

Clinical and Analytical Impact of Moving from Jaffe to Enzymatic Serum Creatinine Methodology

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Background: Identification and monitoring of chronic kidney disease (CKD) requires accurate quantification of serum creatinine. The poor specificity of Jaffe creatinine methods is well documented, and guidelines recommend enzymatic methodology. We describe our experience of moving from Jaffe to enzymatic creatinine methodology. We present comparison of >5000 paired Jaffe and enzymatic creatinine results, examine interferences, and attempt to assess clinical consequences of changing methodology.

Methods: Overall, 5303 serum samples received for routine creatinine measurement were analyzed using Jaffe and enzymatic methods with an Abbott Architect autoanalyzer. Associated results for glucose, total bilirubin, triglycerides, total protein, and hemolytic, icteric, and lipemic indexes were extracted from the laboratory database. CKD staging was estimated for each sample to assess potential clinical effects.

Results: The methods correlated well ($r=0.996$) and showed good agreement (Passing-Bablok fit, $y=0.935x+0.074$). Paired analysis, however, showed significant differences ($P<0.001$), and approximately 20% of results differed by more than $\pm 10\%$. Multivariate analysis demonstrated independent associations between difference in creatinine results, glucose ($P<0.0001$), and hemolytic index ($P=0.009$). Glucose demonstrated positive interference in the Jaffe method, and hemolysis produced negative interference in the enzymatic method. Little or no association was observed with other analytes. CKD staging differed in 4% of samples.

Conclusions: Differences between Jaffe and enzymatic serum creatinine results exceed the recommended 5% target for a significant proportion of samples, particularly at concentrations <1.13 mg/dL ($100\text{ }\mu\text{mol/L}$). Both glucose and hemolysis contribute to the variance in results. Although the clinical impact of these differences seems small, laboratories should continue moving toward enzymatic creatinine estimation to ensure the best estimate of renal function.

INTRODUCTION

Chronic kidney disease (CKD) may affect up to 16% of adults worldwide and is associated with

increased risk of all-cause and cardiovascular mortality, renal disease progression, acute kidney injury (AKI), anemia, bone disorders, and reduced quality of life (1). Identification and monitoring of

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Received May 21, 2019; accepted September 22, 2020.

DOI: 10.1093/jalm/jfaa053

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IMPACT STATEMENT

We have evaluated the move from Jaffe to enzymatic creatinine methodology in a teaching hospital. Samples from general practice, inpatients, and outpatients were studied. We present further evidence of the nonspecificity of the Jaffe method versus the enzymatic method, and observed positive interference from glucose. We also demonstrated negative interference in the enzymatic method from hemolysis. Despite analytical differences in creatinine results between the two methods, our data suggest that clinical effects of the differences would be limited. The enzymatic creatinine method produces more accurate laboratory results and laboratories should work toward using this methodology for assessment of renal function.

CKD is based on estimated glomerular filtration rate (eGFR) and urine albumin excretion (2). Despite its limitations, serum creatinine measurement remains the most practical marker to calculate eGFR (3, 4). Accurate creatinine measurement is thus vital for identification of AKI and correct classification of CKD. Until recently, the preferred method for creatinine measurement was the Jaffe method, which involves the reaction of creatinine with picric acid at alkaline pH (5). Creatinine concentration in the sample is determined spectrophotometrically by measuring the absorbance change due to formation of a creatinine-picric acid complex.

Although simple and inexpensive, Jaffe methodology is nonspecific because alkaline picric acid can react with any compound containing a methylene group (6). Glucose, ketones, and protein can cause falsely elevated creatinine readings, whereas bilirubin can produce falsely low results (7, 8). Several modifications have been used to reduce interference in the Jaffe method (8). One of the more commonly applied changes is kinetic compensation, which involves determining the rate of absorbance change from specific time points during the reaction. If measurements are made when creatinine is the primary contributor to the change in absorbance, interference from

fast- or slow-reacting compounds can be reduced. Glucose, acetoacetate, pyruvate, and other ketoacids react relatively quickly with picric acid compared with creatinine, whereas protein reacts more slowly (9). Measurements can thus be timed to minimize contributions from interfering substances.

Unfortunately, kinetic modifications to the Jaffe method have not completely resolved specificity issues (7, 10). Enzymatic estimation of creatinine was first described in 1937 and is inherently more specific because of the selectivity of enzymes (11, 12). Enzymatic methodology also demonstrates improved imprecision and bias relative to the reference method (isotope dilution mass spectrometry) (13, 14). It should be noted, however, that enzymatic assays are not immune to interference. Greenberg et al. (15) showed that enzymatic assays are less affected by the presence of glucose, β -hydroxy butyrate, acetoacetate, and protein but that hemoglobin and bilirubin may cause falsely low enzymatic creatinine results. Furthermore, the nature of the interference varied depending on the enzymatic method used. A number of drugs have been reported to interfere with enzymatic creatinine assays, and interference from IgM paraproteins has also been observed (16–20).

