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Chronic Kidney Diseases and Nanoparticle Therapeutics

Ravi Kant Upadhyay*

Department of Zoology, DDU Gorakhpur University, Gorakhpur, UP, India

Abstract

Present review article describes main causes of chronic kidney disease a major health problem public health problem round the globe. Disease has multiple etiologies related to sequential pathophysiological stages. It has major concern with chronic changes in renal structure and that severely alter glomerular filtration rate in patients. This article explains CKD biomarkers in brief i.e., serum creatinine, periostin, a matricellular protein discoidin domain receptor 1 (DDR1), a transmembrane collagen receptor of the tyrosine kinase family, Phospholipase D4 (PLD4) renal biomarkers, metabolic biomarkers. The main focus was given on use of nanoparticles for CKD therapeutics. This article describes various metal and metal oxide nanaoparticles, such as cuprous oxide (CONPs), super paramagnetic iron oxide (new SPIO) nanoparticles, silica-coated iron oxide nanoparticle, Vanadium oxide nanoparticles (VONPs, Titanium dioxide and gold, calcifying nanoparticles, colloidal protein-mineral nanoparticles, Liposomal nanoparticles, MITO-Porter, SB-coated NPs, ASc-loaded polymeric nanoparticles, Carbon-coated iron nanocrystal, Nanodiamonds, Sodium-PLGA hybrid nanoparticles, Epidermal growth factor receptor (EGFR)-targeted chitosan (CS) nanoparticles, Photocaged nanoparticles, Mesoporous silica nanoparticles (MSNs Quantum dots (QDs) which are used for drug delivery patients. For successful management of disease progression of diseases, symptoms should analyze by good physician at an eerily stage, by using highly efficacious, sensitive and specific CKD markers. All factors must include knowing the status of disease and chemotherapeutics by using low toxic nanoparticles. Before being used nanoparticles should evaluate in experiment animal models. For future therapeutics metabolomics, kidney transplants and good wound healers are required.

Keywords: Chronic kidney disease; Nanoparticles; CKD therapeutics; Metal and metal oxides; Gold; Silver; Silica; Liposomal nanoparticles

Introduction

Chronic kidney disease (CKD) is a state of gradual loss of kidney function over time. CKD is pathophysiologic process with multiple etiologies, resulting irreversible attrition of nephron and function that frequently leading to end stage disease. CKD is caused by accumulation of nitrogenous waste products which decrease glomerular filtration rate. At early stage of chronic kidney disease pollutants stay in the blood and a percentage of the proteins and supplements are lost in the pee. Uncontrolled glucose level generates high risks to GFR. Disease is characterized by granular surface, decreased function, smaller size and high urine protein while acidosis, sodium retention, excessive rennin production, oligouria, sodium wasting such as solute dieresis and damage are physiological abnormalities mainly observed. Chronic kidney disease (CKD) is inflammation-related. Patients with chronic renal failure who undergo hemodialysis (HD) have some acute adverse effects caused by dialysis-induced oxidative stress, protein adsorption, platelet adhesion, and activation of coagulation and inflammation [1].

Among various causes of CKD are congenital anomalies such as renal hypoplasia, dysplasia, congenital nephritic syndrome, prune belly syndrome, PCKD, RVT and cortical nephrosis. Besides this obstructive uropathy is also one of the important reasons. CKD is also caused due to glomerulonephritis both acquired and inherited. Metabolic disorders such as cystinosis, hyperoxaluria and polycystic kidney disease are also related to CKD. Structural problems such as calculi obstruction, infection, inflammation, familial renal disease and ischemia also display CKD. ESRD is a clinical state or condition in which there has been an irreversible loss of renal function and such patients essentially need renal replacement therapy in order to avoid life threatening uremia. Uremia is a clinical and laboratory syndrome, reflecting dysfunction of all organ systems as a result of untreated or undertreated (dialysis or transplantation) in order to avoid chronic renal failure. Chronic kidney disease (CKD) or chronic renal failure (CRF) encompasses all degrees of decreased renal function, from damaged–at risk through mild, moderate and severe chronic kidney failure. CKD is a worldwide public health problem. In the United States, there is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost. CKD is more prevalent in the elderly population. CKD is associated with an increased risk of cardiovascular disease and chronic renal failure (Figure 1).

Chronic kidney disease is caused due to sever diabetes, high blood pressure and other disorders. Disease progresses with certain changes in physiology of renal functions and eventually leads to kidney failure, which requires dialysis or a kidney transplant to maintain life. Early detection and treatment can often keep chronic kidney disease from getting worse. Treatment methods available are chemotherapy, renal transplantation and stem cell wound healing. For better chemotherapeutics of kidney diseases nanoparticle drug coatings, conjugation, receptor binding are good methods for drug delivery. A bioartificial kidney, which is composed of a membrane cartridge with renal epithelial cells, can substitute important kidney functions in patients with renal failure [2]. Nanowires (NWs) are also used for cellular applications, such as delivery of compounds or sensing platforms [3]. But it is essential to make normal glomerular filtration and use appropriate drug regimens for disruption of glomerular disease (Figure 2).

