Reviewer's report

Title: Exercise as 'precision medicine' for insulin resistance and its progression to type 2 diabetes: A research review

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Reviewer: Derek Ball

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The authors have clearly defined their aims as addressing the role of chronic exercise training plays in the prevention and treatment of IS and progression to diabetes. While the aims are clear the reader then has to negotiate 17 pages of text that attempts to explain the cause of IS by focussing on the role of ectopic fat deposition and the potential effects on mitochondrial function. While this may be of interest to the reader in terms of explaining the potential focus of any subsequent exercise intervention the current format is too long and at times self contradictory.

For example, the reference and evidence provided Page 3 line 25 runs contrary to the statement made on lines 32-39 since the position statement made by the ADA does not clearly identify the genetic predisposition to IS as the primary defect it lists several other environmental and habitual factors with equal weighting.

There is substantial focus on the deposition of intracellular lipids as a primary cause of IS. However, on page 5 line 54-57 the conclusion based on the athletes paradox must be that it is the rate of turnover of IMCL rather than its deposition per se that separates the difference between athletes and a sedentary population that results in IS, a conclusion not reached by the authors.

On Page 6 we are told that simply being the offspring of a diabetic parent will result in a generational defect with regards to IMCL accumulation. There are, however, several studies that demonstrate that the environmental effect from the parental input with regard to both diet and physical activity can account for the incidence of generational diabetes an important observation that appears to be ignored by the authors.

On Page 7 line 14-19 the authors ignore the effects of a lower hexokinase activity as an explanation for IS, an effect reported in ref 50.

On page 7 Line 53-56 the authors discuss the role of mitochondrial respiration and state that the reduced function in T2D patients was associated with glycated haemoglobin, while there might
be a relationship is it meaningful? An explanation of why this important is required to substantiate the comment.

Page 8 line 27-41 The authors refer to work by Oberbach (55) as evidence concerning the relationship between mitochondrial oxidative activity and fibre type distribution. But the current authors have not highlighted that Oberbach's study measured GPDH as a marker of glycolytic enzyme activity without recognising that GPDH would be a poor marker of glycolytic activity and therefore questions the validity of Oberbach's observation.

Page 9 line 45-48. Can the authors explain how a person with severe IR can be classified as otherwise-healthy?

Page 10 line 4-12 Based on the data of Morino their weight loss data suggests that IR is only related to IMCL and has little to do with lipid handling by mitochondrion.

Page 14-17 It is not clear as to why there is an entire section on metabolic flexibility and diet if the focus of the review is aimed at prescription of exercise impacting IS and T2D.

Page 17 lines 54-59 and Page 18 lines 4-17 it is unclear why the authors are discussing sleep and resting RQ.

Page 18 lines 56-59 and Page 19 lines 4-14, the first study to quantify substrate oxidation from intramuscular and extra-muscular sources during exercise at different intensities was conducted by Romijn and coworkers. It is unclear as to why the authors have not included this as the primary reference source and that the work of Jeukendrup et al subsequently adopted the approach of non-isotopic labels to extend these observations.

Page 20 lines 6-7 are the values provided percentages of VO2max?

Page 21 line 9-11, it not clear why it is unfortunate that there are equivocal outcomes from studies.

Page 22 line 19-24. The authors report that it is unclear why there are discrepant findings but appear to fail to recognise that of the three studies cited (105) (48) and (107) they all used a different exercise intensity. Based on the work from the Jeukendrup group the differences in outcomes could be due to the effects that the workload would have on fat catabolism.
Pages 26-28 the authors report the outcomes of several studies but the principal weakness here is the lack of a critique of these studies, for example, while the acute effects of exercise on IS are understood what is the effect of 4 days of inactivity on IS? If the goal of an exercise intervention is to improve IS is it realistic to advocate 4 days of rest? These discussion points are not raised by the authors but raise important questions about the applicability of some of these studies to the notion of precision exercise prescription for IR.

Page 30 The authors discuss the effects of ageing on IS and suggest that IS declines as a function of age citing a study by Clevinger. Is it the case that the trained elderly and the sedentary young subjects did not differ in terms of either ISI or AIR thus suggesting that training has preserved function and not, as suggested, that ageing results in a decline in function regardless of training status?

Minor points

Some of the vernacular used in the text requires tidying up e.g. "full swing", "rally cry" "metabolic demise" "dodged" or "dodge a decline"

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