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ABSTRACT
Acute kidney injury (AKI) and chronic kidney disease (CKD) are posing great threats to global health within this century. Studies have suggested that estrogen and estrogen receptors (ERs) play important roles in many physiological processes in the kidney. For instance, they are crucial in maintaining mitochondrial homeostasis and modulating endothelin-1 (ET-1) system in the kidney. Estrogen takes part in the kidney repair and regeneration via its receptors. Estrogen also participates in the regulation of phosphorus homeostasis via its receptors in the proximal tubule. The ERα polymorphisms have been associated with the susceptibilities and outcomes of several renal diseases. As a consequence, the altered or dysregulated estrogen/ERs signaling pathways may contribute to a variety of kidney diseases, including various causes-induced AKI, diabetic kidney disease (DKD), lupus nephritis (LN), IgA nephropathy (IgAN), CKD complications, etc. Experimental and clinical studies have shown that targeting estrogen/ERs signaling pathways might have protective effects against certain renal disorders. However, many unsolved problems still exist in knowledge regarding the roles of estrogen and ERs in distinct kidney diseases. Further research is needed to shed light on this area and to enable the discovery of pathway-specific therapies for kidney diseases.

ARTICLE HISTORY
Received 18 December 2020
Revised 3 March 2021
Accepted 6 March 2021

KEYWORDS
Estrogen; estrogen receptors (ERs); kidney diseases; acute kidney injury (AKI); chronic kidney disease (CKD)

Introduction
Although estrogen is classically regarded as a reproductive hormone in mammalian species, it also plays an important role in many other physiological processes (e.g., cell growth, development and differentiation, lipid and glucose homeostasis, renal endocrine function, immune function, etc.) [1–5]. The effects of estrogen in physiological and pathophysiological conditions are mediated by two different structural receptor classes, namely, estrogen receptor (ER) α/β and G protein-coupled estrogen receptor (GPER) [6]. Estrogen and its receptors are implicated in the development and progression of various diseases, including cancer, osteoporosis, endometriosis, neurodegenerative disorders, as well as cardiovascular, metabolic, and autoimmune diseases [7–12].

Acute kidney injury (AKI) and chronic kidney disease (CKD) are posing substantial threats to global health. The interdependent relationship between AKI and CKD further adds complexity to the clinical picture [13]. Recent experimental and clinical studies have suggested that estrogen and ERs serve pathophysiological roles in kidney diseases, including AKI, diabetic kidney disease, lupus nephritis, IgA nephropathy, complications of CKD, etc. This review mainly examines the roles of estrogen and its receptors in certain kidney diseases. We also discuss the structures, functions, mechanisms, and modulation of ERs, providing the basis for potential therapeutic interventions.

Structures and functions of ERs
As members of the nuclear receptor family, ERs are found mainly in the nucleus, but also in the cytoplasm and mitochondria [14]. The classical ER subfamily mainly consists of ERα and ERβ [15]. Both of them consist of six functional domains A–F. The NH2-terminal A/B domain contains a ligand-independent transactivation function-1 (AF-1). It’s noteworthy that the transactivation potency of AF-1 varies in a ligand-, cell type-, and promoter-specific manner [3]. The C domain (DNA binding domain) binds to DNA motifs called estrogen response elements (EREs). It also plays a part, to a minor extent, in the stability of ER dimerization [3]. The D domain is a hinge region between the C and E domains. It is involved in ER conformational changes,
interaction with other transcription factors, nuclear translocation, and posttranslational modifications [16–18]. The E domain is identified as the ligand-binding domain (LBD) and the principal dimerization interface of the receptor, which contains a ligand-dependent activation function AF-2 [19,20]. The F domain is the least conserved region with high variability, and many nuclear receptors do not contain such a region [3]. ERα and ERβ share a high degree of conservation in their C and E domains, while the other domains are more divergent [21]. The synergistic effect of AF1 and AF2 is required in the transcriptional regulation mediated by both receptors [22,23]. However, it is still unclear how AF-1 and AF-2 activities are regulated cooperatively by ligands. Recent studies have shown that the AF-2 contains an AF-1 suppression function element and that AF-1 is regulated in an AF-2-dependent manner [24,25].

ERα

In humans, ERα is encoded by the gene ESR1, located on chromosome 6, locus 6q25.1 [26]. ERα is primarily expressed in sex organs (breast, uterus and ovary, testes, epididymis, prostatic stroma), bone, liver, adipose tissue, cardiovascular, and central nervous system (CNS) [27,28]. The classic full-length 67 kDa ERα includes a DNA-binding domain, a ligand-binding domain, and two transcriptional activation functions (AF-1 and AF-2) [3]. In addition, two shorter isoforms (46 kDa ERα46 and 36 kDa ERα36) have been identified. ERα46 lacks the N-terminal region harboring AF-1, whereas ERα36 lacks both AF-1 and AF-2 and encodes a unique 29 amino acid sequence [29,30].

The functional role of ERα was first discovered from a clinical situation where a man bearing a mutation in the ERα gene developed a premature and severe metabolic syndrome [31]. It is now recognized that ERα is a key regulator of energy homeostasis and glucose metabolism and that the ERα pathway might represent a potential therapeutic target for the prevention or treatment of insulin resistance, type 2 diabetes mellitus, and non-alcoholic fatty liver diseases [16,32]. On the other hand, ERα is linked with a variety of cancers and metastases, including breast cancer, cervical cancer, lung carcinoma, and prostate cancer [33–36].

ERβ

In humans, ERβ is encoded by the gene ESR2, located on chromosome 14 (14q23–24), and has five isoforms (ERβ1-5) [37]. These five isoforms exist as a result of alternative splicing of the last coding exon (exon 8). It is noteworthy that ERβ1 is the only full-function isoform with the native LBD and that the other isoforms do not have innate activities in their homodimeric forms but can heterodimerize with ERβ1 and enhance ERβ1-induced transactivation in a ligand-dependent manner [38,39]. ERβ and its isoforms have wider tissue distribution than ERα and they are expressed primarily during embryonic development and in the prostate epithelium, bladder, ovary, colon, lung, adipose tissue, immune system, cardiovascular system, and CNS [27,40,41].

