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Anabolic androgenic steroid-induced hypogonadism, a reversible condition in male individuals? A systematic review

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Abstract

The anabolic–androgenic steroids (AAS) are clinically used as an androgen replacement, in hypogonadism treatment, to induce puberty, and also in the treatment of chronic degenerative diseases. The AAS use out of clinical context is becoming massively, being used merely for aesthetic reasons. AAS abuse may cause severe disarrangement on the HPG axis and generate a significant decrease in testosterone synthesis and secretion by the testes. This review aims to evaluate whether the hypogonadism induced by AAS abuse is reversible and under what circumstances the reversibility is possible. For this, PRISMA guidelines and several databases are used between July and September 2020. Altogether, this systematic review identified and analysed 179 cases of AAS users. Of these, 168 cases had the hypogonadism clearly diagnosed and proven to be linked exclusively to AAS abuse. However, between these 168 cases, only 38 cases presented fully known outcomes and among these, merely in 4, the hypogonadism was completely reversible (2 based on drug therapy) with HPG axis recovery. In conclusion, this review presents evidences that AAS-induced hypogonadism is a seriously underestimated problem, and in the majority of cases, full recovery is very difficult to succeed.

KEYWORDS

AAS, anabolic–androgenic steroids, andrology, drug abuse, hypogonadism, hypothalamic–pituitary–gonadal axis

1 | SUMMARY

Testosterone, a sex hormone, along with other androgens, has a major role in the development of sexual characteristics (masculinising or androgenic effect) and stimulation of muscle protein synthesis, thus promoting hypertrophy (anabolic effect). Due to the effects provided by testosterone, synthetic derivatives of steroid hormones have been developed and used for decades in diverse circumstances. These drugs are used for the treatment of diseases, but also, indiscriminately used without any medical indication for the improvement of performance in sports and particularly for aesthetic reasons (Evans, 2004; Pope et al., 2014; Sagoe et al., 2014).

AAS abuse may cause a severe disarrangement on the HPG axis and consequently, generating a negative feedback, by which occurs a significant decrease in testosterone synthesis and secretion by the testes. This situation usually results in clinical symptoms such as sexual impotence, decreased libido, decreased physical capacity, and even depressive symptoms in a condition medically known as secondary hypogonadism or anabolic steroid-induced hypogonadism (ASIH; Hartgens & Kuipers, 2004; Wu et al., 2010).

Usually, hypogonadism related to AAS abuse is not commonly reported and discussed in medical and academic circles. However, the scientific data indicate that this kind of hypogonadism can be much more common and more problematic than it is usually

TABLE 1 Databases and websites searched (including search terms and conditions) from inception between July and September 2020

	Database or website	Search terms and conditions	Found
1	PubMed	(hypogonadism[Title]) AND steroid[Title], (hypogonadism[Title]) AND anabolic[Title], (hypothalamic-pituitary-gonadal axis[Title]) AND anabolic[Title], hypothalamic-pituitary-gonadal axis[Title]) AND steroid[Title], hypothalamic-pituitary-gonadal axis[Title]) AND hypogonadism[Title]	59
2	ClinicalTrials.gov	Condition: Hypogonadism, Male Title/Acronism: anabolic or steroids or androgenic or abuse or bodybuilder	2
3	PMC	Included in PubMed Search	—
4	MedLine	Included in PubMed Search	—
5	OpenGrey Repository	Hypogonadism	14
6	American Chemical Society Publications	Title: Hypogonadism	0
7	ScienceDirect	Terms: Hypogonadism Title, abstract, keywords: Hypogonadism or Hypogonadism and AAS or Hypogonadism and Anabolic or Hypogonadism and hypothalamic-pituitary-gonadal axis Filters: Research articles, Case Reports	119
8	Web Of Science	(hypogonadism[Title]) AND steroid[Title], (hypogonadism[Title]) AND anabolic[Title], (hypothalamic-pituitary-gonadal axis[Title]) AND anabolic[Title], hypothalamic-pituitary-gonadal axis[Title]) AND steroid[Title], hypothalamic-pituitary-gonadal axis[Title]) AND hypogonadism[Title]	88
9	Lilacs	Included in PubMed Search	—
10	EU Clinical Trials	hypogonadism AND steroid hypogonadism AND anabolic hypogonadism AND androgenic hypogonadism AND hypothalamic-pituitary-gonadal axis	0
11	SCOPUS	(hypogonadism[Title]) AND steroid[Title], (hypogonadism[Title]) AND anabolic[Title], (hypothalamic-pituitary-gonadal axis[Title]) AND anabolic[Title], hypothalamic-pituitary-gonadal axis[Title]) AND steroid[Title], hypothalamic-pituitary-gonadal axis[Title]) AND hypogonadism[Title]	73
12	WHO International Trials Registry	Condition: Hypogonadism Title: anabolic or steroids or androgenic or abuse or bodybuilder	0
13	Google Scholar	allintitle: hypogonadism anabolic, allintitle: hypogonadism steroid, allintitle: hypothalamic-pituitary-gonadal axis hypogonadism, allintitle: hypothalamic-pituitary-gonadal axis anabolic, allintitle: hypothalamic-pituitary-gonadal axis steroid (Excluded patents and citations)	72

pointed (Kanayama et al., 2015). A retrospective database analysis of all 6,033 men evaluated for hypogonadism from 2005 to 2010, identified AAS abuse as the main cause for hypogonadism incidence where 97 men were diagnosed with profound hypogonadism, defined as testosterone 50 ng/dl or less, and among these 97, 42 men (43%) had the AAS abuse as the origin of hypogonadism (Coward et al., 2013).

Thus, considering the AAS abuse a public health problem, due to the fact that hypogonadism caused by AAS abuse is a side effect often underestimated the aim of this systematic review was to identify and to review different studies with focus on AAS abuse related Hypogonadism and, then, bring some light about the reversibility of this condition in men.

