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Review

The role of irisin in kidney diseases

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ABSTRACT

Irisin is a hormone that is produced mainly by skeletal muscles in response to exercise. It has been found to have a close correlation with obesity and diabetes mellitus for its energy expenditure and metabolic properties. Recent research has revealed that irisin also possesses anti-inflammatory, anti-oxidative and anti-apoptotic properties, which make it associated with major chronic diseases, such as chronic kidney disease (CKD), liver diseases, osteoporosis, atherosclerosis and Alzheimer s disease. The identification of irisin has not only opened up new possibilities for monitoring metabolic and non-metabolic diseases but also presents a promising therapeutic target due to its multiple biological functions. Studies have shown that circulating irisin levels are lower in CKD patients than in non-CKD patients and decrease with increasing CKD stage. Furthermore, irisin also plays a role in many CKD-related complications like protein energy wasting (PEW), cardiovascular disease (CVD) and chronic kidney disease-mineral and bone disorder (CKD-MBD). In this review, we present the current knowledge on the role of irisin in kidney diseases and their complications.

1. Introduction

Irisin, a glycosylated protein hormone consisting of 112 amino acid residues, is the cleavage product of fibronectin type III domain-containing 5 (FNDC5), a transmembrane protein of skeletal muscle that is regulated by peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α) [1]. Boström et al. [2] first identified irisin in 2012 and named it after the Greek messenger goddess “Iris”, and since then, it has received attention for its role in metabolism and in metabolic diseases. Irisin is released mainly from skeletal muscle and adipose tissue during exercise or when exposed to cold, making it an adipomyokine [3]. Irisin stimulates browning of white adipose tissue by upregulating browning-related genes, such as uncoupling protein 1 (UCP1) and peroxisome proliferator- activated receptor gamma (PPARγ), regulating the phosphorylation of p38 mitogen-activated protein kinase (p38 MAPK) and extracellular signal-related kinase (ERK) [4–8]. Irisin also promotes the expression of genes associated with lipolysis, leading to the release of glycerol and a reduction in lipid accumulation in adipocytes, thereby improving lipid metabolism [9]. Additionally, it enhances the insulin-mediated glucose uptake capacity of beige fat cells by increasing the expression of Glucose transporter type 4 (GLUT-4) and improves diet-induced insulin resistance in obese adults [10–13]. These unique properties of irisin make it a promising candidate for the treatment of obesity and other metabolic disorders.

Moreover, irisin has been identified in various tissues and has multiple biological functions [14,15]. It participates in a variety of pathophysiological processes, including ameliorating oxidative stress, reducing inflammation, and inhibiting apoptosis [16–18]. Irisin is also involved in the development and progression of several chronic diseases, such as diabetic mellitus (DM) [19], cardiovascular disease (CVD) [20,21], osteoporosis [22], sarcopenia [23]. As all of these diseases are closely related to kidney diseases [24], it is intriguing to investigate the effects of irisin on kidney diseases and their associated complications.

Chronic kidney disease (CKD) is defined as abnormalities of kidney structure or decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1.73 m^2, present for >3 months, with implications for health [25]. Hypertension and diabetes are the most frequent causes of CKD, especially in the elderly. The decline in kidney function leads to a retention of toxins normally eliminated by the kidneys, resulting in uremia. Kidney biopsy can reveal definitive evidence of CKD, displaying common changes such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Presence of proteinuria is the strongest associated factor for the progression of CKD, along with uremic toxin, metabolic acidosis, inflammation, elevated Ang II, insulin resistance, and anorexia. The accumulation of uremic toxins in the circulation and in tissues is linked to the complications in CKD as well,

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including CVD.

2. Circulating irisin levels in kidney diseases

While most cytokines and adipokines tend to increase as kidney function declines, circulating irisin levels decrease in patients with advanced stages of kidney disease, which suggests a correlation between irisin levels and estimated glomerular filtration rate (eGFR) in chronic kidney disease (CKD) patients. In general, CKD patients have lower than normal levels of irisin, and serum irisin concentration tends to decrease as CKD progresses to more advanced stages [26,27], and irisin levels are lower in dialysis patients than in non-dialysis patients [28]. However, the mechanisms that explain the observed associations between irisin levels and the type or severity of kidney disease are likely multifactorial and have yielded inconsistent results in various studies [29].

2.1. Body composition

CKD patients often experience weight loss, progressive muscle weakness, and loss of muscle and fat mass due to reduced physical activity. The prevalence of sarcopenia in CKD patients ranges from 11 % to 28 % [30]. The reduction in muscle mass may contribute to the reduced secretion and expression of irisin in these patients. In obese individuals, serum irisin levels were found to be higher and correlated with weight, body mass index (BMI), waist circumference, and fat mass [31,32], and declined with weight loss [33]. In a study conducted on kidney failure mice, irisin expression in the gastrocnemius muscles decreased [34]. In CKD patients with type 2 diabetes mellitus (T2DM), irisin was associated with fat mass, BMI and eGFR [35]. In dialysis patients, irisin levels positively correlated with lean body mass and percent body fat [36].

Previous studies have observed that the effect of traditional risk factors on CVD in people with CKD varies from the general population; hypertension and elevated cholesterol are not related to reduced survival in advanced CKD, or even exhibit effects in a contrary direction, a phenomenon referred to as reverse epidemiology [37,38]. However, some studies did not find a significant association between irisin and markers of body composition in CKD patients [26,39], yet there was a negative correlation between irisin and these body composition markers in normal subjects, which seems to fit with the reverse epidemiology phenomenon in CKD subjects. Furthermore, despite increasing muscle mass, a resistance exercise training was unable to elevate circulating irisin levels in hemodialysis (HD) patients [40].

