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REVIEW

Molecular and Cellular Mechanisms Linking Chronic Kidney Disease and Sarcopenia in Aging: An Integrated Perspective

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Abstract: Chronic kidney disease (CKD) and sarcopenia are prevalent conditions among the aging population, contributing significantly to morbidity and mortality. CKD exacerbates sarcopenia through complex molecular and cellular mechanisms, including chronic inflammation, oxidative stress, uremic toxin accumulation, protein-energy wasting, and hormonal dysregulation. This review explores the interplay between CKD and sarcopenia, focusing on key pathways such as mTOR signaling, the AMPK-FOXO axis, and myostatin/activin pathways that regulate muscle protein metabolism. Additionally, mitochondrial dysfunction and impaired autophagy emerge as critical contributors to muscle wasting. Clinical implications include identifying biomarkers such as interleukin-6, tumor necrosis factor-alpha, myostatin, and Klotho for diagnosis and monitoring, while potential therapeutic strategies involve targeting the AMPK/mTOR pathway, enhancing mitochondrial function, and inhibiting myostatin activity. Emerging approaches, including multi-omics technologies and AI-driven personalized treatment models, offer innovative solutions for understanding and managing the CKD-sarcopenia axis. This review underscores the need for integrated therapeutic strategies and multidisciplinary collaboration to mitigate muscle wasting and improve outcomes in CKD patients. By bridging molecular insights with clinical applications, this work aims to inform future research and translational efforts in addressing this critical healthcare challenge.

Keywords: chronic kidney disease, sarcopenia, sarcopenia pathophysiology, therapeutic targets

Introduction

Chronic kidney disease (CKD) and sarcopenia, both significantly impacting morbidity and mortality, are prevalent conditions among the elderly. CKD affects over 10% of the global population, with higher prevalence in older adults.[1] Sarcopenia, characterized by the progressive loss of skeletal muscle mass and function, affects approximately 50 million people worldwide, a number projected to rise to 500 million by 2050.[2] The coexistence of CKD and sarcopenia in the aging population exacerbates adverse health outcomes, including increased frailty, disability, and mortality.[3]

The pathophysiological interplay between CKD and sarcopenia involves complex molecular and cellular mechanisms. Chronic inflammation and oxidative stress are central contributors. CKD induces a pro-inflammatory state, elevating levels of cytokines which promote muscle protein degradation and inhibit synthesis. Additionally, CKD-related oxidative stress leads to the accumulation of reactive oxygen species (ROS), causing mitochondrial dysfunction and further contributing to muscle atrophy.[4] Uremic toxins accumulate in CKD and adversely affect muscle cells. These toxins impair mitochondrial function, disrupt protein homeostasis, and induce apoptosis in muscle fibers, thereby accelerating sarcopenia.[5] Moreover, CKD is associated with hormonal imbalances, such as reduced insulin-like growth factor-1 (IGF-1) levels and increased myostatin expression, both of which negatively regulate muscle mass and function.[4,6]

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Understanding the shared mechanisms offers potential avenues for interventions aimed at mitigating muscle wasting and improving clinical outcomes in this vulnerable population. Elucidating the molecular and cellular mechanisms is crucial for developing effective therapeutic strategies to enhance patient outcomes (Figure 1).

Pathophysiological Interplay Between CKD and Sarcopenia

Chronic Inflammation and Oxidative Stress

Chronic low-grade inflammation is the persistence of inflammatory markers, which is one of the features of CKD. It manifests the imbalance between anti-inflammatory and pro-inflammatory substances.[7] Elevated levels of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), promote muscle was the persistence of inflammatory markers. These cytokines decrease protein synthesis in the skeletal muscle, resulting in amplified net catabolism.[8] In addition, these cytokines impair the regenerative ability of satellite cells, hindering muscle repair and growth.[9]