Similar to ERα, ERβ is involved in cellular differentiation, mitochondrial bioenergetics, lipid and glucose metabolisms, energy expenditure, etc. [42–44]. ERβ is generally thought to be a tumor suppressor gene and its expression is dysregulated in different cancers [45–47]. There is an increasing awareness that selective targeting of ERβ signaling pathways might be useful in the treatment of several inflammatory and proliferative diseases [48,49]. Studies support the idea that ERβ agonists can reasonably be used in hormone replacement therapy, early stage prostate and colon cancers, suppression of the immune system without negative effects on bone, and neuroprotection [50].

GPER

In the last decades, studies have suggested that apart from the classical steroid receptors ERα and ERβ, the G protein-coupled estrogen receptor (GPER, formerly known as GPR30) also mediates the effect of estrogen in a rapid signaling pathway [51–53]. As a member of the G-protein coupled receptor superfamily, GPER is localized predominately within intracellular membranes in most cell types [54]. It is widely expressed in numerous tissues and organs, including the vessels, skeletal muscle, brain, heart, kidney, pancreas, and reproductive organs [55,56]. Studies have shown that GPER is involved in many physiological responses, including maintenance of vascular tonicity and blood pressure, reproduction, lipid and glucose metabolisms, immune and inflammatory responses, etc. [57–60]. For instance, mice lacking GPER exhibited metabolic syndrome, such as obesity, impaired glucose tolerance, or dyslipidemia [59,61]. Pharmacological modulation of GPER could promote pancreatic cell survival and improve glucose tolerance [62,63]. The effects of GPER are mediated via multiple signaling pathways, including the activation of adenyl cyclase (AC)/protein kinase A (PKA), epidermal growth factor receptor (EGFR), PI3 kinases, as well as extracellular signal-regulated kinase (ERK) pathways and G protein-coupled pathways [64].
Mechanisms of estrogen action

The mechanisms of estrogen action are categorized into classical (genomic) and rapid (non-genomic) ones. In the classical pathway, estrogen binds to the ERs in the cytoplasm, leading to ER dimerization and translocation to the nucleus, where the estrogen–ER complex interacts with ERE sequences in target genes [16]. This process typically occurs within hours [65]. In recent decades, however, rapid or ‘non-genomic’ effects of estrogen (also termed non-nuclear or membrane initiated steroid signaling) has been reported [66]. This occurs through the ER located in or adjacent to the plasma membrane, or through other non-ER plasma membrane-associated estrogen-binding proteins, which usually takes seconds or minutes [67]. GPER has been identified as one of the main estrogen-sensitive receptors responsible for the rapid non-genomic action of estrogen [68]. The classical (genomic) and non-genomic estrogen signaling pathways are illustrated in Figure 1 [22,69].

Modulation of ERs

Selective estrogen receptor modulators (SERMs) are antiestrogens designed to compete with estrogen and modulate ER activity in a tissue-specific manner [70,71]. For instance, tamoxifen can exhibit antagonistic effect on mammary tissue, whereas it can have agonistic effects on other tissues such as the uterus, bone, and heart [72]. Raloxifene acts as an estrogen agonist in bone and an estrogen antagonist in uterine and breast tissues [73]. Similarly, bazedoxifene functions as a pure antagonist in the breast and an agonist in the bone [74]. Since ERs are nuclear transcription factors involved in the regulation of a variety of physiological and pathological processes in humans, modulation of the receptors either by SERMs or by agonists/antagonists might be beneficial for the prevention and treatment of various diseases [27].

Estrogen and ERs in kidney diseases

Acute kidney injury (AKI)

Gender differences in AKI epidemiology

The incidence of AKI has been steadily increasing, particularly among elderly hospitalized patients [75]. Epidemiological studies suggested that the mortality rates of AKI patients in hospital settings (including intensive care units) ranged from 17.5% to 64.7% [75,76]. As a broad clinical syndrome encompassing different etiologies, AKI is characterized by an abrupt decline of glomerular filtration rate, which is associated with high morbidity and mortality [77]. Various etiologies include pre-renal azotemia, acute tubular necrosis,
acute glomerular/interstitial nephritis, acute vasculitic renal diseases, acute post-renal obstructive nephropathy, and mixed forms [78].

Clinical studies have shown that sex disparities might influence the susceptibility, progression, and therapeutic response to AKI [79–81] and that female sex might have a protective effect on the development of AKI [79,82]. Though a recent retrospective cohort study of AKI complicating acute myocardial infarction-related cardiogenic shock suggested that female sex was independently associated with higher in-hospital mortality, it did mention that women with AKI were older (74 ± 12 years), which highlighted the potential role of estrogen in AKI [83]. Another interesting phenomenon is that compared with females, males were endowed with lower mitochondrial respiratory capacity and poor antioxidant defense system, exhibiting fragmented and smaller mitochondria [84,85]. Given that the disrupted mitochondrial homeostasis plays a prominent role in the pathogenesis of AKI [86], this might partially explain the sex disparities in AKI. The gender dimorphism was also observed in animal experiments where male mice/rats exhibited more severe AKI manifestations than their female counterparts through different mechanisms [87–91].

The role of silent mating type information regulator 2 homolog 1 (SIRT1) in mediating the renoprotective effects of estrogen on AKI has been systematically reviewed recently [92]. Experimental studies have indicated that SIRT1 exerts a protective effect against AKI through regulating oxidative stress, mitochondrial biogenesis, energy metabolism, inflammation and apoptosis [93–97]. The functional interaction between estrogen/ER and SIRT1 has been investigated in different disease models. Estrogen exerts protective effects against inflammation and mitochondrial dysfunction via ERα/SIRT1 pathway [98,99]. SIRT1 acts as an ERα co-activator and is required for modulation of ERα-signaling pathways [100]. In this regard, it is proposed that estrogen through SIRT1 might protect against AKI [92].

