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REVIEW ARTICLE

BLOOD DOPING AND GENE DOPING: A REVIEW ON RECENT TRENDS IN DOPING

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ABSTRACT

The word "Doping" implies to the use of prohibited substances and practices for improving sporting performance of athletes. It includes the misuse of certain techniques and substances for enhancing the performance and endurance level of the athlete. The desire to win, acclamation and associated benefits; drives the athletes towards doping. Athletes in the present age are abusing new substances and methods of doping that are difficult to detect. Blood Doping and Gene doping are the new found trends that pose analytical challenges. Blood doping or induced erythrocythemia helps increasing ones RBC mass to transport more oxygen to muscles for better performance. Gene Doping method uses genes that have the capacity to enhance athletic performance. Analyses of these methods pose limitations due to which these doping methods are trending. This work aims at understanding some recent trends in doping related to prohibited method 'M1' i.e. Manipulation of blood and blood components; and method 'M3' i.e. Gene doping, as stated in 'The 2017 Prohibited List International Standard' by the World Anti-Doping Code; thereby suggesting the best analytical techniques used for the same.

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INTRODUCTION

1. Defining Doping and understanding its reasons

"*Doping*" denotes the use of substances and techniques that are banned by sports workers, primarily athletes, in order to improve their stamina and performance by increasing red blood cells mass, thereby allowing the body to transport more Oxygen to muscles. There is no legal definition of "Doping" thus this offence is defined by the international sports organizations in their own individual manner causing a variation [45]. International Olympic Committee (IOC) defines doping as 'the use of any substance, foreign to the body, and taken with the sole intention of increasing, in an unfair manner, his/ her performance in competition'. Article 1 of WADA (World Anti-Doping Agency) *Code* defines Doping as 'the occurrence of one or more of anti-doping rule violations set forth in Article 2.1 through Article 2.10 of the *Code'* [33]. The word *doping* became a part of the English language by 1933 [40]. The World Anti-Doping Code also defines doping as 'possession, administration or attempted administration of prohibited substances or methods, trafficking or attempted trafficking in any prohibited substance or methods'. It is the desire to win in order to gain appraisal and related benefits that drives the athletes to abuse these substances and methods [42].

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This goal is often achieved by increasing strength or overcoming fatigue with the help of performance-enhancing drugs [50]. It is surprising to know that ancient Olympics in Greece were filled with cases of corruption and doping to such an extent that the games had to be suspended [42]. Since the late 1960s, blood doping, the reinfusion of an athlete's own concentrated oxygenated red blood cells or those of a matched donor, shortly before competition, was alleged to have been used by European runners, cyclists, cross-country skiers and biathletes [50]. Cyclist Lance Armstrong; the Seven-time winner Tour De France 1999 champion was consistently accused of blood doping and had won all the seven matches by cheating. Armstrong was also stripped of the seven Tour de France titles he won from 1999 to 2000.

Blood Doping

Defining Blood Doping

Blood doping also called as induced erythrocythemia, blood boosting or even blood packing. WADA defines it as "the misuse of certain techniques or/and substances to increase one's red blood cells, allowing the body to transport more O_2 to muscles to increase stamina and performance". In aerobic sports disciplines, such as long- distance running, cycling or cross-country skiing, the main factors determining performances are a high delivery of O_2 to the exercising skeletal muscles and its use [27]. 'The 2017 Prohibited List'

given by 'The World Anti-Doping Code' includes Blood Doping under Prohibited Method M_1 i.e. The Manipulation of Blood and Blood Components.

According to this method the following are prohibited:

1. The administration or putting back any quantity of autologous, homologous or heterologous blood, or red blood cell products of any origin into the circulatory system.
2. Enhancing the uptake, transport or delivery of oxygen artificially.
3. Any form of intravascular treatment of the blood or its components by physical or chemical means [33].

The International Olympic Committee (IOC) officially banned blood doping after the 1984 Olympics. In the same year, the USA Olympic Committee declared that seven out of 24 cyclists of the national team who participated in the Olympic Games, used transfusions [32].

