A Systematic review of the literature on the connection between anabolic steroids and Cardiovascular risk.

Abstract

Anabolic Steroids “AS” is a synthetic version of testosterone generated by pharmaceutical industries to deliver a similar biological impact of testosterone. As is used widely for a number of pathological conditions such as anemia and cachexia. Steroids are widely used among patients for autoimmune, respiratory and inflammatory disease. However, it was found that the same item was taken illicitly by athletes, bodybuilder and weightlifter to improve athletic to increase muscle mass and performance. Using overdoses of AS in administration of 50-1000 times higher than those which used in therapeutic purposes can be consider as an alarm of severe side effect of drug abuse. Exceeding use of AS is significantly associated with cardiovascular consequences including hypertension, arrhythmias and hypertrophy. Acute Myocardial Infraction (AMI) was reported as the main widely reported consequences of using Anabolic Steroid AS. (1,2). The causes of AMI varied between Vasospasm, Atherosclerosis, and Hyper-coagulability. Therefore, these causes potential to increase morbidity and mortalityduring overdosing AS especially with a combination with thyroid hormones, growth hormones and insulin. The main aim of this study is to do a literature review of the previous researches to combine the different AS mixture with other components that are potentially used for athletic and aesthetic purposes that can be associated with morbidity and mortality. A number of 20 studies from peer reviewed journals were reviewed in the frame of PRISMA guideline to extract a deep understanding and a panoramic view of the condition of overdosing AS for enhancing sport performance. Data are extracted from each single study and the consensus between studies were shaped as a part of the results and discussion section.

1. Introduction

Myocardial infarction (MI) resulting from drug abuse must be recognized, especially in individuals using anabolic steroids to enhance performance. Adverse effects, such as hepatic and endocrine dysfunction, and cardiovascular issues, have been reported. (1).Steroids widely used,

ranging from treatment in medical emergencies and other diseases to abuse by bodybuilders and other sports players. steroids have different applications, but its overuse leads to serious consequences including cardiac problems. linked to coronary artery disease (CAD), inducing coronary spasm, or by other unidentified mechanisms. (2). However, other risk factors also need to be considered as they are present in more than 50% of coronary artery disease cases.

Anabolic Androgenic Steroid (AASs) is a synthetic version of testosterone and a substance that has been abused and overdosed by athletes for the idea of strengthen their muscles and improve their physical performance. The term anabolic refers to increase male sex physical characteristics and promotes muscles mass and increase accordingly athletic performance (3).AAS is a human-made substance where it worked as androgen receptors but also used widely in treatment of disorders in terms of metabolic and catabolic. At some levels of lacking testosterone, anabolic can also be given for treating chronic diseases. There are different manufactured forms in which they support and optimize muscle growth with no negative consequences on released androgenic (1).Anabolic steroid isgetting an interest of the young males who obsessed of body image and involved in one or more athletics activities and recreational exercises. However, the abuse of it and overdosing can lead to serious consequences on cardiovascular system. The doses taken by athletes consider are much as 5-15 times higher than the one taken for medical purposes. The statistics reported that the number of 18.4% of recreational people overdose anabolic steroid, whereas 13.4% are athletes. These statistics are also including a number of 6.4% males versus 1.6% females (2).whereas, the rate of using steroid increased amongst adolescence to reach between 12% (4). Overdosingsteroid leads to a number of adverse cardiovascular events in which myocardial infraction, stroke can be the obvious results. There is also a number of predictors in which ventricular hypertrophy, hypertension is associated with mortality and morbidity. However, it is a real challenge to estimate the real damage occurred by overdosing steroid due to ethical restriction and lack of information and polypharmacy. Therefore, the adverse effect of AS is scientifically reported in literature. For instance, AS is more likely associated with acute myocardial infarction (1,4),and a number of cases were ended up with mortality with exceeding use of AS. (6) Literature confirmed also a significant correlation between abusing Steroid and turning into aggressive behaviors among those athletes and body builders. As Steroid is used widely in terms of therapeutic treatment. However, in long term it

was found a level of toxicity for a number of body organs including exposing symptoms of association hypertension, liver failure, coronary consequences, and also prostate cancer (2)

The reason of abusing AS can be relied to lack of awareness amongst athletes of AS overdosing physiologic risk. AS overdosing can reach to 50-1000 times as the therapeutic usage. In addition, AS is usually used in combination with different other chemical substances such as testosterone, boldenone, nandrolone and insulin (4).

