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Comparison of Jaffe Method and Enzymatic Method at Measuring Serum Creatinine Level, Creatinine Clearance and Estimated Glomerular Filtration Rate

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ABSTRACT
Background: Correct measuring of blood and urine creatinine level is necessary for identification and tracking of chronic kidney disease (CKD). **Objective:** The aim of this study is a comparison of Jaffe and enzymatic methods for measuring creatinine in serum and in urine, in order to determine whether there are any statistical significant differences between them, and whether they are reflected on creatinine clearance calculation and estimated glomerular filtration rate (eGFR). **Methods:** Creatinine in serum and urine was measured for the group of patients (N=60; female=34, male=26) from 24 to 69 years of age by using Jaffe's method on Dimension RxL biochemical analyzer, and enzymatic method on integrated biochemical and immunochemical analyzer Architect ci8200, and obtained levels are used for creatinine clearance calculation and eGFR. **Results:** The methods correlate well, both in measuring serum creatinine (r_1 = 0.990) and in measuring urine creatinine (r_2 =0.974). There are no statistically significant differences between them (p=0.57). Measuring creatinine using different methods showed no statistically significant differences in the calculated clearances (p=0.93), they significantly correlate (r=0.9722). eGFR, using the MDRD and CKD-EPI formulas, were not statistically significantly different, regardless of the used method. **Conclusion:** Apart from significant correlations between the used methods, the results of using the Jaffe and enzymatic methods showed no significant differences at measuring serum creatinine level, or creatinine clearance and glomerular filtration rate.
Keywords: creatinine, clearance, enzymatic method, Jaffe method.

1. BACKGROUND

Jaffe colorimetric method for measuring creatinine level has been used since 1886, when Max Jaffe noticed forming of red coloring when creatinine reacted with picrine acid in alkaline solution (1).

Although it is non- specific due to its simplicity and low cost, it is still applied in the largest number of laboratories throughout the world (2).

During the measurement, non-creatinine chromogens, such as glucose, acetoacetate, bilirubin and cephalosporins, interfere and can overestimate serum creatinine value. Relative effect of non-creatinine chromogen is higher at lower serum creatinine values. Enzyme method is accepted as better than Jaffe method, due to smaller sample volume necessary for analysis and better specificity, because glucose, acetoacetate and cephalosporins do not interfere in this method, while bilirubin can cause negative interference, which depends on creatinine and bilirubin levels (3).

Most often applied measurement of total kidney function in clinical practice is measuring serum creatinine level. Unfortunately, many factors influence that measurement,

except level of kidney function, and it significantly varies depending on age, gender and muscular mass (4).

Calibration of serum creatinine varies between the laboratories, and calibration errors are reflected on estimated glomerular filtration rate (eGFR) (2). Calibration of serum creatinine, in terms of adjusting these differences, is not standardized among laboratories, which leads to variations in serum creatinine values between them (5).

The gold standard for determining GFR is measuring exogenous substances clearance such as inulin, iohexol and small molecules marked with radioactive isotopes ([51] Cr-EDTA, [99m] Tc-DTPA, [125] I-iothalamate), but these techniques are long-term, require hard work, exposure to radiation and they are expensive (6).

GFR is the most important determinant for CKD identification and classification (7).

GFR in clinical practice is usually based on measurement of serum creatinine level and creatinine clearance calculation, even though the limitations of these measurements are known. Therefore, determining eGFR using formulas based on serum creatinine level is recommended (8).

In order to improve detection of CKD, many laboratories calculate and print in the finding the strength of eGFR by applying formula MDRD (Engl. Modification of Diet in Renal Disease) with each request for measuring serum creatinine level (4).

CKD-EPI (The Chronic Kidney Disease Epidemiology Collaboration) is a research group established by the National Institute of Diabetes and Digestive and Kidney Diseases which developed the CKD-EPI formula for eGFR in adults in 2009 (9).

eGFR using the CKD-EPI formula is more accurate than eGFR using the MDRD formula, at all GFR values, and especially at normal or increased GFR (10).

In order to provide the most accurate assessment of kidney function, clinical recommendation by the National Kidney Disease Education Program is the use of enzymatic specific tests on creatinine which show less bias in comparison with the reference method (11).

2. OBJECTIVE

The aim of this study is a comparison of Jaffe and enzymatic methods for measuring serum and urine creatinine, in order to determine whether there are statistically significant differences between them, and whether they are reflected on creatinine clearance calculation and eGFR.

