Autophagy activation in COL6 myopathic patients by a low-protein-diet pilot trial.


Abstract

A pilot clinical trial based on nutritional modulation was designed to assess the efficacy of a one-year low-protein diet in activating autophagy in skeletal muscle of patients affected by COL6/collagen VI-related myopathies. Ullrich congenital muscular dystrophy and Bethlem myopathy are rare inherited muscle disorders caused by mutations of COL6 genes and for which no cure is yet available. Studies in col6 null mice revealed that myofiber degeneration involves autophagy defects and that forced activation of autophagy results in the amelioration of muscle pathology. Seven adult patients affected by COL6 myopathies underwent a controlled low-protein diet for 12 months and we evaluated the presence of autophagosomes and the mRNA and protein levels for BECN1/Beclin 1 and MAP1LC3B/LC3B in muscle biopsies and blood leukocytes. Safety measures were assessed, including muscle strength, motor and respiratory function, and metabolic parameters. After one year of low-protein diet, autophagic markers were increased in skeletal muscle and blood leukocytes of patients. The treatment was safe as shown by preservation of lean:fat percentage of body composition, muscle strength and function. Moreover, the decreased incidence of myofiber apoptosis indicated benefits in muscle homeostasis, and the metabolic changes pointed at improved mitochondrial function. These data provide evidence that a low-protein diet is able to activate autophagy and is safe and tolerable in patients with COL6 myopathies, pointing at autophagy activation as a potential target for therapeutic applications. In addition, our findings indicate that blood leukocytes are a promising non-invasive tool for monitoring autophagy activation in patients.
KEYWORDS: Bethlem myopathy; Ullrich congenital muscular dystrophy; autophagy; clinical trial; collagen VI; low-protein diet; muscular dystrophies

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