KIDNEY RESEARCH INSTITUTE
A collaboration between Northwest Kidney Centers and UW Medicine

Division of Nephrology
University of Washington

Exercise and CKD: Skeletal Muscle Dysfunction and Practical Application of Exercise to Prevent and Treat Physical Impairments in CKD

Bob Roshanravan MD MS MSPH
Assistant Professor
Division of Nephrology
Kidney Research Institute
University of Washington

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Outline

- Background
  - CKD and the Disablement Process
  - Kidney Disease and Frailty
- Evidence for benefits and risks of exercise in ESRD
- Barriers to exercise
- Safety and Contraindications to exercise
- Individualized exercise prescriptions.

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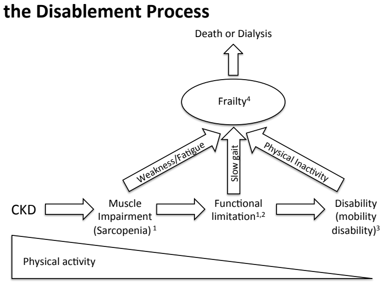
CKD and the Disablement Process



1. Roshanravan B, et al. *Am J Kid Dis.* 2015;65(5):737-747. 2. Roshanravan B, et al. *J Am Soc Neph.* 2013;24(5):822-30.
3. Roshanravan B, et al. *J Gerontol: Med Sci.* 2016 (in press). 4. Roshanravan B, et al. *Am J Kid Dis.* 2012:60(6):912-21.

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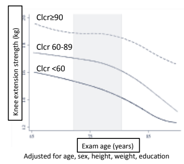
Kidney Disease and Muscle Impairment

CKD ⇨ Muscle Impairment (Sarcopenia)

- Population: Community dwelling older adults in InChianti study
  - Average age 74 ± 6.5 years. 56% female, and 12% with diabetes mellitus
  - Mean ClCr 78 ± 23 mL/min/1.73m²
- Creatinine clearance from 24 hr urine is associated with calf muscle atrophy by Peripheral Quantitative CT
- Lower ClCr associated with faster decline in knee extension strength

	Muscle Density (mg/cm³)		
	No.	Mean (SD)	Adjusted mean difference
ClCr≥90	207	71.7 (3.3)	Reference
ClCr 60-89	410	71.3 (3.4)	-0.10 (-0.62, 0.42)
ClCr<60	179	70 (3.5)	-0.97 (-1.66, -0.28)
Per -10mL/min			-0.15 (-0.26, -0.04)
P value*			0.006
Per 1 yr older age			-0.15 (-0.19, -0.11)

Model adjusted for age, sex, height, weight, site, smoking, education, Diabetes, CAD, total daily animal protein consumption



Adjusted for age, sex, height, weight, education

Roshanravan B, et al. *Am J Kid Dis*. 2015; 65(5):737.

Kidney Disease and Functional Limitation

CKD ⇨ Muscle Impairment (Sarcopenia) ⇨ Functional limitation

- Lower renal function is associated with objective functional limitation (Gait speed) among referred patients with CKD
  - Seattle Kidney Study: Mean age 57±13, GFR_{cysc} 48±18
  - Median follow-up of 3 years IQR [2,4]; Mean visits 3.5±1
  - No ADL disability at baseline

	Baseline gait speed (m/s), Mean (SD)	Adjusted Model Difference in % annual change compared to referent group (95% CI)
GFRcysc	1.0 (0.19)	Reference
60 or greater (n=50)	0.98 (0.22)	-3.18 (-5.31, -1.01)
45-59 (n=67)	0.94 (0.20)	-4.4 (-6.85, -1.89)
30-45 (n=64)	0.95 (0.20)	-6.90 (-9.78, -3.94)
<30 (n=32)		<0.001
P for continuous GFRcysc		

Adjusted for age, sex, race, height, weight, education, smoking, DM, Any CVD (CAD, PVD, stroke), logCRP

ASN 2016 FR-OR027

Kidney Disease and Functional Limitation

CKD ⇨ Muscle Impairment (Sarcopenia) ⇨ Functional limitation

- Objective physical performance assessment:
  - Captures physiologic changes related to chronic illness, aging, and sedentary lifestyle.
  - Identify non-disabled individuals at risk of disability
  - Evaluate change in functioning and health
  - Clinical "vital sign"
- Poor performance on lower extremity tasks associated with future mobility disability, hospitalization, and death in older adults

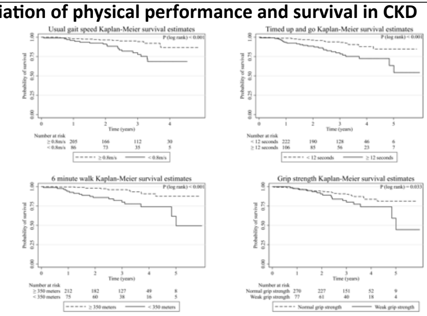
CLINICAL EPIDEMIOLOGY

Association between Physical Performance and All-Cause Mortality in CKD

Baback Roshanravan,* Cassianne Robinson-Cohen,† Kushang V. Patel,‡ Ernest Ayers,*
Alyson J. Littman,†§ Ian H. de Boer,* T. Alp Ikizler,‖ Jonathan Himmelfarb,* Leslie I. Katzel,¶
Bryan Kestenbaum,* and Stephen Seliger** J Am Soc Nephrol 24: 822–830, 2013

	Overall (N=385)	Fast TUAG (N=240)	Slow TUAG (N=122)
Demographic data			
Age, mean ±SD	61±13	57.7±12	66.4±12
Female, No. (%)	63(16)	33(14)	26(21)
Race, No. (%)			
Non-white	146(38)	91(38)	49(40)
Physical examination data, mean ±SD			
Systolic Blood Pressure (mmHg)	132.9±20.7	131.6±19.8	134.2±21.4
BMI (kg/m^2)	31±6.9	30.2±6.3	32.5±7.7
Laboratory Values			
eGFRcysc(ml/min/1.73m^2)*	47.6±23.3	51.7±24.8	41.1±18.3
eGFR CKD-EPI(ml/min/1.73m^2)	41.3±19.3	43.6±19.9	37.8±17.5
Physical Performance, mean ±SD			
4 meter Walk (m/s)	0.9±0.2	1±0.2	0.7±0.2
TUNG (sec)	11.2±4.5	8.8±2	15.9±4.5
6 Minute walk (meters)	400±100.3	436.8±81.9	308.5±78.9
Grip Strength (kg)	36.15±10.6	38.7±10.2	32.4±9.7
Exercise, No. (%)*			
Never	83(26)	41(21)	31(33)
Prevalent Disease, No. (%)			
Diabetes	213(55)	118(49)	75(61)
Any CAD	99(26)	48(20)	41(34)
Disability, No. (%)			
≥1 ADL task	27(8)	13(6)	10(10)
≥1 IADL task*	112(35)	52(26)	49(50)
≥1 Mobility task*	77(24)	26(13)	37(38)

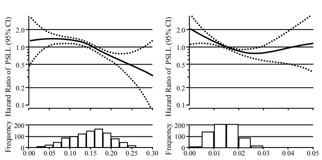
Association of physical performance and survival in CKD



Muscle Impairment and Mobility Disability

CKD ⇒ **Muscle Impairment (Sarcopenia)** ⇒ **Functional limitation** ⇒ **Disability (mobility disability)**

- 1963 community dwelling older adults in Health ABC
  - Mean age 75±2.8 yrs
  - Muscle endurance measured by isokinetic fatigue testing. Total work over 30 repetitions
  - Isometric strength. Peak torque.
  - Outcome: Persistent severe lower extremity limitation (PSLL) – incident severe difficulty or inability to walk ¼ mile on flat surface or ascend 10 steps.



