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REVIEW

Adverse cardiovascular effects of anabolic steroids: pathophysiology imaging

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ABSTRACT

Background Anabolic-androgenic steroids (AAS) are widely abused for enhancing muscle mass, strength, growth and improving athletic performance.

Materials and methods In recent years, many observational and interventional studies have shown important adverse cardiovascular effects of AAS abuse.

Conclusions This review discusses established and future perspectives of novel molecular imaging techniques that may serve as potential tools for early detection of AAS-associated cardiovascular disorders.

Keywords Anabolic-androgenic steroids, cardiovascular, imaging, molecular imaging.

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Introduction

The term 'anabolic-androgenic steroids (AAS)' refers to a group of compounds that are structurally related to testosterone and exert two main physiological effects including muscle growth and masculinization [1]. Since 1940s, AAS therapy has been advocated as substitution therapy of testosterone deficiency and hypogonadism [1]. Moreover, AAS in high doses has been abused with the purpose to enhance muscle mass and improve athletic performance.

AAS administration has been shown to be associated with cardiovascular side effects [2], urogenital problems, that is, gynecomastia, impotency [1], hepatotoxicity [3], hepatocellular carcinoma [4] and neuropsychiatric disorders, that is, aggressiveness and depression [5]. Cardiovascular adverse effects of AAS abuse have been reported sporadically as case reports of hypertension [6], myocardial infarction (MI) and stroke [6], dysrhythmia [7], cardiomyopathy [8], and sudden cardiac death [9] in body builders with long-term AAS abuse in the recent years. Case reports on hard atherosclerotic endpoints (sudden cardiac death, MI or stroke) comprise young AAS abusers without preexistent cardiac risk factors, suggesting that a high AAS dose imposes additional independent risk to conventional cardiovascular risk factors. Parssinen *et al*. [10] reported a more than four times higher incidence of early death in professional athletes abusing AAS compared to the age- and sex-matched general population, in a 12-years prospective observation.

In addition to the potential risk associated with AAS abuse, it is notable that therapeutic treatment with AAS in hypogonadic men has recently been shown to be linked with a higher cardiovascular event rate [11]. This important finding underscores that there is a delicate balance between benefits and risks related to AAS use as a treatment option for patients suffering from androgen deficiency. Adding up clinical AAS use and illegal AAS abuse rates represent a new wave of AAS-associated cardiovascular adverse consequences, in which early diagnosis can reduce health burden.

Molecular imaging is a promising method to target and image certain biomarkers in the process of cardiovascular pathology that can be used for early detection of AAS-associated adverse effects. A number of modalities and tracers are currently being developed that may become useful to delineate functional abnormalities in several pathways involved in AAS-induced cardiovascular injury at the preclinical and clinical level [12,13].

In this study, we review previous literature on cardiovascular side effects associated with AAS (ab)use and promising

molecular imaging techniques that are currently available to reveal the pathological abnormalities at the tissue level.

Pharmaco-epidemiology

Hypogonadism is considered to affect 2–4 million men in the United States [14]. In a recent Endocrine Society clinical practice guideline, AAS replacement therapy was indicated to treat men suffering from hypogonadism correlated with low testosterone blood levels [15]. Next to relevant clinical indications of AAS in physiological doses (28–56 mg/week), illegal abuse of high doses of AAS as a muscle strengthening agent in eugonadal men is reported in high rates, which results in blood levels of androgenic compounds 10–100 times above the physiologic and therapeutic range [16].

The first report of AAS abuse dates from 1954 when members from the Soviet Union's world champion's weight lifting team were found to abuse these substances inadvertently [17]. As late as 1975, AAS abuse was classified as doping. According to the world anti-doping agency report in 2008, AAS were the most commonly identified prohibited drugs among all, comprising 59% of all reported findings. According to a study from 1995, it was suggested that nearly 70% of elite US powerlifters had abused AAS [18]. Unfortunately, AAS abuse occurs frequently not only amongst professional athletes, but also in the general population, particularly high school students. One report demonstrated that the proportion of male population who had abused AAS at least once was up to 4–6·7% in Europe and the USA [19]. More recently, it was estimated that there are more than one million current or ex-abusers of AAS [17].

