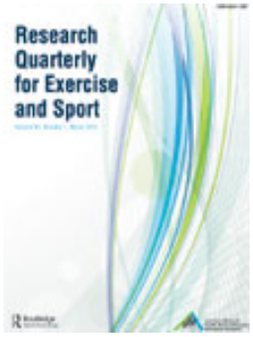

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The Effect of Acute Aerobic Exercise on Biomarkers of Renal Health and Filtration in Moderate-CKD

Jeffrey S. Forsse[a], Matthew N. Peterson[b], Zacharias Papadakis[c], J. Kyle Taylor[d], Burritt W. Hess[e], Nicholas Schwedock[e], D. Crawford Allison[f], Jackson O. Griggs[e], Ronald L. Wilson[f], and Peter W. Grandjean[g]

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ABSTRACT

Purpose: Efficacy of exercise to improve renal health and filtration remains understudied in adults with moderate-stages (stages G3a-b) of chronic kidney disease (CKD). Acute exercise may contribute clinically relevant information for exercise-related augmentation of renal health and filtration in CKD. Urine epidermal growth factor (uEGF) and cystatin C (CyC) are proposed to be more direct biomarkers of renal health and filtration. This study aimed to determine the influence of continuous moderate-intensity exercise (CMIE) and high-intensity interval exercise (HIIE) on traditional and novel biomarkers of renal health and filtration in moderate-stages of CKD. **Methods:** Twenty CKD participants completed 30 minutes of both CMIE and HIIE. Blood and urine samples were obtained pre, 1-hour, and 24-hours post-exercise. Traditional—serum creatinine (sCr) urine creatinine, novel—uEGF, uEGF ratio (uEGFr), and CyC. Estimates of glomerular filtration rate (eGFR)—modification of diet in renal disease (MDRD) and the CKD-Epidemiology (CKD-EPI)—responses were compared pre, 1 hr, and 24 hr post-exercise. **Results:** Relative to pre-exercise measures, uEGF remained unchanged in both exercise conditions. However, uEGFr was 5.4% greater 24-hours after HIIE ($P = .05$), while uEGFr remained unchanged with CMIE. sCr decreased 6 to 19% 1-hour post-exercise in both conditions ($P = .009$). On average renal filtration increased in eGFR-MDRD (7.2 ± 2.0 ml/min/1.73 m^2) ($P = .007$) and eGFR-CKD-EPI (8.6 ± 2.3 ml/min/1.73 m^2) 1-hour post-exercise ($P = .009$). **Conclusion:** By clinical estimates, renal filtration in CKD was not normalized but transiently improved regardless of exercise condition, with HIIE eliciting transient improvements in renal health.

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Acute exercise; chronic kidney disease; continuous moderate-intensity exercise; high-intensity interval exercise; renal filtration; renal health

In the early-to-moderate stages (G3a and b) of chronic kidney disease (CKD), renal dysfunction is difficult to ascertain solely with traditional measurements (Jha et al., 2013; National Kidney Foundation, 2002). Modifications to the vascular and renal endothelium often go unnoticed due to the absence of signs and symptoms (Ju et al., 2015). The current standards for assessing renal filtration measures serum creatinine (sCr) concentrations, albumin, and 24-hour urine collection, with creatinine clearance as the gold standard. However, these methods are indirect measures of renal filtration and can be influenced by various factors such as exercise, dietary intake, hydration, plasma volume, age, medications, and body mass independently of changes in renal filtration (Dharnidharka et al., 2002). Thus, there are limitations to using these assessments to measure acute changes in renal filtration.

More recently, the use of novel biomarker urine epidermal growth factor (uEGF) in conjunction with traditional biomarkers may be beneficial in establishing renal health (Dharnidharka et al., 2002; Ju et al., 2015). uEGF, initiates multiple intracellular pathways that stimulate renal cell growth, survival, replication, and regeneration (Krafts, 2010; Melenhorst et al., 2008). Unlike creatinine, uEGF is produced in the ascending portion of Henle's loop and the distal convoluted tubules (Humes et al., 1989). Therefore, renal health may be measured more directly and specifically via uEGF (Krafts, 2010). When uEGF is factored against urine creatinine as a ratio (uEGF/uCr), the ratio is potentially a more sensitive biomarker to detect transient changes in renal health and the ability of the glomeruli to filter biochemical waste (Ju et al., 2015). The ease and accuracy by which uEGF can be measured supports the utilization as an additional biomarker for renal health assessment. Additionally, uEGF concentrations lack the volatility observed in other biomarkers and the uEGF receptor pathway has been demonstrated to enhance renal outcomes in various models of CKD (Harskamp et al., 2016).