*Adjusted for age, sex, race, site, height, weight, education and eGFRcysc
*N=1963

Roshanravan B, et al. *J Gerontol: Med Sci.* 2016 (in press).
Roshanravan B, et al. *Am Soc Neph.* 2015.

Physical performance tests to help identify functional limitations

Test	Task	Population	Cut-points	Association with outcome	Studies	Resources
Gait speed	Usual walking speed over 3, 4, 7, or 20 meters.	CKD ESRD Older adults	<1m/s <0.8m/s <0.6m/s (dialysis)	Mortality: Each 0.1m/s slower associated with 12% higher risk of death in older adults and 26% higher in CKD	*Roshanravan[29] *Kutner[28] Studenski[43] Afialo[106]	Normative data[107] Normograms for life expectancy by age and gait speed available[43]. Normograms for incident disability by age and gait speed[108].
Timed up and go (TUG)	Get up from seated position, walk 4 meters and return to seated position (Tests balance, walking ability, fall risk)	CKD Older adults	≥12 seconds	Mortality: 81% greater risk if 12 seconds or slower. 8% for each 1 second slower. Associated with falls in older adults	Roshanravan[29] Shumway-Cook[109] Wang[110]	https://www.cdc.gov/steadi/pdf/tug_test-a.pdf Normative data[111]
Short Physical Performance Battery (SPPB)	Test of lower extremity function combining scores from usual gait speed and timed tests of balance and chair stands. Score ranges from 0-12.	Older adults	≤ 8[105] <10[112] Small meaningful change is 0.5 point[113] Substantial change is 1 point[113]	ADL disability, Mobility disability Death in older adults	Guralnik[44,114] Minneci[115]	https://www.irp.nia.nih.gov/branches/leps/sppb/index.htm
6-minute walk distance (6MWD)	Maximal distance covered over 6 minutes. Test of functional exercise capacity	CKD ESRD COPD Older adults	Poor exercise capacity<350 meters[116] Clinically important difference of 50 meters.	Mortality: <350meters associated with 2.82 fold increased risk of death in CKD. 11% reduction in risk of mortality for every 20 meters greater 6MWD in ESRD.	*Roshanravan[29] Veronese[117] Polkey[118] *Torino[119]	Normative data[120]
400meter walk test	Time to walk 400 meters as quickly as possible.	Older adults	Minimum clinically important difference is 28 seconds.[121]	Each additional 1-minute associated with 29% increased risk of mortality and 52% increased risk of mobility limitation.	Newman[122]	

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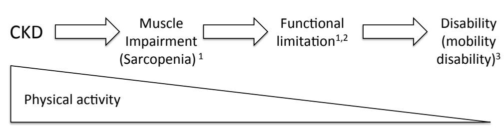
CKD and the Disablement Process



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Frailty phenotype and disability

- Frailty is as terminal clinical syndrome of vulnerability characterized by slow gait, low strength, low physical activity, low energy and weight loss.
- Frailty is associated with risk of disability, hospitalization, and death in older adults

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Frailty Phenotype is common in CKD

Cardiovascular Health Study (mean age 76 years, mean BMI 26.9, 36.8% with disability)		Seattle Kidney Study (mean age 59 years, mean BMI 31.4, 40% with disability)	
Definition	Prevalence	Definition	Prevalence
Self-reported ≥10 pound unintentional weight loss in past year	6%	Self-reported ≥10 pound unintentional weight loss in past 6 months	10%
Lowest sex and BMI specific 20th percentile grip strength	20%	Same absolute cutoffs as CHS[1,17]	16%
Lowest sex specific 20th percentile kilocalories/week	20%	Self reported exercise less than once per week	35%
Positive response to either exhaustion item on CES-D[1]	17%	Lowest 20th percentile exhaustion score on RAND-36[*]	32%
Slowest sex and height specific quintile walking pace	20%	Same absolute cutoffs as CHS;	26%
Frailty	**7%**		**14%**
Intermediate frailty	**47%**		**52%**

Roshanravan B, Khatri M et al. AJKD 2012; 90(6): 912-921

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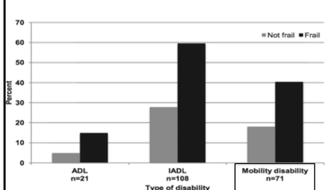
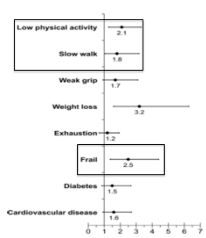
Frailty is a associated with disability and with risk of death or dialysis in CKD





Roshanravan B, Khatri M et al. AJKD 2012; 90(6): 912-921

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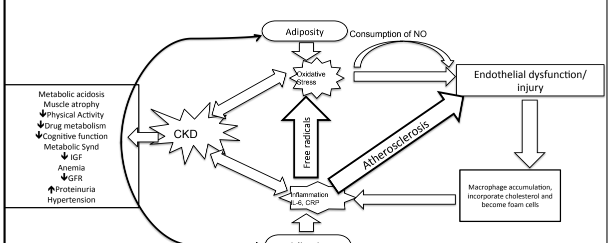
Malnutrition-Inflammation Complex Syndrome in CKD



Adapted from Moinuddin I, Leehey DJ. Adv Chron Kidney Dis. 2008. 15(1):83-96.

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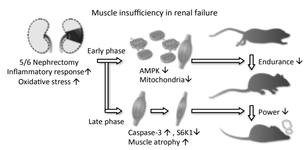
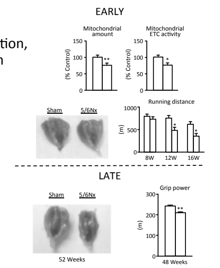
Mitochondrial Impairment Precedes Muscle Atrophy and Functional Limitation

- CKD model: 5/6 nephrectomy of C57Bl/6 mice
- Early changes: Increased oxidative stress, inflammation, decreased endurance, lower mitochondrial function and content without muscle atrophy
- Late changes: muscle atrophy, decreased strength





Tamaki M, et al. *Kid Int*. 2014;85:1330-1339.

