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Pathophysiology of Physical Exercise in Kidney Patients: Unveiling New Players – The Role of Myokines

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Keywords
Physical exercise · Myokines · Chronic kidney disease · Myostatin · Interleukin-6

Abstract
Background: Chronic kidney disease (CKD) is a progressive systemic condition characterized by numerous complications. Among these, alterations in skeletal muscle physiology, such as sarcopenia, are particularly significant, as they are associated with poor outcomes and reduced quality of life. ***Summary:*** Various interventions, including pharmacological approaches and lifestyle modifications have been investigated to slow CKD progression and prevent or treat its complications. Physical exercise, in particular, has emerged as a promising intervention with multiple beneficial effects. These include improvements in physical functioning, increased muscle mass, modulation of metabolic abnormalities, and reduced cardiovascular risk. However, the pathophysiology of physical exercise in patients with kidney disease is complex and remains only partially understood. A crucial advancement in understanding this phenomenon has been the identification of myokines – molecules expressed and released by skeletal muscle in response to physical activity. These myokines can exert both paracrine and systemic effects, influencing not only skeletal muscle physiology but also other processes such as energy metabolism and lipid regulation. ***Key Messages:*** The interplay among skeletal muscle, physical activity, and myokines may act as a pivotal regulator in various physiological processes, including aging, as well as in pathological conditions like cachexia and sarcopenia, frequently observed in CKD patients at different stages, including patients on dialysis. Despite the potential importance of this relationship, only a limited number of studies have explored the relationship between exercise and myokine, and the effect of this interaction on experimental models or individuals with kidney disease. In the following sections, we review and discuss this topic.

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Introduction

Chronic kidney disease (CKD) affects approximately 15% of the general population [1]. CKD patients stages 1 to 5 on conservative therapy or in renal replacement therapy tend to adopt a sedentary lifestyle [2], which correlates with an increased risk of mortality [3]. Moreover, a sedentary lifestyle promotes increased inflammation, oxidative stress, atherosclerosis, vascular calcification, altered lipid metabolism, and insulin resistance [4, 5].

The World Health Organization (WHO) guidelines on physical activity define a sedentary lifestyle as any waking behavior characterized by an energy expenditure of 1.5 metabolic equivalent of the tasks or lower while sitting, reclining, or lying (e.g., watching television or an office job) [6, 7].

Factors such as decreased muscle mass, cardiac dysfunction, and malnutrition contribute significantly to the inactive lifestyle observed in CKD patients [4]. Skeletal muscle, beyond its traditional role in movement, acts as an endocrine organ, producing myokines that regulate various physiological processes [8]. These myokines are secreted during physical activity and play roles in metabolism, insulin sensitivity, and immune function [9].

Promoting exercise and physical activity in CKD patients offers numerous benefits, including improvements in sarcopenia, physical function, mental performance, and quality of life, while also reducing inflammation and oxidative stress [10–13].

However, the precise mechanisms underlying these benefits, particularly the role of myokines, remain incompletely understood [1]. In this review, we aim to provide a comprehensive overview of the role of myokines in CKD patients, specifically focusing on the impact of exercise and physical activity on their pathophysiology.

Physical Exercise in Renal Disease

Physical activity is any bodily movement produced by skeletal muscles that requires energy expenditure. It should be gradually incorporated into the routine of CKD patients [14] to align with the World Health Organization (WHO) guidelines [6], which recommend in adults (aged 18–64 years and including those with chronic conditions) at least 150–300 min of moderate-intensity aerobic physical activity or 75–100 min of vigorous-intensity aerobic physical activity per week. Muscle-strengthening activities involving all major muscle groups are also recommended twice or more times a week at moderate or higher intensity.

Instead, physical exercise is a subset of planned, structured, and repetitive physical activity aimed at improving or maintaining physical fitness. When prescribing exercise in CKD, a patient-centered approach should be followed. This approach considers CKD stage, comorbidities, pharmacologic treatments, patient's goals, and physical capacity. An assessment of the patient's physical function can be performed using tests such as short physical performance battery, 6-min walking test, or five time sit to stand test [15]. Furthermore, due to the high cardiovascular risk of CKD patients, a stress test such as the cardiopulmonary exercise testing (CPET) is also helpful especially if the prescribed exercise is vigorous [16].

The type of exercise can differ from walking, running, cycling, and swimming for aerobic training to the use of weights, elastic bands, kettlebells, and machines but also bodyweight exercises for strength training [17]. Following the American College of Sports Medicine (ACSM) guidelines, which are based on the Frequency Intensity Time Type-Volume Progression (FITT-VP) principle, exercise programs for CKD patients on conservative treatment, dialysis, or kidney transplant recipients can be tailored [18]. Typically, the duration and frequency of training should be 30 min per day, 3–5 days per week. Meanwhile, the exercise intensity should be personalized according to maximum heart rate from exercise testing or by using the rating of perceived exertion (RPE) on the Borg scale (Table 1) [19].

