Expert Opinion

Therapeutic effects of anabolic androgenic steroids on chronic diseases associated with muscle wasting

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Introduction: A variety of clinical conditions are complicated by loss of weight and skeletal muscle which may contribute to morbidity and mortality. Anabolic androgenic steroids have been demonstrated to increase fat-free mass, muscle mass and strength in healthy men and women without major adverse events and therefore could be beneficial in these conditions.

Areas covered: This review provides an overview of clinical trials with anabolic androgenic steroids in the treatment of chronic diseases including HIV-wasting, chronic renal failure, chronic obstructive lung disease, muscular disease, alcoholic liver disease, burn injuries and post operative recovery. Relevant studies were identified in PubMed (years 1950 – 2010), bibliographies of the identified studies and the Cochrane database.

Expert opinion: Although the beneficial effects of AAS in chronic disorders are promising, clinically relevant endpoints such as quality of life, improved physical functioning and survival were mainly missing or not significant, except for burn injuries. Therefore, more studies are needed to confirm their long term safety and efficacy.

Keywords: anabolic androgenic steroids, chronic illnesses, testosterone, weight loss

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1. Introduction

Testosterone has been demonstrated to improve bone mineral density, fat-free mass, prostate volume, erythropoiesis, and sexual function in androgen-deficient men [1]. Also in healthy men supraphysiologic doses of testosterone, especially when combined with strength training, increases fat-free mass, muscle size and strength [2]. In chronic illnesses, such as HIV-wasting, chronic renal failure, chronic obstructive lung disease, muscular disease, alcoholic liver disease, burn injuries and post operative recovery the clinical course is often complicated by loss of weight, skeletal muscle mass and physical dysfunction, which may contribute to increased morbidity and mortality. In these patients, catabolic hormones such as epinephrine and cortisol are increased whereas anabolic hormones such as testosterone are decreased. Anabolic androgenic steroids (AAS), may be expected to improve clinical outcomes. In this review we summarized the clinical literature relevant to the efficacy and safety of AAS in the treatment of chronic diseases including post operative recovery and muscular disease. AAS have been used in the treatment of several other diseases such as age-related androgen deficiency, the treatment of short stature due to Turner's syndrome and constitutional delay of growth and puberty, however, these conditions are beyond the scope of this review.

We preformed our searched on PubMed (1950 – 2010), the Cochrane Database and bibliographies of the identified studies. We searched for Cochrane reviews and randomized, double-blind, placebo-controlled trials with morbidity and mortality

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Article highlights.

- In a variety of chronic illnesses the clinical course is complicated by loss of weight, skeletal muscle mass and physical dysfunction which may contribute to increased morbidity and mortality.
- Anabolic androgenic steroids have been demonstrated to increase weight, fat-free mass and muscle in healthy men and women but also in patients with chronic diseases.
- So far, there is not sufficient evidence that anabolic androgenic steroids improve clinically relevant endpoints such as quality of life, physical functioning and survival in most chronic illnesses.
- Only the use of oxandrolone in patients suffering from burn injury can be recommended.
- Short-term administration of AAS in pharmacological doses appears to be relatively safe.

This box summarizes key points contained in the article.

as major outcomes; however, if these data were unavailable, studies with surrogate endpoints such as body weight, lean body mass (LBM) and muscle mass were included.

2. Physiology

Testosterone has both anabolic and androgenic effects; the anabolic effect of testosterone comprise promoting protein synthesis and nitrogen retention and therefore its administration increases muscle mass and strength. The androgenic effects include developing and maintaining primary and secondary sex characteristics and sexual functions in men [3]. In men testosterone is mainly secreted by the testicular Leydig cells provided adequate stimulations by gonadotropins. The male plasma testosterone concentration ranges between 10 and 30 nmol/l (300 – 1000 ng/dl). In females, circulating testosterone levels are about 10% of those in men, the main sites of secretion are the adrenals and the ovaries. In plasma, about 44% of testosterone is bound to sex-hormone-binding globulin and about 2% is free [4]. According to the free-hormone hypothesis only the non-bound tetosterone is effective, although albumin-bound tetosterone may also become available when the transit time through the target tissue is sufficiently long [5]. The enzyme 5-alpha-reductase catalyzes the conversion of tetosterone into the more potent androgen, dihydrotestosterone [6]. Aromatase can convert testosterone into estradiol, which is responsible for the feminizing side effects of AAS. Nevertheless, estradiol also has important functions in men including inhibition of gonadotropin secretion by the pituitary and the accrual and maintenance of bone mineral density [7]. Without modifications orally taken tetosterone is ineffective due to high first-pass metabolism in the liver. Synthetic derivates of tetosterone can be classified into three groups. Tetosterone with a methyl or ethyl group at position 17 of the molecule is considerably less metabolized by the liver and therefore suitable for oral administration (e.g., methyltestosterone). Esterfication of tetosterone at position 17 makes it less polar and tetosterone-esters are absorbed slowly when injected intra muscular in oil (e.g., tetosterone enanthate and tetosterone propionate). Changes in the A-ring of the tetosterone molecule can be made to prevent its conversion to estradiol or dihydrotestosterone and to modify its interaction with the androgen receptor. By these means the anabolic and androgenic potency can be altered to some extent. So far it has not been possible to produce AAS with only anabolic effects.

