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Monitoring residual kidney function in haemodialysis patients using timed urine collections: validation of the use of estimated blood results to calculate GFR

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Abstract

Objective: With growing recognition of the benefits of preserving residual kidney function (RKF) and use of incremental treatment regimes, the incentive to measure residual clearance in haemodialysis patients is increasing. Interdialytic urine collections used to monitor RKF in research studies are considered impractical in routine care, partly due to the requirement for blood samples before and after the collection. Plasma solute levels can be estimated if patients are in 'steady state', where urea and creatinine concentrations increase at a constant rate between dialysis sessions and are reduced by a constant ratio at each session. Validation of the steady state assumption would allow development of simplified protocols for urine collections in HD patients.

Approach: Equations were derived for estimating plasma urea and creatinine at the start or end of the interdialytic interval for patients in steady state. Data collected during the BISTRO study was used to assess the agreement between measured and estimated plasma levels and the effect of using estimated levels on the calculated glomerular filtration rate (GFR).

Main results: The mean difference between GFR calculated with estimated plasma levels for the HD session after the collection and a full set of measured levels was 2.0% (95% limits of agreement -10.7% to +14.7%, N = 316). Where plasma levels for the session before the collection were estimated, the mean difference was 1.2% (limits of agreement -10.3% to +7.9%, N = 275).

Significance: Using estimated levels for one session led to a clinically significant difference in the calculated GFR for less than 3% of the collections studied. This indicates that the steady state assumption can be used to estimate solute levels when determining GFR from timed urine collections. A pragmatic approach to monitoring RKF in HD would be for patients to collect for approximately 24 hours before routine bloods are taken.

Introduction

Evidence of the benefits of preserved residual kidney function (RKF) in people on dialysis has been accruing for some years. The importance of RKF was first recognised in those treated with peritoneal dialysis, (PD), most notably in the Canada-USA study[1] where survival was 36% higher for each increment of 250 mL in urine volume, but subsequent studies have found similar benefits in the haemodialysis (HD) population. The Netherlands Cooperative Study of Adequate Dialysis (NECOSAD-2) observed that mortality was up to 17 times higher for anuric HD patients than those with measurable RKF, and more recently a US study found that a faster decline in RKF loss during the first year of HD was associated with increased risk of mortality.[2,3] When routinely measured, the time for which clinically significant RKF can be maintained in HD patients has been shown to be comparable with those treated with PD.[4] Other advantages of preserved RKF include improved wellbeing, better quality of life[5] and the reduced need to remove high fluid volumes during dialysis sessions with the associated risks of intra-dialytic hypotension and cardiac stunning.[6]

Although HD guidelines do now allow dialysis dose to be adjusted if patients have sufficient renal clearance, it is still common practice for HD to be initiated at 'full-dose', typically 12 hours/week in three sessions. An important barrier to a more individualised care in haemodialysis patients is that RKF is often not monitored in HD patients.[7] While timed urine collections are carried out routinely in PD patients to measure RKF, they appear to be widely considered as impractical or inaccurate in HD patients, in part due to the cycling of plasma solute levels necessitating the taking of multiple blood samples. As well as impeding the implementation of incremental haemodialysis and the best use of resources, it is likely that this has hindered the conduct of research into interventions to help maintain RKF in HD patients.

Fluid depletion is known to accelerate loss of RKF, so interventions to improve fluid assessment could lead to better preservation of residual function. The BISTRO study (Bio-Impedance Spectroscopy to maintain Renal Output) was a randomized, controlled trial designed to determine whether using bioimpedance technology in setting the target post-dialysis weight can slow the loss of RKF in incident HD patients [Protocol: BMC Nephrol 2017]. [8] Although the primary outcome was time to anuria, of equal importance was the rate of decline of RKF, calculated as a glomerular filtration rate (GFR). The BISTRO protocol involved up to 15 GFR measurements per patient, each requiring a timed interdialytic urine collection and a set of blood samples from which to calculate the average plasma solute levels during the collection interval. This study provided the opportunity to evaluate the use of estimated plasma levels to calculate GFR.