***Corresponding author:** Ravi Kant Upadhyay, Department of Zoology, DDU Gorakhpur University, Gorakhpur, UP, India, Tel: +593-0-987-534; E-mail: rkupadhya@yahoo.com

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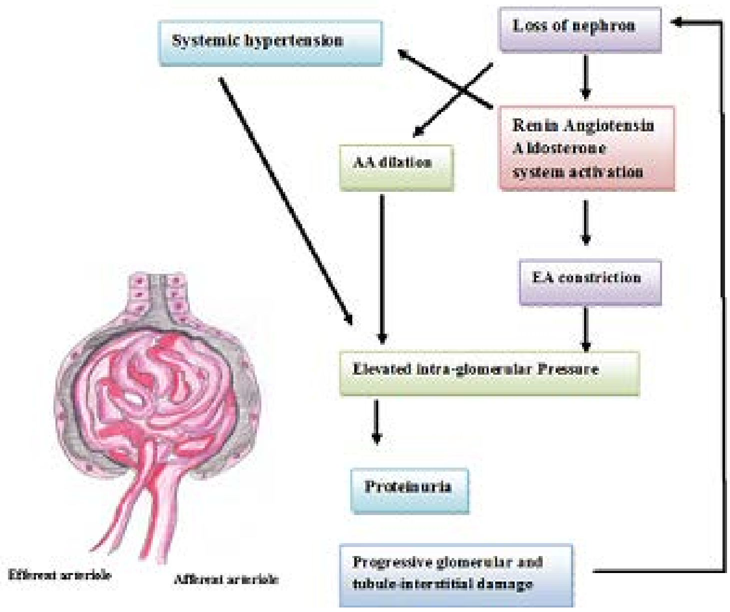

Figure 1: Showing progression of chronic kidney disease.

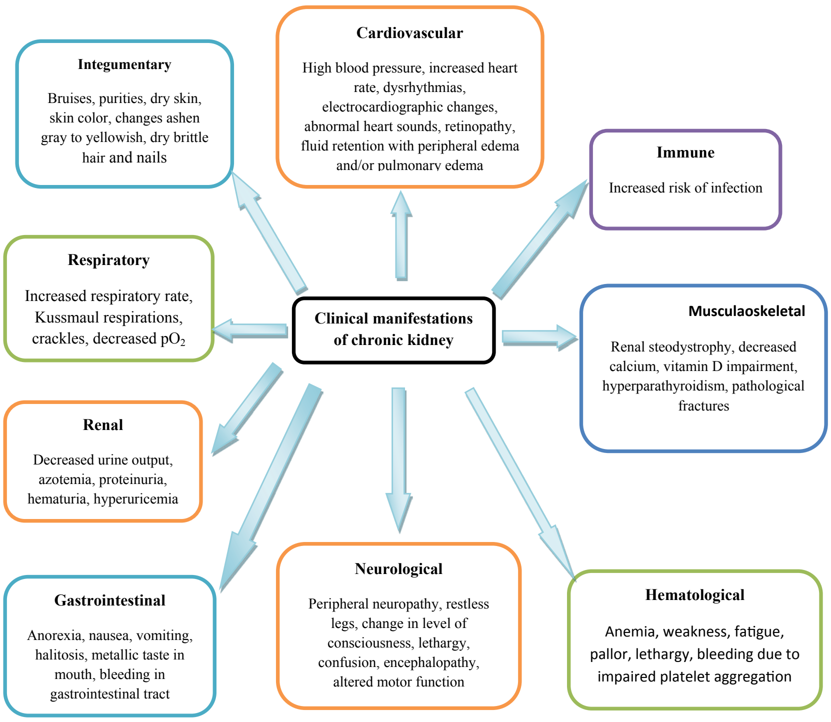

Figure 2: Showing important clinical manifestations of chronic kidney disease.

Causes

There are many causes of CKD, being the congenital anomalies of the kidney and urinary tract and the glomerular diseases very common in paediatric patients. Normally in old age patient's diabetic nephropathy, chronic arterial hypertension and glomerular diseases predominantly occur [4]. Among all causes diabetes and high blood pressure are responsible for up to two-thirds of the CKD cases (Table 1). Very high amount of blood sugar in diabetes causes damage to many organs including the kidneys and heart, as well as blood vessels, nerves and eyes. High blood pressure or hypertension, if uncontrolled, or poorly controlled, leads to cause of a heart attack, strokes and chronic kidney disease (Figure 3). High acid diet and metabolic acidosis also cause chronic kidney disease. Glomerulonephritis is a group of diseases that cause inflammation and damage to the kidney's filtering units. In Polycystic kidney disease large cysts are formed in the kidneys and

