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Abuse of anabolic-androgenic steroids and bodybuilding acne: an underestimated health problem

Bodo Melnik[1], Thomas Jansen[2], Stephan Grabbe[2]
(1) Department of Dermatology, Environmental Medicine and Health Science, Division of Human Sciences, University of Osnabrück, Germany
(2) Department of Dermatology, Venereology and Allergy, University of Essen, Germany

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Summary
Abuse of anabolic-androgenic steroids (AAS) by members of fitness centers and others in Germany has reached alarming dimensions. The health care system provides the illegal AAS to 48.1 % of abusers. Physicians are involved in illegal prescription of AAS and monitoring of 32.1 % of AAS abusers. Besides health-threatening cardiovascular, hepatotoxic and psychiatric long-term side effects of AAS, acne occurs in about 50 % of AAS abusers and is an important clinical indicator of AAS abuse, especially in young men 18-26 years of age. Both acne conglobata and acne fulminans can be induced by AAS abuse. The dermatologist should recognize bodybuilding acne, address the AAS abuse, and warn the patient about other potential hazards.

Introduction
Sports can promote good health as well as pose a health hazard. Various skin diseases can be improved or worsened by sports [1]. Intake or administration of doping agents, especially anabolic-androgenic steroids (AAS) lead to unwanted dermatological effects such as bodybuilding or doping acne with increased seborrhea, striae distensae, gynecomastia, hypertrichosis, hirsutism, androgenetic alopecia, seborrheic dermatitis, cutaneous infections including furunculosis as well as reduction of testicular volume and sperm count (Table 1) [2, 3]. In doping acne the clinical picture ranges from the initial manifestation of acne or a worsening of preexistent acne up to features of acne conglobata or the sudden occurrence of acne fulminans [4–9]. Further, healing of acne may be prevented by anabolic steroids. AAS abuse has detrimental effects on lipid metabolism. The AAS-induced drop of HDL cholesterol and rise of LDL cholesterol increase the cardiovascular risk.
Exacerbation of other skin diseases such as hereditary coproporphyria, linear keloids and psoriasis has been reported as side effects of AAS [10–12]. Therapeutic applications of AAS in dermatology include long-term prophylaxis of hereditary angioedema (danazol, stanozolol), treating cryofibrinogenemia, use of anticatabolic effects in burns and extensive wounds and in wasting syndrome in advanced HIV infection [13–19].
Anabolic ergogenic substances such as AAS and clenbuterol are prohibited for non-therapeutic indications and for use in sports. The World Anti-Doping Agency lists them among prohibited substances and methods [20].

Doping prevalence and anabolic-androgenic steroids
Use of doping agents, especially of AAS, is no longer limited to competitive sports, but has, as medical studies in USA show, spread to leisure sports, especially to fitness sports and bodybuilding [21–34]. The main reason for taking AAS is the identification of adolescents and young adults with the exaggerated ideal body image suggested by western mass media [25, 26, 34]. Striegel et al. [27] estimate that visitors of fitness centers in Germany spend about 85 million

Table 1: Most common clinical side effects of anabolic-androgenic steroids, modified from O´Sullivan et al. [45].

Side effects	Percent (%) of users effected
Changes of libido	61
Mood swings	57
Reduced testicular volume	46
Acne	43
Erectile dysfunction	21
Headaches	9
Edema, water retention	5
Change in hair growth	5

Euros yearly for anabolic ergogenic substances. In the USA, 11 % of boys in grades 11 and 12 consume AAS, as do 2.5 % of girls [24, 30]. In England, 9 % of male fitness studio attendants take AAS [31, 32]. The drugs are known among users as "Sus" and "Deca". "Sus" (sustanon) is a mixture of four testosterone esters, "Deca" is nandrolone decanoate [33].The prevalence of AAS among Australian high school students is reported at 3.2 % [35]. In the subgroup of bodybuilders and weightlifters in Flanders, the prevalence of AAS abuse between 1988 and 1993 was 38–58 % [36]. Doping prevalence among college athletes in the USA is reported to be 17–20 % [26, 32], among amateur bodybuilders even 80 % in men and 40 % in women [24, 29]. An increase in the prevalence in AAS abuse has also been observed in Italy and Sweden [37, 38].