Myokines: A General Overview

It is well-recognized that the skeletal muscle is involved in various physiological processes beyond its mechanical functions, including metabolic regulation, insulin sensitivity, and immune response [20, 21]. A significant advancement in understanding the role of skeletal muscle in these processes has been the identification of myokines, which are cytokines or small peptides produced and released by muscle fibers in response to physical activity [22].

Historically, interleukin-6 (IL-6) was the first molecule directly associated with skeletal muscle [23]. Starting from this initial evidence, the exploration of skeletal muscle as an endocrine organ has been the object of intense research, leading to the identification of various myokines, including myostatin, irisin, interleukin-15 (IL-15), insulin-like growth factor 1 (IGF-1), decorin, among others, with the list continuously expanding [24].

In addition, this scenario has recently become even more intricate with the emergence of the concept that myokines represent just one category elicited by physical

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Table 1. Exercise prescription according to the CKD stage (stages 1–5 CKD-ND, dialysis, and kidney transplant)

	Aerobic training	Resistance training
Stages 1–5 CKD-ND	From moderate (3.0–5.9 METs; RPE 12–14) to vigorous (6.0–8.9 METs; RPE 15–17)	3 sets of 10–15 repetitions of flexion/extension motion of different muscle groups 70% 1-RM
Dialysis	Moderate (3.0–5.9 METs; RPE 12–14)	2/3 set of 8–15 repetitions of flexion/extension motion of different muscle groups 50/60% 1-RM
Kidney transplant	Vigorous (6.0 a 8.9 METs; RPE 15–17)	3 sets of 10–15 repetitions of flexion/extension motion of different muscle groups 70/80% 1-RM

CKD, chronic kidney disease; MET, metabolic equivalent of task; ND, not on dialysis; RPE, rating of perceived exertion on the Borg scale 6-20; 1-RM, maximum weight a subject can lift for a single repetition of a given exercise. [19].

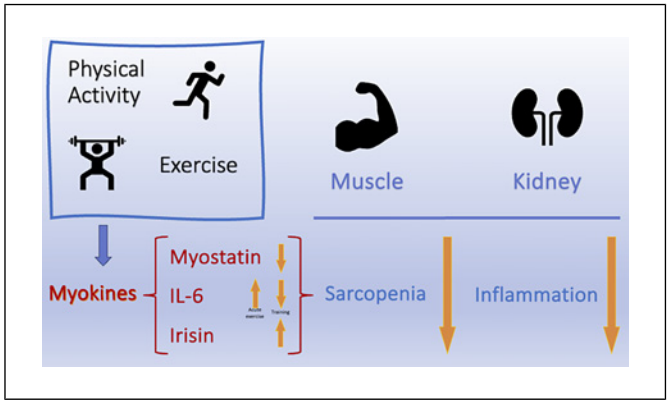

Fig. 1. Exemplificative representation of the potential effects of physical activity and exercise on the most studied myokines in experimental models of renal disease and CKD patients.

exercise. The term "Exerkines" has been introduced to encompass a diverse array of signals released by skeletal muscles in response to acute and chronic exercise [25]. Exerkines may include cytokines, nucleic acids, and metabolites released by other organs and tissues, such as the heart (cardiokines), liver (hepatokines), white adipose tissue (adipokines), brown adipose tissue (batokines), and the nervous system (neurokines).

Focusing on myokines, it should be recognized that beyond the distinct characteristics of individual molecules, they share common features such as secretion by skeletal muscle, modulation by physical activity, and the ability to exert both local and systemic effects. These myokines mediate communication between skeletal muscle and other organs, such as the adipose tissue, liver, and brain, influencing physiological processes and contributing to the pathogenesis of conditions like obesity, diabetes, and neurodegenerative disorders [26–28].

Notably, myokines may also play various roles in the pathogenesis of kidney diseases, participating in the muscle-kidney crosstalk [29]. For instance, molecules such as IL-6, irisin, Myostatin, and FGF21 exhibit differential expression in both experimental and clinical diabetic nephropathy, where they may serve as progression factors or therapeutic targets [30–32].

Furthermore, myokines appear to be implicated in the pathogenesis of vascular alterations related to CKD [33]. However, in addition to their systemic actions, it is crucial to consider the autocrine and paracrine effects of myokines, primarily involved in regulating muscle physiology, including muscle growth, satellite cell proliferation, and lipid metabolism [34].

