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REVIEW

Review of Exercise Interventions to Improve Clinical Outcomes in Nondialysis CKD

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Exercise interventions in chronic kidney disease (CKD) have received growing interest, with over 30 meta-analyses published in the past 5 years. The potential benefits of exercise training in CKD range from slowing disease progression to improving comorbidities and quality of life. Nevertheless, there is a lack of large, randomized control trials in diverse populations, particularly regarding exercise in nondialysis-dependent CKD (NDD). When exercise interventions are implemented, they often lack fundamental features of exercise training such as progressive overload, personalization, and specificity. Furthermore, the physiology of exercise and CKD-specific barriers appear poorly understood. This review explores the potential benefits of exercise training in NDD, draws lessons from previous interventions and other fields, and provides several basic tools that may help improve interventions in research and practice.

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Structured exercise is a promising form of intervention in CKD (Figure 1)[1-12] and has been added to expert clinical care recommendations.[13] Research on the effects of exercise training in CKD has mainly focused on patients on dialysis, with at least 20 meta-analyses (Supplementary Table S1) and an umbrella review[14] published since 2018. Exercise training in patients with NDD, who differ in both clinical care and physiological status, has received relatively less attention. Nevertheless, there have been over a dozen recent meta-analyses on the effects of exercise training on various clinical outcomes in NDD (Table 1).[15-27]

Although systematic reviews represent the highest quality of research on the evidence pyramid, these analyses often report conflicting or null results, and much remains to be learned from well-designed interventional studies. This narrative review will discuss the results of recent meta-analyses, draw lessons from the literature, and direct the reader to other relevant manuscripts and resources. For a similar review in patients on dialysis, see the recent review by Thompson *et al.*[28] and for a quantitative review of exercise across all stages of CKD the clinical practice guidelines published in 2022 by Baker *et al.*[13]

Requirements for Inducing Exercise Training Adaptations

Exercise as medicine is a paradigm that has been around for hundreds if not thousands of years[29]; however, implementation in clinical practice has lagged behind.[30] Basic requirements for inducing training adaptations, such as progressive overload, personalization, and specificity,[31,32] are briefly covered here to facilitate our discussion.

Exercise provides a stimulus to the body by stressing a system (cardiovascular, musculoskeletal, etc.) to a degree greater than it is accustomed to. Although there is an acute response to this "overload" from a single bout of exercise, adaptation requires consistently repeated bouts, known as exercise training. The effects of exercise training are then the sum of the responses to single exercise bouts. As the body adapts, exercise capacity improves, and the amount of stimulus needed to overload the system increases. As a result, exercise training must continually increase in frequency,

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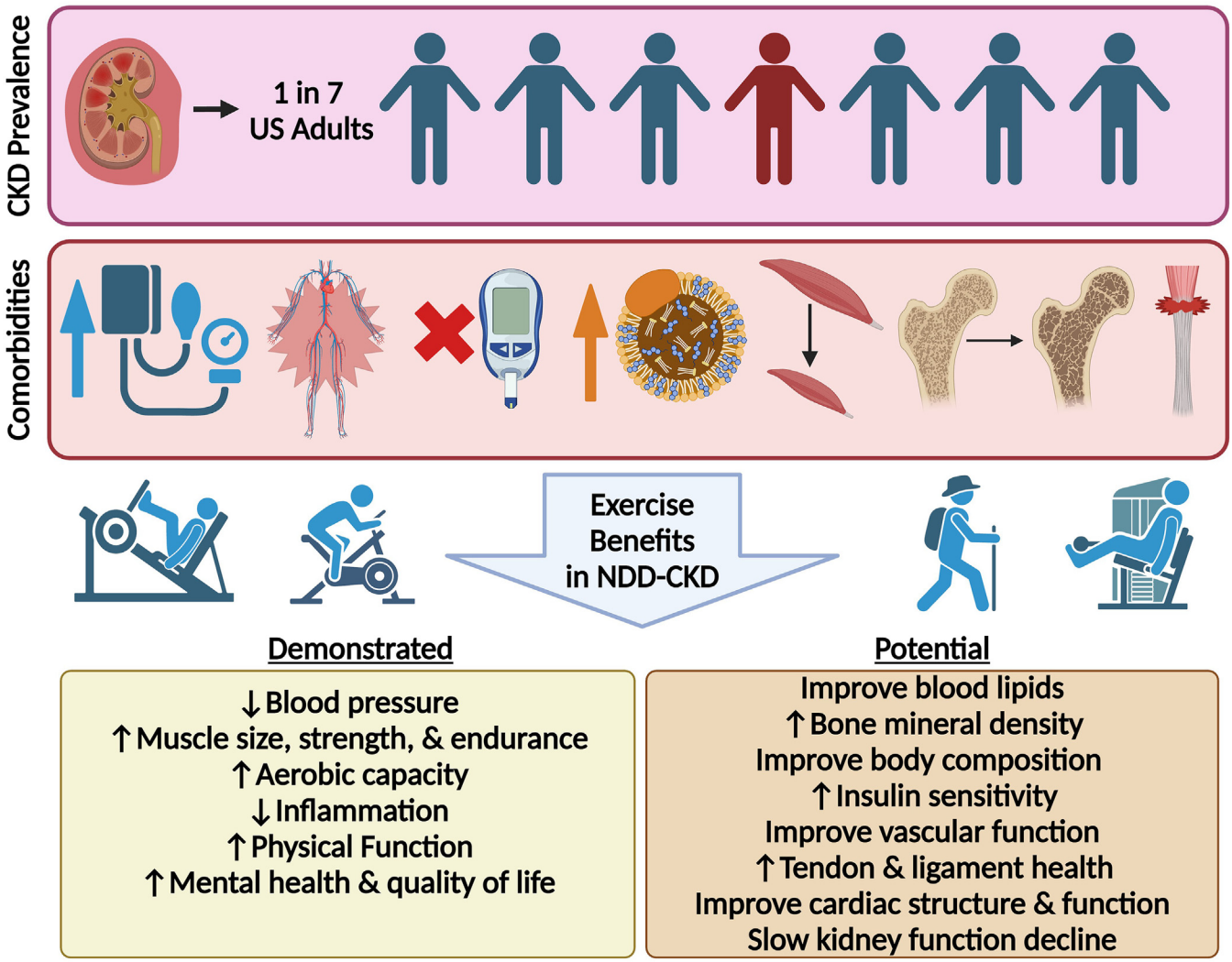

Figure 1. Exercise helps combat pathology in nondialysis chronic kidney disease. More than 1 in 7 US adults are estimated to have chronic kidney disease (CKD) and as many as 9 in 10 are unaware of their condition.[1] Comorbidities are extremely common in CKD, specifically high blood pressure,[2] cardiovascular disease,[3] diabetes,[4] dyslipidemia,[5] muscle wasting,[6] bone abnormalities,[7] and potentially increased susceptibility to tendon injury.[8,9] The coincidence of such broad-ranging pathologies is likely due to the vast physiological roles of the renal system, including the excretion of metabolic waste, termination of humoral signaling, regulation of blood pressure and volume, endocrine signaling, preservation of acid-base and electrolyte balance, maintenance of hematocrit levels, and involvement in the calcium-parathyroid hormone-vitamin D axis. Unsurprisingly, populations with CKD report lower health-related quality of life (HRQL)[10] and have higher rates of hospitalization and mortality compared to healthy populations.[11] Although individuals with nondialysis dependent (NDD) CKD also often exhibit poor exercise capacity,[12] engagement in regular aerobic and resistance exercise can greatly improve health and well-being in this population as covered in this review. Created with BioRender.com.

intensity, volume, or duration (also known as "progressive overload") until the desired physiological outcome is attained.