The doping prevalence in Northern Germany is best represented by the Lübeck study, a survey of 24 fitness studios in Schleswig-Holstein and Hamburg [39]. The average age of the athletes was 27.9 years with users being most frequently (37 %) in the age group 21–25 years. Of the interviewed men 24 % and of the women 8 % admitted to using anabolic drugs. In 94 % potentially highly hepatotoxic substances were taken, mainly procured on the black market, but prescribed by physicians in 14 % (Table 2). As the return of questionnaires in the Lübeck study was 52 %, a much higher rate of use must be anticipated. A recently published report by Striegel et al. [27] from the Institute for Sports Medicine of the University of Tübingen, Germany, revealed the results of a nationwide poll of 113 fitness centers. Of participants, 13.5 % admitted to having used anabolic ergogenic substances at least once. Abuse correlates with cocaine abuse, years of training, frequency of training and showed negative correlation with educational status and alcohol consumption. Especially disturbing is the fact that 48.1 % of the users of anabolic ergogenic agents obtain them through health care providers and 32.1 % of these are under physician supervision.

A similar situation can be found in Sweden. An analysis of 25,835 calls to the anti-doping hotline of the Institute for Clinical Pharmacology of the Huddinge University Hospital in Stockholm from 1993 to 2000 shows that most calls were in regard to side effects of AAS, especially, testosterone, nandrolone decanoate, methandienone and stanozolol [40]. Of the ten most common side effects of AAS, acne was third following psychological changes such as aggression and depression, among clinically visible symptoms it even ranked first (Table 3).

Table 2: Most commonly used anabolic-androgenic steroids in German fitness clubs (Lübeck study), modified from Boos et al. [39].

Anabolic-androgenic steroid (AAS)	Trade name	Cases (%)	Average dose (mg/day)
Methandrostenolone	Dianabol, Metanabol	37.5	36.6
Nandrolone	Deca-Durabolin	37.5	4.0
Testosterone	Systanon, Testoviron	37.5	58.5
Oxandrolone	Anavar, Oxitosona	15.0	25.0
Stanozolol	Winstrol, Stromba	39.0	37.4
Methenolone	Primobolan	27.5	75.6
Other AAS	Omnadren, Proviron	60.9	53.3

Sources of and substance groups of anabolic-androgenic steroids

In the Lübeck study 94 % of abusers took AAS, of these 96 % in oral form and 64 % additionally via a parental route [39]. Among oral drugs, stanozolol, methandrostenolone and oxandrolone predominated. Among parenterally administered AAS, stanozolol, testosterone enanthate and decanoate and nandrolone were favored. Table 2 informs on the frequency of use of the AAS and the average daily dose, which ranged from 35 to 75 mg. The majority of athletes use drug combinations over a period of 7.5 weeks on average as a course of treatment. The drug dose is generally increased up to the middle of the course and tapered again towards the end. A recently published internet-based survey from the USA also shows that of the 207 participants most used AAS in combinations [41].

Table 3: 10 side effects most commonly reported by 4,339 users of anabolic-androgenic steroids in Sweden 1996–2000 [40].

Reported side effects	Number of reports
Aggression	835
Depression	829
Acne	770
Gynecomastia	637
Fear	637
Impotence	413
Testicular atrophy	404
Sleep disturbances	328
Edema	318
Mood swings	302

On average, 3.1 different drugs were used in the 5–10 week course of treatment. Physiological substitution doses were exceeded by a factor of 5 to 29. Diverse bodybuilding online forums and internet services provide exchanges among users, information on procurement, use, combination of drugs, dosages, side effects and, in part, sell products (e.g. www.bodybuilding-online.com, http://steroidanabolic.com./germany/steroideoraldoping.php, www.muscle.de24/de/muskelaufbau/anabolics).

