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How Measuring Glomerular Filtration Rate? Comparison of Reference Methods

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1. Introduction

Glomerular filtration rate (GFR) is considered as the best way to assess global renal function (Gaspari et al., 1997; Stevens & Levey, 2009). Even if GFR estimations (based on creatinine- or cystatin C-based equations) are most often used (see Table 1)(Cockcroft & Gault, 1976; Levey et al., 1999; Levey et al., 2006; Levey et al., 2009), measuring "true" GFR is still important in clinical practice, especially in particular patients (Delanaye et al., 2011a; Delanaye & Cohen, 2008; Stevens & Levey, 2009). In this chapter, we will review the different markers which can be considered as reference methods to measure GFR. Before moving to clinical trials, we have to recall the physiological characteristics of an ideal GFR marker.

2. Clearance concept and ideal marker for glomerular filtration rate

The history of the renal physiology is deeply influenced by the book published by Homer W. Smith in 1951 (Figure 1) : « The kidney: structure and function in health and disease »(Smith, 1951b). In this best-seller of nephrology, Smith compiled all the physiological data (more than 2300 references) which have been published in the scientific literature until 1951. Smith, himself, has largely contributed to the physiological knowledge of the kidney. A large part of this book is dedicated to the GFR measurement. The concept of clearance is well explicated. Actually, the Danish physiologist, Poul Brandt Rheberg was the first to use and define the concept of clearance in 1926 even if this author did not use the word "clearance". Rheberg studied on himself the urea and creatinine clearances to prove that kidney has a filtrating and not only a secreting action (Rehberg, 1926b; Rehberg, 1926a). The term clearance was used for the first time by Möller in 1929 and was then concerning the urea clearance which was proposed as the first evaluation of renal function (Möller et al., 1929). Smith has largely contributed to make popular and classical this concept of clearance to assess GFR (Smith, 1951a). Renal clearance of a substance is defined as the volume of plasma cleared from this substance per time unit (mL/min). Clearance is thus a virtual volume but will permit to apprehend GFR and renal function. However, the concept of clearance is applicable to any internal or external substances. To be considered as a reference method, a marker must have strict physiological characteristics (Smith, 1951b):

1. Marker production and marker plasma concentration must be constant if GFR does not change

2. Marker must be free in plasma (not binding to protein) and must be freely and fully filtrated through the glomerulus
3. Marker is neither secreted nor absorbed by renal tubules
4. Marker must be inert and, of course, not toxic
5. Marker excretion must be exclusively excreted by kidneys
6. Marker must be easily measured in both plasma and urine

Cockcroft

$$GFR\ (mL/min) = \frac{(140 - Age) \times Weight\ (kg)}{7.2 \times SCr\ (mg/dL)} \times 0.85 \text{ if female}$$

4-variable MDRD Study equation

$$GFR\ (mL/min/1.73m^2) = 175 \times SCr\ (mg/dL)^{-1.154} \times Age^{-0.203} \times 0.742 \text{ (if female)} \times 1.21 \text{ for African-American}$$

CKD-EPI study equation

African-American female

Serum creatinine<0.7 mg/dL

$$GFR\ (mL/min/1.73m^2) = 166 \times (SCr/0.7)^{-0.329} \times 0.993^{age}$$

Serum creatinine>0.7 mg/dL

$$GFR\ (mL/min/1.73m^2) = 166 \times (SCr/0.7)^{-1.209} \times 0.993^{age}$$

African-American male

Serum creatinine<0.9 mg/dL

$$GFR\ (mL/min/1.73m^2) = 163 \times (SCr/0.9)^{-0.411} \times 0.993^{age}$$

Serum creatinine>0.7 mg/dL

$$GFR\ (mL/min/1.73m^2) = 163 \times (SCr/0.9)^{-1.209} \times 0.993^{age}$$

Caucasian female

Serum creatinine<0.7 mg/dL

$$GFR\ (mL/min/1.73m^2) = 144 \times (SCr/0.7)^{-0.329} \times 0.993^{age}$$

Serum creatinine>0.7 mg/dL

$$GFR\ (mL/min/1.73m^2) = 144 \times (SCr/0.7)^{-1.209} \times 0.993^{age}$$

Caucasian male

Serum creatinine<0.9 mg/dL

$$GFR\ (mL/min/1.73m^2) = 141 \times (SCr/0.9)^{-0.411} \times 0.993^{age}$$

Serum creatinine>0.7 mg/dL

$$GFR\ (mL/min/1.73m^2) = 141 \times (SCr/0.9)^{-1.209} \times 0.993^{age}$$

Table 1. Creatinine-based equations. SCr: Serum Creatinine, GFR: glomerular filtration rate, MDRD: Modified diet in renal disease, CKD-EPI: Chronic Kidney Disease-Epidemiology group.

Fig. 1. Homer W. Smith

The renal clearance will be easily calculated with the following equation:

$$GFR=([U] \times V) / [P]$$

(where [U] = urinary concentration, [P] = plasma concentration, V = urinary volume)

The calculated value will be then divided by the time interval where the urine collection has been made. *Sensu strict,* the plasma concentration must be sampled from arterial blood but errors induced by venous samples are very limited (Laake, 1954; Handelsman & Sass, 1956; Nosslin, 1965). In the same view, the transit time through the urinary system should also be taken into consideration but, once again, error linked to this transit time is negligible (Ladegaard-Pedersen, 1972; Nosslin, 1965). The method originally proposed by Smith for measuring GFR is not an easy task. Actually, the marker (inulin see below) must be intravenously injected and then perfused at a constant rate to reach stable plasma concentrations. Thereafter, urine collection must be realized, which is a potential source of errors. For this reason, Smith recommended urine collection on 10 and 15 minutes with the use of urinary catheter. Smith recommended three successive collections. The patient was hydrated to assume a sufficient urinary flow though these collections. The mean of the three collection was considered as the GFR measurement (Smith, 1951a). Nowadays, the urine collections are done without urinary catheter and on a longer period of time (60 minutes) to decrease the impact of urine collection errors on the final result (Levey et al., 1991; Robson et al., 1949).

The ideal marker does not exist in the organism (or has still not been discovered if we want to be optimistic). Both urea and creatinine clearance have strong limitations, notably because creatinine is secreted and urea is absorbed by renal tubules (Dodge et al., 1967; Morgan et al., 1978). Therefore, exogenous markers are used to measure GFR. We will successively describe the markers which are still used in clinical practice in 2011: inulin, ^{51}Cr-EDTA, ^{99}Tc-DTPA, iothalamate and iohexol. For every marker, we will describe strengths and limitations both from an analytical and clinical point of view.

3. Inulin

Inulin is still considered nowadays as the gold standard to measure GFR. Smith has deeply studied this marker and makes it the most popular. Inulin is a polymer of fructose which is found in some plants which uses it as energy provider in place of amidon. Its molecular weight is 5200 Da (Gaspari et al., 1997). Some plants are especially rich in inulin: chicory, garlic, leek and Jerusalem artichoke. Humans are not able to metabolize inulin. Because inulin is the first reference method to have been used, its role in the GFR measurement has only be asserted on basis of physiological studies (because the first method is not comparable to any other !). Once again, we often refer to the studies published by Smith and Shannon (New York university)(Smith, 1951a; Smith, 1951c) and by another pioneer Richards (Philadelphia university)(Richards et al., 1934). Inulin was obviously considered as a safe product with any effect on GFR (Shannon, 1934). Inulin is freely filtrated through a semi-permeable membrane which is a strong argument for the absence of binding to protein. This has been shown by Shannon in 1934 (Shannon, 1934) and by Richards in 1937 (Hendrix et al., 1937). In the same publication, Richards proved that inulin was freely and fully filtrated through the glomerulus because he measured the same inulin concentration both in the plasma and the glomerulus of a frog and a salamander (Hendrix et al., 1937). The absence of both tubular absorption and secretion has been demonstrated by an important article published by Shannon in 1934 (Shannon, 1934). In this article, this author showed the