Recently, biomarker cystatin C (CyC) has been promoted as an additional renal marker to produce estimates that are potentially more direct and accurate in assessing acute changes to renal filtration (Macdonald et al., 2006). CyC is produced by all cell types, in all tissues, and is reabsorbed and fully catabolized by tubular cells (Tenstad et al., 1996; Woitas et al., 2000). When compared to serum creatinine, CyC does not bind other blood-borne proteins and is filtered freely at the glomeruli (Odutayo & Cystatin, 2012). Thus, CyC is recommended as a marker to assess acute fluctuations in renal filtration and filtration because CyC does not undergo renal tubular secretion (Odutayo & Cystatin, 2012).

Presently, research studies involving aerobic exercise and individuals with CKD are primarily focused on patients with end-stage renal disease. Therefore, the effect of aerobic exercise

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in populations with early to moderate stage CKD are heavily understudied. Currently, the most commonly recommended aerobic exercise for clinical populations is moderate-intensity steady-state exercise (Fisher et al., 2015; Keteyian et al., 2014; Pattyn et al., 2014). However, the implementation of high-intensity interval exercise (HIIE) aerobic exercise programs in clinical populations is gaining momentum. Therefore, individuals with moderate-stage CKD could potentially elicit similar improvements in renal vasculature health with aerobic exercise interventions, thereby improving renal filtration when assessed with biomarkers uEGF and CyC.

Our purpose was to investigate the effect of an acute bout of HIIE and CMIE aerobic exercise on traditional and contemporary markers of renal health and filtration in individuals with moderate CKD. Secondary aims were to assess whether a single bout of HIIE will produce greater benefits to renal health and filtration when compared to a single bout of continuous moderate-intensity exercise (CMIE). We hypothesized that aerobic exercise would improve traditional and contemporary biomarkers and estimates of renal health and filtration in individuals with moderate CKD and that HIIE will have a greater influence on renal health and filtration when compared to CMIE.

Methods

Participants

This study was part of a larger-scale project that examined variables regarding CKD, acute exercise, flow-mediated dilation, oxidative biomarkers, and hear rate variability (Forsse, Papadakis et al., 2022; Papadakis et al., 2022). Participants were identified from patient databases of local hospitals and medical clinics and were recruited by phone, mail, and physician referral. Participants were included in the study if they were 1) 40 to 75 years old, 2) previously diagnosed with CKD stages G3a and b (GFR, 30–59 mL/min/1.73 m2), 3) engaged in 90 minutes of leisure or work-related activity, 4) nonsmoker, 5) absent of musculoskeletal problems, and 6) able to maintain stable medication use throughout participation. Participants were excluded if 1) BMI was > 35, 2) uncontrolled hypertension, cardiovascular, pulmonary disease, and 3) previously diagnosed as IgA nephropathy, post-infectious glomerulonephritis, HIV nephropathy, focal stenosis, renal artery stenosis, and lupus nephritis. Our patient population recruitment goal was to enroll participants whose CKD diagnosis arose primarily as a secondary diagnosis of hypertension and diabetes.

Study procedure

Prior approval for the study was obtained by the University Institutional Review Board (IRB) for research with human subjects. The study methodology and protocol conform to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval granted by the institution's human research committee. Eligible individuals were provided both verbal and written information regarding the research study. Participants signed and returned the informed consent document and underwent further health screening before admittance into the study (Figure 1).

Health screening

Participants reported to the lab after an 8- to 10-hour fast limited to water ingestion only. Participants were asked to wear standard workout attire. A research study physician reviewed their health history, physician release form, medication guidance, and prior blood records with each participant. After the physician screening, a small venous blood sample was obtained and sent to a Center for Disease Control certified

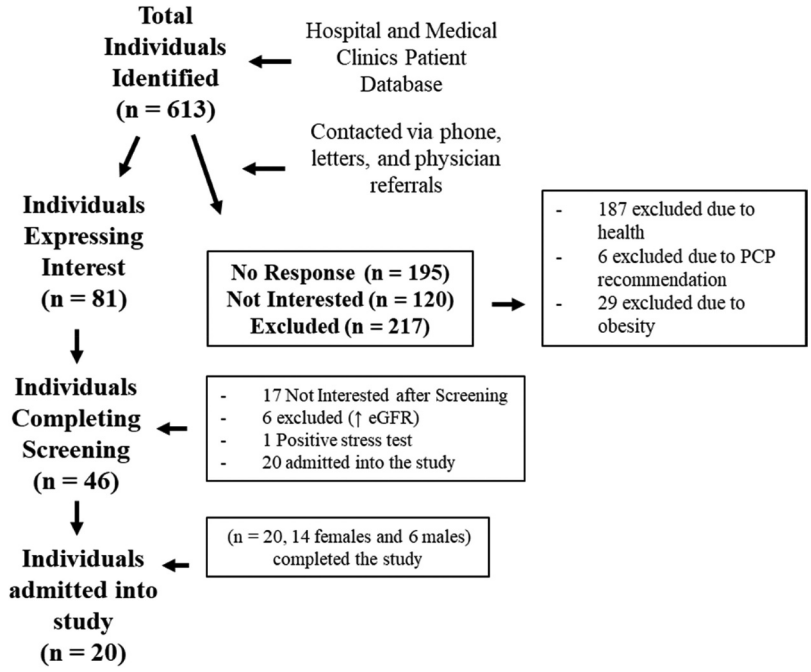

Figure 1. Participant recruitment diagram.

clinical laboratory to confirm prior lab work and verify medical classification of CKD.

