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Project Title: Effect of a 10-week Exercise Class Program on Physical Function and Quality of Life in Individuals with Chronic Kidney Disease

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Summary (250 words max single spaced):
Background: Inactivity in chronic kidney disease (CKD) exacerbates decline of physical function and health-related quality of life (HRQOL). Renal Rehabilitation Programs (RRP) combining education and exercise may mitigate this decline, but clinical effectiveness is unknown.
Objective: Evaluate the effect of a "real-world" RRP on physical function at one year in individuals with CKD.
Design: Quasi-experimental retrospective cohort study using non-equivalent control
Setting and participants: Adults with CKD in the Manitoba Renal Program. Exposed cohort (LKKM) received baseline assessment at Exercise Counseling Clinic (ECC) and attended a 10-week RRP (n=117). Comparison Group 1 (C1) received baseline assessment at ECC, but did not attend RRP over the same time-period (n=167). Comparison Group 2 (C2) included 316 individuals from a concurrent observational study of the same population.
Outcomes: Change in physical function measured by Short Physical Performance Battery Score (SPPB), HRQOL (EuroQol5D/VAS), physical activity level, exercise capacity, and hospitalization rate over one-year.
Results: 53, 40, and 207 completed one-year follow-up in the LKKM, C1, and C2 cohorts, respectively. Baseline median SPPB was 10.5(9-12), 10(8-12), and 9(7-11) in the LKKM, C1, and C2 groups, respectively (P=0.02). Mean change in SPPB over one-year was not significantly different (LKKM=-0.06(2.30); C1=-0.38(1.75); C2=-0.33(2.33); P=0.74). Attendance at RRP predicted improved physical function over one-year in those with SPPB <12 (OR=2.143; P<0.049). Remaining outcome measures showed no significant differences between groups in change over one-year.
Conclusion: A single RRP intervention may be protective against decline in physical function over one-year for individuals with CKD and reduced physical function.

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INTRODUCTION AND BACKGROUND

Approximately 3 million Canadians live with chronic kidney disease (CKD).[1] CKD is classified into 5 stages based on progressive loss of kidney function, measured by estimated glomerular filtration rate (eGFR).[2] Declining kidney function is associated with impaired health-related quality of life (HRQOL)[3] and declining physical function.[4-6] Prevalence of CKD is particularly high in Manitoba, especially in northern and rural communities, affecting between 7.4% to 13.8% of Manitobans.[7] Kidney function, HRQOL,[8,9] and physical function,[10] are lowest in stage 5 CKD, also known as end-stage renal disease (ESRD), which requires renal replacement therapy (RRT), either dialysis or transplant, in order to sustain life. Physical activity levels in CKD patients are also diminished relative to the general population,[11-13] and continue to decline with progressive CKD,[5] reaching lowest levels in ESRD.[14,15] Low levels of physical function and physical activity are predictive of increased risks of all-cause mortality and hospitalization, independent of age and comorbidities.[16-18] In addition, higher rates of physical activity have been associated with slower decline of kidney function.[19] Exercise programming is a strategy to increase physical activity behaviour and has been shown to improve physical function and HRQOL in CKD.[20,21] However, barriers to exercise in the CKD populations, which include fatigue, lack of motivation, and misconceptions regarding safety and effectiveness of exercise, may limit incentive for individuals to participate in exercise on their own.[22,23]

Combining exercise and education classes into a comprehensive renal rehabilitation program (RRP) has the potential to promote habitual exercise, improve physical activity behaviour, and improve disease self-management, which could further protect individuals with CKD from declining health, physical function and quality of life.[24] Combined exercise and education rehabilitation programs may also improve HRQOL by empowering individuals with knowledge to manage their chronic conditions and by functioning as a peer support group.[25] A supervised, outpatient based RRP has been shown to be more effective in improving training volume than independent training[26,27] and has been shown to be a cost-effective intervention in other chronic disease populations.[28] However, only a few evaluations of combined exercise and education interventions have been reported in the CKD population.[27,29]

First, a pragmatic, uncontrolled, observational cohort study evaluated a 12-week program consisting of twice weekly supervised exercise combined with education and additional weekly home-based activity. This study found a significant reduction in symptoms of anxiety and depression and improvements of physical function 20 individuals with stage 3 and 4 CKD after completing the program.[29] Later, Rossi *et al*. conducted a controlled single-centre randomized controlled trial (RCT) evaluation which demonstrated improved physical function and quality of life after a 12-week RRP consisting of twice-weekly guided exercise for individuals with stage 3 and 4 CKD (n=59) as compared to the control group (n=48).[30] Recently, Howden *et al.* completed a year-long efficacy RCT of an 8-week RRP consisting of multidisciplinary lifestyle and comorbidity education and 150 min/week of supervised cardio and resistance training followed by 10 months of prescribed home-based exercise with regular adherence check-in and follow up. Seventy-two patients with stage 3 to 4 CKD participated with 36 each in the intervention and control groups. This study demonstrated increased self-reported activity levels (assessed by the Active Australia Survey), at 6 months of supervised intervention, but a subsequent decrease after 10 months of home-based training, despite a persistent improvement in BMI as compared to controls who received usual care.[27] While these previous investigations show benefit in well-controlled trial settings and immediately after interventions, the real-world effectiveness of a combined exercise and education RRP in preventing decline of physical function and HRQOL in the general CKD population over time has not yet been reported. Further evidence for benefit of such programs is needed to inform the development of exercise and education-based renal rehabilitation therapy into standard clinical care.