Individuals with worse baseline status often show the greatest improvements in response to exercise.[33] However, the stimulus needed for large improvements in low-fit individuals would be insufficient to overload those with greater baseline fitness. Thus, a one-size-fits-all intervention is not appropriate for exercise studies. Training programs must be personalized to individuals by modulating frequency, intensity, time, type, volume, and progression,[34] ideally using the guidance of physiological[35] or performance markers.[36] One approach to optimizing personalization is the "needs analysis". Borrowed from the field of sports performance, a needs analysis is a systematic process for determining the difference between the current state and a goal state to guide intervention design. In Figure 2, we present a needs analysis guide adapted from Scroggs and Simonson[37] for use with patients with CKD.

Much like traditional medicine, the benefits of exercise are dependent on specific physiological mechanisms; however, these are often overlooked. The

Table 1. Significant effects of exercise interventions on clinical outcomes in CKD from recent meta-analyses

Study	CKD stage	Exercise types (Durations)	Evaluated outcomes with significant effects[a] (effect size, 95% confidence intervals, number of studies)
Baião *et al.*,[15] 2023	1–5	AT and/or RT (8–96 wk)	IL-6 (−0.64 SMD[b], −1.01 to −0.27, $n = 5$)
Ferreira *et al.*,[16] 2021	1–3 and HD	AT+RT, guided breathing, Pilates (8–48 wk)	Depression (−0.66 SMD[b], −1.00 to −0.33, $n = 3$), anxiety (−0.78 SMD[b], −1.21 to −0.24, $n = 2$)
Junqué-Jiménenz *et al.*,[17] 2022	3–5	Home-based AT or AT+RT (12–52 wk)	6MWT (44.8 m[b], 30.6–59.0, $n = 5$), sit-to-stand test time (−0.45 SMD[b], −0.64 to −0.26, $n = 3$), timed up-and-go (−0.77 s[b], −1.38 to −0.16, $n = 2$), SF-36 role physical (15.62[b], 5.55–25.69, $n = 3$), SF-36 general health (8.42[b], 2.36–14.47, $n = 3$), HAD scale depression (−1.88[b], −3.05 to −0.71, $n = 1$)
Nakamura *et al.*,[18] 2020	1–5	AT and/or RT (8–78 wk)	Aerobic capacity[c] (2.75 ml/kg/min[b], 1.73–3.76, $n = 4$), timed up-and-go (−0.72 s[b], −1.21 to −0.24, $n = 3$)
Neale *et al.*,[19] 2023	1–5	Unspecified (12–78 wk)	None
Pei *et al.*,[20] 2019	2–5	AT (10–52 wk)	Aerobic capacity (2.08 ml/kg/min[d], 1.1–3.05, $n = 17$), exercise duration (155 s[d], 86–225, $n = 6$), HDL (3.54 mg/dl[d], 0.43–6.65, $n = 6$), SF-36 pain (5.94[d], 1.65–10.23, $n = 6$)
Thompson *et al.*,[21] 2019	NDD 3–5	AT, AT+RT, or Tai Chi (12–156 wk)	Resting SBP after 12–16 weeks (−4.9 mm Hg[b], −8.8 to −1.0, $n = 8$), after 24–26 weeks (−10.9 mm Hg[b], −15.8 to −6.1, $n = 4$), resting DBP after 24–26 weeks (−6.2 mm Hg[b], −10.9 to −1.5, $n = 4$), 24 h ambulatory SBP (−18.0 mm Hg[b], −29.9 to −6.1, $n = 1$), 24 h ambulatory DBP (−9.0 mm Hg[b], −17.7 to −0.29, $n = 1$)
Villanego *et al.*,[22] 2020	NDD 1–5	AT and/or RT (12–52 wk)	Hemoglobin (0.3 SMD[d], 0.1–0.5, $n = 4$), aerobic capacity (2.66 ml/kg/min[d], 1.61–3.71, $n = 9$), 6MWT (56.6m[d], 28.9–84.3, $n = 6$), bicep curl repetitions (6.8[d], 4.9–8.6, $n = 2$), BMI (−0.89 kg/m^2[d], −1.47 to −0.31, $n = 10$), waist circumference (−3.33 cm[d], −5.95 to −0.72, $n = 5$)
Wu *et al.*,[23] 2020	NDD 1–5	AT + RT (5–52 wk)	eGFR (5.01 ml/min per 1.73 m^2[b], 2.37–7.65, $n = 6$; 3.01 ml/min per 1.73 m^2[e], 0.86–5.16, $n = 9$), serum creatinine (−8.57 μmol/l[b], −13.71 to −3.43, $n = 3$; −6.33 μmol/l[e], −10.23 to −2.44, $n = 5$), aerobic capacity (0.55 l/min[b], 0.31–0.80, $n = 2$), SBP (−5.2 mm Hg[e], −7.9 to −2.5, $n = 7$), DBP (−3.6 mm Hg[e], −5.4 to −1.9, $n = 6$)
Wu *et al.*,[24] 2022	NDD 1–5	AT and/or RT (12–52 wk)	BMI (−0.77 kg/m^2[d], −1.31 to −0.23, $n = 14$), waist circumference (−3.11 cm[d], −5.25 to −0.97, $n = 5$), body weight when BMI > 25 (−2.18 kg[d], −3.81 to −0.54, $n = 9$), when intervention > 48 wk (−2.52 kg[d], −4.28 to −0.77, $n = 5$)
Vanden Wyngaert *et al.*,[25] 2018	3–4	AT or AT+RT (12–52 wk)	eGFR (2.16 ml/min per 1.73 m^2[d], 0.18–4.13, $n = 10$), SBP (−5.2 mm Hg[e], −9.4 to −1.0, $n = 8$), aerobic capacity (2.39 ml/kg/min[b], 0.99–3.79, $n = 11$; 1.70 ml/kg/min[e], 0.65–2.74, $n = 11$)
Yang *et al.*,[26] 2020	1–5	AT or AT+RT (12–56 wk)	Urinary albumin-to-creatinine ratio (0.21 SMD[e], 0.04–0.38, $n = 7$)
Zhang *et al.*,[27] 2019	NDD 2–5	AT and/or RT (6–52 wk)	eGFR (2.62 ml/min per 1.73 m^2[d], 0.42–4.82, $n = 12$), SBP (−5.6 mm Hg[d], −9 to −2.2, $n = 9$), DBP (−2.9 mm Hg[d], −3.7 to −2.1, $n = 8$), total cholesterol after interventions[f] < 6 mo (14.6 mg/dl[d], 3.8–25.5, $n = 7$), triglycerides after interventions < 3 mo (−94.8 mg/dl[b], −148.8 to −40.9, $n = 2$), after interventions > 3 mo[f] (45.9 mg/dl[b], 17.8–73.9, $n = 4$), BMI (−1.32 kg/m^2[b], −2.39 to −0.25, $n = 9$),

