Aerobic exercise capacity is maintained over a 5-year period in mild-to-moderate chronic kidney disease: A longitudinal study

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Abstract

Background: Aerobic exercise capacity is reduced in non-dialysis chronic kidney disease (CKD), but little is known about the magnitude of changes in exercise capacity over time. Our main hypothesis was that aerobic ExCap would decline over 5 years in individuals with mild-to-moderate CKD along with a decline in renal function. A secondary hypothesis was that such a decline in ExCap would be associated with a decline in muscle strength, cardiovascular function and physical activity.

Methods: We performed a 5-year-prospective study on individuals with mild-to-moderate CKD, who were closely monitored at a nephrology clinic. Fiftytwo individuals with CKD stage 2–3 and 54 age- and sex-matched healthy controls were included. Peak workload was assessed through a maximal cycle exercise test. Muscle strength and lean body mass, cardiac function, vascular stiffness, self-reported physical activity level, renal function and haemoglobin level were evaluated. Tests were repeated after 5 years. Statistical analysis of longitudinal data was performed using linear mixed models.

Results: Exercise capacity did not change significantly over time in either the CKD group or controls, although the absolute workloads were significantly lower in the CKD group. Only in a CKD subgroup reporting low physical activity at baseline, exercise capacity declined. Renal function decreased in both groups, with a faster decline in CKD (p = 0.05 between groups). Peak heart rate, haemoglobin level, handgrip strength, lean body mass and cardiovascular function did not decrease significantly over time in CKD individuals.

Conclusions: On a group level, aerobic exercise capacity and peak heart rate were maintained over 5 years in patients with well-controlled mild-to-moderate CKD, despite a slight reduction in glomerular filtration rate, mirroring the lack of progression of cardiovascular and muscular dysfunction in this group. In patients with mild-to-moderate CKD, physical activity level at baseline seems to have a predictive value for exercise capacity at follow-up.

Background

We and others have previously shown that aerobic exercise capacity (ExCap), measured as peak oxygen uptake (VO_2peak) or peak ExCap, is already reduced in the early stages of non-dialysis chronic kidney disease (CKD) [1–3]. Reduced VO_2peak is associated with increased mortality in CKD and reduced physical capacity has a negative impact on daily-life activities [4, 5]. Aerobic ExCap is influenced by the function of most organ systems, particularly the cardiovascular and muscular systems. The cause of the reduced ExCap in CKD is likely multifactorial and may differ between different stages of CKD. Anaemia, autonomic dysfunction, vascular dysfunction, cardiac and skeletal muscle abnormalities may all contribute to exercise intolerance in non-dialysis CKD [1, 3, 6–10]. We recently showed that aerobic ExCap in patients with mild to severe CKD stages 2–5 was mainly associated with systemic oxygen delivery factors, in particular peak heart rate (HR) [1].

Although renal function declines over time in most individuals with CKD, the rate of progression differs, and some individuals do not show any progression at all [11, 12]. Surprisingly little is known about how aerobic ExCap and muscle strength and mass change over time in individuals with non-dialysis CKD and how this correlates with changes in renal function. Leikis et al. found that in patients with CKD stages 3–4, both leg strength and VO_2peak declined over a two-year period as glomerular filtration rate (GFR) declined, despite stable haemoglobin levels [13]. The progression of muscle wasting in CKD seems to be highly variable, although few data are available [14]. Physical activity levels of individuals with CKD are generally low and are increasingly reduced in the later stages of CKD [15, 16]. A sedentary lifestyle most likely contributes to a further reduction in aerobic ExCap in patients with CKD, and vice versa.

Given the high incidence of cardiovascular disease in CKD [17] and the higher mortality associated with reduced aerobic ExCap [4, 18], it is of interest to monitor aerobic ExCap. The main aim of this study was to investigate the change in aerobic ExCap over 5 years in individuals with CKD stages 2–3 who were closely monitored at a nephrology clinic. Furthermore, we wanted to study the changes in possible determinants of ExCap in CKD, such as cardiovascular function, muscle strength, lean body mass (LBM), physical activity level and kidney function during the same period of time.

Methods

The current analyses are part of a larger, prospective, single-centre cohort study, PROGRESS 2002, investigating factors impacting the progress of renal insufficiency. The details of this study have been described previously [8].

Study protocol

We included 52 patients with non-dialysis CKD stage 2–3 (CKD; aged 18–65 years) and 54 healthy controls who had completed an exercise test at baseline. The cohort has been monitored over a follow-up of 5 years. GFR was measured by iohexol plasma clearance [19]. During follow-up, GFR measurement by iohexol was repeated in the CKD group. In both CKD and controls, estimated GFR (eGFR) was calculated using the Chronic Kidney Disease–Epidemiology Collaboration (CKD–EPI) equation. This equation was chosen because it has been shown to provide a the most precise estimate of filtration capacity in the range of mild CKD [20]. The methodological considerations have been described in detail elsewhere [21].

