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Androgens for the anaemia of chronic kidney disease in adults (Review)

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[Intervention Review]

Androgens for the anaemia of chronic kidney disease in adults

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ABSTRACT

Background

Anaemia occurs when blood contains fewer red blood cells and lower haemoglobin levels than normal, and is a common complication among adults with chronic kidney disease (CKD). Although a number of approaches are applied to correct anaemia in adults with CKD, the use of androgen therapy is controversial.

Objectives

The aim of this review was to determine the benefits and harms of androgens for the treatment of anaemia in adult patients with CKD.

Search methods

We searched CENTRAL, the Cochrane Renal Group's Specialised Register, the Chinese Biomedicine Database (CBM), CNKI, VIP and reference lists of articles without language restriction. The most recent search was conducted in August 2014.

Selection criteria

All randomised controlled trials (RCTs) that assessed the use of androgens for treating anaemia of CKD in adults were eligible for inclusion.

Data collection and analysis

Two authors independently extracted data and assessed risk of bias in the included studies. Meta-analyses were performed using relative risk (RR) for dichotomous outcomes and mean differences (MD) for continuous outcomes, with 95% confidence intervals (CI).

Main results

We included eight studies that reported data from 181 participants. Study quality was assessed as moderate in six studies, one was low quality, and one was high quality. The small number of included studies, and low participant numbers adversely influenced evidence quality overall.

We found limited evidence (1 study, 24 participants) to indicate that oxymetholone can increase haemoglobin (Hb) (MD 1.90 g/dL, 95% CI 1.66 to 2.14), haematocrit (HCT) (MD 27.10%, 95% CI 26.49 to 27.71), change in albumin (MD 4.91 g/L, 95% CI 3.69 to 6.13), alanine aminotransferase (ALT) (MD 54.50 U/L, 95% CI 43.94 to 65.06), and aspartate aminotransferase (AST) (MD 47.33 U/L, 95% CI 37.69 to 56.97); and decrease high-density lipoprotein (HDL) (MD -15.66 mg/dL, 95% CI -24.84 to -6.48). We also found that compared with erythropoietin alone, nandrolone decanoate plus erythropoietin may increase HCT (3 studies, 73 participants: MD 2.54%, 95% CI 0.96 to 4.12). Compared with erythropoietin (1 study, 27 participants), limited evidence was found to suggest that nandrolone decanoate can increase plasma total

protein (MD 0.40 g/L, 95% CI 0.13 to 0.67), albumin (MD 0.20 g/L, 95% CI 0.01 to 0.39), and transferrin (MD 45.00 mg/dL, 95% CI 12.61 to 77.39) levels. Compared with no therapy (remnant kidney), evidence was found to suggest that nandrolone decanoate can increase Hb (2 studies, 33 participants: MD 1.04 g/dL, 95% Cl 0.66 to 1.41) and HCT (1 study, 24 participants: MD 3.70%, 95% Cl 0.68 to 6.72). Compared with no therapy (anephric), evidence was found (1 study, 5 participants) to suggest that nandrolone decanoate can increase Hb (MD 1.30 g/dL, 95% Cl 0.57 to 2.03), but nandrolone decanoate did not increase HCT (MD 2.00%, 95% Cl -0.85 to 4.85).

However, oxymetholone was not found to reduce blood urea nitrogen (BUN), serum creatinine (SCr), cholesterol, or triglycerides; or increase plasma total protein, prealbumin, or transferrin. No evidence was found to indicate that nandrolone decanoate increased prealbumin or decreased BUN, SCr, AST, ALT, cholesterol, triglycerides, HDL or low-density lipoprotein (LDL). Adverse events associated with androgen therapy were reported infrequently.

Authors' conclusions

We found insufficient evidence to confirm that use of androgens for adults with CKD-related anaemia is beneficial.

PLAIN LANGUAGE SUMMARY

Androgens for the anaemia of chronic kidney disease in adults

Anaemia, which occurs when red blood cell and haemoglobin levels fall below normal, is a common problem among adults with chronic kidney disease (CKD). Anaemia can cause breathlessness, dizziness and chest pain (angina); reduce ability to think clearly; limits ability to exercise; and contributes to sexual problems, poor appetite and reduced quality of life. Anaemia may also cause longer hospital stays, and sometimes death.

There are several approaches to correct anaemia in people with CKD, including drugs to stimulate red blood cell production, dialysis to remove waste and excess water from the blood, blood transfusions, dietary management, and supplementary iron and folate agents.

Other drugs, such as androgens - which are male steroid hormones - may be given in some settings to help reduce undesirable effects of treatments. Another possible benefit of androgen therapy for people with CKD, especially in regions with limited health resources, is that these drugs have lower costs than some other treatments.

We assessed eight small studies that presented data from 181 adults with CKD-related anaemia that investigated use of androgen therapy. Limitations and flaws in the evidence lead to our conclusion that androgen therapy for adults with CKD-related anaemia was not associated with substantial benefits.

SUMMARY OF FINDINGS

Summary of findings for the main comparison.

Nandrolone decanoate plus erythropoietin (rHuEPO) versus erythropoietin (rHuEPO) for the anaemia of chronic kidney disease in adults

Patient or population: adults with the anaemia of chronic kidney disease

Intervention: nandrolone decanoate plus rHuEPO versus rHuEPO

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	rHuEPO	Nandrolone decanoate plus rHuEPO				
Haematocrit (%)		Mean haematocrit in the intervention group was **2.4 higher** (1.04 to 3.77 higher)		73 (3)	⊕⊕⊖⊖ **low**[1]	
Haemoglobin (g/dL)		Mean haemoglobin in the intervention group was **0.44 higher** (0.17 lower to 1.05 higher)		32 (1)	⊕⊕⊖⊖ **low**[2]	
Serum albumin (g/L)		Mean serum albumin in the intervention group was **0.09 lower** (0.24 lower to 0.06 higher)		51 (2)	⊕⊖⊖⊖ **very low**[2]	
Adverse events	**Study population**		**RR 7.72** (1.45 to 41.12)	83 (2)	⊕⊖⊖⊖ **very low**[3]	
	0 per 1000	**0 per 1000** (0 to 0)				
	0 per 1000	**0 per 1000** (0 to 0)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: We are very uncertain about the estimate

Reduce the evidence quality factors: methodology defect, included in the research results of the inconsistency, indirect evidence, inexactness, publication bias.

Increase the level of evidence factor: large effect quantity, confounding factors cannot change effect quantity, or the existing concentration–response relationship.

[1] Few studies included
[2] One study included
[3] High risk of performance bias
Two studies included

BACKGROUND

Description of the condition

Chronic kidney disease (CKD) is a major public health challenge. In the USA, 20 million adults have CKD, and another 20 million are at risk of developing the disease (NKF 2007). Data from NHANES III (1988 to 1994) and USRDS (1998) indicated that prevalence of CKD ranged from 64.3% for stage 1 to 0.2% for stage 5 (NKF 2002).

Anaemia occurs when levels of red blood cells and haemoglobin are reduced. Anaemia is a common complication among people with CKD, and contributes to the burden of disease, causing breathlessness, dizziness, angina, decreased exercise capacity, cognitive and dysfunctions, poor appetite, reduced quality of life, longer hospital stays, and death. Given that numbers of people with CKD are increasing, the public health impact of CKD-associated anaemia is substantial. Anaemia prevalence increases as kidney function decreases. McClellan 2004 reported that anaemia was present in 47.7% of predialysis patients, and Hsu 2002 estimated that the overall burden of CKD-associated anaemia (haemoglobin (Hb) ≤ 11 g/dL) was 610,000 women and 230,000 men in the US population. In 2000, five European countries participating in the Dialysis Outcomes and Practice Patterns Study (DOPPS, Combe 2001) reported that 49% of haemodialysis patients had Hb concentrations below the level recommended by the European Best Practice Guidelines (Geddes 2006). Patients with Hb < 10 g/dL were 29% more likely to be hospitalised than those with Hb levels between 11 and 12 g/dL. The risk of hospitalisation was 4% lower for every 1 g/dL increase in Hb concentration, and mortality risk in these patients was 5% lower for each 1 g/dL increase (Locatelli 2004b).

Description of the intervention

Several approaches are commonly applied to correct anaemia in adults with CKD, including erythropoiesis-stimulating agents (ESAs), dialysis, blood transfusions, nutritional management, iron and folate supplements. ESAs augment erythropoiesis through direct or indirect actions on the erythropoietin receptor, and dialysis can improve anaemia by eliminating some toxins. In the past, iron and folate supplements were mainstay treatments. Although a direct and effective method of treating CKD-related anaemia, blood transfusion carries risk of infection and inducing histocompatibility leukocyte antigens, which may jeopardise future kidney transplant in eligible patients (Eschbach 1989; Ward 1990).

The human erythropoietin (EPO) gene was characterised in 1983 (Lin 1985), and recombinant human EPO (rHuEPO) treatment efficacy was first demonstrated in dialysis patients in 1986 (Winearls 1986). The advent of rHuEPO revolutionised management for people with CKD-associated anaemia and contributed to reducing risks associated with blood transfusion (Cody 2005), sensitisation, and preventing iron overload, and enhancing exercise tolerance, cognitive capacity, sexual function, and quality of life. However, three key issues have been associated with rHuEPO use:

1. Cost: Medicare spending on EPO reached US$1.8 billion in 2004, an increase of 17% from 2003 (USRDS 2006).
2. Risk of pure red cell aplasia (PRCA): a severe, non-regenerative form of anaemia, with selective erythroid aplasia of the bone marrow.
3. Predictable side effects: hypertension, clotting of arteriovenous fistulas, and seizures (Navarro 2003).

Furthermore, rHuEPO may increase cancer mortality risk by stimulating tumour growth (Brian 2005; Henke 2003).

How the intervention might work

Androgens are a class of male steroid hormones that play a major role in the development and maintenance of masculine secondary sexual characters, and which also affect nitrogen metabolism (BOE 2007; Omwancha 2006; Pielecka 2006). Androgens mechanism of action is thought to be due to an increase in EPO synthesis and secretion (Shahani 2009). A positive correlation has been shown between increased Hb and HCT in people treated with androgens (Navarro 2001a; Navarro 2001b; Navarro 2002; Yared 1997).

Adjuvant therapy is often required to help optimise therapeutic response among people with CKD-associated anaemia who are either unresponsive to erythropoiesis-stimulating agents (ESA) or require large doses of ESAs (Navarro 2001a). In some settings, androgens may be administered as adjuvant therapies for people with CKD-related anaemia. Androgens have been reported to increase erythropoiesis, raise plasma EPO concentration in dialysed patients with CKD-anaemia (Teruel 1996a), and elevate Hb concentration in people with CKD (Teruel 1996b). Androgens have also achieved satisfactory results for treating PRCA (Sanchez 2006). Economic cost benefits have been identified for androgen therapy in resource-limited settings (Locatelli 2004a).