Androgen receptor is the main catalyst of the anabolic androgenic effect. Androgen receptor is more widely linked to the body tissues and organs within three main action mechanisms, namely a) direct linkage to the receptor, b) via estrogen receptor through the action of 5-a-reductase, c) via dihydrotestosterone that produced via the auction of 5-a-reductase (5).AASs is a chemical and pharmacological substance of the male Hermon testosterone which is used to increase burst activities in sport.AASs is characterized with a potential impairment of testosterone biosynthesis in the body when it's taken in supra-physiological doses (3), AAS is significantly associated with activating Androgen receptor signaling which is involved in each body tissue. There is a variety of mechanism describes how AASs works in the body. However, the most common mechanism that increase AASs in blood circulation is about administration of testosterone to its synthetic derivatives (6). Therefore, at the normal cases of physiologic level of testosterone, androgen receptors reached to the saturation level, while AASs can stimulate other mechanism rather than activation of androgen receptors. Having high testosterone in the system impacts an antagonist on glucose synthesis and protein catabolism. Overdoses of AASs support displacement glucocorticoidsfrom their receptors (5). This is in turn decrease protein in the muscles which increase the possibilities of muscles growing.Overdosing of AASs binds to number of androgen receptors in which these receptors turned saturated by the time. However, there is two directions in which supervised and unsupervised usage of AASs can be considered. AASs usage under the medical supervision is familiar with medical practices under restricted conditions. Although, a number of athletes overdose not only AASs, but also by adding additional drugs to anabolic steroid such as alcohol, opioids, cocaine, gamma hydroxybutyrate, and marijuana. The combination of mixed group of drugs is associated with the vague to accurately identified the side effect of overdosing a particular drug (2)

1.2 Autopsy findings

Literature reported a variety of consequences of overdosing anabolic steroid including, sudden cardiac death, and coronary artery diseases. It shows also entire damage of myocardial damage due to hypertrophy and small vessels diseases. Based of toxicological investigation using several screening and variety of data analysis on both of blood, hair and urine sample, stanozolol was detected in hair while nandrolone was found in blood (5). Predisposition in myocardial pattern leads to sudden cardiac death. By analyzing a topsy for sudden death cases, it was found associating of taking anabolic steroid and symptoms of testicular atrophy, muscles hypertrophy, and gynecomastia.As Steroid is used widely in terms of therapeutic treatment. However, in long term it was found a level of toxicity for a number of body organs including exposing symptoms of association hypertension, liver failure, coronary consequences, and also prostate cancer (2).

This study aims to explore the extent in which AASs was investigated highlighting the conditions of different cases with various medical treatments. Having different cases diagnosed of abusing steroid based on a variety of symptoms can be presented in differentmedical treatment which helps to better understanding different dimensions of the physical and psychological consequences.

2. Methodology

Data was collected from eleven different medical studies published in peer reviewed journals (Table 1). The included scholarly articles highlight overdosing Steroid by athletes, bodybuilder and weightlifter to improve athletic to increase muscle mass and performance. Data analysis was implanted using both descriptive and contextual data analysis where consensus is reached among studies. Thematic analysis was also used to shape themes and reached the final patterns in the text. PRISMA guideline is presented in the following paragraphs in details.

