ORIGINAL ARTICLE

Comparison of estimated creatinine clearance among five formulae (Cockroft–Gault, Jelliffe, Sanaka, simplified 4-variable MDRD and DAF) and the 24hours-urine-collection creatinine clearance

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Abstract

Background: GFR estimation is of major importance in everyday clinical practice. Usually it is done using one of the many eGFR equations available. In this study we compared in our population four widespread eGFR equations and our own empirical eGFR, with creatinine clearance calculated through a timed urine collection.

Patients and methods: We collected laboratory data of 907 patients from our clinic and outpatient department through a ten-year period and statistically compared the eGFR results between them and with the timed urine collection creatinine clearances.

Results: All eGFR equations gave acceptable approximations to the timed urine collection creatinine clearances. However, in different subpopulations some equations did better than others, without any clear advantage of any equation overall. Surprisingly, our empirical equation named DAF also gave acceptable approximations regardless of age, weight and sex of the patient.

Conclusions: In our population our empirical eGFR method (DAF) gave satisfactory results regarding the monitoring of renal function, compared with four other eGFR methods. We suggest that it could provide a very fast and easy to use means of eGFR calculation. Hippokratia 2010; 14 (2): 98-104

Key words: clearance, creatinine, eGFR, renal failure

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Measuring GFR is widely accepted as the best overall index of kidney function (K/DOQI 2002), and, ideally is performed using inulin or ^{125}I-iothalamate clearance methods. However, these tests are technically impractical and expensive for everyday clinical use. The most common method for assessing GFR is performing a timed urine collection for evaluation of creatinine clearance. This test is also inconvenient and frequently inaccurate as a result of improper collection and overestimation of GFR due to kidney tubular secretion of creatinine[1]. More recently, calculation of eGFR using empirical mathematical formulae has been encouraged as a simple, rapid and reliable means of assessing kidney function. Several GFR prediction equations that take into account the serum creatinine, albumin and certain patient variables (age, gender and body weight) have been shown to generate sufficiently precise, unbiased and easily calculated estimates of GFR (eGFR) although there is still great debate about their accuracy[2-4]. There are no fewer than 46 different prediction equations currently available, although the two most commonly used are the Cockcroft-Gault and the "Modification of Diet in Renal Disease" (MDRD) formulae.

Our aim was to evaluate an empirical method of GFR estimation used in our clinic for the past years by comparing it with some of the most widespread eGFR calculation formulae and with the 24hour urine collection clearance measurements. This was done in order to conclude whether and when the use of an eGFR calculation method is a safe and accurate alternative to the troublesome 24hour urine collection, and which method is the most appropriate for estimating renal function in our population. Our formula was created more than 30 years ago by the first author, empirically, long before the other methods were established, in an attempt to easily assess renal function in a newly diagnosed chronic renal insufficiency (CRI) patient. For simplicity it will be called "DAF" (from the initials of one of the authors).

Patients and methods

Our study included nine hundred and seven (907) patients, from rural and urban territories of Achaia region in Greece, four hundred and eighty seven (486) male, age range 18-97 (median 67.8) years and four hundred and twenty one (421) female, age 18–97 (median 57.9) years with serum creatinines ranging from 0.6 to 17.5 mg/dl). The files of 743 patients (81.94%) came from the Outpatient Department of our Renal Unit and 164 patients (18.06%) came from hospitalized patients in our clinic, over the past ten years. Thus we had complete access to all necessary information. All measurements used in this study are the ones taken when the patients had a stabilized renal function.

The precision and accuracy of the Cockroft–Gault, Jelliffe, Sanaka, simplified 4-variable MDRD and Diamandopoulos' (DAF) formulae were compared with the 24 hours urine collection formula[5-7].

Diamandopoulos' A. formula (DAF)

$$Ccr = \frac{80}{Scr}$$ (use 70 as a numerator for females)

where:

Ccr = clearance rate (mL/min) of creatinine

Scr = serum concentration of creatinine (mg/dL)

The statistical analysis was based on paired t-test using the Origin 4.00™ analysis software and SPSS analysis software. The aim was to compute both the levels of correlation and the levels of differences between the methods. The first approach was made by computing the correlation coefficients between the methods using a non-linear model. The next approach was the use of the paired t-test, because all parameters of the study were numerical, all patients came from the same population and all had paired results. The most appropriate formula would be the one that, when compared with 24-hour urine collection clerarance measurement, would produce the larger p, i.e. the formula that would produce results statistically **insignificant** compared with the 24-hour urine collection clerarance measurement. The staging of the patients was made according to their 24hour urine collections and were classified in the following manner: Stage I, CrCl>90ml/min; Stage II, CrCl 60-90ml/min; Stage III, CrCl 30-59ml/min; Stage IV, CrCl 15-29ml/min; Stage V CrCl<15ml/min.