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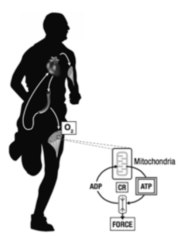
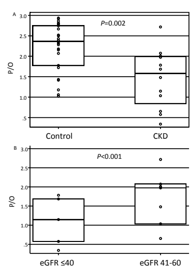
CKD is inefficient muscle mitochondrial metabolism





Roshanravan B, et al. *Am J Kidney Dis*. 2016 Oct;68(4):658-9.

P-value adjusted for age, sex, BMI

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Challenges to exercise

- High prevalence of physical frailty in the kidney disease population may preclude participation in structured physical activity.
- Waning of adherence over time
- **An understanding of a patient's functional status and use of an interdisciplinary approach involving rehabilitative therapies to address functional limitations is vital to providing a feasible, safe, and individualized exercise prescription**

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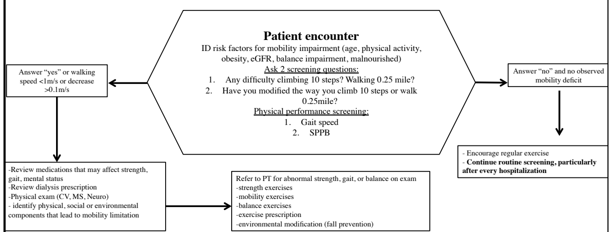
Algorithm for identifying high risk patients for rehabilitative therapies prior to exercise



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Reimbursement for physical therapy

- ICD-10 diagnosis of Sarcopenia: M62.84
  - Deficits in strength: Handgrip (Men <26kg, Women<16kg)
  - Self reported (KDQOL-36 (SF-12 score)<75)
- ICD-10 diagnosis for Impaired mobility: Z74.09
  - Slow walk (Gait speed<1m/s)
  - Self reported difficulty walking ¼ mile or ascending 1 flight of steps

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Overview Benefits of Exercise in ESRD

- Improvements in Muscle structure and function
  - Skeletal muscle hypertrophy with decrease in myostatin mRNA
- Improvements in cardiac function
  - Increased SVI (14%), EF (14%), CO (73%) after 6 months of supervised aerobic exercise. Deligiannis et al. Int J of Cardiology. 1999. 70: 253-66
  - Increased HR variability with decreased sympathetic overactivity at rest with reduced incidence of arrhythmias.
- Improvements in blood pressure
- Improvement in HD Efficiency
  - 11% increase in spKt/V in first month of intradialytic exercise increasing to 19% by 5mo. Parsons TL et al. Arch Phys Med Rehabil. 2006. 87:680-87
- Improvements in Psychological adaptations, QOL, and Nutrition

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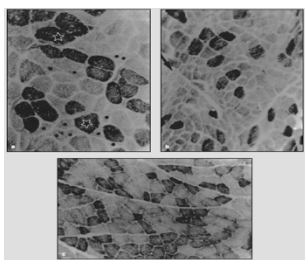
Improved Muscle Fiber Structure

- Prior to exercise:
  - Variable fiber size
  - Large group atrophy mainly of non-oxidative fibers
- After 6 mo combined aerobic and resistance exercise:
  - Increased oxidative fibers
  - Increase muscle fiber area



Kouidi E et al. NDT. 1998. 13:685-99

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Cardiac effects of exercise rehabilitation in hemodialysis patients. Deligiannis A et al. Int J Cardiol. 1999. 70:253-66

- After 6 months of supervised aerobic exercise (n=31)
- Improved HRV and LV function with increased EDVI and ESVI with exercise.

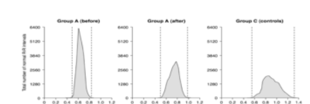

Fig. 1. The heart rate variability (HRV) index records of a haemodialysis patient before and after 6 months of exercise training on the nondialysis days (group A) and of a non-uraemic control (group C) [adapted from Deligiannis et al.,[8] with permission].

LV functional data of group A during stress echo (means±S.D.)

	Baseline		Follow up	
	Rest	Exercise	Rest	Exercise
EDVI[a] (ml/m²)	78.4±25.9	78.9±24.3	84.9±24.5[†]	85.4±23.6[†]
ESVI[a] (ml/m²)	30.6±10.9	26.7±9.5*	30.6±9.8	23.4±8.6*[†]
EF[a] (%)	61.1±6.7	66.4±7.3*	64.1±5.6[†]	73.1±5.6*[†§]
SVI[a] (ml/m²)	47.9±16.4	52.4±17.3*	54.4±16.5[†]	62.2±17.1*[†§]
COI[a] (l/min/m²)	4.2±1.4	6.2±1.8*	4.1±1.0	7.1±1.9*[†§]

[a] EDVI, end-diastolic volume index; ESVI, end-systolic volume index; EF, ejection fraction; SVI, stroke volume index; COI, cardiac output index.

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Exercise during hemodialysis decreases the use of antihypertensive medications

Miller BW et al. AJKD. 2002. 39(4):828-33

- 6 months of in center cycling
- 40 participants and 32 controls
  - 60% completed 6 mo.
- Gradual increase in cycling time. Increasing by 1-5min per session until 30 minutes then increased resistance
- Exercise time increased from 50.7 min/wk to 136.5min/wk per person
- Findings: Decreased mean #BP meds 2.13→1.5 in intervention and 1.91→2.0 in ctrl
  - Intervention group baseline $1687→$1034
  - Control group $1160→$1392

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Improved BP with Exercise

- Improvement in Hct with decreased ESA use
- Most of benefit in BP seen at 3 months
- Annual cost savings of $885/patient/yr

Table 1. Patient Characteristics

	Exercise	Control	P Value
Patients (n)	24	32	
Mean age (y)	52.8 ± 16.0	56.1 ± 15.2	NS
Mean dialysis duration (mon)	20.7 ± 27.5	28.7 ± 25.5	NS
Women (%)	58.3	56.3	NS
African-American (%)	79.2	87.5	NS
Diabetes (%)	25	21.9	NS
Cardiovascular disease (%)*	29.2	21.9	NS
Dialysis noncompliance (treatments/patient/mon)	0.09	0.17	NS
Mean interdialytic weight gain (kg)			
Baseline	2.6 ± 1.5	3.1 ± 1.5	<0.01
Study period	2.8 ± 1.5	3.0 ± 1.8	NS
Hematocrit (%)			
Baseline	34.2 ± 2.8	34.2 ± 3.5	NS
Month 6	35.5 ± 2.4	34.1 ± 2.5	0.05
Epoetin alfa (Epogen) dose (U/wk)			
Baseline	12,030 ± 5,220	12,180 ± 7,590	NS
Month 6	9,240 ± 3,930†	17,010 ± 11,910‡	0.01

NOTE. Mean values are given with ± SD.
Abbreviation: NS, not significant.
*Previous myocardial infarction, coronary artery intervention, or ejection fraction less than 30%.
†P = 0.05 compared with baseline.
‡P = 0.02 compared with baseline.