Given the involvement of myokines in numerous complex pathways, it is not surprising that these molecules have been investigated in physiological processes such as aging and pathological conditions like sarcopenia and CKD [35, 36]. Their expression has specifically been evaluated in experimental and clinical CKD, where modulation, achievable through pharmacological approaches as well as physical exercise [37], may significantly impact multiple processes (Fig. 1; Table 2).

Interleukin-6

The human *IL-6* gene is situated at the p21 region of human chromosome 7. It comprises a 28-amino-acid signal peptide, which, due to varying glycosylation, may manifest as various subtypes with molecular weights ranging from 21.5 to 28 kDa.

Additionally, different IL-6-related signaling pathways have been identified, including the classical pathway, dependent on IL-6 binding to membrane-bound IL-6 receptors (IL-6R), and the trans-signaling pathway, which involves the interaction of soluble IL-6/IL-6R complexes with transmembrane proteins [38].

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Table 2. Basal values of myokine and potential benefits of their modulation in experimental models of renal disease and CKD patients

Myokine	Basal values CKD versus no-CKD (ref)	Potential benefits of modulation (ref)		
		skeletal muscle	nephroprotective role	ancillary benefits
Myostatin*	↑ = [89, 92]	Anti-sarcopenic [75]	Anti-inflammatory [71, 82]	Improved glucose tolerance [71, 82]
IL-6*	↑ [55–57]	N/A	Anti-inflammatory effect [50]	Improved cardio-metabolic profile [138]
Irisin*	↓ [114]	Anti-sarcopenic [111]	Anti-inflammatory [112, 113] Reduced oxidative stress and apoptosis [112, 113] Reduced glomerular hyperfiltration and fibrosis in diabetic nephropathy [32]	Improved glucose tolerance [108] Reduced vascular calcifications [33]
IL-15	↓ [139]	N/A	Anti-inflammatory effect [121] Anti-fibrotic effect [121]	Improved glucose tolerance [119, 120]
BDNF	↓ [140]	N/A	Anti-inflammatory effect [125] Reduced oxidative stress [125]	Improved glucose tolerance [123] Increased fat oxidation [124]
Apelin	↓ ↑ [129, 130]	Anti-sarcopenic [126]	Anti-EndMT [127] Anti-fibrotic [127] Endothelium-dependent vasodilator [128]	–
FGF21	↑ [141]	N/A	Anti-fibrotic [132]	Improved glucose tolerance [133] Improved lipid metabolism [133]
IGF-1*	↓ [136]	Anti-sarcopenic [107]	–	–

IL-6, interleukin-6; IL-15, interleukin-15; BDNF, brain-derived neurotrophic factor; FGF21, fibroblast growth factor 21; IGF-1, insulin-like growth factor 1; EndMT, endothelial-to-mesenchymal transition. N/A = data not available. *Data from clinical studies evaluating the effects of physical exercise in CKD patients are reported in Table 3.

The intricate nature of these molecular pathways likely contributes to the diverse effects of IL-6, which encompass the regulation of inflammation, immune response, hematopoiesis, and metabolism [39–41]. Skeletal muscle is a significant source of IL-6 production, particularly in response to physical exercise [42, 43]. Initially hypothesized to be released by immune cells, subsequent molecular analyses demonstrated a direct production and secretion of IL-6 by skeletal muscle cells, establishing this cytokine as the first member of the myokine family [41, 44, 45].

In resting skeletal muscle, IL-6 mRNA content is low, but both muscle *IL-6* gene and protein expression significantly increased in response to acute exercise in healthy subjects [46]. Notably, these effects are associated with the intensity and duration of exercise rather than muscle injury [47]. When acting as a myokine, IL-6 exerts multiple effects. Initially, during exercise, IL-6 release activates metabolic pathways capable of mobilizing glucose and fatty acids from the liver and adipose tissue to provide energetic substrates for skeletal muscle contraction [48, 49].

Then, higher levels of IL-6 after acute physical exercise may have an anti-inflammatory effect, eventually mediated by decreased levels of tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), along with increased production of the anti-inflammatory cytokines IL-1ra and interleukin-10 (IL-10) [50, 51]. However, the relationship between IL-6 and skeletal muscle is complex and not linear, influenced by lifestyle, and type and duration of training, among other factors [52]. In older individuals, elevated IL-6 levels are associated with poor physical performance and muscle strength [53], while physical activity is linked to decreased muscle inflammation and IL-6 levels [54], suggesting chronic exercise as a potential intervention

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Table 3. Summary of the main clinical studies evaluating the effects of different type of physical exercise in CKD patients at different stages