6MWT, 6-minute walk test; AT, aerobic training; BMI, body mass index; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HAD, hospital anxiety and depression; HD, hemodialysis; HDL, high-density lipoprotein; IL, interleukin; NDD, non-dialysis-dependent CKD; RT, resistance training; SBP, systolic blood pressure; SF-36, Short Form Health Survey for evaluating health-related quality of life; SMD, standard mean difference.
[a] $P \leq 0.05$ and a heterogeneity $I^2 \leq 50\%$ when reported.
[b] Between group analysis of post-intervention values,
[c] By subgroup analysis including only center-based exercise studies.
[d] Between group analysis of the change elicited by intervention.
[e] Within group analysis of the change elicited by intervention.
[f] Effect in a detrimental direction.
Analyses differed in methodology such as comparison type (e.g., within-group vs. between-group), modeling (fixed vs. random effects), etc. Please see corresponding studies for caveats, estimates of clinical significance, and further information when interpreting.

principle of specificity, states that training adaptations are specific to the elicited stimulus.[38] On a macro-scale, specificity can be very simple; if improved sit-to-stand performance is desired, then the muscles involved in sit-to-stand should be exercised in a similar pattern and duration as required by the test. However, specificity becomes more complicated when trying to elicit adaptations such as decreasing chronic inflammation in NDD. It is thus imperative to know the physiological signals, adaptive mechanisms, best training stimulus, and CKD-related pathological barriers that may impede these processes. With this in mind, we have created a specificity chart for several commonly desired adaptations (Figure 3,[39–41] Supplementary Table S2).

Challenges to Successful Exercise Interventions

Exercise adaptations are notoriously variable in healthy individuals.[42] Although these varied responses can be due to genetic differences, they are often the result of inadequate consistency in effort, intensity, and adherence across individuals or differences in baseline status.[33,43,44] The pathological state that accompanies CKD, however, clearly creates further physical, physiological, and practical hurdles to exercise adaptations.

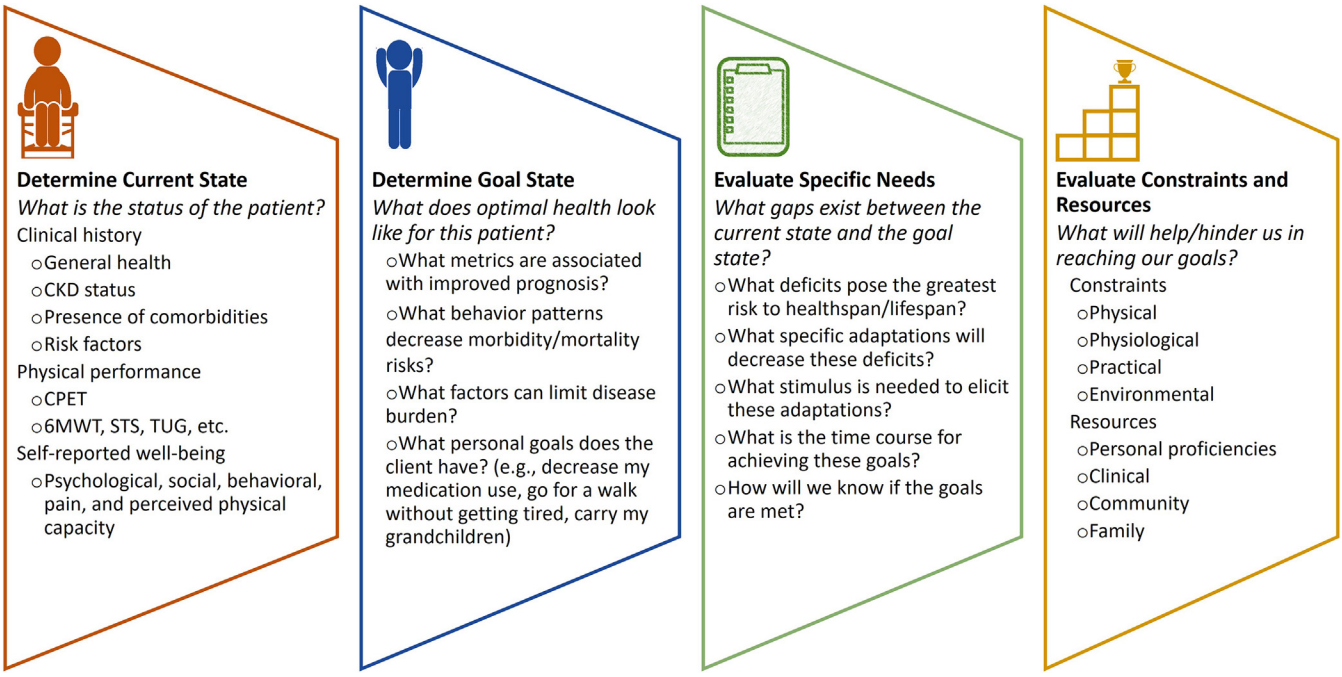

Figure 2. Needs analysis guide for developing exercise interventions for chronic kidney disease patients. Interventions should start with a comprehensive evaluation of patient status. This is followed by the determination of what optimal health looks like, incorporating the desires of both the practitioner and the patient. Next, "needs" can be identified, where a need is the gap between the patient's status and the goal state. Needs should then be prioritized because it may not be possible to give each one equal attention. Finally, the patient and practitioner should work together to evaluate potential constraints and resources that will impact progress. With this needs analysis, the practitioner can then design an intervention that targets an individual's deficits while accounting for their physical limitations and constraints and leveraging their resources. 6MWT, 6-minute walk test; CKD, chronic kidney disease; CPET, cardiopulmonary exercise test; STS, sit-to-stand; TUG, timed up-and-go.