Patients were recruited consecutively from the outpatient clinic at the Department of Renal Medicine at the Karolinska University Hospital during 2002–2009 if they had renal function corresponding to CKD stage 2–3a as defined by the National Kidney Foundation [22]. The controls, matched for age and sex with the CKD 2–3 group, were randomly selected from the Swedish Total Population Register or recruited through the website of the regional University Hospital. The exclusion criteria for all participants were current malignancy, kidney transplantation or kidney donation, or blood-transmitted disease. The inclusion criteria for the controls were absence of kidney disease, cardiovascular disease, diabetes or any chronic medication. After inclusion, all participants underwent clinical investigation, anthropometric

measurement, an exercise stress test, a handgrip strength test, laboratory testing, carotid ultrasound, transthoracic echocardiography and a body composition scan. The participants with CKD were closely monitored and treated aggressively for hypertension, hyperlipidaemia and proteinuria at the Department of Renal Medicine.

The study population and the excluded individuals are presented in Figure 1. Two participants in the CKD group died from cancer before the end of the follow-up period. No patient in the CKD group progressed to renal replacement therapy within the follow-up period. However, several patients were lost to follow-up. At year 5, 49 participants in the CKD group and 43 in the control group participated in the examinations. Forty-six participants in the CKD group and 40 in the control group performed an exercise test; however, one participant with CKD was excluded from the follow-up exercise test analysis because the exercise test was terminated early owing to the occurrence of atrial fibrillation with a high HR. Two other participants with CKD had atrial fibrillation before and during the exercise test; therefore, these individuals were not included in the peak HR analyses.

Fig. 1. Study population at baseline and 5-year-follow up.

The study protocol was reviewed and approved by the Local Ethics Committee and Institutional Review Board of the Karolinska Institutet at the Karolinska University Hospital. All participants gave their written informed consent.

Measurements

Aerobic exercise capacity. A symptom-limited incremental cycle ergometer test on an electronically braked cycle ergometer (RE990; Rodby Innovation AB, Uppsala, Sweden) was administered according to clinical standards. The initial workload and workload increase/minute (10, 15 or 20 W) were individualized with the goal of achieving symptom limitation within 6 to 10 minutes. Participants were instructed to cycle at a speed of 60 rpm and were encouraged to continue cycling until exhaustion. Perceived exertion was reported as the highest rating on the Borg CR10 scale for either leg fatigue, dyspnoea or general exhaustion as a limiting symptom [23]. Aerobic ExCap was defined as the peak workload in W. Continuous 12-lead electrocardiography was used to measure HR and for ST–T-segment monitoring and safety purposes. Resting HR was measured in the supine position before the exercise test. Predicted peak HR was calculated as 220 minus age. HR reserve was defined as the difference between peak and resting HR.

Muscular function. A handheld dynamometer (Grip-A; Takei Scientific Instruments Co., Ltd, Tokyo, Japan) was used to measure maximum voluntary isometric contraction as a measure of handgrip strength. The

test was performed with the participant in a standing position. The measurement was repeated three times using the dominant arm, and the highest value was recorded as handgrip strength.

Cardiac and vascular function. Echocardiography was performed with the participant in the supine left decubitus position and according to current guidelines [24]. The images were acquired using an ultrasound scanner (Sequoia 512; Siemens Medical Solutions, Mountain View, CA, USA) with an appropriate transducer. Cardiac function was evaluated and expressed for systolic left-ventricular (LV) function as ejection fraction (EF), for right-ventricular systolic function as tricuspid annular plane systolic excursion (TAPSE) and for diastolic LV function as an E/é ratio (mitral flow velocity E, divided by tissue LV velocity é). Carotid artery ultrasound was performed to assess arterial stiffness. Measurements of the diameter of the right common carotid artery and calculations of the pressure strain elastic modulus (Ep) were performed according to a standardized protocol [8].

Ambulatory blood pressure monitoring was performed over 24 hours from morning to morning using Spacelab 90217 (Spacelab Healthcare, Issaquah, Washington, USA) and a cuff of appropriate size on the non-dominant arm. Blood pressure was measured three times per hour day and night.

Body composition. Body composition was measured with a whole-body dual-energy X-ray absorptiometry scan to determine LBM (QDR 4500 Discovery A, software version 12.3; Hologic, Bedford, MA, USA). Only the CKD group were examined at follow-up.