Since 2007, the Manitoba Renal Program has offered a 10-week combined exercise and education RRP called “Lean Keen Kidney Machines” (LKKM). We present a pragmatic, quasi-experimental, longitudinal cohort study that evaluates the effectiveness of the Manitoba Renal Program’s ongoing clinical exercise program, the “Lean Keen Kidney Machine” (LKKM program in preventing the decline of physical function and HRQOL in adult patients with CKD. We hypothesize that individuals who attend the LKKM program will have less decline in physical function and HRQOL relative to their peers who do not attend the LKKM program over one year.

MATERIALS AND METHODS

Ethics

The protocol for this study was approved by the Manitoba Health Information Privacy Committee (HIPC), the Winnipeg Regional Health Authority (WRHA) Research Review Committee and the Manitoba Centre for Health Policy (MCHP). Ethics approval was obtained from the University of Manitoba Human Research Ethics Board (HREB), reference number: HS18570 (H2015:149).

Study Design: Retrospective analysis of prospectively collected data using quasi-experimental pre-test post-test non-equivalent control design.

Study Setting and Population: All participants were adults (≥18 years old) with any stage of CKD and registered in the Manitoba Renal Program (MRP), a large provincial renal program responsible for care of individuals with CKD throughout the province of Manitoba. Participant flow and group allocation is depicted in Figure 1.

The ***exposed population (LKKM)*** was comprised of individuals who attended the MRP’s Exercise Counseling Clinic (ECC) between Jan 1, 2011 to March 31, 2016 and were referred to and attended at least 50% of a 10-week LKKM session within a year after their initial ECC appointment.

The ***first comparison group (C1)*** included individuals who attended the ECC between Jan 1, 2011 to March 31, 2016 and were referred to LKKM classes, but did not attend the LKKM program in the year after their baseline assessment.

To account for the threat of self-selection of a motivated sample in the LKKM group, a ***second comparison group (C2)*** was added to the analysis. C2 consisted of a convenience sample of individuals with CKD enrolled in the Canadian Frailty Observation and Interventions Trial (CanFIT) trial, a concurrent longitudinal observational study of frailty status. CanFIT participants underwent similar clinical, physical function, and quality of life evaluations as those performed in the ECC (described below), but did NOT attend the ECC or LKKM classes (Figure 1).[31]

Exercise Counselling Clinic and ECC Research Database

The ECC provides functional assessment, exercise counselling, and medical clearance to exercise for individuals with CKD. Patients referred to the ECC by physicians or allied health staff within the MRP are assessed at baseline and annually at the Wellness Institute at the Seven Oaks General Hospital in Winnipeg. As part of their assessment at the ECC, attendees complete several self-reported questionnaires including a medical and surgical history form, Human Activity Profile, and the EuroQol EQ-5D-3L. At clinic, attendees first meet with a nephrologist who assesses contraindications to exercise. Attendees then complete an assessment of physical capacity that includes the Short Physical Performance Battery (SPPB) and Shuttle Walk Test. Attendees may choose to provide voluntary consent for inclusion of their clinic visit information into the ECC Research Database (ECDB – approved by University of

Manitoba HREB). Subsequently, an individualized exercise plan, taking individual goals, barriers and resources into consideration, is provided by a Certified Exercise Physiologist. As part of this plan, ECC attendees may be referred to the LKKM Program.

Lean Keen Kidney Machine Exercise Class Program

LKKM is a 10-week RRP combining education and exercise, which aims to empower individuals with CKD in Manitoba with the knowledge and confidence to improve their physical function and quality of life through regular exercise and chronic disease self-management. In the program, individuals learn how to exercise safely and how to improve their nutrition, lifestyle, and medication practices. Social support and external motivation is provided by the cohesive nature of the participant cohort, and the encouragement of family or friend supporters to join participants.[32]

The LKKM program is developed and supervised by a Certified Exercise Physiologist. Classes are held weekly at several locations in the city of Winnipeg and consist of 1 hour of education and 1 hour of group fitness activity. Education topics vary by session and include topics such as exercise theory, overview of kidney disease, medications, and nutrition. Exercise sessions also vary in content week to week and generally begin with supervised cardiovascular activity of the participant's choice, such as walking on the track or stationary cycling, followed by strength training using resistance tubing, body weight, free weights, or machines, and conclude with balance exercises and stretching. Participant feedback contributes to the improvement and inclusion of new programming in future iterations.

CanFIT Study Database

The CanFIT study is an ongoing longitudinal cohort study investigating the trajectory of frailty status and its effect on individuals living with CKD in Manitoba.[31] Individuals with all stages of kidney disease attending MRP renal clinics are eligible to participate. Participants are excluded if they have severe visual or hearing impairment. Demographic and clinical information, and results from EQ-5D-3L and SPPB assessment, are collected at baseline and annual follow-up assessments.

