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Original Article

Updated Evidence Report for the Anti-doping research: analysis from 2008 to 2018 for performance-enhancing drugs and gene doping test development

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Abstract
Introduction: Since ancient times, man has always tried to overcome his skills through the use of substances and drugs whose nature has changed over time. From substances of natural origin to those produced in the laboratory up to the use of real methods. Unfortunately, the use of these substances causes harmful effects on health and alters the principle of fair competition in sports. **Methods and Materials:** We have analysed the anti-doping controls (prohibited substances and methods) carried out by the Ministry of Health from 2008 to 2018 (www.salute.gov.it). The literature search was performed on PubMed and Scopus database and Italy Anti-doping official website. The authors have extrapolated test controls and combined the information on the consumption of doping substances in male and female athletes. **Results:** the years 2008 and 2018 recorded the lowest percentage with 2.1% of positives out of a total of 594 tests carried out in these years. From 2009 to 2018 the greatest number of doped athletes is male. Shifting the focus on the consumption of prohibited substances, the most assumed substances are the anabolic agents with an average of 15,4, followed by diuretic and masking agents – 10,3 – and stimulants – 8,5- The other substances have an average of consumption lower than 7. In particular, the lowest number of assumption is recorded for hormones and metabolic modulators – 1,2 - and beta-blocker - 2,7 -. **Conclusion:** The desire for victory has also led to the use of genes to change one's organism forever and irreversibly. Genetic doping is perhaps the most dangerous of methods and certainly the most difficult to discover. To date, in fact, there are no safe and ethical methods that allow to identify genetically modified athletes. In any case, science is attempting to discover new tests precisely to defeat all types of doping
Keywords: Sport, drug, gene doping, doping control.

Introduction

The history of doping, or rather the use of banned substances to improve the sporting represent ancient result (Mazzeo, 2016a). Moreover, the exact date on which the word doping was used is recognized: in 1889 a measure of opium narcotics and tobacco was defined for racehorses in a racecourse in North America. Over time, the belief that medicinal substances can not only heal diseases and eliminate ailments, but improve sports performance, has spread throughout human society (Mazzeo F., 2019d; Barkoukis,et al., 2019). Currently, although there may be a decrease in the number of positive cases of doping tests, there is also the feeling that some athletes are resorting to increasingly sophisticated pharmacological aid practices (Barrie et al., 2019; Mazzeo et al., , 2015).

The Sports Federations, of all nations have sanctioned in their regulation the ban on the use of substances considered to be doping. In particular, the International Olympic Committee (IOC) has defined doping as "the administration or use by any competing athlete of any substance extraneous to the body of any physiological substance taken in abnormal quantities or introduced into the body by an abnormal route with the sole intention of artificially and unfairly increasing performance during the race ".

Furthermore, the use of performance-enhancing substances (PES) by athletes (doping) is a prohibited practice, which is prevalent world-wide. Originally, at the time of the Greco-Roman fighting, people taken natural or animal origins substances – for example various types of plants or sheep's testicles (Mazzeo, 2019a; Montesano et al., 2013). Gradually, artificial drugs and methods were also used (Botrè, 2008; Montesano et al., 2018). In fact, all the people involved in doping have been able to discover ever new enhancement substances and methods (Thevis, 2020; Botrè, 2008). Doping is a really huge and dangerous phenomenon for sport worldwide and for the individual's health. Indeed, it undermines the principle of open and fair competition, disheartens sport's practice and puts the professional under unreasonable pressure (Mazzeo, 2019b; Mazzeo et

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al.,2018). According to Botrè (2008) since 2008, there was a spreading of new doping methods: the gene doping. In fact, following the decoding of the human genome, doping stakeholders have started to apply this knowledge for their own purposes: athletes inject novel or genetically modified material in their body in order to boost their physical performances (Cantelmo, 2019; Neuberger, 2017; Montesano et al., 2016). However, the attention on gene doping began many years earlier. Since 2001 the International Olympic Committee investigates this new method and since 2003 it is prohibited by the World Anti Doping Agency (WADA), although there weren't evidences of gene doped athletes (Mazzeo & Volpe 2016). Moreover, since 2004 the anti-doping authorities has focused their attention on the detection of it. Nowaday, according to the 2020 Prohibited List, for gene and cell doping is meant: "The use of nucleic acids or nucleic acid analogues that may alter genome sequences and/or alter gene expression by any mechanism. This includes but is not limited to gene editing, gene silencing and gene transfer technologies" and "The use of normal or genetically modified cells." (WADA, 2020). Unfortunately, to date, the tests to identify the modification of genes in athletes have encountered enormous difficulties and there are no specific tests (Mazzeo & Volpe 2016).

