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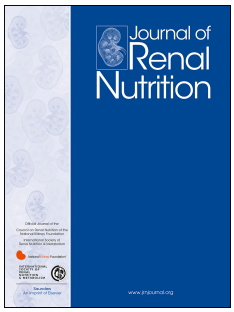

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Muscle atrophy in CKD: A historical perspective of advancements in its understanding.

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ABSTRACT

Objective: This perspective reviews the seminal clinical and experimental observations that led to today's current mechanistic model of muscle protein loss (wasting) in patients with chronic kidney disease (CKD).

Results and conclusion: Early International Society of Renal Nutrition and Metabolism (ISRNM) meetings facilitated discussions and hypotheses about the causes of muscle wasting in CKD. It became widely recognized that wasting is common and correlated with increased risks of mortality and morbidity. Although anorexia and dietary restrictions contribute to muscle loss, several features of CKD-associated wasting cannot be explained by malnutrition alone. The protein catabolism-inducing actions of metabolic acidosis, inflammation, insulin resistance, endocrine disorders and uremic toxins were progressively identified. Continued research to understand the interactions of inflammation, anabolic resistance, mitochondrial dysfunction, exercise, and nutrition on muscle protein turnover in patients with CKD will hopefully accelerate discoveries and treatments to ameliorate muscle wasting as well as the progression of CKD.

Keywords: Chronic kidney disease, muscle atrophy, sarcopenia, protein-energy wasting

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INTRODUCTION

In the 1970s, Drs. Kopple, Massry and colleagues organized meetings of international experts in the USA and Europe to identify abnormalities in the metabolism of proteins, amino acids, lipids, carbohydrates, minerals, and vitamins in patients with renal disease. In 1977, an outcome of those meetings was the formalization of the International Society of Renal Nutrition and Metabolism (ISRNM) with physician-scientists and other leaders in the fields of muscle wasting and CKD installed as leaders of the new society. Early ISRNM congresses facilitated lively discussions about various hypotheses of the causes of muscle protein loss (1-4). It became widely recognized that muscle wasting is common in patients with CKD and it is correlated with increased risks of mortality and morbidity. Although it was agreed that an insufficient food intake due to anorexia and dietary restrictions contribute to muscle loss, several features of CKD-associated wasting cannot be explained by an inadequate diet alone. While this syndrome shares etiologic, cachexia-related features seen in non-CKD populations (e.g., diabetes and heart failure), there are secondary, contributing initiators of muscle protein wasting such as metabolic acidosis, persistent inflammation, insulin resistance, endocrine disorders and uremic toxins that are directly generated by CKD (5). Our review is directed towards presenting a historical research-focused overview of more than half a century of advances in our understanding of the mechanisms that cause losses of muscle proteins in patients with CKD (Figure 1). Many of the cited publications are from past and current members and leadership in the International Society of Renal Nutrition and Metabolism.

UNDERSTANDING MUSCLE ATROPHY IN PATIENTS WITH CKD

The consequence of CKD on muscle mass was recognized as early as the 1830s, when Dr. Richard Bright described evidence of a loss of lean body mass in patients with nephritis. Subsequently, experimental studies and publications detailing clinical observations from the 1930s concluded that excess protein intake initiated uremic symptoms and restricted survival in experimental models of uremia (6). Carmelo Giordano was among the first investigators to identify that dietary protein restriction can be modified to benefit the treatment of patients with CKD. He proposed that "patients with azotemia could utilize their own urea for anabolic purpose" (7). Specifically, he emphasized that dietary protein restriction might promote the utilization of urea nitrogen to improve amino acid metabolism and suppress the generation of nitrogenous waste products. The noted goal of such restriction was to reduce uremic symptoms and prolong life because dialysis was not available to the majority of patients with CKD. It soon became clear that achieving an optimal diet for patients with CKD was not an easy task because ingestion of excessive amounts of dietary protein causes accumulation of circulating uremic toxins including phosphates and acidemia while a diet that is insufficient in protein and energy intake leads to losses of lean body mass.

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These considerations raised obvious questions about what are the limits of dietary protein and other dietary constituents? These questions began to be addressed in a classic clinical investigation that was published in 1973 by Kopple and Coburn (8). They measured the nitrogen balance of patients with CKD who were fed different amounts of dietary protein. The investigators concluded that a dietary protein of 0.6 g/kg/day not only decreases the accumulation of urea/toxins but also provides sufficient amounts of amino acids and energy to prevent losses of muscle proteins. Later in the 1970s, Munro and others reported that muscle

growth and turnover is maintained by a balance of interconnected processes – protein synthesis, protein degradation, amino acid availability plus sufficient energy production and utilization (9).