To provide the most accurate estimation of renal function, analytical performance criteria for creatinine assays were produced by the National Kidney Disease Education Program (21). Clinical guidelines also now recommend the use of specific (i.e., enzymatic) creatinine assays that are zero-biased compared with the reference method (22). In 2017, the Clinical Biochemistry service in Greater Glasgow and Clyde (United Kingdom) moved from kinetic Jaffe to enzymatic methodology for serum creatinine measurement. In this article, we describe our experience of this change through comparison of >5000 paired serum creatinine results generated as part of routine clinical service. We examine the effects of possible interferences and review potential clinical consequences of the change in methodology.

MATERIALS AND METHODS

Samples

5303 serum samples, received over 5 days from general practice, inpatients, and outpatients were processed for creatinine, urea, and electrolytes at Glasgow Royal Infirmary. Samples for serum analytes were collected into serum separator tubes, fluoride oxalate tubes were used for glucose (Greiner Bio-One), and were centrifuged on receipt at 2575g for 10 minutes before analysis. Samples for blood gas analysis were collected into heparinized syringes (Greiner Bio-One) and analyzed immediately. The study design was reviewed and approved by the NHS Greater Glasgow and Clyde Health Board.

Analytical Methods and Calculations

Samples were analyzed on an Abbott Architect c16000 analyzer (Abbott Diagnostics) using the kinetic Jaffe and enzymatic creatinine methods (Supplemental Figure 1), traceable to the isotope dilution mass spectrometry reference method (23, 24). The enzymatic result was regarded as the “true” result. The eGFR was calculated only for

adults ≥ 18 years old using the isotope dilution mass spectrometry traceable modification of diet in renal disease equation, which was in routine clinical use during data collection and analysis (25). The eGFR values >60 are presented numerically for comparison. CKD stages were estimated based on the Kidney Disease: Improving Global Outcomes clinical practice guideline (2). CKD stages were assigned on the basis of a single creatinine measurement, although in practice, 2 measurements 90 days apart are required with urine albumin:creatinine ratios (22). In the absence of urine albumin results, CKD stage 1 or 2, based on an eGFR >60 mL/min per 1.73 m^2 , is presented as “no CKD.”

Using the laboratory information management system (Telepath; DXC) associated values for hemolytic, icteric, and lipemic indexes (HIL; surrogate markers for hemoglobin, bilirubin, and lipids), glucose, total bilirubin, triglycerides, total protein, and request details were extracted (as available) based on sample and patient identification numbers. Concentrations of bilirubin, triglycerides, total protein, and HIL were all measured on an Abbott Architect c16000 analyzer. Glucose results obtained on the same day as creatinine results were included in the study. If multiple glucose results were available, the closest in time to the creatinine measurement was selected. Glucose was measured either using an Abbott Architect c16000 analyzer or a GEM 5000 point-of-care blood gas analyzer (Werfen). Although there is approximately 10% difference between venous plasma and whole-blood glucose measurements, it was concluded that such differences would have minimal impact in this study and that general trends would be preserved across both sample types (26). Only details that accompanied the original request were reviewed to identify potential sources of interference, such as hyperglycemia, paracetamol overdose (for *N*-acetyl cysteine [NAC]), α -methyl dopa and related compounds, or the presence of paraproteins.

Statistical Analysis

Data for glucose, total bilirubin, triglycerides, and HIL were not normally distributed, so they were $\log_{10}$ transformed for statistical analysis. Data were analyzed using univariate correlation analysis, and analytes with P values <0.05 were included in multivariate analysis. Total protein was available for only 187 samples and so was excluded from multivariate analysis. Univariate and multivariate analysis was performed with SPSS software (version 20.1; IBM Corp). Pairwise t -tests and group comparisons (Wilcoxon-Mann-Whitney test) were performed using Analyse-it (version 3.76.5; Analyse-it Software).

RESULTS

Method Characteristics and Interferences

The manufacturer reports similar analytical performance for the Jaffe and enzymatic creatinine assays, with comparable limits of quantification (approximately 0.10 mg/dL [9 μ mol/L]) and linearity (linear to approximately 33.93 mg/dL [3300 μ mol/L]). Total imprecision is reported as $\leq 6.0\%$ and $\leq 3.6\%$ for the Jaffe and enzymatic methods, respectively. Information from the manufacturer regarding interfering compounds suggests that the enzymatic method is more susceptible to negative interference from high concentrations of bilirubin and hemoglobin but is less susceptible to positive interference from glucose and protein. The manufacturer also reports that the enzymatic method suffers from negative interference by α -methyl dopa (antihypertensive) and NAC (antidote for paracetamol overdose) of up to 20% and 10%, respectively (23, 24).

