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THE CURRENT STATE OF NUCLEAR NEPHROLOGY IN MODERN MEDICINE

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ABSTRACT

Glomerular filtration rate (GFR) is the most reliable parameter of renal function. Regarding the complexity of the gold standard inulin clearance, different estimating equations have been developed with CKD-EPI creatinine equation recommended as the most reliable one. In some clinical situations where creatinine based equations might not be valid, alternative methods are needed. Nuclear medicine methods for measuring GFR with 51Cr EDTA and 99mTc DTPA have been widely used for decades. There are different methodologies for the measurement of kidney function with radiopharmaceuticals: urinary clearance, plasma clearance, multiple plasma sampling, slope intercept, single sample plasma equation, slope only, and the gamma camera-based method. Greater precision of measuring GFR is needed in certain clinical situations. The most common are diagnosis and follow up of chronic kidney disease and definition of the beginning of replacement therapy. The assessment of renal function is also important for potential kidney donors. In recent years, with the introduction of new chemotherapeutic drugs and targeted therapy, oncologic patients treated with nephrotoxic drugs have become more commonly referred for measuring GFR. The monitoring of renal function is important during treatment in order to detect the transformation from reversible acute kidney injury to irreversible chronic kidney disease as well as in the cases of renal insufficiency reduce the dosage and prevent accumulation of the drug and avoid dosage related toxic effects. Assessment of kidney function using measured mGFR will be an important milestone in the creation of more accurate and expanding personalized medicine principle in current onconephrology practice.

Keywords: glomerular filtration rate, nuclear medicine methods, nephrotoxicity, onconephrology

INTRODUCTION

The measurement of renal function has been a major field of interest in nuclear medicine(NM). All the functional information achievable with radionuclides are a valuable complement to the morphological imaging techniques such as x-ray, computed tomography, ultrasound or magnetic resonance imaging. NM is unique as it is the only non-invasive method for the assessment of the relative renal split function [1].

GLOMERULAR FILTRATION RATE

Excretion of soluble waste products is achieved by the process of glomerular filtration. Only a few important solutes are excreted through tubular secretion. Thus, the estimation of the glomerular filtration rate (GFR) is the most reliable parameter of renal function.The classic method of GFR measurement is inulin urinary clearance described by Homer Smith in 1937. This remains a gold standard and was used for comparision with other endogenous or exogenous filtration markers. However, because of expensive purified inulin and the time-consuming complex methodology with plasma and urine samples, inulin clearance has never become appropriate for routine clinical practice [2].

GFR ESTIMATING EQUATIONS

GFR equation with creatinine level is practical and easy to perform. The Cockroft Gault equation established in 1976 estimates creatinine clearance using age, sex, body weight and serum creatinine level [3]. There were several limitations, such as an underestimation of the function in advanced age, obese, and edematous patients [4]. In the new approach known as Modification of Diet in Renal Disease (MDRD), a study equation that estimated eGFR has been indexed for body surface area (BSA) [5]. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was developed in 2003, also including individuals from Europe and North America, with and without kidney diseases. The updated version of CKD-EPI from 2009 shows concordance in 80% of cases, including in the Australian population [6]. However, the goal should be to develop more accurate methods that do not require use of race or other demographic features [7]. As the CKD-EPI formula works in ages over 30, there is a special CKiD Schwartz formula that could be used in age group of 2–18 [8].GFR declines after 35 years of age, and the decline is faster in females. Age and gender differences in GFR should be considered additional thresholds important for living kidney donation [9].

There are special clinical situations where creatinine based equations might not be valid and when alternative methods are needed. Cystatin C as a low molecular protein, not correlated with muscle mass or diet, is less dependent on sex, age or race than creatinine. In laboratory practice regarding accuracy, calibration, and precision of creatinine and cystatin C measurement is very important [10]. But inflammation, smoking, thyroid disease, malignant neoplasms and use of glucocorticoids are associated with higher levels of cystatin C. As GFR assessed with cystatin C does not require a local coefficient for racial and ethnic groups, the combination of both should be the best endogenous marker [6]. Kidney Disease Improving Global Outcome (KDIGO) guideline recommends for GFR assessment in initial testing of serum creatinine level and GFR estimating equation [11]. In circumstances where more precise ascertainment of GFR will impact the clinical decision, the use of exogenous markers is worthwhile [12].

