# Exercise in the End-Stage Renal Disease Population

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Many of the known benefits of exercise in the general population are of particular relevance to the ESRD population. In addition, the poor physical functioning that is experienced by patients who are on dialysis is potentially addressable through exercise interventions. The study of exercise in the ESRD population dates back almost 30 yr, and numerous interventions, including aerobic training, resistance exercise training, and combined training programs, have reported beneficial effects. Recently, interventions during hemodialysis sessions have become more popular and have been shown to be safe. The risks of exercise in this population have not been rigorously studied, but there have been no reports of serious injury as a result of participation in an exercise training program. It is time that we incorporate exercise into the routine care of patients who are on dialysis, but identification of an optimal training regimen or regimens, according to patient characteristics or needs, is still needed to facilitate implementation of exercise programs.

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# Why Consider Exercise in Patients with ESRD?

The US Surgeon General issued a landmark report in 1996 that contained the seminal recommendation that "significant health benefits can be obtained by including a moderate amount of physical activity . . . on most, if not all, days of the week" (1). Several of the known benefits of exercise or regular physical activity in the general population are related to areas of specific concern to patients with ESRD, such as reduced risk for cardiovascular mortality, improvement in BP control among hypertensive individuals, better control of diabetes, and improvement in health-related quality of life as a result of enhanced psychologic well-being and improved physical functioning (1-3). Given that cardiovascular mortality is the number-one cause of death among patients with ESRD in the United States and approximately 80% of incident ESRD patients have a history of hypertension (4), there is great potential for mortality reduction as a result of exercise participation in this population. However, epidemiologic research recently uncovered a phenomenon of altered risk factor patterns, sometimes referred to as "reverse epidemiology," that applies to many usual cardiovascular risk factors, including body size, BP, plasma homocysteine, and total and LDL cholesterol (5–9). Therefore, caution is required when extrapolating evidence of benefits in other populations to patients with ESRD. However, the same type of observational data that has yielded paradoxic associations for other risk factors supports a usual relationship between sedentary behavior (10) or low cardiorespiratory fitness (11) and higher mortality among patients with ESRD (Figure 1).

It has been hypothesized that many traditional cardiovascular risk factors exhibit paradoxic associations with mortality in the ESRD population because of associations between usually favorable characteristics and malnutrition or inflammation (8,12). In other words, dialysis patients with protein-energy malnutrition or inflammation are both more likely to have low levels of traditional risk factors such as body weight-for-height, cholesterol, and BP and more likely to have superimposed illnesses that predispose to morbidity and mortality; the malnutrition-inflammation-disease inverse associations may outweigh the more typical negative associations of high levels of these risk factors. Conversely, there is no such inverse association between physical activity and nutritional or inflammatory status or underlying disease. Rather, low levels of physical activity would be expected to be associated with malnutrition, inflammation, and disease, making a typical association between sedentary behavior and higher mortality not surprising. Figure 2 illustrates the parallel associations of sedentary behavior and ESRD with other cardiovascular risk factors and with inflammation, oxidative stress, and endothelial dysfunction and illustrates the areas in which exercise has been beneficial in the general population. This review discusses the extent to which these effects of exercise training have been demonstrated in the ESRD population.

In addition to the possibility of improving cardiovascular outcomes, exercise has the potential to improve physical functioning and health-related quality of life. Low exercise capacity (maximal or peak oxygen consumption) (13–18), muscle wasting (19–21), and poor physical performance (22,23) and functioning (24–27) are also highly prevalent among patients with ESRD and potentially modifiable with exercise interventions (Figure 2). These problems are associated with development of disability, loss of independence, and death among community-

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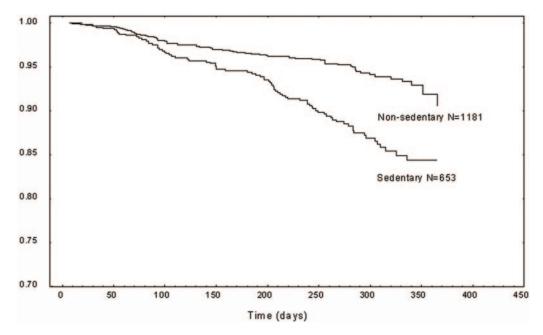


Figure 1. Survival among sedentary and nonsedentary incident dialysis patients.

dwelling elderly people, again raising the possibility that exercise interventions could be especially beneficial to patients with ESRD and could improve survival.

Despite the myriad potential benefits of exercise, dialysis patients are extremely inactive (28), and nephrologists rarely assess patients' physical activity levels or counsel patients to increase activity (29). The lack of exercise assessment and counseling is almost certainly multifactorial, related to such factors as competing medical issues that lead to limited time available for exercise counseling, lack of training in exercise prescription, and fear of adverse events related to exercise in this population. For example, it is possible that, although exercise participation could lead to greater benefits among patients with ESRD than the general population, dialysis patients may also incur greater risk because of underlying heart or musculoskeletal disease. This review focuses on the available data regarding benefits and risks of exercise among patients with ESRD.

# **Aerobic Exercise Training**

Several studies have examined the effects of aerobic exercise training on peak oxygen consumption ( $VO_{2peak}$ ) in this population (16,18,30–45). Although the intensity and the duration of exercise in the studies varies, all have included initial moderate aerobic training progressing to vigorous training for 30 min or more three times per week for  $\geq 8$  wk up to 12 mo (most studies 3 to 6 mo). On average, aerobic exercise training for 8 wk to 6 mo improves  $VO_{2peak}$  by approximately 17% (Figure 3), but there is considerable variability from study to study, and many studies have been uncontrolled (16,18,30,32–36,41,43). Only two of these studies included patients who were on peritoneal dialysis (35,40). Many studies were conducted before the routine use of erythropoietin to control the anemia that is associated with chronic kidney disease (CKD), but the effects of aerobic training seem to be similar among patients who receive

erythropoietin (Figure 3). Therefore, although it is firmly established in the literature that aerobic exercise training increases  $VO_{2peak}$  in patients with ESRD, the total number of patients studied is still relatively small, particularly when one considers only those for whom a control group was also assembled. Furthermore, the improvement in  $VO_{2peak}$  is modest, and patients do not approach predicted age-adjusted  $VO_{2peak}$  levels even after training.