2 | METHODS

This study was registered in the International Prospective Register of Systematic Reviews database (PROSPERO) with registration ID number CRD4202018763. The study design observes the PRISMA guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols; Shamseer et al., 2015).

3 | SEARCH STRATEGY AND DATA MANAGEMENT

Initial analyses were performed using the selected databases (Table 1) without any limitations of language, design or date. The search was performed between July and September 2020 and included the terms: hypogonadism, anabolic, steroid, hypothalamic–pituitary–gonadal axis, abuse and bodybuilder. There were used multiple combinations between the related terms (Table 1). In a second moment, from the reading of the selected articles, among the references, we identified and included 3 more relevant studies for the present review (Figure 1).

All data were compiled in Microsoft Excel 2016 and then in ENDNOTE X7 software.

4 | STUDY ELIGIBILITY CRITERIA

Were eligible for this review clinical trials, case reports, cohorts and studies where the ASIH cases are clearly identified and individualised. The study subjects were men with a history of AAS abuse and presented clinical symptoms and/or laboratory tests compatible with hypogonadism diagnostic. Further details about study eligibility criteria and included or excluded studies are shown in Table 2 and in the PRISMA flowchart diagram (Figure 1).

5 | DATA ABSTRACTION

Two independent blinded authors (JOV and DVP) reviewed each title and abstract for inclusion eligibility. The full-text review was also performed by the same two independent blinded authors (JOV and DVP). After that, the studies selected by both were considered for this review.

6 | RISK OF BIAS IN INDIVIDUAL STUDIES

To avoid or at least minimise the bias incidence, we excluded all studies in which the subjects had other diseases or conditions that could lead to hypogonadism. There were also excluded studies with no clearly characterised hypogonadism or hypogonadism for any other reason than AAS abuse.

Therefore, for this systematic review, they were considered eligible cases exclusively those in which the subjects, after AAS exposure, had total testosterone levels below 300 ng/dl (10.4 nmol/L) and/or presented clinical symptoms of androgen deficiency and/or presented testicular atrophy.

7 | RESULTS

The search results are presented in the PRISMA flow chart (Figure 1) and Systematic review cases outcomes flow chart (Figure 2).

Based on search terms and conditions, we identified a total of 427 results between 13 Internet scientific databases (Table 1; Figure 1). Among these 427 results found, 346 were identified as duplicates. After the duplicates were removed, 81 results remained for detailed analysis.

We searched for the abstracts and full articles of these 81 results. It was identified that 11 of these studies lacked abstracts or full article available on the Internet, and 6 of these 81 results were animal model studies. Consequently, these 17 results were excluded.

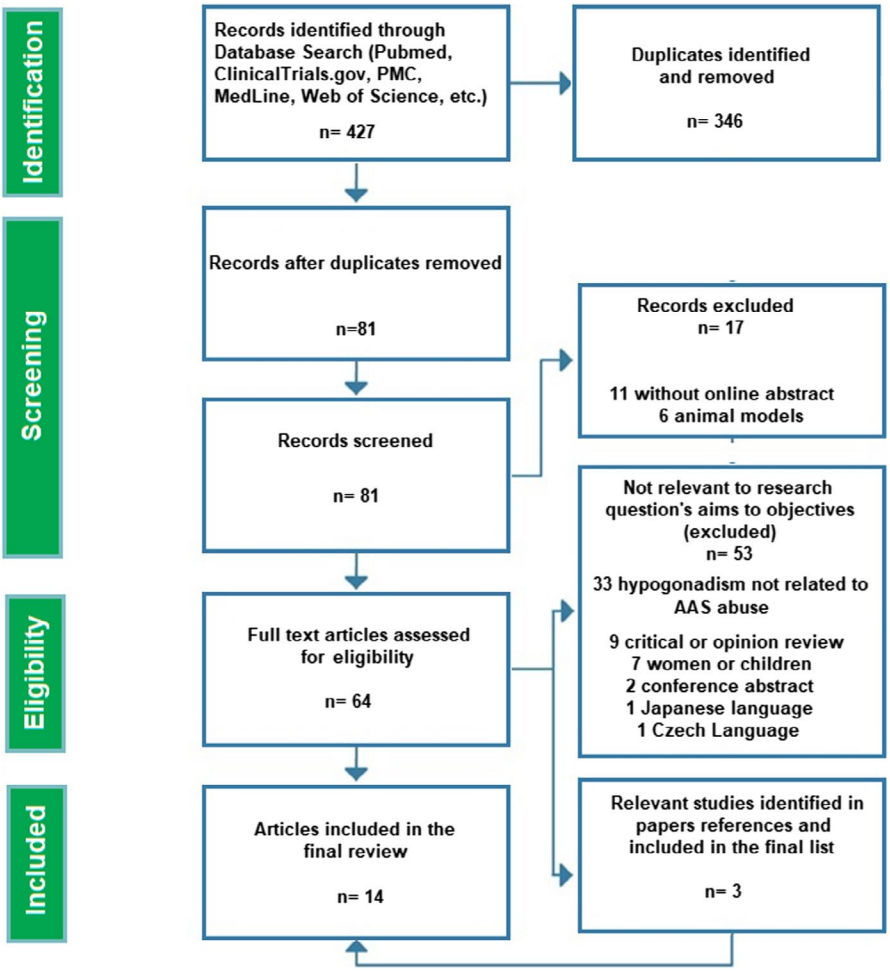

FIGURE 1 PRISMA flow diagram of systematic review search results. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis protocols (Shamseer et al., 2015)

TABLE 2 Study eligibility criteria

INCLUDED STUDIES	CRITERIA	REASONS
POPULATION	Hypogonadal men.	Study subject
EXPOSURE	AAS	The study subject is the hypogonadism caused by AAS abuse.
OUTCOMES	Any	The present review aims to answer if the hypogonadism caused by AAS abuse is reversible. All outcomes are relevant.
STUDY DESIGN	Clinical trial, case report, cohort and studies where the ASIH cases are clearly identified and individualised	Original studies that may describe the hypogonadism caused by AAS abuse, eventual subject treatment and the outcomes.
OTHER CRITERIA	Studies in any time and any language	Increase database.
EXCLUDED STUDIES	**CRITERIA**	**REASONS**
POPULATION	Men without hypogonadism, men with hypogonadism not caused by AAS abuse. Women and animal	Not subject of this investigation. Relevant bias.
EXPOSURE	Presence of other diseases or possible causes for hypogonadism.	Other diseases or causes for hypogonadism could be a relevant bias for this study.
OUTCOMES	N/A	N/A
STUDY DESIGN	Review, Congress, Comment and Response article.	No original or complete data to analyse.
OTHER CRITERIA	Hypogonadism by other causes than AAS abuse. Inability to translate the manuscript into English	Hypogonadism not caused for AAS abuse is not the subject of this investigation. Inability to comprehend the manuscript.

