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The Accuracy of Creatinine Methods Based on the *Jaffé* Reaction: A Questionable Matter

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Summary: The determination of creatinine in serum based on the *Jaffé* reaction was evaluated with four current analysers. In particular, the comparability of results was determined also with survey specimens. Recalibration of 3 out of 4 modifications was necessary, based on the results of patient samples as verified with a HPLC-method. One of the methods proved to give an unacceptable scatter for the results in the lower range (30–150 µmol/l).

A limited interference study (haemoglobin, lipids, bilirubin and acetone) and a method assessment with quality control sera supported the conclusion that the overall accuracy of creatinine methods based on the *Jaffé* reaction is questionable.

Introduction

In a previous article we described the evaluation of four state-of-the-art methods for the measurement of creatinine in serum (1). Two methods were based on the *Jaffé* reaction while the other two used an enzymatic approach. We conlcuded that both enzymatic procedures performed better, and that the two *Jaffé* methods differed in their accuracy.

Because of this study, and in view of earlier experience (2) we felt the need to check the accuracy of the creatinine determinations performed on four analysers currently used in our laboratory.

We restricted ourselves to the comparison of "around normal" samples (30–150 µmol/l), the calibration of the instruments and the most common interferents. We also assessed the methods by applying various quality control samples as used in the years 1992 and 1993 in the Dutch Quality Assessment Scheme (SKZL).

Materials and Methods

Instrumentation

The following instruments were used and calibrated exactly according to the instructions of the various manufacturers:

a) Chem-1 (Bayer-Technicon, U. S. A.)
b) Hitachi 911 (Boehringer Mannheim, Germany)
c) ELAN (Merck, Germany)
d) Dimension AR (DuPont, U. S. A.)

The calibrator creatinine concentrations were as follows:

a) Chem-1:	0 and 814 µmol/l (Technicon Chem-1 SET point Calibrator)
b) Hitachi 911:	0 and 168 µmol/l (BM Calibrator for automated systems)
c) ELAN:	0 and 145 µmol/l (Merck Calibrator SMT)
d) Dimension:	0, 999 and 1971 µmol/l (DuPont Dimension Chem-1 Calibrator)

Patient samples

Serum samples were collected in various departments in the University Hospital Rotterdam. All samples were stored at −70 °C prior to use. We only used non-icteric, non-haemolytic and non-lipaemic specimens for the comparison studies. Samples were divided into two groups. Group I showed a uniform distribution of creatinine values between 40 and 150 µmol/l (40 samples), and group II showed a uniform distribution of values 30 and 900 µmol/l (17 samples).

Creatinine concentrations of all samples were verified with our HPLC reference method (3).

Special samples

For the recalibration of all results we used SRM 909 a_1 and a_2 Human Serum from the National Institute of Standards and Tech-

