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A review of the application of nanoparticles in the diagnosis and treatment of chronic kidney disease

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ABSTRACT

Chronic kidney disease (CKD) poses a great burden to global public health as current therapies are generally ineffective. Early detection and effective therapy are crucial for the future prevention and progression of CKD. Nanoparticles (NPs) vary by particle size, charge, shape and the density of targeting ligands and are associated with enhancement of the pharmacokinetic properties, targetability, or the bioavailability of drugs. Thus, the emergence of NPs in medicine has provided novel solutions to the potential diagnosis and treatment of CKD. This review describes the current experimental research, clinical applications of NPs, the current challenges, and upcoming opportunities in the diagnosis and treatment of CKD.

1. Introduction

Nanoparticles (NPs) refer to minute structures (1–100 nm) in at least one dimension. Nanotechnology encompasses the engineering and manufacturing of NP materials at an atomic or molecular scale [1]. NPs can be produced using both organic and inorganic materials. Organic NPs include polymeric NPs, dendrimer-based NPs, liposomes, and carbon NPs. Inorganic NPs include quantum dots (qdots) NPs, carbon NPs, and magnetic iron oxide particles [2]. Medical nanotechnology involves NPs used in the design, manufacture, regulation, and application of therapeutic drugs or devices [3]. As shown in Fig. 1, NPs have many characteristics and can serve as colloidal dispersions that are made up of an outer shell and an inner core or a matrix structure [4]. In terms of diagnosis, these structures can be used on the surface of a device to improve the sensitivity and selectivity of detection. They can also be used as imaging agents to assist in diagnosis. In terms of treatment, colloidal dispersions consist of an outer shell and an inner core within which the desired drugs, protein, and nucleic acids can be placed (Fig. 1). Furthermore, the NPs could be shielded from the blood components as their surface layer was coated with inert polymers. This technology has certain advantages such as great carrying capacity, long site-specific retention, and effective absorption of active drug agents [3]. The matrix structure of NPs also can encapsulate bioactive compounds such as drugs, proteins and nucleic acids. Their architecture allows for the control of characteristics such as size, charge, shape, and targeting ligands and subsequently improves the biocompatibility and bioavailability of drugs [5,6]. For example, dendrimers are highly branched and easy to modify and are therefore used in various fields [7]. Nanogels can be crosslinked with hydrophilic flexible polymers, and they have a great water retention ability [8]. Ligands such as antibodies, proteins, and nucleic acids can be linked to the NP surface for targeting specific cells or organs. Therefore, this emerging discipline is becoming a promising tool for medical applications, such as biomarkers detection, imaging techniques, drug delivery, gene therapy, chronic disease therapy, antimicrobial agents, tissue engineering and regenerative medicine [9]. The various applications of NPs in medicine are presented in Fig. 2.

Kidney diseases can be mainly divided into acute kidney injury (AKI) and CKD in terms of kidney function progression. AKI is defined as an increase in serum creatinine by $\geq$ 0.3 mg/dL within 48 h or an increase in serum creatinine to $\geq$1.5 times baseline within the previous 7 days or urine volume < 0.5 ml/kg/h for 6 h. It is usually caused by

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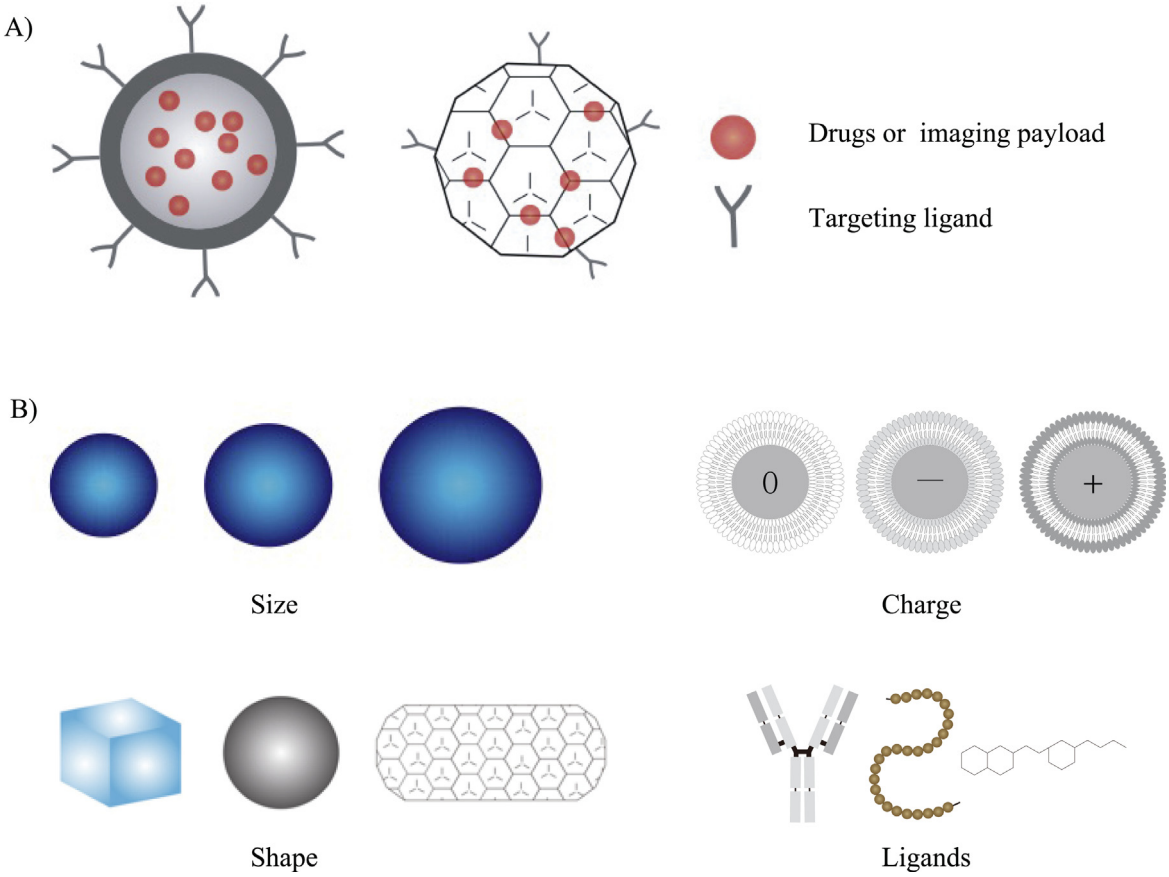

Fig. 1. The composition and properties of nanoparticles. A) Nanoparticles can serve as colloidal dispersions or a matrix structure; B) The features of NPs can be modified by size, charge, shape, and targeting ligands including antibody, peptide and small molecule.

hypovolemia, urinary obstruction, drug poisoning, etc. CKD is defined as a persistent abnormality of kidney structure or function (e.g., glomerular filtration rate [GFR] < 60 mL/min/1.73 m^2 or albuminuria > 30 mg per 24 h) for more than 3 months. Diabetes, hypertension and primary glomerular disease are the most common causes of CKD. They are quite different in terms of definition, causes, and treatment methods. CKD is a worldwide health problem with a prevalence of more than 10%, and a higher prevalence in the elderly [10]. Patients with CKD invariably experience multiple complications and adverse outcomes, which results in a high financial burden to both the affected individuals and society [11]. Thus, early diagnosis of CKD and prompt prevention of disease progression are becoming a public health priority.

A significant amount of research has demonstrated that NPs have exhibited a great capacity for the diagnosis and treatment of CKD. For instance, NPs can provide precise and accurate methods to measure kidney morphology and function and target the delivery of drugs and nucleic acids to specific tissues, which improves renal targeting, retention, and localization. However, few systematic studies of NPs' application in CKD have been conducted. This review focused on the application of NPs in the detection of kidney injury biomarkers and imaging technology. Then we described a novel treatment for CKD and renal replacement therapy for patients with end-stage renal disease (ESRD), as shown in Fig. 3. In the rest of the review, we stated some challenges associated with this technology as well as perspectives.

2. Application of NPs in the diagnosis of CKD

Assessment of early and specific markers is considered crucial for prediction of early onset and the progression of nephropathy. Therefore, an effective intervention therapy could be administered to prevent CKD and reduce complications such as infection, hypertension, anemia and heart failure. However, the traditional diagnostic methods currently available have many limitations such as insensitivity and inconvenience. Therefore, NPs may be important for the early detection of CKD with considerable sensitivity.

2.1. Detection of kidney injury biomarkers

Albuminuria is the risk predictor of incident CKD and CKD progression [12,13]. The routine urinalysis dipstick was positive only when the urinary albumin concentration was > 30 mg/dL. Microalbuminuria could be tested by specific urinary albumin dipsticks or by various specific antibody methods [14]. However, these methods are both insensitive and inconvenient. Surface-enhanced Raman scattering (SERS) with silver/copper/gold NP surface is an emission technology that includes the inelastic scattering of the incident laser energy [15]. SERS has many advantages such as high sensitivity, simple sample processing, rapid analysis, and presence of commercial available portable Raman spectrometers [16]. For example, this technique uses the silver NP surface that absorbs the analyte; thereby, the Raman signal could be enhanced significantly [15]. Stefancu et al. reported that SERS spectroscopy exhibited a strong correlation between the predicted and reference albumin concentrations, with an R^2 and a root-mean squared error of prediction of 0.98 and 2.82, respectively, suggesting that this method is accurate for detecting absolute albuminuria. The extreme low level at 3 μg/ml indicated that this tool is more sensitive in monitoring microalbuminuria than traditional strategy. As reported previously, the detection of the urinary albumin did not require pre-processing of the samples, and this process of detection was very rapid [17]. At present, commercial devices are available that facilitate the

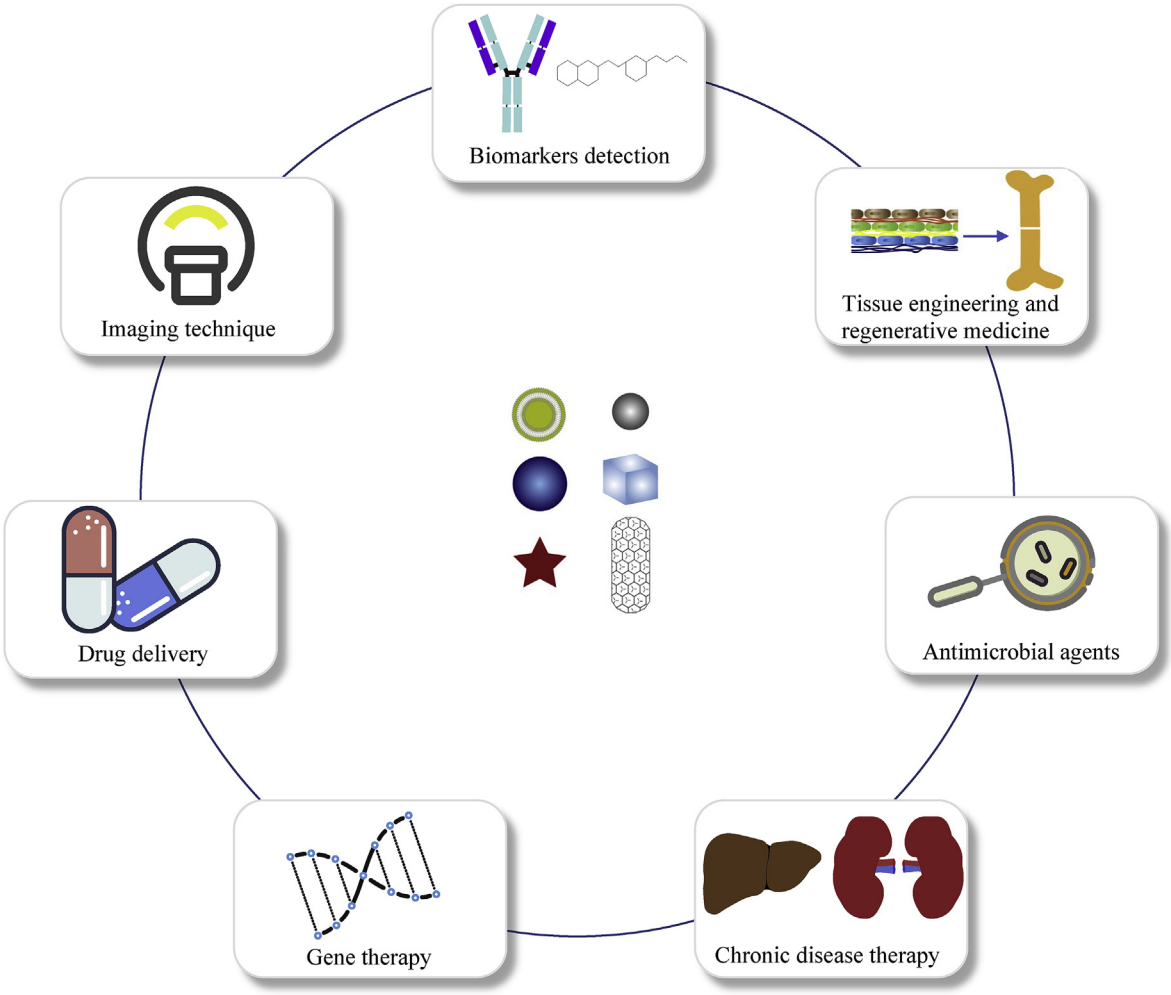

Fig. 2. The various application of nanoparticles in medicine.

