Chapter 05

Role of Nanoparticles in the Treatment of Renal Cancer

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ABSTRACT

The human urinary system consists of two kidneys which are amenable to filtering the blood and releasing metabolic waste in the form of urine through the renal glomerulus. The kidneys face major challenges due to the drug delivery system leading to treatment failure in multiple renal diseases. Since existing treatments for chronic kidney disease (CKD) are mostly unsuccessful, the condition has a significant impact on worldwide public health. Quick detection and appropriate therapy are important for the upcoming thwarting and emergence of CKD. Nanosystems having several physicochemical characteristics such as size, shape, density, surface, and charge with low cytotoxicity, compliant pharmacokinetics, cell internalization, and biodistribution, have shown positive results for renal therapy. Several forms of NPs have been utilized as drug carriers for renal treatment. Conversely, nanoparticles (NPs) having the size of 8nm cannot pass through the kidney. Still, all the nanostructures can be suitable and nontoxic if the nanoparticles' diameter is over the asymptotic value of 6nm for kidney filtration. As a result, the development of NPs in medicine has offered fresh approaches to the possible detection and management of kidney cancer.

KEYWORDS
Nanoparticles, Alternatives, CKD, Treatment, Cytotoxicity

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INTRODUCTION

Cancer is a general term for a group of diseases defined as unbridled division and disruption of cells (Chandraprasad et al., 2022). Many years of intensive work have been devoted to identifying potential cancer risk factors. The genesis of some malignancies has been strongly linked to particular environmental variables including pollution and radiation but detrimental lifestyles like chronic stress, insufficient sleep, poor hygiene, consuming alcohol and sugary drinks, and unhealthy fats critically influence the cancer susceptibility assessment (Marino et al., 2024). Although these outside variables have been identified as important contributors to cancer, it has been difficult to determine how many proto-oncogene mutations, tumor suppressor gene expression patterns, and DNA repair genes are involved (Chen et al., 2020). Exclusively, 5-10% of instances of cancer are caused by genetic factors. Aging also contributes to many distinct cancer forms (Klein, 2021).

In the past few years, the number of renal suffers has greatly grown. Chronic kidney disease (CKD) and acute kidney injury (AKI) are the two main types of renal disorders (Liu et al., 2021). Moreover, it is considered that AKI and CKD are intimately related. In the modern world, the prevalence of renal pelvis and kidney cancer has increased dramatically (Cassell III et al., 2021). Renal cell carcinoma, also known as RCC, is a sneaky tumor that causes around 2% of cancer cases and deaths globally, and its incidence is expected to rise (Padala et al., 2020). The majority of RCCs are found in the kidney's cortex, which is made up of the collecting duct, tubular apparatus, and glomerulus. In terms of histology and behavior, malignancies of the renal pelvises are similar to urothelial (bladder) cancer. Hematuria, flank discomfort, and palpable masses are the "classic triad" of symptoms that just 10% of patients have at first. Additional typical symptoms include weight loss, leukocytosis, and fever. Moreover, around 20% of patients have a range of

paraneoplastic syndromes, such as hypertension brought on by an excess of renin, polycythemia from erythropoietin, Cushing's syndrome from adrenocorticotropic hormone (ACTH), and hypercalcemia from parathyroid-related hormone peptide (Satwikananda et al., 2023). Sometimes, because of tumor involvement and occlusion of the left-side renal vein, a diagnosis of left-sided varicocele raises the possibility of RCC. Surgical resection and ablation of the neoplasm or percutaneous biopsies with immunohistochemistry (IHC) staining are the two methods used to determine systemic therapy, depending on the patient's features and the severity of the illness (Vasiniotis Kamarinos et al., 2022). The immunohistochemical stain for programmed death ligand-1 (PDL1), an immunosuppressive marker, has gained significant predictive power because PD-1 inhibitors, such as pembrolizumab and nivolumab, have been used as the first-line treatment for PDL1-positive metastatic illness (Sekino et al., 2023). About 8.2% of patients had PDL1-positive disease, which is linked to more advanced illness and a worse chance of survival (Cabezón-Gutiérrez et al., 2021). Radiation and chemotherapy are extremely resistant to even PDL1-negative diseases. Various targeted treatments (such as sunitinib, a VEGF tyrosine kinase inhibitor) and immunotherapies (like aldesleukin (IL-2)) are commonly used in the treatment of metastatic illness.