2.2. Uremic toxins

Uremic toxins are classified into three categories: protein-bound solutes, free water-soluble low-molecular-weight solutes, and middle molecules [41].

Protein-bound uremic toxins exhibit a high affinity for plasma proteins, leading to poor clearance through dialysis. Protein-bound uremic toxins mainly include indoxyl sulfate and p-cresyl sulfate, derived from the breakdown of aromatic amino acids intestinal bacteria, which have shown nephrotoxic effects through induction of oxidative stress, inflammation and fibrosis.

Free water-soluble low-molecular-weight uremic toxins account for 46 % of identified uremic toxins, including urea nitrogen, creatinine, trimethylamine N-Oxide (TMAO), asymmetric dimethylarginine (ADMA), et al. They typically exhibit one of the most significant fold changes among uremic solutes in kidney disease patients compared to healthy controls.

Middle molecules uremic toxins with a molecular weight over 500 Da encounter difficulties in being effectively cleared during hemodialysis, including β2-microglobulins, tumor necrosis factor alpha (TNF-α), interleukin-6 (IL-6), et al. There is evidence supporting the involvement of middle molecule in contributing to morbidity and mortality in dialysis patients.

Several studies have observed that the expression of the irisin precursor FNDC5 in skeletal muscle cells and the level of irisin in the cell culture medium decreased when treated with the uremic toxin indoxyl sulfate. This effect is not due to alterations of PGC1-α [42,43]. Urotensin-II (U-II), the strongest known vasoconstrictor peptide ligand, has been reported to be elevated in various kidney diseases [44–47], with serum or urinary U-II levels being higher in patients with severe kidney dysfunction. A study verified that U-II induced skeletal muscle atrophy by upregulating autophagy and directly inhibiting irisin precursor (FNDC5) expression in mouse skeletal cells [48]. Moreover, they demonstrated that the increased U-II levels were accompanied by decreased expression of FNDC5 in chronic kidney failure mice, and FNDC5 expression could be upregulated by knocking out the U-II receptor gene. In non-diabetic peritoneal dialysis (PD) patients, the serum irisin levels were lower than healthy controls and positively associated with dialysis adequacy indices (peritoneal Kt/Vurea and Ccr) [49], indicating that uremic toxins might negatively regulate the expression of irisin. In addition, PD patients present higher serum irisin levels than HD patients, and plasma bicarbonate was independently positively correlated with serum irisin [36,50], suggesting that PD might provide better control of middle molecular and protein-bound uremic toxins and acidosis, which may inhibit irisin secretion. Intriguingly, Ebert T, et al. found a 23 % significant decrease in serum irisin levels after starting HD compared with pre-dialysis levels [26], whereas another study showed a statistically borderline rise in irisin level during HD sessions [51], which could be attributed to decreased intravascular volume after ultrafiltration. Consequently, further studies with larger samples are required to confirm the dialyzable nature of irisin. However, the molecular weight of irisin (12 kDa), close to that of β2-microglobulin, suggests that they may have similar behavior during HD.

2.3. Parathyroid hormone (PTH)

There are several experimental studies providing evidence of molecular coupling and crosstalk between muscle and bone [52], as well as a documented positive correlation between serum irisin levels and long bone mineral density and bone strength [53,54]. Meanwhile, the biological effects of parathyroid hormone (PTH) on irisin also need to be considered. Studies have revealed that PTH levels are inversely correlated with serum irisin levels in postmenopausal women with primary hyperparathyroidism or with osteoporotic fractures after controlling for creatinine levels [55,56], as well as in HD patients [57], and that PTH negatively regulates mRNA and protein expression of FNDC5. This is done by activating extracellular regulated protein kinases (Erk) 1/2 phosphorylation in cultured myotubes [56]. Nonetheless, another study has showed that neither PTH nor 1,25-dihydroxyvitamin D3 affects irisin expression in myotubes [34]. Therefore, the contribution of PTH to the effects of kidney failure on irisin expression is still unclear. Further studies assessing the comprehensive metabolic pathway of irisin, including action receptors, protein-binding rate, and elimination route, will be necessary to obtain a complete understanding of the underlying mechanism of changes in irisin expression in kidney diseases.

3. The effect of irisin on kidney diseases

There is increasing evidence supporting the role of signaling crosstalk connecting skeletal muscle and kidney, and many molecules secreted by skeletal muscle contribute to, or exacerbate a variety of physiological processes in the kidney [58]. As a multifunctional myokine, irisin has been found to be lower in CKD patients, and this is associated with deterioration of kidney function. However, it also participates in several pathophysiological processes, including metabolism, oxidative stress, inflammation, and apoptosis, which may mechanistically have direct beneficial effects on various kidney diseases (Fig. 1). A nationwide cross-sectional data collected from 1115 community-living obese Chinese adults revealed that a high serum irisin level was linked

