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# Evaluation of equations for measuring eGFR based on serum creatinine and 6 cystatin C values in top level rugby players

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## ABSTRACT

Banfi G, Melegati G, Melzi G, Barassi A. Evaluation of equations for measuring eGFR based on serum creatinine and 6 cystatin C values in top level rugby players. *J. Hum. Sport Exerc.* Vol. 5, No. 3, pp. 370-378, 2010. Equations to estimate the glomerular filtration rate (GFR) have recently been advocated over serum creatinine values as a means to more accurately assess kidney function. The Cockcroft-Gault (CG) equation requires a body weight parameter, whereas the Modification of Diet in Renal Disease (MDRD) Study and Mayo Clinic Quadratic Equation (MCQE) formulae do not. We measured the serum creatinine and cystatin C concentrations in male athletes belonging to the Italian National Rugby team. Blood was obtained before the start of training and during competitive season. The serum creatinine level was measured by Jaffe and enzymatic reactions, cystatin C by nephelometry. The same parameters were measured in a control group of male, sedentary and overweight subjects. The concentrations of cystatin C were always into the reference ranges. The concentrations of creatinine were often higher than reference interval. The use of enzymatic method did not improve the specificity. The equations based on cystatin C and creatinine were not correlated. The two equations based on cystatin C were correlated. Two equations based on creatinine values were correlated (MDRD and MCQE); they were not correlated with CG. 29 level athletes, characterized from a high release of creatinine. The use of equations should be accurately evaluated: the CG equation can overestimate the eGFR, the MDRD and MCQE formulae systematically underestimates it. The use of equations to estimate GFR in the general population needs examination of their behaviour in subjects having atypical anthropomorphic characteristics. **Key words:** CREATININE, CYSTATIN C, RUGBY, ATHLETES, EGFR

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## INTRODUCTION

Creatinine is a breakdown product of creatine and phosphorylcreatine, important sources of energy for skeletal muscle (Wyss & Kaddurah-Daouk, 2000). It is usually produced by muscles at a constant rate and excreted almost entirely by kidney filtration. In the steady state, serum creatinine values for an individual are relatively constant and thus are used for determination of renal function. Any rise in serum creatinine value for an individual is usually representative of loss of renal excretory function. Given the simplicity of measurement, the serum creatinine concentration is currently the most widely used and commonly accepted measure of renal function in clinical medicine (Perrone et al., 1992). Serum creatinine levels depend not only on kidney function, but also reflect an individual's existing muscle mass as well. Younger, healthier individuals with a greater muscle mass would thus be expected to produce a larger pool of creatinine and have a higher serum creatinine value compared to frail, older individuals given identical levels of renal excretory function. Sex, race, and ethnic origin also contribute to differences in muscle mass and serum creatinine values.

The measurement of serum creatinine is generally performed by means of the traditional Jaffe reaction (Perrone et al., 1992). The Jaffe method is clearly influenced by non-creatinine compounds, which can contribute 20% to the total creatinine estimation (Perrone et al., 1992). The common reference range for creatinine in the general population is 0.7-1.3 mg/dL (62-115  $\mu\text{mol/L}$ ; the concentrations could be converted from mg/dL to  $\mu\text{mol/L}$  by multiplying by 88.4) for adult males, by using Jaffe (colorimetric reaction) reaction in automated systems (Burtis & Ashwood, 1994). In a recent report based on a wide population, the range was 0.68-1.13 mg/dL (60-100  $\mu\text{mol/L}$ ) for adult males, narrower than the above one (Rustad et al., 2004). No discernment is made in these ranges for age, race or fitness, however. The use of the methods based on an enzymatic reaction could improve the specificity of the measurement because, in this case, it is avoided the interference of the non-creatinine compounds. Cystatin C is not affected by interferences characterizing the creatinine measurement. Thus, the use of cystatin C has been proposed for evaluating eGFR in kidney diseases, but also in paediatric or elder patients.

