Clinical Trials Potpourri

Anabolic Exercise in Haemodialysis Patients: A Randomised Controlled Pilot Study

Kirkman DL, Mullins P, Junglee NA, Kumwenda M, Jibani M, Macdonald JH. J Cachexia Sarcopenia Muscle. 2014;5(3):199–207.

Background: Chronic kidney disease (CKD) causes muscle wasting that increases morbidity and mortality. Resistance exercise has successfully reversed muscle wasting in other cachexic conditions, but its efficacy in CKD remains unclear. This study determined whether resistance exercise, completed during hemodialysis to enhance compliance, could increase muscle volume, strength, and functional capacity among patients with CKD.

Study Overview: In a single-blind study investigators randomized 23 patients with CKD who were on hemodialysis to either an attention control group (SHAM: low-intensity stretching, 3 $d \cdot wk^{-1}$) or a progressive resistance exercise training group (PRET: high-intensity intra-dialytic resistance exercise, 3 $d \cdot wk^{-1}$). After 12 wk, patients assigned to the SHAM group demonstrated statistically and clinically meaningful knee extensor muscle volume loss (–3%). In contrast, patients in the PRET group increased muscle volume (+3%) and strength of the knee extensor muscles. However, these improvements did not translate into increased functional capacity as assessed by sit to stand, get up and go, and walking tests.

Comment: Twelve weeks of high-intensity intra-dialytic resistance exercise training can reverse muscle wasting in patients on hemodialysis. The failure of resistance exercise training to improve functional capacity is inconsistent with other studies of cachexia and warrants further investigation.

Statin Therapy Does Not Attenuate Exercise Training Response in Cardiac Rehabilitation

Rengo JL, Savage PD, Toth MJ, Ades PA. J Am Coll Cardiol. 2014;63(19):2050–1

Background: HMG co-reductase inhibitors (statins) lower cardiovascular events in patients with coronary heart disease (CHD). Beyond their effect on lipids, statins provide benefits through effects on inflammation, the renin-angiotensin system, endothelial function, and arterial compliance. However, statin use is associated with myalgia and fatigue. Furthermore, a recent randomized study reported that statin use attenuated the exercise training response in statin-naïve, overweight subjects at risk for metabolic syndrome following a 12 wk exercise program similar to that used in cardiac rehabilitation (CR). This finding is concerning for CR participants, as baseline aerobic capacity and improvements after participation are correlated with reductions in cardiovascular disease–related and all-cause mortality. Additionally, exercise in conjunction with statin therapy lowers mortality in patients with hyperlipidemia more than either therapy alone. Given the prevalence of statin treatment among patients undergoing CR, the goal of this study was to determine whether its use attenuates the exercise-training response, measured directly by $\dot{V}O_{2peak}$ among patients with CHD attending CR.

Study Overview: Study cohort consisted of consecutive patients with CHD who performed an exercise tolerance test with measurement of peak oxygen uptake ($\dot{V}O_{2peak}$) before and after CR. The cohort was divided into two groups based on statin use throughout the CR program that consisted of three exercise sessions per week for 36 sessions. Of the total cohort of 1,201 individuals, 968 (81%) were in the statin group, and 233 (19%) were in the non-statin group. Groups were similar by sex, smoking status, and rates of type 2 diabetes mellitus. The statin group had significantly lower total cholesterol and low-density lipoprotein cholesterol levels, evincing adherence to the medication. Adherence to exercise training was similar between groups. For both groups, $\dot{V}O_{2peak}$ increased by approximately 17% ($p<0.0001$) after CR. Response to training was nearly identical for the statin and non-statin groups ($+3.2 \pm 3.7$ vs. $+3.1 \pm 3.7$ $mL \cdot kg^{-1} \cdot min^{-1}$, respectively; $p = 0.73$, between groups).

Comment: The results of this study demonstrate that long-term statin use likely does not attenuate effects of aerobic exercise training in patients with CHD.

Angiotensin-Neprilysin Inhibition Versus Enalapril in Heart Failure

McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR; PARADIGM-HF Investigators and Committees. N Engl J Med. 2014;371(11):993–1004.

Background: The renin-angiotensin-aldosterone system (RAAS) is central to the control of systemic vasoconstriction and has been a target for pharmacological therapies for patients with chronic heart failure. These therapies include angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), aldosterone antagonists, and renin inhibitors. A new drug (sacubitril) that inhibits

neprilysin (an enzyme of the RAAS) was evaluated in the recently completed PARADIGM-HF trial.