Studies of the effects of exercise on VO<sub>2peak</sub> have provided important information because they showed that patients with kidney disease could respond physiologically to exercise training in a manner that is similar to other patient groups. However, the qualified success of vigorous aerobic exercise training that is designed to increase  $VO_{2\mathrm{peak}}$  should be put into perspection tive. First, the patients who have been studied to date have generally been the healthiest individuals who receive hemodialysis, usually a small fraction of available patients (33,41), and it is not clear that more typical (i.e., less healthy) patients with kidney disease will be willing or able to undergo vigorous exercise training. Furthermore, it is not clear whether such vigorous training is necessary to derive many of the potential benefits of exercise. Another important caveat to be considered when interpreting the increases in  $VO_{2peak}$  as a result of aerobic exercise training is that the links between change in VO<sub>2peak</sub> and improvements in physical performance, self-reported physical functioning, or health-related quality of life have not been established in this population. Therefore, the extent to which a 17% increase in VO<sub>2peak</sub> actually improves the lives of patients with kidney disease is not clear.

Although the effect of aerobic exercise training on  $VO_{2peak}$  in selected healthy patients who receive hemodialysis has been a major focus of exercise research in the ESRD population, some additional information is available to address other potential benefits of training. Several studies have considered outcomes

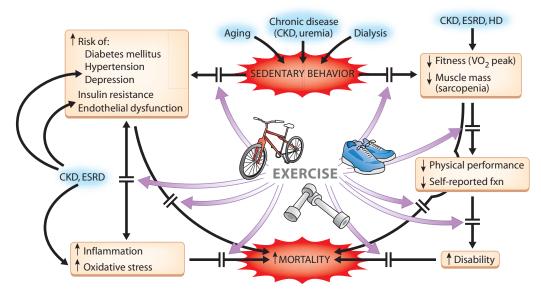


Figure 2. Diagram of potential adverse effects of sedentary behavior and chronic kidney disease and potential beneficial effects of exercise interventions.

in addition to or instead of VO<sub>2peak</sub>, including measures of physical functioning and outcomes not related to physical function. These other outcomes have included anemia, lipid levels, BP control, endothelial function, inflammation, mental health, and health-related quality of life. Although a few small studies have reported an improvement in anemia with vigorous aero-

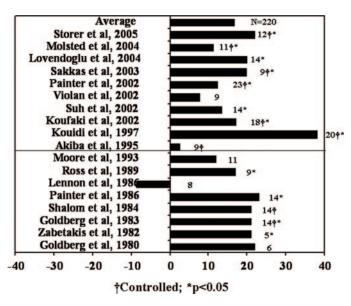


Figure 3. Change in peak oxygen consumption (VO<sub>2peak</sub>) in response to aerobic exercise training programs. Each bar represents a distinct study. The numbers to the right of the bars represent the number of exercising patients available for analysis. \*Change in VO<sub>2peak</sub> was statistically significant;  $^{\dagger}$ the study included a nonexercising control group. Studies above the black line included patients who received erythropoietin.

bic exercise training (30,31), the majority of studies have not reported this benefit (32-34,36). Studies of the lipid effects of vigorous aerobic exercise training have also been mixed, with some showing a decrease in triglyceride (30,31) or an increase in HDL cholesterol (30,31) and others not showing any changes (34-36). Given the small numbers of patients and lack of control groups in most of these reports, the effect of aerobic exercise training on lipid metabolism remains unclear. A recent study assessed the effects of twice-weekly aerobic exercise training on arterial stiffness and insulin resistance (46). Among 11 dialysis patients who completed the 3-mo program, arterial stiffness as measured by pulse wave analysis (augmentation index) decreased, but insulin resistance as measured by the homeostasis model assessment method did not change among the eight participants without diabetes. Few studies have addressed the effects of exercise on markers of inflammation, but one group measured C-reactive protein in 10 patients before and after a 6-mo intradialytic exercise program and found a significant reduction after exercise participation (47).

Two studies were designed specifically to investigate the effects of exercise on BP control in patients who were on hemodialysis (48,49). In the first, patients were nonrandomly assigned to a 6-mo cycling exercise program during dialysis (40 exercisers and 35 control subjects). At the end of 6 mo, 24 (60%) patients were still participating in the exercise program. The patients who completed 6 mo of training had no changes in BP before or after dialysis but were, on average, taking fewer antihypertensive medications to achieve that BP than before the program, whereas the control group did not have any significant change in BP or antihypertensive medications. The second study also involved cycling exercise during HD and enrolled 19 patients, 13 of whom completed at least 3 mo of training.

Predialysis and interdialytic (44 h) ambulatory systolic and diastolic BP decreased after 4 mo of training, a finding that persisted after 6 mo of training. The two studies to date that were specifically designed to evaluate BP control demonstrated a beneficial effect of exercise training.

A few studies have focused on the effects of aerobic exercise training on mental health or health-related quality of life among patients who are on hemodialysis. Carney et al. (50) reported that patients who underwent vigorous aerobic exercise training three times per week for 6 mo (n = 10) reduced their scores on the Beck Depression Index by an average of 4.3 points compared with an increase of 2.5 points in patients who did not exercise (n = 7; P < 0.05). Suh *et al.* (41) conducted a study that involved 14 patients who were on maintenance hemodialysis and underwent moderate-intensity aerobic exercise training three times per week for 12 wk. They reported a trend toward a decrease in depression using a Self-Rating Depression Scale (P = 0.073). In addition, they reported a significant reduction in anxiety and an improvement in quality of life as measured using an ESRDspecific instrument. Kouidi et al. (38) reported a significant improvement in overall quality of life and specifically in depression as measured by the Beck Depression Index after 6 mo of aerobic exercise training in 24 patients. In contrast, Painter et al. (51) included the Medical Outcomes Study Short Form 36-Item questionnaire (SF-36) as a major outcome in a much larger study and found no improvement in the mental health components with 16 wk of aerobic exercise.

