The Anglerfish and Uremic Toxins

Jerome Lowenstein, MD
Excerpted from FASEB 23 June 2011

It is surprising that after 60 years of dialysis for renal failure, the uremic toxin or toxins have not been definitively identified nor the mechanism responsible for their excretion determined. One might say “it all begins with dialysis”. While the clinical features of uremia were many and reasonably well described before dialysis, with the introduction of hemodialysis and peritoneal dialysis, along with the subsequent introduction of erythropoietin for control of anemia, exchange resins for the control of hyperkalemia and hyperphosphatemia and vitamin D for control of secondary hyperparathyroidism and bone disease, the clinical picture of renal failure today is hard to define, and uremia has come to be defined by the measurement of blood urea nitrogen and creatinine [1]. Serum creatinine concentration is employed to estimate glomerular filtration rate, while urea is often assumed to be a surrogate marker for a uremic toxin. Urea and creatinine are both very effectively filtered through dialysis membranes during hemodialysis. Urea kinetics (either Kt/V or URR) are used to judge the adequacy of dialysis. The success of hemodialysis in prolonging the lives of patients with chronic renal failure and the subsequent federal funding of hemodialysis focused attention on the role of filtration in the treatment of uremia and led to an explosion of technol-

How Efficacious Is Exercise Training in ESRD Patients?
A Review of the Evidence From RCCTs

Brandon M. Kistler, MS, RD
Kenneth R. Wilund, PhD

Introduction

Dozens of studies highlighting the benefits of exercise training in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis therapy have been published in the past 20 to 30 years (reviewed in [1-3]). Similar to what is seen in other patients with chronic disease, exercise training in ESRD patients has been shown to improve traditional cardiovascular disease (CVD) risk factors (e.g., plasma lipid profiles, blood pressure), and various metrics related to physical function (e.g., aerobic capacity/VO2max). While the data are impressive in many regards, there are also significant shortcomings, as many were pilot studies with a relatively small number of subjects, the exercise interventions were often short (e.g., 2-3 months), and very few contained randomized control groups. More recently, several longer-term randomized controlled clinical trials (RCTs) examining the efficacy of endurance and/or resistance training have been published. 

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NEWS & VIEWS FROM RRI

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"valuable substances", but these fish still relied on tubular secretion to dispose of toxic wastes. When, in a further adaptation in evolution, they returned to sea water, glomerular filtration no longer served a purpose and glomeruli became smaller, less numerous, and in some instances, e.g., the anglerfish, disappeared entirely [5]. Some marine fish are truly aglomerular, others show a great reduction in the number of glomeruli, and in some instances, e.g., the anglerfish, disappeared entirely [5].

In tubular excretion, on the contrary, apparently all substances share a common element in one of two transport systems because, in all instances in which an adequate examination has been made, the loading of the tubules with one substance depresses the tubular excretion of all other substances in one of two groups [10]. This is presumably a result of competition within the transport system rather than an inhibitory or toxic action, since it is freely reversible [8]. It is now evident that "transport systems" that Smith inferred are membrane transport proteins, OAT1, the PAH transport protein, is localized on the basolateral border of the S2 segment of proximal renal tubular cells and interacts with a wide range of small endogenous substances [10]. OAT3, another member of the family of OAT transporters inhibits a toxic action, since it is freely reversible [8]. It is now evident that "transport systems" that Smith inferred are membrane transport proteins, OAT1, the PAH transport protein, is localized on the basolateral border of the S2 segment of proximal renal tubular cells and interacts with a wide range of small endogenous substances [10]. OAT3, another member of the family of OAT transporters inhibits a toxic action, since it is freely reversible [8].

Several organic anion transporters, OAT1 and OAT3, account for most of the transport of small organic anions across the basolateral membrane of proximal tubular cells, substrate inhibition or competitive inhibition might be important in determining the secretion of putative uremic toxins such as indoxyl sulfate. If residual renal function represents the activity of organic ion transporters that play an important role in the maintenance of patients with end-stage renal disease, drugs which might compete for the OAT1 or OAT3 transporters might be added to those we consider potentially harmful in patients with end-stage renal disease [10].

