The role of exercise in the management of CKD

Drs. Clara Bohm & Stephanie Thompson

April 5, 2022

University of Manitoba

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Objectives

1. Review recent literature on the therapeutic role of exercise in CKD and ESKD

2. Understand common barriers to implementing CKD exercise programs and potential approaches to address them

3. Discuss the role of the health care team in supporting a successful exercise program

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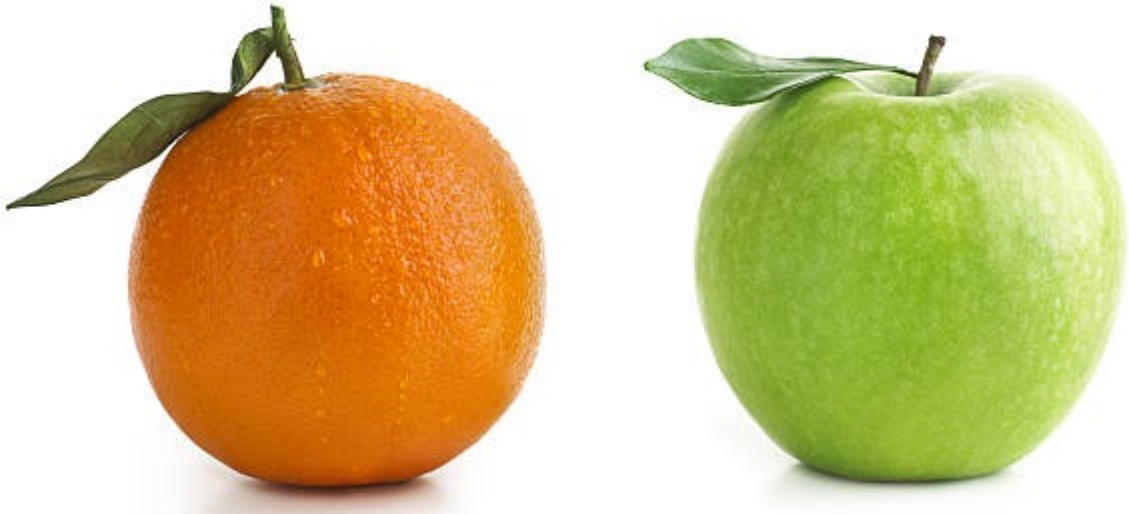
Disclosures

- Dr. Stephanie Thompson
  - None

- Dr. Clara Bohm
  - Received research funding from Hope Pharmaceuticals
  - Ownership interest in Precision Advanced Digital Manufacturing, Inc
  - I am an avid exerciser

Exercise in clinical care: healthy hobby or medical therapy?



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REHAB in other chronic diseases as routine care – WHY THEM?

Cardiac Rehab

<u>63 RCTs; N=14,486</u>

↓ CV death: RR: 0.74 (95% CI: 0.64 to 0.86)

↓ admissions: RR 0.82 (95% CI 0.70 to 0.96)

↑ HRQoL

Low-moderate quality evidence

Anderson et. al. *J. Am. Coll. Cardiol.* 2016

Pulmonary Rehab

↓ Readmission: OR: 0.44 (95% CI: 0.21 to 0.91)

No effect on mortality

<u>65 RCTs; N=3,822</u>

↓ Dyspnea: MD 0.79 (95% CI 0.56 to 1.03)

↑ HRQoL (fatigue, emotional function, mastery)

Mod-high quality evidence

Puhan et. al. *Cochrane reviews.* 2016

McCarthy et al. *Cochrane reviews 2015*

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Exercise programs for CKD are uncommon

Pulmonary rehab

- N=155 facilities with PR in 2015
- 60% are in a hospital setting

Renal Rehab

- Supervised outpatient exercise
- N=7

Camp et al. *Can Respir J*. 2015

Rationale for prescribing exercise in CKD

- Low exercise tolerance is common
  - inversely related to eGFR
  - apparent ~stage 3 CKD
- Low exercise tolerance is both a cause and a consequence of CKD
- The role of exercise in CKD and ESKD management has been identified as a top research priority by patients
- Evidence in general population (CV outcomes, physical fitness, symptoms)

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Manns B et al. Clin J Am Soc Nephrol. 2014.
Hemmelgarn et al. Nephrol. Dial Transplant. 2017

Objective 1:
Evidence of efficacy of exercise training in ESKD

Cochrane Library

Cochrane Database of Systematic Reviews

Exercise training for adults undergoing maintenance dialysis (Review)

Bernier-Jean A, Beruni NA, Bondonno NP, Williams G, Teixeira-Pinto A, Craig JC, Wong G

Cochrane Review 2022

- Adults, maintenance dialysis (HD/PD)
- Structured program of ANY exercise
  - 8 weeks or longer
  - targeting more than a single muscle group
- Comparison = no exercise,"sham," or a co-intervention given to the control
- Patient important outcomes per SONG-HD
  - Death, CV events, fatigue

- 89 RCTS; N=4,291
- N=3,846 included in metanalyses
- 7 studies included PD patients (N=151)
- Exercise intervention primarily aerobic
  - 3 x/wk during HD for 20-40 min
  - moderate perceived exertion
- Intervention duration = 8wks-2 yrs

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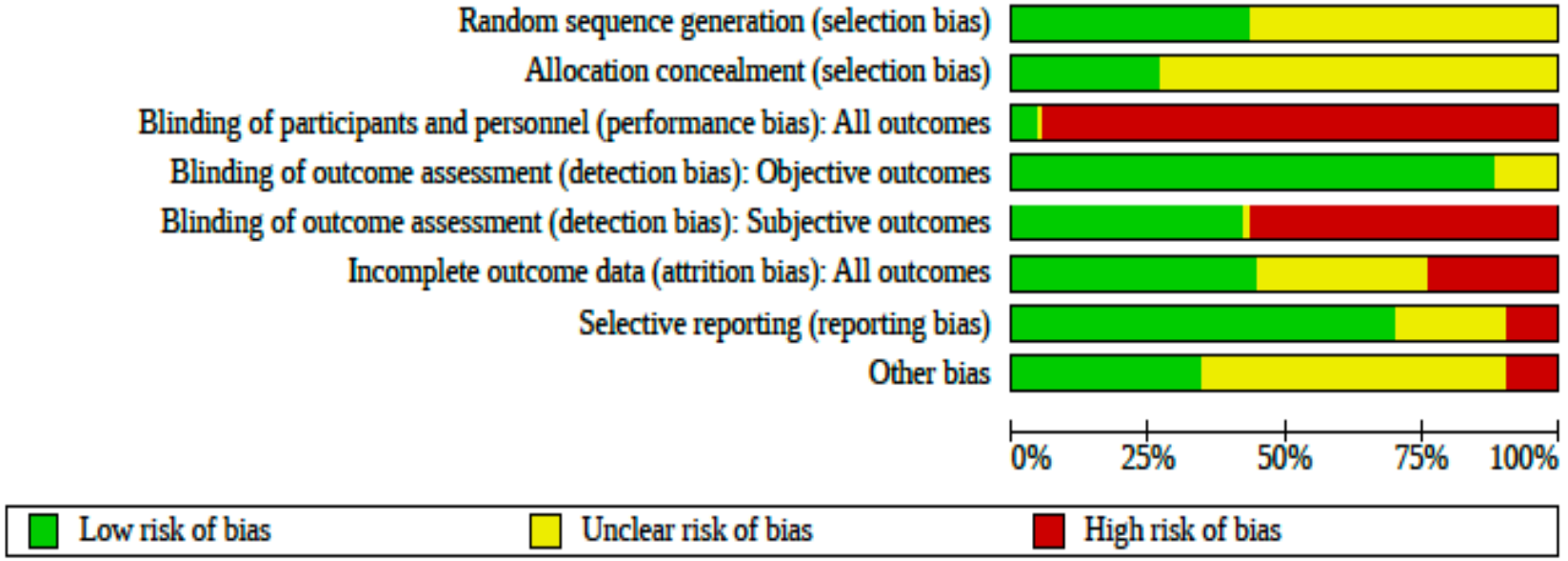
Any exercise versus no exercise or placebo for adults undergoing maintenance dialysis