Beginning in the late 1960s, Jonas Bergstrom and colleagues began their studies of factors regulating electrolytes, glycogen, and amino acid compositions present in muscle biopsies from patients with CKD (10). Among the many important findings from these comprehensive studies, they observed that patients with CKD have a marked decrease in the levels of some essential amino acids (EAA) in muscle biopsies, especially valine (11). This finding stimulated the hypothesis that CKD-mediated losses of muscle proteins are caused by decreased intracellular availability of essential amino acids (EAA), especially three EAA referred to as the branched chain amino acids (BCAA) - leucine, isoleucine and valine. EAA must be acquired from the ingestion of dietary proteins or other exogenous sources. Alternatively, their nitrogen-free carbon skeletons can be supplied and aminated to form EAA that are used to build muscle proteins. These EAA carbon skeletons also are involved in the regulation of nitrogen metabolism. Notably, BCAA regulate protein synthesis and if their availability is limited, there is suppression of protein synthesis and muscle protein wasting occurs (12). If the carbon skeletons of BCAA, denoted as branched chain keto acids (BCKA), are provided in sufficient quantities via dietary manipulation or some other type of supplement, muscle protein losses are suppressed.

In the early 1980s, Mitch, Walser and colleagues built upon the 1970 findings and proposed a new approach to the treatment of patients with CKD. Initially, they compared the effects of daily infusions of alpha-ketoisocaproate, the ketoacid analogue of leucine vs infusion of leucine on urinary urea and total nitrogen excretion during fasting. They observed that nitrogen wasting is suppressed during starvation (13). Next, they reported that when dietary protein is reduced to only 0.3 g protein/kg ideal body weight/day and a ketoacid analog supplement is added to the

dietary regimen, the amounts of EAA are sufficient to synthesize body proteins and block muscle wasting (14). This new dietary approach was clinically well-tolerated and was even linked to slowing of the progression of CKD (15). Additional advances built on these factors. For example, in 1984, Papadoyannakis et al. (16) made a seminal observation that correction of metabolic acidosis improved nitrogen, protein, and potassium balances in uremic subjects, providing the first evidence that metabolic acidosis causes muscle protein wasting.

With the identification of metabolic acidosis as an initiating signal for the muscle wasting in patients with CKD, Mitch and colleagues began using animal models of CKD to investigate underlying mechanisms causing muscle loss. In studies performed in the mid-1980s, rats with a ammonium chloride-induced metabolic acidosis had increases in urinary nitrogen excretion and accelerated catabolism of muscle proteins and branched chain amino acids (i.e., valine) (17). In identically treated rats, protein synthesis was unchanged, a finding that remains unexplained. The group subsequently reported that rats with CKD following subtotal nephrectomy had similar losses of body mass and importantly, increased protein and BCAA degradation but only when the rats developed acidosis (18-20). CKD also impaired insulin-stimulated protein synthesis in muscles. Azotemia per se was excluded as an initiating signal causing muscle protein loss because correction of acidosis restored rates of protein degradation and prevented muscle loss (18). The team also used adrenalectomized animals and isolated muscle preparations to document a co-stimulatory requirement for glucocorticoids (18). These findings in rats have since been validated in patients. Patients with CKD and metabolic acidosis have increased production of glucocorticoids and importantly, a positive correlation between net muscle proteolysis and plasma cortisol levels was documented (21, 22). In subsequent years, physiological and molecular studies provided evidence identifying the specific proteolytic

pathways in muscle that are activated in CKD – the ubiquitin-proteasome system, caspase-3 and autophagy (Fig 2)(23). This activation stems from augmented gene expression of key components of these pathways. These components are collectively referred to as atrophy-inducing genes (i.e., atrogenes).