Disease/disorder	Reason	Effect	Analytical Tests	Therapeutic option
Relapsing nephrotic syndrome	Steroid toxicity is increased	Children and old age both	Urine dipstick tests	Small dose of the steroid prednisolon, chlorambucil
Renal fibrosis	Excessive accumulation of extracellular matrix	Tubular destruction, renal collapse	Increased levels of Ang II modulate fibrosis	Adriamycin, Uranyl nitrate, folic acid
Chronic arterial hypertension and glomerular diseases	Membrano-proliferative glomerulonephritis	Reno-vascular hypertension	Proteinuria, Microalbuminuria	ACE inhibitors, angiotensin receptor blockers, direct renin inhibitors and aldosterone antagonists,
Glomerulonephritis	Acute inflammation of the kidney	Frequent nighttime urination	Creatinine clearance, total protein in the urine	Use of non-steroidal anti-inflammatory drugs, such as ibuprofen (Advil) and naproxen
Hypertensive Nephropathy	Damage to the kidney due to chronic high blood pressure	Glomerular hyper filtration	Protein in the urine (proteinuria	Direct renin inhibitors and aldosterone antagonists
Polycystic Kidney Disease	An inherited kidney disorder	Cysts typically grow 0.5 inches or large, kidney stones, uti-infection	Abdominal CT scan, travenous pyelogram, ultrasound	High blood pressure, pain medication, except Ibuprofen
Renal Parenchymal Disease	Damage in their renal parenchyma	Lupus nephritis, purpura nephritis, IgA nephropathy, etc.	Blood pressure and urea tests	Medicines like glucocorticoid, immuno-suppressor and cytotoxic drug, Blood Purification
FSGS	Attacks the kidney's filtering units (glomeruli) causing serious scarring, leads to permanent kidney damage and even failure	Low Blood Albumin Levels, Proteinuria, Edema	Renal biopsy	Steroid called prednisone or prednisolone
Kidney Failure	In IgA Nephropathy, IgA and immune complex (antibody+antigen) are deposited in the mesangial area of the kidneys.	The disease can affect people of any age although it is more common in men	IgA Nephropathy occurs due to disordered immune system	Urine test, blood test, and kidney biopsy. Immunediagnosis Kidney damage tests. UTP, U-malb, U-TRF, U-IGG, β2-microglobulin, α1-microglobulin, α2-macroglobulin, κ light chain, λ light chain, U-NAG, U-GGT, and Uosm. BUN, Creatinine, UA, β 2-microglobulin, Cyc C, RBP, HCY and PTH. Glomerular hematuria, non-glomerular hematuria and mixed hematuria. Tests for CD4, CD8, NK cells, B cells, T Cells counts etc. Complement test include C3, C4, CH50, C3B, etc.
IgA Nephropathy	Higher amount of IgA lodges in kidney	Purpuric skin rash, arthritis	Cystoscopy, hematuria, CRP or ESR, complement levels, ANA, and LDH. Protein electrophoresis and immunoglobulin levels can show increased IgA in 50% of all patients.	transplants despite the use of ciclosporin, azathioprine or mycophenolate mofetil and steroids
Diabetic Nephropathy	Damage to kidneys caused by diabetes	Igh blood sugar from diabetes can destroy these blood vessels, high cholesterol	Albumin in the urine	Angiotensin-converting enzyme inhibitors also called ACE inhibitors.

Table 1: Showing chronic kidney diseases, reason, possible effect and analytical tests and therapy available.

damage the surrounding tissue. In females during pregnancy narrowing occur in urinary outlets due to weight exerted pressure that prevents normal outflow of urine and causes urine to flow back up to the kidney (Table 1). This causes infections and may damage the kidneys. Formation of kidney stones, tumors or an enlarged prostate gland in men is secondary causes of CKD. CKD High risk groups include those with diabetes, hypertension and family history of kidney failure. Nicotine, a major toxic component of cigarette smoke, is responsible for smoking-mediated renal dysfunction [5]. High-fat diet-induced metabolic syndromes followed by chronic kidney disease caused by intestinal endotoxemia have received extensive attention [6] (Table 2 and Figures 4 and 5).

Symptoms

CKD patient feels more tiredness and have less energy, loss of appetite, trouble in sleeping, muscle cramping at night, have swollen feet and ankles, puffiness around eyes, especially in the morning have dry, itchy skin, need to urinate more often, especially at night. Due to combination of three diseases diabetes, high blood pressure, and genetic defect lead to high risk of CKD (Table 2).

Biomarkers for CKD

Creatinine level is used for early diagnosis and monitoring of progression of chronic kidney disease. Ultrasound or CT scan is performed to find anatomical changes in kidneys and urinary tract. Other tests are used are Albuminuria (AER>30 mg/24 h; ACR>3 mg/mmol, urine sediment abnormalities and tubular disorders. Glomerular filtration rate is best test to measure kidney function. Decreased GFR<60 ml/min/1.73 m^2 is sign of CKD. Reduction in serum α-fetoprotein, calcium phosphate plaques in renal papillae, nanocrystal growth in a supersaturated milieu, plaques containing various calcium and magnesium phosphates are good markers [7]. Renin-angiotensin

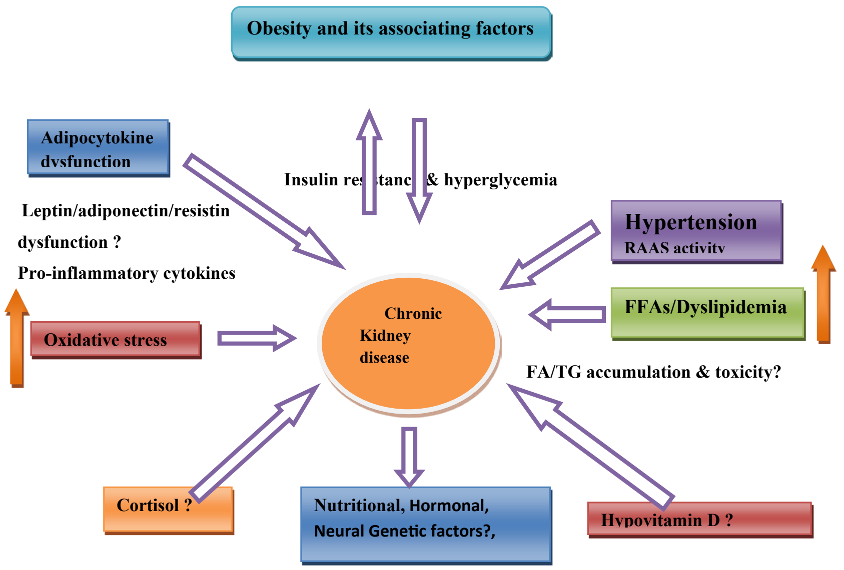

Figure 3: Showing various metabolic and physiological factors responsible for chronic kidney diseases.

