Exercise for Hemodialysis patients: Its NOT about the bike!

Ken Wilund, PhD
Department of Kinesiology and Community Health
University of Illinois at Urbana-Champaign

Global Renal EXercise

TK Cureton Physical Fitness Research Laboratory

Disclosure Information
Ken Wilund

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I have the following financial relationships to disclose:

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I will not discuss off label use and/or investigational use in my presentation.

Learning objectives

- 1) Critically evaluate the literature regarding the benefits of exercise for improving physical function and CVD risk in dialysis patients
- 2) Discuss strengths and limitations of exercise protocols typically prescribed for dialysis patients
- 3) Examine the potential efficacy of novel intervention strategies designed to increase patient participation in exercise and physical activity programs

Exercise training interventions (RCTs) have been shown to consistently and robustly improve which of the following outcomes in hemodialysis patients?

- A) Physical Function and muscle strength
- B) Muscle Mass
- C) Cardiovascular Function
- D) all of the above
- E) none of the above

How much energy do hemodialysis patients typically expend while cycling during dialysis (per 30 minutes)?

- A) < 100 kcal
- B) 100 – 300 kcal
- C) 300 – 500 kcal
- D) > 500 kcal

Preface

- How I look when I think about exercise in dialysis:

- This is NOT a negative talk… but it is a reality check
  - I will start with some skepticism…
  - Then provide reasons for optimism

- Acknowledging reality is important if we want to do better…

The Flowery View: Exercise in CKD ALWAYS WORKS!

CKD Stage	Systematic Reviews and/or Meta-analysis
ALL CKD stages	1) Barcellos CKJ 2015;8(6):753-65; 2) Heiwe AJKD. 2014;64(3 3) Heiwe. Cochrane Reviews. 2011(10):CD003236.
Dialysis	1) Clarkson. AJP 2019 (In press); 2) Sm N. 2005;25(4):352-64.; 4) Chan. A 1165-6; 6)Sheng AJN. 2014;40(5):478-90.; 7) R Clin Rehab. 2018;32(9):1189-202; 9) Chung. J 2019;65(1):4-15. 11) Ferreira 2019 APMR (I 445; 13) Cheema AJN. 2016;44(1):32-45; 14) R Sawant. Phys Can. 2014 16(1): 44-53
Transpl	2-500; ress).

IF IT WORKS SO GREAT ....
THEN WHY IS NOBODY DOING IT ????

Sum **proves muscle strength, physical function, QOL, etc.**

- **Reg** ***ss of stage of disease*** **(non-dialysis CKD, dialysis, transplant)**

- ***Regardless of the mode of exercise (Resistance, endurance, yoga, balance, flexibility)***

The Skeptical View:

- It doesn't always work as well as we want
  - Its not a magic bullet
- IMO: Many have become cheerleaders for mundane exercise prescriptions that produce MODEST/MARGINAL Benefits….
- This is hurting our cause…
  - Its made us (researchers/clinicians) lazy
  - And it's stifling the development of more innovative approaches to exercise

The dirty secret not discussed: *MUCH of the physical fx data is NOT THAT GOOD*

Reference	Exercise Mode	Results
Johansen 2006 JASN 17:2307-14	Intradialytic RT	↑ quadriceps CSA, strength; -no Δ: phys fx, lean mass
Dong 2011 JRN 21(2): 149-59	Peridialytic RT	no Δ: body comp/strength
Kopple 2007 JRN 16(4): 312-24.	Intradialytic RT and ET	no Δ: body comp
Cheema 2007 JASN 18(5): 1594-1601.	Intradialytic RT	Improved muscle "quality" -no Δ: muscle mass; -mixed results: strength/phys fx
Kirkman 2014 JCSM 5(3):199-207.	Intradialytic RT	↑ muscle volume/strength; - no Δ: phys fx
Koh 2010 AJKD 55(1):88-99.	Intra and Interdialytic ET	no Δ: physical fx
Jeong 2019 KI Sep;96(3):777-786	Intradialytic ET	no Δ: physical fx/strength

Data on CV-related outcomes with Ex Training also modest:

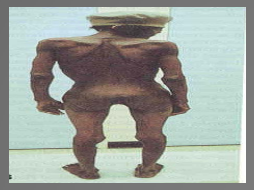
Reference	Mode/population	Results
Toussaint 2008. HI 12:254-63	Intradialytic cycling	"trend" for improved PWV.
Mustata 2004. JASN 15(10):2713-8.	Intradialytic cycling	small improvement in Ai/no controls
Koh 2010. AJKD 55(1):88-99	Intradialytic cycling or home walking	no Δ: BP, PWV
Van Craenenbroeck 2016. AJKD Aug;66(2):285-96.	CKD 3 – 4	no Δ: PWV (CKD 3-4)
Kirkmann 2019 AJP May 1;316(5):F898-F905	CKD 3 – 4	-Improved microvascular fx; -No Δ: central artery stiffness
Jeong 2019 KI Sep;96(3):777-786	Intradialytic cycling	no Δ: PWV, carotid IMT, or systolic fx, Diastolic fx maintained
Shalom 2004. KI, 24: 958-63	Gym exercise 5d/wk	no Δ: cardiac function
Deliagganis. 1999. IJC 70: 253-266	At home exercise	- INCREASED LV mass and Ejection Fraction
Burton CYCLE (In Progress)	Intradialytic cycling	1^0 Hypothesis: Reduced LV mass