How does acidosis cause changes in muscle protein turnover and gene expression? An answer was suggested nearly 70 years ago when studies in dogs revealed that acidosis causes insulin resistance (24). Since the 1990s, studies involving diabetic animals and patients documented changes in muscle protein turnover and activation of proteolytic pathways that were very similar to those found with CKD (25, 26). As with CKD, glucocorticoids were shown to function as a co-stimulatory signal necessary for activation of proteolytic response when insulin anabolic signaling is defective due to insulin absence or resistance. Indeed, a study of mice lacking either insulin receptors or glucocorticoid receptors conclusively demonstrated that both glucocorticoids and impaired insulin signaling are necessary for the development of muscle atrophy (27). It was noted that glucocorticoids directly contribute to the increased expression of atrogenes as well as the development of insulin resistance. Several recent studies involving patients with CKD have provided additional clinical evidence that insulin resistance is a key independent catabolic signal for atrogene expression and sarcopenia in patients with advanced CKD (28-30).

Over the past 3 decades, many research teams have contributed to our understanding of the mechanisms that regulate protein turnover in other disorders associated with muscle loss, including cancer, diabetes, heart failure, pulmonary disease, starvation, disuse and aging. The combined results of those efforts have revealed how a symphony of physiological signals regulate multiple cell signaling pathways and the rates of protein synthesis and degradation (Fig 2) (23). Normal protein balance is regulated through the integration of a variety of nutritional,

neurological, and endogenous endocrine, paracrine and autocrine cues such as dietary intake, movement and exercise status, hormones, cytokines, oxidative stress and other inflammatory molecules, and even dialysis (5, 23, 31). In CKD and other diseases associated with muscle wasting, this balance is disrupted (23, 32). Protein synthesis is frequently suppressed while protein and BCAA degradation are typically activated. Muscle growth and regeneration are also negatively impacted because of actions of CKD signals on muscle precursor cells, namely, satellite or stem cells (Fig 2) (33). Combined, these physiological changes in muscle result in a net loss of lean body mass and concomitant muscle dysfunction.

As mentioned earlier, protein degradation is consistently reported to be activated in patients and animals with CKD. This augmented action is due to changes in gene expression that augment the capacity of the ubiquitin-proteasome system, autophagy and caspase-3 systems (5, 23). Reports about the impact of CKD on protein synthesis in patients have not been as consistent. In studies of Italian patients with CKD and metabolic acidosis, the rate of protein synthesis was increased, whereas the process was in the normal range in patients with normal acid-base balance (21, 34). Others have reported that protein synthesis was elevated or suppressed in patients with CKD with no clear reason for the discrepancies (35, 36). In animals, CKD consistently decreases protein synthesis although mechanisms responsible for the suppression have remained largely unknown until recently (23). In 2020, Zhang et al. (37) provided the first mechanistic evidence about how CKD alters protein synthesis in animals. They reported that CKD enhances the expression of a nucleolar demethylase that reduces ribosomal synthesis and protein translation capacity. This finding is notable because for the first time, epigenetic changes have been linked to muscle loss in CKD.

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In the past few years, discovery of organ-to-organ crosstalk has revealed another regulatory dimension of protein turnover in CKD and possibly other wasting condition (23). Exercise produces beneficial effects on both kidneys and muscle in CKD and they communicate via two-way conversations involving proteins and RNAs. One crosstalk molecule is irisin, a myokine produced in muscle under the control of PGC-1α which is a transcriptional coactivator that is activated by exercise and other anabolic signals (38). Irisin is released from muscle into the circulation where it is taken up by kidney tubule cells. Its actions retarded kidney damage and fibrosis (38). Exercise also influences the tissue production of a variety of microRNAs (miRNAs) which are 18-25 nucleotides long and bind to target mRNAs to inhibit the expression of specific proteins. Quite a few of these microRNAs are produced and released by muscle during exercise (39). Some like miR23a, miR27a, miR26 and miR29, are taken up by kidney cells and improve kidney function by inhibiting the expression of proteins involved in cell damage and fibrotic processes (23). In contrast to exercise, kidney tubular cells negatively influence muscle metabolism during CKD by producing and releasing activin A (40). Activin receptors in the muscle bind released activin A and other members of the TGF-ß superfamily of proteins such as myostatin. Receptor binding of these agonists proteins activates catabolic signaling pathways in muscle fibers and myotubes which negatively impact protein balance by suppressing protein synthesis and increasing protein degradation (23).

LOOKING INTO THE FUTURE

We anticipate there will be a rapid rate of discovery in our understanding of the mechanisms causing muscle loss in CKD which will translate to new treatments that prevent muscle wasting

and the progression of CKD. As in the past, the best approaches to achieving these goals will be to combine nutritional and metabolic approaches with a variety of outcomes. Relevant areas of investigation will include how interactions of chronic inflammation, anabolic resistance, mitochondrial dysfunction, exercise, and nutrition impact muscle protein turnover and the maintenance of muscle mass and function in patients with CKD and patients on dialysis.