Outcome Measures

Primary Outcome

Change in Physical Function at one year as measured by Short Physical Performance Battery Score (SPPB). The SPPB has 3 components: a chair stand test, 3 balance tests (side by side, semi-tandem and tandem), and a 4-metre gait speed test. The SPPB is scored out of 12 with scores in each of the 3 individual components ranging from 0, an inability to complete the test to a maximum performance score of 4.[33] Participant physical function limitations can be classified as severe (0-3), moderate (4-6), mild (7-9), or minimal (10-12) based on total SPPB score.[34] As a measure of lower extremity function, SPPB has been validated in the CKD population to assess physical performance and declining physical function.[31,35,36] SPPB score is sensitive to change with an established minimal clinically important difference (MCID) of between 0.5 and 1 point[37], and is predictive of disability, hospitalization, and mortality.[33,38,39]

Secondary Outcomes

1. *Change in HRQOL* at one year was measured using the EuroQol™ EQ-5D tool, which includes two components, the EQ-5D-3L self-reported questionnaire, and the EQ-5D Visual Analogue Scale (VAS). The EQ-5D-3L asks respondents to rate their health across 5 different dimensions: mobility, self-care, usual activities, pain/discomfort, and

anxiety/depression. Participants report their perceived health status for each dimension on a 3 point Likert-type scale, with 1 representing “no problems”, 2 indicating “some problems”, and 3 indicating “extreme problems” or complete incapacity in that dimension. The EQ-5D-VAS asks participants to report their overall perceived health status from 1, or “worst imaginable” to 100 or “best imaginable”.[40] The EQ-5D has been validated in multiple chronic disease populations including CKD and ESRD[41,42] and normative data for Canadians and the CKD population are available.[43]

2. *Change in Exercise Capacity* at one year was measured in the LKKM and C1 groups only by the Incremental Shuttle Walk Test (ISWT). The ISWT is a timed walking test in which participants walk a 10-metre course at a speed that increases by 0.6 km/h each minute, starting at 1.8 km/h to a maximum of 8.5 km/h at level 12. The ISWT was originally developed and validated in the Chronic Obstructive Pulmonary Disease (COPD) population,[44,45] with an established MCID for COPD patients of 47.5 m,[45] and has been successfully used in the CKD population to evaluate exercise capacity.[29,46] Exercise capacity was not assessed in the CanFIT study.

3. *Change in self-reported physical activity behaviour* at one year was measured in the LKKM and C1 groups using the Human Activity Profile (HAP). The HAP has been used in a variety of clinical populations, including CKD and ESRD, to evaluate self-reported daily physical activity.[47,48] The HAP consists of a 94-item questionnaire of intensity-ranked activities for which the individual reports either they are still doing, have stopped doing, or have never done. There are two components to the HAP: The Maximum Activity Score (MAS), which corresponds to the number of the most aerobically-demanding activity the participant is still doing, and the Adjusted Activity Score (AAS), which approximates usual activity level and incorporates the number of activities the individual is no longer doing into its score.[49] A change in HAP score of approximately 0.5 of the standard deviation of baseline scores has been estimated to indicate a clinically significant difference.[48,50]

   Additionally, the proportion of participants reporting exercising regularly ($\geq$30 min$\geq$3 times per week) was compared between the LKKM and C1 groups at baseline and at one-year follow-up.

4. *Hospitalization* rate and number of admission days over one year were derived from data obtained from the Discharge Admission and Death Hospital Abstracts (Manitoba Health) housed at MCHP.

5. *Mortality*: The proportion of individuals who died over one year was ascertained using data from the Manitoba Health Insurance Registry housed at MCHP.

Data Collection and Management

Demographic, clinical, and outcome data for baseline and one-year follow-up assessments were obtained from the ECDB for the LKKM and C1 groups and from the CanFIT database for the C2 group. To prevent duplication, individuals who were referred to LKKM through the ECC and were also enrolled in CanFIT study were included only in the appropriate ECC study cohort (LKKM or C1, depending on LKKM attendance status) for our analysis.

Data with participant information over the pre-determined study period from the ECDB and CanFIT databases was collated into a single data set. This data set was sent to the Manitoba HIPC for de-identification (scrambled Personal Health Information Number) and subsequently forwarded to the MCHP, where hospitalization data from the Discharge Admission and Death administrative database and mortality data from the Manitoba Health Insurance Registry was added to the dataset. The final dataset was stored at MCHP. All data analysis was performed at MCHP by the study statistician (TF) through a remote access site.

Data Analysis

Descriptive statistics consisting of mean and standard deviation (SD) for normally distributed data, median and interquartile range (IQR) for non-normally distributed data, or proportion for categorical data, were calculated using baseline demographic, clinical, and outcome data to characterize and compare the 3 study groups. Group differences were compared with Analysis of Variance (ANOVA) or Student's T-Test if normally distributed, or using the Kruskal-Wallis or Mann–Whitney U test if not normally distributed. For categorical variables, proportions were compared using Pearson's chi-squared test. Where differences between groups existed, post-hoc pairwise comparisons were completed to identify the significant differences between groups using the Tukey method, or a non-parametric equivalent after Brunner and Puri[51] to account for multiple comparisons. Similar analyses were performed to compare participants who attended one-year follow-up with those who did not.

To evaluate the overall effect of exposure to LKKM, differences between groups at one year and mean changes over one year in SPPB score and EQ-5D-VAS from baseline to follow-up were compared between the three study groups using the statistical procedures described above. Using the same methods, differences between groups and changes over one year in HAP scores and ISWT distance were compared between the LKKM and C1 groups. Additionally, differences between proportions of participants reporting exercising regularly at baseline and one-year follow-up were compared between the LKKM and C1 groups. Data for the HAP scores, ISWT, and exercise status were not available in the C2 group as they were not included in CanFIT baseline or annual follow-up assessments.

