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Reference intervals for serum creatine kinase in athletes

Vassilis Mougios

Background: The serum concentration of creatine kinase (CK) is used widely as an index of skeletal muscle fibre damage in sport and exercise. Since athletes have higher CK values than non-athletes, comparing the values of athletes to the normal values established in non-athletes is pointless. The purpose of this study was to introduce reference intervals for CK in athletes.

Method: CK was assayed in serum samples from 483 male athletes and 245 female athletes, aged 7–44. Samples had been obtained throughout the training and competition period. For comparison, CK was also assayed in a smaller number of non-athletes. Reference intervals (2.5th to 97.5th percentile) were calculated by the non-parametric method.

Results: The reference intervals were 82–1083 U/L (37°C) in male and 47–513 U/L in female athletes. The upper reference limits were twice the limits reported for moderately active non-athletes in the literature or calculated in the non-athletes in this study. The upper limits were up to six times higher than the limits reported for inactive individuals in the literature. When reference intervals were calculated specifically in male football (soccer) players and swimmers, a threefold difference in the upper reference limit was found (1492 vs 523 U/L, respectively), probably resulting from the different training and competition demands of the two sports.

Conclusion: Sport training and competition have profound effects on the reference intervals for serum CK. Introducing sport-specific reference intervals may help to avoid misinterpretation of high values and to optimise training.

METHODS

Subjects

Reference values for serum CK were obtained from 483 male athletes, 245 female athletes, 115 male non-athletes and 122 female non-athletes, all being white, aged 7–44, who visited the laboratory for biochemical monitoring through the measurement of many relevant parameters over the course of 10 years. To be included in the study, subjects had to be apparently healthy, with no known diseases and no major injury or hospitalisation within the past 3 months. Additionally, they should have taken no prescription drugs during the week preceding blood sampling. These criteria were assessed through the administration of a questionnaire. All subjects provided written informed consent to participate in the study, which was conducted in compliance with the Helsinki Declaration of 1975, as revised in 1996, and was approved by the institutional ethics committee.

All athletes were members of Greek sport clubs and had been training for 2–25 years (median 8), undertaking 5–10 training sessions per week (median 6), and exercising 1–2 hours per training session (median 1.6). They practised a wide variety of sports encompassing both endurance and strength/power activities. The sports were running (sprint, middle distance and endurance), jumping, throwing, combined events (triathlon, heptathlon and decathlon), swimming (sprint and middle

Abbreviation: CK, creatine kinase
Reference intervals for serum creatine kinase

distance), cycling, rowing, kayaking, football (soccer), basket-
ball, volleyball, handball, water polo, tennis, table tennis, gymnastics, judo, taekwondo, karate, boxing, weightlifting,
bodybuilding, diving, motocross and snowboarding. Non-
athletes did not participate in any sport training programme.
They were mostly students or employees, performing light-to-
moderate exercise up to three times a week. Physical activity
was assessed through a questionnaire.

Specimens and assay
Subjects provided blood samples in a seated position from an
antecubital vein into plain evacuated tubes in the morning after
an overnight fast and sleep. They refrained from early morning
training to avoid acute exercise-induced shifts in plasma
volume that would affect the CK concentration. No other
intervention in the daily training programme of the athletes
was made. The blood was left to coagulate at room temperature
for 30 minutes and was centrifuged at 1500 g for 10 minutes
to separate the serum, which was analysed immediately or was
stored at –20˚C for up to 1 week prior to analysis. Storage under
these conditions does not affect the CK concentration.17 CK was
assayed spectrophotometrically through the use of commer-
cially available kits that employed optimised conditions in
accordance with the recommendations of the International
Federation of Clinical Chemistry.18 The catalytic concentra-
tion of CK was expressed as U/L at 37˚C.

Calculations and statistics
Since many subjects, especially athletes, visited the laboratory
regularly, each of them provided more than one sample, the
maximum being 19 samples obtained from a swimmer over a
period of 5 years, from adolescence into adulthood, at all
phases of the yearly training and competition programme.
In such cases the median of each individual’s values was used in
the calculation of reference intervals.

Potential outliers were identified by visual inspection of the
reference distribution and were deleted if their distance from
the next, more central value in the distribution exceeded one-
third of the total range of values.21

Reference limits were calculated as the 2.5th and 97.5th
percentiles of the reference collectives according to Solberg21
using the non-parametric method, since most distributions
were significantly different from normal (p <0.05 by the
Kolmogorov-Smirnov test). The 90% confidence intervals (CI)
of each reference limit were also calculated according to
Solberg.21 Reference limits for two groups were declared to
differ if their CI did not overlap (p<0.1).

