TITLE: Exercise in Patients with Chronic Kidney Disease and Kidney Transplant: A Review of the Clinical and Cost-Effectiveness

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CONTEXT AND POLICY ISSUES:

Chronic kidney disease (CKD) refers to persistent impairment of kidney function (> 3 months) that can range from minimal impairment (Stage 1) to kidney failure (Stage 5), the latter requiring dialysis and potentially leading to kidney transplant. It is estimated that 2 million Canadians have kidney disease or are at risk. Between 1998 and 2002, the prevalence of kidney failure in Canada increased by 33% while the incidence increased by 17%. At the end of 2005, almost 20,000 Canadians were receiving dialysis and the number is expected to climb sharply in the future. While no estimate of the economic burden of CKD is available, the average annual cost for dialysis is $55,466/patient (blended rate reflecting all dialysis modalities). The treatment of patients with kidney failure, a subset of the population with CKD, is estimated to consume 1.2% of Canada’s total health expenditures annually.

Numerous health related benefits have been identified in individuals who engage in appropriately structured exercise programs, including those with CKD. The efficacy of exercise for patients with CKD has been studied for 25 years and numerous studies appear to confirm its utility. Despite this finding, exercise has not generally found its way into standard clinical practice for patients in with CKD in most jurisdictions. This report reviews the evidence for the effectiveness of exercise in patients with CKD.

RESEARCH QUESTIONS:

1. What is the evidence of clinical benefit and harm of exercise in patients with chronic kidney disease or kidney transplant?

2. What is the cost-effectiveness of exercise in patients with chronic kidney disease or kidney transplant?

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METHODS:

A limited literature search was conducted of key health technology assessment (HTA) resources, including the PubMed, Cochrane Library (Issue 4, 2008), and University of York Centre for Reviews and Dissemination (CRD) databases; ECRI; EuroScan; and international HTA agencies. A focused Internet search was also completed. Results included articles published between 2003 and October 2008, limited to English language publications. Filters were applied to limit the retrieval to HTAs, systematic reviews (SRs), meta-analyses (MAs), economic studies, and randomized controlled trials (RCTs). In the reference list, internet links are provided where available.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, HTA reports, SRs, and MAs are presented, followed by RCTs and economic evaluations.

SUMMARY OF FINDINGS:

Question #1: Evidence of clinical benefit and harm

Health technology assessments
None were identified.

Systematic reviews and meta-analyses

One SR was identified.\(^5\) Published in 2005, it focused on exercise training in patients receiving maintenance hemodialysis (HD). The objectives of the SR were to (1) systematically review trials of exercise training involving adult patients on HD, (2) provide empirical evidence that exercise can counteract the wasting effects of end stage renal disease (ESRD), and (3) provide recommendations regarding future studies with a view to making exercise prescription more common in this patient population.

Studies were eligible for inclusion if they were RCTs, controlled or uncontrolled trials; and subjects were adults (≥ 18 years) receiving HD for ESRD. Interventions included aerobic and/or resistance training programs ≥ 5 weeks in duration. Outcome measures included a broad range of physiological, psychological, and functional measures potentially responsive to exercise.

The literature search covered the period from 1966 to November 2004. The search identified 34 articles reporting 29 trials including 13 RCTs, seven controlled trials, and nine uncontrolled trials (time series of a single treatment group). Sample size ranged from 7 to 286 (11 to 60 for the RCTs). Overall there was relatively equal gender representation (479 men; 460 women) and a broad representation of age groups (19 to 84). There was considerable heterogeneity in terms of exercise duration, modality, dose, and outcome measures thus precluding meta-analytic techniques.

Intervention duration ranged from 6 weeks to 4 years (7 weeks to 4 years for the RCTs) with the majority being 3 to 6 months. Most trials (19/29) relied solely on aerobic training while others combined aerobic and strength training components. Exercise frequency was three to four times a week for 30 to 60 minutes per session. Aerobic training was typically of moderate intensity while strength training was often of low intensity and focused on the lower limbs. Exercise training occurred during non-dialysis time at training centres and/or home (16 trials), during dialysis (11 trials) or during dialysis and at a training centre and/or home (2 trials). Compliance
was poorly reported and no trials defined compliance *a priori*. Adverse events included hypotension, fatigue, soreness, foot ulcer, and foot pain. One trial also reported an acute gastrointestinal hemorrhage. No trial defined adverse events *a priori*.

