Iohexol Plasma Clearance: Impact of Weighing the Syringe

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Measured glomerular filtration rate (mGFR) measurement is necessary in specific patients and/or specific clinical contexts.[1–3] Plasma clearances are the preferred methods, as they are less costly and cumbersome than urinary clearances.[4] The contrast medium iohexol is the most commonly used worldwide, partly for pragmatic reasons, as this marker is stable, not radioactive, and its measurement is easy, with the possibility of an external quality control.[1,4,5] One goal of the European Kidney Function Consortium (EKFC) is to increase the standardization of GFR measurements. Recently, members of the EKFC have compared plasma versus urinary clearances,[6,7] single versus multiple-sample plasma clearances,[5,8] and the different equations used in multiple-sample methods to model the first (or early) compartment.[9] The plasma clearance is calculated by dividing the amount of iohexol injected by the area under the curve obtained from concentrations at single or multiple times (equations are given in Supplementary Table S1). Comparing the plasma iohexol clearance methods used by different centers, we realized that the amount of injected iohexol was determined differently. Indeed, some centers weighed the syringe of iohexol before and after injection, with the aim to determine the injected dose more correctly than by calculating the theoretically injected volume. When the density of iohexol is known (1.28 for Omnipaque 240 mgI/ml and 1.35 for Omnipaque 300 mgI/ml), the amount of iohexol (in micrograms [μg]) is then easily calculated. As an example, 5 ml of Omnipaque 240 mgI/ml corresponds to the following calculated dose: (weight of syringe before − weight of syringe after) × 518/1.28 × 1000. The final dose of iohexol is thus dependent on the difference of weights before and after injection. Other centers considered only the theoretical volume of injection. As an example, if 5 ml of iohexol 240 or 300 mgI/ml is injected, the amount of iohexol (in micrograms) is as follows: 5 × 518 × 1000 and 5 × 647 × 1000, respectively (518 and 647 being the quantity of iohexol [in milligrams] in each milliliter of Omnipaque 240 and 300, respectively). With this method, the dose of iohexol is fixed. The weight of the injected dose can be obtained from the difference in weight of the syringe before and after injection (= actual weight) or can be calculated from the injected volume (= volume × density). The distribution of the differences in weight from both strategies was centered around zero, and 98.4% (= 4492/4565) were within [−0.5; +0.5 g] (Supplementary Figure S1). In our quest to standardize the iohexol plasma clearance procedure, we investigated the potential differences induced by weighing the syringes (GFR_W) and using iohexol density or by considering the theoretical injected volume (GFR_V). Such a comparison was possible in 3 large cohorts (methods are described in detail in the Supplementary Methods).

Among the 4565 participants, the median age was 53 (percentile [Pct] 25 = 48; Pct 75 = 62) years, the median body mass index (BMI) was 25.7 (Pct 25 = 22.6; Pct

75 = 29.1) kg/m^2, and 46% of the participants were female. The GFR was obtained with the multiple-sample (MS) method in 2941 subjects. For these subjects, the mean GFR$_W$ and GFR$_V$ were 63.56 ± 26.24 and 63.80 ± 26.35 ml/min, respectively. The median paired difference between GFR$_W$ and GFR$_V$ was −0.06 (Pct 2.5 = −3.48; Pct 97.5 = 2.13) ml/min. A concordance within 5% was observed in 96.6% of subjects. The GFR obtained with the single-sample (SS) method was available at time 180 minutes and 240 minutes in 4488 and 3018 subjects, respectively. With the SS method at 180 minutes, the mean GFR$_W$ and GFR$_V$ were 77.59 ± 28.89 and 77.92 ± 29.04 ml/min, respectively. The median paired difference between GFR$_W$ and GFR$_V$ was −0.28 (Pct 2.5 = −3.36; Pct 97.5 = 2.17) ml/min. Concordance within 5% was observed in 94.0% of subjects. With the SS method at 240 minutes, the mean GFR$_W$ and GFR$_V$ were 63.58 ± 24.34 and 63.80 ± 24.42 ml/min, respectively. The median paired difference between GFR$_W$ and GFR$_V$ was −0.07 (Pct 2.5 = −3.06; Pct 97.5 = 1.95) ml/min. Concordance within 5% was observed in 95.0% of subjects. Restricting the analysis to subjects with MS available (n = 2941), mGFR by SS at 180 minutes with GFR$_W$ and GFR$_V$ were 65.32 ± 25.40 and 65.58 ± 25.52 ml/min, respectively. The median paired difference between GFR$_W$ and GFR$_V$ was −0.08 (Pct 2.5 = −3.97; Pct 97.5 = 2.48) ml/min, with a concordance within 5% of 91.0%. The mGFR by SS at 240 minutes with GFR$_W$ and GFR$_V$ were 63.09 ± 24.27 and 63.30 ± 24.35 ml/min, respectively. The

median paired difference between GFR$_W$ and GFR$_V$ was −0.06 (Pct 2.5 = −3.07; Pct 97.5 = 1.97) ml/min, with a concordance within 5% of 94.9%. Concordance was thus significantly higher with the MS method than with the SS at 180 minutes or 240 minutes, and concordance was higher with SS at 240 minutes than at 180 minutes (all pairwise P values <0.0001).