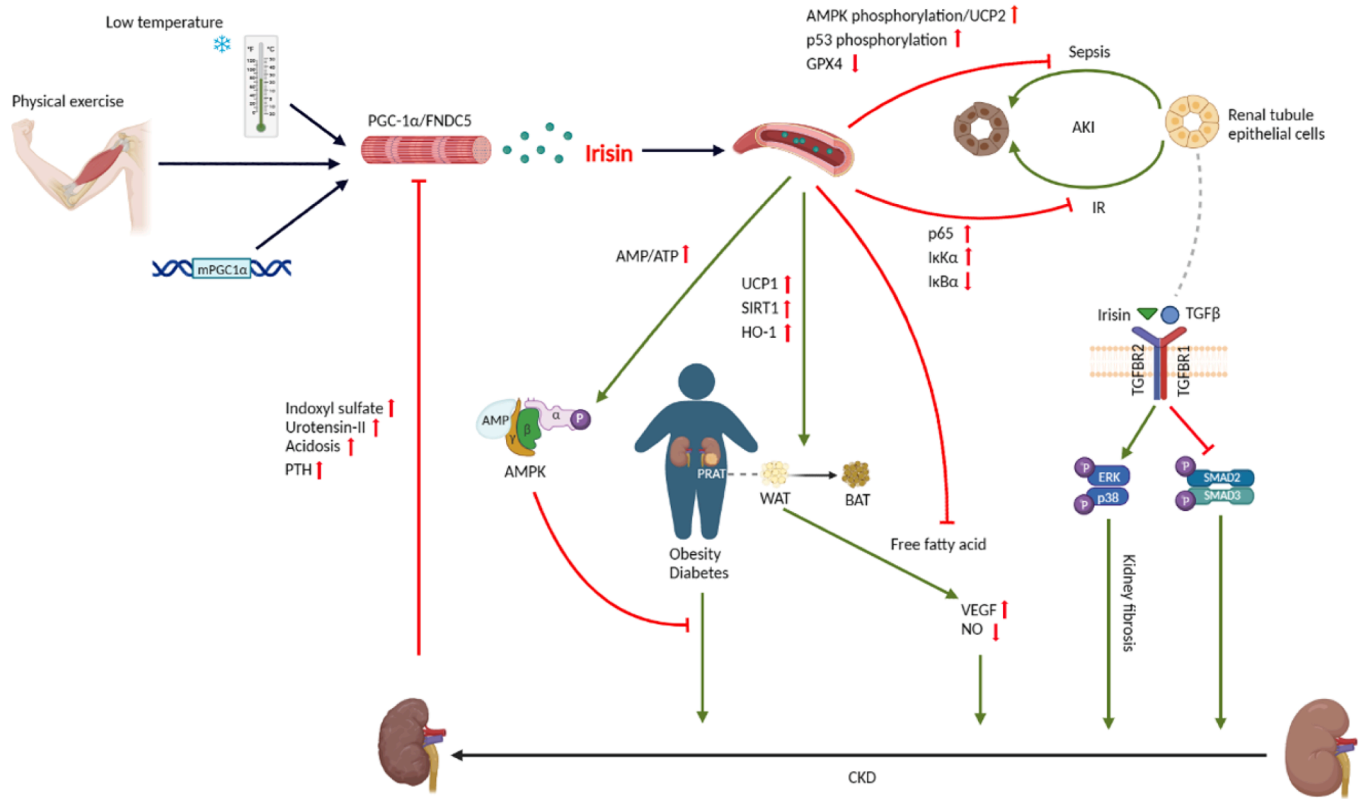

Fig. 1. The effect of irisin on kidney diseases. Irisin is the cleavage product of fibronectin type III domain-containing 5 (FNDC5) that is regulated by peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α). Irisin is released mainly from skeletal muscle during exercise or when exposed to cold. In CKD, indoxyl sulfate, urotensin-II (U-II), acidosis, and parathyroid hormone (PTH) downregulate the expression of irisin. Irisin has effect on various kidney diseases, including acute kidney injury (AKI), kidney fibrosis, diabetic nephropathy and obesity-related chronic kidney disease, through multiple pathways. **Abbreviations**: CKD, chronic kidney disease; AMPK, AMP-activated protein kinase; UCP1, uncoupling protein 1; UCP2, uncoupling protein 2; GPX4, glutathione peroxidase 4; TGF-β1, transforming growth factor-β1; TGFBR1, TGF-β type-1 receptor; TGFBR2, TGF-β type-2 receptor; IR, ischemia–reperfusion; ERK, extracellular signal-related kinase; SIRT1, sirtuin 1; HO-1, heme oxygenase-1; PRAT, perirenal adipose tissue; WAT, white adipose tissue; BAT, brown adipose tissue; VEGF, vascular endothelial growth factor; NO, nitric oxide. Green arrows specify activation, while red arrows show inhibition. Elaborated by Xiejia Li using the Biorender platform. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

to significantly decreased risk of CKD and a marginally decreased risk of albuminuria [59]. Further understanding of the role of irisin in kidney diseases will have significant implications for the pathogenesis, prevention, and treatment of kidney diseases.

3.1. Acute kidney injury (AKI)

AKI is a critical condition characterized by a rapid decline of kidney function, which is a major risk factor associated with the occurrence and development of CKD. It has a high morbidity and mortality rate and is reported to occur in approximately 10–15 % of hospitalized patients and more than 50 % of patients in the intensive care unit [60].

