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Can conditions of skeletal muscle loss be improved by combining exercise with anabolic–androgenic steroids? A systematic review and meta-analysis of testosterone-based interventions

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Abstract

Sarcopenia, cachexia, and atrophy due to inactivity and disease states are characterized by a loss of skeletal muscle mass, often accompanied by reduced levels of anabolic hormones (e.g. testosterone). These conditions are associated with an increase in mortality, hospitalization and worsening in quality of life. Both physical exercise (EX) and anabolic–androgenic steroid (AAS) administration can improve the prognosis of patients as they increase physical functionality. However, there is a gap in the literature as to the impact of these therapies on the gains in strength and muscle mass and their implications for patient safety. Accordingly, we performed a random-effects meta-analysis to elucidate the effects of AAS and/or EX interventions on lean body mass (LBM) and muscle strength in conditions involving muscle loss. A systematic search for relevant clinical trials was conducted in MEDLINE, EMBASE, SCOPUS, Web of Science, and SPORTDiscus. Comparisons included AAS *vs.* Control, EX *vs.* Control, AAS *vs.* EX, AAS + EX *vs.* AAS and AAS + EX *vs.* EX. A total of 1114 individuals were analyzed. AAS increased LBM (effect size [ES]: 0.46; 95% CI: 0.25, 0.68, $P = 0.00$) and muscle strength (ES: 0.31; 95% CI: 0.08, 0.53, $P = 0.01$) when compared to a control group. EX promoted an increase in muscular strength (ES: 0.89; 95% CI: 0.53, 1.25, $P = 0.00$), with no effect on LBM when compared to the control group (ES: 0.15; 95% CI: -0.07, 0.38, $P = 0.17$). AAS did not demonstrate statistically significant differences when compared to EX for LBM and muscle strength. The combination of EX + AAS promoted a greater increase in LBM and muscular strength when compared to AAS or EX in isolation. Qualitatively, AAS administration had relatively few side effects. Significant heterogeneity was found in some analyses, which may be explained by the use of different AAS types and EX protocols. Our findings suggest that AAS administration in cachectic and sarcopenic conditions may be a viable interventional strategy to enhance muscle function when exercise is not a possible approach. Moreover, combining AAS with exercise may enhance positive outcomes in this population.

Keywords Anabolic–androgenic steroids · Exercise · Testosterone · Muscle mass · Strength

1 Introduction

Sarcopenia, cachexia, and atrophy due to inactivity are characterized by a loss of skeletal muscle mass. Each of these conditions results in a metabolic adaptation that leads to an increased protein degradation, decreased rate of muscle protein synthesis, or an alteration in both [1]. It is now recognized that the loss of skeletal muscle mass and strength are associated with an increase in mortality [2, 3], hospitalization [4–6] and worsening in the quality of life [7, 8]; hence, conditions that lead to muscle disfunction have become an important public health issue [9].

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Sarcopenia is broadly defined as an age-related loss of skeletal muscle mass and function; its progression is multifactorial and complex [10]. From 20 to 70 years of age, there is an approximately 30% reduction in muscle mass. This loss results in a decrease in strength, metabolic rate, and aerobic capacity and, consequently, in functional capacity [11]. Newman et al. [12] reported that a loss of muscle function (strength), rather than a loss of mass, is most associated with mortality risk; however, the two variables are interrelated [13]. As a testament to its clinical importance, sarcopenia is now recognized as an independently reportable medical condition [14].

Cachexia is a complex metabolic syndrome associated with several chronic diseases and acute medical conditions [15]. The main clinical feature of cachexia is weight loss in adults, which can be attributed to skeletal muscle loss with or without fat loss [15]. Clinical studies have shown that the preservation of body fatness and skeletal muscle in cachectic patients can decrease mortality risk [16–18].

Exercise (EX) and physical activity are nonpharmacological treatments shown to improve indices of muscle strength and metabolic function in healthy and diseased individuals [19, 20]. EX is the safest and most effective intervention to attenuate or recover some of the lost muscle mass and strength associated with aging [21]. In contrast, limited clinical trials have investigated the impact of exercise training on cachexia. Although the beneficial effects of EX go beyond increasing muscle strength, some patients or even elderly individuals may not benefit from these adaptations due to exercise intolerance (e.g.: frailty, bed rest conditions, cardiorespiratory disability, etc.) [22–25]. Therefore, alternative approaches should be explored to help these individuals achieve a better prognosis.

Testosterone and its derivatives are anabolic–androgenic steroid (AAS) hormones that lead to an increase in muscle mass [26]. Testosterone effects on skeletal muscle mass are dose-dependent, with the administration of supraphysiological doses leading to a substantial increase in muscle strength, which seems to be closely associated with an increase in muscle mass [27].

In several clinical conditions as well as aging, a decline in levels of anabolic hormones, particularly testosterone, can lead to a worse clinical prognosis [28, 29]. Given the role of AAS in improving muscle function, it therefore is speculated that the use of these anabolic agents may increase muscle mass and strength, especially when administered in combination with exercise. It is possible that the increased survival rate in individuals observed with higher levels of blood testosterone is due to better maintenance of muscle mass and strength, which enhances patients' resilience to adverse clinical situations.

Several studies have reported the use of AAS or EX in clinical conditions and sarcopenic states; however, to the best of our knowledge, no meta-analysis has endeavored to compare the effects of AAS and/or EX interventions in conditions where skeletal muscle loss is seen. Thus, the purpose of this meta-analysis is to evaluate the effects of AAS interventions alone or in combination with EX on lean body mass (LBM) (an indicator of muscle mass) and skeletal muscle strength in conditions involving muscle loss.

2 Methods

2.1 Experimental approach to the problem

Inclusion Criteria. *i.* Randomized controlled trials in participants with cachectic clinical conditions or demonstrating age-related skeletal muscle mass loss *ii.* Comparing AAS vs EX vs EX + AAS vs Control. *iii.* Were published in a peer-reviewed, English-language journal *iv.* Were conducted in human populations *v.* Included valid methods for assessing lean body mass and muscle strength.

Exclusion Criteria. i. Studies that did not report data on AAS dosage and EX protocols (frequency, duration and type) were excluded *ii.* Studies with healthy young people or no age-related skeletal muscle mass loss *iii.* Studies that used other pharmacological approaches other than AAS *iv.* Studies that were not written in English, conference abstracts, thesis, or posters.

2.2 Search strategy

The protocol was prospectively registered with Prospective Register for Systematic Reviews (PROSPERO) (CRD42019137133). We followed the guidelines of the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) to carry out this study [30].

In order to identify all clinical trials in which AAS was administered in combination with exercise, we systematically searched multiple online medical databases, including MEDLINE, EMBASE, SCOPUS, Web of Science, and SPORTDiscus from inception through June 2019. The search terms are presented in the supplemental material (Supplementary data A). The initial titles retrieved through the search were independently screened by three authors (JRJ, MNS, and JHF) using the online tool Ryyan [31]. To avoid missing any relevant studies, all reference lists of eligible articles, related reviews, and meta-analyses were hand-searched. We did not include unpublished documents and grey literature, such as conference abstracts, case reports, theses, and patents. The PRISMA flow diagram for study selection is shown in

