



CKJ REVIEW

Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: Why to measure glomerular filtration rate with iohexol?

Pierre Delanaye¹, Toralf Melsom², Natalie Ebert³, Sten-Erik Bäck⁴, Christophe Mariat⁵, Etienne Cavalier⁶, Jonas Björk⁷, Anders Christensson⁸, Ulf Nyman⁹, Esteban Porrini¹⁰, Giuseppe Remuzzi^{11,12}, Piero Ruggenenti^{11,12}, Elke Schaeffner³, Inga Soveri¹³, Gunnar Sterner¹⁴, Bjørn Odvar Eriksen² and Flavio Gaspari¹⁵

¹Department of Nephrology, Dialysis and Transplantation, University of Liège Hospital (ULg CHU), 4000 Liège, Belgium, ²Metabolic and Renal Research Group, UiT The Arctic University of Norway and Section of Nephrology, University Hospital of North Norway, Tromsø, Norway, ³Charité University Medicine, Institute of Public Health, Berlin, Germany, ⁴Department of Clinical Chemistry, Skåne University Hospital, Lund, Sweden, ⁵Department of Nephrology, Dialysis, Transplantation and Hypertension, CHU Hôpital Nord, University Jean Monnet, PRES Université de LYON, Saint-Etienne, France, ⁶Department of Clinical Chemistry, University of Liège Hospital (ULg CHU), Liège, Belgium, ⁷Department of Occupational and Environmental Medicine, Lund University, Lund, Sweden, ⁸Department of Nephrology, Skåne University Hospital, Lund, Sweden, ⁹Department of Translational Medicine, Division of Medical Radiology, Skåne University Hospital, Malmö, Sweden, ¹⁰University of La Laguna, CIBICAN-ITB, Faculty of Medicine, Hospital Universitario de Canarias, Tenerife, Spain, ¹¹Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Istituto di Ricerche Farmacologiche Mario Negri, Centro Anna Maria Astori, Science and Technology Park Kilometro Rosso, Bergamo, Italy, ¹²Unit of Nephrology, Azienda Socio Sanitaria Territoriale (ASST) Ospedale Papa Giovanni XXIII, Bergamo, Italy, ¹³Department of Medical Sciences, Uppsala University, Uppsala, Sweden, ¹⁴Department of Nephrology, Skåne University Hospital, Malmö, Sweden and ¹⁵IRCCS - Istituto di Ricerche Farmacologiche 'Mario Negri', Centro di Ricerche Cliniche per le Malattie Rare 'Aldo e Cele Daccò', Ranica, Bergamo, Italy

Correspondence and offprint requests to: Pierre Delanaye; E-mail: pierre_delanaye@yahoo.fr

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Abstract

A reliable assessment of glomerular filtration rate (GFR) is of paramount importance in clinical practice as well as epidemiological and clinical research settings. It is recommended by Kidney Disease: Improving Global Outcomes guidelines in specific populations (anorectic, cirrhotic, obese, renal and non-renal transplant patients) where estimation equations are unreliable. Measured GFR is the only valuable test to confirm or refute the status of chronic kidney disease (CKD), to evaluate the slope of renal function decay over time, to assess the suitability of living kidney donors and for dosing of potentially toxic medication with a narrow therapeutic index. Abnormally elevated GFR or hyperfiltration in patients with diabetes or obesity can be correctly diagnosed only by measuring GFR. GFR measurement contributes to assessing the true CKD prevalence rate, avoiding discrepancies due to GFR estimation with different equations. Using measured GFR, successfully accomplished in large epidemiological studies, is the only way to study the potential link between decreased renal function and cardiovascular or total mortality, being sure that this association is not due to confounders, i.e. non-GFR determinants of biomarkers. In clinical research, it has been shown that measured GFR (or measured GFR slope) as a secondary endpoint as compared with estimated GFR detected subtle treatment effects and obtained these results with a comparatively smaller sample size than trials choosing estimated GFR. Measuring GFR by iohexol has several advantages: simplicity, low cost, stability and low interlaboratory variation. Iohexol plasma clearance represents the best chance for implementing a standardized GFR measurement protocol applicable worldwide both in clinical practice and in research.

Key words: glomerular filtration rate, iohexol

Introduction

The first part of this review article focused on practical and technical aspects of iohexol plasma clearance [i.e. plasma iohexol analysis and clearance investigation procedures (number of samples and timing)]. In this second part, we focus on the indication of glomerular filtration rate (GFR) measurements in clinical practice as well as in epidemiological and clinical research.