Methods and Techniques of Blood Doping

There are two basic techniques of blood doping; heterologous and autologous blood doping:

Heterologous Blood Doping

In heterologous blood doping, the blood of matched donor is transfused in athlete's body. Though this method is widely used for therapeutic uses, it can pose harm to the athlete's body if the blood is infected.

Autologous Blood Doping

The Autologous blood doping involves removing two units of the athlete's blood, storing the blood and then reinfusing it about seven days prior to the athletic contest. Venesection needs to be performed at least three weeks before reinfusion to allow the subject's hemoglobin to recover to normal levels. Autologous blood doping is difficult to detect. Another method of doping is conventional blood bank method in which whole blood is citrated and refrigerated at 4^oC without addition of preservatives and anti-coagulants, therefore the blood deteriorates steadily and its viscosity increases with increasing brittleness of red blood cells. High glycerol freezing technique is used routinely used for autologous blood transfusion where patient is facing major blood operation and only wish to receive their blood. The blood is centrifuged and glycerol added to the high concentration of red cells which are then frozen at -80^oC in liquid nitrogen. At the time of infusion, cells are washed in order to increase their osmolality to remove glycerol and re-suspended in normal saline and re-infused in a suspension with hematocrit of approximately 50% [28].

Altitude Training Simulations

Other legal ways to increase the number of red blood cells includes simulation of altitude training [43]. During athlete's acclimatization to altitude, his maximum exercise capacity is reduced. To overcome this problem, many athletes were taken to altitude in the weeks prior to the competition. Athletes who reside at sea level are at a disadvantage when competing in endurance events at altitude [18]. This includes using a sleep chamber for 6 to 8 hours/ per day for 2 to 3 weeks, produces substantial increases in serum EPO, reticulocyte count and up to 23% RBC mass leading to improvement in post-altitude endurance performance. An alternative technique to simulate altitude is breathing hypoxic, normobaric gas [32] that pushes the packed cell volume (PCV) to release natural EPO and blood cells, so that more oxygen is absorbed with every breath [43].

Effects of Blood Doping

Erythropoiesis is part of the large process of haematopoiesis, which involves the production of mature cells found in the blood and lymphoid organs [41]. This gives rise to improved vascularization of the muscle resulting in greater oxygen mining from the blood; helping the athlete uptake very high levels of oxygen for sustained periods of endurance work. Blood doping could be ergogenic through its effect on oxygen carriage, blood volume and cardiac output by producing a Polycythemia. Increase in plasma volume allows a greater blood flow to the skin for dissipation of heat. In many forms of endurance exercise, particularly in hot conditions, a significant part of the cardiac output is involved in heat dissipation with blood being shunted through the superficial layers of the skin. Transfusion of 450 ml whole blood on 4 consecutive days decreases submaximal exercise heart rate (in hypoxia) for several weeks, thereby predicting that exercise performance would be increased [27]. The adverse effects of blood doping are increased transfer of infectious disease such as AIDS and hepatitis, if heterologous transfusion is used; it carries risk of intravenous infections such as venous thrombosis, phlebitis and septicaemia. For climbing Mount Everest without supplemental oxygen, a high haematocrit up to 60% would be needed. As the level of hematocrit increases, it increases viscosity of blood. Hyper viscosity associated with high haematocrit levels increases the risk of thrombotic events such as stroke and myocardial infarction. Evidences suggest that, EPO was a key suspect in many deaths [13].

Detection methods

Blood doping virtually disappeared with the arrival of RhEPO in the market at the end of the 1980s. But due to unavailability of detecting methods blood doping has been back in practice [41]. The essential characteristic of any anti doping strategy is the ability to sanction an athlete based identification of a banned substance by subjecting to random, unannounced testing during the weeks before event [9].

Hematologic Passport

Hematologic passport is based on the sequential evaluation of some hematological and biochemical parameters [33]. Erythropoietic substances and RBC parameters are affected by blood doping due to the relationship between Hb mass and physical performance in aerobic sport disciplines for determining high delivery of O_2 to the exercising skeletal muscles [28]. For detection of autologous (self) transfusion, current hematology values for each athlete are compared with past values [1]. Michael Ashenden had proposed that on observing significant deviations from the expected value in progressive logs of each athlete's PCV and hormone concentrations, the athlete should require follow up testing. The Italian Cycling Federation decided in 2000 that all juniors would be tested to provide a baseline PCV and given a

''Hematologic Passport'' which helped them to overcome the detection problems of re-transfused autologous blood [44].