Metabolic and vascular effects of anabolic-androgenic steroids

Lipid profile alteration and early atherogenesis

Therapeutic use of AAS has been shown in many studies to affect the individuals' lipid profile. A meta-analysis including 19 studies and comprising 272 hypogonadal men showed that substitution therapy with intramuscularly administered testosterone results in a decrease in plasma HDL cholesterol levels, which amounted to 0·10 mM [20]. The same results were also demonstrated in a recent meta-analysis including 51 studies on men with low or low-to-normal plasma testosterone levels who received testosterone in different doses as therapy [21]. Moreover, high-dose AAS abuse has been demonstrated to exert unfavourable direct and indirect effects, through AAS-associated hyperhomocysteinaemia [22], on plasma lipid levels. In a nonblinded investigation on 19 bodybuilders, short-term (8 weeks) and long-term (> 14 weeks) high dosages of AAS administration markedly reduced HDL cholesterol [23]. The suppressive effects of AAS administration on HDL plasma levels are dose dependent and depending on the type of AAS and route of administration can result in decrement of 40–70% [24]. The adverse effects of high AAS dosages on plasma levels of LDL cholesterol have been shown in animal and human studies [24,25]. In a study on mice oral AAS administration for 3 weeks increased plasma levels of LDL [25].

Lipid profile impairment is causally implicated in vascular wall injury by promoting inflammatory processes in the arterial wall, macrophage recruitment, and uptake of LDL and oxidized LDL by macrophages which results in foam cell formation [26–28].

Vascular imaging: imaging early atherogenesis

The aforementioned processes, which contribute to establishment and progression of atherosclerotic plaques, can be depicted by molecular imaging techniques. ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) has been studied in a notable number of investigations and has been shown to correlate with the macrophage density in atherosclerotic plaques in humans and in animal models [29]. Additionally, ^{18}F-FDG PET depicts MI subsequent to coronary atherosclerosis. Figure 1 shows a whole body cardiac gated ^{18}F-FDG PET/CT image of a male bodybuilder with abdominal aortic calcification (Fig. 1a) with more extensive FDG uptake in aortic plaques (Fig. 1b) and an inferolateral MI (Fig. 1c) as a result of right coronary artery occlusion.

In a recent study, ^{99m}Tc-interleukin-2 single-photon emissioncomputed tomography (SPECT) was found to be able to depict T-lymphocyte content within atherosclerotic plaques in humans [30]. This technique may enable clinicians to detect active inflammation within the atherosclerotic plaque. Foam cell formation has also been studied using various lipid-based radiotracers. Molecular targeting of oxidized LDL and macrophage uptake of radiolabelled LDL has verified promising targets for visualizing vulnerable atherosclerotic plaques [31,32]. Moreover, a recent pilot study reported feasibility of ultrasmall superparamagnetic particles of iron oxide (USPIO) in detecting inflammation in endothelial cells during atherogenesis with magnetic resonance imaging (MRI) [33]. However, none of the above-mentioned probes and modalities has been applied to monitor AAS-associated vascular inflammation and leucocyte accumulation.

Adhesion molecules expression and platelets aggregation

Although therapeutic and physiological dosages of AAS seem to have beneficial effects on platelet aggregation [34],