We compared age, sex, BMI, and GFR levels of subjects with concordant and discordant GFR results (GFR$_W$ vs. GFR$_V$) in Table 1. Regarding GFR calculated with the MS method, characteristics of patients were not different for those with discordant or concordant results. For the SS methods, subjects with discordant results were older and had lower GFR levels.

To the best of our knowledge, the impact on GFR calculations of weighing the syringe (or not) has not been studied until now. Our results showed a high rate of concordance between the 2 methods, with a vast majority of results concordant within 5%, which is a very stringent criterion. Because of the very large sample size, the bias between GFR$_W$ and GFR$_V$ was statistically significant but was irrelevant from a clinical perspective (<1 ml/min). The impact of weighing the syringe (or not) seems particularly negligible in MS methods, with a rate of concordance reaching 97%. Characteristics of the few subjects with discordant results were not different from those of subjects with concordant results, suggesting that discordant results are probably due to errors or imprecisions in iohexol injection. Also, the median paired difference between

Table 1. Characteristics of patients with concordant versus discordant results (at 5%)

Characteristics	Concordant results	Discordant results	P value
MS (n = 2941)	n = 2842	n = 99	
Age (yr)	54 [40; 64]	55 [40; 62]	NS
Sex (%)	43	43	NS
BMI (kg/m^2)	24.6 [21.5; 28.4]	24.7 [20.9; 28.7]	NS
Weight (kg)	70 [59; 82]	68 [58; 83]	NS
GFR (ml/min)	60 [44; 81]	59 [43; 75]	NS
ΔGFR (ml/min)	−0.03 [−2.67; 1.97]	−3.47 [−13.23; 10.37]	<0.0001
SS at 180 min (n = 4488)	n = 4217	n = 271	
Age (y)	56 [48; 62]	60 [49; 71]	<0.0001
Sex (%)	45	46	NS
BMI (kg/m^2)	25.6 [22.5; 28.9]	25.9 [22.5; 30.7]	NS
Weight (kg)	73 [63; 85]	73 [62; 85]	NS
GFR (ml/min)	80 [58; 100]	44 [32; 59]	<0.0001
ΔGFR (ml/min)	−0.25 [−2.59; 1.88]	−2.54 [−10.31; 10.06]	<0.0001
SS at 240 min (n = 3018)	n = 2875	n = 143	
Age (yr)	54 [41; 63]	59 [47; 72]	<0.0001
Sex (%)	44	46	NS
BMI (kg/m^2)	24.7 [21.6; 28.6]	25.7 [21.9; 30.2]	NS
Weight (kg)	70 [60; 82]	72 [58; 83]	NS
GFR (ml/min)	62 [47; 81]	42 [29; 61]	<0.0001
ΔGFR (ml/min)	−0.05 [−2.34; 1.68]	−2.16 [−11.00; 9.76]	<0.0001

The GFR value is the GFR calculated with syringe weighted. ΔGFR is the difference between GFR obtained by weighing the syringes and GFR obtained by considering the injected volume. Results are expressed as median [percentile 25; percentile 75], except ΔGFR, which is expressed as median [percentile 2.5; percentile 97.5].
BMI, body mass index; GFR, glomerular filtration rate; MS, multiple-sample; NS, not significant; SS, single-sample.

GFR$_W$ and GFR$_V$ in subjects with so-called discordant results remained actually low (Table 1). Of note, if a criterion of concordance of 10% is retained, only 23 results (i.e., 0.8%) were discordant. In the SS methods, the impact of weighing the syringe on the concordance between GFR$_W$ and GFR$_V$ becomes smaller with increasing time-point. Having said that, the concordance with SS remained very high between GFR$_W$ and GFR$_V$ (>90%). Once again, if a concordance within 10% was retained, discordant results were 1.1% at both times 180 minutes and 240 minutes, respectively. Of interest, the SS method at both times 180 minutes and 240 minutes showed higher discordant results at lower GFR levels (~40 ml/min in our cohort). This may be explained by the form of the Jacobsson equation, because, at low GFRs, the iohexol concentration in the SS remains relatively high, which increases the relative error in GFR (the denominator in Jacobsson's error formula becomes smaller). It must be noted that in such a low GFR range, a time-point later than 180 minutes is recommended in SS methods.

The main limitation of the current analysis is that there is no way to evaluate the absolute impact of errors in weighing or volume estimation, because there is no reference. Weighing the syringes is relatively easy and is performed to overcome the possible errors of using the theoretical volume. However, the current analysis demonstrates that both strategies are equivalent. In practice, weighing syringes is important in rare cases in which the volume of iohexol cannot be fully injected for practical reasons. Indeed, even if medical records were checked in patients with discrepancies of more than 5% to verify the volume of iohexol injected, it remains possible that the volume effectively injected was different from the volume defined by the protocol, notably because of difficulties with venipuncture in some patients. This could probably explain gross discrepancies between results observed in a minority of patients.

In this large cohort of subjects with iohexol plasma clearances, we showed that estimating the volume of iohexol injected or weighing the syringes and using iohexol density led to the same GFR results in the vast majority of subjects.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

Table S1. Different equations used in the analysis

Figure S1. Distribution of weight differences (measured or derived from volume).

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