In sports medicine, serum creatinine is widely used for evaluating general health status of athletes, particularly given the critical nature of fluid and electrolyte balance in this setting. Reference values for any biochemical parameter specific to sportsmen have never been established, however. Those used for the general population, including serum creatinine, are routinely applied to athletes. Notably, the values for serum creatinine observed in professional athletes are higher than those found in the general population (sedentary subjects), as demonstrated in a large series of top-level sportsmen competing in eight different sports disciplines (Banfi & Del Fabbro, 2006). The serum creatinine concentration in athletes has been shown to relate to their body mass index (BMI) (Banfi et al., 2006). Some athletes with a low BMI (i.e. cyclists) have serum creatinine concentrations lower than non-physically active subjects (Lippi et al., 2004; Lippi et al., 2006). Conversely, athletes having a high BMI (i.e. rugby players) demonstrate high concentrations of this parameter (Banfi & Del Fabbro, 2006; Banfi et al., 2006).

Creatinine-based equations to estimate the glomerular filtration rate (GFR) have recently been advocated over mere serum creatinine values as a means to more accurately assess kidney function (Lamb et al., 2005; ACCWG, 2005; Myers et al., 2006). The oldest and most commonly used formula proposed for this use is the Cockcroft- Gault (CG) equation (Cockcroft & Gault, 1976). More recently, the Modification of Diet in Renal Disease (MDRD) Study Group and Mayo Clinic Quadratic (Rule et al., 2004) equations were proposed. Body size is not a significant independent variable for the MDRD equation because the GFR estimate is adjusted for body surface area (i.e. 1.73  $\text{m}^2$ ). The 4-variable MDRD formula has been

recommended by expert working groups for the calculating the estimated glomerular filtration rate (eGFR) (Levey et al., 2000; Lamb et al., 2005; ACCWG, 2005; Myers et al., 2006). The MCQE has a diagnostic performance similar to the MDRD, but it should not underestimate GFR into the normal range (Rule et al., 2004).

Cystatin C was proposed for substituting creatinine as an indirect marker of GFR, because it is independent from various sources of interference which characterize creatinine measurement (Perkins et al., 2005). Various equations based on serum cystatin C concentration have been proposed: we tested two of these recently published (Perkins et al., 2005; MacIsaac et al., 2006).

The use of equations to assess kidney function, especially the MDRD formula, has some practical advantages as listed in published recommendations (Lamb et al., 2005; ACCWG, 2005; Myers et al., 2006). However, the validation of these equations was performed in patients suffering from chronic kidney disease (CKD). Use of this equation in healthy individuals has not been validated or defined. In general, GFR estimates using this equation will systematically deviate toward mean (regression to the mean) of the population it was derived from: patients with CKD having lower GFR values. Given these constraints inherent to the MDRD formula, values of eGFR should simply be reported as  $>60$  mL/min/1.73m<sup>2</sup> (Myers et al., 2006).

The objective of the present study was to define the efficacy of serum creatinine and cystatin C values for illustrating the renal function in top level rugby players during a competition season.

## MATERIAL AND METHODS

We measured the serum creatinine concentration in 45 male athletes belonging to the Italian National Rugby team; 16 athletes were tested twice, and 6 three times during the competitive season. The athletes had an age range of 22-32 years; their mean body mass index (BMI) was 27 (SD 1.3) kg/m<sup>2</sup>.

Blood was obtained before the start of training and during competitive season, strictly following preanalytical warnings (Banfi & Dolci, 2003). All the subjects recruited to the study were in the fasting state and had rested for period of 24 h since their last competition or training session. Ethnic origin, geographic residence and dietary habits were identical for all the athletes. Blood drawings were performed in August (before the start of training), November, January, and March. No additional blood was drawn for the research, because the creatinine was one of the routine parameters measured for the evaluation of health status in athletes.

A control group of 18 overweight male subjects (mean BMI: 27.9 kg/m<sup>2</sup>, SD:1.3) has been recruited. The range of age of sedentary subjects was 36-50 years. In the control group serum creatinine was also measured by Jaffe and enzymatic reactions, and cystatin C was measured by nefelometry.

Because serum creatinine was one of the parameters routinely measured for the evaluation of health status in these athletes, no additional blood was drawn for this study. The serum creatinine level was measured by Jaffe reaction in Aeroset c8000 (Abbott, Chicago, USA). The instrument was calibrated against National Institute of Standards and Technology (NIST) human-serum based standard reference material 909. It should be taken into account that the commutability of this product with native sera has not been established for routine methods (Myers et al., 2006). The serum creatinine was also measured by

enzymatic method on Johnson and Johnson Vitros 950. Cystatin C was measured nefelometrically (Dade Behring, Marburg, Germany).