Abbreviations: AAS, anabolic–androgenic steroid; ASIH, androgenic steroid-induced hypogonadism; N/A, not applicable.

A total of 64 studies remained for a complete reading and analysis, considering the inclusion and exclusion criteria (Table 2); from these, 53 studies were excluded from the final results. In 33 studies, the presented hypogonadism was not directly related to AAS abuse by the subjects (studies reported cases of idiopathic hypogonadism, Klinefelter syndrome, Kallmann syndrome, obesity, etc.), 9 studies were opinion articles or critical reviews, 7 had women or children as subjects, 2 referred to abstracts for congresses, and 2 were in languages that we could not translate (Japanese and Czech). In addition, from the 64 studies analysed, 3 relevant papers were identified among the references and included in the final list. Therefore, after the complete reading and considering the inclusion and exclusion criteria, 14 studies were qualified for this review (Figure 1).

Table 3 summarises the 14 studies eligible for this review. There were analysed studies from Brazil (1 study), Slovenia (1 study), Malaya (1 study), UK (4 studies), USA (4 studies), Finland (1 study), Italy (1 study), and Sweden (1 study). The subjects were between 17 and 57 years old with a wide variety of AAS abuse conditions (time, drugs, dose, etc.). The hypogonadism was characterised by clinical symptoms (low libido, erectile dysfunction, etc.) and/or laboratorial examinations (LH, FSH, testosterone, etc.) and/or testicular size (under normal). All kinds of interventions and outcomes were reported, and in the end, considering all available data, it was determined whether or not hypogonadism was reversible.

Overall, this systematic review identified and analysed 179 cases of AAS users (Figure 2). Of these, 168 cases had a clearly diagnosed hypogonadism and proven to be linked exclusively to AAS abuse. However, among these 168 cases, only in 38 cases the outcome was fully known. Among these 38 cases, in merely 4 this condition was completely reversible (2 with drug therapy) with HPG axis recovery. In 34 cases, the hypogonadism was irreversible through subjects remaining with HPG axis disorder associated with clinical symptoms or the need for hormone replacement therapy. In only two cases, the hypogonadism could be reversed without drug treatment.

8 | DISCUSSION

The administration of AAS increases the serum androgens levels to a supraphysiological state, which implies an important derangement on HPG axis and suppression of GnRH, LH, FSH and testosterone (Evans, 2004; Vilar Neto et al., 2018). This disorder results in a reduction of serum testosterone levels and illustrates a secondary hypogonadism, in this case, more specifically known as anabolic steroid-induced hypogonadism (ASIH), which is characterised by the functional incompetence of the testes with subnormal or impaired testosterone synthesis and/or spermatozoa resulting from the exogenous administration of AAS (Hartgens & Kuipers, 2004).

Nevertheless, the AAS abuse is commonly associated with a secondary hypogonadism (ASIH); there are real possibilities of this condition to evolve to a primary hypogonadism (testicular failure). Boregowda et al. report the case of a 40-year-old bodybuilder with a 10-year history of nandrolone, testosterone and growth hormone abuse. Twelve months after discontinuing the drugs, the