Kidney ischemia–reperfusion (IR) is one of the main causes of AKI. Uncoupling protein 2 (UCP2) is a type of mitochondrial inner membrane protein that participates in mitochondrial decoupling and inhibits reactive oxygen species (ROS) formation. It is widely found in the kidney and protects against IR-induced AKI [61,62]. A study [63] in mice subjected to kidney IR surgery showed that serum irisin levels were decreased compared to the control group. However, mice that received an intraperitoneal injection of irisin before IR surgery had a significant decrease in serum creatinine and the AKI predictor kidney injury molecule 1 (KIM-1), as well as UCP2. They also found a lower tubular damage score and less kidney histopathological damage, along with reduced inflammation response and oxidative stress apoptosis. Similar results were obtained in kidney proximal tubular epithelial cells (PTEC) pretreated with irisin before hypoxia/recovery, which showed increased AMP-activated protein kinase (AMPK) mRNA and phosphorylation of AMPK. These results suggest that irisin attenuates IR-induced kidney injury by increasing UCP2 expression through stimulating AMPK phosphorylation.

Ferroptosis is a novel form of programmed cell death that differs from apoptosis, cell necrosis, and autophagy, and is believed to be involved in IR-induced AKI [64]. The inactivation of phospholipid peroxidase glutathione peroxidase 4 (GPX4), a key regulator of lipid ROS, leads to ferroptosis and subsequent intracellular accumulation of lipid ROS. A recent study [65] revealed that the serum irisin levels were downregulated in kidney IR mice, while injection of irisin upregulated GPX4, alleviated kidney injury, reduced inflammatory response, improved mitochondrial function, and reduced endoplasmic reticulum (ER) stress and oxidative stress after IR. In addition, RSL3 (a GPX4 inhibitor) was shown to downregulate GPX4 expression and eliminate the protective effect of irisin on proximal tubule epithelial cells (HK-2).

Consistent with conclusions from the above research, our lab also demonstrated the protective effect of irisin in IR-induced AKI [66]. However, during ATP depletion-repletion in mouse kidney proximal tubular (BUMPT) cells, we detected the induction of irisin precursor FNDC5, along with typical apoptotic morphologies. The peak of FNDC5 expression was observed at 4 h of recovery, after which it decreased. This inconsistency with other studies finding a decrease in FNDC5 may be relate to the systemic or local distribution of FNDC5/irisin and the precise cell types in kidney that express irisin. Knockdown of FNDC5 with siRNA increased apoptosis in BUMPT cells treated with ATP depletion-repletion, while overexpression of both FNDC5 and irisin ameliorated apoptosis, suggesting that FNDC5/irisin has a

cytoprotective or pro-survival effect on kidney tubular cells during ATP depletion-repletion. These results were confirmed in kidney IR mice. We found higher levels of FNDC5 mainly in kidney tubular cells after kidney IR, which was attenuated by intravenous injection of recombinant irisin. Meanwhile, we found p53 activation occurred in BUMPT cells during ATP depletion-repletion and in kidney IR mice, as evidenced by p53 phosphorylation, and p53 activation was suppressed by both FNDC5 overexpression and recombinant irisin. These findings suggest that irisin may protect against IR-induced kidney injury by suppressing p53 phosphorylation.

Sepsis is another major cause of AKI and has been reported to be associated with high incidence of AKI (68.4 %) in hospitalized patients [67]. Inflammation and apoptosis play pivotal roles in the pathogenesis of kidney injury caused by sepsis [68]. A study conducted in lipopolysaccharide (LPS)-treated HK-2 cells to simulate sepsis-induced AKI found that treatment with irisin significantly reversed the increase of inflammatory factors (tumor necrosis factor alpha (TNF-α), interleukin-1 beta (IL-1β)), the decrease of B-cell lymphoma 2 (Bcl-2), the increase of Bcl2-associated X protein (Bax) expression, as well as the number of TUNEL positive cells. The underlying mechanism may be related to nuclear factor-κB (NF-κB), as irisin elevated the expression of p65 and IκKα, and reduced the expression of IκB-α [69].

3.2. Kidney fibrosis

A study has observed that the traditional medicine Dojuksan can increase the expression of PGC1α and FNDC5 in the quadriceps muscle and plasma irisin levels in unilateral ureteral obstruction (UUO) mice, and can improve kidney function by reducing kidney inflammation and tubulointerstitial fibrosis [43]. Peng H et al. validated the protective effects of irisin against kidney fibrosis. They found that muscle-specific overexpression of PGC-1α (mPGC-1α) ameliorate kidney fibrosis and improve kidney function in three well-established mouse kidney injury models, including folic acid treatment, UUO and subtotal nephrectomy [70]; meanwhile, metabolic reprogramming suppression and mitochondrial function improvement were observed. The serum from mPGC-1α mice exhibited similar effects on cultured kidney tubule cells. By detecting mRNA expression and serum levels, they identified that irisin was the determinant factor responsible for the kidney adaptation among several upregulated myokines in muscle of mPGC-1α mice. The incubation of anti-irisin antibody inhibited the protective effect of serum from mPGC-1α mice in kidney tubule cells. Furthermore, treatment with recombinant irisin was able to improve metabolic reprogramming and kidney function, as well as suppress kidney fibrosis in both folic acid injured and subtotal nephrectomy mice. Transforming growth factor-β1 (TGF-β1) is an essential mediator of kidney fibrosis through activating the expression of fibrotic genes and stimulating metabolic reprogramming in kidney tubule cells. This study also found an association between irisin and TGF-β1, whereby irisin was able to interact with TGF-β type-2 receptor (TGFBR2) and interfere with its recruitment to TGF-β type-1 receptor (TGFBR1), thus restraining the phosphorylation of Smad2/3 and facilitate the phosphorylation of ERK and p38 induced by TGF-β1.