All samples were measured in a single batch after calibration. The reproducibility of the method showed a coefficient of variation of 1.8%.

The team studied here did not use creatine supplementation. Diet was controlled by team physicians and it was similar during the whole season, including a mean quantity of 3 g of protein per Kg of body weight.

Regression analysis was used. The probability value of  $p=0.05$  was considered as the significance threshold.

The equations used were

$$CG = \{ [140 - \text{age}] \times \text{weight} / [7.2 \times \text{Scr}/88.4] \}$$

$$\text{MDRD} = 175 \times [(\text{Scr}/88.4)^{-1.154}] \times (\text{age})^{-0.203}$$

$$\text{MCQE} = \exp [1.911 + (5.249/\text{Scr}/88.4) - (2.114 - (\text{Scr}/88.4)^2) - 0.00686 \times \text{age}]$$

$$\text{Cys 1} = (86.7/\text{Cys C}) - 4.2$$

$$\text{Cys 2} = 100/\text{Cys C}$$

## RESULTS

The mean value of Jaffe serum creatinine concentration was 1.23 mg/dL (SD: 0.13), whilst the mean value of enzymatic method was 1.30 (SD: 0.15). The mean value of cystatin C was 0.85 mg/L (SD:0.08).

The serum creatinine values  $>1.3$  mg/dL ( $115 \mu\text{mol/L}$ ) were 19 by using Jaffe reaction and 28 by using enzymatic method. None of the cystatin values was  $>1.2$  mg/L.

The values of creatinine measured by means of both methods and of cystatin C were always ,respectively,  $<1.3$  mg/dl and  $<1.2$  mg/L in control subjects.

The correlations among different equations based on serum cystatin C and creatinine concentrations are collected in the [Table 1](#).

Similar results have been found in sedentary obese male subjects ([Table 2](#)). However, we could remark that CG equations, both based on Jaffe or enzymatic reactions, were statistically different from equations based on cystatin whilst the comparison between these equations was not statistically significant in rugby players.

**Table 1.** Correlation among different methods for estimating GFR in rugby players. Sample size=73. Correlation values are in bold, significance levels in *Italics*. Significance values below 0.05 indicate significant correlations.

CG enz	MDRD enz	Cys C1	Cys C2	MCQE enz	CG Jaffe	MDRD Jaffe	MCQE Jaffe
	<b>0.790</b> <i>&lt;0.01</i>	<b>0.151</b> <i>0.20</i>	<b>0.151</b> <i>0.20</i>	<b>0.790</b> <i>&lt;0.01</i>	<b>0.971</b> <i>&lt;0.01</i>	<b>0.745</b> <i>&lt;0.01</i>	<b>0.744</b> <i>&lt;0.01</i>
MDRD enz		<b>0.277</b> <i>0.017</i>	<b>0.277</b> <i>0.017</i>	<b>0.998</b> <i>&lt;0.01</i>	<b>0.738</b> <i>&lt;0.01</i>	<b>0.935</b> <i>&lt;0.01</i>	<b>0.931</b> <i>&lt;0.01</i>
	Cys C1		<b>1.000</b>	<b>0.271</b> <i>0.021</i>	<b>0.155</b> <i>0.19</i>	<b>0.285</b> <i>0.014</i>	<b>0.279</b> <i>0.017</i>
		Cys C2		<b>0.271</b> <i>0.021</i>	<b>0.155</b> <i>0.19</i>	<b>0.285</b> <i>0.014</i>	<b>0.279</b> <i>0.017</i>
			MCQE enz		<b>0.739</b> <i>&lt;0.01</i>	<b>0.935</b> <i>&lt;0.01</i>	<b>0.935</b> <i>&lt;0.01</i>
				CG Jaffe		<b>0.779</b> <i>&lt;0.01</i>	<b>0.779</b> <i>&lt;0.01</i>
					MDRD Jaffe		<b>0.997</b> <i>&lt;0.01</i>
						MCQE Jaffe	

**Table 2.** Correlation among different methods for estimating GFR in control obese subjects. Sample size=18. Correlation values are in bold, significance levels in *Italics*. Significance values below 0.05 indicate significant correlations.