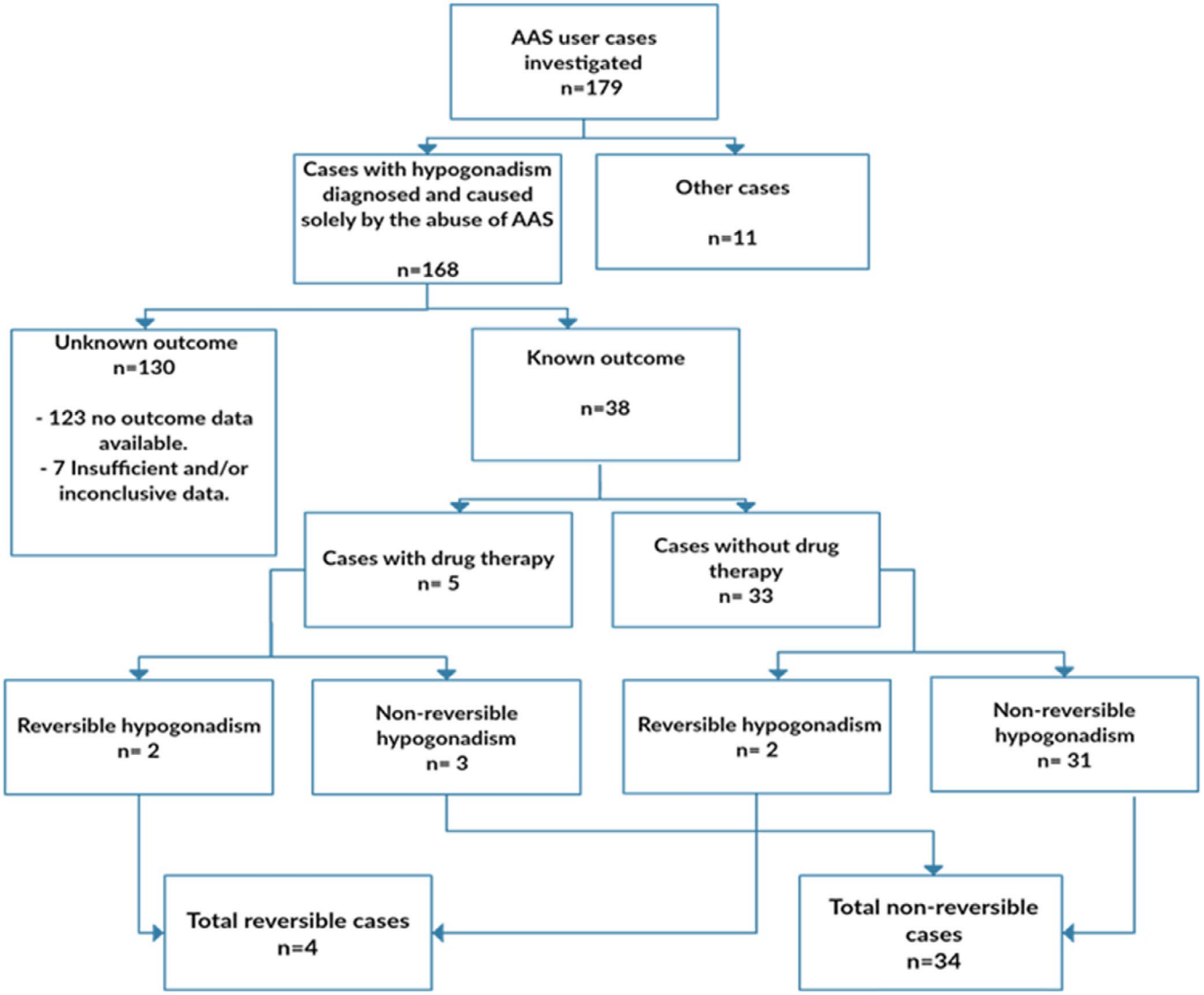

FIGURE 2 Systematic review cases outcomes flow chart

man suffered from low libido, erectile dysfunction and testicular atrophy. Laboratory tests initially confirmed the diagnosis of secondary hypogonadism: FSH = 0.52 U/L, LH = 0.2 U/L, total testosterone = 1.6 nmol/L and azoospermia (0/ml). After 30 months of follow-up, the researchers found a significant increase, with supraphysiological gonadotropin values: FSH = 15 U/L (normal range 1.5–12.4 U/L) and LH = 22 U/L (normal range 1.7–8.6 U/L). Even with this high elevation of gonadotropins levels, his testicles remained incompetent to synthesise testosterone and conclude the spermatogenesis process: total testosterone = 9.6 nmol/L (normal >11 nmol/L) and sperm count = 100,000/ml (normal > 15.000.000/ml). Confirming the diagnosis of primary hypogonadism, at the end of 36 months, gonadotropins further increased (hypergonadotropic hypogonadism), FSH = 16 U/L, LH = 29 U/L and total testosterone decreased even more, testosterone = 7.2 nmol/L. At the end of the study, the patient remained infertile, with testicular atrophy and requiring phosphodiesterase-5 inhibitor to improve his erectile function (Boregowda et al., 2011).

In truth, the pathophysiology of ASIH is certainly much more complex than a simple effect from the negative feedback caused by the excess of androgens. That is because AAS abusers are usually using a blend of high-dose synthetic androgens. In addition to the endocrine disruption, the AAS abuse can also contribute to a primary testicular failure through a direct toxic effect, as suggested by animal studies by Boetcher et al. and Chainy et al. (Boettcher et al., 2011; Chainy et al., 1997; Karavolos et al., 2015; Karila et al., 2004).

Diverging from common sense, the analysed studies in this review clearly show that the deleterious effects of AAS abuse on the HPG axis are not occasional and not necessarily transient. Instead, the recent findings lead us to consider the AAS impact on the HPG axis as an unpredictable and permanent event. Kanayama and collaborators, in a cross-sectional study, investigate 24 (twenty-four) male former long-term AAS users (19 untreated) and compared with the 36 non-AAS-using weightlifters. The 19 untreated AAS users had at least 2 years of cumulative use and had discontinued the AAS use at least 3 months before the laboratorial evaluation. The results showed significantly

TABLE 3 Eligible studies: study, subjects, intervention and outcome description

Author and date	Origin	Study design	Subject	AAS abuse	Hypogonadism characterisation	Intervention	Outcome	Reversible hypogonadism?
Vilar Neto et al. (2018)	BRA	Case report	20-year-old healthy starter bodybuilder	Sustanon 250 mg and nandrolone 100 mg for 4 weeks + Sustanon 500 mg, nandrolone 200 mg and oxymetholone (100 mg/day) for 4 weeks.	FSH = 1.47 mUI/ml, LH = 0.1 mUI/ml and total testosterone = 1.47 ng/ml.	No	After 61 days of steroid withdrawal and no medical treatment, the HPG axis was partially recovered. FSH = 2.1 mUI/ml, LH = 1.8 mUI/ml and total testosterone = 3.5 ng/ml. No clinical symptoms.	YES—after 61 days.
Alibegovic (2018)	SLOVENIA	Case report	57-year-old karate coach	Urine Metabolite Concentration (ng/ml). Metandienone 2,500. Nandrolone 2,200. Mesterolone 16,000. Dehydrochloromethyltestosterone 230	Total testosterone level in the urine was 81.2 nmol/L, and in the serum, it was 109.8 nmol/L. Testícles:Weight: Right testicle = 6.85 g. Left testicle=6.66 g Dimensions: Right testicle = 3.2 × 2.7 cm Left testicle = 3.0 × 2.9 cm	N/A	Signs of excessive aggression. Morphology of testicular hyalinosis showed that the amount of the elastic fibres did not decrease. The subject committed suicide after killing his wife.	N/A
Boregowda et al. (2011)	UK	Case report	40-year-old bodybuilder	Over 10 years: nandrolone, testosterone and growth hormone	12 months after discontinuing the anabolic steroids: FSH = 0.52 U/L LH = 0.2 U/L and total testosterone = 1.6 nmol/L Azoospermia (0/ml) Clinical symptoms: bilateral testicular atrophy (volume, 3 ml), low libido and erectile dysfunction	No	After 30 months of steroid withdrawal: FSH = 15 U/L LH = 22 U/L and total testosterone = 9.6nmol/L and Sperm count = 100.000/ml Clinical symptoms: Continued to have a reduced testicular volume and needed to improve erectile function with a phosphodiesterase−5 inhibitor.	NO—persistent primary hypogonadism (primary gonadal failure and infertility)
Coward et al. (2013)	USA	Study cohort: retrospective and prospective	-Cohort retrospective: 42 profound hypogonadism ASS) -Cohort prospective: 80 men (40.4 ± 8.4 years). Average age of first exposure to AAS was 25.6 ± 7.6 years	-Cohort retrospective: AAS use not detailed. -Cohort prospective The 3 most commonly used AASs:Nandrolone decanoate for 14 months (60 patients), stanozolol for 9.5 months (45 patients), and methandrostenolone for 10.7 months (39 patients)	-Cohort retrospective: Total testosterone 50 ng/dl or less -Cohort prospective: Clinical symptoms: Decreased testicular size, acne, aggressive behaviour and Infertility/low sperm count	-Cohort retrospective: not described -Cohort prospective: TRT	Unknown outcome.	N/A