Since two organic anion transporters, OAT1 and OAT3, account for most of the transport of small organic anions across the basolateral membrane of proximal tubular cells, substrate inhibition or competitive inhibition might be important in determining the secretion of putative uremic toxins such as indoxyl sulfate. If residual renal function represents the activity of organic ion transporters that play an important role in the maintenance of patients with end-stage renal disease, drugs which might compete for the OAT1 or OAT3 transporters might be added to those we consider potentially harmful in patients with end-stage renal disease [10].

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With the insights gained from the anglerfish and the knowledge of membrane transporters, we can look beyond the dialysis membrane at the possible role that measures to reduce the load of toxins generated by the human biome, to bind uremic toxins in the gut, or even measures that might upregulate transporters for uremic toxins in residual nephrons or other epithelia, might serve in the treatment of uremia.
resistance exercise training in ESRD patients have been published [4-9]. While some results from these trials support the notion that exercise training improves physical function and reduces CVD risk, much of the data are impressionistic, or in some cases even negative. As a result, some researchers and clinicians have begun to publicly question the efficacy acquired transporters of exercise training in this population. The primary purpose of this review is to: 1) briefly summarize the findings from recent major RCCTs and other selected studies that have evaluated the efficacy of exercise training on markers of CVD risk and physical function in ESRD patients, 2) discuss potential reasons for some of the equivocal findings from these studies, and 3) discuss the potential for future research to clarify these discrepancies. While not intended to be an exhaustive review of the literature, we have focused on results from several recent studies we believe to be the most significant to date in terms of sample size, intervention length, outcomes measured, and other methodological considerations.

Effects of Exercise Training on Measures Related to Muscle Mass and Physical Function in ESRD

ESRD patients suffer from a variety of co-morbid conditions that contribute to declines in physical functioning. Protein malnutrition, muscle catabolism, and wasting are especially common, and these lead to reduced muscle strength, function, and lower levels of physical activity. Both resistance and endurance exercise training have the potential to improve, or at the very least, prevent declines in physical function in ESRD patients. Indeed, one consistent finding in the exercise-related literature in ESRD patients is that endurance exercise training significantly improves maximal aerobic capacity across a wide range of exercise prescriptions (reviewed in [5]). In a recent review by Johansen, the mean improvement in VO2 peak following endurance exercise training interventions in 19 studies in ESRD patients was around 17% [10]. However, an interesting observation that has been made is that these improvements seem to plateau at levels well below sedentary matched controls. One hypothesis for this is that limitations in aerobic capacity are both peripheral (skeletal muscle) and central (cardiovascular) in nature [11], and that aerobic training alone may not adequately improve peripheral uptake of oxygen. Consistent with this hypothesis, it appears as though exercise interventions that combine both resistance and aerobic training have demonstrated greater improvements in aerobic capacity in this population (reviewed in [12]). Nevertheless, there is evidence that many types of exercise improve maximal oxygen uptake in dialysis patients is an important finding because declines in aerobic capacity and physical function contribute to high levels of physical inactivity in ESRD patients, which in turn contributes to losses in lean mass and ultimately muscle wasting.

Losses in muscle mass are a significant concern because of the strong association between lean body mass and mortality in the dialysis population[13]. Furthermore, reduction in muscle mass may lead to reductions in the ability to perform activities of daily living which may further exacerbate other common comorbidities such as CVD. However, many factors likely contribute to muscle wasting, making it a complex problem to control [14]. Despite numerous well designed and well executed studies attempting to minimize losses in muscle mass in ESRD patients, interventions investigating nutrition, exercise, and combinations of the two have exhibited generally inconsistent or somewhat overwhelming results.