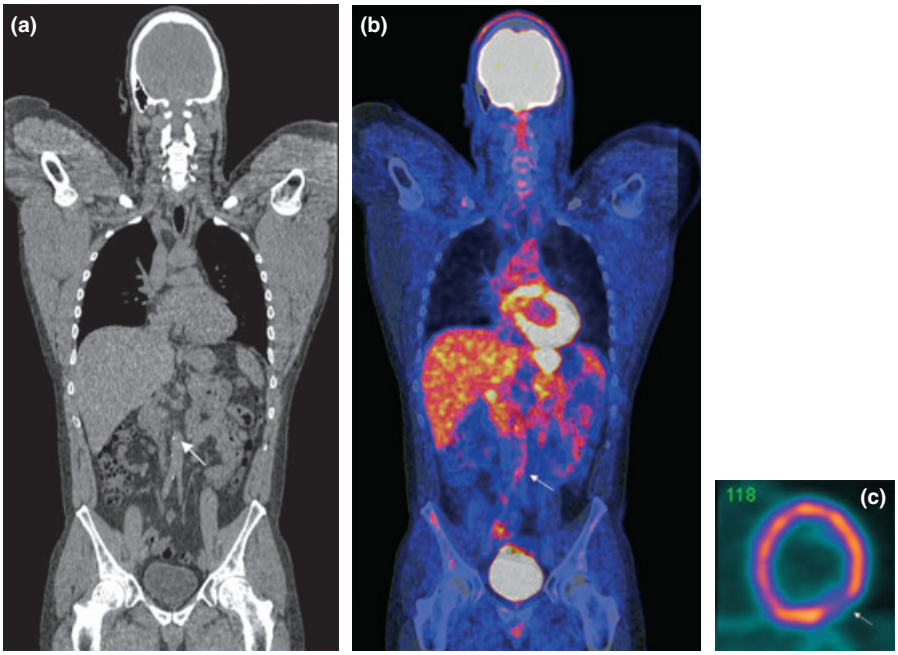

Figure 1 ^{18}F-FDG PET/CT image of androgenic-anabolic steroid-associated atherosclerosis. Whole body ^{18}F-FDG PET/CT of a 40-year-old male body builder with mild abdominal aortic atherosclerosis on CT (a, arrow) and more extensive FDG uptake in soft plaques of abdominal/iliacal arterial tract on PET (b, arrow) and (c) gated myocardial ^{18}F-FDG PET in the same patient indicating an inferolateral infarction (arrow) owing to acute right coronary artery occlusion. FDG, fluorodeoxyglucose; PET, positron emission tomography.

deleterious effects of supraphysiological AAS dosages in promoting expression of adhesion molecules in vessel walls and facilitating platelet–endothelium binding have been reported as a mechanism that contributes to AAS-induced atherosclerosis [19]. Additionally, the role of AAS abuse in thrombogenicity has been reported in some studies. In a study on healthy male volunteers, high-dose AAS treatment (200 mg/week) resulted in increased platelet aggregability as a result of increased thromboxane A2 (TxA2) receptor density [35]. In this study, TxA2 density peaked at 4 weeks after single-dose AAS treatment and returned to baseline density at 8 weeks. The same trend was reported for platelet aggregability, with 5·2% and 7·3% increase after 2 and 4 weeks, respectively. The contrary effects of castration on TxA2 receptor and platelet aggregation were also reported in a cross-sectional case–control study [36]. The effects of AAS on TxA2 receptor density can in part be explained by AAS-associated hyperhomocysteinemia [22,37].

Vascular imaging: imaging adhesion molecules expression

Detection of adhesion molecules expression as an upstream process leading to binding of platelets to the arterial wall can depict atherosclerotic plaque formation at early stages [38]. Vascular cell adhesion molecule-1 (VCAM-1) and integrins provide suitable targets for molecular imaging of adhesion molecules expression. VCAM-1 is expressed by endothelial cells, macrophages and smooth muscle cells [39]. VCAM-1-targeting nanoparticles have been used for signal enhancement in atheromatous arteries of apoE$^{-/-}$ mice, and MRI showed promising results [40]. Recently, the same group labelled the same tetrameric peptide with positron emitter ^{18}Fluoride for PET imaging and was able to demonstrate early atherosclerotic changes in apoE$^{-/-}$ mice [41].