In up to 50 % AAS are obtained on the black market. Sources range from the "house dealer" to users who finance their own need by further selling. The substances are imported via the former Eastern bloc countries. They can also be obtained on vacation in Spanish pharmacies or supermarkets in Thailand [39, 47]. Often anabolic agents from veterinary sources are used. They are often cheaper and easier to obtain, bur carry additional risks as they are not produced with the same care as are drugs for human consumption.

Sources named by the users in the Lübeck survey were in 14 % physicians, in 12 % the trainer, in 16 % pharmacies, in 56 % acquaintances and in 53 % fellow athletes [39]. The latest nationwide data from the Tübingen survey show a shocking participation by health care professionals in distributing AAS to users in 48.1 % of cases [27]. Of these, about one-half receive the substances through physicians' prescriptions and one-third through the pharmacist – often without prescription. It is a very grave situation that about 50 % of AAS are made available by licensed health care providers.

Further correlations exist between consumption of AAS and of other drugs such as alcohol, cigarettes, cocaine, marihuana and chewing tobacco. It probably also paves the way to steroid dependency, as 72 % of users plan to continue taking AAS in the future [43, 44]. This observation confirms the experience gained by an Australian survey that showed that only 19 % of AAS users informed about side effects and their own lab test results by physicians wanted to avoid AAS in the future [45].

Interim results of the "Growing Up Today Study" in the USA with 4,237 boys and 6,212 girls aged 12 to 18 years showed that 4.7 % of boys and 1.6 % of girls already were taking protein drinks, creatine, amino acids, hydroxymethyl butyrate, dehydroepiandrosterone, growth hormone or injectable anabolic steroids at least once weekly to improve their appearance or strength [46]. Media-oriented adolescents wanting to copy the ideals propagated by health magazines are particularly susceptible for diverse supplementation. In the "United States Centers for Disease Control and Prevention's 1997 Youth Risk Behavior Survey" it is shown that certain behavioral peculiarities such as being quarrelsome in girls and taking sexual risks in boys are predictors of future AAS abuse [47].

Pathophysiology of doping or bodybuilding acne

Anabolic-androgenic steroids (AAS) are derivatives of the male hormone testosterone. AAS lead to hypertrophy of sebaceous glands together with increased sebum excretion, increased production of skin surface lipids and an increased population of *Propionibacterium acnes* [2, 48–51]. The mechanism of action of AAS is dependent on the chemical modification of each individual derivative as this affects the affinity to the androgen receptor and the interaction with various steroid-metabolizing enzymes and transport proteins [sex hormone-binding globulin (SHBG)] [58–62]. Regarding interactions of AAS with intracellular steroid receptor proteins, different binding affinities are known [52, 53, 55, 56]. AAS with high binding affinity to the androgen receptor are considered potent androgens such as 19-nortestosterone and methe-nolone; substances with lower binding affinity to the androgen receptor are weak androgens such as stanozolol or fluoxymesterone [56]. Some AAS such as oxymetholone do not bind at all to the androgen receptor and possess other mechanisms of action. Androgen receptors have been found in sebocytes and follicular keratinocytes [57]. It is significant that AAS can be enzymatically converted by steroid-metabolizing enzymes in sebaceous glands and keratinocytes of the follicular epithelium, which posses 3β- and 17β-hydroxysteroid dehydrogenase. The key enzyme of androgen biosynthesis, 5α-reductase, can produce AAS metabolites with a higher receptor binding affinity. The AAS-androgen receptor complex translocates to the cell's nucleus where it modifies protein synthesis of androgen-dependent genes [58, 63]. Even the androgenic prohormone dehydroepiandrosterone (DHEA) plays a role in the pathogenesis of acne, as it is converted into the potent dihydrotestosterone by 3β- and 17β-hydroxysteroid dehydrogenase and 5α-reductase type I found in sebocytes [59–62]. Morphometric analysis of sebaceous glands in AAS-treated athletes in a 4 week training phase showed a significant increase of size of the sebaceous glands by 89.2 % with the number of sebocytes in the differentiating as well as the undifferentiated cell pools both increasing significantly [50].