Oxidative stress, marked by an imbalance between ROS production and antioxidant defenses, is another key factor in CKD.[10] Elevated ROS levels impair cellular components, including lipids, proteins, and DNA, leading to mitochondrial dysfunction and increased muscle cell apoptosis. The resulting mitochondrial impairments reduce ATP production, promote fatigue, and activate signaling pathways that exacerbate muscle protein degradation, aggravating sarcopenia.[4,11,12]

Uremic Toxins and Muscle Atrophy

With a decline in renal function, sulfuric acid accumulates with uremic toxins such as p-cresyl sulfate and indoxyl sulfate accumulate, adversely affecting muscle metabolism. These toxins induce oxidative stress, inflammation and mitochondrial network disintegration in muscle cells, impairing protein synthesis and promoting proteolysis.[13] Uremic toxins also disrupt insulin signaling pathways, reducing glucose uptake stimulated by insulin, weakening insulin signaling pathways by

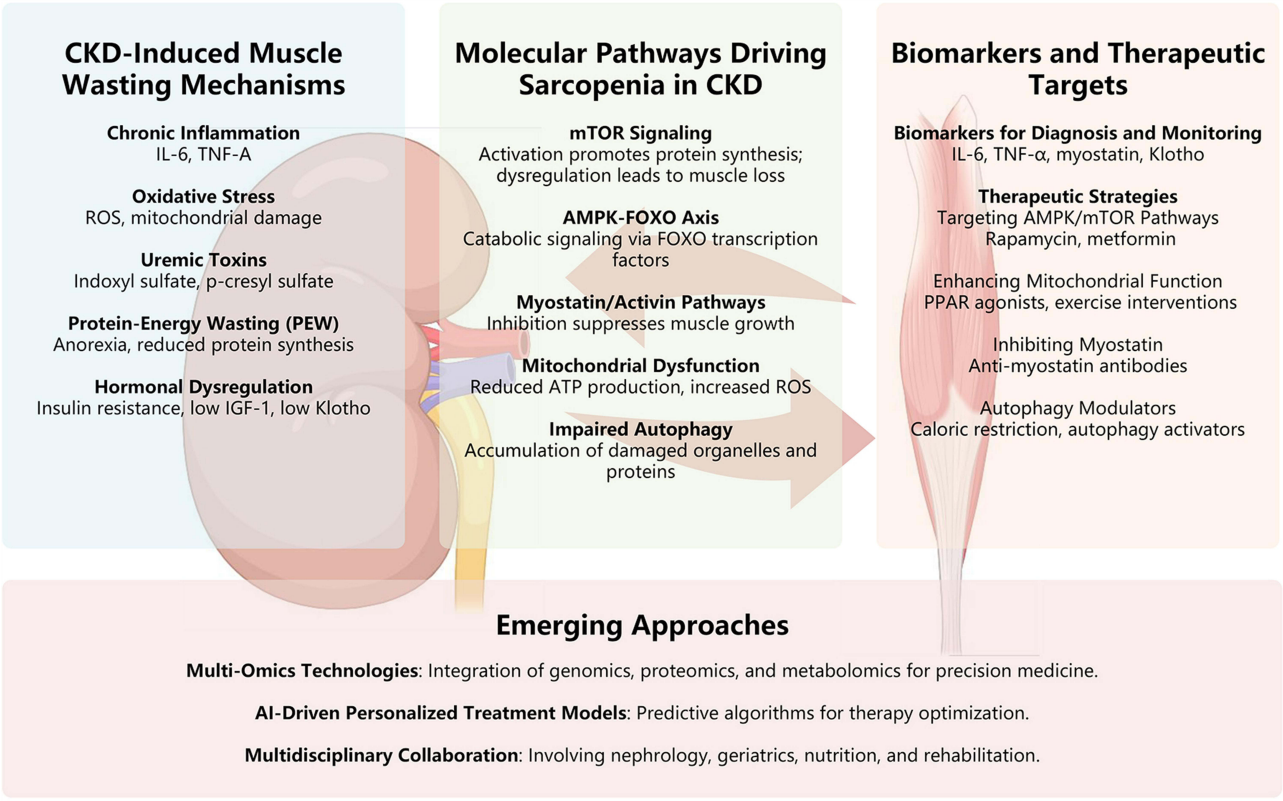

Figure 1 Molecular Pathways and Emerging Strategies for CKD-Induced Sarcopenia: Mechanisms, Biomarkers, and Therapeutic Targets.
Abbreviations: CKD, chronic kidney disease; IL-6, interleukin-6; TNF-α, tumor necrosis factor-alpha; ROS, reactive oxygen species; PEW, protein-energy wasting; IGF-1, insulin-like growth factor-1; mTOR, mammalian target of rapamycin; AMPK, AMP-activated protein kinase; FOXO, Forkhead box O; PPAR, peroxisome proliferator-activated receptor.

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triggering the ERK kinase and further contributing to muscle wasting.[14,15] In addition, uremic toxins promote myocyte l apoptosis and fibrosis by activating pro-apoptotic pathways and stimulating pro-fibrotic factor production.[16] Uremic toxins also contribute to oxidative stress and the stimulation of the production of inflammatory factors, which might be a trigger for renal fibrosis.[17] Furthermore, uremic toxins decrease the formation of myotubes and promote fibrogenic and adipogenic differentiation, which may lead to the accumulation of adipose tissue and fibrosis within skeletal muscles. This fibrotic remodeling weakens muscle structure and function, accelerating the progression of sarcopenia in patients with CKD. High concentrations of uremic toxins, which are indicative of the later stages of CKD, significantly arrest the cell cycle of myoblasts, preventing their proliferation and ultimately causing cell apoptosis.[18]

Protein-Energy Wasting