Flow Cytometry

Nelson *et al.,* (2004) suggested the use of blood group antisera to identify mixed RBC populations in blood samples by flow cytometry [28] as it allows detection of even a single unit of blood transfused, provided that there is at least one antigen mismatch between donor and recipient [33]. A test for detection of allogeneic blood transfusion doping involves blood group antisera to identify mixed RBC populations in blood samples by flow cytometry [46]. Identification of the survival of transfused RBCs in patients by flow cytometry can be determined by capturing its FSC (Forward Scatter Cytometry), SSC (Side Scatter Cytometry) and fluorescence intensity data on the computer. Mixed population of cells with antigenic differences can be analyzed individually via their different levels of fluorescence at the appropriate wavelength, without the need for physical separation [1]. In the analysis of 140 blood samples, no false positive test was obtained signifying a 100% specificity of the method [28]. Based on his studies, Berglund produced an algorithm to detect blood doping from the conventionally refrigerated sample as such blood rapidly increases serum iron and bilirubin, and decreases EPO. Unfortunately the serum EPO is suppressed by physical exercise causing a limitation in its detection [46]. Since the mid-1980s, several other techniques for enhancing blood oxygen-carrying capacity were developed including blood transfusions, administration of Erythropoiesis stimulants, blood substitutes, natural or artificial altitude amenities, and novel gene therapies to enhance the endogenous Erythropoietic response [33].

Gene Doping

Defining Gene Doping

Gene doping is defined as "the non-remedial use of genes and genetic materials that have capability to enhance athletic performance". The artificial gene is administered by direct injection of DNA into muscles; insertion of genetically modified cells; introduction utilizing a virus. Erythropoietin, insulin-like growth factor (IGF) and vascular endothelia growth factor (VEGF) are some of the substances used by athletes to increase their athletic performance [18]. 'The 2017 Prohibited List' given by 'The World Anti-Doping Code' includes Gene doping under Prohibited Method M_3 i.e. Gene Doping. According to this method the following are prohibited:

1. The transfer of polymers of nucleic acids or nucleic acid analogues;
2. The use of normal or genetically modified cells [34].

First addressed in 2001 by the International Olympic Committee and later prohibited in 2003 by the World Anti-Doping Agency (WADA), gene doping has raised concerns for several years; however there is no definitive evidence to support that gene therapy has ever been used as a form of athletic enhancement [12].

Genes used for Doping

Recombinant human erythropoietin (r-HuEPO)

EPO gene is responsible for production of hormone Erythropoietin which is produced mainly in the kidney (90%) and in liver (10%). This gene is mainly used in clinical therapies of thalassemia and chronic anemia due to renal failure. It stimulates the Erythropoiesis in the bone marrow resulting in increased levels of hemoglobin and hematocrit. High level of Hb (Hemoglobin), Hct (hematocrit) and $VO_{2\ max}$ (maximum volume of oxygen) [28] are responsible for an increase transport for oxygen to tissues and hence increases athletic performance. The increased amount of red blood cells leads to high viscosity of blood leading to chances of heart attack [45]. Difficulty in detection adds to its doping advantage [30].

Recombinant Human Growth Hormone (r-HuGH)

Strength and power athletes such as weightlifters and sprinters started using rhGH to improve their muscle strength and decrease body fat [37].

Insulin- like growth factor-1 (IGF-1)

This gene is responsible for muscle mass and size [30]. Use of gene for IGF-1 disproportionately causes strong muscles [45]. It is synthesized by the skeletal muscle itself and acts locally. In a study by Musaro *et al.* (2001) mice induced with IGF-1 gene demonstrated marked muscle hypertrophy and increased injury healing response.