Estrogen and ERs in AKI settings
Renal ischemia–reperfusion injury (IRI). Renal IRI is characterized by a temporary shortage and subsequent restoration of blood supply and oxygen delivery to the kidney, initiating a cascade of deleterious cellular responses leading to ROS generation, inflammation and tubular cell death, leading to AKI [101,102]. As one of the leading causes of AKI, renal IRI often occurs with kidney transplantation, postoperative hypotension, traumatic hemorrhage, cardiovascular surgery, cardiac arrest, and cardiopulmonary resuscitation [103–108].

Clinical studies regarding the association of gender with kidney allograft outcome have mixed results. While some clinical observations suggested that female recipients generally had a better graft function and survival than male counterparts, others indicated that the risk of developing graft failure varied in women stratified by age and donor sex [109–112]. Although the effect of gender disparity in the susceptibility and pathogenesis of IRI in the transplanted kidney is less well established in humans, the majority of experimental studies indicate that females had better outcome of kidney transplantation than males due to increased IRI tolerance [113]. This sex-related differences in IRI-induced AKI might be attributed to the depression of renal sympathetic nervous system with endogenous estrogen and the subsequent reduced regional noradrenaline level [89,114,115]. As expected, the supplementation of estrogen prior to the induction of IRI protected kidney function in female mice and neutered males. Studies also revealed that estrogen administration after cardiac arrest and resuscitation ameliorated AKI in both male and female mice [116,117]. In contrast, testosterone enhances kidney susceptibility to IRI through inhibiting the activation of nitric oxide (NO) synthases and Akt signaling [118]. Notably, renal IRI was exacerbated in female ERα knockout mice [113].

The roles of estrogen and ERs in the signaling mechanisms of IRI-induced AKI have been reported. Estrogen attenuated renal IRI through the activation of peroxisome proliferator-activated receptor γ (PPARγ), a nuclear receptor which plays a vital role in the maintenance of renal metabolic homeostasis [119–121]. The overproduction of renal endothelin-1 (ET-1), which plays a critical role in the initiation of AKI and the subsequent transition to CKD through its two receptors ETa and ETβ, was suppressed with the administration of estrogen in rats challenged with IRI [122–125]. This effect was probably mediated by ERβ and GPER1 in the kidney [126,127]. Estrogen also reduced inflammation and accelerated injured tubular cell regeneration in male rats after IRI-induced AKI [128]. In the uninephrectomized rat model of IRI, the renoprotective effect of estrogen was mediated by the activation of PI3K/Akt pathway followed by increased endothelial nitric oxide synthase (eNOS) phosphorylation in the affected kidneys [129]. Another mechanism might be estrogen-mediated antagonism on N-methyl-D-aspartate receptors (NMDAR) that were expressed in nephrons [130]. The activation of GPER1 also protected the kidney from IRI through enhancing glomerular endothelial barrier function and regulating the content of NO in renal interlobular artery smooth muscle and endothelial cells.
Renal Na\(^+/K^+\)-ATPase is a well-recognized energy-dependent sodium pump which helps maintain the electrolyte and fluid balance via manipulating the transport of certain solutes [133,134]. Under the circumstance of renal IRI, the impaired activity of Na\(^+/K^+\)-ATPase contributed to abnormal hydroelectrolyte status [135,136]. A sex disparity in the alterations of this enzyme was observed following renal IRI, favoring the protective role of estrogen in the stability and modulation of Na\(^+/K^+\)-ATPase upon various renal insults [137,138].

Together, these results demonstrate that there exists a sex dimorphism in IRI-induced AKI. However, the discrepancy between clinical observations and experimental findings regarding this aspect remains to be investigated. Estrogen and ERs might have potential therapeutic implications in the treatment of renal IRI, but recent studies have pointed out that the renoprotective effect of exogenous estrogen becomes evident only when administered at a dose above the physiological level [139]. It has also been doubted that whether the sequelae of renal IRI (i.e., subsequent kidney fibrosis) could actually be brought to a halt by estrogen. Therefore, the therapeutic effect of estrogen and its analogues derived from the existing animal studies needs to be cautiously interpreted when applied to human patients.

**Septic AKI.** Sepsis-induced AKI is the leading cause of AKI in the intensive care unit (ICU) and accounts for nearly half of all AKI events, which is associated with increased mortality and morbidity [106,140]. A multicenter prospective study including 1177 ICU patients with sepsis in 24 European countries reported a 51.2% incidence of AKI with a mortality rate of 41.2% [141]. A multicenter retrospective study of [146,148]. Chinese hospitalized adults found AKI in 47.1% of sepsis cases [142].

Studies regarding the role of estrogen in septic AKI have conflicting results. Feng et al. found that serum estrogen levels were correlated with the severity of renal dysfunction and that increased estrogen levels predicted the development of newly onset AKI within a month [143]. A recent post-hoc analysis of patients with sepsis from the Randomized Evaluation of Normal versus Augmented Level renal replacement therapy (RENAI) trial suggested that female sex was associated with improved survival in septic patients with severe AKI [82]. Trentzsch et al. found that female patients had lower rates of sepsis and renal failure than males following traumatic injury and hemorrhagic shock [144]. Animal studies also demonstrated that estrogen and its selective modulator raloxifene had protective effects on renal function in ovariectomized rats with sepsis through the activation of autophagy [145,146]. Several preclinical studies indicated that the activation of ERs (mainly ER\(\alpha\) and ER\(\beta\)) could regulate inflammatory responses and control sepsis-induced multiorgan dysfunction [147–149].