Physical activity level. Physical activity level was rated by the participants using a four-point scale modified from the Saltin–Grimby Physical Activity Level Scale as follows [25]:

Level 1 = *Regular exercise*: running, swimming, tennis, badminton, gymnastics or similar activity on three or more occasions per week; every session should last at least 30 min and cause sweating.

Level 2 = *Moderate amount of regular exercise*: running, swimming, tennis, badminton, gymnastics or similar activity on 1–2 occasions per week; every session should last at least 30 minutes and cause sweating.

Level 3 = *Light exercise*: walking or cycling or other physical activity during at least 2 h per week, usually without sweating; this includes walking or cycling to/from work, Sunday walks, gardening, fishing, table tennis and bowling or similar activity.

Level 4 = *Sedentary*: mostly reading, watching television, movies or other sedentary activities, or walking, cycling or light exercise for less than 2 h per week.

Blood samples. Haemoglobin, creatinine and high-sensitivity C-reactive protein (hs-CRP) concentration were measured in venous blood obtained using routine laboratory methods at the Karolinska University Laboratory at the inclusion visit before the exercise test.

Statistical analysis

Continuous variables are presented as mean and standard deviation, and categorical variables as number and percentage of the study sample. Variables with a skewed distribution are presented as median and interquartile range. The normality assumption was assessed graphically using histograms. Potential outliers were examined graphically by box plots and their validity were assessed. Logarithmic transformation was performed for variables with a skewed distribution when they were analysed in mixed models. Group comparisons at baseline were performed using Student's *t*-test or Mann–Whitney *U*-test when the assumptions of normality and homogeneity were not fulfilled. For categorical variables, a chi-square test was used. Wilcoxon's signed-rank test for related samples was used to assess the change over time for ordinal data. Statistical significance was defined as a *p*-value < 0.05 for a two-tailed test.

Linear mixed models were considered to be the most suitable method for the analysis of longitudinal data because this method provides effect estimates from the whole study sample provided that the values missing at follow-up are random. Changes over time were analysed in CKD and controls and the changes were compared between the groups by the interaction factor group ´ time in the mixed model. The analyses were adjusted for different background factors (depending on the chosen outcome variable), including age at baseline, sex, height and beta-blocker use.

To analyse longitudinal data where the outcome variables were ordered categoricals, generalized estimating equations (GEE) model were used. The model was set up with the same factors as in the mixed linear model mentioned above. The parameter estimates from the GEE model are presented as odds ratios (OR) and 95% confidence intervals (CI).

Pearson (r) or Spearman (r_s) correlation coefficients were used to analyse the relationship between two variables.

Statistical analyses were performed using IBM SPSS Statistics (version 23.0; IBM, Armonk, NY, USA) and SAS (version 9.3; SAS Institute, Cary, NC, USA) software.

Results

The baseline characteristics of the study participants are summarized in Table 1. The mean age of the whole cohort at entry was 47 years and there were no significant differences between the CKD group and controls in age, sex or body size.

Based on their GFR, 31 individuals in the CKD group were in CKD stage 2 and 21 in CKD stage 3 at baseline. At follow-up, two individuals in the CKD group were in stage 1; nine in stage 2; 27 in stage 3; five in stage 4; and one was in stage 5. Ten individuals in the CKD group had diabetes at inclusion and follow-up and two in the control group had developed diabetes at follow-up. At baseline, 10 individuals in the CKD group were on beta-blocker treatment. At follow-up, this number had increased to 15 and four of the controls had started beta-blocker treatment.

Table 1

Baseline characteristics.

Variable	Controls	CKD	p-value
Subjects (n)	54	52	
Age (years)	48 ± 11	47 ± 11	0.7
Male, n (%)	33 (61)	32 (61)	0.8
Height (cm)	176 ± 9	174 ± 9	0.4
Weight (kg)	77 ± 12	76 ± 16	1
BMI (kg/m^2)	24.9 ± 3.4	25.1 ± 4.0	0.2
Lean body mass (kg)	54 ± 11	52 ± 11	0.5
GFR (mL/min/1.73 m^2)	99 ± 12	60.3 ± 5.2	< 0.001
eGFR (mL/min/1.73 m^2)	96 ± 13.2	59 ± 13	< 0.001
Haemoglobin (g/dL)	14.2 ± 1.2	13.5 ± 1.4	0.02
Hs-CRP (mg/L)	0.89 (0.47–2.1)	1.60 (0.86–3.5)	0.04
Diabetes, n (%)		10 (22)	NA
24-h SBP (mmHg)	124 ± 11	122 ± 14	0.4
24-h DBP (mmHg)	78 ± 8	76 ± 7	0.4
Aetiology of CKD, n (%)			
Familial/hereditary/congenital disease		14 (27)	NA
Primary glomerulonephritis		17 (33)	NA
Secondary glomerular/systemic disease		9 (17)	NA
Miscellaneous/unknown		12 (23)	NA
Medication, n (%)			
Beta blocker		10 (19)	NA
Diuretics		12 (23)	NA