Analytical Comparison

Overall agreement between the enzymatic and Jaffe methods is good (Fig. 1, Supplemental Table 1), although the spread of absolute and relative differences between the 2 methods is large,

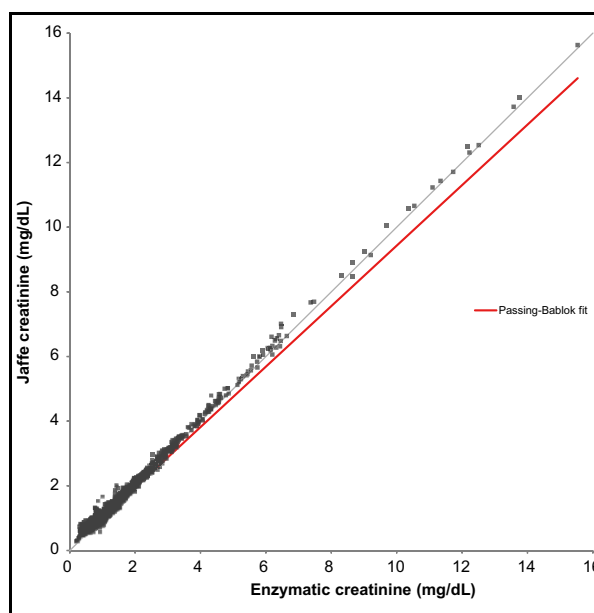
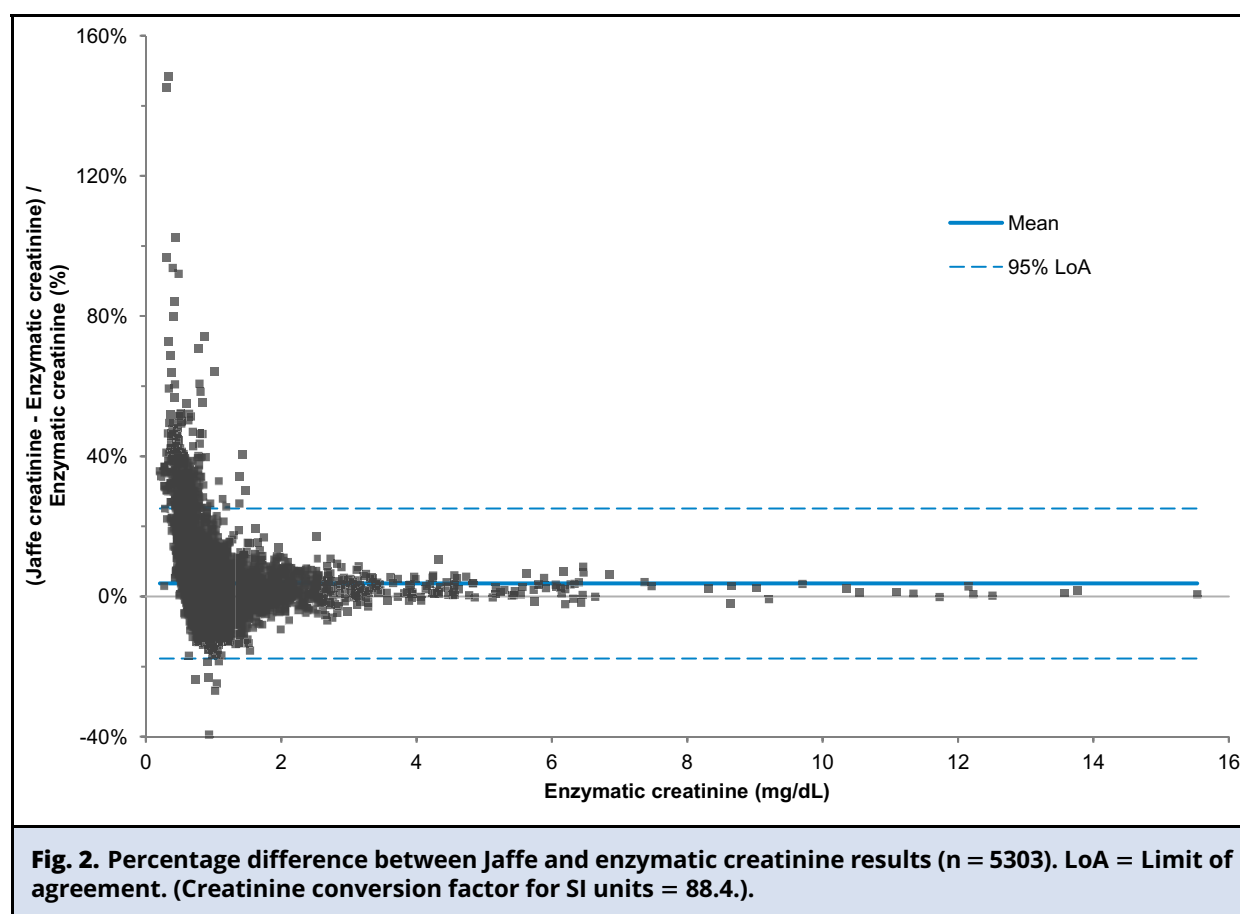