absence of inulin excretion in two types of aglomerular fishes (goosefish, *Lophius piscatorius* and toadfish *Osteichthyes - Lophiidae*). In the same article, Shannon measured GFR by inulin clearance in another type of fish with glomerulus, the dogfish (*Chondrichthyes – Squalidae*). These fishes were then treated with phlorizin which was sensed to block all tubular activity. Although the creatinine clearance in this fish was increased, the inulin clearance was not modified by this treatment (Shannon, 1934). In the same year of 1934, inulin clearance was also measured in aglomerular fish and in dogs by Richards (Richards et al., 1934). The experimentation (measuring GFR with and without phlorizin) was then repeated in man by Smith and Shannon. The results obtained in animals were confirmed in humans. Shannon was the first human who was perfused by inulin in 1935 (Shannon & Smith, 1935; Smith, 1951c). These authors had thus suggested that inulin was not secreted by renal tubules. This assertion will be thereafter confirmed by other authors with the same type of methodology (Shannon & Smith, 1935; Alving et al., 1939; Laake, 1954). Additional arguments were developed in the sixties by animal studies using micropontions in the tubules (Gutman et al., 1965). After intravenous injection, inulin is fully excreted by kidneys in urine (Shannon & Smith, 1935), even if very low concentrations of inulin are found in bile (Höber, 1930; Schanker & Hogben, 1961).

Inulin is doubtless the marker who has been the most investigated from a physiological point of view. In this view, it is logical that inulin is still considered as the gold standard for GFR measurement. Nevertheless, there are limitations to its use in daily practice. Because its relatively high molecular weight (5200 Da), the molecule is relatively viscous and don't quickly reach its volume of distribution. Therefore, only methods using urinary clearance with constant infusion rate seem accurate for this marker. Such methods are more cumbersome. Moreover, inulin is not easily available on the market and remains relatively costly. From our point of view, the most important limitation of inulin is the difficulty linked to its measurement in urine and plasma. Actually, several methods have been proposed and these methods are probably not interchangeable. There is no standardization in inulin measurement. We have shown that GFR results could vary from -10 to +10 mL/min in the same patient only because inulin was measured by a different method (unpublished data). Moreover, most of the methods (except the enzymatic ones) are prone to interferences with glucose measurement which is a limiting factor when measuring GFR in diabetic patients (Little, 1949). Regarding the methods for measuring inulin, we can cite the "acid" methods (Kuehnle et al., 1992; Shaffer & Somogoyi, 1933; Alving et al., 1939; Corcoran, 1952; Rolf et al., 1949; Roe, 1934; Steinitz, 1938; Hubbard & Loomis, 1942; Lentjes et al., 1994; Heyrovsky, 1956; Rolf et al., 1949), the enzymatic methods (Day & Workman, 1984; Delanghe et al., 1991; Jung et al., 1990; Summerfield et al., 1993; Dubourg et al., 2010) and the new methods by high performance liquid chromatography (HPLC) (Ruo et al., 1991; Baccard et al., 1999; Dall'Amico et al., 1995; Pastore et al., 2001). Describing these methods in detail are beyond the scope of this chapter and we propose the readers the following reference if they are interested in this topic (Delanaye et al., 2011b).

4. Preliminary statistical considerations

The use of inulin as GFR marker is justified by physiologic studies. The others markers that will be proposed thereafter will be compared to inulin measurements. Therefore, the use of other markers will be justified not by physiological studies (even if some

physiological studies exist for some markers) but by studies comparing these markers with inulin. Unhopefully, most of these studies comparing different GFR tests lack of strong statistical methodology. Actually, most of the authors have only shown a good correlation between the markers, which is expected but not sufficient. Ratio of new markers results on inulin results are also used (the result being considered as good if ratio is near to 1). The use of such ratio may be misleading (for example, if one method overestimates true GFR in low GFR levels but underestimates GFR in high levels, the ratio will be near to 1 although the method is actually not precise enough). To compare the performance of a new GFR measurement compared to inulin, we need to know the bias (mean difference between the two results) and the precision (standard deviation (SD) around the bias) of this new measurement. Bland and Altman analysis is thus required (Bland & Altman, 1986).

Regarding the other GFR markers, we must also stress that GFR can be measured by plasma clearance and using a bolus injection (instead of constant infusion rate) which makes the GFR measurement much more simple. Method to measure GFR by plasma clearances can be very different (number of samples, timing of samples, mathematical model used). We must keep in mind that results of plasma and urinary clearances are not strictly comparable (plasma clearances overestimate urinary clearances even if the overestimation decreases if plasma samples are drawn after 24 hours) and this must be integrated when these GFR methods are compared (Agarwal et al., 2009; Stolz et al., 2010).

5. ^{51}Cr-EDTA (Ethylenediaminetetra-acetic acid)

5.1 Physiological and analytical data

^{51}Cr-EDTA is an isotopic marker which has a low molecular weight (292 Da). Most of the authors consider that ^{51}Cr-EDTA is not binding to proteins (<0,5% (Brochner-Mortensen, 1978; Bailey et al., 1970; Garnett et al., 1967; Stacy & Thorburn, 1966; Forland et al., 1966; Kempi & Persson, 1975; Forland et al., 1966)) even if Rehling described a binding to protein of 10% (Rehling et al., 1995; Rehling et al., 2001). Due to its low molecular weight, ^{51}Cr-EDTA is freely filtrated through the glomerulus. Physiological studies about renal handling of ^{51}Cr-EDTA are few but it seems that ^{51}Cr-EDTA is neither secreted nor absorbed by renal tubules (Eide, 1970). This absence of secretion and absorption is also confirmed by Forland in dogs (Forland et al., 1966). Regarding the potential extra-renal excretion of ^{51}Cr-EDTA, Garnett described a salivary and a fecal excretion under 1% in one anephric patient (Garnett et al., 1967). Brochner-Mortensen later confirmed the poor fecal excretion (less than 0.1% of the injected dose). Studying the renal excretion and the corporal global radioactivity of 8 healthy subjects after 72 hours, Brochner-Mortensen estimated that 4.5% of the ^{51}Cr-EDTA will be retained in the body, especially in the liver and kidneys (Brochner-Mortensen et al., 1969). The difference between ^{51}Cr-EDTA total clearance and ^{51}Cr-EDTA urinary clearance corresponds to extra-renal clearance of the marker. With this methodology, the same authors estimated extra-renal clearance at 4 mL/min (and this extra-renal clearance remains stable for all GFR ranges)(Brochner-Mortensen & Rodbro, 1976). Jagenburg had also calculated an extra-renal clearance of 2 mL/min in two anuric dialysis patients (Jagenburg et al., 1978). Only, Rehling described a higher extra-renal clearance at 8.4% (Rehling et al., 1995).

Measurement of ^{51}Cr-EDTA by nuclear count is very precise and easy because ^{51}Cr-EDTA half time is long (27 days)(Chantler et al., 1969). The quantity of ^{51}Cr-EDTA injected is

relatively small and therefore the irradiating dose received by the patient is very limited (absorbed dose from 0.011 to 0.0077 mSv according to the radioactive dose injected which is usually 7 MBq). This absorbed dose corresponds to the natural dose of irradiation received in one week and is much lesser than the dose received after thoracic radiography (0.02 mS). Nevertheless, we do not recommend this technique to measure GFR in pregnant women even if authors seem to use it safely (Brochner-Mortensen, 1978; Medeiros et al., 2009; Durand et al., 2006). The dose of EDTA is 1000x lesser than the dose considered as safe (Chantler et al., 1969).

