Dialysis

Systematic Review and Meta-analysis of Exercise Tolerance and Physical Functioning in Dialysis Patients Treated With Erythropoiesis-Stimulating Agents

Kirsten L. Johansen, MD,[1] Fredric O. Finkelstein, MD,[2] Dennis A. Revicki, PhD,[3] Matthew Gitlin, PharmD,[4] Christopher Evans, PhD,[5] and Tracy J. Mayne, PhD[4]

Background: The role of erythropoiesis-stimulating agents (ESAs) in treating the anemia of chronic kidney disease has been reevaluated in view of recent studies suggesting that the use of these agents may be associated with increased morbidity and mortality. This potential increased risk needs to be weighed against the potential benefit of ESAs in improving various aspects of health-related quality of life, in particular, exercise tolerance and physical functioning.

Study Design: A systematic review and meta-analysis of exercise tolerance and physical functioning.

Setting & Participants: Adults on maintenance dialysis therapy.

Selection Criteria for Studies: Outcomes measured before and after ESA treatment were required. Studies of physical function were required to include at least 25 participants.

Intervention: Treatment with any ESA.

Outcomes: Exercise tolerance measured using VO_{2peak} (oxygen consumption per minute at the peak workload during the test), duration of exercise, or 6-minute walk distance or physical functioning assessed using ≥ 1 patient- or clinician-reported outcome measure that included a physical function domain.

Results: 28 articles met criteria for inclusion for evaluation of exercise tolerance, and 14 articles, for physical function. Meta-analysis showed a 23.8% increase in VO_{2peak} from before to after erythropoietin therapy initiation (15 studies) and a nonsignificant 8.2% increase comparing a higher with a lower hemoglobin target (3 studies). For physical functioning, 4 studies met criteria for inclusion in the meta-analysis: there was a 10.5% increase in Karnofsky score from before to after erythropoietin therapy initiation.

Limitations: Many studies of exercise tolerance did not include control groups. A wide variety of instruments was used to assess physical function.

Conclusions: Partial correction of anemia through ESA treatment has a consistent and positive impact on VO_{2peak}. ESA treatment improves patient- and clinician-assessed physical functioning.

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INDEX WORDS: Chronic kidney disease; erythropoiesis-stimulating agents; epoetin alfa; exercise tolerance; quality of life.

Editorial, p. xxx

Recent studies have focused on health-related quality of life (HRQOL) as an important outcome in patients with chronic kidney disease (CKD). This has occurred in part because HRQOL measures have been associated with hospitalizations and mortality in patients with end-stage renal disease (ESRD) maintained on dialysis therapy.[1,2] However, it also has been recognized that HRQOL measures themselves can be viewed as primary outcome measures in studies involving interventions in the care of patients with CKD.[3,4]

HRQOL measures encompass a variety of domains. Exercise tolerance and physical functioning are important aspects of HRQOL. This is particularly true for patients with CKD, who have been documented to have significant decreases in both these domains. Reasons for these decreases likely are multifactorial. Anemia has been associated with impairment in exercise tolerance and physical functioning and likely contributes, at least in part, to patient difficulties. Other potentially important contributors include

From the [1]University of California, San Francisco, CA; [2]Hospital of St. Raphael, Yale University, New Haven, CT; [3]United BioSource Corp, Bethesda, MD; [4]Amgen, Thousand Oaks, CA; and [5]Mapi Values, Boston, MA.

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Address correspondence to Kirsten L. Johansen, MD, University of California, San Francisco, San Francisco VA Medical Center, 4150 Clement St, San Francisco, CA 94121. E-mail: kirsten.johansen@ucsf.edu

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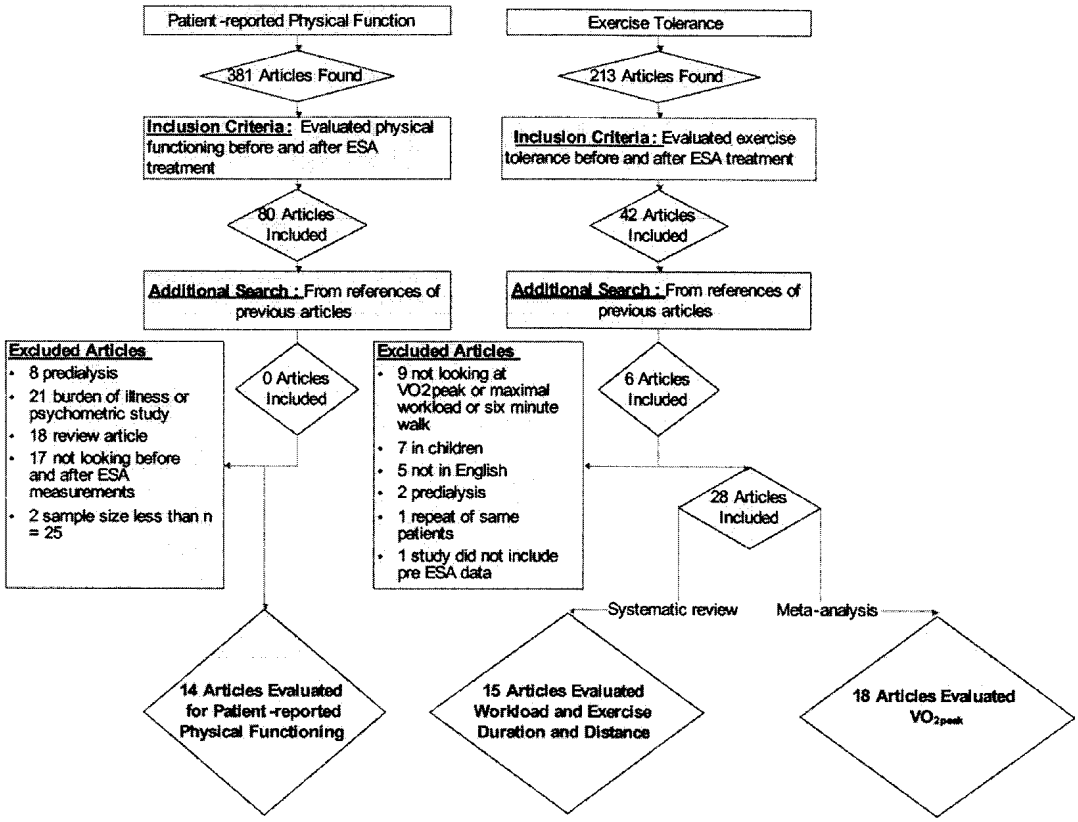

Figure 1. Article selection process. Abbreviations: ESA, erythropoiesis-stimulating agent; Vo_{2peak}, peak oxygen consumption.

lack of physical conditioning because of sedentary behavior, cardiac dysfunction, abnormalities of bone and mineral metabolism, and various psychosocial factors, such as depression.