(Continues)

TABLE 3 (Continued)

Author and date	Origin	Study design	Subject	AAS abuse	Hypogonadism characterisation	Intervention	Outcome	Reversible hypogonadism?
Gill (1998)	UK	Case Report	17-year-old man, starter bodybuilder	Nandralone, Sustanon, Stanazolol and Danazol, doses were not indicated, used for at least six months	Mild an tender gynaecomastia, very scant body hair, reduced testicular size, erectile impotence, severely reduced spermatogenesis, serum testosterone of 0.8 nmol/L and FSH and LH were undetectable	Sustanon was maintained, 250 mg, every two weeks by 15 months, he stopped treatment, and testosterone levels fell from 14 to 8.5 nmol/L. So it was initiate weekly HCG injections on dose of 10,000 UI 1 month, 5,000 UI 1 month, at last 2,500 UI 1 month	Serum testosterone levels and sexual potency returned to normal after three months	Yes, after 30 months of subsequent follow-up, the patient remained clinically and biochemically eugonadal and symptom-free on no treatment.
Martikainen et al. (1986)	FINLAND	Cross-sectional study	Six power athletes[a], mean age 30 years old	Testosterone, Methandienone, Nandrolone, Decanoate, Stanozolol doses were poorly described in use for about 3 months (interrupted three weeks before intervention).	Three weeks after cessation of drug use: Pregnenolone (0.48 ± 0.07 ng/ml), DHEA (6.52 ± 1.41 ng/ml), Progesterone (0.07 ± 0.01 ng/ml), Testosterone (0.85 ± 0.12 ng/ml), Estradiol (0.02 ± 0.003 ng/ml), FSH (1.1 ± 0.03 mUI/ml), and LH (2.6 ± 0.3 mUI/ml).	Single dose of HCG (50 UI/kg) 3 weeks after cessation of AAS use.	Three days after a single dose of HCG (50 UI/kg), the testosterone levels were doubled higher than starting values.	Inconclusive, LH, testosterone and FSH were not evaluated after sufficient time to assess an HPG axis response.
Pirola et al. (2010)	ITALY	Case report	34-year-old man, non-professional bodybuilder	1995 to 2005, in order: Nandrolone (25 mg/day) and Stanazolol (25 mg/day), 8 weeks; Mesterolone (50 mg/day), 15 days; Clomiphene citrate (50 mg/day), 1 week; HCG (2000 UI) three times in a week. 2005 to August 2008, in order: Nandrolone and stanazolol + boldenone (50 mg/day) by three weeks (cycle).	Bilateral testicular atrophy, loss of libido, FSH (1 mUI/ml), LH (<0.5 mUI/ml), estradiol (<10 pg/ml), testosterone (0.3 ng/ml).	Single dose of Triptorelin (100 μg)	Ten days after triptorelin administration testosterone levels raise to 7.0 ng/ml, 1 month after testosterone level was within a normal range, and hypogonadism symptoms disappear.	YES

(Continues)

TABLE 3 (Continued)