Based on GLOBOCAN statistics from 2018, an estimated 403,000 individuals receive a diagnosis of kidney neoplasms a year, accounting for 2.2% of the total number of cancer diagnoses. From these, about 148,800 cases are ascertained in females and 254,500 in males, indicating an about 1.7 relative risk (RR) difference between men and women. Men and women have a cumulative worldwide risk of 0.69% and 0.35%, respectively, of acquiring the condition. As a result, the age-standardized rate (ASR) for men and women is 6.0 and 3.1, with a global average of 4.4. Belarus is the state in the world with the predominant cases of about 16.8/100,000 but the effective incidence in several countries in central Africa is close to or equal to 0. In the developed world, RCC is the seventh utmost type of neoplasm. According to the surveillance, epidemiological research, and results, around 74,000 new cases of renal cancer were detected in the US in 2019, making up 4.2% of all cancer diagnoses. The first reported rate of prevalence was 7.1/100,000 in 1975. Moreover, this led to a 4.9/100,000 incidence rate in 2016. This consistent increase has made renal cancer one of the rapidly growing cancers (Padala et al., 2020).

The primary methods for treating cancer are chemotherapy, irradiation, and surgical excision (Debela et al., 2021). The use of these conventional methods relies on the cancer type and maturation level of the cancer. The core treatment method is chemotherapy used for restricted and metastatic types of cancer which can be applied alone or concocted with the rest of therapies. Although, there are some drawbacks to conventional chemotherapy (Pedziwiatr-Werbicka et al., 2021). Foremost among them is limited aqueous solubility because most chemotherapeutics, whether synthetic or derived from plants, are hydrophobic and need solvents to manufacture the dose form, they can be quite hazardous. The second one is the nondiscrimination of anticancer drugs which can harm quickly reproducing normal cells and are non-selective for tumor cells. Another drawback is multidrug resistance or MDR which is mostly caused by elevated efflux pumps in the cell membrane, such as P-glycoprotein (Pgp), which are in charge of removing different anticancer medications from cells (Catalano et al., 2022).

In the last few years, strong tools for the diagnosis, imaging, and treatment of several illnesses and ailments have been revealed which are nanoparticles (NPs) and nanomedicines. The term "nanotechnology" refers to technology applied at the nanoscale. The ultrafine particles known as nanoscale/nanoparticles range in size from 1 nm to 1000 nm (Prerna and Ratan, 2021). When it comes to highly specialized medical intervention at the molecular level for illness detection, prevention, and therapy, nanomedicine is a significant field within nanotechnology. NPs have the potential to be utilized for molecular targeting and diagnostic imaging of many kidney disorders, such as AKI and CKD (Paluszkiewicz et al., 2021). Nanoparticles and Nanomedicines have specificity, diversity, and efficiency which could handle the difficulty of renal disease treatment. However, obstacles to their systemic administration and tailored distribution have hampered the implementation of nano-based therapies, despite their tremendous potential for treating renal disorders. These obstacles may arise during blood circulation, kidney entrance, or while traveling to specific kidney locations. Luckily, new research has indicated ways to enhance the movement of NPs from the bloodstream to the kidneys and their retention there, potentially resolving both issues.

Researchers conducted a groundbreaking study that demonstrated the ability of polymeric nanoparticles made of poly (methyl methacrylate) (PMMA) to enter renal tissue through systemic circulation. Renal-targeted drug delivery system (DDS) research began in the 1990s. In 1994, actinomycin D-loaded poly (isobutylcyanoacrylate) nanoparticles (NPs) localized in rat mesangial cells were used to describe the first targeted drug delivery method for glomerular mesangial cells. The exponential rise of nanomedicine as a whole has greatly accelerated subsequent research advancements in this area. Targeted nanoparticles (NPs) have emerged as a viable delivery system for tailored therapeutics in preclinical and clinical studies in laboratory settings, both in academia and industry (Oroojalian et al., 2020).

Nanoparticles in Renal Cancer Diagnosis

Evaluation of early and particular indicators is thought to be essential for forecasting the early development and course of nephropathy. Consequently, CKD might be avoided and consequences like infection, hypertension, anemia, and heart failure could be decreased with the use of an efficient intervention therapy (Kalantar-Zadeh et al., 2021). Nonetheless, the conventional diagnostic ways are currently accessible but have some drawbacks such as disruption and insensitivity. That’s why, NPs may be crucial for the rapid detection of CKD with substantial sensitivity. CKD can be detected

in two ways which include nanoimaging and nano-biomakers.