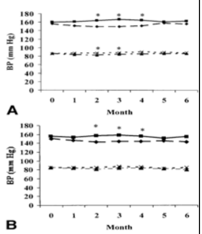

Fig 1. (A) Monthly mean predialysis systolic and diastolic blood pressures (BP) are plotted. No significant difference is seen between the two groups at the conclusion of the 6-month study period. (B) Monthly mean postdialysis systolic and diastolic blood pressures in exercise and control patients are plotted. At 6 months, the difference between the two groups is not statistically significant ($P = 0.12$). *$P < 0.05$ compared with control group. (—◆—) Exercise systolic; (—■—) control systolic; (—▲—) exercise diastolic; (—×—) control diastolic.

Physical functioning and health-related quality of life changes with exercise training in hemodialysis patients.

Painter P et al. AJKD. 2000. 35(3):482-492

- Renal Exercise Demonstration Project (REXDP) performed In 5 clinics in SF bay area.
- Intervention: 8 weeks independent home exercises (IND) followed by 8 wk cycling during HD (ICC)
- Control: units where nurse managers were interested in the project but staff not willing to participate.
- 286 patients on HD for at least 3 months
  - Exclusions: Angina, LE amputation without prosthesis, chronic lung disease with significant desaturation during exercise or shortness of breath at rest, and cerebral vascular disease manifested by TIA.
- Outcomes: Physical function testing, Physical activity assessments, Health related QOL by SF-36

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Intervention

– IND – individualized program with flexibility(5-6x/wk), strengthening (3x/wk), cardiovascular exercises (3-4x/wk).

- Detailed in (Exercise. A Guide for the Dialysis Patient. Patricia Painter. http://www.lifeoptions.org/catalog/pdfs/booklets/exercise.pdf)

– ICC – First session to determine tolerance to cycling and starting duration. Instructions to increase duration gradually by 2-3 min each session and how to adjust based on perceived exertion scale (Borg scale)

- Goal was 30 min of continuous cycling every dialysis session
- Patients encouraged to continue home exercises.

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WORK EFFORT SCALE

6	Rest	
7	Very, Very Light	
8, 9	Very Light	Warm-Up & Cool-Down
10, 11	Fairly Light	
12, 13	Somewhat Hard	Conditioning
14, 15, 16	Hard	Conditioning
17, 18	Very Hard	Slow Down!
19, 20	Very, Very Hard	Slow Down!

How to Use the Work Effort Scale:
Use the scale to rate how hard your exercise feels to you. The number 6 is the work effort you feel just sitting in a chair or doing nothing. As you exercise faster or harder, the work effort will feel harder to you. Check your effort level several times during each exercise session. The same exercises will feel different on different days. As long as you listen to your body, you won't do too much!

Exercise. A Guide for the Dialysis Patient. Patricia Painter. http://www.lifeoptions.org/catalog/pdfs/booklets/exercise.pdf

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Baseline Characteristics

- Cause of renal failure: 43% diabetics, 25.2% HTN, 7.7% GN

Table 1. Baseline Characteristics

Characteristic	Intervention Group	No-Intervention Group
Age (y)	55.9 ± 15.15	52.8 ± 16.8
Women (%)	57.1	65.4
No. of comorbid conditions	3.0 ± 1.4	2.6 ± 1.7
Dialysis adequacy (Kt/V)	1.6 ± 0.46	1.5 ± 0.38
Hematocrit (%)	33.6 ± 4.5	35.0 ± 1.6
Albumin (mg/dL)	3.7 ± 0.39	4.0 ± 0.35
Dialysis prescription (min/wk)	526.4 ± 94.1	533.5 ± 86.9
Time on dialysis (mo)	33.7 ± 35.6	40.2 ± 62.4

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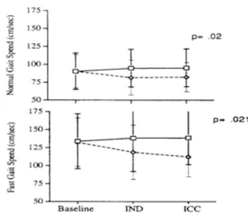
Improvements in QOL and Physical Functioning

Table 3. SF-36 Scale Scores in the Intervention and Nonintervention Groups at Each Testing Time

Scale	Group	Baseline	IND	ICC	F	P
Physical functioning (n = 180)	Intervention	47.7 ± 28.3	52.4 ± 27.7	53.4 ± 27.0	5.69	0.004
	Nonintervention	50.2 ± 24.1	45.2 ± 26.6	44.1 ± 27.6		
Role physical (n = 180)	Intervention	40.4 ± 40.3	54.0 ± 41.7	54.5 ± 21.4	11.12	<0.001
	Nonintervention	62.5 ± 44.2	38.6 ± 42.1	35.2 ± 41.2		
General health (n = 180)	Intervention	45.0 ± 21.9	50.4 ± 22.6	49.1 ± 22.5	2.91	0.050
	Nonintervention	44.7 ± 19.7	48.1 ± 22.1	39.3 ± 19.2		
Bodily pain (n = 180)	Intervention	60.5 ± 28.1	69.6 ± 26.3	66.6 ± 28.6	5.7	0.003
	Nonintervention	68.8 ± 25.9	68.3 ± 24.3	52.7 ± 30.4		
Vitality (n = 180)	Intervention	46.5 ± 23.4	52.8 ± 24.1	52.4 ± 25.5	2.03	0.130
	Nonintervention	45.0 ± 26.2	42.8 ± 21.4	42.1 ± 21.7		
Social functioning (n = 180)	Intervention	67.2 ± 27.6	72.0 ± 27.1	72.7 ± 26.5	2.33	0.090
	Noninvertention	75.0 ± 25.3	69.8 ± 24.3	64.7 ± 30.0		
Role emotional (n = 180)	Intervention	64.0 ± 41.8	70.1 ± 41.6	67.6 ± 42.4	0.466	0.630
	Nonintervention	72.7 ± 41.9	68.2 ± 43.0	71.2 ± 45.2		
Mental health (n = 180)	Intervention	71.5 ± 19.1	73.1 ± 19.5	73.2 ± 19.9	0.519	0.590
	Nonintervention	73.5 ± 16.5	74.6 ± 14.7	71.4 ± 16.0		
PCS (n = 180)	Intervention	35.1 ± 10.8	39.5 ± 10.0	38.3 ± 10.4	10.7	<0.001
	Nonintervention	37.7 ± 8.8	35.5 ± 10.8	31.8 ± 9.6		
MCS (n = 180)	Intervention	48.4 ± 11.0	50.2 ± 11.0	50.7 ± 11.3	0.199	0.820
	Nonintervention	50.9 ± 10.0	50.5 ± 8.8	50.8 ± 9.8		

NOTE. Values expressed as mean ± SD.
Abbreviations: IND, independent exercise; ICC, incenter exercise; PCS, physical component scale; MCS, mental component scale.