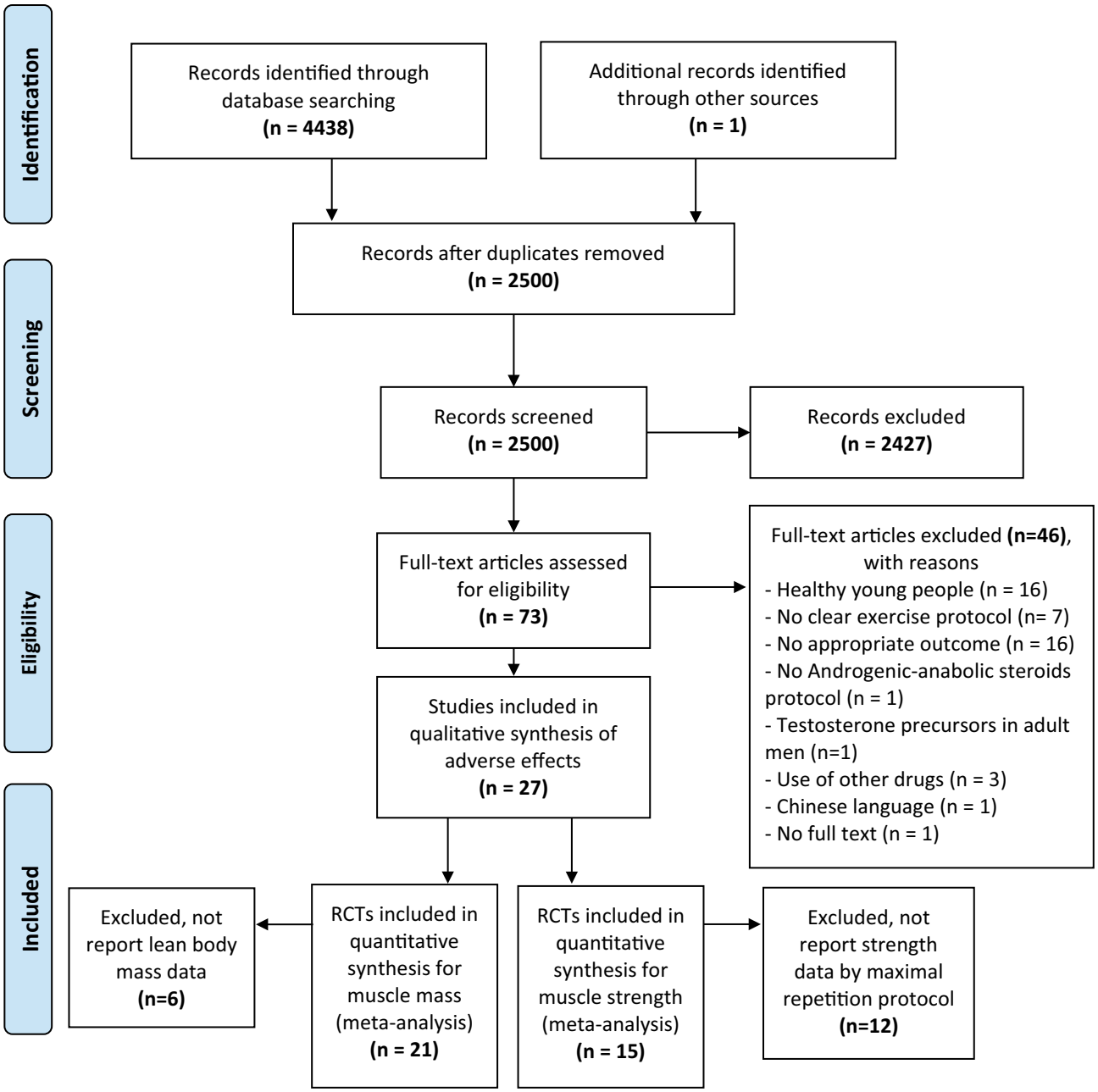

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram. *RCTs* Randomized Controlled Trials

Fig. 1. Out of 4,438 publications retrieved from academic databases, 1,938 were duplicated and then removed. The remaining 2,500 studies were screened (by reading the title and abstract), and 2,427 were considered irrelevant to the purpose of this review. The remaining 73 publications were further analyzed, and 27 studies met our eligibility criteria for qualitative synthesis and reporting of adverse effects (Supplementary data B). We included one study published after our initial search since it met our eligibility criteria [32]. Two studies reported data from the same patients [33, 34]. A meta-analysis for LBM was performed in 21 RCTs, whereby this variable was evaluated via dual-energy x-ray absorptiometry or bioelectrical impedance analysis. A meta-analysis for strength was performed in 15 RCTs, whereby this variable was evaluated by one-repetition maximum (1RM).

2.3 Subjects

A total of 1,114 patients were analyzed across the 27 studies included in this review. Age ranged from 7 to 93 years. Clinical conditions found were: HIV [35–40], chronic obstructive pulmonary disease (COPD) [41, 42], heart failure (HF) [43, 44], spinal cord injury (SCI) [45], kidney failure [46], severe burn [47], obesity [48], hemiplegia [49], and hypogonadism [50]. Seven studies were performed in elderly individuals without a diagnosed clinical condition [32, 33, 51–55] and 1 study was conducted in children and teenagers [47]. Only 1 study was performed in healthy adult men, but it employed a bed rest model that induced atrophy and hence was included in our review [56].

The duration of the exercise intervention protocol ranged from 3 weeks to 12 months. The types of exercise found in the studies were resistance training [32, 33, 35–41, 43–58] steady-state aerobic training [36, 42, 44, 47, 48, 57] and high-intensity intermittent exercise (HIIT) [43, 56]. The administration of testosterone was carried out intramuscularly [32, 35–37, 39–44, 46, 48–50, 55, 56], orally [38, 39, 42, 47, 54, 57, 58] and transdermally [33, 45, 51–53]. Different testosterone formulas were used across the studies, and the dosage and regimen of testosterone ranged from 2 mg per day to 600 mg per week.

2.4 Procedures

Coding of Studies. The studies were read and coded individually by two investigators (HF and JRJ) for the following variables: (a) authors, year of publication, characteristics and clinical conditions of the participants, sample size, sex, and age. The EX protocols were described by (b) type (steady-state aerobic training, resistance training, HIIT), weekly frequency, intensity, volume, and duration of the intervention. The AAS protocols were described by (c) AAS formulation, method of administration, dose, frequency of use, and duration of the intervention; (d) LBM was considered as a surrogate for muscle mass as measured by dual-energy x-ray absorptiometry or bioelectrical impedance analysis; (e) assessment of muscle strength was carried out via maximum dynamic strength testing, with tests categorized based on specificity to the upper limbs or lower limbs; (f) values of mean ± standard deviation (SD) before and after intervention related to the results of LBM and strength; (g) adverse effects reported to the EX and AAS protocols, if any. The coding data were verified between the investigators, and any observed differences were discussed to reach a consensus. A third evaluator (LHM) reviewed the coded data and resolved any conflicts of agreement between investigators.

Calculation of Effect Size. For each LBM and strength outcome, a within-group effect size (ES) i.e.: EX, AAS, EX + AAS, and control was calculated as the difference pretest–posttest, divided by the pooled SD [59]. A study level ES was then calculated as the difference between groups. A small sample bias adjustment was applied to each ES [59]. The sampling variance around each ES was calculated using the sample size in each study and among the groups [60]. This study compared AAS *vs*. Control, EX *vs.* Control, AAS *vs.* EX, AAS + EX *vs.* EX, and AAS + EX *vs.* AAS for LBM or muscle strength outcomes. In studies where more than two time point measurements were performed, we considered only those from the pre- and post-intervention. We used separate data for upper- and lower body total strength when studies presented those measurements.

2.5 Statistical analyses

To account for differences in units of LBM and strength measures, we adopted the Hedge's g-index to characterize ES data [61]. The selection of a random-effects model with Hedges' g criterion was used based on the assumption of a sampling error (within-study error) and between-study variance (high heterogeneity in the studies methodologies). Also, the Hedges' g criterion was selected because it prevents the overestimation of an effect-size when pooling results of fewer than ~ 20 studies [62]. Heterogeneity was assessed using Cochran's Q and I^2 statistics [63]. Meta-regression models were fitted to investigate the sensitivity of treatment effectiveness or efficacy to different study-level moderators (age, sex, type of AAS, testosterone blood levels and duration of intervention with AAS) {Statistical methods for assessing the influence of study characteristics on treatment effects in 'meta-epidemiological' research; Advanced methods in meta-analysis: multivariate approach and meta-regression}. For this analysis, only AAS + EX vs. EX groups were compared in order to evaluate whether the causes of hetogenity could be attributed to AAS treatment. Effect sizes were coded such that positive numbers reflected increasing LBM or strength, and negative values reflected decreasing values in comparison to the respective group. For each dependent measure, we report an ES and the accompanying 95% confidence interval (CI). Effect sizes were categorized as follows: 0.20–0.49, small; 0.50–0.79, medium; 0.80–1.1, large; and ≥ 1.2, very large [62]. Statistical significance was set at $P < 0.05$.

Publication bias was assessed through visual inspection of the funnel plots [64]. In the case of significant publication bias, the trim and fill statistical procedure was calculated and imputed on the right or left side of the plot [65]. This procedure adds or removes studies to balance an asymmetrical

funnel plot. Analyses were conducted using the open-source statistical software package "metaphor" (v3.1.0) in Stata v.16.0 [66].