Really, athletes who participated to the Summer Olympics in Rio de Janeiro may eventually faced a new kind of doping test: one that checks whether they have received performance-enhancing gene therapy. According to the International Olympic Committee's medical and scientific director, samples collected in Rio have been tested for gene doping; at some point, even though the test was not run during the Olympics itself (Barrie et al., 2019; Mazzeo et al., 2019). Though most media attention focuses on doping by professional athletes, there's also a growing doping problem among the general public.

Therefore, there are a variety of drugs and methods which are commonly used in a sports medicine setting. These are usually used to manage pain or in an attempt to reduce inflammation (Schenone et al, 2003; Motola, et al.2001).

Moreover, elite athletes may be subject to drug testing. For these athletes, doctors can be very 'dangerous' people as the use of many common substances can lead to a positive drug test (Mazzeo & Raiola, 2018).

Methods and Materials

We have analysed the anti-doping controls (prohibited substances and methods) carried out by the Ministry of Health from 2008 to 2018 (www.salute.gov.it). The literature search was performed on PubMed and Scopus database and Italy Anti-doping official website. The authors have firstly analysed the data of Italy Anti-doping official website of each single report of the above mentioned Ministry, then they have extrapolated test controls and combined the information on the consumption of doping substances in male and female athletes.

Results

Before analyzing the data in Graphs 1 and 2, it is important to consider the prohibited substances and/or the amount of substance prohibited constantly change: some of them have been eliminated over time while others have been added. For example, pseudoephedrine and norephedrine were removed from the list in 2003 but in 2013, the first substance was reintroduced with a different dosage. Moreover, the number of tests carried out changes from year to year, also considerably and, therefore, the impact of positive athletes on the total number of controlled subjects must be considered.

First of all, although the number of checks was higher in 2011, the highest percentage of positives was recorded in 2014, with 4% of the total (58 positives out of 1427 tests)

In contrast, the years 2008 and 2018 recorded the lowest percentage with 2.1% of positives out of a total of 594 tests carried out in these years

Except for the year 2008, from 2009 to 2018 the greatest number of doped athletes is male. The higher number of male positive is recorded in 2014 and 2015, followed by 2010 with respectively 50 and 47 cases. Differently, the number of positive woman is rather insignificant.

Shifting the focus on the consumption of prohibited substances, the most assumed substances are the anabolic agents with an average of 15,4, followed by diuretic and masking agents – 10,3 – and stimulants – 8,5- The other substances have an average of consumption lower than 7. In particular, the lowest number of assumption is recorded for hormones and metabolic modulators – 1,2 - and beta-blocker - 2,7 -. No tests for gene doping test are programmed.

Discussion

Anti-doping Instruments

The fight against doping in sport is internationally coordinated by the World Anti-Doping Agency (WADA) and its Anti-Doping Code in 2004. From its first draft, the Code has always indicated what is prohibited for doping and what sanctions were foreseen (Gandert, 2019; Mazzeo, 2019). To assist the Agency in the scientific research of new substances and in the identification of cases of violation of the Code, there are the accredited laboratories, the Biological Passport, the Anti-Doping Administration and Management System (ADAMS) and the anti-doping controls on athletes. As concern the laboratories, in order to be accredited by