One of the first RCCTs that examined the effects of exercise training on muscle mass in ESRD patients was the Nandrolone and Exercise Trial (NEXT) conducted by Johansen et al. [5]. This was a 12-week intervention that examined the individual and combined effects of thrice weekly nandrolone decanoate treatment and resistance exercise training on body composition, strength, and function. The resistance training consisted of five lower body resistance exercises using ankle weights three days per week during dialysis. The intensity of the program was fairly vigorous, starting with two sets of each exercise at 60% of each patient’s three repetition max (3RM) strength, progressing to three sets per session, with additional weight added as tolerated. An important finding from this study was that both the nandrolone treatment and resistance training resulted in significant increases in the cross sectional area (CSA) of the main muscle group being exercised—the quadriceps (measured by MRI). The combined treatments had an additive effect. In addition, the groups that received resistance training also had increases in leg muscle strength. By contrast, resistance training surprisingly did not improve several functional measures such as gait speed, stair climbing, or ability to rise from a chair. Furthermore, there was a paradoxical increase in whole body fat mass (assessed by dual-energy X-ray absorptiometry, DXA) in the resistance training group, while lean mass did not change. In summary, this progressive resistance training program had some important benefits (increased quadriceps CSA and strength), but did not improve whole body lean mass or improve performance on several functional tests.

In another recent RCCT called the Progressive Exercise for Anabolism in Kidney Disease (PEAK) Study, Cheema “et al.” investigated a large cohort of patients after 12 weeks of progressive resistance exercise training, compared to a control group receiving usual care[4]. This was another fairly rigorous training program in which 10 different exercises (two sets of eight repetitions for each exercise) were performed with the patients seated in their dialysis chairs three days per week using free weights for upper body exercises and ankle weights for leg exercises. The target rating of perceived exertion (RPE) for each exercise was 15 to 17 of 20 (“hard to very hard”). In contrast to the previous RCCT, thigh cross sectional area (measured by CT scan) did not increase significantly in the resistance trained group (+1.3%, P = NS) compared to the control group (-0.7%, P = NS). This may be due to the fact that the CSA measurements in the PEAK study captured muscles that were not targeted (hamstring) as well as muscle groups that were targeted (quadriiceps) by the exercise intervention. Despite no improvement in muscle CSA, there was a significant improvement in muscle strength, as well as in muscle attenuation, an indicator of muscle quality/lipid infiltration, in the exercising group.

In a continuation of the PEAK study [12], the resistance training intervention was extended out to 24 weeks, while the control group that received usual care for the first 12 weeks crossed over to an identical 12-week resistance training program. Though the changes in muscle mass were again not statistically significant, in the 24 week training group there was a continued trend for an increase in thigh CSA during weeks 12 to 24 (+1.8% vs baseline, P=NS). Surprisingly, thigh CSA continued to decline in the control group during weeks 12 to 24 (-1.4% vs baseline, P=NS). In summary, while muscle strength and exercise capacity did improve in the 24-week training group throughout the trial, the author’s primary conclusion from this study was that resistance training did not improve muscle CSA or quality (lipid content) at 24 weeks. Despite this, the trend for an increase in thigh CSA at 24 weeks and the significant improvements in strength at 12 and 24 weeks are somewhat encouraging.

Kopple et al. also recently conducted a RCCT to examine potential mechanisms by which exercise training improves exercise capacity in ESRD patients[8]. In this study, patients were randomized to one of the following four groups: 1) endurance training continued on next page
alone, 2) resistance training alone, 3) endurance + resistance training, or 4) no training. All exercise sessions were conducted immediately prior to dialysis (three days per week). The endurance training consisted of cycling at a moderate intensity for up to 40 minutes per session. The resistance training consisted of up to two sets of three leg exercises (leg extension, curl, and press) on exercise machines at a resistance up to 80% of their 1RM strength. The combined endurance and resistance exercise group performed approximately 75% of their 1RM strength. The primary outcomes tested included changes in body composition as well as changes in the expression of genes involved in muscle metabolism.