Myokine	Study (Ref)	CKD stage	*n*	Exercise program	Duration	Effects on circulating level	Effects on muscle tissue expression
Interleukin-6	Castaneda et al. [61] (2004)	3–5	14	RT	12 weeks	↓	
	Headley et al. [142] (2012)	2–4	10	Aerobic exercise	12 weeks	NO	
	Viana et al. [58] (2014)	5	13	Acute (walking)	30′	↑	
				Walking training	6 months	↓	
	Watson et al. [59] (2017)	3b–4	7	Acute resistance exercise	1 exercise session		↑
				RT	8 weeks		NO
	Ikizler et al. [60] (2018)	3–4	27	Aerobic exercise	4 months	↓	
	Correa et al. [62] (2021)	2	35	RT	6 months	↓	
	Watson et al. [98] (2022)	3–5	21	Aerobic	Acute (1 session)	NO	↑
			20	Combined	12 weeks		NO
	Kopple et al. [97] (2007)	HD	37	Combined	21 weeks (median)	NO	
	Wilund et al. [63] (2010)	HD	17	Intradialytic cycling	4 months	NO	
	Cheema et al. [67] (2011)	HD	24	RT	12 weeks	NO	
	Liao et al. [64] (2016)	HD	40	Intradialytic cycling	3 months	↓	
	Cruz et al. [65] (2018)	HD	15	Intradialytic cycling	12 weeks	↓	
	Dong et al. [66] (2019)	HD	21	RT	12 weeks	NO	
	Moura et al. [143] (2020)	HD	81	RT	24 weeks	↓	
	Highton et al. [144] (2021)	HD	20	Intradialytic cycling	6 months	NO	
	March et al. [68] (2022)	HD	46	Intradialytic cycling	6 months	NO	
Myostatin	Watson et al. [59] (2017)	3b–4	7	Acute resistance exercise	1 exercise session		↓
				RT	8 weeks		↓
	Zhou et al. [99] (2021)	3–5	151	Combined	12 months	↑	
		3–5	21	Aerobic			

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Table 3 (continued)

Myokine	Study (Ref)	CKD stage	*n*	Exercise program	Duration	Effects on circulating level	Effects on muscle tissue expression
	Watson et al. [98] (2022)				Acute (1 session)	↓	↓
			20	Combined	12 weeks	NO	↓
	Kopple et al. [96] (2006)	HD		RT	8.9 weeks (median)		↓
	Kopple et al. [97] (2007)	HD	37	Combined	21 weeks (median)		↓
Irisin	Moraes et al. [115] (2013)	HD	26	RT	6 months	NO	
	Esgalhado et al. [116] (2018)	HD	15	Acute intradialytic exercise	30′	NO	
IGF-1	Kopple et al. [96] (2006)	HD		RT	8.9 weeks (median)		↑

CKD, chronic kidney disease; HD, hemodialysis; RT, resistance training. Combined exercise program: Aerobic+ RT; NO = no significant changes compared to basal values.

to control inflammation, especially in fragile subjects. In this regard, CKD at different stages (from non-dialysis to dialysis patients) presents a peculiar risk profile, exhibiting a systemic subclinical inflammation, characterized by elevated IL-6 levels, and associated with adverse outcomes, such as cardiovascular disease, sarcopenia, atherosclerosis, bone diseases, and increased mortality [55].

Interestingly, resident renal cells expressing IL-6R may be directly involved by the activation of both classical and trans-signaling IL-6 pathways, which may, in turn, play a role in CKD progression [56]. Moreover, IL-6 is elevated in the muscles of CKD patients, contributing to local and systemic inflammation, which may lead to reduced protein synthesis and increased protein degradation [56, 57]. Considering these factors, various strategies have been proposed to attenuate IL-6 release and production in CKD, including optimal dialysis treatment and lifestyle modifications [34, 37]. Several studies have explored the capacity of different types of exercise interventions to modulate IL-6 levels in the diverse population of CKD patients (Table 3).

Looking at the non-dialysis CKD population, Viana et al. [58] 2014 investigated the effects of physical exercise on inflammatory molecules in advanced CKD. They confirmed a bimodal regulation of IL-6, with plasma IL-6 levels increasing after acute exercise, along with higher levels of IL-10, but decreasing after 6 months of regular walking exercise.

Similar findings were reported in 2017 by Watson et al. in a secondary analysis of a trial conducted on 38 patients with CKD stage 3b–4 randomized to receive an 8-week resistance exercise training intervention [59]. Overall, acute unaccustomed exercise was associated with a large inflammatory response, evidenced by increased gene expression of IL-6, MCP-1, and TNF-α, which was subsequently reduced after training.