Results

The correlation analysis yielded similar results for all eGFR methods, i.e. all methods gave results that had a statistically significant correlation with the 24 hours urine collection clearances. The analysis was done using bivariate correlation between GFR estimation methods as pairs (i.e. each eGFR method compared with the 24hour urine collection clearance) and three different correlation analyses were used, namely Pearson's correlation, Kendall's Tau-b correlation coefficient and Spearman's rho correlation coefficient. All the eGFR methods had a statistically significant correlation (level 0.01) with the 24hour urine collection clearance and thus no safe conclusion derived by this analysis as to which of the methods had a clear advantage among all.

The paired t-test analysis however proved to be more lucrative. Different approaches with groups of different age, gender and stage of renal insufficiency, plus an overall comparison were used in order to get a more global view of the results. It must be emphasized that our data had a normal distribution and its normality was maintained when we divided them in subgroups.

In the five stages of CRI the comparisons per stage and the overall comparison gave the results seen in Table 1. P values of the comparisons are given only when p is larger than 0.05 i.e. when the comparisons yielded results statistically insignificant. MDRD and Cockroft-Gault gave very good approximations to the 24h urine collections clearances in stages V and IV of CRI. However, the results were disappointing in all other stages. DAF gave a very good approximation to the 24h urine collection clearances in stage III (the larger population in our study) but failed to predict accurately in all other stages.

Another approach was made by separating the population into two subpopulations; those over and those under 60 years of age. From this comparison, in two hundred and sixty five patients (n=265) aged <60 years old, independent of sex and staging of CRI the clearance rates of Cockcroft-Gault formula were closer than any other eGFR formula to the 24 hours urine collection (p=0.028). However, the comparison yielded results that were statistically significant for the p<0.05 level, as it can be seen in Table 2.

From the comparison, in six hundred and forty two patients (n=642) aged >60 years old, independent of sex and staging of CRI the rates of DAF were closer than any other eGFR formula, to the 24 hours urine collection (p=0.19). It is interesting that in this comparison the differences were statistically insignificant for the p<0.05 level, i.e. the means of the two methods almost coincided, as it can be seen in Table 3.

Another approach was to compare the methods in different groups of renal function as this was estimated by their 24h urine collections. This way we tried to evaluate all methods in the largest possible subpopulations in order to estimate which of the methods had a clear advantage amongst all. The results are given in the tables in Appendix.

Yet another approach was to compare the eGFR methods in different groups of renal function as this was estimated by their 24h urine collections, this time separating

Table 1: Per stage comparison between methods in our population.

Stages CRI	Population (*n*)	24h urine collection	MDRD	p	Sanaka	p	Cockcroft-Gault	p	Jelliffe	p	DAF	p
V	124	9.45	10.26	0.09	10.5	<0.05	10.29	0.059	9.25	0.63	14.5	<0.05
IV	181	22.31	21.7	0.36	22.21	0.87	22.2	0.86	18.99	<0.05	27.5	<0.05
III	319	44.06	37.93	<0.05	39.4	<0.05	40.14	<0.05	32.6	<0.05	44.5	0.55
II	138	73.27	58.37	<0.05	60.61	<0.05	65.98	<0.05	49.9	<0.05	63.9	<0.05
I	149	118.6	89.00	<0.05	85.7	<0.05	107.71	<0.05	83.51	<0.05	89.6	<0.05
ALL	907	51.4	42.2	<0.05	42.6	<0.05	47.2	<0.05	37.5	<0.05	47.2	<0.05

Table 2: Comparison of eGFR methods in patients under 60 years of age.

Method/Statistics	Mean	SD	SE	P
24h urine collection	76	42.42	2.6	-
Cockroft-Gault	73.07	45.26	2.78	P<0.05
Sanaka	57.36	37.58	2.3	P<0.05
Jelliffe	55.84	35.45	2.17	P<0.05
MDRD	57.11	38.29	2.35	P<0.05
DAF	59.51	36.09	2.21	P<0.05

males and females. Our last approach was the comparison of eGFR methods of male and female populations per CRI stage. All approaches gave similar results, but the corresponding tables are not included.