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Conclusions

- Low intensity independent and in-center exercise is effective in a diverse population with significant comorbidity.
- Specific individualized prescriptions and encouragement from dialysis staff can increases physical performance, and QOL.
- Limitations: Non-randomized with significant selection bias.
  - 10 deaths between baseline and IND
  - 3 deaths and 16 medical complications between IND and ICC
  - No deaths or medical complications thought to be related to exercise

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Exercise, walking capacity, and muscle strength

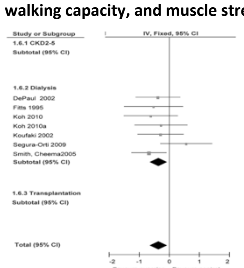

Figure 4. Effects of exercise training on walking capacity. Abbreviations: CI, confidence interval; CKD2-5, chronic kidney disease stages 2-5.

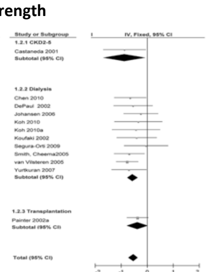

Figure 3. Effects of exercise training on muscular strength. Abbreviations: CI, confidence interval; CKD2-5, chronic kidney disease stages 2-5.

Heiwe S, Jacobson SH. AJKD. 2014; 64(3): 383-393

33

Exercise in Patients on Dialysis: A Multicenter, Randomized, Clinical Trial

Manfredini F, Mallamaci D'Arrigo et al. JASN. 2016.

- The EXerCise Introduction to Enhance performance in dialysis patient trial (EXCITE)
- 6-month personalized, ***home-based walking exercise program*** to improve walking capacity and muscle strength compared to "usual care"
- Excluded participants with limited mobility or high degree of fitness (6 minute walk distance >550meters), exertional angina, or stage 4 NYHA heart failure

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Training customized to level of fitness

- Exercise training on non-dialysis days involved gradual increased intensity of walking cadence.

Functioning Capacity Level	Normal	Moderate	Low	Very Low
6 min distance walked at baseline, m	>300 to ≤550	<300 to >200	<200	<200 +severe symptoms
Number of training sessions per d (always on nondialysis days)	2	2	2	2
Duration of training sessions, min	10	10	10	10
Frequency, times per wk	3	3	3	3
Training speed				
Baseline, km/h	2.8	2.0	1.4	1.4
Miles per h	1.7	1.2	0.9	0.9
wk 1–14, steps/min	72–120	66–100	56–80	56–80
wk 15–24, steps/min	90–120	80–100	60–80	60–80
wk 1–14				
Work/rest time, min	5:1	5:1	5:1	2:1
No. of repetitions	2	2	2	5
wk 15–24				
Work/rest time, min	10:0	10:0	10:0	5:1
No. of repetitions	1	1	1	2

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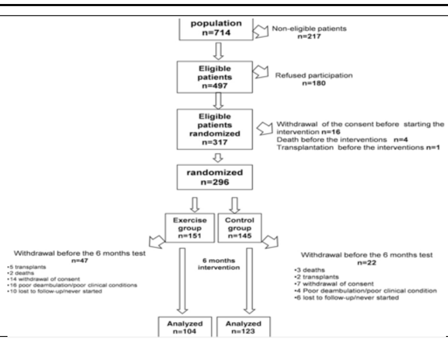

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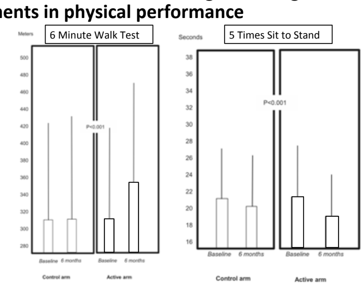
Participant Characteristics

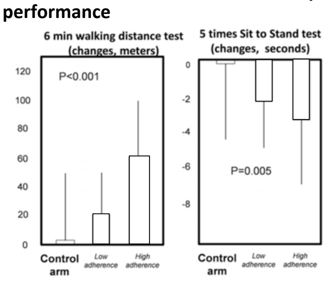
Table 1. Demographic, clinical, and biochemical data of patients that completed the study

	Active Arm (n=104)	Control Arm (n=123)	P Value
Age, yr	63±13	64±14	0.60
Men, %	64	68	0.54
Hemodialysis/CAPD, n	90/14	102/21	0.45
BMI, kg/m^2	26±4	27±6	0.32
Smoking, % (0=no; 1=yes)	18	19	0.93
Diabetes, % (0=no; 1=yes)	18	18	0.88
Systolic BP, mmHg	132±18	127±18	0.06
Diastolic BP, mmHg	72±10	71±12	0.43
HR, beats/min	75±9	74±8	0.51
Total cholesterol, mg/dl	164±39	166±39	0.67
Triglycerides, mg/dl	166±116	160±86	0.68
Hemoglobin, g/dl	11±1	11±2	0.22
Albumin, g/dl	3.9±0.4	3.8±0.5	0.44
Calcium, mg/dl	8.8±0.7	8.9±0.7	0.42
Phosphate, mg/dl	4.9±1.5	4.8±1.4	0.35
PTH, pg/ml	280 (179–456)	283 (156–396)	0.55
Creatinine, md/dl	10.5±2.7	9.8±2.6	0.41
Glycemia, mg/dl	111±64	102±36	0.23
Urea, mg/dl	153±42	148±40	0.33
CRP, mg/L	5.0 (3.1–9.0)	4.6 (3.0–8.0)	0.60
Kt/V hemodialysis	1.42±0.25	1.43±0.30	0.68
Kt/V CAPD	1.96±0.29	1.80±0.60	0.36
Myocardial infarction, %	15	17	0.73
Stroke/transient ischemic attack, %	8	14	0.14
Anginal episodes, %	11	13	0.74
Arrhythmia, %	12	7	0.19
Heart failure, %	17	24	0.24
Peripheral vascular disease, %	7	12	0.16
History of neoplasia, %	22	18	0.52
Antihypertensive therapy, %	77	70	0.27
NYHA class, %			
I	38	34	0.46
II	14	16	
III–IV	4	10	
Mobility, %			
Assisted	4	3	0.56
Independent	96	97	

Exercise is associated with meaningful and significant improvements in physical performance