Why it is important to do this review

Controversy exists about the use of androgens to treat anaemia in people with CKD. The KDOQI guidelines strongly recommend against androgens as adjuvant therapy to ESA treatment in people with CKD-related anaemia. The rationale is that androgens have been associated with adverse effects including acne, virilisation, priapism, hyperglycaemia, liver dysfunction, injection site pain, risk of peliosis hepatis, hepatocellular carcinoma, risk of prostate cancer, and cancer risk in women. Three small, short-term RCTs (Berns 1992; Gaughan 1997; Sheashaa 2005a) explored the possible role of adjuvant androgen therapy with ESA for people undergoing haemodialysis. Recommended Hb levels were not achieved; however, these studies did not enrol participants with ESA hyporesponsiveness (NKF 2006).

OBJECTIVES

The aim of this review was to determine the benefits and harms of androgens for the treatment of anaemia in adult patients with CKD.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) assessing the use of androgens for the treatment of CKD-related anaemia in adults were eligible for inclusion. There was no restriction on language or publication type. The first phases of cross-over RCTs were also eligible for inclusion.

Types of participants

Inclusion criteria

- Adults (aged 18 years or over) with CKD-related anaemia. All CKD stages were included (predialysis, dialysis, and transplant patients). Anaemia and CKD definitions applied by each study were accepted.
- CKD-related anaemia participants with controlled hypertension and cardiac disorders, left ventricular hypertrophy, hypogonadism, kidney-related bone disease, or neurological disorders were included.

Exclusion criteria

- Pregnancy
- Androgen therapy in the six months before study entry
- Anaemia related to causes other than kidney disease, such as folate or B deficiency, sickle cell disease, primary haemolytic anaemia, or multiple myeloma
- Haematological disorders known to cause anaemia
- Iron deficiency (ferritin < 100 ng/mL or transferrin saturation < 20% or both)
- Bleeding
- Known malignancy such as prostate cancer
- Presence of infection or inflammation
- Active ischaemic heart disease
- Uncontrolled hypertension (systolic blood pressure > 190 mm Hg, diastolic > 105 mm Hg)
- Abnormal liver function (positive albumin, bilirubin, alkaline phosphatase (ALP), gamma glutamic transpeptidase (gamma GT), aspartate aminotransferase (AST), alanine aminotransferase (ALT), or prothrombin findings)
- Active hepatitis
- HIV infection
- Study duration less than six months
- Studies in which only one arm received dialysis or transplantation.

Types of interventions

- Any androgen versus no drug or placebo alone
- Any androgen versus routine therapy (e.g. androgens versus EPO)
- Any androgen plus routine therapy versus routine therapy (androgens plus EPO versus EPO)
- Any androgen plus routine therapy versus placebo plus routine therapy (e.g. androgen plus EPO versus placebo plus EPO).

Types of outcome measures

- Mortality
- Measures of anaemia correction (e.g. haemoglobin (Hb) and haematocrit (HCT) values)
- Participant-based quality of life assessment using an internationally validated minimum standard checklist (Efficace 2003; Efficace 2006; Efficace 2007)
- Liver function (e.g. alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values)
- Kidney function (e.g. blood urea nitrogen (BUN) and serum creatinine (SCr) values)
- Lipid profile (e.g. cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) values)
- Total protein, albumin, prealbumin, and transferrin values
- Adverse events: acne, virilisation, priapism, hyperglycaemia, liver dysfunction, prostate cancer, prostate hypertrophy, peliosis hepatis, hepatocellular carcinoma, rash, amenorrhoea, menstrual disorders, enlarged clitoris, excess body hair, increased appetite, increased sexual desire, depression, mania, delirium, acute schizophrenia, cardiovascular adverse events, and other adverse effects including gastrointestinal bleeding, episodes of peritonitis and hydrothorax.

Primary outcomes

- Mortality
- Measures of anaemia correction, such as Hb and HCT values.

Secondary outcomes

- Quality of life assessment using an internationally validated minimum standard checklist (Efficace 2003; Efficace 2006; Efficace 2007)
- Liver function (ALT and AST values)
- Kidney functions (BUN and SCr values)
- Lipid profile (cholesterol, TG, HDL, and LDL values)
- Total protein, albumin, prealbumin, and transferrin values
- Adverse events: acne, virilisation, priapism, hyperglycaemia, liver dysfunction, prostate cancer, prostate hypertrophy, peliosis hepatis, hepatocellular carcinoma, rash, amenorrhoea, menstrual disorders, enlarged clitoris, excess body hair, increased appetite, increased sexual desire, depression, mania, delirium, acute schizophrenia, cardiovascular adverse events, and other adverse effects including gastrointestinal bleeding, episodes of peritonitis and hydrothorax.

Search methods for identification of studies

We searched electronic databases and where necessary corresponded with study authors to obtain additional information.

Electronic searches

We searched the Cochrane Renal Group's Specialised Register (to August 2014) through contact with the Trials' Search Co-ordinator using search terms relevant to this review. The Cochrane Renal Group's Specialised Register contains studies identified from the following sources.

1. Monthly searches of the Cochrane Central Register of Controlled Trials CENTRAL
2. Weekly searches of MEDLINE OVID SP
3. Handsearching of renal-related journals and the proceedings of major renal conferences
4. Searching of the current year of EMBASE OVID SP
5. Weekly current awareness alerts for selected renal journals
6. Searches of the International Clinical Trials Register (ICTRP) Search Portal and ClinicalTrials.gov.

Studies contained in the Specialised Register are identified through search strategies for CENTRAL, MEDLINE, and EMBASE based on the scope of the Cochrane Renal Group. Details of these strategies as well as a list of handsearched journals, conference proceedings and

current awareness alerts are available in the Specialised Register section of information about the Cochrane Renal Group.

We also searched the Chinese Biomedicine Database (CBM), VIP and China National Knowledge Infrastructure (CNKI) (to August 2012).

See Appendix 1 for search terms used in strategies for this review.

Searching other resources

We searched reference lists of identified study reports and the ISI Citation Index database, Science and Social Science Citation Index/ Web of Science Services.

We were unable to contact primary investigators of identified studies for details of additional studies and companies or pharmaceutical firms that produce immunosuppressants used for unpublished data they may possess.

Data collection and analysis

Selection of studies

The search strategy described was used to obtain titles and abstracts of studies that may be relevant to the review. Titles and abstracts were screened independently by two authors who discarded studies that were not applicable; however, studies and reviews that might include relevant data or information on studies were retained initially. Two authors independently assessed retrieved abstracts, and if necessary, the full text of these studies to determine which satisfied the inclusion criteria.

Data extraction and management

Data extraction was carried out independently by two authors using a pre-tested data extraction form. Where more than one publication of one study existed, reports were grouped together and only the publication with the most complete data was used. Where relevant outcomes were only published in earlier versions, these data were used. Any discrepancies between published versions were to be highlighted. Any further information required from the original author was requested by written correspondence. Disagreements were resolved by consensus and with a third author.

Assessment of risk of bias in included studies

The following items were independently assessed by two authors using the risk of bias assessment tool (Higgins 2011) (see Appendix 2).

- Was there adequate sequence generation (selection bias)?
- Was allocation adequately concealed (selection bias)?
- Was knowledge of the allocated interventions adequately prevented during the study (detection bias)?
  - Participants and personnel
  - Outcome assessors
- Were incomplete outcome data adequately addressed (attrition bias)?
- Are reports of the study free of suggestion of selective outcome reporting (reporting bias)?
- Was the study apparently free of other problems that could put it at a risk of bias?

Measures of treatment effect

We analysed data both dichotomous and continuous data in this review. Results for dichotomous data are expressed as relative risk (RR) with 95% confidence intervals (CI). We showed continuous data as mean differences (MD) with 95% CI.

Dealing with missing data

Where necessary, further information required from the original author was requested by written correspondence or telephone. Evaluation of important numerical data such as screened, randomised patients as well as intention-to-treat, as-treated and per-protocol population was carefully performed. Attrition rates, such as drop-outs, losses to follow-up and withdrawals, were investigated. Issues of missing data and imputation methods were critically appraised (Higgins 2011).

Assessment of heterogeneity

Heterogeneity was analysed using a Chi^2 test on N-1 degrees of freedom, with an alpha of 0.05 used for statistical significance and with the I^2 test (Higgins 2003). I^2 values of 25%, 50% and 75% correspond to low, medium and high levels of heterogeneity.

Assessment of reporting biases

We planned to assess for reporting bias by plotting data in a funnel plot.

Data synthesis

Data were pooled using the random-effects model under the assumption that the effects being estimated were not identical throughout, but followed certain distribution patterns. The fixed-effect model was also analysed to ensure robustness of the model chosen and susceptibility to outliers (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

We planned to conduct subgroup analyses based on androgen type, comparators and outcomes, however there were insufficient studies to do this.

Sensitivity analysis

We planned to perform sensitivity analyses to evaluate evidence stability, however there were insufficient studies to do this.

RESULTS

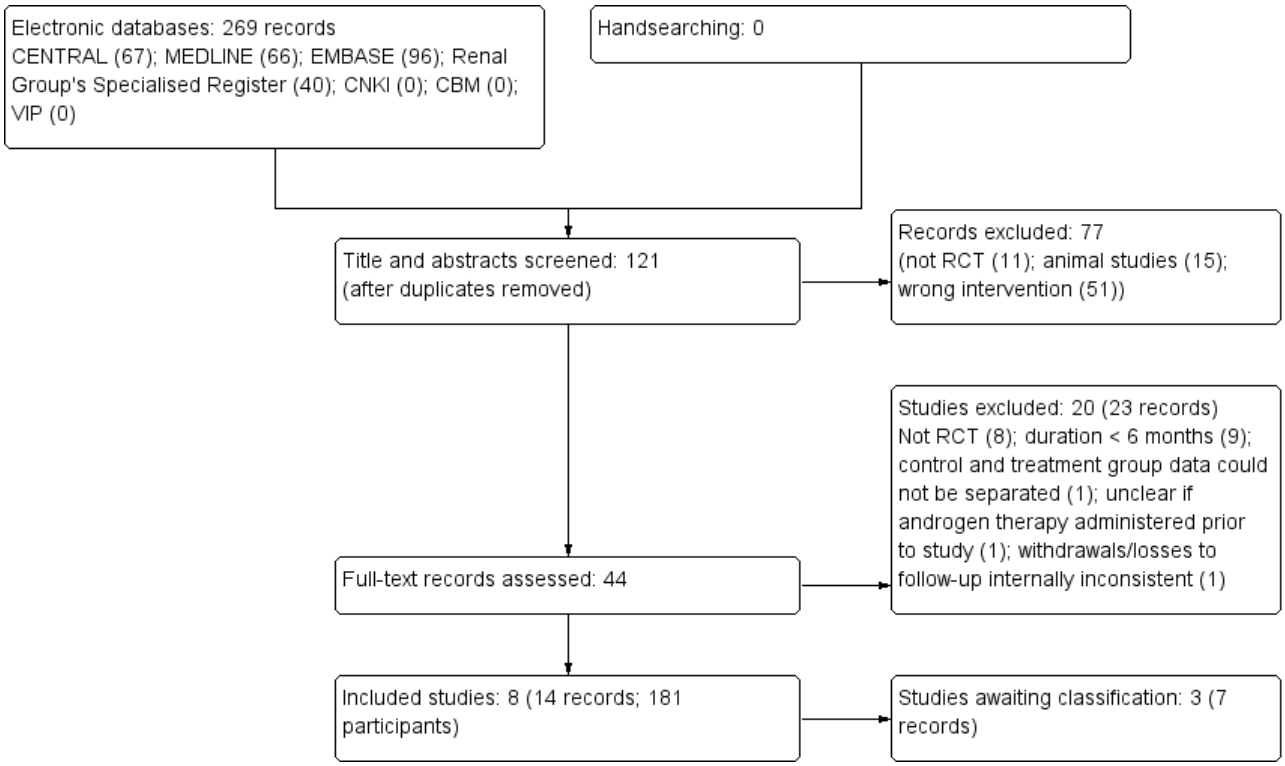
Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

The search strategy described identified 269 records. After removing 148 duplicates, 121 titles and abstracts were assessed, and 77 records were excluded. After further assessment, 20 studies (23 records) were excluded, and three studies (7 records) could not be obtained and are awaiting assessment (Ganguli 2003; Ota 1986; Suzuki 1986). We included eight studies (14 records) in our review (Aramwit 2010; Cattran 1977; Gaughan 1997; Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a; Solomon 1988b) (Figure 1).

