Exercise for Hemodialysis patients: Its NOT about the bike!

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Disclosure Information
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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!

**Summary** – Exercise in CKD improves muscle strength, physical function, QOL, etc.

- **Regardless of stage of disease** (non-dialysis CKD, dialysis, transplant)
- **Regardless of the mode of exercise** (Resistance, endurance, yoga, balance, flexibility)

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Systematic Reviews and/or Meta-analysis</th>
</tr>
</thead>
</table>

IF IT WORKS SO GREAT.... THEN WHY IS NOBODY DOING IT ????
The Skeptical View:

• It doesn’t always work as well as we want
  – It’s not a magic bullet

• IMO: Many have become cheerleaders for mundane exercise prescriptions that produce MODEST/MARGINAL Benefits....

• This is hurting our cause...
  – It’s made us (researchers/clinicians) lazy
  – And it’s stifling the development of more innovative approaches to exercise
<table>
<thead>
<tr>
<th>Reference</th>
<th>Exercise Mode</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Johansen 2006</td>
<td>Intradialytic RT</td>
<td>↑ quadriceps CSA, strength; -no Δ: phys fx, lean mass</td>
</tr>
<tr>
<td>JASN 17:2307-14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dong 2011</td>
<td>Peridialytic RT</td>
<td>no Δ: body comp/strength</td>
</tr>
<tr>
<td>JRN 21(2): 149-59</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kopple 2007</td>
<td>Intradialytic RT and ET</td>
<td>no Δ: body comp</td>
</tr>
<tr>
<td>JRN 16(4): 312-24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheema 2007</td>
<td>Intradialytic RT</td>
<td>Improved muscle “quality”; -no Δ: muscle mass; -mixed results: strength/phys fx</td>
</tr>
<tr>
<td>JASN 18(5): 1594-1601</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kirkman 2014</td>
<td>Intradialytic RT</td>
<td>↑ muscle volume/strength; - no Δ: phys fx</td>
</tr>
<tr>
<td>JCSM 5(3):199-207.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koh 2010</td>
<td>Intra and Interdialytic ET</td>
<td>no Δ: physical fx</td>
</tr>
<tr>
<td>Jeong 2019</td>
<td>Intradialytic ET</td>
<td>no Δ: physical fx/strength</td>
</tr>
<tr>
<td>KI Sep;96(3):777-786</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Data on CV-related outcomes with Ex Training also modest:

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

↓ Quality of Life, ↑ Mortality

LVH/CHF
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: 27 grams/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 it's 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%**