EXOGENOUS MARKERS

Exogenous markers of glomerular filtration are divided in two groups: radiopharmaceutical (51Cr EDTA ethylenediaminetetraacetic, 99mTc DTPA diethylene triamine pentaacetic acid, and 125I iothalamate) and non-radiopharmaceutical (inulin, iodinated contrast agents as iohexol and unlabeled iothalamate) [13].

RADIOPHARMACEUTICALS

There are four stages in GFR measurement using radiopharmaceuticals-preparation, administration, sampling and counting [14]. Molecules of EDTA and DTPA are structurally similar chelating agents, but the radionuclides have different characteristics. 51 Cr has a longer half-life of 27.7 days and a principal gamma emission of 320KeV, while 99mTc has a short half-life of 6.02h and a gamma emission of 140KeV. From the radiation exposure side there is also a significant difference of 0.6mSv and 0.03mSv, respectively, for recommended doses of 3MBq 51Cr EDTA and 10MBq 99mTc DTPA. Regarding the half-life samples with 99mTc DTPA should be measured in the same day. Extrarenal excretion of EDTA is about 4ml/min, and protein binding was constantly decreased with new kit formulations and remained within in the acceptable ranges of

6-12% for EDTA and 5-11% for DTPA. 51Cr EDTA was introduced in 1960 and was widely used in Europe until the end of 2018, when the main global supplier declared termination of the production due to the decreased demand [13]. In the USA, 51Cr EDTA has never been approved by FDA, and iohexol and iothalamate were alternatively used. DTPA as a glomerular filtration agent was recognized in 1960, and was initially labeled with 169Yb and 140La, later with the introduction of in-house kits ready for labeling with 99mTc was considered as GFR agent [15]. In 1974, it was approved by the FDA,but was not widely used until 1980 because of the high protein binding capacity. Since the variability and quantity in protein binding was resolved, it has been used more commonly for GFR measurement, becoming the radiopharmaceutical of choice [15].There have been many studies since 2019 dedicated to the comparison of the two radiopharmaceuticals. A mean difference of 1.4ml/min DTPA clearance tends to exceed EDTA clearance, but the differences are slight and not statistically significantly and are unlikely to be clinically relevant. There are not many studies comparing DTPA with non-radiopharmaceutical agents [15], but data from the comparison of EDTA and DTPA clearance studies are widely accepted as sufficient [16, 17, 18].

PET RADIOPHARMACEUTICALS

There were also attempts with PET tracers [13], 68Ga EDTA and 68Ga NOTA are with comparable results compared with 51Cr EDTA.18F flourodeoxysorbitol is a new functional imaging agent that provides images of high quality, free of background activity like renal plasma flow radiopharmaceuticals. Regarding the cost it could be used only in selected pediatric cases when accurate functional assessment is needed in making decisions about potential removal of the kidney [19]. Adults with malignant lesions of the kidney and marginal renal function may benefit from combined morphological and functional assessment when possibility of partial versus total nephrectomy is being considered.

NM METHODOLOGY OF GFR MEASUREMENT

There are different methodologies for measurement of kidney function with radiopharmaceuticals: urinary clearance, plasma clearance, multiple plasma sampling, slope intercept, single sample plasma equation, slope only and gamma camera-based method (see Table 1).

Urinary clearance is calculated by dividing total amount of substance in urine by the mean plasma concentration during its formation. Urinary clearance with 51Cr EDTA, replaces continuous infusion with single shot and urinary catheterization with collection of twenty-four-hour urine [15]. However, it is rarely used in situations with very low clearance and expanded third spaces.

Plasma clearance of radiopharmaceutical after bolus injection has been used for a long time indirectly measuring renal filtration with disappearance of radiopharmaceutical from plasma [13]. The area under the concentration curve (AUC) for plasma clearance of radiopharmaceutical requires at least three exponential functions. In most cases, a two compartmental model is the appropriate as tracer clearance is a combination of renal clearance and movement from plasma to the remaining extracellular space. After reaching the equilibrium between plasma and extracellular space (usually after two hours), a single exponential decrease remains. AUC is quantified using multiple plasma samples, but is impractical for clinical use [14].