Protein-energy wasting (PEW) is a common complication of CKD, characterized by loss of protein and energy reserves. A variety of factors contribute to PEW, including decreased energy and protein uptake due to dietary restriction or anorexia, increased energy expenditure driven by chronic inflammation, metabolic acidosis, diminished physical activity, decreased anabolism, comorbidities, and the effects of dialysis. Together, these factors create a negative protein and energy balance, leading to the breakdown of muscle proteins and subsequent loss of muscle mass.[19–21] Metabolic abnormalities in CKD, such as insulin resistance and altered amino acid metabolism, further exacerbate muscle wasting. Endothelial dysfunction, oxidative stress, and vitamin D deficiency play significant roles in the development of glucose intolerance and insulin resistance in patients with CKD. Insulin resistance impairs glucose utilization in muscle cells, increasing dependence on protein breakdown for energy.[22,23] Moreover, disorders in amino acid metabolism reduce the availability of the basic resources necessary for muscle protein synthesis, hindering muscle maintenance and growth.[24]

Hormonal Dysregulation

Hormonal dysregulation is a key driver of muscle wasting in patients with CKD. Insulin resistance (IR) is an early metabolic alteration in CKD, resulting from factors such as inadequate glucose elimination, dialysis-related complications, obesity, elevated leptin-to-adiponectin ratio, vitamin deficiencies, and persistent chronic inflammation. IR impairs glucose uptake and protein synthesis in muscle cells, leading to a reduction in anabolism processes.[25] IGF-1 is associated with muscle mass loss in adult patients with CKD. Low IGF-1 levels reduce anabolic signaling through mTOR.[26,27] The decrease in Klotho expression is an early marker of chronic kidney disease. Klotho is an important protein related to anti-aging and disease regulation. Klotho deficiency can exacerbate inflammation and oxidative stress, accelerating the progression of sarcopenia.[28,29] Restoring hormonal balance can improve outcomes in CKD-related frailty.

It is important to recognize that the CKD patient population is highly heterogeneous, encompassing individuals with varying disease stages—from mild impairment to advanced CKD requiring dialysis or transplantation. This diversity significantly influences the prevalence and severity of sarcopenia. For instance, studies have shown that circulating myostatin levels may behave differently at different stages of kidney disease.[30]

Molecular Mechanisms Underpinning CKD-Sarcopenia Axis

The CKD-sarcopenia axis is mediated by complex molecular mechanisms involving disrupted signaling pathways in protein metabolism, mitochondrial dysfunction, and impaired autophagy. These pathways can be used to find potential therapeutic avenues to reduce muscle wasting in patients with CKD.