The comparisons of the results of Cockroft-Gault, Jelliffe, Sanaka, simplified 4-variable MDRD and DAF, and 24hour urine collection with DAF are shown in Figures 1-5. In these figures the reader can see the close correlation between DAF and the other eGFR methods.

This comparison between eGFR equations is very important, first because no one is certain which method gives the most accurate prediction and second because these equations are already in use for years. Cockroft-Gault has been widely used for estimating drug dosing in CRI, and MDRD has been used for staging of CRI.

Furthermore, in order to assure the accuracy of our comparison we added a Bland-Altman analysis of our data. We applied this method to our overall and to our stage III CRI data, the stage in which DAF seemed in greatest concordance with 24h urine collection clearances. For space occupying reasons we limited our comparisons to Cockroft-Gault, MDRD and DAF. The results are given in Figures 6-11. For the analysis we used the Analyze-it® software add-on for Microsoft Excell™. The Bland and Altman analysis also gave these eGFR equations satisfactory results in comparison to 24h urine collection clearances.

In the overall comparisons Bland-Altman analysis shows similar results for the three equations. In the stage III data however, while all three equations gave acceptable correlation with 24h urine collection clearances, DAF had far the smallest bias, a result that comes in accordance with the paired t-test.

Discussion

The estimation of GFR is ideally performed by using inulin or ^{125}I-iothalamate clearance methods. However, these methods are expensive, time-consuming, technically complicated and, in the clinical setting, impractical, to say the least. Cystatin C, a low molecular weight plasma protein, has been proposed as the successor of creatinine for the estimation of GFR. Although some studies have found Cystatin C to be a more accurate marker of GFR, other studies suggested that it does not outmatch creatinine, necessitating further studies[5-10]. One study suggested that GFR estimation for drug dose adjustment was unsatisfactory from Cystatin C and Creatinine[11] while other studies suggested that creatinine measurement itself might be biased due to laboratory variabilities[12-14]. Some nephrologists around the world have adjusted the eGFR equations to their populations[15,16], while some studies have been done in different age groups, i.e. children <14 years and the elderly[17,18,19,20]. Many nephrologists around the world, us included, prefer the less troublesome albeit not so accurate, creatinine clearance measurement through a 24hour urine collection. This method, despite its disadvantages, i.e. probability of improper urine collection and overestimation of GFR due to kidney tubular secretion of creatinine, is the closest measurement one can get to the real GFR in the clinical setting, especially if the patient is hospitalized and a single dose of a pharmacological inhibitor of tubular secretion of creatinine (simetidine or trimethoprime) is administered a few hours prior to the beginning of the timed urine collection. One of the most important aspects of GFR measurement is when a decision has to be made whether the patient must begin dialysis or not. Most experts agree that, except for the cases where other factors indicate immediate initiation of dialysis (i.e. uremic symptoms, pericarditis etc),

Table 3: Comparison of eGFR methods in patients over 60 years of age.

Method/Statistics	Mean	SD	SE	p
24h urine collection	41.27	29.22	1.15	-
Cockroft-Gault	36.6	25.82	1.02	<0.05
Sanaka	36.61	24.61	0.97	<0.05
Jelliffe	29.95	20.22	0.79	<0.05
MDRD	36.07	25.11	0.99	<0.05
DAF	42.12	25.50	1.00	0.19

Appendix

Table 4: Comparison of all methods for patients with creatinine clearance <90 mL/min as estimated by their 24h urine collections, independent of age and sex.

Method/Statistics	mean	SD	SE	p	n
24h urine collection	38.55	21.92	0.79	-	762
Cockcroft -Gault	35.70	22.57	0.81	**< 0.05**	762
Sanaka	43.46	21.09	0.76	**< 0.05**	762
MDRD	33.27	20.55	0.74	**< 0.05**	762
Jelliffe	28.70	17.02	0.61	**< 0.05**	762
DAF	39.12	21.40	0.77	**0.28**	762

Table 5: Comparison of all methods for patients with creatinine clearance <60 mL/min as estimated by their 24h urine collections, independent of age and sex.

Method/Statistics	mean	SD	SE	p	n
24h urine collection	30.88	15.56	0.62	-	624
Cockcroft -Gault	29.01	17.21	0.68	**< 0.05**	624
Sanaka	28.67	16.73	0.67	**< 0.05**	624
MDRD	27.72	15.88	0.63	**< 0.05**	624
Jelliffe	24.01	13.03	0.52	**< 0.05**	624
DAF	33.63	17.21	0.68	**< 0.05**	624

Table 6: Comparison of all methods for patients with creatinine clearance <30 mL/min as estimated by their 24h urine collections, independent of age and sex.