Role of iohexol in clinical practice

It is beyond the scope of this article to review and summarize all clinical settings where measured GFR is recommended [1–3]. Briefly, and as stated in the Kidney Disease: Improving Global Outcomes guidelines [4], additional tests for GFR assessment are needed in specific populations where creatinine-based equations are unreliable, because serum creatinine is largely dependent on muscle mass [5]. Cystatin C can be used as an alternative test but is influenced by other non-GFR-related factors such as obesity, thyroid function and cardiovascular risk factors [6–11]. Thus, measured GFR is recommended for specific patients or subjects with an abnormal muscle mass or body composition, such as anorectic, cirrhotic, obese and renal and non-renal transplant patients [2, 12–17]. If, in daily practice, repeated measurements of GFR in these patient groups are infeasible, at least one GFR measurement will indicate the relationship between serum creatinine (or plasma cystatin C) concentrations and the ‘true’ GFR level. Measured GFR is the only available test to certify GFR levels, and according to the GFR level, to confirm or refute chronic kidney disease (CKD) status. Also, in longitudinal studies, several authors have described the limitations of estimated GFR (eGFR) to adequately assess the true decline in measured GFR [17–21].

Another clear indication for GFR measurement applies when an exact value of GFR is required [4]. The two typical examples are the measurement of GFR before potential living kidney donation or before prescribing a potentially toxic hydrosoluble drug with a narrow therapeutic window, e.g. aminoglycosides or cisplatin [1, 22–24]. Finally, without measured GFR, one pathological condition in nephrology would remain undetected. Abnormally elevated GFR, or hyperfiltration, has been established as an initial pathophysiological step to CKD in patients with diabetes and may also be of importance in common conditions such as

obesity, metabolic syndrome and prediabetes [25, 26]. Importantly, data suggest that treating hyperfiltration with angiotensin-converting enzyme inhibitors could be beneficial [27, 28]. However, it is well accepted that the condition of hyperfiltration can only be correctly detected with measured GFR, as all eGFR equations perform poorly in this specific, highly relevant pathological state [16, 17, 22].

Role of iohexol in clinical research

The role of measured GFR in both clinical epidemiology and clinical research is another important objective of this review.

Clinical epidemiology

Measuring GFR is also feasible in large epidemiological studies. For example, the CRIC (Chronic Renal Insufficiency Cohort), BIS (Berlin Initiative Study), AGES-II (Age, Gene/Environment Susceptibility) and RENIS (Renal Iohexol Clearance Survey) studies are four large observational cohorts with GFR measured by iohexol (CRIC) and iohexol (BIS, AGES-II and RENIS) [29–33]. The RENIS study is interesting since it is a European observational study with a representative sample of the general population in Tromsø, Norway, and GFR measurement has been repeated in the follow-up [26, 31]. The BIS study also measured GFR with iohexol plasma clearance in a large population-based cohort of older patients (mean age 79 years), which also proves the feasibility of performing measured GFR in this fragile age group [32, 34].

Data from numerous epidemiological studies show high but different prevalence rates of CKD in the general population. Moreover, CKD status is associated with mortality, especially cardiovascular mortality [8, 35–38]. However, the vast majority of these epidemiological studies are based on eGFR. It is known that all eGFR equations, based on creatinine and/or cystatin C, have limitations, particularly at high GFR levels [2, 39, 40]. Also, it has been shown that the prevalence of CKD is largely dependent on the equation [Modification of Diet in Renal Disease (MDRD) versus Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) versus Cockcroft–Gault] and biomarker used (creatinine versus cystatin C) [37, 41]. The major limitations of GFR estimations include issues in calibration of the biomarkers [42], different performance of the estimators according to age [43]

and lack of precision in high GFR values [2]. Even if data are limited, we cannot exclude that the prevalence of CKD in the general population, defined as $\text{GFR} < 60 \text{ mL/min/1.73 m}^2$, may be much lower with measured GFR compared with eGFR [31].