5.2 Clinical data

The first studies about ^{51}Cr-EDTA have been published in the sixties, even if studies (but with questionable methodology) had been published before with EDTA marked with ^{14}Cr (Spencer et al., 1958; Foreman & Trujillo, 1954). In 1964, Downes was the first to give ^{51}Cr-EDTA to cows to study the intestinal transit (Downes & Mcdonald, 1964). In 1966, Stacy and Thorburn are the first to inject ^{51}Cr-EDTA to lambs for measuring GFR. They reported a good correlation with inulin clearance in the animal model (ratio ^{51}Cr-EDTA/inulin was 0,95)(Stacy & Thorburn, 1966). The first scientists who will be interested in GFR measurement by ^{51}Cr-EDTA in humans are English (Garnett et al., 1967; Favre & Wing, 1968; Garnett et al., 1967; Heath et al., 1968; Lavender et al., 1969). It must be underlined that nearly all studies published on this marker are coming from Europe because ^{51}Cr-EDTA is not available in USA (not approved by the FDA)(Brandstrom et al., 1998). The first author who studied ^{51}Cr-EDTA in humans is Garnett who was nuclearist in Southampton. These first data were published in The Lancet in 1967 (Garnett et al., 1967). This author injected one unique dose of ^{51}Cr-EDTA and described a mono-exponential decrease in ^{51}Cr-EDTA concentrations after 30 minutes. This author already evoked the plasma clearance (and the bolus injection) to measure GFR with ^{51}Cr-EDTA. Unhopefully, Garnett did not compare his results to inulin clearance but only to creatinine clearance. However, Garnett performed and compared 56 ^{51}Cr-EDTA urinary clearances with inulin urinary clearances. He found a correlation of 0.995 and asserted that ^{51}Cr-EDTA result were between ±5% of the inulin results which was really excellent. Thereafter, several studies were published on the same topic to compare performances of inulin clearance with urinary or plasma clearance of ^{51}Cr-EDTA. We resumed these studies in Table 2, restricting the data to studies in adults. However, once again, the following conclusions will be drawn from studies having used the most adequate statistical methods. Globally, the performance of ^{51}Cr-EDTA is good. Chantler, in 1969, showed that results of urinary clearance of ^{51}Cr-EDTA was within 5% of the results of inulin (Chantler et al., 1969). This excellent concordance between urinary clearances of ^{51}Cr-EDTA and inulin will be later confirmed by Froissart. This author showed a bias of +3 mL/min (^{51}Cr-EDTA thus slightly overestimating inulin) and a precision of ± 4 mL/min (95% of the ^{51}Cr-EDTA results will be + or – 8 mL/min around the bias)(Froissart et al., 2005b). The best study comparing ^{51}Cr-EDTA plasma clearance with inulin clearance is certainly published by Medeiros in 2009 (Medeiros et al., 2009). This author showed that bias between the two GFR was 3±6 mL/min. This is one of the rare studies where accuracy 30% results are given (defined as the percentage of patients having a ^{51}Cr-EDTA GFR within 30% of inulin GFR). Accuracy 30% for plasmatic clearance of ^{51}Cr-EDTA is 93%. The higher performance is obtained when late blood samples (at 6 or 8 h) are considered.

References	Sample	Population	GFR range (mL/min/ 1.73 m²)	GFR methods	Statistics	Results
(Garnett et al., 1967)	56	NA	± 0 to 180	Urinary clearance and constant infused rate	Regression Correlation	=1.075x-3.06 0.995
(Heath et al., 1968)	39	Healthy CKD Calcium troubles	10 to 150	Urinary clearance and constant infused rate	Correlation	0.995 ^{51}Cr-EDTA underestimates by de 14-16%
(Favre & Wing, 1968)	20	CKD	6 to 187	Urinary clearance and constant infused rate	Ratio Correlation BAr	1.02 0.992 1.5±8.7
(Lavender et al., 1969)	100 clearances in 28 subjects	CKD	± 0 to 150	Urinary clearance and constant infused rate	Ratio Regression Correlation	0.96 ± 0.0027 =0.96x+0.26 0.994
(Brochner-Mortensen et al., 1969)	17	2 healthy	± 10 to 130	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : plasmatic clearance: on 5 hours, samples every 15 min	Correlation Regression	0.974 =1.017x+1.6
(Chantler et al., 1969)	21	CKD	± 10 to 160	Urinary clearance and constant infused rate	Correlation Regression Ratio	0.977 =1.004x-0.032 1.004±0.013
(Stamp et al., 1970)	65 clearances in 56 subjects	15 healthy 41 calcium troubles	± 20 to 140	Urinary clearance and constant infused rate	Correlation Regression Ratio	0.91 =0.98x+6.5 0.96±0.02
(Ditzel et al., 1972)	20	NA	6 to 166	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : plasmatic clearance: samples at 5,10, 15, 20, 30, 60, 90, 120, 150, 180, 210, 240 min	Correlation Regression BAr	0.97 =0.85x+11.42 1.5±11.7
(Lingardh, 1972)	25	Healthy and CKD	±8 to 120	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : plasmatic clearance: samples timing not available	Correlation Regression Mean difference	0.984 =1.099x+4.96 6.2 mL/min

(Brochner-Mortensen, 1973)	89 clearances in 9 subjects	Healthy, before and after hyperglycemia	130 to 150	Urinary clearance and constant infused rate	Ratio	0.9±0.01
(Hagstam et al., 1974)	29	CKD	± 30 to 160	Urinary clearance and constant infused rate	Correlation Regression Ratio	0.97 =0.855x+7.555 0.96±0.07
(Hagstam et al., 1974)	31	CKD	± 30 to 160	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : plasmatic clearance: samples at 180, 200, 220 et 240 min + BM correction	Correlation Regression Ratio	0.97 =0.961x+2.908 1±0.11
(Winterborn et al., 1977)	16	Children and 4 healthy adults	± 5 to 120	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : urinary clearance:	Correlation Regression	0.99 =0.96x+3.5
(Jagenburg et al., 1978)	17	Severe CKD	2.6 to 11	Urinary clearance	Correlation Regression	0.97 =1.05x-0.3
(Rehling et al., 1986)	19	Nephrectomy	11 to 76	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : plasmatic clearance: 5 samples between 3 and 5 h+BM correction	Correlation Regression SD around the mean difference	0.96 =0.86x+2.4 4.3 mL/min
(Froissart et al., 2005b)	111	NA	NA	Urinary clearance and constant infused rate	BA	2.7±3.5
(Froissart et al., 2005a)	22	NA	NA	Urinary clearance and constant infused rate	BA	4±4.9
(Medeiros et al., 2009)	44	Renal grafted	±15 to 80	Inulin: urinary clearance and constant infused rate ^{51}Cr-EDTA : plasmatic clearance: samples at 2, 4, 6, 8 h + BM correction	t-test Correlation BA Exactitude 30%	NS 0.94 2.5±6.1 90.9%

Table 2. Studies comparing ^{51}Cr-EDTA with inulin. NA: not available, CKD: chronic kidney disease subjects, BA: Bland and Altman analysis, BAr: Bland and Altman analysis re-calculated by us, BM: Brochner-Mortensen.

5.3 Strengths and limitations

^{51}Cr-EDTA clearance was the first published alternative to inulin. Among the strengths of this marker, we have to underline the good performance of GFR measurement comparing to inulin (or to other markers). Physiological profile can also be considered as satisfying. This marker is yet easy to measure (especially according to its long half-life) and the precision of the measurement appears excellent. The costs, compared to other GFR markers, are acceptable. One important limitation is linked to the fact that ^{51}Cr-EDTA GFR must be done in a Nuclear Medicine department. The most important limitation of this marker is the non-use in USA, where ^{51}Cr-EDTA is not recognized by the FDA.

6. ^{99}Tc-DTPA (Diethylenetriaminepenta-acetic acid)

6.1 Physiological and analytical data

Like ^{51}Cr-EDTA, ^{99}Tc-DTPA is an isotopic marker with a low molecular weight (393 Da)(Durand et al., 2006). DTPA may be labeled with another isotopic marker (^{113m}Indium (Johansson & Falch, 1978; Reba et al., 1968; Piepsz et al., 1974), ^{169}Ytterbium (Perrone et al., 1990; Russell et al., 1985)) but technetium 99 is the most used up to now. The ^{99}Tc-DTPA is also used in Nuclear Imagery (isotopic nephrogram) for instance to measure separately the function or the right and left kidney (Biggi et al., 1995; Hilson et al., 1976; Kainer et al., 1979). However, we will only discuss GFR measurement based on plasma and/or urinary methods with ^{99}Tc-DTPA. GFR can also be estimated with external counting using gamma camera (namely the "Gates" method) (Gates, 1984; Russell, 1987) but this method is not precise enough to be considered as a reference method for measuring GFR. For some authors, the GFR estimation given by the Gates method is even less performing than the creatinine clearance (Owen et al., 1982; Goates et al., 1990; van de Wiele C. et al., 1999; Ma et al., 2007; Mulligan et al., 1990; Galli et al., 1994; Ginjaume et al., 1985; Rodby et al., 1992; Tepe et al., 1987; Aydin et al., 2008; De Santo et al., 1999; Fawdry et al., 1985; Durand et al., 2006).

