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INVITED REVIEW

SERUM CREATININE CONCENTRATIONS IN ATHLETES: ARE THEY NORMAL?

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ABSTRACT

BANFI, G. Serum creatinine concentrations in athletes: are they normal? Brazilian Journal of Biomotricity, v. 4, n. 3, p 157-164, 2010. In sports medicine, creatinine is used for evaluating general health status of athletes. In the present review, different aspects of the behaviour of creatinine values in sportsmen are summarized. The reference values for common biochemical and haematological parameters used for athletes are the same commonly used for general population. The serum concentration of creatinine could sometimes apparently pathological in some athletes and the interpretation of these values should consider the sportsmen status. In fact, the values of serum creatinine in athletes are higher than those reported in sedentary people. However, the population of sportsmen is not homogeneous, and some differences are evident among athletes competing in different sport disciplines. The creatinine values are affected from acute exercise, which modifies renal flow. The sport discipline is an additional variable for interpreting creatinine values, which can show values lower than those measured in sedentary people in endurance athletes. The creatinine values are modified in some sport disciplines during competitive season, showing increases when activity is more intense. Cystatin C, a low molecular weight that is freely filtered through the glomerulus and almost completely reabsorbed and catabolized by tubular cells, could be used in athletes, while it is virtually independent from body mass.

Keywords: creatinine, MDRD, athletes, glomerular filtration rate

INTRODUCTION

The concentration of creatinine in serum is the most widely used and commonly accepted measure of renal function in clinical medicine. Reference values of biochemical parameters specific for sportsmen have never been defined and those used for the general population, included serum creatinine level, are routinely applied to athletes. The common reference range for creatinine in the general population is 0.7-1.3 mg/dL (62-115 μmol/L) for adult males, by using Jaffé reaction in automated systems.

In sports medicine, creatinine is used for evaluating general health status of athletes, particularly in events where hydroelectrolytic balance is crucial level. The study of the behaviour of serum creatinine and its reference interval is mandatory to avoid misinterpretation of athletes' values which are sometimes higher than the thresholds

Brazilian Journal of Biomotricity, v. 4, n. 3, p. 157-164, 2010 (ISSN 1981-6324)

established for general population.

The reference values commonly used for athletes are those defined in general, sedentary people. The athletes are usually thought to be physically normal and health by definition, but high workload for training and psychophysical stress due to competitions could modify the homeostasis, inducing apparently pathological biochemical and haematological values.

Surprisingly, serum creatinine values have been studied and reported in few papers concerning athletes. Moreover, few reports are concerning the applications of equation, based on creatinine values, in sportsmen. The use of these equations is now recommended by international medical associations (MYERS et al 2006), although their use in individuals characterized from normal glomerular filtration rate is still discussed (LAMB et al., 2005).

Creatinine is nonenzymatically derived from creatine. Creatine turnover rates in normal men are constant, representing 1.6% of the total creatine pool per day (BURTIS and ASHWOOD, 1994). Thus, the creatinine quantity produced and released from an individual could be calculated, considering the total muscle mass, which is the most important determinant of the creatine pool size because it contains about 98% of the total quantity of creatine in the body. It is clear that creatinine concentration in blood, which is used as parameter of glomerular filtration rate (GFR), could be influenced by body mass, diet (content of meat in diet), analytical methods. Jaffe method, commonly used for measuring creatinine, is simple, cheap, easily adapted to automated systems. However, the method is interfered by molecules other than creatinine until 20% of the total amount. For this reason, enzymatic methods, and, recently, the calibration of all the methods against gas chromatography-isotope dilution mass spectrometry are recommended (MYERS et al., 2006). The origin of creatinine from creatine and from muscles is usually claimed for justifying the differences between men and women (BURTIS and ASHWOOD, 1994). Surprisingly, the relation between muscles mass and creatinine was not extensively studied.

The different aspects of the relationship between creatinine values and sport activities have been described in review (BANFI et al, 2009).

We report here some researches which are of particular interest for sport physician and trainer to interpret creatinine and creatinine-based equations values in athletes.

Creatinine values in professional athletes

The concentrations of serum creatinine in athletes are higher than those found in sedentary people. Banfi and Del Fabbro (2006) recruited 220 elite athletes: 15 triathletes of the Italian National Team, 29 basketball players of a Italian First Division team, 35 cyclists from two professional teams, 13 racing motorcyclists of a professional team, 27 soccer players of a Italian First Division team, 23 sailors of a America's Cup yacht, 34 alpine skiers of the Italian National Team, and 44 rugby players of the Italian National Team. The athletes were all males and the age range was 17-36 years.