Author and date	Origin	Study design	Subject	AAS abuse	Hypogonadism characterisation	Intervention	Outcome	Reversible hypogonadism?
Jarow and Lipshultz (1990)	USA	Case report	Case 1:36-year-old man, competitive bodybuilder. Case 2:39-year-old man, weight lifter competitor in the past.	Case 1: Testosterone cypionate (200mg/week), nandrolone decanoate (200 mg/week), methandrostenolone (30 mg/day), in 6 months a year for the last 4 years. Discontinued use 6 weeks before this study. Case 2: Testosterone cypionate (200 mg/week), oxandrolone (2 tablets/day), methandrostenolone (20 mg/day). Discontinued use 2 and a half year before this study.	Case 1: Fructose-positive azoospermia, serum FSH and LH were not detectable; low testosterone (10 nmol/L), and low prolactin normal. GnRH stimulation revealed a severely blunted response of pituitary gland function, even one year after stop steroids use. Case 2: low serum testosterone (6nmol/L) and normal serum LH, FSH, and prolactin. Normal sperm count, with normal motility and morphology. 2 years history of decreased libido.	Case 1: HCG injections (time and doses note specified) Case 2: None of the treatment was acquired.	Case 1: Sperm count in 3 million sperm/ml, normal mobility, and morphology. 9 months since begun the treatment the subject got his wife pregnant. Case 2: Not related.	Case 1: No, despite the reversibility of azoospermia and infertility, even after 1 year of steroid withdrawal, the GnRH test revealed a highly compromised response from the pituitary gland. Case 2: No, even after 3 years of steroid withdrawal, the GnRH test revealed a blunted response of the pituitary gland.
Coxon (2016)	UK	Case report	38-year-old man	The patient reported that has used steroid at high doses for 7—8 years, discontinued use 3 years previously.	Erectile dysfunction, low serum testosterone levels (7 nmol/L), free testosterone (80 pmol/L), and LH (1.5 UI/L). Moderate sperm count reduced.	Clomiphene citrate (50 mg) on alternate days for three months.	Three months later serum testosterone (9.2 nmol/L) and free testosterone (151 pmol/L) remained below the expected.	NO
Kanayama et al. (2015)	USA	Cross-sectional study, naturalistic.	Male weightlifters (35–55 years old). 36 AAS non-users, and 24 long-term AAS former users (13 with pronounced hypogonadism).	At least 24 months of lifetime use of AAS.	AAS users: Total testosterone 319 ng/dl; Free testosterone 107 pg/ml; FSH 4.7 mIU/ml; LH 3.9 mIU/ml, significantly smaller testicular volumes. Hypogonadism was evidence by Sexual Desire questionnaire. AAS non-users: Total testosterone 449 ng/dl; Free testosterone 132 pg/ml; FSH 5.2 mIU/ml; LH 4.6 mIU/ml.	No	No treatment related by authors.	NO
Flanagan and Lehtihet (2015)	SWEEDEN	Randomised clinical trial	26 men, 8 healthy normogonadotropic, 5 IHH, and 13 FAU (documented cessation for at least 7 months)	Insulin, GH, IGF-1, thyroid hormone, testosterone, nandrolone, methandienone, and stanozolol; The median dose of testosterone was 2000mg per week (range 750–6000 mg)	The hypogonadism was assessed by clinical observations. The FAU group had testosterone levels <10 nmol/L. The GnRH stimulation test was performed, a single IV dose of 100μg followed by an IM dose of 5,000 U of HCG.	No	After the first administration of GnRH, the LH levels were similar in FAU and IHH groups. FAU males had lower LH levels than healthy men. 72 hr after IM dose of 5,000 U of HCG, testosterone levels of control group raised to 20.9 nmol/L, IHH, 16.8 nmol/L, and FAU, 9.7 nmol/L.	NO

(Continues)

TABLE 3 (Continued)

Author and date	Origin	Study design	Subject	AAS abuse	Hypogonadism characterisation	Intervention	Outcome	Reversible hypogonadism?
Gazvani et al. (1997)	UK	Case report	Case 1:31-year-old amateur bodybuilder. Case 2:33-year-old keen bodybuilder. Case 3:27-year-old bodybuilder. Case 4:28-year-old bodybuilder	Drugs and doses not described. Case 1: Last five years on steroids. Case 2: Using AAS. Case 3: AAS abuse history. Case 4: Over 4 years AAS abuse history.	Case 1:6 years of secondary infertility history because of azoospermia. Reduced testicular volume, FSH = 0.6 U/I, LH = 2.8 U/I, and testosterone = 3.7 nmol/L. Case 2: diagnosis of primary infertility due to azoospermia and reduced testicular volume. Six months of AAS abstinence FSH was 1.9 U/L, LH 4.3 U/L, and testosterone = 1.3 nmol/L. Case 3: Primary infertility of 3 years and azoospermia. (hypogonadism not characterised). Case 4:1 year of primary. infertility due to azoospermia., reduced testicular volume. FSH 0.7 U/L, LH 1.2 U/L and testosterone 4.2 nmol/L.	Case 1: No. Case 2: No. Case 2: No. Case 2: No.	Case 1:18 months after stopping steroid abuse, there was found improvement in sperm profile and FSH was 2.6 U/L, LH 5.1 U/L, and testosterone 6.6 nmol/L. 20 months after cessation of steroid abuse, the subject got his wife pregnant. Case 2:20 months after stopping steroid abuse, there was found improvement in sperm profile and FSH was 2.3 U/L, LH 3.71 U/L, and testosterone 11.2 nmol/L. Case 3:20 months after stopped steroid abuse, there was found an enormous improvement in sperm profile. 22 months after cessation of steroid abuse, the subject got his wife pregnant. Case 4:6 months after stopping steroid abuse, there was found improvement in sperm profile, FSH was 0.9 U/L, LH 1.5 U/L, and testosterone 11.2 nmol/L. 9 months after cessation of steroid abuse, the subject got his wife pregnant.	Case 1: No, despite the reversibility of azoospermia and infertility, low testosterone remains. Case 2: Yes. Case 3: Inconclusive. (Reversible azoospermia and fertility). Case 4: No, despite the reversibility of azoospermia and infertility, the HPG axis remains disturbed.
Menon (2003)	Malaya	Case report	37-year-old amateur bodybuilder with hypogonadotropic hypogonadism	10 years on AAS abuse. Testosterone cypionate, methandrostenolone, oxandrolone, testosterone propionate, oxymetholone, nandrolone decanoate, and methenolone enanthate.	Testicular atrophy, erectile dysfunction, azoospermia, and infertility. (FSH 0.5 U/L, LH 0.9 U/L, testosterone: 7 nmol/L	Three times a week injections of 10,000 IU of hCG (Profasi; Serono) and daily injections of 75. IU of hMG (Humegon; Organon) for 3 months.	One month on treatment: dramatic improvement in his semen profile. FSH 5 U/L, LH 8 U/L, testosterone: 21 nmol/L). 2 months on treatment: erectile function recovered. No improvement in testicular volumes. 10 months after starting the treatment, the subject got his wife pregnant.	Inconclusive. Despite the reversibility of azoospermia and infertility, the gonadotropin profile was not evaluated after treatment, and testicular volume was compromised even after 2 months of treatment.