Height and weight were measured using a calibrated stadiometer scale (Seca, Chino, CA). Waist circumference was measured horizontally at the umbilicus. Body composition (e.g., lean, fat, and bone tissue) was measured by dual-energy x-ray absorptiometry (Hologic, Marlborough, MA). Each participant performed a standardized maximal graded exercise test (Bruce/Modified Bruce) on a treadmill (TrackMaster, Newton, KS) to estimate cardiovascular fitness and hemodynamic responses to exercise of increasing intensity. Heart rate, blood pressure, ECG, and rating of perceived exertion (RPE) were monitored throughout the test. Respiratory gases (VO_2 and VCO_2) were measured continuously using an integrated respiratory gas analysis system (ParvoMedics, Sandy, UT). The exercise test began with 5 minutes of warm-up at a walking pace that was comfortable for the participant. The speed and incline of the treadmill was increased every 3 minutes until the participant reached volitional fatigue. The test was stopped at the participant's request, if we observed signs or symptoms that warrant test termination, or attainment of respiratory exchange ratio (RER) of 1.15 or greater. The results of the test were used to determine the safety of participation in our experimental protocol and if cleared to participate. Resting and peak VO_2 and heart rates were used to calculate the appropriate exercise intensities for experimental exercise sessions.

Study design

We employed a within subject, randomized cross-over study design with two exercise conditions. Participants each served as their own control and were randomly assigned to start either HIIE or CMIE, in a counterbalanced order, with a minimum three-day washout period between conditions. Each exercise condition required three blood and urine sampling time points during a 24-h period. Power analysis was performed in G-Power and revealed that the study needed 20 participants to be statistically powered based on setting the confidence level at 0.95 and statistical power at 0.80 in order to achieve a moderate-high effect size.

Exercise protocol

In the CMIE experimental condition, exercise consisted of treadmill walking at 2% incline and a speed eliciting 60 to 65% of $VO_{2reserve}$ (VO_2R) for 30 minutes. In the HIIE experimental condition, participants were asked to complete 30 minutes of exercise in 5-min intervals. Each interval included 3 minutes of submaximal but vigorous exercise at 90% of peak VO_2R and 2 minutes of slow walking at 20% VO_2R. Participants exercised at 60 to 65% VO_2R for the first and last 2 ½ minutes of this 30-min exercise session with 5-min intervals in between. Each of the exercise sessions were similar in duration, average intensity (60 to 65% of VO_2R), and caloric expenditure (Figure 2).

Blood pressure and heart rate

Baseline heart rate and blood pressure were recorded prior to the start of each exercise session. Heart rate was continuously monitored throughout the entire exercise protocol using Polar H7 heart rate monitor (Polar, Bethpage, NY). Blood pressure was obtained using manual blood pressure equipment (American Diagnostic Corporation, Hauppauge, NY) by experienced clinicians.

Biochemical analysis and calculations

Research participants reported to the lab after an 8- to 12-hr fast. Participants were encouraged to practice stable dietary

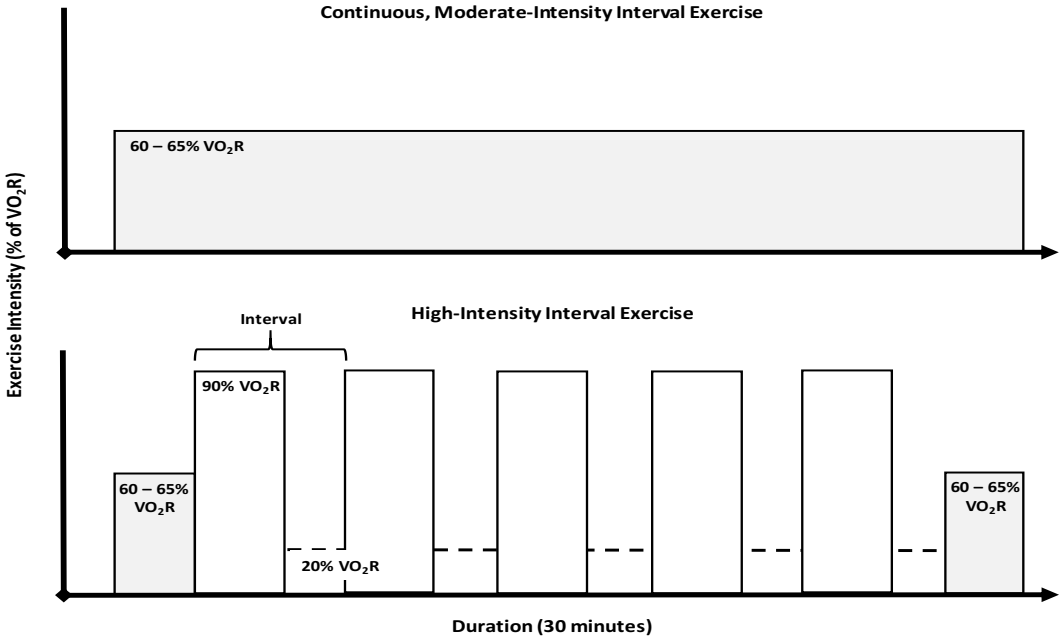

Figure 2. Exercise protocol for High-intensity interval exercise (HIIE) and Continuous moderate-intensity exercise (CMIE).