The slope intercept method or the one pool method are simplifications of AUC method considering AUC is predominantly determined by the second exponential. The monoexponential curve method works with a few plasma samples between two and four hours, when equilibrium is achieved and the calculation of apparent volume of distribution is correlated with slope intercept GFR [20]. Single sample plasma equations are divided into two groups, first with functions that compare empiric correlation between apparent volume of distribution and GFR, and others based on functions derived from the coefficients subsequently determined from the measurements [21].From many formulas, Fleming's based on Jacobson theory,

where volume of apparent distribution is given as a ratio of absolute applied activity to plasma concentration and BSA is preferred [22]. The last BCNM guideline from 2018 recommends Fleming's equation, with estimated GFR suggested, to guide the timing of plasma samples [23]. The international guidelines technique has systematic differences between one sample and two-samples methods for estimating GFR. If GFR is > 100ml/min/1.73m3, the simple sample will be adequate. The one sample method is based on the one compartment model, with the correction of non-immediate mixing and non-uniform distribution of the tracer. The single sample method as further simplification, where accuracy depends on how exactly distribution volume is known and at what time blood sample is taken [21]. For lower GFRs, at least another sample should be taken between 3 and 24h, but more preferably the next day [24]. The gamma camera-based method measures GFR directly from the renal uptake and urinary excretion. A widely known and used Gates technique requires a minimum 6-minute imaging protocol without plasma sampling, using data from full and empty syringes and population-based correction of renal depth. The percentage of renal uptake was empirically correlated within 24h of creatinine clearance. Many studies dealing with the comparison of 51Cr EDTA and 99mTc DTPA plasma clearances compared with Gates show the latter as very imprecise [25, 26, 27]. Precision was slightly better using 20-minute plasma samples after a 20-minute study [28]. The combination method has been proposed for a more accurate split function. Despite the development of commercial gamma camera software methodologies for measuring GFR, they have never been recommended.

NM METHODS FOR SPECIFIC PATIENTS' GROUP (LOW GFR, EXPANDED THIRD SPACE)

In patients with a low GFR slope, intercept method could not be reliably applied. In patients with GFR<25ml/min/1.73m2, samples between 2 and 4 hours were found to have absolute error of 11.3 ml/min, so further sampling at 2,4,8 and 24 hours after the injection would be necessary [24]. Also, clinical situations with expanded third space, edematous conditions with ascites and pleural effusions prolong the time of equilibration with plasma, so in these patients' urinary collection is recommended or alternatively multiple plasma samples up to 24 hours. In the last BNMS guideline, the Brochner Mortensen correction was advised for GFR measurement in patients with expanded third space [23, 29].

ADVANCED NM METHODS (EFFECTIVE RENAL PLASMA FLOW-ERPF, QUANTITATIVE SPECT/CT)

There were attempts to obtain more data from NM studies that use 99mTc DTPA for measuring ERPF and GFR, since estimation of ERPF is important in some clinical situations, such as diabetes mellitus and hypertension, and this could be done using the Schlegel gamma camera method [30]. The quantitative SPECT/CT hybrid system allows for a more accurate measurement of GFR

Table1. *Overview of NM methods for GFR measurement*

Reference	Method	Application remarks
15,	Urinary clearance	inconvenient for patients
	Plasma clearance	
13, 14, 23,	• multiple plasma samples	inconvenient for patients
13, 14, 23,	• few samples (2-3)	with slope intercept method
21, 22,	• single plasma sample	timing depends on function
25, 26, 27, 28	Gamma camera-based method	improved precision with additional plasma sample
23,24,	NM method for specific groups (low GFR, expanded third space)	late plasma samples because of the prolonged equilibration
30,	Effective renal plasma flow	in special clinical situations
31,	Quantitative SPECT/CT	in precision medicine

than conventional planar scintigraphy with a manual GFR quantitation method based on a deep learning approach to the 3D segmentation of the kidney parenchyma on CT. Segmentation methods were found useful in specific cases of urolithiasis or multicystic dysplastic kidney, as they could represent regional functional deterioration by obstructing urinary stones and subsequent improvement after stone removal procedures. SPECT/CT technology might be the future path to precision nuclear medicine regarding the measurement of regional GFR [31].