WADA for anti-doping purposes, they must have certain technological advancement requirements: all over the world there are only 30 laboratories choosed by WADA (WADA, 2020b). The laboratories analyse the biological sample, fix the prohibited quantitative of doping substances and determine cases, criteria and methodologies of anti-doping tests too (Mazzeo, et al 2018; Montesano et al,2020). The ADAMS is an on-line database system with which it is possible the global monitoring of the athlete by comparing various information: laboratory results, therapeutic use exemptions (TUEs) and anti-doping rule violations (Greene, 2019). It allows the sharing of information amongst the organizations too. As regards anti-doping controls, there are two ways to detect the presence of a doping substance in biological samples of an athlete. The first one, the Biological Passport, is an indirect detection tool. It allows to understand if an athlete has taken doping substances, through the recording and monitoring of biological, haematological, endocrinological and localization data too (Devriendt, 2019; Houlihan, 2019; Mazzeo, F., 2020). The latter is a direct detection tool and consists of tests on biological samples. Figure 1 showed when scientists retested athletes' samples in 2016 with more sensitive methods, they found a higher rate of doping than initially reported.

Anti doping test

According to the art. 5 of 2015 Wada Code – with 2019 amendments and in now in force - , doping test shall be undertaken in order to discover doped athletes (Wada, 2015; Duval, 2016). It represents a fundamental moment to safeguard the integrity of the values of sport - first of all the fair competition - and to protect the health of athletes (Mazzeo, 2019b). The anti-doping authorities establish urine and/or blood tests (Mazzeo, 2018). All operations relating to the collection and the storage of biological samples are meticulously performed according to specific protocols in order to preserve the health and privacy of the athletes and the certainty of the results (Waddington et al.,, 2019; WADA 2014). Biological samples are analysed exclusively in WADA accredited laboratories. The Code establishes that athletes can be tested at any time and in any place. After being chosen for the tests, they are conducted in special sterile room, informed about the biological sample collection procedure and on the possibility to choose the sample kit (WADA 2014 ; Elbe & Overbye et al., 2014). Furthermore, in order to protect the athlete's privacy and to make the samples anonymous, to each athlete is assigned a code so the accredited laboratory doesn't know the identity of the controlled people. The tests are carried out in the presence of the doping control officer (DCO) who records all the information relating to the athlete - state of health, last location, last physical activity and any transfusions or taking drugs -, and to the operations carried out until the end of the test, including the athlete's collaborative or non-collaborative conduct (WADA, 2014). As concern the urine analysis, in order to avoid tampering and / or falsification of the sample, the DCO, of the same sex of the athlete, must ensure the direct passage of the urine from the body to the sample (WADA, 2014). The minimum quantity must be 90 ml which can be produced even in several moments, always under the supervision of the staff (Elbe & Overbye et al., 2014; Kojima, 2016). With regard to the blood sample, the athlete must position himself comfortably with feet on the ground for at least 10 minutes before the sample. He can choose from three samples collection kit. The Blood Control Officer (BCO) disinfects the skin where to take the sample. He has a maximum of three attempts to withdraw the minimum quantity required for the test (WADA,2016). The DCO or BCO must ensure that all procedures are clear, understandable and visible to the athlete (Kojima et al., 2016; Stella et al., 2005; WADA, 2014).

Gene doping test

Several methodologies have been proposed to the identification of genetically doped athletes. This has always been a highly discussed topic. Specifically, it was objected that routine tests were unable to detect the presence of modified genetic material in the athletes' bodies (Brzeziańska, 2014) Moreover, until today, there aren't specifics WADA standardized methods (Guilherme, 2007). The only probable alternative could be tissue sampling but this type of control as well as being highly expensive involves ethical problems, linked to the invasiveness of the control (Hermann, 2014; Breivik, 2005).

Furthermore, this kind of test could be able only to identify the direct injection of genes in the desired target organ but it is not valid in case of transfer of the human origin gene due to the equality of genes between donor and recipient. In this case, only the protein level in blood could be indicative for doping abuse but genes may be turned on and off by taking specific drugs (Baoutina, 2010).