intake, medication use, and refrain from any moderate or strenuous physical activity 48 hours prior to completing each exercise session for this study. Participants were offered a 16 oz glass of water after completing each exercise session. Participants were not allowed to consume any caloric content during their time at the lab. Blood samples totaling 2.7 tbsp (40 ml) each were obtained by venipuncture into the most prominent vein site in the antecubital space. Samples were obtained before exercise and again at 1 h after exercise. Another blood sample, equivalent to the other experimental samples, was obtained 24-hours after each exercise condition. All blood samples were collected into 10 ml red-top (no additive) and 4 ml purple-top (KEDTA additive) vacuum-pressured specimen tubes.

A small amount of blood from each sample was immediately drawn into heparinized capillary tubes for estimating hematocrit in order to correct for shifts in plasma volume due to sweating during the exercise sessions (Beaumont, 1973). Blood samples were placed on ice immediately and allowed to clot for 30 minutes. Samples were centrifuged at 3500 RPMs for 15 minutes. Serum and plasma were recovered from the red-top and purple-top tubes, respectively, allocated into separate storage tubes and stored at −80°C until analysis.

Urine samples were collected in a sterile container before exercise and again 1 and 24 h after exercise. Participants were sent to the restroom with a specimen cup and asked to provide a urine sample as they voided their bladder. Participants returned to the lab with the sealed specimen cup and handed it to one of the study investigators. Upon collection, the sample was put on ice for 30 minutes then centrifuged for 5 minutes at 1000 RPMs. The urine samples were separated into plastic storage tubes and stored at −80°C until analysis.

sCr and CyC concentrations were determined using standard ELISA procedures (R&D Systems, Minneapolis, MN, and Arbor Assays, Ann Arbor, Michigan) to calculate changes in renal filtration. uEGF concentrations were determined using (R&D Systems, Minneapolis, MN) ELISA kit, and urine creatinine concentrations used colorimetric assays (Enzo Life Sciences Inc., Farmingdale, NY) to calculate changes in renal health. uEGF was divided by urine creatinine and $\log_2$ transformed as a ratio to characterize changes in renal health according to a paper by Ju et al. (Ju et al., 2015)

Statistical analysis

Univariate analysis of baseline variables was determined to be normally distributed prior to statistical analysis. Significant differences in exercise were determined by two factor repeated measures ANOVA (condition x time). The first factor, exercise condition, had two levels, HIIE and CMIE. The second factor, sampling time, three levels (baseline, one- and twenty-four-hour post-exercise). The dependent variables of interest to analyze kidney health and filtration were uEGF, (uEGF/uCr) $\log_2$ as a ratio, sCr, uCr, and CyC. Differences between changes in HIIE and CMIE were calculated. Duncans new multiple range test was used to determine significant time effects. Within each condition, response effect sizes were calculated as mean differences from pre-exercise and using the pooled standard deviation between measurement points with 95% confidence intervals (CI). Significance for all tests was set at a priori ≤ 0.05 level. Research data are presented as mean ± standard error. All statistical procedures were carried out using SAS software version 9.4 and IBM SPSS Statistics 26.

Results

Participants

Twenty participants (14 females and 6 males) with diagnosed CKD stages G3a-b met entry criteria and completed the entire study. Baseline participant demographics and physiological characteristics are displayed in Table 1. There were no reported adverse events, cardiovascular events, or hospitalizations as a result of the research intervention.

Exercise session

Participants achieved exercise intensities of 17.8 ± 3.8 mL/kg/min of VO_2R (three minutes of the upper intensity interval) for HIIE and 13.7 ± 2.8 mL/kg/min of VO_2R for CMIE. When averaging three minutes of 90% VO_2R with two minutes of 20% VO_2R (62% combined) and comparing it to 60 to 65% VO_2R, there were no significant differences in work rate

Table 1. Baseline demographics and medication use.