3. HIV

In HIV-infected patients increasing weight loss has been found to be significantly associated with decreased survival, as well as with reduced quality of life [8]. In both HIV-positive men and women, tetosterone levels have been directly correlated with muscle mass [9] and hypogonadism is common in men with HIV infection, particularly those with AIDS [10].

The effectiveness of a variety of AAS has been studied in patients infected with HIV (**Table 1**). A Cochrane review from 2005 included 13 clinical trails with both HIV-infected men and women, eugonadal and hypogonadal. The combined results demonstrated that AAS increases LBM (weighted mean difference: 1.3 kg) and total weight (weighted mean difference: 1.1 kg) in HIV-infected patients with weight loss, although a significant heterogeneity was present for the random-effect model (probably due to multiple sources of variability across the studies, including differences in study populations, differences in interventions and differences in the methods of determining the changes). However if only studies with a high quality score (based on randomization, blinding and description of withdrawals and dropouts) were selected the authors found a greater increase in LBM and body weight without significant heterogeneity. Furthermore, in trials in which a supraphysiological androgen dose was tested, a larger treatment effect was seen than in those with a physiological replacement dose. No significant effect was seen in numbers of death and withdrawals due to adverse events [11]. Two, later published, large randomized placebo-controlled trials studying 262 and 303 HIV-infected men with weight loss respectively, underscored the conclusions obtained from the Cochrane review [12,13]. However, in one trial, no effect of androgen treatment on the Health-related quality of life or total work output was seen [12].

4. Chronic renal failure

AAS and transfusions were the mainstay treatment for anemia due to kidney disease prior to the introduction of recombinant erythropoietin. Despite the widespread success of recombinant erythropoietin in chronic renal failure, there has been enduring interest in the use of AAS because of their potential to improve the nutritional status in these patients. Patients with chronic renal failure commonly suffer from reduced

Table 1. Efficacy of Anabolic androgenic steroids (AAS) in chronic diseases associated with muscle wasting.

Ref.	Number of patients (sex)	Study design	Study duration (intervention)	Efficacy (AAS vs control)	Comments
HIV					
[11]	781 (male and female)	13 Randomized, double-blind, placebo-controlled trials	Varying duration and interventions	LBM: ↑ (weighted mean difference: 1.3 kg) Body weight: ↑ (weighted mean difference: 1.1 kg) Number of deaths: = Withdrawals due to adverse events: =	LBM and body weight had a significant heterogeneity for the random-effect model
[12]	262 (male)	Randomized, double-blind, placebo-controlled trial	12 weeks (OX daily; 20, 40, or 80 mg)	Body weight: ↑ [1.1 P, 1.8 (20 OX), 2.8 (40 OX), 2.3 kg (80 OX] BCM: ↑ [0.45 P, 0.91(20 OX), 1.5 (40 OX), and 1.8 kg (80 OX] QOL: = Treadmill testing: =	At 12 weeks, only the gain in weight at the 40-mg dose of OX and the gain in BCM at the 40- and 80-mg doses of OX were greater than those in the placebo group
[13]	303 (male)	Randomized double-blind placebo-controlled trial	12 weeks (ND 150 mg or testosterone 250 mg every 2 weeks)	Body weight: ↑ (mean increase: 1.48 kg) FFM: ↑ (mean increase: 1.34 kg) Perception of benefit: ↑ (ND group compared with both the placebo and the testosterone groups)	The mean increase in weight in the ND group was significantly better compared with the testosterone group
Chronic renal failure					
[16]	29 (male and female)	Randomized double-blind placebo-controlled trial	6 months (ND 100 mg weekly)	LBM: ↑ (ND: 4,5; P: 1.9 kg) Serum creatinine levels: ↑ (ND: +168; P: -4.0 mmol/l) Stair-climbing test: ↑ (ND: 36.5 – 32.7; P: 38.7 – 42.1 seconds) Peak oxygen consumption: ↑ (not significant) Grip strength: = Fatigue: ↓ (The only significant change in quality of life)	Two of the three women who received ND required dosage reduction

= No difference; BCM: Body cell mass; C: Control; EX: Exercise; FFM: Fat free mass; FIM: Functional independence measure; IM: Intramuscular; LBM: Lean body mass; MVICT: Maximal voluntary isometric contraction testing; ND: Nandrolone decanoate; OX: Oxandrolone; P: Placebo; QOL: Quality of life; T: Testosterone; TBSA: Total body surface area.