Identified benefits of exercise in patients on HD include improved cardiorespiratory functioning, muscle architecture and control, metabolic syndrome components (e.g., blood pressure, fasting glucose), dialysis adequacy, alleviation of depression, and improved quality of life (QOL) scores. The authors concluded, “...there is sufficient empirical published evidence to support the addition of exercise recommendations to clinical guidelines...” (p.363)

No formal evaluation of the quality of included studies is evident but methodological shortcomings and knowledge gaps in the literature were acknowledged by the SR authors. Limitations in statistical methods, limited involvement of blinded assessors, and incomplete reporting of participant characteristics, interventions and outcome measures were all noted with regard to the included RCTs. The external validity of the RCTs was also questioned given that the majority of included RCTs (9/13) excluded patients with diabetes which is a leading cause of ESRD.

**Randomized controlled trials**

Six relevant publications reporting on five RCTs were identified that were either published subsequent to or not captured in the SR described above:

**Castaneda et al.** described the results of an RCT examining the impact of a 12-week resistance training program on the malnutrition-inflammation syndrome complex in CKD. Subjects included patients > 50 years of age with moderately severe CKD who were not on dialysis (n=26). The active treatment group (n=14) engaged in supervised resistance training using five pneumatic training machines three times/week for 45 minutes. Participants performed three sets of eight repetitions on each machine (chest and leg press, latissimus pull down, knee extension and flexion) with training intensity targeted at 80% of a participant’s one repetition maximum. Control subjects (n=12) performed only the stretching and flexibility exercises used by the treatment group. All participants were asked to follow a low protein diet beginning 8 weeks before randomization and continuing through the intervention period.

Participants in the exercise group showed reductions in systemic inflammation as measured by serum C-reactive protein (CRP) and interleukin-6 compared with control subjects (*P*=0.01). In addition, patients in the exercise group showed significant benefits in muscle fibre cross-sections (*P*<0.05) and muscle strength (*P*=0.001). The authors noted limitations to their RCT including the small sample size and that fact that their results may not be generalizable to patients with other stages of kidney disease or different dietary regimes. However, they concluded that resistance training may reverse malnutrition-inflammation complex syndrome in patients with CKD.

**Van Vilsteren et al.** examined the effects of a 12-week low-to-moderate intensity exercise program on 25 variables related to physical fitness, health-related QOL, physiological measures, and behavioural change in a population of sedentary patients on HD (n=96). Exclusion criteria included cardiovascular disease, use of β-blockers, unstable angina, and orthopaedic complaints. The active treatment group (n=53) participated in both strength and aerobic training. The strength training component occurred prior to dialysis sessions and involved 40 minutes of calisthenics, step, flexibility, and low weight resistance exercises. The aerobic component included 20 to 30 minutes of cycling during the first 2 hours of HD sessions.
two to three times/week. Exercise intensity targeted ~60% of individual maximum capacity. The treatment group also received exercise counseling to improve exercise adherence. No reference is made to any form of intervention in the control group.

Results showed significant ($P<0.05$) positive change in seven variables (reaction time, lower extremity muscle strength, vitality, general health perception, health change, Kt/V [a measure of dialysis adequacy], and stage of change [a measure of readiness to adopt new behaviour]). There were no significant differences between groups in the other 18 outcome measures and no significant changes occurred in the control group. The authors concluded that even short-term activity improves some outcome measures in patients on HD.

Yurtkuran et al. reported the results of an RCT examining the effects of a 12-week yoga-based program in a population of patients receiving HD (n=37).\textsuperscript{8} Eligibility criteria included HD $\geq$ 6 months and an average musculoskeletal pain score of 2 on a 0 to 10 scale. There were many exclusion criteria related to cardiovascular, liver and orthopedic disorders, and diabetes; 75% of patients screened for eligibility were excluded.

The active treatment group (n=19) performed breathing and postural exercises under supervision in the HD unit 30 minutes/day, twice a week. Both the intervention group and the control group (n=18) were trained to perform range of motion exercises at home for 10 minutes each day. Outcome measures focused on pain, fatigue, sleep disturbance, and grip strength as well as 10 biochemical variables.

The treatment group showed significant improvements relative to the control group in 10 outcome measures including pain ($P=0.03$), fatigue ($P=0.008$), sleep disturbance ($P=0.04$), grip strength ($P=0.006$), urea ($P=0.02$), creatinine ($P=0.007$), alkaline phosphatase ($P=0.02$), cholesterol ($P=0.02$), erythrocyte count ($P=0.04$), and hematocrit count ($P=0.03$). Changes in the remaining four outcome measures (calcium, phosphorus, HDL-cholesterol and triglycerides) were not significant. The authors concluded that yoga-based exercise could have a role in the treatment of patients on HD but they called for larger RCTs to confirm the generalizability of their findings.

