Is high-density lipoprotein-based therapy an option for the treatment of muscle damage in Facioscapulohumeral muscular dystrophy?

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Facioscapulohumeral muscular dystrophy (FSHD) is an inherited myopathy due to a genetic mutation on the 4q35 chromosome. The mutation leads to loss of methylation in the 4q35 region that, in turn, is permissive for DUX4 expression, a gene that is silenced in the healthy adult population. DUX4 functions as a transcription factor, driving expression of proteins involved in oxidative stress, cell death and inflammatory response pathways. DUX4 expression in skeletal muscle increases fibre disorganisation, loss of contraction capacity, and ultimately death. At present, there is no cure for FSHD and only limited effective therapies. High-density lipoproteins (HDLs) are well-characterized for their antioxidant and anti-inflammatory properties and currently HDL-based therapies are in clinical trial for other oxidative stress-related diseases.

We hypothesized that HDL treatment may be effective against DUX4-induced oxidative stress in skeletal muscle in both early and progressive models of the disease. To test this hypothesis, C2C12 mouse skeletal cells were cultured in 4% and 20% O_2 conditions and were subsequently transfected with a DUX4 expression vector or control vector for 48 hours to induce an oxidative stress, FSHD-like phenotype. For the final 4 hours, the cells were treated with HDL particles (32μM, the physiologic circulating concentration) or vehicle (Milli-Q).

DUX4 was highly expressed in transfected cells, with no expression in control transfected cells (determined by mRNA and western blot analysis) and it was this expression of DUX4 which induced the oxidative stress phenotype. The levels of oxidative stress were shown to be significantly reduced in both 4% and 20% O_2 conditions by 59.9% and 91.4%, respectively, with HDL treatment. In keeping with reduced oxidative stress, HDL treatment also decreased cell death significantly by 63.1% and 75.5% in 4% and 20% O_2 culture conditions, respectively. Furthermore, DUX4 expression resulted in a disrupted myotube formation, and this was also improved following HDL treatment in 20% O_2. In conclusion, our early results *in vitro* support that HDL is a potential therapy for FSHD.