2.1 Searching strategy

2.1.1 Keywords

A systematic literature review was conducted using PRISMA guideline (7). As the first phase of secondary data collection, Conducting the searching phase has been processed within identification of a number of keywords including “Anabolic steroids, myocardial infarction,

steroids, bodybuilder, athletics, heart disease, cardiovascular". Boolean parameters were also used to combine these keywords which provides more opportunity for searching strategy. A number of 215 studies have been presented, whereas 11 relevant studies were finally included.

2.1.2 Databases

The academic data bases of "PubMed, Google scholar, web of science" were used for finding research papers from peer reviewed journals indexed with Q1 and Q2. The relevant academic databases were selected for its relevancy for medical research and steroid studies. Google scholar was also selected to reach to medical databases and recognized well-cited research papers.

2.2 Selection criteria

Research papers written in English were selected. The inclusion criteria include also full text papers, studies which are published in peer reviewed journals are also considered. Papers are available only in abstracts are excluded. Such research written in other languages than English is excluded. Papers which are research papers are only included. However, other types of papers such as communication, review, technical report are excluded.

2.3 Research quality

All selected papers were reviewed against the quality standards. Sufficient and systematized data collection are considered high priority for high-established research papers. In order to maintain the overall research quality, research paper published in Q1 and Q2 journals are highly considered within inclusion list.

Table 1. Studies overviews

Author	**Region**	**Aims**	**Method**	**Results**	**Themes**
Sivalokanathan et al., (2021)	UK	To what extent performance-enhancing drugs mainly caffeine and steroid impact cardiovascular activities.	Literature review	Caffeine has no direct impact on Cardiovascular system. However, Anabolic Steroid failed to negate the adverse consequences that associated it with cardiovascular	Caffein and steroid on cardiovascular consequences

				illnesses.	
Jain and Goel, (2020)	India	Talking a case report of a younger man that struggle out of sever lifted side chase due to overdosing anabolic steroid. CAD disease seems to be for elderly group of population. However, new upward trend of body builder increases the possibility of taking proteins, amino acids and steroid to fasten the process of muscles building.	Case report	There is a significant association between abusing steroid and perceiving cardiovascular consequences. avoidance of taking steroid reduce the risk of Coronary artery diseases CAD.	Steroid on coronary artery diseases.
Johnson et al. (2023)	USA	The abuse of using Anabolic androgenic steroid for better body muscles, physical appearance and sexual function. This report aims to investigate ischemic stroke in a young individual who abuse taking stanozolol and clenbuterol for body builder context.	Case report	By investigating the patient was found that he was consuming testosterone and stanozolol for a number of weeks which leads to left sided weaknesses, ringing in the ear and slurred speech resulting failing in bathroom. Anticoagulant therapy was conducted by giving a heparin drip per cardiac protocol.	Steroid on ischemic stroke
Hernández-Guerra *et al.*(2019)	Spain	Investigating the abuse of Anabolic for a number of 6 months Steroid on a young athlete in a sudden death cases after coming back from a party	Case report	After receiving cardiorespiratory arrest, the forensic autopsy was conducted and the body show the following observations: a) external examination of the body show hypertrophy of muscles, while b) internal examination show cardiomegaly with sever coronary atherosclerosis. B) at histology acute myocardial faction was observed while blood results show existence of ethanol, stanozolol, nandrolone, and testosterone	Impact of Anabolic Android on cardiovascular activities
Heydari et al., (2020)	Iran	Aorta dissection is one of injury caused by having supra physiologic doses of steroid. This happens by weakening the connective tissue. The case of bodybuilder was investigated and all examinations of laboratory exams were conducted	Case report	Findings show that abusing steroid is significantly associated with determinate effect on myocardium. Results also reveal that overdosing steroid for exercising people may lead to aortic dissection.	Steroid on aortic dissection