Integrins, that is, αvβ3 integrin, are adhesion molecules that are expressed following endothelial cell injury, as well as at more progressed stages of atherosclerotic plaque formation during neo-angiogenesis [38]. αvβ3 integrin has high binding affinity to arginine–glycine–aspartate (RGD) amino acid sequence facilitating cell–extracellular matrix interactions. It has been shown in many oncological and myocardial remodelling studies that radiotracers based on RGD can be applied targeting αvβ3 integrin [42,43]. One recent report showed that ^{18}F-RGD PET can show atherosclerotic changes in apoE$^{-/-}$ mice [44]. In that report, quantified measures of ^{18}F-RGD uptake were correlated with ^{18}F-FDG PET measures. However, none of the tracers on adhesion molecules has currently been applied to investigate AAS-associated vascular injury.

Impaired vasodilatation

Although endogeneous testosterone has been shown to exert vasodilatory effects [45], AAS use in hypogonadal men has been shown to result in paradoxical pro-atherogenic vasoconstrictive effects [46]. It was shown that testosterone therapy in hypogonadal men is correlated with impaired vasodilation, independently from lipid profile measures [46]. Supraphysiological doses of AAS have also shown to exert similar effects on vasoreactivity in human and animal studies [47,48]. In a study on rabbits treated with AAS for 4, 8 and 12 weeks, it was shown that both endothelium-dependent and endothelium-independent pathways of vasodilatation are inhibited in the thoracic aorta [47]. In a study on male body-builders who abused AAS for 3–4 years, vasodilatation was significantly lower than that of ex-abusers and controls [48]. AAS abuse in body builders independently of the other factors impaired endothelium-independent vasodilator pathways. It was also shown that a 3-month period of abstinence results in a degree of improvement in vascular function. Moreover, long-term therapy with supraphysiological doses of AAS in female-to-male transsexuals has shown to result in decreased vasodilation independent of the effects of age, lipid profile and vessel size [49].

The mechanisms through which AAS induces deleterious effects on vasodilatation are not sufficiently investigated. However, endothelial injury as a result of lipid profile alterations and establishment of atherosclerosis could explain the impairment in endothelium-dependent pathway through decreased NO production. Also, the increase in TxA2 receptor density in vessel walls as a result of AAS treatment results in impaired endothelial-independent vasodilator pathways [50]. Further studies should be carried out to reveal more information on cellular and molecular processes related to the role of AAS on vasoreactivity.

Imaging impaired vasodilatation

The cold pressure test (CPT) is known to be a useful tool to demonstrate endothelial dysfunction [51]. Cold exposure induces vasodilatation in coronary arteries, but paradoxically results in vasoconstriction in dysfunctional arteries. This paradoxical effect can be measured by myocardial perfusion imaging agents such as the PET tracers ^{15}O-water and ^{13}N-ammonia [52] (Fig. 2). Performing CPT could reveal early vascular effects of AAS abuse in humans.

In summary, metabolic and vascular adverse effects of AAS abuse can be classified as:

1 Alterations in the lipid profile, especially decreased serum HDL levels and hyperhomocysteinaemia contributing to endothelial damage.
2 Increased platelets adhesion to vascular wall.
3 Vasospastic effects and impaired vasodilatation.

Myocardial effects

Myocardial hypertrophy

The role of AAS abuse in myocardial hypertrophy has been shown in animal and human studies. In a recent investigation on rats treated with high-dose nandrolone for 8 weeks, electrical remodelling and increasing myocytes nuclei diameter in the