Doses of injected ^{99}Tc-DTPA are totally safe (10 MBq)(Kempi & Persson, 1975; Durand et al., 2006). If the GFR measurement is coupled with nephrogram, the radioactive dose is however 40 to 200x higher than a simple GFR measurement with ^{51}Cr-EDTA (Kempi & Persson, 1975; Griffiths et al., 1988). The half-life of ^{99}Tc-DTPA is short (6.05 h) which imposes that the GFR measurement is realized quickly after the samplings, which is a practical inconvenient compared to ^{51}Cr-EDTA (Owen et al., 1982). The ^{99}Tc-DTPA measurement is as precise as other isotopic methods. The most relevant critic regarding ^{99}Tc-DTPA is its potential binding to protein. This aspect has been debated in the literature. Some authors described a binding to plasma proteins from 2 to 13%, which implies an underestimation of GFR, especially when GFR is measured by plasmatic clearance (Kempi & Persson, 1975; Agha & Persson, 1977; Klopper et al., 1972; Biggi et al., 1995; Houlihan et al., 1999; Rehling et al., 2001). These high percentages could however been explained by the lack of purity of the first available preparations of ^{99}Tc-DTPA (Rootwelt et al., 1980; Rehling et al., 2001; Fleming et al., 2004; Carlsen et al., 1980; Russell et al., 1983; Kempi & Persson, 1975). This hypothesis has been well illustrated in 1980 by Carlsen who studied and compared ^{51}Cr-EDTA clearances with 4 different commercial preparations of ^{99}Tc-DTPA. This author showed different results according to the preparation used (Carlsen et al., 1980). The binding to protein may also be studied by different methodologies (ultrafiltration, electrophoresis, precipitation, *in vitro* or *in vivo,* in humans or in animals etc)(Rehling et al.,

2001; Russell et al., 1983; Jeghers et al., 1990). For example, Rehling found a binding to protein of 10-13% but this author was also the only one who found a significant and comparable binding to protein for ^{51}Cr-EDTA and iothalamate (Rehling et al., 2001). The subject is finally still debated (Jeghers et al., 1990). Another potential critic about ^{99}Tc-DTPA is the very poor available data on its physiological handling. A study in a dog model argued for the absence of tubular secretion and reabsorption (Klopper et al., 1972).

6.2 Clinical data

There are hopefully much more clinical studies comparing ^{99}Tc-DTPA with other markers. After the preliminary study published by Hauser (Hauser et al., 1970), the performances of ^{99}Tc-DTPA clearance was studied from the seventies. Klopper may be considered as one of the pioneers with this markers (Klopper et al., 1972). The first studies were however comparing ^{99}Tc-DTPA with iothalamate and the samples were limited (Table 6)(Klopper et al., 1972; Rootwelt et al., 1980). The first study comparing ^{99}Tc-DTPA with inulin was published in 1984 (Rehling et al., 1984). In table 3, we resumed the results of studies comparing ^{99}Tc-DTPA with the gold standard method in adults. Two studies have compared with good statistical methods the urinary clearance of ^{99}Tc-DTPA and inulin. In the study published by Lewis in 1989, the bias was excellent bias (near to 0) but the precision was not satisfying (± 18 mL/min)(Lewis et al., 1989). One year later, Perrone showed excellent concordance between urinary clearances of ^{99}Tc-DTPA and inulin in 13 chronic kidney disease (CKD) patients. However, the results were less impressive in the 4 healthy subject where ^{99}Tc-DTPA clearances overestimate (+12 mL/min) inulin clearances. Definitive conclusion about the performance of ^{99}Tc-DTPA plasmatic clearance is difficult to draw and we clearly need additional studies on this topic.

6.3 Strengths and limitations

^{99}Tc-DTPA presents the advantages and inconvenient of other isotopic methods (see ^{51}Cr-EDTA paragraph). The dosage of the marker is relatively cheap and precise. His short half-time makes it a few less practicable than ^{51}Cr-EDTA. Among the most important advantages of ^{99}Tc-DTPA, we underline the fact that it is the only marker that can be coupled with nephrogram to give separated function between the two kidneys (Durand et al., 2006). Physiological data to confirm its role as a reference marker are however clearly lacking. We also think that global performance of ^{99}Tc-DTPA compared to inulin is probably a few less than the ^{51}Cr-EDTA, especially with plasma clearances (at least in part because ^{99}Tc-DTPA is binding to proteins).

7. Iothalamate

7.1 Physiological and analytical data

Iothalamate is an ionic contrast product which was particularly used for urography. Iothalamate is derived from the tri-iodobenzoic acid. Its molecular weight is 637 Da (Schwartz et al., 2006) and it is freely distributed into the extracellular volume (Visser et al., 2008). From a historical point of view, iothalamate was not the first contrast agent used to measure GFR. Other derivates from tri-iodobenzoic acid had been tested at the end of the fifties. Diatrizoate (Hypaque) was proposed by some authors as a potential GFR marker because it is fully excreted by the kidneys (Meschan et al., 1963; Burbank et al., 1963; Stokes et al., 1962; Mcchesney & Hoppe, 1957). However, other authors suggested that

References	Sample	Population	GFR range (mL/min/ 1.73 m²)	GFR methods	Statistics	Results
(Rehling et al., 1984)	20	Nephrectomy	11 to 76	Inulin: urinary and plasma clearance with bolus ^{99}Tc-DTPA: Urinary and plasma clearance: samples at 5, 10, 20, 40, 60, 90, 120, 150, 180, 210, 240, 270, 300 min	Wilcoxon Ratio urinary plasma ^{99}Tc-DTPA and urinary clearance of inulin Correlation Regression	urine : $p<0.05$ plasma : $p<0.05$ 0.97 0.97 =0.93x+6.8
(Shemesh et al., 1985)	45	NP	±10 to 140	Inulin: urinary clearance and constant infused rate ^{99}Tc-DTPA urinary clearance	Correlation Ratio	0,969 1,02±0,14
(Notghi et al., 1986)	37	Healthy and CKD	7 to 182	Inulin: urinary clearance and constant infused rate ^{99}Tc-DTPA plasma clearance: samples at: 60 and 150 min	Correlation Regression	0.77 =0.94x+33.7
(Petri et al., 1988)	NA	Lupus	23 to 123	Inulin: urinary clearance and constant infused rate ^{99}Tc-DTPA: urinary clearance with bolus	Correlation Regression r^2	0.96 =x+4.4 0.93
(Lewis et al., 1989)	29	10 heart grafted 11 renal grafted 10 donors	10 to 117	Inulin: urinary and plasma clearance with bolus ^{99}Tc-DTPA: urinary clearance with bolus	Correlation Regression BAr	0.85 =0.84x+8.4 0±18

(Perrone et al., 1990)	13 4	CKD Healthy 2 successive days	±5 to 130	Inulin: urinary clearance and constant infused rate ^{99}Tc-DTPA urinary clearance with bolus	Wilcoxon or t-test Correlation BA	P<0.001 from 0.93 to 0.98 Day 1 +0.5±3 Day 2 -2±3 Inulin (day 1 and 2): 108±14 96±8 ^{99}Tc-DTPA (day 1 and 2) 122±24 108±17
(Wharton, III et al., 1992)	18	Intensive care and CKD	2 to 69	Inulin: urinary clearance and constant infused rate ^{99}Tc-DTPA urinary clearance with bolus	Correlation Regression	0.85 =1.12x
(Gunasekera et al., 1996)	15	NA	±25 to 160	Bolus and plasma clearance for inulin and ^{99}Tc-DTPA: 6 samples within the first hours, 3 or 4 samples between 2 and 4 h	Correlation Regression	=0.98x-0.4 0.98