The role of erythropoiesis-stimulating agents (ESAs) in treating the anemia of patients with CKD has been reevaluated in view of recent studies suggesting that use of these agents may be associated with increased morbidity and mortality.[5,6] However, several investigators have suggested a benefit of ESAs in improving various aspects of the HRQOL in patients with CKD, particularly in the domains of exercise tolerance and physical functioning.

The purpose of the present study is to review the available published evidence of the effect of ESA treatment on exercise tolerance and physical functioning in patients with CKD maintained on dialysis therapy.

METHODS

Review Strategy

We performed a systematic review of the literature for the impact of ESA therapy on exercise tolerance and patient functional outcomes in patients with ESRD. A systematic search was conducted using MEDLINE and EMBASE (Fig 1). The search was limited to articles published in the English language and during the period between 1988 (the first year ESAs were approved by the US Food and Drug Administration for use in the United States) and 2008. Search terms for kidney disease included "chronic renal failure" or "chronic renal insufficiency" or "kidney failure, chronic" (medical subject heading) or "renal insufficiency, chronic" (medical subject heading) or "end stage renal disease" or dialysis or "hemodialysis" or "haemodialysis"; for ESAs, "Epoetin Alfa" or "erythropoietin"; for exercise tolerance, "exercise" or "physical function" or "walking"; and for physical function, "physical functioning" or "physical status" or "physical performance" or "functional status" or "health-related qualify of life" or "HRQL" or "HRQOL" or "quality of life" or "QOL." Articles were identified for the review if they met the following inclusion criteria: (1) adults

with ESRD receiving dialysis, (2) treatment with any approved ESA, (3) functional and/or physical function measures, and/or (4) exercise tolerance measures. Study designs included randomized clinical trials and observational studies as long as pre- and posttreatment measures of exercise tolerance or physical functioning scores were reported. Studies not published in English were excluded, as well as those including only children or patients with CKD not yet requiring dialysis therapy. In addition, for the review of physical function outcomes, we excluded studies with sample sizes < 25. This exclusion was not applied to studies of exercise tolerance because most studies identified had small sample sizes.

Exercise Tolerance End Points

Studies that included maximal or submaximal exercise testing or a 6-minute walk test were considered to address the end point of exercise tolerance. In these studies, maximal exercise testing was performed using a variety of protocols based on either bicycle ergometry with increasing resistance or treadmill walking with increasing speed and/or grade. The most commonly reported outcome from these studies was VO_{2peak}, or oxygen consumption per minute at the peak workload during the test. However, several studies reported duration of testing, distance walked, or maximal workload achieved during testing instead of or in addition to VO_{2peak}, and these outcomes also were extracted.

The 6-minute walk test has been used in clinical trials for > 25 years as a direct measure of submaximal exercise tolerance and as a surrogate for maximal oxygen consumption. Participants are asked to walk as far as possible within a 6-minute period, and distance walked is recorded.[7-9] The validity, reliability, and responsiveness of the 6-minute walk test has been evaluated in populations including patients with heart failure, after myocardial infarction, with chronic obstructive pulmonary disease, and with ESRD.[9-15]

Exercise testing results often were available for only a subset of study participants within studies with other primary outcomes. In these cases, we reported the study design and number of participants relevant to the exercise outcomes.

Physical Function End Points

For physical functioning outcomes, studies were included if study participants were assessed using ≥ 1 patient- or clinician-reported outcome measure that included a physical function domain. The most frequently used measures of physical functioning were the Karnofsky Performance Scale (KPS), Kidney Disease Questionnaire (KDQ), Sickness Impact Profile (SIP), and the 36-Item Short-Form Health Survey (SF-36). The KPS is a clinician-rated measure of functional outcomes and consists of a 100-point ordinal scale anchored at "death" (score of 0) and "normal, no complaints, no evidence of disease" (score of 100).[16] The KPS has been used frequently in ESRD studies,[17,18] and KPS scores have been shown to be a good predictor of mortality[19,20] and to correlate highly with patient-reported measures of physical function.[21,22]

The SIP is a generic health status measure that evaluates changes in behavior associated with illness.[23,24] The SIP was designed to be applicable across different diseases and contains 12 separate domain subscales. The physical summary scale includes the body care and movement (23 items), ambulation (12 items), and mobility (10 items) subscales. A lower SIP score indicates higher functioning. The content and construct validity and reliability of the SIP have been shown in numerous studies,[25] including ESRD.[26,27]

The KDQ consists of 26 questions grouped into 5 domains: physical symptoms, fatigue, depression, relationship with others, and frustration.[26] The physical symptoms scale asks patients to select 6 symptoms most important for them and then rate on a 7-point Likert-type scale the degree to which each symptom has caused problems or difficulties in the past 2 weeks. Higher KDQ physical symptom scores indicate better function. The KDQ's content and construct validity and reliability have been shown in a dialysis population.[26]

The SF-36 is a generic health status measure that includes 8 domains: Physical Functioning, Role–Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role–Emotional, Mental Health, and a single health transition item. There is good evidence supporting the reliability and validity of the SF-36 in general and chronic disease populations,[28] including ESRD.[29] Only the Physical Functioning domain of the SF-36 was used in this analysis. A higher score indicates better HRQOL.