Fig. 1. Passing-Bablok regression analysis of 5303 creatinine results measured by Jaffe and enzymatic methods. Red line indicates Passing-Bablok fit, $y = 0.9354x + 0.074$. Gray line indicates $y = x$. Pearson correlation coefficient = 0.996. (Creatinine conversion factor for SI units = 88.4.).

particularly below creatinine concentrations of 1.13 mg/dL (100 μ mol/L) (Fig. 2). A pairwise t -test showed a statistically significant difference between enzymatic and Jaffe creatinine results ($P < 0.001$). Of the 5303 samples, 1079 (20%) Jaffe creatinine results differed from the enzymatic result by either -10% or less or $+10\%$ or more (Table 1). Median concentrations of glucose, total protein, triglycerides and lipemic index were slightly higher in the group with $+10\%$ or more versus -10% or less. Bilirubin concentration and hemolytic and icteric indexes were similar between the 2 groups.

Univariate analysis demonstrated significant correlations between the percentage difference in creatinine result from the 2 methods and glucose, triglycerides, total protein, and HIL ($P < 0.01$ in each case) (Table 2). Only bilirubin did not show a statistically significant relationship. Multivariate



analysis demonstrated independent associations between creatinine difference (as percentage) and both glucose ($P < 0.0001$, $\beta = 0.565$) and the hemolytic index ($P = 0.009$, $\beta = 0.103$).

Analytical Interference in the Jaffe Method

Glucose concentrations were available for 1589 samples (27%). Figure 3A and Supplemental Table 2 demonstrate a positive correlation between glucose concentration and percentage difference in creatinine and suggest that this effect becomes more apparent above glucose concentrations of approximately 270 mg/dL (15 mmol/L). Wilcoxon group comparison showed a statistically significant difference in Jaffe creatinine values associated with glucose concentrations ≤ 108 or

>270 mg/dL (≤ 6 or >15 mmol/L; $P < 0.0001$) but did not show a difference for enzymatic creatinine values ($P = 0.6449$).

Ten samples were identified from patients with possible hyperglycemic states (diabetic ketoacidosis or hyperosmolar hyperglycemic state). Jaffe creatinine was on average 37% higher than the enzymatic result in these patients, and the average glucose was 400 mg/dL (22 mmol/L) (Supplemental Table 3). In general, the data show that the difference in creatinine result increases with glucose concentration. In one of these samples, the creatinine difference was only 6% with a glucose concentration of 384 mg/dL (21.1 mmol/L). Measured creatinine values in this sample were 3.53 mg/dL (312 μ mol/L) in the Jaffe method and

Table 1. Characteristics of samples in which the Jaffe creatinine differed from the enzymatic creatinine by either +10% or more (939 samples from 837 patients) or –10% or less (140 samples from 131 patients).

Difference in Creatinine	+10% or More		–10% or Less	
	Median	Range	Median	Range
Jaffe creatinine, mg/dL (μmol/L)	0.72 (64)	0.28–4.79 (25–423)	0.87 (77)	0.53–1.31 (47–116)
Enzymatic creatinine, mg/dL (μmol/L)	0.62 (55)	0.20–4.32 (18–382)	1.00 (88)	0.63–1.54 (56–136)
Difference (Jaffe – enzymatic), mg/dL (μmol/L)	0.11 (10)	0.05–0.64 (4–57)	–0.11 (–10)	–0.37 to 0.08 (–33 to –7)
Difference (Jaffe – enzymatic), %	17	10–148	–11	–39 to –10
eGFR ^a (Jaffe), mL/min/1.73 m ²	89	9–254	78	38–140
eGFR (enzymatic), mL/min/1.73 m ²	108	10–365	68	32–112
Glucose, mg/dL (mmol/L)	115 (6.4)	34–795 (1.9–44.1)	88 (4.9)	50–182 (2.8–10.1)
Total bilirubin, mg/dL (μmol/L)	0.5 (9)	0.1–31.0 (2–530)	0.5 (8)	0.1–10.5 (2–179)
Triglycerides, mg/dL (mmol/L)	177 (2.0)	44–4159 (0.5–47.0)	124 (1.4)	53–345 (0.6–3.9)
Total protein (g/L)	73	60–83	67	58–73
Hemolytic index (g/L)	0.06	0.00–15.16	0.05	0.00–1.61
Icteric index, mg/dL (μmol/L)	0.7 (11.5)	0.0–32.7 (0–560)	0.7 (11.8)	0.1–28.7 (2–490)
Lipemic index (g/L)	0.06	0.0–6.2	0.02	0.00–0.44