The Painter study, called the Renal Exercise Demonstration Project (51), was unique in its large size and its focus on physical performance and health-related quality of life as the primary outcome measures rather than VO<sub>2peak</sub>. The study included 286 patients and included an 8-wk home-based training intervention followed by 8 wk of cycling exercise during dialysis sessions. Home-based training included recommendations for strengthening and flexibility exercises as well as walking or stationary cycling of gradually increasing duration three to four times per week. Cycling during dialysis was begun for as long as tolerated at an intensity that was determined by patients' level of perceived exertion. Patients were encouraged to increase cycling time to a goal of 30 min per session and to increase intensity as tolerated on the basis of perceived exertion. Outcomes included physical performance measures such as gait speed, 6-min walk distance, and ability to stand from a chair as well as self-reported physical functioning using the SF-36. The authors were able to demonstrate that physical performance and health-related quality of life improved with exercise training and declined in those who were not assigned to the exercise interventions. For example, the Physical Functioning (PF) score of the SF-36 increased 12% in the group that was assigned to exercise and decreased 12% in the control group. The authors noted that the impact of these interventions was more profound in the patients who had worse functioning at baseline (52). The intervention did include a recommendation to do low-intensity strengthening exercises in addition to aerobic exercise training, but this aspect of the program was not directly supervised even during the dialysis center training phase of the study, and fewer than 10% of the patients reported following this recommendation. For these reasons, it seems likely that the majority of the reported benefits can be ascribed to aerobic exercise training. This study demonstrated that a broader and less heavily selected group of patients who are on hemodialysis could participate in exercise training with improvements in functioning. In fact, from the point of view of physical performance and self-reported functioning, it seems that patients who are less able stand to benefit more from beginning an exercise program.

Other, more recent studies have also included measures of physical function other than VO<sub>2peak</sub>. For example, Molsted et al. (44) conducted a 5-mo study of twice-weekly aerobic exercise training. Among the 11 patients who completed the exercise program, there was an improvement in the PF score and the Physical Component Summary score of the SF-36. In a study of aerobic cycling exercise during dialysis in 12 patients, Storer et al. (45) reported improvements in muscle strength and fatigability among exercisers compared with a nonexercising control group. This perhaps surprising increase in strength in response to aerobic exercise was accompanied by changes in skeletal muscle growth factors, including a decrease in myostatin mRNA and increase in IGF-1 receptor in the eight patients with paired muscle biopsies, suggesting that these patients may be so deconditioned that even aerobic training provides a stimulus for muscle hypertrophy (53). However, muscle hypertrophy was not actually observed among the small number (n = 5)of patients in whom fiber size was measured before and after exercise. Finally, the exercising patients significantly improved their physical performance on tasks such as stair climbing, walking 10 m, and a timed up-and-go test, although these tests were not performed by the nonexercising control subjects for comparison.

The movement away from VO<sub>2peak</sub> as a primary outcome of aerobic exercise training has been accompanied by a movement toward administering exercise programs during dialysis treatments. There are several reasons that exercise training during dialysis is particularly attractive. First, there is the possibility of better adherence to a regimen that does not include extra visits, a possibility that was borne out in one comparative study (54). Second, hemodialysis sessions typically represent a period of forced inactivity and thereby may directly contribute to the poor functioning of this population. Therefore, exercise during dialysis represents an opportunity to reverse the potentially negative impact of dialysis (55). Third, it is possible that exercise could improve solute removal during dialysis by increasing blood flow to muscle and leading to greater efflux of urea and other toxins into the vascular compartment, where they can be removed (56). Indeed, several studies have shown that shortterm bouts of exercise or long-term exercise training can increase urea removal (47,56-58). However, these potential benefits must be balanced by the possibility of reduced exercise tolerance during dialysis as a result of fluid and electrolyte shifts and the possibility that exercise could exacerbate dialysisassociated hypotension. Nevertheless, beneficial effects of intradialytic exercise have been observed, and exercise is well

tolerated within the first 1 to 2 hours of dialysis sessions (17,34,39).

#### **Resistance Exercise**

Muscle strength is an important determinant of physical performance and ability to live independently in the geriatric population (59,60). Patients who receive dialysis are weak compared with healthy sedentary control subjects (19,61–65), and it is likely that weakness is an important limitation to physical functioning in patients with kidney disease. We previously showed that muscle strength was an important predictor of gait speed in patients who were on dialysis (19), and Diesel *et al.* (66) showed that isokinetic muscle strength was an important determinant of VO<sub>2peak</sub> in a group of patients who were on dialysis. Therefore, it seems likely that resistance exercise training could be of benefit to these patients, and it is surprising that few studies have focused on resistance exercise training or included resistance training as part of the program.

Headley et al. (67) reported on the results of a 12-wk resistance exercise training program in a group of 10 patients who were on hemodialysis. The program consisted of two supervised training sessions per week during which, after a 5- to 10-min warm-up period, patients performed eight to nine weight-machine exercises that were designed to strengthen the whole body. In addition to supervised training sessions, patients were given Theraband (Hygenic Corp., Akron, OH) exercise bands and instructed to follow at home once per week a video that covered nine exercises. At the end of the training program, the patients increased their peak torque of the leg extensors of the dominant leg at the 90°/s velocity by 12.7  $\pm$  3.6%, but there was no significant change in peak torque at 120°/s or 150°/s or in grip strength in either hand. Patients improved on several physical performance tests after the training, including a 6-min walk test, normal and maximum gait speed, and time to complete a sit-to-stand test 10 times. There were no complications or injuries related to the exercise training.

