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Scholarly Review

Physical functioning in end-stage renal disease patients: Update 2005

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Abstract

Physical functioning in patients with end-stage renal disease treated with dialysis is low, whether measured using objective laboratory measures, physical performance testing, or self-reported measures. Peak oxygen uptake (VO_{2peak}), self-reported functioning measures, and physical activity levels are independent predictors of mortality in these patients. Cardiovascular exercise training studies result in improvements in VO_{2peak}, physical performance tests, and self-reported functioning. Resistance exercise training improves muscle strength. Exercise training may have positive benefits on other factors that are important clinical issues in dialysis patients, including cardiovascular risk profile, oxidative stress, and inflammation. Endothelial function, a surrogate marker of atherosclerosis, has been shown to improve with exercise training in dialysis patients. Although there have been numerous recent studies on benefits of exercise, few dialysis clinics or nephrologists provide encouragement or programs as a part of their routine care of their patients. There are many national guidelines that include exercise or increasing physical activity as a part of the treatment of many conditions that are relevant in dialysis patients, including hypertension, hyperlipidemia, and high cardiovascular disease risk. The nephrology community continues to state concern for outcomes; however, a simple, low-tech intervention that has many benefits to their patients (i.e., encouragement, recommendations, and opportunity for increasing physical activity) has not been adopted as part of the standard care. Adoption of routine counseling and encouragement for physical activity has the potential to improve outcomes, improve physical functioning, and optimize quality of life and overall health of dialysis patients.

Key words: Physical functioning, exercise capacity, exercise training

INTRODUCTION

The first publication that demonstrated low level of exercise capacity in a hemodialysis patient appeared in 1977.[1] Since then it has been well documented in many studies that patients with end-stage renal disease (ESRD) treated with dialysis are limited in their ability to perform physical exercise, with levels of exercise capacity reported to be 60% to 70% of age-expected levels.[2] Despite significant progress in technological aspects of renal replacement therapy and medical advances, patients remain limited physically, which negatively impacts overall health, quality of life, and outcomes (i.e., hospitalizations, mortality). Since the publication of the first randomized clinical trial of exercise training in hemodialysis patients,[3] there have been some key studies that have demonstrated the importance of this neglected part of ESRD patient care. This presentation is a review of what we know about exercise and physical functioning in ESRD in 2005.

In discussing literature related to exercise, it is important to clarify terms. *Physical activity* is defined as bodily movement that is produced by the contraction of skeletal

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muscle and that substantially increases energy expenditure. *Physical fitness* is a set of attributes that people have or achieve that relates to the ability to perform physical activity. One of these attributes is *cardiorespiratory fitness* (often referred to as *exercise capacity*), which relates to the ability of the cardiac, circulatory, and respiratory systems to supply and use oxygen during sustained physical activity.[4] *Physical functioning* is best defined as an individual's ability to perform activities required in their daily lives.[5,6] Physical functioning is determined by many factors, including physical fitness (cardiorespiratory fitness, strength, and flexibility), sensory function, clinical condition, environmental factors, and behavioral factors.[5,6] *Exercise training* is the planned, structured, and repetitive bodily movement done to improve or maintain one or more components of physical fitness or other health benefits.[4] Increased *physical activity* can be considered exercise training, although increased physical activity also can result from unstructured increases in movements throughout the day. It is also important to understand the concept of *specificity of training*, which means benefits obtained from exercise training are specific to the type of training performed. For example, the elegant study reported by Kouidi *et al*.[7] showed dramatic improvements in muscle histology, whereas other studies have not. The training program implemented by Kouidi was a combination of cardiovascular exercise (aerobic) and resistance training. Most studies have only been of the cardiovascular type of exercise and have not reported changes in muscle strength or muscle fiber histologic changes.

MEASUREMENT OF FUNCTIONING

Given the multiple determinants of physical functioning (i.e., cardiorespiratory fitness, strength, sensory function, clinical status, environmental and behavioral factors),[5,6] it is clear that no one measure can cover all areas. Thus, the measurement is complicated and should be tailored to specific populations and specific characteristics of interest. Assessment of functioning can range from objective laboratory measures of cardiorespiratory fitness to questionnaires on self-report of physical functioning, which include questions relating to the ability to perform activities that range from basic self-care to household activities and more strenuous tasks.

Cardiorespiratory fitness is objectively measured using laboratory measures of oxygen uptake during a maximal exercise test performed on a cycle ergometer or treadmill (VO_{2max}). VO_{2max} may be estimated from submaximal tests, but these estimations have limitations. There are criteria for achievement of VO_{2max},[8] many of which are not achieved by patients with chronic disease who are often limited by symptoms such as skeletal muscle weakness or shortness of breath. In such cases, the measure of exercise capacity should be referred to as peak oxygen uptake (VO_{2peak}) or symptom-limited VO_{2peak}.

Self-reported physical functioning can be assessed using questionnaires, such as the physical functioning scale on the SF-36 Health Status Questionnaire,[9,10] which assess level of difficulty performing activities of daily living (ADL), instrumental ADL, and more strenuous activities. The growing interest in physical functioning in older and diseased populations has led to development of tests that measure physical performance of standardized tasks such as walking (6-min walk, gait speed), balancing, reaching, rising from a chair, and climbing stairs.[11,12] These tests are referred to as physical performance tests and are not direct measures of cardiorespiratory fitness, strength, or flexibility, but are indicators of these physical fitness measures.

PHYSICAL FUNCTIONING IN DIALYSIS PATIENTS

Physical functioning as measured by objective laboratory measures, performance-based measures, and self-report is low in patients treated with dialysis. In patients who are able to perform symptom-limited maximal exercise testing, the values for peak oxygen uptake (VO_{2peak}) are severely reduced, averaging about 60% of age-predicted values[2,13–17] ranging from 17.0[7] to 28.6 mL/kg/min.[18] The specific limitations to VO_{2peak} in patients treated with dialysis have not been identified and are potentially numerous.[19] Painter *et al*. showed significant improvement in VO_{2peak} within 8 weeks after successful transplant. This improvement occurred without exercise training or significant improvements in hematocrit. Anemia associated with renal disease has always been implicated in the limited VO_{2peak}, and in the early trials of recombinant human (rHu)-erythropoietin (EPO) treatment, several studies measured VO_{2peak}. When increasing hematocrit from 17 to 20% up to 30 to 33%, there is a corresponding increase in VO_{2peak}.[20–23] The increase in VO_{2peak} per increase in hematocrit, however, is blunted compared to that observed in normal healthy subjects whose hematocrit was manipulated through phlebotomy and/or reinfusion of packed red cells[24–27] (Figure 1). Likewise, in the study by Painter *et al*.[19] in which hematocrit was increased using rHu-EPO from 33% up to 40% to 42%, there was no change in VO_{2peak},

