Kidney and Blood Pressure Research

Research Article

Kidney Blood Press Res
DOI: 10.1159/000520103

Received: August 4, 2021
Accepted: September 27, 2021
Published online: November 25, 2021

Maximal Exercise Capacity in Chronic Kidney Disease Stage 4–5 Patients Transitioning to Renal Replacement Therapy or Continuing Conservative Care: A Longitudinal Follow-Up Study

Tapio Hellman[a] Roosa Lankinen[a] Markus Hakamäki[a] Niina S. Koivuviita[a] Jussi Pärkkä[b] Petri Kallio[b, c] Kaj Metsärinne[a] Mikko J. Järvisalo[d, e]

[a]Kidney Center, Turku University Hospital and University of Turku, Turku, Finland; [b]Department of Clinical Physiology, Turku University Hospital and University of Turku, Turku, Finland; [c]Paavo Nurmi Centre & Unit for Health and Physical Activity, University of Turku, Turku, Finland; [d]Department of Anaesthesiology and Intensive Care, Turku University Hospital and University of Turku, Turku, Finland; [e]Department of Intensive Care, Turku University Hospital and University of Turku, Turku, Finland

Keywords
Chronic kidney disease · Ergometry test · Renal replacement therapy · Exercise capacity

Abstract
Introduction: Chronic kidney disease (CKD) is associated with impaired maximal exercise capacity (MEC). However, data are scarce on the development of MEC in CKD stage 4–5 patients transitioning to renal replacement therapy (RRT). ***Methods:*** We explored the change in MEC measured in watts (Wlast4) with 2 consecutive maximal bicycle stress ergometry tests in 122 CKD stage 4–5 patients transitioning to dialysis and transplantation in an observational follow-up study. ***Results:*** Mean age was 58.9 ± 13.9 years and 43 (35.2%) were female. Mean time between the baseline and follow-up ergometry tests was 1,012 ± 327 days and 29 (23.8%) patients had not initiated RRT, 50 (41.0%) were undergoing dialysis, and 43 (35.2%) had received a kidney transplant at the time of the follow-up ergometry test. The mean Wlast4 was 91 ± 37 W and 84 ± 37 W for the baseline and follow-up ergometry tests, respectively ($p < 0.001$). The mean Wlast4 declined between the baseline and follow-up ergometry tests in patients not requiring RRT ($p = 0.001$) and transplant recipients ($p = 0.005$), but not in dialysis patients ($p = 0.478$). There were no differences in the ratio of Wlast4 of the follow-up to the baseline ergometry tests (ΔWlast4) between patients on different treatment modalities at the time of the follow-up test ($p = 0.097$). Mean capillary blood bicarbonate was significantly associated with ΔWlast4 after adjusting for age and treatment modality in the multivariate linear regression analysis (β = 0.226, $p = 0.012$). ***Conclusion:*** MEC declined or remained poor in advanced CKD patients transitioning to RRT or continuing conservative care in this observational study. Mean capillary blood bicarbonate was independently associated with the development of MEC.

Introduction

Impairment of maximal exercise capacity (MEC) is common in chronic kidney disease (CKD) and is associated with mortality [1–3]. Attenuated MEC has been demonstrated across all stages of CKD including dialysis

karger@karger.com
www.karger.com/kbr

Correspondence to:
Tapio Hellman, tapio.hellman@tyks.fi

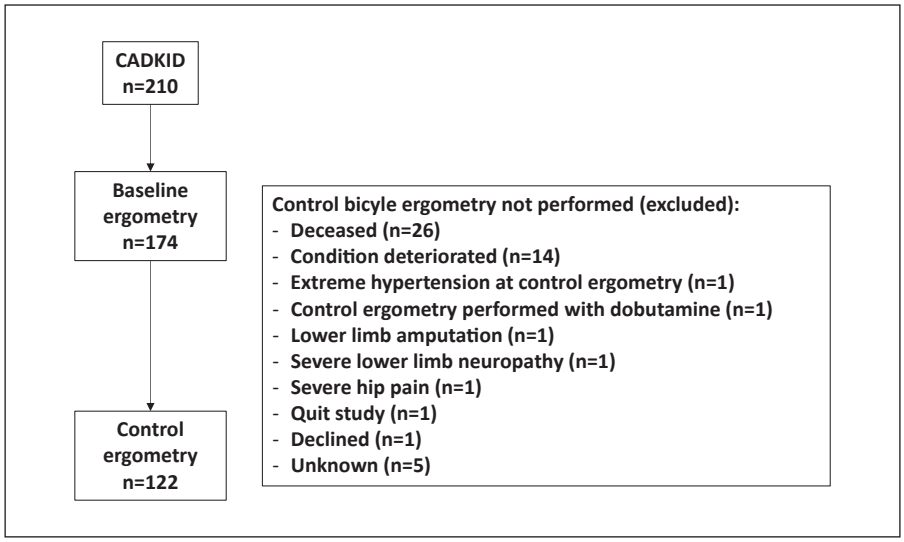

Fig. 1. Flowchart of the study patients. CADKID, Chronic Arterial Disease, quality of life and mortality in chronic KIDney injury.