Metnod/Statistics	mean	SD	SE	p	n
24h urine collection	17.08	7.35	0.42	-	305
Cockcroft -Gault	17.36	10.38	0.59	**0.52**	305
Sanaka	17.45	10.15	0.58	**0.39**	305
MDRD	17.05	10.36	0.59	**0.93**	305
Jelliffe	15.03	8.37	0.47	**< 0.05**	305
DAF	22.25	11.83	0.67	**< 0.05**	305

Table 7: Comparison of all methods for patients with creatinine clearance <15 mL/min as estimated by their 24h urine collections, independent of age and sex (this table is of course identical to the stage V of table 2).

Method/Statistics	mean	SD	SE	p	n
24h urine collection	9.45	3.37	0.29	-	124
Cockcroft -Gault	10.29	5.08	0.45	**0.059**	124
Sanaka	10.50	5.63	0.50	**< 0.05**	124
MDRD	10.26	5.69	0.51	**0.09**	124
Jelliffe	9.25	4.67	0.41	**0.63**	124
DAF	14.51	7.03	0.63	**< 0.05**	124

the time to begin chronic dialysis is when GFR drops bellow 15 ml/min. Most of the time this final decision is made through the 24hour urine collection method as this method is considered among nephrologists as a gold standard of GFR estimation[21].

Except for these cases however there are many other cases when a fast and accurate GFR estimation has to be made. Thus, in the outpatient setting, drug-dose adjustments, the use or avoidance of certain drugs, information about possible complications of radio-contrast agents or simply informing the patients upon their renal function status, are some of the circumstances where a general practitioner - physician needs an alternate, faster and easier to use method of estimating GFR. But which method is the most appropriate?

It would be easy to suggest that we could use different formulae for men and women, different levels of plasma creatinine and/or different age groups but such an assumption would make the eGFR approach more complicated. After all, the ideal method of eGFR has to fulfill certain requirements. First of all it has to be accurate enough as to place the patient's CRI status in its correct

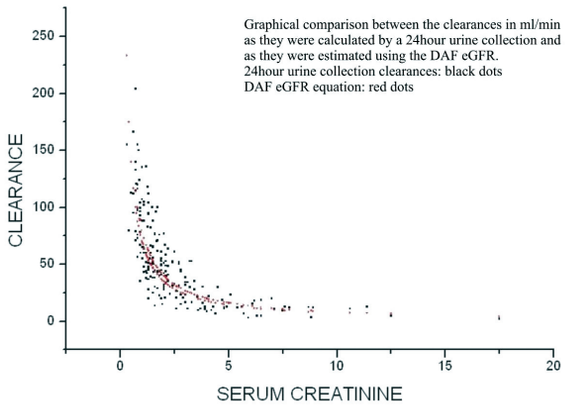


Figure 1: We can see the overall graphical comparison of the clearance rates between the 24hour urine collection (black dots) and the Diamandopoulos' formula (DAF, red dots). Here the rates of the DAF are clearly inside the rates of the 24hour urine collection.

stage, second, it has to be easy to calculate (ideally without the use of a calculator) and, third, it has to demand as little data as possible. By definition, and according to our study, all methods fulfill the first requirement, while DAF clearly surpasses the other methods in the second and third requirements.

The DAF formula is based on a simple assumption, i.e. if creatinine has a steady rate of production then serum creatinine must have a direct relation to creatinine clearance. Since the declining of renal function leads to a decline of creatinine clearance and a concomitant increase of serum creatinine, we assume that these changes are analogue and thus they can be represented by a simple formula such as:

Serum Creatinine X Creatinine Clearance = Constant[22]

As a constant for this formula we used the lowest values of creatinine clearance in the normal range of our laboratory, i.e. 80 for men and 70 for women. Thus the formula became:

Serum Creatinine X Creatinine Clearance = 80 for men and 70 for women
and
Creatinine Clearance = 80 / Serum Creatinine (70 for women)

If, for example, a woman has a serum creatinine 3.3 mg/dl, we estimate her Creatinine Clearance as 70 / 3.3 = 21.2 ml/min.