The control group was represented by 100 males with the same age range. Sedentary, non obese, apparently healthy males, without biochemical and haematological signs of diseases were selected. Mean values of 1.1 ± 0.2 mg/dL in the whole group of athletes and of 1.0 ± 0.1 mg/dL in controls have been reported. The mean values in the different sports groups were: 0.99 ± 0.07 mg/dL in triathletes, 1.15 ± 0.07 mg/dL in basketball players, 0.93 ± 0.07 mg/dL in cyclists, 0.92 ± 0.09 mg/dL in motorcyclists, 1.27 ± 0.09 mg/dL in soccer players, 1.08 ± 0.11 mg/dL in sailors, 1.15 ± 0.10 mg/dL in skiers, and

azilian Journal of Biomotricity, v. 4, n. 3, p. 157-164, 2010 (ISSN 1981-6324)

1.30 ± 0.11 mg/dL in rugby players.

The differences between physically active and inactive subjects are demonstrated for professional athletes coming from eight different sports, showing different characteristics of aerobic/anaerobic metabolism, different training loads and frequency of competitions, different length of competitions, and different periods of training and competitions through the year. It should be outlined that the distribution of the serum creatinine concentrations in athletes population showed characteristically mean concentrations lower than those observed in sedentary people below the threshold of 1 mg/dL, and much higher above 1 mg/dL. The distribution, in other terms, is not homogeneous.

The interpretation of creatinine values in athletes should consider that the behaviour of this parameter could be different from general population.

It is crucial to avoid misinterpretation, additional medical evaluations, and unnecessary modifications of diet and hydration.

Relationship between creatinine values and body mass index in athletes.

A study concerning the relation between muscle mass and serum creatinine and body mass index in athletes has been described by Banfi et al. (2006). Serum creatinine was measured in 151 professional athletes. They belonged to rugby Italian national team (n=44), to triathlon Italian national team (n=9), to soccer Italian first division team (n=27), to America's Cup yacht crew (n=22), to alpine ski Italian national team (n= 34), to a ProTour cycling team (n= 24).

The range of athletes' age was 17-35 years. Blood drawings were performed before the start of training and competitions season, strictly following preanalytical warnings. A positive correlation occurs between BMI and serum creatinine ($r=0.48$, $p<0.001$). The rugbyists, who showed the highest values of BMI (28.83 ± 2.41 kg/m^2), showed laso the highest values of serum creatinine (1.31 ± 0.12 mg/dL). At the contrary, cyclists, who were characterized from low BMI (21.33 ± 1.21 kg/m^2) had correspondingly lowest concentrations of serum creatinine (0.91 ± 0.07 mg/dL).

We remark that the correlation was found in sports characterized by different kind of training, competitive season, involvement of aerobic and anaerobic metabolisms and was connected to the peculiar status of professional sport activities. The interpretation of creatinine values in sportsmen must consider the specific sport that athlete performs. In some aerobic sports (cyclism, triathlon) the BMI values are highly homogeneous, whereas in others (sailing, rugby) the values are heterogeneous. In these sports, there are athletes with different anthropometric characteristics. In the rugby, for example, forwards generally have higher BMI than backs or, in soccer, goalkeepers have BMI higher than other players. The lean mass is not crucial for defining creatinine values, as described in wide populations (SWAMINATHAN et al, 1986). Cyclists and triathletes, typically characterized from low fat tissues percentages have lowest creatinine values, whereas rugby players with relatively high fat tissues have higher values, confirming the previous findings described in the general population. It should mean that the homeostatic values of creatinine are related to the body size, but also to other physiological mechanisms, as the effect of increasing volume of distribution: it is known that total body water is closely related to body mass (SWAMINATHAN et al, 2000).

azilian Journal of Biomotricity, v. 4, n. 3, p. 157-164, 2010 (ISSN 1981-6324)

Relationship between creatinine values and type of sport discipline

Endurance athletes, usually characterized from low BMI, could show serum creatinine concentrations lower than those of sedentary controls: 0.79-0.98 mg/dL for Nordic skiers (n=37) and 0.72-0.95 mg/dL for cyclists (n=80) against an interval of 0.82-1.06 mg/dL for controls (n=60) (LIPPI et al 2004). Serum creatinine concentrations in cyclists lower than those observed in controls were confirmed in 50 professional athletes in comparison with 35 sedentary people (0.93 ± 0.14 vs 0.98 ± 0.10 mg/dL; p=0.044) (LIPPI et al, 2006).