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<table>
<thead>
<tr>
<th>Screened</th>
<th>N=337</th>
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<tbody>
<tr>
<td>Enrolled &amp; Completed Baseline Testing</td>
<td>N=138</td>
</tr>
<tr>
<td><strong>Randomization</strong></td>
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<tr>
<td>Control</td>
<td>N=44</td>
</tr>
<tr>
<td>Completed 6-m testing</td>
<td>N=36</td>
</tr>
<tr>
<td>Completed 12-m testing</td>
<td>N=34</td>
</tr>
<tr>
<td><strong>Dropped from CON due to (n=10):</strong></td>
<td></td>
</tr>
<tr>
<td>- Transplant, n=3</td>
<td></td>
</tr>
<tr>
<td>- Death, n=2</td>
<td></td>
</tr>
<tr>
<td>- Moved, n=2</td>
<td></td>
</tr>
<tr>
<td>- GI issues, n=1</td>
<td></td>
</tr>
<tr>
<td>- Poor compliance,</td>
<td></td>
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<tr>
<td>Whey Protein</td>
<td>N=45</td>
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<td>Completed 6-m testing</td>
<td>N=45</td>
</tr>
<tr>
<td>Completed 12-m testing</td>
<td>N=38</td>
</tr>
<tr>
<td><strong>Dropped from Whey due to (n=7):</strong></td>
<td></td>
</tr>
<tr>
<td>- Transplant, n=1</td>
<td></td>
</tr>
<tr>
<td>- Death, n=4</td>
<td></td>
</tr>
<tr>
<td>Whey + Exercise</td>
<td>N=49</td>
</tr>
<tr>
<td>Completed 6-m testing</td>
<td>N=36</td>
</tr>
<tr>
<td>Completed 12-m testing</td>
<td>N=29</td>
</tr>
<tr>
<td><strong>Dropped from Whey + EX due to (n=20):</strong></td>
<td></td>
</tr>
<tr>
<td>- Poor compliance, n=3</td>
<td></td>
</tr>
<tr>
<td>- CV events, n=4</td>
<td></td>
</tr>
<tr>
<td>- Infection, n=1</td>
<td></td>
</tr>
<tr>
<td>- Opted out, n=4</td>
<td></td>
</tr>
<tr>
<td>- Death, n=1</td>
<td></td>
</tr>
<tr>
<td>- Chemotherapy, n=1</td>
<td></td>
</tr>
<tr>
<td>- Moved, n=2</td>
<td></td>
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<tr>
<td>- Protein intolerance, n=1</td>
<td></td>
</tr>
</tbody>
</table>
**Baseline Data: these are NOT the sickest patients in the clinic**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=34)</th>
<th>Whey (n=38)</th>
<th>Whey + EX (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BMI (m/kg²)</strong></td>
<td>31 ± 7.6</td>
<td>32.9 ± 8.1</td>
<td>32.9 ± 8.4</td>
<td>.654</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td>57 ± 12.4</td>
<td>56.2 ± 14.8</td>
<td>52.8 ± 10.2</td>
<td>.441</td>
</tr>
<tr>
<td><strong>Gender (% M)</strong></td>
<td>63.2</td>
<td>55.0</td>
<td>73.9</td>
<td>.429</td>
</tr>
<tr>
<td><strong>Diabetes (%)</strong></td>
<td>47.4</td>
<td>65.0</td>
<td>50.0</td>
<td>.481</td>
</tr>
<tr>
<td><strong>Vintage (months)</strong></td>
<td>48.0</td>
<td>38.0</td>
<td>33.8</td>
<td>.379</td>
</tr>
<tr>
<td><strong>Albumin (g/dL)</strong></td>
<td>4.04 ± 0.33</td>
<td>4.02 ± 0.30</td>
<td>4.04 ± 0.35</td>
<td>.979</td>
</tr>
<tr>
<td><strong>SBP (mm/Hg)</strong></td>
<td>139 ± 25.8</td>
<td>142 ± 12.6</td>
<td>131.1 ± 20.6</td>
<td>.196</td>
</tr>
<tr>
<td><strong>DBP (mm/Hg)</strong></td>
<td>79 ± 13.6</td>
<td>75.6 ± 12.3</td>
<td>77.9 ± 11.4</td>
<td>.702</td>
</tr>
</tbody>
</table>
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 (Aᵢ)

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 \textit{systolic} function, though trend for improved \textit{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 Shad Ireland:
  
  - Age 11 – kidney failure, starts dialysis
  
  - Age 20 – 2 failed transplants, weighed 75 pounds…, became captivated 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?

4 Primary steps:

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

Traditional Exercise Programs for HD

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

“OR”

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

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

Fang et al. 2019. Blood Purification
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

Exercise Prescription for Life
4-5 days a week of some physical activity
Dr. Benjamin Levine
(these can be done in any order)

1 Day
1 hour - something fun!

1 Day
4 mins high intensity
3 mins recovery
repeat 4x

2 - 3 Days
30 minute moderate intensity

Plus
Any day - 30 minute strength training

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

| A) Standard, Simplistic HD Exercise Prescription: |
| ~ 30 minutes/3 days/week, low-to-moderate intensity, mandated |

*GET AWAY FROM THIS*

A) Intradialytic Cycling
   - OR
   - 2) Resistance Training
   - OR
   - 3) Walking Program

B) Proposed Alternative Approach:
   - Comprehensive lifestyle modification supported by family & clinicians
   - 1) Low Intensity/Fun Activities & 2) Intradialytic Exercise & 3) Out-of-clinic/Higher Intensity Exercise

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
  – 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...
QUESTIONS?

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• Mohamed Ali, M.D. (UIC)
• Eddie McAuley, PhD (UIUC)

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