The statistical methods that we used in our work are

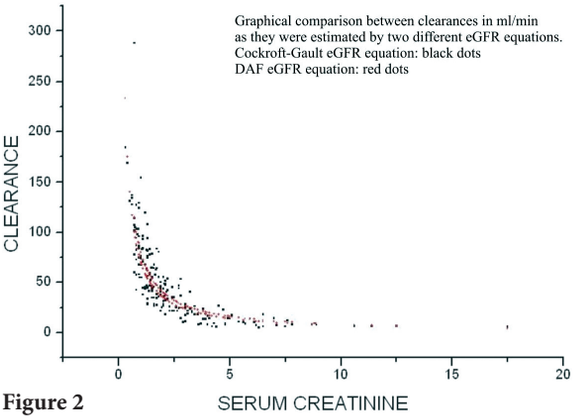
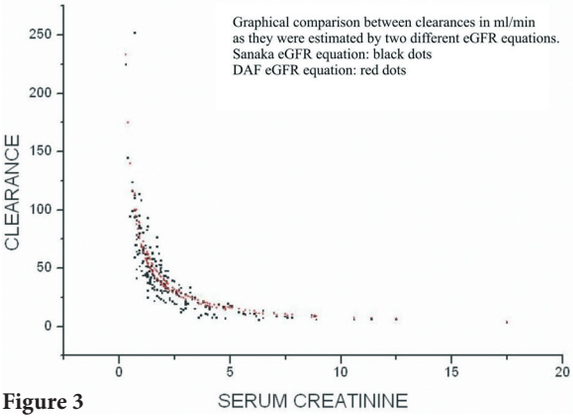


Figure 2



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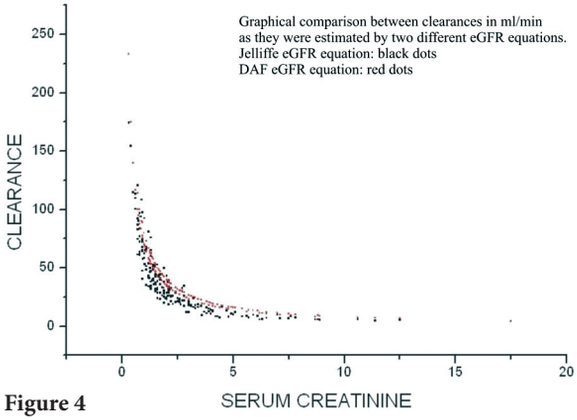


Figure 4

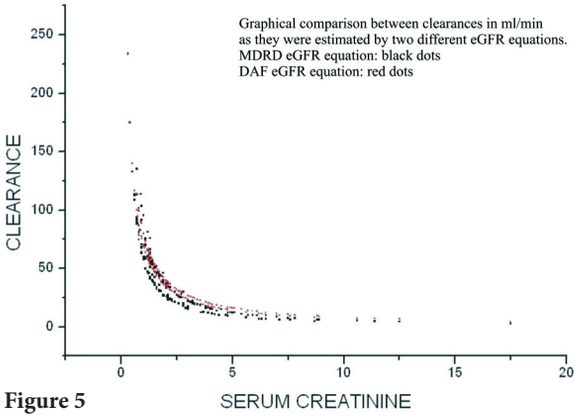


Figure 5

Figures 2 to 5: The reader can see the close correlation between DAF and the other eGFR methods. DAF lays in almost the same trajectory with Cockroft-Gault and Sanaka, while giving slightly higher GFRs than SMDRD and Jelliffe.

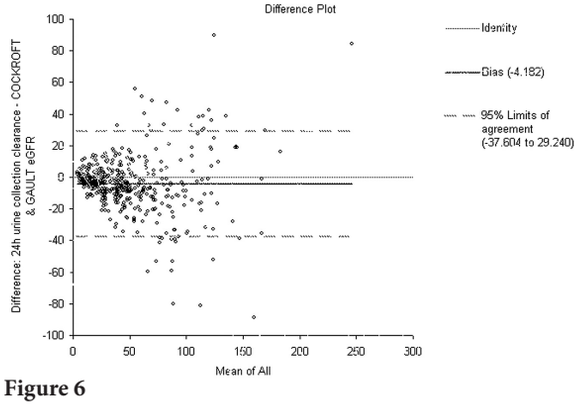
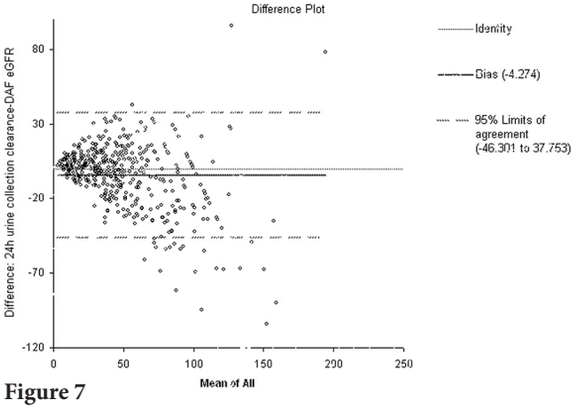