Summary of the literature on exercise training in CKD:

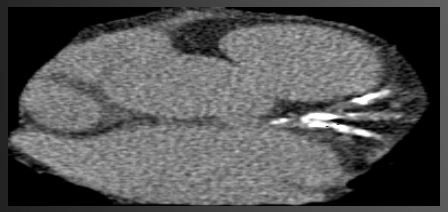
- Most studies are small and/or lack control groups
- Improvements in muscle size, strength, and physical function are modest/inconsistent…. (but improvements are there)
- CV benefits are especially weak or absent
- ***We have amazing anecdotes (which keeps us going)***
- If we are going to improve our data… we have to admit its not ideal…. AND FIND A BETTER WAY FORWARD

Should we really be surprised?
Think About What We Are Asking Exercise To Do!

Malnutrition, Inflammation,
oxidative Stress, "Uremic-toxins"



CVD ↔ Muscle Wasting/Functional Declines ↔ CKD-BMD

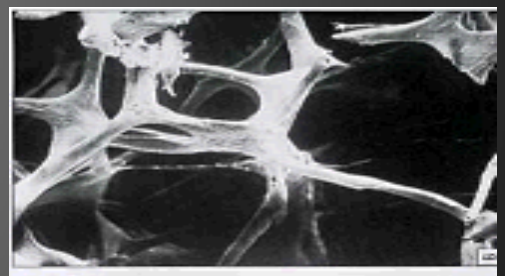


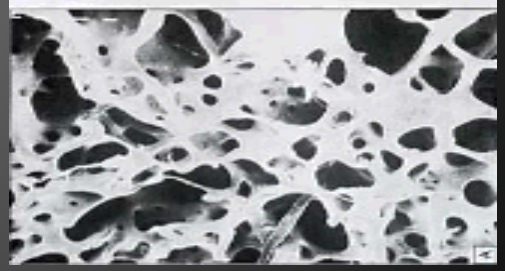
Vascular
Calcification

Minerals (Ca, P)

Arterial Stiffness

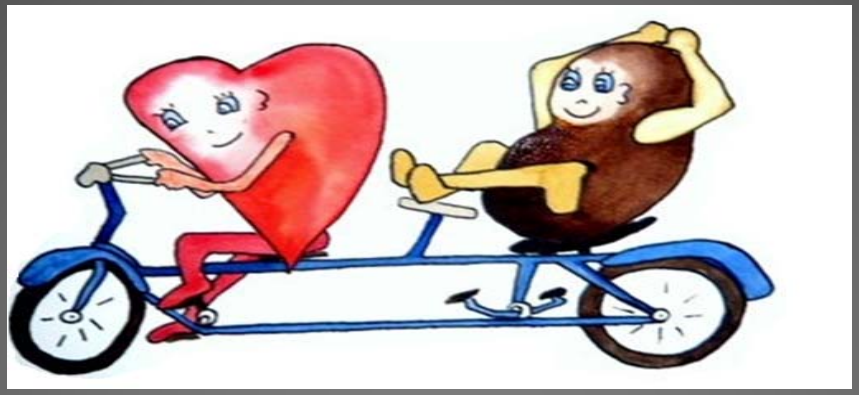
LVH/CHF





↓ Quality of Life, ↑ Mortality

To Illustrate the difficulties…



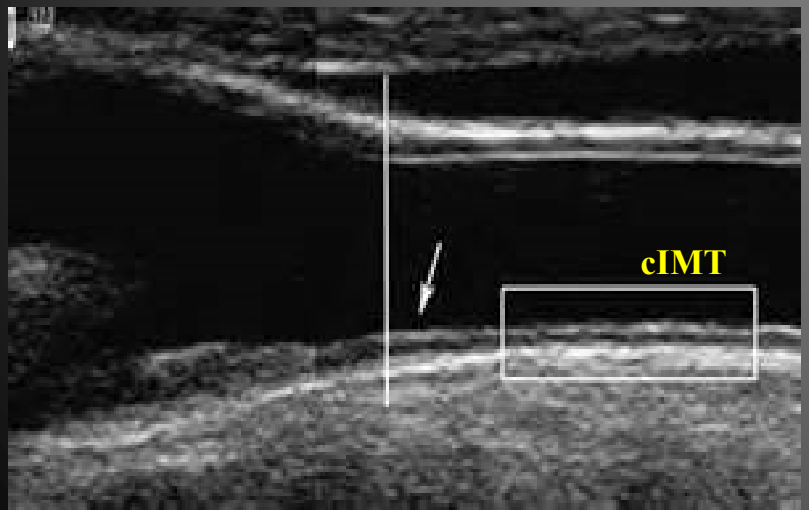
- Efficacy of Intra-Hemodialytic Oral Protein and Exercise (IHOPE)
- Jeong et al. KI 2019 Sep;96(3):777-786