Myostatin gene (MSTN)

Myostatin (MSTN), or growth and differentiation factor 8 (GDF-8), is a member of the transforming growth factor (TGF-β) family which acts at physiological levels to limit muscle mass [50]. It prevents the uncontrolled growth of skeletal muscles. This gene is used in treatment of muscular dystrophy [30]. Removal of this gene might cause tears or fractures of bones [45]. Mosher *et al* performed artificial mutation in myostatin gene in racing Whippet dogs which resulted in 'double muscled' dogs with significantly less fat mass. These dogs showed markedly improved racing performance [30]. The first case of a human mutation in the MSTN gene was described in 2004 by Schuelke *et al.* where, a German athlete gave birth to a child with extraordinary musculature (mainly in the arms and legs) compared to a child of the same age [50].

Vascular Endothelial Growth Factor (VEGF)

This gene stimulates the production of new blood vessels [47]. It provides additional blood flow to the heart, lungs, muscles and other organs, therefore delaying exhaustion. Endorphins and Enkephalins are used pain-relief drugs for athlete's body. This gene is an alternative to chemical drugs; which are taken for relief from pain [30].

Methods of Gene Doping

Viral method is most efficient method of gene transfer; but it requires a large commitment of financial resources to ensure the highest safety precautions are met. Another method is through ex vivo introduction, which involves removing a group of cells from the patient that are related to the disease [37]. The steps that made feasible and triggered a new era in the manufacturing of synthetic EPO were the isolation and characterization of the human DNA region that codifies endogenous EPO, and the creation of a complementary mold copy of the same region (c-DNA). All RhEPO produced by

different manufactures have different analogies, because they come from different sources of synthesis [4].

Risks involved in Gene Doping

With genetics in sports, athletes would not need to strive or make sacrifices to obtain good results causing the loss of the sport practice spirit and the loss of popularity of sport. Integration of viral vectors into the host genome carries the risk of insertional mutagenesis post humanism or trans-humanism. Gene Doping is not only causing harm to the athlete's health but also to others; means to the future individual [45]. Gene therapy might develop leukemia and shows flu like symptoms [30].

Detection of Gene Doping

There are many possible methods of detecting gene doping. Artificially manipulated genes are likely identical to naturally occurring genes and its products [37]. The research has yielded several different prospective methods for testing; including "muscle biopsy" and "Indirect measurement of enzymes or proteins" [45] and techniques such as microarray or sequence-based transcriptional profiling and proteomic and metabolomic analyses that can define molecular "signatures" of exposure to specific doping agents, or families of drugs, or methods. These help to identify disturbance in physiology [18]. The easiest test is the molecular test-to detect insertion vector in the plasma and other body fluids; but the disadvantage of this test is vectors have short half life. Therefore, the test should be carrying out in short period of time. Muscle biopsy at the site of the injection is reliable method for detection of gene doping provided that the athlete submits readily since this method is invasive [17].

Another method is 'genetic bar code method' or 'labeling of gene transfer products'. The engineered genes do not contain introns. This fact can be used in detecting gene doping by using molecular tests, but the disadvantage of this technique is it requires tissue sampling like muscle biopsies. This method of testing is invasive in nature so very unlikely to be accepted by athletes and sporting authorities. Structural differences between endogenous and RhEPO can be detected by this technique [37]. The review of the work done by François Lasne and colleagues (2004) suggested that in a comparative study of the iso-electric profiles of physiological Epo and Epo resulting from in vivo gene transfer in primates, it was found that the induction of exogenous Epo resulted in over expression and

Table 1. Detection techniques of Blood Doping and Gene Doping suggested by different authors