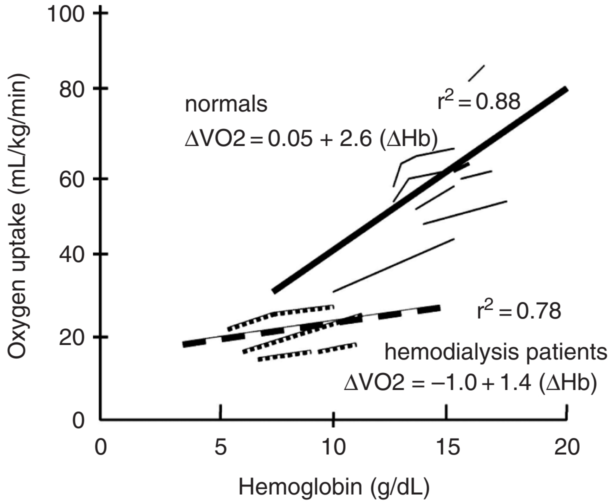

Figure 1 Changes in VO_{2peak} responses in healthy normal individuals and hemodialysis patients with manipulation of hematocrit (Hb = hemoglobin). Reprinted with permission.[123]

unless the patients were involved in exercise training (Figure 4). In fact, even with this near-normalization of hematocrit, VO_{2peak} remained surprisingly low compared to age-predicted values (mean, 56.8 ± 20.6% of age and sex predicted levels).

It is documented that these patients have low cardiac output responses to exercise, primarily because of a blunted heart rate. They also may be limited by endothelial dysfunction,[28] which may affect the ability to divert cardiac output to the working muscles during exercise. The blunted heart rate response and/or endothelial dysfunction may be related to autonomic dysfunction; however, this has not been well documented.[29] It is also widely evident that these patients have abnormal muscle function, both metabolic and structural.[7,30] Thus, although anemia may be the most obvious contributor to the limited VO_{2peak}, it appears that once hematocrit is treated to levels above 30%, there is no further benefit in normalizing it, in terms of exercise capacity, and other interventions, particularly exercise training may be needed to improve muscle function[7] to optimize utilization of the increased oxygen delivery resulting from the increased hematocrit levels.

The reported values for VO_{2peak} are for those patients who are physically capable to perform the test. It is possible that more than 50% of patients are physically not capable of performing a symptom-limited exercise test. Most studies have only included patients at the highest functional levels and have excluded patients with comorbidities such as diabetes or cardiovascular disease (CVD). Thus, most patients are well below these reported levels of VO_{2peak}. Although there are many patients who have comorbid medical conditions that may contribute to limited exercise capacity, the markedly low functioning in the best of the patients indicates that there is a need to intervene to increase functioning. To put these levels of VO_{2peak} in perspective, patients with congestive heart failure are classified as moderate severity if the VO_{2peak} levels are between 16 and 20 mL/kg/min.[31]

In patients who may not be able to perform symptom-limited exercise testing, physical performance testing may provide an indication of levels of functioning. Physical performance testing results are also low in dialysis patients.[32–37] Johansen *et al*.[33] reported that compared to age-matched healthy controls, gait speed was significantly lower in hemodialysis patients (100.2 ± 33.2 vs. 149.2 ± 35.3 cm/s). In a group of renal transplant candidates, gait speed was reported to be 77% of normal age-expected values,[32] and in a group of 131 hemodialysis patients who were more representative of the general dialysis population, gait speed was reported to be 66.1% of normal age-expected values.[35,36] Lower extremity function as measured by sit-to-stand testing was found to be severely limited in 111 patients, averaging less than 25% of normal age-predicted values.[35,36]

Self-reported physical functioning is the most commonly reported assessment in dialysis patients. Self-reported physical functioning (as measured by the SF-36 Health Status Questionnaire) is also severely limited.[33,35,36,38] The Physical Function (PF) scale is reported to be between 30[35,36] and 56,[33] averaging around 44[33,35,36,38,39] (on a scale of 0–100), all significantly below reported age norms.[9] The Physical Component scale (PCS) in dialysis patients is consistently reported to be 35,[35,38,39] well below the age norm of 50.[40] Other self-report instruments used in dialysis patients also report levels of physical functioning that are significantly lower than age-predicted norms.[41] Figure 2 demonstrates how limited dialysis patients' reported physical functioning is compared to documented levels in other chronic disease populations (using the PF scale of the SF-36 questionnaire).

SIGNIFICANCE OF LOW PHYSICAL FUNCTIONING

As early as 1997, DeOreo[38] reported that the self-reported physical functioning scores were predictive of outcomes. They reported in a historical prospective analysis of a large sample (n = 1000) of hemodialysis patients.

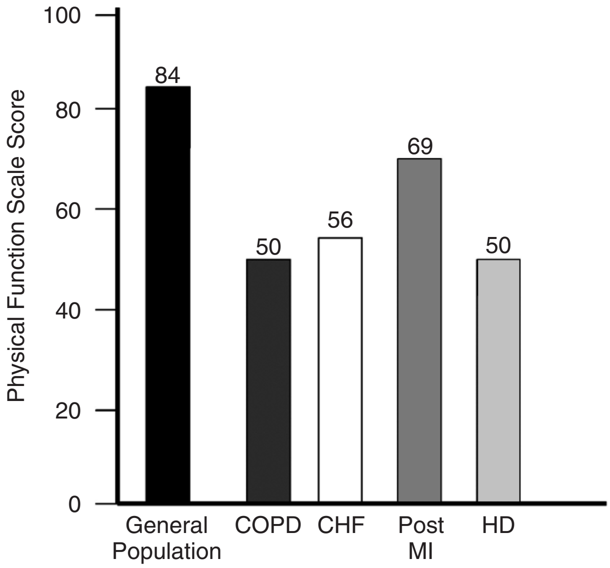

Figure 2 SF-36 Physical Function Scale Scores in several chronic disease populations: COPD = chronic obstructive pulmonary disease; CHF = congestive heart failure; MI = myocardial infarction; HD = hemodialysis. Adapted data from Ware *et al.*[40]

Those patients who scored below the median (< 34) on the PCS on the SF-36 questionnaire were twice as likely to die and 1.5 times more likely to hospitalized. This measure was as predictive of mortality as protein catabolic rate or Kt/V_{urea}. They concluded that for every 5-point increase in the PCS, there was a corresponding 10% increase in the probability of survival.

Knight *et al.*[42] reported the predictive values (hazard ratio for 1-year mortality) of the self-reported functioning (PCS on the SF-36) in 15,000 dialysis patients. They showed that compared to patients with a PCS score of > 50, those with PCS score of < 20 had a hazard ratio of 1.97; those with PCS of 20–29 had a hazard ratio of 1.62; and those with a PCS score of 30–39 had a hazard ratio of 1.32. Those who had a decline in PCS over 1 year had additional increase risk in mortality as evidenced by a hazard ratio of 1.25 per 10-point decline in PCS score. From this data set, Lowrie[43] earlier reported that for every 1-point increase in PCS there was a 3.5% improvement in the odds of death.

