Accurate assessment of renal function prior and after peptide receptor radionuclide therapy

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SUMMARY

Peptide receptor radiation therapy (PRRT) with radiolabeled octreotide analogs is effective treatment in patients with somatostatin receptor-positive neuroendocrine tumors. The kidneys are critical organ during PRRT because of peptide reabsorption, retention, and prolonged irradiation in the proximal tubules. We presented results of kidney functions tests in four patients before and after PRRT with ^{90}Y-DOTATOC and ^{177}Lu-DOTATATE, with special reference to the pathophysiology of preexisting multiple risk factors for kidney impairment. We conducted several methods routinely used in clinical practice to determine kidney function - serum creatinine, serum cystatin C, creatinine clearance (CrCl) through 24 hours of urine collection and mathematical equations for prediction of glomerular filtration rate (GFR). A very accurate measurement of kidney function (GFR and effective renal plasma flow) was done by radioactive tracers - ^{99}Tc- diethyl triamine pentaacetic acid and ^{131}I ortho-iodohippurate plasma clearance. Beside PRRT nephrotoxicity, patient age, preexisting kidney disease, and chronic comorbidities contribute to the risk of renal impairment. Because clinically relevant differences were assessed between calculated values and the real situation, mathematical calculation of GFR or CrCl did not seem to be appropriate to assess individual renal function precisely enough.

Key words: *Neuroendocrine Tumors; Kidney Function Tests; Glomerular Filtration Rate; Receptors, Peptide; Radiopharmaceuticals*

INTRODUCTION

Peptide receptor radionuclide therapy (PRRT) with radiolabeled somatostatin analogues such as [^{90}Y-DOTA0,Tyr3]-octreotide (^{90}Y-DOTATOC) and [^{177}Lu-DOTA0,Tyr3]-octreotate (^{177}Lu-DOTATATE), is a promising tool in the management of patients with inoperable or metastasized neuroendocrine tumors (1). These compounds are able to irradiate tumors and their metastases via the internalization through specific receptor subtype, generally over-expressed on the cell membrane (2, 3). The radiolabeled somatostatin analogues that are being used in PRRT are predominantly cleared by the kidneys. The small peptides are filtered by the glomeruli and most of the activity is excreted via the urine. However, about 2% of the total dose is reabsorbed by megalin/cubulin system in the proximal tubular cells. After transport to the lysosomes, the (metabolized) radioligand is retained there, resulting in prolonged kidney irradiation (4). Despite kidney protection with positively charged aminoacids, which compete for drug transporters, renal damage may become evident for months and years after receptor radionuclide therapy, especially after ^{90}Y-DOTATOC (5, 6).

Renal impairment (RI) in patients with malignancy is often multifactorial and it is clinically useful to consider cancer-independent comorbidities as underlying causes (7). Patients with inoperable or metastasized neuroendocrine tumors often have risk factors such as age, pre-existing hypertension, or diabetes that increase the probability of RI. Therefore, individual assessment of renal function is important before PRRT therapy. Functional coupling between glomerular filtration rate (GFR) and tubular function is largely dependent on the "positive" glomerulotubular balance and the "negative" tubuloglomerular feedback, which ensure integrated regulation of whole nephron function (8). GFR is the best measure of overall renal function and is central to the National Kidney Foundation (NKF) classification and staging diagnosis of chronic kidney disease (CKD). Normal GFR varies according to age, sex, and body size between 120 and 130 ml/min/1.73m^2 and declines with age (9). It is relatively constant under standard conditions and, as opposed to tubular secretion, is independent of the urine flow. Because GFR may be reduced before the onset of symptoms of renal failure, its assessment enables earlier diagnosis and therapeutic interventions in patients at risk. Moreover, the level of GFR is a strong predictor of the time of onset of kidney failure as well as the risk of complications of chronic kidney disease (10). As a clearance method, inulin has been considered as the gold standard for a long time, but this method is expensive and time-consuming because it requires constant infusion, bladder catheterization (for good reproducibility), significant blood sample volume and its use is limited to investigational research. The measurement of GFR can be obtained by means of radioactive tracers exclusively eliminated by the glomerulus (11). Chromium-51 ethylenediaminetetraacetic acid (^{51}Cr-EDTA) is probably the best tracer for that purpose, because of the tight binding of ^{51}Cr to EDTA and the low protein binding of the compound. However, it is not universally available. A valuable alternative is the use of technetium-99m diethyl triamine pentaacetic acid (^{99m}Tc-DTPA), providing that the purity is guaranteed. There is a high positive correlation (r - 0.98) between inulin clearance and the clearance of ^{99m}Tc-DTPA. DTPA clearance values are about 5% lower than the clearance of inulin. Total effective renal plasma flow (ERBF), which represent extraction efficiency of active secretory structures of the kidney, can be measured by a widely accepted method of determining the clearance of hippuran (ortho-iodohippurate acids marked radioiodine).