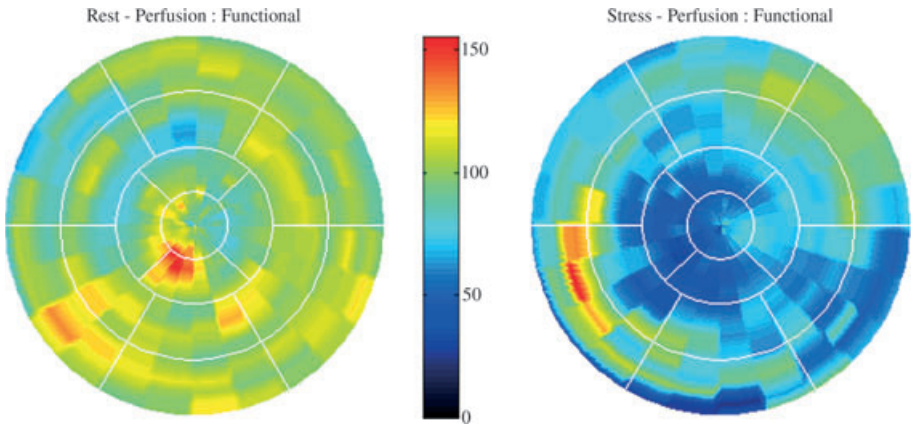

Figure 2 Polarmap of rest ^{13}N-ammonia (left) and stress ^{13}N-ammonia (right) positron emission tomography of the left ventricle in a patient with chest pain. The colour bar indicates the perfusion level (mL/min/100 g myocardial tissue). During stress myocardial perfusion is reduced at the apical, anteroseptal and infero-lateral region compared with the rest situation. The calculated absolute stress/rest perfusion ratio was 1·28 (normal > 2). Coronary angiography showed normal coronaries. In this patient, microvascular disease was diagnosed.

AAS group suggested early stages of myocardial hypertrophy [53]. Significant increase in left ventricular mass index, ranging from 7% to 24%, has been shown in studies on rats treated with low-dose and high-dose AAS for 8–10 weeks [54,55]. Another study on the AAS treatment for 3 weeks in mice subjected to aerobic training and sedentary mice showed that high-dose AAS treatment in sedentary mice results in increased ventricular mass index by 25% [25]. Adverse effects of AAS administration in this study were counteracted by aerobic exercise, suggesting more risk of AAS abuse in nonathlete abusers.

Also, many case reports of sudden cardiac death in athletes who abused AAS have shown clinically important left ventricular hypertrophy [6,9]. Association between AAS abuse and echocardiographical detected myocardial hypertrophy has been shown in a study on athletes who chronically abused AAS (median = 24 months) [56]. In this study, hypertrophic index (interventricular septum plus posterior wall thickness divided by the internal diameter) was significantly higher in AAS (ex-), abusers compared with nonuser athletes. Moreover, the extent of AAS abuse was linearly correlated with mean left ventricular wall thickness.

Although the mechanisms responsible for left ventricular hypertrophy in AAS abusers are not well-understood, it has been shown that long-term AAS abuse increases peripheral vascular resistance [55], blood pressure [57] and myocardial sympathetic nerve activity [58], which can explain mechanical stress-induced myocardial hypertrophy in AAS abusers. Moreover, androgen receptors which are responsible for AAS-induced hypertrophic effects on skeletal muscles are also present in myocytes and result in increased protein anabolism within myocardial cells and interstitium [25,54]. In a study on rats treated with high-dose AAS for 10 weeks, increased left ventricular mass was shown to be a result of both myocardial cell hypertrophy and interstitial fibrosis. Both effects were further effectively inhibited by losartan, which suggest the role of renin–angiotensin system (RAS) in increase in left ventricular mass [54]. It has been shown that in AAS-treated rats, angiotensin-1 (AT1) receptor expression increases 60–120% comparing with nontreated groups. However, it is not yet investigated whether AAS treatment directly enhances RAS activity or the process of the mechanical stress-induced hypertrophy is the trigger.

Imaging pathophysiology of myocardial hypertrophy

Owing to the role of RAS in AAS-associated cardiac mass change, detection of RAS activity in early stages of myocardial injury would predict future myocardial adverse outcomes in AAS (ab)users. Recently, Verjans *et al.* [59] in a study on post-MI mice have shown that ^{99m}Tc-losartan uptake increases 2·4-fold after MI compared to control animals. This promising result, in targeting AT1 receptor, could provide a valuable tool to investigate the early stages of AAS-associated cardiac pathogenesis in abusers and animal models *in vivo*.