Variable (N = 20)	Mean ± SD
Age (yrs)	62.0 ± 10
Height (cm)	167.1 ± 8.6
Weight (kg)	80.9 ± 15.8
BMI (kg/m^2)	28.8 ± 4.3
Waist (cm)	98.9 ± 12.7
BF (%)	37.3 ± 8.3
SBP (mmHg)	125.4 ± 10.7
DBP (mmHg)	81.4 ± 5.1
HR (bpm)	71.3 ± 11.5
Creatinine (mg/dL)	1.11 ± 0.2
$eGFR_{Cr}$ (mL/min/1.73 m^2)	51.5 ± 6.5
Glucose (mg/dL)	117.0 ± 70.2
Albumin (g/dL)	4.13 ± 0.8
Total Cholesterol (mg/dL)	173.7 ± 36.3
LDL (mg/dL)	91.9 ± 28.8
HDL (mg/dL)	50.7 ± 15.2
Triglycerides (mg/dL)	155.9 ± 53.2
VO_2 (ml/kg/min)	19.4 ± 4.6
Medications	**Users (total n = 20)**
ARB	3 (20)
ACE inhibitor	6 (20)
α-Blocker	2 (20)
β-Blocker	4 (20)
Diuretic	6 (20)
Oral diabetic	7 (20)
Insulin	1 (20)
Statin	10 (20)
Steroids	2 (20)
T3/T4	3 (20)

All values are described as mean ± standard deviation along with minimum and maximum values, and ranges.

Abbreviations and definitions: ACE = angiotensin-converting enzyme; ARB = angiotensin II receptor blocker; BF = Body fat; BMI = Body mass index; DBP = Diastolic blood pressure; $eGFR_{Cr}$ = estimated glomeruli filtration rate serum creatinine; HDL-C = High-density lipoprotein cholesterol; HR = Heart rate; LDL-C = Low-density lipoprotein cholesterol; SBP = Systolic blood pressure; TC = Total cholesterol; TG = Triglycerides; VO_2 = oxygen uptake; Waist = Waist circumference.

Table 2. Exercise demographics.

Variable	HIIE	CMIE
Time (min)	30 (3:2)	30
65% VO_2 (L/min)	1.1 ± 0.5	1.1 ± 0.4
65% VO_2 (mL/kg/min)	13.8 ± 2.8	13.7 ± 2.9
90% VO_2 (mL/kg/min)	17.4 ± 3.8	-
HR (bpm)	119.2 ± 17.1	116.0 ± 17.6
Speed (mph)	2.7 ± 0.8	2.2 ± 0.6
Grade (%)	8.2 ± 3.2	4.8 ± 3.3
RPE	7.5 ± 1.0	5.9 ± 1.0

All values are described as Mean ± Standard Deviation.
Abbreviations: Avg. = average; kcal = kilo calorie; MAP = Mean arterial pressure; RPE = rate of perceived exertion; VO_2 = oxygen uptake.

between conditions (P= .92). A total of 149.6 ± 43.8 kcal were expended during HIIE and 139.6 ± 40.7 kcal during CMIE with no significant differences between conditions (P= .39). There were no significant changes in plasma volume over the course of each exercise condition. Also, the average exercise heart rate was not significantly different between each condition (P= .28). All participants were able to tolerate and complete each 30-minute exercise session without stopping regardless of CKD stage (Table 2).

Primary renal outcomes in response to exercise

Changes in blood and urine markers for each exercise condition are listed in Table 3. uEGF was significantly decreased one-hour post-exercise in both conditions and returned to baseline within 24 hours after exercise in both conditions (P = .01). uEGF was normalized to uCr as a ratio $\log_2$ (uEGF/uCr) to estimate changes in renal health. There were no significant changes in uEGF/uCr ratio after one-hour post-exercise; however, at 24-hours uEGF/uCr ratio was 5.4% higher (P = .05) in HIIE when compared to baseline with a moderate effect size (ES) of 0.56. CMIE returned to baseline after 24-hours post-exercise with no significant changes. When comparing CMIE and HIIE, there was a significant difference between condition (P = .04).

sCr was significantly decreased post-exercise in both exercise conditions (P = .01) with a large ES of 1.09 for HIIE and a low ES 0.20 for CMIE. When sCr was corrected for shifts in plasma volume, sCr was significantly lower than baseline for 24 h after exercise (P = .01). uCr was also significantly lowered in the hours post-exercise regardless of exercise condition (P= .03) with an ES of 0.43 (HIIE) and 0.76 (CMIE).

CyC concentrations remained unchanged at one and 24 h after both exercise conditions (P = .79 and p = .84). However, there was a difference between exercise conditions at one-hour post-exercise (P = .01) with CMIE producing higher levels, while no differences were observed between conditions at 24 h (P = .39). CyC concentrations were corrected for shifts in plasma volume with no statistically significant changes between time points.

The modification of diet in renal disease (MDRD) and CKD-epidemiology (CKD-EPI) equations were utilized to measure eGFR using sCr concentrations (Figure 3(a,b)). eGFR was significantly increased in both exercise conditions in the hours post-exercise (MDRD P = .01 and CKD-EPI P = .01), with no differences between conditions. Both conditions were pooled together, with MDRD and CKD-EPI producing large ES (2.41 and 2.01) in altering renal filtration. When HIIE and CMIE were separated and compared for the MDRD equations, HIIE produced a large ES of 2.11, and CMIE ES 1.59. eGFR remained elevated above baseline for 24 h post-exercise in both conditions. eGFR equations for CyC concentrations were used with only CyC and in conjunction with sCr. eGFR for both CyC and CyC/sCr remained unchanged across exercise condition and time (P= .11 and P = .40).