Outcome	Absolute effect (95% CI)	Number of participants (studies)	Certainty of the evidence	Comment
HRQoL: Physical component Score (PCS) of SF-36; Scale: 0 to 100 Follow up: range 2 to 12 months	Mean PCS was 4.1 points higher with exercise (1.9 to 6.4 higher)	656 (17)	LOW	Any exercise may improve the physical component score of HRQoL
***Fatigue** Follow up: range 2 to 12 months	Unable to pool	326 (6)	LOW	Based on the direction of the effect, any exercise may reduce fatigue
Depression Follow up: range 2 to 12 months	SMD for depression was 0.62 SD lower with exercise (1.00 to 0.24 lower)	490 (11)	MODERATE	Any exercise probably improves depression. Greater effect + 4 months of exercise training (SMD -1.26, 95% CI -1.80 to -0.72)
Functional capacity Assessed: 6MWT Follow up: range 2 to 6 months	Mean 6MWT was 49.9 metres further with Exercise (37.2 to 62.6)	827 (19)	MODERATE	Any exercise probably improves functional capacity
Pain Assessed: SF-36 Scale: 0 to 100 Follow up: range 3 to 12 months	The mean pain score was 5.3 points higher with exercise (0.1 lower to 10.7 higher)	872 (15)	LOW	Any exercise may reduce pain but the effect estimate is imprecise
***Death** Follow up: 3 years	RR 0.95 (0.56 to 1.62)	296 (1)	VERY LOW	From a 6 month walking intervention High lost to follow up
***Cardiovascular events**			No studies	

Study quality was down graded due to short duration of interventions and follow up



Adverse events

- Poorly reported, only 15% of studies included AEs as outcomes
- No deaths
- Shortness of breath, MSK injury, soreness

Bernier-Jean A et al Cochrane Library, 2022

Symptoms in Individuals on Dialysis

- Symptoms are common
  - 30-80% of individuals on dialysis have at least one symptom
- Symptom burden is high
  - Number of symptoms endorsed per individual = **6-20**
- Most frequent symptoms
  - Fatigue (~80%)
  - Poor sleep, pain, muscle cramping, itch, decreased appetite, drowsiness and dry skin (>50%)
  - Restless legs syndrome, difficulty concentrating, anxiety and depression (>30%)

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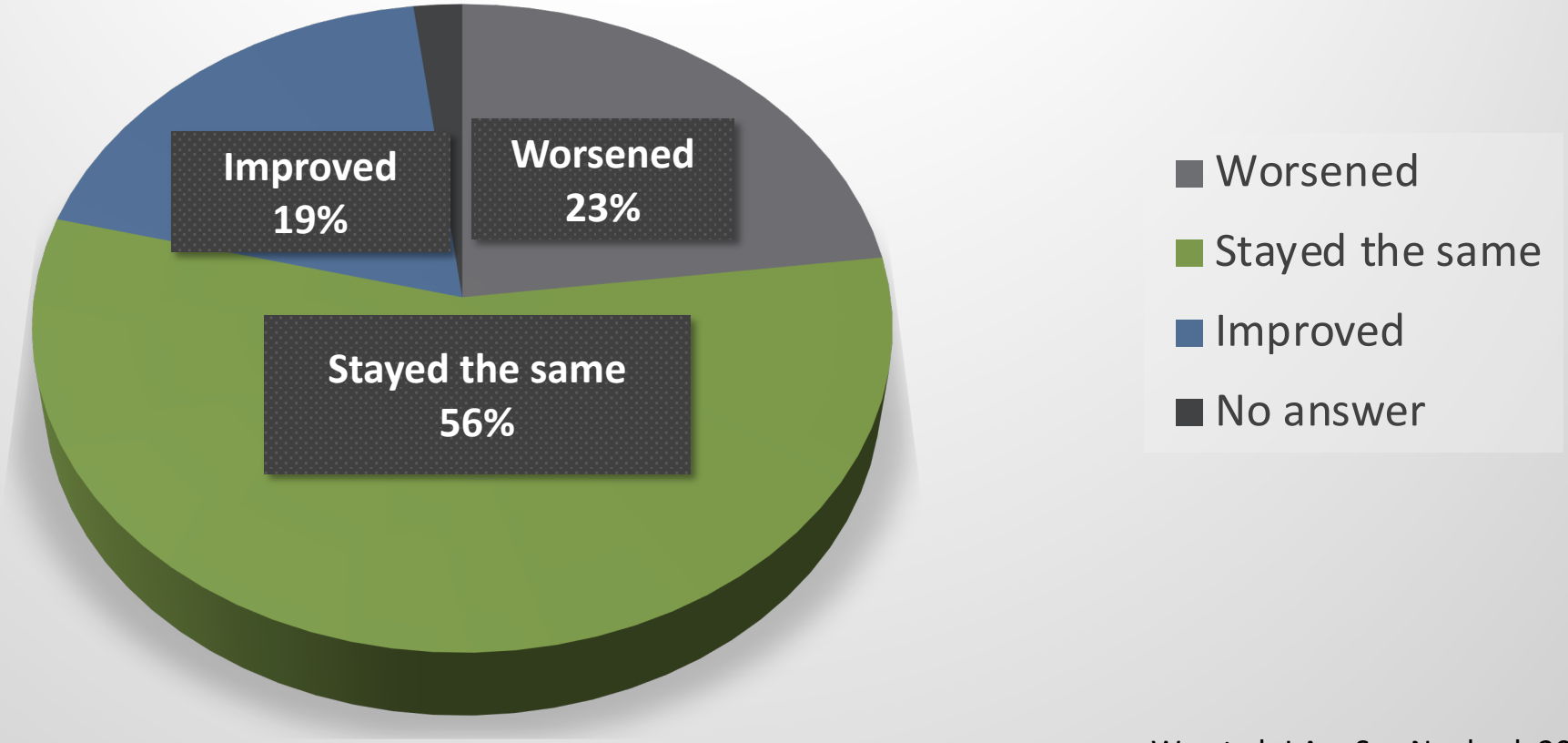
Almutary H et al. J Renal Care. 2013;39:140-50
Weisbord SD et al. JASN, 2005; 16:2487-94)