In 2018, Ikizler TA et al. randomized 122 participants with CKD stages 3 and 4 to receive a 4-month intervention with aerobic exercise in combination with caloric restriction. They found that each intervention was independently associated with an improved pro-inflammatory metabolic milieu, and a significant reduction of IL-6 concentrations [60].

Conversely, the effects of resistance training were investigated in 2004 by Castaneda C. et al. [61] in 26 non-dialysis patients on a low-protein diet. They found that resistance training reduced inflammation and improved nutritional status.

Similarly, Correa et al. [62] in patients with stage 2 CKD observed that a 6-month resistance training program improved both uremic parameters and inflammatory markers, including IL-6, and notably, delayed the progression of kidney disease. However, the potential

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exercise-mediated IL-6 modulation has also been tested in HD patients with nonuniform results.

For instance, in 2010, Wilund et al. [63] found no effects on inflammatory markers of intradialytic exercise training prescribed in 17 HD patients. On the opposite, Liao et al. [64] in 40 HD patients randomized to exercise (cycling) for 3 months observed significant improvements in serum albumin levels, body mass index, and IL-6.

More recently, these findings have been confirmed by Cruz et al., [65] who found a reduction in IL-6 serum levels after 12 weeks of intradialytic aerobic training. However, several other studies have shown that progressive intradialytic resistance training did not affect IL-6 circulating levels [66–68].

Finally, a recent meta-analysis showed that different types of exercise interventions in CKD patients are associated with a significant decrease in pro-inflammatory molecules, including IL-6, C-reactive protein, and TNF-α, along with an increase in IL-10 [69]. However, subgroup analysis showed that the effects of exercise on reducing IL-6 are more prominent in non-dialysis CKD patients and when interventions lasted more than 16 weeks.

Undoubtedly, the heterogeneity of patient populations and interventions (type of exercise, duration) renders the interpretation of the results of these studies and others with similar aims difficult to make. Therefore, while exercise intervention seems to be a reliable strategy to modulate IL-6 in CKD patients, defining the right target population and implementing an adequate program to promote improvements in clinical outcomes remains to be determined.

Myostatin

Myostatin, also known as growth and differentiation factor-8 (GDF8), belongs to the transforming growth factor-β (TGF-β) family and was first identified in 1997. It is initially synthesized as an inactive 375 kDa precursor (pre-pro Mstn) and undergoes processing to produce a 12.5/26 kDa mature peptide [70]. Myostatin acts by binding to type II activin receptor IIB, which activates intracellular pathways, including Smad proteins and mitogen-activated protein kinases (MAPKs), regulating essential cellular processes like cell differentiation and inflammation [71]. Skeletal muscle cells are the primary source of total body myostatin, serving as the principal negative regulator of muscle growth. Its expression is downregulated by physical activity, yet it exerts detrimental effects on muscle growth by influencing various cell types, including satellite cells and myofibers.

Primarily acting on myofibers, myostatin inhibits myogenesis, reducing the gene expression of molecules involved in skeletal muscle development through the inhibition of the IGF-1/Akt/mTOR pathway [72]. Additionally, it can enhance muscle loss by activating proteolysis and autophagy through the upregulation of the ubiquitin-proteasome system and inhibiting satellite cell proliferation and differentiation [73]. Myostatin's role as a potential mediator and biomarker of aging and sarcopenia is evident through experimental models showing a significant negative correlation between *Mstn* gene expression and muscle mass and strength in older animals and adults [74]. Coherently, the inhibition or knockout of muscle expression of myostatin has demonstrated beneficial effects during aging and in reducing the extent of sarcopenia [75].

However, contradictory results have emerged regarding serum myostatin levels in the elderly population, suggesting a discrepancy between muscle and systemic Mstn expression and effects [76]. In con trast to sarcopenia, cachexia, characterized by weight loss and severe wasting associated with inflammation and metabolic derangements, represents a pathological condition observed in chronic diseases such as cancer, heart failure, liver cirrhosis, and CKD [77].

Experimental and clinical studies have hypothesized myostatin's role in cachexia, observing correlations between systemic Mstn overexpression in adult mice and muscle and fat loss, typical features found in cachectic patients [78–81].

Beyond muscle production, myostatin is expressed in various tissues, including adipose tissue, liver, kidney, and bone. Accumulating evidence suggests its implications in physiological and pathological processes, including energy metabolism, bone mineralization, inflammatory-related vascular alterations, insulin resistance, and obesity [71, 82].

Myostatin is also directly expressed in the human kidney, in both glomerular and tubulointerstitial compartments. This expression is upregulated in diabetic nephropathy and directly correlated with interstitial fibrosis [83]. Moreover, myostatin expression is also upregulated in the arterial wall of CKD patients, where, similarly to its effects observed in skeletal muscle, it may induce ubiquitin-mediated proteolysis of intracellular proteins, thus influencing vascular structure [84].

