Letter to the Editor

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Is creatine kinase an ideal biomarker in rhabdomyolysis? Reply to Lippi et al.: Diagnostic biomarkers of muscle injury and exertional rhabdomyolysis (https://doi.org/10.1515/cclm-2018-0656)

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To the Editor,

With interest we have read the opinion paper by Lippi et al. [1] regarding diagnostic biomarkers of muscle injury and exertional rhabdomyolysis. We fully agree with the authors that creatine kinase (CK) is by far the most popular biomarker in this respect. However, we do not share the authors' enthusiastic view of CK being an almost perfect rhabdomyolysis biomarker.

Creatine kinase activity is measured in serum or plasma. In assessing the extent of rhabdomyolysis, one would expect that the amplitude of the biomarker signal in plasma reflects the amount of tissue damage. However, in the case of CK many factors are unfavourable to make this assumption:

1. Tissue distribution of CK activity shows marked differences amongst human muscles: specific CK activity may strongly vary between 228 U/g (diaphragm) and 3000 U/g (m. rectus abdominis) [2].
2. It is commonly assumed that mechanical stress disrupts plasma membranes to an extent that allows muscle enzymes to leak from the cell into the extracellular space. However, this does not fully explain changes in muscle enzyme activity in the blood after exercise. Apart from this mechanically induced membrane damage, under critical metabolic conditions, ATP consuming enzymes like CK are "volitionally" expulsed by muscle cells in order to prevent cell death [3]. Subjects can be classified into high responders and low responders. In high responders, the cross-sectional area and volume of the quadriceps femoris muscle were significantly lower than in low responders, and mobilization of free fatty acids tended to be lower in high responders [4].
3. CK activity not only depends on the number of released enzyme molecules into the circulation, but strongly depends on extracellular glutathione concentration. CK is a brittle enzyme containing a large number of free thiol groups, which are very prone to oxidation. Because the life-span of a protein is 1.4 times the biological half-life, CK stays ±22 h in the plasma before deactivation and elimination [2]. During the time the enzyme stays in the circulation, CK is prone to oxidative stress and degradation processes that may produce an irreversible reduction of its catalytic activity *in vivo* before blood sampling. The classical solution used by vendors to treat the sample with reducing agents such as N-acetylcysteine is only partly efficient to restore enzyme activity [5]. In rhabdomyolysis, extracellular glutathione concentration is often reduced [6], which hampers the correct assessment of muscle damage. In subjects recovering from eccentric exercise, those with low plasma total glutathione levels had a smaller plasma CK response and a faster recovery from eccentric exercise compared with subjects having high plasma total glutathione levels [7]. As CK is mainly metabolized by liver macrophages [8], the plasma half-life of CK increases in severe liver insufficiency.
4. Posttranscriptional CK modification: Posttranscriptional action of carboxypeptidase N (CN, EC 3.4.17.3) further degrades the CK-M chain, leading to additional CK heterogeneity. CN activity in serum is characterized by a large inter-individual variation, in particular under pathological conditions [9]. It is clear that the specific activity rapidly decreases, as illustrated by the steady increase in the activation energy of CK following its release into plasma [10, 11].

In the literature, numerous findings of unexpectedly low serum CK activity have been reported in intensive care

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patients [12]. These conditions may lead to an underestimation of the myocardial infarct size when serum CK activity measurements are used. In intensive care patients, low CK values are associated with an increased mortality, illustrating its poor quality as an injury marker [12].

The lack of a gold standard model for quantitatively assessing muscle injury has given way for surrogate muscle injury markers. Realizing that overselling CK as a muscle trauma biomarker will further reduce the interest in other biomarkers of muscle injury, we would like to highlight that the popularity of CK as a muscle tissue damage biomarker is not completely warranting a correct quantitative interpretation in all cases. In particular in the case of major comorbidities, CK cannot always be regarded as a reliable biomarker for muscle injury. We therefore recommend adding additional (even less popular) biomarkers of muscle damage in doubtful cases.

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