Parkerson and Gutman[41] showed very similar relationships between outcomes of mortality, hospitalization, and self-reported physical functioning using the Duke Health Profile questionnaire. All of these relationships take case mix into consideration in the statistical analyses.

Sietsema *et al.*[44] reported the prognostic value of exercise capacity as measured by VO_{2peak} in 175 ambulatory hemodialysis patients over a 3.5-year follow-up period. The analysis was based on the difference between those above and below the median value of VO_{2peak} of 17.5 mL/kg/min. The deaths per group were statistically lower in the group with higher values (4/88 or 5% compared to 19/88 or 22%; $p = 0.02$). They also reported that exercise capacity was the strongest predictor of survival over the 3.5-year follow-up, even when corrected for other contributing variables.

Although there are no data relating physical function test scores to outcomes in dialysis patients, there is a significant amount of observational data in the elderly that clearly documents that the loss of mobility and lower extremity function (as measured by tests of gait speed, sit to stand, and balance) results in higher rates of institutionalization, hospitalization, morbidity, and mortality.[45,46] The Established Populations for Epidemiologic Studies of the Elderly (EPESE), a very large study (n > 5000) sponsored by the NIA, has established a large database of functional measures of lower extremity function (i.e., gait speed, standing balance, sit to stand), which have been shown to be highly predictive of morbidity, mortality, hospitalization, and institutionalization in elders with arthritis,[47] CVD,[48] peripheral artery disease,[49] and general aging.[50]

Physical activity levels in ESRD

Most dialysis patients are sedentary.[35,51,52] Data from the Renal Exercise Demonstration Project[35] showed that 59% of 286 hemodialysis patients participated in no physical activity beyond basic ADL. Johansen *et al.*[51] reported that physical activity as measured by accelerometry (activity monitor) was significantly low in 39 hemodialysis patients compared to age-matched sedentary healthy controls (53.1 vs. 186.6 arbitrary units; $p < 0.001$). In this study, physical activity declined in the dialysis patients at a rate of 3.4% per month over a 12-month period.[33] Data from the USRDS Dialysis Morbidity and Mortality Study survey were used by O'Hare *et al.*[52] to dichotomize patients into sedentary (never or almost never participate in physical activity during leisure time) and nonsedentary (participation in some physical activity during leisure time). Of a total sample of 4024 patients, 12.4% were unable to ambulate or transfer. Of the 2264 who had physical activity data, 35% were categorized as sedentary. Eleven percent of the sedentary patients died over the 1-year follow-up period compared to 5% of the nonsedentary patients ($p < 0.001$). The patients classified as sedentary at study initiation showed a 62% greater risk of mortality over 1 year compared with nonsedentary patients with adjustment for other variables associated with survival in this group (perception of general health, cardiac disease, peripheral vascular disease, creatinine, hematocrit, dialysis modality, education level, male sex, diabetes, phosphorous level).

The Renal Exercise Demonstration Project[35] was a study that was designed to provide physical activity information and encouragement to a group of 286 patients who were quite representative of the general dialysis population, in that the mean age was 55.9 ± 15.1 years, and 43.7% had renal failure attributed to diabetes mellitus. There was a mean of three comorbid conditions, including CVD and other common conditions. Physical activity levels were categorized into four levels: ADL only; calisthenics (stretching/strengthening exercises); some cardiovascular exercise (< 20 min/session and/or three times per week), and recommended cardiovascular exercise (> 20 min/session and ≥ 3 times/week). Changes in physical activity participation are shown in Figure 3. At baseline, nearly 60% did only ADL. This decreased with the intervention to 6.4% at the end of the intervention. Those reporting the recommended levels of cardiovascular exercise was 12% at baseline and increased to 45% at the end of the

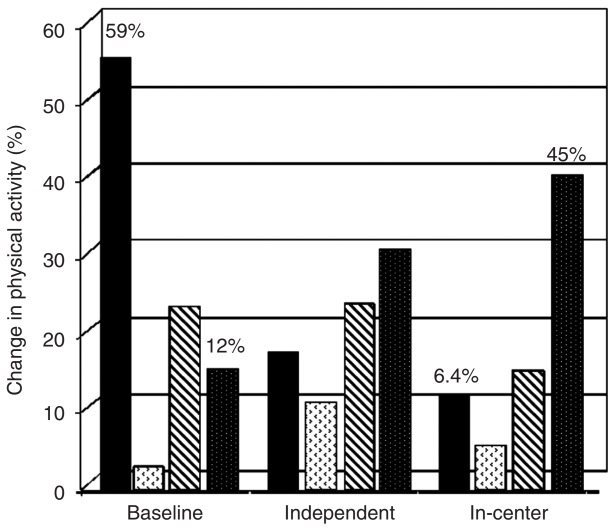

Figure 3 Changes in physical activity in the Renal Exercise Demonstration Project Exercise Intervention Group. (■) ADL only; (▨) stretching/strengthening exercises; (▧) some cardiovascular exercise (i.e. < 20 min/session and/or fewer than 3 days/week); (■) recommended cardiovascular exercise (at least 20 min/session; 3 or more days/week). Reprinted with permission.[35]

intervention. The frequency and duration of exercise in those categorized as recommended cardiovascular exercise increased from 23.7 min/session 3.2 days/week of participation to an average of 4.1 days/week for 38.4 min/session at the end of the study. This clearly demonstrates that dialysis patients will increase their physical activity if given specific information and encouragement to do so. There was an effort to include documentation of activity as a routine part of the predialysis assessment by the dialysis staff, and patient participation was greater in those clinics where this was accomplished.

Exercise training in dialysis patients

There are many exercise training studies in hemodialysis patients and several in peritoneal dialysis. Cardiovascular exercise training has conclusively been shown to result in increased exercise capacity ranging from 5 to 42% increases in VO_{2peak}.[3,7,19,53–59] Most exercise training studies that include measurement of VO_{2peak} as the outcome include the highest functioning patients, with exclusion of patients with diabetes and/or cardiovascular comorbidities. Thus, many are not generalizable to the overall dialysis population. What is striking in all of these studies, however, is the low level of VO_{2peak} in these higher functioning patients, suggesting some physiologic limitation imposed by the renal disease and/or the dialysis treatment. One such limitation may be anemia. In a randomized trial of normalization of hematocrit plus 5 months of exercise training in hemodialysis patients, Painter *et al.*[19] showed that the only significant factor in changing VO_{2peak} was exercise training—not normalizing hematocrit. The exercise group in the normal hematocrit group increased VO_{2peak} by a mean of 15.6 ± 11.3% and the usual hematocrit exercise group increased by 9.6 ± 21.1%. There were no changes in either control group (either in usual hematocrit or normalized hematocrit group) (Figure 4). Although mortality outcomes were not measured in this study, 10% of the subjects in the exercise groups had a change in VO_{2peak} from less than or equal to 17.0 mL/kg/min to values greater than 17.0 mL/kg/min. Using the data from Sietsema *et al.*,[44] this change may have resulted in improved mortality in those low functioning patients.