2.6 Methodological quality

We used the Cochrane risk of bias tool to evaluate the internal validity of results in the studies included in this review (Review Manager 5.3). Two researchers (MNS and JHF) reviewed the publications of selected trials to determine whether the investigators used appropriate methods to: (1) generate a random allocation sequence (selection bias), (2) conceal the sequence of treatment allocation from trial investigators and participants before the trial (selection bias), (3) mask participants and investigators from the knowledge of treatment allocation during the trial (performance bias and detection bias), and (4) deal with missing outcome data (attrition bias). We consistently rated the selective outcome reporting domain as 'unclear' as there was inadequate information available in the trials to evaluate planned versus reported outcomes.

3 Results

3.1 Effect on lean body mass

Twenty-one studies were included in the LBM analysis. Pooled results showed an increase in LBM in individuals receiving AAS when compared to control or placebo (ES: 0.46; 95% CI: 0.25, 0.68, $P=0.00$; Fig. 2a). LBM did not differ in EX when compared to control (0.15; -0.07, 0.38, $P=0.17$; Fig. 2b). AAS intervention did not demonstrate a difference in LBM when compared to EX (0.20; -0.17, 0.57, $P=0.29$; Fig. 2c). An increase in LBM was seen in AAS + EX group when compared to EX alone (0.46; 0.21, 0.72, $P=0.00$; Fig. 2d) and when compared to AAS alone (0.37; 0.09, 0.65, $P=0.00$; Fig. 2e). The funnel plot analysis was performed for all comparisons (Supplementary data C), and evidence of asymmetry was seen only in the AAS + EX *vs.* AAS comparison, and the respective computation of trim and fill analysis consequently was performed. (Supplementary data C; Fig. S1e).

3.2 Effect on muscle strength

Fifteen studies were included in the strength analysis. Pooled results showed that AAS promoted an increase in muscle strength when compared to control (0.31; 0.08, 0.53, $P=0.01$, Fig. 3a). Similarly, EX alone promoted an increase in muscle strength when compared to control (0.89; 0.53, 1.25, $P=0.00$, Fig. 3b). Muscle strength did not differ between AAS and EX (-0.53; -1.07, -0,00, $P=0.05$, Fig. 3c). An increase in muscle strength was seen in AAS + EX when compared to EX alone (0.42; 0.10, 0.74, $P=0.00$; Fig. 3d) and when compared to AAS alone (1.02; 0.53, 1.51, $P=0.00$, Fig. 3e). The funnel plot analysis was performed for all comparisons (Supplementary data D), and evidence of asymmetry was seen only in the AAS + EX *vs.* EX comparison, and the respective computation of trim and fill analysis consequently was performed (Supplementary data D; Fig. S2e).

3.3 Meta-regression

The results from the meta-regression model are presented in Supplementary data E. Considering the overall effects, and taking into account participants age (> 60 years; < 60 years), sex (man; woman); study duration (time, $t \leq 3$ months; 3 months $< t \leq 6$ months, and $t > 6$ months); blood testosterone levels change (increase or decrease/no changed) and AAS type (anabolic/androgenic ratio < 2 or anabolic/androgenic ratio > 2 followng Kicman [67] classification), the only significant variable found to explain the heterogeneity in AAS + EX vs. EX interaction was the AAS type in the LBM outcome (coefficient: 1.419 95% CI [0.367; 2.471]; $z=2.64$ $P=0.008$). None of these variables explained the heterogeneity in muscle strength.

3.4 Testosterone blood levels

The results from fourteen studies that measured testosterone blood levels pre-and post-intervention in men are summarized in Fig. 4.

According to Travison et al. [68], who have established the reference ranges for total testosterone in men, only one study in this review reported that the mean basal testosterone levels in the intervention group (before testosterone administration) were lower than the 2.5th percentile for men, at their respective ages [33]. The mean of testosterone blood levels was increased above the 97.5th percentile for men in two studies [32, 36]. Gharahdaghi et al. [32] administered Sustanon® (250 mg per week) in elderly individuals (65–75 years), and Grinspoon et al. [36] administered testosterone enanthate (200 mg per week) to HIV-infected men. Four studies did not find any changes in testosterone levels after the intervention with anabolic androgenic steroids [39, 45, 48, 56]. Sartorio et al. [48] reported no changes in testosterone levels after 3 weeks of nandrolone undecanoate administration (80 mg per week) in obese women. Ferreira et al. [42] was the only study that reported a decrease in testosterone levels after treatment with Durateston® ("attack" dose) and stanozolol

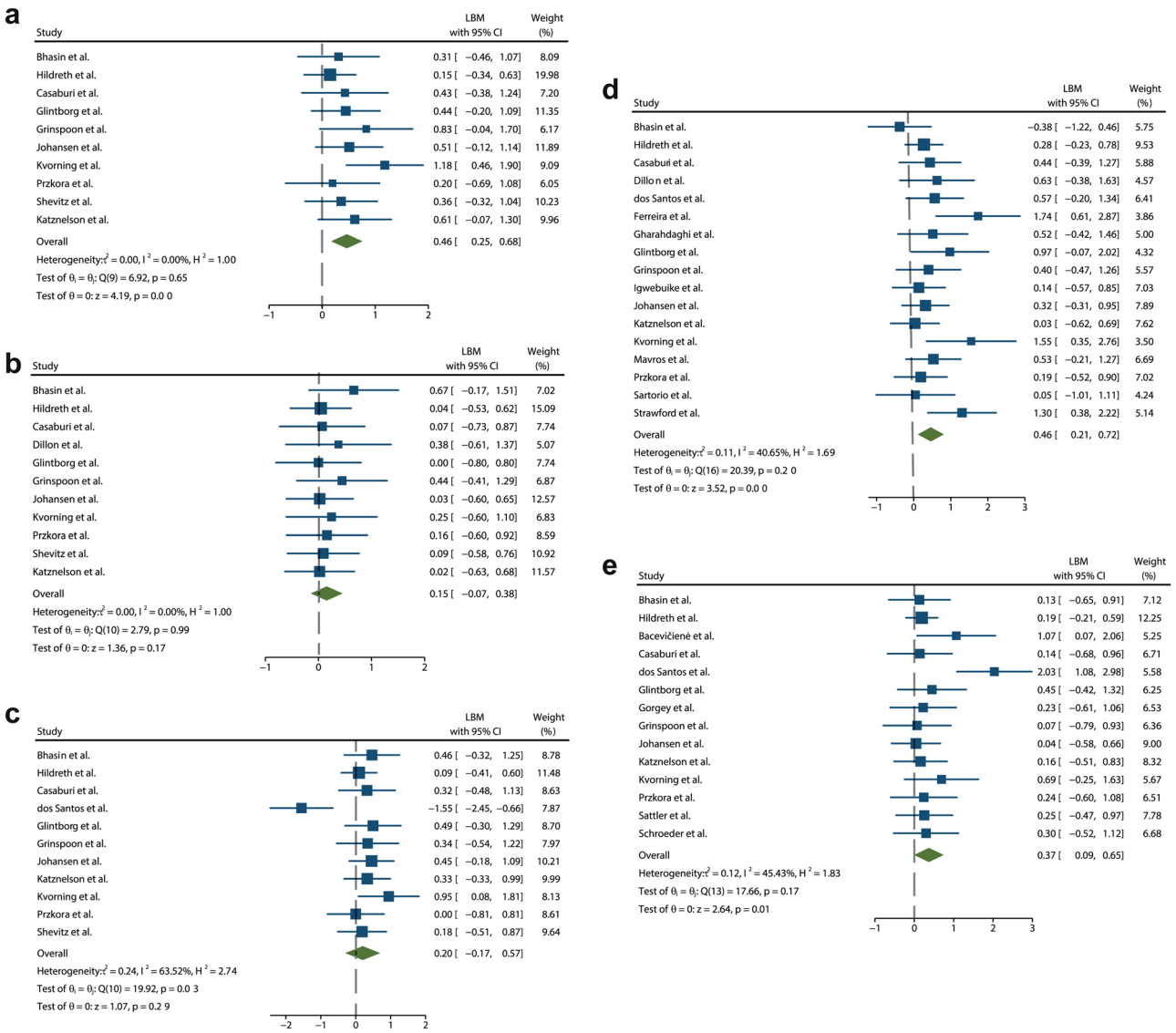

Fig. 2 (**a**) Forest plot for Lean Body Mass (LBM) from AAS intervention *vs.* Control. Values in the right of the vertical dashed line favor Anabolic–Androgenic steroids (AAS), while on the left favor Control group. Low heterogeneity in this comparison was detected (Q = 6.92, $P = 0.65$). (**b**) Forest plot for Lean Body Mass (LBM) from EX intervention *vs.* Control. Values in the right of the vertical dashed line favor EX, while on the left favor Control group. Low heterogeneity in this comparison was detected (Q = 2.79, $P = 0.99$). (**c**) Forest plot for Lean Body Mass (LBM) from AAS intervention *vs.* EX. Values in the right of the vertical dashed line favor AAS, while on the left favor EX interventions. High heterogeneity in this comparison was detected (Q = 19.92, $P = 0.03$). (**d**) Forest plot for Lean Body Mass (LBM) from AAS + EX *vs.* EX. Values in the right of the vertical dashed line favor AAS + EX, while on the left favor EX group. Low heterogeneity in this comparison was detected (Q = 20.39, $P = 0.20$). (**e**) Forest plot for Lean Body Mass (LBM) from AAS + EX *vs.* AAS. Values in the right of the vertical dashed line favor AAS + EX, while on the left favor AAS group. Low heterogeneity in this comparison was detected (Q = 17.66, $P = 0.17$). Values are the individual and pooled effect sizes (95% CI) from those studies that measured LBM