patients and kidney transplant recipients compared to healthy controls [1–5]. Moreover, MEC has been shown to further deteriorate with time especially in patients with advanced CKD with or without maintenance dialysis dependency, whereas in mild to moderate CKD and in transplant recipients exercise tolerance seems to remain more stable [6–9]. However, very limited data exist on the development of MEC in advanced CKD patients transitioning to different treatment modalities of renal replacement therapy (RRT). An observational study published in 1987 showed an improvement in MEC in 20 end-stage renal disease patients following kidney transplantation [10]. However, in the study by Painter et al. the sample size was limited and no control group was included. A more recent study in 2020 by Lim et al. explored the change in MEC before and after transplantation in 81 kidney transplant recipients as well as in wait-listed CKD and hypertensive non-CKD controls [11]. In line with the findings by Painter et al., MEC improved in kidney transplant recipients in the study by Lim et al. However, the study patients were fairly young and only modestly comorbid possibly not reflecting the general CKD stage 4–5 population. Thus, we sought to investigate the development and determinants of MEC measured using repeated maximal bicycle stress ergometry tests in consecutively recruited CKD stage 4–5 patients transitioning to dialysis and transplantation in an observational follow-up cohort study.

Materials and Methods

This prespecified analysis is a part of the ongoing prospective Chronic Arterial Disease, quality of life and mortality in chronic KIDney injury (CADKID) study (http://www.ClinicalTrials.gov NCT04223726) protocol assessing arterial disease, quality of life, and mortality in patients with CKD stage 4–5. The primary study cohort comprised 210 study patients consecutively recruited between 2013 and 2017. All included patients were ≥18 years of age and had CKD stage 4–5 with estimated glomerular filtration rate (eGFR) <30 mL/min per 1.73 m^2 calculated using the Chronic Kidney Disease Epidemiology Collaboration equation.

This is a follow-up study of the previously published report of the CADKID study on the determinants of maximal stress ergometry performance in 174 non-dialysis CKD stage 4–5 patients [12]. All study patients in the initial report were scheduled for a follow-up maximal stress ergometry test within a time interval of 3 years from baseline. A total of 52 patients, most of whom (26 patients) perished, did not perform the follow-up ergometry test and were excluded from the study (shown in Fig. 1). Altogether 122 study patients completed the 2 consecutive stress ergometry tests and comprised the patient cohort of the present study. The study cohort was then divided into 3 subgroups (no RRT, dialysis, and transplant patients) according to the treatment modality at the time of the follow-up stress ergometry test. Different dialysis modalities (hemodialysis vs. peritoneal dialysis) were not segregated in the dialysis patient group.

Maximal Stress Ergometry Test and Biochemical Data

In line with the previous report and clinical standards, the maximal stress ergometry test was performed as an incremental, symptom-limited bicycle exercise test at the Department of Clinical Physiology of the research hospital. The primary test workload for each participant was modeled according to an estimated maximum workload (using datasets of the Mini Suomi study [13] as a reference) and a targeted test duration of 6–10 min. All tests were preceded by a 30-s warm-up phase during which the target speed of 60 rpm was reached. The workload was increased automatically

10–20 W per minute by the ergometry software until symptom limitation within 6–10 min. The study patients were instructed to maintain a cycling speed of 60 rpm and encouraged to persist until exhaustion. The mean workload of the last 4 min of maximal stress (Wlast4) in watts was collected along with maximal heart rate, metabolic equivalent of task, and maximal oxygen uptake for all patients. As the study protocol did not include a complete spiroergometry, the metabolic equivalent of task and maximal oxygen uptake values were derived from the achieved workload in watts by the ergometry software. The Borg scale (score range 6–20 with 6 indicating very light exertion and 20 indicating extremely hard exertion) was used to assess the intensity of exercise [14]. Furthermore, all patients underwent echocardiography at rest prior to the stress ergometry test using a commercially available ultrasound system (Vivid E9; GE Vingmed Ultrasound, Horten, Norway) with a 3.5-MHz phased-array transducer (M5S). Left ventricular ejection fraction, left ventricular end-diastolic diameter, and left ventricular mass index were collected for all patients in line with clinical standards.

All the study patients were periodically followed up in the kidney center of the research hospital. Thus, extensive serial biochemical data provided by Turku University Hospital laboratory service (TYKSLAB) were collected for each patient every 3 months encompassing the time interval between the baseline and follow-up ergometry tests. The mean of all the collected values of each laboratory test was used in the analyses.

As MEC assessment in watts has been used successfully in prior studies on exercise tolerance of CKD patients [8, 15], Wlast4 was chosen as the base for the primary outcome measure. Wlast4 has been previously described as a measure of MEC in ergometry [13]. The values considered normal for expected maximal exercise performance measured as watts are derived and extrapolated from large datasets of the Mini Suomi study. The algorithms for Wlast4 expected exercise performance are incorporated in the cycle ergometer software and used in day-to-day clinical work. The use of Wlast4 was deemed to better represent MEC as the measure takes into account a larger portion of the final phase of the ergometry test in contrast to a single achieved peak workload measure. Thus, primary outcome of the study was the change in MEC defined as the ratio of Wlast4 of the follow-up to the baseline ergometry tests (ΔWlast4).

Ethics

The study was approved by Medical Ethics Committee of the Hospital District of Southwest Finland, and all procedures were in accordance with the Helsinki Declaration. All patients provided written informed consent before entering the study.