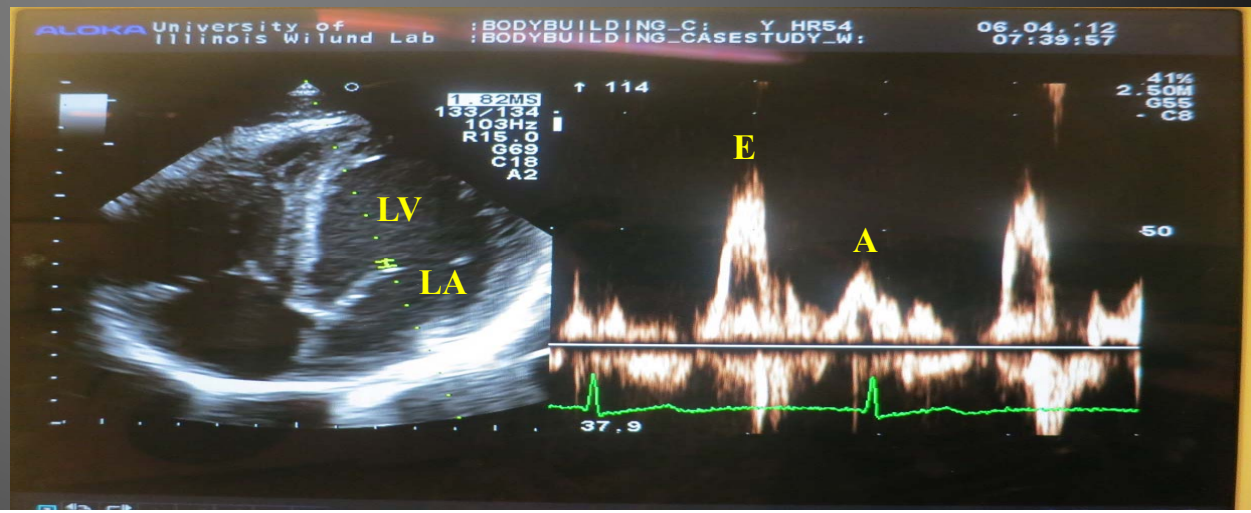
- N ~ 150 HD patients randomized to 3 groups *for 1 year*:
  - Control
  - Intradialytic WHEY Protein supp: 27grams/session
  - Intradialytic Whey + Endurance Exercise: 45 min cycling/session, RPE 12-13

Primary Hypotheses in IHOPE

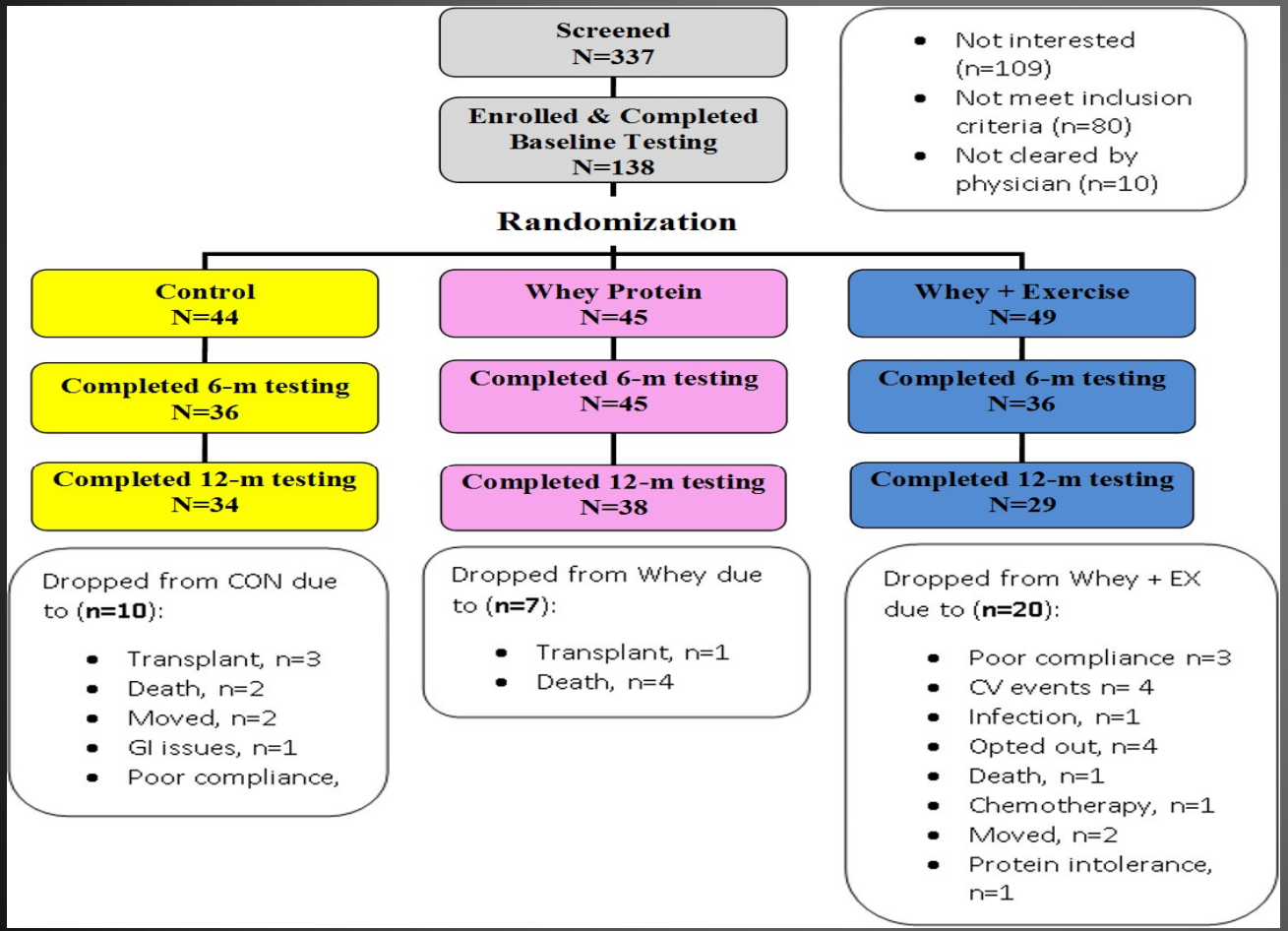
- **Aim 1: PRO and EX will have additive beneficial effects on physical function**
  - *Primary outcome was shuttle walk test (proxy for aerobic capacity)*