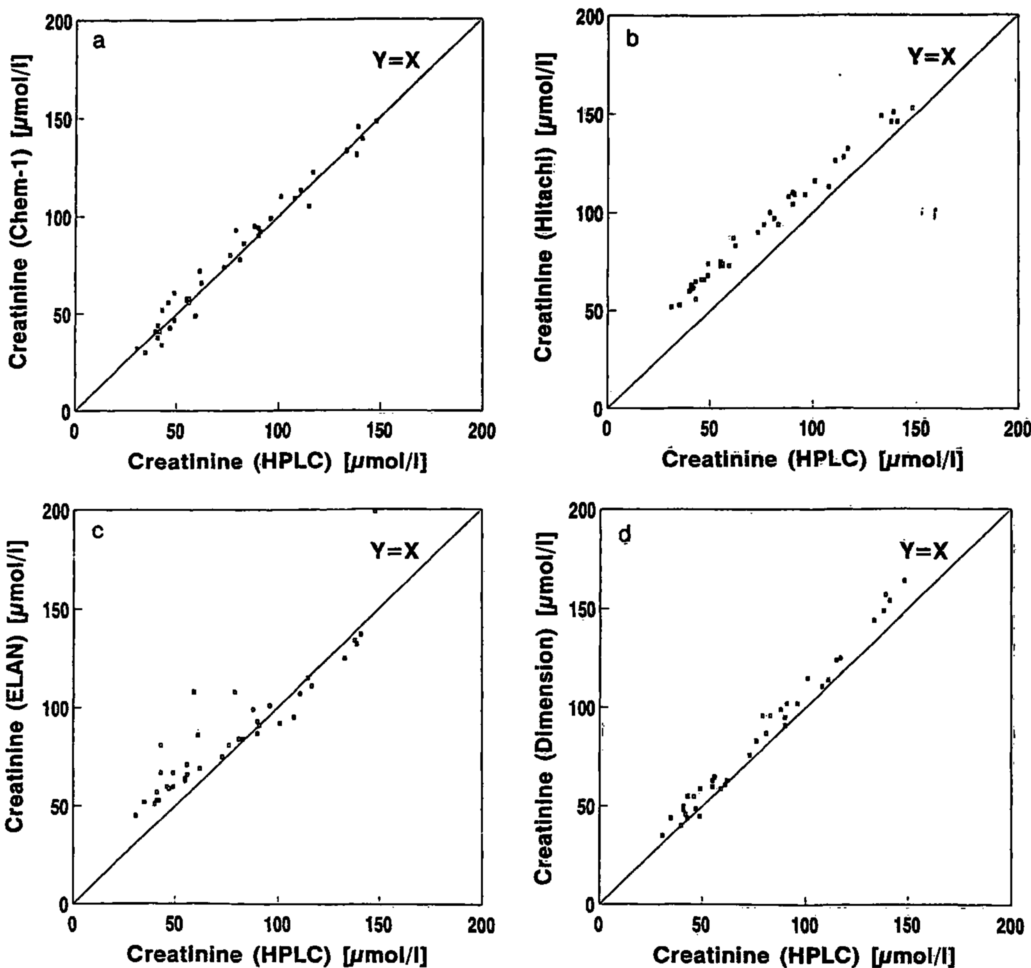

Fig. 1 Graphical presentation of the uncorrected results from patient samples obtained with the various methods.

Tab. 1 Results SRM 909 Human Serum samples

Sample	Creatinine (µmol/l)				
	Stated value	Chem-1	Hitachi 911	ELAN	Dimension
909 a_1	84	90	104	97	84
909 a_2	463	470	454	403	470

Remarks:
1. Stated value = value National Institute of Standards and Technology (NIST)
2. Analyser values = average of 6–8 measurements on two consecutive days

Tab. 2 Regression equations before and after correction

	Regression equation	
	Before correction	After correction
Chem-1	y = 1.05x	y = 1.00x − 10
Hitachi 911	y = 0.93x + 23	y = 1.00x − 5
ELAN	y = 0.79x + 24	y = 0.97x − 3
Dimension	y = 1.05x + 3	y = 1.02x

Remarks:
1. Correction was done with both SRM samples
2. The graph consisted of 17 data points in the range 30–900 µmol/l
3. All coefficients of correlation were at least 0.99

nology (Gaithersburg, U. S. A.). The samples used for the recovery study came from the Dutch Quality Assessment Foundation (SKZL). They were used in the quality control schemes in 1992 and 1993. Seven were of human origin and seven of animal origin.

Interference study

A restricted interference study was done with spiked albumin solutions as described earlier (2). We only studied the influence of haemoglobin, lipids (Intralipid®) and acetone (0–13.6 mmol/l).

The influence of bilirubin was checked with 9 very icteric serum samples.

Statistical analyses

Regression analysis was performed according to *Passing & Bablok* (4).

Results

Actual situation

All patients samples, groups I and II, were measured in duplicate together with both the SRM 909 samples. In

Tab. 3 Interference study

	Chem-1	Hitachi 911	ELAN	Dimension
Haemoglobin	±	0	0	0
Lipids	0	0	0	0
Acetone	+	+	+	++

Remarks:
1. Haemoglobin: 0 – 10 – 20 – 50 – 70 – 100 μmol/l
2. Lipids: Intralipid® dilutions ranging from non-lipaemic to lipaemic (6 measurements)
3. Acetone: 0.0 – 3.4 – 6.8 – 10.2 – 13.6 mmol/l
4. 0 = no influence
± = moderate influence
\+ = strong influence
++ = very strong influence

figure 1, the results of group I samples on all four analysers are plotted against the results of our HPLC method.

Calibration

Both SRM serum samples were measured 6–8 times in total on two consecutive days. The results are given in table 1.

Using the regression lines calculated from the data in table 1, all the results of groups I and II were recalculated. Table 2 shows only the group II data, which represent a comparison between the actual (= manufacturer set) and the real (= SRM based) calibration graph.