Study Overview: Investigators randomized 8,442 patients with heart failure, NYHA class II to IV symptoms, and an ejection fraction ≤40% to receive either enalapril (an ACE inhibitor) or an experimental drug that contained both sacubitril and valsartan (an ARB). During 27 mo of follow-up, the risk of cardiovascular-related death or heart failure hospitalization was 20% lower among the sacubitril/valsartan group compared to the enalapril group. The sacubitril/valsartan group also experienced significantly fewer heart failure-related symptoms and physical limitations as measured by the Kansas City Cardiomyopathy Questionnaire.

Comment: The prevalence of heart failure continues to increase and mortality rate remains high, with ~50% survival at 5 yr after diagnosis. It has been nearly 10 yr since the U.S. Food and Drug Administration (FDA) has approved a new drug for these patients. The results from the PARADIGM-HF trial are promising that this dry spell may end.

Cardiac Rehabilitation Improves Functional Capacity and Patient Reported Health Status in Patients With Continuous-Flow Left Ventricular Assist Devices: Rehab-VAD Randomized Controlled Trial

Kerrigan DJ, Williams CT, Ehrman JK, Saval MA, Bronsteen K, Schairer JR, Swaffer M, Brawner CA, Lanfear DE, Selektor Y, Velez M, Tita C, Keteyian SJ. JACC Heart Fail. 2014;2(6):653–9

Background: Reduced functional capacity and health status are independent predictors of mortality in patients with heart failure. Cardiac rehabilitation (CR) improves both and is related to improved outcomes in these patients. However, there is a paucity of data describing the effects of CR in patients with a left ventricular assist device (LVAD).

Study Overview: Individuals with a recently implanted LVAD were randomized in a 2:1 fashion to participate in 6 wk of CR versus usual care (UC). Prior to randomization 26 patients with a continuous flow LVAD performed the following tests: the Kansas City Cardiomyopathy Questionnaire (KCCQ), a cardiopulmonary exercise test (CPX), the six minute walk (6MW), and a single-leg extension maximal isokinetic test. Exercise was well tolerated with only one untoward event in >300 sessions. Following 6 wk of CR, subjects in the CR group showed improvements in peak $\dot{V}O_2$ (+10%), CPX treadmill time (+3.1 min), KCCQ score (+14.4), 6MW (+52 m), and leg strength (+17%). Change in peak $\dot{V}O_2$ and 6MW were not significantly different from the UC group. There were significant differences between groups for change in leg strength, KCCQ score, and CPX treadmill time.

Comment: This study represents one of the first randomized trials of exercise training in patients with a continuous flow LVAD. The lack of difference in change in peak $\dot{V}O_2$ and 6MW may be due to spontaneous improvements in function as a result of improved forward flow in both groups. The results of this trial support the benefits of CR for patients with an LVAD.

The Effect of Rate of Weight Loss on Long-Term Weight Management: A Randomized Controlled Trial

Purcell K, Sumithran P, Prendergast LA, Bouniu CJ, Delbridge E, Proietto J. Lancet Diabetes Endocrinol. 2014;2(12):954–62

Background: Popular opinion suggests that individuals who lose weight rapidly are at increased risk for rapid weight regain. Consistent with this opinion, guidelines recommend gradual weight loss (e.g., 2 lbs or 1 kg per wk). However, data supporting the benefits of gradual weight loss over rapid weight loss is lacking.

Study Overview: Investigators randomized 200 subjects (18 to 70 yr) with body mass index of 30 to 45 $kg \cdot m^{-2}$ to a program designed to achieve 15% weight loss either rapidly (over 12 wk) or gradually (over 36 wk), both followed by a 12 mo maintenance program. The primary outcome was change in weight at the end of this 12 mo period. Among subjects who initially lost at least 12.5% of their weight and completed the study, weight regain was not significantly different for subjects in the rapid weight loss group (mean weight regained = 71%) compared to the gradual weight loss group (mean weight regained = 71%).

Comment: These data contradict the contention that weight regain is worse following rapid weight loss compared to gradual weight loss. For some patients, rapid weight loss (if achieved) may provide greater and quicker reinforcement of weight loss efforts. In addition, rapid weight loss may assist the morbidly obese, who often have musculoskeletal limitations to exercise, to increase their physical activity sooner; further enhancing weight loss efforts.

Effects of Exercise Training on Outcomes in Women With Heart Failure: Analysis of HF-ACTION (Heart Failure—A Controlled Trial Investigating Outcomes of Exercise Training) By Sex

Piña IL, Bittner VB, Clare RM, Swank A, Kao A, Safford R, Nigam A, Barnard D, Walsh MN, Ellis SJ, Keteyian SJ; For the HF-ACTION Investigators. JACC HF. 2014;2(2):180–6.