Therefore, myostatin may potentially play a significant role in the pathogenesis, progression, and onset of complications in CKD patients. In this regard, one of the most typical aspects of patients with CKD, particularly those undergoing HD, is the high prevalence of

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malnutrition and muscle wasting, which directly correlates with morbidity and mortality [85].

Malnutrition and muscle wasting, whose components have been synthesized in the definition of protein energy wasting (PEW) syndrome, are multifactorial conditions with a complex physiopathology [86, 87]. Myostatin overexpression may contribute to these conditions, supported by data indicating the association between its upregulation and inflammation in the skeletal muscle of CKD murine models and in human CKD muscle biopsies [88, 89].

Moreover, inflammatory cytokines and uremic toxins, such as TNF-α and indoxyl sulfate, induce Mstn, thus promoting protein catabolism [90]. Therefore, Mstn may constitute a link between inflammation and PEW in CKD patients [91]. However, also in CKD patients, data on circulating Mstn levels seem in contradiction with those reported in skeletal muscle [92, 93].

Given its substantial regulatory effects on muscle growth and metabolism, inhibiting or modulating myostatin signaling has been explored as a potential therapeutic strategy in various clinical conditions, focusing on improving muscle mass and performance status in patients with sarcopenia and cachexia. Currently, physical exercise remains the most effective and safe intervention to modulate Mstn muscle expression. Resistance exercise training has demonstrated beneficial effects in attenuating the progression of sarcopenia, improving muscle size and strength, and decreasing *Mstn* gene expression in animal models, healthy individuals, and patients with chronic heart failure [94, 95]. Specific effects of physical exercise on myostatin muscle expression or systemic levels in kidney disease patients have been scarcely investigated (Table 3).

In 2006, Kopple et al. [96] reported the secondary analysis of a randomized interventional study testing the effects of 8-week resistance training in a cohort of HD patients undergoing muscle biopsy. The authors observed that, following training, there was an increase in the gene expression of IGF-I, IGF-I receptor, and IGF binding proteins (IGFBPs), while Mstn expression significantly decreased (-51%). One year later, the same group reported similar results testing different forms of exercise training (endurance, strength, or a combination) in 51 HD patients [97]. After about 21 weeks, they found that all the exercise programs improved physical performances and reduced body fat content, while significantly increasing IGF-I and IGFBPs and reducing *Mstn* gene expression.

More recently, the effects of exercise on muscle Mstn expression have also been tested in non-dialysis-dependent CKD patients. In the previously mentioned study by Watson, it was found that muscle gene expression of Mstn was significantly suppressed from baseline following both acute exercise and resistance training in patients with CKD stage 3b–4 [59].

These data were then confirmed later by the same group in a larger cohort [98]. Despite the promising results, only one study has prospectively evaluated the relationship between training and circulating Mstn in CKD patients. This study, part of the Renal Exercise (RENEXC) trial, demonstrated that 12 months of exercise training increased lean mass and decreased fat mass in 151 CKD non-dialysis-dependent patients [99]. However, the prevalence of sarcopenia was unchanged, and most interestingly, plasma myostatin levels were significantly positively correlated with muscle mass and physical performance and further increased after training, suggesting that circulating myostatin reflects muscle mass content rather than being a marker of muscle wasting [100]. The role of myostatin in sarcopenia pathogenesis has prompted exploration of pharmacological approaches. While inhibition in aged mice has shown increased muscle mass and strength, direct inhibition in humans, including HD patients, has yielded limited results. Multitarget strategies focusing on inhibiting myostatin receptor or downstream pathways appear more promising, though these therapeutic strategies are still far from clinical application.

Irisin

Irisin represents one of the first identified and most studied myokines. It derives from the cleavage of fibronectin type III domain-containing 5 protein (FNDC5) and ones released into the bloodstream, after binding to its receptor integrin aV/b1/5, it can mediate pleiotropic functions in several tissues and organ systems through the adenosine 5'-monophosphate-activated protein kinase (AMPK), the focal adhesion kinase (FAK), and the MAPK signaling pathways [101].

It is vigorously produced after acute physical exercise, and by activating downstream pathways in an autocrine manner, it plays a key regulatory role in muscle growth and differentiation of myoblasts [102]. Notably, there is conflicting evidence about the effects of chronic exercise on irisin production [103], but recent metanalysis suggest the importance of the type of training performed: chronic resistance training programs seem to lead to an increase in irisin levels comparable to that obtained with acute exercise [104, 105]. The strict relationship with muscle physiology has allowed to identify circulating irisin as a biomarker for muscle mass and performance, taking into

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consideration its significantly lower levels in patients with sarcopenia [106].