Tab. 4 Results of all icteric serum samples

Sample	Bilirubin (μmol/l)	Creatinine (μmol/l)				
		HPLC	Chem-1	Hitachi 911	ELAN	Dimension
1	229	64	57	45	33	77
2	153	62	61	50	37	75
3	159	72	66	66	54	82
4	191	101	86	85	69	116
5	138	52	43	42	34	67
6	158	50	47	43	42	70
7	910	122	218	16	0	130
8	124	60	48	49	41	74
9	124	36	22	28	49	41

Remarks:
1. The results were corrected with SRM 909

Recalculation of all group I results gave an improvement in accuracy.

Tab. 5 Results of all survey samples

Sample	Creatinine (μmol/l)				
	HPLC	Chem-1	Hitachi 911	ELAN	Dimension
1	74	72	86	75	67
2	90	112	118	102	108
3	91	82	102	90	93
4	120	310	213	328	293
5	70	48	71	65	57
6	138	129	136	115	129
7	33	157	113	199	145
8	85	76	93	79	68
9	56	207	142	221	179
10	122	141	141	116	134
11	77	67	89	83	71
12	41	23	52	43	37
13	134	162	159	134	161
14	92	124	124	107	112

Remarks:
1. All samples were used in surveys in The Netherlands during 1992 and 1993
2. Samples 1, 4, 5, 6, 7, 9 and 12 were human and 2, 3, 8, 10, 11, 13 and 14 animal
3. The results were not corrected with SRM 909

Interference study

The results of interference by haemoglobin, lipids and acetone in albumin solution (creatinine concentration 100 μmol/l) are given in table 3 while the measurements of the icteric serum samples are tabulated in table 4.

Recovery

All recovery experiments with quality control samples are described in table 5. We only used specimens with HPLC-values between 30 and 150 μmol/l.

Discussion

Since creatinine is important in clinical medicine, it is frustrating that the overall accuracy is still inadequate, despite all the modifications and improvements. It follows from all our evaluation work that we produce erroneous creatinine results every day. The number of errors

is not known, but fortunately we feel that most of them will not effect patient care. However, we cannot accept the analytical errors found in our study, despite its limited design. In this respect, our study confirms the results of the study reported by *Vassault* et al. (5), although this was designed differently. As a multicentre survey, it described the actual situation in France with regard to creatinine determination, with the aim of proposing a selected method. No firm conclusion could be drawn, except a negative one regarding the imprecision and inaccuracy. It is clear from figure 1 in our study that three methods were calibrated wrongly (Hitachi 911, ELAN and Dimension) while one (ELAN) also showed a large scatter.

Table 1 shows the improvements after recalibration with both SRM samples. We wondered whether the results obtained after recalibration could meet objective accuracy criteria. Applying 4.4% (6) as a maximal allowable deviation in 95% of the experiments, we found that 58% of the results for group I samples in the Chem-1 to be acceptable, for the Hitachi 55%, for the ELAN 23%, and for the Dimension 75%. It is stressed again that all samples were taken at random from our routine production, and they showed no visible peculiarities.

Most of the deviating results were found in the lower range (< 60 µmol/l) which makes all methods questionable for paediatric work.

The question arises as to what more we can expect from creatinine methods based on the *Jaffé* reaction. This topic has been intensively studied by several groups (7–13), unfortunately without firm conclusions, taking into account all the interference problems that may be encountered with clinical specimens. A limited example of variability due to interference is shown in tables 3 and 4.

We therefore have to accept that there is at the moment no *Jaffé* modification that is completely satisfactory. There is much literature to confirm this (14, 15).

One solution may be the application of more specific enzymatic methods. Without doubt this would mean an improvement in accuracy, as we have also shown (1). Many laboratories changed over in the last five years from *Jaffé* reaction-based methods to one of the enzymatic procedures. In the Netherlands only 4% of laboratories used enzymatic methods in 1989; in 1994 this is 14% (the majority of methods being so-called dry-chemistry). German surveys show nearly 10% in 1989 and about 35% now.

