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LETTER

Low *versus* high carbohydrates in the diet of the world-class athlete: insights from McArdle's disease

Burke *et al.* have elegantly shown in world-class race walkers undergoing a 3 week period of intense training that, compared with a diet providing high carbohydrate (CHO) availability (8.6 g kg^{-1} day^{-1}), a low CHO diet (< 1.0 g kg^{-1} day^{-1}) impaired performance, in part due to worsened exercise economy (Burke *et al.* 2017). Their study adds valuable information to the field of sports nutrition given the ongoing debate (also in the mass media) about which dietary pattern is more suitable for endurance athletes. Recent alternatives to the 'classic' high CHO approach, such as diets with periodic or chronic low CHO availability, are receiving growing attention.

No universal recommendation can be given to athletes regarding dietary CHO content. Personalised nutrition appears to be the wiser approach. Yet it should always be considered that any diet resulting in very low glycogen levels is likely not only to preclude achievement of top-level endurance sports performance, but also to impair the ability to perform intense endurance exercise in general. This phenomenon is best illustrated by the results of research conducted with elite athletes, such as the valuable study by Burke and coworkers, as well as by studies on patients with McArdle's disease (glycogenosis type V). This rare, often ignored disorder can provide mechanistic insight into the importance of muscle glycogen for intense endurance exercise performance.

McArdle's disease is a pure myopathy caused by inherited deficiency of the skeletal-muscle isoform of glycogen phosphorylase, 'myophosphorylase', encoded by the *PYGM* gene. Because this enzyme catalyses the breakdown of glycogen into glucose 1-phosphate in muscle fibres, patients are unable to obtain energy from their muscle glycogen stores, with the remaining body tissues retaining normal metabolic function (Santalla *et al.* 2014). McArdle's disease therefore represents an excellent model with which to study the biological consequences of exercising with unavailability of muscle glycogen, and is arguably the paradigm of exercise intolerance, typically consisting of acute 'crises' of fatigue and muscle stiffness and contractures upon the start of endurance exercise such as brisk walking. Such crises are frequently accompanied by marked muscle damage or rhabdomyolysis (see below for the potential implications of the latter phenomenon) (Santalla *et al.* 2014).

The poor aerobic capacity of McArdle's patients (e.g. mean peak oxygen consumption ($\dot{V}_{O_2peak}$) in Spanish patients = 18.2 ± 6.5 ml kg^{-1} min^{-1} (range 5.9, 37.8)) and the intolerance to endurance sports in virtually all of them (Lucia *et al.* 2012) is consistent with the classic findings reported by Scandinavian scientists 50 years ago that decreasing pre-exercise muscle glycogen reserves by dietary and/or exercise manipulation severely decreases tolerance to fatigue during endurance exercise (Bergstrom *et al.* 1967). Observations in McArdle's patients are also consistent with the vital role that glycogen-derived ATP plays in key muscle functions whose failure might accelerate onset of fatigue. One such function is Ca^{2+} handling by the sarcoplasmic reticulum (Ortenblad *et al.* 2013), which is affected both in patients (Nogales-Gadea *et al.* 2012) and in the genetically manipulated mouse model of McArdle's disease that we recently generated (harbouring the commonest *Pygm* genotype causing the disorder among Caucasians, *p.R50X/p.R50X*; Fiuza-Luces *et al.* 2016). Further, the endurance capacity of *p.R50X/p.R50X* mice is much lower (~48%) than that of healthy (wild-type (*wt*)/*wt*) mice and, although in mice heterozygous for the *p.R50X* mutation (*p.R50X/wt*) the ability to utilise glycogen is not totally blocked (~50% of normal), their endurance capacity remains considerably reduced (by ~18%) when compared with their *wt*/*wt* peers (Brull *et al.* 2015).

A main consequence of the low CHO diet in the study by Burke *et al.* was impaired walking economy (Burke *et al.* 2017). In this regard, the oxygen consumed by the muscles of McArdle's patients is not converted into the expected power production, as shown by the very low gross mechanical efficiency values of these individuals during submaximal bicycling, i.e. 13% *vs* 19% in their age/gender-matched healthy controls (Mate-Munoz *et al.* 2007). The main reasons for this phenomenon are likely to be excessive muscle recruitment and increased dependence on fat metabolism owing to the inherited block in muscle glycogen metabolism since CHO is a more efficient fuel than fat in terms of generating ATP per mole of oxygen (Santalla *et al.* 2014).