Statistics

The results are reported as mean ± standard deviation and median (interquartile range [IQR]) for normally distributed and skewed variables, respectively, while categorical variables were reported with absolute and relative (percentage) frequencies. Normality in continuous variables was tested with Kolmogorov-Smirnov and Shapiro-Wilk tests.

The comparisons between the variables of the baseline and follow-up ergometry tests within the whole study cohort, and for the subgroups separately, were performed using the Wilcoxon signed rank test or Paired-Samples *T* Test according to the distribution of the ratio of each variable of the follow-up to the baseline ergometry tests. The comparisons between different subgroups (no RRT, dialysis, and transplant patients) were performed using the one-way ANOVA and Kruskal-Wallis tests for normally distributed and skewed covariates, respectively, and with a post-hoc Bonferroni correction to allow for multiple pairwise comparisons. Categorical variables were compared using the Pearson χ^2 test. The association between treatment modality and change in Wlast4 during follow-up was also explored using repeated measures ANOVA (Proc Mixed, SAS Institute Inc.) and followed by adjustment for age and eGFR at baseline. The correlation/clustering between repeated measurements within a subject was taken into account by using an unstructured correlation structure, based on Akaike's and Bayesian information criterion examination.

The univariate associations between the dependent variable and tested covariates were separately analyzed using linear regression models. The covariates with a univariate association at $p < 0.10$ significance level with the dependent variable (online suppl. Table. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520103) were entered in the multivariate linear regression model. The entered covariates included use of calcium channel blockers (dihydropyridines), mean left ventricular end-diastolic diameter of the baseline and follow-up echocardiographies, and mean capillary blood bicarbonate. Only 1 antihypertensive medication was included in the multivariable model to avoid multicollinearity, and mean capillary blood bicarbonate was selected out of the acid base analyses results due to the most significant univariate association. The multivariable model was adjusted by entering age and treatment modality at the time of the follow-up ergometry test as covariates. Potential existence of multicollinearity was assessed by examining variance inflation factors. The combined missingness in the whole study cohort data was <0.3%, and no data were missing in the multivariable model.

All analyses were 2-sided and $p < 0.05$ was considered statistically significant. IBM SPSS Statistics software version 26.0 and SAS version 9.3 (SAS Institute Inc.) were used to perform all analyses, as appropriate.

Results

Altogether 122 study patients underwent the baseline and follow-up maximal bicycle stress ergometry tests and were included in this study. Mean age was 58.9 ± 13.9 years and 43 (35.2%) were female. Baseline eGFR was 13.2 ± 3.5 mL/min/1.73 m^2 in the whole cohort, and the patients not receiving RRT during the study had slightly higher baseline eGFR compared to others (Table 1). Mean time between the baseline and follow-up ergometry tests was 1,012 ± 327 days. A total of 29 (23.8%) patients had not initiated RRT, 50 (41.0%) were undergoing maintenance dialysis, and 43 (35.2%) had received a kidney transplant at the time of the follow-up ergometry test. The mean dialysis vintage was 675 ± 282 and 961 ± 351 days in the patients receiving dialysis and transplanted patients at the time of the follow-up ergometry test, respectively. The mean kidney transplant vintage at the

Table 1. Baseline characteristics, medications, and mean follow-up biochemical data between the ergometry tests of the study patients according to treatment modality at the time of the follow-up ergometry test

	No RRT (*N* = 29)	Dialysis (*N* = 50)	Transplant (*N* = 43)
Age, mean (median), years	70 (72)	59 (61)$^{\alpha}$	52 (52)$^{\beta,\Omega}$
Female	7 (24.1)	20 (40.0)	16 (37.2)
BMI	26.9 (24.7–28.8)	28.1 (24.6–32.6)	25.2 (23.0–30.1)
eGFR, mL/min/1.73 m^2	15 (12–18)	12 (11–14)$^{\alpha}$	12 (11–14)$^{\beta}$
Smoking	11 (37.9)	23 (46.9)	17 (39.5)
Hypertension	28 (96.6)	50 (100)	42 (97.7)
Diabetes	9 (31)	21 (43)	14 (32.6)
Heart failure	6 (20.7)	8 (16.0)	1 (2.3)$^{\beta,\Omega}$
Atrial fibrillation	8 (27.6)	8 (16.0)	0 (0)$^{\beta,\Omega}$
CAD	5 (17.2)	5 (10.0)	2 (4.7)
Stroke	3 (10.3)	3 (6.0)	4 (9.3)
PAD	0 (0)	7 (14.0)	3 (7.0)
Medications			
Betablocker	20 (69.0)	39 (78.0)	28 (65.1)
Calcium channel blocker	19 (65.5)	43 (86.0)$^{\alpha}$	37 (86.0)$^{\beta}$
Insulin	4 (13.8)	15 (30.0)	13 (30.2)
Statin	13 (48.3)	30 (60.0)	28 (65.1)
Calcium carbonate, mg	1,000 (500–1,000)	1,000 (500–1,000)	1,000 (1,000-1,000)
Sodium bicarbonate, mg	2,000 (1,250–2,500)	2,000 (1,375–3,000)	2,500 (2,000–4,625)
Biochemical data			
Hemoglobin, g/L	120 (113–129)	112 (108–120)$^{\alpha}$	117 (112–122)
Creatinine, µmol/L	364 (282–386)	522 (423–611)$^{\alpha}$	391 (331–534)$^{\beta,\Omega}$
Urea, mmol/L	21.4 (16.2–25.0)	20.0 (17.6–23.6)	18.0 (15.4–19.6)$^{\beta,\Omega}$
Albumin, g/L	36.3 (±2.6)	32.7 (±3.7)$^{\alpha}$	34.0 (±2.8)$^{\beta}$
Ionized calcium, mmol/L	1.23 (±0.05)	1.21 (±0.06)	1.24 (±0.06)$^{\Omega}$
Phosphorus, mmol/L	1.25 (1.14–1.43)	1.51 (1.40–1.73)$^{\alpha}$	1.45 (1.30–1.55)$^{\beta}$
Parathyroid hormone, ng/L	154 (92–210)	279 (210–398)$^{\alpha}$	222 (152–320)$^{\beta}$
HbA1c, mmol/mol	37 (33–40)	35 (31–51)	34 (31–49)
pH	7.39 (7.36–7.42)	7.39 (7.37–7.42)	7.39 (7.36–7.40)
Carbon dioxide, kPa	5.1 (4.8–5.5)	5.2 (4.9–5.5)	5.1 (4.9–5.4)
Bircarbonate, mmol/L	22.7 (21.5–24.8)	23.7 (22.2–24.9)	23.0 (21.5–24.2)
Ferritin, µg/L	256 (119–371)	397 (249–530)$^{\alpha}$	317 (247–534)
Transferrin saturation, %	25.5 (21.7–30.1)	24.5 (22.8–27.4)	28.2 (23.2–31.6)