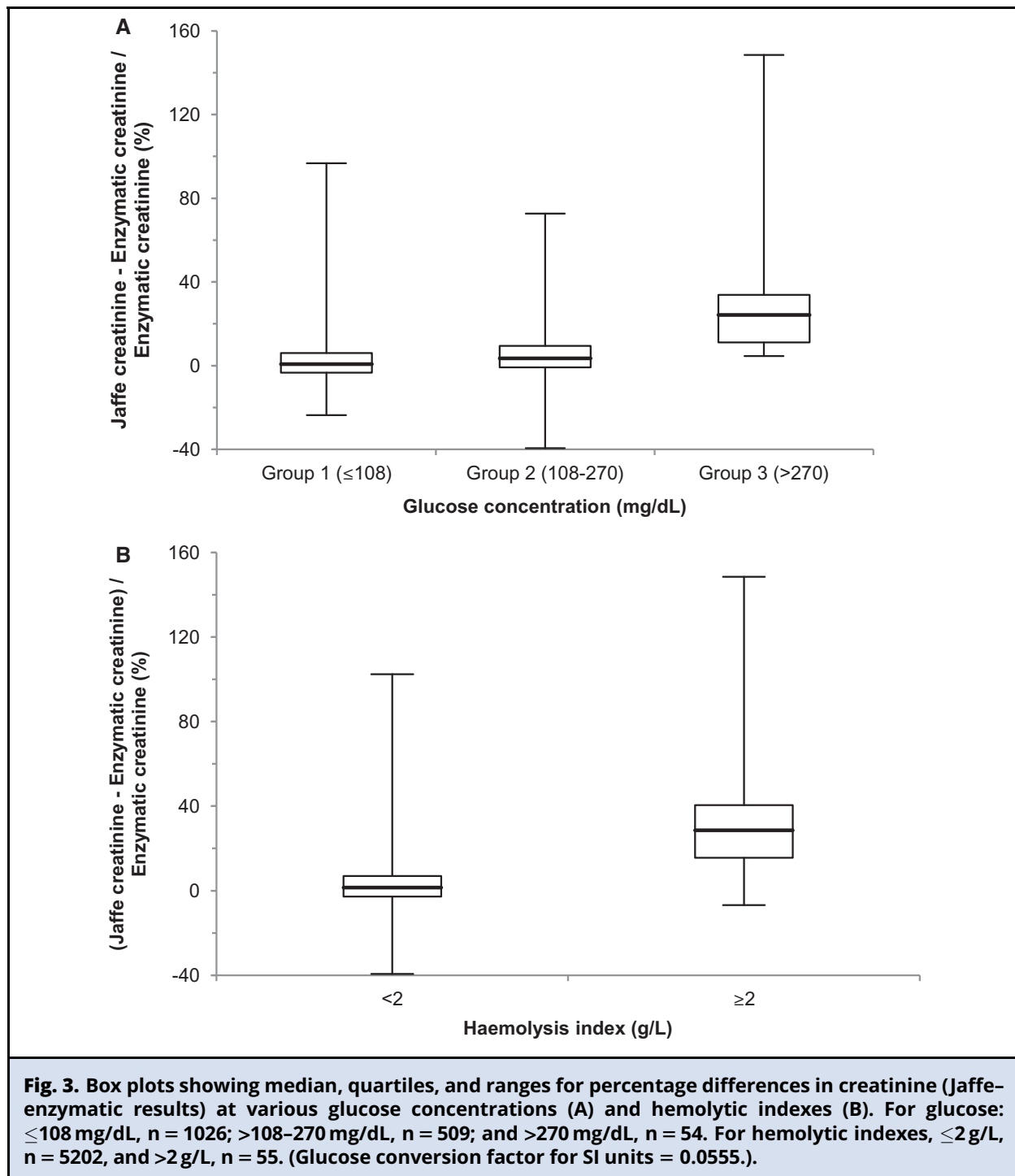
^aeGFR, estimated glomerular filtration rate.**Table 2. Univariate analysis showing correlations between the percentage difference in Jaffe and enzymatic creatinine values and analytical interferences.**

Interference	Pearson Correlation coefficient	P (2-Tailed)	n
Log ₁₀ glucose	0.505	<0.0001	1589
Log ₁₀ bilirubin	–0.009	0.556	4236
Log ₁₀ triglycerides	0.262	<0.0001	840
Total protein (g/L)	0.244	0.001	187
Log ₁₀ hemolytic index	0.140	<0.0001	4998
Log ₁₀ icteric index	–0.036	0.009	5224
Log ₁₀ lipemic index	0.100	<0.0001	4373

3.34 mg/dL (295 μmol/L) in the enzymatic method. Creatinine results from other patients ranged from approximately 0.45 to 1.70 mg/dL (40–150 μmol/L) in the Jaffe method and 0.34 to 1.13 mg/dL (30–100 μmol/L) in the enzymatic method.