Information Synthesis

The content of relevant articles was summarized, including first author and date of publication, study type, sample size, instrumentation, hemoglobin (Hb) target, and duration of follow-up. Exercise tolerance and physical functioning outcomes are reported as percentage of change from baseline.

A meta-analysis was performed for percentage of difference in VO_{2peak}. Because study design could influence the estimate, meta-analyses were performed separately for studies evaluating pre– versus post–ESA therapy initiation and studies evaluating lower versus higher Hb targets. Heterogeneity among studies was assessed using the Q statistic. Because no heterogeneity was found (P for Q statistic ≥ 0.05), we conducted fixed-effects meta-analyses to combine these outcomes across included studies, estimating overall raw point estimates of each risk factor and their associated 95% confidence intervals (CIs). Random-effect results also were performed. Exercise tolerance articles that did not evaluate VO_{2peak} were reviewed and described separately.

For physical functioning outcomes, meta-analysis was performed for 4 of the KPS studies (the Delano[30] study was excluded from the meta-analysis because it did not contain information regarding uncertainty [standard error, standard deviation, or P value]). Results of the KDQ physical symptom scores, SIP physical symptom scores, and SF-36 physical function scores were not subject to a meta-analysis because there was missing information or uncertainty, study designs were different (cohort vs randomized controlled trial), or there were differences in the treatment target. When there was sufficient information, effect sizes were calculated for these studies.

RESULTS

Exercise Tolerance Studies

Two hundred thirteen potential articles were identified. Five studies were excluded from our review because of non-English language. After review of article abstracts, complete texts for 48 articles was reviewed. Based on this more in-depth evaluation, 28 articles were included in this systematic review and meta-analysis. Information about each study is listed in Table 1.

The reviewed articles include most (n = 23) small studies evaluating pre– versus post–ESA therapy initiation in patients started on epoetin alfa therapy for the first time.[30,31,35-44,46-48,50-57] In these studies, the average number of participants was 13, with a range of 7-29 and a total of 301. Starting Hb concentration ranged from 5.9-8.3 g/dL. The target (when a target was reported) typically was in the range of 10-12 g/dL, and the average increase in Hb level in the studies of dialysis patients was 58%. Five studies compared 2 different target Hb levels, 4 (excludes McMahon et al,[32] 1992) of which assigned participants randomly to the different groups and assessed outcomes in a double-blinded fashion.[33,34,45,49] These studies included 762 participants, most of whom were contributed by a single large study (n = 596) in which the primary exercise-related outcome was 6-minute walking distance.[34] The Canadian Erythropoietin Study Group[33] (CESG; 1990) randomly assigned patients to 3 groups: placebo, target Hb level of 9.5-11 g/dL (low), and target Hb level of 11.5-13 g/dL (high), 87 of whom completed a treadmill test and 93 of whom completed a 6-minute walk. Parfrey et al[34] (2005) randomly assigned patients already receiving epoetin alfa to continue treatment with epoetin alfa with a target Hb level of 9.5-11.5 g/dL or higher doses of epoetin alfa designed to achieve a target Hb level of 13.5-14.5 g/dL.

VO_{2peak} Outcomes

Nineteen studies[30,32,35-37,39-41,44-46,48,49,52-57] were found for VO_{2peak}, but only 18 (excludes Bocker et al,[54] 1988) studies met the criteria for inclusion in the meta-analysis. Baseline values for VO_{2peak} were ~50%-60% of age-predicted norms for sedentary individuals,[58] indicating that these patients were limited in exercise tolerance. The pooled estimate from 15 studies suitable for meta-analysis comparing pre– versus post–ESA therapy initiation for change in VO_{2peak} was 23.8% (95% CI, 18.56-28.97; Fig 2). Three studies compared change in VO_{2peak} after continued usual epoetin alfa treatment between lower versus higher Hb targets.[32,45,49] One study reported a significant increase in VO_{2peak} at the higher target, 1 reported a nonsignificant increase, and 1 reported a nonsignificant decrease. Meta-analysis results for these studies are shown in Fig 3, and the pooled estimate of differences in VO_{2peak} was 8.2% (95% CI, −5.25 to 21.63).

Workload, Duration, and Distance of Exercise

The average change in maximal workload (10 studies) with initiation of ESA therapy (25.8%) was similar in magnitude to the average change in VO_{2peak}[35-38,41,43,47,50,52,53,55,57]; however, the average change in exercise duration (12 studies) was greater (43.4%).[30,33,38,40,43,44,46-48,50,51,56] Two studies reported changes in submaximal rather than maximal workload, and the average change was 45.6%.[42,54] Finally, 3 studies reported changes in the distance walked in 6 minutes.[31,33,34] The CESG found a significant increase in 6-minute walking distance in the combined epoetin-alfa groups compared with placebo ($P = 0.02$); however, there was no significant difference between the high- and low-Hb-target groups. Harris et al[31] found increases of 28.4% at 6 months and 52% at 1 year. In Parfrey et al[34] (2005), the lower-target group increased walking distance by 4.3% compared with a 6.5% increase in the high-Hb group ($P = 0.45$).

Physical Function Studies

Three hundred eighty-one potential articles including measures of physical functioning were identified. After review of article abstracts, complete texts for 80 articles were reviewed. Based on this more in-depth evaluation, 14 articles were included in this systematic review. Information about each study is listed in Table 2.