Description	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Amount of kidney remaining at each stage	normal or increased GFR (>90 mL/min/1.73 m^2)	Mild reduction in GFR (60-89 mL/min/1.73 m^2)	Moderate reduction in GFR (45-59 mL/min/1.73 m^2)	Severe reduction in GFR (15-29 mL/min/1.73 m^2)	Kidney failure (GFR <15 mL/min/1.73 m^2 or dialysis)
Major disorders	Anemia, including functional iron deficiency, Blood pressure	Calcium absorption decreases,	Dyslipidemia/heart failure	Hyperkalamia, hyperparathyroidims	Hyperphosphatemia, left ventricular hypetrophy, metabolic acidosis,malnutrition potential
Kidney damage	More than 90%	60-89%	30-59%	15-20%	Less than 15%
Description of each stage	Early kidney damage	Worse kidney damage with reduced function	Even worse damage with less function	Kidney function much severely affected	End stage renal disease, kidney failure
Symptoms	No symptom, urea and cretainine levels normal	No symptoms, urea and creatinine levels normal or mildly elevated	Tiredness, poor appetite, itching, creatinine level rises, excess of urea	Tiredness, poor appetite, itching get worse	Poor sleeping of night, difficulty in breathing, itchiness, vomiting, high level of urea and creatinine
Treatment options	Therapeutic reversal is possible	Monitor creatinine level, blood pressure, restoration of kidney function	Intensive care, with good therapeutic options, diet control and metabolic control	Use dialysis, Receive and early transplant	Start renal replacement therapy, regular dialysis or transplantation

Table 2: Five stages of chronic kidney diseases with symptoms and therapeutic options available.

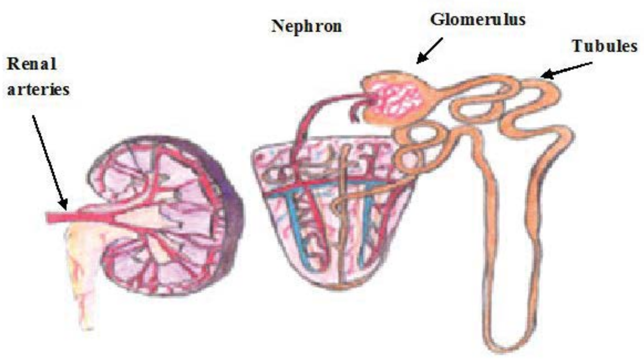

Figure 4: Structure of a diseased nephron.

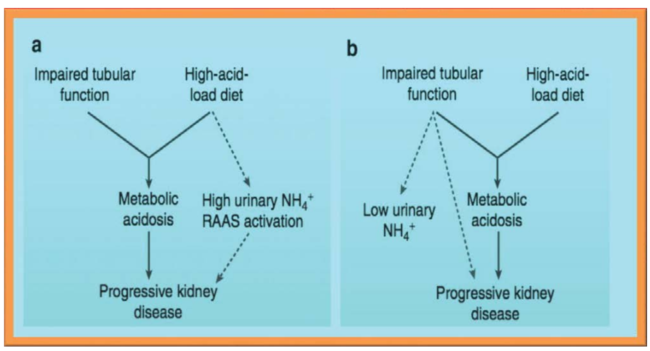

Figure 5: Showing impaired kidney functions due to high acid diet and metabolic acidosis.

system (RAS) and the immune-inflammatory mediators including level of cytokines are good indicators of pathophysiology of CKD [4]. Phospholipase D4 (PLD4) is a single-pass transmembrane glycoprotein, is among the most highly upregulated genes in murine kidneys subjected to chronic progressive fibrosis, it is a good biomarker of CKD [8]. Among potential endogenous biomarkers are creatinine, CysC and urine albumin to creatinine ratio. It improves risk stratification for kidney disease progression and mortality. Kidney injury molecule and neutrophil gelatinase-associated lipocalin are considered reasonable biomarkers in urine and plasma to determine severity and prognosis of CKD [9]. Blood urea nitrogen increases with the protein diet but extra nitrogen causes problem to kidney filtration mainly GFR [10] (Table 2). B2-microglobulin (11.8 kDa) constitutes a classIHLA, is present in all nucleated cells in the body. It also found in immune cells like lymphocytes and monocytes. It can freely filter through glomeruli and is reabsorbed and metabolized in the proximal tubule. Plasma B2-M is a good endogenous marker of GFR [11].

Use of Nanoparticles

New advanced therapeutic methods are evolved in clinical sciences. These are discovered with increasing translation of nanomedicines. Use of nanodevices has wider role in renal disease therapy. Recent advancements in the field of tissue regeneration and stem cell therapy have provided novel solutions to treat kidney diseases [12]. Tailoring of nanomedicines in terms of kidney retention and binding to key membranes and cell populations associated with renal diseases is now possible. These can greatly enhance their localization, tolerability and efficacy [12]. Advancements have been seen at three level fabrications of new nanomaterials, coatings and discovery of new drug delivery vehicles for biodistribution of therapeutic agents deep into the kidney tissues. Still there is a need for of new strategies regarding the design of ideal glomerular filtration rate agents and renal clearable nanoparticles [13]. There is a need to reduce material toxicities of nano-devices, to make them non-invasive when used for restoration of kidney function and diagnosis of disease. There is need to develop new simple biophysical agents and diagnosing kidney disease. For effective treatment of renal diseases organ surrounding microenvironment influence distribution and elimination of nanoformulations. Therefore, nanoparticulate design must be non-toxic and efficient drug delivery system [14]. Most of the metal nanoparticles show acute nephrotoxicity, accumulate in the kidney and put potential chronic effect [15]. Therefore, drugs are incorporated into nanocarriers and could be used for drug targeting [16]. Nanocomplexes/nanoparticles are also used as kidney disease markers and are therapeutically more feasible [17].