Categorical values in parentheses are % unless stated otherwise. Continuous variables are expressed as mean (±SD) or median (IQR) for normally distributed and skewed covariates, respectively. The biochemical data are the calculated cumulative means of the follow-up blood tests regularly collected every 3-month intervals between the baseline and follow-up ergometry tests. BMI, body mass index; eGFR, estimated glomerular filtration rate; CAD, coronary artery disease; PAD, peripheral artery disease; HbA1c, glycosylated hemoglobin; RRT, renal replacement therapy; SD, standard deviation; IQR, interquartile range. $^{\alpha}$ No RRT versus dialysis group $p < 0.05$. $^{\beta}$ No RRT versus transplant group $p < 0.05$. $^{\Omega}$ Dialysis versus transplant group $p < 0.05$.

time of the follow-up ergometry test was 481 ± 295 days in the transplant recipients.

The baseline characteristics, medications, and mean follow-up biochemical data are summarized in Table 1 and data for the baseline and follow-up ergometry tests in Table 2. The mean Wlast4 in the whole study cohort was 91 ± 37 W and 84 ± 37 W for the baseline and follow-up ergometry tests, respectively ($p < 0.001$). The Borg scale scores were 19 (IQR 0) and 19 (IQR 0) for the baseline and follow-up ergometry tests, respectively, indicating that maximal exertion was achieved in both tests. However, Borg scale data were available in only 39/122 (32.0%) and 43/122 (35.2%) patients for the baseline and follow-up ergometry tests, respectively. Transplant recipients had higher age, sex, and body-size corrected Wlast4 at baseline and follow-up ergometry tests than others (transplant recipients (70 ± 18 W for the baseline ergometry and 65 ± 20 W for the second ergometry test)) versus no

Table 2. Echocardiography data at rest and stress ergometry data for the baseline and follow-up ergometry tests

	No RRT (*N* = 29)	Dialysis (*N* = 50)	Transplant (*N* = 43)
Ergometry test baseline			
EF, %	65 (60–69)	64 (60–70)	65 (63–69)
LVEDD, mm	53 (52–56)	54 (50–60)	53 (48–56)
LVMI	108 (85–125)	100 (89–130)	88 (81–110)
Wlast4, W	87 (±25)	81 (±40)	106 (±35)$^{\beta,\Omega}$
Wlast4%, %	59 (±17)	54 (±22)	70 (±18)$^{\Omega}$
Max heart rate, /min	125 (±20)	119 (±25)	137 (±24)$^{\Omega}$
MET, units	4.7 (4.1–5.2)	4.6 (3.6–5.4)	5.7 (5.0–7.3)$^{\beta,\Omega}$
VO2max, mL/(kg·min)	16.3 (14.4–21.6)	16.0 (12.5–19.1)	20.1 (17.4–27.0)$^{\beta,\Omega}$
Ergometry test follow-up			
EF	63 (60–69)	63 (58–69)	66 (64–70)$^{\Omega}$
LVEDD	53 (52–57)	54 (51–58)	52 (48–55)
LVMI	99 (88–128)	108 (93–123)	98 (87–111)
Wlast4, W	78 (±26)	78 (±44)	96 (±33)$^{\beta}$
Wlast4%, %	54 (±17)	53 (±24)	65 (±20)$^{\Omega}$
Max heart rate, /min	117 (±21)	122 (±27)	131 (±23)
MET, units	4.3 (3.6–4.9)	4.2 (3.7–5.3)	5.5 (4.8–6.5)$^{\beta,\Omega}$
VO2max, mL/(kg·min)	14.9 (12.4–17.2)	14.9 (12.9–18.6)	19.2 (15.7–22.7)$^{\beta,\Omega}$
Ergometry test Δ			
Time between tests, days	899 (±215)	956 (±313)	1,151 (±360)$^{\beta,\Omega}$
Wlast4 ratio	0.90 (0.79–0.93)	1.0 (0.84–1.15)	0.91 (0.78–1.05)