During a 12-week power training with AAS administration the sebum secretion rate rose significantly from 0.989 ± 0.191 µg/cm^2/min to 1.171 ± 0.076 µg/cm^2/min [49]. The relative distribution

of the main lipid classes of sebum (free fatty acids, squalene, triglycerides, wax esters) on the forehead showed no significant difference before or after AAS use. A significant increase in cholesterol to 4.2 ± 0.7 % compared to the initial level of 2.4 ± 0.1 % was observed. Beyond effects of androgens on the androgen receptor, other nuclear receptors, the peroxisome proliferator-activated receptors (PPAR), are involved in development, proliferation and differentiation of sebocytes. The nuclear receptors PPAR-γ, PPAR-α and PPAR-δ induce lipogenesis and differentiation of sebocytes during various differentiation phases [54, 64]. Here, androgen-induced gene expression of PPAR-γ_1 appears to play an important role in sebocyte differentiation. AAS increase sebum synthesis directly by binding to the androgen receptor of the sebocyte and indirectly by induction of the nuclear hormone receptor PPAR-γ_1, whose natural ligand 15-deoxy-Δ12, 14-prostaglandin J2 was recently identified in sebocytes of hamsters and in adipocytes [65, 66]. Plewig and Luderschmidt [67] observed that hamster sebocytes were similar to human sebocytes in terms of size, turnover time and androgen dependency. Iwata et al. [66] recently showed that 15-deoxy-Δ12,14-prostaglandin J2 is an important effector of lipogenesis in hamster sebocytes. It increases triglyceride production by increasing the activity of diacylglycerol acyl transferase (DGAT), the rate-determining enzyme of triglyceride synthesis. Production of 15-deoxy-Δ12, 14-prostaglandin J2 is via COX-2- and cytochrome-P-450-mediated metabolic pathways. AAS are indirectly involved in prostaglandin metabolism in lipogenesis through increased expression of PPAR-γ_1. Pharmacological manipulation of prostaglandin metabolism opens new ways in acne therapy and sebum suppression, as was shown for the 5-lipoxygenase inhibitor zileuton by Zouboulis et al. [68–71]. Zileuton inhibits the synthesis of leukotriene B4, the natural ligand of PPAR-α [72], which is also involved in lipogenesis in sebaceous glands [54, 64].

Clinical features of doping acne

Administration of AAS leads to stimulation of the sebaceous glands even in individuals who already display seborrhea. The spectrum of AAS-induced sebaceous gland diseases ranges from the appearance or exacerbation of seborrhea, the development of acne up to the development of acne papulopustulosa, acne conglobata or acne fulminans (Figures 1 and 2). Acne conglobata or acne fulminans can develop under exogenous AAS even in the absence of previous acne [4, 5, 7, 8, 73]. Further, AAS-induced acne can be worsened by oral or parenteral administration of vitamin preparations containing high doses of vitamin B2, B6 and B12 [74]. Iatrogenic administration of testosterone or other AAS to treat excessive height in children and adolescents can cause acne conglobata or acne fulminans just as in doping acne (Figure 2) [5, 6, 75, 76]. Associated psychological disturbances, gynecomastia, striae distensae, edema, increased body mass index and decrease in testicular volume point to doping acne [40].

When suspecting doping acne, drug-induced acneiform exanthemas, especially due to halogens, B vitamins, lithium salts, isoniazid, glucocorticosteroids or tetracyclines, should be considered as a differential diagnosis. They are usually monomorphous consisting of follicular papules and pustules and lacking primary comedos [77].