Dose dependent association of exercise with improvement in physical performance



Study	Population	Intervention/control	Result	Monitoring	Adherence/AE
Leehey et al, 2016	Obese diabetic patients with CKD 2-4 (n=36)	12 weeks of supervised exercise training (3x/wk) followed by 40 weeks of supervised home exercise + diet intervention Aerobic 3x/wk (60 minutes) Resistance 3x/wk (20-30 min) Control – dietary counseling at baseline	Increased Walking capacity (treadmill time) at 12 weeks compared to control (+4.3min vs -0.2 min; P=0.03). Effect of exercise not significant after 52 weeks (P=0.14).	Exercise + diet: Weekly phone calls and encouraged to meet with trainer once monthly Control: 9 follow-up telephone calls	4 lost to follow-up in exercise and 0 in control. No serious adverse events.
Howden et al, 2015[124]	CKD 3-4, plus >1 uncontrolled cardiac risk factor (n=83)	12 months aerobic and resistance based on ACSM guidelines. Aerobic 5x/wk (moderate intensity >30min) Resistance 2x/wk (moderate intensity) Control – usual care	Increased 6 minute walk distance of 54 meters after 12 months (vs -3m in control) Preserved grip strength (P=0.03) Preserved timed up and go Increased VO_{2peak} &Exercise capacity Increased physical activity.	Nurse practitioner follow-up at 1 month to monitor impact of exercise on BP, blood glucose. Exercise physiologist assessed BP and blood glucose levels (in DM) prior to gym session.	70% adherence 3 lost to follow-up and 1 discontinued in training group 3 lost to follow-up and 3 discontinued in control. No serious adverse events
Greenwood et al, 2015[125]	Stage 3-4 CKD (n=20)	12 month of aerobic and resistance training, 3x/wk (2x/wk supervised, 1x/wk home) Aerobic exercise (recumbent stationary bike) with intensity of 80% heart rate reserve Resistance training 80% of 1 repetition maximum (goal of 3 sets of 8-10 rep).	Increased VO_{2peak} Primary outcome: Improved kidney function Secondary outcome: Decreased pulse wave velocity	40-minute session with renal physiotherapist at baseline to discuss exercise and personal goals. Weekly phone calls to encourage self-managed exercise and assess RPE.	79% adherence 2 training group dropped out (1 started PD and 1 emigrated) No serious adverse events noted.
Kouidi et al, 2009[126]	ESRD on dialysis (n=63) Excluded diabetes	10 month supervised in-center aerobic and resistance exercise. Aerobic in-center cycling Target RPE of 13 out of 20. Heartrate on exercise 60-70% of maximum. Isometric & isotonic resistance exercise of abdomen and lower limbs 30 minutes while in seated position gradual increase to 3 sets of 15 repetitions	Increased Exercise time Increased VO_{2peak} Increased Left Ventricular Ejection Fraction Improved heart rate variability	2 exercise trainers specialized in physical rehabilitation supervised training sessions. Continuous heart rate monitoring telemetrically during exercise	88.3% adherence 59 completed study (2 discontinued in training and 2 lost to follow-up in control). No complications

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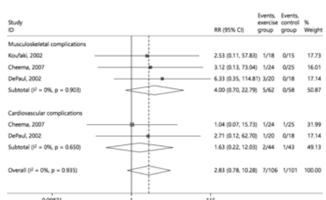
Risks of Exercise

- No studies specifically designed to assess risk of exercise in ESRD
- Recent metanalysis: Among all intradialytic exercise studies only 3 cardiovascular events reported (2 in exercise and 1 in control) related to hypotension.



Sheng K, et al: Intradialytic Exercise in Hemodialysis Patients: a Systematic Review and Meta-Analysis. Am J Nephrol 2014; 40:478-90

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Outline

- Background
  - CKD and the Disablement Process
  - Kidney Disease and Frailty
- Evidence for benefits and risks of exercise in ESRD
- Barriers to exercise
- Safety and Contraindications to exercise
- Individualized exercise prescriptions.

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Barriers to exercise

- Patient related:
  - Poor physical function, comorbidity, psychological
  - Logistical
- Structural barriers:
  - Not prioritized by healthcare team
  - Lack of support from kidney health providers/dialysis staff
  - Lack of peer support
  - Lack of resources (exercise specialist)

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Patient-perceived barriers to adopting exercise

Table 3. All emerged themes of barriers to promotion/provision of PA and rehabilitation services in units as reported by 120 respondents

Reported themes of barriers	n (%)
Money/funding	42 (35)
Lack of time	37 (30.8)
Lack of qualified personnel (physio or other exercise professional) for this role	32 (26.6)
Lack of physical resources or difficulty with existing resources (e.g. dialysis beds, exercise equipment)	20 (16.6)
Lack of interested/motivated patients due to ill health and lack of awareness	14 (11.6)
Prioritisation of other services/lack of vision	14 (11.6)
Lack of motivated medical staff	10 (8.3)
Lack of leadership and professional advice on how to organise a unit with rehab in mind	7 (5.8)
Lack of space	6 (5)
Lack of hard research evidence, lack of knowledge about available offered services within organisations, culture, obstruction by health and safety management	<5

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Safety and Contraindications

- Diabetics: postpone if blood sugars >250 or <100
- Prone to hypoglycemia: check blood sugar before, during and after exercise. Have snack available
- Avoid aquatic exercise if open wounds
- Instruction on avoiding valsalva maneuver during strength training
- Postpone/stop exercise if patients experience dizziness, severe headache, or fluctuating HR, BP responses
- Consult MD if experiencing hypotensive episodes and symptoms after dialysis and exercise.

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Safety and Contraindications

- Cardiovascular: Unstable CAD, decompensated heart failure, unstable arrythmias, severe and symptomatic aortic stensosis, uncontrolled hypertension (>180/110) and aortic dissection.
- Pulmonary: severe pulmonary hypertension (PASP>55mmHg)
- Diabetic patients on beta blockers may develop hypoglycemia and have masked symptoms in hot and humid environment (recommend reduce intensity).
- Vasodilators (alpha blockers, clonidine, nitrates, hydralazine): Predispose to hypotension after exercise . Recommend prolonged cool down period to prevent hypotension.

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Outline

- Background
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Individualized exercise prescriptions

- Individualized to the patient's physical function with an emphasis placed on regular engagement and evaluation of progress
- Health evaluation including assessment of baseline function, and addressing potential safety concerns
  - Patients with symptoms suggestive of cardiac disease or with known disease should undergo exercise testing before participation in vigorous exercise training programs.
  - For moderate exercise history, physical exam and possible EKG testing may be adequate.

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Health Evaluation

- Medical evaluation: health history, physical exam, assessment of cardiovascular disease risk factors and physical function
  - Physical performance assessed in HD patient mid-week non-dialysis day
  - Referral to rehabilitative therapy if appropriate prior to start of exercise regimen
- Referral to cardiac rehabilitation for patients with symptomatic heart failure (EF<35%), acute MI within preceding 12 months, CABG, stable angina, recetne history of heart valve replacement, coronary stenting and heart or lung transplant.

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When is structured and supervised exercise prescription necessary?

- Poor functioning in ADL
- Severe muscle weakness and function
- Symptoms of CV and respiratory discomfort during ADL
- Fear of exercise and lack of confidence
- No previous exercise experience

51

Expert opinion

Koufaki P, Greenwood S, Painter P. Journal of Sports Sciences. 2015. 33(18):1902-1907.

ACSM's Guidelines for Exercise testing and Prescription, 8th ed. 2010. 166-7.