Metal and Metal Oxide Nanoparticles

Metal and metal oxide such as cuprous oxide is used to make nanoparticles (CONPs). These not only selectively induce apoptosis of tumor cells *in vitro* but also inhibit the growth and metastasis of melanoma by targeting mitochondria with little hepatic and renal toxicities in mice [18]. This effectiveness of CONPs inhibits melanoma progress through multiple pathways, especially through targeting melanoma stem cells [18]. Super paramagnetic iron oxide (new SPIO) nanoparticles are taken up by visceral organs and showed a unique MRI contrast pattern in the kidney. SPIO are also detected in the mesangial cells of renal corpuscles. SPIO can be potentially be used as a new contrast agent for evaluation of kidney function as well as immunune function [19]. SPIONs produce a decrease in blood pressure and a natriuresis but the rate of fluid filtration in the kidney was not significantly affected [20]. Titanium dioxide (TiO(2) do not effect hepatic and renal functions after 7 days [21]. But a very low dose of TiO (2-S210) significantly superoxide dismutase (SOD) activity of plasma and glutathione peroxidase (GSH-PX) activity of kidney. Silica-coated iron oxide nanoparticle functionalized with dithiocarbamate groups (IONP) exposure induces innate immune function responses [22].

Iron Oxide Nanoparticles (SPION)

Super paramagnetic iron oxide nanoparticles (SPION) have wider biomedical and diagnostic applications [23]. Super paramagnetic iron oxide nanoparticles showed iron-induced oxidative stress and toxicity [24]. But SPIONs stabilized with Dextran-coated iron oxide (D-IONPs) nanoparticles dextran (D-IONPs) did not cause any toxicological effect on renal and liver function [23]. Aqueous-phase iron-oxide nanoparticles (IO NPs) with glutathione (GSH) act as anti-oxidant in the human body and do not affect cortical-medullary anatomy and restore renal physiological functions. These could be used as long-circulating MRI contrast agents due to their immense bio-targeting potential [25].

Vanadium Oxide Nanoparticles (VO NPs)

Vanadium oxide nanoparticles (VO NPs) are used to trace CKD but these effect functions of the heart and the immune system [26]. S- and C-VO NPs decreased the number of WBCs at the higher dose, while total protein and albumin levels.

Titanium Dioxide Nanoparticles

Titanium dioxide (TDN) nanoparticles are widely used in many industries as well as in medicine and pharmacology [27]. Tiron a synthetic vitamin E analog is a mitochondrial targeting antioxidant. It ameliorates oxidative stress and inflammation when used in titanium dioxide nanoparticles (TiO_2 NPs) and induce nephrotoxicity in male rats [28]. TiO_2 NPs treated rats showed marked elevation of renal indices, depletion of renal antioxidant enzymes with marked increase in MDA concentration as well as significant up-regulation in fibrotic biomarkers TGFβ1 and MMP9. TiO_2 NPs treated rats significantly attenuate the renal dysfunction through decreasing of renal indices, increasing of antioxidant enzymes activities, down-regulate the expression of fibrotic genes [28]. Polyacrylic acid (PAA) metal-oxide nanoparticles (TiO_2, CeO_2, Fe_2O_3, ZnO) exposure in goldfish negatively affects neutrophils [29].

Gold Nanoparticles (GNPs)

Gold nanoparticles (AuNPs) have a wide range of applications in various fields. Gold nanoparticles (GNPs) have shown promising applications in targeted drug delivery and contrast imaging. GNPs play prominent role in a number of biomedical applications like imaging, drug delivery, and cancer therapy. These show unique optical features and biocompatibility [30] but cause *in vitro* cytotoxicity [31]. Two types of GNPs porous gold nanoparticles (PGNPs) and solid gold nanoparticles (SGNPs) have been fabricated. Administration of synthesized PGNPs increases the levels of aspartate aminotransferase (AST), alkaline phosphate (ALP), serum creatinine and blood glucose, whereas that of SGNPs increases the levels of AST, ALP and blood glucose [30]. Biogenic gold nanoparticles are orally administered to retain the hepatic enzymatic markers, serum lipid levels and followed by renal biochemical profile in the rats. GNPs treated rats displayed an elevated level of lipid peroxidation, superoxide dismutase, glutathione peroxidase, and catalase enzymatic activity. GNPs treated rat able to alleviate the hyperglycemic condition due to the enzymatic activity of catalase [32]. These GNPs treated rats did not show histological injury in the hepatic, renal, and pancreatic tissues. GNPs caused an acute phase induction of proinflammatory cytokines in cortex and medulla of rat kidneys [31]. Gold nanoclusters (Au NCs) are highly advantageous as used in medical diagnostics and therapies. These show efficient renal clearance and high tumor uptake [33]. Negatively charged glutathione-protected Au NCs displayed lower excretion and increased tumor uptake , whereas positively charged clusters caused transient side effects on the peripheral blood system [33]. AuNPs@AK particles showed decrease in fibronectin expression and attenuated renal fibrosis, and reduced inflammatory response. These act in a very short time and show reducing risk of adverse effects and are good therapeutic option for treatment of CKD patients [1]. AuNPs showed modulatory effects on an antioxidant system in male Wistar diabetic rats with autism spectrum disorder (ASD). AuNPs improved many of the oxidative stress parameters (SOD, GPx and, CAT), plasma antioxidant capacity (ORAC) and lipid profile relative to the other parameters. These do reversibility of the pancreatic B cell in group IV which may reflect the regenerative capacity of AuNPs [34,35]. GQ poly (d,l-lactide-co-glycolide)-loaded gold nanoparticles precipitated with quercetin (GQ) restore the metabolic disorders caused by high-fat diet, which suppresses insulin resistance, lipid metabolic imbalance, and proinflammatory cytokine production. These prevent kidney injury by inhibition of TLR4/NF-κB and oxidative stress, further increasing superoxide dismutase activity [6].