- **Aim 2: PRO and PRO+EX will have additive beneficial effects on CV structure and function:**
  - *PWV, carotid stiffness, cIMT, LV Systolic and Diastolic Function*





The Study Consort… tells us why its so hard to get good data



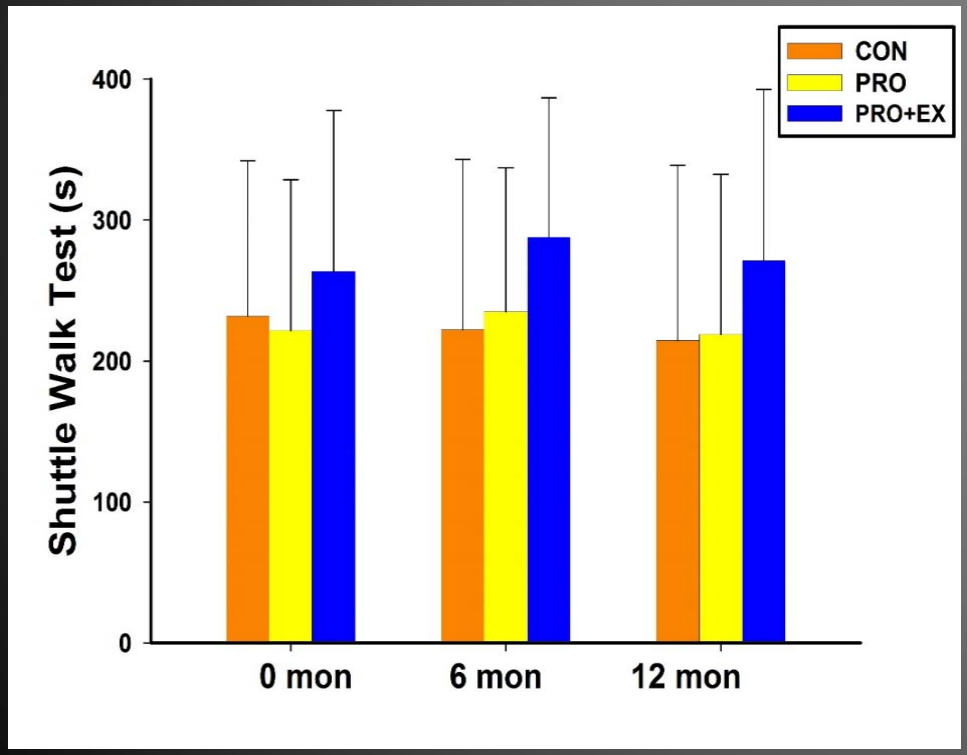
- Age: 55 (29-81)
- Gender: 58% male
- Race: 84% A.A.
- Dropout rates:
  - CON = 23%
  - PRO = 16%
  - **PRO+EX = 41%**