Our group recently completed a randomized 2 × 2 factorial trial of resistance exercise training and anabolic steroid administration in 79 patients who were receiving maintenance hemodialysis (68). Interventions included lower extremity resistance exercise training for 12 wk during hemodialysis sessions three times per week using ankle weights and double-blinded weekly nandrolone decanoate (100 mg for women; 200 mg for men) or placebo injections. Sixty-eight patients completed the study. Exercise did not result in a significant increase in lean body mass, but quadriceps muscle cross-sectional area as measured by magnetic resonance imaging increased in patients who were assigned to exercise (P = 0.01) and to nandrolone (P < 0.0001) in an additive manner. Patients who exercised increased their strength in a training-specific manner, and exercise was associated with an improvement in self-reported physical functioning (P = 0.04 compared with nonexercising groups), but there was no change in walking or stair-climbing time related to exercise participation. A trial of a similar intradialytic resistance training that also includes upper body exercises was recently completed as well (55), but the results have not yet been published. A preliminary report in abstract form suggests that C-reactive protein was reduced at the end of a 12-wk program (69).

#### Combined Resistance and Aerobic Exercise

Kouidi et al. (21) enrolled seven patients who were receiving long-term hemodialysis into a 6-mo exercise rehabilitation program that included aerobic exercise and strengthening exercise. The program consisted of 90-min sessions three times per week on nondialysis days. Specifically, the training routine included a 10-min warm-up followed by 50 min of aerobic exercises, 10 min of low-weight resistance exercise, 10 min of stretching exercises, and 10 min of cool-down. They examined the effect of this program on VO<sub>2peak</sub> and on muscle morphology. The program resulted in an average increase in VO<sub>2peak</sub> of 48%, an increase that is greater than any program involving aerobic exercise training alone (Figure 2). They also reported a remarkable improvement in muscle atrophy, with a 25.9% increase in the mean area for type I fibers and a 23.7% increase in mean area of type II fibers. Although they characterized their training program as "mainly of aerobic type," the notable muscle hypertrophy and the stunning improvement in  $VO_{2peak}$  suggest that the strength training portion may have contributed important additive or synergistic effects to the aerobic training. It is possible that muscle atrophy in some patients with ESRD is so severe as to limit VO<sub>2peak</sub> because of the small mass of working muscle. Unfortunately, the design of this study did not allow the separate contributions of aerobic and resistance training to be delineated.

The same group of investigators also examined heart rate variability before and after the same exercise training program in 30 exercising patients and 30 sedentary control subjects (70). They found that heart rate variability increased among the exercisers, suggesting improved autonomic control of the heart and reduced risk for arrhythmia.

A couple of other studies of mixed exercise interventions included control groups. Mercer et al. (71) conducted a nonrandomized, controlled trial of an exercise rehabilitation program that occurred during a 12-wk period and included a combination of intermittent aerobic exercise on a cycle ergometer and a local muscular endurance circuit of eight exercises. A total of 212 patients were potentially available to participate, but only 22 volunteered and were eligible. Thirteen were slated for the exercise, but only seven completed the study. These patients showed improvements in performance of a 50-m walk (15  $\pm$ 5.8%), stair climbing (22  $\pm$  11%), and stair descent (18  $\pm$  12%) after the exercise intervention. DePaul et al. (72) conducted a randomized trial of a mixed-exercise intervention among patients who were on hemodialysis and were receiving erythropoietin. The intervention consisted of progressive resisted isotonic quadriceps and hamstrings exercise and training on a cycle ergometer three times weekly for 12 wk. Cycling exercise was performed during dialysis, and weight training took place before or after dialysis according to patient preference. Twenty patients were randomly assigned to the exercise group, 15 of whom were available to be retested after 12 wk. The exercise group increased the workload at which their rating of exertion on the Borg scale (73) was "somewhat strong" by 20 ± 18 W,

compared with an increase of 6 ± 13 W for the control group (P = 0.02). At 12 wk, the intervention group also increased their combined hamstring and quadriceps strength by  $46.7 \pm 49.3$  lb  $(P = 0.02 \ versus \ control \ group)$ . There were no significant or clinically important differences in disease-specific quality of life or performance on a 6-min walk test between the study groups. The authors noted that the group was particularly high functioning at baseline, with scores on the PF scale of the SF-36 and on the 6-min walk test that were close to reported values for healthy groups and significantly higher than baseline scores in the Renal Exercise Demonstration Project (51), in which it was noted that patients with lower functioning at baseline improved to a greater degree (52). Finally, two studies focused on Tai Chi among patients who were undergoing peritoneal dialysis (74,75). One reported an improvement in self-reported physical functioning (74), and the other reported an improvement in mental health scores (75).

#### Risks of Exercise

The most common risk of exercise participation in the general population is musculoskeletal injury; the most serious risks are those of cardiac origin, ranging from dysrhythmia to ischemia to sudden death. The risk of both types of adverse events is higher with high-intensity exercise than with submaximal exercise (76).

No studies have been specifically designed to assess the risk of exercise among patients with CKD; available information comes from case reports and from mentions of adverse effects that occurred during studies of the effects of exercise. Musculoskeletal risk may be increased in patients with CKD as a result of hyperparathyroidism and bone disease. Their bone disease may place them at higher risk for fracture (77), and spontaneous quadriceps tendon ruptures have been reported (78-80), probably as a result of poorly controlled secondary hyperparathyroidism. However, it is possible that weight-bearing or strengthening exercises could, in the long run, decrease the risks for falls and increase bone density, further lowering the risk for fracture. The up-front risks for injury can be minimized by including a warm-up period in exercise sessions, by avoiding high-impact activities, and by beginning training programs at lower intensity and progressing gradually as tolerated. These strategies have been used in many of the studies reviewed in this article with great success, because the number of adverse events that were associated with exercise testing and training has been extremely low. Furthermore, improved muscle strength and overall fitness that are achieved through an appropriately prescribed program of progressive exercise could reduce the likelihood of injury during exercise and associated with falls, possibly lowering the overall risk for musculoskeletal injury (76). Specific studies that are designed to assess the balance of risks and benefits of exercise training among patients with CKD would be of great value.