Cardiac function

Anabolic-androgenic steroids abuse has been shown to affect the cardiomyocyte survival and heart function in cell cultures, animal models and humans [55,60]. Beutel *et al.* [55] were the first to investigate the effects of AAS administration on cardiac output in animal models. In their study, three groups of rats were treated with vehicle, low-dose AAS or high-dose AAS, for 8 weeks, and the groups were compared with regard to cardiac output. The results showed that AAS treatment in high doses results in significant decrease in cardiac output comparing with low-dose AAS and control groups (107, 154 and 121 mL/min, respectively). In this study, no significant differences in cardiac output were observed between low-dose AAS and the control groups as a result of significant decrease in peripheral resistance in low-dose AAS administered mice. However, peripheral resistance in rats receiving high-dose AAS was significantly higher compared to low-dose AAS and control groups which is in agreement with paradoxical effects of high-dose AAS on vasodilation. A recent study reported that both diastolic and systolic functional parameters are impaired in AAS abuser athletes comparing with nonabuser athletes [60]. In this study, echocardiography in AAS abusers showed a significantly lower ejection fraction (50% vs. 59%), longitudinal strain (16·9% vs. 21%) and radial strain (38·3% vs. 51%) compared to AAS nonabusers. A similar trend was observed in diastolic functional parameters.

The mechanisms of high-dose AAS-associated heart dysfunction are still not thoroughly investigated. However, some studies showed deleterious molecular and cellular effects of high-dose AAS administration on myocardium which overlap early injury pathways of heart failure. It is known that in hypertrophic myocardium, hypertrophy can be linked with any of the heart failure signalling pathways, resulting in heart failure [61]. It has also been shown that AAS indirectly mediates the processes that precede mitochondrial damage, apoptosis and sarcomere disruption. In a study on rats treated with AAS, it was shown that lesions compatible with early stages of heart failure, such as swollen mitochondria and disintegrated contractile units, were present in myocardium as early as 3 weeks after treatment [62]. Association between AAS abuse and apoptosis has been studied in rat ventricular myocytes exposed with different doses of AAS and showed that AAS exposure results in dose-dependent myocardial apoptotic cell death [63]. In another animal study with rabbits that were treated with daily supraphysiological doses of AAS for 60 days, apoptotic lesions and higher caspase-3 activity were noticed in treated animals [64]. Fibrosis is known as a

process leading to heart failure. It has also been reported that high-dose AAS treatment in small animal models is associated with interstitial collagen deposition and fibrosis [54,65]. Fibrosis is assumed to occur initially as an adaptation in myocardial hypertrophy to preserve the function of the ventricles and, thereafter, as a repair mechanism to compensate apoptotic myocardial cell loss [54]. In one study on rabbits treated with daily oral high doses of AAS for 3 months, the AAS-treated group showed myocardial interstitial fibrosis associated with higher caspase-3 activity [65]. Local RAS activity which has been shown to be activated in high-dose AAS treatment in rats [54] induces interstitial fibrosis and has been shown to be a key signalling pathway for heart failure [66].

Imaging pathophysiology of impaired heart function

Pro-apoptotic effects of AAS-(ab)use can be further investigated *in vivo* by apoptosis targeting tracers such as ^{99m}Tc-Annexin-A5 [67]. Annexin-A5 has high affinity to phosphatidylserine, a protein which is expressed during apoptosis on cell membrane. Feasibility of ^{99m}Tc-annexin-A5 has been shown in detecting myocardial apoptosis in patients with acute allograft rejection [67].

Significance of RAS system activation in AAS-associated heart failure can be explored by further *in vivo* investigations on human and animals, using ^{99m}Tc–losartan SPECT. Future studies are warranted to better explain the mechanisms and feasibility of nuclear medicine techniques for pathophysiological understanding of AAS-induced myocardial injury.

Cardiac arrhythmia

Cardiac arrhythmias are associated with AAS abuse. Most commonly, atrial fibrillation but also ventricular tachycardia and ventricular fibrillation has been described secondary to AAS abuse in human case reports [68]. In a study on rats treated with high-dose nandrolone for 10 weeks, heart rate variability measurements revealed a reduction in parasympathetic activity compared with the vehicle-treated group [53]. Sympathetic indices were also higher in the AAS-treated group. It was also shown that AAS-treated animals show prolonged action potentials as a result of reduced density of transient potassium outward current (Ito) in the left ventricle. This change can be explained by left ventricular hypertrophy as well as by downregulation of expression of Ito membrane channels.