(12 mg per day) in COPD patients; after this intervention mean testosterone blood levels values fell below the 2.5th percentile for men (Fig. 4).

Two studies in women who received dehydroepiandrosterone (DHEA) and were submitted to exercise exhibited an increase by 2–3 times in testosterone levels [57, 58]. Conversely, Villareal, and Holloszy [58] did not observe any change in testosterone blood levels when men received DHEA and were submitted to exercise (Fig. 4). Although DHEA is a hormonal precursor of testosterone, we have included these studies since an increase in testosterone levels in women was reported. According to testosterone

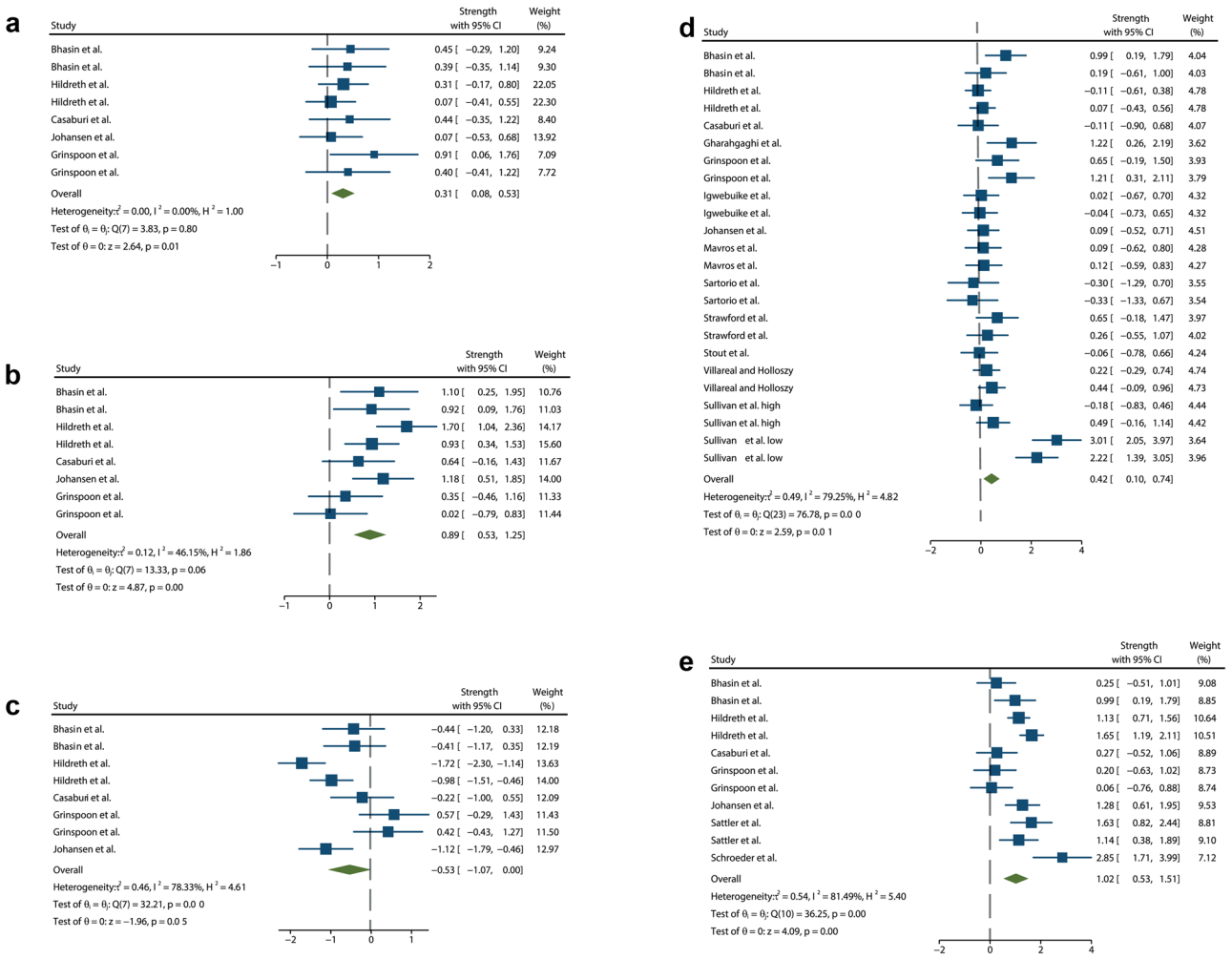

Fig. 3 (**a**) Forest plot for muscle strength from AAS *vs.* Control. Values in the right of the vertical dashed line favor AAS, while on the left favor Control. Low heterogeneity in this comparison was detected (Q = 3.83, *P* = 0.80). (**b**) Forest plot for muscle strength from EX *vs.* Control. Values in the right of the vertical dashed line favor EX, while on the left favor Control group. Low heterogeneity in this comparison was detected (Q = 13.33, *P* = 0.06). (**c**) Forest plot for muscle strength from AAS *vs.* EX. Values in the right of the vertical dashed line favor AAS, while on the left favor EX group. High heterogeneity in this comparison was detected (Q = 32.21, *P* = 0.00). (**d**) Forest plot for muscle strength from AAS + EX *vs.* EX. Values in the right of the vertical dashed line favor AAS + EX, while on the left favor EX group. High heterogeneity in this comparison was detected (Q = 76.78, *P* = 0.00). Note: Sullivan's study divided into high and low load exercises protocols. (**e**) Forest plot for muscle strength from AAS + EX *vs.* AAS. Values in the right of the vertical dashed line favor AAS + EX, while on the left favor AAS group. High heterogeneity in this comparison was detected (Q = 36.25, *P* = 0.00). Values are the individual and pooled effect sizes (95% CI) from those studies that measured muscle strength. Data from the upper and lower strength was separately analyzed when measured

reference values for women [69], only Villareal and Holloszy [58] reported an increase in testosterone plasma levels above the 97.5th percentile post-intervention.

3.5 Side effects and adverse experiences

Table 1 summarizes the studies that reported side effects from testosterone administration. Only 3 studies did not evaluate any well-known biomarkers or adverse effects that may be altered during testosterone administration [33, 50, 53]. Six studies reported no adverse effects related to AAS [32, 45–48, 58]. However, these latter studies did not specify which adverse events were monitored. An increase in hemoglobin levels or hematocrit were reported in 8 studies after AAS intervention [35–37, 41, 51, 52, 55, 56]. ALT, AST, GGT, ALB were measured in 9 studies, and all of these enzymes were in a normal range [35–38, 41, 42, 47, 49, 54]. PSA was measured in 9 studies, and no increase above reference values was reported [35, 36, 40, 41, 51, 52, 55, 56, 58]. Eleven studies performed a lipidic analysis, and no differences were reported in LDL,