Table 1. Efficacy of Anabolic androgenic steroids (AAS) in chronic diseases associated with muscle wasting (continued).

Ref.	Number of patients (sex)	Study design	Study duration (intervention)	Efficacy (AAS vs control)	Comments
[17]	79 (male and female)	Randomized double-blind placebo-controlled 2 × 2 factorial trial	12 weeks (ND (100 mg for women; 200 mg for men) and/or lower extremity resistance exercise training)	Body weight: ↑ (ND: 2.5; EX: 1.6; P: 0; ND + EX: 1.8 kg) LBM: ↑ (ND: 3.3; EX: -0.3; P: -0.1; ND + EX: 3.0 kg) Muscle size: ↑ (ND: 4.2; EX: 1.2; P: -3.5; ND + EX: 6.7 cm^2) Muscle strength: ↑ (not significant; ND compared with placebo) Gait speed, stair climbing, or rising from a chair: = QOL: =	
COPD					
[22]	217 (male and female)	Randomized double-blind placebo-controlled trial	8 weeks [nutritional therapy with or without ND (men 50; women 25 mg; every 2 weeks)]	Body weight: ↑ (2.5 kg for both nutritional therapy and ND Muscle mass: ↑ (nutritional therapy + ND was more in favour than nutritional therapy alone group) Maximal inspiratory mouth pressure: ↑ (only significant in the nutritional therapy + ND group)	Patients were prestratified into a depleted and a non-depleted group. Data shown is for the depleted group. However, although smaller, similar favourable effects of AAS on body composition were seen in the non-depleted group
[23]	23 (male)	Randomized double-blind placebo-controlled trial	27 weeks (250 mg of testosterone IM at baseline and 12 mg of oral stanozolol a day)	Body weight: ↑ (ND: 1.8; P: -0.4 kg) LBM: ↑ Anthropometric measures of arm: ↑ Thigh circumference ↑ Maximal inspiratory mouth pressure: ↑ (not significant) Endurance exercise capacity: =	
[24]	63 (male)	Randomized double-blind placebo-controlled trial	8 weeks (ND 50 mg every 2 weeks)	FFM: ↑ (ND: 1.7; P: 0.3 kg) Muscle function: = Exercise capacity: = Health status: =	The *post hoc* analysis showed that the impaired respiratory muscle function and exercise capacity caused by low-dose oral glucocorticosteroids as maintenance medication could be restored by ND treatment

= No difference; BCM: Body cell mass; C: Control; EX: Exercise; FFM: Fat free mass; FIM: Functional independence measure; IM: Intramuscular; LBM: Lean body mass; MVICT: Maximal voluntary isometric contraction testing; ND: Nandrolone decanoate; OX: Oxandrolone; P: Placebo; QOL: Quality of life; T: Testosterone; TBSA: Total body surface area.

Table 1. Efficacy of Anabolic androgenic steroids (AAS) in chronic diseases associated with muscle wasting (continued).

Ref.	Number of patients (sex)	Study design	Study duration (intervention)	Efficacy (AAS vs control)	Comments
[25]	16 (male and female)	Randomized double-blind placebo-controlled trial	16 weeks (ND men 50; women 25 mg every 2 weeks)	Body weight: = LBM: = Distance walked on 6 min: = Physiological function: = QOL: =	
Muscular disease					
[30]	40 (male patients with myotonic dystrophy)	Randomized double-blind placebo-controlled trial	12 months (testosterone enanthate 3 mg/kg/week)	LBM: ↑ (data not shown) Muscle mass: ↑ (data not shown) Muscle strength: =	
[32]	51 (male patients with Duchenne dystrophy)	Randomized double-blind placebo-controlled trial	6 months (OX 0.1 mg/kg/day)	Average muscle score: ↑ (not significant; OX: +0.035; P: -0.140) Arm muscle strength: ↑ (OX: +0.243; P: -0.141) Leg muscle strength: = Quantitative muscle tests: ↑ (OX: +0.784; P: -2.933)	
[33]	19 (male and female patients with inclusion body myositis)	A double-blind, placebo-controlled, crossover design	8 months (OX 20 mg a day)	Whole-body MVICT: ↑ (borderline significant (p = 0.06) OX: 15.5; P: 4.1 kg Upper-extremity MVICT: ↑ (OX: 6.3; P: 2.5 kg Lower extremity MVICT: = Stair climbing ↑ (a median of 1 step on average with OX versus no change with P)	Only 13 of the 19 enrolled patients completed the entire study, dropouts were predominantly due to difficulties in travelling
Alcoholic liver disease					
[37]	499 (male and female)	Five randomised clinical trials	Varying duration and interventions	Mortality: = Liver-related mortality: = Liver complications: = Liver histology: = Liver biochemistry: =	

= No difference; BCM: Body cell mass; C: Control; EX: Exercise; FFM: Fat free mass; FIM: Functional independence measure; IM: Intramuscular; LBM: Lean body mass; MVICT: Maximal voluntary isometric contraction testing; ND: Nandrolone decanoate; OX: Oxandrolone; P: Placebo; QOL: Quality of life; T: Testosterone; TBSA: Total body surface area.