Baseline Data: these are NOT the sickest patients in the clinic

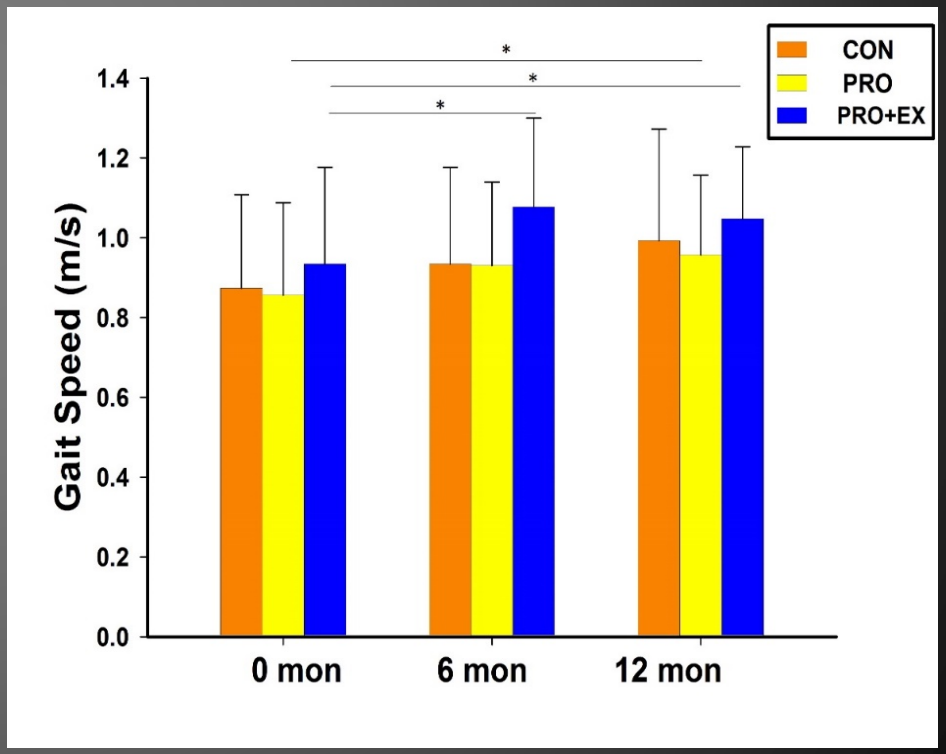
	Placebo (n=34)	Whey (n=38)	Whey + EX (n=29)	p
BMI (m/kg^2)	31 ± 7.6	32.9 ± 8.1	32.9 ± 8.4	.654
Age (years)	57 ± 12.4	56.2 ± 14.8	52.8 ± 10.2	.441
Gender (% M)	63.2	55.0	73.9	.429
Diabetes (%)	47.4	65.0	50.0	.481
Vintage (months)	48.0	38.0	33.8	.379
Albumin (g/dL)	4.04 ± 0.33	4.02 ± 0.30	4.04 ± 0.35	.979
SBP (mm/Hg)	139 ± 25.8	142 ± 12.6	131.1 ± 20.6	.196
DBP (mm/Hg)	79 ± 13.6	75.6 ± 12.3	77.9 ± 11.4	.702

Results - Aim 1: No changes in Physical Function

Primary Outcome:
No Change in Shuttle Walk performance

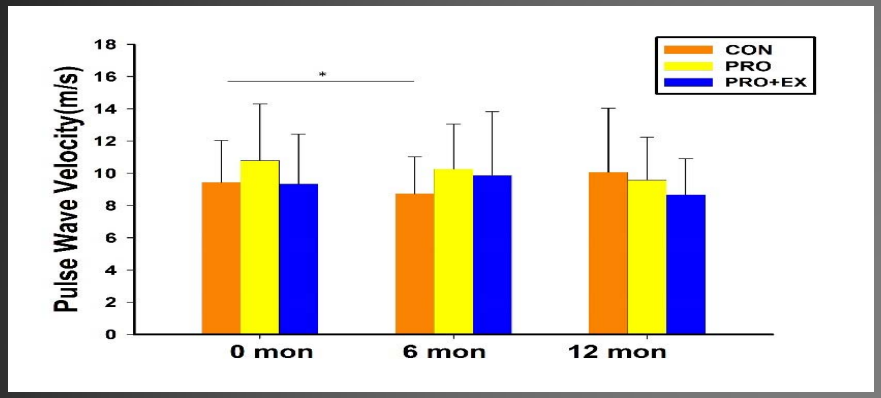


Secondary Outcome:
Modest improvement in normal gait speed

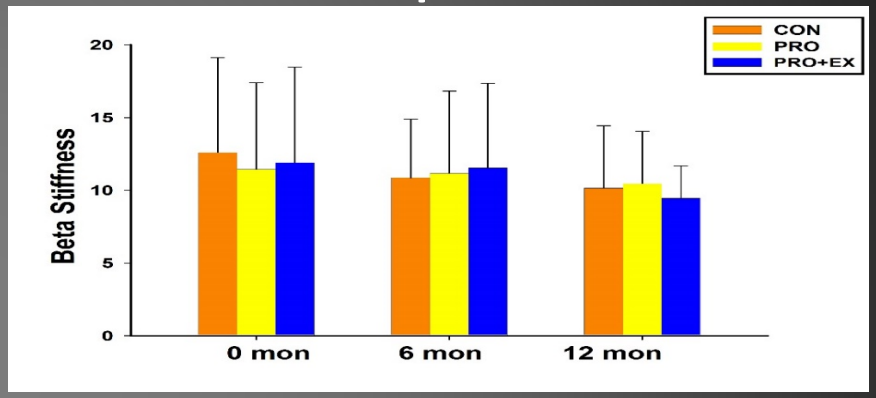


Results from Aim 2:
No Changes in Measures of Arterial Stiffness or structure (cIMT)