point-of-care screening of microalbuminuria [16]. Recently, a simple disposable electrochemical immunosensor (Fig. 4) was also developed for the point-of-care testing of microalbuminuria, wherein gold NPs were used on the electrodes to enhance the biocompatibility and conductivity of this sensor and novel PS/Ag/ab-HSA nanoprobes (polystyrene nanoparticle core with silver nanoshells covalently conjugated to the HSA antibodies) were prepared on the surface of electrode by dielectrophoresis. This point-of-care platform could perform tests anywhere from the home to the bedside and the data is transferred wirelessly to electronic equipment or the cloud for early detection and monitoring of CKD [18].

Other than microalbuminuria, a novel nanotechnology-based

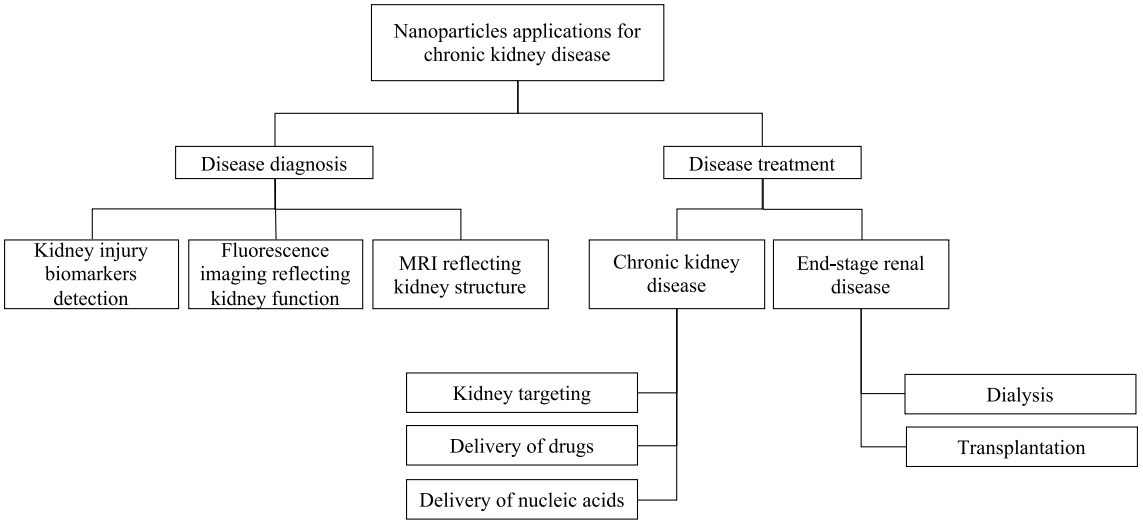

Fig. 3. Diagrammatic sketch for different applications of nanoparticles in chronic kidney diseases.

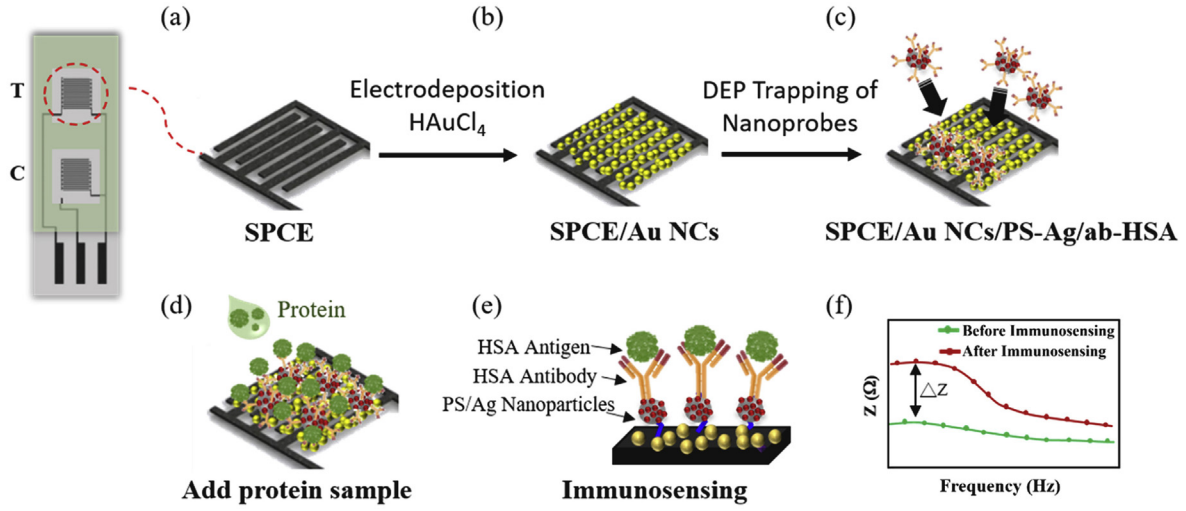

Fig. 4. Schematic illustration of systematic protocol for immunosensor fabrication and operation. (Reprinted with permission from Ref. [18] Copyright 2019: Elsevier.).

multianalyte point-of-care device could quantitatively measure hemoglobin, serum albumin, urine creatinine, and glycosylated hemoglobin, which might be extended to other protein markers (glycated albumin and serum creatine) [19]. By comparing the tested results from this device with laboratory results, the device has been proved useful for detecting early diabetic kidney disease and, in the future, could be used in remote developing nations [20].

Promising biomarkers such as cystatin C (CysC), N-acetyl-β-D-glucosaminidase (NAG) and kidney injury molecule-1 (KIM-1) were effective predictors for CKD [21–23]. A growing body of research has indicated that NPs could be used to amplify the response of an immunosensor in the detection of these biomarkers [24–28]. A disposable amperometric immunosensor was developed to detect CysC in human serum using a sandwich-type assay. They used a layer-by-layer construction approach applying Au NPs to produce an amplified response, which allowed the immunosensor to measure CysC with sensitivity [26]. Wang et al. proposed a novel "light-switch" molecule of the Ru (II) complex ([Ru(dcbpy)2dppz]2+-DPEA) with self-enhanced electrochemiluminescence (ECL) properties [24]. This molecule was almost non-emissive in an aqueous solution; however, when intercalated into the DNA duplex, it became brightly luminescent. They combined this ECL self-enhanced molecule with DNA nanotechnology, to offer an effective signal amplification method that determined NAG which is a characteristic biomarker of diabetic nephropathy. This detection method has been reported to be very sensitive with a linear range of 0.1 pg/mL to 1 ng/mL [24]. Similarly, an ECL biosensor was constructed to determine the levels of KIM-1, a biomarker of early renal injury that reflected the process of renal injury and recovery. Pt NPs were then applied to improve the electron transfer efficiency [28]. Thus, nanotechnology is a promising tool with high sensitivity and efficiency that could improve and complement the current clinical examination methods for CKD, thereby facilitating an earlier intervention.

2.2. Noninvasive fluorescence kidney functional imaging technique

Glomerular filtration rate (GFR) directly describes kidney function. However, this type of detection is inconvenient and poses the risk of acute kidney injury caused by the contrast agent iohexol required for this procedure. Physicians routinely apply the CKD-epidemiology collaboration (CKD-EPI) formula to estimate GFR, which was referred to as eGFR. However, a minor part of creatinine could be absorbed and secreted by the tubular cells, which declined the efficiency in detecting CKD in the early and late-stage, whereas various fluorescent NPs, including qdots, gold and silica NPs, were found to provide four distinct advantages over current methods in the evaluation of GFR. First, they did not cause toxicity or interfere with metabolism in vivo. Second, the absorption and emission wavelengths were in the visible region, and more favorable in the near-infrared range. Third, they were completely filtered by the glomeruli while not being secreted or absorbed via the tubules [29]. Fourth, these NPs were easy to produce and relatively inexpensive [30].

Examples of commercially available nanomaterials are fluorescent semiconductor nanocrystals (also known as qdots), which have been widely applied in the biological field [31]. Furthermore, highly-sensitive and inexpensive near-infrared fluorescence imaging had been widely used in investigating many diseases, such as cancer [32,33]. Nevertheless, noninvasive fluorescence imaging of renal insufficiency and staging are still in the preclinical phase of research [33]. Yu et al. used renal-clearable near-infrared-emitting glutathione-coated gold NPs (GS-AuNPs) as a contrast agent in fluorescence imaging of the kidneys to assess kidney function. They found this nanotechnology was viable for assessing kidney dysfunction noninvasively, reporting the dysfunction stages, and even revealed adaptive functioning in mice with unilateral obstructive nephropathy (UUO) [34]. Moreover, they successfully identified the dysfunction occurring in kidney stages that fitted with renal damage evaluated via pathological findings [34]. Because conventional markers such as serum creatinine and blood urea nitrogen (BUN) could not reveal the renal dysfunction of UUO accurately, this nanotechnology can serve as a powerful kidney function imaging tool. Initially, they applied GS-AuNPs in the fluorescence imaging of kidney clearance kinetics in normal mice to prove that they were non-toxic and did not affect metabolism in vivo [35]. The kidneys of mice revealed no structural alterations and found a very low accumulation in the background tissues [35]. Gold NPs coated by glutathione exhibited the emission wavelength (~800 nm), which was in the near-infrared range and was visible [36]. The hydrodynamic diameter of GS-AuNPs (3.3 ± 0.4 nm) was lower than the renal filtration threshold (6–8 nm), so they could be removed out of the body through the kidneys efficiently [37]. Many renal-clearable NPs are currently available, including AuNPs, copper nanoparticles (CuNPs), iron oxide NPs, silica NPs (SiNPs), carbon dots and palladium nanosheets, which makes the application of NPs in noninvasive renal imaging possible [38–42]. SiNPs with fluorescent anti-CD11b have also been utilized as an imaging tool for assessing inflammation and fibrosis at a high intensity in animal models of UUO [43]. Importantly, NP imaging accurately determines the kidney dysfunction stages and evaluates renal inflammation and fibrosis, indicating that this technology can be used to detect the renal function and invasively investigate the pathology in