Methods

Determination of residual GFR

In dialysis patients, GFR is usually calculated from the mean of the renal urea and creatinine clearances (K_rU and K_rC), normalised to a body surface area (BSA) of 1.73 m^2:

$$GFR = \left(\frac{K_rU + K_rC}{2}\right) \times \frac{1.73}{BSA}\ mL/min/1.73m^2 \quad (1)$$

The renal clearance for a solute from a timed urine collection is calculated using:

$$K_r = \frac{C_{urine} \times V_{urine}}{C_{p\_TAC} \times T_{urine}}\ mL/min \quad (2)$$

where C_{urine} is the concentration of the solute in the urine and C_{p_TAC} is the time-averaged concentration of the solute in the plasma during the collection. All concentrations are in mmol/L. V_{urine} and T_{urine} are the volume and duration of the timed urine collection (in mL and minutes respectively).

If a linear increase in solute concentration is assumed, C_{p_TAC} is simply the concentration at the midpoint of the collection. For a full interdialytic urine collection, C_{p_TAC} is the mean of the concentration of the solute at the end of session before the collection (C_{reb}) and the concentration at the start of the next session ($C_{preNext}$).

$$C_{p\_TAC} = \frac{C_{reb} + C_{preNext}}{2} \quad (3)$$

Pre- and post-dialysis plasma levels (C_{pre} and C_{post}) are required for the session before the collection to allow correction for rebound using the Tattersall formula[9]:

$$C_{reb} = C_{pre} \times \left(\frac{C_{post}}{C_{pre}}\right)^{\frac{T_d}{T_d - T_p}} \quad (4)$$

Where T_d is the dialysis time in minutes and t_p is the 'patient clearance time' for the solute (35 and 66 minutes for urea and creatinine respectively). Figure 1 shows the concentration profile during the interdialytic interval.

The standard protocol used to collect the data needed to calculate K_rU and K_rC in BISTRO was a full interdialytic collection which required patients to collect their urine throughout the interdialytic interval. A modified protocol was introduced to accommodate patients, for example those working, who wished to remain in the study but were not able to carry out the urine collections as specified above. For a 'partial interdialytic' collection, the three blood samples were taken as for the full interdialytic collection but the patient collected urine for a minimum of 24 hours at the most convenient time during the

interval between the sessions. They recorded the time they emptied their bladder before starting the collection and the last time they collected their urine in the canister. The equation used to calculate C_{p_TAC} for a partial interdialytic collection is given in Supplementary Materials Appendix A.

Estimation of plasma solute levels using the steady state assumption

When a patient is in 'steady state' with stable muscle mass and dialysis prescription, plus reasonably consistent daily protein and fluid intake, their plasma urea and creatinine concentrations will be reduced by the same fraction (R_{HD}) during each HD session and will increase with a constant gradient (G_c) between sessions (see Figure 1). With a constant concentration gradient, plasma urea and creatinine throughout the week can be predicted using the pre- and post-dialysis levels from one session, as described in Supplementary Materials Appendix B. This approach to predicting solute levels is adapted from the UK Renal Association guideline published in 1997.[10] G_c combines the solute generation rate and distribution volume, allowing the weekly concentration profile to be modelled without the use of sophisticated computation[11]. If the steady state assumption is valid, allowing the use of estimated plasma levels, GFR can be calculated for a urine collection with blood samples taken at the session before or after.

Validation of the use of estimated compared to measured plasma levels in GFR calculations

An audit of the procedure to monitor GFR during the BISTRO study provided the data required to assess the effect of using estimated plasma levels in two scenarios. For scenario A, the pre- and post-dialysis plasma levels were measured for the session before the collection and used to estimate the pre-dialysis levels for the next session. For scenario B, pre-dialysis plasma levels were measured for the session after the collection and used, together with pre- and post-dialysis levels from another session, to estimate the post rebound levels for the last session. For each patient with sufficient data, GFR was calculated for one collection with a complete set of urine data and measured plasma levels (GFR_{meas}), then recalculated using the estimated plasma levels for each scenario. The equations are for a patient on thrice weekly dialysis. The derivation of these equations, and the equivalent equations for twice weekly dialysis, can be found in Supplementary Materials Appendix B.