Cardiovascular diseases such as myocardial infarction (MI) can induce chronic kidney impairment. A study found that irisin expression increased with improved kidney function in MI mice after aerobic exercise training, and that irisin can alleviate oxidative stress and apoptosis induced by H_2O_2 in vitro through activating the AMPK-Sirtuin1-PGC-1α pathway. This suggests that improvement of aerobic exercise on MI-induced kidney injury is partially mediated by irisin [71].

3.3. Diabetic nephropathy

A meta-analysis of 23 studies has revealed that serum irisin levels are significantly lower in patients with T2DM and gestational DM (GDM) [72], and that the duration of DM is an independent determinant of irisin levels [73]. Another meta-analysis of 13 studies has showed that lower serum irisin levels are associated with more severe albuminuria and lower eGFR in T2DM patients [74]. However, there are inconsistent findings regarding whether irisin levels are elevated or reduced in type 1 diabetes mellitus (T1DM) patients compared to healthy individuals [72,75].

Since physical exercise is one of the important treatments for DM, and irisin is an exercise-induced factor, a study aimed to determine the renoprotective action of muscle irisin secretion induced by physical exercise in DM [76]. They found that physical exercise reduced classical diabetic kidney morphological abnormalities and albuminuria in streptozotocin (STZ)-induced DM rats, along with an elevation of FNDC5-irisin expression in skeletal muscle. These effects were prevented by treatment with an irisin receptor (αV class integrin) inhibitor (CycloRGDyK). In further mechanistic research in HK-2 cells, it was found that the elevation of collagen IV and fibronectin induced by high glucose was prevented by both serum from exercised diabetic subjects and recombinant irisin in a dose-dependent manner, which were associated with AMPK activation. It suggests that the kidney protective effect induced by physical exercise in DM may be mediated by irisin/AMPK pathway.

3.4. Obesity-related chronic kidney disease (OB-CKD)

Obesity exacerbates hypertension as a risk factor for CKD by inducing vasoconstriction and promoting salt and water retention. Additionally, obesity worsens glucose intolerance and insulin resistance, further elevating the risk of CKD. The impact of obesity on the kidney involves the activation of novel intrarenal inflammation pathways, recruiting professional immunologic cells through metaflammation. Notably, obesity-related glomerulopathy has emerged as a distinctive pathological variant of focal segmental glomerulosclerosis [77]. OB-CKD, which is characterized by glomerular hypertrophy and microalbuminuria, has generated a great deal of interest due to the obesity pandemic. Previous studies have disclosed that perirenal adipose tissue (PRAT) is a predictor of microalbuminuria in obese patients [78] and is associated with OB-CKD [79,80]. PRAT-derived free fatty acid (FFA) can induce impaired vascular endothelial growth factor-nitric oxide (VEGF-NO) axis [81], while various adipokines released from PRAT have effects on glomerular endothelial function and kidney arteries [82]. Han F et al. [83] observed significant increases in body weight, fat mass and PRAT in high-fat diet (HFD) mice. However, intraperitoneal injection of irisin improved metabolic parameters (improved glucose homeostasis and reduced FFA levels) and ameliorated kidney injury (reduced albuminuria, reversed glomerular hypertrophy, mesangial proliferation, glomerular fibrosis and lipid accumulation), as well as attenuated oxidative injury and inflammation. Furthermore, irisin enhanced the downregulation of some proteins related to browning of white adipose tissue including uncoupling protein 1 (UCP1), sirtuin 1 (SIRT1) and heme oxygenase-1 (HO-1) in PRAT of HFD mice. An ex vivo study showed that glomeruli treated with PRAT-derived conditioned medium (PRAT-CM) exhibited higher vascular endothelial growth factor (VEGF) and lower nitric oxide (NO) production, but these changes were reversed by treatment with irisin, indicating that irisin may regulate VEGF-NO axis and mediate kidney protection. These results suggest that irisin may regulate PRAT browning, glomerular endothelial function, oxidative stress and inflammation to exert a kidney protective effect in OB-CKD.

4. The effect of irisin on CKD-related complications

Irisin deficiency has been implicated in the development of muscle atrophy, endothelial dysfunction (ED), vascular calcification (VC), and pathologic bone metabolism, which are all intricately linked to some important complications of kidney diseases, including protein energy wasting (PEW), cardiovascular disease (CVD) and chronic kidney

disease-mineral and bone disorder (CKD-MBD) (Fig. 2).

4.1. Sarcopenia

Sarcopenia is prevalent in patients with chronic kidney disease (CKD) and is associated to increased cardiovascular mortality. Several associated factors for the progression of CKD, including uremic toxin, metabolic acidosis, inflammation, and anorexia, can lead to skeletal muscle protein breakdown and muscle atrophy. Moreover, the levels of serum irisin are significantly lower in HD and PD patients, particularly those with sarcopenia, when compared to healthy individuals [84,85]. Therefore, irisin may serve as an independent predictor of sarcopenia in dialysis patients.