Signaling Pathways in Muscle Protein Metabolism

mTOR Pathway in Protein Synthesis Regulation

The mechanistic target of rapamycin (mTOR) is a central regulator of cell growth and protein synthesis. In skeletal muscle, activation of mTOR complex 1/2 (mTORC1/2) stimulates protein synthesis by phosphorylating key substrates such as eukaryotic initiation factor 4E-binding proteins (4E-BPs) and ribosomal S6 kinases (S6Ks), thereby enhancing translation initiation. This results in elevated protein translation and synthesis, thereby fostering muscle growth. Growth factors, amino acids, and mechanical stimulation activate mTORC1 to promote muscle hypertrophy.[31] Conversely, inhibition of mTORC1 leads to decreased protein synthesis and muscle atrophy. In CKD, heightened production of

ROS and impaired mitochondrial function are prevalent, leading to oxidative stress. This stress is a key factor in triggering muscle atrophy in advanced CKD patients by inhibiting the mTOR pathway and its downstream targets, which in turn suppresses protein synthesis.[32]

AMPK-FOXO Axis in Protein Degradation

AMP-activated protein kinase (AMPK) acts as an energy sensor that is activated in the presence of low cellular energy. Activation of AMPK inhibits mTORC1, thereby reducing protein synthesis. AMPK also modulates protein synthesis by suppressing the activity of eukaryotic elongation factor 2 (eEF2).[33] Additionally, activation of AMPK leads to dephosphorylation and nuclear translocation of forkhead box O (FOXO) transcription factor. In the nucleus, FOXO induces the expression of muscle-specific E3 ubiquitin ligases, such as atrogin-1 and muscle RING-finger protein-1 (MuRF1), which promote protein degradation through the ubiquitin-proteasome system. This coordinated regulation ensures that when energy is insufficient, protein synthesis is downregulated, and protein degradation is upregulated, leading to muscle atrophy.[34]

Myostatin/Activin Pathway in Inhibition of Muscle Growth

Myostatin and Activin are both members of the transforming growth factor-beta (TGF-β) superfamily and are a negative regulators of muscle growth. They inhibit skeletal muscle growth and differentiation by engaging with the activin type IIB receptor (ACTRIIB) activates SMAD2/3 signaling pathways to modulate gene transcription.[35] Moreover, myostatin inhibits the Akt/mTOR pathway by activating SMAD2/3 signaling pathways to reduce protein synthesis and enhances the expression of atrogin-1 to promote protein degradation.[36] Elevated levels of myostatin are associated with muscle wasting status, and inhibition of myostatin has been shown to increase muscle mass, highlighting its critical role in muscle homeostasis.[37]

Role of Mitochondrial Dysfunction

Disruption of Mitochondrial Dynamics and Muscle Energy Metabolism

Mitochondria play a vital role in energy production in skeletal muscle. Disruptions in mitochondrial dynamics, including imbalances in division and fusion processes, can impair mitochondrial function, leading to reduced ATP production and increased production of ROS.[38] Impairment of muscle energy metabolism due to mitochondrial dysfunction in skeletal muscle is linked to muscle weakness, poor exercise tolerance, and fatigue mitochondrial dysfunction in skeletal muscle.[39] Concurrently, within the context of CKD, there is a deficiency in mitochondrial dynamics coupled with elevated mitochondrial oxidative stress, which in turn, fuels the advancement of CKD. Maintaining proper mitochondrial dynamics (fusion and fission process shaping mitochondrial morphology) is crucial for muscle health, and its disorders involve a variety of muscle-wasting conditions.