Population	Frequency	Intensity	Time	Type	Special considerations
CKD and ESRD	Wk 1-2: 2/wk Wk 3-5: 3/wk	Moderate (RPE 11-13 on scale of 6-20), 55-70% max HR Moderate (RPE 11-16), 55-90 % of max HR	20min/day (or bouts of 3-5 min of intermittent exercise)	**Aerobic** (cycling, walking, swimming)	For patients on beta blockers use RPE instead of HR Patients on vasodilators (e.g. alpha-blockers, CCB) would require extended cool-down period after exercise Arms with active dialysis access can be exercised during non-dialysis times PD patients may have more effective exercise with smaller dwell volumes, although fluid in the abdomen is not a contraindication to exercise
	Wk 1-2: 2/wk Wk 3-5: 2/wk	60-70% of 1-RM	Minimum of 1 set of 10-15 repetitions. Gradually increase to 2-4 sets Choosing 8-10 different exercises to work major muscle groups. Rest 2-3min between sets Rest>=48hrs between sessions	**Resistance** (multi-joint exercises affecting more than one muscle group and targeting agonist and antagonist muscles)	
	5/wk		10 min/day	**Flexibility** (Combine it with Aerobic and Resistance when possible)	
Modifications for initial aerobic activity based on baseline activity using pedometer[128]					
Sedentary	3-5/wk	Light-moderate (RPE 3-6 on a scale of 0-10)	20-30min/day	Walking 3000-3500 steps	
Minimal physical activity/ no exercise/moderate to highly deconditioned	3-5/wk	Light to moderate (RPE 3-6 on a scale of 0-10)	30-60 min/day	Walking 3000-4000 steps	
Sporadic physical activity/ no or suboptimal exercise/ moderate to mild deconditioned	3-5/wk	Moderate to hard (RPE 6-8 on a scale of 0-10)	30-90min/day	Walking >3000-4000 steps (goal >5400-7900 steps and total of ~150min/wk moderate intensity)	

Practical Implications

- Assessment of baseline level of physical function and mobility limitation should be assessed prior to initiating exercise.
- Exercise should be recommended at a low-moderate level relative to the individual's level of fitness rather than absolute scale
- Gradual stepwise approach to increasing physical activity over time using multiple bouts of physical activity (≥5-10min).
- Exercise during dialysis should be limited to first 2 hrs to avoid hypotension.
- Encourage both aerobic and strength training and help create an activity plan that identifies recommended levels of physical activity for a specific person and describes how the person intends to meet them.
- Regular follow-up with healthcare team to encourage exercise and adjust antihypertensive and insulin needs.

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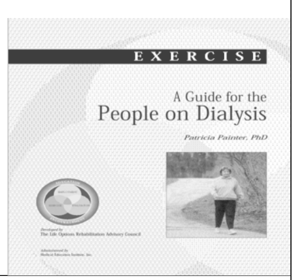
Resources

- Exercise. A Guide for the Dialysis Patient. Patricia Painter. http://www.lifeoptions.org/catalog/pdfs/booklets/exercise.pdf
- https://www.kidney.org/atoz/content/stayfit



Conclusions

- Kidney disease is associated with functional limitation linked with disability and death
- Exercise improves physical functioning and QOL estimate
- Exercise can improve cardiac risk factors
- Exercise can improve dialysis efficiency and may reduce medication burden.
- Individualized prescription to the patient's physical function with an emphasis placed on regular engagement and evaluation of progress
- In those without contraindication, exercise should be recommended at a low-moderate level relative to the individual's level of fitness rather than absolute scale.
- Gradual stepwise approach to increasing physical activity over time using multiple bouts of physical activity (≥5-10min).

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KIDNEY RESEARCH INSTITUTE
A collaboration between Northwest Kidney Centers and UW Medicine

Division of Nephrology
University of Washington

Thank You

NIH National Institute of Diabetes and Digestive and Kidney Diseases

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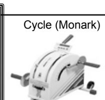
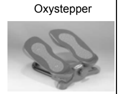
Cycle (Monark)



Oxystepper



Hand Weights

Ankle Weights

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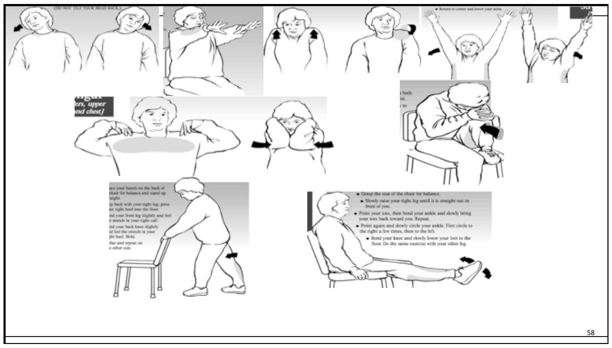

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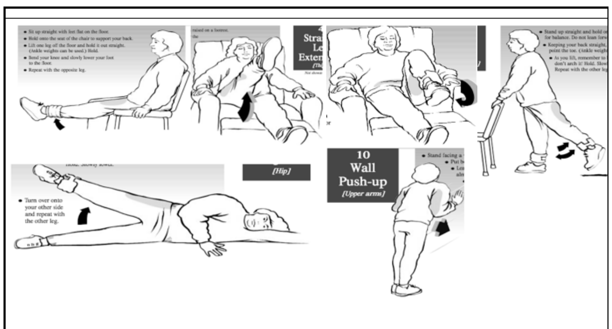

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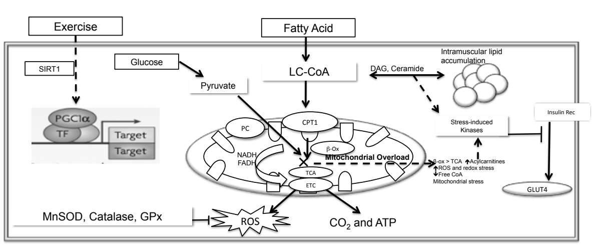
Basics of Mitochondrial Metabolism



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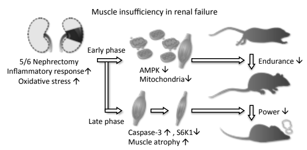
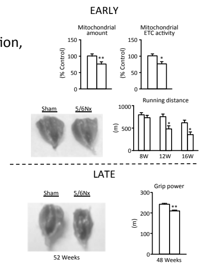
Mitochondrial Impairment Precedes Muscle Atrophy and Functional Limitation

- CKD model: 5/6 nephrectomy of C57Bl/6 mice
- Early changes: Increased oxidative stress, inflammation, decreased endurance, lower mitochondrial function and content without muscle atrophy
- Late changes: muscle atrophy, decreased strength





Tamaki M, et al. *Kid Int*. 2014;85:1330-1339.

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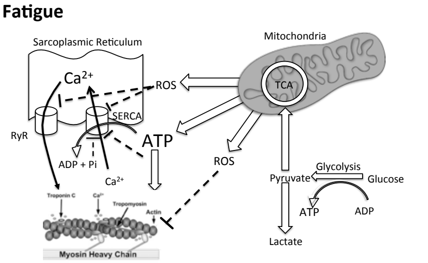
Decreased ATP Production and Increased Oxidative Stress Lead to Fatigue



Adapted from Allen DG, Lamb GD, Westerblad H. *Physiol Rev*. 2008;88:287-332.