Physical inactivity is one of the strongest predictors of physical disability in older persons.[60,61] Although there are no data on elderly dialysis patients, the increasing age of patients on dialysis make the data in the general population of older persons relevant to the nephrology community. Regular physical exercise has been shown in longitudinal observational studies to extend longevity and to reduce risk of physical disability in later life.[62–66]

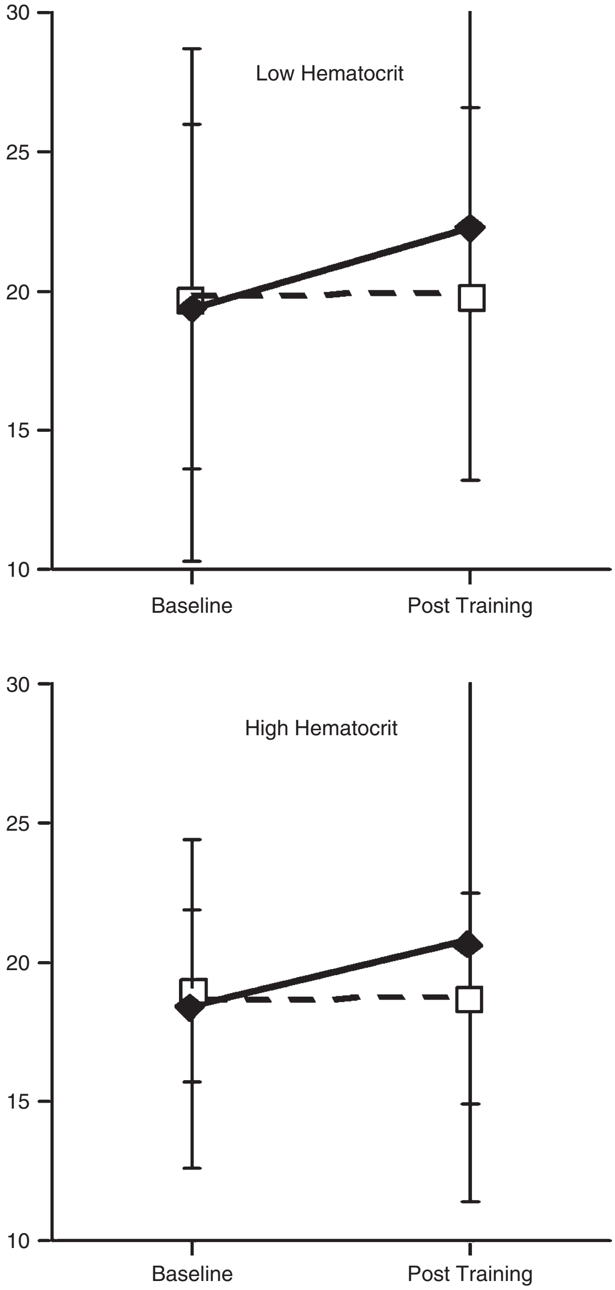

Figure 4 Changes in VO_{2peak} after 5 months of cardiovascular exercise training in exercise and no exercise groups in two hematocrit treatment groups. (◆) Exercise training; (□) no exercise training. Reprinted with permission.[19]

In the EPESE studies of 6200 older persons free of baseline disability, those with a low level (lower tertile) of regular physical activity were 1.8 times more likely to develop disability in ADL or mobility over 6 years than those with a high level (upper tertile) of physical activity.[63] The benefit of cardiovascular exercise on physical function in older populations may be through direct effect on impairments such as muscle strength online[7] low cardiorespiratory fitness,[68] and impaired balance[69] or through prevention of disabling diseases such as CVD. There have been several randomized clinical trials that have demonstrated beneficial effects of physical exercise programs in diseased and/or frail older adults. The Fitness and Arthritis in Seniors Trial (FAST) studied 439 community dwelling older adults with knee osteoarthritis. Self-reported physical function was significantly improved in those participating in an 18-month cardiovascular exercise training or resistance exercise training program compared to those participating in a health education program. The FAST programs also resulted in improved walking speed and balance.[47] There have been other studies in patients with chronic obstructive pulmonary disease[70] and heart failure[71] in which cardiovascular exercise training improved physical function and distance walked in 6 min. Frail older adults have shown significant improvements from resistance exercise programs and structured exercise programs, specifically in improved mobility, gait speed, and muscle strength.[72,73]

Cardiovascular exercise training has also been shown to result in significant improvement on physical performance tests in dialysis patients.[35–37] In the Renal Exercise Demonstration Project,[35,36] there were significant differences in the change over time in normal and fast gait speed and sit to stand tests between the exercise intervention group and no intervention group (Figure 5). The changes were most pronounced in patients who had low self-reported physical function scores (SF-36 PCS scale). This demonstration project clearly indicates that the natural course is for deterioration of physical functioning over time. Thus, *maintenance* of functioning is a positive outcome that can certainly be obtained with increasing physical activity.

The Renal Exercise Demonstration Project also resulted in significant improvements in self-reported physical functioning in the exercise intervention group (Figure 6). All four physical scales on the SF-36 improved in the exercise intervention group and either showed no change or deterioration in the no-intervention group. Thus the PCS score (a composite of the individual scale scores) was significantly improved as a result of the exercise intervention. It is not known whether changes in self-reported functioning resulting from exercise training results in improved outcomes; however, if the relationship between the PCS score and probability of survival and/or odds of death holds, the mean increase in PCS score of 7 points in the demonstration project in the

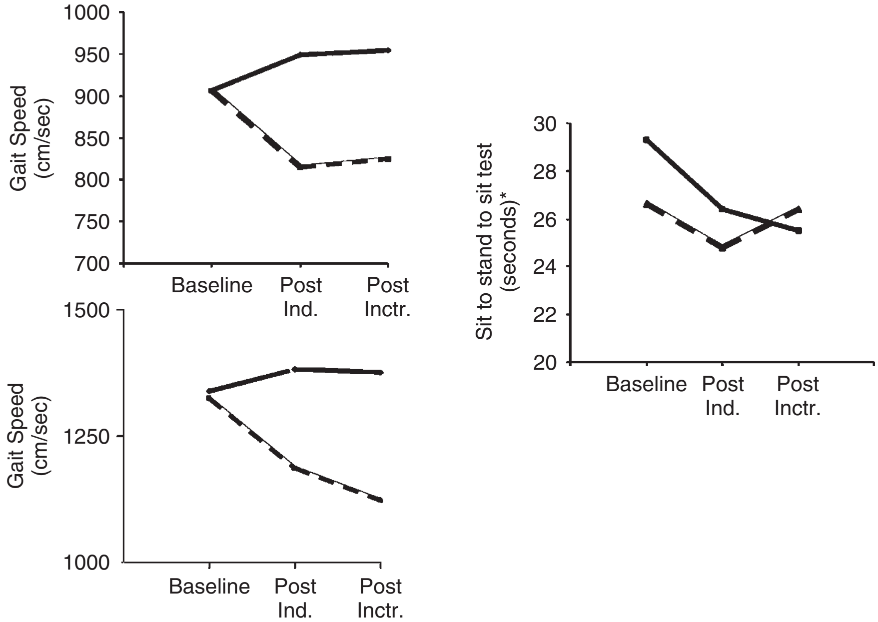

Figure 5 Changes in physical function tests in exercise intervention and no intervention groups in the Renal Exercise Demonstration Project. (—) Exercise intervention; (- - -) no intervention. Time by intervention interactions: normal gait speed $p = 0.019$; fast gait speed $p = 0.005$; sit-to-stand test $p = 0.004$. Reprinted with permission.[35]