Table 1. Efficacy of Anabolic androgenic steroids (AAS) in chronic diseases associated with muscle wasting (continued).

Ref.	Number of patients (sex)	Study design	Study duration (intervention)	Efficacy (AAS vs control)	Comments
[38]	273 (male)	Randomized double-blind placebo-controlled trial	6 months (OX 80 mg/day for 30 days followed by OX 40 mg/day for 60 days accompanied by high-calorie, high-protein food supplementation; P was accompanied by low-calorie, low-protein food supplementation)	Mortality: = (total group) Mortality in patients with moderate malnutrition: ↓ (at 6 months: OX: 79.7%; P: 62.7% patients alive)	Subgroup analysis should be interpreted with caution
Burns					
[41]	20 (male and female)	Randomized double-blind placebo-controlled trial	Patients were monitored until transferred to a rehabilitation facility, an average Time period of 33 ± 9 days (OX 20 mg/day)	Weight loss: ↓ (OX: 3; P: 8 kg) Nitrogen loss: ↓ (OX: 4; P: 13 kg) Healing time of a standardized donor site ↓ (OX: 9; P: 13 days)	
[42]	81 (male and female)	Randomized double-blind placebo-controlled trial	Patients were monitored until transferred, an average time period of 37 ± 3 days (OX 20 mg/day)	Length of hospital stay: ↓ (OX: 31.6; P: 43.3 days) Length of hospital stay indexed to TBSA burn: ↓ (OX: 0.88; P: 1.29 days) (deaths excluded)	The study was stopped halfway because of a significant difference between groups found on interim analysis
Surgical recovery					
[47]	25 (male)	Randomized double-blind placebo-controlled trial	Preoperative T enanthate (600 mg weekly for 4 weeks)	Length of hospital stay: ↓ (non significant; T: 5.9 P:6.8 days) Ability to stand: ↑ (day 3; T: 5.2; P: 4.0 FIM score) Walking: = (only small trend in favour of T) Stair climbing: = (only small trend favour of T)	
[48]	29 (female)	Randomized double-blind placebo-controlled trial	4 weeks or until discharge (ND 2 mg/kg)	Weight: = LBM: = Length of hospital stay: = Strength and cognitive function: =	

= No difference; BCM: Body cell mass; C: Control; EX: Exercise; FFM: Fat free mass; FIM: Functional independence measure; IM: Intramuscular; LBM: Lean body mass; MVICT: Maximal voluntary isometric contraction testing; ND: Nandrolone decanoate; OX: Oxandrolone; P: Placebo; QOL: Quality of life; T: Testosterone; TBSA: Total body surface area.

muscle mass [14], which has been shown to correlate with increased mortality [15].

A small randomized clinical trail studying 29 men and women treated with nandrolone decanoate (100 mg once weekly; of the three women who received nandrolone two required dosage reduction because of amenorrhea and acne, respectively) or placebo showed that patients treated with nandrolone decanoate gained in LBM, increased in serum creatinine levels, (suggesting increased muscle mass), had a reduction in their reported symptoms of fatigue and decreased the mean time required for a walking and stair-climbing test as compared with those receiving placebo [16]. Additionally, a larger (79 patients) randomized double-blind placebo-controlled study showed that patients who received nandrolone decanoate (100 mg for women; 200 mg for men weekly) increased in weight, LBM and predialysis serum creatinine concentration. However, none of the muscle strength parameters improved significantly and neither exercise nor nandrolone decanoate was associated with improvements in physical performance tests. Virilizing side effects in women were not reported despite the high dose of nandrolone decanoate used in this study [17].

