Role of Skeletal Muscle Mitochondrial Dysfunction in CKD

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Muscle wasting and frailty in CKD are clinically well established. The role of the mitochondria, which are essential to produce ATP required for contraction and cellular metabolism, is emerging as a possible explanation for accelerated loss of muscle and, hence, decline in functional ability in patients with CKD. Mechanisms for muscle wasting in patients with CKD include impaired growth of new muscle fibers possibly through impaired satellite cell function, suppression of protein synthesis, and stimulation of protein degradation through the ubiquitin-proteasome system (1).

In their observational study, Gamboa *et al.* (2) tested the hypothesis that mitochondrial dysfunction is present prior to initiation of maintenance dialysis and could differentiate between patients with moderate to severe CKD, patients on maintenance dialysis, and healthy controls. In their successful quest to examine quadriceps mitochondrial function, they performed ^{31}P magnetic resonance spectroscopy and obtained skeletal muscle tissue by biopsy in a subset of patients on maintenance dialysis and controls to examine mitochondria morphology and markers of mitochondrial fusion and fission. Data on the phosphocreatine recovery kinetics indicated that recovery time is longer in patients with maintenance dialysis than controls, which remained significant after controlling for hemoglobin levels. This *in vivo* evidence of mitochondrial dysfunction correlated with lower eGFR, which the authors suggest is the uremic environment gradually damaging the mitochondria.

In an earlier report, the authors presented findings that skeletal muscle of patients with CKD stage 5 had lower mitochondrial volume density, lower mitochondrial DNA copy number, and higher BCL-2/adenovirus interacting protein 3 (BNIP3, a mitophagy inducer) content than controls (3). Moreover, there are structural abnormalities, mitochondrial swelling, and abundant intracellular lipofuscin granules in mitochondria of patients with CKD, further suggesting mitophagy, a cellular process that removes damaged mitochondria (3). Yet, mitochondrial dysfunction is not limited to occurring exclusively in skeletal muscle and could reflect systemic or other tissue dysfunction. In fact, mitochondrial DNA copy number in PBMC decreased with increasing severity of CKD (2). The kidneys have a high oxygen consumption, and mitochondrial count and mitochondrial damage in the kidney itself will alter kidney function. Importantly, a reduction in mitochondrial DNA copy number is associated with higher all-cause mortality adjusted for kidney function and cardiovascular disease risk factors, higher infection-related mortality risk, and increased hospitalization due to infection in patients with CKD (4).

There are several mechanisms by which mitochondrial dysfunction could influence severity of CKD. The authors performed additional experiments examining systemic inflammation and oxidative stress, key contributors to mitochondrial dysfunction. A few central inflammatory markers, including IL-6 and TNF-α, were higher in patients on maintenance dialysis than controls. The investigators measured coenzyme Q10 (CoQ10) levels and the ratio of reduced to oxidized form of CoQ10 (or CoQ10 redox ratio), a validated marker of oxidative stress, and they reported that the total CoQ10 and reduced CoQ10 were lower in patients on maintenance dialysis compared with controls, providing additional support of oxidative stress in CKD. It is possible that additional inflammatory markers other than those measured are increased, that pathways are upregulated, and that the source of inflammation and oxidative stress is adipose tissue and skeletal muscle, in addition to blood cells.

Although numerous factors influence the mitochondria, one's exercise capacity and physical activity level are significant contributors, advocating the consideration of these important covariates in studies of mitochondrial function. A higher mitochondrial content in skeletal muscle leads to a greater ability to produce ATP and, therefore, improves exercise capacity and muscular endurance. Gamboa *et al.* (2) measured physical performance by a 6-minute walk test. As recognized by the authors, patients and controls were not selected to be sedentary, and the 6-minute walk distance may not reflect true differences in physical activity levels across groups. The authors conclude that worsening of kidney function affects mitochondrial function independent of physical performance. It is not clear if results would be independent of aerobic capacity or if exercise training can modify mitochondrial dysfunction in patients with CKD. A study of patients with CKD not on dialysis who participated in a 12-week combined aerobic and resistive training program showed that skeletal muscle citrate synthase activity, mitochondrial mass, and gene expression of transcription factors involved in mitochondrial biogenesis did not change significantly with

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exercise training (5). Although this may conflict with numerous studies demonstrating positive effects of exercise training on mitochondrial function in adults without advanced kidney disease, it may signify irreversible damage in patients with CKD not on dialysis.

Finally, we should consider muscle composition to weave into the mitochondrial schematic. Intramuscular fat increases with age, but inactivity, illness, and disease also contribute to intramuscular fat accumulation, which can have implications for loss of muscle and physical function (6). High levels of intramuscular fat may also impair mobility and increase the risk for developing a disability, which has ramifications for patients with CKD. In their study, phosphocreatine recovery was associated with increased intramuscular fat after adjusting for age, body mass index, race, and sex. Given that intramuscular fat is amenable to change *via* interventions of exercise, calorie restriction, and combinations of weight loss and exercise training, it is possible that levels of intramuscular fat could be modified in this patient population by changing sedentary behavior and dietary intake and that this could translate to improved mitochondrial function.

How important are the mitochondria to physical function and muscle wasting in patients with CKD? Longitudinal studies that follow patients with CKD and examine physical performance and skeletal muscle tissue changes while measuring aerobic capacity, muscular strength, and body composition, specifically lean tissue mass, are necessary to fully tackle this question. Given that numerous factors such as aging, physical activity, and other comorbidities contribute to mitochondrial dysfunction, these factors would require examination in conjunction with comprehensive measures of the mitochondria. With an admirable goal that their findings will lead to the development of therapeutic targets for frailty and sarcopenia in CKD, Gamboa *et al.* (2) provide us with some early and novel insight into the role of skeletal muscle mitochondrial function in patients with CKD.

Disclosures

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