low-functioning patients would translate to an increase in the probability of survival by 14% (using data of DeOreo[38]) or an improvement in the odds of death of 24.5% (using the data of Lowrie *et al.*[74]). This possibility clearly justifies a randomized clinical trial of increasing physical functioning in dialysis patients.

Health benefits of increasing physical activity

Many studies have shown positive health benefits from increased physical activity without structured exercise training. Regular physical activity may benefit a number of conditions that affect survival in the general population, many of which have been outlined in the literature.[4] Benefits of physical activity outlined in this report that are relevant to dialysis patients include reduction in CVD risk; prevention or delay in the development of hypertension and improvement of blood pressure in those with hypertension; reduction of the risk of developing diabetes; maintenance of muscle strength and joint structure and function; preservation of strength in older adults and help to maintain independent living status and reduction of the risk of falling; relief of symptoms of depression and anxiety; and enhancement of psychological well-being by improving physical functioning in persons compromised by poor health. There may be other benefits of regular physical activity that could positively impact other factors that are of concern in dialysis

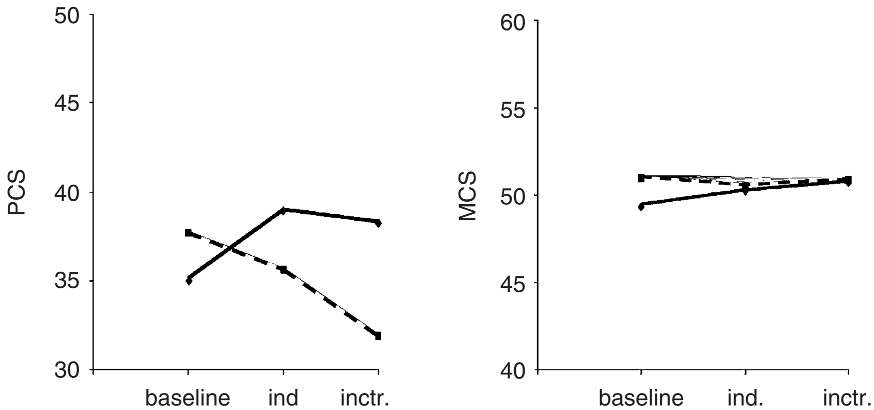

Figure 6 Changes in the physical and mental composite scale scores on the SF-36 in the Renal Exercise Demonstration Project. (—) Exercise intervention; (- - -) no intervention. Time by intervention interactions: PCS $p < 0.001$; MCS $p = \text{NS}$. Reprinted with permission.[35]

patients, specifically muscle wasting, cardiovascular risk, oxidative stress, and chronic inflammation.

Muscle wasting and muscle strength

Skeletal muscle atrophy is a significant problem in hemodialysis patients and is a significant predictor of morbidity and mortality in these patients and may be a significant contributor to limitations in physical functioning.[74] Johansen *et al*.[75] reported that contractile mass is reduced in hemodialysis patients compared to healthy age-matched controls. The reduction was associated with the reduced muscle strength. Kouidi *et al*.[7] reported impressive reversal in muscle atrophy assessed by morphometric analysis of muscle fibers obtained from muscle biopsy. The exercise training program was fairly intensive and involved combined cardiovascular and strengthening (through calisthenics and low weight resistance exercises) 90 min per session three times per week for 6 months in a supervised setting. They observed a 29% increase in fiber area, as well as favorable changes in ultrastructure and capillary and mitochondrial density. Headley *et al*.[76] reported that muscle strength can be increased with resistance training in hemodialysis patients. After 12 weeks of resistance training, there was an increase in quadriceps peak torque (measure of strength) of 12.7% and improvements in 6-minute walk distance, maximal walking speed, and the sit-to-stand test. Currently there is a randomized clinical trial of 30 hemodialysis patients (PEAK Study) under way in Australia.[77]

Muscle wasting is both dialysis and non-dialysis-related. Decreased dietary intake, sedentary lifestyle, and hemodialysis-associated catabolism are all important.[78] Pupim *et al*.[78] demonstrated that cycling exercise during dialysis enhances the anabolic effects of intradialytic parenteral nutrition. Exercise for 15 min initiated 15 min after starting of the dialysis session resulted in the increased uptake of amino acids and net muscle protein accretion by two-fold compared to intradialytic parenteral nutrition alone. These results are consistent with well-documented anabolic effects of cardiovascular exercise in healthy subjects, in which increased muscle amino acid uptake and muscle protein accretion in healthy subjects has been observed following an acute bout of exercise and following exercise training of the cardiovascular type.[79,80]

Cardiovascular risk

Regular cardiovascular exercise also has a positive influence on cardiovascular risk profile. In hemodialysis patients, early studies showed improvements in fasting glucose, insulin levels, and blood pressure with exercise training.[81,82] Reductions in blood pressure have been reported with cardiovascular exercise training by Hagberg *et al*.[83] and Painter *et al*.[56] with reductions in antihypertensive medication requirements. With the use of EPO for treatment of anemia, it is not known whether exercise training can override the vasoconstrictive side effects of EPO therapy. In the randomized clinical trial of exercise training plus normalization of hematocrit in hemodialysis patients,[19] there were no differences in blood pressure between the groups; however, there was a significant difference in total peripheral resistance during exercise, with the exercise groups showing significantly greater drops in vascular resistance during exercise (P. Painter, unpublished data). Miller *et al*.[84] reported a careful assessment of blood pressure responses to a program of 6 months of cycling exercise during hemodialysis in 40 patients, with 35 nonexercising controls. There were no statistical differences in predialysis or postdialysis blood pressures between the two groups at baseline or at 6 months; however, 13 (54%) of the exercise group had a reduction in antihypertensive medication use over the 6 months compared to 4 patients in the control group ($p = 0.008$). The mean relative benefit of exercise was a 36% reduction in antihypertensive medications with an average annual cost savings of $885/patient-year ($p = 0.005$) in the exercise group.