Gold Nanorods

Gold nanorods have the potential to localize the treatment procedure by hyperthermia and influence the fluorescence. These show dual capabilities as photothermal agents and autofluorescence enhancer to track cell death [36]. When the PEGylated nanorods are internalized inside the cells through endocytosis, the transverse plasmonic peak combined with the enhanced absorption and scattering properties of the nanorods can enhance the autofluorescence emission intensity from the cell. Nano sized OMVs are also effective mediators of long distance communication *in vivo*. These show good biodistribution and deposit in outer membrane vesicles (OMVs)-bacterial extracellular vesicles-with immune-modulatory functions is performed [37]. Single-walled carbon nanotubes (SWCNTs) have been used to deliver single-stranded (ssDNA) [35]. Nude multi-walled carbon nanotubes s-MWCNTs and s-MWCNTs-PEG displayed good *in vitro* and *in vivo* biocompatibility. These are used as carrier for drug delivery [38].

Gadolinium (Gd) Nanoparticles

Gadolinium based nanoparticles coated with silica are used as MRI bioimaging agent [39]. Though, Gd^{3+} ions put some adverse side effects such as renal failure, pancreatitis or local necrosis. Similarly, silica coated magnetic nanoparticles showed biosafety because it avoids GdOHCO3 degradation into harmful products (such as Gd^{3+} ions) at physiological conditions [39]. Silica nanoparticles show viability of cultured human embryonic kidney cells (HEK293) [40].

Silver Nanoparticles

Silver nanoparticles (AgNPs) are increasingly and extensively being applied for biomedical purposes. Nanosilver, as colloidal silver, shows harmful effects on liver and brain and skin irritation [41]. Prolonged treatment of AgNPs also led to the activation of cell proliferative, survival and proinflammatory factors (Akt/mTOR, JNK/Stat and Erk/NF-κB pathways and IL1β, MIP2, IFN-γ, TNF-α and RANTES) and dysfunction of normal apoptotic pathway [42]. Iodide-modified silver nanoparticles were used as the enabler for sensitive measurements of urine proteins [43]. These assist in identification of high-risk AKI type based on common urinary biomarkers [43]. AgNPs may have potential to adversely affect the kidney functions as well as capability to cause myriad of cellular damage [44].

Selenium Nanoparticles

Selenium is a metalloid and shows some characteristics of a metal and some of a non-metal. Ginger *Zingiber officinale* selenium nanoparticles (SeNPs) with whole-body low-dose gamma radiation (γ-R) showed protective effect against nicotine-induced nephrotoxicity in male albino rats. Selenium nanoparticles with low level of ionizing radiation exposure ameliorate nicotine-induced inflammatory impairment in rat kidney [5]. SeNPs in synergistic interaction with γ-R induce anti-oxidant-mediated anti-inflammatory activities [5]. Selenium nanooparticles showed chemoprotective effects in subchronic cadmium chloride exposure animals. Se-NPs appear to be effective in ameliorating the adverse neurological and nephrotoxic effects induced by CdCl2 partially through the scavenging of free radicals, metal ion chelation, averting apoptosis and altering the cell-protective pathways [45]. Cadmium (Cd) exposure leads to production of reactive oxygen species (ROS), which are associated with Cd-induced neurotoxicity and nephrotoxicity [45]. Lead selenide nanoparticles (nano PbSe) cause oxidative damage to the kidney in rats [46]. Selenium accumulates in the kidney and shows potential chronic effects and induces acute nephrotoxicity in mice [15].

Mineralo-Organic Nanoparticles

Mineralo-organic nanoparticles form in various human body fluids, including blood and urine. These nanoparticles possibly formed within renal tubules and increase in size in supersaturated urine [46]. These mineralo-organic nanoparticles found in blood may induce kidney stone formation via an alternative mechanism in which the particles translocate through endothelial and renal epithelial cells to reach urine. These nano particles can be used in early detection and treatment of ectopic calcifications and kidney stones [46]. In addition, renal epithelial cell injury facilitates crystal adhesion to cell surface and serves as a key step in renal stone formation [47].

Calcifying Nanoparticles

Calcifying nanoparticles isolated from patients with kidney stones are cytotoxic to human bladder cancer cells [48]. These nanoparticles were cytotoxic to EJ cells, more so than nanohydroxyapatites. Calcifying nanoparticles induced greater autophagy and apoptosis than nanohydroxyapatites. It happens due to production of intracellular reactive oxygen species. Calcifying nanoparticles can trigger bladder cancer cell injury by boosting reactive oxygen species production and stimulating autophagy and apoptosis [48].