Physical Challenges

Physical challenges are defined here as factors that make the act of regularly exercising more difficult. Individuals with CKD are afflicted with muscle wasting,[6,45–47] neurocirculatory dysregulation,[48] pulmonary dysfunction,[49] and a lower aerobic capacity,[50,51] all likely leading to decreased physical function[52] and exercise intolerance.[53] In focus groups of nonexercising patients with stage 3–4 CKD, fatigue is the most common self-reported barrier to exercise.[54] Perceived fatigue is higher in patients with NDD than in healthy controls even in the absence of greater muscle fatigue (i.e., a decline in strength with prolonged contractions).[55] Nevertheless, there is growing evidence of impaired muscle energetic function in CKD[56] that may contribute to physical limitations. This impairment is evident even during submaximal exercise whether[57,58] or not[59,60] an oxygen (O_2) delivery limitation also exists and may be due to a build-up of harmful serum metabolites such as kynurenine.[61,62] Compared to healthy controls, individuals with NDD demonstrate a lower muscle oxidative capacity, which is strongly associated with poorer 6-minute walk test (6MWT) performance.[63,64] NDD also leads to greater mitochondrial uncoupling at rest,[64,65] which increases the amount of O_2 needed to generate energy. Greater uncoupling during exercise would cause increased O_2 consumption, which has been associated with slower walking speeds and greater fatigability in older adults.[66,67]

Across patients with CKD, decrements in muscle mass,[68] physical function,[69] aerobic[70] and exercise capacity[71] increase with disease severity. Other factors such as the degree of bicarbonate deficiency or metabolic acidosis further contribute to impairments in muscle oxidative capacity,[64] muscle endurance, and exercise blood pressure (BP) regulation.[72] Mobility impairment[73] and musculoskeletal pain[74] are also common, which may make certain exercises more difficult. Thus, many disease-related complications may contribute to decreased physical capacity in CKD. Designing interventions that stimulate exercise adaptation with minimal duration may help limit fatigue-related deterrence. For example, just two 14-minute sessions of high-intensity interval training per week for 12 weeks was sufficient to increase absolute aerobic capacity by approximately 10% in severely obese non-CKD individuals.[75] Due to the significant heterogeneity of CKD symptoms,[76] blanket implementation of exercise programs will likely lead to inconsistent adherence

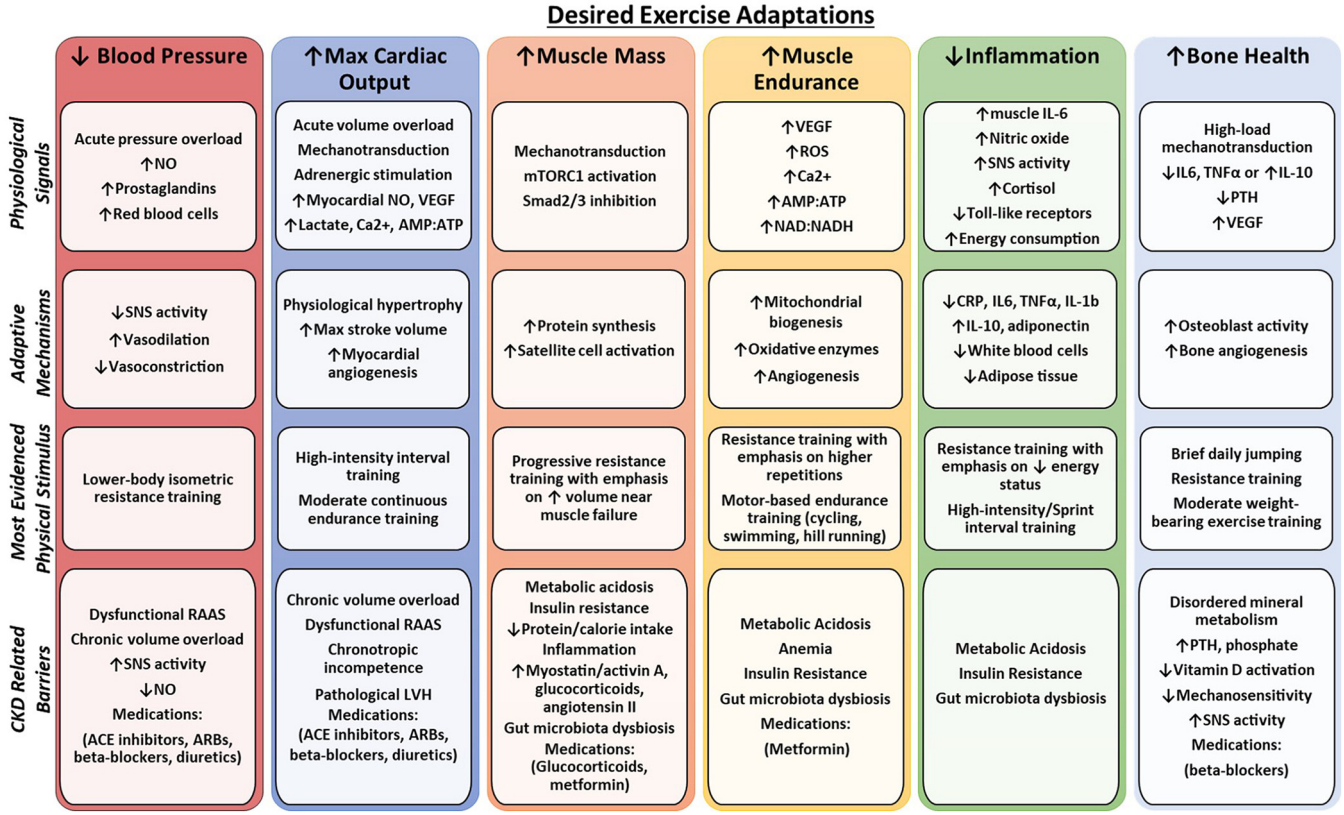

Figure 3. Specificity chart template for organizing important factors for exercise prescription in chronic kidney disease. This chart is not meant to be absolute or comprehensive but can serve as a template that can be edited and added to in conjunction with the needs analysis. For more information regarding exercise adaptations and their molecular signals, see recent reviews by Dent *et al.*,[39] Egan and Sharples,[40] and McGee and Hargreaves.[41] ACE, angiotensin-converting enzyme; AMP, adenosine mono-phosphate; ARBs, angiotensin receptor blockers; ATP, adenosine tri-phosphate; CRP, C-reactive protein; IGF, insulin-like growth factor; IL, interleukin; LVH, left ventricular hypertrophy; mTORC, mammalian target of rapamycin complex; NAD, nicotinamide adenine dinucleotide; NO, nitric oxide; PTH, parathyroid hormone; RAAS, renin angiotensin aldosterone system; ROS, reactive oxygen species; SNS, sympathetic nervous system; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor. Additional resources can be found in Supplementary Table S2.

and personalization may need to be valued over standardization. Providing modified or alternative exercises and pain management strategies may keep this from impeding participation. Because the physical capacity to perform exercise is an inherent prerequisite for training, interventions in CKD may need to be initiated at intensities that would normally be considered suboptimal for health benefits and progressed over time.