The reviewed articles included randomized clinical trials (3 double-blind and 3 open label)[26,33,49,59-61] and single-cohort observational studies.[18,21,30,31,62-64] Only 2 studies[30,31] included sample sizes < 30, and the remaining observational studies included 57-487 participants followed up for 3-12 months. Overall

Table 1. Summary of Descriptive Information and Research Methods for Exercise Tolerance Articles (lowest to highest target)

Reference	Description	Baseline VO_{2peak}	Treatment Target	Instruments[a]	Follow-up (mo)
Harris et al[31] (1991)	EPO cohort study (n = 24)	NA	Hb, 9-10 g/dL	6-min walk test (distance walked)	6 & 12
McMahon et al[32] (1992)	RCT crossover study[b] (n = 12)	17.4 ± 2.6	Hb, 9 g/dL & Hb, 12 g/dL	Progressive cycle ergometer test[a] (VO_{2peak})	4
CESG[33] (1990) & Laupacis et al[26] (1991)	RCT[b]; placebo (n = 30) vs EPO low (n = 40) vs EPO high (n = 40)	NA	Placebo: NA EPO low: Hb, 9.5-11.0 g/dL EPO high: Hb, 11.5-13.0 g/dL	6-min walk test (distance walked) Exercise stress test (duration of exercise)	6
Parfrey et al[34] (2005)	RCT[b]; EPO low (n = 300) vs EPO high (n = 296)	NA	EPO low: Hb, 9.5-11.5 g/dL EPO high: Hb, 13.5-14.5 g/dL	6-min walking test (distance walked)	18
Barany et al[35] (1993)	EPO cohort study (n = 21)	1.24 ± 0.39 L/min	Hb, 10 g/dL	Progressive cycle ergometer test[a] (maximal workload, VO_{2max})	7-12
Mayer et al[36] (1988)	EPO cohort study (n = 8)	16.0 ± 3.4	Hb, 10 g/dL	Progressive cycle ergometer test[a] (VO_{2peak})	1.5-4
Metra et al[37] (1991)	EPO cohort study (n = 10)	21.4 ± 4.2	Hb, 10 g/dL	Progressive cycle ergometer test[a] (maximal workload, VO_{2peak})	1-3
Topuzovic[38] (1999)	EPO cohort study (n = 17)	NA	Hb, 10 g/dL	Progressive cycle ergometer test[a] (maximal workload, duration of exercise)	Until target reached
Tsutsui et al[39] (1989)	EPO cohort study (n = 29)	22.4 ± 4.2	Hct, 30%	Symptom-limited maximal treadmill test by standard Bruce protocol (duration of exercise, VO_{2max})	Until target reached
Macdougall et al[40] (1990)	EPO cohort study (n = 10)	19.1 ± 7.0	None stated (achieved Hb > 10 g/dL)	Progressive cycle ergometer test[a] (duration of exercise, VO_{2peak})	4
Rosenlof et al[41] (1989)	EPO cohort study (n = 9)	15.7 ± 1.7	Hb ≥ 10 g/dL	Progressive cycle ergometer test[a] (maximal workload, VO_{2peak})	Until target reached
Delano[30] (1989)	EPO cohort study (n = 11)	1.045 L/min	Hct, 31.5%	Treadmill: modified Balke protocol (duration of exercise, VO_{2max})	24
Braumann et al[42] (1991)	EPO cohort study (n = 12)	NA	Hct, 30%-35%	Progressive cycle ergometer test[a] (submaximal workload at heart rate of 130 beats/min)	2.4 ± 0.6
Juric et al[43] (1995)	EPO cohort study (n = 19)	NA	Hb, 10-12 g/dL	Progressive cycle ergometer test[a] (maximal workload, duration of exercise)	3.4 ± 1.4
Macdougall et al[44] (1990)	EPO cohort study (n = 7)	11.3 ± 3.2	Hb, 10-12 g/dL	Progressive cycle ergometer test[a] (duration of exercise, VO_{2peak})	4
McMahon et al[45] (2000)	RCT[b] crossover study (n = 14)	1.62 ± 0.22 L/min	Hb, 10 g/dL & Hb, 14 g/dL	Progressive cycle ergometer test[a] (VO_{2peak})	4

(Continued)

Table 1 (Cont'd). Summary of Descriptive Information and Research Methods for Exercise Tolerance Articles (lowest to highest target)

Reference	Description	Baseline VO_{2peak}	Treatment Target	Instruments[a]	Follow-up (mo)
Robertson et al[46] (1990)	EPO cohort study (n = 19)	0.98 ± 0.33	Hct, 32%-38%	Progressive cycle ergometer test[a] (duration of exercise, VO_{2max})	2-3
Davenport et al[47] (1992)	EPO cohort study (n = 11)	NA	Hb, 11 g/dL	Progressive cycle ergometer test[a] (maximal workload, duration of exercise)	3.1[c]
Lundin et al[48] (1991)	EPO cohort study (n = 10)	15.1 ± 5.3	Hct, 35%	Progressive cycle ergometer test[a] (duration of exercise, VO_{2peak})	3
Painter et al[49] (2002)	RCT[b]; low Hb (n = 14) vs low Hb + exercise (n = 9) vs normal Hb (n = 10) vs normal Hb + exercise (n = 12)	Low Hb: 19.8 ± 6.2 High Hb: 20.0 ± 4.1	Low Hb: Hct, 30%-33% High Hb: Hct, 40%-42%	Treadmill testing: branching protocol (VO_{2peak})	5.6
Wizemann et al[50] (1992)	EPO cohort study (n = 7)	NA	Hct, 35%	Progressive cycle ergometer test[a] (maximal workload, duration of exercise)	Until target reached
Hase et al[51] (1993)	EPO cohort study (n = 9)	NA	Hb, 12 g/dL	Symptom-limited maximal treadmill test: standard Bruce protocol (duration of exercise)	3
Akiba et al[52] (1995)	EPO cohort study (n = 18)	18.4	ΔHb, +4-5 g/dL	Progressive cycle ergometer test[a] (maximal workload, VO_{2max})	3
Barany et al[53] (1991)	EPO cohort study (n = 9)	1.16 ± 0.36 L/min	None stated	Progressive cycle ergometer test[a] (maximal workload, VO_{2max})	12
Bocker et al[54] (1988)	EPO cohort study (n = 16)	NA	No target	Progressive cycle ergometer test[a] (submaximal workload at heart rate of 130 beats/min, VO_{2max} [not meta-analyzed for VO_{2max}])	2.3 (1.6-3.3)[d]
Grunze et al[55] (1990)	EPO cohort study (n = 8)	1.19 ± 0.25	None stated	Progressive cycle ergometer test[a] (maximal workload, VO_{2max})	6
Lewis et al[56] (1993)	EPO cohort study (n = 9)	18.7 ± 4.2	None stated	Weber treadmill protocol (duration of exercise, VO_{2max})	5.4
Marrades et al[57] (1996)	EPO cohort study (n = 8)	25.4 ± 4.6	None stated	Progressive cycle ergometer test[a] (VO_{2peak})	NA

Note: Hb and Hct values are reported as seen in the publication (an estimate of Hb can be converted to Hct by multiplying by 3; an estimate of Hct can be converted to Hb by dividing by 3). Conversion factor for Hb in mg/dL to g/L, ×10.