The exact mechanisms responsible for the roles of estrogen and ERs in septic AKI remain to be elucidated. Further studies are needed to uncover the potential roles of estrogen and ERs in mediating the gender differences in septic AKI. Though a majority of experimental studies have demonstrated the salutary effects of estrogen and ER agonists on the outcome of sepsis-induced multiple organ failure including AKI, clinical investigations have not reached a consensus in this respect. The remaining gap between the bench and the bedside prompts us to take into consideration the different clinical study protocols. For example, the hormonal status or the level of estrogen of a patient at the time of sepsis may have an effect on the clinical outcome [150,151]. Studies providing information regarding hormonal status (oral contraceptives, menstrual cycle, and hormone replacement therapy) at the time of patient enrollment are encouraged. It is important to note that kidney is just one of the many involved organs in sepsis and that the overall effects of estrogen in other organs or systems need addressing. Also, fluid resuscitation and antibiotics are still the mainstay of treatment for patients with sepsis and, therefore, estrogen-related therapies may be developed for the best interests of the individual patient.

**Drug-induced AKI.** Drug-induced AKI accounts for 0.7% to 26% of cases with AKI among hospitalized patients [152–154]. Various drugs that are metabolized in the kidney and cleared via glomerular filtration and/or tubular secretion may induce AKI from a variety of mechanisms [155]. In the proximal tubules, apical transport of the aminoglycosides and basolateral transport of cisplatin increase the risk for AKI [156]. Acute interstitial nephritis is another form of drug-induced AKI, which typically develops from medications that incite an allergic reaction (e.g., antibiotics, proton pump inhibitors, non-steroidal anti-inflammatory drugs, etc.) [157–159].

Studies regarding the sex differences in the susceptibility to drug-induced AKI have conflicting results. While some suggested that females were more vulnerable to aminoglycoside- and cisplatin-induced nephrotoxicity, others found no such gender disparities [160–162]. At least in the field of drug-induced acute
interstitial nephritis, epidemiological characteristics showed a female preponderance [159,163]. This might be attributed to gender differences in the expression of drug transporters on proximal renal tubules [164]. However, the issue of gender differences in the susceptibility to nephrotoxins is far more nuanced. There is actually no impact of gender on the protein levels of some key drug transporters in human kidney samples, as revealed by liquid chromatography-tandem mass spectrometry-based targeted proteomics [165,166]. On the other hand, sex differences in the expression of kidney genes responsible for the metabolism of certain drugs have been confirmed in experimental studies [164,167]. For example, females could better handle mercuric chloride-induced tubular injury because of their correspondingly increased renal expression of organic anion transporter 1/3 (OAT1/3) and multidrug resistance-associated protein 2, leading to higher excretion of mercury and less likelihood of AKI [168]. A sex hormone dependent pattern of the expression of OAT2 was also observed in mouse and rat kidneys (i.e., OAT2 could be upregulated by estrogen and progesterone) [169].

The roles of estrogen and ERs in drug-induced AKI have been investigated. Preclinical studies demonstrated that young females exhibited decreased susceptibility to cisplatin-induced AKI, highlighting the potential role of estrogen [154,170,171]. Moreover, estrogen and GPER1 agonist G-1 had protective effects against human tubular epithelial cell injury induced by methotrexate [172]. In a rat model of heavy metal-induced AKI, tamoxifen prevented mercury-induced toxicity on mitochondrial energy-dependent functions in the kidney [173]. In contrast, fulvestrant, an ERα down-regulator, exacerbated kidney injury in rats with AKI induced by gentamicin [174,175]. Further studies are warranted to determine the roles of estrogen and ERs in drug-induced AKI.

It is well established that renal tubules are very susceptible to various insults including a range of commonly used drugs [176]. However, there exist distinct differences regarding the vulnerability to certain drugs among different segments of tubules or regions of the kidney. Whether or not estrogen or ERs confer comprehensive protection within the kidney is still unknown. Besides, drug-induced nephropathy can also be accompanied by other organ disorders such as hepatotoxicity and thrombocytopenia [177,178]. Management of these comorbidities, therefore, is equally important. A physician should have a high index of suspicion for the risk factors associated with drug-induced AKI in that the underlying health conditions of the patients may have a great impact on the clinical outcome. Correcting risk factors and treating underlying diseases should be emphasized.

**Chronic kidney disease (CKD)**

**Gender differences in CKD epidemiology**

According to the 2017 KDIGO guidelines, CKD is defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health [179]. Major causes of CKD include diabetic nephropathy, IgA nephropathy, lupus nephritis, and membranous nephropathy [180,181]. Epidemiological studies suggested that females experienced slower renal function decline than males, possibly owing to the protective effect of estrogen or the damaging effect of testosterone [182,183]. Studies also revealed that premenopausal women (particularly those less than 45 years old) who underwent bilateral oophorectomy were at higher risk of developing CKD [184], highlighting the renoprotective effect of estrogen [185,186]. On the other hand, CKD itself is associated with hypothalamic–pituitary–ovarian dysfunction, which results in the earlier onset of menopause in uremic women [187]. The estrogen-based hormone replacement therapy seems to ameliorate renal dysfunction and delay CKD progression in postmenopausal patients, which might be partially due to the increased renal NO production and reduced oxidative stress [188–190]. Similarly, animal studies also indicated that the progression of kidney disease was slower in females.

**Estrogen and ERs in CKD settings**

**Diabetic kidney disease (DKD).** As a major microvascular complication of diabetes mellitus, DKD is the most common cause of end-stage renal disease (ESRD) in developed countries. DKD has severe individual and societal consequences, owing to its high morbidity, mortality, and health-care costs [191]. Clinical studies regarding the sex-specific differences in the prevalence and progression of DKD are inconsistent. While some studies reported a higher incidence of DKD and subsequent ESRD in male population, others suggested a female predominance, or no such differences [192–194]. Different study protocols (e.g., age, race, types of diabetes, etc.) and confounding factors might explain this inconclusive link between sex and DKD [195]. The role of sex hormones including estrogen in the setting of DKD has not yet been determined. Nevertheless, a majority of studies have shown that an imbalance of sex hormones does exist among both
male and female patients with diabetes [196,197]. On the other hand, animal studies supported the concept of renal protection in DKD with estrogen [198–200].