The risk for cardiac events during maximal exercise testing is low, on the order of 0.5 per 10,000 tests for death and 3.6 per 10,000 tests for myocardial infarction, estimates that are based on tests that were conducted in healthy and diseased populations (76,81–83). No data specifically address the risks in pa-

tients with kidney disease. It is likely that their risk is higher than in the healthy general population because of the high prevalence of risk factors for cardiac disease and known cardiac disease, but their risk is probably not significantly higher than the risk in populations that undergo diagnostic tests for cardiovascular disease. Again, no untoward cardiac events have been reported in any of the published studies of exercise testing in patients with ESRD, and, although these patients were a highly select group, the risk seems to be low (76). The risk for cardiac events during submaximal exercise (*i.e.*, training) is even lower than that for maximal testing (84). Although the risk for a cardiac event is transiently increased during exercise, overall, that risk is attenuated in individuals with higher levels of habitual physical activity (76).

A major purpose of medical screening before exercise participation is to determine which patients are at increased risk for cardiovascular events. However, all patients with ESRD or advanced CKD are at increased risk for cardiopulmonary disease. Therefore, the existing guidelines provide little assistance in determining whether exercise testing should be performed before initiation of an exercise program or which patients should be tested (76,85). The necessity for testing should be related to the proposed intensity of training and the patient's symptom or disease status. Patients with symptoms suggestive of cardiac disease or with known disease should undergo exercise testing before participation in vigorous training programs (85). However, many of the reported studies of moderate-intensity exercise training in patients with kidney disease have relied on history, physical examination, and, in some cases electrocardiographic testing to determine whether patients may participate in exercise training programs without adverse events, suggesting that this strategy is appropriate when moderate-intensity training is involved.

In addition to proper medical screening, some disease-specific considerations may reduce risk. Attention to patients' volume status and BP control is important in this population. Patients with ESRD should have their dry weight assessed frequently to avoid volume overload and may tolerate exercise best either during dialysis or on a day after a dialysis session.

# **Conclusions**

There is an ever-expanding body of literature related to the effects of exercise among patients with ESRD, and, recently, the quality of studies is improving. Returning to Figure 2 and the potential benefits of exercise in this population, there are now ESRD-specific data to suggest that exercise can improve many indicators of physical functioning, such as fitness, muscle mass, physical performance, and self-reported physical functioning. Fewer data are available to address cardiovascular indices. However, preliminary evidence suggests that exercise can enhance the management of hypertension, reduce inflammation, and improve endothelial function.

Why, then, has exercise not been broadly applied in this population? Until recently, lack of published position statements about exercise in this population may have limited enthusiasm for a focus on exercise. However, the recently published Kidney Disease Outcomes Quality Initiative (K/DOQI)

clinical practice guidelines on management of cardiovascular disease state that, "all dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity" (guideline 14.2) (86). The lack of randomized data on outcomes such as survival is also often cited as a reason that physical activity has not been incorporated into the routine care of dialysis patients (87,88). Although there is no doubt that larger studies of the effects of exercise interventions on survival and quality of life are needed, there is now more compelling evidence to support the benefits of exercise in the dialysis population than there is to support several other commonly used therapies, such as "statins" (87). Perhaps a larger barrier to implementation of exercise programs in the dialysis population is the lack of a clearly defined "best" program. This review has synthesized results from a myriad of different exercise programs of varied intensity, duration, and exercise modality. Given this remarkable variety, it seems that almost any method of increasing activity in this population is likely to be beneficial, but the nephrology community is desperately in need of comparative studies to determine the extent to which less vigorous activity is beneficial and to set forth a regimen or counseling program that can be broadly applied and incorporated into the routine care of our patients.

In the meantime, we should strive to follow the K/DOQI guidelines and encourage our patients to increase their level of physical activity. The first step toward increasing patients' activity level is assessment. Clinicians should determine whether patients are performing at least 30 min of moderate activity on three or more days per week. If not, then barriers to increasing activity should be investigated, including specific questions about musculoskeletal limitations and potential cardiac limitations such as dyspnea or chest pain. Musculoskeletal limitations can be further assessed and addressed through referral to a physical therapist. Cardiovascular symptoms warrant dry weight assessment and/or stress testing. Once these potential contraindications to exercise have been eliminated, patients should be encouraged to begin a walking program, starting with 10 to 30 min/d, 3d/wk at a moderate difficulty level as tolerated. Patients should then be encouraged to increase their walking time to at least 30 min on 3 d/wk or more, keeping the intensity at a moderate level (or a perceived exertion of "somewhat hard") (73). The success of such a program is likely to be enhanced by regular and ongoing physician or dialysis personnel assessment and encouragement of participation in physical activity. In addition, use of pedometers may increase participation by facilitating goal setting and providing tangible evidence of progress (89,90). Physical activity programs within the dialysis setting have the potential to be of great benefit as well, and the principles of implementation are similar to those outlined for a walking program (initial assessment, starting at a low level as tolerated, and gradual progression toward goals). However, it is impractical to consider such a program without universal support of dialysis staff, because the burden of maintaining an in-center exercise program falls largely on the clinical staff.

#### Disclosures

None.