Table 3. Studies comparing ^{99}Tc-DTPA with inulin. NA: not available, CKD: chronic kidney disease subjects, BA: Bland and Altman analysis, BAr: Bland and Altman analysis re-calculated by us, BM: Brochner-Mortensen.

diatrizoate (as other derivates from tri-iodobenzoic acid) was secreted by renal tubules (Woodruff & Malvin, 1960; Harrow, 1956; Winter & Taplin, 1958). In 1961, Denneberg is the first to compare diatrizoate labeled with I^{131} and inulin in human (Denneberg et al., 1961). This author described a higher renal excretion and then confirmed that diatrizoate is secreted by renal tubules (Denneberg et al., 1961). Diatrizoate was still studied by some authors in the next years but the interest has definitively moved from diatrizoate to iothalamate (Burbank et al., 1963; Morris et al., 1965; Dalmeida & Suki, 1988; Owman & Olin, 1978; Donaldson, 1968).

As we will describe in the next paragraph, interest in iothalamate as a GFR marker has grown from the mid-sixties with the studies proposed by Sigman (Sigman et al., 1965a;

Sigman et al., 1965b). For this author, the binding of iothalamate to protein is less than 3% (Sigman et al., 1965b). Such result was confirmed by most of the authors thereafter (Anderson et al., 1968; Gagnon et al., 1971; Blaufox & Cohen, 1970; Prueksaritanont et al., 1986; Back et al., 1988b), except for Maher and Rehling (see ^{99}Tc-DTPA chapter)(Rehling et al., 2001; Maher & Tauxe, 1969). Rapidly, Sigman has proposed to move from labeling with I^{131} to labeling with I^{125}. I^{125} is actually more stable (Elwood & Sigman, 1967; Maher et al., 1971). I^{125}-Iothalamate is thus an isotopic method which is precise and safe. The half-life of ^{125}I is 60 days (Perrone et al., 1990). Physiological data on iothalamate have been published after the first clinical studies by Sigman. Iothalamate was then studied in aglomerular fishes and only 3% of injected iothalamate was found in urine. The absence of tubular secretion and reabsorption was confirmed in a dog model (Griep & Nelp, 1969). However, these reassuring results were not confirmed by Odlind in 1985. This author actually observed in rats a tubular secretion of iothalamate (comparing with ^{51}Cr-EDTA and using inhibitors of tubular secretion). In the same view, Odlind described, in 6 healthy subjects, that iothalamate clearance overestimates inulin clearance and that this overestimation is reversible after inhibition of tubular secretion by probenecid (Odlind et al., 1985). In anephric patients, Cangiano described an extra-renal excretion of iothalamate that reached 4 to 8 mL/min. This extra-renal excretion fall to 0 after thyroid saturation by iodine (Cangiano et al., 1971). A potential limited extra-renal clearance of iothalamate was thus suggested in the thyroid. Evans described a clearance of iothalamate of 3.1±1.8 mL/min in 7 dialysis patients (among these, 5 were anuric). In animal models, a limited biliary excretion is suggested by some authors (Owman & Olin, 1978; Prueksaritanont et al., 1986). Comparing the total (i.e. plasma) and the renal clearance of iothalamate in healthy subjects, Back calculated the extra-renal clearance at 6 mL/min (Back et al., 1988b). In the same experience, Dowling calculated extra-renal clearance at 10 ml/ml, which was constant for all the GFR levels (sample of 26 patients)(Dowling et al., 1999). In this last study, the plasma clearance was measured until 180 min, which may be considered as too short (Dowling et al., 1999). Visser has also calculated the urinary excretion of iothalamate on 24 h and estimated the extra-renal excretion at 14±12% (Visser et al., 2008). Such values of extra-renal clearances are thus not so negligible, especially when it is considered in patients with severe CKD. Actually, the relative importance of this extra-renal clearance will be higher when the GFR is yet low (Visser et al., 2008).

Iothalamate is a safe product but, of course, it will be not used in subjects presenting a known "true" allergy to contrast products (Heron et al., 1984). Regarding the isotopic method, the radioactive dose got by the patient is also very low (lower than the dose got for thorax radiography)(Hall & Rolin, 1995; Bajaj et al., 1996).

Because its relatively low molecular weight, iothalamate is a good marker (just like ^{51}Cr-EDTA) to be used in simplified protocols. Cohen was the first to use the bolus method instead of the constant rate infusing method in 1969 (Cohen et al., 1969). Several authors have showed that iothalamate could be used in plasma clearance (LaFrance et al., 1988; Welling et al., 1976; Back et al., 1988b; Gaspari et al., 1992) even if results are not fully comparable to urinary clearances (Agarwal et al., 2009). It must also be underlined that iothalamate is the only one marker which is frequently used with subcutaneous injection (Israelit et al., 1973). It had actually been shown that plasma iothalamate concentrations remain constant 60 to 90 min after a subcutaneous injection (so, equivalent to the constant

infusion rate method but much easier) (Israelit et al., 1973; Adefuin et al., 1976; Tessitore et al., 1979; Sharma et al., 1997).

Iothalamate can yet be measured by "cold" non-isotopic methods. The first "cold" dosage of iothalamate was proposed in 1975 by Guesry (Guesry et al., 1975). This author used fluorescent excitation analysis or X ray fluorescence (XRF), which will be also used for iohexol measurement (see below). In this technique, iodine atoms are ionized by americanum. When the iodine atom comes back to neutral status, it will emit X ray that will be then quantified (Guesry et al., 1975). Guesry found an excellent correlation between isotopic and XRF iothalamate measurement. Iothalamate concentration can also be determined by electrophoresis but, to the best of our knowledge, this technique is only used in the Mayo Clinic (Wilson et al., 1997). The most used methods to measure iothalamate are HPLC methods (Boschi & Marchesini, 1981). The HPLC method seems specific, sensible and reproducible (CV intra-day lower than 2% and CV inter-day lower than 6%) (Boschi & Marchesini, 1981; Prueksaritanont et al., 1984; Weber et al., 1985; Reidenberg et al., 1988; Back et al., 1988b; Gaspari et al., 1991; Dowling et al., 1998; Agarwal, 1998; Kos et al., 2000; Agarwal et al., 2003; Farthing et al., 2005; Bi et al., 2007). A new technique based on mass spectrometry has recently been proposed to measure iothalamate (Seegmiller et al., 2010). These authors have compared 51 GFR results given by this new technique and by electrophoresis. The results are excellent in term of correlation and bias (0.8%). The SD around the bias, namely the precision, is however less negligible at 13.7%. That means that 95% of the results measures in the same patient may vary from ± 28% according the way iothalamate has been measured. Iothalamate measurement remain very stable (for two months at room temperature and at –4 and -20°C and for 1 year at -80°C) (Weber et al., 1985; Seegmiller et al., 2010).

7.2 Clinical data

Iothalamate (Conray°) was used as GFR marker for the first time by Sigman from the New York University in 1965 (Sigman et al., 1965a; Sigman et al., 1965b). In these articles, Sigman used iothalamate labeled with ^{131}I and compared its clearance with inulin clearance in 10 patients in the first publication (Sigman et al., 1965a) and in 16 in the second one (Sigman et al., 1965b). On this limited sample, Sigman described a ratio iothalamate/inulin near to 1, even though the ranges of this ratio are from 0.74 à 1 in the first study (Sigman et al., 1965a) and from 0.937 à 1.138 in the second one (Sigman et al., 1965b). These first interesting results were then confirmed by the same authors with ^{125}I-iothalamate (Elwood & Sigman, 1967). Other authors published thereafter their own data comparing performance of inulin and iothalamate clearances. We resumed the results obtained in adults in Table 4. It is probably right to write that iothalamate has been the most studied GFR marker and the marker for which several comparisons to inulin exist. Other authors have confirmed the good performance of iothalamate urinary clearances, especially in CKD patients (Maher et al., 1971; Perrone et al., 1990; Skov, 1970). In healthy subjects, the results are however more questionable and iothalamate seems to overestimate inulin (+20 mL/min)(Perrone et al., 1990) although precision is not optimal ±11 mL/min, as illustrated in the study by Botev (Botev et al., 2011). Data regarding the performance of the iothalamate plasma clearance are less numerous but is seems that bias is acceptable. However, precision is not optimal, especially in higher GFR levels. Additional studies could be of interest for the plasmatic method (Agarwal, 2003; Mirouze et al., 1972).

