The authors are commended for generating an interesting and thought provoking empirical study investigating the effects of anabolic responses upon mitochondrial physiology. The contributing bioenergetic rationale behind the study is novel. This study seems to be the third paper/investigation using a subset of individuals used within an original investigation. The results presented are of interest, and provide a justification for further investigation(s) to be undertaken in this area.

Key questions and comments

A key message from the current paper i.e. the response of MYOZ1 seems driven by 2-3 large responders from the group. Was an outlier test run on the data? If not, I'd be interested to see the results of one that could be run. Regardless, a limitation of the current study is the small sample size from the perspective of the stance of MYOZ1 as a biomarker. Whilst the authors acknowledge that validation of this hypothesis, and further mechanistic insight being required, I feel that it is important to acknowledge this variability in relation to the sample size as a cautionary outcome towards the interpretation of the MYOZ result.

The original study where the subset of participants in this are drawn from did not detect any group (supplementation)-based differences in VL thickness of whole-body muscle mass. However, individual supplementation group based pre-post increases were identified e.g. Type 1 increase in PLA and SPC, type II in LEU, WPC and SPC, and further increases spanning nuclei, and time and G*T responses in satellite cell accretion. At minimum, these findings need mentioning in this paper as considerations, since an established body of evidence supports the roles of nuclei and satellite cell responses in contributing towards the 'anabolic' responses to training.

Can the authors provide details of the supplementation group breakdown towards the HI and LOW groups here?

Minor comments

Abstract
The sentence "Myofibrillar protein levels of genes related to new myofibril formation as well as whole lysate PGC1-α protein levels were also assessed" is unclear at present, please revise to e.g. "Proteins relating to myofibril formation, as well as whole lysate PGC1-α protein levels were assessed"

Please add an absolute or relative statistic including its standard deviation, for the magnitude change over time and cluster differences in citrate synthase activity, and add the standard deviation statistic to the stated +25% increase in MOZ-1 result.

Line 63; highlight that you're referring to MPS as existing from a whole/mixed fraction

Line 76; reword to clarify that you're referring to the genes that code for the aforementioned proteins to increase myofibril protein content

Line 85; you've not explicitly mentioned any biomarkers of volume of function yet, so reword to clarify that you're referring to biomarkers of volume and/or function

Line 143; please clarify whether you are referring to 4-15% gels as graded gels, or separate gels over a 4-15% range.

Western blotting

Please add clarification as to whether the statistical analysis on western blot proteins was conducted on raw densiometry data i.e. POST raw densiometry result from target of interest divided by ponceau density, related to the same approach from PRE, or whether statistical analysis was conducted upon relative % or fold changes.

Line 210; please clarify whether you are referring to 4-15% gels as graded gels, or separate gels over a 4-15% range.

Why Coomassie for MHC and actin Vs Ponceau for others?

Statistical analysis
Please state the reasoning for the use of Mean +/- SE, despite the use of parametric statistics

Results
Line 268; remove the "(mean +/- SE)" reference as this is already mentioned in line 263.

Line 292-294; please clarify that the positive association referred to was based on the pooled samples. My interpretation is that it is, but clarification of this would be of benefit.

Discussion
Lines 385-398; for balance I suggest the authors also cite and note the study from Porter and colleagues (https://www.ncbi.nlm.nih.gov/pubmed/25539479) that did show enhanced qualitative and quantitative mito responses after 12 weeks of training, utilising high-resolution respiration approaches as eluded to not being possible in this instace.

Figures
The authors are commended for the presentation of both cluster mean and individual data throughout

Figure 2; why is the representative image of coomassie staining not from an example participant from the study, similar in principle to what is provided in figure 3? In the potential absence of the use of a housekeeping protein, an example coomassie stain from 1-2 individuals in the current analysis would be highly recommended.