BMI body mass index; bpm beats per minute; CKD chronic kidney disease; eGFR glomerular filtration rate estimated by CKD–EPI; ESA erythropoiesis-stimulating agents; GFR glomerular filtration rate measured by iohexol clearance; HR heart rate; hs-CRP high-sensitivity C-reactive protein; n number; 24-h SBP/DBP average 24-h systolic/diastolic blood pressure

Values reported as number (percentage), mean ± standard deviation or median (interquartile range). P-value: t-test, Mann–Whitney U-test (continuous variables) or chi-square (categorical values).

Variable	Controls	CKD	p-value
ACE inhibitors		22 (42)	NA
Angiotensin II blockers		21 (39)	NA
Calcium-channel blockers		10 (19)	NA
ESA		1 (2)	NA
Oral cortisone		2 (4)	NA
Iron supplementation		4 (8)	NA
Functional measurements			
Peak workload (W)	238 ± 60	193 ± 63	< 0.001
Peak HR (bpm)	177 ± 11	161 ± 24	< 0.001
Peak RPE	8.6 ± 1.3	9 ± 1.3	0.2
Handgrip strength (kg)	44 ± 12	40 ± 11	0.08

BMI body mass index; bpm beats per minute; CKD chronic kidney disease; eGFR glomerular filtration rate estimated by CKD–EPI; ESA erythropoiesis-stimulating agents; GFR glomerular filtration rate measured by iohexol clearance; HR heart rate; hs-CRP high-sensitivity C-reactive protein; n number; 24-h SBP/DBP average 24-h systolic/diastolic blood pressure

Values reported as number (percentage), mean ± standard deviation or median (interquartile range). P-value: t-test, Mann–Whitney U-test (continuous variables) or chi-square (categorical values).

Renal function and blood analyses

At baseline, GFR measured by iohexol clearance was 60.3 ± 5.2 mL/min/1.73 m^2 in CKD and 99.5 ± 12.5 mL/min/1.73 m^2 in the controls ($p < 0.001$). At follow-up, measured GFR in the CKD group was 50.2 ± 16.9 mL/min/1.73 m^2, a mean decline of 17% over 5 years. eGFR values at baseline and follow-up were calculated by CKD–EPI for both CKD and controls. A significant decrease in eGFR was seen between baseline and year 5 for both groups; the difference in the change in eGFR over time between the groups was borderline significant (interaction group · time, $p = 0.05$) (Table 2). The annual rate of decline in eGFR was 1.8 mL/min/1.73 m^2 in the CKD group and 0.8 mL/min/1.73 m^2 in the control group.

Haemoglobin was significantly lower in the CKD group than in controls at both time points, but increased significantly over time in both groups. This change did not differ significantly over time between the groups (Table 2). However, separate analyses in men and women using the paired samples t-test showed that haemoglobin increased significantly in women (p = 0.001) but not in men (p = 0.2).

Hs-CRP was higher in the CKD group than in controls at each time point, but no significant change over time was seen in either CKD or controls.

Table 2. Functional measurements at baseline and 5-year follow-up.

Exercise test results

Aerobic ExCap and peak HR were both significantly lower in CKD than in controls at both time points, and did not change significantly over time in neither CKD nor controls (Table 2, mixed model with values adjusted for covariates). In CKD, there was a non-significant average decline in ExCap of 2.6%. The non-significant decline in peak HR in the CKD group was 0.6%. In controls, the mean values of ExCap showed a non-significant decrease of 1.7% and peak HR significantly decreased by an average of 2.3%. There was no significant difference in the rating of perceived exertion (RPE) between the groups at baseline. At follow-up, the mean ratings were 8.3 for CKD and 8.5 for controls (p = 0.7 between groups).

Muscle strength and lean body mass

Handgrip strength was significantly lower in CKD than in controls at baseline, but not at follow-up (Table 2, mixed model). The difference in the change over time between the two groups was borderline significant (p = 0.06), with a significant reduction in the control group. LBM did not differ significantly between groups at baseline (CKD 52.8 kg; controls 53.5 kg, p = 0.3, analysed by linear mixed model) and increased from 52.8 kg to 54.5 kg (p = 0.02) at follow-up in the CKD group. Mean values were adjusted for the covariates of age at baseline, sex, height and weight at baseline. Weight increased from 75.7 kg to 78.3 kg (p = 0.006, paired samples t-test) in the CKD group.