Background: Women have been underrepresented in prior studies exercise training in patients with heart failure (HF). An analysis of the HF-ACTION trial by sex provides insights into the effects of exercise training on fitness and clinical outcomes in women with HF.

Study Overview: The HF-ACTION trial prospectively randomized 2,331 patients (661 women) with HF and ejection fraction ≤35%, to either usual care or exercise training. Women had lower baseline peak oxygen consumption ($\dot{V}O_2$) than men (13.4 vs. 14.9 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively). Peak

$\dot{V}O_2$ increased similarly in women and men following 3 mo of exercise training (mean ± SD; 0.9 ± 2.2, and 0.8 ± 2.7 $mL \cdot kg^{-1} \cdot min^{-1}$, respectively; p = 0.42) despite lower exercise volume in women (median 70 vs. 81 min per wk, respectively). Compared to the usual care group, exercise training was associated with a 26% lower risk for all-cause mortality/hospitalization in women, but not men.

Comment: HF-ACTION data represent the largest database of women with HF enrolled in a trial of exercise training. These findings support the addition of exercise training to other evidence-based medical therapies for women with HF. The effects of exercise training on clinical outcomes in women with HF with preserved ejection fraction remain unexplored.

The Effect of an EDTA-Based Chelation Regimen on Patients With Diabetes Mellitus and Prior Myocardial Infarction in the Trial to Assess Chelation Therapy (TACT)

Escolar E, Lamas GA, Mark DB, Boineau R, Goertz C, Rosenberg Y, Nahin RL, Ouyang P, Rozema T, Magaziner A, Nahas R, Lewis EF, Lindblad L, Lee KL. Circ Cardiovasc Qual Outcomes. 2014;7:15–24.

Background: Chelation therapy using ethylene diamine tetraacetic acid (EDTA) infusion was developed to treat lead poisoning. It has been advocated since the 1950s as a method to reduce atherosclerosis and prevent myocardial infarction by calcium removal. Today, tens of thousands of chelation treatments are provided to individuals wishing to reverse their heart disease and lower event risk.

Study Overview: The National Institutes of Health (NIH) funded a study to assess chelation treatment to lower the risk of myocardial infarction, coronary revascularization, stroke, angina, and death among patients with a history of myocardial infarction. In this subgroup analysis, patients >50 yr with diabetes received 40 infusions of EDTA (n = 322) or placebo (n = 311) over a 40 to 70 wk period were assessed. Compared to the placebo group, subjects in the EDTA group had a lower risk of a major cardiovascular event (25% vs. 38%, p<0.001) and all-cause mortality (10% vs. 16%, p = 0.011). Because this study represents a sub-analysis, the current findings are insufficient to recommend chelation therapy as a treatment for patients with a history of myocardial infarction and diabetes.

Comment: Clinical exercise physiologists work daily with patients who suffer a myocardial infarction. These patients may have questions about chelation therapy as part of their treatment regimen. This study, although promising, should not be used to provide advice regarding chelation treatment. There is risk to chelation therapy, including kidney damage, arrhythmia, and possible death. It is likely that a follow-up study will be performed to assess the reproducibility of these results. Until then, adequate information regarding the risk-to-benefit ratio of chelation therapy cannot be provided to patients.

Dose-Response Relation Between Exercise Duration and Cognition

Chang Y, Chuc, Wang C, Wang Y, Song T, Tsai C, Etnier JL. Med Sci Sports Exerc. 2015; 47:159–65.

Background: Exercise, brain plasticity, and cognitive function have received much attention over the past decade. This includes several studies that have shown a modest relationship between performing an acute bout of exercise and improved cognitive performance. However, less information is known about the relationship between duration of exercise and cognitive performance. Knowledge in this area is needed to better understand the mechanisms responsible for the exercise-cognition relationship, as well as possibly help guide the development of an exercise prescription aimed at improved cognitive performance.

Study Overview: Twenty-six males between the ages of 20 and 22 yr living in Taiwan completed three bouts of moderate intensity (~65% heart rate reserve) cycling of 10, 20, and 45 min in duration. A 30 min period of reading served as control. Cognitive function was assessed by the STROOP Test. Results showed that 20 min of moderate intensity exercise was associated with significantly improved cognitive performance, as measured by both shorter response time and higher accuracy. However, improved performance was not observed with the 10 or 45 min exercise bout.

Comment: The relationship between cognitive performance and exercise has rightfully drawn much attention and more is needed as the number of people entering older age increases. A better understanding of how exercise might act, either temporarily or permanently, to alter mental status and cognitive performance is important and deserving of additional research.