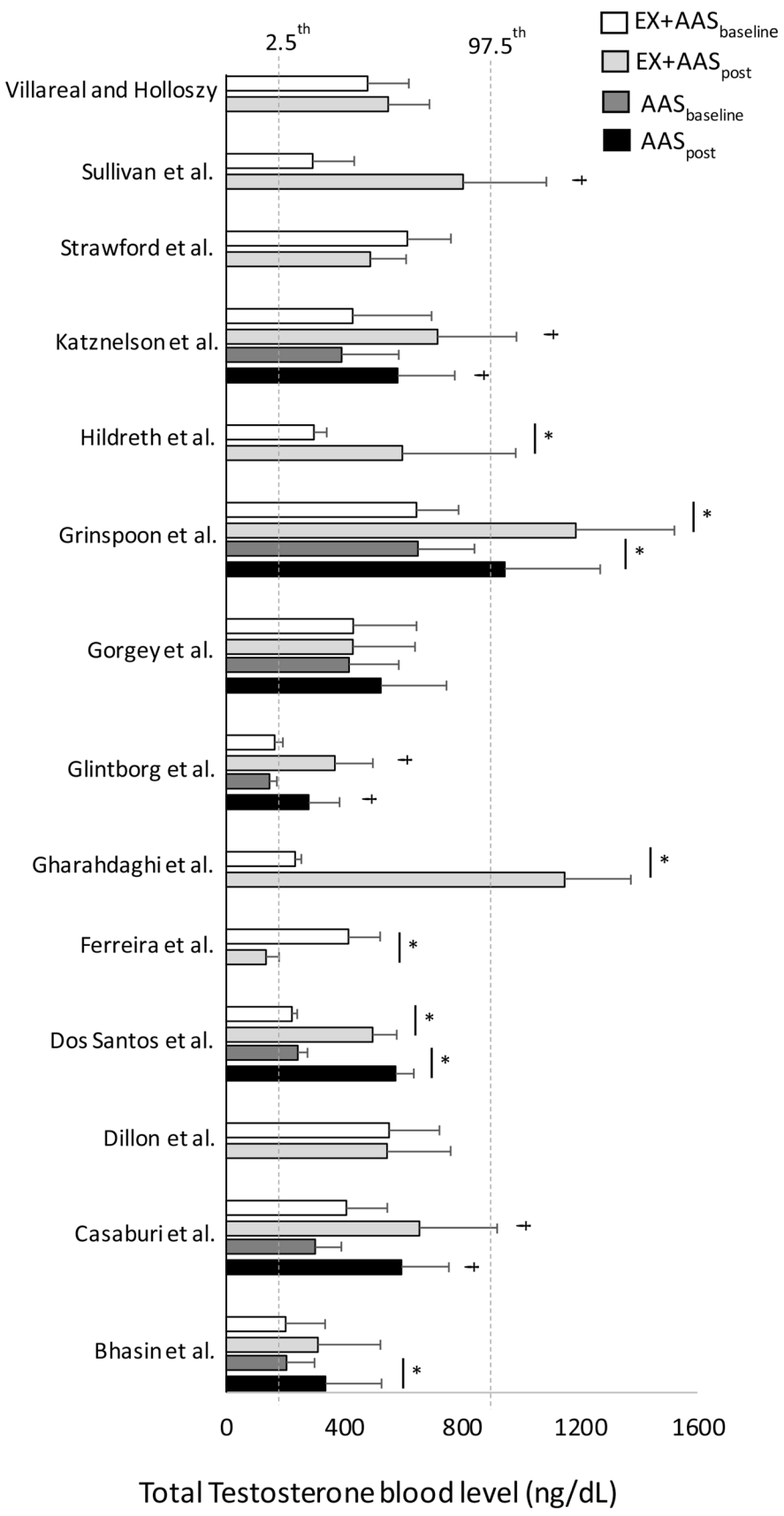

Fig. 4 Testosterone blood levels from studies included in this meta-analysis. Values are mean ± SD from baseline and post -anabolic–androgenic-steroids intervention measurements. The dashed lines represent the 2.5th and 97.5th percentiles (192 ng/dL and 902 ng/dL, respectively), according to Travinson et al. [68] * *vs.* baseline ($P < 0.05$); † *vs.* placebo or control group ($P < 0.05$). The values from placebo or control group are not represented in the graph

Table 1 Side effects and changes in biomarkers

Study	Side effects and biochemical markers
Bacevičienė et al.	No side effects measured in this study
Bhasin et al.	Six percent increase in hemoglobin levels in EX + AAS group ($P < 0.05$) and a 14% increase in the AAS group ($P = 0.04$) when compared pre-post intervention; The authors reported no changes in these biomarkers when compare AAS (EX + AAS, AAS) and placebo (EX + placebo and placebo) groups: bilirubin, ALT, AST, TG, LDL, PSA, $CD4^+$, and $CD8^+$ counts and HIV RNA; Acne (1 case in AAS groups; 1 case in placebo groups). Breast enlargement (1 case in AAS groups)
Casaburi et al.	About 7% increase in hemoglobin levels in EX + AAS and AAS groups when compared pre-post intervention ($P < 0.05$). Only one subject exhibited hemoglobin levels higher than 18 g/dL at the end of the intervention in the AAS group (Hb levels decreased during postintervention observation); The authors reported no changes in these biomarkers when comparing all groups: ALT, AST, GGT, ALP, PSA, TC, and HDL; Increase Cr levels in the EX + AAS group pre-post intervention ($P < 0.05$)
Dillon et al.	Increase in hematocrit at Head-Down Bed Rest (i.e., effects of time) ($P < 0.05$); The authors reported no changes in these biomarkers when comparing EX + AAS and placebo (EX + placebo, placebo) groups: TC, HDL, LDL, VLDL, and PSA; TC decreased in EX + AAS after 14 days of bed rest when compared to placebo; TG and VLDL decreased during Head-Down Bed Rest (i.e., effects of time) ($P < 0.05$)
Dos Santos et al.	The authors related a decrease in heart rate ($P < 0.05$) and there were no changes in SBP and DBP in all groups during the intervention
Ferreira et al.	The authors related no changes in these biomarkers within groups, between groups, or across time: electrolytes, glucose, calcium, phosphorus, magnesium, total protein, ALB, blood cell count, PAP, and prostate size
Gharahdaghi et al.	No side effect was measured in this study; The authors related no adverse events during or after completion of the study
Glintborg et al.	No side effects measured in this study
Gorgey et al.	The authors reported that no adverse events were observed; The authors related no changes in these biomarkers between all groups: lipid panel, CRP, TNF-α or FFA
Grinspoon et al.	Only in the AAS group was found a decrease of TC levels ($P < 0.05$); AAS groups (AAS and EX+AAS) were found an increase in hematocrit from baseline ($P < 0.05$); The authors reported that breast tenderness or gynecomastia developed in 3 patients: 2 AAS groups (EX + AAS and/or AAS) and 1 placebo groups (EX + placebo and/or placebo). Adverse effects on prostate hypertrophy, acne, mood swings, and polycythemia were not observed in the study
Hildreth et al.	The higher-range AAS (7,5-10 g/day of Testosterone gel) group exhibited an increase in HCT when compared with lower-range AAS (2,5-7 g/day of Testosterone gel) ($P = 0.008$); There was no significant increase in PSA levels in any group; The authors related there were no differences in the frequency of prespecified adverse events[a] between placebo groups (EX + placebo and/or placebo) and AAS groups (EX + AAS and/or AAS) except for HCT (more frequent in AAS groups); The authors related fewer cardiovascular events[b] among AAS groups (EX + AAS and/or AAS) in comparison with placebo groups (EX + placebo and/or placebo) ($P = 0.001$)
Igwebuike et al.	No changes in these biomarkers were found in any group: fasting glucose, insulin, HDL, LDL, and TG from baseline
Johansen et al.	No side effects were reported in the study
Katznelson et al.	No patient had HCT > 52%; No change was found in the following biomarkers for any of the groups: TC, LDL, HDL, TG, and PSA; The authors related that PSA levels were increased in 4 subjects using AAS (2 in EX + AAS and 2 in AAS), but in 3 of them the levels returned to normal at follow up, the other one was lost to follow-up
Kvorning et al.	No side effects measured in this study
Mavros et al.	The authors related that the EX + AAS group had a reduction in HDL ($P = 0.02$) and an increase in ALT ($P = 0.02$)
Przkora et al.	According to the authors, no adverse effects were noted, such as hirsutism or increased liver enzymes
Sartorio et al.	According to the authors, no side effects were observed during the study
Sattler et al.	Two subjects who received AAS developed acneiform lesions, both had a history of acne; Increase Hb levels in AAS and EX + AAS groups ($P < 0.001$). A significant increase in the ALT levels AAS group ($P = 0.002$), but according to the authors, no patient in either group had an increase in any liver test above normal and any evidence of hepatitis. ALB levels decrease in EX + AAS ($P = 0.001$). A decrease in TC in the AAS group from baseline ($P = 0.03$); No change was noted in these biomarkers in any groups: blood urea nitrogen and TG from baseline