To account for a potential ceiling effect in participants with a perfect SPPB score (12) at baseline, a post-hoc ANOVA and logistic regression model were constructed using study participants with baseline SPPB score <12 similar to a method used by Hardy *et al*.[52] A post-hoc logistic regression model using stepwise selection was constructed to determine predictors of improvement in 1 point or more in SPPB score among those with a baseline SPPB score of <12. The primary predictor was study exposure group (LKKM vs. pooled C1 and C2 groups). Other variables added to the model included age, sex, albumin, hemoglobin, diabetes, and total SPPB score at baseline.

Mean numbers of hospital admission days were compared between groups using ANOVA. A negative binomial regression model was used to compare rate of hospitalization between groups over one year since baseline assessment. Mortality rates over one year were also compared between groups, but had to be excluded from analysis to comply with MCHP policy requiring the output of all statistical analyses to contain more than 6 individuals per cell.[53]

A *P*-value of <0.05 was considered statistically significant for all analyses. All data management, programming, and analyses were performed using SAS® version 9.4 (Carey, NC).

RESULTS

Of a total of 284 records extracted from the ECDB, 53 and 40 individuals had completed one-year follow-up by 31 March 2016 and were included in the analysis of the LKKM and C1 groups, respectively. Of a total of 410 records extracted from the CanFIT database, 207 had completed one-year follow-up by 31 March 2016 and were included in the analysis of the C2 group. Follow-up rates by group were: LKKM: 45.3%, C1: 30.1%, and C2: 65.5% (Figure 2).

Comparison of Groups at Baseline

Group Baseline Characteristics

Baseline characteristics of individuals who returned for follow-up are reported in Table 1. The exercise group and the two comparison groups were generally similar in baseline characteristics. The C1 group was younger at 55.6 years (SD 13.0), than the LKKM group at 63.3 years (SD 11.7) and the C2 group at 63.3 years (SD 15.6); $P<0.0084$. The C1 group had a higher mean BMI at 32.5 kg/m^2 (SD 9.2) than the C2 group at 29.7 kg/m^2 (SD 6.1). Baseline kidney function, as measured by median eGFR, was higher in the LKKM group at 25 mL/min/1.73 m^2 (IQR 12-36), than both the C1 group at 9 mL/min/1.73 m^2 (IQR 5-22.5), and the C2 group at 16 mL/min/1.73 m^2 (IQR 9-22). Proportion of participants on RRT at baseline was highest in the C1 group at 57.5% versus the LKKM and C2 groups at 24.5% and 28.0% respectively; P<0.001. Baseline lab values for albumin, calcium, phosphate and parathyroid hormone (PTH) differed statistically between groups, but the magnitudes of differences were not clinically significant.

Characteristics of participants who returned for follow-up and those who did not return for follow-up were similar. Mean hemoglobin was statistically, but not clinically, higher among those who returned for follow-up at 115.26 g/L (SD 16.78) than those who did not at 112.74 g/L (SD 16.41); $P<0.0461$, and proportion of individuals with hypercholesterolemia was higher in the group that returned for follow-up at one year (62.54%), than those who did not (53.54%); $P<0.019$. There was no statistically significant difference in outcome measures at baseline between participants who returned for a follow-up and those who did not (data not shown).

Comparison of Outcomes

Change in Physical Function as Measured by SPPB

Baseline median SPPB total score was higher in the LKKM group at 10.5 (IQR: 9-12), than in the C2 group at 9 (IQR: 7-11); $P<0.0202$ (Table 2). Differences between groups in SPPB total score persisted at one year with the LKKM group retaining a higher SPPB median total score of 11 (IQR: 9-11); than the C2 group median total score of 9 (IQR: 6-11); $P<0.019$. There was no significant difference between groups in mean change in SPPB total score over one year (Table 2).

Predictors of Change in SPPB Over One Year

Logistic regression modeling among those with a baseline SPPB score <12, showed that the LKKM exposed participants were approximately 2-fold more likely than participants who were not exposed to LKKM (pooled C1 and C2) to improve in physical function over one year (Table 3). This finding was supported by a stepwise regression model that adjusted for effects of known modifiers of physical function: age, sex, albumin, hemoglobin, diabetes comorbidity, and total SPPB score at baseline. In this model, only LKKM attendance was found to be an important predictor of improved physical function at one year among individuals with a baseline SPPB score of <12 (OR 2.143; 95% CI: 1.003, 4.580; $P<0.049$).

Health-Related Quality of Life (HRQOL)

There was no significant difference between groups in EQ-5D-VAS score at one year. Mean change in EQ-5D-VAS score at one year did not differ significantly between the exposed and comparison groups (Table 2). Due to small numbers in cells, a comparison of proportions improving, maintaining, or declining in EQ-5D-3L domains between groups could not be completed.[53] Proportion of individuals endorsing any symptoms were similar in the 5 domains of the EQ-5D-3L between study groups at baseline and follow-up (Table 4).

Physical Activity Behaviour

There was no significant difference between the LKKM and C1 groups in HAP MAS or HAP AAS at one year, nor was there any significant difference in mean change in HAP MAS or HAP AAS over one year (Table 2). A significantly greater proportion of participants reported exercising regularly in the LKKM group (59%), than the C1 group (41%) at one-year follow-up (Table 5).