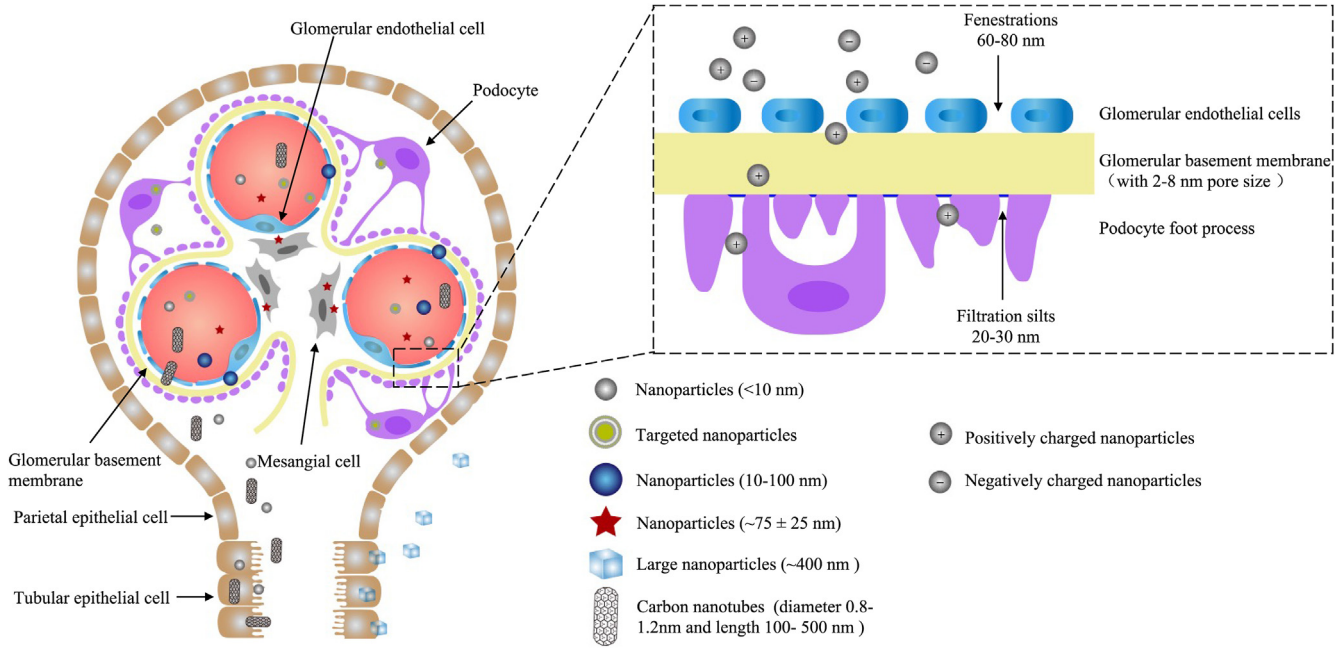

Fig. 5. Schematic structure of the kidney glomerulus and the glomerular filtration barrier. As shown, nanoparticles (< 10 nm) could reach tubular epithelial cells easily. 10–100 nm nanoparticles could be designed size for glomerular deposition and particles of ~75 ± 25 nm size for mesangial cells. Modified nanoparticles can target podocytes specially. The large nanoparticles (~400 nm) could reach the proximal tubule cells via the peritubular capillary. Moreover, carbon nanotubes (length 100–500 nm and diameter 0.8–1.2 nm) directly headed for proximal tubule cells. Expanded portion showed three layers of glomerular filtration barrier: endothelium with fenestration (60–80 nm), glomerular basement membrane (2–8 nm pore), and epithelial podocytes with filtration slit (20–30 nm). It is negatively charged and repels negatively charged nanoparticles.

the future.

2.3. NPs-based magnetic resonance imaging (MRI) reflects the structural information in the kidney

Currently, renal biopsy is the best method to diagnose and evaluate kidney disease. It is considered as the only link between the diagnosis of renal disease and its pathological conditions of the kidney. However, a biopsy is an invasive procedure, which puts patients at risk for hematoma; thus it is an impractical measure for use in follow up [44]. Furthermore, mismatches between the very small obtained specimen and the overall kidney condition have occurred because of the limited extent of renal tissue involvement [45]. Thus, nano-MRI could provide solutions to the limitations of conventional modalities and might be the next step in renal biopsy [46]. Moreover, it is noninvasive and assesses the overall condition of the kidneys and would be a viable measure for use in follow up. In the development of nanoscale detection technologies, iron oxide NPs are regarded as a promising alternative to nephrotoxic gadolinium-based MRI contrast agents [47]. Iron oxide particles could be used in both functional (quantitative perfusion, quantitative glomerular filtration rate, and estimation of tubular function) and cellular imaging (intrarenal phagocytosis in inflammatory nephropathy) [48,49]. Inflammatory cells including macrophages absorb iron oxide, and the T2-weighted MRI signal decreased in these areas of high cell populations [50]. The signal intensity of each kidney was measured using different types of nephropathies prior to and 24 h after injection of the iron oxide. The cortical signal intensity decreased significantly in the nephrotoxic nephritis rats. In contrast, the signal intensity loss was seen in all renal compartments in response to the diffuse interstitial lesions in the obstructive nephropathy model, indicating NP-based MRI can help in diagnosing different types of nephropathies [51]. Similar results have been reported in human studies [52]. Hauger et al. also injected iron oxide intravenously to detect and characterize macrophages infiltrated in native and transplanted kidneys. The patients with cortical macrophage infiltration in their kidneys presented a 33% ± 18% mean cortical signal decrease, as revealed by T2-weighted images. In three patients with ischemic acute tubular necrosis, an intense (42 ± 18%) signal decline was exclusively observed in the medulla [52]. Given that macrophages infiltration is one of the characteristics of inflammation, signal decline due to uptake by macrophages can provide the information of renal inflammation and injury. By detecting the intensity and area of MRI signal, different nephropathies can be identified and differentiated. Though the safety of frequent use of iron oxide NPs remains unknown, its preclinical pharmacokinetic and safety appears to be satisfactory in view of the application prospect of this method as a single-dose diagnostic agent for human MRI [53]. As NP-enhanced MRI could provide both structural and functional information for the kidneys, it could be used to assess renal inflammation and differentiate between different kidney diseases clinically.

3. Application of NPs in the treatment of CKD

CKD results in loss of renal function and even renal failure. In contrast to more acute inflammatory glomerulonephritis where immunosuppression could potentially even cure disease, no currently available therapies can reverse the loss of renal function in CKD [54]. At present, only limited therapeutic strategies are available to slow down the progress of CKD. Supportive treatment includes angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB), and other conservative treatments [55,56]. In addition, immunosuppressive therapy comprises glucocorticoid, cyclophosphamide, cyclosporin, mycophenolatemofetil and rituximab. However, there is a need for markedly more targeting therapies with few side effects to slow down the progression of CKD. NPs play an important role in terms of serving as kidney-targeting transport system for several classes of drugs and nucleic acids.

3.1. Kidney targeted treatment

Kidney targeted therapy could improve the therapeutic drug efficacy and reduce toxicity. The nephron, which is the structural and functional unit of the kidney, is composed of the glomerulus and tubule system. The glomerulus is made up of a tuft of blood capillaries and the mesangium (mesangial cells and the extracellular matrix). The glomerular filtration barrier comprises three layers: glomerular endothelial cells (GECs), glomerular basement membrane (GBM), and podocytes (Fig. 5). The first layer is composed of the GECs that are characterized by numerous transcellular holes and fenestrations (60–80 nm) filled with an endothelial glycocalyx [57]. It restricts the circulating plasma components from entering the endothelial cell membranes through a filamentous structure and strong negative charge [58]. The next layer is a 300-nm thick connective tissue membrane with a 2-8-nm pore size; it comprises collagen IV, laminin, nidogen, and negatively charged heparan sulfate proteoglycans [59–61]. These layers produce an interwoven meshwork to filter small molecules according to charge and size. The podocytes are firmly attached to the GBM and have interdigitating foot processes, forming 20-30-nm-wide filtration slits [62]. This barrier is the final size-selective filter in albumin.

NPs can be designed to target specific cells or tissues via tailoring the particle size, charge, shape, and density of the targeted ligands (Table 1). The size of NPs significantly influences cellular uptake, blood circulation half-life, and targeting [63]. NPs of an average size of 100 nm have a longer half-life period than NPs of smaller or larger sizes. Smaller particles penetrated the kidneys more readily, but those < 10 nm were more likely to be removed by renal excretion and phagocytosis [63]. Thus, by tailoring the size of the NPs, there is potential to target different cells (Fig. 5). Research has shown that NPs with diameters of approximately 75 ± 25 nm targeted the renal mesangium, whereas larger NPs (> 100 nm) could not enter the mesangium due to the size limitation created by the fenestrations of GECs [64]. Studies have also focused on targeting the renal tubule, and have designed NPs (< 10 nm) small enough to get past the glomerular filtration barrier and be internalized by the epithelial cells [65,66]. In vivo, 5 nm dextran-based NPs and dendrimer NPs were both filtered, and then absorbed by the tubular epithelial cells in a time and dose-dependent fashion [66]. However, large NPs (~400 nm), which were much larger than the fenestrations of the GBM, were found to target the proximal tubules selectively. This result suggested that the NPs are internalized by the proximal tubule epithelial cells at basal side via passing through the peritubular capillaries [67].

The surface charge of the NPs has a bearing on glomerular filtration rate. NPs with different surface charges could be combined with the circulation proteins or other charged molecules, which led to an increase in hydrodynamic size. Furthermore, they interacted with the glomerular capillary wall, which is negatively charged [68]. Thus, this interaction could be another strategy to attain kidney-targeting. Cationic ferritin NPs (13 nm) were accumulated in the GBM of the rat; however, the negatively charged ferritin NPs were not [69]. Similarly, the siRNA NPs in circulation could access the GBM and preferentially deposited there because of their positive surface charge [70]. Studies have indicated that with NPs of < 5.5 nm, the charge is a primary determinant of kidney uptake. Negatively charged quantum dots (~3.7 nm) accumulated in the mesangial cells, with only a few found in the urine. While similar sized cationic quantum dots were excreted directly into the urine [71].

The shape of NPs has a significant impact on the performance and biological distribution in vivo, as they need to be successfully transported and bound to their designated target. Different shapes have been developed, such as cubic, spherical, hexagonal, helical, and rods. Cylindrical shape is the only shape affected by blood flow [72]. Rod structure has exhibited enhanced tumor penetration compared to other shapes [73]. Spherical NPs are cleared less slowly than non-spherical NPs due to their aspect ratio and dimension; however, they migrate to the vessel walls less efficiently [74]. For example, the single-walled carbon nanotubes with a length of 100–500 nm and a diameter of 0.8–1.2 nm were rapidly filtered by the glomerular, reabsorbed by the tubules partially, and translocated into the nuclei of proximal tubular cells (Fig. 5). Mathematical modeling suggested the trend of flow compared with the orientation of the NPs allowed for clearance via the glomerular pores [75]. Similarly, in the renal injury models induced by cisplatin, carbon nanotubes targeted therapeutic siRNA to proximal tubule cells to reduce the injury [76]. Thus, appropriate shapes could be designed to target podocytes in the future to alleviate albuminuria in CKD.

Active targeting of NPs involves the conjugation of targeting ligands to the surface of NPs, which improved the specificity of therapy under identical physical conditions such as size, charge, and shape [77]. These ligands included antibodies, antibody fragments, peptides, aptamers and small molecules. Various ligands were designed to target the corresponding receptors of mesangial cells, GECs, GBM, podocytes and tubular cells, respectively, which have been listed in Table 1. The well-studied ligands include E-selectin antibody, Ac2-26 peptide, cyclopeptide, angiotensin I/II, modified polymyxin, and their corresponding receptors include E-selectin, collagen IV, αvβ3 integrin receptor, angiotensin II receptor and megalin, respectively. At the onset of glomerulonephritis in mice, E-selectin was specifically expressed on the endothelial cells. Therefore, coating the liposomes with an antibody against E-selectin, could successfully suppress this expression in the GECs and reduce albuminuria [78]. Studies have shown that NPs containing a specific peptide Ac2-26 bind to a collagen IV target subendothelial collagen IV [79]. Because collagen IV was produced by GECs or podocytes and both these cells are present on the surface of GBM, the podocytes and GECs can be repaired by targeting the GBM.

Table 1
Characteristics of NPs with renal targeting.