Figure 1. Flow diagram showing study selection



Included studies

We included eight studies that enrolled 194 adults with CKD-associated anaemia, of whom 181 completed the studies. Study populations were small, ranging from 9 to 37 participants (average = 24.25 participants). Studies were conducted in Thailand, USA, Egypt, Canada, Spain, Korea and Greece.

We found a substantial bias favouring inclusion of males (M/F: 107/24) in the five studies that reported gender (Aramwit 2010; Cattran 1977; Gaughan 1997; Navarro 2002; Sheashaa 2005a). Participants' sex was not reported in three studies (Kim 1999a; Koronis 2000; Solomon 1988b).

Participants' ages ranged from 25 to 78 years. Mean participant age was not reported in three studies (Kim 1999a; Koronis 2000; Solomon 1988b)

All studies recruited participants with CKD-related anaemia (Aramwit 2010; Cattran 1977; Gaughan 1997; Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a; Solomon 1988b). Dialysis interventions included peritoneal dialysis for at least three months (Aramwit 2010); continuous peritoneal dialysis for at least six months (Navarro 2002); haemodialysis (Gaughan 1997; Kim 1999a; Koronis 2000; Sheashaa 2005a; Solomon 1988b); or chronic dialysis (Cattran 1977). Blood chemistry requirements varied, but included Hb concentration < 11 g/dL; serum ferritin concentrations of at least 100 ng/mL; serum transferrin saturations of at least 20%. Iron parameters also varied, as did Hb and HCT levels.

All studies were of six months duration. Intervention arm participants received androgens administered as subcutaneous (SC) or intramuscular (IM) injections (nandrolone decanoate), or oral tablets (oxymetholone). Study drug doses and frequencies were: 50 mg tablet twice daily (Aramwit 2010); nandrolone decanoate 200 mg IM once weekly (Cattran 1977; Navarro 2002); nandrolone decanoate 100 mg IM once weekly (Solomon 1988b); nandrolone decanoate 100 mg IM plus rHuEPO 1500 U intravenously (IV) once weekly (Gaughan 1997); nandrolone decanoate 100 mg IM plus rHuEPO 2000 U SC (Kim 1999a); nandrolone decanoate 100 mg IM plus rHuEPO 1000 U SC every 15 days (Koronis 2000); and nandrolone decanoate 50 mg IM plus rHuEPO 1000 U SC twice weekly (Sheashaa 2005a). Only Aramwit 2010 reported three month follow-up. Four studies investigated nandrolone decanoate plus rHuEPO versus rHuEPO alone as the control (Gaughan 1997; Kim 1999a; Koronis 2000; Sheashaa 2005a); one study investigated nandrolone decanoate versus rHuEPO alone as the control drug (Navarro 2002); two studies investigated no therapy as the control (Cattran 1977; Solomon 1988b); one study investigated oxymetholone plus rHuEPO versus placebo plus rHuEPO as the control drug (Aramwit 2010).

Four studies (Aramwit 2010; Navarro 2002; Sheashaa 2005a; Cattran 1977) reported Hb and HCT levels as indicators of anaemia correction; Kim 1999a and Koronis 2000 reported HCT levels only; Solomon 1988b reported Hb levels only.

Aramwit 2010 and Navarro 2002 reported kidney function (BUN and SCr values). Aramwit 2010 also reported liver function measures (AST and ALT values) and lipid profile indicators (TG, HDL, LDL values); and Gaughan 1997 reported TG only.

Four studies (Aramwit 2010; Gaughan 1997; Navarro 2002; Sheashaa 2005a) reported serum albumin. Aramwit 2010 and Navarro 2002 reported total protein; and Navarro 2002 reported prealbumin and transferrin levels.

Four studies reported adverse events, including: gastrointestinal bleeding (Aramwit 2010); hydrothorax (Navarro 2002); acne (Gaughan 1997); menstrual disorders and excess body hair (Sheashaa 2005a).

Four studies reported no drop-outs, withdrawals or losses to follow-up (Kim 1999a; Koronis 2000; Sheashaa 2005a; Solomon 1988b). Gaughan 1997 reported that one participant withdrew after developing an active mycobacterium tuberculosis infection; Aramwit 2010 and Navarro 2002 both reported two participants discontinued treatment. Cattran 1977 reported that eight participants did not complete the study (21.6%).

Excluded studies

We excluded 20 studies; of these eight were not RCTs (Buchwald 1977; Diez 1997; Gascon 1999; Lee 2002; Logan 2005; Mora 2001; Solomon 1987; von Hartitzsch 1976); nine were fewer than six months duration (Aggarwal 2005; Aslanhan 2001; Ballal 1991; Berns 1992; Eiam-Ong 2007; Hendler 1974; Mirahmadi 1979; Saxena 1997; Williams 1974); treatment and control group data were indistinct in Naik 1978; it was unclear if androgen therapy had been administered to participants during the six months preceding the study (Neff 1981); reported withdrawals/losses were internally inconsistent in Brockenbrough 2006; and Solomon 1988b investigated an intervention outside the scope of this review. See Characteristics of excluded studies.

Risk of bias in included studies

Aramwit 2010 was assessed as a high quality study; six were judged to be of moderate quality (Gaughan 1997; Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a; Solomon 1988b); and Cattran 1977 was low quality. Summaries of quality assessments are presented in Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

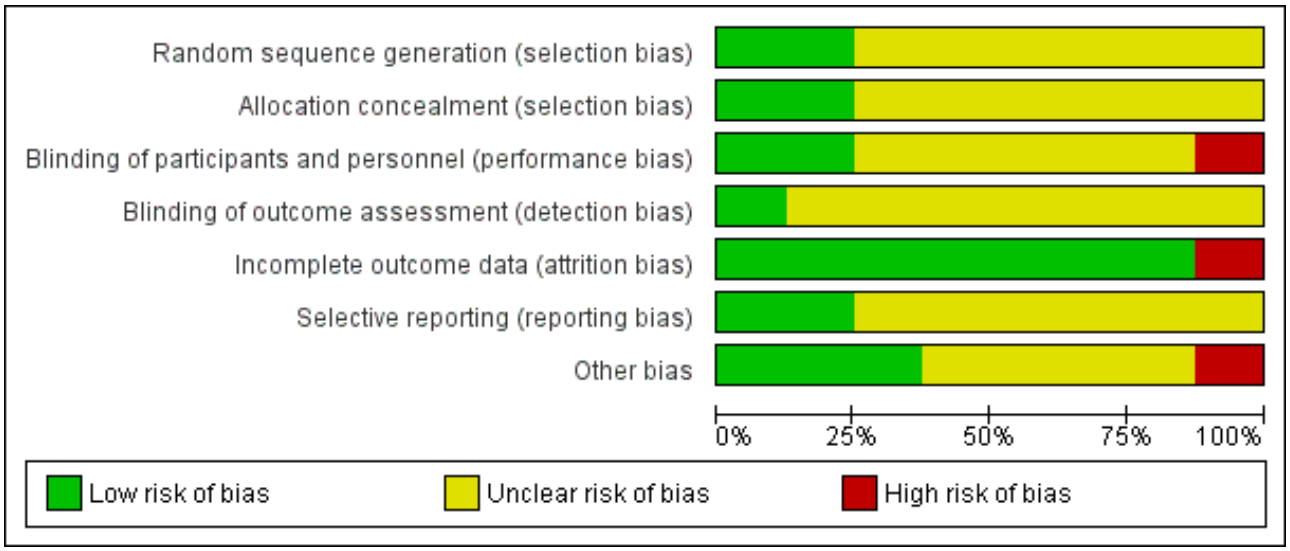
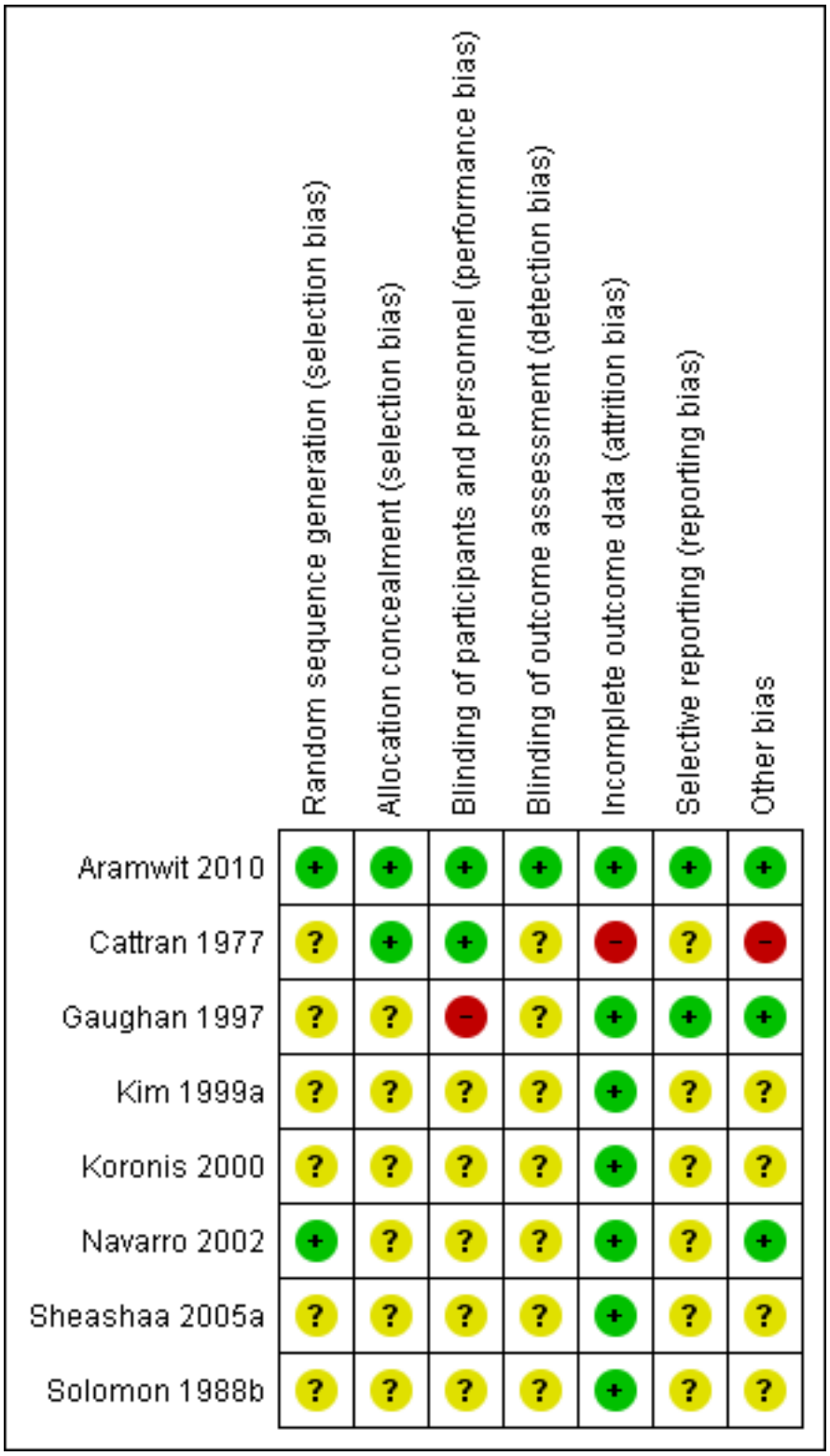