Cardiovascular function

At baseline, LV diastolic function (E/é ratio), was significantly lower in the CKD group compared with controls, although within normal values; while LV systolic function (EF), right ventricular systolic function (TAPSE) and vascular stiffness (Ep) did not differ significantly between groups (Table 2, mixed model). E/é, EF, TAPSE and Ep did not change significantly over 5 years in the CKD group, nor was the change over time significantly different from that in controls (Table 2). E/é increased and EF decreased in controls from baseline to follow-up with values remaining within the normal range.

Self-reported physical activity

The results of this analysis are presented in Table 3. Self-reported physical activity levels differed between groups at baseline with controls being physically more active than CKD patients. At follow-up,

there was no significant difference in physical activity level between groups. Individuals with CKD reported higher physical activity levels at follow-up compared with baseline while controls reported lower physical activity levels at follow-up compared with baseline. The interaction group x time was statistically significant (p = 0.0002), indicating that the two groups differed regarding their change in physical activity level over time.

Table 3. Change in physical activity (PA) level between baseline and 5-year follow-up.

	Odds ratio	Confidence interval	P-value
[a]CKD: Follow-up vs. baseline	2.12	1.26–3.56	0.0047
[b]Controls: Follow-up vs. baseline	0.54	0.35–0.84	0.0057
[c]CKD vs. controls at baseline	0.42	0.21–0.86	0.0169
[d]CKD vs. controls at follow-up	1.66	0.77–3.63	0.2008

CKD chronic kidney disease.
[a] CKD: Odds for increased PA at follow-up compared with baseline.
[b] Controls: Odds for increased PA at follow-up compared with baseline.
[c] Odds for higher PA in CKD group compared with controls at baseline.
[d] Odds for higher PA in CKD group compared with controls at follow-up. Results are analysed using a generalized estimation equation. The results are based on 188 observations from 106 subjects. P-value: chi-square test.

Correlations between the change in ExCap and physiological measurements

Correlations between the change in aerobic ExCap and changes in selected physiological and biochemical measurements were analysed for the CKD group. There were significant correlations between the change in ExCap and changes in peak HR and handgrip strength (r = 0.5 and 0.3 respectively, p = 0.001 and 0.03 respectively, n = 43 and 45 respectively). The change in measured GFR was significantly correlated with the change in aerobic ExCap in CKD (r = 0.3, p = 0.03, n = 42). However, when eGFR was used, the correlation between the change in eGFR and the change in ExCap was not significant (r = 0.06 and p = 0.7, n = 44). The change in physical activity level did not correlate to the change in ExCap (r_s = − 0.05 and p = 0.7, n = 45), nor did the change in haemoglobin level, Hs-CRP level, E/é or EP (r = 0.1, 0.03, − 0.08 and − 0.01 respectively, p = 0.4; 0.9, 0.6 and 0.9, respectively, n = 45, 42, 43 and 43, respectively). For controls, there were no significant correlations between the change in ExCap and changes in peak HR, handgrip strength and eGFR (r = 0.1, 0.1 and − 0.3 respectively, p = 0.5, 0.5 and 0.06, respectively, n = 40, 40 and 39, respectively).

Discussion

In this study we analysed changes in aerobic ExCap and known determinants over a 5-year period in individuals with mild-to-moderate CKD compared with healthy individuals. Individuals with CKD were recruited from a dedicated nephrology clinic and closely monitored. In these patients, aerobic ExCap, peak HR, handgrip strength, LBM, haemoglobin level and cardiovascular function were all maintained over 5 years, despite a 17% reduction in GFR over time.

To the best of our knowledge, this is the first study to evaluate the change in aerobic ExCap over time in CKD patients compared with healthy controls. As expected, eGFR decreased more in CKD patients than in controls ($p = 0.05$). Aerobic ExCap is expected to decline with age, with an average 5–20% decline per decade in cross-sectional studies of healthy individuals, while longitudinal studies show a greater decline in older individuals compared with younger people [26, 27]. The mean change in ExCap in our study was almost 3% over 5 years in the CKD group and a little less in the control group. Our study included some younger individuals (< 35 years old), which could explain the modest decline compared with those seen in previous studies of healthy individuals. An important finding from our study is that ExCap did not decline more rapidly in the CKD group attending a nephrology clinic than in the controls. Reductions in peak HR and peripheral oxygen utilization but not stroke volume appear to mediate the normal age-associated decline in aerobic ExCap [26–28]. The expected decline in peak HR with normal aging is not as pronounced as the decline in aerobic ExCap of 4–6% per decade that was reported by Fleg et al. [28], which is similar to our data for the controls. The reduction in peak HR in the CKD group was only 0.6%. For the CKD group, there was a significant correlation between the change in ExCap over 5 years and the change in peak HR, which was not seen in the control group. This suggests that peak HR, or the possibility of achieving a high peak HR, could be an important factor influencing ExCap in this CKD group. Peripheral oxygen utilization and maximal stroke volume were not measured in our study, however a measure of diastolic function, E/é, decreased in controls but not in CKD patients over 5 years. Diastolic dysfunction may lead to an inability to increase stroke volume at exercise through the Frank–Starling mechanism and a preserved diastolic function at rest might indicate that maximal stroke volume was also preserved.