Abbreviations: CESG, Canadian Erythropoietin Study Group; EPO, epoetin alfa; Hb, hemoglobin; Hct, hematocrit; NA, not applicable; RCT, randomized controlled trial; VO_{2peak}, peak oxygen consumption; VO_{2max}, maximal oxygen consumption.

[a]Progressive cycle ergometer and treadmill protocols vary.

[b]Double blinded.

[c]Median.

[d]Mean and range.

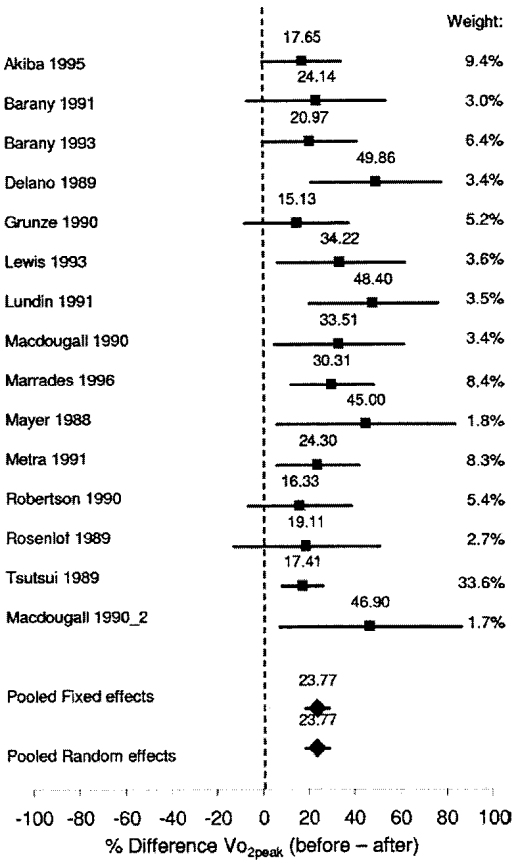

Figure 2. Forest plot of pre–versus post–erythropoesis-stimulating agent comparison studies of VO_{2peak}. Note: Weight is calculated as the reciprocal of the variance (V_i) of the outcome estimate of from the i^{th} study. Abbreviation: VO_{2peak}, peak oxygen consumption.

sample sizes for clinical trials ranged from 48-416, and only a single clinical trial was placebo controlled.[26,33]

Clinician-Rated Functional Outcomes

Five articles were identified that used the KPS to evaluate functional status after treatment with an ESA (Table 3).[18,21,30,31,64] Improvements of 3.7%-25.8% in KPS scores were seen at 3-6 months, and after 10-12 months, improvements from baseline ranged from 13.2%-16.9%. In the Evans et al[18] (1990) study, KPS scores improved 16.7% during 10 months. There were no clear differences in improvement in KPS scores between partial anemia correction (Hb < 11.5 g/dL; 10.4% to 16.9%) and higher anemia correction groups (Hb > 12.0 g/dL; 3.7% to 16.7%). Four studies were suitable for meta-analysis; the pooled estimate comparing pre– versus post–ESA therapy initiation for change in KPS score was 10.5% (95% CI, 4.74-16.32) in the random-effects model (Fig 4).

Patient-Reported Physical Functioning

Twelve articles were found that examined patient-reported physical function measures after treatment with an ESA.[18,21,26,33,49,59-65] Most of these studies used the KDQ,[26,33,59-61] SIP,[21,26,33,64] or SF-36[6,62,63,65] as the health outcome measure. Studies using the KDQ physical symptoms scale as an end point found 19.3%-44.4% improvements between baseline and 6-month follow-up (Table 4). After 12 months, changes of 17.2%-31.8% were seen in KDQ physical symptom scores. In the CESG placebo-controlled clinical trial, the epoetin alfa–treated groups showed 35.9%-44.4% improvements in KDQ physical symptoms scores compared with only 9.5% in the placebo group. Partial anemia correction groups reported improvements of 6.3%-44.4% in KDQ physical function scores compared with improvements of 17.2%-35.9% in the higher correction target groups (Hb > 12.0 g/dL).

Studies using the SIP physical score detected a 24.0%-61.9% improvement in physical activities and functioning after ESA treatment (Table 5).

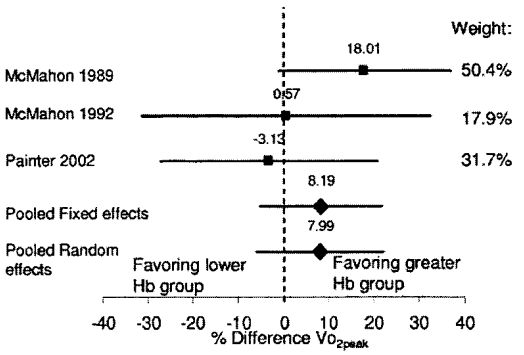

Figure 3. Forest plot of studies of VO_{2peak} that compare 2 hemoglobin (Hb) levels achieved with erythropoiesis-stimulating agent treatment. Note: Weight is calculated as the reciprocal of the variance (V_i) of the outcome estimate of from the i^{th} study. Abbreviation: VO_{2peak}, peak oxygen consumption.