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Allocation

Although all studies reported that participants were randomised, six did not provide sequencing details (Cattran 1977; Gaughan 1997; Kim 1999a; Koronis 2000; Sheashaa 2005a; Solomon 1988b). Aramwit 2010 and Navarro 2002 used computer-generated random number tables, and although Aramwit 2010 did not report allocation concealment methods, it was likely that concealment was adequate; investigators were not actively involved in treatment, and physicians involved in participants' care were

unaware of study outcome parameters. Allocation concealment was not adequately reported by the remaining seven studies (Cattran 1977; Gaughan 1997; Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a Solomon 1988b).

Blinding

Aramwit 2010 and Cattran 1977 were double-blinded, placebo-controlled studies; Gaughan 1997 was an open-label study. Blinding was not reported in the remaining five studies (Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a; Solomon 1988b).

Incomplete outcome data

Outcome data were reported clearly in seven studies (Aramwit 2010; Gaughan 1997; Kim 1999a; Koronis 2000; Navarro 2002; Solomon 1988b; Sheashaa 2005a), among which drop-out rates and losses to follow-up were lower than 10%; and hence, risk of attrition bias was assessed as low. Cattran 1977 reported a drop-out and loss to follow-up rate of 21.6% (8/37 participants), and was assessed at high risk of attrition bias.

Selective reporting

Investigators involved in two studies were contacted to obtain study protocols (Aramwit 2010; Gaughan 1997). Although protocols were not provided, it was clear that the published reports included all expected outcomes, and were assessed at low risk of reporting bias.

Reporting was insufficient in six studies and was assessed as unclear risk of selective reporting (Cattran 1977; Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a; Solomon 1988b).

Other potential sources of bias

Participant demographic data were comparable and protocols were approved by relevant ethics committees in two studies (Aramwit 2010; Gaughan 1997). It was unclear if a protocol was completed for the study by Navarro 2002, and ethics approval was not reported. Cattran 1977 secured participants' informed consent but neither demographic data nor ethics approval were reported, and was determined to be at high risk of bias.

Participant demographic data were similar between arms in three studies (Kim 1999a; Koronis 2000; Sheashaa 2005a), but informed consent, protocols and ethics approval were not reported. Signed informed consent and demographic data were not reported in Solomon 1988b.

Effects of interventions

See: **Summary of findings for the main comparison**

We analysed reported data on androgens plus routine therapy versus routine therapy alone, androgens plus routine therapy versus placebo plus routine therapy, androgens versus routine therapy, and androgens versus no drug. Androgens assessed were nandrolone decanoate and oxymetholone.

Baseline participant characteristics were clearly reported in six studies (Aramwit 2010; Gaughan 1997; Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a).

None of the included studies reported on death or quality of life.

Nandrolone decanoate plus rHuEPO versus rHuEPO alone

Four studies investigated nandrolone decanoate plus rHuEPO versus rHuEPO alone (Gaughan 1997; Kim 1999a; Koronis 2000; Sheashaa 2005a).

Haemoglobin and haematocrit

Sheashaa 2005a reported no significant difference in Hb (Analysis 1.1 (1 study, 32 participants): MD 0.44 g/dL, 95% CI -0.17 to 1.05).

Compared to rHuEPO alone nandrolone decanoate plus rHuEPO significantly increased HCT (Analysis 1.2 (3 studies, 73 participants): MD 2.54%, 95% CI 0.96 to 4.12); I^2 = 17%)

Albumin and triglycerides

There was no significant difference in serum albumin at the end of treatment (Analysis 1.3 (2 studies, 51 participants): MD -0.09 g/dL, 95% CI -0.24 to 0.06; I^2 = 0%).

Gaughan 1997 reported no significant difference in serum triglycerides at the end of treatment (Analysis 1.4 (1 study, 19 participants): MD 34.00 mg/dL, 95% CI -74.70 to 42.70).

Adverse events

Gaughan 1997 reported no differences in acne between the groups (Analysis 1.5.1 (1 study, 19 participants): RR 3.30, 95% CI 0.15 to 72.08). Sheashaa 2005a reported no differences in menstrual disorders (Analysis 1.5.2 (1 study, 32 participants): RR 11.0, 95% CI 0.66 to 183.79) or excess body hair (Analysis 1.5.3 (1 study, 32 participants): RR 11.0, 95% CI 0.66 to 183.79) between the groups.

Oxymetholone plus alpha rHuEPO versus placebo plus alpha rHuEPO

Aramwit 2010 investigated oxymetholone plus alpha rHuEPO versus placebo plus alpha rHuEPO.

Haemoglobin and haematocrit

Aramwit 2010 reported oxymetholone plus rHuEPO significantly increased Hb when compared to rHuEPO alone (Analysis 2.1 (1 study, 24 participants): MD 1.90 g/dL, 95% CI 1.66 to 2.14) and HCT (Analysis 2.2 (1 study, 24 participants): MD 27.10%, 95% CI 26.49 to 27.71).

Liver and kidney function

Aramwit 2010 reported oxymetholone plus rHuEPO significantly decreased ALT (Analysis 2.3.1 (1 study, 24 participants): MD 54.50 U/L, 95% CI 43.94 to 65.06 and AST levels (Analysis 2.3.2 (1 study, 24 participants): MD 47.33 U/L, 95% CI 37.69 to 56.97). No improvement in kidney function was apparent with either intervention measured in terms of BUN (Analysis 2.4.1 (1 study, 24 participants): MD -0.94 mmol/L, 95% CI -4.02 to 2.14) or SCr (Analysis 2.4.2 (1 study, 24 participants): MD 261.60 µmol/L, 95% CI -37.76 to 560.96).

Lipid profile and albumin

Aramwit 2010 reported no significant differences in total cholesterol (Analysis 2.5.1 (1 study, 24 participants): MD -26.16 mg/dL, 95% CI -63.86 to 11.54), TG (Analysis 2.5.2 (1 study, 24 participants): MD -47.80 mg/dL, 95% CI -117.41 to 21.81) or LDL (Analysis 2.5.4 (1 study, 24 participants): MD -1.11 mg/dL, 95% CI

-31.80 to 29.58), but a significant decrease was reported for HDL (Analysis 2.5.3 (1 study, 24 participants): MD -15.66 mg/dL, 95% CI -24.84 to -6.48)

A significant increase in change in serum albumin was reported for oxymetholone plus rHuEPO (Analysis 2.6 (1 study, 24 participants): MD 4.91 g/L, 95% CI 3.69 to 6.13)

Adverse events

Aramwit 2010 reported no significant differences in adverse effects (Analysis 2.7 (1 study, 24 participants): RR 1.18, 95% CI 0.08 to 16.78).

Nandrolone decanoate versus rHuEPO

Navarro 2002 investigated nandrolone decanoate versus rHuEPO.

Haemoglobin and haematocrit

Navarro 2002 reported no significant change in Hb (Analysis 3.1 (1 study, 27 participants): MD 0.10 g/dL, 95% CI -0.28 to 0.48) or HCT (Analysis 3.2 (1 study, 27 participants): MD 0.40%, 95% CI -0.77 to 1.57).

Total protein, pre-albumin, transferrin and albumin

Navarro 2002 reported nandrolone decanoate significantly increased total protein (Analysis 3.3 (1 study, 27 participants): MD 0.40 g/L, 95% CI 0.13 to 0.67), transferrin (Analysis 3.5 (1 study, 27 participants): MD 45.00 mg/dL, 95% CI 12.61 to 77.39) and albumin (Analysis 3.6 (1 study, 27 participants): MD 0.20/L, 95% CI 0.01 to 0.39); but not prealbumin (Analysis 3.4 (1 study, 27 participants): MD 1.00 mg/dL, 95% CI -3.53 to 5.53).

Kidney function

Navarro 2002 reported nandrolone decanoate did not significantly decrease BUN (Analysis 3.7.1 (1 study, 27 participants): MD -9.00 mg/dL, 95% CI -18.13 to 0.13) or SCr (Analysis 3.7.2 (1 study, 27 participants): MD 0.80 mg/dL, 95% CI -0.88 to 2.48).

Adverse events

Navarro 2002 reported that one participant in the nandrolone decanoate group developed peritonitis, and one participant in the rHuEPO group experienced exacerbation of CKD-related anaemia. There was no statistical difference in adverse effects between groups (Analysis 3.8 (1 study, 27 participants): RR 1.08, 95% CI 0.07 to 15.50).

Nandrolone decanoate versus no therapy

Cattran 1977 and Solomon 1988b investigated nandrolone decanoate versus no drug. Cattran 1977 investigated the effects of nandrolone decanoate versus no drug therapy among remnant kidney patients (15/9 intervention/control) and anephric participants (3/2 intervention/control).

Haemoglobin and haematocrit

Nandrolone decanoate significantly increased Hb (Analysis 4.1 (2 studies, 33 participants): MD 1.04 g/dL, 95% CI 0.66 to 1.41; I^2 = 0%). Cattran 1977 reported nandrolone decanoate significantly increased HCT (Analysis 4.2 (1 study, 24 participants): MD 3.70%, 95% CI 0.68 to 6.72). Cattran 1977 also reported the effects in anephric participants and reported a statistically significant increase in Hb with nandrolone decanoate (Analysis 5.1 (1 study, 5 participants): MD 1.30 g/dL, 95% CI 0.57 to 2.03), but no significant difference in HCT (Analysis 5.2 (1 study, 5 participants): MD 2.00%, 95% CI -0.85 to 4.85).