3. RESPONDENTS AND METHODS

Respondents

There were 60 patients of both genders included in the study (female n=34; male n= 26), aged from 24 to 69 years, hospitalized at the Clinics for Internal Diseases, University Clinical Center in Tuzla (UCC Tuzla), whose serum samples and 24-hour urine were delivered to the Institute of Biochemistry, Polyclinics of Laboratory Diagnostics, UCC Tuzla for measuring creatinine concentration and clearance level.

Creatinine clearance test for all the respondents was made for the purpose of assessments of kidney function. Patients in the study were identified through a unique identification number, and no personal information was used, except the mandatory information for identification (age, gender) and heights and weight which were necessary for the creatinine clearance test for which they were referred to the laboratory.

The Ethical Committee consent was previously obtained for all the analysis made, in accordance with the University Clinical Center in Tuzla procedure for the aforementioned type of study.

Methods

Creatinine clearance is calculated according to equation

$$C = \frac{U \cdot V}{S} \cdot t \ (12)$$

in which U is the creatinine level in urine (µmol/L), V volume of 24-hour urine (mL), S serum creatinine level (µmol/L), and t mumber of minutes in a day (1440). The result has been corrected by factor in accordance to the "ideal" body surface (1.73m ^{2}), whereas A is the body surface of the respondents calculated on the basis their heights and weight. The clearance results are expressed as mL/min/1.73 m ^{2} (12).

eGFR was calculated using medical calculator QxMD Online Calculator which estimates GFR by including data (serum creatinine level, age, sex and race in the MDRD formula and the CKD-EPI formula) (13-14).

Statistical data analysis

Computer program Excel 2010 MS Office, as well as programming package SPSS 20.0 and Medcalc 11 are used to display results and statistical data analysis. All the variables were tested to determine if they are normally distributed by using the Kolmogorov-Smirnov test (KS test). Comparison between the methods is done using standard sequence of tests – t-test to determine if there is an average difference between measured values, correlation test with calculating coefficient concordances to determine if there is a relationship between the two methods.

Finally, Passing- Bablok regression analysis with determination of regression equation with intercept A and slope B along with the corresponding reliability interval and with Cumsum test for linearity were done. Statistical hypotheses were tested on the significance level of ☐ 0.05, i.e. the difference among samples was considered significant if p<0.05.

4. RESULTS

A group of 60 respondents, 24-69 years of age, consisted of 34 female respondents and 26 male respondents, whose results of the examined parameters were tested to determine normal distribution using the Kolmogorov-Smirnov test. Average age of respondents was 56.80±10.39; body weight 77.80±11.45 and body height 170.18±10.40.

Serum creatinine levels measured using Jaffe and enzymatic methods were compared, and an average difference of 6.63 µmol /L (%95 CI=-16.28 to 29.54) is found between the methods, which was not proved to be

	Urine Creatinine (mmol/24h)		Serum creatinine (µmol/L)	
	Jaffe method	Enzymatic method	Jaffe method	Enzymatic method
Number of the respondents	60	60	60	60
Arithmetic middle	10.25	10,20	117.65	111.02
Standard deviation	3.05	2.93	64,42	62,29
Minimum	5.00	5.00	51	47
Maximum	20.00	20.00	298	309
	t=0.09; df = 118; p=0.93		t=0.57; df = 118; p=0.57	

Table 1. Comparison of serum and urine creatinine levels measured using Jaffe and enzymatic method

Creatinine clearance (ml/min/1.73m^2)		
Jaffe method	Enzymatic method	
Number of the respondents	60	60
Arithmetic middle	68,70	72.30
Standard deviation	32.04	34.07
Minimum	13.00	15.00
Maximum	131.00	136.00
t=0.59; df = 118; p = 0.55		

Table 2. Creatinine clearance measured using Jaffe and enzymatic method

statistically significant (t=0.57; df =118; p=0.57).

Subsequently, correlation between these two methods was done, and significant correlation of 0.99 (p<0.0001) was found, with coefficient concordance R^2=0.98 (%95 CI=0.976-0.99).