Gagliano-Jucáand Basaria, (2019)	USA	Investigating the mechanism behind the ergogenic effect of Anabolic Asteroid as using it abusively amongst athletes and those who seeking for improving their body image.	Review	Investigating and reviewing in details endogenic drugs and its testosterone. It is also. Investigating its ability to exert tissue androgenic effects as it binds to androgen receptor. Finding out the verse impact of using AAS on vascular system and overall body health status.	Steroid and its impact on myocardial condition.
Tan*et al.* (2020)	USA	Investigating the overdosing of Anabolic steroid on the young man 25	Case report		
Seara et al. (2020)	Brazil	The aim of this study is to investigate the impact of overdosing Anabolic Steroid on myocardial infarction.	Review	Overdosing AS can have a negative consequence on cardiovascular system including, hypertension, hypertrophy, and arrhythmias. The challenge of reaching the cause of symptom can be due to the combination between steroid and other growth hormones but also taking insulin.	Review on the impact of AS on cardiovascular system.
Favretto et al. (2022)	Italy	To identify the cause of the death for a body builder person who found dead in hotel room	Death cause examination: toxicological investigation/ forensic medical investigation	Abusing steroid leads to death. The measurement of hair analysis leads to better identify the overdosing Anabolic steroid.	overdosing AS
Fadah et al. (2023).	USA	Investigation the supra physiological uses of ASS on cardiomyopathy	Review		
Liu et al. (2019)	China	This study aims to investigate the correlation between abusing AAS and its direct effect on cardiovascular system risks.	Data was collected within a literature review by selecting peer reviewed articles from well-established databases such as PubMed & biotechnology information databases.	There is an association between overdosing AAS and having adverse effects on cardiovascular system. There was consensus amongst studies that cause-effect relationship can be found for those who abuse AAS and developing relevant diseases.	Review on the impact of AS on cardiovascular system.

3. Results

Data is analyzed in terms of two different level of data analysis, namely conducting descriptive data analysis including research bibliometrics, whereas contextual data analysis is also considered to reach the consensus among the included research.

3.1 description data analysis

Bibliometric research has been presented in this section in terms years of publications, methodology and data collection. Studies regions are also highlighted.

3.1.1 country of studies

Based on our inclusion criteria, The UK is more likely more interested in investigation of steroid abusing cases (36%) whereas abusing cases was less likely investigated in the countries of USA, Spain, Iran, India, Italy and China. Findings indicate that abusing steroid is an essential approach for medical research, since a large number of athletes using it for empowering their performance and for showing off purposes.

3.1.3 Research year of publication

Since academicians and researchers started to be interested in steroids over the last century, this interest continues to remain recent. As response, the included research was published over the last five years. This reflects the continuous of overdosing steroid among bodybuilders and athletes. However, the confirmed medical negative consequences and mortalities. This adds additional responsibilities on medical care services to continue investigation and provide abusers with appropriate guidelines.

3.1.4 Research methods for selected study

Research of abusing steroid has a particular structure in terms of data collection. It was found that research is more likely identify a specific case report and giving more detailed information of determining symptoms and medical treatment. Treating individual cases assess to deep understanding each circumstance and being able to compare similarities and differences to reach to a standardized medical guideline to assist medical treatment of each case. However, a number of research collected the data through conducting literature review. On the other hand, combination between case report and literature review were another reported research design for steroid research.

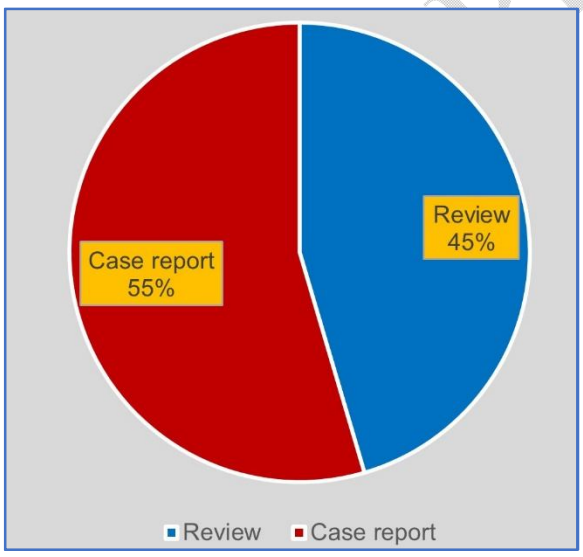

Fig1. Research methods and data collection (n=11)

