarantees free medical care to the indigent. Nobody can be forced to a specific medical treatment unless required by law. law may in no case violate the limits imposed by respect for the human person. "*

One of the first issues that comes up when considering whether, when, and how results from genetic studies will be exploited for gene doping purposes is whether gene doping is "right. While many people agree with WADA's position that gene doping threatens the integrity of sports competition, others think differently. Whether or not it is right to use DNA for enhanced athletic performance will likely be a subject of fiery debate for years to come [28].

Therefore, it seems that gene doping is intended in the near future to remain hidden and spread very quickly among athletes. The field of gene therapy, and by extension, gene doping, is full of unpredictable and dangerous results [27-29].

Preventive measures

Most athletes will not have enough background knowledge to fully understand the potential health hazards imposed by gene doping. Therefore, it is importance that athletes and their supporting staff will be educated on this subject in order to prevent the use of gene doping. Athletes will receive information on the potential benefits of gene doping from the mass media such as newspapers, magazines and television. They will be tempted to try such a new therapy, especially when they are informed that such a form of doping may be almost impossible to detect. Athletes should be made aware of the risks involved in gene doping when used in an uncontrolled athletic setting without compromising the great possibilities that gene therapy offers for the treatment of certain illnesses. Elite athletes and athletes in gyms appear to be the primary target groups. In order to develop an effective strategy for the prevention of gene doping, national as well as international coordination is required.

We need to develop new analytic methods and biological molecular techniques in anti-doping laboratories, and design programs that avoid the non therapeutic use of genes.

Declaration of interest

The authors report no conflicts of interest.

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