In routine clinical practice, indirect methods are used to approximate GFR. The most frequently applied approximation is endogenous serum creatinine concentration (SCr). According to the guidelines of the NKF–Kidney Disease Outcomes Quality Initiative (K/DOQI), prediction equations taking into account Scr and given variables for creatinine production, such as age, gender, body weight, race, are recommended for GFR estimate in

clinical practice. The most widely used are the Cockcroft-Gault (C-G) and the Modification of Diet in Renal Disease (MDRD), as well as a modified MDRD equation called the Chronic Kidney Disease Epidemiology Collaboration (CKDEPI) (12, 13). Creatinine clearance (CrCl) measurement, through 24-h urine collection, is also used to estimate renal function; however, the reliability of this method is very much dependant on accurate and complete urine collection. Cystatin C has been suggested as an alternative marker of the GFR, sensitive in early and mild changes of GFR. It has advantages over serum creatinine because of its claimed "constant" rate of production and its intrarenal handling, being freely filtrated, completely reabsorbed, and, then catabolized by the tubular epithelial cell (14). Proteinuria (albuminuria) is additional biomarker to classify stages of CKD in view of its additional clinical predictive ability above and beyond estimated GFR (10).

We present results of kidney functions tests in four patients before and after PRRT of neuroendocrine tumors with reference to differences between measured and estimated parameters of renal function, as well as on the pathophysiology of preexisting risk factors for kidney impairment.

METHOD

Measurement of renal function parameters

GFR was measured as technetium-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) clearance with a single injection technique with a two-point sampling approach at 180 min and 240 min post-injection (37 MBq) according to the slope intercept method described by Russell et. (15). Quality control of ^{99m}Tc-DTPA preparations was performed with thin layer chromatography and showed a high labeling efficiency (>95%). Effective renal plasma flow (ERPF) was determined by the clearance of ^{131} I-hippuran (12 MBq) in two blood samples taken at 20 and 30 minutes, according to Blaufox's method (16). The measured GFR (mGFR) and ERPF values were expressed as ml/min/1.73m^2. Variations in these parameters were compared to reference values (expected values for the sex and age) and express as percentage. Differential separate clearance left to right kidney was calculate from dynamic scintigraphy after injection of ^{99m}Tc-DTPA (L:D). A blood sample for creatinine measurement was taken in the morning directly prior to the DTPA clearance. Serum creatinine was determined according to the kinetic Jaffe's method, using an automated biochemical analyzer (Olympus AU400) and commercially available assay kits by the same manufacturer. Reference range for women was 30–96 μmol/L; for men < 50 years 30–110 μmol/L; and for men > 50 years 30–127 μmol/L. Serum cystatin C (ScysC) have been determined by an immunoturbidimetric method on the same analyzer (Olympus AU400) with Diazyme commercially available assay kits, with the reference range 0.50–1.03 mg/L.