References	Sample	Population	GFR range (mL/min/1.73 m²)	GFR methods	Statistics	Results
(Sigman et al., 1965a)	10	NA	70 to 108	Inulin: urinary clearance and constant infused rate ^{131}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin BAr	1.06 (0.74 to 1.23) 6±13
(Sigman et al., 1965b)	24 clearances in 16 subjects	NA	2 to 167	Inulin: urinary clearance and constant infused rate ^{131}iothalamate : urinary clearance and constant infused rate	t-test Ratio It/inulin BAr	NS 1.005 (from 0.937 to 1.138) 0.7±4
(Elwood & Sigman, 1967)	26 clearances in 21 subjects	NA	27 to 136	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin BAr	1 (from 0.93 to 1.09) 1±3
(Malamos et al., 1967)	19	Healthy and CKD	NA	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin Correlation (urinary) Regression	1.01±0.19 0.979 It=1.09inulin-0.65
(Anderson et al., 1968)	18	11 CKD and 8 healthy	3 to 139	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Regression BAr	=0.9x+6.7 -0.7±13

(Maher & Tauxe, 1969)	15	hypertensive	±55 to 120	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin Regression	0.92 (0.81 to 1.04) Inulin=1.08It
(Skov, 1970)	43 65 clearances in 22 subjects 38 clearances in 13 subjects 24 clearances in 8 subjects	CKD GFR<5 ml/ GFR between 5 et 15 mL/min GFR between 15 et 25 mL/min		Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus and urinary clearance	Ratio It/inulin Correlation Regression BAr	Group 1 0.98±0.06 0.999 =0.972+0.01 0±0 Group 2 1 0±1 Group 3 0.92±0.071 0.968 =1.083+3.46 -2±1
(Gagnon et al., 1971)	78 clearances in 24 subjects	NA	±10 to 180	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin	1.01
(Cangiano et al., 1971)	49 clearances in 18 subjects	NA	±30 to 150	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin Correlation Regression	1.07 0.94 =1.06+1.17
(Maher et al., 1971)	198	NA	±5 to 150	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Bias Regression	-2.09 Inulin=1.022It+0.537

(Mirouze et al., 1972)	36 clearances in 23 subjects	hypertensive	±5 to 120	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Ratio It/inulin Correlation Regression	1.44±0.13 0.96 =1.18+8.43
(Mirouze et al., 1972)	15	hypertensive	±80 to 140	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : plasma clearance: samples at 5, 10, 15, 20, 40, 60, 80, 100 et 120 min + correction	Ratio It/inulin Correlation Regression	1.23±0.16 0.77 =1.06+1.18
(Israelit et al., 1973)	22	20 CKD 2 healthy	6 to 125	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus SC and urinary clearance	Ratio It/inulin Correlation Regression	1.05±0.04 0.97 =1.054-3.069
(Rosenbaum et al., 1979)	7 healthy 9 renal grafted 8 donors after donation		96 to 147 35 to 87 42 to 98	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus and urinary clearance	Ratio It/inulin BAr	1.02±0.04 1.43±0.08 1.23±0.04 -1±13 -7±14 -4±13
(Ott, 1975)	84	CKD and donors	±10 to 150	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : urinary clearance and constant infused rate	Correlation Regression	0.932 =1.04+2.11

(Ott, 1975)	100	CKD and donors	±5 to 150	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus SC and urinary clearance	Correlation Regression	0.982 =1.02-0.61
(Tessitore et al., 1979)	30	15 creatinine<1 mg/dL 15 creatinine<20 mg/dL	NA	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus SC and urinary clearance	Ratio It/inulin Correlation	1.07±0.05 0.96
(Notghi et al., 1986)	76 clearances in 40 subjects	Healthy and CKD	±10 to 180	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus SC and urinary clearance	Correlation Regression	0.86 =0.8x+19.5
(Petri et al., 1988)	NA	Lupus	23 to 123	Inulin: urinary clearance and constant infused rate Iothalamate (XRF): bolus and urinary clearance	Correlation Regression r^2	0.99 =0.9x-2.1 0.99
(Perrone et al., 1990)	13 4	CKD Healthy Two successive days	±5 to 130	Inulin: urinary clearance and constant infused rate ^{125}iothalamate : bolus SC and urinary clearance	Wilcoxon or t-test Correlation Means	P<0.001 from 0.93 to 0.98 Inulin : 108±14 day 1 96±8 day 2 ^{125}iothalamate 127±12 day 1 120±7 day 2
(al Uzri et al., 1992)	5	healthy	120 to 165	Inulin: urinary clearance and constant infused rate Iothalamate (HPLC): bolus and urinary clearance	ratio	1.00±0.06

(Isaka et al., 1992)	23	CKD	10 to 130	Inulin: urinary clearance and constant infused rate Iothalamate (HPLC): bolus and urinary clearance	Correlation Slope with 0 intercept	0.98 1.05±0.01
(Agarwal, 2003)	12 clearances in 3 subjects	CKD	± 20 to 110	Inulin: urinary clearance and constant infused rate Iothalamate (HPLC): plasma clearance on long time with insulin pomp	Bias (Inulin-It) CV	0.8 19.9%
(Botev et al., 2011) Data from 5 studies (Anderson et al., 1968; Elwood & Sigman, 1967; Perrone et al., 1990; Rosenbaum et al., 1979; Skov, 1970)	94	See above	± 5 to 140	See above	Correlation Regression BA (It-Inulin)	0.97 =1.04+2.334 +4.6±11

Table 4. Studies comparing iothalamate with inulin. NA: not available, CKD: chronic kidney disease subjects, BA: Bland and Altman analysis, BAr: Bland and Altman analysis re-calculated by us, BM: Brochner-Mortensen, HPLC: high pressure liquid chromatography, It: iothalamate, SC: subcutaneous, XRF: X ray fluorescence.

7.3 Strengths and limitations

Iothalamate can be measured either by HPLC or XRF methods or by isotopic methods. This is the only one marker where this choice is possible. However, there is no evidence that all the techniques of measurement are fully equivalent. Iothalamate is certainly the marker that has been the most deeply studied from a physiological point of view (with inulin). Unhopefully, there are strong reasons to believe that iothalamate is secreted by renal tubules. Moreover, extra-renal clearance of iothalamate is not so negligible. These limitations are confirmed by most of the clinical studies showing that iothalamate slightly overestimates inulin clearance, especially in the high levels of GFR. A clinical limitation concerns the patients who are allergic to contrast product. This marker remains however

important because it is the most used marker in USA. For example, iothalamate has been used in trials having built the new creatinine-based equations (Levey et al., 1999).