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PRACTICAL APPLICATION

Although insufficient food intake due to anorexia and dietary restrictions contribute to muscle loss, it is evident that several features of CKD-associated wasting cannot be explained by an inadequate diet alone. Preventing/treating metabolic acidosis, inflammation, insulin resistance, endocrine disorders and uremic toxins as well as promoting physical exercise should be a common practice in care of patients of CKD. Understanding the interactions of inflammation, anabolic resistance, mitochondrial dysfunction, exercise, and nutrition on muscle protein turnover and the maintenance of muscle mass in patients with CKD will accelerate the rate of discovery and lead to new treatments to prevent/treat muscle wasting as well as the progression of CKD.

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FIGURE LEGENDS

Fig. 1. Timeline of some highlighted discoveries that have contributed to our understanding of the causes of muscle protein loss in patients with CKD.

Fig. 2. A mechanistic model of muscle protein loss. Initiating signals, including acidosis, excess glucocorticoids, chronic inflammation and myostatin/activin-A, indicated on the left, impact muscle cells to alter insulin/IGF-1 and other cell signaling pathways. Signaling becomes abnormal and expression of atrogenes increase which lead to higher activities of the ubiquitin-proteasome and other proteolytic systems in muscle. Disturbed signaling also negatively impacts muscle protein synthesis and muscle progenitor cell functions. CKD enhances the expression of a nucleolar demethylase NO66. NO66 produces epigenetic changes which reduce ribosomal synthesis and overall protein translation capacity in CKD. Finally, discovery of organ-to-organ crosstalk has revealed another regulatory dimension of protein turnover in muscle. Molecules such as irisin, myostatin, miRNAs, and activin-A mediate important intercellular communication between kidney, muscle, and other organs that affects positive or negative cellular changes. Altogether, these changes in protein turnover and muscle regeneration result in muscle atrophy.

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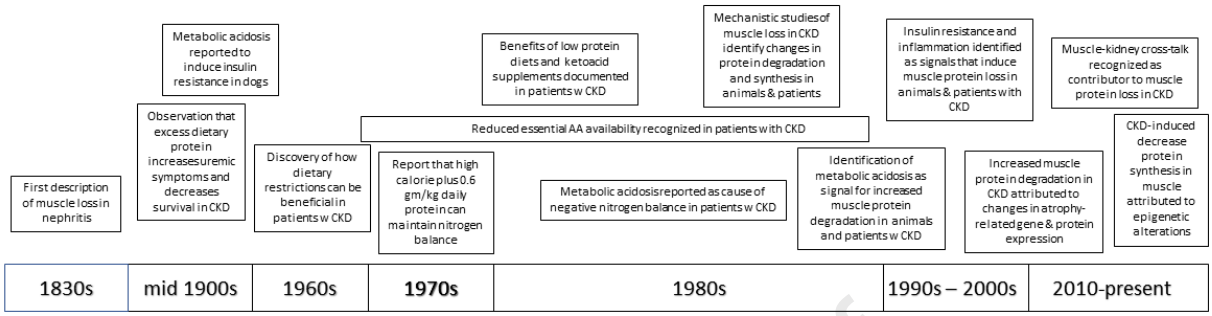
Fig 1.