Creatinine clearance (expressed as mL/min/1.73 m^2 of body surface area (BSA)) was calculated from 24-h urine.

CrCl= (UCr x 24h urine volume (ml))/(SCr x 1440 (min/day))

UCr- urine creatinine (μmol/L), SCr– serum creatinine (μmol/L)

BSA (m^2) = 0.0235 x height (cm)$^{0.42246}$ x weight (kg)$^{0.51456}$ (17)

Estimated GFR (eGFR) was calculated using the prediction equations for Cockcroft-Gault (C-G), MDRD and CKD-EPI (18, 19)

The prediction equation used for calculating GFR from ScysC has determined by the Particle-Enhanced Turbidimetric Immunoassay (PETIA) is as follows (19): CYS C - GFR (mL/min/1.73m2) = 84.69 × [cystatin C (mg/L)]$^{-1.68}$ (20).

Body mass index (BMI) was calculated by formula BMI= weight (kg)/ height (m^2)

Case No. 1

The first case was a 73-years old man, with recurrence of carcinoid in mediastinal areas, three years after surgical treatment for mediastinal tumor (PH finding atypical carcinoid insular + solid cell type). In Table 1 are the results of kidney function test before and 6 months after therapy with ^{90}Y DOTATOC a 3.7 GBq. Baseline, measured parameters of kidney function mGFR and ERPF were significantly reduces compared to normal expected values. Prominent decrease of ERBF (-56%) was probably due to long lasting hypertension and systemic vascular damage. Laboratory tests SCr, ClCr, and eGFR overestimate real basal level of kidney function. CYS C – GFR showed high accuracy to mGFR. After PRRT, mGFR fell for 16%, SCr rises above normal range indicating clinical manifestation of RI. Differential separate clearance left to right kidney indicated that mild renal impairment was symmetrical.

Table 1. Results of kidney function test - Case No I

KIDNEY FUNCTION TEST	BASELINE	6 MONTHS AFTER PRRT
SCr (μmol/L)	120	134
CrCl (ml/min)	68	54
C-G	51	46
MDRD	55	48
CKD-EPI	51	45
ScysC (mg/l)	1.77	2.64
CYS C – GFR	43	23
^{99m}Tc- DTPA	46 (-40%*)	31 (-60%*)
^{131}I orthoiodohippurate	202 (-56%*)	186 (-65%*)
L:R	47% : 53%	45% : 55%
Filtration fraction	0.22	0.16
BMI(kg/m^2)	22	21

MDRD, CKD-EPI, CYS C-GFR, clearance of $^{99mTc-DTPA}$ and ^{131}I orthoiodohippurate are expressed in mL/min/1.73m^2

*reduction compared to the normal expected values in relation to sex and ageL:D – differential separate clearanece left to right kidney calculate from dynamic scintigraphy (^{99m}Tc- DTPA)

Case No. 2

The second case was a 56-years old patient, with unresectable disseminated well-differentiated neuroendocrine rectosigmoidal carcinoma with of deposit diffuse liver and peritoneal carcinomatosis (Ph certificates). Baseline, all tests of kidney function was normal (Table 2). After PRRT (^{90}Y DOTATOC a 3.7 GBq) CrCl and C-G underestimates kidney function, while MDRD, CK-EPI and CYS C – GFR, as mGFR and ERBF, were normal indicating that there has been no deterioration of kidney function. This patient had no underlying disease. As in all presented patients, changes in body weight had influence on SCr and calculated values of GFR.