Categorical values in parentheses are % unless stated otherwise. Continuous variables are expressed as mean (±SD) or median (IQR) for normally distributed and skewed covariates, respectively. The biochemical data are the calculated cumulative means of the regularly collected follow-up blood tests of the study patients. EF, ejection fraction; LVEDD, left ventricular end-diastolic diameter; LVMI, left ventricular mass index; Wlast4,mean workload of the last 4 min of maximal stress; Wlast4%, the mean proportional workload of the last 4 min of the age, sex, and body-size predicted value; MET, metabolic equivalent of task; VO2max, maximal oxygen uptake; RRT, renal replacement therapy; SD, standard deviation; IQR, interquartile range. $^{\alpha}$ No RRT versus dialysis group $p < 0.05$. $^{\beta}$ No RRT versus transplant group $p < 0.05$. $^{\Omega}$ Dialysis versus transplant group $p < 0.05$.

RRT and dialysis groups together (56 ± 21 W for the baseline ergometry and 53 ± 22 W for the second ergometry test) ($p < 0.01$ for both comparisons). Furthermore, the mean Wlast4 decreased in the patients not requiring RRT ($p = 0.001$) and transplant recipients ($p = 0.003$) while no significant change in Wlast4 between the baseline and follow-up ergometry tests was observed in patients receiving dialysis ($p = 0.322$) (shown in Fig. 2). The maximum heart rate decreased in the patients not receiving RRT ($p = 0.008$) while no change in achieved maximum heart rate was observed in dialysis or transplant patients (Table 2). There were no differences in the ΔWlast4 of the follow-up and baseline ergometry tests between the study groups ($p = 0.10$). The decline in Wlast4 from the baseline to the follow-up ergometry test in the whole study population remained significant when examined using repeated measures ANOVA (F 14.63, $p < 0.01$). Treatment modality, however, was not associated with the change in Wlast4 from baseline to follow-up in repeated measures ANOVA before (F 1.86, $p = 0.16$) or after adjustment for age and baseline eGFR ($F = 1.99$, $p = 0.14$). The mean interval between the ergometry tests was shorter in patients not receiving RRT and dialysis patients compared to transplant recipients ($p < 0.05$ for both comparisons) (Table 2).

Univariate associations between risk factors and ΔWlast4 are shown in online supplementary Table 1. The delay between the baseline and follow-up ergometry tests, dialysis vintage, or time from transplantation at the time of the follow-up ergometry test were not associated with ΔWlast4 in the univariate models. In the multivariable linear regression analysis, mean capillary blood bicarbonate remained significantly associated with ΔWlast4 after adjusting for age and treatment modality at the time of the follow-up ergometry test (β = 0.226, $p = 0.012$). The results remained unaltered when the time interval between the ergometry tests was included in the model.