Analytical Interference in the Enzymatic Method

The hemolytic index also demonstrated a positive correlation with percentage difference in creatinine (Fig. 3B, Supplemental Table 4). Wilcoxon group comparison showed no difference in Jaffe



creatinine values associated with hemolytic indexes of < 2 or ≥ 2 g/L ($P = 0.0826$) but did show a difference for enzymatic creatinine values

($P = 0.0007$), suggesting that hemolysis causes a significant negative bias in the enzymatic method relative to the Jaffe method.

One patient in this data set received NAC. Two samples from this patient showed the enzymatic creatinine was 11% and 13% lower than the Jaffe result, in keeping with data from the manufacturer. Three paraprotein-containing samples were identified from clinical details. One sample with an IgG κ (21 g/L) and 2 with IgM λ paraproteins (14 and 23 g/L, respectively). All samples were from different patients. The difference in creatinine results in these 3 samples was $\leq 7\%$. No patients were identified as having received α -methyl dopa or related compounds (dopamine, dobutamine).

Chronic Kidney Disease Staging

The number of samples assigned to each CKD category was similar for both the Jaffe and enzymatic creatinine methods; however, classification differed in 205 of 5243 samples from 196 adult patients (Table 3). No patients were reclassified by >1 stage, and the majority of reclassifications were between no CKD and CKD3. Assuming the enzymatic creatinine result produces the correct classification, there were 106 reclassifications to a less severe CKD stage (82 samples were reclassified from CKD3 to no CKD, 21 from CKD4 to CKD3, and 3 from CKD5 to CKD4). Ninety-nine samples were reclassified to a more severe CKD stage (94 samples were reclassified from no CKD to CKD3 and 5 from CKD3 to CKD4).

The median glucose concentration for samples reclassified from CKD3 (Jaffe) to no CKD

(enzymatic) was 193 mg/dL (10.6 mmol/L), and for those reclassified from no CKD (Jaffe) to CKD3 (enzymatic), it was 105 mg/dL (5.8 mmol/L). This result is consistent with the finding that positive interference from glucose in the Jaffe method could generate a more severe CKD classification. Other analytes did not show clear associations across the groups. It was also noted that 67% of patients with mismatched CKD stages were female, whereas only 55% samples overall were from female patients.

DISCUSSION

Current recommendations are to use specific enzymatic methods for creatinine measurement; however, a significant proportion of laboratories in the United Kingdom still use Jaffe methodology. In May 2018, data from the United Kingdom National External Quality Assessment Service (UK NEQAS) showed that of the UK laboratories in the general chemistry scheme measuring creatinine, 212 were using traditional Jaffe methods and 276 enzymatic methods (F. MacKenzie, personal communication, May 16, 2018). The most likely reason for this is the cost of the enzymatic assay, although this may improve as more laboratories change methodology.

This article has presented analysis of a large data set generated by a routine clinical biochemistry laboratory. Enzymatic creatinine results have been used as the comparator because that approach is the recommended methodology and shows better agreement with the reference method (13, 21). The data demonstrate good agreement between the Abbott Architect Jaffe and enzymatic serum creatinine methods; however, bias for a significant number of Jaffe creatinine results compared with the enzymatic method exceeds the recommended limit of $<5\%$ (21). Indeed, 20% of Jaffe creatinine values measured in

Table 3. Number of samples assigned to CKD stages based on Jaffe and enzymatic creatinine values.

Enzymatic Jaffe	No CKD	CKD stage 3	CKD stage 4	CKD stage 5	Total
No CKD	3794	82	0	0	3876
CKD stage 3	94	930	21	0	1045
CKD stage 4	0	5	214	3	222
CKD stage 5	0	0	0	100	100
Total	3888	1017	235	103	5243

this study differed from the enzymatic result by more than $\pm 10\%$.

The primary contribution to this bias appears to be poor specificity of the Jaffe method. Glucose demonstrated a significant independent correlation with the difference in creatinine results between the 2 methods. The data clearly show positive interference from glucose in the Jaffe method, with no effect in the enzymatic method. This finding is in accordance with information provided by the manufacturer and in published literature and is likely to be due to a direct reaction of glucose with picric acid in the Jaffe method (6–8, 27).