CG enz	MDRD enz	Cys C1	Cys C2	MCQE enz	CG Jaffe	MDRD Jaffe	MCQE Jaffe
	<b>0,788</b> <i>&lt;0.01</i>	<b>0,588</b> <i>0.01</i>	<b>0,588</b> <i>0.01</i>	<b>0,834</b> <i>&lt;0.01</i>	<b>0,929</b> <i>&lt;0.01</i>	<b>0,725</b> <i>&lt;0.01</i>	<b>0,789</b> <i>&lt;0.01</i>
MDRD enz		<b>0,580</b> <i>0.012</i>	<b>0,580</b> <i>0.012</i>	<b>0,937</b> <i>&lt;0.01</i>	<b>0,670</b> <i>&lt;0.01</i>	<b>0,899</b> <i>&lt;0.01</i>	<b>0,722</b> <i>&lt;0.01</i>
	Cys C1		<b>1,000</b>	<b>0,586</b> <i>0.011</i>	<b>0,567</b> <i>0.014</i>	<b>0,578</b> <i>0.012</i>	<b>0,519</b> <i>0.027</i>
		Cys C2		<b>0,586</b> <i>0.011</i>	<b>0,567</b> <i>0.014</i>	<b>0,578</b> <i>0.012</i>	<b>0,519</b> <i>0.027</i>
			MCQE enz		<b>0,712</b> <i>&lt;0.01</i>	<b>0,835</b> <i>&lt;0.01</i>	<b>0,891</b> <i>&lt;0.01</i>
				CG Jaffe		<b>0,775</b> <i>&lt;0.01</i>	<b>0,786</b> <i>&lt;0.01</i>
					MDRD Jaffe		<b>0,741</b> <i>&lt;0.01</i>
						MCQE Jaffe	

## DISCUSSION AND CONCLUSION

While GFR cannot be measured directly, the most accurate means to assess it involves use of exogenous filtration markers such as inulin and iothalamate. However, as measurement of GFR using these markers is cumbersome and expensive, utility of these assays in clinical practice is limited. Conversely, steady state balance between production and urinary excretion of the endogenous marker, creatinine, has made it a simple and easy procedure to evaluate kidney function.

The serum creatinine concentration is the most widely used and commonly accepted measure of renal function in clinical medicine. The common reference range for creatinine in the general population corresponds to 0.7-1.3 mg/dL for adult males (Perrone et al., 1992). Reference values for serum creatinine specifically applicable to sportsmen have never been defined, however. In our experience, athletes are frequently observed to have higher creatinine values, at times in excess of 1.3 mg/dL or what would be considered "normal". We previously studied a large number (n=220) of elite male athletes who participated in one of eight discrete sports, each characterized by different aerobic/anaerobic activities, competitive seasons, training, and anthropometric values. We found that serum creatinine values were higher in these sportsmen than in age-matched sedentary subjects (Banfi & Del Fabbro, 2006).

Recently, the use of serum creatinine has been criticized because its serum value is affected by many factors independent from GFR including age, gender, body size, diet, drugs, and analytical method of measurement (Myers et al., 2006). Estimating equations that combine serum creatinine concentrations with known external factors affecting creatinine measurement have been proposed as more accurate means to evaluate GFR. The currently recommended equation to estimate GFR is the abbreviated (4-variable) MDRD formula (Cockcroft & Gault, 1976; Lamb et al., 2005; ACCWG, 2005; Myers et al., 2006). However, estimating equations are recognized as being potentially inaccurate in populations that are different from those in whom the equations was developed (i.e. CKD). In a healthy population of 365 potential kidney donors (205 women), these equations were found to underestimate GFR by 14 mL/min (CG) and by 29 mL/min/1.73 m<sup>2</sup> (MDRD) (Rule et al., 2004). Lower values of eGFR (i.e. <60 mL/min/1.73m<sup>2</sup>), as such, are seen having greater validity (Myers et al., 2006). In diabetic patients the predictive performance of equations based on cystatin C, MDRD and CG were equivalent (MacIsaac et al., 2006).

The use of Jaffe or enzymatic creatinine methods did not supply significant differences. The use of enzymatic methods should increase the specificity of creatinine measurements, avoiding or at least minimizing the influence of interfering substances characterizing the colorimetric reaction, but the calibration which "adapts" the data to improve the correlation of results due to commercial and marketing reasons often cancel the differences, as demonstrated also a National survey (Ceriotti et al., 2007).