Exercise Capacity

There was no significant difference between the LKKM and C1 groups in ISWT distance at one year. Comparison of group mean change in ISWT showed no difference in change in ISWT distance over one year between participants who attended LKKM and those who did not (Table 2).

Hospitalization

No significant difference between study groups was observed in mean number of hospital admission days over one year (LKKM=2.0754 (5.42); C1=4.4750 (10.04); C2=5.2367 (18.94); *P*=0.45). Negative binomial regression modelling showed that there was no statistically significant difference in hospitalization rates over one year between the group exposed to LKKM and the two comparison groups *(P*=0.55).

DISCUSSION

This pragmatic quasi-experimental retrospective cohort study found no significant differences in change in physical function between the group that was exposed to the 10-week combined exercise and education RRP (LKKM) and the two comparison groups in our primary analysis. However, regression analysis did demonstrate an effect of LKKM attendance for individuals with less than perfect physical function at baseline. Approximately one-third of the participants in the LKKM group had a perfect SPPB total score (i.e. SPPB score = 12) at baseline, restricting the ability of the SPPB to detect any improvement in physical function over one year. When individuals with a perfect SPPB score of 12 at baseline were removed from our analysis, logistic regression analysis showed that individuals with reduced physical function (SPPB Score <12) who attended LKKM had an approximately 2-fold higher likelihood of improved physical function over 1 year than those individuals with SPPB Score <12 in the comparison groups who did not attend the LKKM program, even when adjusted for other known modifiers of physical function such as age, sex, physical function and comorbidities. Thus, it is likely that the impact of LKKM exposure on physical function was limited by a ceiling effect in this study. Similar ceiling effects have been reported as a limitation of the SPPB in the measurement of physical function of diverse and higher functioning populations in several studies.[52,54,55]

In addition to the ceiling effect, our sample size only had 17% power to detect what may have been a small, but clinically significant difference in change in SPPB score of approximately

0.5[37] between the LKKM and both comparison groups over 1 year. It is possible that with a greater number of participants, this difference between groups would have emerged as statistically significant.

The relatively high proportion of individuals in the LKKM group (40%) who were exercising regularly at baseline may have muted the overall potential effect of the LKKM intervention on physical function and HRQOL. Although there was a substantial improvement of 20% in the proportion of LKKM attendees reporting exercising regularly one year after baseline, due to the relatively large proportion of LKKM attendees who already exercised at baseline (40%; Table 5), the overall increase in volume of exercise over one year may not have been sufficient to noticeably improve overall population estimates for physical function and HRQOL in the LKKM group relative to the comparison groups.

HRQOL, as measured by the EQ-5D-VAS, was maintained in the LKKM group, consistent with the reported protective effect of exercise on HRQOL.[20] Surprisingly, both comparison groups also maintained HRQOL over one year of CKD progression by the same measure. Because study entry in the CanFIT study and referral to ECC often follow referral to the MRP, it is possible that coincident with baseline assessment, some of the participants in the comparison groups began to receive more frequent and renal-focused healthcare, which can contribute to the maintenance of HRQOL in the CKD population.[56,57]

No differences were seen in change in physical activity behaviour between groups as measured by the HAP. The HAP measures self-reported physical activity in terms of types of activities that the individual is doing on a regular basis, and is therefore sensitive to loss of physical function resulting in disability,[48] but it is not especially sensitive changes in volume of weekly exercise.[58] However, a change in proportion of individuals reporting regular exercise was observed in the LKKM exposed group, but not in the C1 comparison group suggesting that LKKM did increase regular exercise behaviour. Alternatively, the LKKM attenders may have inherently been a more motivated group than the non-attenders and therefore more likely to participate in additional exercise over time.

Change in exercise capacity as measured by the ISWT did not differ between groups. Despite the large variability in the mean ISWT distances, and the relatively high proportion of individuals not completing the ISWT either at baseline or 1 year follow-up, it is can be estimated that based on our observed standard deviation of ISWT differences between baseline and 1 year, and our minimum sample size of 30 individuals, that our study had 76% power to detect a MCID of 47 m.[45] Furthermore, differences in the proportion of individuals not completing the ISWT at either baseline or one-year follow-up were similar between the LKKM group (17%) and the C1 group (25%), reducing the likelihood of attrition bias.

Limitations

The quasi-experimental design of this study is a potential source of bias. Participants were initially referred to the ECC based on patient request, or on physician perception that exercise counselling would be of benefit; thus, the formation of the LKKM group from individuals who self-selected to attend the LKKM exercise program raises a threat of selection bias of a motivated sample in the direct comparison of the LKKM group and C1 comparison groups. The C2 group, composed of individuals who were not referred to the ECC, was included in the comparison to account for this potential source of bias.

While mostly similar at baseline, there were important differences between the three groups, which necessitate caution when interpreting comparisons. Kidney function was lowest in the C2 group, which had the greatest proportion of participants on RRT at baseline, and highest in the LKKM group, suggesting that participants who were referred to LKKM, but who did not attend, had reduced kidney function at baseline compared to those who were referred to LKKM and did attend. This also suggests that ESRD was a barrier to LKKM attendance.