However, as expected by its myokine role, beyond musculoskeletal homeostasis, irisin is also involved in many other regulatory pathways, including liver and glucose metabolism, white fat browning and neuroprotection. Noticeably, evidence is recently mounting for what concerns the role played by irisin in the field of kidney diseases.

First of all, it is important to underline that irisin is involved in kidney protection more broadly and indirectly by counteracting oxidative stress and glucose intolerance, which conspicuously contribute to renal damage and CKD progression [107]. In an in vivo model, treatment with irisin was shown to improve glucose tolerance and diet-induced obesity [108]. More specifically, for what concerns diabetic nephropathy, Wang et al. have found decreased levels of circulating irisin in diabetic patients with micro- and macroalbuminuria compared to those with normal albuminuria. Of note, the myokine's serum concentration showed, respectively, a linear and an inverse relationship with glomerular filtration rate and proteinuria [32].

Recently, Formigari et al. have shed light on the potential involvement of irisin in physical exercise-mediated nephroprotection in diabetic nephropathy. In an in vivo model of diabetic rats, 8 weeks of aerobic physical exercise hindered the development of glomerular hypertrophy and fibrosis. This finding was linked with an increased irisin expression in the muscle and with an activation of the AMPK pathway in the kidney. Of note, treatment with an irisin receptor inhibitor (CycloRGDyK) counteracted the irisin-mediated nephroprotective effects observed after physical exercise, such as the reduction of albuminuria and the glomerular expression of fibronectin and collagen IV [109].

Renal fibrosis represents the pathophysiological hallmark of CKD. The treatment with irisin of tubule cells incubated with a well-known mediator of kidney damage, TGFβ, leads to suppression of downstream signaling pathways of TGFβ and increased aerobic metabolism. Moreover, the same authors showed that the administration of irisin to an in vivo model of kidney fibrosis and CKD was associated with an improvement of both kidney histopathology and function [110]. CKD is notoriously associated with vascular calcifications, which represent one of the main causes of high cardiovascular risk in this population. Irisin treatment was shown to protect against medial vascular smooth cell calcifications in vitro and in a CKD mouse model by reducing inflammation and pro-inflammatory cell death [33]. The same research group has very recently described how irisin may be able to counteract PEW. The use of irisin in mouse models of CKD-related muscle atrophy led to reduced fatty acid oxidation and apoptosis and consequently to an improvement of skeletal muscle atrophy [111]. Of note, there is evidence that irisin plays a nephroprotective role in the context of acute kidney injury, as well. Liu et al. [112] have shown in vitro and in vivo irisin expression in kidney tubule cells during ischemia-reperfusion-injury (IRI) conditions. The authors showed an autocrine renal defense mechanism mediated by irisin leading to decreased oxidative stress and inflammation. This finding was confirmed in another recent paper in which irisin pretreatment allowed for a dampening of apoptosis, inflammation, and oxidative stress in mouse renal tissue subjected to IRI [113].

Recently, Wen et al. [114] have found decreased irisin plasma levels in patients affected by advanced CKD compared to healthy subjects. The authors have identified reduced muscle mass and circulating uremic toxins as factors possibly responsible for this reduction.

For what concerns the effects of physical exercise on irisin levels in CKD patients, evidence is still scarce and derives solely from studies conducted on hemodialytic patients. Notably, no difference was observed in plasma irisin levels of hemodialysis patients after both an intradialytic resistance training program of 6 months and after acute intradialytic exercise sessions [115, 116]. In conclusion, whether induced by physical exercise or as a recombinant drug, in the future irisin may represent a promising therapeutic agent in renal diseases, mainly – but not only – aimed at reducing the high cardiovascular risk which characterizes CKD patients.

Other Myokines

Myostatin, irisin, and IL-6 are the most well-known myokines in the field of renal diseases. Nevertheless, other promising ones are gaining interest and evidence such as IL-15, brain-derived neurotrophic factor (BDNF), apelin, fibroblast growth factor 21 (FGF21), and IGF-1, which production and release are significantly upregulated by physical exercise.

IL-15 is a cytokine member of the interleukin-2 superfamily involved in skeletal muscle fiber growth and myocyte differentiation [117]. Studies on mice and humans showed an augmented production and secretion of IL-15 in skeletal muscle after physical exercise [118]. Of note IL-15 seems to act positively on metabolic diseases enhancing glucose uptake and tolerance [119, 120]. Moreover, in a unilateral ureteral obstruction model, treatment with IL-15 was recently associated with a

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reduced inflammatory milieu and myofibroblasts-mediated fibrosis [121].