Change in Symptom Burden with Hemodialysis

N = 698



Wu et al. J Am Soc Nephrol, 2004

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Symptoms: Under Recognized and Poorly Treated

- Providers
  - Underreported 97% of symptoms
  - Underestimated symptom severity in 63%

- Symptoms are poorly treated
  - Few effective treatments exist
  - Hesitation to take more pills
    - High pill burden
    - Side effects of medication
    - Attribution of symptoms to acute events

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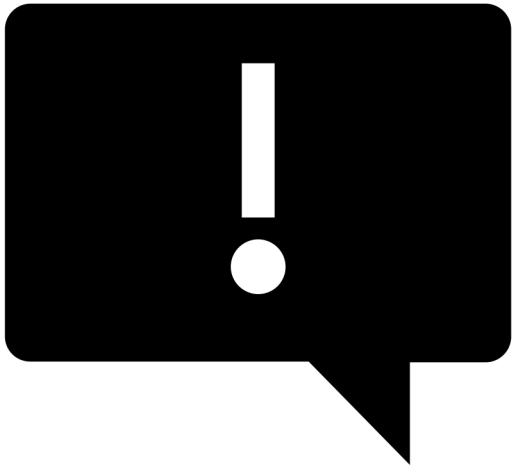
Weisbord SD et al. Clin J Am Soc Nephrol 2007;2:960-7
Davison S et al. Kidney Int 2015;88:447-59
Chiu YW et al. Clin J Am Soc Nephrol 2009;4:1089-96
Pena-Polanco JE et al. Clin J Am Soc Nephrol 2017

Symptom Rx: Priority for Individuals Receiving Dialysis

- Improvement of symptom burden identified as key research priority in Canada
- Key outcomes for future studies in international prioritizing exercises:
  - Fatigue/energy
  - Sleep
  - Anxiety/stress, depression, frustration
  - Cramping
  - Decreased appetite



Manns B et al. Clin J Am Soc Nephrol 2014;9:1813-21
Urquhart-Secord R et al. Am J Kidney Dis 2016;68:444-54
Evangelides N et al. Am J Kidney Dis 2017
Flythe J et al. Clin J Am Soc Nephrol 2018;13: 735–745

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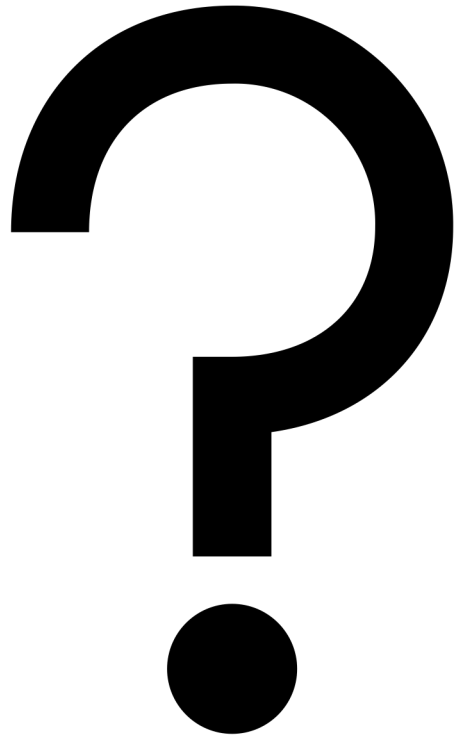
Why Exercise for Symptoms?



- Evidence in general population
  - Anxiety, depressive symptoms, sleep
- Non-pharmacologic
  - better acceptance
- Opportunity for exercise during HD
  - “Lap time”; supervision
- Physiologic Plausibility/Potential Treatment
  - Restless legs, cramping, sleep, anxiety

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Systematic Review & Meta-Analysis: Effect of Aerobic Exercise on Symptoms in Hemodialysis

P: Adults on maintenance hemodialysis

I: Aerobic exercise for > 8 weeks at least twice weekly for at least 20 min/session

C: Usual care; no or sham exercise

O: Change in any dialysis-related symptom

- Restless legs syndrome, muscle cramps, pruritis, pain
- Depressive symptoms, anxiety, sleep disturbance, fatigue
- Nausea, vomiting, decreased appetite

S: Randomized controlled trials

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Hargrove N et al. Clin J Am Soc Nephrol 2021; 16(4) 560-574

Effect of aerobic exercise on hemodialysis-related symptoms in adults undergoing maintenance hemodialysis

CJASN
Clinical Journal of the American Society of Nephrology

Systematic review and meta-analysis

MEDLINE
PubMed
Cochrane
CENTRAL
CINAHL
PsycINFO
SPORTDiscus
EMBASE
PEDro
Scopus

1960 or inception until 15 April 2020

3048 studies screened

15 RCTs assessed the effects of aerobic exercise on 1 or more HD symptoms

2 studies
Restless Legs Syndrome (RLS)

9 studies
Depression

4 studies
Sleep disturbance

1 study
Muscle cramping

4 studies
Anxiety

1 study
Fatigue

Aerobic exercise demonstrated improvement in symptoms of RLS, muscle cramping, and fatigue as compared to non-exercise controls

Meta-analysis

-7.57
(95%CI -8.25, -6.89)

Greater reduction in Beck Depression Inventory (BDI) score with exercise as compared to controls

Conclusion in adults on maintenance hemodialysis, aerobic exercise appears to improve several HD-related symptoms, including RLS, symptoms of depression, muscle cramping, and fatigue.