Table 1 (continued)

Study	Side effects and biochemical markers
Schroeder et al.	According to the authors, there were no new or worsening urinary symptoms, increases in blood pressure, the occurrence of edema or onset of cardiorespiratory symptoms; No change was noted in these biomarkers in any groups: blood urea nitrogen and PSA
Shevitz et al.	According to the authors, no adverse effects were noted such as hirsutism, deepening voice, sexual dysfunction, menstrual change (among women) or gynecomastia (among men) in the AAS group; The authors found an increase in liver function in 2 subjects (biomarkers and study group not reported)
Shimodozono et al.	The authors related no changes in the following biomarkers in the AAS group from baseline: bilirubin, total protein, LDL, sodium, potassium, fasting blood glucose, and HCT. An increase in AST and LDH was seen in the AAS group ($P<0.05$), but still below the normative limits. ALT values above normal were observed in two subjects and GGT in one subject in the AAS group. Significant decrease in HDL ($P<0.05$), TG ($P<0.01$), and blood urea nitrogen ($P<0.05$) below the normative limits were observed between baseline and 6 weeks period of intervention with AAS
Stout et al.	The authors reported no changes in these biomarkers between groups and from baseline: NT pro-BNP, IL-6, hs-CRP, sICAM, sVCAM. With the exception of the decrease of TNF-α in EX + placebo group from baseline ($P<0.05$); There were no significant changes between groups (placebo and AAS) and from baseline in cardiac outcomes (atrial and ventricular diameter and function)
Strawford et al.	The authors reported a decrease in HDL levels in the AAS group when compared to placebo ($P<0.001$); Mood swings were reported by 8 subjects (5 in the AAS group and 3 in the placebo group). An increase in libido during the study was reported by 4 subjects (2 in the AAS group and 2 in the placebo group). Four subjects reported anxiety and 1 reported nausea in the AAS group
Sullivan et al.	Hb slightly greater in the AAS group when compared to the placebo group ($P=0.056$); According to the authors the PSA levels do not increase in the AAS group in comparison with the placebo group
Villareal and Holloszy	According to the authors, no serious adverse events were related during the course of the study. PSA levels did not change between AAS and placebo groups and from baseline

AAS anabolic–androgenic steroid, *ALB* Albumin, *ALP* alkaline phosphatase, *ALT* alanine transaminase, *AST* aspartate transaminase, *Cr* creatinine, *CRP* C-reactive protein, *DBP* diastolic blood pressure, *EX* Exercise, *FFA* Free fat acid, *GGT* gamma-glutamyltransferase, *Hb* hemoglobin, *HCT*, hematocrit, *HDL* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *LDH* lactate dehydrogenase, *LDL* low-density lipoprotein cholesterol, *NT pro-BNP* N-terminal pro-brain natriuretic peptide, *PAP* prostatic acid phosphatase, *PSA* prostate-specific antigen, *SBP* systolic blood pressure, *sICAM-1* soluble intercellular adhesion molecule, *sVCAM* soluble vascular cell adhesion molecule, *TC* total cholesterol, *TG* triglycerides, *TNF-α* tumor necrosis factor-alpha, *VLDL* very-low-density lipoprotein

[a]HCT > 54%; Increase of ≥ 0.75 ng/mL over baseline at any time point (confirmed by a second measurement in 2 weeks); American Urological Association symptom score ≥ 20; AST or ALT > 2 times the upper limit of normal; Somnolence (Epworth Sleepiness Score > 16); Hypoxia (defined as arterial oxygen saturation by pulse oximetry < 88%)

[b]Acute coronary syndrome; Arrhythmia; Aortic aneurysm; Syncope/presyncope

VLDL, and triglycerides [35–37, 39, 41, 45, 49, 52, 54, 56, 57]. However, two studies reported a decrease in HDL levels [39, 49]. Two studies measured cardiac function and remodeling, and no changes were reported in these parameters [43, 44].

3.6 Study quality

Cochrane risk-of-bias from included studies in this meta-analysis is shown in Supplementary data F. Two studies were judged to have a risk of selection bias and one of reporting bias.

4 Discussion

Muscle mass can be broadly defined as the quantity or volume of skeletal muscle, whereas strength is related to muscle contraction capacity. One longitudinal study has shown that the age-related reduction of muscle strength is more predictive of mortality over the years than the reduction of muscle volume [12]. However, recent evidence has shown that skeletal muscle tissue is an endocrine organ that can synthesize and secrete approximately 600 substances (a.k.a. myokines), and the role of these substances in whole-body physiology is of emerging interest [70]. For instance, clinical studies have shown that the preservation of skeletal muscle in cachectic patients can decrease mortality risk, hence promoting a better prognosis [16–18]. In addition, several studies have reported a positive relationship between low muscle mass and mortality among older adults [71–74].

The present meta-analysis aimed to review the effects of AAS and AAS + EX on LBM and muscle strength in clinical and skeletal muscle loss conditions. Herein, we show that AAS administration promotes an increase in both LBM and muscle strength, while EX alone promotes an increase only in muscle strength when compared to controls in the studied population. When AAS is combined with EX, an

increase in LBM and muscle strength is seen over and above that achieved with AAS or EX alone. Although the effect of using AAS alone does not differ from the isolated effects of EX (-0.53; -1.07, -0.00, $P = 0.05$), the effect size heavily favored EX. Therefore, when used separately, EX appears to be more effective in promoting increased strength when compared to the use of AAS alone in conditions involving muscle loss. A meta-analysis by Andrews et al. [75] found similar results, reporting that healthy individuals exhibited an additional increase in muscle mass and strength when exercise was performed in combination with AAS administration compared to exercise alone.

The majority of the participants included in this review exhibited decreased physical activity either due to a clinical condition or exercise intolerance [22–24]. In agreement with our findings, two separate meta-analyses have shown that an exercise intervention was able to increase muscle strength but not LBM in sarcopenic elderly individuals [76] and sarcopenic obese individuals [77].

Although exercise is often chosen as the first-line treatment for several diseases associated with muscle atrophy [19, 20], many patients already have experienced significant muscle loss in these conditions [78], becoming intolerant to exercise (e.g.: frailty, bed rest conditions, cardiorespiratory disability, etc.) to the extent that exercise is a difficult treatment option [23, 24, 76]. The pooled data from our study showed a lack of evidence that exercise per se promotes significant changes in muscle mass when compared to the control group. This evidence suggests that, in several clinical conditions, patients may not benefit from an exercise intervention, and AAS administration could provide an alternative to a better prognosis. We did not perform a subanalysis to differentiate or compare ES between resistance training and aerobic training, as only two studies with an exercise component did not employ resistance training protocols. The interventions with only aerobic training and placebo promoted an increase in LBM in one study [44] and remained unchanged in another [42]. Although resistance training is considered the gold-standard intervention for gaining muscle mass, we cannot determine whether it has a greater effect compared to aerobic exercise in the population studied herein based on available data.

In clinical conditions, such as HIV, renal failure, heart failure, COPD, bed-rest, etc., cachexia can be a debilitating factor that may lead to treatment resistance and poor prognosis [79–81]. Moreover, exercise may not be an option to treat and help individuals with these conditions due to impaired mobility and/or exercise intolerance [23–25, 78]. Considering that AAS administration alone promoted an increase in both LBM and muscle strength, which is in agreement with the meta-analysis by Skinner et al. [82], it is feasible to consider the use of AAS in patients confined to physical inactivity. A recent meta-analysis conducted with burn patients (pediatrics and adults) found that resistance exercise did not statistically increase muscle strength and LBM, suggesting AAS might be a viable alternative in this population [83]. However, it should be noted that although the strength increases did not reach statistical significance, the effect size heavily favored the use of resistance exercise (SMD = 0.74) and the confidence intervals also indicated a positive benefit (CI = -0.02 to 1.50).

Two clinical studies not included in this review have pointed out that AAS administration in patients with cancer and liver failure promoted beneficial effects on muscle strength and muscle mass [84, 85]. Elderly individuals who underwent a 3-year hormone therapy replacement regimen exhibited similar results [86]. Moreover, AAS provision in elderly individuals was able to reduce the recurrence of hospitalization in both sexes [87, 88]. Two meta-analyses conducted with HIV/AIDS patients [89] and another with HF patients [90] reported that AAS treatment was able to increase muscle strength in the former patients and physical capacity in the latter individuals.