Table 2. Summary of Descriptive Information and Research Methods for Physical Function Articles

Reference (year)	Description	Treatment Target[a]	Instruments	Follow-up (mo)
		Randomized Controlled Trials		
CESG[33] (1990) & Laupacis et al[26] (1991)	RCT[b]; placebo (n = 30) vs EPO low (n = 40) vs EPO high (n = 40)	Placebo: NA EPO low: Hb, 9.5-11.0 g/dL EPO high: Hb, 11.5-13.0 g/dL	KDQ physical; SIP physical summary	6
Painter et al[49] (2002)	RCT[b]; low Hb (n = 14) vs low Hb + exercise (n = 10) vs normal Hb (n = 12) vs normal Hb + exercise (n = 12)	Low Hb: Hct, 30%-33% Normal Hb: Hct, 40%-42%	SF-36 physical function	5.6
Muirhead et al[59] (1992)	RCT[c]; IV EPO (n = 38) vs SC EPO (n = 45)	Hb, 10.5-12.5 g/dL	KDQ physical	6
Foley et al[60] (2000)	RCT[c]; EPO low (n = 73) vs EPO high (n = 73)	EPO low: Hb, 9.5-10.5 g/dL EPO high: Hb, 13-14 g/dL	KDQ physical	12
Furuland et al[61] (2003)	RCT[c]; EPO subnormal (n = 124) vs EPO normal (n = 115)	EPO subnormal: Hb, 9.0-12.0 g/dL EPO normal: Hb, 13.5-16.0 g/dL	KDQ physical	12
		Cohort Studies		
Fukuhara et al[62] (2008)	EPO/DAR cohort study (n = 487)	None stated (switch study)	SF-36	1.75-4
Delano[30] (1989)	EPO cohort study (n = 29)	Hct, 31.5%	KPS	24
Evans et al[18] (1990)	EPO cohort study (n = 333)	Hct, 32%-38%	KPS; Nottingham Health Profile Mobility	4, 10
Harris et al[31] (1991)	EPO cohort study (n = 28)	Hb, 9.0-10.0 g/dL	KPS	6, 12
Levin et al[63] (1993)	EPO cohort study (n = 324)	None stated (achieved Hct, 30%)	SF-36 physical function	4
Moreno et al[64] (1996)	EPO cohort study (n = 57)	None stated (achieved Hct, 29%)	KPS; SIP physical summary	3, 6
Beusterien et al[65] (1996)	EPO cohort study (n = 484)	None stated (achieved Hct, 30%)	SF-36 physical function	3.5
Moreno et al[21] (2000)	EPO cohort study (n = 156)	Hb, 13.0 g/dL	KPS; SIP physical summary	6

Note: Conversion factor for Hb in mg/dL to g/L, ×10.

Abbreviations: CESG, Canadian Erythropoietin Study Group; DAR, darbepoetin alfa; EPO, epoetin alfa; Hb, hemoglobin; Hct, hematocrit; IV, intravenous; KDQ, Kidney Disease Questionnaire; KPS, Karnofsky Performance Scale; NA, not applicable; RCT, randomized controlled trial; SC, subcutaneous; SF-36, 36-Item Short-Form Health Survey; SIP, Sickness Impact Profile.

[a]Hb and Hct values are reported as seen in the publication (an estimate of Hb can be converted to Hct by multiplying by 3; an estimate of Hct can be converted to Hb by dividing by 3).

[b]Double blinded.

[c]Open label.

For example, the CESG[53] clinical trial (1990), 1 of the few placebo-controlled randomized clinical trials comparing epoetin alfa treatment, showed improvements of 59.4%-61.9% in SIP physical scores from baseline to 6 months. The placebo group showed only a 14.3% improvement in SIP physical scores during this same period. Partial anemia correction groups reported improvements of 59.4% in KDQ physical function scores compared with improvements of 61.9% in the higher correction target groups (Hb > 12.0 g/dL).

When the SF-36 physical functioning scale was used as an end point, a significant improvement of 8.9% was observed after 49-180 days of initiating ESA treatment[65] (Table 6). During a briefer period of 7-14 weeks, improvements of 2.6%-8.4% were observed for physical functioning scores.[64] In Painter et al[49] (2002), only participants who received exercise training and epoetin

Table 3. Cohort Studies of ESA Impact on KPS Scores

Reference	Treatment Target	KPS Score		
		Baseline	Follow-up	Change (%)
Delano[30] (1989)	Hct, 31.5% (n = 29)	76	12 mo: 86	12 mo: 13.2
Evans et al[18] (1990)	Hct, 32%-38% (n = 329)	67, from original score of 3.3 (1.3)[a]	4 mo: 72.3, from original score of 2.77 (1.3)[a] 10 mo: 72.5, from original score of 2.75 (1.2)[a]	4 mo: 16.1 (ES = 0.40) 10 mo: 16.7 (ES = 0.41)
Harris et al[31] (1991)	Hb, 9.0-10.0 g/dL (n = 28 at 6 mo; n = 24 at 12 mo)	77	6 mo: 85 12 mo: 90	6 mo: 10.4 12 mo: 16.9
Moreno et al[64] (1996)	None stated (achieved Hct, 29%) (n = 57)	68.4 (1.8)	3 mo: 78.6 (1.6) 6 mo: 81.0 (1.4)	3 mo: 22.1 (ES = 1.05) 6 mo: 25.8 (ES = 1.22)
Moreno et al[21] (2000)	Hb, 13.0 g/dL (n = 115)	75.6 (2.7)	6 mo: 78.4 (2.8)	6 mo: 3.7 (ES = 1.04)

Abbreviations: ES, effect size; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; KPS, Karnofsky Performance Status.

[a]Scores for Evans et al[18] (1990) were transformed to KPS scores using the formula (100 – (Evans score × 10).

alfa improved their physical functioning; there was no increase in physical function in the normal-Hb group compared with the control group.

Other Measures of Function and Activity

Three additional studies, which examined the impact of epoetin alfa in patients with ESRD, used other measures of functional ability and activity level. Evans et al[18] (1990) showed no significant benefit of ESA therapy using the Nottingham Health Profile mobility score. Adamson and Eschbach[66] (1989) conducted an observational study of 309 participants receiving dialysis who were initiated on epoetin-alfa therapy.[66] The percentage of participants who reported being "very active" increased from 19.8% at baseline to 37.7% at 6 months and 35.5% at 10 months ($P < 0.01$). Barany et al[35] (1993), using a single-question global physical activity score, observed a significant increase in physical activity in ESA-treated patients compared with controls.