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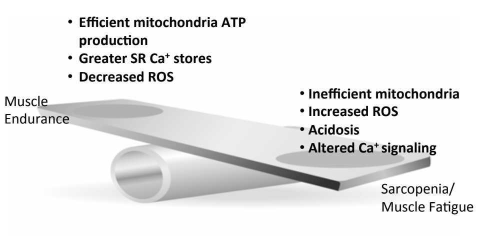
CKD and Fatigue: Potential Mechanisms



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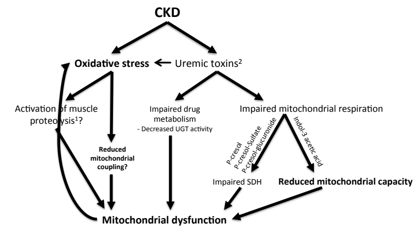
Mitochondrial Dysfunction in Kidney Disease



1. Mutsaers HAM, et al. *Biochimica et Biophysica Acta.*1832(2013)
2. Talbert EE, Powers SK. *J Appl Physiol*. 2013;115:529-538.

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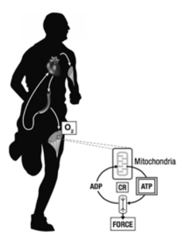
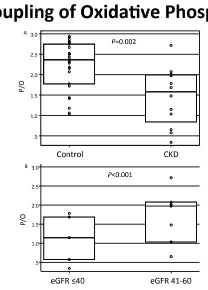
CKD is Associated With Uncoupling of Oxidative Phosphorylation





Roshanravan B, et al. *Am J Kidney Dis*. 2016 Oct;68(4):658-9.

P-value adjusted for age, sex, BMI

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CKD Muscle Mitochondrial ENergetics and Dysfunction (MEND) Study

CKD negatively affects normal functioning of skeletal muscle: Leads to objective fatigue and weakness
Purpose: Understand how CKD affects muscle mitochondria, an essential component of skeletal muscle cells

- ^{31}PMRS measuring phosphocreatine dynamics during exercise of the tibialis anterior muscle
  - Exercise protocol: rapid dorsiflexion as fast as possible for 20 seconds targeting 50% breakdown of PCr (pH>6.8)
  - 14 minutes of recovery
- Muscle endurance testing: isometric force time integral
- Older adult controls (>65 years): 45 leg MRS

	CKD (n=19)	Control (n=45)
Female, No (%)	10 (53)	26 (57)
Age	64 ±11	71 ±4
BMI	30 ±6	25 ±3
GFR (MDRD)	37 ±13	>60
Diabetes, No (%)	5 (26)	0

Unpublished observations

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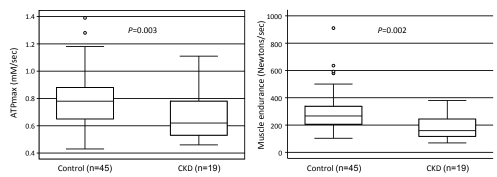
CKD MEND: Preliminary Results

- Lower mitochondrial capacity (ATPmax) in tibialis anterior muscle of patients with CKD
- Lower muscle endurance and preserved muscle strength in CKD compared to controls



P value adjusted for age and sex
Unpublished observations

Summary of RCT of exercise training

Authors (year) country	n	Study groups (n)	Exercise intervention: delivery	modality	prescription	duration	Outcomes: variable	% change	p value
Goldberg et al. [24] (1983) Goldberg et al. [25] (1986) Harter et al. [26] (1985) USA	25	exercise (n = 14) control (n = 11)	NDT	AER	walking, cycle erg. 50–80% VO_{2peak} 45–60 min, 3×/week	12 months	VO_{2peak}	+17–21%	≤0.01[b]
							GXT duration	+26%	≤0.01[b]
							plasma triglyceride	–29–33%	≤0.01[b]
							VLDL triglyceride	–30–38%	≤0.05[b]
							VLDL cholesterol	–16%	≤0.02[b]
							HDL	+16–20%	≤0.05[b]
							glucose disappearance rate	+35–42%	≤0.02[b]
							insulin affinity	+25–70%	≤0.01[b]
							hematocrit	+27%	≤0.02[b]
							RBC mass	+27%	≤0.01[b]
							hemoglobin	+16–20%	≤0.01[b]
							basal insulin levels	–21%	≤0.05[b]
							RBC survival	+46%	≤0.02[b]
							Beck depression inventory	–42%	≤0.01[b]
Deligiannis et al. [31] (1999) Greece	60	exercise (n = 30) control (n = 30)	NDT	COMBO	calisthenics, aerobics, swimming or ball games, and strength exercise 50–70% VO_{2peak}, 90 min, 3–4×/week	6 months	VO_{2peak}	+41%	< 0.05[b]
							GXT duration	+33%	< 0.05[b]
							HRV index	+31%	< 0.05[b]
							SD of R-R interval	+18%	< 0.05[b]
							R–R interval length	+18%	< 0.05[b]
							n patients, with HRV index <25	–40%	< 0.05[a]
							n patients with arrhythmias (Lown class >II)	–33%	< 0.05[a]
Deligiannis et al. [32] (1999) Greece	38	exercise 1 (n = 16)	NDT	COMBO	calisthenics, steps, up to 70 min, and strength exercise, 3×/week	6 months	exercise 1		
							left ventricle mass index	+11%	≤0.05[a]
							ejection fraction	+12%	≤0.01[a]
							stroke volume index	+23%	≤0.05[a]
							cardiac output index	+20%	≤0.05[a]
		exercise 2 (n = 10) control (n = 12)	HB	AER	cycle ergometer 30 min at 50–60% HR_{max}, >5×/week		exercise 2 no significant adaptations vs. control group		
Konstantinidou [35] (2002) Greece	48	exercise 1 (n = 16)	ND	COMBO	aerobic training 50–70% VO_{2peak}, 60 min and strength exercise, 3×/week	6 months	exercise group 1		
							VO_{2peak}	+43%	≤0.05[a]
							GXT duration	+33%	≤0.05[a]
							VE_{peak}	+41%	≤0.05[a]
							VO_{2AT}	+37%	≤0.05[a]
		exercise 2 (n = 10)	ID	COMBO	cycle ergometer Borg RPE=13 60–90 min, and lower body strength exercise 3×/week		exercise group 2		
							VO_{2peak}	+24%	≤0.05[c]
							GXT duration	+22%	≤0.05[c]
							VE_{peak}	+12%	≤0.05[c]
							VO_{2AT}	+18%	≤0.05[c]
		exercise 3 (n = 10) control (n = 12)	HB	AER	cycle erg., 50–60% HR_{max}, 30 min, 5×/week		exercise group 3		
							VO_{2peak}	+17%	≤0.05[c]
							GXT duration	+14%	≤0.05[c]
							VE_{peak}	increase	≤0.05[c]
							VO_{2AT}	+8%	≤0.05