As a myokine, irisin can regulate skeletal muscle metabolism and alleviate muscle atrophy. Previous studies have indicated that exercise can increase the levels of circulating irisin in both humans and experimental animal models. For instance, a study has demonstrated that recombined irisin can protect against muscle mass decline in the hindlimb-suspended mice and preserve the fiber cross-sectional area [86]. Nevertheless, it has been observed that a resistance exercise training program fails to raise plasma irisin levels beyond the extent of muscle mass increase [40]. This suggests that exercise may not be the primary factor associated with circulating irisin levels in dialysis patients, as uremic toxin and dialysis treatment may significantly affect the modulation of irisin expression in skeletal muscle. Further studies are required to investigate the influence of irisin on sarcopenia in CKD patients.

4.2. Chronic kidney disease-mineral and bone disorder (CKD-MBD)

CKD patients commonly develop mineral and bone disorder, characterized by imbalances in calcium, phosphate and PTH homeostasis, and also encompasses abnormalities in bone turnover, mineralization and volume, as well as vascular or other soft tissue calcifications.

An increasing body of evidence indicates that skeletal muscles impact bone metabolism through the secretion of myokines, including irisin [52,87,88]. Previous studies have revealed that a reduction of irisin in skeletal muscles is correlated with osteopenia in unloading and androgen-deficient mice [89,90]. Irisin has a beneficial effect on upregulating pro-osteoblastic genes, increasing osteoblastic bone formation, and inhibiting osteoclastic bone resorption in mice [22]. These findings suggest that irisin may act as the molecular transducer responsible for the muscle-bone crosstalk.

Clinical evidence indicates that CKD-induced osteoporosis mainly impacts cortical bone. A study showed a significant reduction in the expression of irisin in the gastrocnemius muscles of 5/6 nephrectomy (Nx) mice, with a positive correlation to cortical, but not trabecular, bone mass density (BMD) at the femurs [33]. Administration of irisin alleviated the reduction of cortical BMD and alkaline phosphatase (ALP) expression at the femurs in Nx-induced kidney failure mice.

Hyperparathyroidism is partly responsible for the occurrence of cortical porosity in CKD [91]. Serum PTH showed a negative correlation with cortical bone parameters, and prolonged exposure to high PTH levels could result in selective cortical bone loss in individuals undergoing dialysis [92]. Irisin was found to downregulate PTH-receptor mRNA expression in osteoblasts [54]. The noteworthy inverse correlation between irisin and PTH and ALP, respectively observed in both HD and PD patients, indicate that irisin may restrain bone resorption, alleviate bone-vascular interaction, and protect vascular function [93].

Vascular calcification (VC) is a prevalent condition in individuals with CKD and is recognized as one of the risk factors for CVD [94]. The development of VC is significantly influenced by impaired bone metabolism and dysfunction of the bone-vascular axis [95].