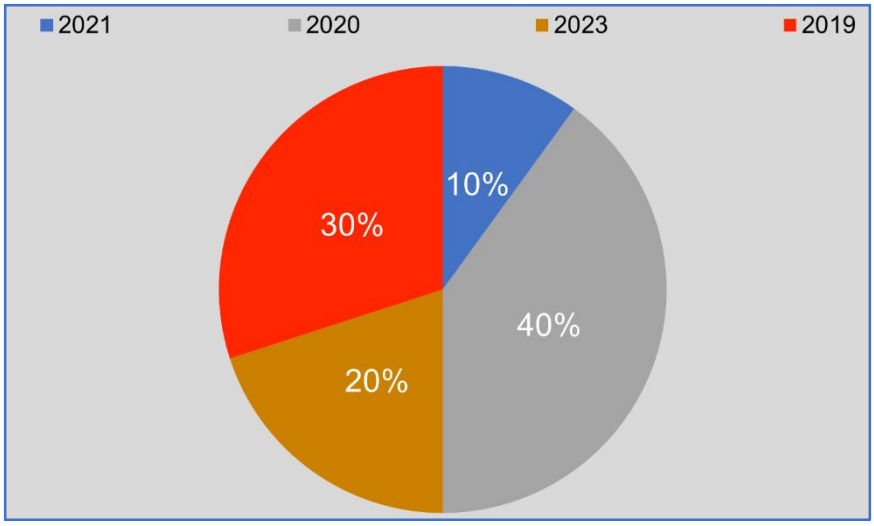

Fig2. Studies by published year (N=11)

3.2 Contextual data analysis

Studies provides a number of adverse consequences of overdosing steroid but also a various medical treatment

3.2.1 UK context

In a comparison study of reporting Steroid and Caffein for their continuous usage impact on cardiovascular disease and causing sudden death for overdosing. (8) Founds that while caffein has no impact on changing the structure of myocardium, the storied on the other hand has occurred many changes. Cardiovascular changes include elevation in blood changes. In additional, the toxicity of myocardial is also associated with ventricular function, arterial thrombosis. Caffeine has no direct impact on Cardiovascular system. However, Anabolic Steroid failed to negate the adverse consequences that associated it with cardiovascular illnesses.

3.2.3 India context

Regarding Steroid on coronary artery diseases, talking a case report of a younger man that struggle out of sever lifted side chase due to overdosing anabolic steroid. CAD disease seems to be for elderly group of population. However, new upward trend of body builder increases the possibility of taking proteins, amino acids and steroid to fasten the process of muscles building.There is a significant association between abusing steroid and perceiving cardiovascular consequences. avoidance of taking steroid reduce the risk of Coronary artery diseases CAD (9).

3.2.4 USA context

In another case report was conducted in USA for a younger individual, he was kept for 20 minutes in emergency unit due to sever left-sided chest pain. By discovering his medical history, it was discovered abusing and overdosing anabolic steroid. The motivation of consuming such amount was due to upward trend among young people to raise their awareness of body build. To achieve this target, they are more likely to consume unsupervised doses of anabolic steroid and a variety of different proteins and other synthetic supplements (14).

Linking Steroid on ischemic stroke, the abuse of using Anabolic androgenic steroid for better body muscles, physical appearance and sexual function. This report aims to investigate ischemic stroke in a young individual who abuse taking stanozolol and clenbuterol for body builder context.By investigating the patient was found that he was consuming testosterone and stanozolol for a number of weeks which leads to left sided weaknesses, ringing in the ear and slurred speech (10).