An important finding from this study was that exercise training resulted in several beneficial changes in mRNA levels that should promote muscle anabolism. Most of these beneficial transcriptional changes were related to increases in the anabolic protein IGF-I and reductions in the protein synthesis inhibitor myostatin. Despite improvements in these markers of muscle turnover, there were no changes in body composition (whole body or regional lean and fat mass) as assessed by DXA or bioelectrical impedance. In summary, similar to the NEXT[5] and PEAK[4, 12] studies, there were both positive and negative findings, making it difficult to evaluate the efficacy of exercise in ESRD patients based on these data.

One potential concern with exercising patients with ESRD is that many are in a perpetual catabolic state, and hemodialysis further stimulates protein loss and catabolism[15].

While acute exercise is obviously an energy expending process, chronic exercise training is generally considered an anabolic intervention. Indeed, several studies involving acute exercise interventions indicate that exercise transiently improves muscle protein turnover in ESRD patients. Furthermore, acute nutritional supplementation and exercise appear to have additive effects on whole body and muscle protein metabolism over the course of a single dialysis session (reviewed in[16]). Recently, Dong et al. conducted a 6-month randomized trial to examine the chronic effects of nutritional supplementation and a consistent resistance training on body composition and strength in ESRD patients[17]. In this study, patients were randomized to one of two groups: 1) oral, intradialytic nutritional supplementation, or 2) nutritional supplementation + resistance exercise training. Patients in the resistance training group performed three sets of 12 repetitions on a leg press machine at an intensity of 60% of their 1RM strength immediately before their dialysis session three days per week. Unfortunately, there were no significant differences between groups in terms of change in body mass, total lean mass, leg lean mass, or leg strength at six months. When data from the nutrition only and nutrition + resistance exercise group were combined, there was a significant increase in 1RM leg strength compared to baseline; however, lean mass was still not significantly increased over baseline levels. Because the study did not include a control group that did not receive a nutritional supplement, it was not possible to discern if the reported improvements in muscle strength and mass were due to the nutritional supplement or the resistance exercise training preserved strength or body mass compared to a group receiving usual care. In addition, several measures of leg strength and physical function also improved significantly in the resistance training group. It is noteworthy that the improvements in strength and body composition in this study were so robust, given the inconsistent findings from the exercise training studies reviewed above that have used higher intensity exercise protocols. This finding warrants additional studies comparing the effects of different exercise training intensities on muscle strength and function.

In summary, while some of the results from the above studies indicate positive effects of exercise training on body composition and physical function, many of these results are somewhat disappointing in terms of the quantity and consistency of improvements. There are a variety of potential reasons for these seemingly equivocal results. For one, the exercise prescriptions that have been used in some of these studies may have been below the threshold at which significant anabolic adaptations may occur. A majority of exercise studies in ESRD patients have used intradialytic training, which is often preferred for a variety of reasons, including reducing patient burden and improving exercise compliance[18]. Indeed, each of the RCCTs reviewed above utilized exercise training protocols that occurred either during, or immediately preceding, the patient’s dialysis session. Considering the multiple co-morbid conditions and severe decline in physical function that many ESRD patients suffer from, a more appropriate goal may be to simply maintain their health and functioning relative to a control group getting usual care. The length of the exercise intervention in each of these studies was between three and six months, which may not have been sufficient to fully capture expected declines in the control group. In fact, trends for improvements in strength, function, and body composition were noted in several of these studies, and it is possible that statistically significant differences may have been seen had the interventions been extended for 9 to 12 months or longer. While this would be ideal, high dropout rates and low compliance with interventions are common in this population due primarily to...
high morbidity and mortality rates. As a result, conducting longer-term interventions in this population will be extremely challenging.