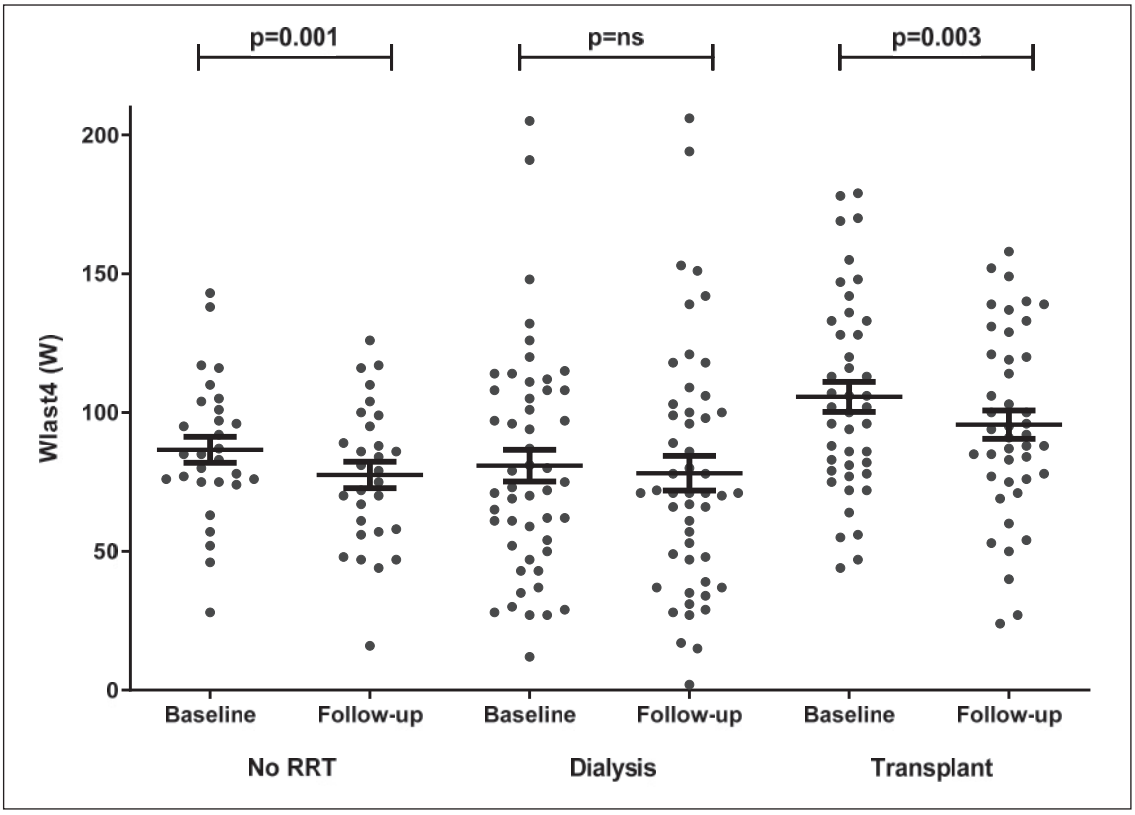

Fig. 2. The development of mean Wlast4 between the baseline and follow-up ergometry tests according to treatment modality at the time of the follow-up ergometry test. The comparisons were performed using Wilcoxon signed rank test and paired-samples *T* test, as appropriate. Wlast4, mean workload of the last 4 min of maximal stress in watts; RRT, renal replacement therapy.

Discussion

In this large observational prospective follow-up cohort study, overall MEC declined in CKD stage 4–5 patients transitioning to RRT or continuing conservative care during a mean follow-up of ca. 3 years. The attenuation of exercise tolerance was, however, limited to patients not receiving RRT and transplant recipients while MEC remained poor and similar to baseline in patients who had initiated and continued on maintenance dialysis. However, there were no significant differences in ΔWlast4 between study patients with different treatment modalities at the time of the follow-up ergometry test. Interestingly, mean capillary blood bicarbonate was independently associated with ΔWlast4.

This is the first study to explore the development of MEC in a large real-world observational cohort of CKD stage 4–5 patients transitioning to dialysis and/or transplantation or continuing on conservative renal care. Prior studies have primarily described the change in MEC within specific patient populations not transitioning to other treatment modalities [6–9]. One previous study exploring the development of exercise tolerance in end-stage renal disease patients receiving kidney transplants published in the late 1980s by Painter et al. [10] enrolled only 20 patients, that is, less than half the number of transplant patients included in the present study and was too small to draw definite conclusions. More recently, Lim et al. compared the change in MEC in 81 kidney transplant recipients to cohorts of wait-listed CKD and hypertensive non-CKD patients and demonstrated an improvement in exercise tolerance after transplantation. However, the mean age of the transplant recipients was 43 years, and few comorbidities were observed in the study [11]. Strikingly, we observed a substantial decline in MEC in CKD patients who underwent kidney transplantation in contrast to the findings in prior studies [9–11]. Furthermore, the change in exercise tolerance was comparable between treatment modalities and numerically similar between patients not receiving RRT and

transplant recipients (Table 2). There are multiple possible explanations for this finding. First, the transplant recipients in our study were older and had more cardiovascular comorbidities compared to prior studies [9–11]. The criteria for kidney transplant eligibility were strict in 1987 compared to contemporary criteria. Second, the patients in the previous studies were more specifically selected, whereas the patients in our study were recruited consecutively representing a real-world cohort of patients known to lead a sedentary life style [16]. Third, the dialysis vintage in the transplant recipients of our study was substantial (mean >2.5 years), possibly contributing to the poor MEC at the follow-up ergometry test. However, our findings do not rule out the possibility of cessation in MEC decline after transplantation as ergometry tests were performed at only 2 separate time points and only once following transplantation. Exercise tolerance appears to be better sustained in younger transplant recipients with or without exercise training intervention while beneficial effects of exercise training in improving MEC have been demonstrated also in older transplanted patients with a wide range in kidney transplant vintage [9, 17].

Overall, the MEC was poor in this study as the mean Wlast4 ranged between 53% and 65% of the age, sex, and body-size predicted value in the follow-up ergometry test regardless of treatment modality (Table 2). Unsurprisingly, transplant recipients had higher age, sex, and body-size corrected MEC at both baseline and follow-up ergometry tests compared to others. The finding probably reflects the high level of cardiovascular comorbidity in our study as virtually all patients were hypertensive, over a third had diabetes, and almost half had a history of smoking (Table 2). In line with this reasoning, it is plausible that MEC did not decline significantly in the dialysis group as these highly comorbid patients are the frailest of CKD patients with the poorest baseline exercise tolerance and, thus, have the least MEC "in reserve" to lose. The association between mortality and impaired MEC has been shown in several studies on different subsets of CKD patients as well as in our previous work [1–3, 18]. Although exercise training has been demonstrated to improve MEC in CKD patients with and without RRT, data are inconsistent whether ameliorated MEC through physical training improves survival [17, 19–21]. There are, however, consistent data that exercise training is safe and improves quality of life in CKD and transplant patients [17, 19, 22]. Thus, it is reasonable to strive to counter MEC decline associated with CKD and recommend regular exercise training and enforce early physical rehabilitation after kidney transplantation as stated in current guidelines [23].