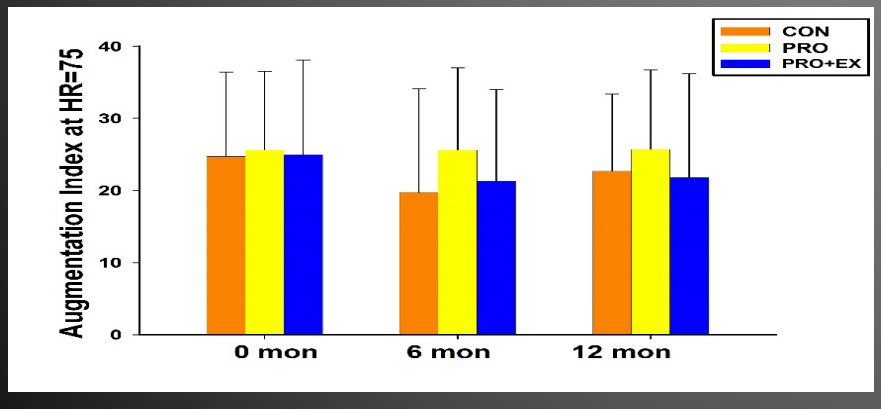
PWV



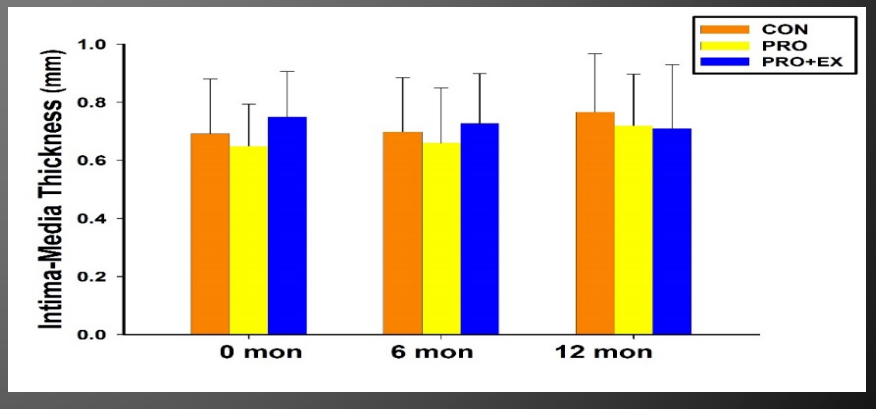
Carotid β Stiffness



Augmentation Index (A_i)



Carotid IMT



Summary/Conclusions

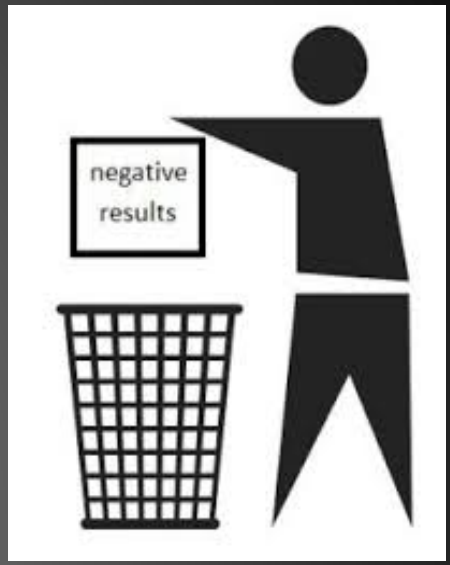
Effects of 12 months of: 1) OPS or 2) OPS + EX:

- Modest trends for improvements in some functional/strength measures
- No changes in Arterial structure/function
- No change in cardiac *systolic* function, though trend for improved *diastolic* function

- Control group did NOT get worse (with exception of diastolic fx)
- Dropout was significant (41% in EX group)

- We could have "spun" a more positive story….
  But to what end?

Why all the negative/modest/equivocal data?



- 1) Has exercise volume and intensity been too low?
  - avg energy expenditure: 35-70 kcal/session…in some studies
  - avg power output: ~17 watts… in several studies

- 2) Are CKD patients too sick?
  - Are arteries too calcified?
  - Do metabolic disturbances (e.g., acidosis, anemia) inhibit muscle and/or cardiovascular adaptations?

- 3) Is inhibiting progression all we can hope for? May need longer trials

- 4) Complex Nutritional concerns MUST be addressed:
  - anemia, chronic volume overload

If you are now doubting the efficacy of exercise in CKD…

- Read story of
- Age 11 – kidr
- Age 20 - 2 fa ted watching triathlon

- 2004 – completed 1st Ironman Triathlon (and many more since)
- ***Take home message:*** **this stuff works…** ***but we have to get them to do more… and start earlier!***

An anecdote from my lab

- Patient (D.J.) ~ 35 year old A.A. male. Sedentary, obese, HTN, diabetes, IDWG ~ 5 kilos
- Randomized to EXERCISE group in IHOPE trial. Horrible compliance…
- Saw him one Monday…. IDWG was 15 kg
- Cramping Friday. Got saline, Got thirsty, DRANK THIS:

- Finished study… Saw zero benefits… we took bike away
- After 2-3 weeks, he asked for the bike back…Started cycling 1-2 hours/session, changed his diet… lost 40 pounds and got a transplant.
- DJ is contributing to the "negative" data from my NIH-funded RCT
- Take home message: this exercise stuff CAN work…if prescription/adherence is good

How is exercise “normally” prescribed in HD?

<u>4 Primary steps</u>:

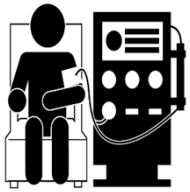
- 1) clinic purchases expensive bike
- 2) Nurse/tech sticks bike in front of patients 3x/week during dialysis
- 3) Beg patient to pedal
- 4) Give up. Watch bike collect dust in storage room
- Even if we could get them to pedal… would it matter?
- *Is this how YOU exercise?*

How much exercise are patients typically getting?