In the next issue, we will review the effects of exercise training on cardiovascular disease risk in end-stage renal disease patients, draw conclusions from the presented aspects and discuss future directions for the study and application of exercise training in end-stage renal disease patients [TO BE CONTINUED]

**Literature Cited**


### Day 1
**Wednesday, January 25, 2012**

**11:30-12:30am**
**Breakfast**

- **Speaker:** Peter Kostko, MD
- **Facility Information:** Rural Research Institute, New York, NY

**12:00-1:15pm**
**Welcome**

- **Speaker:** Madhukar Purohit, MD
- **Facility Information:** University of Missouri, Columbia, MO

**1:15-1:30pm**
**Novel PD solutions—what are the clinical implications?**

- **Speaker:** John Jarema, MD
- **Facility Information:** Charité University Hospital, Berlin, GERMANY

**1:30-1:45pm**
**Implementing programs for ARF in developing countries**

- **Speaker:** Mary Cohen, MD, MPH, MIA
- **Facility Information:** Rural Research Institute, New York, NY

**1:45-1:50pm**
**Long-term care of the kidney transplant recipient**

- **Speaker:** Heidi M. Schreiber, MD
- **Facility Information:** Vanderbilt University Medical Center, Nashville, TN

**2:00-2:15pm**
**Discussion**

**2:15-2:30pm**
**Break**

- **Speaker:**
- **Facility Information:**

**2:30-3:45pm**
**Renal replacement therapy in gestational ESRD patients—a clinical approach**

- **Speaker:** Janan P. Kousouch, MD, PhD
- **Facility Information:** University of Pennsylvania, THE NETHERLANDS

**3:45-4:00pm**
**Can physical and occupational rehabilitation make a difference to outcomes?**

- **Speaker:** S. Yorke Josep, MD
- **Facility Information:** University Health Network, Toronto, ON, CANADA

**4:00-4:15pm**
**What are the considerations for RRT decisions in ESKDF?**

- **Speaker:** Christopher R. Bugg, MD, FACP
- **Facility Information:** Northwest Kidney Centers, Seattle, WA

**4:15-4:30pm**
**Keynotes: Endoscopists in the progress of CKD—bystander or culprit?**

- **Speaker:** Chris W. Pickrova, MD
- **Facility Information:** University of Nottingham, Derby, UK

**4:30-4:45pm**
**Discussion**

**4:45-5:00pm**
**Lunch**

**5:00-6:15pm**
**What are the impacts so far of the bundle on patient care?**

- **Speaker:** Franklin M. Paulus, MD, FACP
- **Facility Information:** Fresenius Medical Care, Waltham, MA

**6:15-6:30pm**
**Debate: Quantification of phosphate and calcium balance is necessary to correct bone mineralization in HD patients**

- **Speaker:** Frank Czoch, MD (yes)
- **Facility Information:** University of California, San Francisco, CA

- **Speaker:** David A. Brandony, MD (no)
- **Facility Information:** University of Rochester, Rochester, NY

**6:30-6:45pm**
**A critical evaluation of blood volume measurements during hemo dialysis**

- **Speaker:** C.P. Friesen, MD, PhD
- **Facility Information:** University Medical Center Groningen, Groningen, THE NETHERLANDS

**6:45-7:00pm**
**Discussion**

**7:00-7:15pm**
**Welcome Celebration**

### Day 2
**Thursday, January 26, 2012**

**7:30-8:00am**
**Breakfast**

- **Speaker:** William H. Frank, MD
- **Facility Information:** Cleveland Clinic, Cleveland, OH

**8:00-8:30am**
**Psychosocial in immunological renal diseases: where, when, and how**

- **Speaker:** Charles D. Pasci, FACP
- **Facility Information:** Imperial College London, UK

**8:30-9:45am**
**The challenges of providing RRT in demographically diverse centers**

- **Speaker:** Thomas A. Gomes, MD, FASN
- **Facility Information:** Mayo Clinic in Florida, Jacksonville, FL

**9:45-10:00am**
**Unrecognized dialysis dectoring: a problem avoiding procrastination of Jeffrey J. Snyder, MD, FPHQ**

- **Facility Information:** Fresenius Medical Care, Calestion, FL

**10:00-10:15am**
**Discussion**

**10:15-10:30am**
**Break**

**10:30-11:45am**
**Genetics of vascular calcification: basic science and clinical implications**

- **Speaker:** Marthae Bosch MD
- **Facility Information:** Translational Medicine Branch, National Institutes of Health, Bethesda, MD