Regarding Steroid and its impact on myocardial condition, investigating the mechanism behind the ergogenic effect of Anabolic Asteroid as using it abusively amongst athletes and those who seeking for improving their body image. Investigating and reviewing in details endogenic drugs and its testosterone. It is also. Investigating its ability to exert tissue androgenic effects as it binds to androgen receptor. Finding out the verse impact of using AAS on vascular system and overall body health status. (13, 15).

3.2.5 Spain context

Regarding Impact of Anabolic Android on cardiovascular activities, Investigating the abuse of Anabolic for a number of 6 months Steroid on a young athlete in a sudden death case after coming back from a party. After receiving cardiorespiratory arrest, the forensic autopsy was conducted and the body show the following observations: a) external examination of the body show hypertrophy of muscles, while b) internal examination show cardiomegaly with sever coronary atherosclerosis. B) at histology acute myocardial faction was observed while blood results show existence of ethanol, stanozolol, nandrolone, and testosterone (11).

3.2.6Iran context

Aorta dissection is one of injury caused by having supra physiologic doses of steroid. This happens by weakening the connective tissue. The case of bodybuilder was investigated and all examinations of laboratory exams were conducted. Findings show that abusing steroid is significantly associated with determinate effect on myocardium. Results also reveal that

overdosing steroid for exercising people may lead to aortic dissection. Regarding symptoms, Retrosternal pain for more than 30 minutes, anxiety, cold sweating, delirium. Short about treatment, taking nitroglycerin for providing relief of angina pectoris, Sternotomy was performed and large hematoma was removed. After operation the patients was weaned from inotropic drugs. Combination usage of steroid growth hormone and testosterone for bodybuilding purposes (12).

3.2.7Brazil context

Regarding Review on the impact of AS on cardiovascular system, the aim of this study is to investigate the impact of overdosing Anabolic Steroid on myocardial infarction. Overdosing AS can have a negative consequence on cardiovascular system including, hypertension, hypertrophy, and arrhythmias. The challenge of reaching the cause of symptom can be due to the combination between steroid and other growth hormones but also taking insulin. (4).

3.2.8Italy context

To identify the cause of the death for a body builder person who found dead in hotel room. Abusing steroid leads to death. The measurement of hair analysis leads to better identify the overdosing Anabolic steroid. Clenbuterol, a long-acting selective beta2 agonist: Blood (1 ng/ml) and Urine (1 ng/ml),Hair (25 pg./mg). Confirmed also abusing steroid. Conducting a number of laboratory tests on Urine (), blood and hair. This measurement includes the following medical tests: “gas chromatography–mass spectrometry (GC-MS), liquid chromatography-high resolution mass spectrometry (LC-HRMS) and liquid chromatography–tandem mass spectrome- try (UPLC-MS/MS)”. As a result, steroid was found in Urine (202 ng/ml), testosterone was also positive (T/E = 11) (2).

3.2.9China context

This study aims to investigate the correlation between abusing AAS and its direct effect on cardiovascular system risks. Data was collected within a literature review by selecting peer reviewed articles from well-established databases such as PubMed & biotechnology information databases. There is an association between overdosing AAS and having adverse effects on cardiovascular system. There was consensus amongst studies that cause-effect relationship can be found for those who abuse AAS and developing relevant diseases (16).

4. Discussion

The results find out several adverse cardiovascular events cause by overdosing anabolic steroid. These consequences include hypertension, left ventricular hypertrophy and cardiomegaly. Such changes, remodeling and ramifications of cardiovascular change can be observed in terms of a number of arise indicators such as lipid profile alteration, myocardial toxicity, venous thrombosis and reduced in ventricular physical functions (14)Arrhythmias is a mother consequence of abusing anabolic steroid. It is a challenge to report such results in a wide range study due to the issue of standardization and the varieties of each study conditions. Studies reported that the direct impact of steroid can be fibrosis and left ventricular hypertrophy (3,9).In addition, it is also challengeable to measure sole impact of steroid or its combination with other illicit drugs. One of challenges also when investigation the athlete's heart is to ensure the real causes of left ventricular reduces functions. It is due to sport exercising or it is due to overdosing steroid. On the other hand, the risk factor of not taking steroid such as hypogonadism, depression can be a reason for steroid addiction. However, getting addicted to steroid raises the risks of hypertension and insulin resistance (16).