Nanoimaging

Kidney function is directly described by glomerular filtration rate (GFR). However, the contrast agent iohexol, which is used for this operation, might cause acute renal damage, making this form of detection uncomfortable. The CKD-epidemiology collaborative (CKD-EPI) formula, often known as eGFR, is frequently used by doctors to estimate GFR. However, tubular cells could absorb and secrete a small amount of creatinine, which reduced their ability to detect CKD in its early and late stages (González-Nicolás et al., 2024). In contrast, different fluorescent NPs, such as Q-dots, gold, and silica NPs, have been identified to offer four unique advantages over existing techniques in the assessment of GFR (Bhatt et al., 2024). Firstly, they did not produce any toxicity or disrupt in vivo metabolism. Secondly, the wavelengths of absorption and emission were in the visible range, with the near-infrared area being more favorable. Thirdly, glomeruli can completely filter them but cannot be absorbed and secreted through the tubules. NPs were convenient to develop and also affordable. Fluorescent semiconductor nanocrystals, or Q-dots, are examples of commercially accessible nanomaterials that have been extensively used in the biological area. Moreover, a variety of disorders, including cancer, have been extensively studied using extremely sensitive and reasonably priced near-infrared fluorescence imaging. However, preclinical research on noninvasive fluorescence imaging for renal insufficiency and staging is currently ongoing. Glutathione-coated gold nanoparticles (GS-AuNPs), which are renal-clearable and produce near-infrared light, have been employed by several scientists as a contrast agent in renal-function fluorescence imaging. In rats exhibiting unilateral ureteral obstruction (UUO), they discovered that this nanotechnology was effective for reporting the phases of kidney impairment and for noninvasively monitoring kidney disease (Huang, 2020). Additionally, they were able to pinpoint the malfunction that was present in kidney phases that corresponded with renal impairment as determined by pathological evidence. It is verified nowadays that both blood urea and serum creatinine are insufficient to identify renal impairment but nanomedicine can act as a potential identifier for this act. At first, they used GS-AuNPs to demonstrate that they were harmless and had no effect on metabolism in vivo by fluorescent imaging renal clearance kinetics in healthy mice. However, there are no structural changes and also discovered a very low deposition in the supporting tissues shown by the kidneys of mice. The visible and IR ranges having wavelengths of (~800nm) were emitted from gold NPs coated with glutathione. GS-AuNPs could be effectively eliminated from the body through the kidneys because of their smaller diameter (Ma et al., 2020). Currently, there are a variety of renal-clearable NPs accessible, including carbon dots, palladium nanosheets, iron oxide NPs, copper nanoparticles (CuNPs), silica NPs (SiNPs), and AuNPs, making the use of NPs in noninvasive-kidney-imaging-feasible. Significantly, NP imaging assesses renal tenderness and fibrosis as well as correctly identifies the phases of kidney failure, suggesting that this technique may be utilized in the future to both identify renal function and invasively study pathology (Paluszkiewicz et al., 2021).

Nano-Biomarkers

The risk factor for incident CKD and the advancement of CKD is albuminuria. The standard dipstick for urinalysis was only positive when the level of albumin in the urine was more than 30 mg/dL (Sumida et al., 2020). Urine albumin dipsticks or different specific antibody techniques can be used to test for microalbuminuria. However, these methods are inappropriate and insensitive. Raman spectrometers are readily accessible for purchase, and SERS offers several benefits including high sensitivity, easy sample preparation, quick analysis, and rapidity (Kołątaj et al., 2020). For instance, this method makes use of the analyte-absorbing silver NP surface, which might greatly increase the Raman signal. The minor value shows the authenticity of this procedure than any other conventional methods for tracking microalbuminuria. As previously reported, urine albumin may be detected relatively quickly and without the need for sample pre-processing. Currently, commercial tools that provide microalbuminuria point-of-care screening are accessible. The biological compatibility and conductivity of the newly developed disposable electrochemical immunosensor for point-of-care microalbuminuria testing were improved by the use of Au nanoparticles on the electrodes. Nowadays dielectrophoresis has been used to prepare new types of mixed Nps that are covalently attached to the antibodies. Another advantage of this technology is that you can take samples from anywhere even from the house of the patients and send data to the electronic machines for early CKD identification (Ma et al., 2020).

