Measured GFR in Routine Clinical Practice—The Promise of Dried Blood Spots

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Accurate determination of glomerular filtration rate (GFR) is crucial for the diagnosis of kidney disease. Estimated GFR (eGFR) calculated by serum creatinine and/or cystatin C is a mainstay in clinical practice and epidemiologic research but lacks precision and accuracy until GFR <60 mL/min/1.73 m^2. Furthermore, eGFR may not precisely and accurately represent changes in GFR longitudinally. The lack of precision and accuracy is of concern in populations at high risk for kidney disease, as the dissociation between changes in eGFR and GFR may lead to missed diagnoses of early kidney disease. Therefore, improved methods to quantify GFR are needed. Whereas direct measures of GFR have been too cumbersome for screening and ambulatory care, a practical method of measuring GFR by iohexol clearance using dried capillary blood spots exists. In this review, we examine the current literature and data addressing GFR measurements by dried capillary blood spots and its potential application in high-risk groups.

Key Words: Glomerular Filtration Rate, Iohexol, Iothalamate, Dried blood spots

INTRODUCTION

Estimated or measured glomerular filtration rate (GFR) is an essential tool for health care providers taking care of patients at risk of kidney disease. Accurate ascertainment of GFR is crucial for the diagnosis of early kidney disease, which may manifest as hyperfiltration (GFR greater than 2 standard deviations above the mean GFR in normal, healthy individuals)[1] or rapid GFR decline (annual GFR loss greater of >3 mL/min/1.73 m^2).[2] Additionally, an accurate GFR is critical for the diagnosis of CKD (GFR <60 mL/min/1.73 m^2).[3]

GFR can be directly measured by the clearance of exogenous filtration markers (e.g., inulin and iohexol) or calculated indirectly by the clearance of endogenous filtration markers (e.g., serum creatinine and cystatin C). Estimated GFR (eGFR) calculated by serum creatinine and/or cystatin C remains the most widely used method in clinical practice and epidemiologic research. Despite advances in GFR assessment, current estimates of GFR by endogenous filtration markers lack precision (i.e., too much random error) and accuracy (i.e., too much systematic error) before CKD stage 3 (GFR < 60 mL/min/1.73 m^2).[4] In addition, longitudinal changes in eGFR may not reflect changes in measured GFR (mGFR).[5,6]

The lack of precision and accuracy is of concern in populations at high risk for kidney disease, as the dissociation between changes in eGFR and GFR represents a missed opportunity to diagnose early kidney disease. Accordingly, there is a need for improved screening methods to identify subtle changes in kidney function. While direct measures of GFR have been too cumbersome for screening and ambulatory care, a practical method of measuring GFR by iohexol clearance using dried capillary blood spots (DBS) exists.[7,8] In 2006, Niculescu-Duvaz and colleagues[7] demonstrated that iohexol clearance measured on DBS on filter paper provided GFR measurements comparable to the iohexol plasma clearance but at a significantly reduced time and cost. We demonstrated that GFR by iohexol clearance using DBS on filter paper measured GFR accurately in adults[9] and was feasible in an outpatient setting with adolescents[10] with type 1 diabetes. While this method is ideally suited for patients with diabetes who routinely prick their fingers to obtain glucose readings, we believe this method could also be translated to screening for early kidney disease in other populations at high risk of stages of kidney disease. Examples include bone marrow transplant patients on immunotherapy, HIV patients on antiretroviral therapy (ART), pregnant women with CKD and obesity, and patients for whom GFR status has implications for medication dosing. In this review, we examine the current literature and data addressing GFR measurements by DBS and its potential application in high-risk groups.

Measurement of Glomerular Filtration Rate

GFR is measured as the clearance of exogenous filtration markers that are eliminated exclusively by glomerular filtration, including inulin, iohexol, iothalamate, technetium 99m diethylenetriamine pentaacetic acid, and chromium 51-ethylenediamine tetraacetic acid. A major shortcoming of plasma clearance is the need for patients to remain inpatient/in-clinic for several hours for repeated blood collections to calculate the clearance curve accurately GFR measurements, by plasma clearance techniques, therefore remain impractical and expensive with common methodologies (e.g., iohexol or inulin by plasma clearance or nuclear kidney scans) and are not routinely

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performed in clinical practice or large-scale clinical research.

Consequently, GFR is typically estimated by endogenous filtration markers (i.e., serum creatinine and/or cystatin C). Although estimated GFR is sufficient for clinical decision making in many circumstances, particularly when GFR is < 60 mL/min/1.73 m^2,[11] patients at risk of early kidney disease when GFR is normal-to-elevated would benefit from having their GFR measured using more accurate and precise techniques. The early diagnosis of declining kidney function may be important due to the potential for early interventions aimed at delaying the progression of kidney disease. Early intervention is one rationale for the Preventing Early Renal Loss (PERL) study in which change in GFR measured by iohexol is the study end point.[12] Therefore, to diagnose early kidney disease, accurate and precise diagnostic tools applied in the clinical setting are necessary.