Nicholas Hargrove, Nada El Tobgy, Olivia Zhou, et al. ***Effect of Aerobic Exercise on Dialysis-Related Symptoms in Individuals on Maintenance Hemodialysis***. CJASN doi: 10.2215/CJN.15080920. **Visual Abstract by Edgar Lerma, MD, FASN**

Unclear to High Risk of Bias

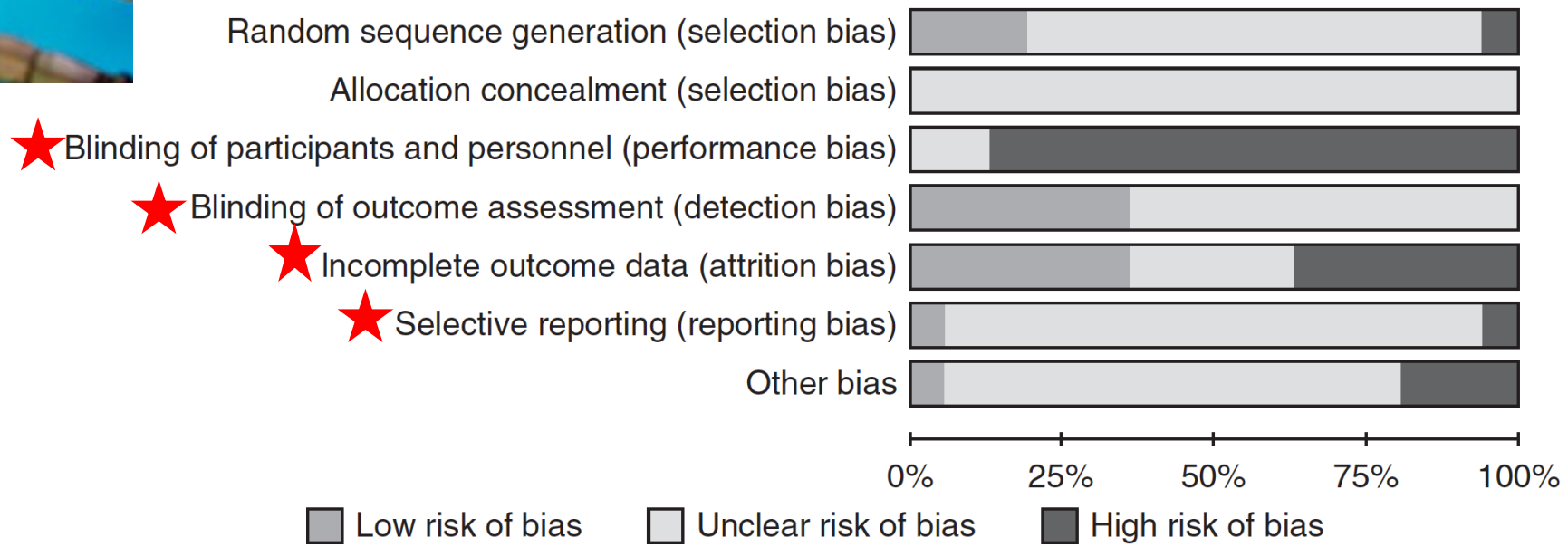

Figure 4. | Risk of bias summary for individual studies.

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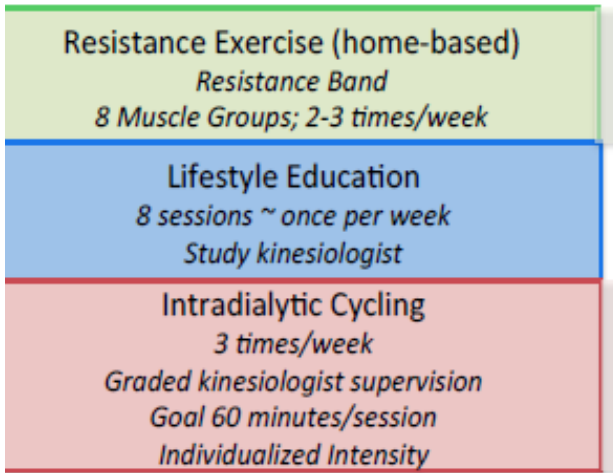
Hargrove N et al. Clin J Am Soc Nephrol 2021; 16(4) 560-574

“Renal Rehab” Study

- Single Centre RCT
- Effect of exercise rehabilitation on symptom burden in hemodialysis
- Population: Adults on maintenance HD
- Intervention: 6-month supervised exercise rehabilitation program
- Primary Outcome: Dialysis Symptom Index (DSI) symptom burden score
  - Modified DSI (11 symptoms most likely to improve)
  - Endurance (Shuttle walk), Frailty (Fried), HRQOL (EQ5D-5L)
- N = 150
- Delays in recruiting due to COVID
- Last patient enrolled 1 month ago – completed 2023



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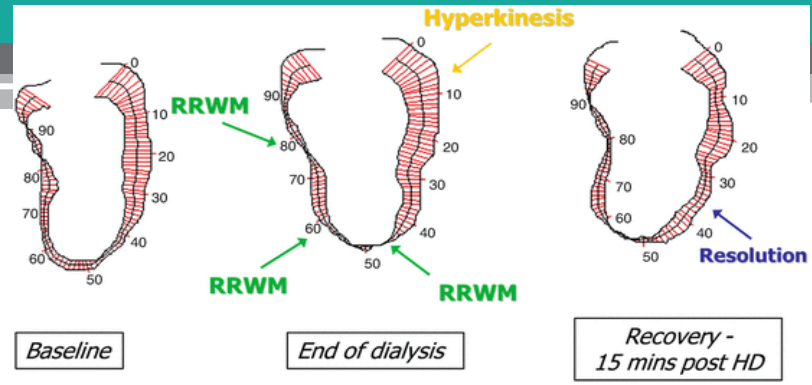
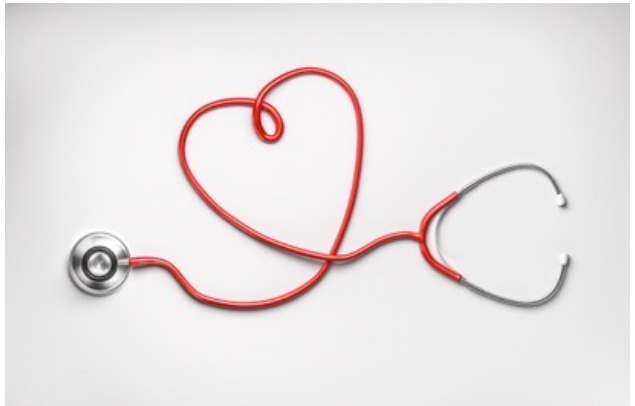
Myocardial Stunning and Symptoms



- Reduced myocardial blood flow → cardiac regional wall motion abnormalities
  = Myocardial Stunning
- Recurrent stunning occurs in 2/3 of in-centre HD patients
- Associated with chronic cardiac injury and adverse events



- Reduced perfusion of vital organs leads to worsening HD-related symptoms
  - Nausea and vomiting, cramping, fatigue, “fogginess”
  - ↑ RWMA at the end HD associated with ~2-fold risk of severe post-HD fatigue

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McGuire S et al. Clin Kidney J. 2019; Burton JO et al Clin J Am Soc Nephrol. 2009; McIntyre CW et al. Clin J Am Soc Nephrol. 2008; Dubin R et al. Nephrol Dial Transplant. 2013; Eldehni et al. Semin Dial. 2012; Jakob SM et al. Crit Care Med. 2001