5. Chronic obstructive pulmonary disease (COPD)

Weight loss and muscle wasting are common complications of COPD. Weight loss in patients with COPD leads to impairment of physical performance, disability, and greater mortality [18,19]. Also, low circulating levels of testosterone are common in males with chronic obstructive pulmonary disease, especially in those receiving maintenance oral glucocorticosteroid therapy [20,21]. The largest randomized double-blind, placebo-controlled trail was conducted by Schols *et al.* including 203 patients (male and female). These patients were pre-stratified into a depleted (body weight less then 90% and/or a fat-free mass less then 67% (men)/63% (women) of ideal body weight) and a non-depleted group. In the depleted patients both nandrolone decanoate (women 25 mg; men 50 mg; every 2 weeks) and nutritional therapy alone induced a similar significant body weight gain as compared with placebo. However, measurements of body composition indicated a larger increase in muscle mass in the nandrolone decanoate group whereas weight gain in the nutritional group consisted mainly of fat mass. Although weight gain was less in the non-depleted patients, similar favorable effects of AAS on body composition were seen. Also, the maximal inspiratory mouth pressure improved significantly more in the nandrolone-decanoate-treated patients [22]. Two smaller studies provided evidence in the same line as the previous study. In the study conducted by Ferreira *et al.* undernourished male COPD patients who received treatment (250 mg of testosterone intramuscularly at baseline and 12 mg of oral stanozolol daily for 27 weeks) increased in body mass index (BMI), LBM and anthropometric measures of arm and thigh circumference as compared with those receiving placebo. However, there was no significant changes in endurance exercise capacity [23]. The study of Creutzberg *et al.* showed that a short-term course of nandrolone decanoate (50 mg every two weeks) had an overall positive effect relative to placebo on fat free mass in 63 male patients with COPD. Maximal inspiratory mouth pressure and maximal isokinetic work of the lower extremities increased significantly in the nandrolone decanoate group when compared with baseline, however not with placebo. The *post hoc* analysis showed that the impaired respiratory muscle function and exercise capacity caused by low-dose oral glucocorticosteroids as maintenance medication could be restored by nandrolone decanoate treatment [24]. However, a controlled trial conducted by Sharma *et al.* in 16 patients with severe COPD who did not participate in a structured rehabilitation program, nandrolone-decanoate-treated patients (men 50 mg, women 25 mg every two weeks) did not gain significantly more weight and did not show improvement in physiological function or quality of life as compared with those receiving placebo [25]. Although the effects of androgen treatment in patients with COPD are relatively consistent, the clinical benefit for the treated patients is controversial. The studies conducted so far in COPD patients have used relatively low doses of androgens and, knowing the dose-dependent effects of nandrolone decanoate or testosterone on muscle mass and strength, the administration of higher doses may be expected to result in larger gains. However, this remains to be determined.

6. Muscular disease

Despite the potential of AAS to increase muscle mass and strength, only a few clinical trials have studied the effects of AAS in patients with muscular disease. The few studies published to date were mainly targeted at improving muscle strength in patients with muscular dystrophies (MD). MD are a clinically and genetically heterogeneous group of diseases characterized by skeletal muscle wasting but there is also an association of MD with reduced plasma androgen levels [26]. Curative therapy is not available, corticosteroids (prednisone and deflazacort) are the only drugs with convincing evidence of slowing the progression of MD [27,28]. Unfortunately, the side effects of prolonged corticosteroid therapy, especially weight gain and growth retardation in children have limited the long-term use [29].

In 1989 Griggs *et al.* conducted a placebo-controlled clinical trail studying 40 male MD patients who randomly received testosterone enanthate (3 mg/kg/week) or placebo. Although LBM and muscle mass increased, muscle strength did not increase after 12 months in the testosterone-enanthate-treated group [30]. A randomized, double-blind, placebo-controlled trial by Fenichel *et al.* was executed to confirm the results of a pilot study, which showed improvements in average muscle score in 10 boys with Duchenne MD treated with oxandrolone for 3 months [31]. This study

showed a trend but not a significant change in the average manual muscle strength score after treatment with oxandrolone (0.1 mg/kg/d for six months). However, the arm muscles did significantly increase in strength and the mean improvement in quantitative muscle was also significantly increased as compared with placebo [32]. Only one randomized, double-blind, placebo-controlled, trial studied the effects of AAS in patients with other muscular diseases. Rutkove *et al.* conducted a crossover trail in patients with inclusion body myositis. Patients received oxandrolone (20 mg a day) or placebo for 12 weeks followed by a minimum 2-month washout period, followed by 12 weeks of the alternative treatment. Despite a large number of dropouts (only 13 of the 19 enrolled patients completed the entire study, mainly due to difficulties in travelling to the study center) the authors found a borderline significant effect of oxandrolone in improving whole-body strength and a significant effect in improvement in upper-extremity strength in the oxandrolone group [33].

7. Alcoholic liver disease

Malnutrition is common in patients with alcoholic liver disease. Malnutrition is associated with development of serious complications (ascites, encephalopathy and hepatorenal syndrome), as well as the overall mortality [34]. In men with alcoholic cirrhosis plasma concentrations of free (non-protein-bound) testosterone and bioavilable (non-sex-hormone-binding-globulin-bound) testosterone are mostly decreased and levels of estrogens are often increased [35,36]. These findings suggest a possible role for AAS in the treatment of alcoholic liver disease.