Over time, different alternatives have been proposed, unfortunately all characterized by invasive approaches. Recently, WADA works to implement the information in the Biological Passport through the identification of the genes necessary to improve sports performance (Mazzeo & Volpe, 2016 ;de Boer, 2019; Wada, 2020c). Indeed, the periodic detection of some proteins is able to identify any abnormal alterations in the gene expression which could result as a suspicion of gene doping. Unfortunately, it is possible to do this examination only within approximately 60 days after administration of any doping substance, thus it is not possible consider it an effective and valid method (Mahendru et al., 2019).

More important than the ethical implications of gene doping, some experts say, is the fact that gene doping could be dangerous, and possibly even fatal.

Conclusion

First of all, we have to consider that gene doping can be dangerous and detrimental to health. Indeed, there is a risk that the modification of the body through the use of gene therapy may cause various diseases such as cancer and have an impact on future generations, too. In particular, the genetic material, created in illegal laboratories without any controls on sanitary conditions, could be contaminated with chemicals and other impurities from the production and purification process (Mazzeo et al., 2018; Elbe & Overbye, 2014.).

Currently, it is very difficult the identification of athletes who have adopted the genes. Indeed, the detection of chemicals or associated viral particles may involve tissue sampling and it will be unlikely that athletes will be forced to give consent to this procedure, given the invasive nature of the biopsies needed to present. Furthermore, many forms of genetic doping do not require the direct injection of genes in the desired target organ. 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 (Ritchie & Henne, 2018; Montesano et al., 2019).

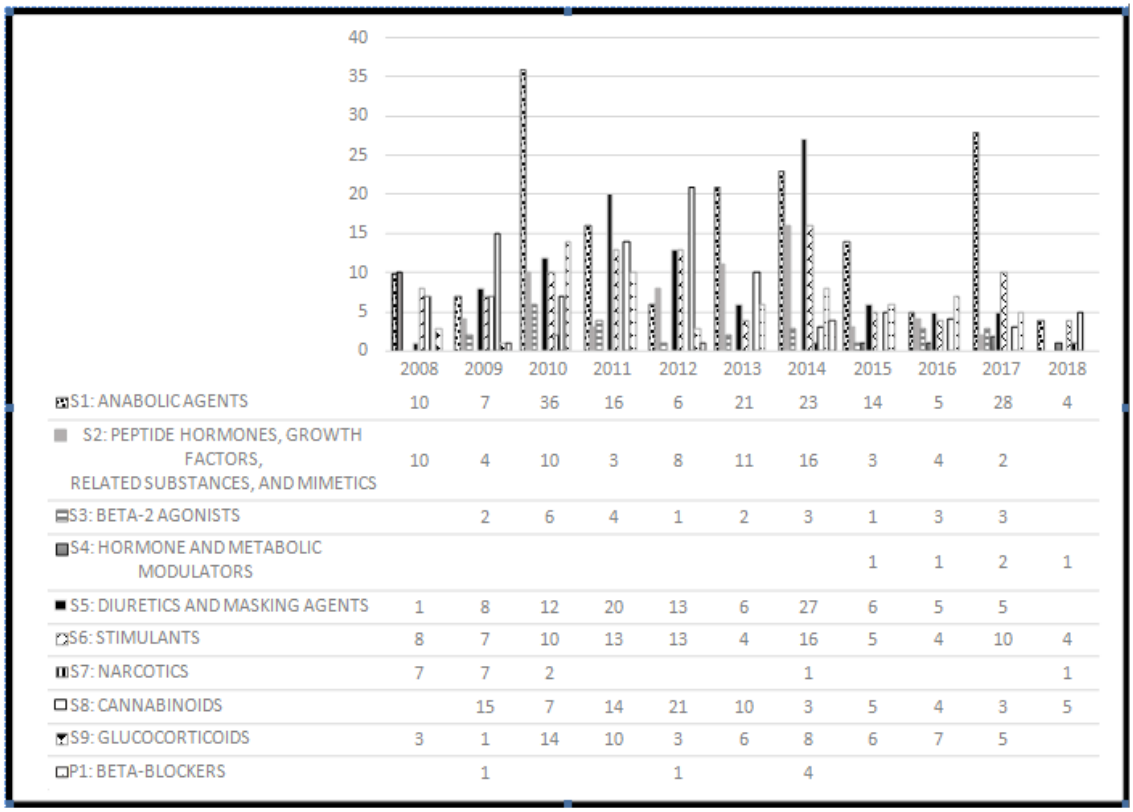
At any rate, there is an additional problem linked to the circumstance that the work on the standardization of reliable tests to detect gene doping is uncompleted. The scientific and medical communities should support the activities of the World Anti-Doping Agency (WADA) in developing new methods of gene doping detection and updating the lists of banned agents. In addition to educational programmers for athletes, and development of tests for gene doping detection, an individual method of gene doping control should be introduced, in which each athlete would be the self-reference baseline. In the case of such an approach it would be necessary to collect in an individual athlete database the results of his/her tests (biochemical and haematological), and possibly the expression profile of genes that can be potentially used for gene doping, to monitor it over time. UCI (Union Cycliste Internationale), WADA and IAAF (International Association of Athletics Federations) have already introduced a project known as the Athlete Passport to gather individual athlete testing data (WADA 2009–2013) (Mazzeo, 2016b). In the future, such a personalized method of doping control may be the main method of combating this complex problem. In summary, to prevent the development of gene doping, international sports organizations should conduct numerous educational campaigns among athletes, pointing to the risks and ethical problems associated with its use (Waddington & Møller, 2019).