Variability in the time from LKKM program completion to post-intervention evaluation between participants may also partially explain the limited magnitude of effect of the RRP intervention in our study. The time from completion of the LKKM program to the follow-up assessment differed between individual participants by up to 10 months. In contrast, previous evaluations of RRPs in CKD have assessed changes in physical function and HRQOL directly following the completion of the intervention program, with continually applied external motivation to facilitate exercise adherence from participant baseline to follow-up.[27,29,30]

As a longitudinal cohort study relying on participants to return for follow-up, this study suffered from low follow-up rates. Follow-up rates were disproportionately higher in the C2 comparison group because the CanFIT study had researchers meet participants for follow-up as part of regular clinic visits, while the LKKM and C2 groups required participants to return for follow-up voluntarily. Despite low follow up, baseline characteristics and outcome measures were similar between those who returned for follow-up and those who did not, reducing the threat of attrition bias.

Strengths

To our knowledge, the presented study is the first pragmatic evaluation of the clinical effectiveness of a combined exercise and education program as an intervention to prevent the decline of physical function and HRQOL in individuals with CKD over one year. Furthermore, of recent evaluations of combined exercise and education RRPs, this study had the largest total sample size.[27,29]

The diversity of the study population in terms of age, sex, race, CKD stage, and comorbidities, resulted in a sample that was more characteristic of the general CKD population[1] than previous investigations which were focused on CKD stages 3 and 4[27,29,30]. This study included participants from early CKD through ESRD, as well as a representative proportion of comorbidities, and drew from a racially and socially diverse population, maximizing the generalizability of the results to a wider range of the Canadian CKD population.[1]

This study provides clinical evidence of the effectiveness of referral to an RRP with participants registering for and completing the program in a way that more faithfully reflects the time course and adherence to a RRP prescription. Though the effect of the intervention is modest, it is bolstered by the fact that there was a lasting effect of a single intervention under clinical conditions.

Future Investigations

This study adds to growing evidence that referral to a single round of a combined exercise and education RRP appears to be helpful in preventing decline of physical function in individuals with CKD and supports referral of individuals with CKD to RRP in clinical care.[27,29,30] Future investigations should determine whether this beneficial effect lasts for greater than one year, whether repeat attendance at RRP sessions has added benefit, and if benefits to physical function with RRPs translate into long-term decreases in adverse events such as hospitalization and mortality rates. In addition, in view of relatively low rates of adherence to an exercise prescription, (41% in this study) there is need for investigation into how barriers to attendance can be overcome, especially for patients on dialysis, who were less likely to attend LKKM than non-dialysis patients in our study. Finally, future investigations of the benefit of RRPs in the maintenance of physical function in the early stages of CKD should incorporate measures of physical function that are sensitive to changes in a greater range of physical capacity and less prone to ceiling effects than the SPPB.

Conclusion

This pragmatic evaluation of a clinical exercise program, demonstrated that attendance at LKKM was associated with improved physical function over one year among individuals with CKD who had reduced physical function at baseline. Furthermore, attendance at LKKM promoted a lasting change in the proportion of individuals exercising regularly. The results of our study suggest that for individuals with CKD and reduced physical function, attending even a single course of a 10-week clinical RRP helps to increase exercise activity leading to prolonged improvements in physical function. These results provide further evidence that attending combined exercise and education RRPs can help to mitigate the decline of physical function in individuals with CKD.