#### References

- Office of the US Surgeon General: Physical Activity and Health: A Report of the Surgeon General, Washington, DC, US Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, 1996
- Sato Y, Nagasaki M, Nakai N, Fushimi T: Physical exercise improves glucose metabolism in lifestyle-related diseases. Exp Biol Med (Maywood) 228: 1208–1212, 2003
- 3. Willey KA, Singh MA: Battling insulin resistance in elderly obese people with type 2 diabetes: Bring on the heavy weights. *Diabetes Care* 26: 1580–1588, 2003
- 4. US Renal Data System: USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, Bethesda, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, 2006
- Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 63: 793–808, 2003
- 6. Johansen KL, Young B, Kaysen GA, Chertow GM: Association of body size with outcomes among patients beginning dialysis. *Am J Clin Nutr* 80: 324–332, 2005
- 7. Kalantar-Zadeh K, Kilpatrick RD, McAllister CJ, Greenland S, Kopple JD: Reverse epidemiology of hypertension and cardiovascular death in the hemodialysis population: The 58th annual fall conference and scientific sessions. *Hypertension* 45: 811–817, 2005
- 8. Suliman M, Stenvinkel P, Qureshi AR, Kalantar-Zadeh K, Barany P, Heimburger O, Vonesh EF, Lindholm B: The reverse epidemiology of plasma total homocysteine as a mortality risk factor is related to the impact of wasting and inflammation. *Nephrol Dial Transplant* 22: 209–217, 2007
- 9. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15: 458–482, 1990
- 10. O'Hare AM, Tawney K, Bacchetti P, Johansen KL: Decreased survival among sedentary patients undergoing dialysis: Results from the dialysis morbidity and mortality study wave 2. *Am J Kidney Dis* 41: 447–454, 2003
- 11. Sietsema KE, Amato A, Adler SG, Brass EP: Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. *Kidney Int* 65: 719–724, 2004
- 12. Kopple JD: The phenomenon of altered risk factor patterns or reverse epidemiology in persons with advanced chronic kidney failure. *Am J Clin Nutr* 81: 1257–1266, 2005
- 13. Painter P, Messer-Rehak D, Hanson P, Zimmerman SW, Glass NR: Exercise capacity in hemodialysis, CAPD, and renal transplant patients. *Nephron* 42: 47–51, 1986
- Barnea H, Drory Y, Iaina A, Lapidot C, Reisin E, Eliahou H, Kellerman JJ: Exercise tolerance in patients on chronic hemodialysis. *Isr J Med Sci* 16: 17–21, 1980
- 15. Beasley C, Smith D, Neale T: Exercise capacity in chronic renal failure patients managed by continuous ambulatory peritoneal dialysis. *Aust N Z J Med* 16: 5–10, 1986
- 16. Moore GE, Brinker KR, Stray-Gundersen J, Mitchell JH: Determinants of VO2peak in patients with end-stage renal

- disease: On and off dialysis. Med Sci Sports Exerc 25: 18–23, 1993
- 17. Moore GE, Parsons DB, Stray-Gundersen J, Painter PL, Brinker KR, Mitchell JH: Uremic myopathy limits aerobic capacity in hemodialysis patients. *Am J Kidney Dis* 22: 277–287, 1993
- 18. Violan MA, Pomes T, Maldonado S, Roura G, De la Fuente I, Verdaguer T, lloret R, Torregrosa JV, Campistol JM: Exercise capacity in hemodialysis and renal transplant patients. *Transplant Proc* 34: 417–418, 2002
- Johansen KL, Shubert T, Doyle J, Soher B, Sakkas GK, Kent-Braun JA: Muscle atrophy in patients receiving hemodialysis: Effects on muscle strength, muscle quality, and physical function. *Kidney Int* 63: 201–207, 2003
- McIntyre CW, Selby NM, Sigrist M, Pearce LE, Mercer TH, Naish PF: Patients receiving maintenance dialysis have more severe functionally significant skeletal muscle wasting than patients with dialysis-independent chronic kidney disease. Nephrol Dial Transplant 21: 2210–2216, 2006
- Kouidi E, Albani M, Natsis K, Megalopoulos A, Gigis P, Guiba-Tziampiri O, Tourkantonis A, Deligiannis A: The effects of exercise training on muscle atrophy in haemodialysis patients. *Nephrol Dial Transplant* 13: 685–699, 1998
- 22. Johansen KL, Chertow GM, da Silva M, Carey S, Painter P: Determinants of physical performance in ambulatory patients on hemodialysis. *Kidney Int* 60: 1586–1591, 2001
- 23. Brodin E, Ljungman S, Hedberg M, Sunnerhagen KS: Physical activity, muscle performance, and quality of life in patients treated with chronic peritoneal dialysis. *Scand J Urol Nephrol* 35: 71–78, 2001
- DeOreo PB: Hemodialysis patient-assessed functional health status predicts continued survival, hospitalization, and dialysis-attendance compliance. *Am J Kidney Dis* 30: 204–212, 1997
- Lowrie EG, Curtin RB, LePain N, Schatell D: Medical outcomes study short form-36: A consistent and powerful predictor of mortality in dialysis patients. *Am J Kidney Dis* 41: 1286–1292, 2003
- 26. Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK: Health-related quality of life as a predictor of mortality and hospitalization: The Dialysis Outcomes and Practice Patterns Study (DOPPS). Kidney Int 64: 339–349, 2003
- 27. Unruh M, Benz R, Greene T, Yan G, Beddhu S, DeVita M, Dwyer JT, Kimmel PL, Kusek JW, Martin A, Rehm-McGillicuddy J, Teehan BP, Meyer KB; Group HEMO Study: Effects of hemodialysis dose and membrane flux on health-related quality of life in the HEMO Study. *Kidney Int* 66: 355–366, 2004
- 28. Johansen KL, Chertow GM, Ng AV, Mulligan K, Carey S, Schoenfeld PY, Kent-Braun JA: Physical activity levels in patients on hemodialysis and healthy sedentary controls. *Kidney Int* 57: 2564–2570, 2000
- Johansen KL, Sakkas GK, Doyle J, Shubert T, Dudley RA: Exercise counseling practices among nephrologists caring for patients on dialysis. Am J Kidney Dis 41: 171–178, 2003
- 30. Goldberg AP, Hagberg JM, Delmez JA, Haynes ME, Harter HR: Metabolic effects of exercise training in hemodialysis patients. *Kidney Int* 18: 754–761, 1980
- Goldberg AP, Geltman EM, Hagberg JM, Gavin JR, Delmez JA, Carney RM, Naumowicz A, Oldfield MH, Harter HR:

- Therapeutic benefits of exercise training for hemodialysis patients. *Kidney Int* 24: S303–S309, 1983
- Zabetakis PM, Gleim GW, Pasternack FL, Saraniti A, Nicholas JA, Michelis MF: Long-duration submaximal exercise conditioning in hemodialysis patients. *Clin Nephrol* 18: 17–22, 1982
- Shalom R, Blumenthal JA, Williams RS, McMurray RG, Dennis VW: Feasibility and benefits of exercise training in patients on maintenance dialysis. *Kidney Int* 25: 958–963, 1984
- 34. Painter PL, Nelson-Worel JN, Thornbery MM, Hill DR, Shelp WR, Harrington AR, Weinstein AB: Effects of exercise training during hemodialysis. *Nephron* 43: 87–92, 1986
- Lennon DL, Shrago E, Madden M, Nagle F, Hanson P, Zimmerman S: Carnitine status, plasma lipid profiles, and exercise capacity of dialysis patients: Effects of a submaximal exercise program. *Metabolism* 35: 728–735, 1986
- Ross DL, Grabeau GM, Smith S, Seymour M, Knierim N, Pitetti KH: Efficacy of exercise for end-stage renal disease patients immediately following high-efficiency hemodialysis: A pilot study. *Am J Nephrol* 9: 376–383, 1989
- 37. Akiba T, Matsui N, Shinohara S, Fujiwara H, Nomura T, Marumo F: Effects of recombinant human erythropoietin and exercise training on exercise capacity in hemodialysis patients. *Artif Organs* 19: 1262–1268, 1995
- 38. Kouidi E, Iacovides A, Iordanidis P, Vassiliou S, Deligiannis A, Ierodiakonou C, Tournaktonis A: Exercise renal rehabilitation program: Psychosocial effects. *Nephron* 77: 152–158, 1997
- 39. Painter P, Moore G, Carlson L, Paul S, Myll J, Phillips W, Haskell W: Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. *Am J Kidney Dis* 39: 257–265, 2002
- 40. Koufaki P, Mercer TH, Naish PF: Effects of exercise training on aerobic and functional capacity of end-stage renal disease. *Clin Physiol Funct Imaging* 22: 115–124, 2002
- 41. Suh MR, Jung HH, Kim SB, Park JS, Yang WS: Effects of regular exercise on anxiety, depression, and quality of life in maintenance hemodialysis patients. *Ren Fail* 24: 337–345, 2002
- 42. Sakkas GK, Sargeant AJ, Mercer TH, Ball D, Koufaki P, Karatzaferi C, Naish PF: Changes in muscle morphology in dialysis patients after 6 months of aerobic exercise training. *Nephrol Dial Transplant* 18: 1854–1861, 2003
- 43. Levendoglu F, Altintepe N, Okudan N, Ugurlu H, Gokbel H, Tonbul Z, Guney I, Turk S: A twelve week exercise program improves the psychological status, quality of life and work capacity in hemodialysis patients. *J Nephrol* 17: 826–832, 2004
- 44. Molsted S, Eidemak I, Sorensen HT, Kristensen JH: Five months of physical exercise in hemodialysis patients: Effects on aerobic capacity, physical function and self-rated health. *Nephron Clin Pract* 96: c76–c81, 2004
- Storer TW, Casaburi R, Sawelson S, Kopple JD: Endurance exercise training during haemodialysis improves strength, power, fatigability and physical performance in maintenance haemodialysis patients. *Nephrol Dial Transplant* 20: 1429–1437, 2005
- Mustata S, Chan C, Lai V, Miller JA: Impact of an exercise program on arterial stiffness and insulin resistance in hemodialysis patients. *J Am Soc Nephrol* 15: 2713–2718, 2004

- 47. Zaluska A, Zaluska WT, Bednarek-Skublewska A, Ksiazek A: Nutrition and hydration status improve with exercise training using stationary cycling during hemodialysis (HD) in patients with end-stage renal disease (ESRD). *Ann Univ Mariae Curie Sklodowska [Med]* 57: 342–346, 2002
- 48. Miller BW, Cress CL, Johnson ME, Nichols DH, Schnitzler MA: Exercise during hemodialysis decreases the use of antihypertensive medications. *Am J Kidney Dis* 39: 826–833, 2002
- 49. Anderson JE, Stewart KJ, Hatchett L: Effect of exercise training on interdialytic ambulatory and treatment-related blood pressure in hemodialysis patients. *Ren Fail* 26: 539–544, 2004
- Carney RM, Templeton B, Hong BA, Harter HR, Hagberg JM, Schechtman KB, Goldberg AP: Exercise training reduces depression and increases the performance of pleasant activities in hemodialysis patients. *Nephron* 47: 194– 198, 1987
- 51. Painter P, Carlson L, Carey S, Paul SM, Myll J: Physical functioning and health-related quality-of-life changes with exercise training in hemodialysis patients. *Am J Kidney Dis* 35: 482–492, 2000
- 52. Painter P, Carlson L, Carey S, Paul SM, Myll J: Lowfunctioning hemodialysis patients improve with exercise training. *Am J Kidney Dis* 36: 600–608, 2000
- 53. Kopple JD, Cohen AH, Wang H, Qing D, Tang Z, Fournier M, Lewis M, Casaburi R, Storer T: Effect of exercise on mRNA levels for growth factors in skeletal muscle of hemodialysis patients. J Ren Nutr 16: 312–324, 2006
- 54. Konstantinidou E, Koukouvou G, Kouidi E, Deligiannis A, Tourkantonis A: Exercise training in patients with end-stage renal disease on hemodialysis: Comparison of three rehabilitation programs. *J Rehabil Med* 34: 40–45, 2002
- Cheema BS, O'Sullivan AJ, Chan M, Patwardhan A, Kelly J, Gillin A, Fiatarone Singh MA: Progressive resistance training during hemodialysis: Rationale and method of a randomized-controlled trial. *Hemodialysis Int* 10: 303–310, 2006
- Parsons TL, Toffelmire EB, King-VanVlack CE: Exercise training during hemodialysis improves dialysis efficacy and physical performance. *Arch Phys Med Rehabil* 87: 680– 687, 2006
- 57. Kong CH, Tattersall JE, Greenwood RN, Farrington K: The effect of exercise during haemodialysis on solute removal. *Nephrol Dial Transplant* 14: 2927–2931, 1999
- 58. Parsons TL, Toffelmire EB, Vlack CE King-Van: The effect of an exercise program during hemodialysis on dialysis efficacy, blood pressure, and quality of life in end-stage renal disease patients. Clin Nephrol 61: 261– 274, 2004
- 59. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, Scherr PA, Wallace RB: A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. *J Gerontol* 49: M85–M94, 1994
- Potter JM, Evans AL, Duncan G: Gait speed and activities of daily living function in geriatric patients. Arch Phys Med Rehabil 76: 997–999, 1995