Creatinine levels measured in 24-hour urine were compared using Jaffe and enzymatic methods. An average difference of 0.05 mmol/24h (%95 CI=-1.03 to 1.13) is found between the methods, which was not statistically

difference between the methods. On the other hand, the slope B was 0.95 (%95 CI=0.89 to 1.0) including value 1 in CI, which again implies that there were no differences by proportional type between the 2 methods. The belonging regression equation read:
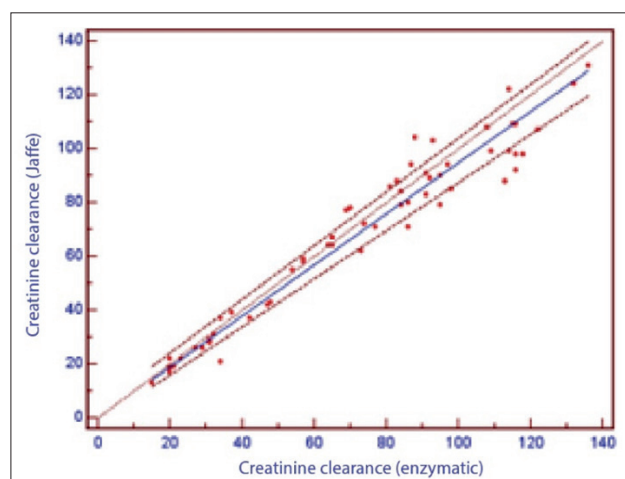
Klirens (Jaffe) = -0,0385 + 0,9487 x Klirens (enz)

Cusum test for linearity showed no significant deviation from linearity (p>0.05). A graphic representation of this analysis with a good matching between the two methods is given in Figure 1.

Solid blue line- regression direction; dashed red lines- reliability intervals; dotted line red line-ideal direction y=x

eGFR between Jaffe and enzymatic methods were compared according to the CKD-EPI formula, and an average difference of 3.34 ml/min/1.73m^2 (%95 CI) between the methods is found, which was not statistically significant (t=0.583; df =118; p=0.560), as shown in Table 3.

eGFR between two formulas (CKD-EPI to MDRD) were compared using enzymatically determined creatinine value, and using Passing-Bablok regression which

	eGFR MDRD (ml/min/1.73m^2)		eGFR CKD-EPI (ml/min/1.73m^2)	
	Jaffe method	Enzymatic method	Jaffe method	Enzymatic method
Number of the respondents	60	60	60	60
Arithmetic middle	66,32	72.07	66.43	69,77
Standard deviation	32.01	35,40	30,68	32.02
Minimum	15.00	14.00	14.00	14.00
Maximum	157.00	157.00	118.00	124.00
	t=0.933; df = 118; p=0.35		t=0.583; df = 118; p=0.560	

Table 3. Comparison of eGFR according to MDRD and according to CKD-EPI formula between Jaffe and enzymatic methods

significant (t=0.09; df =118; p=0.93). Next, correlation between these two methods was done, and significant correlation of 0.974 (p<0.0001), with coefficient concordance R^2=0.973 (%95 CI=0.955-0.983) was found, which is shown in Table 1.

Creatinine clearance values measured by Jaffe and enzymatic methods were compared. An average difference of 3.6 ml//1.73m^2 (%95 CI=-8.35 to 15.56) was found between the methods, which was not statistically significant (t=0.59; df =118; p=0.55). Next, correlation between these two methods was done, and significant correlation of 0.9722 (p<0.0001), with coefficient concordance R^2=0.965 (%95 CI=0.943-0.978) was found.

For the purpose of comparison of these two methods of creatinine clearance measuring, the Passing- Bablok regression analysis was used. The intercept A of -0.039 (%95CI=-2.0 to 3.97) was obtained, i.e. the CI did include value zero, which implies that there was no systematic

Figure 1. Passing-Bablok regression model for creatinine clearance comparison measured with Jaffe and enzymatic methods;

showed intercept A from 0 and slope B from 1 values, but with significant deviation from linearity according to Cusum test (p<0.01) , which indicated absence of linear matching results, as shown in Table 3.

5. DISCUSSION

Group of respondents hospitalized at the Clinics for Internal Diseases, UCC Tuzla included in this study, is a representative random sample as encountered in the clinic practice every day. Standardization implied serum creatinine calibration with SRM 967, as a secondary reference material of routine methods, levels of which were measured by NIST (National Institute for Standard and Technology) using reference methods (GC-IDMS; LC-IDMS).