Another consequence of blocked glycogenolysis, with potential clinical implications, is muscle damage, especially after hard exertion (sometimes leading to rhabdomyolysis), as reflected by high levels of intramyocellular proteins (e.g. creatine kinase [CK]) in the blood of McArdle's patients (their CK levels are usually >1000 U l^{-1}, well above the normal upper limit; 200 U l^{-1}; Lucia *et al.* 2012). Although mechanistic explanations that fully account for this phenomenon remain elusive, one reason might be down-regulation of Na^+–K^+ pumps in patients' muscles (Haller *et al.* 1998), which are fuelled by glycogenolysis-dependent ATP and are responsible for maintaining cellular volume and integrity (Santalla *et al.* 2014). Interestingly, muscle damage might further impair the efficiency of muscle contractions (Warren *et al.* 1996), as reflected by impaired running economy (Calbet *et al.* 2001).

It would have been interesting to assess the effects of the different diets on muscle damage markers in the study by Burke *et al.* Further research might determine whether low CHO diets can increase muscle damage (and subsequent risk for rhabdomyolysis), especially during a demanding endurance training approach that is gaining adepts among Westerners (partly for its advocated health benefits while taking up little time), the so-called high intense interval training ('HIIT').

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References

Bergstrom J, Hermansen L, Hultman E & Saltin B (1967). Diet, muscle glycogen and physical performance. *Acta Physiol Scand* **71**, 140–150.

Brull A, de Luna N, Blanco-Grau A, Lucia A, Martin MA, Arenas J, Marti R, Andreu AL & Pinos T (2015). Phenotype consequences of myophosphorylase dysfunction: insights from the McArdle mouse model. *J Physiol* **593**, 2693–2706.

Burke LM, Ross ML, Garvican-Lewis LA, Welvaert M, Heikura IA, Forbes SG, Mirtschin JG, Cato LE, Strobel N, Sharma AP & Hawley JA (2017). Low carbohydrate, high fat diet impairs exercise economy and negates the performance benefit from intensified training in elite race walkers. *J Physiol* **595**, 2785–2807.

Calbet JA, Chavarren J & Dorado C (2001). Running economy and delayed onset muscle soreness. *J Sports Med Phys Fitness* **41**, 18–26.

Fiuza-Luces C, Nogales-Gadea G, Garcia-Consuegra I, Pareja-Galeano H, Rufian-Vazquez L, Perez LM, Andreu AL, Arenas J, Martin MA, Pinos T, Lucia A & Moran M (2016). Muscle signaling in exercise intolerance: insights from the McArdle mouse model. *Med Sci Sports Exerc* **48**, 1448–1458.

Haller RG, Clausen T & Vissing J (1998). Reduced levels of skeletal muscle Na^+K^+-ATPase in McArdle disease. *Neurol* **50**, 37–40.

Lucia A, Ruiz JR, Santalla A, Nogales-Gadea G, Rubio JC, Garcia-Consuegra I, Cabello A, Perez M, Teijeira S, Vieitez I, Navarro C, Arenas J, Martin MA & Andreu AL (2012). Genotypic and phenotypic features of McArdle disease: insights from the Spanish national registry. *J Neurol Neurosurg Psychiatry* **83**, 322–328.

Mate-Munoz JL, Moran M, Perez M, Chamorro-Vina C, Gomez-Gallego F, Santiago C, Chicharro L, Foster C, Nogales-Gadea G, Rubio JC, Andreu AL, Martin MA, Arenas J & Lucia A (2007). Favorable responses to acute and chronic exercise in McArdle patients. *Clin J Sport Med* **17**, 297–303.

Nogales-Gadea G, Consuegra-Garcia I, Rubio JC, Arenas J, Cuadros M, Camara Y, Torres-Torronteras J, Fiuza-Luces C, Lucia A, Martin MA, Garcia-Arumi E & Andreu AL (2012). A transcriptomic approach to search for novel phenotypic regulators in McArdle disease. *PloS One* **7**, e31718.

Ortenblad N, Westerblad H & Nielsen J (2013). Muscle glycogen stores and fatigue. *J Physiol* **591**, 4405–4413.

Santalla A, Nogales-Gadea G, Ortenblad N, Brull A, de Luna N, Pinos T & Lucia A (2014). McArdle disease: a unique study model in sports medicine. *Sports Med* **44**, 1531–1544.

Warren GL 3rd, Williams JH, Ward CW, Matoba H, Ingalls CP, Hermann KM & Armstrong RB (1996). Decreased contraction economy in mouse EDL muscle injured by eccentric contractions. *J Appl Physiol* **81**, 2555–2564.

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