Scenario A

For the scenario where pre- and post-dialysis plasma levels (C_{pre} and C_{post}) were available for the session before the collection, the pre-dialysis levels for the next session were estimated using:

$$C_{preNext} = C_{pre} \times R_{HD} + G_c \times T_{int} \quad (5)$$

Where T_{int} is the interdialytic interval during which the collection took place. R_{HD}, the concentration reduction fraction during HD, is the ratio of the post-dialysis solute concentration corrected for rebound (using equation 4) to C_{pre}:

$$R_{HD} = \frac{C_{reb}}{C_{pre}} = \left(\frac{C_{post}}{C_{pre}}\right)^{\frac{T_d}{T_d - T_p}} \quad (6)$$

For thrice weekly dialysis G_c, the concentration gradient, is calculated from C_{pre} and R_{HD} using:

$$G_c = \frac{C_{pre} \times \left(1 - {R_{HD}}^3\right)}{T_{int} \times {R_{HD}}^2 + T_{intNext} \times R_{HD} + T_{intLast}} \quad (7)$$

Where $T_{intNext}$ and $T_{intLast}$ are, respectively, the interdialytic intervals after and before the interval during which the collection took place. C_{p_TAC} and the clearances for urea and creatinine were then calculated with the estimated $C_{preNext}$ and used to determine GFR_{estA}.

Scenario B

For the scenario where the pre-dialysis plasma levels ($C_{preNext}$) were available for the session after the collection, the post-rebound levels for the last session were estimated using:

$$C_{reb} = C_{preNext} \times {R_{HD}}^3 + G_c \times T_{intNext} \times {R_{HD}}^2 + G_c \times T_{intLast} \times R_{HD} \quad (8)$$

As the BISTRO protocol did not include post-dialysis blood samples for the session after the collection, for scenario B, R_{HD} was determined using pre- and post-dialysis solute concentrations for the session before another collection, ideally with the same treatment time (a 'matched' session).

In scenario B, G_c is calculated from $C_{preNextl}$ and R_{HD} from the matched session using:

$$G_c = \frac{C_{preNext} \times \left(1 - {R_{HD}}^3\right)}{T_{intNext} \times {R_{HD}}^2 + T_{intLast} \times R_{HD} + T_{int}} \quad (9)$$

C_{p_TAC} and the clearances for urea and creatinine were then calculated with the estimated C_{reb} and used to determine GFR_{estB}.

Selection of the validation dataset

The BISTRO study was registered in April 2016, ISCCTN Number: 11342007) and ethics approval obtained through the UK Integrated Research Application System (Project number 20613).[8] The inclusion criteria for BISTRO are described in detail in the published protocol. Deliberately pragmatic, there were few exclusions, but these included being unable to give consent, expected survival <6 months, certain multiple limb amputations and an inability to manage study procedures, including urine collections. Patients were screened within 3 months of commencing haemodialysis. Those who passed at least 500 mL of urine in the short interdialytic period (or had a calculated GFR >3mL/min/1.73m^2, see

below) were randomised and asked to carry out urine collections every month for the first 3 months, then every other month until they left the study.

Where available, one admissible interdialytic urine collection was included in the validation dataset for each patient who had been screened for the BISTRO study prior to the quality control audit in 2019. To be admissible for the validation exercise, the collection had to have a complete set of urine data and measured plasma levels. Collections were excluded where there was clear indication of incorrect labelling of pre or post blood samples, transcription errors or sample dilution. The BISTRO protocol did not require documentation of problems or changes in the delivery of dialysis that meant the patient would not be in steady state, but where such issues were recorded the collection was excluded.

For each patient with at least one admissible collection, the one closest to month 3 of the study was selected. Month 3 was chosen as it was hoped that problems with collections would have been identified and addressed by then, and that a wide range of GFR would be covered. The last admissible collection was selected for patients who had not yet reached month 3 of the trial, including those who were screened but did not meet the entry criteria. If the collection for month 3 was inadmissible or not fully documented, the closest admissible collection before or after month 3 was selected.