Physiological Challenges

Physiological challenges include CKD features that have the potential to impair the adaptative responses to exercise training. These include chronic uremia, metabolic acidosis, inflammation, insulin resistance, electrolyte imbalance, volume overload, endothelial dysfunction, low hematocrit, acid-base and mineral disturbances, etc. In general, these can be separated into mechanisms that may inhibit aerobic or resistance training adaptations.

Currently, there is insufficient evidence to determine whether CKD blunts aerobic training adaptations, though cardiovascular limitations seem likely (see the Aerobic Capacity section). Kirkman *et al.* [77] found that patients with NDD (mean ± SD estimated glomerular filtration rate, eGFR = 44 ± 12 ml/min per 1.73 m^2) obtained only half of the increase in aerobic capacity reported in the general aging population in response to 12 weeks of aerobic training. However, this trial used control data from separate studies and thus could not account for training effort, intensity, adherence, or baseline status and medication use. Evidence of blunted molecular responses to aerobic exercise that may impact adaptation is scarce. One study of muscle gene expression responses to a single bout of cycling found similar, but less pronounced, mRNA changes in patients with end-stage CKD compared to healthy individuals ($r = 0.79$; $P < 0.01$). However, this was a small study ($n = 5$) that also relied on external control data, making consistency hard to verify.[78] Another study found 1 microRNA (miR-146a; associated with inflammation) that exhibited a varying response to maximal exercise between healthy and CKD (eGFR = 46 ± 23) subjects; however, the relevance of this finding remains unclear.[79]

Limited data suggest that muscle hypertrophic signaling may be blunted by CKD; however, impaired muscular adaptation has not been directly shown in humans. Aberrant molecular signaling in CKD leads to altered protein turnover and muscle wasting, purportedly due to chronic inflammation, metabolic acidosis, elevated glucocorticoids, and other mechanisms that have been extensively reviewed.[45-47,80-82] Many proposed mechanisms involve insulin/IGF-1 resistance and impaired IRS-1/PI3K/Akt signaling, which are upstream of one of the main muscle hypertrophy pathways, mTORC1.[83,84] In animal models of CKD, basal deficiencies in IRS-1/PI3K/Akt signaling, increased protein degradation, and decreased protein synthesis have been reported.[85,86] However, 7 days of chronic muscle overload in 5 of 6 nephrectomized rats has been reported to fully activate IRS-1/PI3K/Akt pathways, resulting in hypertrophy similar to controls.[85] Although a deeper evaluation of these data reveals remaining deficiencies in mTORC1 and IRS-1 phosphorylation and questionable responses of total IRS-1 compared to other reports.[87] A similar study by Wang *et al.* [86] found that chronic muscle overload improved but did not completely rescue muscle size and hypertrophy signaling in 5 of 6 nephrectomized mice. Although these data demonstrate the potential for impaired resistance training adaptation, one of the only human training studies that compared NDD (GFR = 17 ± 5) to healthy controls found similar increases in quadriceps strength (∼2.4-fold) and endurance (∼1.5-fold) between groups.[88]

Practical Challenges

Practical barriers to exercise in CKD include insufficient funding for renal exercise programs, a lack of renal education opportunities for the public and practitioners, and poor accessibility of exercise equipment.[89] Patients with NDD in particular do not benefit from the greater presence of exercise professionals and programs that have fortunately been implemented in many hemodialysis clinics.[90] Well-designed home-based exercise programs may help circumvent some of these challenges. For example, Sian *et al.* [91] elicited improvements in cardiorespiratory fitness, exercise tolerance, BP, and cholesterol through just 4 weeks of unsupervised home-based high-intensity interval training in a general older adult population.[91] In addition, a small meta-analysis (n = 8 trials) of home-based exercise in CKD shows limited but consistent evidence of improvements in physical function and self-reported health metrics.[17] Given the complexities of exercise prescription in special populations, many kidney health providers feel inadequately trained to advise patients on physical exercise.[92] The Global Renal Exercise Network (https://grexercise.kch.illinois.edu/) suggests that increasing the number of exercise professionals in renal care programs is the most effective strategy for removing exercise barriers in CKD.[89] In addition, there is a disproportionate burden of CKD on low-resourced and minority communities,[93] requiring investigators and practitioners to address disparities in access to education, nutrition, exercise equipment, and health care to improve outcomes equitably. This includes a special emphasis on enrolling participants from these underrepresented groups into clinical trials to ensure the generalizability of findings.

Results and Lessons From Previous Interventions

Despite the growing acceptance of exercise as an effective intervention in CKD[94] and over 20 years of related research,[95] there is still a lack of large, randomized control trials investigating the benefits of exercise in NDD. The 13 meta-analyses in Table 1 collectively cited only approximately 47 unique trials in NDD, most of which involved fewer than 50 participants. Therefore, there is a paucity of data to draw strong conclusions from. Furthermore, across meta-analyses, there is inconsistent use of postintervention values versus change from baseline for calculating effect size (ES), thereby likely increasing variability in the findings. Given the challenges of exercise research, it may be advantageous to view even inconsistently demonstrated outcomes as potential benefits that can be obtained with adequate interventional design. With this in mind, we herein present a range of the purported benefits of exercise in NDD, though they differ in strength of evidence.

Physical Function

Impaired physical function is common in CKD and is associated with worse clinical outcomes, including increased risk of cardiovascular disease and mortality.[52,73,96-98] In NDD specifically, a meta-analysis by Ribeiro *et al.* [99] found that low physical performance in NDD results in a mortality hazard ratio of 2.04. Of the meta-analyses in Table 1, exercise training was found to improve 6MWT distance in 2 of 4 analyses (ES = 44.8 m and 56.6 m), timed up-and-go in 2 of 2 (ES = −0.77s and −0.72s), and sit-to-stand in 1 of 3 (−0.45 standardized mean difference, SMD). When the trials used in these meta-analyses are evaluated individually, improvements in 6MWT, sit-to-stand, and timed up-and-go are more consistently shown.[100-105] At least 7 studies[100-106] have demonstrated changes in 6MWT distances greater than the minimally clinically significant change of approximately 30 m suggested for older adults with pathologies or pulmonary hypertension.[107,108] Two of these studies also found significant

improvements in self-reported physical function and perception of energy or fatigue,[100,103] supporting the use of these tests as metrics of overall physical well-being. Furthermore, in a retrospective longitudinal study of patients with CKD (eGFR = 30 ± 27), improvement in an incremental shuttle walking test greater than 50 m was related to a significantly lower risk of morbidity and mortality compared to "nonimprovers" and unexercised controls.[109] Together, the currently available data suggest that exercise can improve physical function, which may lead to better long-term patient outcomes, and thus is a worthwhile target for intervention.