8. Iohexol

8.1 Physiological and analytical data

Iohexol is a non-ionic contrast product, mainly used for myelography. Its molecular weight is 821 Da (Olsson et al., 1983; Schwartz et al., 2006). Iohexol is chronologically the last marker proposed for measuring GFR. Actually, the first human was receiving iohexol in 1980 (Aakhus et al., 1980). In this study, it was shown that the substance was safe and fully excreted by the kidneys (this assertion will be criticized thereafter, see below). However, these authors also describe (but data are not available) a higher urinary clearance of iohexol than ^{51}Cr-EDTA (Aakhus et al., 1980). The details of these comparison studies were published three years after (see clinical data)(Olsson et al., 1983). In the same study, the authors confirm that iohexol is distributed through the extracellular volume, which will be confirmed by other authors (including in CKD patients and in obese subjects) (Friedman et al., 2010; Nossen et al., 1995; Edelson et al., 1984; Back et al., 1988b; Olsson et al., 1983). Iohexol has not effect *per se* on GFR (Olofsson et al., 1996). Binding to protein seems very limited for iohexol. The first study described a binding to protein of only 1.5% (Mutzel et al., 1980). This will be thereafter confirmed (Back et al., 1988b; Krutzen et al., 1984). Physical properties of iohexol make it a good candidate to be used in simplified protocols like plasma clearance (Thomsen & Hvid-Jacobsen, 1991; Gaspari et al., 1995; Edelson et al., 1984). Contrary to the prior studies (Aakhus et al., 1980), several authors have shown that extra-renal clearance of iohexol is limited but not null (Arvidsson & Hedman, 1990; Krutzen et al., 1984). Back calculated at 6.2 mL/min the difference between total and urinary clearance of iohexol in healthy subjects (Back et al., 1988b). Frennby observed an extra-renal clearance lower than 2 mL/min in 6 anuric dialysis patients (Frennby et al., 1994; Frennby et al., 1995). These last very low results were also found by Nossen in 16 patients with severe CKD. Their mean measured GFR was 14 mL/min and the extra-renal clearance was estimated at 10% (Nossen et al., 1995). In 16 healthy subjects, Edelson estimated the extra-renal clearance of iohexol at 5% (Edelson et al., 1984). Contrary to iothalamate, there are very few physiological studies on the renal tubular handling of iohexol.

As for iothalamate, iohexol can be measured by several different techniques. Among these, HPLC and XRF are the most used ones. HPLC was historically the first method used (Aakhus et al., 1980) and described (Krutzen et al., 1984). As we have shown, iohexol measurements by HPLC are sensitive, specific and reproducible (Back et al., 1988c; Farthing et al., 2005; Cavalier et al., 2008). The high performance of such dosage notably enables the use of iohexol low doses and the measurement on finger-prick samples (Krutzen et al., 1990; Niculescu-Duvaz et al., 2006; Mafham et al., 2007; Cavalier et al., 2008; Aurell, 1994). Iohexol measurement is also pretty stable at room temperature and at -20°C(Krutzen et al., 1984; O'Reilly et al., 1988). Measurement of iohexol by XRF method is less validated and probably less performing, especially in low plasma concentrations (O'Reilly et al., 1986; Back & Nilsson-Ehle, 1993; Effersoe et al., 1990; Brandstrom et al., 1998; Aurell, 1994). We will not discuss into details the other methods for measuring iohexol: capillary electrophoresis (Shihabi & Constantinescu, 1992) and mass spectrometry (Lee et al., 2006; Annesley & Clayton, 2009; Denis et al., 2008; Stolz et al., 2010). The safety of iohexol is now confirmed (Heron et al., 1984; Aurell, 1994), notably by the largest series of iohexol

measurements in Sweden (1500 GFR measurements/y)(Nilsson-Ehle & Grubb, 1994; Nilsson-Ehle, 2002). This safety profile is, at least in part, explained by the low dose of iohexol injected, and by the exclusion of patients with contrast products allergy.

8.2 Clinical data

The results of the first clinical study on iohexol as a reference GFR marker will be published in 1983 (Olsson et al., 1983). Actually, GFR was measured in 10 healthy subjects with urinary clearances of iohexol and ^{51}Cr-EDTA. In this study, the iohexol clearance was significantly higher than the ^{51}Cr-EDTA clearance (110 versus 96 mL/min). In this first study, large dose of iohexol was injected to the patient (from 375 to 500 mg I/kg)(Olsson et al., 1983). Thereafter, the doses of iohexol used will be drastically reduced but it has been well described that the physiologic handling of iohexol was identical if different dosages are used (Back et al., 1988a). In table 5, we resumed the study results having compared the performance of iohexol to inulin in adult subjects. To the best of our knowledge, only two studies have compared urinary clearances of iohexol and inulin. The results seem excellent but Bland and Altman analysis have not been realized (Brown & O'Reilly, 1991; Perrone et al., 1990). Contrary to other markers, iohexol plasmatic clearances have been the most studied. The relatively worst results obtained by Erley are explained by the patients included (Erley et al., 2001). Actually, the patients hospitalized in intensive care are prone to develop edema and, in this situation, plasmatic clearances are not accurate, whatever the marker (Skluzacek et al., 2003). The study published by Gaspari demonstrated a good performance of iohexol plasma clearance compared to inulin but the number of samples was high and these samples were drawn lately (after 10h)(Gaspari et al., 1995).

References	Sample	Population	GFR range (mL/min/1.73 m²)	GFR methods	Statistics	Results
(Lewis et al., 1989)	29	10 heart grafted 11 renal grafted 10 donors	9.6 to 116.8	Inulin: urinary clearance and constant infused rate Iohexol (XRF) Plasma clearance: bolus and samples after 3 and 4	Correlation Regression Ratio	0.86 =0.85x+8.79 1.09±0.06
(Brown & O'Reilly, 1991)	30	NA	±10 to 125	Inulin: urinary clearance and constant infused rate Iohexol (XRF) urinary clearance and plasma clearance: samples at 3 and 4 h +BM correction	Correlation Regression Ratio	Urinary 0.986 =0.998-2.309 Plasma 0.983 =0.947+4.92 =1.102±0.286

(Gaspari et al., 1995)	41	CKD	6 to 160	Inulin: urinary clearance and constant infused rate Iohexol (HPLC) Plasma clearance, samples at 5, 10, 20, 30, 45, 60, 90, 120, 180, 240, 300, 450, 600 min	Correlation Regression BA	0.97 =0.994x+2.339 1.02±7
(Erley et al., 2001)	31	intensive care	±10 to 130	Inulin: urinary clearance and constant infused rate Iohexol (XRF) Plasma clearance: samples at 150, 195, 240 + 360 min if estimated GFR under 30 mL/min	Correlation Regression BA	=0.971x+7.65 r^2=0.96 (Io-inulin) =8.67±7.21
(Sterner et al., 2008)	20	healthy	106 to 129	Inulin: urinary clearance and constant infused rate Iohexol (HPLC) Urinary clearance and constant infused rate	Wilcoxon	Not different

Table 5. Studies comparing iohexol with inulin. NA: not available, CKD: chronic kidney disease subjects, BA: Bland and Altman analysis, BAr: Bland and Altman analysis re-calculated by us, BM: Brochner-Mortensen, HPLC: high pressure liquid chromatography, Io: iohexol, SC: subcutaneous, XRF: X ray fluorescence.

8.3 Strengths and limitations

Iohexol is probably the easiest way to measure GFR. It can be used in all patients (except in patient with true allergy to contrast product). Its measurement by HPLC is probably one of the most precise compared to other cold method (inulin and iothalamate). Iohexol is the less expensive marker and the cost of HPLC is also low. More important, it must be underlined that an external quality control does exist for iohexol measurement (Equalis, Sweden). From unpublished data, it can be concluded that the inter-laboratory CV for iohexol measurement is very low (less than 5%). Such results don't exist for iothalamate and inulin, and, at least for inulin, we think that such good inter-laboratory results would not be reached (personal

data). The limitations of iohexol are the lack of strong physiological data (notably regarding the tubular handling of the marker) and the relatively few studies having compared iohexol with inulin. More studies have actually compared iohexol with other GFR markers.