Mortality, quality of life and adverse events were not reported.

DISCUSSION

Summary of main results

We found limited evidence to suggest that androgens may confer positive effects to increase Hb, HCT and serum albumin.

Studies by Kim 1999a, Koronis 2000 and Sheashaa 2005a comparing nandrolone decanoate plus rHuEPO with rHuEPO alone reported increased HCT levels. Sheashaa 2005a reported no significant increase in Hb. There was insufficient evidence to discern if nandrolone decanoate plus rHuEPO increased serum albumin and decreased rates of adverse events.

Findings reported by Aramwit 2010 in a comparison of oxymetholone plus rHuEPO with placebo plus rHuEPO indicated significant increases in Hb, HCT, serum albumin, AST and ALT; and a significant decrease in HDL. There was insufficient evidence to discern if oxymetholone plus rHuEPO decreased BUN, SCr, cholesterol, TG, LDL and adverse events.

In a comparative analysis of nandrolone decanoate with rHuEPO, Navarro 2002 reported a statistically significant increase in total protein, transferrin, and serum albumin. BUN was decreased but not significantly. There was insufficient evidence to assess if nandrolone decanoate had an effect in increasing Hb, HCT, prealbumin, and decreasing SCr and adverse events.

Cattran 1977 and Solomon 1988b, comparing nandrolone decanoate with no therapy, reported increased Hb levels. In a subgroup analysis of participants with remnant kidney status. Cattran 1977 reported that compared with no therapy, nandrolone decanoate significantly increased HCT levels. In a further subgroup analysis in anephric participants, a significant increase in Hb was reported, but there was no change in HCT. Evidence was insufficient to demonstrate if nandrolone decanoate increased HCT in anephric patients.

There was limited evidence to indicate that oxymetholone may increase Hb, HCT, plasma albumin, AST, and ALT; and decrease HDL, cholesterol, triglyceride, and LDL. Evidence was insufficient to determine if oxymetholone had an effect in decreasing BUN, SCr, and LDL or in increasing plasma total protein, prealbumin, and transferrin. There was no evidence to demonstrate that androgens decreased BUN or SCr.

Nandrolone decanoate may have an effect in increasing Hb, HCT, plasma total protein, plasma albumin, and transferrin, but there was is insufficient evidence to demonstrate increases prealbumin or decrease in BUN, SCr, AST, ALT, cholesterol, triglyceride, HDL, or to decrease LDL. Reporting was suboptimal, and it remains unclear whether oxymetholone and nandrolone decanoate conferred significant adverse effects among adults with CKD-related anaemia.

We were unable to determine if:

1. dose-effect relationships exist in relation to androgens and CKD-related anaemia in adults;
2. time-effect relationships exist in relation to androgens and CKD-related anaemia in adults;
3. androgens-erythropoietin relationships exist in relation to androgens and CKD-related anaemia in adults.

Overall completeness and applicability of evidence

Based on the eight small included studies, scant evidence was identified in relation to the efficacy or safety of androgens for adults with CKD-related anaemia. Evidence was flawed by sparseness, methodological and reporting quality in most studies. More adequately powered and robust study designs would help to clearly determine the role of androgens for adults with CKD-related anaemia compared with other therapies. There was a marked absence of reporting of mortality and quality of life, and although there was some reporting of adverse effects, the small study cohorts may have meant that studies were underpowered to capture rates accurately. Our findings of adverse events reporting did not equate with those cited in the KDOQI guidelines (NKF 2006).

Quality of the evidence

Evidence quality and reporting were suboptimal (Summary of findings for the main comparison). Results were not robust, studies inadequately powered, and methodological processes were absent or flawed in many instances. Randomisation was claimed, but methods not reported in six included studies (Cattran 1977; Gaughan 1997; Kim 1999a; Koronis 2000; Sheashaa 2005a; Solomon 1988b). Similarly, allocation concealment was mentioned, but detailed description was not included in those six studies.

Blinding procedures were unclear in five studies (Kim 1999a; Koronis 2000; Navarro 2002; Sheashaa 2005a; Solomon 1988b) and reported as open-label in Gaughan 1997.

Consequently, there was a high risk of selection, performance and detection biases. Our efforts to clarify and expand on reported data by contacting study authors did not obtain significant or sufficient additional data to enhance our assessments.

Potential biases in the review process

We assessed that six of the eight included studies were of suboptimal methodological quality, although it is possible that these deficits may relate wholly or partly to lack of adequate reporting. Nevertheless, there was significant likelihood of presence of selection, performance, and detection biases in the evidence.

Agreements and disagreements with other studies or reviews

Adamu 2012 conducted a review that compared androgen therapy and EPO use for the treatment of people with CKD-related anaemia while focusing on implications for developing countries. Similar methodological approaches were applied in both reviews, and both looked at nandrolone decanoate versus rHuEPO and measures of anaemia correction such as haemoglobin, total protein and liver function.

There were differences in study inclusion criteria: we excluded reviews fewer than six months duration, which were eligible for inclusion by Adamu 2012; we included eight studies (181 participants) and Adamu 2012 included four studies (114 participants). Only one study was common to both reviews (Navarro 2002). Interventions investigated also differed: we investigated androgens versus EPO; androgens versus no drug or placebo alone; androgens plus EPO versus EPO; androgens plus EPO versus placebo plus EPO. Adamu 2012 considered nandrolone versus EPO and nandrolone plus EPO versus EPO. There were also differences in outcome measures. We sought kidney function measures (BUN and SCr values), lipid profiles (TG, HDL, LDL values), albumin, prealbumin, and transferrin values; while Adamu 2012 sought only blood pressure as an outcome measure.

Although there were some similarities in reported results, there were also differences. Our finding based on limited evidence suggesting that nandrolone decanoate may increase Hb and HCT was not reported by Adamu 2012, who found that total protein and blood pressure were increased. However, both reviews found that there was significant change in total protein increase associated with nandrolone decanoate versus rHuEPO; there was no change in liver function.

AUTHORS' CONCLUSIONS

Implications for practice

Oxymetholone may help to correct anaemia and increase albumin among adults with CKD-related anaemia by increasing ALT and AST, and decreasing HDL levels. However, evidence quality was poor, and we were unable to confirm if oxymetholone could reduce BUN, SCr, cholesterol, or TG. Furthermore, it could not be established if oxymetholone increased plasma total protein, prealbumin, or transferrin. Limited evidence suggested that nandrolone decanoate may increase HCT, plasma total protein, plasma albumin, and transferrin.

There was no compelling evidence to indicate if nandrolone decanoate increased Hb or prealbumin, or decreased BUN, SCr, AST, ALT, cholesterol, TG, HDL, adverse events, or LDL.

Suboptimal study quality meant that evidence to support the use of androgens in adults with anaemia of CKD was not identified.

Implications for research

Large, multicentre RCTs investigating androgens for anaemia of CKD in adults are required. Future investigators should ensure that people at all CKD stages are recruited, and assessment of a comprehensive range of targeted androgen therapies is undertaken. Triallists should plan measure changes in symptom relief, quality of life, and rate of CKD progression to end-stage kidney disease.

Reporting of mortality, quality of life and adverse events outcomes is required. Future studies should explore if occurrence of relative EPO insufficiency is a possible rationale for using androgens for adults with CKD-related anaemia, and whether prolonged or short courses of androgen therapy is of greater benefit. The most suitable dosages of androgens should also be explored for adults living with CKD-related anaemia.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aramwit 2010

Methods	• Study design: placebo-controlled RCT • Study duration: NS • Duration of follow-up: 6 months
Participants	• Country: Thailand • Setting: single centre • Diagnosis not clearly stated; participants had adequate PD ≥ 3 months; clinical examination included residual kidney function (24 h urine) and HCT levels; HCT levels ranged from 30% to 36%; serum ferritin concentrations ≥ 100 ng/mL and serum transferrin saturations ≥ 20%; 69 patients were screened and 26 CAPD patients met inclusion criteria; 43 patients were excluded from the study • Number (randomised/analysed): treatment group (12/11) control group (14/13) • Mean age ± SD (years): treatment group (55.08 ± 9.97); control group (54.14 ± 10.88) • Sex (M/F): treatment group (10/1); control group (10/3) • Exclusion criteria: all other caused of anaemia; active ischaemic heart disease, hepatic problems, or infections during study; received carnitine or > 1000 mg/d vitamin C; patients left the study if they could not comply with the treatment, were not willing to continue, or if the physician opined that the treatment was no longer necessary
Interventions	Treatment group • Oral oxymetholone: 50 mg tablet taken twice/d • rHuEPO: dose not specified • Duration: 6 months Control group • Placebo: taken twice/d • rHuEPO: dose not specified • Duration: 6 months
Outcomes	• Measures of anaemia correction: Hb, HCT • Liver function: ALT, AST • Kidney function: BUN, SCr • Lipid profile: cholesterol, TG, HDL, LDL • Total protein, albumin

Aramwit 2010 *(Continued)*

	• Other tests: glucose • Adverse effects: gastrointestinal bleeding, hydrothorax
Notes	• Prealbumin and transferrin not reported • Gender of participants who dropped out was not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation using computer-generated random sampling table
Allocation concealment (selection bias)	Low risk	Not reported; however, allocation concealment was performed, because the investigators were not actively involved in the treatment of the participants and the physicians who took care of the participants were not informed of the outcome parameters
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Neither physicians nor participants had knowledge of drug allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not reported detail in the article. An e-mail was sent to the author, who told us that the outcomes were assessed in a blinded manner
Incomplete outcome data (attrition bias) All outcomes	Low risk	After enrolment 2 participants withdrew: one oxymetholone group participant withdrew because of gastrointestinal bleeding; a blood transfusion was administered in the fourth month of the study. One EPO group participant withdrew during the fifth month of the study due to hydrothorax
Selective reporting (reporting bias)	Low risk	Investigators reported that although the study protocol was available, we were unable to obtain a copy. However, it was clear that the published reports included all expected outcomes
Other bias	Low risk	Signed informed consent obtained from all participants. The study was approved by the Ethics Committee of the Institute Review Board at Phramongkutklao Hospital, Thailand. Overall, participant demographic data were similar in both arms

Cattran 1977

Methods	• Study design: cross-over RCT • Study duration: NS • Study follow-up: 6 months
Participants	• Country: Canada • Setting: single centre • Male patients; chronic HD for at least 6 months • Number randomised/completed (remnant kidney/anephric): 37/29; treatment group (15/3); control group (9/2) • Age range: 25 to 66 years • Sex (M/F): 37/0

Cattran 1977 *(Continued)*

	• Exclusion criteria: NS
Interventions	Treatment group • Nandrolone decanoate: 200 mg IM weekly • Duration: 6 months Control group • No therapy Co-interventions • Aluminium hydroxide for phosphate control • Daily oral supplement containing 150 mg of elemental iron • 2.5 mg of folic acid
Outcomes	• Hb • HCT
Notes	ALT, AST, BUN, SCr, cholesterol, TG, HDL, LDL, mortality, BUN, SCr, total protein, albumin, pre-albumin, and transferrin were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Mentioned randomisation, but not detailed
Allocation concealment (selection bias)	Low risk	Allocation concealment mentioned
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	High risk	8 participants withdrew after enrolment
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting to enable assessment
Other bias	High risk	Signed informed consent obtained from all subjects. Participant demographic data not reported. No indication that ethics approval was sought or granted