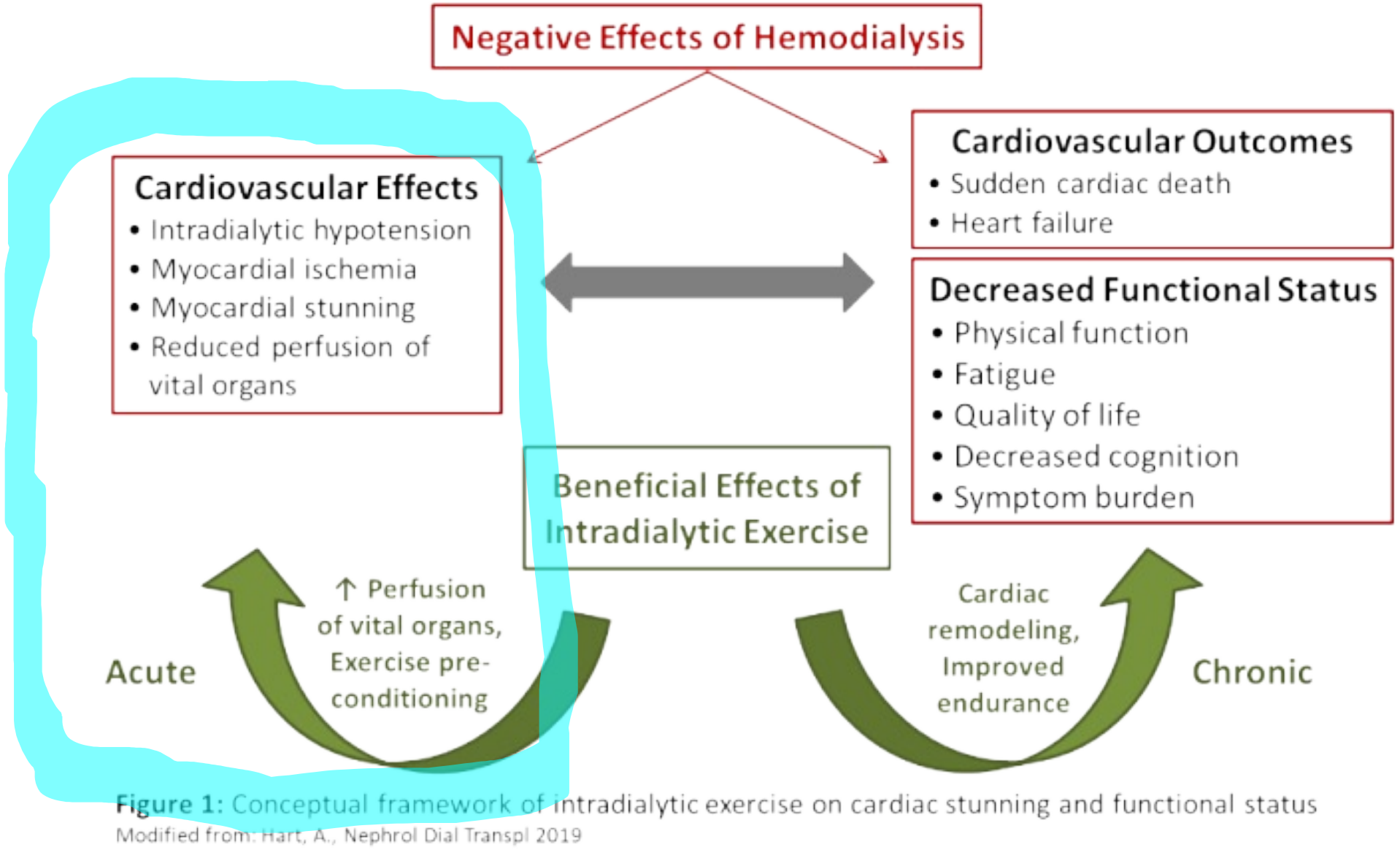

Figure 1: Conceptual framework of intradialytic exercise on cardiac stunning and functional status
Modified from: Hart, A., Nephrol Dial Transpl 2019

Modified from: Hart A, Johansen KL. Nephrol Dial Transplant. 2019;34(11):1816-1818

Less Stunning with Intradialytic Exercise then with HD alone

- Cross-sectional study
- People enrolled in clinical intradialytic cycling program
- 1 control; 1 exposure (exercise) visit in same week
- Stunning measured using echocardiograms
- N = 19

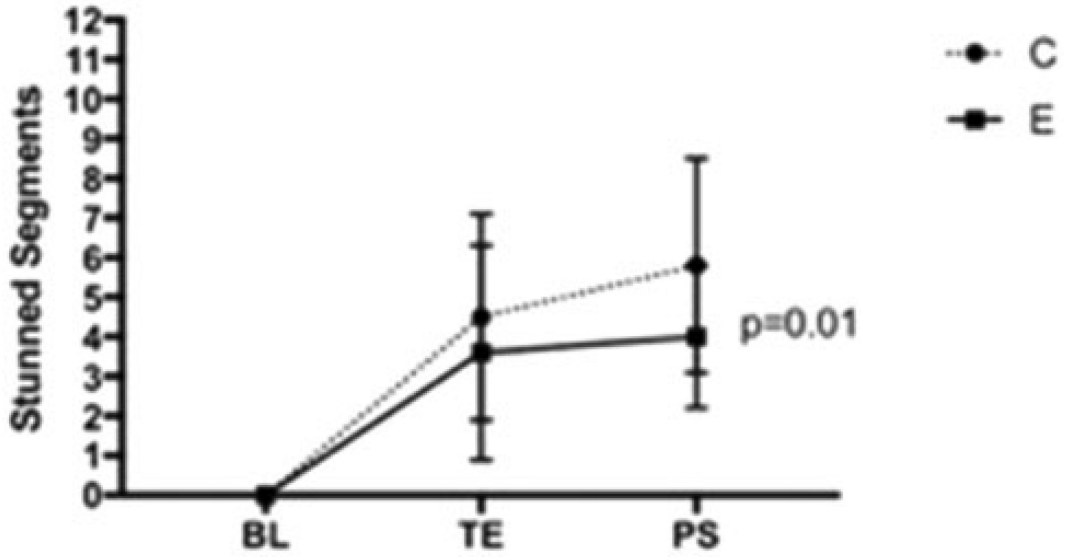

FIGURE 2: Number of stunned segments at each echocardiogram time point in control and exposure visits.

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Penny et al. Nephrol Dial Transplant 2019

Evolution of exercise trials in CKD: intradialytic exercise and myocardial stunning

Trial of **I**ntradialytic **C**ycling **K**idney **E**xercise **R**ehabilitation for Cardiac **S**tunning in **H**emo**d**ialysis (**TICKERS_HD**)

Does intradialytic aerobic exercise improve HD-induced ***myocardial stunning*** *compared to usual care?*

Design: RCT (7 sites) with 1-to-1 parallel design Winnipeg, Halifax, London, Calgary, Edmonton, Champaign IL, Adelaide Australia

Study Population: Adults, chronic in-centre HD for > 3 months; no intradialytic exercise in last 6 months; N=160

Intervention: Standard care plus 12 weeks cycling during HD

Secondary outcomes: high sensitivity TnT, fatigue, symptoms, feasibility

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CIHR IRSC

A randomized controlled trial to investigate the effects of intra-dialytic cycling on left ventricular mass.