The neurotrophin BDNF recently emerged as a myokine linked with protective effects in diabetes and obesity [118]. The extent of its muscular release after acute and especially chronic physical exercise are yet to be elucidated [122], but the metabolic beneficial effects are well ascertained. Treatment of diabetic mice with BDNF enhances glucose metabolism in the diabetic muscle and leads to decreased blood glucose levels [123]. An increased BDNF production in the skeletal muscle after contraction results in an AMPK-dependent fat oxidation showing a myokine's beneficial role in energy homeostasis. Interestingly, BDNF circulating levels were found low both in obese and diabetic patients [124]. Finally, a recent paper by Asfar et al. described a strong association between CKD, inflammation, and oxidative stress and proposed BDNF as a promising biomarker, considering that BDNF low levels are linked with sarcopenia, depression, and reduced exercise capacity in CKD patients [125].

As previously stated, skeletal muscle atrophy is a well-known complication of CKD. Apelin is a myokine with a direct anti-sarcopenic effect. Enoki et al. [126] showed a two-phase trend in apelin's production in a CKD mouse model with an increased expression in the early stages of CKD (8 weeks after 5/6 nephrectomy) and a reduction in myokine's expression in later stages. Interestingly, treatment with apelin led to an improvement in CKD-induced sarcopenia.

Moreover, a recent paper described an in vitro and in vivo nephroprotective role played by apelin, consisting in an anti-endothelial-to-mesenchymal (EndMT) transition and anti-fibrotic effect via the inhibition of TGFβ/Smad signaling [127]. It is interesting to point out that this myokine seems to be also involved in the pathophysiology of acute kidney injury by exerting an endothelium-dependent vasodilator effect [128].

Few data have been reported in human CKD, where apelin circulating levels have been found both under and upregulated when compared with healthy subjects. The potential clinical implications of these findings and the effects of physical exercise in CKD remain to be clarified [129, 130].

The hormone FGF21 is mainly produced in the liver but also by the skeletal muscle during physical exercise [131]. The beneficial role played by FGF21 as a metabolic regulator is well known and confirmed in therapeutic studies [132]. Moreover, its involvement in hindering the histopathological alterations found in diabetic nephropathy was observed [133].

Of note, increased levels of FGF21 were found in CKD models and patients affected by CKD, but the pathophysiological meaning and the implications of these findings still need to be elucidated [134]. IGF-1 is a growth hormone (GH) essential for bone and tissue development. Alterations of the GH/IGF-1 axis and the high-affinity IGFBP activity were observed in renal diseases. In particular, an overactivation was found in the early stages of diabetic nephropathy and autosomal polycystic kidney disease [135, 136], whereas resistance to GH/IGF-1 was observed in CKD, which may be due to metabolic acidosis, inflammation, and uremia [137]. Interestingly, physical exercise is positively associated with IGF-1 production, as also found by Kopple et al. [96] The authors observed an increase in the skeletal muscle expression of IGF-1 and IGFBPs after exercise training in dialysis patients, which was associated with a reduction in body fat and an increase in fat-free mass.

Moreover, there is evidence of a key role played by IGF-1 in the anabolic response observed after physical exercise in CKD and hemodialysis patients [107]. As outlined above, all these exercise-induced cytokines and peptides have been acknowledged as myokines with a promising role in the field of kidney diseases. Nevertheless, the knowledge about their involvement in humans and in the different stages of CKD has to be deepened.

Conclusions

The identification and characterization of myokines have marked a significant advancement in comprehending the intricate pathophysiology of skeletal muscle. In particular, the modulation of myokines by physical exercise may partially elucidate the role of physical activity in muscular physiology, as well as its impact on metabolism and other systemic processes.

Experimental and clinical data indicate that, in CKD patients, physical exercise may serve as a potent regulator of both muscle and systemic myokine effects. These regulatory mechanisms hold promise for having a positive influence on conditions such as sarcopenia, malnutrition, metabolic dysregulation, and chronic inflammation in this patient population. Moreover, through the regulation of myokines, physical exercise may contribute to a delayed progression of kidney disease.

Hence, while myokines can be potential therapeutic targets, physical exercise emerges as an even more formidable tool for improving patient outcomes. However, also considering the lack of specific data for other CKD

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patient populations, such as those undergoing peritoneal dialysis and kidney transplantation, further research is needed to identify the most effective type of exercise, determine which patients stand to benefit the most and optimize the integration of physical exercise with pharmacological and non-pharmacological interventions.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization: D.P. and P.E.; methodology: D.P.; resources: L.M.; data curation, L.M. D.V., and F.B.; writing – original draft preparation; P.E., D.P. Y.B. and C.M.; writing – review and editing: E.R. and F.V. All authors have read and agreed to the published version of the manuscript.

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