Mean capillary blood bicarbonate was independently associated with ΔWlast4 in our study. This finding is relevant as low bicarbonate levels have been associated with poor physical performance in prior studies in patients with or without CKD [24, 25]. In this context, it is not a surprise that bicarbonate was associated with ΔWlast4 as MEC remained poor or declined further in the study cohort. In previous studies, the bicarbonate measurements have been performed on single or few samples [24, 25] whereas our current data demonstrate an association between ΔWlast4 and mean bicarbonate levels of serial measurements taken every 3 months throughout the whole follow-up interval during most of which the study patients were uremic or undergoing dialysis. Nevertheless, the mean bicarbonate in each subgroup remained within reference range reflecting the correction of acidosis with alkali supplementation in clinical practice in the research hospital (Table 2). However, correction of bicarbonate levels with alkali has not been associated with improved physical performance in CKD patients whereas some data exist on the positive effect of sodium bicarbonate supplementation on physical exercise performance in athletes [26, 27]. The clinical significance and implications of bicarbonate on MEC in CKD patients remain unclear and warrant further research.

This study has the limitations of an observational study. The sample size was moderately limited in comparison to the initial cohort of the study on ergometry performance [12] due to mortality and morbidity of the study patients. Baseline eGFR was slightly higher in the patients not receiving RRT in this real-world study. The difference, however, was small and unlikely to skew the findings on the development of MEC as the great majority of patients were in CKD stage 5 at baseline and the mean time interval between the ergometry tests was almost 3 years. Furthermore, the lack of a significant treatment group effect on the development in Wlast4 through follow-up remained unaffected by adjustment for age and baseline eGFR in repeated measures ANOVA. Furthermore, no measured data on upper limb muscle strength or day-to-day physical activity were available. However, the maximal stress bicycle ergometry test provides solid data on lower limb muscle strength and cardiorespiratory performance. As the study protocol did not include a complete spiroergometry, true maximal oxygen uptake or respiratory exchange ratio were not collected and Borg scale data were available in only a third of the study patients, the maximality of the study stress ergometry test was more subjective. Nevertheless, all

patients were persistently encouraged to continue cycling until exhaustion. Furthermore, the patients were extensively studied and the ergometry tests performed according to the same standards in the same department of the research hospital. Furthermore, extensive follow-up biochemical data were collected providing good and reliable data quality on study patients transitioning to RRT or continuing conservative care. Despite these limitations, we believe that these data can guide future research and offer insight on the importance of exercise tolerance in CKD patients initiating dialysis or receiving transplants. Somewhat surprisingly MEC remained at a lower level even after a year following kidney transplantation compared to that observed in the predialysis phase. In light of this finding, there seems to be an unrecognized need for long-term physical rehabilitation of kidney transplant patients following transplantation. The recent prospective randomized multicenter EXCITE trial showed that a personalized walking exercise program at home improves the physical performance of dialysis patients and reduces their rate of hospitalization [28] and similar programs may be warranted for transplant patients.

In conclusion, MEC declined or remained poor in this observational prospective study on CKD stage 4–5 patients transitioning to dialysis or transplantation or continuing conservative care. Mean capillary blood bicarbonate was independently associated with the change in exercise tolerance in this study.

Acknowledgment

We would like to thank biostatistician Eliisa Löyttyniemi, MSc, for statistical consultation.

Statement of Ethics

The study (reference No. T05/024/20) received approval of the Medical Ethics Committee of the Hospital District of Southwest Finland and the Ethics Committee of the National Institute for Health and Welfare. The study adheres to the Declaration of Helsinki. All patients provided written informed consent before entering the study.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

Funding Sources

This study was supported by research grants from the Finska Läkaresällskapet, Helsinki, Finland, the Perklén Foundation, Helsinki, Finland, and the Aarne Koskelo Foundation, Helsinki, Finland. None of the funding bodies were involved in designing of the study; collection, analysis, or interpretation of data; or writing of the report.

Author Contributions

T.H., R.L., M.H., N.K., J.P., P.K., K.M., and M.J.J. designed the study and were responsible for the data collection. T.H. performed the statistical analysis and drafted the manuscript. T.H., R.L., M.H., N.K., J.P., P.K., K.M., and M.J.J. revised the manuscript.

Data Availability Statement

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

References

1 Roshanravan B, Robinson-Cohen C, Patel KV, Ayers E, Littman AJ, de Boer IH, et al. Association between physical performance and all-cause mortality in CKD. J Am Soc Nephrol. 2013;24(5):822–30.
2 Sietsema KE, Amato A, Adler SG, Brass EP. Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease. Kidney Int. 2004;65(2):719–24.
3 Ting SM, Iqbal H, Kanji H, Hamborg T, Aldridge N, Krishnan N, et al. Functional cardiovascular reserve predicts survival pre-kidney and post-kidney transplantation. J Am Soc Nephrol. 2014;25(1):187–95.
4 Van Craenenbroeck AH, Van Craenenbroeck EM, Van Ackeren K, Hoymans VY, Verpooten GA, Vrints CJ, et al. Impaired vascular function contributes to exercise intolerance in chronic kidney disease. Nephrol Dial Transplant. 2016;31(12):2064–72.
5 van den Ham EC, Kooman JP, Schols AM, Nieman FH, Does JD, Franssen FM, et al. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. Am J Transplant. 2005;5(8):1957–65.
6 Leikis MJ, McKenna MJ, Petersen AC, Kent AB, Murphy KT, Leppik JA, et al. Exercise performance falls over time in patients with chronic kidney disease despite maintenance of hemoglobin concentration. Clin J Am Soc Nephrol. 2006;1(3):488–95.
7 Zhang L, Luo H, Kang G. Longitudinal study of physical activity with various methods in maintenance hemodialysis patients. Hemodial Int. 2021;25(2):249–56.
8 Wallin H, Jansson E, Wallquist C, Hylander Rössner B, Jacobson SH, Rickenlund A, et al. Aerobic exercise capacity is maintained over a 5-year period in mild-to-moderate chronic kidney disease: a longitudinal study. BMC Nephrol. 2020;21(1):475.
9 Painter PL, Hector L, Ray K, Lynes L, Dibble S, Paul SM, et al. A randomized trial of exercise training after renal transplantation. Transplantation. 2002;74(1):42–8.