A Cochrane review published in 2006 included five randomized clinical trails with a total of 467 patients with alcoholic liver disease (447 males and 20 females). The studies mainly used oxandrolone as treatment. The combined results demonstrated no significant effect of AAS on mortality, liver complications, liver histology, and liver biochemistry [37]. However, there is one randomized double-blind placebo-controlled trail which demonstrated that a subgroup of patients (moderate malnutrition) improved survival in patients receiving oxandrolone [38]. Nevertheless, this should be interpreted with caution.

8. Burns

Burn injury is associated with extreme hypermetabolism and catabolism that induces loss of LBM and strength [39]. Mean testosterone levels in male patients with severe burn injuries are usually diminished [40]. AAS may therefore attenuate hypermetabolism or blunt the catabolic response associated with burn injury and potentially improve outcome.

A randomized double-blinded placebo-controlled trail in patients with major burns showed that weight loss and daily nitrogen loss decreased significantly during oxandrolone (20 mg/day) treatment. The healing time of a standardized donor site also decreased significantly [41]. Additional evidence for the efficacy of AAS in patients with burns was provided in a multicenter placebo-controlled clinical trail. This study, in 81 adult patients (male and female) with burn injuries showed that treatment with oxandrolone (10 mg every 12 h) decreased length of hospital stay by 28%. The study was terminated halfway because of a significant difference between groups found on interim analysis [42].

9. Surgical recovery

Post operative recovery is characterized by a catabolic state and malnutrition [43,44]. Additionally, muscle strength has an important role in the recovery from a joint replacement operation. Therefore, treatment with AAS has been studied to improve outcomes after surgery. Mainly older patients were studied because of the age-related decline in endogenous androgens in both men and women [45,46], slower recovery, increased morbidity and mortality and reduced muscle strength in older patients.

In a randomized double-blinded placebo-controlled trail 25 elderly men undergoing elective knee replacement received preoperative testosterone enanthate (600 mg weekly) or placebo for four weeks. In the testosterone-enanthate group mean length of hospital stay reduced nonsignificantly, the ability to stand improved significantly and there was a trend towards improvements in walking and stair climbing as compared with the placebo-treated group [47]. However, a controlled pilot study including 29 frail elderly females with hip fractures who received either nandrolone decanoate (2 mg/kg, weekly) or placebo for four weeks showed no detectable benefits from treatment with nandrolone decanoate [48].

10. Side effects

Many adverse events associated with AAS use/abuse have been reported. These range from cardiovascular events to hepatotoxic, renal, reproductive/endocrine, dermatological, psychological and behavioural effects [49,50]. These effects however, are mainly described in casuistic reports of patients who abuse AAS. In the clinical trails discussed in this review, adverse events, when reported, were usually described as mild and reversible. Events were mainly application site reactions (pain, skin irritation, hematoma at the injection site) or consistent with the androgenic nature of AAS; acne, mild hirsutism, breast tenderness, clitoral enlargement, reduction in testicular size, increased libido, increased aggressiveness/irritability, mood swings, adverse liver function tests, elevated hematocrit and an altered lipid profile. If liver enzymes were increased, the degree of change was usually mild and no reason to interrupt treatment. Elevated hematocrit is dose-dependent and rarely leads to discontinuation of treatment. However, in patients with COPD AAS may aggravate polycythemia. Reduction in high-density lipoprotein (HDL)

and increase in low-density lipoprotein (LDL) cholesterol levels are frequently seen. It is not known whether this adversely affects cardiovascular risk, however, since AAS are usually administered for limited periods, the effects on lipid profile are mostly transient. In the reviewed studies, there was no report of hypertension or development of edema and only one patient was reported to have an elevated prostate-specific antigen.

Recently, a testosterone substitution trial in elderly men with low testosterone levels and impaired mobility was discontinued due to a significantly increased number of cardiovascular adverse events in the testosterone-treated group. [51] This was unexpected since a recent meta-analysis of testosterone-substitution trials did not shown increased cardiovascular risk in testosterone-treated men [52]. Although these conflicting results need further evaluation in larger controlled trials, it seems prudent to withhold high-dose androgen treatment in older men with high cardiovascular risk.

11. Expert opinion

Disease is associated with a catabolic state, resulting in weight loss and loss of muscle strength, contributing to functional impairment and excess morbidity and mortality. Androgens have a dose-dependent anabolic effect on muscle mass and strength and may potentially prevent some of the adverse effects of chronic disease and thus improve outcome. Supplementation of testosterone in older frail men with age-related hypogonadism is associated with mild to moderate improvement of body composition, however, clinically meaningful positive effects on muscle strength and function are mostly absent. Short-term administration of AAS in pharmacological doses has been shown to increase muscle mass and muscle strength in young and older men with relatively few side effects. However, probably due to the fear of side effects, mainly obtained from casuistic reports of AAS abuse by athletes, the potential efficacy of AAS in patients with chronic conditions has not been extensively studied. Additionally, due to their strong virilizing effects their use is primarily limited to males. Nevertheless, virtually all studies executed in chronically ill patients provided evidence for a clinically meaningful and statistically significant increase in weight, muscle mass and fat-free mass without major adverse events. However, drawing firm conclusions form these studies is difficult. The studies were underpowered to detect a benefit of treatment on mortality. Although most studies detected a significant increase in muscle mass or strength, the clinical benefit for the individual patient is not always evident in terms of rehabilitation, quality of life or survival. Furthermore, straightforward conclusions are hampered by the large heterogeneity between the studies, including various diseases, different drugs and a large range of doses.