A revolutionary multianalyte point-of-care device based on nanotechnology may be used to test hemoglobin, serum albumin, urine creatinine, and glycosylated red blood cells in addition to microalbuminuria. It may also be expanded to monitor additional protein indicators such as glycated albumin and serum creatine. This gadget helps identify diabetic kidney disease early on by comparing test findings with laboratory data; in the future, it may be utilized in distant underdeveloped countries. Cystatin C (CysC), kidney injury molecule-1 (KIM-1), and N-acetyl- β-D-glucosaminidase (NAG) are promising biomarkers against CKD (Jana et al., 2022). Research on the use of NPs to enhance an immunosensor's response in the identification of these biomarkers is becoming more and more extensive. A sandwich-style assay was used to produce an inexpensive amperometric immunosensor to identify CysC in human serum. Researchers applied Au NPs layer-by-layer to check the CysC response and achieved excellent results. A new Ru (II) complex molecule having self-enhanced electrochemiluminescence (ECL) capabilities, called $[Ru(dcbpy)2dppz]^{2+}$-DPEA, was also recommended. When this molecule was introduced into the DNA duplex, it became brilliantly luminous (Ma et al., 2020). They discovered NAG, a unique biomarker of diabetic nephropathy, by using DNA nanotechnology in combination with an ECL self-enhanced

molecule to provide an effective signal amplification approach. Similarly, KIM-1 level biomarkers are being used along with ECL biosensors for early renal damage. Then, Pt NPs are pertinent to enhance the efficiency of electron transfer (Yu et al., 2022). So overall, nanotechnology is a very effective and sensitive instrument that has the potential to determine the early and accurate CKD diagnosis.

Nanoparticles in Renal Cancer Therapy

Quick advancements in nanotechnology for the creation of nanomedicine agents have enormous potential to enhance cancer treatment strategies. Products in the nanomedicine space provide the chance to develop complex targeting techniques and multifunctionality. New cancer treatments have been developed and improved using a broad variety of nanoparticles based on lipids, synthetic polymers, and organic, inorganic, or glycan substances (Aghebati-Maleki et al., 2020). They have been examined for the treatment of renal cancer, such as; Drug delivery systems, nano surgery, and gene nanotherapy.

Nanoparticles for Drug Delivery in Renal Cancer

NPs have been extensively studied for the transport of many kinds of medications because of their effective and safe specific drug delivery characteristic. NPs increased the medications' targetability, bioavailability, and pharmacokinetic qualities (Lee et al., 2023). Recently, it was demonstrated that thapsigargin NPs might effectively cure CKD by activating FoxO1 and Nrf2. Through the activation of Nrf2 and FoxO1, thapsigargin NPs prevented oxidative stress-induced cell death in human kidney tubular epithelial cells in vitro. Conversely, siRNA-mediated suppression of Nrf2 and FoxO1 increased the cytotoxicity caused by oxidative stress. It has been observed that thapsigargin NPs improved renal damage in an adenine diet-induced CKD rat model in vivo, suggesting that it is a viable treatment to stop or slow the course of CKD (Ma et al., 2020).

Natural polyphenol resveratrol has anti-inflammatory properties that help with several renal disorders. However, the poor pharmacological properties of the compound reduce its applications. Consequently, a unique technique was employed to get over these restrictions, and NPs loaded with resveratrol were created. For example, the KIM-1 antibody that is present in the epithelial cells of the kidney KIM-1 antibody was overloaded with coupled with NPs and improved targetability. Resveratrol-loaded nanoparticles (NPs) were used to treat HK-2. This led to decreased toxicity, prolonged and regulated drug release, and inhibition of the inflammasome NLRP3, and IL-1β, two key players in kidney inflammation (Zhao et al., 2021). Adenine-induced CKD mice had elevated BUN and creatinine levels. The treated patients have low creatinine levels and they recovered earlier as compared to the patients that are treated with simple drugs. Creatinine levels were lowered and tubulointerstitial damage was lessened in the CKD animals after being treated with resveratrol-loaded NPs or KIM-1-resveratrol-loaded NPs (Singh et al., 2022).