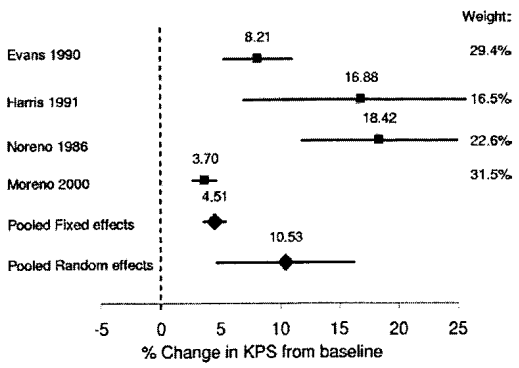

Figure 4. Forest plot of studies of the Karnofsky Performance Scale (KPS) that compare 2 hemoglobin levels achieved with erythropoiesis-stimulating agent treatment. Note: Weight is calculated as the reciprocal of the variance (V_i) of the outcome estimate of from the i^{th} study.

DISCUSSION

The findings in the present study emphasize the importance of ESA therapy in improving the exercise tolerance and physical functioning of dialysis patients.

The impairment in exercise tolerance of patients with ESRD patients is well documented. Reasons for this impairment are multifactorial, but anemia likely has a significant contributory role. In general, studies comparing exercise tolerance before and after the treatment of anemia with ESA therapy show an increase in exercise tolerance. However, studies comparing ESA therapy to achieve higher versus lower Hb targets did not show a benefit of higher targets.

Factors other than anemia contribute to the impaired exercise tolerance of dialysis patients. Marrades et al[57] in 1996 compared exercise tolerance in ESA-treated patients with ESRD with that of healthy controls and concluded that exercise tolerance after correction of anemia was much less than that of healthy sedentary individuals. This appears to be true even after normaliza-

Table 4. Randomized Controlled Trials of ESA Impact on KDQ Physical Symptom Scores

Reference	Treatment Target	KDQ Physical Symptom Score		
		Baseline	Follow-up	Change (%)
CESG[33] (1990)	Placebo (n = 30)	4.2	6 mo: 4.6	6 mo: 9.5
	EPO low: Hb, 9.5-11.0 g/dL (n = 40)	3.6	6 mo: 5.2	6 mo: 44.4
	EPO high: Hb, 11.5-13.0 g/dL (n = 40)	3.9	6 mo: 5.3	6 mo: 35.9
Muirhead et al[59] (1992)	IV EPO: Hb, 10.5-12.5 g/dL (n = 38)	4.3 (1.2)	24 wk: 5.2 (1.2)	24 wk: 20.9 (ES = 0.75)
	SC EPO: Hb, 10.5-12.5 g/dL (n = 45)	4.3 (1.1)	24 wk: 5.3 (1.1)	24 wk: 23.3 (ES = 0.91)
Foley et al[60] (2000)	EPO low: Hb, 9.5-10.5 g/dL (n = 73)	3.68	48 wk: 4.39 (at 24 wk); 4.85	48 wk: 19.3 (at 24 wk); 31.8
	EPO high: Hb, 13-14 g/dL (n = 73)	3.49	48 wk: 4.28 (at 24 wk); 4.59	48 wk: 22.6 (at 24 wk); 31.5
Furuland et al[61] (2003)	EPO subnormal: Hb, 13.5-16.0 g/dL (n = 55)	3.83	48 wk: 4.49	48 wk: 17.2
	EPO normal: Hb, 9.0-12.0 g/dL (n = 62)	4.00	48 wk: 4.25	48 wk: 6.3

Note: Conversion factor for Hb in mg/dL to g/L, ×10.

Abbreviations: CESG, Canadian Erythropoietin Study Group; ESA, erythropoiesis-stimulating agent; EPO, epoetin alfa; Hb, hemoglobin; Hct, hematocrit; IV, intravenous; KDQ, Kidney Disease Questionnaire; SC, subcutaneous.

[a]Hb and Hct values are reported as seen in the publication (an estimate of Hb can be converted to Hct by multiplying by 3; an estimate of Hct can be converted to Hb by dividing by 3).

tion of Hb levels with ESA therapy. The available evidence does not suggest much additional improvement in exercise tolerance with normalization of Hb levels beyond that seen with partial correction of anemia. Furthermore, it was noted by several investigators that the increase in exercise tolerance was less than expected given the fractional change in Hb levels, suggesting that factors other than anemia likely contribute to the poor exercise tolerance of patients with ESRD.

Consistent with the exercise tolerance studies, clinician- or patient-reported measures of physical functioning showed improvements associated with partial correction of anemia. The magnitude of this effect varied by the measure used to assess physical functioning. For example, studies using the KPS, a clinician-rated measure, observed 13%-17% improvements. However, physicians' perceptions of patients' symptoms often are limited.[67] More dramatic changes were noted with patient-reported assessments of physi-

Table 5. ESA Impact on SIP Physical Scores

Study	Treatment Target	Baseline	Follow-up	Change (%)
	Randomized Controlled Trial			
CESG[33] (1990)	Placebo (n = 30)	4.9	6 mo: 4.2	6 mo: 14.3
	EPO low: Hb, 9.5-11.0 g/dL (n = 40)	6.4	6 mo: 2.6	6 mo: 59.4
	EPO high: Hb, 11.5-13.0 g/dL (n = 40)	6.3	6 mo: 2.4	6 mo: 61.9
	Cohort Studies			
Moreno et al[64] (1996)	None stated (achieved Hct, 29%) (n = 57)	15.4	3 mo: 11.3 6 mo: 9.6	3 mo: 26.6 (ES = 0.30) 6 mo: 37.7 (ES = 0.43)
Moreno et al[21] (2000)	Hb, 13.0 g/dL (n = 156)	5.4	6 mo: 4.1	6 mo: 24.0 (ES = 1.08)

Note: Conversion factor for Hb in mg/dL to g/L, ×10.