	Characteristics	Renal target and receptor
Size	~75 nm gold NPs	Mesangium [64]
	5 nm dextran-based NPs	Renal tubular epithelial cells [66]
	5 nm dendrimer NPs	Renal tubular epithelial cells [66]
	~400 nm PLGA–PEG NPs	Proximal tubule epithelial cells [67]
Charge	Cationic ferritin NPs	Glomerular basement membrane [69]
	SiRNA NPs	Glomerular basement membrane [70]
	Negatively-charged quantum dots	Mesangial cells [71]
	Cationic quantum dots	Tubular epithelial cells [71]
Shape	Carbon nanotubes (100–500 nm and diameter of 0.8–1.2 nm)	Proximal tubular cell [75,76]
Surface ligands	E-selectin antibody	E-selectin/Glomerular endothelial cells [78]
	Ac2-26 peptide	Collagen IV/Glomerular basement membrane [79]
	Cyclo peptide	αvβ3 integrin receptor/Podocyte [80]
	Angiotensin I/II	Angiotensin II receptor/Mesangial cells [81]
	Modified polymyxin	Megalin/Proximal tubule epithelia cells [85]

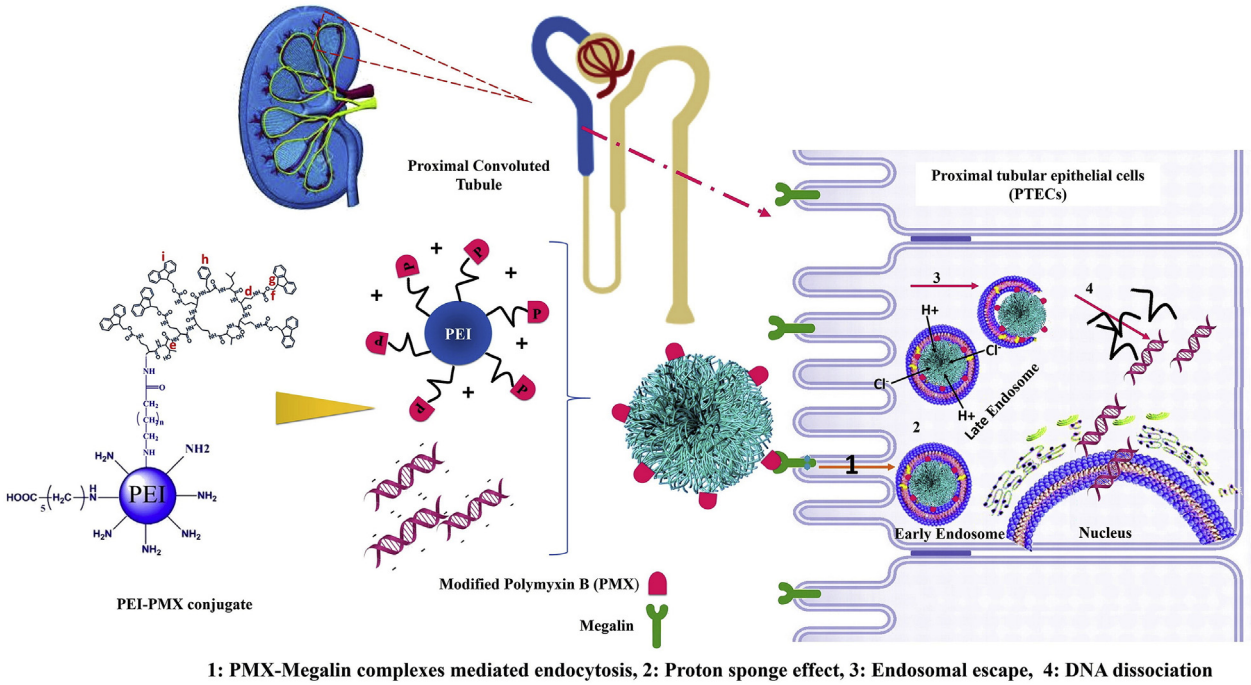

Fig. 6. Schematic illustration of megalin-mediated delivery of modified-polymyxin-PEI conjugates to PTECs. (Reprinted with permission from Ref. [85] Copyright 2017: Elsevier.).

Cyclopeptide was able to selectively bind with the αvβ3 integrin receptor on the podocytes, and the cyclo-modified quantum dots have been shown to be internalized by the podocytes [80]. Thus, this may be a potential method for targeted therapies of podocyte-associated diseases. Recently, NPs used to target mesangial cells for the presence of angiotensin-converting enzyme on the surface have been developed, which are pivotal to diabetic nephropathy. This method used angiotensin I as a proligand and angiotensin II as a secondary ligand, which triggered the NP uptake in the mesangial cells by binding in a second stage to the angiotensin type II receptor [81]. Targeting drugs to the proximal tubular cells can be an attractive approach to treat tubulointerstitial fibrosis by minimizing the risks of adverse side effects and enhancing the efficacy of the antifibrotic drugs [82]. Megalin has been identified as a multi-ligand receptor that is expressed in the apical membrane of proximal tubule epithelial cells and plays an important role in the endocytosis of the cells [83]. Several studies have probed the megalin receptor for specifically delivering the drugs to the kidneys [84,85]. As showed in Fig. 6, Oroojalian et al. synthesized megalin-targeted nanocomposites of modified-polymyxin–polyethylenimine (PEI) conjugates for the delivering an EGFP plasmid to improve the biocompatibility, cell specificity, and stability of drugs used to treat tubulointerstitial fibrosis. Both in vivo and vitro experiments showed that modified polymyxi–PEI/DNA NPs could target kidney cells that express megalin effectively and had improved the efficiency of transfection [85] (Table 1).

3.2. NPs can be used to deliver drugs

NPs possess an efficient and safe selective drug delivery property (Fig. 1a), which is why they have been widely investigated for the delivery of various types of drugs. NPs improved the pharmacokinetic properties and enhanced the targetability and bioavailability of drugs. Recently, thapsigargin NPs proved to be viable for treating CKD by activating Nrf2 and FoxO1. In vitro, thapsigargin NPs protected human kidney tubular epithelial cells from oxidative stress-induced cell death by activating Nrf2 and FoxO1, whereas the oxidative stress-induced cytotoxicity was enhanced by siRNA-mediated inhibition of Nrf2 and FoxO1. In vivo, thapsigargin NPs reportedly ameliorated renal injury in an adenine diet-induced CKD mouse model [86], indicating that it is a promising therapy to prevent or interfere with CKD progression.

Resveratrol is a natural polyphenol that elicits beneficial effects on several renal diseases through an anti-inflammatory mechanism [87]. However, poor pharmacokinetic properties such as low aqueous solubility, low photostability, and poor bioavailability limited the application of this polyphenol [88]. Thus, a novel method was used to overcome these limitations, and resveratrol-loaded NPs were constructed. NPs were conjugated with the KIM-1 antibody, which was highly upregulated on the surface of the injured kidney epithelial cells, which enhanced targetability [89]. The treatment of HK-2 with resveratrol-loaded NPs resulted in lower toxicity, allowed sustained and controlled release of drugs, and inhibited the NLRP3 inflammasome and IL-1β, which play central roles in kidney inflammation. CKD mice induced by adenine presented high BUN and creatinine levels. Following treatment with resveratrol-loaded NPs or KIM-1-resveratrol-loaded NPs, the creatinine levels were reduced, and the tubulointerstitial injury was alleviated in the CKD models. The KIM-1-resveratrol-loaded NPs exhibited a more favorable effect, and thus, it was concluded that these NPs could prevent CKD via targeting injured kidney cells and attenuating the NLRP3 inflammasome, which showed better therapeutic effects and less side effects than the traditional treatment methods [90]. Several natural herbs have reportedly inhibited fibrosis and CKD progression, but when treated alone, the effects were limited because of poor bioavailability and non-specificity [91]. Salvianolic acid B is extracted from the traditional herb Danshen, which inhibits the TGF-β1-induced myofibroblast phenotype and restores the epithelial morphology in the human kidney proximal tubular cell line [92]. Reports had shown that when salvianolic acid B-phospholipid complex was encapsulated into NPs, the oral bioavailability and gastrointestinal absorption were improved [93]. Therefore, in the near future, nanotechnology could be used in TCM herbal medicines to potentially treat CKD.

The initial medication for the treatment of iron deficiency anemia was ferrous sulfate (FeSo4). However, the use of FeSo4 had several drawbacks, including a low absorption rate, poor bioavailability, and

serious side effects [94]. Thus, some studies used iron oxide magnetic NPs to treat iron deficiency anemia in an effort to overcome these disadvantages [95,96]. Furthermore, liposomal NPs were also used for drug delivery. Liposomal NPs enhanced iron absorption and solved some of the noncompliance problems [97].

CKD was frequently accompanied by hyperphosphatemia [98]. The currently prescribed phosphate binders on the market have several drawbacks, such as a high risk of hypercalcemia, high cost, low-to-moderate efficacy, and adverse gastrointestinal effects [99]. A phosphate binder based on iron-ethylenediamine with nanoporous silica (Fe-EDA-SAMMS) had been chosen for substrates and Fe (III) deposition methods to overcome these limitations. Compared with other common phosphate binders, the Fe-EDA-SAMMS material possessed an improved phosphate-binding capacity, a faster phosphate-binding rate, a broader operating pH window, and was significantly less affected by the other anions [100]. Importantly, several nanodrugs have already been approved for hyperphosphatemia applications by the US Food and Drug Administration (FDA), such as sevelamer carbonate [101].

3.3. NPs deliver nucleic acids

Apart from delivering the drugs, NPs can also be applied to deliver the nucleic acids to the specific target, such as siRNA, mRNA, and DNA. Thus, by combining nucleic acids with NPs, a biocompatible, stable, and modifiable delivery system can be formulated, which can cure chronic kidney disease. Connective tissue growth factor (CTGF), which is the important molecule in chronic fibrotic diseases, provided a unique strategy for siRNA target therapy [102]. Khaja et al. produced a biocompatible and cheap sterically stabilized phospholipid NPs (SSLNPs), then combined the siRNA against CTGF with NPs. This nanocarrier could load and transport enough siRNA against CTGF to treat the renal tubular epithelial cells, which showed favorable pharmacokinetic properties and became a stable system for targeting fibrotic kidney diseases [103]. Both p38α mitogen-activated protein kinase (MAPK) and p65 contributed to the inflammatory injury in the kidneys [104]. Recently, Wang et al. designed a liposomal NP siRNA co-delivery system that loaded both p38α MAPK and p65 siRNA to reduce the kidney injury. Liposomes were selected for the siRNA delivery because of their biocompatibility, biodegradability, cheapness, modifiability and high carrying capacity [105]. Experiments showed that the liposome siRNA co-delivery had glomerulus targeting and retention capabilities and could efficiently silence p38α MAPK and p65. In mouse IgA nephropathy models, the proteinuria, inflammation, and excessive extracellular matrix deposition were markedly relieved. This co-delivery system provided a new method of glomerulus targeting and could be a promising way to treat other inflammatory diseases [106].

mRNA could be used as a replacement therapy for treating hereditary renal diseases and other kidney diseases. Delivering mRNA by NPs was less expensive and more stable, and provided an alternative treatment for diseases. Fabry disease is a rare inherited lysosomal storage disorder led by mutations in the gene (GLA) encoding the lysosomal enzyme a-galactosidase A [107,108]. Patients with enzyme deficiency are at a higher danger of developing CKD and cardiovascular disease [109]. Enzyme replacement therapies are currently used for treating Fabry disease but are costly and have negligible efficacy [110]. Recently, an alternative approach was developed by constructing nanoparticles-formulated with mRNA for delivering the therapeutic human GLA sustainably in vivo. This study indicated that the serum GLA protein levels had increased significantly, and the clinically relevant biomarkers reduced by delivering the human GLA mRNA into mice. Their research took advantage of the inner features of an mRNA-based approach to produce the hGLA protein at very high levels for several days, resulting in more favorable therapeutic properties than the enzyme replacement therapies [111].

Plasmid DNA (pDNA) delivery, as a gene method, exhibited lower immune response and toxicity in vivo [112]. NPs have the ability to deliver pDNA to the targeted organ or cells effectively [113,114]. Conversely, it could prevent pDNA from DNase digestion in the blood circulation [115]. Tsai et al. combined anti-miRNA plasmids and iron oxide/alginate NPs for conjugating with anti-kidney antibodies. MRI and in vivo imaging systems showed that these nanocomposites could target the renal tubular cells specifically, and that anti-miRNA released by the nanocomposites inhibites cyst formation and cell proliferation which are characteristics of the autosomal dominant polycystic kidney disease [116]. These findings indicate that NPs can be a promising strategy for the treatment of CKD and other gene mutation-caused diseases.