There have been no *randomized* trials to study the effects of exercise training on cardiovascular risk profile in dialysis patients. The very high prevalence of risk factors for CVD and the high rates of CVD would certainly justify such an intervention trial or trial of multiple risk factor interventions, which have been proven effective in reducing cardiovascular risk in other high-risk populations.[85] The Cardiovascular DOQI[86] guidelines specifically recommend that, "All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity." This guideline is based on the abundant data in other high-risk populations on the positive impact of regular physical activity on CVD risk.

Exercise and vascular function

Sheer stress (increased blood flow) is a potent stimulus for nitrous oxide release. Thus, measures such as vascular response to a change in flow (i.e., following transient vascular occlusion) serves as a stimulus for NO release, and the vascular response to this release can be measured using ultrasound (flow-mediated dilation [FMD]).

Brachial artery FMD has been correlated with coronary endothelial function as measured during cardiac catheterization,[87,88] and FMD predicts risk for future cardiovascular events in patients with chest pain[89] and has become a surrogate marker for cardiovascular morbidity and mortality. Cardiovascular exercise training has been shown to improve vascular endothelial function as measured by FMD in men with coronary artery disease. The FMD was 7.9% at baseline and 11.1% ($p < 0.05$) after 12 weeks of a standard cardiac rehabilitation program. This improvement in FMD was associated with increased plasma nitrate, nitrite levels, plasma 8-isoprostane-$F_2\alpha$, and plasma superoxide dismutase activity.[90] Similar improvements in vascular endothelial function have been demonstrated with exercise training in adult ESRD patients treated with hemodialysis. Mustata *et al*.[91] reported reduced arterial stiffness as measured by radial artery pressure waveform analysis in 11 patients after a 3-month cardiovascular exercise training program. The arterial stiffness measure was 17 μm at baseline and improved to 12.2 μm at the end of the intervention ($p = 0.01$). After cessation of the exercise training, the arterial stiffness measures reverted to preexercise levels. Rus *et al*.[92] reported similar findings following localized handgrip exercise training (squeeze a rubber ring 10 times/min for 30 min per day) for 8 weeks in 14 adult hemodialysis patients. FMD was 6.0 ± 0.4% at baseline and improved to 10.3 ± 0.7% ($p < 0.001$) at 8 weeks.

Exercise and inflammation

There are several epidemiologic studies that demonstrate a significant relationship between physical activity and markers of inflammation in adults. Higher levels of physical activity are cross-sectionally associated with lower levels of C-reactive protein (CRP), white blood cell count, and fibrinogen.[93] Abrahmson and Vaccarino[93] studied a large sample of 3638 apparently healthy men and women under 40 years who participated in the third National Health and Nutrition Examination Study. They reported that, compared to those engaging in physical activity 0 to 3 times per month, those who participated in physical activity 4 to 21 times per month had significantly reduced odds of having an elevated CRP level (odds ratio, 0.77) and for those who exercised 22 or more times per month, the odds were further reduced (odds ratio, 0.63). Similar associations were observed for white blood cell count and fibrinogen levels. Likewise, Alber *et al*.[94] measured CRP in more than 2800 subjects at baseline in the pravastatin inflammation/CRP evaluation study. They showed that CRP levels decreased progressively with increasing levels of physical activity ($p < 0.001$). This relationship between levels of strenuous activity participation and CRP levels remained when controlled for other factors that affect CRP, such as smoking, history of CVD, body mass index, high-density lipoprotein cholesterol, blood pressure, and age. In an intervention study of moderate intensity exercise over 6 months in 43 subjects at risk for having ischemic heart disease, Smith *et al*.[95] showed a significant ($p < 0.0010$) 58.3% reduction in blood mononuclear cell production of atherogenic cytokines (IFN-γ, TNF-α, and IL-1β) and a 35.9% increase in the production of atheroprotective cytokines (TGF-β, IL-4, and IL-10). There was also a 35% decrease in serum levels of CRP. These changes were independent of any modification of other associated risk factors and were directly correlated with the total number of hours subjects spent doing exercises of repetitive, lower body motion. The atheroprotective cytokines that were increased in this study are those that inhibit cell-mediated immune reactions of the type seen in atherosclerotic lesions, primarily by suppressing macrophage and lymphocyte function.

CRP levels have been reduced with progressive resistance exercise training in a randomized trial in 34 hemodialysis patients.[96] The resistance training group performed two sets of 10 exercises with free weights, targeting all major muscle groups, 3 times per week, during routine HD. The limb containing the vascular access was exercised just before each treatment session, whereas all other training was performed during dialysis sessions. LogCRP significantly decreased in the resistance training group compared to the control group ($f = 4.426$, $p = 0.047$). Reduced logCRP was correlated with improved strength ($r = -0.428$, $p = 0.042$), thigh muscle CSA ($r = -0.670$, $p < 0.001$), Mini-Nutritional Assessment Score ($r = -0.531$, $p = 0.006$), albumin ($r = -0.613$, $p = 0.001$), prealbumin ($r = -0.705$, $p < 0.001$), body mass ($r = -0.414$, $p = 0.040$), and protein catabolic rate ($r = -0.415$, $p = 0.049$).[96] Because CRP is a strong predictor of outcomes in dialysis patients,[97] further investigation of this positive effect of resistance exercise training is warranted.

Exercise and oxidative stress

Regular cardiovascular exercise results in protective adaptations such as decreased blood pressure, reduced platelet aggregation and adhesiveness, and increased coronary blood flow. These protective adaptations may be mediated, in part, by up-regulation of the basal levels of

NO production, which is thought to occur because of sheer stress on the endothelium. Up-regulation of NO production has been observed in cardiovascular exercise training studies.[98] Additionally, acute cardiovascular exercise increases NO production to facilitate blood flow, which has, in turn, been shown to up-regulate the expression of superoxide dismutase in vascular smooth muscle cells.[99] Although an acute bout of exercise may impose a mild oxidant stress, the repeated bouts of exercise on a regular basis is thought to initiate adaptations that reduce oxidative insult, such as reducing O_2^- production and up-regulating antioxidant enzymes.[99,100] Data in non-ESRD subjects have shown that 12 weeks of cardiovascular endurance exercise training resulted in increases in the basal activity of erythrocyte antioxidant enzymes and decrease neutrophil O_2^- production during exhaustive exercise.[101] The molecular mechanisms involved in the protective effects of exercise training are not known. Evidence suggests, however, that at least some of the atheroprotective effects on risk factors for CVD associated with cardiovascular exercise could be due to adaptations that minimize oxidative stress (i.e., increase antioxidant capacity) and/or that increase the availability of NO.[102]