Abusing Anabolic Androgen Steroid has potential adverse impact on a variety of body organs and systems including musculoskeletal, cardiovascular, hepatic, neuroendocrine and dermatologic consequences. Regarding musculoskeletal, it was reported that abusing steroid may impact on enlarging 9-fold of body tendons. It is also associated with enlarging skeletal muscle mass and strengths. Androgen receptors have direct impact on myocardium and vascular muscles. Cardiovascular physiology safety under the condition of physiological testosterone remains controversial (4,17.18).Cardiovascular adverse effects including the higher risk of arrhythmias, hypertension, myocardial disfunction, impaired systolic and diastolic function. Regarding hepatic organs, it was reported that having supra physiologic doses of steroid has such impact on elevation on hectic origin. The duration of 17α-alkylated AAS release hepatotoxicity in the blood. In terms of Neuropsychiatric, increasing aggressive behavior is associated with androgen withdraw. It was also observed a number of suicidal attempts also as consequence. In addition, dermatologic symptoms were also observed for those who overdose steroids with increasing of acne vulgaris and folliculitis. (16,18,19,20)

There is different arguments and questions remain opens in the majority of the analyzed studies must be transferred into future research. For instance, abusing steroid studies were mostly conducted as case report, rather than conducting formal eepidemiologica research. This can be an argument for accuracy and integrity of research results. Those who overdosing steroid, they are also consuming another number of chemical substances and drugs. Therefore, it is always challengeable to decide the adverse consequences of death is only about abusing steroid or not about consuming other drugs (2).Supra-physiological doses of AAS confirmed a significant association with left ventricular failure. However, studies that identified the impact of AAS on right ventricular remain limited (2,12,14)

Studies shows a number of risk factors associated with overdosing steroid. AAS toxicity can significantly exceeding therapeutic level. Increasing the risk of complication by talking multiple steroids in cycles. blood pressure elevation is another risk that studies have reported. Abusing AAS can lead to raise blood pressure in which known as hypertension. Retention of sodium, water and development of angiotensin in which blood vessels. Elevated blood pressure generates physical strains on heart and arteries (13,16,21). As responses, heart attack and cardiovascular diseases are subject to developed.Dyslipidemia is another well-recognized adverse effect of overdosing steroid. Changing in lipid profiles with increased level of low-density of lipoprotein, cholesterol imbalance. As consequence, coronary arteries diseases can be developed. Heart Rhythm Disturbances can be also other risks of injecting steroid from unreliable resources (4). In addition, metabolic effects are significantly associated with cardiovascular diseases. Using AAS should be under medical supervision of physicians through the lowest effective doses. For those have been using steroid before, personalized cardiovascular diseases prevention plan must be considered.

5. Conclusions

Overdosing steroid among bodybuilder and athletes poses a significant risk for cardiovascular diseases. The misuse of steroid can lead to a significant reverse effect including, increased blood pressure, heart rhythm disturbances, cholesterol imbalances and overall cardiovascular diseases. Literatures show a different case with a variety of symptoms treated in uncommon medical treatments. There is a remained arguments regarding the steroid consuming for improving sport performance regarding the doses, resources, duration, symptom developed and whether these

symptoms extracted from consuming pure steroid or was the combination with other medical substances. Recommendation for future research to conduct a longitudinal study over different generation for observing the changes in consuming steroid and the associated needs and behaviors but also psychological circumstance.

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