The higher risk of mortality associated with decreased GFR is another hot topic in clinical epidemiology [4, 36, 44]. Once again, associations between cardiovascular risk and CKD have been described with eGFR in the vast majority of patients. This fact could lead to confusion or false-positive associations, as eGFR may include variables such as gender, ethnicity, weight and age that are *per se* risk factors for cardiovascular morbidity and mortality and often referred to as 'non-GFR determinant'. The different weights of these factors in different equations might explain differences in the magnitude of association between cardiovascular outcomes and eGFR [45, 46]. Some authors have suggested a closer association between mortality and the Cockcroft–Gault equation compared with the MDRD study equation [45]. The fact that age is handled differently mathematically in the two equations could explain the discrepancies. The association between eGFR and mortality also varies with the biomarker considered. For cystatin C–versus creatinine-based equations, an increased hazard ratio for all-cause mortality was found for $\text{eGFR} < 85 \text{ mL/min/1.73 m}^2$ based on cystatin C, but when the eGFR was based on creatinine, the hazard ratio increased when $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ [47, 48].

Also, the classical association between the MDRD (or CKD-EPI) equation and mortality is U-shaped, with a higher mortality at high GFR values. This U-shaped association has not been found when cystatin C–based equations were investigated [36, 44, 49]. Overall, it is virtually impossible to know whether this U-shaped association is (i) a mathematical artefact, (ii) due to hyperfiltration (true elevated GFR) or (iii) due to sarcopenia and falsely low creatinine concentrations. Measured GFR has recently been discredited because it was insufficiently able to predict mortality compared with creatinine- or cystatin C–based equations [50]. Using measured GFR is, however, the only way to really study the potential link between decreased renal function and cardiovascular or total mortality, being sure that this association is not due to confounders, i.e. non-GFR determinants of biomarkers [muscle mass (serum creatinine), traditional cardiovascular risk factors (cystatin C) and non-traditional cardiovascular risk factors (creatinine and cystatin C)] [6, 7, 9, 51–53].

Clinical research

In nephrological trials, the classic clinical endpoints are mortality, end-stage renal disease or doubling of serum creatinine. However, these are relatively rare events developing over a long period of time, especially in low-risk patients. For this reason, clinical studies in nephrology require large sample sizes and a long follow-up time. Therefore, several authors proposed so-called surrogate markers instead of 'true' endpoints. GFR and albuminuria are the two most reliable surrogate markers to use [54]. However, eGFR lacks precision, especially at high GFR levels, and is, as mentioned above, not only dependent on GFR, but also on non-GFR determinants included in the equations. Moreover, several authors have described large discrepancies between slopes based on measured GFR versus eGFR [17–21]. The majority of these studies have shown that the decline in measured GFR is underestimated by eGFR. For these reasons, detection of potential differences in GFR slopes between two groups (e.g. one treated with active therapy and the other with placebo) requires larger sample sizes with eGFR than with measured GFR. An example is the trial of belatacept in renal transplant patients,

which showed a benefit of belatacept therapy when measured GFR was used, whereas a non-significant difference was observed with eGFR [55]. Importantly, the number of patients with measured GFR in the three groups was relatively small ($n = 32$ in the intensive belatacept group, $n = 37$ in the less intensive group and $n = 27$ in the cyclosporine group). Another illustrative example is the ALADIN (A Long-Acting Somatostatin on Disease Progression in Nephropathy due to Autosomal Dominant Polycystic Kidney Disease) trial in which the efficacy of somatostatin in polycystic kidney disease was studied. The slope of measured GFR was an important secondary endpoint. The authors were able to show that the slope of measured GFR was significantly different between treatment groups ($n = 36$ and 34 in the active and placebo arm, respectively) [56]. Such important results would have been missed if only eGFR had been used [21]. A similar trial with similar results was published using tolvaptan. The authors also showed a significantly different slope in eGFR after 3 years of follow-up between the tolvaptan and placebo groups, but had to include 1445 patients to detect this significant difference [57].

The lack of precision of eGFR is also particularly important in the context of drug dosage adaptation. It is beyond the scope of this article to discuss all the limitations of equations in this context [58]. Due to these limitations, the European Medicines Agency now recommends that 'a method accurately measuring GFR using an exogenous marker [should be] used in pharmacokinetic studies in subjects with decreased renal function' [59].

Conclusions

In conclusion, both in clinical practice and in research, measured GFR is considered too rarely. Nephrology is certainly the only discipline where a gold standard measurement is so uncommonly used. Measuring GFR by iohexol has several advantages: simplicity, low cost, stability and low interlaboratory variation. We are convinced that iohexol plasma clearance is the best chance to implement a standardized GFR measurement protocol that would be applicable worldwide both in clinical practice and in research. Even if it is not as perfect as the 'gold standard' method (inulin urinary clearance), iohexol plasma clearance appears to provide the best compromise between physiology, reliability and feasibility.

Conflict of interest statement

None declared.

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