Selective Androgen Receptor Modulators (SARM's) have been developed in an attempt to obtain the desired effects of androgens while minimizing the unwanted effects on the prostate and cardiovascular outcomes. Although exciting, efficacy and safety of these compounds remains to be determined.

In conclusion, treatment of patients suffering from chronic conditions with AAS appears to be relatively safe and outcomes based on surrogate endpoints are promising. However, larger studies, with adequate follow up are needed before firm recommendations can be made. Based on current knowledge, only the use of oxandrolone in patients suffering from burn injury can be recommended.

Declaration of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

Bibliography

1. Snyder PJ, Peachey H, Berlin JA, et al. Effects of testosterone replacement in hypogonadal men. J Clin Endocrinol Metab 2000;85:2670-7
2. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. N Engl J Med 1996;335:1-7
3. Kuhn CM. Anabolic steroids. Rec Prog Horm Res 2002;57:411-34
4. Dunn JF, Nisula BC, Rodbard D. Transport of steroid hormones: binding of 21 endogenous steroids to both testosterone-binding globulin and corticosteroid-binding globulin in human plasma. J Clin Endocrinol Metab 1981;53:58-68
5. Mendel CM. The free hormone hypothesis: a physiologically based mathematical model. Endocr Rev 1989;10:232-74
6. Sundaram K, Kumar N, Monder C, Bardin CW. Different patterns of metabolism determine the relative anabolic activity of 19-norandrogens. J Steroid Biochem Mol Biol 1995;53:253-7
7. de Ronde, Pols HA, van Leeuwen JP, de Jong FH. The importance of oestrogens in males. Clin Endocrinol (Oxf) 2003;58:529-42
8. Bhasin S, Javanbakht M. Can androgen therapy replete lean body mass and improve muscle function in wasting associated with human immunodeficiency virus infection? JPEN J Parenter Enteral Nutr 1999;23:S195-201
9. Grinspoon S, Corcoran C, Lee K, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. J Clin Endocrinol Metab 1996;81:4051-8
10. Dobs AS, Dempsey MA, Ladenson PW, Polk BF. Endocrine disorders in men infected with human immunodeficiency virus. Am J Med 1988;84:611-16

11. Johns K, Beddall MJ, Corrin RC. Anabolic steroids for the treatment of weight loss in HIV-infected individuals. Cochrane Database Syst Rev 2005:CD005483

12. Grunfeld C, Kotler DP, Dobs A, et al. Oxandrolone in the treatment of HIV-associated weight loss in men: a randomized, double-blind, placebo-controlled study. J Acquir Immune Defic Syndr 2006;41:304-14

13. Gold J, Batterham MJ, Rekers H, et al. Effects of nandrolone decanoate compared with placebo or testosterone on HIV-associated wasting. HIV Med 2006;7:146-55

14. Woodrow G, Oldroyd B, Turney JH, et al. Whole body and regional body composition in patients with chronic renal failure. Nephrol Dial Transplant 1996;11:1613-18

15. Kato A, Odamaki M, Yamamoto T, et al. Influence of body composition on 5 year mortality in patients on regular haemodialysis. Nephrol Dial Transplant 2003;18:333-40

16. Johansen KL, Mulligan K, Schambelan M. Anabolic effects of nandrolone decanoate in patients receiving dialysis: a randomized controlled trial. JAMA 1999;281:1275-81

17. Johansen KL, Painter PL, Sakkas GK, et al. Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: a randomized, controlled trial. J Am Soc Nephrol 2006;17:2307-14

18. Laaban JP, Kouchakji B, Dore MF, et al. Nutritional status of patients with chronic obstructive pulmonary disease and acute respiratory failure. Chest 1993;103:1362-8

19. Gray-Donald K, Gibbons L, Shapiro SH, et al. Nutritional status and mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;153:961-6

20. Reid IR, Wattie DJ, Evans MC, Stapleton JP. Testosterone therapy in glucocorticoid-treated men. Arch Intern Med 1996;156:1173-7

21. Kamischke A, Kemper DE, Castel MA, et al. Testosterone levels in men with chronic obstructive pulmonary disease with or without glucocorticoid therapy. Eur Respir J 1998;11:41-5

22. Schols AM, Soeters PB, Mostert R, et al. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. Am J Respir Crit Care Med 1995;152:1268-74