Study	Frequency	Intensity/Time	Results	Comment/Calculated Work rate*
Koh 2010 RCT n=70	-3x/wk -6 months	-30-45 min -Mod intensity	-No Δ 6-min walk test or PWV	Avg Energy expenditure: End of study: 35 kcal/session
Kopple 2007 RCT, n = 80	-3x/wk -21 weeks	-20 -40 min -Mod intensity	-No Δ body comp. -Improved markers muscle metabolism	Avg energy expenditure: Baseline: 37 ± 7 kcal/session End: 79 ± 17 kcal/session
Bohm 2014 RCT, n=60	-3x/wk -24 weeks	-30 - 60 min -Low intensity	-No Δ VO2peak, Or 6-min walk	Avg Energy expenditure: Baseline: 8W*30 min = 3.5 kcal/session End: 20W*60 min = 17.2 kcal/session
Toussaint 2008 X-over, n=19	-3x/wk -3 months	-30min -Self-determined intensity	Trend for improved PWV	Avg Energy expenditure: 73 kcal/session (throughout)

How do HD exercise Rx's compare to PA guidelines?

Traditional Exercise Programs for HD

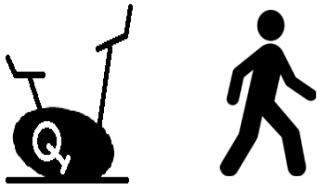


Intradialytic Exercise

Out-of-Clinic Exercise

Endurance Training

Intradialytic cycling or home walking
60 – 135 min/week
Low-mod intensity

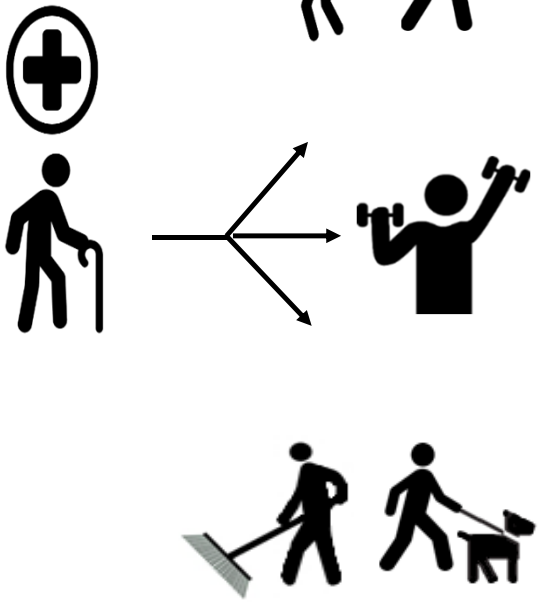


"OR"

Resistance Training
2 – 3 days/week
Low-mod intensity

Fang et al. 2019. Blood Purification

Exercise/PA Recs for Elderly/Chronic Disease



Endurance Training

> 150 min/week moderate aerobic exercise
OR
>75 min/week vigorous

"AND"

Resistance Training
≥2 days/week

"AND"

Lifestyle PA
Regular/recreational
Daily

A plan to move Forward:
The GREX "Move More" Initiative

- GREX: The Global Renal Exercise Network
  - Researchers, clinicians, and patient partners from > 25 countries

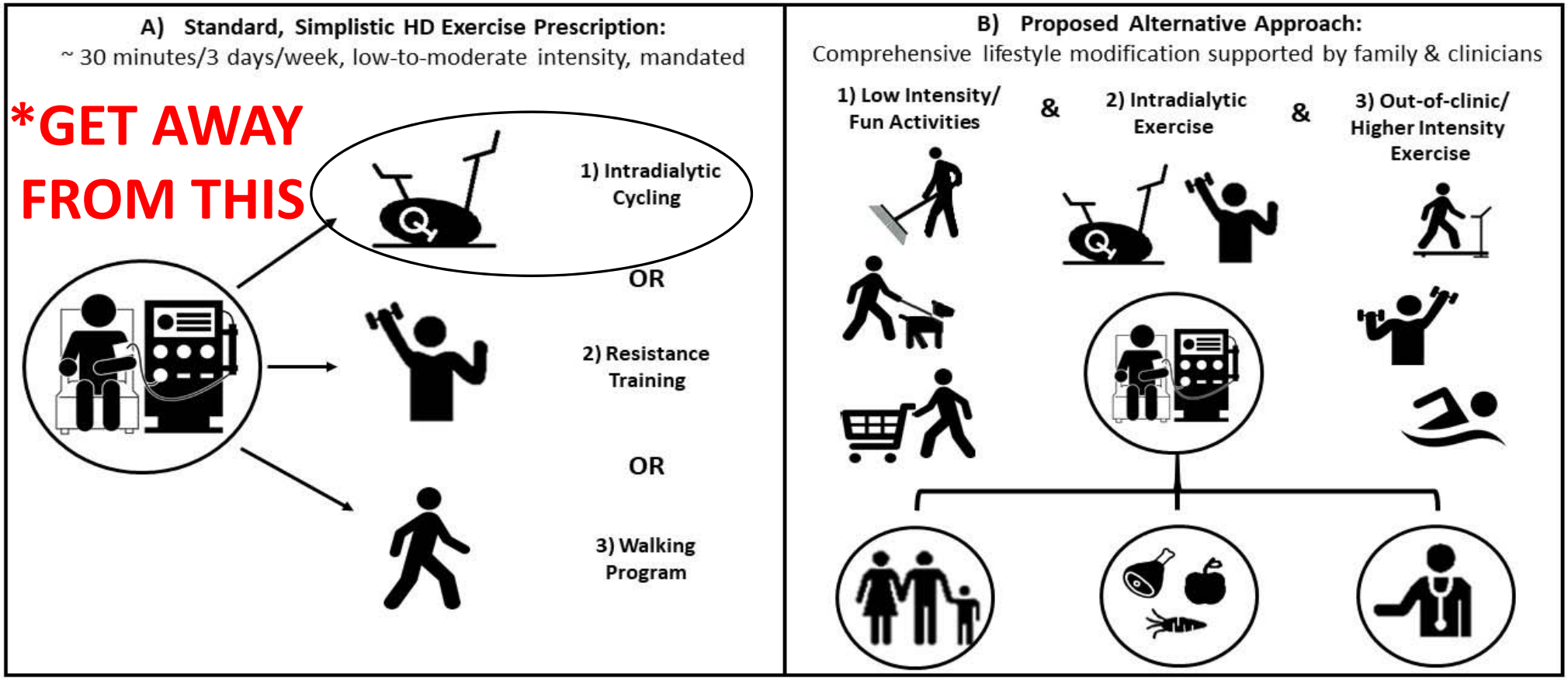
- Goals of the GREX "Move More" Initiative:
  - Rethink how we prescribe "exercise" in CKD: Focus on getting patients to MOVE MORE, by any means necessary
  - Must discuss barriers and goals, and give patients the autonomy to decide what activities to engage in
  - "Inundate clinics in a culture of physical activity/wellness"
  - Develop a certification program to train students for renal rehab