Gaughan 1997

Methods	• Study design: open-label RCT • Study duration: September 1993 to February 1995

Gaughan 1997 *(Continued)*

	• Study follow-up: 6 months
Participants	• Country: USA • Setting: single centre • HD patients • Number (randomised/analysed): treatment group (10/9); control group (10/10) • Mean age ± SD (years): treatment group (53.7 ± 16.7); control group (45.3 ± 15.4) • Sex (M/F): treatment group (7/2); control group (4/6) • Exclusion criteria: deficiency, sickle cell disease, primary haemolytic anaemia, or multiple myeloma; previous nephrectomy; active gastrointestinal bleeding; active ischaemic heart disease,; abnormal liver function; uncontrolled hypertension; iron deficiency (ferritin < 100 ng/mL or transferrin saturation < 15% or both; infection with the human immunodeficiency virus; known malignancy; presence of inflammation or infection; doubtful compliance as a result of alcohol abuse, drug abuse, or poor motivation
Interventions	Treatment group • Nandrolone decanoate: 100 mg IM weekly • Alpha rHuEPO: 1500 U IV at the end of each HD session • Duration: 26 weeks Control group • Alpha rHuEPO: 1500 U IV at the end of each HD session • Duration: 26 weeks
Outcomes	• TG • Albumin • Transferrin • Adverse events: acne
Notes	• Mortality, Hb, HCT, ALT, AST, BUN, SCr, cholesterol, HDL, LDL and total protein not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation claimed, but detail not provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	One ND arm participant withdrew: active injection with mycobacterium tuberculosis. It was not reported that skin tuberculin tests were undertaken for study participants

Gaughan 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	Investigators reported that although the study protocol was available, we were unable to obtain a copy. However, it was clear that the published reports included all expected outcomes
Other bias	Low risk	Signed informed consent was obtained from all participants. Study protocol approved by the Institutional Review Board at Thomas Jefferson University Hospital. Overall, participant demographic data were similar between groups

Kim 1999a

Methods	• Study design: parallel RCT • Study duration: NS • Study follow-up: NS
Participants	• Country: Korea • Setting: single centre • HD patients; HCT < 24% • Number: treatment group (12); control group (12) • Age: NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group • Nandrolone decanoate: 100 mg IM, twice monthly • Alpha rHuEPO: 2000 IU SC, twice weekly • Duration: 6 months Control group • Alpha rHuEPO: 2000 IU SC, twice weekly • Duration: 6 months
Outcomes	• HCT
Notes	• Mortality, Hb, ALT, AST, BUN, SCr, cholesterol, HDL, LDL, albumin, transferrin, total protein, and adverse events were not reported • Abstract report only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported, but not described
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported

Kim 1999a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Investigators did not respond to a request for the protocol; Insufficient reporting to enable assessment
Other bias	Unclear risk	Signed informed consent not reported. Ethics Committee approval not reported. Demographic data similar between groups

Koronis 2000

Methods	• Study design: RCT • Study duration: NS • Duration of follow-up: 6 months
Participants	• Country: Greece • Setting: • Male anaemic HD patients • Number: treatment group (9); control group (8) • Age: NS • Sex (M/F): 17/0 • Exclusion criteria: NS
Interventions	Treatment group • Nandrolone decanoate: 200 mg IM every 15 days • Alpha rHuEPO 1000 IU SC, 3 times weekly • Duration: 6 months Control group • Alpha rHuEPO 1000 IU SC x three times weekly • Duration: 6 months
Outcomes	• HCT
Notes	• Mortality, Hb, ALT, AST, BUN, SCr, cholesterol, HDL, LDL, albumin, transferrin, total protein, and adverse events not reported • Abstract report only

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported, but not detailed
Allocation concealment (selection bias)	Unclear risk	Not reported

Koronis 2000 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data reported
Selective reporting (reporting bias)	Unclear risk	Investigators did not respond to a request for the protocol; Insufficient reporting to enable assessment
Other bias	Unclear risk	Signed informed consent not reported. Demographic data not reported. Ethics Committee approval not reported

Navarro 2002

Methods	• Study design: parallel RCT • Study duration: performed over 2 years • Duration of follow-up: 6 months
Participants	• Country: Spain • Setting: single centre • Male CAPD patients; Hb < 11 g/dL, serum ferritin ≥ 100 ng/mL, serum transferrin saturations ≥ 20% • Number (randomised/analysed): treatment group (14/13); control group (15/14) • Mean age ± SD (years): treatment group (62 ± 7); control group (60 ± 8) • Mean time on dialysis ± SD (months): treatment group (17 ± 7); control group (15 ± 6) • Sex (M/F): 29/0 • Exclusion criteria: previously treated with nandrolone, rHuEPO, theophylline derivatives or steroids; received blood transfusions; anephric; illness requiring hospitalisation of single episode of peritonitis in previous 3 months; malignancy; active infection; immunological disease
Interventions	Treatment group • Nandrolone decanoate: 200 mg IM, once weekly • Duration: 6 months Control group • rHuEPO: initial dose 50 U/kg/wk SC for 6 months ◦ According to anaemia response, dose modified to reach and maintain concentration 11 to 13 g/dL
Outcomes	• Measures of anaemia correction: Hb, HCT • Kidney function: BUN, SCr • Total protein, serum albumin, prealbumin, transferrin • One episode of peritonitis
Notes	• Lipid profile decreases were reported in article; however, detailed data were not provided • Liver function was stated to be stable in the article; however, detailed data were not provided

Navarro 2002 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised using a computer-generated random sampling table
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated clearly
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated clearly
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants withdrew (1 each from ND and EPO groups): who respectively developed peritonitis and kidney transplant
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting to enable assessment
Other bias	Low risk	All participants signed informed consent. Overall, participant demographic data between arms were similar

Sheashaa 2005a

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 months
Participants	• Country: Egypt • Setting: single centre • Anaemic HD patients (Hb < 9.5 g/dL); adequate HD (Kt/V > 1.2/session); sufficient nutrition; received parenteral iron • Number: treatment group (16); control group (16) • Mean age ± SD (years): treatment group (44.1 ± 12.5); control group (38.2 ± 14.9) • Sex (M/F): treatment group (8/8); control group (12/4) • Exclusion criteria: received EPO or androgen therapy in the preceding 6 months.
Interventions	Treatment group • Nandrolone decanoate: 50 mg IM x twice weekly • Alpha rHuEPO: 1000 U SC, three times weekly • Duration: 6 months Control group • Alpha rHuEPO: 1000 U SC, 3 times weekly • Duration: 6 months

Sheashaa 2005a *(Continued)*

Outcomes	• Measures of anaemia correction: Hb, HCT • Serum albumin • Adverse effects: menstrual disorders, excess body hair
Notes	• Mortality, ALT, AST, BUN, SCr, cholesterol, HDL, LDL, transferrin, total protein, and pre-albumin not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All participants accounted for in analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting to enable assessment
Other bias	Unclear risk	Signed informed consent not reported. Ethics Committee approval not reported. Participant demographic data similar between groups

Solomon 1988b

Methods	• Study design: parallel RCT • Study duration: NS • Duration of follow-up: 6 months
Participants	• Country: USA • Setting: single centre • HD patients • Number: treatment group (5); control group (4) • Age: NS • Sex (M/F): NS • Exclusion criteria: NS
Interventions	Treatment group • Nandrolone decanoate: 100 mg IM, once weekly • Duration: 6 months

Solomon 1988b *(Continued)*

	Control group • No therapy
Outcomes	• Hb
Notes	• Mortality, HCT, ALT, AST, BUN, SCr, cholesterol, HDL, LDL, albumin, transferrin, total protein, and adverse events not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomisation reported, but not detailed
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not clearly stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not clearly stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data reported
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting to enable assessment
Other bias	Unclear risk	Signed informed consent not reported. Demographic data not reported. The study was approved by the Human Studies Subcommittee of the Veterans' Administration Medical Center of West Haven

ALT - alanine aminotransferase; AST - aspartate aminotransferase; BUN - blood urea nitrogen; CAPD - continuous ambulatory peritoneal dialysis; Hb - haemoglobin; HCT - haematocrit; HD - haemodialysis; HDL - high-density lipoprotein; EPO - erythropoietin; IM - intramuscular; LDL low-density lipoprotein; ND - nandrolone decanoate; rHuEPO - recombinant human erythropoietin; SC - subcutaneously; SCr - serum creatinine; TG - triglyceride

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aggarwal 2005	Study duration less than six months
Aslanhan 2001	Study duration less than six months
Ballal 1991	Study duration less than six months
Berns 1992	Study duration less than six months

Study	Reason for exclusion
Brockenbrough 2006	RCT. Reported withdrawals/losses in the text were not consistent with table 1 and table 2 data
Buchwald 1977	Not RCT
Diez 1997	Not RCT; wrong intervention
Eiam-Ong 2007	Study duration less than six months
Gascon 1999	Not RCT
Hendler 1974	Study duration less than six months
Lee 2002	Not RCT
Logan 2005	Not RCT
Mirahmadi 1979	Study duration less than six months; wrong intervention
Mora 2001	Not RCT
Naik 1978	Could not separate treatment group and control group data in the report
Neff 1981	Unclear if participants received androgen treatment in the six months before entry into the study
Saxena 1997	Study duration less than six months
Solomon 1987	Not RCT
von Hartitzsch 1976	Not RCT
Williams 1974	Study duration less than six months

RCT - randomised controlled trial

Characteristics of studies awaiting assessment *[ordered by study ID]*

Ganguli 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	Insufficient information to determine relevance to this review

Ota 1986

Methods	

Ota 1986 *(Continued)*

Participants	
Interventions	
Outcomes	
Notes	Insufficient information to determine relevance to this review

Suzuki 1986

Methods	
Participants	
Interventions	
Outcomes	
Notes	Unable to obtain a copy of this paper

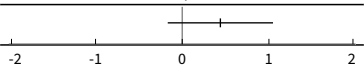
DATA AND ANALYSES

Comparison 1. Nandrolone decanoate + rHuEPO versus rHuEPO

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Haematocrit	3	73	Mean Difference (IV, Random, 95% CI)	2.54 [0.96, 4.12]
3 Serum albumin	2	51	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.24, 0.06]
4 Triglycerides	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Adverse events	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 Acne	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Menstrual disorders	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Hirsutism	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

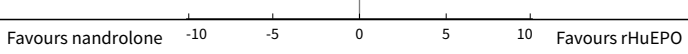
Analysis 1.1. Comparison 1 Nandrolone decanoate + rHuEPO versus rHuEPO, Outcome 1 Haemoglobin.