The roles of estrogen and ERs in DKD have been investigated. It was reported that the deficiency of estrogen (ovariectomy) could exacerbate renal pathological manifestations (e.g., glomerulosclerosis and tubulointerstitial fibrosis) in rats with diabetes induced by streptozotocin (STZ). The supplementation of estrogen or raloxifene attenuated these changes through reducing lipid peroxidation and oxidative stress [199,201,202]. Similarly, in male diabetic mice with or without orchiectomy, estrogen effectively inhibited DKD progression (e.g., reduced glomerulosclerosis, albuminuria and glomerular hyperfiltration) [198]. In a model of spontaneous DKD, the estrogen treatment attenuated mesangial expansion and glomerular basement membrane (GBM) thickening but failed to ameliorate proteinuria and glomerulosclerosis in male Otsuka-Long-Evans-Tokushima-Fatty rats [203]. Mechanistic studies showed that estrogen exerted its renoprotective effect on DKD through upregulating matrix metalloproteinase (MMP)-2 and MMP-9 to accelerate the degradation of extracellular matrix (ECM) [204]. In addition, estrogen attenuated albuminuria and ECM deposition by regulating the expression of transforming growth factor-β1 (TGF-β1) and its downstream signaling pathway [205]. Moreover, both estrogen and raloxifene ameliorated albuminuria and mesangial expansion in ovariectomized db/db mice, possibly via inhibiting TGF-β1-induced fibronectin transcription and activator protein-1 (AP-1) activity [206].

ERα gene polymorphisms have been associated with the risks of developing CKD with type 2 diabetes mellitus in the African American population and of developing DKD in girls with type 1 diabetes [207,208]. ERα and its splice variants exhibited protective effects against DKD induced by STZ in female mice, as evidenced by reduced glomerular size, hyperfiltration, macrophage infiltration, and proteinuria [209]. The ERα signaling was proposed as one of the renal signaling pathways involved in the pathogenesis of DKD and might be a promising target for the treatment of nephropathy in diabetic patients [210].

Since glomerular mesangial cell (MC) and podocyte injuries are involved in the progression of proteinuria and DKD, quite a few studies have focused on the effects of estrogen and ERs on modulating these cellular processes [211]. Both ERα and ERβ are expressed in human/murine MCs and podocytes [212,213]. It was demonstrated that estrogen played a protective role in the regulation of proliferation and apoptosis of these cells via its receptors. For example, estrogen could increase the degradation of ECM to slow the progression of DKD through upregulating MMP-9 in MCs [213]. It also inhibited podocyte apoptosis through binding to ERβ, which was associated with the activation of the JAK2/STAT3 signaling pathway [214]. Moreover, estrogen or tamoxifen could improve albumin excretion, reduce glomerular size, and decrease matrix accumulation via upregulating the expression of ERβ and down-regulating TGF-β in podocytes from db/db mice [215]. Podocytes isolated from these mice had a higher level of F-actin and lower level of caspase-9, indicating that estrogen might protect against podocyte injury in DKD through regulating both actin cytoskeleton and apoptosis [216]. In ERα knockout mice, podocyte injury (increased desmin and decreased nephrin and Wilms tumor-1) and apoptosis developed, and the estrogen treatment could prevent these changes via the activation of extracellular signal-regulated protein kinase (ERK) signaling pathway [217,218].

Studies regarding the role of GPER1 in DKD are limited. GPER1 agonist icariin was reported to exert protective effects against oxidative stress and fibrosis in male rats with DKD induced by STZ [219]. GPER1 was crucial in regulating MC migration and ECM production in response to TGF-β1 [220]. It was through GPER1 that icariin reduced the deposition of type IV collagen and fibronectin induced by high glucose in human/rat MCs by inhibiting TGF-β/Smad and ERK1/2 signaling pathways [221]. The activation of GPER1 also inhibited high glucose-induced podocyte apoptosis by modulating Bcl-2 expression and mitochondrial translocation [222].

The altered renin–angiotensin system (RAS) plays a crucial role in the context of DKD. Male STZ-induced diabetic mice administered with angiotensin II had more prominent albuminuria, glomerular hypertrophy and mesangial expansion than females [223]. Female rats had lower levels of albuminuria and renal angiotensinogen (AOGEN) mRNA compared with male rats in the development of STZ-induced DKD [224]. This indicates the sex dimorphism regarding RAS in DKD, highlighting the potential role of estrogen in this disease.

In brief, a majority of experimental studies back up the idea that estrogen might play a protective role in DKD through attenuating glomerular MC and podocyte injuries via its receptors and through its sex dimorphism in RAS. However, many controversies and questions remain regarding the roles of sex hormones in the pathophysiology and progression of DKD. The imbalance of sex steroids (e.g., estrogen versus testosterone) has been confirmed in the setting of diabetes from clinical trials, which suggests that restoration of hormonal
homeostasis is far more important than just supplying estrogen as is done in most of the animal studies. Diabetes mellitus, especially type 2, is recognized as the cardiovascular disease equivalent and is associated with other end-organ complications such as retinopathy and neuropathy. The potential role of estrogen or ERs in these aspects has yet to be investigated. Moreover, the complexity and diversity of signaling networks involved in diabetes require more drugs developed to specifically target these dysregulated pathways.

**Lupus nephritis (LN).** As one of the most severe manifestations of systemic lupus erythematosus (SLE), LN is characterized by proteinuria, hematuria and progressive renal dysfunction. It affects over half of all patients diagnosed with SLE and is a major risk factor for overall morbidity and mortality [225]. The female to male incidence of SLE mounts to nine during the fourth decade of life and declines subsequently until the seventh or eighth decade, disproportionately affecting women of reproductive age [226].