RESULTS
The distribution of CK values in the four study groups is shown
in fig 1. Male athletes had the widest distribution followed by
female athletes and male non-athletes.

Table 1 presents the reference limits and their CI for each
group. Both the lower and the upper reference limits for male
athletes were higher than the corresponding reference limits for
male non-athletes, with non-overlapping CI. The same was the
case for female athletes and non-athletes. Males had higher
reference limits than females in both athletes and non-athletes,
again with non-overlapping CI. In contrast, the lower and
upper reference limits of female athletes and male non-athletes
did not differ significantly (they had overlapping CI).

DEPENDENCE ON AGE
Reference values tended to be higher in the centre of the age
range of the subjects (from about 12 to about 30 years) in all
four groups. However, the differences from the values at the
edges of the age range were not large enough to justify any
attempt to partition the data and establish separate reference
intervals. In addition, values obtained from the same individu-
als over the course of up to 5 years showed no consistent
tendency.

Dependence on sport
Within the group of male athletes two sports had high enough
numbers of subjects to let one calculate specific reference
intervals and thus partly examine the issue of dependence on
sport. The sports were football, with 182 subjects, and
swimming, with 93 subjects (fig 2). The lower reference limits
(with CI in parentheses) were 83 (53–84) U/L for football
players and 70 (61–89) U/L for swimmers. The upper reference
limits were 1492 (924–1908) and 523 (435–543) U/L, respec-
tively.

DISCUSSION
As presented in the introduction, the serum CK concentration
serves as an index of both overexertion and adaptation of the
muscular system to repeated bouts of exercise. As such, CK is
one of the top choices of athletes and coaches when requesting
a biochemical profile, although the interpretation of CK values
is not always straightforward. This laboratory has previously
shown that CK is higher in athletes than in non-athletes,
whether they are male or female, juvenile or adult.2 The aim of
the present study was to contribute to the elucidation of what
the serum CK concentration means for an athlete by providing
reference intervals to be used mainly by sports medicine
practitioners and coaches in daily practice. It is because of this
that no intervention in the training programme of the athletes
during the days preceding blood sampling was attempted.
Given the fact that serum CK remains elevated for several days
post-exercise, the values used in this analysis should be
considered as the cumulative effect of recent training sessions
in conjunction with the repeated-bout effect.25

The upper reference limits for CK in male and female athletes
were twice those for male and female non-athletes. This is in
agreement with the differences reported for the mean values in
a previous study from this laboratory.2 It is noteworthy that the
upper reference limits in the non-athletes of this study are
among the highest in the literature. In particular, Wu,26 Wong et
al.,27 and Schumann and Klauke28 have proposed limits that are
under 350 U/L in males and under 200 U/L in females. Miller et
al.29 and Stro¨mme et al.30 have proposed limits (males, 391 and
398; females, 240 and 207 U/L, respectively) whose CI overlap
with the CI of the limits in this study. Finally, the limits
proposed by Lev et al.31 are either slightly higher than (532 U/L
in males) or very close to the ones in this study (248 U/L in
females).

The major reason for the discrepancies among studies that
have determined reference limits for CK in non-athletes
(including the present study), as also suggested by Stro¨mme
et al.,32 is probably the physical activity level of the subjects.
Among the lowest upper reference limits were the ones
determined in hospitalised subjects,33 whereas the highest
limits were determined in moderately active, physically fit
military subjects.34 As far as the present study is concerned, the
non-athletes were all ambulatory, and, although not participat-
ing in any sport training programme, many were physically
active, engaging in light-to-moderate physical activity up to
three times a week, as mentioned in the Methods section. Such
activity is widely advocated as beneficial to health. On this basis
it may be necessary to revise the reference intervals for CK in
the general population. These intervals should not be based on
subjects who are physically inactive (or, what is more, hospitalised)
but on subjects who lead a healthy lifestyle that
includes regular physical activity. Thus, in addition to introduc-

REFERENCES
25 Stro¨mme et al.

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cing reference intervals for athletes, the present study may contribute to establishing more relevant reference intervals for CK in the general population.

Gender affected the reference interval for CK in athletes, the upper reference limit for males being more than twice as high as that for females. This is in agreement with the differences in mean and maximal values seen in other studies and is in line with the existence of sex-specific reference intervals for CK in the general population. These differences may be explained by the higher CK content of men’s muscle than that of women’s muscle, although other factors, such as muscle membrane permeability, CK clearance rate and lymph activity cannot be excluded.

Age (within the range of 7–44) did not seem to affect the reference interval for CK in athletes considerably. This is agreement with the statement that age does not appear to influence the degree to which serum enzyme concentrations increase with exercise and is in line with the absence of age-specific reference intervals for CK in the general population within the aforementioned range.

