Innovations in Nephrology

Rady Children's Hospital San Diego

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PEOPLE

Dr. Peter Yorgin: Lupus expert and active researcher

Peter Yorgin, M.D., is the clinical director of the Division of Nephrology at Rady Children's Hospital-San Diego and a clinical professor of pediatrics at UC San Diego School of Medicine. He has been responsible for the vision behind the development and expansion of the division.

Dr. Yorgin also co-directs the Joint Nephrology/Rheumatology Lupus Clinic, which he launched with rheumatologist Robert Sheets, M.D., in 2011 to provide coordinated care in a single visit for the sickest lupus patients. The multidisciplinary clinic includes nurses, social workers and a dietitian.

Along with lupus nephritis, Dr. Yorgin's primary clinical interests are glomerular diseases, tuberous sclerosis and continuous renal replacement therapy. Currently, he has multiple research projects, including the impact of rapid exchange of continuous renal replacement therapy (RECRRT), using ShareSource Connect as a means of quality control, and new tools to assess nutrition in children with chronic kidney disease. Along with his own research, he has a particular interest in supporting the research careers of young pediatric nephrology faculty and fellows.

Prior to coming to Rady Children's in 2009, Dr. Yorgin was recruited by Loma Linda University, where he was the director for pediatric dialysis and pediatric resident international elective rotations. Previously, he conducted clinical research at Stanford University, in which he described new dialysis techniques and post-transplant anemia in children and adult kidney transplant recipients. Earlier in his career, after completing his pediatric nephrology fellowship at the University of Minnesota and Stanford University, he was recruited to launch the Division of Nephrology in the Department of Pediatrics at the University of Arizona.

RESEARCH

Vitamin D therapy for muscle wasting and fibrosis in CKD-

associated cachexia

The laboratory of Robert Mak, M.D., Ph.D., chief of Rady Children's Division of Nephrology and a professor of pediatrics at UC San Diego School of Medicine, has found that vitamin D supplementation ameliorates muscle wasting and fibrosis in mice with chronic kidney disease (CKD)-associated cachexia, suggesting that vitamin D repletion, specifically 25D repletion, could be an efficacious therapeutic strategy.

Muscle wasting in CKD has multiple causes, including malnutrition, inflammation, uremia, metabolic disturbances and likely vitamin D insufficiency. In addition to its classic function of maintaining calcium and phosphate homeostasis, vitamin D also plays a very extensive role as a cell differentiating and anti-proliferative factor with actions in a variety of tissues, including renal, cardiovascular, immune systems and muscles. Patients with CKD are often 25-hydroxyvatamin D3 (25D) and 1,25 dihydroxyvitamin D3 (1,25D) insufficient.

The researchers investigated whether vitamin D repletion could ameliorate muscle wasting and fibrosis in vitamin D insufficient CKD mice. CKD in mice was induced by two-stage 5/6 nephrectomy. CKD and sham mice were treated with 25D (75 µg/kg per day), 1,25D (60 ng/kg per day), 25D+1,25D (75 µg/kg per day and 60 ng/kg per day, respectively) or ethylene glycol as vehicle for six weeks. Serum and blood chemistry and energy homeostasis parameters were measured. The effects of vitamin D repletion were studied on skeletal muscle fiber size (soleus and tibias anterior fiber cross-sectional area) and in vivo muscle function (grip strength and rotarod activity) in CKD mice.

The lab also quantified the effects of vitamin D repletion on muscle expression of key molecules associated with myogenesis, skeletal muscle regeneration and muscle mass regulation as well as inflammatory cytokines in CKD mice. In addition, Dr. Mak and his colleagues profiled the effects of vitamin D repletion on skeletal muscle fibrosis by measuring soleus collagen content and muscle fibrotic and anti-fibrotic gene expression in CKD mice.

Vitamin D supplementation was shown to normalize serum 25D, 1,25D and 25D+1,25D concentrations in CKD mice. Additionally, it improved energy homeostasis, corrected lean mass loss, attenuated perturbations of muscle and brown adipose tissue adenosine triphosphate (ATP) and uncoupling proteins content as well as over-expressed muscle thermogenic genes and pro-inflammatory cytokines and pro-fibrotic genes in CKD mice. The lab identified differential effects of 25D versus 1,25D repletion in CKD mice. 25D repletion normalized energy expenditure, soleus and tibialis anterior muscle fiber area, soleus muscle collagen content , brown adipose tissue ATP content, muscle insulin-like

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(IGF-I) protein content, muscle IL-1 protein content and muscle pro-fibrotic Smad-3 mRNA expression; whereas 1,25D repletion improved but did not normalize these parameters.

Figure 1

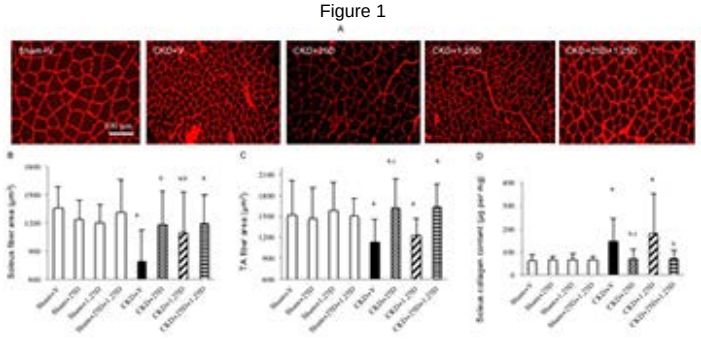

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Figure 1: Skeletal muscle histomorphometry, muscle fiber area and collagen content in CKD mice. Representative photomicrographs of soleus immunohistochemical sections labeled with a polyclonal antibody to laminin with magnification X 200 (A). Soleus muscles average fiber area (B). Soleus muscles average fiber area (C) and muscle collagen content (D).

An abstract will be presented at the American Society of Nephrology's annual meeting in November.

RESEARCH

Depression in patients with lupus, other chronic diseases

Using a depression questionnaire, Dr. Peter Yorgin (see "People" story) has identified depression in nearly half of adolescent patients seen in Rady Children's Joint Nephrology/ Rheumatology Lupus Clinic. Recently, he analyzed data from screenings at other specialty clinics.

Dr. Yorgin pioneered the first use of a depression questionnaire by an outpatient clinic at Rady Children's when he used a screening tool to identify depression in lupus patients. Data from this screening (given to 60 lupus patients during their visit) revealed that 48 percent had a diagnosis of depression discoverable in their electronic medical record. Of these patients, 23 percent had moderate depression and 7 percent had moderately severe depression. Most concerning, two of the patients had suicidal thoughts and required urgent evaluations.

Based on these findings, the screening tool was made available to

other specialty clinics at the Rady Children's. The Hospital later switched to a different depression questionnaire, the PHQ-2, since it took less time to administer. The PHQ-2 is now administered by a medical assistant at every outpatient visit. Additionally, a behavioral pathway was created to make it easier for patients to obtain outpatient psychological services.

Recently, Dr. Yorgin analyzed data from screenings at six specialty clinics. Looking at PHQ-2 data from 9,399 patient encounters, he found that depression screenings were positive in 4.6 percent of all patient visits and suicide screenings were positive in 1.4 percent. Rheumatology and pulmonary patients were found to have the highest frequency of depression, while kidney transplant patients had the lowest.

Dr. Yorgin is now starting to evaluate how quality of life surveys correlate with PHQ-2 screening in kidney transplant patients.