Long-term studies have shown that the use of AAS, via testosterone replacement therapy (TRT), can increase survival rate in some clinical conditions [91, 92]. However, it remains undetermined whether this longer rate of survival is associated with an increase in strength or muscle mass once AAS perform many other functions in the body, such as improving insulin resistance [92] and reducing the occurrence of anemia [91]. Further studies are needed to clarify the underlying reasons why AAS may help to improve clinical prognosis in conditions of cachexia and sarcopenia.

Regarding the combination of AAS + EX, the studies included in this review indicate that any additional increase in testosterone plasma between the range of 2.5^{th}—97.5^{th} percentile induced by AAS intervention is capable of promoting an increase in LBM and muscle strength when compared to EX or AAS alone. Therefore, our results do not support the need to attain supraphysiological blood testosterone levels to increase muscle mass and strength in this population.

4.1 Side effects of AAS

The duration of the AAS regimens in the studies included herein ranged from 3 to 12 months. Overall, the controlled use of AAS for this period did not appear to cause adverse effects that would contraindicate its use to combat muscle loss in a clinical population. It should be noted that the use of AAS in sports has been associated with liver, heart, and kidney damage [93–95]. However, these athletes often abuse anabolic agents, taking supraphysiological doses that result in testosterone levels values as high as 2,000 ng/dL

[96]. Long-term supraphysiological testosterone levels produce toxicity in several tissues, although the mechanism underlying these effects are not fully elucidated. In this review, only two studies reported an increase in testosterone levels above the normal physiological range [32, 36], and these studies did not observe any severe adverse effects.

Conversely, there are some reports that AAS administration exerts cardioprotective effects when testosterone levels remain in a normal range [97]. When AAS is combined with exercise, one could speculate that fewer adverse effects would be reported than an intervention with AAS alone since exercise is known to promote a healthy lipid profile and improve cardiovascular function [98–100]. This hypothesis warrants further study.

One of the concerns of the use of AAS in RCTs to promote gains in muscle strength and muscle mass is its known adverse effects, which are usually related to the abuse of AAS in non-clinical practices. However, the studies included in this review reported few or no side effects from AAS administration. Several studies from our qualitative analysis did not show significant changes in serum levels of biomarkers such as liver enzymes (AST, ALT, GGT), bilirubin or albumin, lipid profile (total cholesterol, HDL, LDL, TG, VLDL), hemoglobin, hematocrit or PSA. Likewise, no cardiovascular changes (diameter and atrial and ventricular function) or adverse effects related to androgenism were found, such as hirsutism, deepening of the voice, gynecomastia (men) or menstrual changes (women) (see in Table 1).

Although our qualitative analysis of the use of AAS does not report significant adverse effects, we cannot exclude the possibility that these effects may occur, especially in outcomes that are not sensitive or specific to the biomarkers analyzed by the studies. In addition, it should be noted that the duration of the included studies were relatively short (≤ 1 year); the long-term adverse effects and safety of AAS use in the studied population have yet to be fully documented. Some guidelines have an absolute contraindication to the use of AAS (referring to TRT) in men with untreated prostate or breast cancer, as well as severe heart failure. In addition, there is a relative contraindication in men with severe low urinary tract symptoms and haematocrit > 48% -50% [101, 102].

4.2 From hypogonadism to eugonadal: a viewpoint beyond consensus

When the individuals included in this review also exhibit low levels of testosterone (HIV/AIDS, COPD, heart failure, kidney failure, elderly), it is feasible to consider an AAS intervention to obtain some of the beneficial effects of exercise. The only study conducted with hypogonal individuals in our review showed that EX + T undecanoate had an additional effect on muscle mass in relation testosterone therapy alone [50]. Also, a meta-analysis from Chen et al. [103] has shown that EX increased muscle strength, but not muscle mass, in prostate cancer patients undergoing androgen deprivation therapy, a condition of induced hypogonadism. These works are in agreement with our findings in which EX plus AAS is crucial to increase muscle mass in hypogonadal men.

Recently, the European Academy of Andrology (EAA) proposed the term functional hypogonadism to refer to the clinical situation with signs and symptoms similar to classic hypogonadism, but with more subtle aspects, nonspecific symptoms and generally without evident signs of androgen deficiency. Hypogonadism is common in several clinical conditions such as those analyzed in this review. According to the EAA consensus statement, in the absence of symptomatic hypogonadism, TRT is not recommended to improve morbidity, mortality and physical capacity/function in various clinical conditions [102]. Another consensus by the Endocrine Society has a similar position on the topic [101]. Therefore, it would be expected that the benefits of TRT would be restricted only to individuals with hypogonadism.

It is necessary to understand that sarcopenia and cachexia clinical conditions are not exclusive to patients with hypogonadism [14, 15]. Eugonadal individuals can suffer from these dysfunctions and have a worse prognosis; however, they conceivably would not adopt any therapy, since the consensus does not advocate a sufficient benefit for TRT in these cases. AAS therapy involves a broad group of drugs, which do not always have the same function as TRT [67]. The use of other AAS, such as oxandrolone or nandrolone decanoate, as a possible therapy for eugonadal individuals should be considered. Usually, consensus statements in endocrinology are directed towards the treatment of hypogonsadism and other consensus statements, such as those for sarcopenia [104] and cachexia [105], for example, do not contemplate the possible use of AAS. As highlighted in Fig. 4, the AAS therapy does not always induce changes in testosterone hormone levels and only two studies obtained supraphysiological levels.

4.3 Study limitations

Research-based evidence is lacking as to what testosterone plasma levels are required to promote beneficial adaptations when combined with EX in healthy individuals [106, 107]. The studies included in this review did not analyze the response to acute changes in plasma testosterone levels and its consequences for adaptations induced by the EX. In healthy individuals, acute EX-induced testosterone hormonal elevations seem not to contribute to gains

in strength and muscle mass [108]. Furthermore, in the studies included in this review, the EX protocols alone did not promote a significant change in endogenous baseline testosterone levels, so it is unlikely that any individual with hypogonadism will become eugonadal or *vice-versa*, only performing EX. Usually, drastic hormonal changes, such as exercise-induced male hypogonadism, are common in athletes undergoing strenuous training routines and not in EX protocols described in this review [109].

Dose, testosterone formulations, and administration routes may all influence specific outcomes. For instance, a recent meta-analysis found that intramuscular testosterone injection was more effective than transdermal delivery for increasing muscle strength and mass [82]. Moreover, Bhasin et al. [110] noted a positive correlation between testosterone dose and an increase in muscle strength and mass. Different testosterone formulations exhibit a distinct anabolic/androgenic ratio. For example, testosterone enanthate has a ratio of 1, while the decanoate of nandrolone has a ratio of 11 [67]. According to our meta regression, AAS type explains the heterogeneity in AAS + EX vs. EX interaction in the LBM outcome (coefficient: 1.419 95% CI [0.367; 2.471]; z = 2.64 $P = 0.008$). Moreover, testosterone molecules have different pharmacokinetics, which can promote supraphysiological levels of plasma testosterone, hence increasing adverse effects [111]. Our meta-analysis was not able to account for these complexities.

Differences in exercise protocols included in our study also need to be taken into account when attempting to draw evidence-based conclusions. Although only two studies did not perform resistance training [42, 44], which has well-established effects on increasing muscle mass and strength [112], there is no consensus on which exercise protocol is better for the clinical conditions reviewed herein. In healthy individuals, resistance training with high loads (> 60% 1 RM) was shown to be more effective in increasing muscle strength when compared to lighter loads [112]. This may have implications for the results heterogeneities of the studies, as not all EX protocols were performed with high load resistance training. In addition, several other training variables can influence responses, such as recovery time between sets [113], frequency [114] and training volume [115]. These variables go beyond the ability to be analyzed quantitatively by our study.

Although the present review and meta-analysis considered that skeletal muscle dysfunction was present in the studies included, the individuals were not submitted to a specific evaluation to diagnose cachexia or sarcopenia according to the newest guidelines and consensus [14, 15]. Moreover, AAS interventional protocols, such as dose, formulation, and route of delivery, should be addressed in future RCTs to establish the safest regimen in specific clinical conditions to achieve the desired prognosis.