4. Application of NPs in the management of ESRD

A significant number of patients with CKD will progress to ESRD, which necessitates dialysis or kidney transplantation [117]. This condition is associated with a major change in their quality of life, as well as a series of complications. Thus, nanomaterials might one-day lead to fewer complications and improved quality of life.

4.1. Dialysis

NPs could improve the efficacy and reduce the adverse effects of hemodialysis. Magnetically assisted hemodialysis was introduced to remove the target toxins. This type of NPs was based on conjugates made from biocompatible ferromagnetic NPs and a targeted binding substance. The experiments revealed that this new method exhibited a greater removal rate and overall removal efficiency than conventional hemodialysis, and it could be used to remove toxins that could not be done with conventional treatment [118]. The use of a plasmon-induced dialysate comprised of Au NPs-treated water instead of conventional deionized water was an innovative breakthrough. This dialysate treatment reduced the removal time of 70% BUN and creatinine, which were reduced by 47% and 59%, while NO that was induced by the lipopolysaccharide was suppressed [119]. Additionally, nanotechnology could also reduce the side effects led by hemodialysis, such as dialysis-induced oxidative stress, protein absorption, and plate adhesion [120–122]. Chen et al. designed multi-functional decorated gold NPs and used an artificial kidney to simulate efficient hemodialysis. It reduced the acute adverse effects, and also decreased dialysis-induced oxidative stress [123]. Peritoneal dialysis, nanotechnology also could reduce the side effects. A nanoconjugate Apaf-1 inhibitor might protect the mesothelial cells from cytokine-induced injury and quaternary ammonium polyethyleneimine, and therefore, NPs might be used as antibacterial agents for peritonitis [124,125].

4.2. Transplantation

Only a relatively small proportion of patients are able to receive kidney transplants because of the scarcity of available donor organs. Novel methods being tested include implantable artificial kidneys, which incorporate a high-efficiency filter made of silicon nanotechnology and a bioreactor of cultured renal tubule epithelial cells. These filters had slit-like pores, similar to the glomerular slit diaphragms, which showed great selectivity at a given value of permeability [126]. This implantable artificial kidney simulated the arrangement of the glomerular–tubule of the kidney was implanted into the vascular system, which utilized the patient's blood pressure to pump blood into the NP filters with membranes that mimicked the slit-shaped pores of the podocytes, and then via the bioreactor containing living tubular cells. However, challenges such as how to sustain a clot-free filtration and a stable differentiated phenotype of tubule cells still exist [127].

5. Conclusions and perspectives

Nanotechnology is a promising tool for the diagnosis of early CKD and monitoring of CKD progression to ensure that prompt prevention and therapy strategies are immediately undertaken. This tool has provided some biomarkers such as microalbuminuria, hemoglobin, serum albumin, urine creatinine, glycosylated hemoglobin, CysC, NAG and KIM-1 and has amplified effective signals using SERS, etc. Furthermore, NP imaging could measure kidney dysfunction stages and assess the inflammation and fibrosis of the kidneys, which might replace invasive renal biopsies in the future. Also, this technology could be used to treat CKD and ESRD patients. By tailoring the NP size, charge, shape, and surface ligand, we could design the proper transport to deliver both drugs and nucleic acids. In addition, NPs could reduce complications and improve existing renal replacement therapy. As the progress of nanotechnology advances, several NPs have already been marketed, while many are still in preclinical trials. Challenges exist regarding bringing the NPs closer to clinical translation. Thus, efforts are still required for improving the in vivo stability, kidney targeting, biodistribution, metabolism, and reduction in nanotoxicity. We believe that collaboration is required between nephrologists and nanotechnologists so that appropriate targeting and therapeutic methods could be translated more readily from the bench to the hospital bed.

Declaration of competing interest

None.

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References

[1] O.C. Farokhzad, R. Langer, Impact of nanotechnology on drug delivery, ACS Nano 3 (2009) 16–20, https://doi.org/10.1021/nn900002m.
[2] S.H. Lee, J.B. Lee, M.S. Bae, D.A. Balikov, A. Hwang, T.C. Boire, I.K. Kwon, H.J. Sung, J.W. Yang, Current progress in nanotechnology applications for diagnosis and treatment of kidney diseases, Adv. Healthcare Mater. 4 (2015) 2037–2045, https://doi.org/10.1002/adhm.201500177.
[3] E.S. Ali, S.M. Sharker, M.T. Islam, I.N. Khan, S. Shaw, M.A. Rahman, S.J. Uddin, M.C. Shill, S. Rehman, N. Das, S. Ahmad, J.A. Shilpi, S. Tripathi, S.K. Mishra, M.S. Mubarak, Targeting cancer cells with nanotherapeutics and nanodiagnostics: current status and future perspectives, Semin. Canc. Biol. (2020), https://doi.org/10.1016/j.semcancer.2020.01.011.
[4] C. Brede, V. Labhasetwar, Applications of nanoparticles in the detection and treatment of kidney diseases, Adv. Chron. Kidney Dis. 20 (2013) 454–465, https://doi.org/10.1053/j.ackd.2013.07.006.
[5] L. Palmerston Mendes, J. Pan, V.P. Torchilin, Dendrimers as nanocarriers for nucleic acid and drug delivery in cancer therapy, Molecules 22 (2017), https://doi.org/10.3390/molecules22091401.
[6] R.T. Chacko, J. Ventura, J. Zhuang, S. Thayumanavan, Polymer nanogels: a versatile nanoscopic drug delivery platform, Adv. Drug Deliv. Rev. 64 (2012) 836–851, https://doi.org/10.1016/j.addr.2012.02.002.
[7] F. Abedi-Gaballu, G. Dehghan, M. Ghaffari, R. Yekta, S. Abbaspour-Ravasjani, B. Baradaran, J.E.N. Dolatabadi, M.R. Hamblin, PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy, Appl. Mater Today 12 (2018) 177–190, https://doi.org/10.1016/j.apmt.2018.05.002.
[8] J.P. Rolland, B.W. Maynor, L.E. Euliss, A.E. Exner, G.M. Denison, J.M. DeSimone, Direct fabrication and harvesting of monodisperse, shape-specific nanobiomaterials, J. Am. Chem. Soc. 127 (2005) 10096–10100, https://doi.org/10.1021/ja051977c.
[9] G.R. Rudramurthy, M.K. Swamy, Potential applications of engineered nanoparticles in medicine and biology: an update, J. Biol. Inorg. Chem. 23 (2018) 1185–1204, https://doi.org/10.1007/s00775-018-1600-6.
[10] S. Luo, M.E. Grams, Epidemiology research to foster improvement in chronic kidney disease care, Kidney Int. 97 (2020) 477–486, https://doi.org/10.1016/j.kint.2019.11.010.
[11] R. Saran, B. Robinson, K.C. Abbott, L.Y.C. Agodoa, J. Bragg-Gresham, R. Balkrishnan, N. Bhave, X. Dietrich, Z. Ding, P.W. Eggers, A. Gaipov, D. Gillen, D. Gipson, H. Gu, P. Guro, D. Haggerty, Y. Han, K. He, W. Herman, M. Heung, R.A. Hirth, J.T. Hsiung, D. Hutton, A. Inoue, S.J. Jacobsen, Y. Jin, K. Kalantar-Zadeh, A. Kapke, C.E. Kleine, C.P. Kovesdy, W. Krueter, V. Kurtz, Y. Li, S. Liu, M.V. Marroquin, K. McCullough, M.Z. Molnar, Z. Modi, M. Montez-Rath, H. Moradi, H. Morgenstern, P. Mukhopadhyay, B. Nallamothu, D.V. Nguyen, K.C. Norris, A.M. O'Hare, Y. Obi, C. Park, J. Pearson, R. Pisoni, P.K. Potukuchi, K. Repeck, C.M. Rhee, D.E. Schaubel, J. Schrager, D.T. Selewski, R. Shamraj, S.F. Shaw, J.M. Shi, M. Shieu, J.J. Sim, M. Soohoo, D. Steffick, E. Streja, K. Sumida, M. Kurella Tamura, A. Tilea, M. Turf, D. Wang, W. Weng, K.J. Woodside, A. Wyncott, J. Xiang, X. Xin, M. Yin, A.S. You, X. Zhang, H. Zhou, V. Shahinian, US renal data system 2018 annual data report: epidemiology of kidney disease in the United States, Am. J. Kidney Dis. 73 (2019), https://doi.org/10.1053/j.ajkd.2019.01.001 A7-a8.
[12] H. Reichel, J. Zee, C. Tu, E. Young, R.L. Pisoni, B. Stengel, J. Duttlinger, G. Lonnemann, B.M. Robinson, R. Pecoits-Filho, D. Fliser, Chronic kidney disease progression and mortality risk profiles in Germany: results from the chronic kidney disease outcomes and practice patterns study, Nephrol. Dial. Transplant. (2020), https://doi.org/10.1093/ndt/gfz260.
[13] R.G. Nelson, M.E. Grams, S.H. Ballew, Y. Sang, F. Azizi, S.J. Chadban, L. Chaker, S.C. Dunning, C. Fox, Y. Hirakawa, K. Iseki, J. Ix, T.H. Jafar, A. Kottgen, D.M.J. Naimark, T. Ohkubo, G.J. Prescott, C.M. Rebholz, C. Sabanayagam, T. Sairenchi, B. Schottker, Y. Shibagaki, M. Tonelli, L. Zhang, R.T. Gansevoort, K. Matsushita, M. Woodward, J. Coresh, V. Shalev, Development of risk prediction equations for incident chronic kidney disease, JAMA (2019), https://doi.org/10.1001/jama.2019.17379.
[14] W.F. Keane, G. Eknoyan, Proteinuria, albuminuria, risk, assessment, detection, elimination (PARADE): a position paper of the National Kidney Foundation, Am. J. Kidney Dis. 33 (1999) 1004–1010, https://doi.org/10.1016/s0272-6386(99)70442-7.
[15] P.A. Mosier-Boss, Review of SERS substrates for chemical sensing, Nanomaterials 7 (2017), https://doi.org/10.3390/nano7060142.
[16] G. McNay, D. Eustace, W.E. Smith, K. Faulds, D. Graham, Surface-enhanced Raman scattering (SERS) and surface-enhanced resonance Raman scattering (SERRS): a review of applications, Appl. Spectrosc. 65 (2011) 825–837, https://doi.org/10.1366/11-06365.
[17] A. Stefancu, V. Moisoiu, C. Bocsa, Z. Balint, D.T. Cosma, I.A. Veresiu, V. Chis, N. Leopold, F. Elec, SERS-based quantification of albuminuria in the normal-to-mildly increased range, Analyst 143 (2018) 5372–5379, https://doi.org/10.1039/c8an01072b.
[18] M.O. Shaikh, P.Y. Zhu, C.C. Wang, Y.C. Du, C.H. Chuang, Electrochemical immunosensor utilizing electrodeposited Au nanocrystals and dielectrophoretically trapped PS/Ag/ab-HSA nanoprobes for detection of microalbuminuria at point of care, Biosens. Bioelectron. 126 (2019) 572–580, https://doi.org/10.1016/j.bios.2018.11.035.
[19] V. Kumar, D.M. Kashyap, S. Hebbar, R. Swetha, S. Prasad, T. Kamala, S.S. Srikanta, P.R. Krishnaswamy, N. Bhat, Aza-heterocyclic receptors for direct electron transfer hemoglobin biosensor, Sci. Rep. 7 (2017) 42031, https://doi.org/10.1038/srep42031.
[20] V. Kumar, S. Hebbar, A. Bhat, S. Panwar, M. Vaishnav, K. Muniraj, V. Nath, R.B. Vijay, S. Manjunath, B. Thyagaraj, C. Siddalingappa, M. Chikkamoga Siddaiah, I. Dasgupta, U. Anandh, T. Kamala, S.S. Srikanta, P.R. Krishnaswamy, N. Bhat, Application of a nanotechnology-based, point-of-care diagnostic device in diabetic kidney disease, Kidney Int. Rep. 3 (2018) 1110–1118, https://doi.org/10.1016/j.ekir.2018.05.008.
[21] X.F. Zeng, D.X. Lu, J.M. Li, Y. Tan, Z. Li, L. Zhou, Z.Q. Xi, S.M. Zhang, W. Duan, Performance of urinary neutrophil gelatinase-associated lipocalin, clusterin, and cystatin C in predicting diabetic kidney disease and diabetic microalbuminuria: a consecutive cohort study, BMC Nephrol. 18 (2017) 233, https://doi.org/10.1186/s12882-017-0620-8.
[22] F. Dieterle, E. Perentes, A. Cordier, D.R. Roth, P. Verdes, O. Grenet, S. Pantano, P. Moulin, D. Wahl, A. Mahl, P. End, F. Staedtler, F. Legay, K. Carl, D. Laurie, S.D. Chibout, J. Vonderscher, G. Maurer, Urinary clusterin, cystatin C, beta2-microglobulin and total protein as markers to detect drug-induced kidney injury, Nat. Biotechnol. 28 (2010) 463–469, https://doi.org/10.1038/nbt.1622.
[23] M.L. Alter, A. Kretschmer, K. Von Websky, O. Tsuprykov, C. Reichetzeder, A. Simon, J.P. Stasch, B. Hocher, Early urinary and plasma biomarkers for experimental diabetic nephropathy, Clin. Lab. 58 (2012) 659–671.
[24] H. Wang, Y. Yuan, Y. Zhuo, Y. Chai, R. Yuan, Sensitive electrochemiluminescence immunosensor for detection of N-Acetyl-beta-d-glucosaminidase based on a "Light-Switch" molecule combined with DNA dendrimer, Anal. Chem. 88 (2016) 5797–5803, https://doi.org/10.1021/acs.analchem.6b00357.
[25] H. Wang, Y. Yuan, Y. Zhuo, Y. Chai, R. Yuan, Self-enhanced electrochemiluminescence nanorods of tris(bipyridine) ruthenium(II) derivative and its sensing application for detection of N-Acetyl-beta-d-glucosaminidase, Anal. Chem. 88 (2016) 2258–2265, https://doi.org/10.1021/acs.analchem.5b03954.
[26] P. Lopes, E. Costa-Rama, I. Beirao, H.P.A. Nouws, A. Santos-Silva, C. Delerue-Matos, Disposable electrochemical immunosensor for analysis of cystatin C, a CKD biomarker, Talanta 201 (2019) 211–216, https://doi.org/10.1016/j.talanta.2019.04.006.
[27] F. Zhang, H. Zhong, Y. Lin, M. Chen, Q. Wang, Y. Lin, J. Huang, A nanohybrid composed of Prussian Blue and graphitic C3N4 nanosheets as the signal-generating tag in an enzyme-free electrochemical immunoassay for the neutrophil gelatinase-associated lipocalin, Mikrochim. Acta 185 (2018) 327, https://doi.org/10.1007/s00604-018-2865-8.
[28] H. Yang, H. Wang, C. Xiong, Y. Chai, R. Yuan, Highly sensitive electrochemiluminescence immunosensor based on ABEI/H2O2 system with PFO dots as enhancer for detection of kidney injury molecule-1, Biosens. Bioelectron. 116