The matched sessions required for scenario B were taken from the closest available collection to the month selected for the validation dataset with plausible pre- and post-dialysis plasma levels for the session before the collection and a similar dialysis time. If there were equally close collections from before and after the selected month, the earlier one was used.

Statistical analysis

Descriptive statistics (mean and standard deviation) were used to compare the measured and estimated solute levels and the parameters derived from them (time averaged plasma concentration, renal clearance and GFR). The Bland and Altman method[12], where differences and 95% confidence limits of agreement are expressed as percentages of the values, was also used to assess the agreement and between GFR calculated using the full set of measurements and with the estimated levels. A difference of less than 10% or 0.5 mL/min/1.73m^2, whichever is larger, was considered to be clinically acceptable for monitoring GFR.

Results

Data from 346 patients recruited by 29 of the 32 BISTRO participating centres from across the UK (England, Wales, Northern Ireland and Scotland) were audited for data quality checks in 2019. The QC data included patients who did not have sufficient residual function to be randomised when screened, as well as patients who had been followed up for more than a year.

316 patients (median age 63, range 23 to 89 years; 71% male; 91% white) had at least one admissible interdialytic collection when their data was submitted. The admissible collection closest to month 3 of the study was selected for the validation dataset, as described in the methods. This was the month 3 collection for 142 patients. An earlier collection was selected for 77 patients who had not reached month 3 (including 20 who were not randomised). The closest collection to month 3 was selected for 97 patients who did not have an admissible collection at month 3 due to issues with the urine collection (25), lack of documentation or records showing a disrupted dialysis regime (15), missing blood results (40) and implausible plasma levels (17). The majority of the collections included in the validation dataset (93%) were full interdialytic collections and 95% of these were carried out over 2 days. The remaining 7% were partial interdialytic collections. The matched session required for the simulation in scenario B was available for 275 of the 316 patients.

For the selected collections, the mean GFR_{meas} was 3.7 mL/min/1.73m^2 (range 0.1 to 20.0 mL/min/1.73m^2). Tables 1 and 2 show the mean and standard deviation for the solute levels, time averaged concentrations, renal clearances and GFR in the two scenarios. There was a tendency to underestimate the pre-dialysis concentration for the session after the urine collection and to overestimate the post-rebound concentration for the session before. The discrepancy was halved in the time averaged concentration as would be expected when the estimate is combined with a measured value.

For scenario A, the mean difference between GFR_{estA} and GFR_{meas} as a percentage of GFR_{meas} was 2.0% (95% limits of agreement -10.7% to +14.7%). For scenario B, the mean difference between GFR_{estB} and GFR_{meas} was -1.2% (limits of agreement -10.3% to +7.9%). Only 9 (3%) of GFR_{estA} and 6 (2%) of GFR_{estB} differed from GFR_{meas} by more than 0.5 mL/min/1.73m^2 (or 10% if this was larger).

Figures 2 and 3 show the correlation and differences between the GFRs calculated with estimated and measured blood levels for scenarios A and B. A subsequent review of the outliers (difference >10%) showed changes in creatinine levels that suggested that these patients had missed a session or changed shifts and were not in steady state.

Discussion

Although there was no requirement to ensure that BISTRO participants were in a stable dialysis regime we found good agreement, over a wide range of RKF, between GFR calculated using the measured plasma levels and using levels estimated by assuming the patients were in steady state. The difference between GFR_{meas} and GFR calculated with estimated levels was clinically acceptable for 97% of patients when $C_{preNext}$ was estimated (scenario A) and 98% when C_{reb} was estimated (scenario B).

This validation exercise supports the use of protocols for urine collections where blood samples are taken at only one session. The logical choice would be to take blood samples at the session when the patient returns the canister having completed the collection. The agreement with GFR_{meas} was slightly better for scenario B, even though GFR_{estB} relied on data from a matched session at least a month earlier or later. Closer agreement might be expected if the HD reduction fraction had been determined using pre- and post-dialysis levels for the session after the collection, which would be the case if the collection was timed to end with the routine bloods.