- 61. Bohannon RW, Smith J, Barnhard R: Grip strength in end stage renal disease. *Percept Mot Skills* 79: 1523–1526, 1994
- 62. Fahal IH, Ahmad R, Edwards RH: Muscle weakness in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 16: S419–S423, 1996
- 63. Spindler A, Paz S, Berman A, Lucero E, Contino N, Penalba A, Tirado S, Santana M, Zeballos AC: Muscular strength and bone mineral density in haemodialysis patients. *Nephrol Dial Transplant* 12: 128–132, 1997
- 64. McElroy A, Silver M, Morrow L, Heafner BK: Proximal and distal muscle weakness in patients receiving hemodialysis for chronic uremia. *Phys Ther* 50: 1467–1481, 1970
- 65. Fahal IH, Bell GM, Bone JM, Edwards RH: Physiological abnormalities of skeletal muscle in dialysis patients. *Nephrol Dial Transplant* 12: 119–127, 1997
- Diesel W, Voakes TD, Swanepoel C, Lambert M: Isokinetic muscle strength predicts maximum exercise tolerance in renal patients on chronic hemodialysis. *Am J Kidney Dis* 16: 109–114, 1990
- 67. Headley S, Germain M, Mailloux P, Mulhern J, Ashworth B, Burris J, Brewer B, Nindl B, Coughlin M, Welles R, Jones M: Resistance training improves strength and functional measures in patients with end-stage renal disease. *Am J Kidney Dis* 40: 355–364, 2002
- 68. Johansen KL, Painter PL, Sakkas GK, Gordon P, Doyle J, Shubert T: Effects of resistance exercise training and nandrolone decanoate on body composition and muscle function among patients who receive hemodialysis: A randomized, controlled trial. J Am Soc Nephrol 17: 2307– 2314, 2006
- 69. Smith B, Cheema B, O'Sullivan A, Pang G, Lloyd B, Patwardhan A, Chan M, Gillin A, Kelly J, Fiatarone Singh M: Resistance training during hemodialysis reduces C-reactive protein. Results from a randomized controlled trial of progressive exercise for anabolism in kidney disease (the PEAK Study). J Am Geriatr Soc 53: S13–S14, 2005
- 70. Deligiannis A, Kouidi E, Tourkantonis A: Effects of physical training on heart rate variability in patients on hemodialysis. *Am J Cardiol* 84: 197–202, 1999
- 71. Mercer TH, Crawford C, Gleeson NP, Naish PF: Low-volume exercise rehabilitation improves functional capacity and self-reported functional status of dialysis patients. *Am J Phys Med Rehabil* 81: 162–167, 2002
- 72. DePaul V, Moreland J, Eager T, Clase CM: The effectiveness of aerobic and muscle strength training in patients receiving hemodialysis and EPO: A randomized controlled trial. *Am J Kidney Dis* 40: 1219–1229, 2002
- 73. Borg GA: Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 14: 377–381, 1982
- 74. Ling K, Wong FSY, Chan W, Chan S, Chan EPY, Cheng Y: Effect of a home exercise program based on Tai Chi in patients with end-stage renal disease. *Perit Dial Int* 23[Suppl 2]: S99–S103, 2003
- Mustata S, Cooper L, Langrick N, Simon N, Jassal SV, Oreopoulos DG: The effect of a Tai Chi exercise program on quality of life in patients on peritoneal dialysis: A pilot study. *Perit Dial Int* 25: 291–294, 2005
- Copley JB, Lindberg JS: The risks of exercise. Adv Ren Replace Ther 6: 165–171, 1999
- 77. Alem AM, Sherrard DJ, Gillen DL, Weiss NS, Beresford SA, Heckbert SR, Wong C, Stehman-Breen C: Increased risk of

- hip fracture among patients with end-stage renal disease. *Kidney Int* 58: 396–399, 2000
- 78. Shah MK: Simultaneous bilateral quadriceps tendon rupture in renal patients. *Clin Nephrol* 58: 118–121, 2002
- Jones N, Kjellstrand CM: Spontaneous tendon ruptures in patients on chronic dialysis. Am J Kidney Dis 28: 861–866, 1996
- Ryuzaki M, Konishi K, Kasuga A, Kumagai H, Suzuki H, Abe S, Saruta T, Takami H, Tashiro M: Spontaneous rupture of the quadriceps tendon in patients on maintenance hemodialysis-report of three cases with clinicopathological observations. Clin Nephrol 32: 144–148, 1989
- 81. VanCamp SP, Peterson RA: Cardiovascular complications of outpatient cardiac rehabilitation programs. *JAMA* 256: 1160–1163, 1986
- Haskell WL: Cardiovascular complications during exercise training of cardiac patients. Circulation 57: 920–924, 1978
- 83. Gibbons LW, Mitchell TL, Gonzalez V: The safety of exercise testing. *Prim Care* 21: 611–629, 1994
- 84. Thompson PD, Funk EJ, Carleton RA, Sturner WQ: Inci-

- dence of death during jogging in Rhode Island from 1975 through 1980. *JAMA* 247: 2535–2538, 1982
- American College of Sports Medicine: Guidelines for Exercise Testing and Prescription, Philadelphia, Williams & Wilkins, 1995
- 86. National Kidney Foundation: K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis* 45[Suppl 3]: S1–S154, 2005
- 87. Painter P, Johansen KL: Improving physical functioning: Time to be a part of routine care. *Am J Kidney Dis* 48: 167–170, 2006
- Cheema BS, Smith BC, Fiatarone Singh MA: A rationale for intradialytic exercise training as standard clinical practice in ESRD. Am J Kidney Dis 45: 912–916, 2005
- 89. Tudor-Locke C, Bassett DR: How many steps/day are enough? Preliminary pedometer indices for public health. *Sports Med* 34: 1–8, 2004
- Croteau KA: A preliminary study on the impact of a pedometer-based intervention on daily steps. Am J Health Promot 18: 217–220, 2004

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