Discussion

To our knowledge, our study is the first to utilize uEGF and uEGF/uCr $\log_2$ as a ratio to acutely determine changes in renal health and filtration in moderate CKD with acute bouts of aerobic exercise. We hypothesized that HIIE would have a greater influence on transient changes in renal health when compared to CMIE. Our findings suggest that an acute bout of HIIE can transiently improve renal health in individuals with moderate CKD. When we normalized uEGF to uCr as a ratio, the ratio of uEGF/uCr $\log_2$ returned to baseline within

Table 3. Results of changes in renal markers.

HIIE									
Variables	BSLN	1-HR	24-HR	F	P	1-HR 95% CI	24-HR 95% CI	1-HR ES	24-HR ES
uEGF (ng/ml)	10.25 ± 1.77	6.91 ± 1.07[a]	10.58 ± 1.20	7.39	0.01	2.85–6.96	8.28–12.87	0.86	0.09
uEGF/uCr (ng/mg)	3.88 ± 0.17	3.83 ± 0.17	4.09 ± 0.19[a]	4.84	0.05	3.66–3.99	3.90–4.27	0.14	0.53
uCr (mg/dL)	6.27 ± 0.45	4.82 ± 0.69[a]	6.21 ± 0.72	3.61	0.03	3.50–6.13	4.82–7.59	0.43	0.03
sCr (mg/dL)	1.45 ± 0.04	1.17 ± 0.05[a]	1.34 ± 0.06[a]	5.87	0.01	1.06–1.27	1.15–1.52	0.84	1.09
CyC (ng/ml)	1320.42 ± 52.79	1283.53 ± 79.54	1370.05 ± 116.52	0.23	0.79	1131.58–1435.47	1153.38–1586.71	0.08	0.14
CMIE									
uEGF (ng/ml)	12.58 ± 2.23	8.45 ± 1.55[a]	10.72 ± 1.66	4.84	0.04	5.47–11.42	7.53–13.90	0.50	0.22
uEGF/uCr (ng/mg)	4.08 ± 0.22	4.15 ± 0.16	4.05 ± 0.20	0.54	0.59	3.99–4.30	3.85–4.24	0.16	0.06
uCr (mg/dL)	5.32 ± 0.38	4.2 ± 0.61[a]	5.45 ± 0.65	2.73	0.04	4.82–7.59	4.20–6.69	0.76	0.30
sCr (mg/dL)	1.44 ± 0.07	1.36 ± 0.06[a]	1.38 ± 0.08	5.38	0.01	1.18–1.53	1.15–1.60	0.19	0.20
CyC (ng/ml)	1510.25 ± 117.61	1577.13 ± 105.82	1451.57 ± 60.51	0.16	0.84	1356.43–1689.08	1342.57–1560.90	0.03	0.15

All values are described as mean ± standard error.
Abbreviations and definitions: 1-HR = One Hour Post-exercise; 24-HR = Twenty-four Hour Post-exercise; BSLN = Baseline; CI = Confidence Interval; ES = Effect Size; sCr = Serum Creatinine; CyC = serum cystatin C; uCr = Urine Creatinine; uEGF = Urine Epidermal Growth Factor; and uEGF/uCr ratio.
[a]< 0.05 indicates significant differences in outcome measures from baseline to that time.

24 hours in CMIE; however, the ratio of uEGF/uCr $\log_2$ increased by 5.4% at 24 h post-exercise in the HIIE condition. Therefore, for the first time, our study showed that renal health transiently improved after an acute bout of HIIE, with an acute bout of HIIE positively altering renal health at 24 hours. Thus, the uEGF/uCr ratio appears to be a more sensitive assessment for quantifying acute renal health changes with exercise than traditional assessment methods. Also, when uEGF is assessed independently of uEGF/uCr ratio, there is an observed decrease in uEGF concentrations one-hour post-exercise in both HIIE and CMIE. Our findings may seem contradictory to those of Konradsen et al. (Konradsen & Nexø, 1988), who reported increases in uEGF after a single bout of aerobic exercise. However, this study was limited to healthy, fit individuals who had different physiological characteristics than our participants. Potentially uEGF may have transiently decreased then increased between 1- and 24 h post-exercise, returning to normal values at 24 h. Therefore, the results of our study indicate a transient influence in renal health via uEGF with HIIE; however, our results are limited to the 24-h post-exercise period. Additionally, there may be a compounding effect observed with the implementation of aerobic training studies (frequency and intensity) on biomarker uEGF and uEGFr pathway that are not elucidated in our study.