Cheema et al. conducted an RCT examining the effect of prolonged (24 weeks) versus short-duration (12 weeks) progressive resistance training (PRT) on muscle wasting in patients on HD (n=49).\textsuperscript{9,10} Major eligibility criteria included age $\geq$ 18 years, HD $> 3$ months, no medical contraindications to exercise, independent ambulation, and Kt/V $\geq$ 1.2. The study was conducted in two phases and was designed to provide a comparison of 12 weeks of PRT to usual care (no instruction to exercise or access to equipment)\textsuperscript{9} as well as the effect of 12 versus 24 weeks of PRT. In phase 1 the active treatment group (n=24) participated in PRT while the control group (n=25) received usual care. Phase 2 began at 12 weeks when the control group crossed over and began active treatment as well. PRT sessions occurred during HD 3 times/week and were supervised by an exercise physiologist. Exercises were performed in a seated or supine position and involved completing two sets of eight repetitions of each of 10 PRT exercises. Exercise intensity was hard to very hard.

Primary outcome measures were thigh muscle cross-sectional area and intramuscular lipid content while secondary outcomes included muscular strength, exercise capacity, and CRP level. In the 12-week PRT group, statistically significant improvements occurred for the treatment group in intramuscular lipid content ($P=0.04$), muscle strength ($P=0.002$), and CRP level ($P=0.02$) versus usual care.\textsuperscript{9} Although the 24-week PRT group showed some gains on most measures relative to the 12-week PRT group, no statistically significant change occurred.
in any measure. The authors noted a number of limitations including the lack of a no-exercise control group, location of the study at a single site and unblinded assessment of secondary measures. Large scale RCTs were called for.

Petraki et al. reported the results of an RCT examining the effects of exercise on cardiac baroreflex sensitivity in a population of patients on HD (n=43). Exclusion criteria included unstable hypertension, congestive heart failure, arrhythmias, recent myocardial infarct, angina, diabetes, liver disease, or a history of syncope. The active treatment group (n=22) performed 60 minutes of aerobic exercise (cycling) and 30 minutes of strength and flexibility exercises three times weekly during HD for 7 months. Exercise intensity was targeted to be somewhat hard. Two control groups, 21 HD patients and 20 age-sex matched healthy sedentary volunteers, continued their normal routines. Outcome measures included indices of cardiac baroreflex activity and cardiorespiratory efficiency. All indices of baroreflex activity improved significantly (P<0.05) in the treatment group versus the HD control group as did most measures of cardiorespiratory efficiency. The authors identified the need for additional studies to determine if these changes have any impact on cardiovascular morbidity and mortality in patients on HD.

Limitations

In addition to the absence of studies addressing patients with kidney transplants and only one study addressing patients with pre-dialysis CKD, a number of challenges exist regarding the available evidence. Most studies involved only a single site, were small in size, and were highly selective in terms of patient enrollment. In particular, most studies excluded patients with diabetes who represent a significant proportion of patients with CKD. As well, exercise type, intensity and duration displayed such variability as to preclude comparison of results or determination of the appropriate exercise prescription. Although most studies reported positive results, the implications of the results for disease progression, morbidity and mortality remains unclear. As noted in the SR, most of the RCTs do not satisfy current standards of reporting.

Question #2: Cost-effectiveness

No studies addressing the cost-effectiveness of exercise in CKD patients were identified.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

CKD represents a significant burden for both patients and the health system. Patients with CKD, especially those in kidney failure, experience high morbidity and mortality rates and poor health-related QOL. There is a relatively small pool of literature addressing the efficacy of exercise in the treatment of these patients although one group of experts asserts that virtually all the studies published over the past three decades have demonstrated that exercise is safe and beneficial in this population.

In contrast to the pool of literature addressing the efficacy of exercise in patients with CKD, especially those on HD, there appears to be no literature addressing the cost-effectiveness of exercise programs in this patient group. Although the absolute cost of an exercise program might not be large, it is clear that the cost could vary considerably depending on whether the program depended on low intensity interventions such as yoga-based exercises or more aggressive programs using sophisticated machinery such as PRT.

Despite the appeal of exercise programs in patients with CKD, decision-makers will want to consider several key issues evident in the literature. The available evidence appears to favour...
exercise programs that are carried out during HD but beyond this it provides decision-makers and planners with no guidance as to the optimal program design or exercise prescription (i.e., exercise type, intensity and duration). Perhaps more significant, the available evidence does not make a link between exercise-induced improvements in various intermediate outcome measures and reduced morbidity or mortality and only seldom makes the link to health-related QOL.

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