Table 2. Results of kidney function test - Case No II

KIDNEY FUNCTION TEST	BASELINE	6 MONTHS AFTER PRRT
SCr (μmol/L)	70	81
CrCl (ml/min)	93	68
C-G	82	71
MDRD	107	90
CKD-EPI	100	93
ScysC (mg/l)	1.1	0.93
CYS C – GFR	89	117
99mTc- DTPA	95**	110**
^{131}I orthoiodohippurate	550**	540**
L:R	44%:56%	49%:51%
Filtration fraction	0.18	0.21
BMI(kg/m^2)	19,3	21

MDRD, CKD-EPI, CYS C-GFR, clearance of ^{99m}Tc- DTPA and^{131}I orthoiodohippurate are expressed in mL/min/1.73m^2

**normal expected values in relation to sex and age

Case No. 3

Our third case was a 63-years old woman after surgical resection for carcinoid tumor of the small intestine with multiple metastatic spread to the liver. PRRT was conducted in following order: I PRRT (90Y DOTATOC a 1.85 GBq/ 177Lu DOTATATE a 1.85 GBq), II PRRT (90Y DOTATOC a 2.15 GBq / 177Lu DOTATATE a 2.76 GBq), and III PRRT (177Lu DOTATATE a 5.5 GBq). Observing measured values of GFR and ERBP by radionuclide clearances in table No.3, baseline kidney function was normal with mild reduction of ERBF (possible due to recurrent urinary tract infection in previous period). During long-term follow-up mGFR remained stable, reduction was not significant (≤ 10%) in relation to the normal expected values in relation to sex and age, while differences in calculated values of GFR were significant, mostly overestimating actual renal function. CYS C – GFR underestimate renal function after I PRRT and in the further period; after laboratory testing we excluded hyperthyroidism as a possible cause of increased ScysC.

DISCUSSION

Kidneys represent the critical organs due to radiosensitivity to the doses during PRRT, particularly after ^{90}Y-DOTATOC. This effect is particularly marked after ^{90}Y-DOTATOC due to the higher energy and wider range of beta particle penetration of ^{90}Y in tissue (Emax: 2.27 MeV, Rmax: 11 mm). ^{177}Lu, whose beta particles possess lower energy and shorter penetration power in tissue (Emax: 0.49 MeV, Rmax: 2 mm), results in lower kidney doses and, therefore, a reduced occurrence and severity of renal toxicity (20). In PRRT the site of histological damage is, amongst other factors, dependent on the particle size range of the radionuclide used. In the case of ^{90}Y, radiation damage is mostly in the glomeruli, as evidenced by the picture of thrombotic microangiopathy. For radionuclides with shorter ranges, such as the beta emitter ^{177}Lu the damage is predominantly in the tubules with no or less damage in the glomeruli. Only 2% of the radioligand is retained in the proximal tubular cells, resulting in prolonged kidney irradiation (21). The co-administration of positively charged amino acids such as L-lysine and/or L-arginine competitively inhibiting the proximal tubular re-absorption of the radiopeptide results in a reduction in the renal dose ranging from 9% to 53% (22).

Plasma sample radionuclide clearances enable accurate (low bias and high precision) and reproducible measurements of GFR and therefore allow detection of hyperfiltration and early renal impairment (11). Accurate measurement by clearance of exogenous filtrated markers often is considered too complex and, therefore, surrogate markers, such as serum values of endogenous markers, are used in routine practice. Historically, urea was the first marker used to formally assess kidney function. Increased concentrations of urea may be observed in a number of settings in cancer patients not directly related to alterations in GFR, such as increased dietary protein intake, hypercatabolism, corticosteroid use, or gastrointestinal bleeding. SCr supplanted urea for the assessment of kidney function in the mid-1900s and remains the most widely used laboratory test to estimate GFR (12). Creatinine is freely filtered by the glomerulus and is not reabsorbed by the renal tubules; however, it is