10 Painter P, Hanson P, Messer-Rehak D, Zimmerman SW, Glass NR. Exercise tolerance changes following renal transplantation. Am J Kidney Dis. 1987;10(6):452–6.
11 Lim K, Ting SMS, Hamborg T, McGregor G, Oxborough D, Tomkins C, et al. Cardiovascular functional reserve before and after kidney transplant. JAMA Cardiol. 2020;5(4):420–9.
12 Lankinen R, Hakamäki M, Metsärinne K, Koivuviita N, Pärkkä JP, Saarenhovi M, et al. Association of maximal stress ergometry performance with troponin T and abdominal aortic calcification score in advanced chronic kidney disease. BMC Nephrol. 2021;22(1):50.
13 Arstila M, Impivaara O, Mäki J. New ergometric reference values for clinical exercise tests. Scand J Clin Lab Invest. 1990;50(7):747–55.
14 Fletcher GF, Balady GJ, Amsterdam EA, Chaitman B, Eckel R, Fleg J, et al. Exercise standards for testing and training: a statement for healthcare professionals from the American Heart Association. Circulation. 2001 Oct 2;104(14):1694–740.
15 Wallin H, Asp AM, Wallquist C, Jansson E, Caidahl K, Hylander Rössner B, et al. Gradual reduction in exercise capacity in chronic kidney disease is associated with systemic oxygen delivery factors. PLoS One. 2018 Dec 19;13(12):e0209325.
16 Vallance JK, Johnson ST, Thompson S, Wen K, Lam NN, Boyle T, et al. Prevalence and correlates of accelerometer-based physical activity and sedentary time among kidney transplant recipients. Can J Kidney Health Dis. 2019;6:2054358119882658.
17 Calella P, Hernández-Sánchez S, Garofalo C, Ruiz JR, Carrero JJ, Bellizzi V. Exercise training in kidney transplant recipients: a systematic review. J Nephrol. 2019;32(4):567–79.
18 Lankinen R, Hakamäki M, Metsärinne K, Koivuviita NS, Pärkkä JP, Hellman T, et al. Cardiovascular determinants of mortality in advanced chronic kidney disease. Am J Nephrol. 2020;51(9):726–35.
19 Nakamura K, Sasaki T, Yamamoto S, Hayashi H, Ako S, Tanaka Y. Effects of exercise on kidney and physical function in patients with non-dialysis chronic kidney disease: a systematic review and meta-analysis. Sci Rep. 2020;10(1):18195.
20 Painter P, Moore G, Carlson L, Paul S, Myll J, Phillips W, et al. Effects of exercise training plus normalization of hematocrit on exercise capacity and health-related quality of life. Am J Kidney Dis. 2002;39(2):257–65.
21 Greenwood SA, Castle E, Lindup H, Mayes J, Waite I, Grant D, et al. Mortality and morbidity following exercise-based renal rehabilitation in patients with chronic kidney disease: the effect of programme completion and change in exercise capacity. Nephrol Dial Transplant. 2019;34(4):618–25.
22 Rossi AP, Burris DD, Lucas FL, Crocker GA, Wasserman JC. Effects of a renal rehabilitation exercise program in patients with CKD: a randomized, controlled trial. Clin J Am Soc Nephrol. 2014;9(12):2052–8.
23 Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int. 2013(Suppl 3):1–150.
24 Yenchek R, Ix JH, Rifkin DE, Shlipak MG, Sarnak MJ, Garcia M, et al. Association of serum bicarbonate with incident functional limitation in older adults. Clin J Am Soc Nephrol. 2014;9(12):2111–6.
25 Abramowitz MK, Hostetter TH, Melamed ML. Association of serum bicarbonate levels with gait speed and quadriceps strength in older adults. Am J Kidney Dis. 2011;58(1):29–38.
26 Witham MD, Band M, Chong H, Donnan PT, Hampson G, Hu MK, et al. Sodium bicarbonate to improve physical function in patients over 60 years with advanced chronic kidney disease: the BiCARB RCT. Health Technol Assess. 2020;24(27):1–90.
27 Hadzic M, Eckstein ML, Schugardt M. The impact of sodium bicarbonate on performance in response to exercise duration in athletes: a systematic review. J Sports Sci Med. 2019;18(2):271–81.
28 Manfredini F, Mallamaci F, D'Arrigo G, Baggetta R, Bolignano D, Torino C, et al. Exercise in patients on dialysis: a multicenter, randomized clinical trial. J Am Soc Nephrol. 2017 Apr;28(4):1259–68.