Traceability in measuring serum creatinine, obtained by standardization of the same, does not solve analytical interferences caused by non-specificity of the test. Traceability can not be achieved unless the routine methods are the same, or at least very similar in terms of specificity (15). Neither did Jaffe method, nor the other modifications of original Jaffe method or even enzymatic method, cannot be freed from weak specifics and reproducibility (16).

Failure to resolve interlaboratory discrepancies in measuring serum creatinine is explained by the fact that standardization is not correction for analytical non-specificity, as is the case with Jaffe method. In spite of numerous attempts to improve characteristics of Jaffe reaction, non- specificities still remain (17-18).

In our study, by comparing serum creatinine levels measured using Jaffe and enzymatic methods, an average difference of 6.63 µmol /L (%95 CI=-16.28 to 29.54) was found between the methods, which was not statistically significant (t=0.57; df =118; p= 0.57), as shown in Table 1. We found a significant correlation of 0.99 (p<0.0001) between these two methods, with coefficient concordance R ^{2}=0.98 (%95 CI=0.976-0.99). Other authors (3) also came to similar results in the study which compared serum creatinine values measured using Jaffe and enzymatic methods with 318 subjects.

Unlike our study, the mentioned study also examined the influence of interfering substances, glucose and bilirubin. They found that, in the measured serum creatinine values, there were no statistically significant differences in the absence of interfering substances (glucose < 6.93 mmol/L; bilirubin < 17 µmol/L) between Jaffe and enzymatic methods. In the presence of interfering substances (glucose > 6.93 mmol/L, bilirubin >17 µmol/L), higher serum creatinine values were measured in Jaffe method compared to enzymatic method, but that difference proved not to be statistically significant (19).

Robert Schmidt and associates state that Jaffe method is subject to bias due to interfering substances (loss of analytical specificity). The risk of wrong CKD classification is the highest at the reference range of 60 ml/min/1.73 m ^{2}. However, the risk of wrong classification due to bias is much lower than the risk of wrong classification due to biological variation. Jaffe method can represent low risk in selected populations, if the eGFR results close to

reference range of 60 ml/min/1.73 m ^{2} are interpreted with caution (20).

By comparing the creatinine levels measured in 24-hour urine, in our study, an average difference of 0.05 mmol/24h (%95 CI=-1.03 to 1.13) was found between Jaffe and enzymatic methods, which was not statistically significant (t=0.09; df =118; p=0.93).

The biggest problem with measuring creatinine clearance, as an estimated glomerular filtration rate, is correctly collected 24-hour urine. Since the 24-hour urine is usually collected without supervision, it happens that collection of urine is not complete and, for that reason, it is possible to make a wrong conclusion about kidney function.

Universal application of estimated glomerular filtration rate formulas, with appropriate benefit for the patient, requires standardization in measuring creatinine (21, 22).

Comparing estimated glomerular filtration rate according to MDRD formula (eGFR MDRD, as shown in Table 3), as well as comparing glomerular filtration rate according to CKD-EPI formula (eGFR CKD-EPI, as shown in Table 3) between Jaffe and enzymatic methods, we didn't find any statistically significant differences.

Authors state that all deficiencies of empirical formula MDRD and the method for creatinine can also be attributed to creatinine clearance. It should also be noted that both creatinine clearance and eGFR are only estimates of kidney function (23).

In other, earlier published studies, Levey and associates (14), and Stevens and associates also indicate that the CKD-EPI formula is more accurate than the MDRD formula for estimated GFR, especially with higher levels of GFR (24).

From the conducted study, we conclude that for limited number of patients, Jaffe and enzymatic methods do not show significant differences in measuring serum and urine creatinine. Jaffe and enzymatic methods of measuring serum creatinine correlate well, they have linear relationship, but disproportionate systematic difference between them is present, threrefore, clinical decision should be based on reference values for an individual method.

There are no significant differences in the measured values of urine creatinine between modified Jaffe and enzymatic methods. Jaffe and enzymatic methods of measuring urine creatinine correlate well, they have linear relationship and proportional systematic mistake between them is not present. Calculated clearances of endogenous creatinine clearances, by using serum and urine creatinine values measured using Jaffe and enzymatic methods, show no significant differences and show high level of correlation, so that the distribution of the patients according to stages of chronic kidney disease is not different when the serum creatinine is measured using different methods**.**

6. CONCLUSION

Estimated glomerular filtration rate according to MDRD and CKD-EPI formula, using serum creatinine

values measured using Jaffe and enzymatic method, show no statistically significant differences and have high level of correlation.

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