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FIGURES AND TABLES

Figure 1: Group allocation

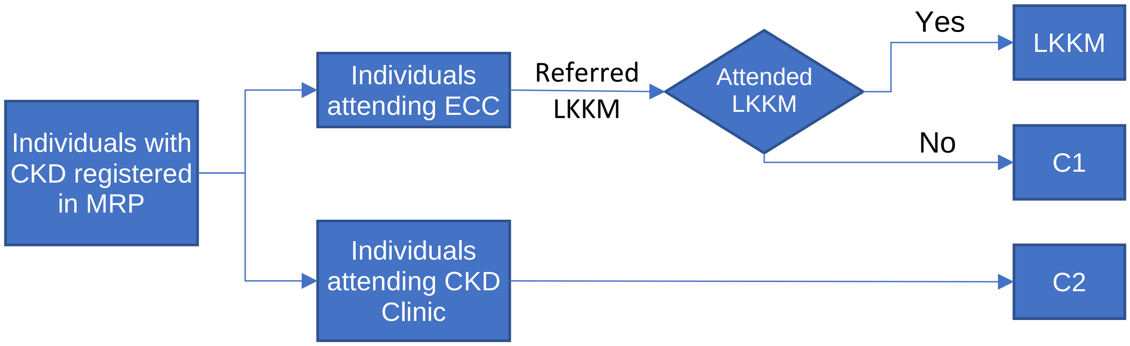

Figure 2: Participant flow diagram

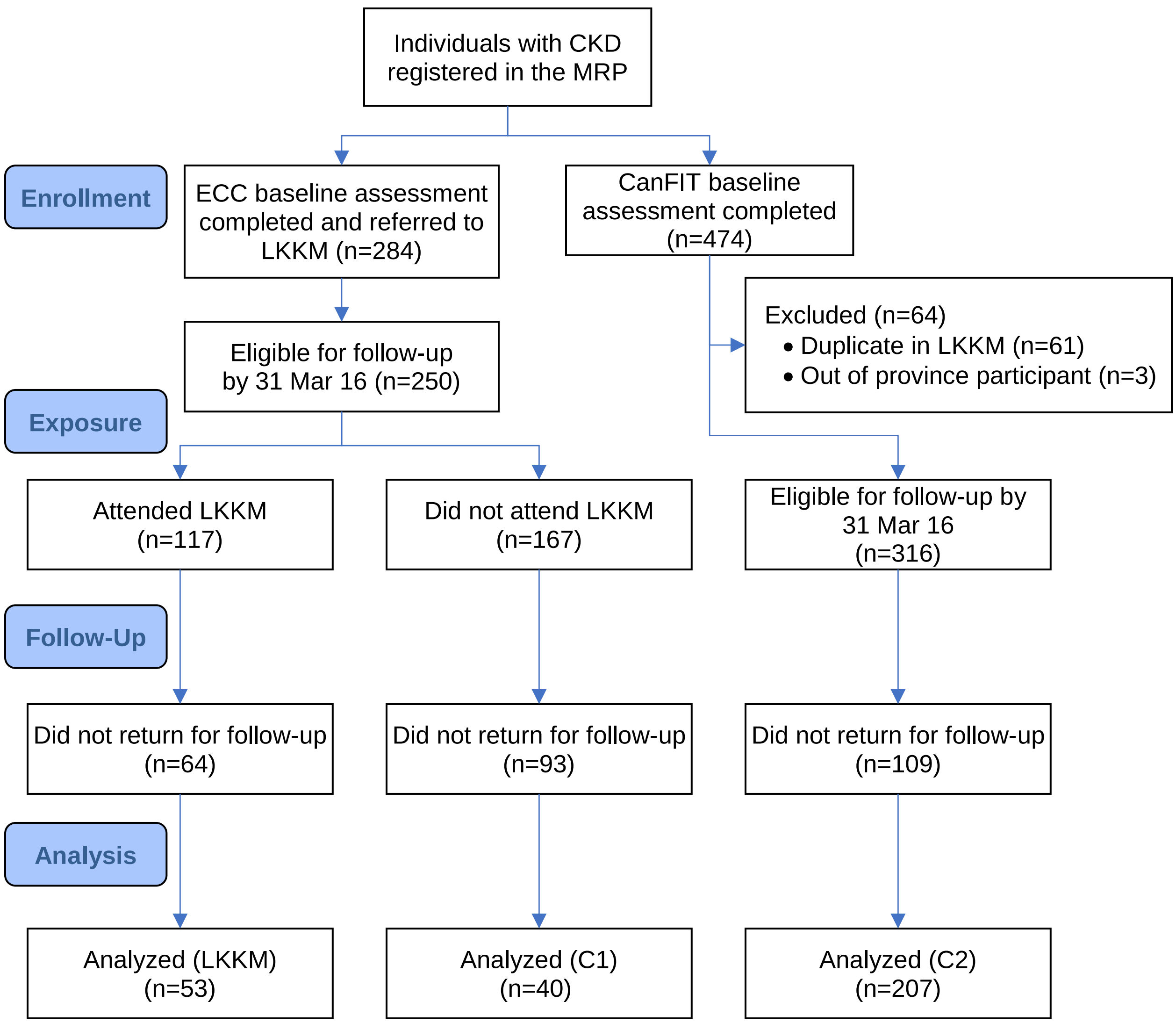

Table 1: Comparison of all participants, by group, at baseline, in individuals with one-year follow-up

	LKKM n = 53	C1 n = 40	C2 n = 207	*P*-value
Age (years)	63.3 (11.7)[a]	55.6 (13.0)[c]	63.3 (15.6)	0.008
BMI (kg/m^2)	31.25 (6.54)	32.49 (9.16)[c]	29.65 (6.08)	0.029
Race, non-white % (No.)	23% (10)	26% (9)	27% (54)	0.90
Sex, male % (No.)	51% (27)	65% (26)	60% (125)	0.34
Systolic BP (mmHg)	137.8 (18.2)	137.5 (23.1)	137.9 (21.0)	0.99
Diastolic BP (mmHg)	74.7 (12.2)	75.4 (11.0)	75.7 (13.3)	0.89
Arthritis % (No.)	38% (20)	33% (13)	40% (82)	0.68
Diabetes % (No.)	57% (30)	60% (24)	58% (120)	0.95
High cholesterol % (No.)	68% (36)	63% (25)	61% (126)	0.66
IHD % (No.)	21% (11)	23% (9)	18% (38)	0.80
PVD % (No.)	13% (7)	18% (7)	17% (36)	0.76
Renal Replacement Therapy % (No.)	25% (13)[a]	58% (23)[c]	28% (58)	<0.001
Smoker (ever) % (No.)	34% (18)	43% (17)		0.40
Walk support % (No.)	27% (14)	32% (12)	28% (21)	0.89
Albumin (g/L)	35.0 (4.61)	33.3 (5.78)	35.6 (5.17)	0.039
Calcium corrected (mmol/L)	2.40 (0.18)	2.43 (0.18)	2.35 (0.16)	0.007
Creatinine (µmol/L)	215[a,b] (146-426)	481 (189-785)	306 (210-514)	0.002
eGFR- MDRD (mL/min/1.73 m^2)	25[a,b] (12-36)	9 (5-22.5)	16 (9-22)	<0.001
Hemoglobin (g/L)	119.1 (17.60)	114.4 (17.87)	114.5 (15.38)	0.16
Phosphate (mmol/L)	1.37 (0.41)	1.57 (0.51)	1.40 (0.34)	0.025
PTH (ng/L)	155 (88.5-236)	176 (118-431)	171 (91-277.5)	0.35