Reducing the requirement for blood samples is an important step towards a pragmatic protocol for measuring RKF in HD patients. The other step is to reduce the collection time. The preference for full interdialytic collections for HD patients is based on concerns that the GFR is suppressed by haemodialysis, although there are few publications to support this. The most frequently cited paper indicating an increase in GFR during the interdialytic interval is from 1995,[13] in an era when target weight was routinely set to the lowest weight that the patient could tolerate and post-dialysis fluid depletion would have been the norm. To enable patients who could not collect for the full interdialytic interval to remain in the study, urine collections of at least 24 hours were accepted for BISTRO. We were not able to make a comparison of partial and full interdialytic collections (this would require patients to switch to a new canister at a known time during the collection). However, collecting for a convenient period may be more accurate than collecting for the full interval as the patient can empty their bladder naturally and they are less likely to forget to use the canister or overfill it. If acceptable to the patient, it is preferable to carry out the collection towards the end of the interdialytic interval as this minimises the time for which the urine is stored and, where blood samples are taken after the collection, the impact of any error in estimating the post rebound levels for the previous session. In patients with substantial RKF, collecting for the shorter interdialytic interval reduces the possible overestimation of GFR due to the non-linear (asymptotic) concentration rise (see Supplementary Materials Appendix A).

In incremental dialysis, adjustments to the dialysis prescription are made using K_rU, rather than GFR. The agreement between K_rU, determined using equation 2, with the time averaged urea concentration calculated using measured and estimated plasma levels was similar to that for GFR. An alternative method for estimating C_{p_TAC} for urea was published by Daugirdas [14] shortly after the BISTRO protocol

was finalised. In this method, urine is collected for a minimum of 24 hours ending just before the HD session where a pre-dialysis (and ideally post-dialysis) blood sample is taken. C_{p_TAC} for urea is estimated using an empirical (best-fit) equation derived using formal urea kinetic modelling to construct the interdialytic plasma urea profile for a range of hypothetical dialysis regimes[11].

$$C_{p\_TAC} = \mathrm{C_{preNext}} \times [1.075 - (0.0038 \times \mathrm{URR} + 0.059) \times T_{\mathrm{urine}} / T_{\mathrm{int}}] \quad (10)$$

Where the urea reduction ratio, URR, is (C_{pre} – C_{post}) / C_{pre} expressed as a percentage.

For the full interdialytic collections used to validate scenario B, the Daugirdas equation gave a slightly higher C_{p_TAC} (and a slightly lower K_rU) than we obtained using the steady state assumption where URR was high (over 0.75).

The Daugirdas method offers a quick way to obtain K_rU from a urine collection timed to coincide with the end of the interdialytic interval. For collections carried out earlier in the interval, or when GFR is required, the equations in this paper can be used. Our data suggest that urine volume should not be used as a surrogate for GFR or K_rU. For the 60 patients with GFR_{meas} between 3 and 4 mL/min/1.73m^2 in the validation dataset (typically with K_rU 2 to 3 mL/min) the mean urine output was 680 mL/day but this varied from 220 to 1470 mL/day. The urine urea concentration in this cohort varied from 25 to 181 mmol/L. The factors contributing to this variation include hydration and fluid intake, which can vary for an individual as well as between patients, making residual urine output a poor indicator of RKF.

Conclusion

The good agreement between GFR_{meas} and GFR calculated with estimated plasma levels for the session before or after the urine collection validates the steady state assumption, and the use of estimated levels when calculating GFR from timed interdialytic urine collections. This allows the protocol for urine collections to be simplified and, for the BISTRO study, justifies the use of estimates where blood samples have been missed.

To monitor RKF in HD patients, we suggest using timed collections of about 24 hours in the dialysis interval before routine blood samples are scheduled. If this is not convenient, a pre-dialysis blood sample from the session after the collection can be used, together with pre- and post-dialysis plasma levels from a matched session. Other than noting the start and end times, the collection procedure is the same as for PD patients. Ideally, patients should keep to the same timing (which will usually be towards the end of the interdialytic interval) and not undertake collections if their dialysis regime has recently been changed or disrupted.