23. Ferreira IM, Verreschi IT, Nery LE, et al. The influence of 6 months of oral anabolic steroids on body mass and respiratory muscles in undernourished COPD patients. Chest 1998;114:19-28

24. Creutzberg EC, Wouters EF, Mostert R, et al. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. Chest 2003;124:1733-42

25. Sharma S, Arneja A, McLean L, et al. Anabolic steroids in COPD: a review and preliminary results of a randomized trial. Chron Respir Dis 2008;5:169-76

26. Harper P, Penny R, Foley TP Jr, et al. Gonadal function in males with myotonic dystrophy. J Clin Endocrinol Metab 1972;35:852-6

27. Mendell JR, Moxley RT, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med 1989;320:1592-7

28. Bonifati MD, Ruzza G, Bonometto P, et al. A multicenter, double-blind, randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy. Muscle Nerve 2000;23:1344-7

29. Walter MC, Lochmuller H. Novel approaches to treat muscular dystrophies. Expert Opin Investig Drugs 2001;10:695-707

30. Griggs RC, Pandya S, Florence JM, et al. Randomized controlled trial of testosterone in myotonic dystrophy. Neurology 1989;39:219-22

31. Fenichel G, Pestronk A, Florence J, et al. A beneficial effect of oxandrolone in the treatment of Duchenne muscular dystrophy: a pilot study. Neurology 1997;48:1225-6

32. Fenichel GM, Griggs RC, Kissel J, et al. A randomized efficacy and safety trial of oxandrolone in the treatment of Duchenne dystrophy. Neurology 2001;56:1075-9

33. Rutkove SB, Parker RA, Nardin RA, et al. A pilot randomized trial of oxandrolone in inclusion body myositis. Neurology 2002;58:1081-7

34. Mendenhall C, Roselle GA, Gartside P, Moritz T. Relationship of protein calorie malnutrition to alcoholic liver disease: a reexamination of data from two Veterans Administration Cooperative Studies. Alcohol Clin Exp Res 1995;19:635-41

35. Gluud C, Bahnsen M, Bennett P, et al. Hypothalamic-pituitary-gonadal function in relation to liver function in men with alcoholic cirrhosis. Scand J Gastroenterol 1983;18:939-44

36. Gluud C. Serum testosterone concentrations in men with alcoholic cirrhosis: background for variation. Metabolism 1987;36:373-8

37. Rambaldi A, Gluud C. Anabolic-androgenic steroids for alcoholic liver disease. Cochrane Database Syst Rev 2006:CD003045

38. Mendenhall CL, Moritz TE, Roselle GA, et al. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. Hepatology 1993;17:564-76

39. Tredget EE, Yu YM. The metabolic effects of thermal injury. World J Surg 1992;16:68-79

40. Dolecek R, Dvoracek C, Jezek M, et al. Very low serum testosterone levels and severe impairment of spermatogenesis in burned male patients. Correlations with basal levels and levels of FSH, LH and PRL after LHRH + TRH. Endocrinol Exp 1983;17:33-45

41. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. J Crit Care 2000;15:12-17

42. Wolf SE, Edelman LS, Kemalyan N, et al. Effects of oxandrolone on outcome measures in the severely burned: a multicenter prospective randomized double-blind trial. J Burn Care Res 2006;27:131-9

43. Patterson BM, Cornell CN, Carbone B, et al. Protein depletion and metabolic stress in elderly patients who have a

fracture of the hip. J Bone Joint Surg Am 1992;74:251-60

44. Hedstrom M, Saaf M, Dalen N. Low IGF-I levels in hip fracture patients. A comparison of 20 coxarthrotic and 23 hip fracture patients. Acta Orthop Scand 1999;70:145-8

45. Harman SM, Metter EJ, Tobin JD, et al. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab 2001;86:724-31

46. Laughlin GA, Barrett-Connor E. Sexual dimorphism in the influence of advanced aging on adrenal hormone levels: the Rancho Bernardo Study. J Clin Endocrinol Metab 2000;85:3561-8

47. Amory JK, Chansky HA, Chansky KL, et al. Preoperative supraphysiological testosterone in older men undergoing knee replacement surgery. J Am Geriatr Soc 2002;50:1698-701

48. Sloan JP, Wing P, Dian L, Meneilly GS. A pilot study of anabolic steroids in elderly patients with hip fractures. J Am Geriatr Soc 1992;40:1105-11

49. Evans NA. Current concepts in anabolic-androgenic steroids. Am J Sports Med 2004;32:534-42

50. Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. Sports Med 2004;34:513-54

51. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. N Engl J Med 2010;363:109-22

52. Fernandez-Balsells MM, Murad MH, Lane M, et al. Adverse effects of testosterone therapy in adult men: a systematic review and meta-analysis. J Clin Endocrinol Metab 2010;95:2560-75

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