Aerobic Capacity

Aerobic capacity is the maximal amount of O_2 an individual can intake, deliver, and utilize during exercise. Individuals with CKD have lower aerobic capacity than healthy controls[51] which worsens with disease progression[50] and is associated with increased cardiovascular burden[110] and mortality.[111] Five of 5 meta-analyses in Table 1 found a significant effect of exercise training on aerobic capacity (ES = 2.08–2.75 ml/kg/min).[18,20,22,23,25] Improvements in aerobic capacity as little as 6% have been suggested to be clinically significant[25,112,113] and a critical cut point of 17.5 ml/kg/min has been shown to predict mortality.[111] One of the more impressive improvements in aerobic capacity in NDD (eGFR = 38 ± 13), an increase of 5.8 ml/kg/min, was elicited by Van Craenenbroeck *et al.*[114] through 3 months of cycling for 4 daily 10-minute sessions at 90% of anaerobic threshold heart rate. The volume of this intervention (40 minutes daily) is significantly greater than most other interventions (30 minutes 2–3 d/wk), likely leading to a greater effect. Whether the use of multiple shorter exercise sessions across the day in this study impacted the results is not clear; however, the efficacy of similar, brief albeit vigorous exercise has been explored in other trials and warrants consideration.[115,116] No specific aerobic exercise program has demonstrated superiority for increasing aerobic capacity, and several meta-analyses suggest practically equivocal effects of moderate-intensity continuous and high-intensity interval training in general and overweight or obese populations.[117,118] Due to its complexity and interaction with kidney disease, we discuss the physiology of aerobic capacity in more detail here.

Aerobic capacity is generally considered to be limited by cardiovascular function (O_2 delivery) and improvements with training are attributed to increases in maximal cardiac output.[119,120] This is because in healthy individuals, the oxidative capacity (maximal O_2 consumption) of muscle normally exceeds O_2 delivery during whole-body exercise.[120,121] In order to improve aerobic capacity in NDD, it is important to understand how the disease could impair both O_2 delivery and use.[30] In a cross-sectional study, Wallin *et al.*[71] found that stroke volume, peak heart rate, and hemoglobin concentration are lower in NDD compared to controls and concluded that O_2 delivery is the main determinant of aerobic capacity decline with disease progression. Wallin *et al.*[71] study, however, did not include measures of O_2 utilization needed to evaluate the role of peripheral O_2 use, such as arterial venous O_2 difference. In a similar evaluation, Chinnappa *et al.*[122] found that arterial venous O_2 difference was a better predictor of aerobic capacity in NDD ($R = 0.78$) compared to cardiac output ($R = 0.74$). They further suggested that in NDD, aerobic capacity reflects the ability of skeletal muscle to extract O_2 and not cardiovascular function. This claim is surprising given that in their data, peak cardiac output mirrored the aerobic capacity decline with disease status. In addition, their study showed no difference in peak arterial venous O_2 difference between the NDD and healthy control groups, which does not support a muscular impairment. Although arterial venous O_2 difference did explain more of the variance in aerobic capacity in NDD ($R^2 = 0.61$) compared to healthy controls ($R^2 = 0.38$) or heart failure patients ($R^2 = 0.32$), this difference may instead be attributed to the varying degrees of anemia in CKD.

Several factors contribute to O_2 delivery limitations in NDD. Maximal heart rate, which is generally not modifiable through exercise training, is classically decreased in CKD.[123] This deficit resolves within 2 months of kidney transplant,[124] suggesting that the uremic milieu may blunt the cardiac adrenergic response.[125] Training-induced increases in plasma volume and hematocrit are 2 major adaptations that improve cardiac output and O_2 delivery and thus aerobic capacity.[43,126] Patients with CKD, however, commonly suffer from chronic plasma volume expansion without compensatory increases in hematocrit,[127] which could restrict their adaptive ability. The prevalence of low hematocrit progressively increases from 8% to 53% across CKD stages,[13,14,28–30,128] likely due to declines in erythropoietin production. In patients on dialysis, normalizing hematocrit (increasing the O_2–carrying capacity of the blood) improves aerobic capacity, both alone[58,129] and when combined with exercise.[58,95] However, improvement in hematocrit even to normal levels with these agents does not restore aerobic capacity to the level of healthy controls.[58,95] Furthermore, caution must be taken with the use of exogenous erythropoiesis-stimulating agents to improve hematocrit because they significantly increase the risk of thrombovascular events and mortality.[130]

In summary, impaired O_2 delivery in NDD likely limits aerobic capacity; however, the impact of impaired muscle O_2 use is unclear.[71,122] Furthermore, several physiological factors in NDD may prevent exercise training-induced improvements in aerobic capacity, and methods for overcoming these are limited. Nevertheless, there is consistent evidence that exercise training can lead to clinically meaningful improvements in aerobic capacity in NDD[18,20,22,23,25] and further research on optimizing interventions is warranted. Of note, evaluating changes in absolute (l/min) along with relative (ml/kg/min) values will help researchers isolate the effects of changes in physiological function from those of altered body composition.

BP

Hypertension is prevalent in CKD and is considered one of its main causes.[1] Of the 7 meta-analyses in Table 1 evaluating BP, 4 found significant benefits of exercise training on resting systolic BP (ES = −4.9 to −10.9 mm Hg), and 3 on resting diastolic BP (ES = −2.9 to −6.2 mm Hg).[21,23,25,27] Although the effects of exercise training on BP are inconsistent and may vary with intervention duration,[21] several of the analyzed studies demonstrate impressive BP reductions.[100,101,131] Aoike *et al.* [100,101] found that home-based or center-based walking exercise 3 times per week for 24 weeks reduced systolic BP by approximately 13 to 14 mm Hg, versus no change in the control group (eGFR = ∼28 ± 11). The intensity of this intervention was personalized using a heart rate monitor and cardiopulmonary exercise test results. Further, the workouts were progressed by increasing duration at weeks 4 and 8, potentially adding to their effectiveness. A study by Leehey *et al.*[131] utilized similar intervention methods resulting in a 17 mm Hg reduction in mean systolic BP (eGFR = 44 ± 36); however, the nonexercise group saw a similar change, highlighting the importance of study run-ins to normalize standard of care. Other pitfalls that may lead to null findings include well-controlled BP at baseline,[132,133] confounding medications, the use of an automated sphygmomanometer, and low study power.[134,135] Exercise as a means to improve BP is well-documented in other populations, with 2 meta-analyses of 93 and 270 trials concluding that isometric resistance training is the most effective mode.[136,137] The Edwards *et al.* [136] analysis found mean reductions from baseline in resting systolic BP of 4.1, 4.5, 4.6, 6., and 8.2 mm Hg following high-intensity interval, aerobic, dynamic resistance, combined, and isometric resistance training respectively. Both analyses also found greater effects in individuals with higher baseline BP. Thus, exercise training has the potential to improve BP in NDD; however, baseline BP and medication should be controlled for and the use of isometric exercises should be explored in exercise studies targeting BP.