Table 3. Results of kidney function test - Case No III

KIDNEY FUNCTION TEST	BASELINE	6 MONTHS AFTER I PRRT	6 MONTHS AFTER II PRRT	6 MONTHS AFTER III PRRT
SCr (μmol/L)	80	65	78	71
CrCl (ml/min)	104	55	80	85
C-G	60	93	77	71
MDRD	65	85	69	77
CKD-EPI	67	87	70	78
ScysC (mg/l)	1,1	1,8	1,4	1,5
CYS C – GFR	86	40	58	55
99mTc- DTPA	76 **	68***	65***	70***
^{131}I orthoiodohippurate	405 (- 20 %*)	380 (- 25 %*)	350 (- 28 %*)	360 (- 25 %*)
L:R	48%:52%	52%:48%	52%:48%	54%:46%
Filtration fraction	0.18	0.17	0.19	0.19
BMI(kg/m^2)	22,1	22	22.3	22

MDRD, CKD-EPI, CYS C-GFR, clearance of 99mTc- DTPA and131I orthoiodohippurate are expressed in mL/min/1.73m2

*reduction compared to the normal expected values in relation to sex and age

**normal expected values in relation to sex and age

***non significant reduction (≤ 10%) in relation to the normal expected values in relation to sex and age

secreted at variable rates. The problem is the fact that tubular secretion of creatinine is increased proportionally relative to its glomerular filtration as kidney function declines, resulting in a significant overestimation of true GFR. As a result, an increase in serum creatinine may not be observed until a substantial decrease in GFR has occurred ''creatinine blind range''. Additional limitations to the use of serum creatinine to estimate GFR arise from the substantial variability in between-person and within-person creatinine generation influenced by physical condition and nutrition. In an attempt to account for this variation, several serum creatinine–based equations have been developed to estimate GFR (8, 10). Prediction equations are more reliable than 24-hour creatinine clearance because most patients do not collect timed urine samples accurately. Creatinine clearance can vary up to 27% in routine clinical practice (day-to-day coefficient of variation) (12). Compared with the clearance method, these formulae based on serum values appear to be simpler, less costly, and easily available. Looking at possible comorbidites in cancer patients, prediction equations are not validated for the detection of early decline of GFR in patients with risk factors, such as patients with incipient and overt diabetic nephropathy, patients with a normal Scr with known CKD or cardiovascular disease. In such cases, GFR can be markedly underestimated with large bias and a poor accuracy within 30%. Considering KDIGO recommendation, in patients with cancer plasma sample radionuclide clearance measurements may be necessary at extremes of age, such in elderly and children, at extremes of body size (obesity, or low body mass index < 18.5 kg/m2), in severe malnutrition (23). GFR should also be measured when dosing with anticancer drugs, which have high toxicity and which are excreted by the kidney (7). ScysC is more sensitive marker for early and mild changes of GFR, but it may be increased in settings of increased metabolic rate because of increased cell turnover, such as hyperthyroidism, use of glycocorticoid and patients with malignant diseases (24). ScysC has been showed to decrease in hypothyroidism (19). Renal function loss may become clinically evident 1 to 5 years after receptor radionuclide therapy (22). Measurement of progression of radiation induces nephropathy using estimated GRF based on serum creatinine is difficult since substantial changes in secretion, generation, and extra-renal metabolism of creatinine can occur and will lead to false measures of lower degrees of progression. ScysC has been reported to rise faster than creatinine after a fall in GFR, enabling earlier identification of AKI. Several cystatin C–based equations to estimate GFR appear to be simpler and more accurate than creatinine-based equations (25). However, mild renal function impairment is common and best monitored with radionuclide clearance.

CONCLUSION

The determination of overall renal function by means of plasma sample radionuclide technique provides insight into the glomerular tubular balance, an information significantly more accurate than the nonradioactive traditional measurements, especially for clearance values above 60 ml/min/1.73 m^2 and for monitoring the disease. It represent a noninvasive approach (one intravenous injection and two blood samples), delivering a rather negligible amount of radiation. Early recognition of impaired renal function and presence of risk factors, particularly hypertension and diabetes, should suggest appropriate treatment that can slow down the progression of disease and prevent the development of kidney associated complications.

Conflict of interest

We declare no conflicts of interest.

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