While both aerobic ExCap and peak HR are known to be more reduced in the later stages of CKD than in the earlier stages [1, 3, 29], only one small study has reported the changes in aerobic ExCap over time in non-dialysis CKD patients [13]. That study found a reduction in VO_2peak of 9% over two years, a stable haemoglobin level and a fall of 28% in the calculated creatinine clearance. As a decline in leg strength paralleled the reduction in VO_2peak, the authors speculated that the reduction in VO_2peak was likely related to intrinsic muscle changes. However, peak HR decreased with a mean value of 9 over only two years, which may also have influenced aerobic ExCap in that study. The difference between the results of our study compared with that study may in part be explained by the higher mean GFR in our study (at baseline, 60 versus 31 mL/min/1.73 m^2) and the smaller decline in GFR over time. Furthermore, handgrip strength and LBM did not decrease over 5 years in the CKD group in our study. Grip strength is known to be reduced in non-dialysis CKD patients [1, 30, 31] and to further decrease in conjunction with the progression of CKD [31]. Muscle wasting seems to be more pronounced in patients with dialysis-

dependent CKD than in those with non-dialysis CKD [32]. However, John et al. [14] showed a highly variable course of the change in muscle cross-sectional area over two years, and the rate of muscle loss was actually more pronounced in non-dialysis CKD patients than in patients on dialysis. Compared with the non-dialysis CKD group in our study, the non-dialysis CKD group in the study by John et al. had more advanced CKD with a substantially lower eGFR (16 mL/min/1.73 m^2), which might explain the discrepancy between the results.

Overall, at the group level, the individuals with CKD in our study were very stable in all measured parameters: i.e., cardiovascular, muscular and haematological. Cardiac function and vascular stiffness showed no significant change over time in the CKD group, while the controls significantly decreased their cardiac diastolic and systolic function and their peak HR. The changes in the control group can be considered to be the result of normal aging. Data from our group show that in the same cohort, daytime systolic blood pressure did not increase over 5 years in the CKD group, while a small but significant increase was seen in the controls [33]. According to the Fick principle, aerobic ExCap is the result of oxygen delivery and oxygen extraction mechanisms, which are highly dependent on the function of the cardiovascular system and skeletal musculature. Given the lack of progression in outcomes representing the function of these systems, it is not surprising that aerobic ExCap did not decrease significantly in the CKD group. A reduced level of physical activity may contribute to a decline in ExCap, but physical activity actually increased in the CKD group, perhaps further contributing to the maintenance of their ExCap. The opposite was seen in the control group, who significantly decreased their physical activity over 5 years.

The participants with mild-to-moderate CKD in our study were recruited from a dedicated nephrology clinic and showed well-controlled blood pressure over time [33]. The CKD group was monitored more closely than the controls, with aggressive treatment of hypertension, hyperlipidaemia and proteinuria. These factors may explain the fact that this group could maintain their cardiovascular and muscular function and thereby their aerobic ExCap. The mean decline in GFR over time was comparable to or a little lower than values reported in other studies [12, 34, 35]. Interestingly, Jones et al. reported that GFR decline slowed significantly following referral to a nephrology clinic, indicating that interventions to slow progression of CKD are important and beneficial. The decline of GFR in the control group was not more pronounced than expected in healthy individuals [36].

There are some important limitations of our study. The study groups were relatively small at baseline and were further reduced at follow-up. To overcome the problem with subjects lost to follow-up, statistical analyses were performed using linear mixed models to compensate for missing values. We measured aerobic ExCap as peak workload and not VO_2peak during exercise. However, given the linear relationship between exercise load and oxygen uptake during cycle ergometry [37], and the fact that the tests were performed according to the same protocol at both time-points with similar high RPEs, we believe our results are a valid measurement of the true changes in aerobic ExCap and peak HR over time.