9. Studies comparing reference methods

In Table 6, we resumed the results of studies comparing reference markers (other than inulin). We selected studies in adults. We focused on studies having used the best statistical methods to analyze the results, i.e. the Bland and Altman analysis. It is difficult to interpret results from studies having compared different markers but also different methods (for example, plasmatic clearance of iothalamate with urinary clearance of ^{51}Cr-EDTA) because it is impossible to affirm that potential differences are due to difference in markers or to difference in methods. Another limitation of several studies is the relatively small sample of subjects included. If we take into account these two limitations, we can stress on some interesting results showing good concordance (bias±SD) between plasma clearances of ^{51}Cr-EDTA and ^{99}Tc-DTPA (1.91±6.1 mL/min), and between plasma clearances of ^{51}Cr-EDTA and iohexol (-0.16±6.17 mL/min in (Brandstrom et al., 1998), 4±7.9 mL/min in (Bird et al., 2009), 2±9.2 (Lundqvist et al., 1997), and -0.6±3.6 mL/min in (Pucci et al., 2001)).

References	**Sample**	**Population**	**GFR range (mL/min/1.73 m²)**	**GFR methods**	**Statistics**	**Results**
(Odlind et al., 1985)	11	Nephrectomy and CKD	37 to 137	Cp of Cr and ^{125}It: samples at 180, 210 and 240 min + BM correction	Wilcoxon Ratio It/Cr BAr It-Cr	It higher (p<0.001) 1.13 12±7.5
(Lewis et al., 1989)	29	10 heart grafted 11 renal grafted 10 donors	10 to 117	Cu of Dt and Io (XRF): samples at 3 and 4 h after bolus	Correlation Regression Ratio BAr Dt-Io	0.89 Io=0.89Dt+6.5 1.08±0.06 -0.7±14.8
(Goates et al., 1990)	16	NA	21 to 156	Cu ^{125}It: Cu after bolus IV and infusion Cp of Dt: samples at 60 and 180 min+ BM correction	Correlation BAr Io-Dt	0.99 3.2±6.1
(Effersoe et al., 1990)	15	urography	22 to 110	Cp of Io (XRF), Cr and Dt : samples at 0, 10, 20, 30, 120, 180, 240 and 300 min	Regression Correlation BA : Cr-Io Dt-Io Cr-Dt	Io=0.97Dt-11 0.96 Io=1.01Cr+8 0.95 -10.8±7.9 -9.4±6.9 -0.7±10.4

(Gaspari et al., 1992)	19	CKD	7 to 148	Cp of Cr and It (HPLC): bolus IV and samples at 5, 10, 20, 30, 40, 50, 60, 90, 120, 180, 240, 300, 450 and 600 min	Correlation Regression BAr It-Cr	0.995 It=1.007Cr-0.303 -0.1±4.7
(Lundqvist et al., 1994)	31	Para or tetraplegic	±70 to 130	Cp of Cr and Io (XRF): samples à 180, 210, 240 and 270 minutes+ BM correction day 1 and 2	BA Cr-Io	Day 1 : +2.1±10.2 Day 2 : +0.9±5.9
(Galli et al., 1994)	50	NA	±15 to 160	Cp of Cr and Dt: samples at 60 and 180 min	Regression BA Dt-Cr	Dt=0.982Cr+3.2 1.91±6.1
(Sambataro et al., 1996)	17	Diabetic	7 to 105	Cu of Cr and It (HPLC)	Regression BAr It-Cr	It=0.979Cr-3.04 1.3±5
(Lundqvist et al., 1997)	77	Urography	±25 to 125	Cp of Cr and Io (XRF): samples at 180, and 240 or 270 min+ BM correction	Correlation Regression BA (Io-Cr)	0.918 Io=0.892Cr+6.28 2±9.2
(Brandstrom et al., 1998)	49	GFR>40	±40 to 125	Cp of Cr and Io (HPLC and XRF): samples at 150, 195 and 240 min + BM correction	Regression Correlation BA Cr-Io	XRF Io=1.03Cr-1.79 0.97 0.58±4.95 HPLC Io=1.05Cr-4.43 0.96 -0.16±6.17
(Pucci et al., 1998)	32	Diabetic	13 to 151	Cp of Cr and Io (HPLC): samples at 5, 10, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300 + 360 and 420 if creatinine>2 mg/dL + 1440 min if>5mg/dL	Regression Correlation BA Cr-Io	0.995 Io=0.978Cr+2.45 -0.6±3.6

Houlihan (Houlihan et al., 1999)	21	Diabetic	50 to 145	Cp of Dt and Io (XRF): samples at 120, 165 and 210 for Dt samples at 120, 150, 180, 210 and 240 min for Io + BM correction	Regression Correlation BA Io-Dt	Io=0.9938Dt+4.916 0.97 4.3±7.7
(Pucci et al., 2001)	41	Diabetic	29 to 150	Cp of Cr and Io (HPLC): samples at 5, 10, 15, 30, 60, 90, 120, 150, 180, 210, 240, 270, 300 + 360 and 420 if creatinine>2 mg/dL + 1440 min if>5mg/dL	Regression Correlation BA Cr-Io	Type 1 Io=0.978Cr+0.132 0.999 Type 2 0.987 Io=0.078Cr+2.352 BA :-0.42±3.69
Bird (Bird et al., 2009)	56 19	CKD healthy	±15 to 140	Cp of Cr and Io (XRF): samples at 20, 40, 60, 120, 180 and 240 min	BA Cr-Io	4±7.9

Table 6. studies comparing different reference methods (other than inulin), NA = not available, BA: Bland and Altman, BAr: Bland and Altman recalculated by us, BM: Brochner Mortensen,Cr: ^{51}Cr-EDTA, Dt: ^{99}Tc-DTPA, Io: iohexol, It: iothalamate, Cp: plasma clearance, Cu: urinary clearance, IC: constant infusion rate, IB: bolus injection, IV: intravenous, SC: subcutaneous, AUC: area under the curve, NS: not significant, HPLC: high pressure liquid chromatography, XRF: X ray fluorescence.

10. Conclusions and perspectives

In this chapter, we reviewed all the reference methods available in 2011 to measure GFR. Among these methods, inulin clearance can certainly be considered as the gold-standard because it is historically the first method used and because this marker is certainly the best characterized from a physiological point of view. However, inulin is expensive and commercial sources are limited (Gaspari et al., 1997). Due to its high molecular weight, there are doubts to use inulin in simplified plasma clearance (urinary clearances with constant infusion rate remain necessary but are very cumbersome). Measurement of plasma inulin is neither easy nor standardized. For all these reasons, the use of inulin is and will always be relatively marginal. In 2011, it is maybe time to move from the perfect physiological marker (inulin) to markers, maybe less perfect in the renal physiologic handling, but less costly, easier to use everywhere in the world and with a standardized measurement. From our point of view, iohexol is probably the best marker with the best balance between

physiological characteristics and practical advantages. Additional studies comparing references markers seem necessary in 2011. It seems also important to underline that GFR measurement is also subject to its own imprecision and to biological variation (Kwong et al., 2010). Therefore, it is illusionary to expect differences between different GFR methods of less than 10% (±2SD around the bias) and accuracy 10% over 85-90%. We must also keep these results in mind when we analyze the studies testing the performance of the creatinine-based equations (Kwong et al., 2010).

11. References

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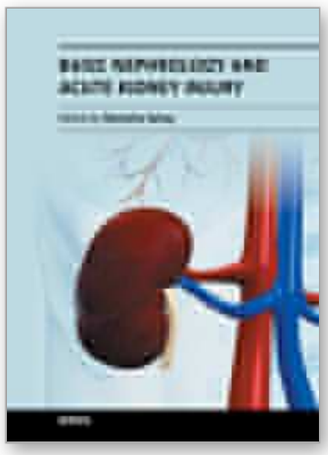

Basic Nephrology and Acute Kidney Injury

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The first section of the book covers the basics of nephrology and second section focuses on acute kidney injury. This easy to reference text examines the physiological and biochemical aspects of renal diseases - all in one convenient resource. Experts in the field discuss topics of increasing concern in nephrology including newer methods of assessing renal function. The field of acute kidney injury in nephrology is a rapidly evolving one with research translating into clinical guidelines and standards. This text brings together experts to provide an authoritative reference for management of AKI in various clinical settings. Pregnancy related AKI is an important entity which has also been discussed in detail. The recent advances in the field of critical care AKI have been incorporated as well and help the reader to update their knowledge.

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