The predominance of females among patients with SLE underlines a pathogenic role for female hormones including estrogen [227]. Though mixed results exist regarding whether exogenous estrogen (either oral contraceptives or hormone replacement therapy) may increase the risk for SLE, endogenous estrogen and ERs have been confirmed to be associated with the modulation of both innate and adaptive immune responses in SLE [228–230]. The development and function of immune cells such as T/B cells and plasmacytoid dendritic cells (DCs), as demonstrated by a large body of literature, can be directly influenced by estrogen [231,232]. For instance, estrogen can interfere with the normal tolerance of naive DNA-reactive B cells and amplify the activation of autoreactive B cells [233,234]. Clinical studies further revealed that a baseline sex-biased difference of differentially expressed genes (DEGs) in B cells existed between healthy females and males, and that some of the DEGs were relevant to estrogen-induced type I interferon (IFN)/B cell activator factor (BAFF) signaling pathway [235,236]. Moreover, estrogen could stimulate the expression of CD40 ligand, a molecule involved in the pathogenesis of LN, in peripheral T cells isolated from patients with SLE [232,237]. The detrimental impact of estrogen on SLE was also confirmed by its inhibitory effect on T cell apoptosis, thus allowing for the persistence of autoreactive cells [231]. One randomized controlled trial evaluating the efficacy of fulvestrant in SLE patients found that selective ERs blocking could reduce disease activity as revealed by decreased expression of T cell activation markers and improved SLE disease activity index (SLEDAI) [238]. Interestingly, studies conducted from different nations have shown that male SLE patients had more severe disease patterns and worse prognoses compared with females. For instance, renal involvement, especially type IV LN with nephrotic syndrome, was more frequent in males [239–247].

In murine models of lupus, female mice were more susceptible to the development of glomerulonephritis [248] and the estrogen treatment accelerated the progression of LN [249]. This sex discrepancy suggests a potential role for estrogen in this autoimmune disease. A majority of animal studies concluded that estrogen might play a detrimental role in the pathogenesis of LN. The estrogen treatment could induce a lupus phenotype with kidney damage in wild-type mice and resulted in more immune cells expressing ERα (e.g., CD4⁺ and CD8⁺ T cells, dendritic cells, and macrophages) in autoimmune-prone mice [250]. The administration of estrogen to lupus-prone mice increased the levels of BAFF as well as anti-C1q and anti-dsDNA antibodies, and expanded the population of self-reactive idiotypic B and T cells, thereby accelerating the progression of glomerulonephritis in lupus [249,251]. Through binding to ERs, environmental estrogens (e.g., diethylstilbestrol and bisphenol-A) that mimic estrogenic activity also enhanced autoantibody production and IgG immune complex deposition in the kidney in lupus-prone mice after orchietomy [252].

Studies of ERs in the pathogenesis of LN and other immune-mediated glomerular diseases have mixed results. Those in favor of the detrimental role of ERs argued that ERα acted in a B cell-intrinsic manner to promote B cell activation specifically in female lupus-prone mice, and that its deletion in B cells attenuated autoantibody production and glomerular immune complexes [253]. Furthermore, ERα knockout female mice developed less severe nephritis induced by nephrotoxic serum while manifesting normal autoimmune humoral response [12]. Similarly, other studies indicated that ERα deficiency conferred protection against proteinuria and tubular injury in female lupus-prone mice [254,255]. However, Scott et al. pointed out that previously reported ‘ERα knockout mice’ were not in fact ERα null but expressed an N-terminally truncated ERα (ERα short, similar to an endogenously expressed ERα46 variant), and that these mice were protected from LN after ovariectomy only if supplemented with estrogen [256,257]. This suggested that the ERα short protein had a protective role in LN and that endogenous ERα variants might represent a potential therapeutic target. Likewise, Shim et al. suggested that mice lacking ERα
rather than lacking ERβ developed autoimmune glomerulonephritis, proteinuria, and plasma cell infiltration in the kidney without antigen challenge [258]. Clinical data have shown that ERα polymorphism is associated with SLE susceptibility in the overall and Asian populations as well as the renal and cutaneous involvements [259–261].

Mechanistic studies regarding the roles of estrogen and ERs in LN and immune-mediated glomerular injury are limited. Estrogen was reported to enhance the activation of conventional DCs through modulating IFN-dependent and independent pathways in both wild-type and lupus-prone mice [262]. ERα was required for Toll-like receptor (TLR)-induced inflammation and the generation of both plasmacytoid DCs and interleukin-17 (IL-17) producing cells, all of which were implicated in SLE [263,264]. Another possible mechanism was that it was through ERα that the estrogen induced the expression of tumor necrosis factor-like weak inducer of apoptosis (TWEAK) and aggravated LN [265].

In conclusion, epidemiological studies and the majority of animal studies highlight the possibility of the involvement of estrogen/ERs in the pathophysiology of LN. The specific mechanisms underlying its role require further investigation. A recent study revealed that aberrant posttranslational modification of steroid receptors including ERα in T cells contributed to the gender-bias of SLE and that targeting ERα could improve the symptoms of lupus patients [266]. Since there are limited clinical trials investigating the efficacy of ERα antagonism in these patients, this pioneering finding may provide a novel molecular basis for future precision treatment.

IgA nephropathy (IgAN). IgAN is the most common glomerulonephritis globally leading to ESRD [267]. Mesangial hypercellularity with deposition of IgA-containing immune complexes is one of the key pathological features.

Male gender was an independent risk factor for developing ESRD in IgAN and male patients presented with worse clinicopathologic manifestations than females [268,269]. Consistently, an animal study suggested that trichothecene vomitoxin (VT)-induced IgAN had a male predilection in B6C3F1 mice and that these males had more severe disease patterns [270]. To further investigate the role of estrogen in IgAN, a study found that castration of female B6C3F1 mice increased the severity of VT-induced IgAN, but supplementation with estrogen did not attenuate this effect but rather increased disease severity [271].