In contrast to glucose, hemolysis appears to cause negative interference in enzymatic creatinine measurement. Comparisons showed no significant change in Jaffe creatinine results with increasing hemolytic index but demonstrated a significant decrease in the enzymatic method. Although this finding is in accordance with the information from the manufacturer and the published literature, it is perhaps a less well-known source of interference (15). The manufacturer reports a 7% negative bias at a hemoglobin concentration of 10 g/L in the enzymatic method, and a 5% positive bias in the Jaffe method. The manufacturer recommends hemolytic index cutoffs of 5 g/L for the Jaffe method and 10 g/L for the enzymatic method, above which serum creatinine results should not be reported. Our data suggest enzymatic creatinine results could be significantly lower when the hemolytic index is ≥ 2 g/L, which could affect patient care, especially in pediatrics.

No significant independent correlations with the difference in creatinine between the 2 methods were observed for bilirubin, triglycerides, or the icteric and lipemic indexes. Recovery data from the manufacturer suggest that bilirubin and lipid (in the form of Intralipid, Fresenius Kabi AB, Sweden) can cause negative interference in the enzymatic method, and bilirubin interference has been reported in the literature (15). We identified

weak correlations between the icteric and lipemic indexes and difference in creatinine from the enzymatic and Jaffe methods, and no association with bilirubin concentration. In the case of bilirubin and the icteric index, it is possible that this study did not contain samples with sufficiently high bilirubin concentrations to demonstrate this effect. The maximum total bilirubin concentration in this study was 30.99 mg/dL (530 μ mol/L), and only 7 of 4233 bilirubin results were >23.39 mg/dL (>400 μ mol/L), whereas the manufacturer reports negative effects on recovery at bilirubin concentrations of 66.01 mg/dL (1129 μ mol/L; unconjugated) and 26.02 mg/dL (445 μ mol/L; conjugated). Similarly for triglycerides and the lipemic index, only 2 of 736 triglyceride concentrations were >1769.69 mg/dL (>20 mmol/L). In contrast to the icteric index, which generally correlates well with bilirubin concentration, the lipemic index is based on the addition of soy-based Intralipid to serum samples, which may not consistently replicate the effects of endogenous lipemia (28, 29).

α -Methyldopa and related compounds, and NAC have been reported to produce negative interference in enzymatic creatinine values (30). Results from the single patient in this data set who received NAC agree with the manufacturer, with reductions in enzymatic creatinine results of approximately 12%. The literature, however, suggests that interference from NAC would not occur at concentrations expected during treatment (31). No evidence of dopamine-based treatment was identified in this data set. Published case studies describe interference in the final step of the enzymatic reaction (Trinder reaction) (Supplemental Figure 1) by phenindione and ethamsylate (16, 17). No significant interference from these compounds is reported by the manufacturer, and neither drug was identified in this study. Further work would be required to evaluate the impact of such drugs on creatinine measurement in our hospital.

It is almost certain that there are interferences in the enzymatic method that have yet to be

identified. Since moving to the enzymatic method, the authors have identified 1 case of negative interference from an IgM paraprotein (21 g/L) and observed negative interference due to significantly elevated triglycerides (approximately 8100 mg/dL [92 mmol/L]; data not shown). Both are rare but important factors about which clinical laboratories should be aware. The nature of paraprotein interference is likely to be patient-specific. Only 3 paraprotein-containing samples (ranging from 14 to 23 g/L) were identified in this study and showed no evidence of interference. Additional work will be undertaken to identify the potential scope of this problem, which could highlight patients for whom enzymatic creatinine measurement may be unreliable for monitoring renal function.

Although analytical differences were observed between creatinine results produced by the Jaffe and enzymatic methods, the data suggest that the clinical impact of these differences may be relatively small. The average difference in creatinine values associated with glucose concentrations >270 mg/dL (>15 mmol/L) was approximately 0.24 mg/dL (21 μ mol/L; 54/5303 samples). Because the enzymatic creatinine concentration was lower than the Jaffe creatinine in these samples, it could mean that some patients who would previously have been identified as having AKI would no longer fall into this category with the enzymatic method. Although the numbers are small, early management of hyperglycemia and “pre-renal” AKI are often similar (i.e., intravenous fluids); therefore, we believe this is unlikely to have a significant clinical impact on patient management at our institution. It should be noted that overestimation of creatinine with the Jaffe method could have a more pronounced clinical effect in general practice among poorly controlled diabetic patients or patients with low creatinine (e.g., in children or patients with low muscle mass). Indeed, the difference in measured creatinine between the 2 methods is more pronounced at enzymatic creatinine concentrations $\leq$ 1.13 mg/dL ($\leq$ 100 μ mol/L), where

the Jaffe creatinine is on average 5% higher (range, –39% to 148%, $n=4151$) than the enzymatic results compared with an average of 1% higher (range, –15% to 41%, $n=1152$) for concentrations >1.13 mg/dL (>100 μ mol/L). Figures 1 and 2 show that agreement between the 2 methods is much better at higher creatinine concentrations, consistent with the literature (32). We observed 1 patient with plasma glucose of 380 mg/dL (21.1 mmol/L) for whom the difference in creatinine results was only 6%. In this case, measured creatinine was approximately 3.39 mg/dL (300 μ mol/L) in both assays. It is possible that the positive effect of glucose on Jaffe creatinine values is limited, and thus the relative contribution at higher creatinine concentrations is less significant.