CKD-Associated Mitophagy Impairment and Muscle Atrophy

Mitophagy, which involves the selective removation of impaired mitochondria through the autophagy-lysosome pathway, plays a crucial role in maintaining mitochondrial integrity and quality control.[40] In CKD, impaired mitophagy caused by FOXO activation leads to dysfunctional mitochondria accumulation, exacerbates oxidative stress and promotes muscle cell apoptosis.[41] Defective mitophagy disrupts cellular homeostasis by failing to clear damaged mitochondria, leading to muscle atrophy. Enhancing mitophagy has been proposed as a therapeutic strategy to prevent muscle wasting in patients with CKD.[40,42]

Dysregulated Autophagy and Cellular Homeostasis

Importance of Autophagy in Maintaining Muscle Cell Health

Autophagy is a cellular process that degrades and recycles damaged organelles and proteins, maintaining tissue and cellular homeostasis. In skeletal muscle, satellite cells act as muscle stems and play a crucial role in muscle regeneration. Autophagy can affect satellite cells through various metabolic and stress-related cellular signals, thus affecting the regeneration process of muscle.[43] Proper autophagic activity prevents the accumulation of damaged proteins and organelles, which can otherwise lead to muscle dysfunction and atrophy.[43,44]

CKD-Induced Autophagy Suppression and Muscle Cell Degeneration

Uremic toxins associated with CKD promote systemic and vascular inflammation, oxidative stress and aging, are associated with systemic inflammation and metabolic disturbances that can inhibit autophagy in muscle cells. Inhibition of autophagy leads to the accumulation of damaged cellular components, promoting myocyte degeneration and atrophy.[13,45,46] Restoring autophagic activity in patients with CKD may help preserve muscle mass and function including aging muscles, muscular dystrophies, and mitochondrial myopathies by enhancing the clearance of defective cellular constituents.[47]

Clinical Implications and Translational Perspectives

Given the detrimental impact of CKD-associated sarcopenia on patient outcomes,[48] grasping its clinical and translational aspects is key to effective diagnosis and treatment. Identifying reliable biomarkers and developing targeted therapies are pivotal in managing CKD-related sarcopenia. Integrating exercise, nutrition, pharmacology and other interventions within a multidisciplinary framework holds promise for mitigating muscle wasting and enhancing patient well-being.

Biomarkers for CKD-Related Sarcopenia

Inflammatory Markers: IL-6 and TNF-α

Elevated levels of pro-inflammatory cytokines, such as IL-6 and TNF-α, have been implicated in the pathogenesis of sarcopenia among CKD patients. Pro-inflammatory cytokines, by upregulating calpain, E3 ligases, and NF-κB, and by locally inhibiting IGF-1 and insulin to enhance FOXO activation and diminish AKT activity, promote muscle protein catabolism and contribute to muscle wasting.[32,49] Studies have shown that increased serum IL-6 and TNF-α levels are positively correlated with the development of sarcopenia in patients with CKD patients. Higher concentrations of these cytokines are associated with greater muscle degradation in this population.[32,48] Grosicki et al found that lowering IL-6 offers an attractive treatment to keep skeletal muscle healthy.[50]

Myostatin and Klotho as Diagnostic and Monitoring Indicators

Myostatin, a negative regulator of muscle growth, has been found to have elevated levels in patients with CKD, leading to muscle atrophy.[51] Inhibition of myostatin has the potential to increase muscle mass, indicating its potential as a therapeutic target.[52] Klotho, an anti-aging protein predominantly expressed in the kidneys, exhibits reduced levels in CKD, with a progressive decline corresponding to advancing stages of CKD. Decreased levels of Klotho are associated with adverse outcomes, including muscle wasting.[28,53] Therefore, both myostatin and Klotho serve as potential biomarkers for the diagnosis and monitoring of sarcopenia in patients with CKD.