Template for a More Comprehensive (yet simple) Exercise Rx

Proposed by Ben Levine (UTSW) in lieu of traditional exercise Rx for healthy adults

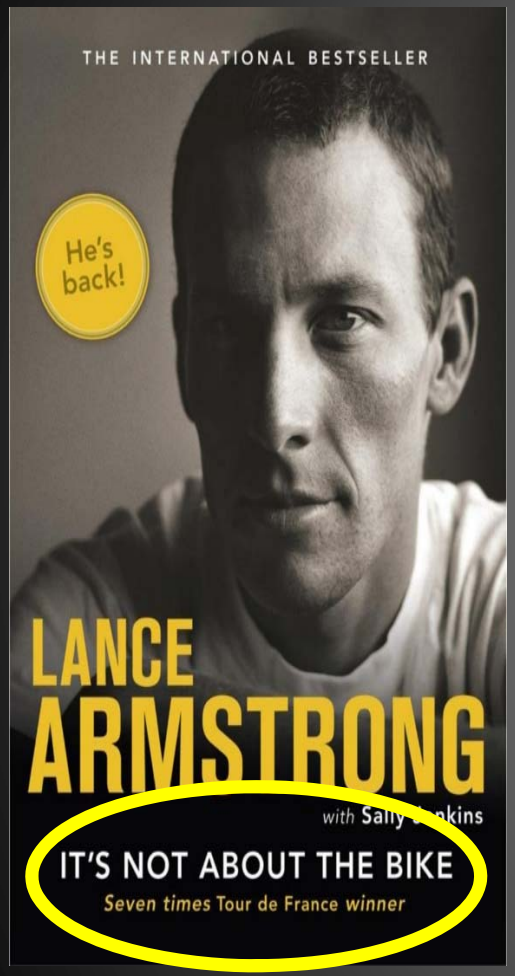
What should a modified Exercise Rx look like in HD?

Figure 1: Standard vs Novel Exercise/Physical Activity Prescription for HD patients



Wilund et al. 2019. Exercise and Sport Science Reviews

How do we get there?



- 1) Assess the patient. Do they need pre-habilitation?
  - Physical therapy, treatment for depression, nutrition management (anemia, volume control…)
- 2) Find out what the patients WANT to do, or are WILLING to do
  - *See* Tawney et al 2000. AJKD 36(3): 581-91.
  - Give PATIENTS the autonomy to choose activities
- 3) Inquire about how to get family/friends involved.
  - The SOCIAL aspects of exercise are CRITICALLY important
- 4) Need culture change at clinic
  - "Inundate clinics in culture of physical activity"
  - If Nephrologists mandate it… it can happen (e.g., Mexico City)

Summary/Take Home Message

- Exercise Rx has to be more than sticking a bike in front of patients. Until we change this, we will continue to see modest benefits, in small percentages of patients
- The key to getting patients to move more is addressing barriers.
  - Many will need "pre-habilitation"
- Exercise Rx should first focus on getting patients to simply **MOVE MORE**.
  - What are they WILLING/Able to do?
- Start by identifying lifestyle PA in which the patient prefers to engage
  - Progress to simple aerobic activities that include more walking, and then to activities that build strength.
- Patients progress should be evaluated, and goals adjusted, as progression is seen.
- NEPHROLOGISTS must mandate the culture change. And the clinic will follow…

Global Renal EXercise

QUESTIONS?

Renal and Cardiovascular Disease Research Laboratory
U of Illinois at Urbana-Champaign

Collaborators

- Bo Fernhall, PhD (UIC)
- Shane Phillips, PhD (UIC)
- Mohamed Ali, M.D. (UIC)
- Eddie McAuley, PhD (UIUC)

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