CYCLE-HD

Study Design & Participants

130 prevalent hemodialysis patients
Age = 57.2 years

Prospective, cluster-randomized, open-label, blinded endpoint study

3 hemodialysis units = total of 6 clusters for randomization

Intervention

Standard care + intradialytic cycling (n=65)
6-months

Standard care (n=65)
6-months

Primary outcome: Change in LV mass from baseline between groups measured using cardiac MRI

Results

Intradialytic cycling led to a reduction in left ventricular mass (-11.1g; p<0.0001)

Intradialytic cycling also led to improvements in both T1 mapping and pulse wave velocity (p<0.001 for both)

Participants completed 71.7% of exercise sessions and maintained exercise intensity

51 SAEs reported during the study, none were assessed as related to the intervention

CONCLUSION:

A 6-month program of intradialytic cycling significantly improves LV mass; it is safe, deliverable and well tolerated.

kidney INTERNATIONAL ISN

Graham-Brown et al, 2020

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Role of exercise in the management of *non-dialysis* CKD?

- Improvements in physical function, walking capacity, fitness, several domains of QoL with exercise training

- Similar issues re: study quality

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Role of exercise in outcomes relevant to CKD - Blood pressure?

Systematic review	Exercise versus control (SBP mmHg) 95%CI
Thompson 2019	-4.33 (-9.04, 0.38)
Zhang 2019	-5.61 (-8.99, -2.23)
Van den Wyngaert 2018	1.22 (-4.45, 6.90)
Yamamoto 2021	-0.75 (-1.24, -0.26)
Villanego 2020	-1.68 (-6.80, 3.44)

Role of exercise in outcomes relevant to CKD – CKD Progression

- ~ 6 systematic reviews with conflicting findings
- Short duration, inappropriate statistical analyses, non-measurement of true renal function
- However, no harm to GFR

Could it work?

- Anti-inflammatory effect of myokines (IL-6)
- Decreased sympathetic nervous activity
- Reduced oxidative stress

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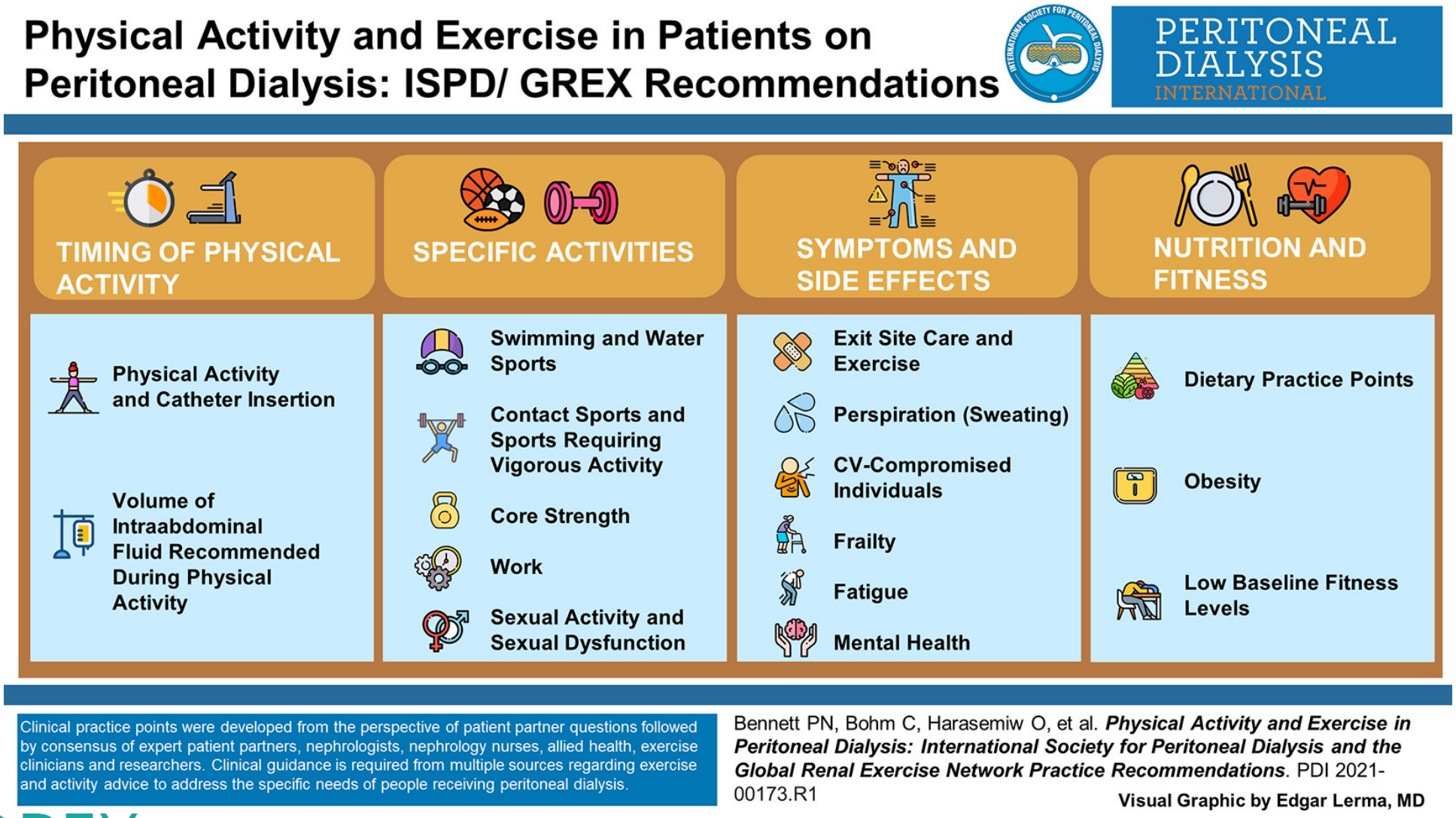
Viana et al. J Am Soc Nephrol. 2014
Gleeson et al. Nat Rev Immunol. 2011

What about Peritoneal Dialysis?



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Graphical Abstract This is a visual representation of the abstract.

Summary slide key points

- Exercise training improves physical function and fitness
- Good rationale and supporting evidence for symptoms in HD
- Restless legs and depressive symptoms ”good” evidence
  - Aerobic exercise more evidence than resistance
  - Longer programs may be better
- Cardiovascular benefits to exercise
  - Clinically important benefits still uncertain but to come
- Shift in CKD exercise literature to address *relevant outcomes*
- Important gaps remain for PD, CKD

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So then let’s get moving then…..