Different sports have quite different demands in terms of strength, speed, endurance, flexibility and technique. Training programmes are tailored to meet these often conflicting demands and to provide the perfect mix of abilities that will enable an athlete to excel. Thus, although introducing reference intervals for CK in athletes is in itself an advance over having reference intervals in the general population only, asking for sport-specific reference intervals is a legitimate request. The available data permitted a partial response to this request, that is, the introduction of reference intervals in male football players and swimmers. Interestingly, the upper reference limit in football players was almost three times the upper reference limit in swimmers. This may be related to the nature of football. Football training and playing involves a great deal of

![Figure 1](https://www.bjsportmed.com)

**Figure 1** Distribution of serum CK values in male and female athletes and non-athletes.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Reference limits and 90% confidence intervals (CI) for serum creatine kinase (U/L, 37°C) in male and female athletes and non-athletes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>Lower reference limit</td>
</tr>
<tr>
<td>Male athletes</td>
<td>82</td>
</tr>
<tr>
<td>Female athletes</td>
<td>47</td>
</tr>
<tr>
<td>Male non-athletes</td>
<td>45</td>
</tr>
<tr>
<td>Female non-athletes</td>
<td>25</td>
</tr>
</tbody>
</table>
weight-bearing activities, which include eccentric (lengthening) contractions of the leg muscles, such as during landing after a jump or when abruptly stopping while sprinting. Eccentric contractions are known to cause more muscle injury than concentric (shortening) contractions, resulting in higher increases of serum CK. In addition, football playing can induce muscle damage due to mechanical impact with other players. Finally, football training and competition are often performed under harsh environmental conditions, and football games are among the longest (90 minutes) and most energy-demanding sporting activities. In contrast, swimming training and competition involve mainly non-weight-bearing activities and concentric contractions of the upper and lower limb muscles, causing minor muscle damage and only small increases in serum CK. In addition, there is no muscle-damaging physical contact with other swimmers. Finally, swimming training and competition take place mostly in the protective environment of a swimming pool, and most swimming events last only a few minutes.

CONCLUSION

In summary, by analysing serum samples from 483 male athletes and 245 female athletes of a variety of sports, I have calculated the following reference intervals for the catalytic concentration of CK: males, 82 to 1083 U/L; females, 47 to 513 U/L. The upper limits of these intervals are twice the upper limits reported for moderately active non-athletes in the literature or calculated in the non-athletes of this study. The difference from the upper limits reported for inactive individuals in the literature (171 U/L for males and 145 U/L for females) is more dramatic, being more than sixfold in males and threefold in females. The difference between physically active and inactive non-athletes suggests the need for a revision of the reference intervals in the general population in accordance with the guidelines for regular exercise as part of a healthy lifestyle. When reference intervals were calculated specifically in male football players and swimmers, a threefold difference in the upper reference limit was found (1492 vs 523 U/L, respectively), which may be explained by the heavier training and competition burden placed on football players.

The findings of the present study indicate profound effects of sport training and competition on the reference intervals for serum CK. Introducing specific reference intervals in athletes and, further, reference intervals according to sport may protect physicians from misinterpreting high CK values as pathological ones. Additionally, it may help coaches to establish decision limits for CK as guidelines in optimising training, in conjunction with other widely used parameters (such as blood lactate). In principle, coaches could maximise training adaptations and performance gains by employing training loads resulting in CK values close to the upper reference limits. However, exceeding these limits might signal an increased risk for overexertion or injury.

Figure 2  Distribution of serum CK values in male football players and swimmers.

What is already known on this topic

- The serum concentration of creatine kinase (CK) is used as an index of skeletal muscle fibre damage in sport and exercise.
- Normal values have been established in the general population.
- Since athletes have higher values than non-athletes, comparing the values of athletes to the normal values established in non-athletes is pointless.

What this study adds

- This study introduces reference intervals for CK in male and female athletes, as well as specific reference intervals in male football (soccer) players and swimmers.
- These intervals may protect physicians from misinterpreting high CK values as pathological ones.
- They may help coaches to establish decision limits as guidelines in optimising training.
Finally, the findings of the present study may indicate introduction of reference intervals for CK in other sports and introduction of reference intervals for other blood parameters in athletes. Target parameters should be the ones upon which physical activity has a moderate-to-large effect, as identified in studies from many laboratories.\(^1\,^3\,^5\) The establishment of specific reference intervals in athletes will set the framework for a more accurate evaluation of the training load and training status in the direction of both protecting an athlete’s health and enhancing his or her performance. Additionally, it will increase the value of monitoring athletes through clinical laboratory tests and motivate sport clubs and individual athletes to seek such monitoring on a regular basis.

Competing interests: None declared.

REFERENCES