The data observed by using Jaffe and enzymatic methods both in CG, MDRD and MCQE equations have high coefficients of correlation: the choice of enzymatic methods is not nowadays recommended because of calibration which induces an artificial increase of the measured values.

Cystatin C, a low molecular weight that is freely filtered through the glomerulus and almost completely reabsorbed and catabolized by tubular cells has been proposed as a reliable marker of GFR. The cystatin C values in rugby players were into reference interval and their distribution was narrower than this of creatinine. The use of cystatin C could be recommended in evaluating athletes, especially when their body mass is very high, influencing the measurement of the creatinine and its clinical interpretation. The use of two different equations based on the cystatin C concentrations produced equivalent data. The results



obtained by using cystatin C equations are higher than MDRD values but lower than CG ones, confirming the better stability and narrower distribution of cystatin values than the creatinine ones. Our results support the conclusion of Herget-Rosenthal et al. (2007), who stated that eGFR calculated with the MDRD and CG equations have to be valued cautiously in anthropometric extremes, where cystatin C measurement may provide valuable information.

We found good agreement between MCQE and MDRD, although a statistically significant difference exists when the two equations are correlated. The agreement between MCQE and MDRD was present for both enzymatic and colorimetric methods for creatinine measurement. We remarked that a correlation did not exist between the two equations based on cystatin C and the equations based on creatinine values (MDRD, CG, and MCQE).

A significant difference was evident between CG and MDRD, showing an overestimation of CG and an underestimation of MDRD. In rugby players, characterized from high BMI, we confirm previous descriptions of discrepancies between CG and MDRD.

While the CG equation can overestimate the eGFR in healthy overweight subjects, the MDRD formula systematically underestimates it, particularly in individuals with increased BMI, such as elite athletes.

The literature is replete with evidence demonstrating the limitation on use for both equations. When obesity is present (body mass index  $> 30 \text{ kg/m}^2$ ), no reliable GFR estimation can be obtained using either equation (Rule et al., 2004). Moreover, the gross overestimation in obese subjects by using the CG equation suggests an urgent need for further validation of GFR equations in the obese, as stated by Lamb et al. (2005).

Verhaeve et al found that the CG equation markedly underestimated GFR in lean subjects and clearly overestimated GFR in obese subjects (Verhaeve et al., 2005). Conversely, better accuracy might be better achieved in matching the GFR formula to the population surveyed. The MDRD has been shown to be preferable in elderly patients, whereas CG may be preferable in subjects younger than 65 years (Rule et al., 2004).

The similar results observed in athletes and in nonathletes by using equations corroborate the literature data. Only a different behaviour among equations was observed in the two studied groups, i.e. when CG and cystatin-based equations were compared. It is probably due to the higher age of the subjects into control group.

The significant differences noted between eGFR values that we found by using the equations in athletes, both before and during the competitive season, confirm the possible overestimation of eGFR by the CG and underestimation by the MDRD formulae compared to the creatinine clearance results (Rule et al., 2004; Bostom et al., 2002; Vervoort et al., 2002), as also demonstrated in top-level cyclists at rest (Lippi et al., 2008).

The Australasian Creatinine Consensus Group guidelines stated that adjusted GFR estimates are adequate except in patients with a body size that is very different from average (ACCWG, 2005). It should be noted that this is true not only for obese subjects ( $\text{BMI} > 30 \text{ Kg/m}^2$ ), but also for healthy subjects with BMI values in the range  $25\text{-}30 \text{ Kg/m}^2$ . We confirmed these data by measuring cystatin on sedentary overweight male subjects, having an age range similar of this of athletes.



The use of cystatin C for monitoring renal function in athletes characterized from high BMI should be recommended.

The use of equations to estimate renal excretory function should be recommended in chronic kidney disease, but not in the general population until further studies will examine their behaviour in different populations having atypical anthropomorphic characteristics. This is particularly important for professional athletes who show a wide range of serum creatinine concentrations, sometimes higher than reference intervals extrapolated from general population, even from group of subjects having similar BMI, and also fluctuations of the parameter during the competitive season (Banfi et al., 2009).

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