Several methods exist to measure GFR including inulin, which has been used for decades as a gold standard measure of GFR. However, inulin is not widely available, is difficult to measure, and requires either collection of urine or constant infusion for best results—both of which add significant difficulties for widespread practice.[13,14] Several radioisotopes exist, such as ^{99m}Tc-DTPA, chromium 51-ethylenediamine tetraacetic acid, and ^{125}Iothalamate, but as radioisotopes their use outside of research investigations is problematic due to logistics, cost, and exposure to radiation, especially in asymptomatic young adults and/or adolescents. In contrast, iohexol and nonradioactive iothalamate are nonionic, low osmolar contrast agents that are not absorbed, metabolized, or secreted by the kidney. Low toxicity is reported in radiology practice (contrast x-rays) for iohexol in which doses that are 10-50 times higher than for GFR determination are used.[13,14] Our institutions have safely measured GFR by iohexol clearance over 1000 times without safety issues in the Prevent Early Renal Loss (PERL) study.[12] In fact, for over 20 years, publications have argued that iohexol is a gold standard measure of GFR.[15] The Advanced Research and Diagnostic Laboratory at University of Minnesota has successfully assayed iohexol to determine GFR in 2226 research participants from 2011 to 2016.

CLINICAL SUMMARY

- Estimates of GFR by serum creatinine and cystatin C are inaccurate at normal to elevated GFR range.
- GFR by iohexol and iothalamate clearance in dried blood spots provides a practical and accurate method to measure GFR.

MEASURED GLOMERULAR FILTRATION RATE BY DRIED BLOOD SPOTS

Measuring GFR by iohexol clearance using DBS is practical and feasible, and studies in people with and without diabetes mellitus demonstrate that iohexol clearance using DBS provides GFR measurements comparable to iohexol plasma clearance but at a significantly reduced patient and staff time.[7,8,10] GFR measured in DBS (GFR-DBS) was comparable to GFR plasma clearance of iohexol and more accurate, precise and less biased than eGFR by CKD-EPI creatinine, CKD-EPI cystatin C, and CKD-EPI creatinine-cystatin C in adults with type 1 diabetes,[9] similar to previous studies[7,8] (Fig. 1). Additionally, GFR-DBS offers a more convenient and less biased approach to quantify GFR, as the bias in the GFR-DBS measurements (2 or 5 spots) compared to GFR plasma iohexol was minimal and similar to that previously reported in nondiabetic subjects.[7,8] Better methods to measure GFR would more effectively detect early GFR decline and reduce both false positive and negative results of GFR screening compared to current eGFR methods. Recently, the American Diabetes Association recommended annual estimation of GFR in adolescents with diabetes.[16-19] Feasibility of translating the GFR-DBS method to the ambulatory setting was also demonstrated in a small sample of adolescents with type 1 diabetes (T1D).[10] We demonstrated less variability of GFR-DBS compared to eGFR by Bouvet and Schwartz in adolescents with type 1 diabetes.[10] All adolescent participants agreed or strongly agreed that the iohexol injection and DBS collection were preferable to an overnight urine sample.[10] The multicenter PERL Study is in the process of validating the GFR-DBS method in adults with type 1 diabetes.

Whereas the GFR-DBS method is ideally suited for patients with diabetes mellitus who routinely prick their fingers to obtain glucose measurements, GFR-DBS is an easily adapted methodology with promise for wide applicability to research and clinical practice in populations at high risk of kidney disease. For example, this method was recently applied in men with or at risk for HIV infection to assess GFR.[20]

GFR-DBS by iohexol clearance could be incorporated into current clinical research or annual screening tests by placement of a peripheral IV for blood sampling followed by injection of iohexol and removal of the IV prior to a regularly scheduled clinic visit. This would significantly reduce the time required for a standard iohexol GFR study from 4-5 hours. Self-collection of DBS could be performed as an outpatient, and the filter paper could then be mailed back to the laboratory.[8,10] The relative simplicity of the GFR-DBS method and superior results compared to eGFR suggests that this or similar methodology may improve upon current practices used to ascertain GFR, which are either not feasible or effective in identifying early kidney function loss clinically. Figure 2 illustrates the steps we employed in our studies to measure GFR by the GFR-DBS methodology. Another potential advantage of GFR-DBS is the low cost—iohexol (approximately $20.00 per 10 mL vial of 300 mg/mL iohexol), filter paper to collect DBS, and shipping and handling of filter paper are all inexpensive. However, high throughput assays at certified clinical laboratories must be developed to permit