Conclusions

Individuals with mild-to-moderate CKD maintained their aerobic ExCap over a 5-year-period. Known determinants of aerobic ExCap such as peak HR, haemoglobin level, muscle strength and cardiac diastolic function were also preserved over the 5 years. Possible explanations for this include attendance at a specialist nephrology clinic with tight monitoring and an increase in self-reported physical activity level over 5 years.

Abbreviations

CI, confidence interval; CKD: Chronic kidney disease; CKD–EPI, Chronic Kidney Disease–Epidemiology Collaboration; E/é: Mitral flow velocity E divided by tissue LV velocity é; EF: Ejection fraction; eGFR: Estimated GFR; Ep: Pressure strain elastic modulus in the carotid artery; ExCap: Exercise capacity; GEE, Generalized estimating equations; GFR: Glomerular filtration rate; Hs-CRP: high-sensitivity C-reactive protein; HR: Heart rate; LBM: Lean body mass; LV: Left ventricular; OR, odds ratio; RPE: Rating of perceived exertion; TAPSE: tricuspid annular plane systolic excursion; VO_2peak: Peak oxygen uptake

Declarations

Ethics approval and consent to participate

The study protocol was reviewed and approved by the Local Ethics Committee and Institutional Review Board of the Karolinska Institutet at the Karolinska University Hospital. All participants gave their written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

HW performed all statistical analyses and prepared the original draft of the manuscript. HW, AR, ME and EJ interpreted the data and contributed to substantial revision of the manuscript. SJ, CW, BHR and ME designed the study and contributed to data acquisition. All authors read and approved the final manuscript.

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Table

ıctional measurements at baseline and 5-year follow-up.

	Controls						*CKD*		
	Baseline (n = 54)	**Year 5**	***P*-value time[a]**	**Baseline** (n = 52)	**Year 5**	***P*-value time[a]**	***P*-value group[b]**	***P*-value group*time[c]**	**Covariates[d]**
/)	237 (225–249)	233 (221–245) n = 40	0.3	195 (184–207)	190 (178–202) n = 45	0.2	< 0.001/< 0.001	0.8	Age, sex, height
	175 (171–179)	171 (167–176) n = 40	0.04	161 (157–165)	160 (155–164) n = 43	0.3	< 0.001/0.001	0.4	Age, BB medication
	99 (94–104)	102 (96–107) n = 40	0.4	91 (86–96)	89 (84–95) n = 43	0.5	0.03/0.002	0.2	Age, BB medication
g)	44(43–46)	43 (41–44) n = 40	0.006	41 (39–42)	41 (39–42) n = 48	0.8	< 0.001/0.07	0.06	Age, sex, height
	65 (63–68)	61 (59–64) n = 41	<0.001	62 (60–65)	61 (58–63) n = 45	0.1	0.06/0.7	0.1	*
	5.0 (4.7–5.4)	5.7 (5.3–6.1) n = 43	<0.001	5.6 (5.3–6.0)	5.9 (5.6–6.3) n = 46	0.06	0.01/0.3	0.1	Age
	2.5 (2.4–2.6)	2.5 (2.4–2.6) n = 43	0.4	2.3 (2.2–2.4)	2.4 (2.3–2.5) n = 45	0.09	0.06/0.2	0.6	*
p	5.8 (5.4–6.3)	6.0 (5.5–6.6) n = 43	0.5	6.5 (5.8–7.1)	6.8 (6.2–7.4) n = 47	0.4	0.06/0.08	1	Age
'3	96 (92–100)	92 (87–96) n =	0.03	59 (55–62)	50 (46–54) n =	<0.001	< 0.001/< 0.001	0.05	

		43			47				
n	14.2 (13.8–14.5)	14.7 (14.3–15.0)	0.002	13.6 (13.3–13.9)	13.9 (13.6–14.2)	0.04	0.01/0.001	1	Sex
		n = 40			n = 49				
	1.0 (0.7–1.3)	1.0 (0.8–1.3)	0.9	1.9 (1.4–2.6)	1.8 (1.4–2.4)	0.8	0.002/0.006	0.8	
		n = 43			n = 49				

BB beta-blocker; *bpm* beats per minute; *CKD* chronic kidney disease; *E/é* left-ventricular early filling velocity/early diastolic myocardial velocity (a variable of left-ventricular diastolic function); *eGFR* glomerular filtration rate estimated by CKD–EPI; *Ep* pressure strain elastic modulus in the carotid artery; *HR* heart rate; *hs-CRP* high-sensitivity C-reactive protein; *LV* left ventricular; *LVEF* left-ventricular ejection fraction; *n* number; *RV* right ventricular; *TAPSE* tricuspid annular plane systolic excursion (a variable of right-ventricular systolic function).