The polymorphism of ERα gene might be associated with the pathogenesis of IgAN [272]. Among several pathways regulating the proliferation of MCs in IgAN, ERα acted as a hub protein that could affect a set of proteins and transcription factors involved in the disease process [273]. A recent study using bioinformatics analysis based on the Gene Expression Omnibus database found that some of the key genes upregulated in IgAN were linked with the estrogen signaling pathway [274]. Another study reported that the expression of glomerular ERα in IgAN renal tissue decreased with the increasing severity of disease, proposing ERα as an independent factor affecting the prognosis of patients with IgAN [275]. Further studies are needed to elucidate the roles of estrogen and its receptors in the pathogenesis of IgAN.

Other CKD models. In animal models of CKD, estrogen was reported to exert protective effects against renal pathologies (e.g., glomerular hypertrophy, atrophic tubules, loss of podocytes, etc.) through attenuating oxidative stress and inflammation [276–278]. In the aging Dahl salt-sensitive (DSS) rats with ovariectomy, estrogen could attenuate glomerulosclerosis and tubulointerstitial fibrosis [279]. Spontaneously hypertensive stroke-prone (SHRSP) rats with uninephrectomy treated with estrogen had reduced albuminuria, glomerulosclerosis, and tubulointerstitial fibrosis [276]. Estrogen also preserved the contralateral kidney function in rats with unilateral ureteral obstruction (UUO), as revealed by reduced expressions of TGF-β and α-smooth muscle actin (∝-SMA) [280]. As a SERM, tamoxifen conferred protection against kidney fibrosis induced by UUO via modulation of ERα-mediated TGF-β1/Smad pathway [281]. Its anti-fibrotic effect was also confirmed in a model of chronic nephropathy (hypertensive nephrosclerosis by chronic inhibition of NO synthesis) where treated rats had less albuminuria, glomerulosclerosis and interstitial fibrosis than untreated ones [282].

The role of ERs has also been investigated. In an adenine-induced CKD model, male rats developed more severe kidney damage than female ones, which might be associated with decreased renal expression of ERα [283]. However, a study using cotton rats to simulate the spontaneous CKD in the elderly population showed that both ERα and ERβ were strongly present in the renal tubules, which correlated with renal cystic lesions, inflammation and fibrosis [284]. Renal tubular epithelial cell regeneration and proliferation contribute to chronic kidney fibrosis, which ultimately leads to CKD [285,286]. Estrogen participated in the renal tubular regeneration process by modulating cell proliferation through the activation of both ERα and GPER1 receptor [287]. The role of ERα in kidney regeneration
and growth was further confirmed in an animal model, where ERα knockout female mice exhibited reduced compensatory kidney growth [288].

Taken together, a majority of the studies suggest that estrogen might exert protective effects against CKD through ameliorating renal fibrosis and that SERMs might be a group of drugs of interest for CKD. However, pharmacokinetics in CKD should be taken into account because of the altered renal and non-renal drug clearance in this population [289]. SERMs such as tamoxifen and raloxifene have been confirmed to be associated with the risks of deep vein thrombosis and pulmonary embolism [290, 291]. The long-term safety and efficacy of these agents need to be investigated. Besides, little progress has been made regarding the prevention and reversal of kidney fibrosis up to now. Whether these drugs confer protection to CKD patients is still unclear.

Complications of CKD

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

CKD-MBD is a major complication of CKD characterized by biochemical abnormalities, bone disorders, and vascular/soft tissue calcification, contributing to cardiovascular disease and mortality [292]. The abnormal metabolisms of calcium, phosphorus, parathyroid hormone (PTH), and vitamin D are key disturbances in CKD-MBD [293].

Physiologically, estrogen takes part in the regulation of phosphorus homeostasis by activating ERα/ERβ-mediated phosphate transporter NaPi-IIa in kidney proximal tubules [294]. Studies regarding the impact of estrogen on phosphate metabolism are mainly confined to the general population. The endogenous estrogen levels in older men were inversely associated with serum phosphorus levels [295]. Consistently, postmenopausal women receiving estrogen treatments had lower serum levels of phosphorus by increasing the urinary excretion of phosphorus [296]. Another SERM, bazedoxifene, could reduce serum phosphorus levels, thereby improving renal functions in postmenopausal osteoporotic women without severe renal insufficiency [297].

CKD-associated osteoporosis is more prominent in postmenopausal uremic patients, highlighting the potential role of estrogen in the disease process [298, 299]. For instance, raloxifene was effective in improving bone mineral density (BMD) in postmenopausal osteoporotic women with CKD [300–303]. Further studies revealed that ERα gene polymorphism might dictate the different outcomes of BMD in postmenopausal hemodialysis patients who received raloxifene [304]. Animal studies showed that the deficiency of estrogen (ovariectomy) contributed to the impaired fixation of titanium implants in the femurs and further bone loss in the mandibles of uremic mice (5/6 nephrectomy) [305, 306]. In an animal model of progressive CKD (male Cy+/ rats with autosomal dominant cystic kidney disease), raloxifene improved skeletal material properties (those independent of bone mass) and structural properties [307]. Mechanistic studies revealed that estrogen could inhibit PTH-stimulated osteoclast-like cell formation through blocking both the cAMP-dependent protein kinase (PKA) and the calcium/PKC pathway [308, 309].

Vascular calcification is highly prevalent in the CKD population, which is associated with major adverse cardiovascular events. Hyperphosphatemia and the abnormality of renin–angiotensin–aldosterone system are contributing factors for this phenomenon [310, 311]. Studies focusing on the effects of estrogen on phosphate/angiotensin II-induced vascular smooth muscle cells (VSMCs) proliferation revealed that estrogen and raloxifene prevented the mineralization of VSMCs [312]. Further analysis revealed that this protective effect was mediated by the transactivation of growth arrest-specific gene 6 (Gas6) and upregulation of liver kinase B1 (LKB1) in the presence of ERα [313, 314]. A randomized controlled trial suggested that estrogen, which had a favorable effect on oxidative stress, might protect against atherosclerotic cardiovascular disease in postmenopausal women with ESRD on hemodialysis [315].

