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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?

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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 confute 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 wellas 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 muscule 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 iothalamate (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 GFR <60 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 eGFR <85 mL/min/1.73 m^2 based on cystatin C, but when the eGFR was based on creatinine, the hazard ratio increased when eGFR was <60 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.

References

1. Stevens LA, Levey AS. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol* 2009; 20: 2305–2313
2. Delanaye P, Mariat C. The applicability of eGFR equations to different populations. *Nat Rev Nephrol* 2013; 9: 513–522
3. Gaspari F, Perico N, Remuzzi G. Measurement of glomerular filtration rate. *Kidney Int Suppl* 1997; 63: S151–S154
4. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. *Kidney Int Suppl* 2013; 3: 1–150
5. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. *Clin Chem* 1992; 38: 1933–1953
6. Schei J, Stefansson VTN, Mathisen UD *et al*. Residual associations of inflammatory markers with eGFR after accounting for measured GFR in a community-based cohort without CKD. *Clin J Am Soc Nephrol* 2016; 11: 2802–2886

7. Knight EL, Verhave JC, Spiegelman D *et al*. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. *Kidney Int* 2004; 65: 1416–1421
8. Coresh J, Selvin E, Stevens LA *et al*. Prevalence of chronic kidney disease in the United States. *JAMA* 2007; 298: 2038–2047
9. Stevens LA, Schmid CH, Greene T *et al*. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009; 75: 652–660
10. Naour N, Fellahi S, Renucci JF *et al*. Potential contribution of adipose tissue to elevated serum cystatin C in human obesity. *Obesity (Silver Spring)* 2009; 17: 2121–2126
11. Fricker M, Wiesli P, Brandle M *et al*. Impact of thyroid dysfunction on serum cystatin C. *Kidney Int* 2003; 63: 1944–1947
12. Delanaye P, Cavalier E, Radermecker RP *et al*. Cystatin C or creatinine for detection of stage 3 chronic kidney disease in anorexia nervosa. *Nephron Clin Pract* 2008; 110: c158–c163
13. Luis-Lima S, Marrero-Miranda D, González-Rinne A *et al*. Estimated glomerular filtration rate in renal transplantation: the nephrologist in the mist. *Transplantation* 2015; 99: 2625–2633
14. Masson I, Flamant M, Maillard N *et al*. MDRD versus CKD-EPI equation to estimate glomerular filtration rate in kidney transplant recipients. *Transplantation* 2013; 95: 1211–1217
15. Beben T, Rifkin DE. GFR estimating equations and liver disease. *Adv Chronic Kidney Dis* 2015; 22: 337–342
16. Bouquegneau A, Vidal-Petiot E, Vrtovsnik F *et al*. Modification of Diet in Renal Disease versus Chronic Kidney Disease Epidemiology Collaboration equation to estimate glomerular filtration rate in obese patients. *Nephrol Dial Transplant* 2013; 28: iv122–iv130
17. Gaspari F, Ruggenenti P, Porrini E *et al*. The GFR and GFR decline cannot be accurately estimated in type 2 diabetics. *Kidney Int* 2013; 84: 164–173
18. Rule AD, Torres VE, Chapman AB *et al*. Comparison of methods for determining renal function decline in early autosomal dominant polycystic kidney disease: the consortium of radiologic imaging studies of polycystic kidney disease cohort. *J Am Soc Nephrol* 2006; 17: 854–862
19. Xie Y, Bowe B, Xian H *et al*. Rate of kidney function decline and risk of hospitalizations in stage 3A CKD. *Clin J Am Soc Nephrol* 2015; 10: 1946–1955
20. Gera M, Slezak JM, Rule AD *et al*. Assessment of changes in kidney allograft function using creatinine-based estimates of glomerular filtration rate. *Am J Transplant* 2007; 7: 880–887
21. Ruggenenti P, Gaspari F, Cannata A *et al*. Measuring and estimating GFR and treatment effect in ADPKD patients: results and implications of a longitudinal cohort study. *PLoS One* 2012; 7: e32533
22. Bouquegneau A, Vidal-Petiot E, Moranne O *et al*. Creatinine-based equations for the adjustment of drug dosage in an obese population. *Br J Clin Pharmacol* 2016; 81: 349–361
23. Pai MP, Nafziger AN, Bertino JS Jr. Simplified estimation of aminoglycoside pharmacokinetics in underweight and obese adult patients. *Antimicrob Agents Chemother* 2011; 55: 4006–4011
24. Dooley MJ, Poole SG, Rischin D *et al*. Carboplatin dosing: gender bias and inaccurate estimates of glomerular filtration rate. *Eur J Cancer* 2002; 38: 44–51
25. Chagnac A, Weinstein T, Korzets A *et al*. Glomerular hemodynamics in severe obesity. *Am J Physiol Renal Physiol* 2000; 278: F817–F822
26. Melsom T, Schei J, Stefansson VTN *et al*. Prediabetes and risk of glomerular hyperfiltration and albuminuria in the general nondiabetic population: a prospective cohort study. *Am J Kidney Dis* 2016; 67: 841–850
27. Ruggenenti P, Porrini EL, Gaspari F *et al*. Glomerular hyperfiltration and renal disease progression in type 2 diabetes. *Diabetes Care* 2012; 35: 2061–2068
28. Brenner BM, Lawler EV, Mackenzie HS. The hyperfiltration theory: a paradigm shift in nephrology. *Kidney Int* 1996; 49: 1774–1777
29. Denker M, Boyle S, Anderson AH *et al*. Chronic Renal Insufficiency Cohort Study (CRIC): overview and summary of selected findings. *Clin J Am Soc Nephrol* 2015; 10: 2073–2083
30. Eriksen BO, Melsom T, Mathisen UD *et al*. GFR normalized to total body water allows comparisons across genders and body sizes. *J Am Soc Nephrol* 2011; 22: 1517–1525
31. Eriksen BO, Mathisen UD, Melsom T *et al*. Cystatin C is not a better estimator of GFR than plasma creatinine in the general population. *Kidney Int* 2010; 78: 1305–1311
32. Schaeffner ES, Ebert N, Delanaye P *et al*. Two novel equations to estimate kidney function in persons aged 70 years or older. *Ann Intern Med* 2012; 157: 471–481
33. Inker LA, Okparavero A, Tighiouart H *et al*. Midlife blood pressure and late-life GFR and albuminuria: an elderly general population cohort. *Am J Kidney Dis* 2015; 66: 240–248
34. Schaeffner ES, van der Giet M, Gaedeke J *et al*. The Berlin initiative study: the methodology of exploring kidney function in the elderly by combining a longitudinal and cross-sectional approach. *Eur J Epidemiol* 2010; 25: 203–210
35. Hallan SI, Vikse BE. Relationship between chronic kidney disease prevalence and end-stage renal disease risk. *Curr Opin Nephrol Hypertens* 2008; 17: 286–291
36. Matsushita K, van der Velde M, Astor BC *et al*. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. *Lancet* 2010; 375: 2073–2081
37. Brück K, Jager KJ, Dounousi E *et al*. Methodology used in studies reporting chronic kidney disease prevalence: a systematic literature review. *Nephrol Dial Transplant* 2015; 30: iv6–iv16
38. Brück K, Stel VS, Gambaro G *et al*. CKD prevalence varies across the European general population. *J Am Soc Nephrol* 2016; 27: 2135–2147
39. Eriksen BO, Tomtum J, Ingebretsen OC. Predictors of declining glomerular filtration rate in a population-based chronic kidney disease cohort. *Nephron Clin Pract* 2010; 115: c41–c50
40. Levey AS, Stevens LA, Schmid CH *et al*. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; 150: 604–612
41. Delanaye P, Cavalier E, Moranne O *et al*. Creatinine- or cystatin C-based equations to estimate glomerular filtration in the general population: impact on the epidemiology of chronic kidney disease. *BMC Nephrol* 2013; 14: 57
42. Coresh J, Eknoyan G, Levey AS. Estimating the prevalence of low glomerular filtration rate requires attention to the creatinine assay calibration. *J Am Soc Nephrol* 2002; 13: 2811–2812
43. Pottel H, Hoste L, Dubourg L *et al*. A new estimating glomerular filtration rate equation for the full age spectrum. *Nephrol Dial Transplant* 2016; 31: 798–806
44. Hallan SI, Matsushita K, Sang Y *et al*. Age and association of kidney measures with mortality and end-stage renal disease. *JAMA* 2012; 308: 2349
45. Sederholm Lawesson S, Alfredsson J, Szummer K *et al*. Prevalence and prognostic impact of chronic kidney disease in