Despite the difficulties noted above, it seems that winter 2019 has brought important changes (WADA, 2019a; Brown. 2019). In fact, WADA and IOC enthusiastically announced important developments in the search for doping substances and in genetic doping (WADA, 2019a; IOC, 2019). The first one regards the implementation of a particular blood test which uses the Dried Blood Spot (DBS) method, that could be considered a revolutionary weapon in the fight against doping (WADA, 2019a; IOC, 2019; Kojima, 2016, Thevis, 2020,). Differently from the "traditional" blood tests, DBS involves the use of a drop of blood through a simple puncture on the finger. This method, could also be preferred by athletes as an alternative to the inconvenience of the classic collection method. Others advantages is linked to the reduction of costs associated with the transport and storage of the biological sample and the less degradation of it (WADA, 2019a; Thevis, 2020). The last one - and very important - news is that the research on genetic sequencing, financed by the IOC and conducted by Professor Yannis Pitsiladis, are leading to good results (IOC, 2019; Wang, 2017). The Pitsiladis's research, started in 2006, involves identifying the changes in the body's genetic signature after a transfusion or taking a banned product that increases the production of red blood cells - including erythropoietin (EPO), the most widely used drug used to increase the sports performance - (Yan, 2017; Pitsiladis, 2014). The great novelty and importance of Pitsiladis' work is the discovery that there are approximately 21,000 genes in the body and several hundred are activated when an athlete has taken on EPO or has undergone a blood transfusion. This change in the athlete's genetic signature will remain detectable for weeks - perhaps months - after the use of these types of doping. (Wang, 2017; Yan, 2017). The studies, now in the final phase, will lead to a test for the detection of genetic doping which, if approved by WADA, can be used already in Tokyo Olympic Games 2020 (IOC, 2019).

The field of gene therapy, and by extension, gene doping, is full of unpredictable and dangerous. The therapies need to be proven and the research is still at only an experimental stage as Savulescu says, "in the spirit of sport."