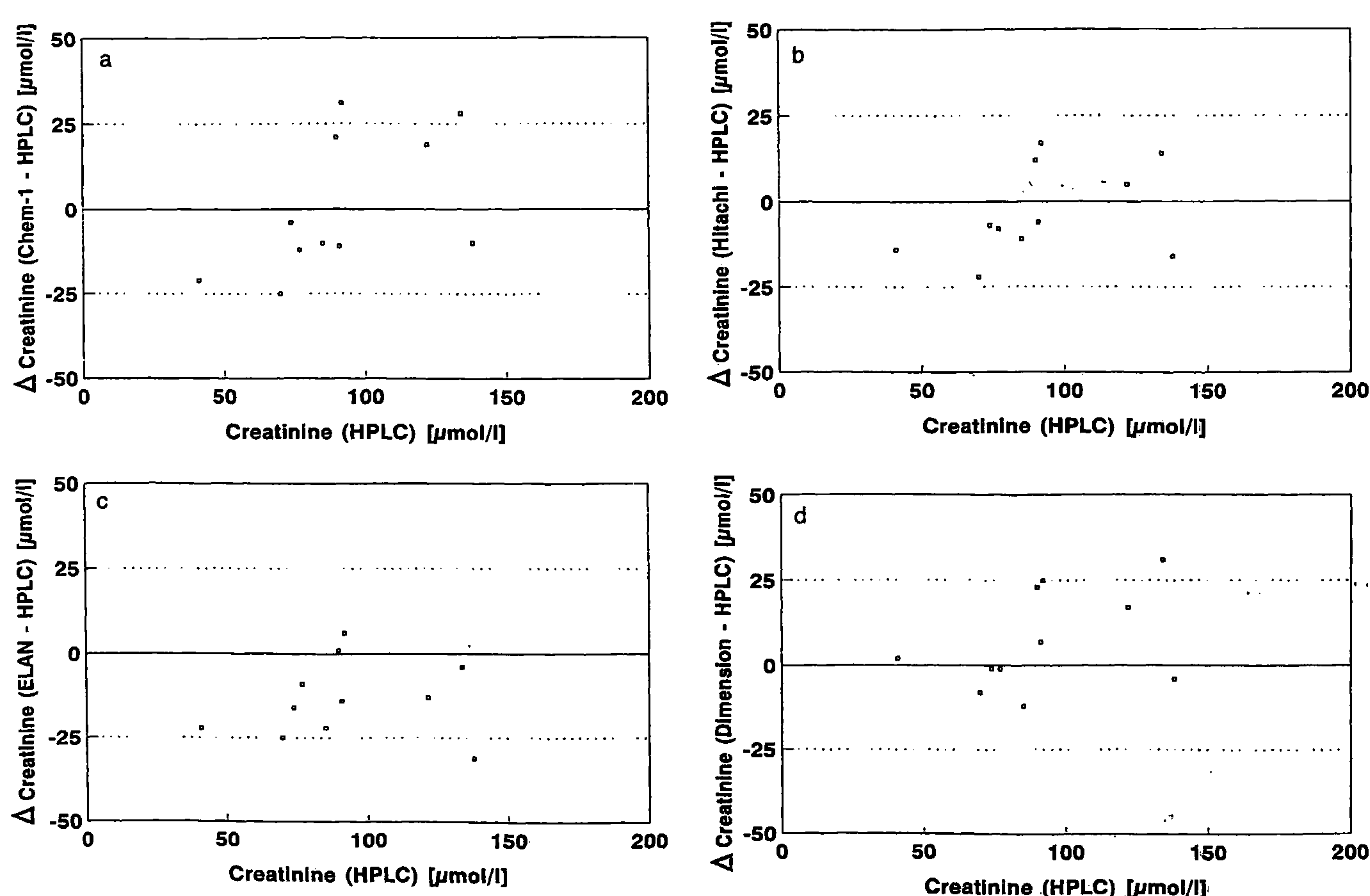

Fig. 2 Residual creatinine values (corrected) of control samples against the creatinine (HPLC) concentration for the methods under study.

Unfortunately, enzymatic creatinine methods are also prone to interference (1, 16) though less than *Jaffé* methods. As suggested by *Bacon* et al. a possible solution is a combination of an enzymatic and a kinetic approach (17).

A second drawback that needs to be overcome is the high cost of enzymatic creatinine reagents.

Finally, we wish to discuss the external assessment of creatinine methods. It is clear from table 5 that only well-documented samples can be used in surveys. When the presentation of the data is redesigned and the extreme outliers are omitted (samples 4, 7 and 9) the picture presented in figure 2 still confirms this observation.

We are aware that the number of samples we used was limited. Nevertheless, it raises the question of the value of surveying the *Jaffé* reaction-based creatinine determination with varying control samples.

In this respect it is also worthwhile to mention the work of *Kenny* (18) who analysed various creatinine methods, predominantly based on the *Jaffé* reaction. In his effort to explain the large variation seen in surveys performed with samples spiked with interfering substances, he detected various reaction patterns.

Finally, the determination of creatinine deserves critical and constructive attention from the clinical chemical professional. However, this also holds for manufacturers. Manufacturers should be obliged to provide sufficient analytical and clinical evaluation information, at least for the most important laboratory quantities. Sometimes they do. It is, unfortunately, not common practice.

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