Traditional biomarkers of renal filtration were assessed to determine the influence of aerobic exercise on renal filtration. We hypothesized that a short bout of acute aerobic exercise would increase renal filtration and that HIIE would have a more significant influence than CMIE. In previous studies, when eGFR was calculated using sCr, eGFR remained relatively unchanged following aerobic exercise in multiple populations (Hiraki et al., 2013; Virvidakis et al., 1986). In our study, during each exercise intervention, sCr was measured and found to significantly decrease post-exercise in both conditions at one and 24 h post-exercise. When correcting for shifts in plasma volume due to sweat loss, sCr remained lower in both conditions for 24 h. On average, corrected sCr remained 10.3% lower with HIIE and 7.6% with CMIE at 24 h when compared to baseline. sCr concentrations were used to calculate eGFR using MDRD and CKD-EPI equations. On average, MDRD eGFR increased by 16.6%, and CKD-EPI increased by 18.9% one-hour post-exercise compared to baseline. eGFR approached baseline after 24 hours in both conditions. These results suggest that glomerular filtration was transiently improved after aerobic exercise independent of exercise conditions. Additionally, when comparing the results of our study to similar studies done in healthy populations, improvements observed in renal health and filtration appear to be more isolated to CKD, whereas aerobic exercise in healthy populations appears to have a ceiling effect (no changes) on renal health and filtration (Forsse, Buckley et al., 2022). Table 4 provides the equations used to determine eGFR.

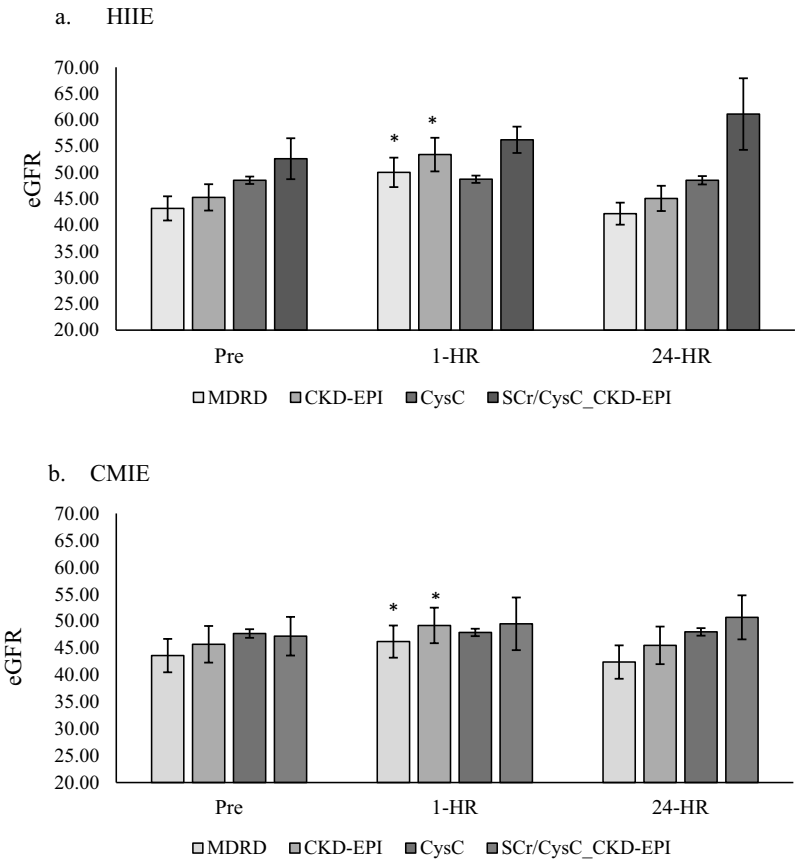

Figure 3. (a,b) Changes in eGFR from baseline—post-exercise in high-intensity interval exercise (HIIE) and continuous moderate-intensity exercise (CMIE). Abbreviations: Chronic kidney disease epidemiology (CKD-Epi), estimates of glomerular filtration rate (eGFR), modification of diet in renal disease (MDRD), and serum creatinine/serum cystatin C_CKD-Epi.All data is presented as mean + SE.* Indicates significant differences (P = .05) between time points and conditions.

Researchers and practitioners have long questioned the reliance on sCr to determine changes in eGFR due to a high rate of variance in creatinine production and concentrations (Dharnidharka et al., 2002; Knight et al., 2004; Solomon & Segal, 2008; Stevens et al., 2008). Henceforth, over the last few decades alternative markers, have been explored to assist in estimating renal filtration, the most common being CyC. In our study, CyC concentrations were used independently and in conjunction with sCr to determine changes in eGFR after acute bouts of HIIE and CMIE. In both exercise conditions, eGFR was calculated using serum CyC, which remained unchanged at one and 24 h post-exercise. eGFR was also calculated using both creatinine and CyC with no significant changes across time or condition. These results are similar to Greenwood et al. (Greenwood et al., 2015), who demonstrated no changes in eGFR with CyC and sCr/CyC after 12-months of aerobic exercise and resistance training in individuals with CKD stages G3 and G4. However, our study differed in the patient population, exercise modality, and exercise intensity and improved sCr eGFR by 10.9 mL/min/1.73 m^2 on average after a single bout of aerobic exercise. In contrast, Greenwood et al. (Greenwood et al., 2015) observed a smaller increase of 7.8 mL/min/1.73 m^2 in eGFR. Due to the novelty of exercise and renal filtration in CKD stages G3a and b, the mechanisms relating to these similarities are elusive. Potentially, the dose of exercise prescribed (HIIE vs. CMIE) could have influenced the increase in renal filtration via changes in vascular endothelial function of the renal system (Forsse et al., 2018; Peterson et al., 2019).