(Continues)

TABLE 3 (Continued)

Author and date	Origin	Study design	Subject	AAS abuse	Hypogonadism characterisation	Intervention	Outcome	Reversible hypogonadism?
Turek et al. (1995)	USA	Case report	37-year-old former bodybuilder with a 4-year history of primary infertility, low serum testosterone and decreased libido.	5 years on AAS abuse ended 5 years before referral. He had commonly used 2 or 3 steroid preparations together in cycles of 14 to 16 weeks followed by an equal period of abstinence. The most common AAS was injectable nandrolone decanoate and oral stanozolol.	Testicular atrophy, azoospermia, and infertility. Testosterone=160 ng/dl.	Tamoxifen (10 mg. twice daily) and injections of 2,000 IU of hCG (three times a week) for 4 weeks followed by 3,000 IU (three times a week) of hCG for 3 months.	1 month on treatment: testosterone = 287 ng/dl. 3 months on treatment: testosterone=325 ng/dl, sperm profile improved, and the subject got his wife pregnant. Two months later, due to the development of painful gynaecomastia, human chorionic gonadotropin was discontinued, and intramuscular testosterone was prescribed.	No. Despite the reversibility of azoospermia and infertility, the subject still needs an exogenous testosterone replacement.

Abbreviations: AAS, anabolic androgen steroids; AMH, anti-Mullerian hormone; DHEA, dehydroepiandrosterone; FAU, former androgen use; FSH, follicle-stimulating hormone; GH, growth hormone; GnRH, gonadotropin-releasing hormone. AAS, anabolic–androgenic steroids; HCG, human chorionic gonadotropin; hMG, human menopausal gonadotropins; HPG, hypothalamic–pituitary–gonadal; IGF-1, insulin-like growth factor 1; IHH, idiopathic hypogonadotropic hypogonadism; im, intramuscular; iv, intravenous; LH, luteinising hormone; N/A, not applicable; SHBG, sexual hormone-binding globulin; TRT, testosterone replacement therapy.

[a]This article just refers to subjects as 'power athletes'.

smaller testicular volume and lower total testosterone levels in the former AAS users compared to nonusers. However, 13 (54%) of the 24 former AAS users demonstrated pronounced symptoms of anabolic steroid-induced hypogonadism, what sure requires special attention (Kanayama et al., 2015). In a different approach, Jarrow et al. investigated two case reports involving former AAS users. The study demonstrated from GnrH stimulation tests that even after 3 years of AAS withdrawal, the pituitary response was still largely compromised. In one case, even with HCG treatment, the pituitary response was clearly compromised. On the other case, the test showed no response from the pituitary gland (Jarow & Lipshultz, 1990).

Despite important studies, reviews, guidelines and even medical algorithm already been published (Bagatell & Bremner, 2003; Bagatell & Bremner, 1996; Dandona & Rosenberg, 2010; Tatem & Beilan, 2020), the management of ASIH patient is still a complicated question. Clomiphene citrate, human chorionic gonadotropin (HCG), tamoxifen and anastrozole are the main drugs normally recommended in an attempt to treat the incidence of hypogonadism and infertility in AAS users. In fact, there are relevant data which show the use of HCG and clomiphene citrate associated with meticulous medical and laboratory monitoring as an efficient treatment in hypogonadism and even effective in preventing or mitigating the AAS abuse impairment on testes and HPG axis (Tatem & Beilan, 2020).

Unfortunately, the continued absence of conclusive studies does not allow definitive guidelines on how to treat ASIH (Nieschlag & Vorona, 2015). The literature proposes that the interruption of the use of AAS can be carried out basically in four ways: immediate interruption without medical therapy, discontinuation associated with clomiphene therapy, discontinuation associated with HCG therapy, and exchange of the use of AAS not prescribed by testosterone prescribed by doctors. Important to elucidate that these are still 'off-label' approaches, once US Food and Drug Administration (FDA) has not approved the use of clomiphene, hCG, or testosterone for the treatment of AAS withdrawal, and there are no clinical trials of medical therapy for this condition (Anawalt, 2019).

Human chorionic gonadotropin (HCG) has been shown to be an important alternative in endogenous testosterone recovery in men who have lost their ability to produce this hormone, to normalise sexual potency, and in improving the symptoms of hypogonadism (Gill, 1998; Habous et al., 2018). Unlike other medications, an important distinction of HCG is its action directly on the testicle, causing an immediate response (Coviello et al., 2005; Toscano et al., 1983). In addition, it is very important to report that in men, HCG therapeutic application has been more recurrent mainly due to an increase on the abuse of AAS and the hypogonadism cases (Rahnema et al., 2014).

However, the success of HCG use in the treatment of AAS-related hypogonadism is not certain. Martikainen et al. investigated six young power athletes who used a single dose of HCG (50 UI/kg) 3 weeks after cessation of AAS abuse (prior AAS abuse, total testosterone values were 6.85 ± 2.09 pg/ml and 3 weeks after AAS discontinuation reduced to 0.85 ± 0.12 pg/ml). Three days after HCG

(50 UI/kg) administration, testosterone levels increased by two times; however, it was not possible to confirm the reversibility of hypogonadism in this case. LH, FSH and T levels have not been dosed for a longer period, and the nonelevation of androstenedione serum values, even after HCG stimulation, could mean that there was no stimulus of the 17β-hydrosteroid enzyme, making the elevation in serum testosterone values only a transient event (Martikainen et al., 1986). Similarly, Menon (2003) noted that the regular use of HCG injections (3×/weeks; 1,000 IU), even combined with another drug to induce testosterone synthesis (human menopausal gonadotropins—hMG; 75 IU) for 3 months, resulted in no conclusive results on the reversibility of hypogonadism. In this case, there was no observable change in testicular volume after treatment and gonadotropin profile also was not evaluated after HCG therapy (Menon, 2003).