To sum up, the myocardial effects of AAS abuse can be summarized in three different categories including:

1 Myocardial hypertrophy as result of
   (a) Elevated muscle sympathetic nerve activity.
   (b) Direct anabolic effects of AAS.
   (c) Renin–angiotensin system activity induced collagen deposition and interstitial fibrosis.
2 Left ventricular dysfunction as result of
   (a) AAS-induced myocardial hypertrophy.
   (b) Mitochondrial damage and apoptosis as consequences of Ca^{2+} signalling.
   (c) Renin–angiotensin system activity and fibrosis.
3 Cardiac arrhythmias as result of increased myocardial mass and reduction.

Conclusions

There are only few studies focusing on the mechanisms responsible for AAS abuse-associated cardiovascular pathology. Nonetheless, some case reports, cross-sectional human studies, and some animal reports have demonstrated an adverse role of AAS abuse on the vascular wall and the myocardium. The wave of now middle-aged ex-AAS abusers and the increasing group of the elderly AAS users necessitates more detailed documentation of the underlying pathophysiology to enhance insight into the delicate balance between benefit and harm. Owing to the obvious ethical reasons, prospective double-blinded human studies are not easily justified. Accordingly, retrospective case–control studies of cohorts and prospectively follow-up of such cohorts seem to be

Table 1 Overview of cardiovascular pathology associated with androgenic-anabolic steroid (AAS) (ab)use and appropriate detecting techniques

	AAS effect	Imaging technique (modality)
Vascular	Endothelial dysfunction [46]	CPT (PET) [51]
	Adhesion molecules exposure	VINP-4 (MRI) [40]
	VCAM-1 [39]	^{18}F-4V (PET) [41]
	$\alpha_v\beta_3$integrin [38]	^{18}F-RGD (PET) [42]
	Leucocyte recruitment and foam cell formation	^{18}FDG (PET) [29] ^{99m}Tc-II2 (SPECT) [30] USPIO (MRI) [33]
Myocardial	Apoptosis [63]	^{99m}Tc-Annexin-V(SPECT) [67]
	RAS activity [54]	^{99m}Tc-losartan (SPECT) [59]
	Hypertrophy	Echocardiography [54]
	Dysfunction	Echocardiography [55,60]

CPT, cold pressure test; FDG, fluorodeoxyglucose; MRI, magnetic resonance imaging; PET, positron emission tomography; RAS, renin–angiotensin system; SPECT, single-photon emission computed tomography; USPIO, ultra-small superparamagnetic particles of iron oxide; VCAM-1, vascular cell adhesion molecule-1.

the most feasible strategy for human studies to obtain more conclusive epidemiologic data.

In addition to the above-mentioned imaging techniques (summarized in Table 1), future studies on AAS-specific pathophysiological processes and molecular imaging techniques of AAS-associated cardiovascular disease would provide clinicians diverse diagnostic tools for early detection, evaluation and monitoring of adverse cardiovascular consequences of AAS abuse. For instance, dehydroepiandrosterone (DHEA) mediates its action via multiple signalling pathways involving specific membrane receptors and via transformation into androgen and oestrogen derivatives (e.g., androgens, oestrogens, 7α and 7β DHEA, and 7α and 7β epiandrosterone derivatives) acting through their specific receptors and is associated with ischaemic heart disease, endothelial dysfunction and atherosclerosis. These pathways include also sigma receptors (sigma-1) expression. The specific sigma receptor PET ligand ^{11}C-SA4503 may be a method to quantify the androgen receptor expression of the vascular system to evaluate the atherosclerotic status in relation with AAS abuse [69]. This may lead to selective non-invasive diagnostic imaging in relatively young population of AAS abusers as promising tools for AAS-related atherosclerosis development which can be complemented with blood sampling.

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