Several investigations have demonstrated an inverse relationship

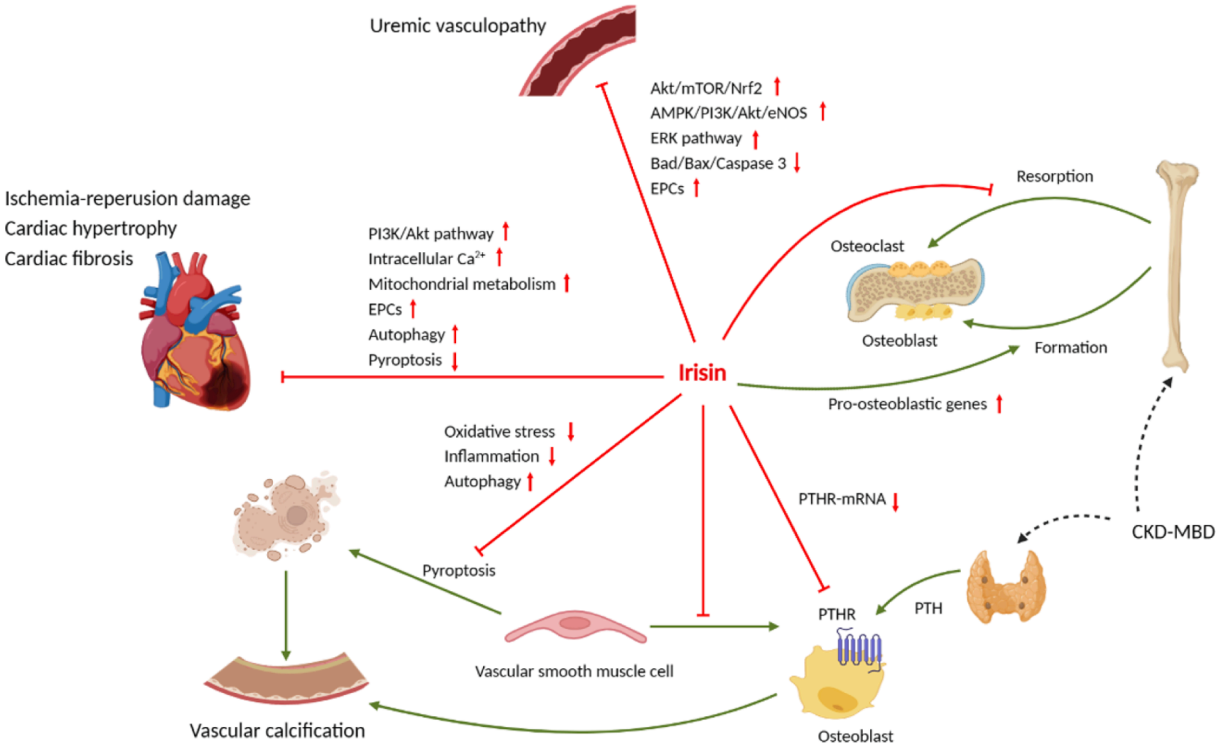

Fig. 2. The effect of irisin on CKD-related complications. **Abbreviations**: CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; PTH, parathyroid hormone; PTHR, parathyroid hormone receptor; AKT, RAC-gamma serine/threonineprotein kinase; mTOR, Mechanistic target of rapamycin; Nrf2, Nuclear factor erythroid 2-related factor 2; AMPK, AMP-activated protein kinase; PI3K, phosphoinositide 3-kinases; eNOS, endothelial nitric oxide synthase; ERK, extracellular signal-related kinase; EPCs, endothelial progenitor cells. Green arrows specify activation, while red arrows show inhibition. Elaborated by Xiejia Li using the Biorender platform. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

between serum irisin levels and prevalence and progression of VC both in general population [96] and in individuals receiving renal replacement treatment [57,85,97].

Despite a lack of clarity on the role of irisin in CKD-associated VC and its underlying mechanism, the existence of an interplay between irisin, PTH, and bone metabolism implies that irisin may exert bone-related vasculoprotection. The core driver of VC is the phenotypic change involving vascular wall constituent cells toward manifestations similar to those undergone by osteoblasts. It is postulated that irisin can reduce the amount of calcium in circulation by boosting osteoblast differentiation or inhibiting the transformation of vascular smooth muscle cells (VSMCs) into osteoblasts [57]. In addition, VSMC pyroptosis activated by oxidative and inflammatory stress has been demonstrated to be a crucial event in the pathogenesis of VC in CKD. Irisin can enhance autophagy and reduce reactive oxygen species (ROS) production in β-glycerophosphate (β-GP)-treated VSMCs, protect against pyroptotic cell death, as well as alleviate aorta calcification in CKD mice [98].

4.3. Cardiovascular disease (CVD)

People with CKD are at high risk for CVD even in the early stages of CKD [99]. Many studies have consistently demonstrated an association between reduced eGFR and occurrences of fatal or nonfatal CVD, including congestive heart failure, myocardial infarction, stroke, and peripheral vascular disease. Within the CKD context, three primary pathological forms of CVD are evident: atherosclerosis, arteriosclerosis or disease of the large vessels, and structural modifications in the myocardium, including eccentric left ventricular hypertrophy (LVH), concentric LVH, and left ventricular remodeling. Even marginal reductions in renal function and minimal levels of albuminuria are indicative of an elevated risk of cardiovascular (CV) events and premature mortality, and the risk of CV events increases continuously with further CKD progression. Substantial evidence revealed the potential role of irisin in CVD. Irisin is highly secreted in the myocardium, and low serum irisin levels were observed to be associated with high expression level of markers representing myocardial injury [100]. The reduced irisin levels help to reduce ATP utilization and improve energy supply to the ischemic myocardium as compensation for the myocardial hypoxia after infarction [101]. However, if the myocardial ischemia and hypoxia intensify, a significant loss of myocardium occurs, and this further exacerbates the reduction in irisin levels, which induces ventricular remodeling and ultimately results in heart failure [102,103]. Patients with atrial fibrillation (AF), chronic heart failure or coronary artery disease (CAD) exhibit lower levels of irisin when compared to controls [104–107]. Additionally, individuals with T2DM who have lower irisin levels are associated with a 1.6 times higher risk of CVD [108]. In the setting of CKD, studies have demonstrated that elderly patients with CKD stage 3–5 with high serum irisin levels had lower CVD risk [109], whereas low irisin levels in HD patients associated with increased mortality of cardiovascular and cerebrovascular diseases (CCVD) [110]. These findings suggest that irisin may have an important role in the pathophysiological process of CVD and can serve as a marker of CVD outcomes in CKD.

The cardiomyocytes, while serving as a crucial origin of irisin, is also a direct target of irisin. Irisin has anti-hypertensive effects mediated by improving endothelial function through the AMPK-protein kinase B-endothelial nitric oxide synthase-nitric oxide (AMPK/Akt/eNOS/NO) pathway [84] and activating nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant in the paraventricular nucleus (PVN) [111]. Meanwhile, several investigations have demonstrated that irisin has protective effect on myocardium against ischemia–reperfusion damage via facilitating angiogenesis [112] and regulation of mitochondrial function [113], stimulating cardiomyocyte metabolism and differentiation in mice through the phosphoinositide 3-kinases-protein kinase B (PI3K-AKT) pathway and calcium signaling [114], and boosting myocardial repair mediated by cardiac progenitor cells [115]. Irisin further alleviates cardiac hypertrophy and fibrosis induced by pressure overload and angiotensin II by regulating AMPK-mTOR signaling pathway [116], activation of autophagy and suppression of pyroptosis [117].

Moreover, irisin presents effects on maintaining the functional integrity of vascular endothelium and preventing the early stage of uremic vasculopathy. Some studies found a negative association between irisin levels and many leukocyte adhesion molecules (LAMs) that are upregulated during endothelial injury [118,119], as well as the intima-media thickness of carotid artery (cIMT) [120]. Administration of exogenous irisin exhibited several beneficial effects, including reducing the production of oxidative stress mediators by up-regulating the Akt/mTOR/Nrf2 pathway [121], promoting endothelial-dependent vasodilation through the activation of the AMPK/PI3K/Akt/eNOS pathway [84,122,123], increasing endothelial cell viability by activating the ERK proliferation pathway and down-regulating the pro-apoptotic Bad/Bax/Caspase 3 pathway [112,124,125], increasing the number and migration of circulating endothelial progenitor cells (EPCs) [126,127], and regulating endothelial and perivascular adipose tissue (PVAT) functions [128]. These actions can lead to the remodeling of endothelial barriers and recovery of vessel function after cardiovascular injury.