Abbreviations: CESG, Canadian Erythropoietin Study Group; EPO, erythropoietin; ES, effect size; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; SIP, Sickness Impact Profile.

[a]Hb and Hct values are reported as seen in the publication (an estimate of Hb can be converted to Hct by multiplying by 3; an estimate of Hct can be converted to Hb by dividing by 3).

Table 6. ESA Impact on SF-36 Physical Function Scores

Reference	Treatment Target[a]	Baseline	Follow-up	Percentage of Change (ES)
	Randomized Controlled Trial			
Painter et al[49] (2002)	Low Hb: Hct, 30%-33% (n = 14)	78	5 mo: 76	5 mo: −2.6%
	Low Hb + exercise: Hct, 30%-33% (n = 9)	72	5 mo: 83	5 mo: 15.3%
	Normal Hb: Hct, 40%-42% (n = 10)	74	5 mo: 65	5 mo: −13.9%
	Normal Hb + exercise: Hct, 40%-42% (n = 12)	63	5 mo: 77	5 mo: 22.2%
	Cohort Studies			
Levin et al[63] (1993)	None stated (achieved Hct, 30%) (n = 324)	45.3	4 mo: 49.8	4 mo: 9.9%
Beusterien et al[65] (1996)	None stated (achieved Hct, 30%) (n = 484)	44.0 (27.4)	14 wk: 47.9 (28.9)	14 wk: 8.4% (ES = 0.14)
Fukuhara et al[62] (2008)	No Hb stated (switch study) (n = 487)	77.4	7-14 wk: 79.4	7-14 wk: 2.6% (ES = 0.10)

Note: Conversion factor for Hb in mg/dL to g/L, ×10.

Abbreviations: ES, effect size; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; Hct, hematocrit; SF-36, 36-Item Short Form Health Survey.

[a]Hb and Hct values as seen in the publication (an estimate of Hb can be converted to Hct by multiplying by 3; an estimate of Hct can be converted to Hb by dividing by 3).

cal functioning. For example, 1 placebo-controlled clinical trial that used the KDQ and SIP to assess physical functioning[26,33] showed much more striking changes in physical functioning. KDQ physical scores increased 36%-44% in the ESA-treated groups, but increased only 9.5% in the placebo group. Similarly, SIP physical scores improved 59%-62% in ESA-treated groups and only 14% in the placebo group.

Physical functioning improvements varied with Hb targets across different studies. Importantly, it is clear from these studies that full correction of anemia does not result in additional improvements in patient assessments of physical functioning compared with partial anemia correction. This observation supports 2 recent articles suggesting that maximal improvements in HRQOL in patients with CKD occur with Hb level increases into the 10-12– or 11-12–g/dL range with only blunted improvements occurring with increases in Hb levels to > 12 g/dL.[68,69]

The exact mechanism for the association between change in Hb levels and improvement in exercise tolerance and physical functioning is not clear. This improvement may be linked to increased oxygen transport after increases in Hb levels. However, other factors likely contribute to the decreased exercise tolerance and physical functioning, including lack of physical conditioning because of sedentary behavior, cardiac dysfunction, abnormalities of bone and mineral metabolism, and various psychosocial factors, such as depression.

Several limitations should be considered when interpreting this review. As a result of phase 2 placebo-controlled studies using epoetin alfa, it was deemed unethical to not treat patients; therefore, most studies did not include a placebo control group. Therefore, few randomized placebo-controlled clinical trials have been completed evaluating the impact of ESA treatment on exercise tolerance or physical functioning end points. Thus, it was necessary to include studies that did not randomly assign patients to treatment or did not include control groups in our analysis. In addition, the funding source was not reported for many articles; thus, separate analyses comparing outcomes based on funding source were not possible. All studies that reported funding reported either full industry support (n = 13) or partial support (eg, patient care funds or free study drug; n = 11). Five studies were excluded

from our review because of non-English language, which has the potential to introduce bias. However, all were small nonrandomized studies with a pre-post erythropoietin design. Of these, 4 clearly stated in the abstract that there was improvement in exercise tolerance, and the fifth did not include an abstract in English to allow us to make this determination. Therefore, we do not consider it likely that their exclusion biased our results toward a more robust increase in VO_{2peak}.

Studies examining exercise tolerance included participants who were considerably younger and healthier than the present US dialysis population[70] and had to be able to perform exercise tolerance tests, potentially limiting the generalizability of the findings. In addition, there is heterogeneity in Hb levels before and after ESA treatment and in the methods for evaluating exercise tolerance (eg, progressive cycle ergometer test and treadmill testing). Furthermore, lack of a non–ESA-receiving control group in the studies of initiation of ESA therapy is a serious limitation and could result in overestimation of the improvement attributable to ESA administration. In addition, we cannot rule out the possibility of publication bias, particularly in light of the generally small sample sizes of the investigations of exercise tolerance. However, the large number of studies showing consistent benefit across different types of exercise testing leads us to conclude that partial correction of anemia leads to significant improvement in exercise tolerance in patients with ESRD.

In the studies of physical function we reviewed, a number of different patient-reported physical function outcome measures were used, and because of differences in their item content, these instruments may be measuring different aspects of physical functioning. However, the consistency of findings across different measures provides some confidence in the review results. Finally, variations in clinical study designs and data collection schedules may impact on outcomes across the different studies reviewed.

This systematic review and meta-analysis found evidence for improvement in exercise tolerance and clinician- and patient-reported measures of physical functioning. For exercise tolerance, partial correction of anemia through ESA treatment has a consistent and positive impact on VO_{2peak} and other measures in patients with ESRD. Consistent with exercise tolerance findings, ESA treatment improves patient- and clinician-reported physical functioning using a variety of measures. No additional increases occur with Hb levels > 12 g/dL in exercise tolerance and physician-reported physical function. However, increases in Hb levels > 12 g/dL were associated with smaller improvements in patient-reported physical function. Correction of anemia does not restore exercise tolerance or physical functioning to levels similar to those of individuals with normal kidney function.

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