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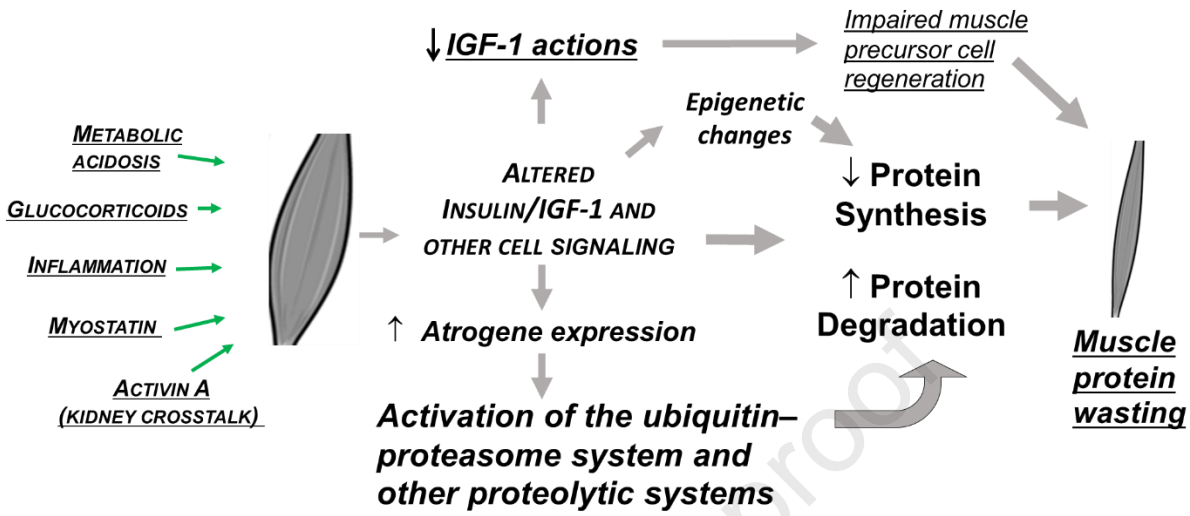

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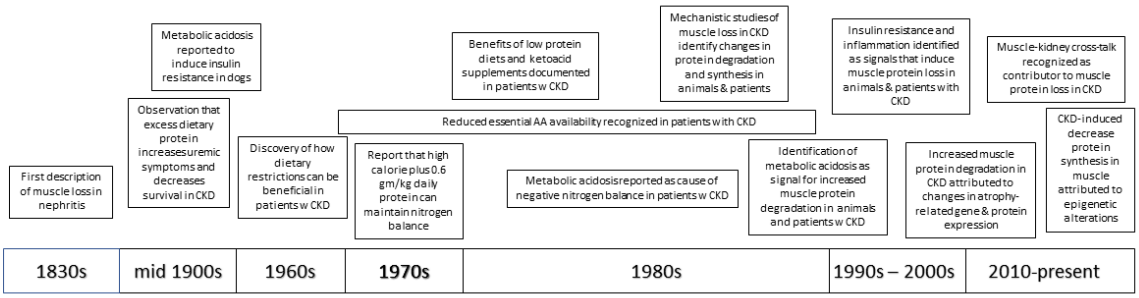

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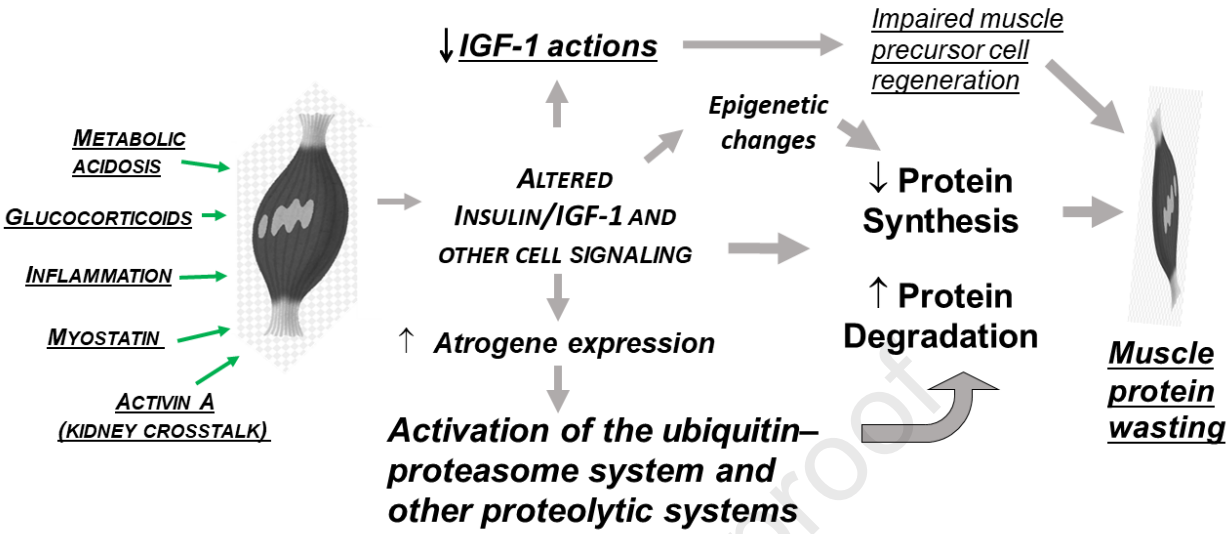

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