(2018) 16–22, https://doi.org/10.1016/j.bios.2018.05.032.
[29] M. Takeda, S. Khamdang, S. Narikawa, H. Kimura, Y. Kobayashi, T. Yamamoto, S.H. Cha, T. Sekine, H. Endou, Human organic anion transporters and human organic cation transporters mediate renal antiviral transport, J. Pharmacol. Exp. Therapeut. 300 (2002) 918–924, https://doi.org/10.1124/jpet.300.3.918.
[30] J. Huang, N. Gretz, Light-emitting agents for noninvasive assessment of kidney function, ChemistryOpen 6 (2017) 456–471, https://doi.org/10.1002/open.201700065.
[31] X. Michalet, F.F. Pinaud, L.A. Bentolila, J.M. Tsay, S. Doose, J.J. Li, G. Sundaresan, A.M. Wu, S.S. Gambhir, S. Weiss, Quantum dots for live cells, in vivo imaging, and diagnostics, Science 307 (2005) 538–544, https://doi.org/10.1126/science.1104274.
[32] H. Wang, Q. Mu, K. Wang, R.A. Revia, C. Yen, X. Gu, B. Tian, J. Liu, M. Zhang, Nitrogen and boron dual-doped graphene quantum dots for near-infrared second window imaging and photothermal therapy, Appl. Mater Today 14 (2019) 108–117, https://doi.org/10.1016/j.apmt.2018.11.011.
[33] F.J. Penna, J.S. Chow, B.J. Minnillo, C.C. Passerotti, C.E. Barnewolt, S.T. Treves, F.H. Fahey, P.S. Dunning, D.A. Freilich, A.B. Retik, H.T. Nguyen, Identifying ureteropelvic junction obstruction by fluorescence imaging: a comparative study of imaging modalities to assess renal function and degree of obstruction in a mouse model, J. Urol. 185 (2011) 2405–2413, https://doi.org/10.1016/j.juro.2011.02.015.
[34] M. Yu, J. Zhou, B. Du, X. Ning, C. Authement, L. Gandee, P. Kapur, J.T. Hsieh, J. Zheng, Noninvasive staging of kidney dysfunction enabled by renal-clearable luminescent gold nanoparticles, Angew Chem. Int. Ed. Engl. 55 (2016) 2787–2791, https://doi.org/10.1002/anie.201511148.
[35] M. Yu, J. Liu, X. Ning, J. Zheng, High-contrast noninvasive imaging of kidney clearance kinetics enabled by renal clearable nanofluorophores, Angew Chem. Int. Ed. Engl. 54 (2015) 15434–15438, https://doi.org/10.1002/anie.201507868.
[36] J. Liu, M. Yu, C. Zhou, S. Yang, X. Ning, J. Zheng, Passive tumor targeting of renal-clearable luminescent gold nanoparticles: long tumor retention and fast normal tissue clearance, J. Am. Chem. Soc. 135 (2013) 4978–4981, https://doi.org/10.1021/ja401612x.
[37] M. Yu, J. Zheng, Clearance pathways and tumor targeting of imaging nanoparticles, ACS Nano 9 (2015) 6655–6674, https://doi.org/10.1021/acsnano.5b01320.
[38] A.A. Burns, J. Vider, H. Ow, E. Herz, O. Penate-Medina, M. Baumgart, S.M. Larson, U. Wiesner, M. Bradbury, Fluorescent silica nanoparticles with efficient urinary excretion for nanomedicine, Nano Lett. 9 (2009) 442–448, https://doi.org/10.1021/nl803405h.
[39] X. Huang, F. Zhang, L. Zhu, K.Y. Choi, N. Guo, J. Guo, K. Tackett, P. Anilkumar, G. Liu, Q. Quan, H.S. Choi, G. Niu, Y.P. Sun, S. Lee, X. Chen, Effect of injection routes on the biodistribution, clearance, and tumor uptake of carbon dots, ACS Nano 7 (2013) 5684–5693, https://doi.org/10.1021/nn401911k.
[40] Z. Zhou, L. Wang, X. Chi, J. Bao, L. Yang, W. Zhao, Z. Chen, X. Wang, X. Chen, J. Gao, Engineered iron-oxide-based nanoparticles as enhanced T1 contrast agents for efficient tumor imaging, ACS Nano 7 (2013) 3287–3296, https://doi.org/10.1021/nn305991e.
[41] S. Tang, M. Chen, N. Zheng, Sub-10-nm Pd nanosheets with renal clearance for efficient near-infrared photothermal cancer therapy, Small 10 (2014) 3139–3144, https://doi.org/10.1002/smll.201303631.
[42] S. Yang, S. Sun, C. Zhou, G. Hao, J. Liu, S. Ramezani, M. Yu, X. Sun, J. Zheng, Renal clearance and degradation of glutathione-coated copper nanoparticles, Bioconjugate Chem. 26 (2015) 511–519, https://doi.org/10.1021/acs.bioconjchem.5b00003.
[43] T. Shirai, H. Kohara, Y. Tabata, Inflammation imaging by silica nanoparticles with antibodies orientedly immobilized, J. Drug Target. 20 (2012) 535–543, https://doi.org/10.3109/1061186x.2012.693500.
[44] C.M. Yuan, R.M. Jindal, K.C. Abbott, Biopsy: observation time after kidney biopsy: when to discharge? Nat. Rev. Nephrol. 5 (2009) 552–554, https://doi.org/10.1038/nrneph.2009.147.
[45] P.D. Walker, The renal biopsy, Arch. Pathol. Lab Med. 133 (2009) 181–188, https://doi.org/10.1043/1543-2165-133.2.181.
[46] H.T. Khosroshahi, B. Abedi, S. Daneshvar, Y. Sarbaz, A. Shakeri Bavil, Future of the renal biopsy: time to change the conventional modality using nanotechnology, Int. J. Biomed. Imag. (2017) 6141734, https://doi.org/10.1155/2017/6141734 2017.
[47] K.L. Stabi, L.M. Bendz, Ferumoxytol use as an intravenous contrast agent for magnetic resonance angiography, Ann. Pharmacother. 45 (2011) 1571–1575, https://doi.org/10.1345/aph.1Q431.
[48] N. Grenier, M. Pedersen, O. Hauger, Contrast agents for functional and cellular MRI of the kidney, Eur. J. Radiol. 60 (2006) 341–352, https://doi.org/10.1016/j.ejrad.2006.06.024.
[49] C. Corot, P. Robert, J.M. Idee, M. Port, Recent advances in iron oxide nanocrystal technology for medical imaging, Adv. Drug Deliv. Rev. 58 (2006) 1471–1504, https://doi.org/10.1016/j.addr.2006.09.013.
[50] C. Egger, C. Cannet, C. Gerard, C. Debon, N. Stohler, A. Dunbar, B. Tigani, J. Li, N. Beckmann, Adriamycin-induced nephropathy in rats: functional and cellular effects characterized by MRI, J. Magn. Reson. Imag. 41 (2015) 829–840, https://doi.org/10.1002/jmri.24603.
[51] O. Hauger, C. Delalande, C. Deminiere, B. Fouqueray, C. Ohayon, S. Garcia, H. Trillaud, C. Combe, N. Grenier, Nephrotoxic nephritis and obstructive nephropathy: evaluation with MR imaging enhanced with ultrasmall superparamagnetic iron oxide-preliminary findings in a rat model, Radiology 217 (2000) 819–826, https://doi.org/10.1148/radiology.217.3.r00dc04819.
[52] O. Hauger, N. Grenier, C. Deminere, C. Lasseur, Y. Delmas, P. Merville, C. Combe, USPIO-enhanced MR imaging of macrophage infiltration in native and transplanted kidneys: initial results in humans, Eur. Radiol. 17 (2007) 2898–2907, https://doi.org/10.1007/s00330-007-0660-8.
[53] P. Bourrinet, H.H. Bengele, B. Bonnemain, A. Dencausse, J.M. Idee, P.M. Jacobs, J.M. Lewis, Preclinical safety and pharmacokinetic profile of ferumoxtran-10, an ultrasmall superparamagnetic iron oxide magnetic resonance contrast agent, Invest. Radiol. 41 (2006) 313–324, https://doi.org/10.1097/01.rli.0000197669.80475.dd.
[54] M.D. Breyer, K. Susztak, The next generation of therapeutics for chronic kidney disease, Nat. Rev. Drug Discov. 15 (2016) 568–588, https://doi.org/10.1038/nrd.2016.67.
[55] A. Meguid El Nahas, A.K. Bello, Chronic kidney disease: the global challenge, Lancet 365 (2005) 331–340, https://doi.org/10.1016/S0140-6736(05)17789-7.
[56] P. Sharma, R.C. Blackburn, C.L. Parke, K. McCullough, A. Marks, C. Black, Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers for adults with early (stage 1 to 3) non-diabetic chronic kidney disease, Cochrane Database Syst. Rev. (2011) Cd007751, , https://doi.org/10.1002/14651858.CD007751.pub2.
[57] S.C. Satchell, F. Braet, Glomerular endothelial cell fenestrations: an integral component of the glomerular filtration barrier, Am. J. Physiol. Ren. Physiol. 296 (2009) F947–F956, https://doi.org/10.1152/ajprenal.90601.2008.
[58] F.E. Curry, R.H. Adamson, Endothelial glycocalyx: permeability barrier and mechanosensor, Ann. Biomed. Eng. 40 (2012) 828–839, https://doi.org/10.1007/s10439-011-0429-8.
[59] J.H. Suh, J.H. Miner, The glomerular basement membrane as a barrier to albumin, Nat. Rev. Nephrol. 9 (2013) 470–477, https://doi.org/10.1038/nrneph.2013.109.
[60] Y.S. Kanwar, M.G. Farquhar, Presence of heparan sulfate in the glomerular basement membrane, Proc. Natl. Acad. Sci. U. S. A. 76 (1979) 1303–1307, https://doi.org/10.1073/pnas.76.3.1303.
[61] S. Ogawa, Z. Ota, K. Shikata, K. Hironaka, Y. Hayashi, K. Ota, M. Kushiro, N. Miyatake, N. Kishimoto, H. Makino, High-resolution ultrastructural comparison of renal glomerular and tubular basement membranes, Am. J. Nephrol. 19 (1999) 686–693, https://doi.org/10.1159/000013543.
[62] A.T. Lahdenkari, K. Lounatmaa, J. Patrakka, C. Holmberg, J. Wartiovaara, M. Kestila, O. Koskimies, H. Jalanko, Podocytes are firmly attached to glomerular basement membrane in kidneys with heavy proteinuria, J. Am. Soc. Nephrol. 15 (2004) 2611–2618, https://doi.org/10.1097/01.ASN.0000139478.03463.D9.
[63] N. Hoshyar, S. Gray, H. Han, G. Bao, The effect of nanoparticle size on in vivo pharmacokinetics and cellular interaction, Nanomedicine 11 (2016) 673–692, https://doi.org/10.2217/nnm.16.5.
[64] C.H. Choi, J.E. Zuckerman, P. Webster, M.E. Davis, Targeting kidney mesangium by nanoparticles of defined size, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 6656–6661, https://doi.org/10.1073/pnas.1103573108.
[65] L. Sancey, S. Kotb, C. Truillet, F. Appaix, A. Marais, E. Thomas, B. van der Sanden, J.P. Klein, B. Laurent, M. Cottier, R. Antoine, P. Dugourd, G. Panczer, F. Lux, P. Perriat, V. Motto-Ros, O. Tillement, Long-term in vivo clearance of gadolinium-based AGuIX nanoparticles and their biocompatibility after systemic injection, ACS Nano 9 (2015) 2477–2488, https://doi.org/10.1021/acsnano.5b00552.
[66] A.V. Nair, E.J. Keliher, A.B. Core, D. Brown, R. Weissleder, Characterizing the interactions of organic nanoparticles with renal epithelial cells in vivo, ACS Nano 9 (2015) 3641–3653, https://doi.org/10.1021/acsnano.5b00428.
[67] R.M. Williams, J. Shah, B.D. Ng, D.R. Minton, L.J. Gudas, C.Y. Park, D.A. Heller, Mesoscale nanoparticles selectively target the renal proximal tubule epithelium, Nano Lett. 15 (2015) 2358–2364, https://doi.org/10.1021/nl504610d.
[68] F. Oroojalian, F. Charbgoo, M. Hashemi, A. Amani, R. Yazdian-Robati, A. Mokhtarzadeh, M. Ramezani, M.R. Hamblin, Recent advances in nanotechnology-based drug delivery systems for the kidney, J. Contr. Release 321 (2020) 442–462, https://doi.org/10.1016/j.jconrel.2020.02.027.
[69] K.M. Bennett, H. Zhou, J.P. Sumner, S.J. Dodd, N. Bouraoud, K. Doi, R.A. Star, A.P. Koretsky, MRI of the basement membrane using charged nanoparticles as contrast agents, Magn. Reson. Med. 60 (2008) 564–574, https://doi.org/10.1002/mrm.21684.
[70] J.E. Zuckerman, C.H. Choi, H. Han, M.E. Davis, Polycation-siRNA nanoparticles can disassemble at the kidney glomerular basement membrane, Proc. Natl. Acad. Sci. U. S. A. 109 (2012) 3137–3142, https://doi.org/10.1073/pnas.1200718109.
[71] X. Liang, H. Wang, Y. Zhu, R. Zhang, V.C. Cogger, X. Liu, Z.P. Xu, J.E. Grice, M.S. Roberts, Short- and long-term tracking of anionic ultrasmall nanoparticles in kidney, ACS Nano 10 (2016) 387–395, https://doi.org/10.1021/acsnano.5b05066.
[72] E. Blanco, H. Shen, M. Ferrari, Principles of nanoparticle design for overcoming biological barriers to drug delivery, Nat. Biotechnol. 33 (2015) 941–951, https://doi.org/10.1038/nbt.3330.
[73] V.P. Chauhan, Z. Popovic, O. Chen, J. Cui, D. Fukumura, M.G. Bawendi, R.K. Jain, Fluorescent nanorods and nanospheres for real-time in vivo probing of nanoparticle shape-dependent tumor penetration, Angew Chem. Int. Ed. Engl. 50 (2011) 11417–11420, https://doi.org/10.1002/anie.201104449.
[74] F. Gentile, C. Chiappini, D. Fine, R.C. Bhavane, M.S. Peluccio, M.M. Cheng, X. Liu, M. Ferrari, P. Decuzzi, The effect of shape on the margination dynamics of non-neutrally buoyant particles in two-dimensional shear flows, J. Biomech. 41 (2008) 2312–2318, https://doi.org/10.1016/j.jbiomech.2008.03.021.
[75] A. Ruggiero, C.H. Villa, E. Bander, D.A. Rey, M. Bergkvist, C.A. Batt, K. Manova-Todorova, W.M. Deen, D.A. Scheinberg, M.R. McDevitt, Paradoxical glomerular filtration of carbon nanotubes, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 12369–12374, https://doi.org/10.1073/pnas.0913667107.
[76] S. Alidori, N. Akhavein, D.L. Thorek, K. Behling, Y. Romin, D. Queen, B.J. Beattie, K. Manova-Todorova, M. Bergkvist, D.A. Scheinberg, M.R. McDevitt, Targeted