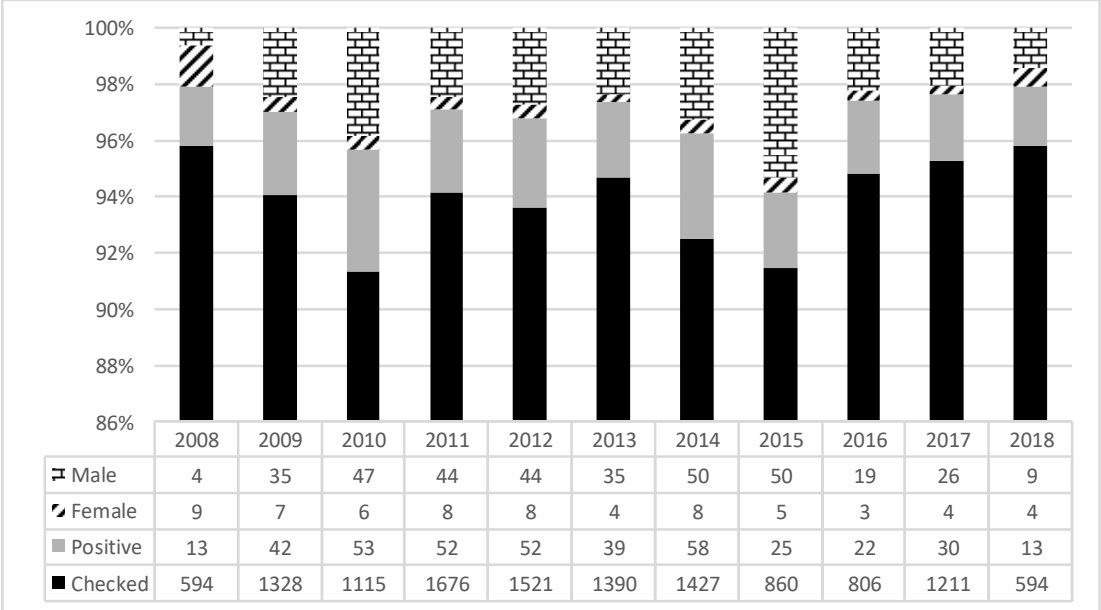
Disclosure statement

No potential conflict of interest was reported by the authors.



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
S1: ANABOLIC AGENTS	10	7	36	16	6	21	23	14	5	28	4
S2: PEPTIDE HORMONES, GROWTH FACTORS, RELATED SUBSTANCES, AND MIMETICS	10	4	10	3	8	11	16	3	4	2	
S3: BETA-2 AGONISTS		2	6	4	1	2	3	1	3	3	
S4: HORMONE AND METABOLIC MODULATORS								1	1	2	1
S5: DIURETICS AND MASKING AGENTS	1	8	12	20	13	6	27	6	5	5	
S6: STIMULANTS	8	7	10	13	13	4	16	5	4	10	4
S7: NARCOTICS	7	7	2				1				1
S8: CANNABINOIDS		15	7	14	21	10	3	5	4	3	5
S9: GLUCOCORTICOIDS	3	1	14	10	3	6	8	6	7	5	
P1: BETA-BLOCKERS		1			1		4				

Graphic 1: Spread of doping substances



	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018
Male	4	35	47	44	44	35	50	50	19	26	9
Female	9	7	6	8	8	4	8	5	3	4	4
Positive	13	42	53	52	52	39	58	25	22	30	13
Checked	594	1328	1115	1676	1521	1390	1427	860	806	1211	594

Graphic 2: Number of doped athletes from 2008 to 2018 breakdown by gender

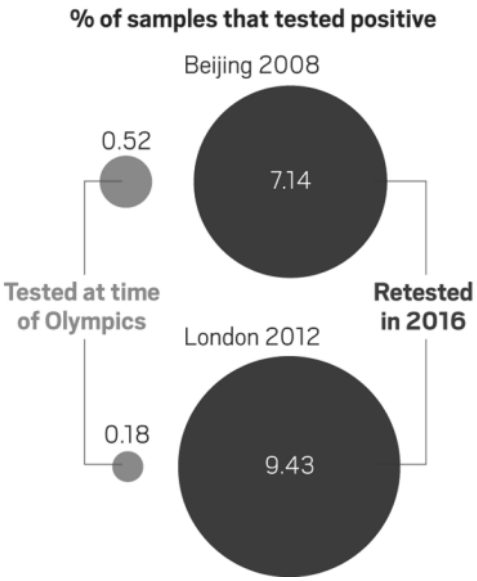


Figure 1

Busted

When scientists retested athletes' samples in 2016 with more sensitive methods, they found a higher rate of doping than initially reported.

Note: Not all samples originally tested during the Olympics were retested in 2016. For example, there were 5,051 samples tested in 2012 in London. In 2016, 403 of those were retested.
Sources: World Anti-Doping Agency and Arne Ljungqvist

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