Numerous natural herbs have slowed the course of CKD and fibrosis, but their benefits were insufficient when used alone. A compound known as salvianolic acid B is derived from the conventional herb, and it is used to recover the epithelium of the human renal proximal tubular cell and suppress the cancer-producing cells (Liang et al., 2024). Studies have demonstrated that salvianolic acid B-phospholipid group encapsulation into nanoparticles (NPs) enhanced its oral bioavailability and intestinal absorption. That's why, CKD can be treated potentially by using nanotechnology in TCM herbal medicines. The initial treatment was ferrous sulfate ($FeSO_4$) for deficiency of iron. Moreover, the ferrous sulfate ($FeSO_4$) use had some limitations like poor bioavailability, low absorption rate, and adverse effects. Nonetheless, liposomal NPs are also applicable to the drug delivery process. Liposomal NPs improved the absorption of iron and resolved certain noncompliance issues. CKD was often associated with hyperphosphatemia. The phosphate binders have some disadvantages, including a significant risk of hypercalcemia, a high price tag, a low to moderate level of effectiveness, and unfavorable gastrointestinal side effects. To overcome these drawbacks, Fe (III) deposition methods and phosphate binders reliant on iron-ethylenediamine with nonporous silica (Fe-EDA-SAMMS) were selected for substrates. The Fe-EDA-SAMMS material had a greater capacity to bind phosphate, a faster rate of phosphate binding, a wider pH operating window, and was far less impacted by the other anions than other typical phosphate binders. Several nanodrugs, including sevelamer carbonate, have previously received approval from the US FDA (Food and Drug Administration) for use in hyperphosphatemia (Ma et al., 2020).

Nano Surgery

Femtosecond laser systems, nanotweezers, nanoneedles, and nano-knives are the nanodevices that are applicable to reduce the disruption of adjacent tissues at the stage of unitary cells (Paluszkiewicz et al., 2021). Nanoneedles can offer the appropriate and safe local dispatch of active materials through a transdermal way. The efficiency of anticancer treatment can be increased by directly delivering drugs into the cytoplasm of cells through the use of diamond nanoneedle arrays. Nano tweezers can control the both adjusting and operating of nanostructures. Silicon nano tweezers were used in medicine, for instance, to manipulate DNA molecules and make them easier to characterize. The nano-knives, which made a 20 nm incision, were a revolutionary tool in neurosurgery that made it possible to isolate and sever a single axon during peripheral nerve surgery. With its ability to irreversibly electroporate solid tumors, the nano-knife seems to be a breakthrough weapon in oncology.

The surgery processes mainly orthopedic and nano surgery are designed by the participation of NMs (Sedra et al.,

2021). Because of their superior biocompatibility, titanium-based NMs are utilized in the manufacture of implants, which can lessen postoperative discomfort and hasten the healing of wounds. NMs have been used in dentistry as well. Antibacterial silver, chitosan, copper oxide, or zinc oxide nanoparticles are great substrates for composite adhesives. Consequently, titanium oxide nanotubes make up the implant's surface (Liu et al., 2020).

Gene Nanotherapy

Gene therapy is another area of medicine that is quickly expanding because of nanotechnology; research in this field focuses on changing gene expression. The transfer of small interfering RNA (siRNA) to cells using nanocarriers such as lipid NPs is one method utilized to alter gene expression. Here, translation is prevented by siRNA's degradation of the target mRNA, which results in gene silence (Huang and Xiao, 2022). One such lipid-based nucleic acid-lipid nanoparticle that targets the growth factor for vascular endothelial cells is ALN-VSP (Alnylam). Using RNA interference, patients with advanced solid tumors have their production of KSP and VEGF downregulated when NPs are coupled with siRNAs that target these two proteins. Treatment for malignant conditions including brain tumors and neurodegenerative disorders can be greatly improved by targeted molecular therapy, which alters the expression of certain genes. Mutating the gene for P-glycoprotein, a protein that exports drugs out of cells and helps to remove numerous foreign substances, is another advantage of molecular targeted therapy that may help to solve the multi-drug resistance issue (Emran et al., 2022). The cytotoxicity of chemotherapeutic drugs towards cancer cell lines can be improved by developing a nanosystem for the simultaneous administration of siRNA (lowering the level of expression of P-glycoprotein genes) and an anti-cancer agent utilizing mesoporous silica NPs (Paris and Vallet-Regí, 2020).

Conclusion

A promising method for early CKD diagnosis and tracking the disease's course to ensure that treatment and preventative measures are implemented right away is nanotechnology. Nanosystems are better than other therapeutic and diagnostic methods because it provide invaluable insights by identifying and selecting specific disease areas. Some biomarkers, including hemoglobin, serum albumin, urine creatinine, glycosylated hemoglobin, CysC, NAG, and KIM-1, have been supplied using this technique. Additionally, effective signals have been enhanced using SERS, among other methods. Moreover, NP imaging can detect the kidney malfunctioning phases and also determine the fibrosis and inflammation of the kidney which could relegate the intrusive renal therapies eventually.

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