fibrillar nanocarbon RNAi treatment of acute kidney injury, Sci. Transl. Med. 8 (2016) 331ra339, https://doi.org/10.1126/scitranslmed.aac9647.
[77] F. Alexis, E. Pridgen, L.K. Molnar, O.C. Farokhzad, Factors affecting the clearance and biodistribution of polymeric nanoparticles, Mol. Pharm. 5 (2008) 505–515, https://doi.org/10.1021/mp800051m.
[78] S.A. Asgeirsdottir, P.J. Zwiers, H.W. Morselt, H.E. Moorlag, H.I. Bakker, P. Heeringa, J.W. Kok, C.G. Kallenberg, G. Molema, J.A. Kamps, Inhibition of proinflammatory genes in anti-GBM glomerulonephritis by targeted dexamethasone-loaded AbEsel liposomes, Am. J. Physiol. Ren. Physiol. 294 (2008) F554–F561, https://doi.org/10.1152/ajprenal.00391.2007.
[79] N. Kamaly, G. Fredman, M. Subramanian, S. Gadde, A. Pesic, L. Cheung, Z.A. Fayad, R. Langer, I. Tabas, O.C. Farokhzad, Development and in vivo efficacy of targeted polymeric inflammation-resolving nanoparticles, Proc. Natl. Acad. Sci. U. S. A. 110 (2013) 6506–6511, https://doi.org/10.1073/pnas.1303377110.
[80] K. Pollinger, R. Hennig, M. Breunig, J. Tessmar, A. Ohlmann, E.R. Tamm, R. Witzgall, A. Goepferich, Kidney podocytes as specific targets for cyclo(RGDfC)-modified nanoparticles, Small 8 (2012) 3368–3375, https://doi.org/10.1002/smll.201200733.
[81] S. Maslanka Figueroa, A. Veser, K. Abstiens, D. Fleischmann, S. Beck, A. Goepferich, Influenza A virus mimetic nanoparticles trigger selective cell uptake, Proc. Natl. Acad. Sci. U. S. A. 116 (2019) 9831–9836, https://doi.org/10.1073/pnas.1902563116.
[82] M.E. Dolman, S. Harmsen, G. Storm, W.E. Hennink, R.J. Kok, Drug targeting to the kidney: advances in the active targeting of therapeutics to proximal tubular cells, Adv. Drug Deliv. Rev. 62 (2010) 1344–1357, https://doi.org/10.1016/j.addr.2010.07.011.
[83] G. Wicher, M. Larsson, A. Fex Svenningsen, E. Gyllencreutz, L. Rask, H. Aldskogius, Low density lipoprotein receptor-related protein-2/megalin is expressed in oligodendrocytes in the mouse spinal cord white matter, J. Neurosci. Res. 83 (2006) 864–873, https://doi.org/10.1002/jnr.20774.
[84] S. Gao, S. Hein, F. Dagnaes-Hansen, K. Weyer, C. Yang, R. Nielsen, E.I. Christensen, R.A. Fenton, J. Kjems, Megalin-mediated specific uptake of chitosan/siRNA nanoparticles in mouse kidney proximal tubule epithelial cells enables AQP1 gene silencing, Theranostics 4 (2014) 1039–1051, https://doi.org/10.7150/thno.7866.
[85] O. F, R. AH, M. F, N. AH, S. WT, A. KR.M.J.M. science, M.f.b.a. engineering C, Efficient megalin targeted delivery to renal proximal tubular cells mediated by modified-polymyxin B-polyethylenimine based nano-gene-carriers, 79 (2017), pp. 770–782, https://doi.org/10.1016/j.msec.2017.05.068.
[86] F.Y. Cheng, Y.H. Lee, Y.H. Hsu, I.J. Chiu, Y.J. Chiu, Y.F. Lin, H.W. Chiu, Promising therapeutic effect of thapsigargin nanoparticles on chronic kidney disease through the activation of Nrf2 and FoxO1, Aging (Albany NY) 11 (2019) 9875–9892, https://doi.org/10.18632/aging.102437.
[87] S.H. Hong, H.J. Lee, E.J. Sohn, H.S. Ko, B.S. Shim, K.S. Ahn, S.H. Kim, Anti-nephrolithic potential of resveratrol via inhibition of ROS, MCP-1, hyaluronan and osteopontin in vitro and in vivo, Pharmacol. Rep. 65 (2013) 970–979, https://doi.org/10.1016/s1734-1140(13)71078-8.
[88] N. Summerlin, E. Soo, S. Thakur, Z. Qu, S. Jambhrunkar, A. Popat, Resveratrol nanoformulations: challenges and opportunities, Int. J. Pharm. 479 (2015) 282–290, https://doi.org/10.1016/j.ijpharm.2015.01.003.
[89] T. Ichimura, E.J. Asseldonk, B.D. Humphreys, L. Gunaratnam, J.S. Duffield, J.V. Bonventre, Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells, J. Clin. Invest. 118 (2008) 1657–1668, https://doi.org/10.1172/JCI34487.
[90] Y.F. Lin, Y.H. Lee, Y.H. Hsu, Y.J. Chen, Y.F. Lin, F.Y. Cheng, H.W. Chiu, Resveratrol-loaded nanoparticles conjugated with kidney injury molecule-1 as a drug delivery system for potential use in chronic kidney disease, Nanomedicine 12 (2017) 2741–2756, https://doi.org/10.2217/nnm-2017-0256.
[91] Y. Zhong, Y. Deng, Y. Chen, P.Y. Chuang, J. Cijiang He, Therapeutic use of traditional Chinese herbal medications for chronic kidney diseases, Kidney Int. 84 (2013) 1108–1118, https://doi.org/10.1038/ki.2013.276.
[92] G. Yao, L. Xu, X. Wu, L. Xu, J. Yang, H. Chen, Preventive effects of salvianolic acid B on transforming growth factor-beta1-induced epithelial-to-mesenchymal transition of human kidney cells, Biol. Pharm. Bull. 32 (2009) 882–886, https://doi.org/10.1248/bpb.32.882.
[93] Q. Peng, T. Gong, J. Zuo, J. Liu, D. Zhao, Z. Zhang, Enhanced oral bioavailability of salvianolic acid B by phospholipid complex loaded nanoparticles, Pharmazie 63 (2008) 661–666.
[94] Z. Tolkien, L. Stecher, A.P. Mander, D.I. Pereira, J.J. Powell, Ferrous sulfate supplementation causes significant gastrointestinal side-effects in adults: a systematic review and meta-analysis, PloS One 10 (2015) e0117383, , https://doi.org/10.1371/journal.pone.0117383.
[95] D.I. Pereira, S.F. Bruggraber, N. Faria, L.K. Poots, M.A. Tagmount, M.F. Aslam, D.M. Frazer, C.D. Vulpe, G.J. Anderson, J.J. Powell, Nanoparticulate iron(III) oxo-hydroxide delivers safe iron that is well absorbed and utilised in humans, Nanomedicine 10 (2014) 1877–1886, https://doi.org/10.1016/j.nano.2014.06.012.
[96] Y. Shen, L. Posavec, S. Bolisetty, F.M. Hilty, G. Nystrom, J. Kohlbrecher, M. Hilbe, A. Rossi, J. Baumgartner, M.B. Zimmermann, R. Mezzenga, Amyloid fibril systems reduce, stabilize and deliver bioavailable nanosized iron, Nat. Nanotechnol. 12 (2017) 642–647, https://doi.org/10.1038/nnano.2017.58.
[97] M.M. Fathy, H.M. Fahmy, A.M.M. Balah, F.F. Mohamed, W.M. Elshemey, Magnetic nanoparticles-loaded liposomes as a novel treatment agent for iron deficiency anemia: in vivo study, Life Sci. 234 (2019) 116787, https://doi.org/10.1016/j.lfs.2019.116787.
[98] J. Floege, Phosphate binders in chronic kidney disease: an updated narrative review of recent data, J. Nephrol. (2019), https://doi.org/10.1007/s40620-019-00689-w.
[99] S.M. Moe, G.A. Block, C.B. Langman, Oral phosphate binders in patients with kidney failure, N. Engl. J. Med. 363 (2010) 990, https://doi.org/10.1056/NEJMc1005274 author reply 990.
[100] T. Sangvanich, W. Ngamcherdtrakul, R. Lee, J. Morry, D. Castro, G.E. Fryxell, W. Yantasee, Nanoporous sorbent material as an oral phosphate binder and for aqueous phosphate, chromate, and arsenate removal, J. Nanomed. Nanotechnol. 5 (2014), https://doi.org/10.4172/2157-7439.1000222.
[101] C.L. Ventola, Progr. Nanomed.: Approv. Invest. Nanodrugs, P t. 42 (2017) 742–755.
[102] A.M. Salazar-Montes, L.D. Hernandez-Ortega, M.S. Lucano-Landeros, J. Armendariz-Borunda, New gene therapy strategies for hepatic fibrosis, World J. Gastroenterol. 21 (2015) 3813–3825, https://doi.org/10.3748/wjg.v21.i13.3813.
[103] F. Khaja, D. Jayawardena, A. Kuzmis, H. Onyuksel, Targeted Sterically Stabilized Phospholipid siRNA Nanomedicine for Hepatic and Renal Fibrosis, Nanomaterials vol. 6, (2016), https://doi.org/10.3390/nano6010008.
[104] J.R. Timoshanko, J.D. Sedgwick, S.R. Holdsworth, P.G. Tipping, Intrinsic renal cells are the major source of tumor necrosis factor contributing to renal injury in murine crescentic glomerulonephritis, J. Am. Soc. Nephrol. 14 (2003) 1785–1793, https://doi.org/10.1097/01.asn.0000073902.38428.33.
[105] R. Kanasty, J.R. Dorkin, A. Vegas, D. Anderson, Delivery materials for siRNA therapeutics, Nat. Mater. 12 (2013) 967–977, https://doi.org/10.1038/nmat3765.
[106] Y. Wang, Q. Wu, J. Wang, L. Li, X. Sun, Z. Zhang, L. Zhang, Co-delivery of p38alpha MAPK and p65 siRNA by novel liposomal glomerulus-targeting nano carriers for effective immunoglobulin a nephropathy treatment, J. Contr. Release 320 (2020) 457–468, https://doi.org/10.1016/j.jconrel.2020.01.024.
[107] O. Motabar, E. Sidransky, E. Goldin, W. Zheng, Fabry disease - current treatment and new drug development, Curr. Chem. Genom. 4 (2010) 50–56, https://doi.org/10.2174/1875397301004010050.
[108] T. Kubo, Fabry disease and its cardiac involvement, J. Gen. Fam. Med. 18 (2017) 225–229, https://doi.org/10.1002/jgf2.76.
[109] R. Schiffmann, D.A. Hughes, G.E. Linthorst, A. Ortiz, E. Svarstad, D.G. Warnock, M.L. West, C. Wanner, Screening, diagnosis, and management of patients with Fabry disease: conclusions from a "kidney disease: improving global outcomes" (KDIGO) controversies conference, Kidney Int. 91 (2017) 284–293, https://doi.org/10.1016/j.kint.2016.10.004.
[110] R. El Dib, H. Gomaa, R.P. Carvalho, S.E. Camargo, R. Bazan, P. Barretti, F.C. Barreto, Enzyme replacement therapy for Anderson-Fabry disease, Cochrane Database Syst. Rev. 7 (2016) Cd006663, , https://doi.org/10.1002/14651858.CD006663.pub4.
[111] F. DeRosa, L. Smith, Y. Shen, Y. Huang, J. Pan, H. Xie, B. Yahalom, M.W. Heartlein, Improved efficacy in a Fabry disease model using a systemic mRNA liver depot system as compared to enzyme replacement therapy, Mol. Ther. 27 (2019) 878–889, https://doi.org/10.1016/j.ymthe.2019.03.001.
[112] L. Jin, X. Zeng, M. Liu, Y. Deng, N. He, Current progress in gene delivery technology based on chemical methods and nano-carriers, Theranostics 4 (2014) 240–255, https://doi.org/10.7150/thno.6914.
[113] J. Liu, T. Meng, M. Yuan, L. Wen, B. Cheng, N. Liu, X. Huang, Y. Hong, H. Yuan, F. Hu, MicroRNA-200c delivered by solid lipid nanoparticles enhances the effect of paclitaxel on breast cancer stem cell, Int. J. Nanomed. 11 (2016) 6713–6725, https://doi.org/10.2147/ijn.S111647.
[114] A. Kheirolomoom, C.W. Kim, J.W. Seo, S. Kumar, D.J. Son, M.K. Gagnon, E.S. Ingham, K.W. Ferrara, H. Jo, Multifunctional nanoparticles facilitate molecular targeting and miRNA delivery to inhibit atherosclerosis in ApoE(-/-) mice, ACS Nano 9 (2015) 8885–8897, https://doi.org/10.1021/acsnano.5b02611.
[115] A.J. Kim, G.F. Woodworth, N.J. Boylan, J.S. Suk, J. Hanes, Highly compacted pH-responsive DNA nanoparticles mediate transgene silencing in experimental glioma, J. Mater. Chem. B 2 (2014) 8165–8173, https://doi.org/10.1039/c4tb00559g.
[116] Y.C. Tsai, I.L. Teng, S.T. Jiang, Y.C. Lee, Y.Y. Chiou, F.Y. Cheng, Safe nanocomposite-mediated efficient delivery of MicroRNA plasmids for autosomal dominant polycystic kidney disease (ADPKD) therapy, Adv. Healthcare Mater. 8 (2019) e1801358, , https://doi.org/10.1002/adhm.201801358.
[117] A.S. Go, G.M. Chertow, D. Fan, C.E. McCulloch, C.Y. Hsu, Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization, N. Engl. J. Med. 351 (2004) 1296–1305, https://doi.org/10.1056/NEJMoa041031.
[118] D. Stamopoulos, P. Bouziotis, D. Benaki, C. Kotsovassilis, P.N. Zirogiannis, Utilization of nanobiotechnology in haemodialysis: mock-dialysis experiments on homocysteine, Nephrol. Dial. Transplant. 23 (2008) 3234–3239, https://doi.org/10.1093/ndt/gfn189.
[119] H.C. Chen, H.C. Lin, H.H. Chen, F.D. Mai, Y.C. Liu, C.M. Lin, C.C. Chang, H.Y. Tsai, C.P. Yang, Innovative strategy with potential to increase hemodialysis efficiency and safety, Sci. Rep. 4 (2014) 4425, https://doi.org/10.1038/srep04425.
[120] V. Liakopoulos, S. Roumeliotis, X. Gorny, E. Dounousi, P.R. Mertens, Oxidative stress in hemodialysis patients: a review of the literature, Oxid. Med. Cell Longev. (2017) 3081856, https://doi.org/10.1155/2017/3081856 2017.
[121] G.A. Kaysen, T. Greene, B. Larive, R.L. Mehta, R.M. Lindsay, T.A. Depner, Y.N. Hall, J.T. Daugirdas, G.M. Chertow, The effect of frequent hemodialysis on nutrition and body composition: frequent Hemodialysis Network Trial, Kidney Int. 82 (2012) 90–99, https://doi.org/10.1038/ki.2012.75.
[122] J.T. Daugirdas, A.A. Bernardo, Hemodialysis effect on platelet count and function and hemodialysis-associated thrombocytopenia, Kidney Int. 82 (2012) 147–157, https://doi.org/10.1038/ki.2012.130.
[123] H.C. Chen, C.Y. Cheng, H.C. Lin, H.H. Chen, C.H. Chen, C.P. Yang, K.H. Yang, C.M. Lin, T.Y. Lin, C.M. Shih, Y.C. Liu, Multifunctions of excited gold nanoparticles