Muscle Strength, Endurance, and Size

Muscle strength is the maximal capacity to generate force and muscle endurance is the ability to sustain force. Low muscle strength and mass are prevalent in approximately 20% of patients with NDD[138] and are associated with increased mortality (hazard ratio = 1.46 and 1.38).[99] Handgrip strength, knee extensor strength, and bicep curl repetitions were the only muscle-specific outcomes evaluated in the analyses in Table 1.[17,18,22] Maximal bicep curl repetitions (in 30s) alone was found to improve with training (ES = 6.8 repetitions)[22] and was used as an indicator of muscle endurance in 2 studies.[100,101] However, unless participants were reaching failure prior to 30s, this measure may more accurately reflect contraction speed and not endurance. Although this difference may seem trivial, the training methods for increasing endurance and contraction speed are different and such discrepancies in training or testing could lead to erroneous null findings. In the meta-analyses of knee extensor[18] and handgrip strength,[17] 3 of the 5 analyzed trials found significant improvements from baseline that were not seen in controls.[139-141] The 2 trials that failed to increase strength had a brief period (8–12 weeks) of supervised resistance training, followed by a much longer period of at-home training without a standardized plan or progression[110,142] (a fundamental component of training[31]). In contrast, 1 of the positive trials elicited 29% to 47% increases in upper and lower body strength through 12 weeks of progressive resistance training, despite patients (GFR = 25) being on a low-protein diet.,[141] A major difference here was that all training was supervised by an exercise physiologist. Another study found that 8 weeks of supervised progressive resistance training resulted in an approximately 13% increase in isokinetic strength as well as significant increases in rectus femoris cross-sectional area and volume (eGFR = 29, range: 19–32).[140] We found 5 resistance training studies with muscle outcomes not included in the analyses in Table 1. The 3 that implemented supervised in-center progressive resistance training showed robust changes in muscle size and strength in just 12 weeks.[88,143,144] The other 2 studies[145,146] used 12-month home-based interventions and only the one that was progressed remotely by a physiotherapist elicited significant (though modest) improvements in strength.[145]

Muscle adaptations reflect the demands imposed by training. For example, to improve muscle endurance, exercise should involve repetitive or prolonged

contractions to produce metabolic stress in the target muscle, a stimulus for endurance adaptations.[147,148] Cycling then, may be more effective than running at increasing leg muscle endurance because the muscles are used as a motor as opposed to a strut[149] imposing a greater energy demand. Although exercise training improves muscle strength, endurance, and size, each involves a different combination of stimuli and adaptations that can be targeted through specific approaches. Collective analysis of resistance training interventions suggests that if muscle growth (hypertrophy) is the goal, then the volume of work near failure should be maximized; and, if increases in muscle strength are desired, training at higher loads is beneficial.[150] An important caveat regarding resistance training is that muscular adaptation only occurs in the utilized tissue (knee extension exercise will not increase handgrip strength).[151] Factors released into serum during exercise, such as growth hormone and insulin-like growth factor, have not been shown to elicit hypertrophy or strength changes in unexercised muscle.[152,153]

Overall, there is a shortage of resistance exercise research in the NDD population. Although available meta-analyses do not identify a strong effect of exercise training on muscle function in NDD, a careful reading raises questions as to the validity of this conclusion. Results from a number of studies have shown that well-designed interventions can increase muscle strength and size in NDD in as few as 12 weeks.[88,139-141,143,144] Therefore, the design of a resistance training program (e.g., supervision and progression) appears more important than duration for eliciting adaptations. Training should be specifically chosen based on the desired adaptation and target muscles, as adaptations demonstrate mode[154] and location specificity.[152,153] In terms of muscle testing, most physical function tests involve multiple nonmuscular components (balance, coordination, cardiovascular fitness, etc.) making them nonideal for evaluating muscle function. Thus, care should be taken when selecting muscle outcome measures, suggestions for which can be found in articles from Beaudart[155] and Buckinx.[156]

Inflammation and Oxidative Stress

Chronic inflammation is a well-accepted component of CKD[157] and is associated with mortality across all stages of the disease.[158] Exercise training has well-demonstrated antiinflammatory effects in other populations,[159] and although there is an acute proinflammatory response to unaccustomed exercise in NDD, 8 weeks of training alleviates this response.[160] Only 2 meta-analyses[15,24] in Table 1 evaluated the effects of exercise training on inflammatory markers. One found no effect of exercise on interleukin (IL)-6 or C-reactive protein (CRP) levels in NDD[24] and the other found changes in IL-6 (ES = −0.64 standardized mean difference) but not C-reactive protein, IL-10 (antiinflammatory), or tumor necrosis factor-α in a subgroup analysis of NDD.[15] The latter study also found that resistance, but not aerobic or combined exercise, significantly decreased C-reactive protein and tumor necrosis factor-α and increased IL-10 in an analysis that pooled results from dialysis and NDD.[15] Interestingly, one of the main suggested mechanisms for the antiinflammatory effect of exercise is the transient elevation in IL-6 it causes, which purportedly triggers a post-exercise increase in IL-10 and suppression of tumor necrosis factor-α.[159,161,162] Muscle is responsible for the majority of this IL-6 spike during exercise, rising 1 to 100-fold depending on exercise type[163] and it is believed to be stimulated by sensors of a low-energy state.[161,164] It is thus unsurprising that exercise of greater intensity and duration is associated with greater IL-6 responses.[163] At least 4 exercise studies in NDD have shown convincing reductions in basal IL-6 (∼2.2–4.2 pg/ml) using resistance[165,166] or aerobic training.[167,168] In a similar vein, acute increases in oxidative stress with exercise are an important signal for exercise adaptions, and chronic exercise training can decrease oxidative stress.[169] Available studies in stage 3–4 CKD measuring the effects of exercise on oxidative stress in NDD show conflicting results with one finding a reduction in F2-isoprostane levels[168] and the other finding no effect.[170] Nevertheless, a recent meta-analysis containing mostly hemodialysis studies found that exercise training improves oxidative stress markers, including malondialdehyde, advanced oxidation protein products, superoxide dismutase, and F2-isoprostanes, making this an area worthy of further research.