Objective 2:
Common barriers to exercise in CKD and potential approaches to address them

Barriers to exercise for people with CKD: the need to change policy

ORIGINAL RESEARCH

Global Policy Barriers and Enablers to Exercise and Physical Activity in Kidney Care

Barriers and examples of enablers

- Funding→ mandate physical activity metrics in renal care
- Service provision → include clinical algorithms for non-exercise professionals
- Regulations and legislation →process of accreditation
- Guidelines and research →multicenter collaborations
- Environmental & social → promote exercise in the clinics
- Communication & marketing →collaboration with nephrology associations, industry

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Bennett et al. Journal of Renal Nutrition. 2021

We know many of the barriers to IDE at the person level…

Patients

FearofInjury
NoSupport
Cost
FATIGUE
NoTime
Transportation
How?What
NeedExerciseCompanion
Weakness
ShortnessofBreath

Physicians and unit staff

NOTIME
TooBusy
FearofInjury
KeepTheRoutine
How?What
NoExpertise
SedentaryCulture
LowPriority
PatientsNotInterested

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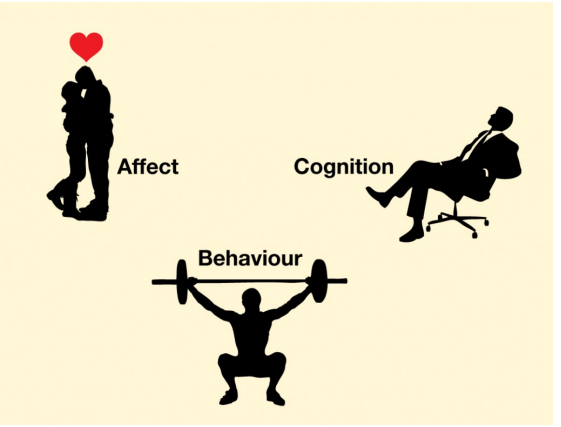
Thompson et al. CJASN. 2016
Jhamb et al. BMC Nephrol. 2016
Castillo et al. Nephrol Dial Tranplant. 2022
Heiwe et al. Implement Sci. 2012
Delgado et al. Nephrol Dial Transplant. 2012

Implementation Science - Using a systematic approach to address barriers to intradialytic exercise program delivery

- Qualitative study
  - Interviews with HD healthcare providers and patients (N=43)
  - 12 unique HD sites



- Theory driven approach
  - Identified barriers and enablers according to factors known to influence behaviour change (Theoretical Domains Framework - TDF)
  - Mapped factors to behaviour change techniques to develop strategies to support intradialytic exercise program delivery

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Castillo G et al. Nephrol Dial Transplant 2022 37:558-574

Table 1. Description of theoretical domains included in the TDF version 1 [37, 38]

Domain	Description
Knowledge	An awareness of the existence of something (including knowledge of condition/scientific rationale)
Skills	An ability or proficiency acquired through practice
Social/professional role and identity	A coherent set of behaviors and displayed personal qualities of an individual in a social or work setting
Beliefs about capabilities	Acceptance of the truth, reality or validity about an ability, talent or facility that a person can put to constructive use
Beliefs about consequences	Acceptances of the truth, reality or validity about outcomes of a behavior in a given situation
Motivation and goals	Mental representations of outcomes or end states that an individual wants to achieve
Memory, attention and decision processes	The ability to retain information, focus selectively on aspects of the environment and choose between two or more alternatives
Environmental context and resources	Any circumstance of a person's situation or environment that discourages or encourages the development of skills and abilities, independence, social competence and adaptive behavior
Social influences	Those interpersonal processes that can cause individuals to change their thoughts, feelings or behaviors
Emotion	A complex reaction pattern involving experiential, behavioral and physiological elements by which the individual attempts to deal with a personally significant matter or event
Behavioral regulation	Anything aimed at managing or changing objectively observed or measured actions
Nature of behavior	Direct experience/past behavior including routine, automatic or habitual behavior

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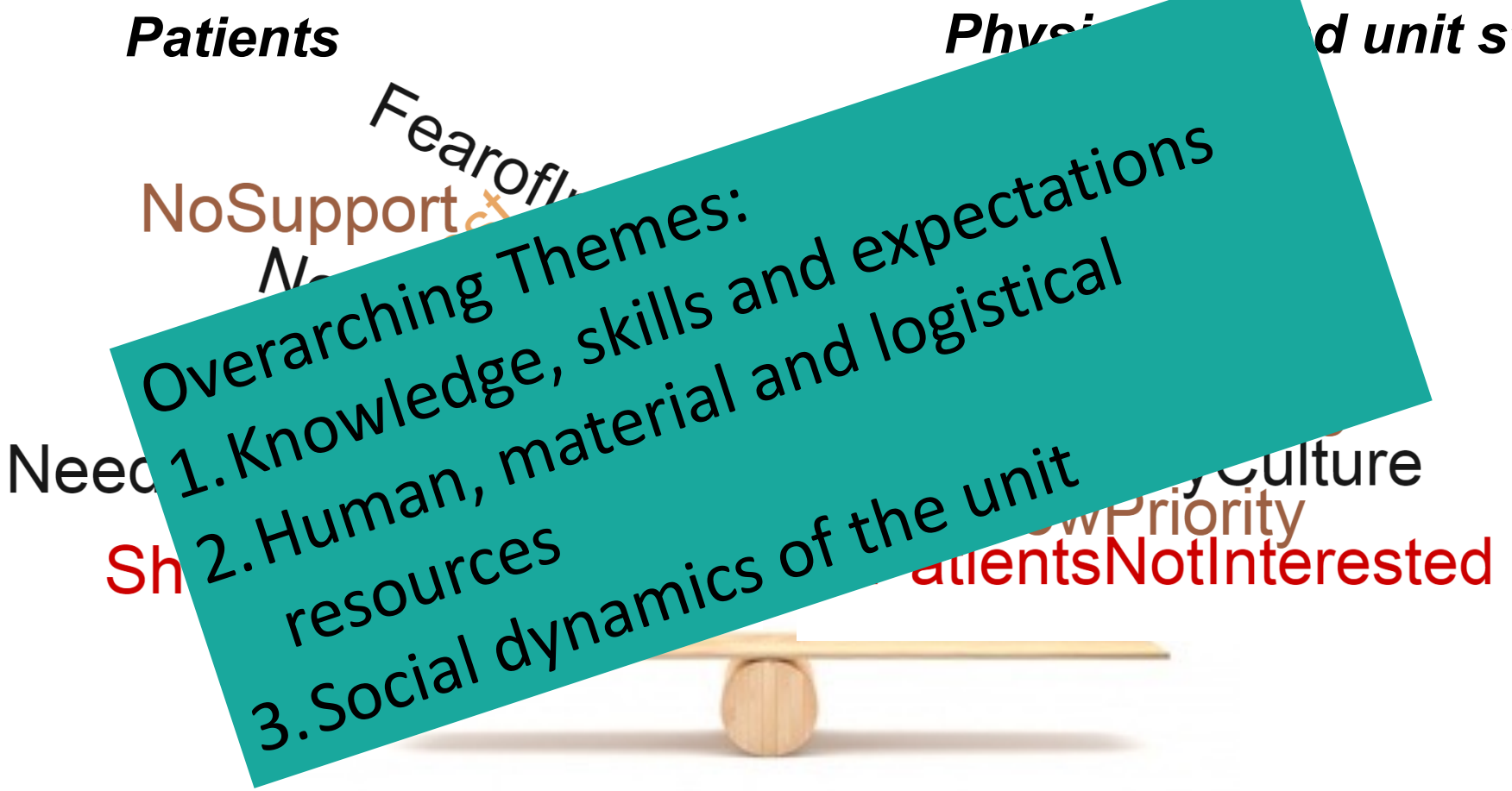
Implementation Science - Using a systematic approach to address barriers to intradialytic exercise program delivery