The kind of sport and related different anthropometrical characteristics of athletes induce different ranges of creatinine concentrations. The levels of creatinine in cyclists are very stable during the competitive season, whilst in athletes competing in other sports the concentrations show modifications.

Creatinine values during training and after acute exercise

There are some papers which describe the modifications of serum creatinine values during training and acute exercise. Generally, the serum creatinine concentrations are not significantly influenced by training and competition (SAENGSIRISUWAN et al, 1998, KRATZ et al, 2002), even in extreme sports (FALLON et al, 1999). In Thai boxers (n=20; age =14-17 years), the creatinine values during normal training, intensive training and after a match were not statistically different from the values of the control group. Differences were not described also for creatinine clearance, with the exception for the value observed after a match, which was significantly lower when compared with this reported in the control group and with the previous values of the same athletes registered during the training period, probably because of changes in renal haemodynamics (reduction of renal blood flow) during the fight (SAENGSIRISUWAN et al, 1998).

In sixteen volunteers participating to the First Race Across the Alps, a ultraendurance cyclism race of 509 km at an altitude of 300-2750 m, including 11 mountain passes, serum creatinine values showed a statistically significant increase immediately after the end of the effort, in comparison with the values observed before the start of the race. The mean values, however, fell always into reference intervals (1.26 ± 0.21 after race, 0.95 ± 0.17 before) and returned at baseline level after 24 hours from the end of the race (0.94 ± 0.17). The authors outlined the importance of adequate fluid replacement by professional ultramarathon cyclists who had taken a total fluid amount of 17 L during the race. The negative correlation (p=0.02) between the rise of serum creatinine and the athlete's training kilometres performed during the year preceding the race remarks the importance of training to smooth and attenuate the level and duration of renal impairment (NEUMAYR et al, 2005).

The decrease of serum creatinine when training regimens are heavier and competitions more frequent cannot be associated with modifications of the muscular mass and can be explained with modifications of blood flow and/or fluid volume as hypothesized in the case of modifications of creatinine and urea after efforts in endurance athletes.

Creatinine values during a competitive season

A study reported the behaviour of creatinine values during a competitive season in athletes belonging to different sport disciplines.

The mean concentration of serum creatinine at rest was 1.31 mg/dL in rugby players (BMI= 28.9 ± 2.3), 1.14 mg/dL in skiers (BMI = 25.8 ± 1.9), and 0.92 in cyclists (BMI=

azilian Journal of Biomotricity, v. 4, n. 3, p. 157-164, 2010 (ISSN 1981-6324)

21.3 ± 1.3), confirming that the values are correlated to mass.

Analysis of variance showed significant differences among groups of athletes practising different sports. The analysis for repeated measures demonstrated significant differences for rugby ($p<0.005$) and ski ($p<0.02$), but not for cycling ($p=0.25$). The different training regimen and characteristics of sport are relevant for interpreting creatinine values. The serum creatinine concentration showed a significant decrease when training regimens were heavier and competitions more frequent in rugby players and skiers (BANFI et al 2008).

Influence of laboratory methods

The laboratory methods could be crucial for correctly interpreting the creatinine concentrations. The values reported in the scientific literature in athletes were obtained by using the traditional Jaffe reaction. The use of enzymatic method did not improve, however, the results. On 127 sera obtained from 57 toplevel rugby players during the 2005-2006 competitive season (May, August, November, January) creatinine concentrations have been measured by using Jaffe method and an enzymatic method. Paradoxycally, higher values were supplied by enzymatic method (1.28 ± 0.14 mg/dL) when compared with the traditional one 1.22 ± 0.13 mg/dL. The recalibration procedures performed by producers for minimizing the intermethod differences probably induced this result (BANFI et al, 2009).

The use of standardized methods for measuring creatinine is mandatory for harmonizing values (MYERS et al, 2006)

Creatinine-based equations

Recently, the use of equations for estimating GFR was recommended (LAMB et al, 2005; MYERS et al, 2006). The equations include creatinine concentrations but also include additional variables which are known to influence creatinine measurement and interpretation. Among equations, the Cockcroft and Gault (CG, 1976) formula was proposed some years ago and widely used, but now the MDRD formula (LEVEY et al, 2000) is recommended (MYERS et al, 2006). MDRD could be of particular value in sport medicine because it is not influenced by body mass (LAMB et al, 2005). Only in cyclists GFR was estimated by an equation: the creatinine clearance was calculated in ultramarathon cyclists by CG formula, evidentiating a significant decrease immediately after the race (85 ± 19 mL/min) of estimated GFR (eGFR), compared with the basal value (114 ± 27 mL/min). The recovery was reached in a period of 24 hours from the end of race (113 ± 28 mL/min). The decline of creatinine clearance (18%) was already described in recreational cyclists after a race (NEUMAYR et al, 2003).