Values reported as mean (95% confidence interval). *P*-value: linear mixed models. Mean values are adjusted for covariates.

[a] Significance of the change over time in the control group and the CKD group, respectively.

[b] Significance of the difference between the control group and the CKD group at baseline/year 5.

[c] Significance of the difference in change over time between the CKD group and the control group.

[d] Baseline values are used as fixed covariates.

[e] Values presented in the table are the calculated anti-logs of the log-scale estimates that were used in linear mixed models analyses.

* Age was tested as a covariate but was not significant.

Figures

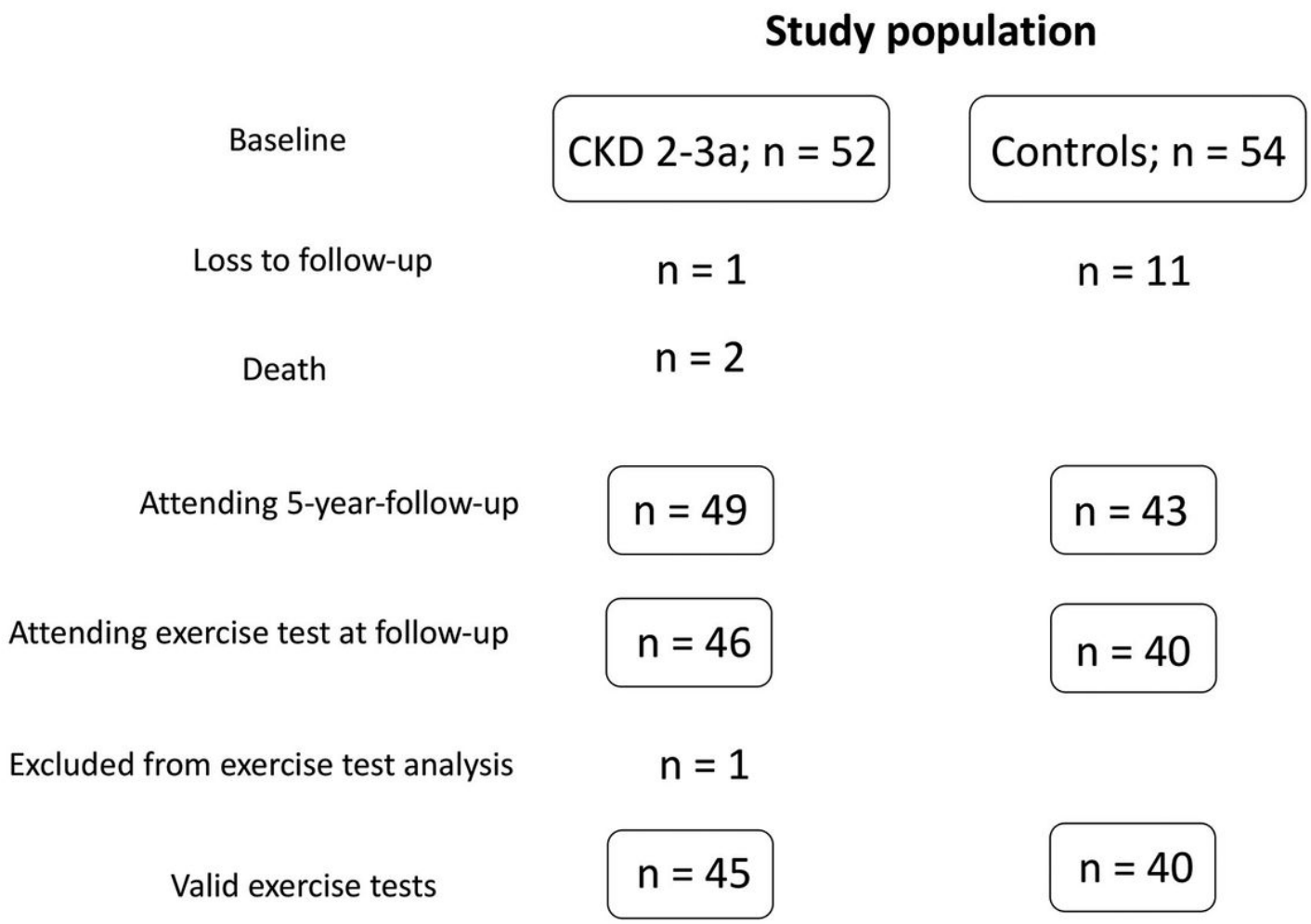

Figure 1

Study population at baseline and 5-year-follow up.

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