


See related article, “Fourteen Monogenic Genes Account for 15% of Nephrolithiasis/Nephrocalcinosis,” on pages 543–551.

**Electroacupuncture Therapy for Muscle Atrophy in CKD: Is There a Needle in the Haystack?**

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Muscle wasting is highly prevalent among patients with CKD. The cellular mechanisms of muscle atrophy have been identified, yet definitive treatment to prevent or reverse this complication is not fully in sight. Despite proven efficacy in persons without kidney disease, resistance exercise training has not consistently and convincingly been shown to improve lean body mass in patients with CKD.1 Several novel interventions, such as blocking the Stat3 signaling pathway by C188–9 and inhibiting myostatin using anti-myostatin peptide and miRNA-27, are being explored, offering a glimmer of hope.

In this issue of JASN, Hu et al.2 report their results of studying the effects of low-frequency electrical stimulation (LFES) in mice with CKD-induced muscle atrophy. Specifically, the investigators treated 5/6-nephrectomized mice and control mice with LFES for 15 days. In CKD mice, LFES prevented soleus and extensor digitorum longus muscle weight loss and loss of hind-limb muscle grip. LFES countered the CKD-associated decline in the IGF-1 signaling pathway and led to increases in markers of protein synthesis and myogenesis. LFES acutely increased the expression of inflammatory cytokines (IFN-γ and IL-6), which was accompanied by infiltration of muscle with M1 macrophages in the early phase followed by M2 macrophages 2 days later. The IGF-1 expression in the muscle was temporally related to accumulation of M2 macrophages. The authors also noted that expression of miRNA-1 and -206, which inhibit IGF-1 translation, decreased in the acute response phase after LFES and increased at a later phase. Hu et al. concluded that LFES ameliorates CKD-induced skeletal muscle atrophy by upregulation of the IGF-1 signaling pathway.

While these findings are interesting and novel, many unanswered questions still remain regarding the mechanism of action and utility of LFES in the clinical setting. For example, which component of LFES is key to this effect, the acupuncture or the electrical stimulation? In the metaphysical concept, acupuncture is based on the belief that energy or chi travels through hypothetical channels called “meridians.” Disturbance of chi causes disease, which could be restored by inserting needles in specific points of the body. There is no supporting scientific evidence for the existence of chi life force or meridians. However, a National Institutes of Health consensus conference concluded that there was positive evidence for its effectiveness for certain conditions.3 Electroacupuncture treatment is an acupuncture method that uses stimulation of acupuncture needles with a low-frequency microcurrent. Electroacupuncture increases blood flow and oxygenation of skeletal muscles4 and has been applied for recovery from skeletal muscle fatigue and musculoskeletal disorders. Onda et al.5 showed that acupuncture with and without electrical stimulation ameliorated skeletal muscle atrophy in mice that were subjected to hind-limb suspension. Acupuncture down-regulated the genes involved in muscle breakdown (atrogin-1 and muscle RING-finger protein-1) and upregulated Akt1 and Transient receptor potential cation channel subfamily V member 4, which are positive regulators of protein synthesis. In another study, Takaoka et al.6 demonstrated that electroacupuncture treatment induced satellite cell proliferation in nonatrophic skeletal muscle through the suppression of myostatin expression.

Does LFES mediate its effect through modulation of microRNA (miRNA) expression? miRNAs are small noncoding
RNAs that are key regulators of gene expression. Individual miRNA may contain multiple binding sites complementary to a variety of miRNAs, resulting in a complex network that regulates multiple cellular functions. Skeletal muscle–enriched miRNAs (myomiRs) miR-1, miR-133a, miR-133b, miR-206, miR-208, miR-208b, miR-486, and miR-499 are important regulators of myogenesis. For instance, miR-29, which inhibits myogenesis, is decreased in the skeletal muscle of mice with CKD. In the study by Hu et al., miR-1 and miR-206 were transiently decreased by LFES but subsequently increased. Repression of these miRNAs promotes muscle hypertrophy by increasing IGF-1 expression. It is well known that insulin/IGF-1 promotes phosphorylation of mediators, such as insulin receptor substrate 1, PI3K, and Akt, leading to net increase in protein synthesis. Thus, LFES may restore the disturbed IGF-1 signaling in CKD through a miRNA-dependent mechanism.

What is the consequence of LFES-induced inflammation? We showed that IL-6 expression is increased in skeletal muscle of patients with ESRD and could play an important role in muscle protein catabolism. Proinflammatory cytokines stimulate phosphorylation of Stat3 resulting in suppression of insulin/IGF-1 signaling and activation of myostatin leading to muscle atrophy. Activation of cytokines and chemokines recruits macrophages to the site of injury. Initial influx of inflammatory M1 macrophages is essential for removal of debris, which is replaced subsequently by M2 macrophages. The latter promotes tissue repair and regeneration. Phenotypic transition from M1 to M2 macrophage is driven by downregulation of proinflammatory cytokines and upregulation of anti-inflammatory cytokines. While transient activation of cytokines within physiologic limits is essential for skeletal muscle remodeling, sustained activation of proinflammatory cytokines in the pathologic range could be detrimental, causing muscle atrophy. The effect of repeated intermittent low-level activation by LFES on muscle metabolism needs further study.

Does LFES constitute a safe alternative to exercise? If proven effective and safe, this technique may prove to be invaluable for the bedridden patients, those in wheelchairs, and patients who otherwise cannot exercise. However, acupuncture and electrical stimulation are not without complications. Adverse effects ranging from infection to rhabdomyolysis have been reported in literature. While the results from this study are promising, more questions remain to be answered before LFES is ready for prime time: Is the anabolic effect of LFES local and confined to the muscle being stimulated or systemic in nature? How many muscle groups need to be treated to achieve demonstrable increase in lean body mass? What is the optimal frequency and intensity of stimulation? Is the effect of LFES sustained with long-term use? While all these questions remain to be answered, there is at least reason to hope that a potential treatment for CKD–associated muscle atrophy is on the horizon.

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**DISCLOSURES**

None.

**REFERENCES**

Measuring Intradialytic Hypotension to Improve Quality of Care

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A significant fall in BP during dialysis, so-called intradialytic hypotension (IDH), is an important clinical problem. IDH is common, occurring in 15%–20% of treatments.1 IDH is often associated with distressing symptoms such as lightheadedness, weakness, muscle cramps, and nausea and vomiting. As could be imagined, reducing blood flow to vital organs, even transiently, is associated with a panoply of organ damage, including myocardial stunning, ischemic damage to the white matter of the brain, and perhaps disruption of the gastrointestinal barrier against endotoxins with increased inflammation. Severe IDH has been associated with a variety of catastrophes. It is likely linked to intradialytic arrhythmias, and may precipitate these, as well as myocardial infarction. Case reports of intestinal infarction, as well as of IDH-induced blindness due to retinal ischemia, have been reported. Arteriovenous access thrombosis is seen more commonly in patients with IDH.3 Finally, in patients with residual kidney function, repeated ischemic insults to a kidney unable to autoregulate its blood flow may hasten the progression to anuria and loss of the substantial advantages that even small amounts of residual kidney function provide. Some of the cardiovascular event risk associated with IDH may be a reflection of underlying comorbidity. The risk of IDH increases markedly at low values of predialysis BP,1,4 and low predialysis BP has itself been associated with cardiovascular disease and increased short-term mortality.

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