However, contrasting findings have also been reported. Some studies found a positive association between serum irisin levels and blood pressure, cIMT and higher risk for CVD [7,129]. It was postulated that irisin levels may be secreted by adipose or skeletal muscle in response to metabolic diseases in order to mitigate their deleterious effects on the vasculature as a compensatory mechanism. Therefore, the impaired compensation or reduced sensitivity to irisin in advanced stages of metabolic disorders might compromise the protective role of irisin and contribute to the perpetuation of inflammatory response and endothelial injury [130]. Moreover, the role of irisin may vary throughout the different stages of CVD [20]. As of now, investigations of the association between irisin and CVD in the CKD population remains limited, and further studies are needed to elucidate the role of irisin and the precise mechanisms involved.

5. Future prospects

With mounting evidence indicating that serum irisin concentrations decrease in patients with chronic kidney disease (CKD) and decline further with the progression of CKD stages, several studies have demonstrated links between irisin and kidney diseases, due to the close association between metabolic disorders with the underlying mechanism and multiple complications of kidney diseases. However, some studies have yielded conflicting conclusions, and a majority of them have only been conducted on animals. Furthermore, most available enzyme-linked immunosorbent assay (ELISA) kits employing polyclonal antibodies have been shown to lack specificity [131]. A particular research group noted variability in irisin concentrations when employing ELISA kits from the same manufacturer. Inconsistent standards in the validation of antibodies have precipitated a pervasive “reproducibility crisis” [132], resulting in incongruent findings, which has raised concerns about the validity of ELISA kits. Prioritizing research on the development of a monoclonal antibody specifically targeting irisin is crucial. Recently, a company introduced a pioneering sandwich ELISA featuring a monoclonal antibody [133]. However, the antibody s specificity for human irisin in plasma/serum samples remains unverified, and the intra- and inter-assay reproducibility has not been appropriately assessed, posing a significant challenge to in vivo investigations. Calibrated mass spectrometry was anticipated to be the “gold standard” for identifying the existence of plasma irisin and its concentration. A study explored the detection of human irisin in blood through the application of quantitative mass spectrometry. They synthesized irisin peptides as internal standards, and incorporated a valine enriched with stable isotopes (six ^{13}C atoms) [134]. However, another group utilizing the same

method quantified irisin concentrations in samples of human cerebrospinal fluid, but did not observe the presence of irisin in human plasma [135]. The observed disparities reveal a considerable level of methodological variability and raise significant concerns regarding the meaningful interpretation of minor differences between groups of individuals based on single measurements for each person. Furthermore, the preparation of plasma or serum samples for mass spectrometry requires the removal of highly abundant proteins such as albumins and immunoglobins, which results in variable amounts of retained proteins for analysis and hinders reproducible quantification [136]. As the field of irisin research continues to evolve, there is a need for progress in measurement techniques to provide more accurate and reproducible results.

Irisin appears to be a promising therapeutic target for some metabolic diseases as its capacity to stimulate energy expenditure and regulate metabolic process potentially could have a positive effect on clinical outcomes by ameliorating underlying disorders. Although exercise was initially assumed to induce the secretion of irisin, recent studies have demonstrated that the elevation of irisin levels varies based on the type, intensity, and duration of exercise, as well as the age of the participants. Additionally, the upregulation of FNDC5 mRNA expression following exercise is not consistent, and the short half-life of irisin further complicates the issue [137–139]. Consequently, the efficacy of exercise as an ideal approach to promote irisin release remains a subject of debate. Moreover, it has been proposed that exercise may enhance kidney function, and yet no conclusive study has demonstrated that physical exercise can decelerate the decline in kidney function among CKD patients [140].

Several animal studies indicate that administering irisin directly is advantageous for metabolic and potentially non-metabolic illnesses [141]. Nevertheless, these preclinical findings should be approached with care since metabolic conditions vary significantly between rodents and humans. Additionally, it is important to note that irisin may cause certain side effects during treatment. Excessive irisin has been observed to be linked to the onset of puberty [142], promote ROS generation and apoptosis of cardiomyocytes under hypoxic conditions [143], and may hasten cachexia since it is a potential promoter of energy expenditure.

6. Conclusion

The discovery of irisin has provided novel perspectives for exploring the pathophysiological processes of diverse metabolic and non-metabolic disorders. Subsequent research is imperative to gain a thorough understanding of irisin's distinct influence on human pathophysiology, particularly in the context of kidney diseases, and to elucidate the underlying mechanisms. Furthermore, the establishment of a more precise and standardized measurement technique for irisin is essential. This would not only facilitate the conduct of clinical studies on irisin but also enable a comprehensive exploration of irisin's potential as a therapeutic target.

Author contributions

Xiejia Li designed and wrote the draft of the manuscript. Bengt Lindholm edited the manuscript.

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CRediT authorship contribution statement

Xiejia Li: Conceptualization, Funding acquisition, Writing – original draft. **Bengt Lindholm:** Writing – review & editing.

Data availability

No data was used for the research described in the article.

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