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Castillo G et al. Nephrol Dial Transplant 2022 37:558-574

Systematic approach to addressing barriers

- Feasibility assessment tool
  - Checklist of feasibility factors units advised to consider before launching IDE program

- Concrete solutions to barriers to program delivery unit specific strategies to support program delivery
  - Barriers/Enablers – *Uncertainty about risks and benefits of exercise*
  - TDF Domain – *Knowledge/Beliefs about consequences*
  - Suggested behaviour change technique – *Provide information about health consequences*
  - Suggested operationalization– *Provide patients and staff with access to information re: risks & benefits*

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Castillo G et al. Nephrol Dial Transplant 2022 37:558-574

Objective 3:
Role of health care team in supporting a successful CKD exercise program

What is the role of the healthcare team in a CKD exercise program?

- Most kidney care providers are not exercise specialists

- Role is primarily supportive or

  "*not to get in the way*"

WHAT DOES *THAT* MEAN?

1. Reframe advice to emphasize what can be done
2. Recognize where exercise has a therapeutic role
3. Advocate for exercise resources

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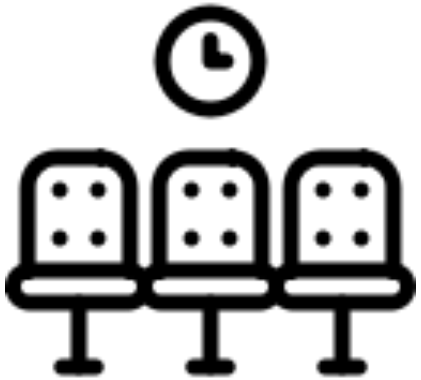
Let’s talk about implementation outside of the unit..



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Moorman et al. CJASN. 2019

Building capacity in exercise science through collaboration

MISSON: To foster **collaborative** research and **innovation** across **multiple disciplines** to develop effective and feasible strategies to increase physical activity and exercise participation in order to **optimize health outcomes** in people with kidney disease

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Extra Slides

Box 1. Feasibility tool for introducing IDE into a given unit

Knowledge, skills and expertise
What training can be provided to existing unit staff?

- Are the unit leadership aware of current evidence for IDE?
- How will risks and benefits of IDE be communicated to staff and patients?
- Do staff have the capacity to undertake skills training?
- Do staff have the capacity to employ learned skills?
- What kind of support can be provided at the bedside?
- What guidance will be provided to aid staff in identifying patients?
- Will rationales for inclusion/exclusion criteria be provided?
- What experience do staff have with exercise equipment and IDE interventions?
- Will staff be trained to conduct assessments and how to make adjustments to exercise plans?

What expertise do unit staff have access to?

- Will the unit have access to an exercise professional?
- Will an exercise professional be available to set up the intervention?
- Will an exercise professional deliver the intervention?
- Who will deliver the intervention beyond the trial?
- Will staff support the IDE intervention if the unit has access to an exercise professional?

Human, material and logistical resources
What kind of unit (academic, community and satellite) is being considered for an IDE intervention?

- Do they have a history of previous IDE programs?
- How often are nephrologists present in the unit?
- What is the inpatient:outpatient ratio?
- What is the nursing staff:patient ratio?
- What does a typical nurse assignment involve?

What staff are available to contribute to an IDE program?

- Is now a good time? How saturated is the unit with other ongoing practice changes?
- How much time do staff feel they have to devote to another practice change?
- How do staff characterize their workload?
- What is the current division of labor and how do staff feel about it?
- Are there dialysis aides, personal support workers, exercise professionals, students or volunteers available?

What equipment is present in the unit?

- What equipment, if any, is available (e.g. what bike models)?
- What are staff and patient perceptions of existing exercise equipment? Does equipment need to be replaced or supplemented?
- Will the chosen equipment interfere/conflict with dialysis setup (e.g. will the bike model preclude the use of certain bed/chair models)?
- How are patients assigned to chairs/beds? How will this impact equipment set up?
- How will incompatible equipment be addressed?

How will the layout of the unit impact exercise set up?

- How far away are potential equipment storage areas?
- How much time is needed to retrieve equipment?
- Is there sufficient space for equipment to be moved around (e.g. bikes to be wheeled around in a cart)?

What staff are available to contribute to an IDE program?

- Is now a good time? How saturated is the unit with other ongoing practice changes?
- How much time do staff feel they have to devote to another practice change?
- How do staff characterize their workload?
- What is the current division of labor and how do staff feel about it?
- Are there dialysis aides, personal support workers, exercise professionals, students or volunteers available?

What equipment is present in the unit?

- What equipment, if any, is available (e.g. what bike models)?
- What are staff and patient perceptions of existing exercise equipment? Does equipment need to be replaced or supplemented?
- Will the chosen equipment interfere/conflict with dialysis setup (e.g. will the bike model preclude the use of certain bed/chair models)?
- How are patients assigned to chairs/beds? How will this impact equipment set up?
- How will incompatible equipment be addressed?

How will the layout of the unit impact exercise set up?

- How far away are potential equipment storage areas?
- How much time is needed to retrieve equipment?
- Is there sufficient space for equipment to be moved around (e.g. bikes to be wheeled around in a cart)?

When is the best time to set up exercise equipment?

- How are staff breaks organized?
- How much time is equipment set up expected to take?
- How can the time needed to set up equipment be integrated in

Social dynamics of the unit

What is the likelihood of engaging champions?

- Are there easily identifiable champions in the unit's leadership team? Among frontline staff? Among patients?
- Does the unit leadership have the capacity to support a new intervention?
- Do nephrologists support IDE? Are they willing to endorse and champion an IDE intervention?
- Will frontline staff champions be allocated time to complete champion-related tasks?
- What training do champions need to complete their champion duties?
- How socially engaged are champion contenders? How likeable are champion contenders?

What communication avenues are available for sharing patient stories and outcomes?

- What patient stories can be shared with unit staff and other patients?
- What opportunities are there for showcasing patients who exercise?
- What kind of intervention progress and outcome data can be shared with staff and patients?
- How can feedback mechanisms be integrated into the intervention?

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