INTRADIALYTIC EXERCISE

Cheema *et al*.[103] have made an elegant argument for incorporation of regular intradialytic exercise into the routine dialysis care. They argue that the practice of using stationary cycles during the hemodialysis treatment is safe, in that there have been no reported untoward events in any of the reported studies. The experience of the present author using cycling during dialysis is extensive, with exercise training in more than 400 hemodialysis patients. There have been no untoward events, andit is clear that there are no negative hemodynamic effects; in fact, systolic blood pressure stabilizes during the exercise time and patients typically experience less cramping and hypotensive episodes (personal experience). Cycling during dialysis has been shown to be effective in improving exercise capacity in several controlled studies[55,56] and in a randomized controlled trial.[19] Exercise training during dialysis has also been shown to reduce antihypertensive medication requirements.[56,84]

For many years, it was thought the exercise had no effect on the dialysis treatment per se. Recent studies, however, have demonstrated that cycling exercise during the treatment results in increased solute removal. Vaithilingham *et al*.[104] reported statistically greater weekly phosphate removal in 12 patients who exercised during dialysis compared to those who did not exercise. Exercise also increased midweek urea reduction ratio (although not statistically). The phosphate removal with exercise was similar to increasing dialysis time by 1 hr per session. Kong *et al*.[105] studied 11 patients who were on paired dialysis sessions: one with exercise and the other as a control. The rebound of urea, creatinine, and potassium were reduced significantly with exercise treatment. The rebound of urea dropped from 12.4 to 10.9%, creatinine from 21.2 to 17.2%, and potassium from 62 to 44%. Kt/V_{urea} and reduction ratios of all three solutes also increased significantly. These authors concluded that the improvement in dialysis adequacy with exercise training was equivalent to extending the length of the hemodialysis treatment by 30 min. The mechanism of these increases in clearance with exercise is thought to be dilation of vasculature within the skeletal muscles. At rest, muscle blood flow is minimal, rendering a very large percent of the body tissue unexposed to dialysis. During exercise, muscle blood flow increases in proportion to the relative intensity of the exercise effort,[106] thus increasing the tissue mass that is exposed to the dialysis treatment. The improved clearances that are achieved with cardiovascular exercise during the treatment plus the increases in physical functioning and other possible benefits certainly make the recommendation of incorporation of intradialytic exercise as a part of the routine treatment proposed by Cheema *et al*.[103] worth considering.

Physical activity recommendations in the nephrology community

The Life Options Renal Rehabilitation Advisory Council was established in 1993 with the goal of identifying barriers to rehabilitation in patients with ESRD treated with dialysis. Rehabilitation was defined as, "A coordinated program of medical treatment, education, counseling and dietary and exercise regimens designed to maximize the vocational potential, functional status and quality of life of dialysis patients."[107] The focus of the Life Options Initiative is to develop "bridges" to the barriers to renal rehabilitation. The bridges (core principles) identified are: 1) encouragement to adopt a positive bias toward rehabilitation on the part of the patient, dialysis team members, and families; 2) education for all patients and families about kidney disease, treatment options, self-care, employment; 3) exercise to prevent physical deterioration resulting from reduced activity; 4) employment goals to maintain their current jobs whenever possible and assuring access to vocational rehabilitation when needed; and 5) evaluation of rehabilitation outcomes to guide treatment and policy decisions. This group is committed to developing educational materials and promoting changes in practice within the dialysis and nephrology community in regards to rehabilitation. One of the first educational initiatives was to develop an educational program for exercise for the dialysis patient.[108] Before developing this guide, several focus groups were conducted among various professionals involved in the dialysis process to assess awareness and need for and limitations of an exercise program for dialysis patients.[109] Eight focus groups (two each with hemodialysis patients, nurse/managers of freestanding dialysis centers, social workers, and nephrologists) were held. The focus groups discussed the following: the current physicians' "prescription for exercise"; the role of the individual members of the management team in recommending or developing an exercise plan; the concept of an integrated exercise program and appropriate elements it should contain; the perceived benefits of such a program; and the potential barriers to adoption. A summary of these groups is beyond the scope of this review; however, the following recommendations came from the summary:

1 Although most health-care professionals agree that an integrated program of exercise as a part of the patients' rehabilitation is beneficial, there must be involvement by the nephrologist in incorporating this into the overall patient care. Nurses and social workers also need information on how to encourage and reinforce patient efforts.
2 Any program must be easily accessible. Evaluation of each center is necessary to assess space, staffing, etc., and a program must be flexible enough to accommodate units with a variety of physical and staff resources.
3 Any program must be introduced as a normal part of dialysis and a segment of the overall treatment plan.
4 Any plan must cover a wide variety of patient levels and interests. All ages and body types should be included in a variety of exercises ranging from walking to moving arms in the chair. The plan must include realistic expectations, beginning slowly with gradual progression.
5 A concomitant program of staff education and motivation is recommended to encourage health care professionals to value exercise to personally get involved in the program.
6 Tangible rewards should be presented to patients who successfully participate.

The Life Options *Exercise for the Dialysis Patient: A Comprehensive Program* was published and distributed to all dialysis clinics in the United States in 1995. Since that time, two surveys have been published that reveal practices related to exercise in dialysis clinics. In June 2000, the Rehabilitation Committee of the ESRD Network of New York (Network 2) surveyed the 200 dialysis clinics in the Network to learn about their exercise programs, to identify units with successful programs, and to identify factors that may be barriers to developing successful programs.[110] Ninety-one percent of the units (n = 182) returned the survey. Fourteen percent (26 units) offer an exercise program. On average, 20 patients per unit participate, most while dialyzing. There is about 25% patient drop out owing primarily to medical problems, loss of interest, and staff shortages. The major barriers identified were: 1) nephrologists were either not interested or not convinced of the benefits of exercise for their patients; 2) nephrologists were concerned about the safety of exercise; 3) staffing issues were of concern, including funding and lack of time; and 4) patients lack information about the benefits of exercise.

A second survey was performed by the Life Options Advisory Council staff in cooperation with the ESRD Network of Texas and Council of Nephrology Social Workers of North Texas.[111] The survey used the Unit Self Assessment Tool (USAT), which was developed to quantify and catalog ongoing rehabilitation efforts within dialysis clinics. The tool is a self-scored checklist of 100 possible rehabilitation activities, which was organized according to the five core principles of rehabilitation (above). The Exercise category consisted of 20 activities divided into levels of difficulty or complexity, each of which was given 1 point for scoring. Thus, the highest possible score for the exercise category was 20. A total of 169 centers completed the survey (68% response rate). Exercise practice was the lowest of all rehabilitation practices, with a mean of 3.7 ± 2.9 activities in the units. Only 21% of facilities had any advanced exercise activities (i.e., support of local fitness events among renal patients; providing for exercise programming outside of the unit; providing in-center, organized fitness activities during dialysis).