Author and Year	Detection Technique Used	Limitations of Technique
Wolfgang Jelkmann and Carsten Lundby (2015); Lippi et al. (2006); Unal et al. (2004)	Athlete's Biologic Passport or Hematological passport	The measuring devices, processing of the analytical data and the assessment of abnormal parameters to be the result of doping; the applicability in sports practice; the impact on research.
Wolfgang Jelkmann and Carsten Lundby (2015); Lippi et al. (2006); Arndt et al. (2004)	Allogenic transfusion: a.Direct detection of blood or urine samples b.(for transfusion)- flow cytometry Autologous transfusion: c.Indirect detection (for autologous blood transfusion)	May give false-positive results. It does not detect autologous transfusion.
Truong HB and Ip EJ (2012), Robinson et al. (2006), Haisma et al. (2006), Bento et al. (2003)	RhEpo detection a.Direct method:- isoelectric technique based on hyposulfated sugar concentration in urine b. Indirect method: Measuring various parameters like Hct, serum erythropoietin concentration, sTFR, reticulocytes, 1.ON model- measures RhEPo shortly after use. 2.OFF model- identify RhEPo weeks after stoping treatment	Time consuming, expensive. Need for blood, need for counter analysis.
Dr. kamble et al. (2012), Haisma et al. (2006)	Molecular tests to detect Insertion vectors in the plasma and other body fluids of a person	Vectors (Plasmids and virus vectors) have very short half life. Therefore, we need to carry out these tests with relatively shorter intervals and with regular testing regimes.
Haisma et al. (2006)	'Genetic bar code method' or labeling of gene transfer products	Need for the complete Cooperation of scientists, ethicists, athletes, sports authorities, medical practitioners, professional societies and none the less, public.
	The engineered genes do not contain introns. This fact can be used in detecting gene doping molecular tests	Involve tissue sampling like muscle biopsies. Invasive nature- not accepted by athletes
Baoutina et al. (2010)	PCR assays to detect small amount of Epo	cDNA–EPO sequence is modified by insertion of small introns in a targeted exon/exon junction or by site-directed mutagenesis of sequences for primers and/or probe annealing.
Mayne et al. (2008), Fore et al. (2010)	Muscle biopsy	Invasive and the majority of athletes would not be willing to undergo this test before or after training orcompetition.
	Indirect measurement of enzymes or proteins	These levels may be increased or decreased due to the gene that has been altered in the cells.
	Proteonomic Database- method of testing that would be specific to each athlete.	Require consistent measuring of various Proteins and hormones in the blood and comparing them to reference levels.
Brand et al. (2014)	Indirect test- implicit attitude test (IAT) and Picture-based doping-BIAT Direct test- PEAS(The Performance Enhancement Attitude Scale)	Reaction time can be changed

thus a different isoelectric pattern than the endogenous form was observed [12]. Difficulties in detection are due to the fact that EPO is a complex macromolecule, present in low concentrations in biologic fluids, with quite a similar structure to its endogenous form, which made impossible for one to accurately identify its illicit use for a long time. Two mathematic models were designed with the use of data from placebo and RhEPO: the ON model, to identify current RhEPO users, and the OFF model, which was intended to identify the athlete who had recently discontinued RhEPO administration. At the same time, a direct test to detect RhEPO was developed by Paris doping control lab, based on subtle differences between RhEPO and physiologic EPO carbohydrate residues [4]. Even with advanced biotechnology, gene doping may not always be detected thus giving an advantage to this technique [12]. The problem with measuring gene product levels is that it fails to distinguish doped athletes from athletes with natural genetic mutations that cause them to have high levels without artificial enhancement [17]. The detection methods should be highly specific, sensitive and be properly validated to be able to withstand legal scrutiny [2]. The development of detection methods at the global scale, educating the athletes regarding the risks of gene doping and re-evaluating the existing regulations for gene therapy are the few preventive measures that should be undertaken [30].

RESULTS AND DISCUSSION

Athletes are tempted to use prohibited substances in order to improve their strength. These prohibited substances are not only used by athletes in the world of sports but also amongst individuals, mostly young ones, who are engaged in sports recreationally. Some drugs like erythropoietin and growth hormones, and methods like autologous blood transfusion are very difficult to detect as they mimic naturally present hormones in body. This is the main drawback of all the detection tests which are derived for the purpose of offering fair-play to all the athletes [44]**.** Gene doping is providing WADA and other anti-doping organizations with their greatest challenge in the fight to preserve clean competition [37]. The study of Deckx *et al.* (2012) concluded that 94% respondents thought that gene doping was equivalent to cheating. However, lack of similar studies with regard to doping and gene doping suggested that, there is a need for sociological, behavioral and ethical research to query the attitudes of athletes to the use of doping in sports. As there is a need to overcome the problem of doping in sports to achieve fair play, the scope for analysis of Prohibited Substances and Prohibited Methods is widened. Athletes are indulging in the use of new drugs that can alter their physiology and can mask their presence. Being active in the field of Research related to Doping is crucial now, thereby stating that this study has practical scope in future.

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