decorated artificial kidney with efficient hemodialysis and therapeutic potential, ACS Appl. Mater. Interfaces 8 (2016) 19691–19700, https://doi.org/10.1021/acsami.6b05905.

[124] B. Santamaria, A. Benito-Martin, A.C. Ucero, L.S. Aroeira, A. Reyero, M.J. Vicent, M. Orzaez, A. Celdran, J. Esteban, R. Selgas, M. Ruiz-Ortega, M.L. Cabrera, J. Egido, E. Perez-Paya, A. Ortiz, A nanoconjugate Apaf-1 inhibitor protects mesothelial cells from cytokine-induced injury, PloS One 4 (2009) e6634, , https://doi.org/10.1371/journal.pone.0006634.

[125] A. Ortega, S. Farah, P. Tranque, A.V. Ocana, S.H. Nam-Cha, N. Beyth, C. Gomez-Roldan, R. Perez-Tanoira, A.J. Domb, F.C. Perez-Martinez, J. Perez-Martinez, Antimicrobial evaluation of quaternary ammonium polyethyleneimine nanoparticles against clinical isolates of pathogenic bacteria, IET Nanobiotechnol. 9 (2015) 342–348, https://doi.org/10.1049/iet-nbt.2014.0078.

[126] D.M. Kanani, W.H. Fissell, S. Roy, A. Dubnisheva, A. Fleischman, A.L. Zydney, Permeability - selectivity analysis for ultrafiltration: effect of pore geometry, J. Membr. Sci. 349 (2010) 405, https://doi.org/10.1016/j.memsci.2009.12.003.

[127] M. Salani, S. Roy, W.H.t. Fissell, Innovations in wearable and implantable Artificial kidneys, Am. J. Kidney Dis. 72 (2018) 745–751, https://doi.org/10.1053/j.ajkd.2018.06.005.