Therapeutic Targets

Development and Application Prospects of Myostatin Inhibitors

Targeting the myostatin/activin pathway has emerged as a promising therapeutic strategy for sarcopenia. Clinical studies investigating myostatin inhibitors have demonstrated potential benefits in increasing muscle mass and improving physical performance.[54] Although studies utilizing animal models have illustrated the beneficial effects of myostatin inhibitors, many clinical trials with human subjects have failed to replicate these outcomes.[37] Therefore, further research is needed to establish their efficacy and safety in patients with CKD.

Drugs Enhancing Mitochondrial Function: PPAR Agonists

Peroxisome proliferator-activated receptors (PPARs) are a group of nuclear receptors that function as ligand-activated transcription factors within the larger superfamily of nuclear receptor proteins and play a crucial role in regulating energy metabolism and mitochondrial function.[55] PPAR agonists, particularly PPAR-γ agonists like pioglitazone, have shown therapeutic effects in various kidney conditions.[56] These agents may improve muscle metabolism and reduce sarcopenia by enhancing mitochondrial function.[57]

Small Molecule Interventions Targeting the AMPK/mTOR Pathway

The AMP-activated protein kinase (AMPK)/mechanistic target of rapamycin (mTOR) pathway is integral to muscle protein synthesis and degradation.[33] AMPK is crucial for preserving cellular well-being and function, as it promotes autophagy to eliminate impaired organelles and proteins, and enhances mitochondrial biogenesis, which are often diminished in sarcopenic muscles. Modulating this pathway through small molecule interventions provides a potential therapeutic approach for sarcopenia in CKD. Activating AMPK can promote autophagy and mitochondrial biogenesis, while inhibiting mTOR can reduce protein degradation.[58,59] They are also capable of modulating muscle protein metabolism by influencing the insulin signaling in muscle cells.[60]

Integrated Management Strategies

Combining resistance exercise with nutritional interventions has shown positive effects on sarcopenia measures in CKD patients. Exercise stimulates muscle protein synthesis, while adequate nutrition provides the necessary substrates for muscle growth.[61,62] Physical exercise, including both aerobic and resistance training, is key to combating sarcopenia in CKD patients. Although the aggregated data from Heiwe and Jacobson's systematic review indicated that exercise training can improve exercise capacity in adults with chronic kidney disease, the inconsistent findings, particularly in quality of life outcomes, underscore the need for individualized exercise programs tailored to the specific characteristics and disease stages of CKD patients.[63] Given the significant heterogeneity among CKD patients, tailored intervention strategies are essential. Early-stage patients may benefit primarily from preventive exercise and nutritional interventions, whereas patients with advanced CKD or dialysis might require more comprehensive, multimodal therapeutic approaches. Moreover, differences in molecular profiles, such as varying levels of biomarkers like myostatin and Klotho, underscore the need for stratified analyses in future clinical trials to optimize personalized treatment strategies. Pharmacological treatments targeting specific molecular pathways can further enhance these effects, suggesting a synergistic approach to managing CKD-related sarcopenia.[64,65] Addressing sarcopenia in CKD requires a comprehensive approach involving nephrologists, dietitians, physiotherapists, and other healthcare professionals. Multidisciplinary management ensures that patients receive tailored interventions encompassing medical treatment, dietary planning, and physical rehabilitation, ultimately improving outcomes and quality of life.[66] Individualized comprehensive intervention based on the results of the patient's Comprehensive Geriatric Assessment (CGA) is expected to improve the prognosis of patients.[67,68]

Future Directions

CKD and sarcopenia share overlapping molecular pathways that require innovative research approaches for deeper understanding and effective clinical translation. Future studies should focus on leveraging emerging technologies, addressing existing challenges, and integrating multidisciplinary insights.