Figure 6



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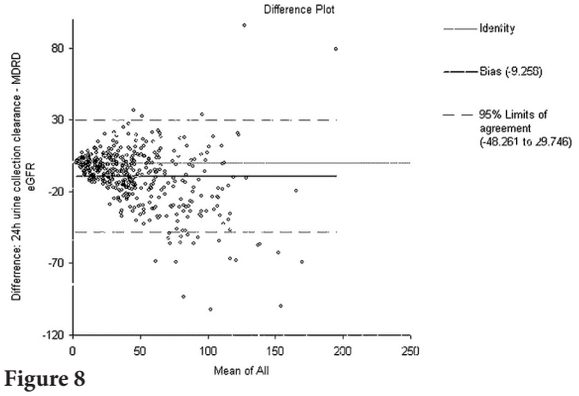

Figure 8

Figures 6 to 8: We see that in the overall comparisons, Bland-Altman analysis shows similar satisfactory results for the three equations.

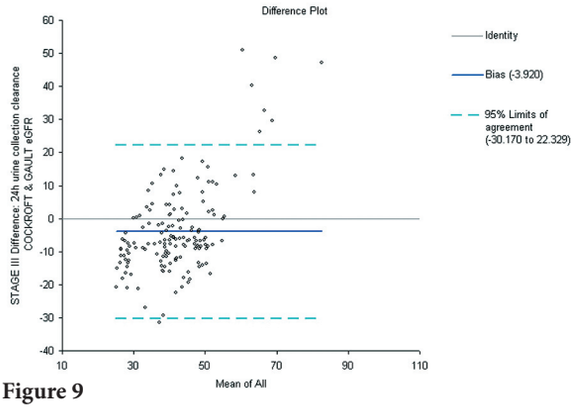

Figure 9

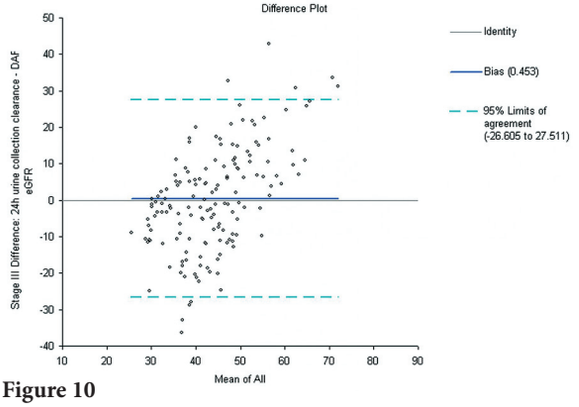

Figure 10

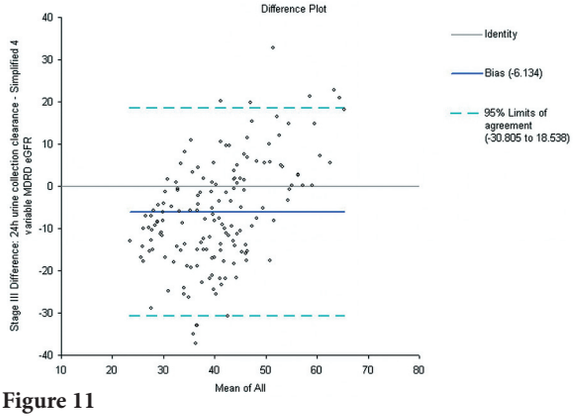

Figure 11

Figures 9 to 11: In the stage III data, while all three equations gave acceptable correlation with 24h urine collection clearances, DAF had far the smallest bias, a result that comes in accordance with the paired t-test.

considered valid for comparisons of clinical measurements[23]. Of course one cannot underestimate the probable differences in populations other than our own and this formula should be evaluated in other populations as well.

Conclusion

Based on our results, the simplicity of DAF, i.e. a simple division of a constant with serum creatinine, the pretty good estimation of renal function that DAF offers and the minimal input data it requires, we recommend its use as a first approach tool for estimating GFR, regardless of age, weight and sex. Despite the fact that it fails to accurately predict renal function (and this so happens with all other eGFR equations as well), since it still places, in most cases, the renal function in its correct CRI stage it could provide a very fast and easy to calculate means of eGFR measurement.

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