MRI IN THE MEASUREMENT OF GFR

Radionuclide methods are acceptable but when considering ionizing radiation, there are attempts to be substituted with other methods, especially in pediatric practice. In MRI molecular gadolinium was used as a contrast (Gd DOTA or Gd DTPA) with predominant glomerular filtration without tubular secretion or reabsorption. Although it poses great potential for accurate measurement of GFR, it has not been validated enough to be recommended in routine clinical practice [32]. Recently, motion robust radial volumetric interpolated breath hold examination (VIBE) dynamic control enhanced MRI has shown good correlation with serum creatinine and 99mTc DTPA plasma samples [33].

CLINICAL INDICATIONS

GFR is a standard measure of renal function. High quality medical care needs accurate measurement of GFR.There are certain clinical scenarios where greater precision of measuring GFR is needed. The most common are diagnosis and follow up of chronic kidney disease and definition of the beginning of replacement therapy. Another very common use is in the assessment of renal function of potential kidney donors [34, 35]. In recent years, with the introduction of new chemotherapeutic drugs and targeted therapy, patients treated with nephrotoxic drugs (cisplatin, cyclosporin), the calculation of doses for renally excreted drugs (carboplatin) have become more commonly used for measuring GFR. Assessment of renal function is also very important in the estimation of single kidney GFR in unilateral or bilateral hydronephrosis, pre- and post-intervention (medical or surgical), especially before nephrectomy.

NM IN NEPHROONCOLOGY

Malignancy can cause renal impairment by both direct and indirect mechanisms. Direct renal injury could be caused in renal cell carcinoma where cancer cells destroy renal parenchyma, or prostatic and ureteric carcinoma, which cause renal outflow obstruction. In multiple myeloma, precipitation of toxic immunoglobulin molecules in tubular cells causes tubular atrophy. Barai et al. compared 1373 cancer patients (excluding urological and hematological malignancies) with 1089 potential living kidney donors as healthy controls. 99mTc DTPA plasma clearance with two samples (60 and 180minutes) was performed. In cancer patients GFR was lower, but this was explained on account of the higher mean age and physiological decline in GFR by 0.7-1ml per year. From their data, malignancy, per se, could not cause any decline in glomerular filtration capacity [36]. On the other hand, neoplastic and renal diseases are closely related to each other because of increased risk of cancer in patients with end stage renal disease (most commonly prostate, renal or cervical cancer) and also development of kidney disease caused by the treatment with nephrotoxic drugs. Nephrotoxicity (NT) develops when kidney specific detoxification and excretion are compromised by the action of endogenous and mostly exogenous toxins. Understanding the mechanisms of NT is very helpful in producing drugs with reduced side effects. Mechanisms for drug induced NT include changes in glomerular hemodynamics, tubular cell toxicity, inflammation, crystal nephropathy, rhabdomyolysis and thrombotic microangiopathy [37]. Acute renal failure is the most common complication as it develops in 12-49% of terminally cancer patients. The cancer patients often need radiographic examinations, so they are more prone to develop contrast induced acute kidney injury (CI-AKI). Serum concentration of some tumor markers (CA-125, CYFRA 21-1, NSE,SCC-Ag, fPSA, CEA, Chromogranin A and β2microglobulin are increased in patients with impaired renal function). Different markers of renal damage have been used in clinical practice: high molecular weight proteins (albumin,

transferrin, immunoglobulin G), proteins with enzymatic activity (alanine aminopeptidase,alkaline phosphatase, αglutathione S transferase, γ–glutamyl transpeptidase, π–glutathione S-transferase, N-acetyl D-glucosaminidase), kidney injury molecule1 (KIM-1), neutrophil gelatinase associated lipocalin (NGAL), cytokines (interferons, interleukins, tumor necrosis factor, colony stimulating factor and several other growth factors), clusterin, osteopontin and type IV collagen [35]. The most promising among them is NGAL, as its level correlates with the renal damage and the progression of tumor disease [38].