Study or subgroup	Nandrolone decanoate N	Nandrolone decanoate Mean(SD)	rHuEPO N	rHuEPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sheashaa 2005a	16	10.4 (0.6)	16	10 (1.1)		0.44[-0.17,1.05]



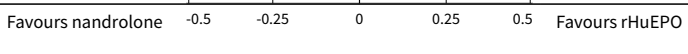
Analysis 1.2. Comparison 1 Nandrolone decanoate + rHuEPO versus rHuEPO, Outcome 2 Haematocrit.

Study or subgroup	Nandrolone decanoate N	Nandrolone decanoate Mean(SD)	rHuEPO N	rHuEPO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Kim 1999a	12	29.8 (3.1)	12	26.2 (4)		25.86%	3.6[0.74,6.46]
Koronis 2000	9	35.9 (5)	8	31.9 (1.8)		18.24%	4.04[0.54,7.54]
Sheashaa 2005a	16	32.8 (2.3)	16	31.2 (2.7)		55.9%	1.56[-0.18,3.3]
Total ***	**37**		**36**			**100%**	**2.54[0.96,4.12]**
Heterogeneity: Tau^2=0.38; Chi^2=2.42, df=2(P=0.3); I^2=17.31%							
Test for overall effect: Z=3.15(P=0)							



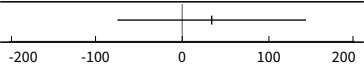
Analysis 1.3. Comparison 1 Nandrolone decanoate + rHuEPO versus rHuEPO, Outcome 3 Serum albumin.

Study or subgroup	Nandrolone decanoate N	Nandrolone decanoate Mean(SD)	rHuEPO N	rHuEPO Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Gaughan 1997	9	4 (0.4)	10	4.1 (0.2)		31.6%	-0.1[-0.37,0.17]
Sheashaa 2005a	16	3.4 (0.3)	16	3.5 (0.2)		68.4%	-0.09[-0.27,0.09]
Total ***	**25**		**26**			**100%**	**-0.09[-0.24,0.06]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.95); I^2=0%							
Test for overall effect: Z=1.22(P=0.22)							



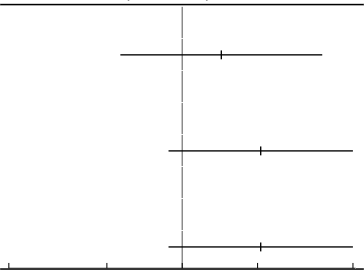
Analysis 1.4. Comparison 1 Nandrolone decanoate + rHuEPO versus rHuEPO, Outcome 4 Triglycerides.

Study or subgroup	Nandrolone decanoate N	Nandrolone decanoate Mean(SD)	rHuEPO N	rHuEPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Gaughan 1997	9	198 (145)	10	164 (86)		34[-74.7,142.7]



Analysis 1.5. Comparison 1 Nandrolone decanoate + rHuEPO versus rHuEPO, Outcome 5 Adverse events.

Study or subgroup	Nandrolone decanoate n/N	rHuEPO n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.5.1 Acne				
Gaughan 1997	1/9	0/10		3.3[0.15,72.08]
1.5.2 Menstrual disorders				
Sheashaa 2005a	5/16	0/16		11[0.66,183.79]
1.5.3 Hirsutism				
Sheashaa 2005a	5/16	0/16		11[0.66,183.79]

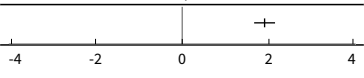


Comparison 2. Oxymetholone + rHuEPO versus placebo + rHuEPO

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Haemoglobin g/dL	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Liver function	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3.1 AST	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
3.2 ALT	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Kidney function	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 BUN [mmol/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4.2 SCr [µmol/L]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5 Lipid profile	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5.1 Total cholesterol [mg/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Triglycerides [mg/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 HDL [mg/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 LDL [mg/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
6 Change in serum albumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

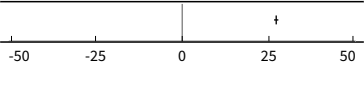
Analysis 2.1. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 1 Haemoglobin g/dL.

Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Aramwit 2010	11	12.9 (0.3)	13	11 (0.3)		1.9[1.66,2.14]



Analysis 2.2. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 2 Haematocrit.

Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Aramwit 2010	11	38.1 (1)	13	11 (0.3)		27.1[26.49,27.71]



Analysis 2.3. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 3 Liver function.

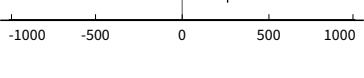
Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.3.1 AST						
Aramwit 2010	11	70.9 (12.5)	13	23.6 (11.5)		47.33[37.69,56.97]
2.3.2 ALT						
Aramwit 2010	11	75.6 (14)	13	21.1 (12)		54.5[43.94,65.06]

Analysis 2.4. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 4 Kidney function.

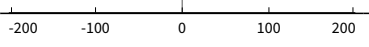
Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.4.1 BUN [mmol/L]						
Aramwit 2010	11	16.3 (3.2)	13	17.3 (4.4)		-0.94[-4.02,2.14]
2.4.2 SCr [µmol/L]						
Aramwit 2010	11	1195.9 (420.8)	13	934.3 (306.6)		261.6[-37.76,560.96]

Analysis 2.5. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 5 Lipid profile.

Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
2.5.1 Total cholesterol [mg/dL]						
Aramwit 2010	11	149 (43.3)	13	175.2 (50.9)		-26.16[-63.86,11.54]
2.5.2 Triglycerides [mg/dL]						

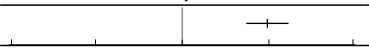


Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Aramwit 2010	11	110.2 (56.2)	13	158 (112.6)		-47.8[-117.41,21.81]
2.5.3 HDL [mg/dL]						
Aramwit 2010	11	33.4 (10.3)	13	49 (12.7)		-15.66[-24.84,-6.48]
2.5.4 LDL [mg/dL]						
Aramwit 2010	11	88.9 (35.5)	13	90 (41.3)		-1.11[-31.8,29.58]



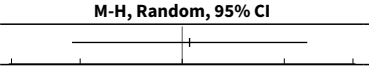
Analysis 2.6. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 6 Change in serum albumin.

Study or subgroup	Oxymetholone N	Oxymetholone Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Aramwit 2010	11	2.7 (1.5)	13	-2.2 (1.6)		4.91[3.69,6.13]



Analysis 2.7. Comparison 2 Oxymetholone + rHuEPO versus placebo + rHuEPO, Outcome 7 Adverse effects.

Study or subgroup	Oxymetholone n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Aramwit 2010	1/11	1/13		1.18[0.08,16.78]



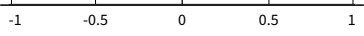
Comparison 3. Nandrolone decanoate versus EPO

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
3 Plasma total protein	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4 Prealbumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
5 Transferrin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
6 Serum albumin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7 Kidney function	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
7.1 BUN [mg/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
7.2 SCr [mg/dL]	1		Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

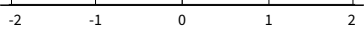
Analysis 3.1. Comparison 3 Nandrolone decanoate versus EPO, Outcome 1 Haemoglobin.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Navarro 2002	13	11.8 (0.4)	14	11.7 (0.6)		0.1[-0.28,0.48]



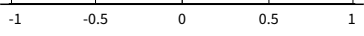
Analysis 3.2. Comparison 3 Nandrolone decanoate versus EPO, Outcome 2 Haematocrit.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Navarro 2002	13	35.1 (1.5)	14	34.7 (1.6)		0.4[-0.77,1.57]



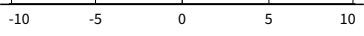
Analysis 3.3. Comparison 3 Nandrolone decanoate versus EPO, Outcome 3 Plasma total protein.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Navarro 2002	13	6.7 (0.4)	14	6.3 (0.3)		0.4[0.13,0.67]



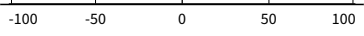
Analysis 3.4. Comparison 3 Nandrolone decanoate versus EPO, Outcome 4 Prealbumin.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Navarro 2002	13	33 (6)	14	32 (6)		1[-3.53,5.53]



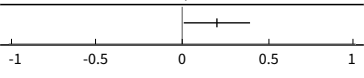
Analysis 3.5. Comparison 3 Nandrolone decanoate versus EPO, Outcome 5 Transferrin.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Navarro 2002	13	237 (57)	14	192 (18)		45[12.61,77.39]



Analysis 3.6. Comparison 3 Nandrolone decanoate versus EPO, Outcome 6 Serum albumin.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Navarro 2002	13	3.8 (0.2)	14	3.6 (0.3)		0.2[0.01,0.39]

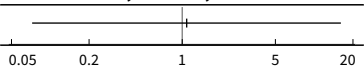


Analysis 3.7. Comparison 3 Nandrolone decanoate versus EPO, Outcome 7 Kidney function.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	EPO N	EPO Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
3.7.1 BUN [mg/dL]						
Navarro 2002	13	49 (10)	14	58 (14)		-9[-18.13,0.13]
3.7.2 SCr [mg/dL]						
Navarro 2002	13	9.7 (2.5)	14	8.9 (1.9)		0.8[-0.88,2.48]

Analysis 3.8. Comparison 3 Nandrolone decanoate versus EPO, Outcome 8 Adverse effects.

Study or subgroup	Nandrolone n/N	EPO n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Navarro 2002	1/13	1/14		1.08[0.07,15.5]

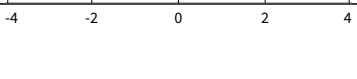


Comparison 4. Nandrolone decanoate versus no therapy (remnant kidney patients)

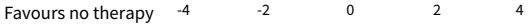
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haemoglobin	2	33	Mean Difference (IV, Random, 95% CI)	1.04 [0.66, 1.41]
2 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 4.1. Comparison 4 Nandrolone decanoate versus no therapy (remnant kidney patients), Outcome 1 Haemoglobin.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	No therapy N	No therapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Cattran 1977	15	7.7 (0.4)	9	6.7 (0.5)		95.41%	1[0.62,1.38]
Solomon 1988b	5	9.8 (1.5)	4	7.9 (1.2)		4.59%	1.82[0.07,3.57]
Total ***	**20**		**13**			**100%**	**1.04[0.66,1.41]**
Heterogeneity: Tau^2=0; Chi^2=0.8, df=1(P=0.37); I^2=0%							

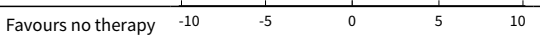


Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	No therapy N	No therapy Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=5.42(P<0.0001)							



Analysis 4.2. Comparison 4 Nandrolone decanoate versus no therapy (remnant kidney patients), Outcome 2 Haematocrit.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	No therapy N	No therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cattran 1977	15	24.6 (1.4)	9	20.9 (4.5)		3.7[0.68,6.72]

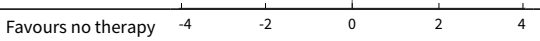


Comparison 5. Nandrolone decanoate versus no therapy (anephric patients)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Haemoglobin	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2 Haematocrit	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

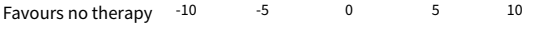
Analysis 5.1. Comparison 5 Nandrolone decanoate versus no therapy (anephric patients), Outcome 1 Haemoglobin.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	No therapy N	No therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cattran 1977	3	5.7 (0.2)	2	4.4 (0.5)		1.3[0.57,2.03]



Analysis 5.2. Comparison 5 Nandrolone decanoate versus no therapy (anephric patients), Outcome 2 Haematocrit.