Treatment and preventive measures

The most important measure in doping acne is the immediate cessation of exogenous administration of AAS. Treatment of the various acne forms conforms to the general guidelines for treating acne [78]. Systemic retinoids are first-line therapy for acne conglobata or acne fulminans. Isotretinoin is the most potent sebosuppressive agent. Possible liver damage induced by AAS must be taken into consideration. When AAS abuse is detected, the physician should give detailed counseling on the long-term risks of AAS abuse and provide for professional psychological intervention. AAS abuse can be confirmed by detecting the substances and their metabolites in urine and, more recently, by gas chromatography-mass spectrometry of hair [79].

Risks of long-term abuse of anabolic-androgenic steroids

The cardiovascular toxicity of AAS is known; an exhaustive and up-to-date review is found by Dhar et al. [80]. The sudden cardiac death of two bodybuilders with long-term AAS use should not go unmentioned [81]. Psychiatric complications of AAS abuse such as increased aggression and depression should be viewed in a sociological context and from the point of view of safety in driving and handling machines [82]. An autopsy study by the Institute for Forensic Medicine of the Swedish Karolinska Institute on 52 AAS abusers proved the association of AAS abuse and the abuse of other psychoactive substance in 79 % of the cases [83]. AAS can also pave the way to opiate dependency [84]. In comparison to other drug abusers, AAS abusers died at a significantly earlier age of 24.5 years, more frequently due to murder or suicide and possessed a higher body mass index.

Underestimating the dangers of anabolic-androgenic steroids by physicians

The uncritical and careless approach to non-therapeutic use of AAS is evident in the Lübeck study [39] and in the recently published Tübingen study [27], where 14 % and 32.1 % of physicians, respectively, played an assisting role in AAS abuse. Similar results were obtained in an Australian survey of 143 general practitioners in Sydney [85]. Two percent of physicians admitted to prescribing AAS for bodybuilding, 6 % were inclined to do the same if requested. Of the Australian colleagues, 77 % showed interest in obtaining more information on effects and side effects of AAS.

Conclusions

Law makers are concerned about the increased use of doping agents and methods by sportsmen and –women in the whole field of sports and the resulting dangers to health and to the future of sports [Law to the Agreement of November 16, 1989 against Doping (of March 3, 1994, BGBl. II p. 334)]. In the declaration of the new version of the Attachment to the Agreement of November 16, 1989 against Doping of January 21, 2002, anabolic-androgenic steroids are listed in the group of illicit drugs in the chapter "C" [63]. Nevertheless, use of anabolic-androgenic steroids has reached a troubling high prevalence in leisure sports and bodybuilding in Germany. Due to the cult of body image propagated by the mass media and the internet marketing of these substances, further increases in AAS abuse can be anticipated.

