Reviewer's report

Title: Biomarkers of peripheral muscle fatigue during exercise

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Reviewer: Hans Degens

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Major essential comments:
The paper describes several types of conditions as muscle fatigue. This causes confusion. The first is a sense of continuously feeling tired, even before exercise is performed, and the other skeletal muscle fatigue that develops with ongoing contractile activity of the muscle as occurs during exercise. I think it is important to clearly distinguish these two ‘fatigues’ throughout the manuscript. There is even a third issue and that is that skeletal muscle may be more fatiguable in disease states, adding further to the confusion. Maybe the author could subdivide the manuscript into three sections dealing with each of these types of fatigue.

In the section of inflammation I have the impression that the author is speaking about muscle weakness rather than muscle fatigue. These things need all to be clearly distinguished in the manuscript!

References not always correct. Please check carefully throughout the manuscript.

Minor essential comments:
In the abstract say that the biomarker must be WITHOUT appreciable diurnal variations.

Page 3 Exercise section: The first sentence can be deleted.

Page 4 Exercise-induced muscle fatigue: Opening sentence: although a muscle may still produce appropriate force during prolonged activity, fatigue may still be there as the capacity to generate force is diminished. I would say: Fatigue is the decreased ability to generate force or power during ongoing contractile activity. Power is maybe more important than force.

This section also does treat muscle fatigue and a sensation of tiredness as one and the same thing. Please note that also during submaximal aerobic exercise muscle fatigue develops that is not necessarily reflected by a sensation of tiredness, but a reduced ability to develop force and power.

I think that most of the factors that contribute to fatigue in Table 1 are factors that do actually cause a sensation of tiredness, rather than muscle fatigue. It is in many of those cases that muscle fatigue does occur earlier during contractile activity, so you could say that the muscle is more fatiguable or less fatigue resistant. So may be you could change the heading into: ‘Factors that contribute to an earlier onset of muscle fatigue’ or ‘Factors that contribute to feeling tired’.
Page 4 section ‘Fatigue versus muscle damage’ I do not think ref 6 is appropriate to reflect that muscles contain different fibre type. I suggest to refer to e.g. one of the reviews from the 80’s or 90’s by D Pette, which will also discuss the myosin ATPase method. Further a good section!

Section on page 6 and 7 also mixes up damage and muscle fatigue. While ATP depletion may cause fatigue it is more often a problem of Pi accumulation as [ATP] may be constant when force decreases (see e.g. review by Jones DA J Physiol 2009). The inflammatory changes themselves may not necessarily cause muscle fatigue, but maybe more a reflection of damage that occurred during exercise.

Page 8: I doubt whether serum lactate indicates an inability to convert oxygen into energy. I think it is more reflecting that the aerobic ATP generation is insufficient for the generation of the required ATP and needs to be supplemented with anaerobic ATP generation. After exercise the aerobic energy metabolism is adequate again.

Line 10 of ‘Lactate’ section: what is the 70-90% a percentage off? VO2max?

Second paragraph of ‘Lactate’ section. Lactate, you say, does also increase in patients. I guess what you want to say here is that it increases at lower (relative) workloads.

Page 21: Could you specify what the sensitivity/specificity refer to: is the to diagnose the mitochondrial disorder or the fatiguability of the muscle?

There is a rather simple way to assess fatigue and that is to determine the maximal force a muscle (group) can generate after contractile activity compared the force/power the muscle could generate before the onset of contractile activity. This is the usual way of determining fatigue resistance (See e.g. Burke et al., J Physiol, 1973).

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
'I declare that I have no competing interests’