Emerging Research Areas

Single-Cell and Multi-Omics Approaches in CKD-Sarcopenia Research

Advances in single-cell transcriptomics, proteomics, and metabolomics offer unprecedented insights into the heterogeneity of tissues affected by CKD and sarcopenia. Single-cell RNA sequencing (scRNA-seq) enables the profiling of individual cell populations, uncovering cell-specific molecular changes that drive muscle wasting and kidney dysfunction. These approaches can identify novel biomarkers and therapeutic targets, such as cell-specific regulatory pathways and transcription factors.[69,70]

Multi-omics integration, which combines genomics, epigenomics, proteomics, and metabolomics, provides a holistic view of the sarcopenia and CKD.[71,72] Such integrative analyses can map interactions between muscle and kidney tissues at the systemic level, offering insights into the interplay of inflammation, metabolic dysregulation, and mitochondrial dysfunction.

AI-Driven Personalized Treatment Models

With the development of artificial intelligence (AI), it is possible to explore the personalized treatment of CKD and sarcopenia and has important clinical significance. Machine learning algorithms can process large datasets to predict

disease and prognosis, stratify patients based on risk, and recommend targeted interventions.[73] A research study that used eight distinct machine learning approaches to forecast CKD-related outcomes, based on a range of demographic, clinical, and comorbidity data, has uncovered potential predictive markers that may impact CKD progression, in addition to recognized indicators of adverse CKD prognosis.[74] AI can also integrate diverse datasets from imaging, molecular diagnostics, and clinical assessments, creating dynamic predictive models.[75]

Multidisciplinary Collaboration

Effective management of CKD and sarcopenia necessitates multidisciplinary collaboration among nephrologists, geriatricians, nutritionists, and rehabilitation specialists. This integrated approach addresses multifaceted issues, including nutritional deficiencies, muscle function decline, and comorbidities, through tailored interventions.[76,77] Such collaboration improves patient outcomes by combining expertise in medical care, dietary optimization, and physical therapy.[78]

Challenges

Data Heterogeneity and Biological Complexity

CKD and sarcopenia are influenced by a multitude of factors, including genetics, environmental exposures, and comorbidities. The heterogeneity of patient populations poses significant challenges for translational research. Variations in age, disease stage, and treatment history can confound the interpretation of molecular data.[79,80] Additionally, the complex interplay between kidney and muscle tissues involves numerous signaling pathways, making it difficult to isolate causative mechanisms.[81] Efforts to standardize data collection and harmonize analytical methods are crucial to addressing these challenges.[82,83] Developing robust frameworks for multi-omics data integration and implementing standardized protocols in clinical and preclinical studies will improve reproducibility and reliability.

Need for Multicenter, Longitudinal Studies

Efforts have been undertaken to devise medications targeting muscle deterioration by focusing on the molecular pathways involved in sarcopenia associated with chronic kidney disease. Despite favorable outcomes observed in preclinical animal studies, most subsequent clinical trials in humans have failed to achieve similar positive results, with a significant number of these initiatives exhibiting only marginal benefits.[64,84] Translating molecular insights into clinical practice requires multicenter, large-scale longitudinal studies. Such studies enable the validation of biomarkers and therapeutic targets across diverse populations and provide insights into disease progression. Long-term follow-up is critical to evaluating the efficacy of interventions and understanding their impact on outcomes like frailty, mobility, and mortality. Collaborative research networks can facilitate data sharing, ensuring that findings are generalizable and applicable across settings. Additionally, global consortia focusing on CKD and sarcopenia can drive innovation and accelerate the implementation of new diagnostic and therapeutic strategies.

Conclusion

In conclusion, an integrated perspective on the molecular and cellular mechanisms linking CKD and sarcopenia in aging reveals that chronic inflammation, oxidative stress, mitochondrial dysfunction, and impaired autophagy collectively disrupt muscle protein homeostasis and accelerate muscle wasting. Key pathways, including the myostatin/activin axis, AMPK/mTOR signaling, and defective mitophagy, offer promising therapeutic targets, yet the translation of these insights into effective treatments remains challenged by patient heterogeneity and complex disease interactions. Multidisciplinary collaboration, advanced technologies and multicenter, longitudinal studies are essential for validating biomarkers and optimizing personalized interventions to improve patient outcomes.

Data Sharing Statement

All data generated or analysed during this study are included in this published article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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