Still regarding the use of intramuscular injections of HCG, apparently, azoospermia and infertility reversibility seem to be more likely to be achieved than complete recovery of the HPG axis. Turek et al. demonstrate that HCG administration, associated with tamoxifen, was able to reverse azoospermia and infertility, but the HPG axis remained impaired. In this study, tamoxifen (10 mg two doses a day) and injections of 2,000 IU of hCG (three times a week) for 4 weeks followed by 3,000 IU (three times a week) of hCG for 3 months were used as treatment for a 34-year-old man with a history of AAS abuse for 5 years and 4 years history of primary infertility and decreased libido. Although his wife successfully became pregnant 3 months after starting therapy, the man still needs exogenous testosterone administration to maintain adequate man pattern response (Turek et al., 1995). Still, in a series of four cases involving AAS users, diagnosed with azoospermia and infertility and followed conservatively (without drug therapy), Gazvani et al. observed an expressive sperm concentration improvement with full fertility recovery in all cases. That was further confirmed by the fact that 3 (three) subjects were able to get their partners pregnant, 1 of them already after 9 (nine) months of AAS withdraw. However, despite long-term follow-up (18 months), only 1 subject achieved a fully recovering HPG axis functionality (Gazvani et al., 1997).

In fact, there is strong evidence that two things are extremely decisive for an individual's ability to regain the capacity of synthesising and secreting normal testosterone levels and reverse ASIH. The age of the patient and the length of time in which endogenous testosterone synthesis was compromised. Previous evidence suggests a possible reversibility in younger men related to an efficient 'elastic axis' being able to recover gonadotropin-releasing hormone (GnRH) pulsation and gonadotropin secretion more competently (Moretti et al., 2007; Rahnema et al., 2014). In a case report previously published by our research group, we observed the case of a young bodybuilder who was able to spontaneously recover his endogenous testosterone synthesis even after major HPG axis disruption and severe impairment in LH, FSH and testosterone levels. Most likely, this spontaneous recovery was only possible due to two conditions: the patient was only 19 years old and used AAS for only 8 weeks (Vilar Neto et al., 2018).

The question about the ASIH reversibility is certainly a controversial issue. Two of the main studies already published on the theme reached divergent conclusions (Handelsman & Shankara-Narayana, 2020). Rasmussen et al. examined the question from a detailed cross-sectional study where 33 former AAS abusers were compared with current AAS abusers and a control group. The study data showed significantly lower total and free testosterone levels in AAS abusers compared to nonusers (control group) subjects ($p < .01$). The former AAS abusers group also had higher proportions of participants with depressive symptoms (24.2%), erectile dysfunction (27.3%) and decreased libido (40.1%) than the other two groups ($p < .05$). Two things about the former AAS abusers group are very significant: The elapsed duration since AAS cessation (geometric mean, 95% CI) was 2.5 years, 57.6% of the subjects reported having regularity used HCG, and 33.3% reported the use of aromatase-inhibiting drugs during AAS cycles. These data suggest that a relatively long recovery time and drugs administration as an attempt to mitigate the AAS abuse impact on the testicles and HPT axis was not enough to solve or prevent the problem. In conclusion, the authors claim that 'AAS abusers exhibited biochemical and functional ASIH several years after AAS cessation' (Rasmussen et al., 2016).

In the other hand, Nandini Shankara-Narayana and collaborators also through a meticulous cross-sectional study came to the conclusion that 'Suppressed testicular and cardiac function due to androgen abuse is effectively fully reversible'. In this work, a group formed by 31 past AAS users were compared with two other groups: 41 current AAS users and 21 nonusers (control). The results show some interesting data, especially when we observe that in this study the past AAS users group had 300 days (median) since last AAS use versus 902 days (geometric mean (95% CI)) in the Rasmussen study. Even that way, Nandini Shankara-Narayana found that the past users group as well as the control group had no record of infertility issues and with the exception of testis volume and serum sex hormone-binding globulin (SHBG), no significant differences were found in androgenic evaluation between the control group and the AAS past users group. Serum FSH, LH, testosterone DHT, estradiol, estrone and DHEA were similar in both groups. Even the incidence of acne, gynaecomastia and temporal hair loss were similar between these groups (Shankara-Narayana et al., 2020).

These discrepancy studies results (full recovery in shorter time vs. no recovery in long time) show that the question of reversibility of ASIH is not a trivial matter and certainly very well-controlled studies will be necessary for a definitive answer to this question. Nevertheless, it is important to note that the present systematic review may be limited by the small number of studies on the topic and that the published studies themselves may be biased if we consider that there could exist a tendency to highlight and to publish negative outcome cases.

9 | CONCLUSION

The present review shows that AAS abuse-induced hypogonadism is still a poorly studied health issue. Even searching among 13 scientific databases, only 14 related studies could be selected for this review.

Our data analyses showed that deleterious effects of AAS abuse on the endogenous testosterone synthesis are not occasional and not necessarily transient. Therefore, hypogonadism is an expected event for AAS users and it is a serious and underrated problem. In addition, this condition may be the cause of fertility problems, depression, low libido and sexual impotence in men.

The ASIH does not seem to have its origin and problematic exclusively related to negative feedback and HPG axis disorder. The simultaneous use of different types of AAS, in high doses and for a prolonged period of time, may also be associated with primary testicular failure, which could contribute to explain the cases in which recovery was not possible.

The analysed cases in this review suggest that the ASIH is a reversible condition; however, the time required and the success rate are uncertain and essentially depend on patient age and how long he was exposed to supraphysiological androgens levels, and certainly medical and pharmacological intervention is key factors to achieve recovery.

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CONFLICT OF INTEREST

The authors declare that there were no conflicts of interest in the realisation of this research.

AUTHOR CONTRIBUTIONS

José de Oliveira Vilar Neto provided the main idea and helped in data collection, data analysis, and preparation of the manuscript. Daniel Vieira Pinto, Juan de Sá Roriz Caminha and Elizabeth De Francesco Daher contributed to data analysis and preparation of the manuscript. Carlos Alberto da Silva helped in data collection and preparation of the manuscript. Robson Salviano De Matos, Carlos Antônio Bruno da Silva, Felipe Rocha Alves, Saulo Chaves Magalhães and Júlio César Chaves Nunes Filho gave assistance in data analysis.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analysed in this study.

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