Calciprotein Particles (CPPs), Colloidal Protein-mineral Nanoparticles

Calciprotein particles (CPPs), colloidal protein-mineral nanoparticles composed of solid-phase calcium phosphate and serum protein fetuin-A found in blood. These were found component of chronic kidney disease-mineral and bone disorder (CKD-MBD) [49]. Serum CPP Fetuin-A supply contribute to the pathophysiology of mineral metabolism and moderately impaired renal function.

Aptamers

The aptamers can be selected from large library of random oligonucleotides. These are used in targeted therapy that requires the application of effective carriers to counter the renal clearance effect and/or functional cargo to exert therapeutic action [50].

Liposomal Nanoparticles

Liposomal nanoparticles are versatile drug delivery vehicles that show great promise in cancer therapy. It is used as a targeting moiety with highly efficient 89Zr liposome-labeling method based on a rapid ligand exchange reaction between the membrane-permeable 89Zr(8-

hydroxyquinolinate)4 complex and the hydrophilic liposomal cavity-encapsulated deferoxamine (DFO) [51]. Liposomal nanoparticles DOXIL® [52] are commonly used in treatment of adult cancers. These exhibit improved safety profile compared to their free drug counterparts. These are non-invasive and are used to target solid tumors. These show wider stratification and used as personalized cancer nanomedicine [52]. Similarly, cholesterol-conjugated G(3)R(6)TAT (CG(3)R(6)TAT) formed cationic nanoparticles via self-assembly, caused no-significant damage to the liver and kidney functions nor interfered with the balance of electrolytes in the blood [53].

Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are used in alternative drug delivery system compared to emulsions, liposomes and polymeric nanoparticles [54]. These show necropsies in tissues and effect hepatic and renal functions. These mediate inflammatory response in experimental animals. M. alternifolia essential oil (tea tree oil or TTO) is used to prepare solid lipid nanocarrier made with essential oil of Melaleuca (nanoTTO) and terpinen-4-ol (terp-4-ol). In investigation it was found that the TTO, nanoTTO and terp-4-ol were not toxic to liver and kidneys since hepatic and renal functions were not affected [55].

MITO-Porter

MITO-Porter is a liposome used for mitochondrial delivery. It is used in cancer therapeutic strategy by delivering anticancer drugs directly to mitochondria. Most anticancer drugs are intended to function in the nuclei of cancer cells. If an anticancer drug could be delivered to mitochondria, the source of cellular energy could be destroyed, resulting in the arrest of the energy supply and the killing of the cancer cells [56] MITO-Porter system can be used to treat drug-resistant cancers [56].

SB-coated NPs

Sulfobetaines (SBs) are a class of zwitterionic surfactants with a reputation for enhancing colloidal stability at high salt concentrations. The low hydrodynamic size of the SB micelles and SB-coated NPs showed efficient renal clearance [57]. SB amphiphiles can stabilize alkanethiol-coated GNPs in physiologically relevant buffers at concentrations well below their CMC, with size increases corresponding to single-particle encapsulation [57].

ASc-loaded Polymeric Nanoparticles

S. cumini (ASc) and ASc-loaded polymeric nanoparticles (NPASc) decrease glucose (56%), cholesterol (33%) and creatinine (51%) levels; serum (16%) and pancreatic (46%) AOPP and renal (48%) [58]. Asialoglycoprotein receptor (ASGPR)-targeted doxorubicin hydrochloride (Dox) nanoparticles (NPs) are used to treat hepatocellular carcinoma (HCC). Polyethylene sebacate (PES)-Gantrez® AN 119 Dox NPs showed extensive tumor necrosis, reduced collagen content, reduction in serum α-fetoprotein ($p<0.05$). [59]. Hence, high efficacy coupled with greater safety portrayed Pul Dox NPs as a promising nanocarrier for improved therapy of HCC [59].

Multifunctional DNA Carriers

Multifunctional DNA carriers (MDCs) which self-assemble with DNA to form structured nanoparticles that possess virus-like functions for cellular trafficking [60]. MDCs interact with cellular nuclear transport proteins gene expression in growth-arrested human embryonic kidney cells. These show lower cytotoxicity, than lipid and polyethyleneimine vectors. NSOM-based direct fluorescence-topographic imaging is unique and powerful for elucidating nanoscale distribution of specific cell-surface molecules in membrane fluctuations [61].

Carbon-Coated Iron Nanocrystal

Carbon-coated iron nanocrystal (CCIN) showed acute toxicity in mice effects on hepatic, renal and hematological functions. CCIN is characterized by low acute toxicity and mild side effects on the hepatic, renal and hematological functions within a certain dose range [62]. The median lethal dose (LD (50)) of CCIN particles given by intravenous injection was 203.8 mg/kg in mice.

Nanodiamonds

Diamond is a metastable allotrope of carbon. MNDs are used for the development of new technologies of hemodialysis and plasmapheresis for binding and removal of viral particles from the blood of infected patients [63].

Sodium-PLGA Hybrid Nanoparticles

Enoxaparin sodium-PLGA hybrid nanoparticles (EPNs) are made by introducing the negative polymer of enoxaparin sodium (ES) to form an electrostatic complex with the cationic drug. DOX It shows high encapsulation efficiency (93.78%) [64]. These nanoparticles showed the excellent sustained-release characteristics of DOX-loaded EPNs (DOX-EPNs) *in vivo* pharmacokinetics. EPNs can be used in aqueous solution of DOX antitumor drug with enhanced oral bioavailability [64]. KS-loaded PLGA vitamin-E-TPGS microparticles (MPs) and nanoparticles (NPs) showed rapid renal clearance, which results in serious nephrotoxicity/ototoxicity [65]. KS is polycationic and shows poor oral absorption half-life (2.5 h). These KS-loaded PLGA (poly (lactic-co-glycolic acid) vitamin-E-TPGS microparticles (MPs) and nanoparticles (NPs) can use to reduce the dosing frequency and dose-related adverse effect.