Study or subgroup	Nandrolone N	Nandrolone Mean(SD)	No therapy N	No therapy Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Cattran 1977	3	17 (0.6)	2	15 (2)		2[-0.85,4.85]



APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	1. MeSH descriptor Androgens explode all trees 2. androgen*:ti,ab,kw 3. *testosterone:ti,ab,kw 4. nandrolone:ti,ab,kw 5. oxandrolone:ti,ab,kw 6. oxymetholone:ti,ab,kw 7. stanozolol:ti,ab,kw 8. (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) 9. renal insufficiency:ti,ab,kw 10.MeSH descriptor Renal Insufficiency, Chronic explode all trees 11.MeSH descriptor Renal Replacement Therapy explode all trees 12.(chronic next kidney or chronic next renal):ti,ab,kw 13.(endstage next kidney or endstage next renal):ti,ab,kw 14.(end next stage next kidney or end next stage next renal):ti,ab,kw 15.(CKD or CKF or CRD or CRF):ti,ab,kw 16.(ESKD or ESRD or ESKF or ESRF):ti,ab,kw 17.dialysis:ti,ab,kw 18.h*emodialysis:ti,ab,kw 19.(kidney next transplant* or renal next transplant*):ti,ab,kw 20.(kidney next allograft* or renal next allograft*):ti,ab,kw 21.(kidney next graft* or renal next graft*):ti,ab,kw 22.(PD or CAPD or CCPD or APD):ti,ab 23.(#9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22) 24.(#8 AND #23) 25.an*emi*:ti,ab,kw 26.(low next iron or low next h*emoglobin):ti,ab,kw 27.(#25 OR #26) 28.(#24 AND #27)
MEDLINE (Ovid SP)	1. exp Androgens/ 2. androgen$.tw. 3. testosterone.tw. 4. dihydrotestosterone.tw. 5. nandrolone.tw. 6. oxandrolone.tw. 7. oxymetholone.tw. 8. stanozolol.tw. 9. or/1-8 10.Renal Insufficiency/ 11.exp Renal Insufficiency, Chronic/ 12.exp Renal Replacement Therapy/ 13.(chronic kidney or chronic renal).tw. 14.(endstage renal or endstage kidney).tw. 15.(end stage renal or end stage kidney).tw. 16.(CKD or CKF or CRD or CRF).tw. 17.(ESKD or ESRD or ESKF or ESRF).tw. 18.dialysis.tw. 19.(haemodialysis or hemodialysis).tw.

(Continued)

	20.(kidney transplant$ or renal transplant$).tw. 21.(kidney allograft$ or renal allograft$).tw. 22.(kidney graft$ or renal graft$).tw. 23.(PD or CAPD or CCPD or APD).tw. 24.or/10-23 25.and/9,24 26.Anemia/ 27.Anemia, Iron-Deficiency/ 28.an?emi$.tw. 29.(low iron or low haemoglobin or low hemoglobin).tw. 30.or/26-29 31.and/25,30
EMBASE (Ovid SP)	1. exp Androgen/ 2. androgen$.tw. 3. dihydrotestosterone.tw. 4. nandrolone.tw. 5. oxandrolone.tw. 6. oxymetholone.tw. 7. stanozolol.tw. 8. testosterone.tw. 9. or/1-8 10.Chronic Kidney Disease/ 11.Kidney Failure/ 12.exp Renal Replacement Therapy/ 13.exp Kidney Transplantation/ 14.(chronic kidney or chronic renal).tw. 15.(endstage renal or endstage kidney).tw. 16.(end stage renal or end stage kidney).tw. 17.(CKD or CKF or CRD or CRF).tw. 18.(ESKD or ESRD or ESKF or ESRF).tw. 19.dialysis.tw. 20.(haemodialysis or hemodialysis).tw. 21.(kidney transplant$ or renal transplant$).tw. 22.(kidney allograft$ or renal allograft$).tw. 23.(kidney graft$ or renal graft$).tw. 24.(PD or CAPD or CCPD or APD).tw. 25.or/10-24 26.and/9,25 27.Anemia/ 28.Iron Deficiency Anemia/ 29.an?emi$.tw. 30.(low iron or low haemoglobin or low hemoglobin).tw. 31.or/27-30 32.and/26,31
Chinese databases (CBM, VIP and CNKI)	1. (Androgens OR testosterone OR nandrolone OR oxandrolone OR oxymetholone OR anadrol OR stanozolol OR stanazolol).ti,ab,kw 2. (renal anemia OR renal anaemia OR kidney anemia OR kidney anaemia).ti,ab,kw 3. adults.ti,ab,kw 4. (random OR randomization OR randomisation OR randomize).ti,ab,kw

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Appendix 2. Risk of bias assessment tool

Potential source of bias	Assessment criteria
Random sequence generation Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence	*Low risk of bias:* Random number table; computer random number generator; coin tossing; shuffling cards or envelopes; throwing dice; drawing of lots; minimization (minimization may be implemented without a random element, and this is considered to be equivalent to being random).
	High risk of bias: Sequence generated by odd or even date of birth; date (or day) of admission; sequence generated by hospital or clinic record number; allocation by judgement of the clinician; by preference of the participant; based on the results of a laboratory test or a series of tests; by availability of the intervention.
	Unclear: Insufficient information about the sequence generation process to permit judgement.
Allocation concealment Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	*Low risk of bias:* Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study (e.g. central allocation, including telephone, web-based, and pharmacy-controlled, randomisation; sequentially numbered drug containers of identical appearance; sequentially numbered, opaque, sealed envelopes).
	High risk of bias: Using an open random allocation schedule (e.g. a list of random numbers); assignment envelopes were used without appropriate safeguards (e.g. if envelopes were unsealed or non-opaque or not sequentially numbered); alternation or rotation; date of birth; case record number; any other explicitly unconcealed procedure.
	Unclear: Randomisation stated but no information on method used is available.
Blinding of participants and personnel Performance bias due to knowledge of the allocated interventions by participants and personnel during the study	*Low risk of bias*: No blinding or incomplete blinding, but the review authors judge that the outcome is not likely to be influenced by lack of blinding; blinding of participants and key study personnel ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding or incomplete blinding, and the outcome is likely to be influenced by lack of blinding; blinding of key study participants and personnel attempted, but likely that the blinding could have been broken, and the outcome is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Blinding of outcome assessment Detection bias due to knowledge of the allocated interventions by outcome assessors.	*Low risk of bias:* No blinding of outcome assessment, but the review authors judge that the outcome measurement is not likely to be influenced by lack of blinding; blinding of outcome assessment ensured, and unlikely that the blinding could have been broken.
	High risk of bias: No blinding of outcome assessment, and the outcome measurement is likely to be influenced by lack of blinding; blinding of outcome assessment, but likely that the blinding could have been broken, and the outcome measurement is likely to be influenced by lack of blinding.
	Unclear: Insufficient information to permit judgement
Incomplete outcome data Attrition bias due to amount, nature or handling of incomplete outcome data.	*Low risk of bias:* No missing outcome data; reasons for missing outcome data unlikely to be related to true outcome (for survival data, censoring unlikely to be introducing bias); missing outcome data balanced in numbers across intervention groups, with similar reasons for missing data across groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk not enough to have a clinically relevant impact on the intervention effect esti-

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	mate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes not enough to have a clinically relevant impact on observed effect size; missing data have been imputed using appropriate methods.
	High risk of bias: Reason for missing outcome data likely to be related to true outcome, with either imbalance in numbers or reasons for missing data across intervention groups; for dichotomous outcome data, the proportion of missing outcomes compared with observed event risk enough to induce clinically relevant bias in intervention effect estimate; for continuous outcome data, plausible effect size (difference in means or standardized difference in means) among missing outcomes enough to induce clinically relevant bias in observed effect size; 'as-treated' analysis done with substantial departure of the intervention received from that assigned at randomisation; potentially inappropriate application of simple imputation.
	Unclear: Insufficient information to permit judgement
Selective reporting Reporting bias due to selective outcome reporting	*Low risk of bias:* The study protocol is available and all of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported in the pre-specified way; the study protocol is not available but it is clear that the published reports include all expected outcomes, including those that were pre-specified (convincing text of this nature may be uncommon).
	High risk of bias: Not all of the study's pre-specified primary outcomes have been reported; one or more primary outcomes is reported using measurements, analysis methods or subsets of the data (e.g. subscales) that were not pre-specified; one or more reported primary outcomes were not pre-specified (unless clear justification for their reporting is provided, such as an unexpected adverse effect); one or more outcomes of interest in the review are reported incompletely so that they cannot be entered in a meta-analysis; the study report fails to include results for a key outcome that would be expected to have been reported for such a study.
	Unclear: Insufficient information to permit judgement.
Other bias Bias due to problems not covered elsewhere in the table	*Low risk of bias:* The study appears to be free of other sources of bias.
	High risk of bias: Had a potential source of bias related to the specific study design used; stopped early due to some data-dependent process (including a formal-stopping rule); had extreme baseline imbalance; has been claimed to have been fraudulent; had some other problem.
	Unclear: Insufficient information to assess whether an important risk of bias exists; insufficient rationale or evidence that an identified problem will introduce bias.

HISTORY

Protocol first published: Issue 1, 2008
Review first published: Issue 10, 2014

Date	Event	Description
11 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

- Study selection – Qianchun Yang, Minawaer Abudou
- Extraction of data from studies - Qianchun Yang, Taixiang Wu
- Quality assessment – Qianchun Yang, Taixiang Wu and Xisheng Xie
- Enter data into RevMan – Qianchun Yang, Xisheng Xie

- Carried out the analysis – Qianchun Yang, Minawaer Abudou and Taixiang Wu
- Interpreted the analysis – Qianchun Yang, Taixiang Wu and Xisheng Xie
- Drafted the final review – Qianchun Yang, Minawaer Abudou, Taixiang Wu and Xisheng Xie
- Disagreement resolution – Taixiang Wu

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- The Second Clinical College, Guangzhou University of Chinese Medicine, China.

External sources

- Cochrane Renal Group, Australia.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In addition to the bibliographic databases listed in the protocol for this review, we also searched the Chinese Biomedicine Database (CBM). This search did not identify any records for assessment.

INDEX TERMS

Medical Subject Headings (MeSH)

Androgens [*therapeutic use]; Anemia [blood] [*drug therapy] [etiology]; Cholesterol [blood]; Erythropoietin [therapeutic use]; Hematocrit; Nandrolone [analogs & derivatives] [therapeutic use]; Nandrolone Decanoate; Oxymetholone [therapeutic use]; Randomized Controlled Trials as Topic; Renal Insufficiency, Chronic [*complications]; Triglycerides [blood]

MeSH check words

Adult; Humans