**11:45-12:00pm**
**Use of mineralization retarder blockers in pre-dialysis CKD, needs and concerns**

- **Speaker:** Philip J. Kimmuly, MD
- **Facility Information:** University of North Carolina at Chapel Hill, Chapel Hill, NC

**12:00-1:15pm**
**Debate: PD if it is a real option is a preferred option for the US**

- **Speaker:** Joanne M. Berg，“MD, FRCPC”
- **Facility Information:** John J. Stroks, MD, FASSM (yes)

**1:15-1:30pm**
**Debate: ARF as a sign of infection is a preferred option for the US**

**1:30-1:45pm**
**Lunch**

**1:45-2:30pm**
**Keynote: Sodium sodium blood cell death—pathophysiology and clinical aspects**

- **Speaker:** Folker Lang, MD
- **Facility Information:** Erlanger-Kurt University of Tubingen, Tuubingen, GERMANY

**2:30-2:45pm**
**Volume control—is it more difficult in PD than in HD?**

- **Speaker:** John Bunker, MD
- **Facility Information:** Weka Fores Medical Center, Winston Salem, NC

**2:45-3:00pm**
**Discussion**

**3:00-3:15pm**
**Break**

**3:15-4:30pm**
**Cemarities**

**3:30-3:45pm**
**The difficult vascular access case problem**

- **Speaker:** Alexander S. Yost, MD
- **Facility Information:** University of Minnesota School of Medicine, Minneapolis, MN

**3:45-4:00pm**
**Sudden death in dialysis patients: are there significant modifiable factors?**

- **Speaker:** Patrick H. Fox, MD, FAKDS
- **Facility Information:** Duke University Medical Center, Durham, NC

**4:00-4:15pm**
**Diagnosis of cardiovascular disease in CKD**

- **Speaker:** Peter A. McColough, MD, FHM
- **Facility Information:** St. John Providence Health System, Providence, RI

**4:15-4:30pm**
**Discussion**

### Day 3
**Friday, January 27, 2012**

**7:30-8:30am**
**Breakfast**

**8:30-9:00am**
**The role of CKD in health status and quality of life**

- **Speaker:** Peter Kostko, MD
- **Facility Information:** Rural Research Institute, New York, NY

**9:00-9:30am**
**Blood pressure (BP) history trends in HD patient outcomes**

- **Speaker:** Len Uruyana, FACP
- **Facility Information:** Rural Research Institute, New York, NY

**9:30-10:45am**
**Debate: Division of bypass after the IDEAL study: Clinical judgment is most important**

- **Speaker:** Daniel E. Vones, MD, FReS (yes)
- **Facility Information:** Tiber Medical Center, Boston, MA

**10:45-11:00am**
**Discussion**

**11:00-11:15am**
**Break**

**11:15-12:30pm**
**Oral presentations of the three best abstracts**

**12:30-1:30pm**
**Outcomes in the frequent hemodialysis network (PHN) trials**

- **Speaker:** Christopher T. Capell, MD, FACP
- **Facility Information:** Transplantation and Nephrology, Toronto, ON, CANADA

**1:30-1:45pm**
**Blood pressure modulation**

- **Speaker:** John Zhang, MD, FACP
- **Facility Information:** University of Illinois at Chicago, Chicago, IL

**1:45-2:00pm**
**Purification**

- **Speaker:** John Zhang, MD, FACP
- **Facility Information:** University of California, Davis, CA

**2:00-2:15pm**
**Dialysis after the PHN trial: volume control, dose and who else?**

- **Speaker:** Michael V. Ross, MD, MSCG
- **Facility Information:** Wake Forest University School of Medicine, Winston Salem, NC

**2:15-2:30pm**
**Discussion**
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