In conclusion, these results suggest that estrogen and SERMs are of clinical significance in the management of CKD-MBD through attenuating biochemical abnormalities, bone disorders, and vascular calcification. Potential adverse effects of these agents are still to be alerted, especially in hemodialysis patients. Although there were no reported breast cancer or thromboembolism associated with the use of raloxifene by the aforementioned studies, the long-term safety and efficacy of SERMs need to be confirmed by larger prospective studies with longer follow-ups. Moreover, the mainstays of therapy for CKD-MBD are dietary phosphorus restriction, modification of dialysis prescriptions, phosphate binders, calcitriol or vitamin D analogs, and calcimimetics [316]. Parathyroidectomy (PTX) is considered when patients develop drug resistance or side effects [317]. Recent studies also confirmed the feasibility and efficacy of microwave ablation treatment for patients ineligible for PTX [318, 319]. Therefore, more studies are warranted to evaluate whether there is an
additional benefit of adding estrogen or SERMs to the established treatment regimen.

**Uremic coagulopathy**

Epidemiological studies revealed an increased susceptibility to major bleeding events in dialysis patients [320,321]. Potential etiologies include platelet dysfunction, dysfunctional von Willebrand factor, decreased production of thromboxane, uremic toxins, and anemia [322,323]. The bleeding tendency in uremic patients was further complicated or exacerbated by their comorbidities and medications (e.g., hypertension, atrial fibrillation with warfarin therapy, cerebrovascular disease with anticoagulants) [318,324–326]. For patients who were refractory to routine interventions for uremic bleeding, conjugated estrogens might be another option [327–329]. Overall, there lacks concrete data regarding the efficacy of estrogen in the prevention and treatment of bleeding in CKD patients. Most of the studies investigating the hemostatic effect of estrogen were confined to the general population, particularly in the setting of recurrent bleeding from arteriovenous malformations, and still there were conflicting results [330,331]. Several case reports have suggested that estrogen, as part of the hormonal therapy, might be effective in the management of recurrent bleeding or hematoma in uremic patients [332–334]. An animal study suggested that estrogen could shorten the prolonged bleeding time in uremic rats and that this hemostatic effect was neutralized by ER antagonists [335]. A possible hypothesis was that the impaired L-arginine-NO signaling under uremic conditions led to acute endogenous deprivation of estrogen and resulted in inhibited platelet aggregation and adhesion [336–338].

The long-term effects of estrogen as a component of hormone therapy in postmenopausal women have been well described by the Women’s Health Initiative trial and related studies, and a consensus has been reached that women who start hormone therapy within 10 years of menopause onset may have less risk of thromboembolic complications [339,340]. However, this notion should be taken prudently in CKD population, as suggested by KDOQI guidelines and several studies [341–343]. CKD is an established risk factor for venous thromboembolism [344,345]. Patients with CKD are at high risk for thromboembolic events due to endothelial dysfunction and retention of indolic solutes [346,347]. Estrogen can cause thrombosis through elevating the levels of prothrombotic factors and decreasing the levels of protein S and antithrombin [348]. Because of the altered drug pharmacokinetics in patients with CKD, exogenous estrogen treatment might be associated with an increased risk of arteriovenous access thrombosis [348–350]. Likewise, an animal study suggested that the estrogen supplementation in rats with renal impairments produced thrombotic microangiopathic lesions in the kidneys [351].

The dual effect of estrogen in uremic coagulopathy needs further investigation. Clinical application of estrogenic agents in the treatment of uremic bleeding requires more explorations. The risk–benefit ratio of estrogen in postmenopausal women with advanced CKD is still unknown and clinical trials addressing this issue are needed.

**Conclusions and research gaps**

Beyond its conventional role in the reproductive system, estrogen also functions in diverse developmental and physiological processes through its different receptors. Estrogen and ERs are crucial in maintaining mitochondrial homeostasis and modulating ET-1 system in the kidney, which points forward to their indispensable roles in normal kidney function. In kidney proximal tubules, estrogen takes part in the regulation of phosphorus homeostasis via its receptors. Estrogen and modulation of ERs have been shown to exert anti-oxidative stress and anti-fibrosis effects in CKD models. On the other hand, studies have revealed the involvement of estrogen and ERs signaling pathways in some autoimmune kidney disorders such as LN.

In light of these findings, the altered or dysregulated estrogen/ERs signaling pathways contribute to a variety of diseases (Table 1). Moreover, given the fact that sex dimorphism exists in certain renal disease entities revealed by epidemiological studies, the roles of estrogen and ERs cannot be overemphasized in the pathogenesis and prognosis of kidney diseases. Indeed, clinical and experimental studies have shown that the level of estrogen or ERs gene polymorphism influences the susceptibilities or dictates the outcomes of several renal diseases. Based on the evidence provided in this review, we propose the concept that targeting estrogen/ERs signaling pathways, either by agonizing or by antagonizing, might works in patients with certain kidney diseases.

However, many gaps exist in knowledge regarding the roles of estrogen and ERs in distinct kidney diseases and further research is necessary to address these areas. The gender differences in the setting of AKI does not necessarily mean this is the case in every single cause for AKI. Likewise, the functional role of estrogen or ERs
The benefits of SERMs have been witnessed in patients at the long way to go before it can be applied to clinical trials. There have been several studies showing estrogen and ERs are involved in the renoprotective effects in several experimental models, there is still a long way to go before it can be applied to clinical trials. The benefits of SERMs have been witnessed in patients with CKD, however, adverse events and long-term outcomes should be assessed.

The therapeutic potential of targeting estrogen/ERs signaling pathways remains to be tested. Moreover, by no means does targeting these mechanisms fully tackle renal disorders, considering the complex signaling networks involved. Further experimental and clinical studies are warranted to comprehensively understand the roles of estrogen and ERs in different kidney diseases.
Acknowledgments

The authors would like to thank Wei Gong, Mi Bai and Yan Guo for assistance with integrating information and formatting the manuscript.

Disclosure statement

The authors declared no conflict of interest.

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