If a pragmatic protocol such as this is adopted in routine care, it will underpin awareness of the preservation of RKF and facilitate the implementation of incremental haemodialysis.[15] For research

studies looking at changes in GFR, such as BISTRO, this type of protocol will make the organisation of collections considerably easier.

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Table 1: Descriptive statistics (mean and standard deviation) for Scenario A

Scenario A (N= 316)	Measured values only	With estimated $C_{preNext}$	Discrepancy
$C_{preNext}$ urea (mmol/L)	17.1 ± 5.4	16.8 ± 5.1	-0.3 ± 2.3
C_{p_TAC} urea (mmol/L)	11.9 ± 4.0	11.7 ± 3.8	-0.1 ± 1.2
K_rU (mL/min)	2.7 ± 2.0	2.7 ± 2.0	0 ± 0.3
$C_{preNext}$ creatinine (µmol/L)	593 ± 201	575 ± 196	-18 ± 52
C_{p_TAC} creatinine (µmol/L)	442 ± 153	433 ± 151	-9 ± 26
K_rC (mL/min)	5.7 ± 4.4	5.8 ± 4.4	0.1 ± 0.5
GFR (mL/min/1.73m^2)	3.7 ± 2.7	3.8 ± 2.7	0.1 ± 0.3

Table 2: Descriptive statistics (mean and standard deviation) for Scenario B

Scenario B (N = 275)	Measured values only	With estimated C_{reb}	Discrepancy
C_{reb} urea (mmol/L)	6.8 ± 2.8	7.1 ± 2.9	0.3 ± 1.4
C_{p_TAC} urea (mmol/L)	12.1 ± 3.8	12.2 ± 3.9	0.1 ± 1.9
K_rU (mL/min)	2.8 ± 2.0	2.8 ± 2.0	0 ± 0.2
C_{reb} creatinine (µmol/L)	295 ± 113	312 ± 123	17 ± 46
C_{p_TAC} creatinine (µmol/L)	449 ± 152	457 ± 157	8 ± 23
K_rC (mL/min)	5.7 ± 4.2	5.6 ± 4.3	-0.1 ± 0.5
GFR (mL/min/1.73m^2)	3.7 ± 2.6	3.7 ± 2.6	0.0 ± 0.2

Captions for Figures:

Figure 1.

Diagrammatic presentation of solute concentration changes used in conjunction with a timed-urine collection. The pre-dialysis (C_{pre}), post-dialysis (C_{post}) and rebound concentrations (C_{reb}) for the session before the collection and pre-dialysis concentration for the session after ($C_{preNext}$) are used to calculate the reduction fraction (R_{HD}) and the time averaged solute concentration during the interdialytic urine collection (C_{p_TAC}). C_{pre}, R_{HD} and the regime-dependent interdialytic intervals are used to calculate the concentration gradient (G_c) (see text for calculations).

Figure 2. Comparison between GFR_{est} and GFR_{meas} for Scenario A (estimated pre-dialysis levels for the session after the urine collection). (Left panel, correlation coefficient, Right panel Bland and Altman plot).

Figure 3. Comparison between GFR_{est} and GFR_{meas} for Scenario B (estimated post-rebound levels for the session before the urine collection). (Left panel, correlation coefficient, Right panel Bland and Altman plot).

Figure 1. Graphical representation of solute concentration changes over the course of a full Interdialytic urine collection.