The influence of body mass in equations is crucial, because the eGFR could be highly different by using CG and MDRD formulae: For example, in 19 toplevel rugby players who have high BMI (28.9 ± 2.5 kg/m^2), before the start of training and competitions, CG gave a mean value of eGFR of 123 ± 17 mL/min, whilst MDRD gave a value of 72 ± 8 mL/min. The use of equations in healthy population should be still established: the National Kidney Disease Education Program currently recommends that eGFR above 60 mL x ml/min^{-1} x $(1.73\ m^2)^{-1}$ be reported simply as ">60 mL x ml/min^{-1} x $(1.73\ m^2)^{-1}$" rather than a discrete numeric value (MYERS et al, 2006).

The athletes could a physiological model for studying and applying equations for eGFR.

azilian Journal of Biomotricity, v. 4, n. 3, p. 157-164, 2010 (ISSN 1981-6324)

The interpretation of serum creatinine concentrations in athletes, in conclusion, could not be performed by using the usual reference intervals.

The use of reference ranges specific for athletes should not be recommended because the athletes population is not homogeneous.

The use of general population reference ranges should not be recommended in sports medicine, to avoid misinterpretation of data and unnecessary further investigation, especially when serum creatiine value is higher than the upper limit of the reference interval. This does not necessarily imply that specific reference ranges should be calculated for athletes, also for creatinine: the individuality index (ratio between intra- and inter-individual variability) of creatinine is 0.33, lower than the values of 0.60, universally considered the threshold for classifying a reference range useful in a population.

Role of cystatin C

The use of parameters different from creatinine could aid the evaluation of renal function in athletes. 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. This parameter is not influenced by some variables which are confounding creatinine measurement, e.g. age, gender, and body mass index, although some doubts have been reported (WETMORE et al, 2010).

A study demonstrated that the cystatin C values in rugby players were into reference interval and their distribution was narrower than this of creatinine (BANFI et al, 2009b). The use of cystatin C can be a real and attractive alternative to the use of creatinine and their equations.

Conclusion

The monitoring of athletes should be done by consecutive creatinine assessments, using as basal one the value observed before the start of training and competitions, but considering the sport performed and body mass index. The study of serum creatinine values and eGFR in athletes should be encouraged for evaluating the behaviour of the parameter in healthy individuals characterized by high muscular mass, controlled diet, and heavy modifications of renal blood flow during training and competitions.

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Serum concentrations of toxic mineral in controls and athletes at the start and the end of the 6 months of the study; a = As; b = Be = c = Cd; d = Pb; As = arsenic; Be = beryllium; Cd = cadmium; Pb = lead; AG: athletes group; CG: control group. Full size image. Significant differences were observed between groups, with higher values of As, Cd, Pb in AG ($p < 0.05$).Â First, all the serum and urinary concentrations of toxic metals obtained in this study were in the normal range, so that none of the subjects presented a health risk [28 , 29]. Creatinine production is proportional to the muscle mass of the individual and in the absence of any renal pathology, creatinine excretion rates are constant, and not modified by physical exercise or by variations in catabolism. Serum creatinine concentrations in athletes: are they normal? Giuseppe Banfi IRCCS Galeazzi and School of Medicine, University of Milano, Milano, Italy. Corresponding author: Giuseppe Banfi, PhD IRCCS Galeazzi, via Galeazzi 4, 20161 Milano, Italy giuseppebanfi@supereva.it. Submitted for publication: May 2010.Â The serum concentration of creatinine could sometimes apparently pathological in some athletes and the interpretation of these values should consider the sportsmen status. In fact, the values of serum creatinine in athletes are higher than those reported in sedentary people. However, the population of sportsmen is not homogeneous, and some differences are evident among athletes competing in different sport disciplines. Submersion - serial measurements of serum creatinine are recommended in all submersion victims to monitor for the development of acute renal impairment. Suspected acute renal failure - measurement is particularly useful in renal failure because it is minimally affected by protein intake, hydration, and protein metabolism.Â With normal renal excretory function, the serum creatinine level should remain constant and normal. The creatinine level is affected minimally by hepatic function. The creatinine is used as an approximation of the glomerular filtration rate (GFR). In general, a doubling of creatinine suggests a 50% reduction in the GFR. The BUN/creatinine ratio is a good measurement of kidney and liver function.