STEMI from a gender perspective: data from the SWEDEHEART register, a large Swedish prospective cohort. *BMJ Open* 2015; 5: e008188
46. Matsushita K, Mahmoodi BK, Woodward M *et al*. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012; 307: 1941–1951
47. Shlipak MG, Matsushita K, Arnlov J *et al*. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med* 2013; 369: 932–943
48. Delanaye P, Glassock RJ, Pottel H *et al*. An age-calibrated definition of chronic kidney disease: rationale and benefits. *Clin Biochem Rev* 2016; 37: 17–26
49. Shlipak MG, Katz R, Sarnak MJ *et al*. Cystatin C and prognosis for cardiovascular and kidney outcomes in elderly persons without chronic kidney disease. *Ann Intern Med* 2006; 145: 237–246
50. Hsu CY, Propert K, Xie D *et al*. Measured GFR does not outperform estimated GFR in predicting CKD-related complications. *J Am Soc Nephrol* 2011; 22: 1931–1937
51. Melsom T, Fuskevåg OM, Mathisen UD *et al*. Estimated GFR is biased by non-traditional cardiovascular risk factors. *Am J Nephrol* 2015; 41: 7–15
52. Mathisen UD, Melsom T, Ingebretsen OC *et al*. Estimated GFR associates with cardiovascular risk factors independently of measured GFR. *J Am Soc Nephrol* 2011; 22: 927–937
53. Rule AD, Bailey KR, Lieske JC *et al*. Estimating the glomerular filtration rate from serum creatinine is better than from cystatin C for evaluating risk factors associated with chronic kidney disease. *Kidney Int* 2013; 83: 1169–1176
54. Coresh J, Turin TC, Matsushita K *et al*. Decline in estimated glomerular filtration rate and subsequent risk of end-stage renal disease and mortality. *JAMA* 2014; 311: 2518–2531
55. Vincenti F, Larsen C, Durrbach A *et al*. Costimulation blockade with belatacept in renal transplantation. *N Engl J Med* 2005; 353: 770–781
56. Caroli A, Perico N, Perna A *et al*. Effect of longacting somatostatin analogue on kidney and cyst growth in autosomal dominant polycystic kidney disease (ALADIN): a randomised, placebo-controlled, multicentre trial. *Lancet* 2013; 382: 1485–1495
57. Torres VE, Chapman AB, Devuyst O *et al*. Tolvaptan in patients with autosomal dominant polycystic kidney disease. *N Engl J Med* 2012; 367: 2407–2418
58. Park EJ, Wu K, Mi Z *et al*. A systematic comparison of cockcroft-gault and modification of diet in renal disease equations for classification of kidney dysfunction and dosage adjustment. *Ann Pharmacother* 2012; 46: 1174–1187
59. EMA. Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/02/WC500162133.pdf. 2014

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