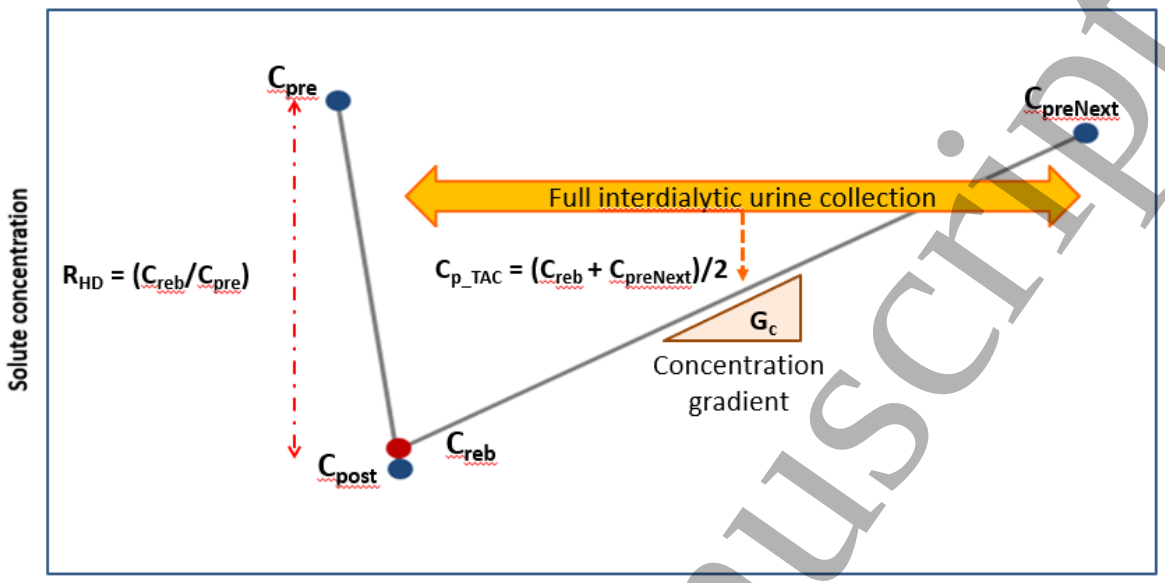

Figure 2. Comparison between GFR_{est} and GFR_{meas} for Scenario A (estimated pre-dialysis levels for the session following the urine collection).

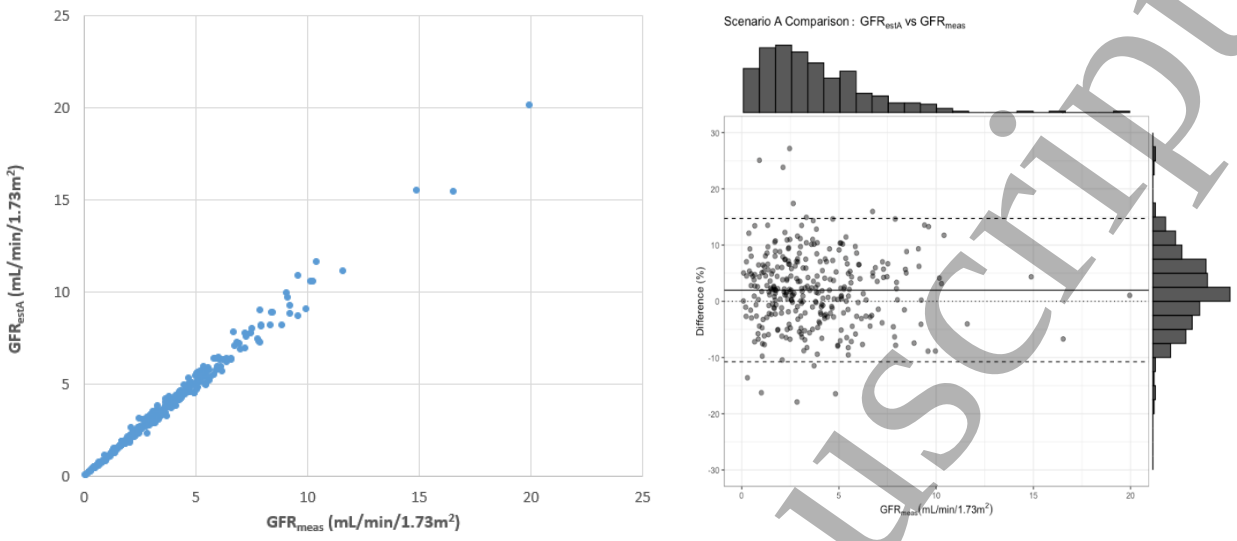

Figure 3. Comparison between GFR_{est} and GFR_{meas} for Scenario B (estimated post-rebound levels for the session before the urine collection).