Note: Continuous variables are expressed as Mean (SD) or Median (IQR). Categorical variables are expressed as % (N).
Data not available in group is indicated with a blank cell.
Pairwise comparisons: [a]LKKM vs C1 – $P<0.05$; [b]LKKM vs C2 – $P<0.05$; [c]C1 vs C2 – $P<0.05$
Data for CHF, hypertension, lung disease, and stroke proportions were analyzed but suppressed due to cell values <6, per MCHP policy[53]

Table 2: Comparison of outcome measures in participants with follow-up at baseline and one year

	Baseline				**One year**				**Mean change over one year**			
	LKKM n=53	**C1** n=40	**C2** N=207	***P*-value**	**LKKM** n=53	**C1** n=40	**C2** N=207	***P*-value**	**LKKM n=53**	**C1 n=40**	**C2 N=207**	***P*-value**
SPPB Total	10.5[b] (9-12) [52]	10 (8-12) [39]	9 (7-11) [207]	0.02	11[b] (9-11) [49]	9 (7-12) [37]	9 (6-11) [204]	0.019	-0.06 (2.30) [48]	-0.38 (1.75) [37]	-0.33 (2.33) [204]	0.74
SPPB Total Score for baseline <12	10 (7-11) [35]	9 (8-10) [29]	8 (5-10) [162]	0.051	10[b] (9-11) [33]	9 (7-11) [27]	8 (5-10.5) [160]	0.012	0.31 (2.61) [32]	-0.26 (1.83) [27]	-0.23 (2.52) [160]	0.5075
EQ-5D-VAS	62.9 (18.3) [52]	59.6 (18.4) [39]	62.1 (19.6) [189]	0.7041	62.2 (20.0) [52]	61.3 (20.3) [35]	66.3 (17.9) [202]	0.1729	-0.47 (21.30) [51]	0.76 (22.04) [34]	4.43 (21.47) [184]	0.29
HAP MAS	66.9 (13.7) [51]	65.3 (16.5) [38]		0.62	69.0 (11.7) [51]	65.2 (17.2) [34]		0.23	1.53 (8.36) [49]	0.24 (10.74) [33]		0.54
HAP AAS	57.4 (17.0) [49]	50.4 (19.9) [37]		0.082	55.2 (17.3) [51]	52.3 (19.9) [33]		0.47	-3.00 (9.46) [47]	0.48 (9.23) [31]		0.11
Shuttle-walk (m)	236.4 (125.3) [52]	228.1 (155.6) [37]		0.78	236.9 (111.7) [45]	228.1 (158.1) [31]		0.78	-9.77 (65.40) [44]	-29.33 (68.68) [30]		0.22

Note: Continuous variables are expressed as Mean (SD) if normally distributed, or expressed Median (IQR) if not normally distributed.
Number of included in analysis indicated by [N].
Data not available in group is indicated with a blank cell.
Pairwise comparisons: [a]LKKM vs C1 – $P<0.05$; [b]LKKM vs C2 – $P<0.05$; [c]C1 vs C2 – $P<0.05$.

Table 3: Logistic regression model: improvement in SPPB for participants with baseline SPPB<12

Effect	**Odds Ratio**	**95% Wald Confidence Limits**	
LKKM attendance	2.241	1.025	4.899
Age	0.987	0.965	1.009
Sex	1.213	0.686	2.146
Albumin	0.979	0.923	1.038
Hemoglobin	1.003	0.985	1.021
Diabetes	1.181	0.647	2.155
SPPB Total Score at Baseline	0.960	0.866	1.064

Table 4: Comparison of proportion of participants endorsing any impairment in EQ-5D-3L dimensions at baseline and one year between study groups

	Baseline				**One-year follow-up**			
	LKKM n=53	**C1** n=40	**C2** n=207	***P*-value**	**LKKM** n=53	**C1** n=40	**C2** n=207	***P*-value**
Mobility % (No.)	40.4% (21)	62.5% (25)	47.4% (91)	0.10	46.2% (24)	61.1% (22)	51.7% (106)	0.38
Self-care % (No.)	23.1% (12)	20.0% (8)	9.9% (19)	0.023	17.3% (9)	21.6% (8)	8.3% (17)	0.024
Usual activities % (No.)	44.2% (23)	52.5% (21)	22.4% (43)	<0.001	41.2% (21)	50.0% (18)	25.9% (53)	0.004
Pain/discomfort % (No.)	63.5% (33)	74.4% (29)	55.2% (106)	0.068	71.2% (37)	77.8% (28)	50.2% (103)	<0.001
Anxiety/depression % (No.)	37.3% (19)	50.0% (20)	29.7% (57)	0.041	43.1% (22)	38.9% (14)	28.3% (58)	0.083

Note: Proportions are % and number endorsing any disability in that dimension, i.e. domain score >1. Proportions compared between groups using chi-square.

Table 5: Proportion of participants reporting regular exercise at baseline and one year

	Exercise at baseline	***P*-value**	**Exercise at one year**	***P*-value**
LKKM Group % (No.) currently exercising	40% (20)	0.69	60% (29)	0.027
C1 Group % (No.) currently exercising	36% (14)		35% (13)	
Total currently exercising % (No.)	38% (34)		49% (42)	

Note: Proportions are % and number reporting they are currently exercising ≥30mins≥3x/week at specified period. Proportions exercising compared between LKKM and C1 group at specified period using chi-square test.

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