We recently confirmed that staff within the dialysis clinics are not routinely encouraging patients to participate in regular physical activity.[112] One-hundred dialysis staff with direct patient care responsibilities (nursing staff, patient care technicians, dieticians, or social workers) in five clinics completed questionnaires to assess encouragement for physical activity practices. Thirty-one percent of staff rated the levels of physical functioning of their patients as “excellent” or “very good” with only 17% rating functioning “poor” or “very poor.” Forty -five percent stated that at least half of their patients would benefit from increasing physical activity. Thirty-four percent never ask about physical limitations and 24% never or rarely encourage patients to be more physically active. Only 32% state that they regularly encourage patients to be active. Predictors of low physical activity encouragement among dialysis staff were: 1) job position (i.e., not professionally trained); 2) agreement with the statement, “It is not my responsibility to help patients increase their physical functioning”; 3) a perception of a lack of skills for motivating patients to exercise; and 4) agreement with the statement “dialysis patients lack motivation to exercise.” It is clear from these data that, although patient care staff think exercise is important and they want their patients to improve their levels of functioning, no consistent training is provided or policies/responsibilities are in place within the units for staff to either assess functioning or encourage exercise.

Exercise counseling practices among nephrologists caring for patients on dialysis were the topic of a survey reported by Johansen *et al*.[113] The investigators surveyed a total 505 nephrologists attending the Meeting of the American Society of Nephrology (October 2001), 277 of whom were from the United States. Although 98.6% of the US nephrologists stated that physical activity is beneficial for patients on dialysis, only 48.9% often ask about physical activity, and only 28.5% routinely prescribe exercise for their patients. Additionally, only 4.3% of the nephrologists provide written material about exercise to their patients. Characteristics that were significantly associated with noncounseling behavior in multivariate analysis were no time for physical activity counseling ($p < 0.0001$), not confident in counseling ability ($p = 0.005$), physical activity not as important as other medical concerns ($p = 0.051$), younger age of physician ($p < 0.0001$), male sex ($p = 0.013$), and lower percentage of practice that was primary care ($p = 0.035$). The authors suggest that these findings are consistent with the emphasis in medical training and practice guidelines such as the Dialysis Outcomes Quality Initiative (DOQI) on management of the dialysis procedure and of specific side effects of kidney disease and not on physical functioning. New DOQI guidelines recently published on management of CVD include guidelines specific to physical activity.

A smaller group of nephrologists completed a questionnaire at the 2003 World Congress of Nephrology.[114] This survey indicated that 95% agreed on the fact that the sedentary lifestyle is an important risk factor in chronic kidney disease patients; 78% thought that it is the responsibility of the nephrologist to advise the patients about physical activity. Thirty-three percent stated that they offered in-center exercise training programs and 15% said patients participate in out-center exercise groups. The Ruhr area of Germany appears to have the most active programs, where 20% of all hemodialysis patients are involved in intradialytic exercise programs. Currently 50% of units in this area of Germany are prescribing exercise, where participation rates have reached 75%. Germany appears to have a health-care system that provides the largest financial support for such interventions.

EXISTING RECOMMENDATIONS FOR EXERCISE

The “disconnect” between nephrologists’ view of the importance of physical activity for their patients and the lack of actual practice of providing programs for exercise for patients in the clinics or even recommendations as a part of the routine care is curious. Cheema *et al*.[103] suggested that the lack of support from expert advisory bodies, private advocacy groups, industry, and the health-care professional communities will be required if such practices are to become routine. There are several national guidelines in the United States, however, that recommend increased physical activity as the first line of treatment of several medical concerns that are important in dialysis patients. Specifically increased physical activity is included in the guidelines for treatment of hypertension,[115] hyperlipidemia,[116] patients with known cardiac disease or at high risk for developing cardiac disease,[117] and the general population.[4] There are also specific recommendations for patients with renal failure. The Renal Physician’s Association Clinical Practice Guidelines “Preparing Patients for Renal Replacement Therapy” states, “If a patient has GFR < 30 mL/min/1.73m^2 and does not engage in regular physical activity, then s/he should receive counseling and encouragement to increase physical activity.” Also, in the new KDOQI guidelines for CVD in dialysis patients, there is a guideline that states, “All dialysis patients should be counseled and regularly encouraged by nephrology and dialysis staff to increase their level of physical activity.”[86] Thus it appears that there are sufficient guidelines to recommend increased levels of physical activity for this patient group based on the high risk for CVD. The relationship of low functioning and outcomes should also be a compelling reason for the nephrology community to incorporate increased physical activity as a routine part of the patient care.

CHALLENGES

The challenge in the United States and likely in other countries is finding the resources to provide counseling and encouragement as a routine part of the patient care, whether that is in the physician's office or at the dialysis clinic. Intradialytic exercise is an ideal setting to provide the opportunity for increased physical activity, since patients are there three times/week using their time quite unproductively. With training and commitment from the leadership of the clinic, the environment could become a supportive and encouraging place to provide motivation for regular activity, and the clinical supervision may put the concerns of medical risk (which are minimal) at bay. Providing exercise at the dialysis location (either before the treatment or during the treatment) will facilitate participation because it is convenient, supported as part of the routine care, and an expectation of the treatment of the kidney disease. Missing the opportunity for productive use of the dialysis treatment time is disappointing. The Renal Exercise Demonstration project, however, clearly showed that patients can significantly improve functioning through an independent home exercise prescription. Thus, many patients can increase physical activity in their homes and/or participate in programs in the community. They must, however, be given a very clear message from the nephrology provider that this is an important part of the treatment for their kidney disease and their personal responsibility for maintaining their overall health. Ongoing encouragement and support are important in this patient group who often are anxious and depressed, making it difficult to start and maintain a program of regular physical activity. This presents an interesting dilemma for the nephrology community, because it is has been shown that exercise is as effective as either primary adjunctive therapy in the treatment of depression in the general population[118–121] and has been shown to improve psychological status in dialysis patients.[122] In elderly adults in the general population, improving their ability to perform ADL and maintain independence in their homes improves psychological profiles.[119,121] It may be the case that depression may render many patients unable to independently initiate a program of physical activity; thus greater levels of encouragement and monitoring may be needed.

SUMMARY

Clearly more research is needed in the form of randomized clinical trials to determine the effect of regular exercise on outcomes in dialysis patients. Much of nephrology practice, however, is based on epidemiologic and associative data from large databases and not randomized clinical trials. Thus, the excuse for not including exercise as a part of the routine care cannot be the lack of randomized clinical trials. The strong, independent association of low physical functioning and outcomes and the knowledge that physical functioning can be improved through exercise should be evidence enough to make efforts to determine the best and most efficient way to provide exercise counseling and encouragement and facilitate participation in regular physical activity in dialysis patients. The implications of the lack of movement to provide such programs as standard practice is a loss of patients' independence, increased need for institutional care, reduced quality of life, cardiovascular morbidity, and death. Now that the technological issues related to maintaining life on dialysis are familiar and successful, it behooves the nephrology community to work toward optimizing quality of life, functioning, and outcomes in their patients.

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