The severity of CKD may influence changes in renal health and filtration with aerobic exercise. Our research participants' average baseline eGFR was 51.5 ± 6.5, which is substantially higher than previously reported studies. Headley et al. (Headley et al., 2014) average eGFR was 47.0 ± 12.0, Howden et al. (Howden et al., 2013) average eGFR 38.4 ± 8.8, and Greenwood et al. (Greenwood et al., 2015) had an average eGFR of 36.6 ± 10.1. Also, the current CKD criteria have recently changed since the completion of our study. Thus, the magnitude of the response in eGFR and renal health changes may be linked to CKD severity.

The exercise capacities of our study participants were a representation of current CKD populations. With an average VO_{2max} of 19.4 ± 4.6 ml/kg/min, their cardiorespiratory fitness levels were lower than healthy populations but comparable to related CKD cohorts VO_{2max} of 14.9 ± 1.1 and 19. 6 ± 6.7 ml/kg/min (Headley et al., 2014; Leehey et al., 2009). The exercise conditions were designed to stimulate the renal vasculature via improved endothelial function. The work rates of both HIIE and CMIE were calculated and comparable to one another (Table 2). On average, heart rate, VO_2, and caloric expenditure did not differ between HIIE and CMIE. Even with lower cardiorespiratory fitness levels, all participants in our study were able to safely and effectively complete both exercise conditions. Upon completing both exercise sessions, participants were asked which one they preferred. Anecdotally, the majority of participants preferred and enjoyed the HIIE more than the CMIE. Participants stated, "HIIE was not as boring as CMIE, and they felt better after HIIE." These results further support the use of incorporating HIIE into exercise recommendations for populations with CKD.

Table 4. eGFR equations.

Equation	
Serum Creatinine (MDRD)	$eGFR = 175 * (sCr)^{-1.154} * (Age)^{-0.203} * (0.742$ if female) * (1.212 if African American)
Serum Creatinine (CKD-EPI)	$eGFR = 141 * \min(sCr/\kappa, 1)^{\alpha} * \max(sCr/\kappa, 1)^{-1.209} * 0.993^{Age} * 1.018$ [if female] * 1.159 [if black]
Serum Cystatin C	$eGFR = 127.7 * CyC^{-1.17} * age^{-0.13} *$ (0.91 if female) * (1.06 if black)
Serum Creatinine/Cystatin C	$eGFR = 177.6 * sCr^{-0.65} * CyC^{-0.57} * age^{-0.20} *$ (0.82 if female) * (1.11 if black)

Standard equations are referenced in the literature and by National Kidney Foundation (Stevens et al. 2008).

Abbreviations and definitions: α = −0.329 (females) or −0.411 (males); κ = 0.7 (females) or 0.9 (males); min = indicates the minimum of sCr/κ or 1; max = indicates the maximum of sCr/κ or 1; sCr = serum creatinine (mg/dL); CyC = serum cystatin C.

Limitations

The results of this study are limited to overweight or obese men and women with CKD stages G3a-b, who participated in regular low-moderate amounts of physical activity. Participants were asked to maintain regular medication use, diet, and physical activity habits through the course of the study, and to our knowledge, were able to comply with our request. However, it is possible that variation in these outside factors could have influenced our results.

Renal blood flow was not measured with ultrasound due to anatomical and methodological difficulty assessing the renal artery. Although assessing renal blood flow could have provided an additional dimension in assessing kidney filtration, we presumed that renal blood flow would respond similarly to healthy individuals. Not measuring urine-specific gravity before and after exercise due to the small aliquots of urine obtained during each measurement point was also a potential limitation.

Conclusions

This study demonstrated that for the first-time renal health can be transiently improved in patients with moderate CKD following a short acute bout of HIIE when using uEGF/uCr as a ratio. Our findings indicate that HIIE appears to be safe and achievable for individuals with moderate CKD. Also, renal filtration can be transiently improved after an acute bout of either HIIE or CMIE in individuals with moderate CKD. However, our findings are limited and require more in-depth studies targeting specific mechanisms that influence cellular renal health with various aerobic exercise types. Further research is needed into training studies focused on early-to-moderate stages of CKD to better understand the underlying mechanisms into improving and treating renal decline. Results from our study assist in laying the foundation for further research into this much needed area of research.

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Ethical approval statement

All authors acknowledge ethical responsibility for the content of the manuscript and will accept the consequences of any ethical violation

IRB approval

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