Finally, the studies included in this review are restricted to English language publications and are associated with different clinical conditions and/or age with loss of muscle function. The analysis of a specific clinical condition (e.g. only men with hypogonadism or patients with COPD or HIV) would dramatically reduce the number of included studies and, consequently, hinder a detailed quantitative analysis on the effectiveness of EX and AAS. We also highlight that for the same clinical condition, there may be individuals with different characteristics in relation to muscle function and testosterone levels, which in turn may result in differential responses to the use of EX and AAS for the same clinical comorbidity.

5 Conclusion: can conditions of skeletal muscle loss be improved by combining exercise with anabolic–androgenic steroids?

Our study analyzed the effects of AAS and AAS + EX interventions on LBM and muscle strength in clinical conditions associated with muscle loss. Short-term AAS administration exhibits a positive effect on LBM and muscle strength, with few adverse effects reported. The combination of AAS + EX was superior to EX or AAS interventions alone for increasing muscle mass and strength (Fig. 5). To our knowledge, this is the first meta-analysis to assess AAS interventions and exercise in clinical conditions. Our analyses indicate that individuals with an impaired capacity for physical activity may achieve a clinical benefit from AAS interventions. Also, EX, in combination with short-term AAS intervention, helps to maximize results in the studied population.

Given evidence that muscle loss conditions (sarcopenia and cachexia) lead to a worsened clinical prognosis, and added to the fact that the EX [116, 117] and the use of AAS [91, 92] may increase survival in some clinical conditions, our findings provide promising evidence that afflicted patients may obtain positive benefits from EX + AAS therapy or only AAS, if exercise is not a viable option (Fig. 6). In addition, AAS therapy appears to be relatively safe to use in a controlled clinical setting, whereby biomarkers and adverse reactions are monitored by a clinician. The benefits of restoring muscle mass, strength and, consequently, improving patients prognosis and survival, can outweigh the associated risks. However, the long-term effects of clinical AAS administration remain undetermined, and the potential for adverse responses with continued use cannot be ruled out.

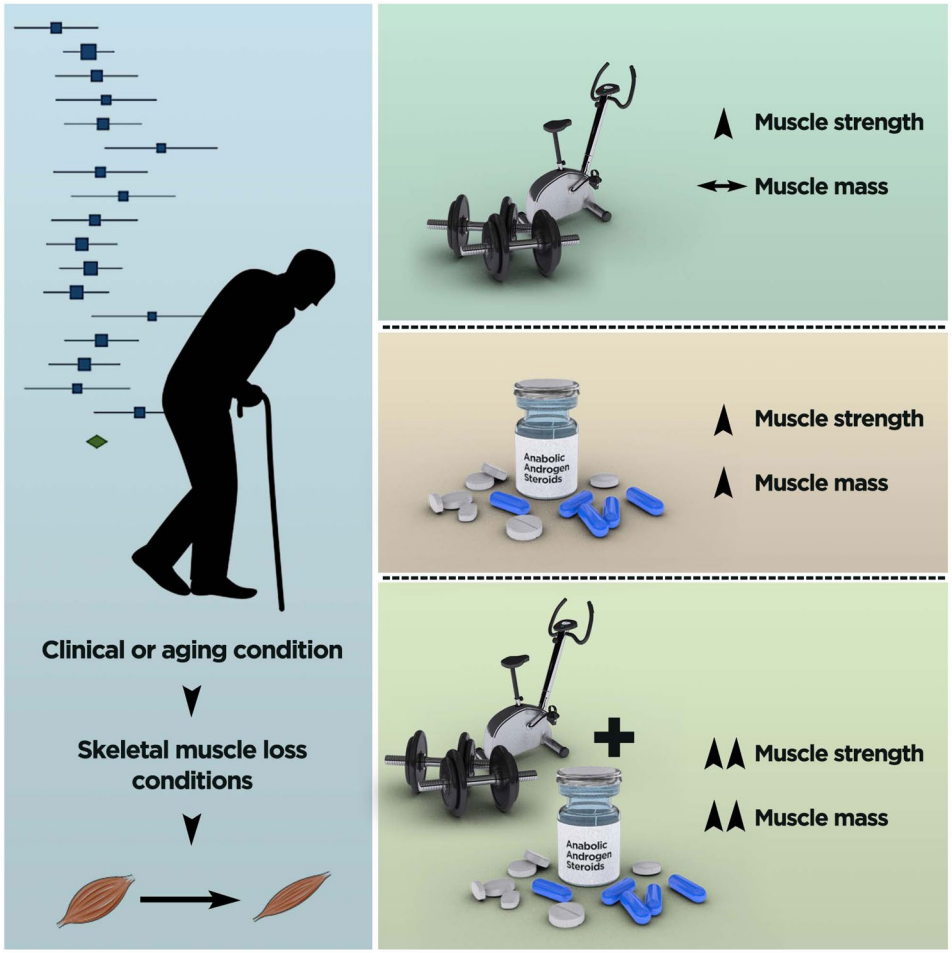

Fig. 5 Highlights of the main results in our meta-analysis: Association of therapies (AAS + EX) promote greater increase in muscle mass and strength. Exercise therapy alone may not be a satisfactory option for many patients

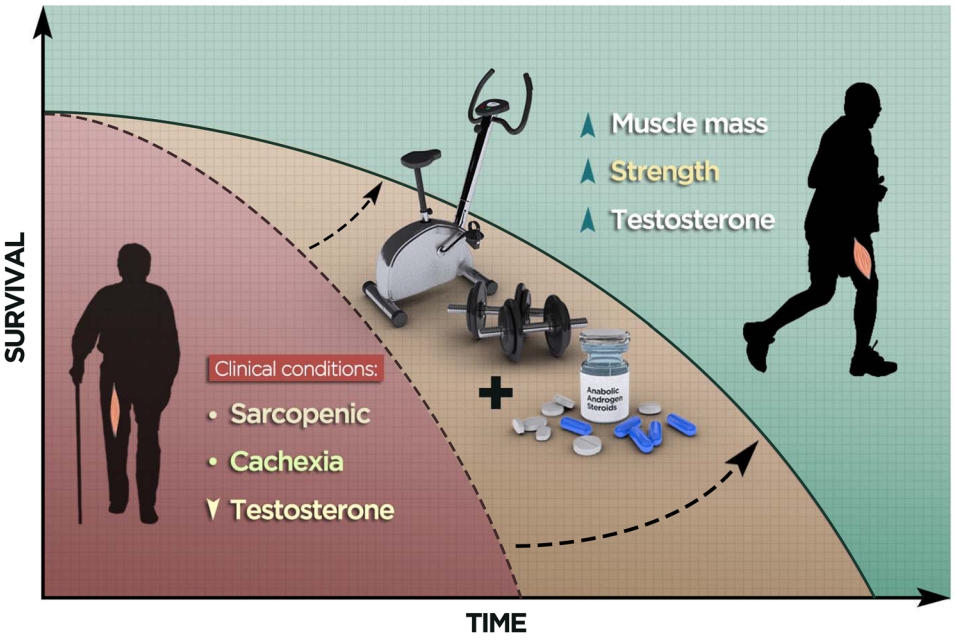

Fig. 6 Sarcopenic and cachectic patients have lower survival and decrease endogenous testosterone blood levels. Therefore, it is speculated that reversing these conditions with the use of AAS and EX may increase the survival of numerous clinical conditions

Abbreviations 1RM: One maximal repetition; AAS: Anabolic–androgenic steroid; AIDS: Acquired Immunodeficiency Syndrome; ALB: Albumin; ALT: Alanine transaminase; AST: Aspartate transaminase; COPD: Chronic Obstructive Pulmonary Disease; DHEA: Dehydroepiandrosterone; EAA: European Academy of Andrology; ES: Effect size; EX: Exercise; GGT: Gamma-glutamyltransferase; HDL: High-density lipoprotein; HF: Heart Failure; HIIT: High-intensity intermittent exercise; HIV: Human Immunodeficiency Virus; LBM: Lean body mass; LDL: Low-density lipoprotein; PRISMA: Preferred Reporting Items of Systematic Reviews and Meta-Analysis; Q: Cochran's Q test; RCTs: Randomized Controlled Trials (RCTs); PSA: Prostate specific antigen; SCI: Spinal Cord Injury; TG: Triglycerides; TRT: Testosterone replacement therapy; VLDL: Very low-density lipoprotein

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Declarations

Conflicts of interest The authors declare that they have no competing interests.

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