Kidney Function

Four of 9 meta-analyses in Table 1 found a significant effect of exercise training on at least 1 metric of kidney function.[23,25-27] The variation in methods of calculating ES, study weighting, and grouping, and the large number of different metrics used do not instill confidence in these collective results. For example, the impact of exercise training on eGFR from a study by Leehey *et al*.[131] in stage 2–4 CKD is assigned an ES of 1 by 2 analyses[22,27] and −2.41 by another.[25] The clinical relevance of these findings is also difficult to determine because it is dependent on the length of intervention and the expected rate of kidney function decline. Many individual studies have suggested that exercise can improve or slow kidney function decline in patients with NDD.[102,134,141,166,171-176] Unfortunately, most

studies do not evaluate the rate of renal function decline before intervention and lack the sample size to account for baseline variation. This makes it difficult to determine whether the observed improvement is real or an artifact of insufficient randomization. Furthermore, GFR is typically estimated, introducing other confounders such as the independent effects of exercise and muscle mass on creatinine levels; an issue which may be remedied through the use of cystatin C-based estimates.[177] More potentially convincing evidence comes from an ancillary analysis of the LIFE study, which included 1199 older adults, 66% of whom had an eGFR of <60 ml/min per 1.73 m^2 (mean, 54 ± 17).[178] This analysis found that a 2-year exercise intervention led to approximately 0.5 ml/min per 1.73 m^2 per year slower decline in eGFR compared to health education alone.[178] Mechanistically, it is easy to postulate that exercise may benefit kidney function indirectly by decreasing BP and inflammation or improving diabetic symptoms. Another potential mechanism is muscle-kidney crosstalk via muscle-secreted extracellular vesicles, growth factors, and myokines or exercise-induced cytokines ("exerkines").[179,180] To date, studies interrogating muscle-kidney crosstalk have only taken place in animal models, where such pathways are easier to observe,[181-183] but this area warrants further attention. Thus, though mechanistically plausible, the strength of the evidence for exercise-induced improvements in kidney function is modest due to limitations in the sample size and methodology of current studies. This sentiment is echoed and greatly expanded upon in a recent review by Davies *et al.*,[184] to which we refer the reader.

Adverse Events

Five of the meta-analyses in Table 1 aggregated data on adverse events in analyzed trials.[16-18,23,26] Only 1 reported finding any adverse events related to exercise[18] and all reported events were from a singular trial (including several cases of hypotension due to weight loss, and 1 case each of chest pain while exercising, knee pain, Achilles pain, joint pain while exercising, and rapid atrial fibrillation with hospitalization).[168] We have found no citations of exercise safety concerns specific to NDD and various forms of exercise, including aerobic, resistance, and high-intensity interval training have been directly assessed by various literature and found to be safe.[13,105,106,185,186] Resources for performing exercise safely are provided by the Global Renal Exercise Network[187,188] and the American College of Sports Medicine.[34]

Gaps in Knowledge

Gaps exist in understanding exercise's effect on bone health, optimal exercise dosing, and the use of nutritional and pharmacologic therapeutics to improve exercise adaptation. We found only 1 study on exercise and bone health in NDD (eGFR = 27 ± 11), which showed no benefit of a 24-week walking program on serum bone metabolism markers, likely due to the low mechanical load.[189] Nevertheless, exercise represents a promising therapy for combating bone dysfunction when impact exercise or resistance training is used.[190-193] Another interesting area that needs evaluation is the minimum effective dose of exercise, because decreasing exercise frequency or duration may help increase adherence. One of the few studies on exercise dosing showed that after 12 weeks, resistance training for 1 versus 3 sessions per week resulted in equal improvements in isometric strength, physical function, and self-reported uremic symptoms in stage 3 CKD.[143] Only muscle cross-sectional area and pennation increased with greater frequency. Larger, longer-duration interventions are needed.

Strategies to enhance the effect of limited protein intake on exercise-induced anabolism such as maximizing essential amino acid content,[194] supplementing with surplus ketoanalogues,[195] and optimizing protein timing[196] lack evidence in NDD and warrant investigation. Supplementing with sodium bicarbonate (to decrease acidosis[197,198]), dietary nitrate (to improve exercise efficiency[199]), iron (to improve muscle function[200]), vitamin D (to promote musculoskeletal[201] and cardiovascular function[202]), and coenzyme-Q and nicotinamide riboside (to combat mitochondrial dysfunction[203]) has received some attention in the CKD literature; however, it requires further research. Creatine, which may become a conditionally essential nutrient in CKD,[204] is one of the best-evidenced supplements for exercise performance[205,206] and could help combat sarcopenia, osteoporosis, and frailty.[207] Creatine supplementation does not damage healthy kidneys.[208] If creatine supplementation is shown to be safe for diseased kidneys, exploration of its use may be beneficial, although this treatment may necessitate substituting cystatin-C for serum creatinine in GFR calculations.

Incretin-mimetics may improve physical function and have gained popularity as weight loss drugs,[209] but their efficacy in conjunction with exercise remains to be tested in patients with CKD. A recent study in obese patients with heart failure with preserved ejection fraction demonstrated improvements in 6MWT performance.[210] Given the high prevalence of diastolic heart failure and obesity in patients with CKD these treatments appear promising. Semaglutide has been shown to improve renal end points[211] and lead to substantial weight loss; however, its impact on exercise adaptation remains to be explored. However, caution is

advised because potential adverse responses have been reported,[212] and induction of weight loss may not benefit some patients with CKD.

Further Considerations for Research and Practice

Optimizing interventional studies is crucial for increasing the use and efficacy of exercise in CKD. The expanding use of smart devices could be leveraged to collect physical activity data, administer surveys, and encourage adherence.[213] A group from the UK recently developed a free digital platform for physical activity and emotional well-being intervention in CKD populations ("Kidney Beam", https://beamfeelgood.com/kidney-disease) which significantly improved mental health and sit-to-stand test performance in just 12 weeks.[214-216] Although clinical trials using these platforms in regions with a universal health care system hold promise, they require validation in regions with alternative health care systems and racially and socioeconomically diverse patient populations to determine the generalizability and identify barriers to implementation. Furthermore, trials may benefit from the inclusion of attention control groups (with health education similar to the AWARD study[106]) to identify benefits attributable to exercise alone. The use of healthy control groups may also help delineate the effects of CKD pathophysiology from the efficacy of the intervention and potentially identify new therapeutic targets.

Concluding Remarks

Despite significant physical, physiological, and practical barriers, exercise training has been shown to consistently improve physical function and aerobic capacity; frequently improve BP and muscle function; and occasionally have beneficial effects on inflammation, oxidative stress, and kidney function. In addition, meta-analyses have suggested several benefits of exercise training not discussed here (Table 1). Other potential benefits such as improved bone health remain underexplored. To date, exercise interventions have often lacked the basic requirements for inducing adaptation, namely progressive overload, personalization, and specificity. We present here several resources (Figures 2 and 3, and references throughout) to aid in avoiding these pitfalls. Future interventions may also benefit from including exercise supervision, greater sample sizes, and better control of participant baseline status. Although the number of well-designed studies of exercise training in NDD is growing, we must not wait to implement personalized progressive exercise programs into patient care. In general, the risk of exercise is low and its inclusion in practice and policy has the potential to immediately affect the health and quality of life of the patient population. There is an urgent need to ensure programs are effective in limited-resource environments and underrepresented groups, which represent a disproportionately large and underserved portion of the patient population.

DISCLOSURE

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Recent systematic reviews meta-analyses evaluating exercise interventions in hemodialysis patients.

Table S2. Specificity table: additional resources.

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