In patients with malignant diseases during the treatment, renal function could be impaired, as chemotherapeutic drugs are secreted in unmetabolized active form and the therapeutic window is usually narrow. Quite often, MDRD do not register a decrease in GFR that would be sufficient enough to require dose adjustment. Creatinine guided formulas are also not suitable for dose assessment. Also, CKD EPI is not accurate enough and should be replaced with NM methods in chemotherapy dosing purposes.CKiD formulas significantly overestimates GFR in patients after stem cell transplantation [11]. Neither creatinine nor cystatin C clearance accurately measure GFR changes during and after chemotherapy treatment. NM GFR would be appropriate for accurate GFR measurement and necessary for dose adjustment. Measuring GFR is becoming very important in oncology for the adjustment of the doses of renal-excreted drugs.The evaluation and monitoring of renal function is worthwhile throughout treatment with NT drugs. GFR correlates with clearance of carboplatin. Thus, submaximal chemotherapy could be avoided in patients with high carboplatin clearance and could prevent overdose in patients with reduced clearance.

Many chemotherapeutic and targeted agents cause NT (see table 2).

NT has become an increasingly important factor limiting efficacy of cancer treatment. Renal function should be monitored before starting chemotherapy. GFR below 60ml/min/1.73m2 and creatinine clearance below 30ml/min seen in severe chronic kidney disease requires safety measures with use of anti-cancer treatment. Most of these effects are reversible, but some of them as doxorubicin, cisplatin, ifosfamide, methotrexate and pemetrexed may present longer duration of NT [39]. Platinum group chemotherapeutic agents (cisplatin/carboplatin) are among these with the most serious NT. GFR could not be measured by creatinine clearance as it could be affected by slow muscle loss due to chronic illness, corticosteroids, or malnutrition. Plasma creatinine does not show increase unless GFR decreases by 50%,and thus alternative methods for GFR measurement are worthwhile.48-72h after cisplatin administration there is impaired proximal and distal tubular reabsorption and increased vascular resistance. Serum Cystatin C and 99mTc DTPA with two samples were determined in 20 patients before and after chemotherapy. The values correlated before treatment, but after chemotherapy GFR values obtained by radionuclide measuring method declined, so the authors concluded that NM method should be method of choice in the assessment of NT in patients receiving cisplatin [40]. Carboplatin regimens remain the first line of treatment for gynecological cancers and quite often are used repeatedly. Carboplatin is almost exclusively excreted via glomerular filtration with

Table 2. *Nephrotoxic drugs used in oncology*

Groups of Drugs (Classes)	Drugs
Alkylating agents	Cyclophosphamide. Iphosphamide
Cytotoxic agents	Cisplatin, Carboplatin
Antimetabolites	Methotrexate, pemetrexed, Gemcitabine
Vinca alkaloids	Vincristine, Vinblastine
Antitumor antibiotics	Doxorubicin, Mitomycin C
Proteasome inhibitors	Bortezomib, Carfilzomib
EGFR inhibitors	Cetuximab, Panitumumab
mTOR inhibitors	Temsirolimus
B-Raf inhibitors	Vemurafenib
Antiangiogenesis VEFG and VEGFR inhibitors	Bevacizumab, Sorafenib, Sunitnib
Immune Checkpoint Inhibitors	Imipimumab, Pembrolizumab, Nivolumab
CAR-T therapy	

negligent tubular reabsorption or secretion allowing dosage based on GFR.This enables predictable exposure important to minimize toxicity and to optimize efficacy [41]. GFR based chemotherapy dose calculation is mostly with CamGFR modeled GFR [42] on a square root scale using non IDMS (an isotope dilution mass spectrometry) creatinine and patient's biometric data. From 2011 to 2015 on the FDA's site on adverse effects due to anticancer targeted therapy 2943 adverse effects were reported. 47,3% were metabolic disturbances, renal impairment was reported in 42.2%, and hypertension in 10.5%. The most frequent metabolic disturbance was hypokalemia. The most common adverse effects due to the use of Ipilimumab and Cetuximab [43].

