J Physiol 0.0 (2020) pp 1–2

The Journal of Physiology

CROSSTALK

Rebuttal from Marlou L. Dirks, Benjamin T. Wall and Francis B. Stephens

Marlou L. Dirks, Benjamin T. Wall and Francis B. Stephens

Department of Sport and Health Sciences, College of Life and Environmental Sciences, University of Exeter, Exeter, UK

Email: m.dirks@exeter.ac.uk

Edited by: Francisco Sepúlveda

Linked articles: This article is part of a CrossTalk debate. Click the links to read the other articles in this debate: https://doi.org/10.1113/JP278219, https://doi.org/10.1113/JP279714, https://doi.org/10.1113/JP278220.

Goodpaster (2020) has presented a convincing case for a role of specific subcellular species of ceramides and diacylglycerols in the development of insulin resistance (IR). Indeed, a 2016 *Journal of Physiology* CrossTalk by our opponent presented a similarly eloquent argument for ceramides based on pharmacological, genetic and cross-sectional studies (Summers & Goodpaster, 2016). We refer readers to the 2016 CrossTalk for a robust opposing view, but would like to add that more recent research has confirmed that pharmacological interventions, e.g. myriocin, have off-site effects, and might even improve insulin sensitivity independently of ceramides (Pillon *et al.* 2018; Appriou *et al.* 2019). The 2016 opposing view also overlooked that the insulin sensitising effect of pharmacological and gene knockout models that lower lipid is usually restricted to the liver, whereas skeletal muscle remains largely unaffected (Holland *et al.* 2007; Li *et al.* 2011). Thus, whereas we wholeheartedly agree that intramuscular lipid is often associated with IR, we still contend that clear causation has not been demonstrated by the arguments presented (Goodpaster, 2020).

It can be tempting to infer causation from this large body of associative data (Goodpaster, 2020); however, the demonstration of a clear disassociation between intramuscular lipid accumulation and IR refutes a causal relationship. Specifically, as outlined in our initial argument, we and others have demonstrated that physical inactivity rapidly leads to IR, and often in the absence of changes in specific ceramide species implicated in IR (e.g. C16:0 and C18:0; Dirks *et al.* 2016). Crucially, none of the human intervention studies in our opponent's proposal have accounted for habitual physical activity. Moreover, all of the human studies referenced were cross-sectional in nature or used physical activity to improve peripheral IR, and we are unaware of any time-course studies in humans that have the temporality to delineate changes in IR from lipid accumulation. Of course, it could be argued that physical inactivity causes a physiological decline in muscle glucose uptake, and that intramuscular lipid-induced IR is pathophysiological. However, given that physical inactivity has been implicated in epidemiological studies and randomized controlled trials as a major cause for IR independently of obesity (Lee *et al.* 2012), and eventually leads to intramuscular lipid accumulation, we cannot rule out that intramuscular lipids are innocent bystanders and that there is no 'athlete's paradox'. Clearly, well-controlled time-course studies directly targeting specific lipid species are required to support the paradigm that intramuscular lipids *per se* (and exclusively) cause IR.

Call for comments

Readers are invited to give their views on this and the accompanying CrossTalk articles in this issue by submitting a brief (250 word) comment. Comments may be submitted up to 6 weeks after publication of the article, at which point the discussion will close and the CrossTalk authors will be invited to submit a 'Last Word'. Please email your comment, including a title and a declaration of interest, to jphysiol@physoc.org. Comments will be moderated and accepted comments will be published online only as 'supporting information' to the original debate articles once discussion has closed.

References

Appriou Z, Nay K, Pierre N, Saligaut D, Lefeuvre-Orfila L, Martin B, Cavey T, Ropert M, Loreal O, Rannou-Bekono F & Derbre F (2019). Skeletal muscle ceramides do not contribute to physical-inactivity-induced insulin resistance. *Appl Physiol Nutr Metab* **44**, 1180–1188.

Dirks ML, Wall BT, van de Valk B, Holloway TM, Holloway GP, Chabowski A, Goossens GH & van Loon LJ (2016). One week of bed rest leads to substantial muscle atrophy and induces whole-body insulin resistance in the absence of skeletal muscle lipid accumulation. *Diabetes* **65**, 2862–2875.

Goodpaster BH (2020). CrossTalk proposal: Intramuscular lipid accumulation causes insulin resistance. *J Physiol*, https://doi.org/10.1113/JP278219.

Holland WL, Brozinick JT, Wang LP, Hawkins ED, Sargent KM, Liu Y, Narra K, Hoehn KL, Knotts TA, Siesky A, Nelson DH, Karathanasis SK, Fontenot GK, Birnbaum MJ & Summers SA (2007). Inhibition of ceramide synthesis ameliorates glucocorticoid-, saturated-fat-, and obesity-induced insulin resistance. *Cell Metab* **5**, 167–179.

Lee IM, Shiroma EJ, Lobelo F, Puska P, Blair SN, Katzmarzyk PT; Lancet Physical Activity Series Working Group (2012). Effect of physical inactivity on major non-communicable diseases worldwide: an analysis of burden of disease and life expectancy. *Lancet* **380**, 219–229.

Li Z, Zhang H, Liu J, Liang CP, Li Y, Li Y, Teitelman G, Beyer T, Bui HH, Peake DA, Zhang Y, Sanders PE, Kuo MS, Park TS, Cao G & Jiang XC (2011). Reducing plasma membrane sphingomyelin increases insulin sensitivity. *Mol Cell Biol* **31**, 4205–4218.

Pillon NJ, Frendo-Cumbo S, Jacobson MR, Liu Z, Milligan PL, Hoang Bui H, Zierath JR, Bilan PJ, Brozinick JT & Klip A (2018). Sphingolipid changes do not underlie fatty acid-evoked GLUT4 insulin resistance nor inflammation signals in muscle cells. *J Lipid Res* **59**, 1148–1163.

DOI: 10.1113/JP279715

Summers SA & Goodpaster BH (2016). CrossTalk proposal: Intramyocellular ceramide accumulation does modulate insulin resistance. *J Physiol* **594**, 3167–3170.

Additional information

Competing interests

No competing interests declared.

Author contributions

All authors have read and approved the final version of this manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

Funding

None.

Keywords

insulin resistance, intramuscular lipid accumulation, muscle disuse