Nanoparticle (NP) formulation DICLO-NP shows reduce renal necrosis without influencing other side effects or drug characteristics [66]. Mercapto-modified mesoporous silica nanoparticles (MSNS) MSNS-6MP/CDDP is able to completely eliminate liver, kidney and heart toxicities induced by CDDP alone or CDDP plus 6MP. Cisplatin is provided to cancer treatment but it exhibits serious cardiac and renal toxicities [67].

EGFR-Targeted Chitosan (CS) Nanoparticles

The epidermal growth factor receptor (EGFR)-targeted chitosan (CS) nanoparticles are versatile delivery system used for silencing the essential mitotic checkpoint gene Mad2 and induce cell death. However, combination of both Mad2 siRNA-loaded CS nanoparticles strategy with chemotherapeutic agents such as cisplatin constitutes an efficient and safe approach for the treatment of drug resistant tumors [68].

RNAi-Based Therapeutics

RNAi is safe and effective therapy for patients with the rare disease, primary hyperoxaluria (PH). RNAi target idiopathic stone disease [69]. Similarly, siRNA potentiate the enhanced permeability and retention effect-based strategy. Lipid nanoparticles bind to VEGF receptor 2 on tumor endothelial cells was inhibited by liposomal siRNA [70].

Ferritin Based Nanoparticle

Horse-derived ferritin-based nanoparticles are also used in MRI for clinical diagnostics [71]. The reporter nanoparticles are also engineered from a novel two-staged stimuli-responsive polymeric material with an optimal ratio of an enzyme-cleavable drug or immunotherapy (effector elements) and a drug function-activatable reporter element [72]. Amorphous silica (SiO2) is used in biopharmaceutical and industrial fields. SiNPs causes oxidative stress, inflammation, and DNA damage in several major organs [73]. The delivery of siRNA is made to find out liver and kidney functions [74,75].

Photocaged Nanoparticles

The anticancer drug chlorambucil was protected by coupling with Pe(OH)4 to form photocaged nanoparticles (Pe(Cbl)4). These Pe(OH)4 nanoparticles do not show toxic effect on major organs under the experimental conditions [76]. Mn-NPs are also used for delivery of drugs to the target organ [77].

Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSNs) are ideal nanocarriers which have important bioapplications such as drug, gene, and protein delivery. MSNs are used as carriers for cancer diagnosis and therapy. MSNs are genotoxic to normal human cells, leading to changes in the expression of some genes. This genotoxicity may cause cellular dysfunction and certain benign diseases [78]. Cationic liposomes of Lipofectamine 2000 are used for cellular uptake of MSNs. These cationic liposomes combining with MSNs show cytotoxicity of both *in vitro* and *in vivo* [79]. But endocytosis efficiency of MSNs in human embryonic kidney 293T cells was greatly increased using Lipofectamine 2000 compared with controls ($P<0.001$). These also show no apparent cytotoxicity to human renal 293T cells [79]. Micellar nanoparticles are fabricated from asymmetrically functionalized β-cyclodextrin (β-CD) based star copolymers covalently conjugated with doxorubicin (DOX), folic acid (FA) and DOTA-Gd moieties. These are used for integrated cancer cell-targeted drug delivery and magnetic resonance (MR) imaging contrast enhancement [80].

Quantum Dots

Quantum dots (QDs) are well known for their potential application in biosensing, *ex vivo* live-cell imaging and *in vivo* animal targeting. Bioconjugated QDs, i.e., captopril-conjugated QDs (QDs-cap) are intraperitoneally administered. They reach to target organs via systemic blood circulation into liver, spleen, kidney and brain [81]. Multifunctional DNA carriers (MDCs) that self-assemble with DNA and form structured nanoparticles. These virus-like particles functions for cellular trafficking [60]. These nanoparticles interact with cellular nuclear transport proteins gene expression in growth-arrested human embryonic kidney cells. These show lower cytotoxicity, than lipid and polyethyleneimine vectors. NSOM-based direct fluorescence-topographic imaging is used to elucidate nanoscale distribution of specific cell-surface molecules in membrane fluctuations [61]. Ultra-small super paramagnetic iron oxide (USPIO)-enhanced dynamic MRI detection is used to visualize renal rejection after kidney transplantation [82]. Iron oxide and gadolinium-based particles are used for the non-invasive *in vivo* detection of macrophage infiltration into inflamed areas by magnetic resonance imaging (MRI). These have high clinical applications mainly in kidney transplantation [83].

Conclusion

In fabrication of nanoparticles toxicity of metal should be reduced, it must be biocompatible and non-invasive. Quality of coated material should be highly therapeutic, easily soluble and permeable and show good biodistribution. Hence, molecular efficacy, sensitivity and specificity of drug and nanoparticle should be tested. After administration of nanoparticle, its design should provide clear diagnosis and more accurate quantitative assessment of drug dose level after release into body organs. As nanomaterials are developed and applied, their potential for health hazards needs to be determined. Besides, conventional markers of CKD new category of renal biomarkers, metabolic biomarkers are needed. It will need integration of metabonomic technology with traditional methods. Before, administering drugs, toxicological behavior of biomedical nanomaterials should know. New biomarkers should reno-protective show accurate diagnosis and display high predictive value. These should workable for renal transplant recipients and therapeutic targets in CKD patients.

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