In September 2011, the US FDA issued a drug safety communication warning about the risk of acute kidney injury with zoledronic acid and pamidronate, the most common biphosphonates (BPs) used in oncology [44]. Even BP with safer renal profile might produce serious nephrotoxicity. As the BP effects are dose dependent and infusion time dependent toxicity could be limited increasing intervals between doses [45]. However, all BPs can potentially cause acute tubular necrosis, but there are cases with nephritic range proteinuria and collapsing variant of focal segmental glomerulosclerosis [44]. Large binational cohort study with 98807 patients treated with BP demonstrated a modest increased risk of chronic kidney disease progression [46]. Current guidelines include the assessment of renal status in dosing with monitoring of renal function especially in GFR group between 30 and 60ml/min [44].

Conclusion: The use of nuclear medicine in renal studies has significantly declined since the beginning of nuclear nephrology, although split function was the main advantage over other invasive techniques available for the assessment of individual renal function. As the diagnostic of renovascular hypertension and follow up of renal transplants have been replaced with color Doppler ultrasound, interest for nuclear medicine studies in that field significantly declined [16].On the other hand, with all disadvantages with formulas, estimated GFR patients require alternative methods for more accurate assessment of kidney function. This is of utmost importance in the treatment of oncology patients [10]. GFR assessment is very important in clinical practic as as the kidney complications because of cancer or its treatment are becoming more prevalent in current oncology. Measurement of GFR is essential to individualize chemotherapy dosage and to allow optimized treatment. Despite the development of chemotherapeutic drugs and targeted therapy drug, NT has become an important factor that limits efficacy of cancer treatment [39]. In situations where there is a narrow therapeutic window, accurate assessment of GFR is needed to avoid treatment failure from under dosing and toxicity from over dosing. Monitoring is important during the treatment to detect the transformation from reversible acute kidney injury to irreversible chronic kidney disease and in the cases of renal insufficiency reduce the dosage and prevent accumulation of the drug and avoid dosage related toxic effects [41]. Even though there is no ideal marker of renal function available to anticipate complications and to enable better treatment decisions [47]. Amplifying the assessment of kidney function beyond creatinine or cystatin C, using measured mGFR is reducing misclassification and will be an important milestone in the creation of more accurate and expanding personalized medicine in current nephrology practice [7].

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Резиме

ПРИМЕНА НА НУКЛЕАРНАТА НЕФРОЛОГИЈА ВО СОВРЕМЕНАТА МЕДИЦИНА

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Одредување на гломеруларна филтрациска рата е најсигурниот параметар за процена на бубрежната функција. Со оглед на комплексноста на златниот стандард инулин клиренс, поставени се повеќе формули, меѓу кои CKD-EPI се смета за најсигурна. Во одредени клинички состојби каде што формулите базирани на нивото на креатинин се недоволно прецизни, се применуваат алтернативни методи. Нуклеарномедицинските методи со одредување на ГФР со помош на 51Cr EDTA и 99mTc-DTPA се користат со децении. Постојат повеќе методи за определување на бубрежната фукција со помош на радиофармацевтици: уринарен клиренс, плазма клиренс, мултипни плазма примероци, крива со пресметан пораст, равенка со единичен примерок, крива на пораст и метода базирана на активност измерена под гама-камера. Одредени клинички состојби бараат прецизно одредување на ГФР: пациенти со намалена бубрена функција пред започнување на заместителна терапија и процена на бурежната функција кај донори на бубрези. Последните години со сè поголема примена на хемотерапија и таргет-терапија во онкологијата се појавува проблемот на нефротоксичност, за кој ќе биде потребна прецизна процена на бубрежната функција, особено во услови кога акутната лезија може да премине во хронична, трајно намалена бубрежна функција. Во услови на намалена функција треба да се приспособи дозата на лекот за да се намалат токсичните ефекти, со што се создаваат услови за примена на современиот принцип на персонализирана медицина во онкологијата.

Клучни зборови: гломеруларна филтрациона рата, нуклеарно медицински методи, нефротоксичност, онколошка нефрологија