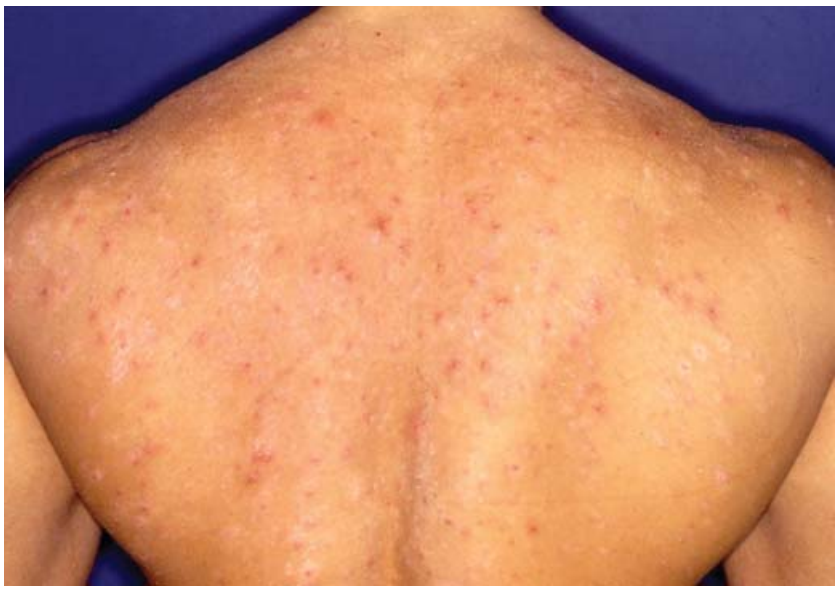

Figure 1: Acne papulopustulosa induced by anabolic-androgenic steroids.

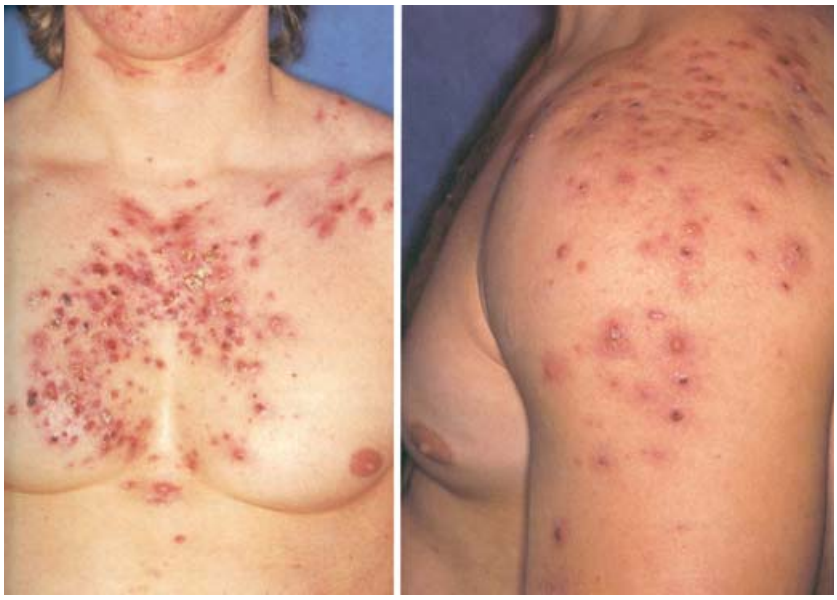

Figure 2: Acne conglobata induced by anabolic-androgenic steroids.

As 50 % of users develop doping acne, the physician should recognize this as an indicator of drug abuse. Dermatologists play an important role here. In young men with persistent acne and adults with late-type acne a detailed history should be taken and appropriate lab tests performed. The serious health risks of AAS abuse must be taken more seriously by physicians, as AAS abuse may lead to steroid dependency and possibly to further drug consumption. It is therefore very disturbing, that about half of all AAS are obtained with the assistance of physicians and pharmacists. This runs contrary to physicians' moral obligations and should lead to a broad debate among physicians. Non-therapeutic use of AAS will otherwise become the most frequent cause of iatrogenic disease due to drug abuse [86, 87]. Continued medical education and a broad consensus among physicians can help curb the mass consumption of anabolics and the resulting health risks. Preventive measures in the USA in the form of gender-specific, team-oriented instruction of sports groups have been successful [88, 89].

Dedication

We thankfully dedicate this article to our (Melnik & Jansen) academic teacher, Prof. Dr. med. Dr. h.c. Gerd Plewig, for his teaching and his extensive scientific contributions on acne and sebaceous gland diseases on the occasion of his retirement. <<<

Conflict of interest

None.

Correspondence to

Prof. Dr. B. Melnik
Dermatology Office
Eickhoffstraße 20–22
D-33330 Gütersloh, Germany
Tel.: +49-52 41-98 80-80
Fax: +49-52 41-25 80-1
E-mail: melnik@t-online.de

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