Assessment of CKD stages also suggested a relatively small clinical impact. CKD stage classifications calculated from the 2 methods differed in only 4% of samples, predominantly between no CKD and CKD3. A small number of changes between stages 3 and 4 were also observed. It is unlikely that a single result in this range of creatinine concentrations would have a significant effect in terms of treatment or referral to specialist care because classification of CKD requires >1 abnormal result over a period of 3 months. In addition, it was noted that the proportion of samples from female patients whose CKD stage was reclassified was higher than the proportion in the overall data set. The reasons for this result are unclear, and further investigation is required to ascertain whether it is significant.

Relatively few studies have looked at the clinical consequences of moving from Jaffe to enzymatic creatinine methodology. Schmidt et al. (33) observed discordance between eGFR determined from enzymatic and Jaffe creatinine methods and identified a misclassification rate of approximately 4%. The work of Schmidt et al. studied creatinine results from a single platform in outpatients and, similar to the data presented here, noted that the majority of misclassifications occurred at an eGFR of approximately 60 mL/min per 1.73 m² with no

consistent direction of discordance. Drion et al. (32) asserted that the risks associated with a change from CKD3 (eGFR 57 mL/min per 1.73 m²) to stage 2 (eGFR 62 mL/min per 1.73 m²) are similar but demonstrated significant differences in CKD staging ranging between 1% and 42% for eGFR values of 45 to 60 mL/min per 1.73 m². Drion and coworkers examined Jaffe and enzymatic creatinine results from different analytical platforms across multiple laboratories. The former of these 2 studies agrees well with the data presented here in terms of misclassification rate, and it seems likely that results from a single center or using a single analytical platform will be more consistent.

The conclusion of Schmidt et al. (33) was that the risk of misclassification using the Jaffe method could be acceptable in an outpatient setting. Although this may be possible, it contradicts current guidelines. In addition, given the degree of interference from glucose and other compounds in the Jaffe method, the enzymatic method is likely to be safer, more reliable, and more robust in a laboratory providing acute services (22). Measurement of urine creatinine was not performed in this study; however, it would be interesting to examine the differences between

creatinine clearance determined from Jaffe and enzymatic methods and the clinical effects.

In conclusion, this robust data set generated from a large number of patient samples shows that agreement between the Jaffe and enzymatic serum creatinine methods in a single routine laboratory is generally good. The data further confirm the nonspecificity of the Jaffe method, especially at lower concentrations of creatinine. We demonstrated that the enzymatic creatinine method is less susceptible to positive interference from glucose and that hemolysis can cause negative interference, which requires further assessment and discussion with the manufacturer. Although the clinical impact of these analytical differences appears to be reassuringly small, it is important that laboratories continue to move toward more specific enzymatic analysis of creatinine to produce the most accurate results possible for diagnosis and monitoring of renal disease.

SUPPLEMENTAL MATERIAL

Supplemental material is available at *The Journal of Applied Laboratory Medicine* online.

Nonstandard Abbreviations: CKD, chronic kidney disease; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; HIL, hemolytic, icteric, and lipemic indexes.

Author Contributions: All authors confirmed they have contributed to the intellectual content of this paper and have met the following 4 requirements: (a) significant contributions to the conception and design, acquisition of data, or analysis and interpretation of data; (b) drafting or revising the article for intellectual content; (c) final approval of the published article; and (d) agreement to be accountable for all aspects of the article thus ensuring that questions related to the accuracy or integrity of any part of the article are appropriately investigated and resolved.

N.R. Syme and D. Talwar conceived the study design. N.R. Syme performed data analysis and prepared the first draft of the manuscript. D.C. McMillan performed univariate and multivariate analysis. K. Stevens and C. Stirling provided clinical assessment of the data. All authors provided intellectual content of critical importance to the work described and contributed to all revisions of the manuscript.

Authors' Disclosures or Potential Conflicts of Interest: Upon manuscript submission, all authors completed the author disclosure form. Disclosures and/or potential conflicts of interest: **Employment or Leadership** C. Stirling, NHS GG+C Health Board. **Consultant or Advisory Role** None declared. **Stock Ownership** None declared. **Honoraria** None declared. **Research Funding** None declared. **Expert Testimony** None declared. **Patents** None declared.

Role of Sponsor: No sponsor was declared.

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