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Effect of age and long-term disuse on proteome of human skeletal muscle

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Motivation and Aim: In normal conditions, skeletal muscle accounts for 30-40 % of body mass. The main function of skeletal muscles is to maintain posture and movement; in addition, with the normal level of physical activity, skeletal muscle plays a significant role in the regulation of carbohydrate and fat metabolism in the organism and positively affects the functioning of various systems (cardiovascular, nervous, etc.). Skeletal muscle tissue undergoes pronounced changes with aging, in particular, the amount of mitochondria and muscle mass decreases, which leads to a decline in strength, endurance, fat and carbohydrate oxidation rate, and insulin sensitivity. Chronically reduced physical activity is one of the key factors inducing these changes. The aim of this work is to investigate the effect of chronic decrease in physical activity (disuse) on the human skeletal muscle proteomic profile and to compare these changes with those induced by age.

Methods and Algorithms: In order to investigate the effects of ageing (the combined effects of 'normal' ageing and pathological processes), older adults (72[69-77] years, n=37) with primary knee/hip osteoarthritis, a model of aging with chronic disuse and inflammation, were compared with young healthy adults (35[28-38] years, n=15). The effects of chronic long-term disuse were studied by comparing young adults with primary knee/hip osteoarthritis (39[37-42] years; n=8) with young healthy individuals. Biopsy samples from *m. vastus lateralis* were taken from all volunteers for proteomic profile studies for panoramic quantitative (isobaric labelled) mass spectrometry based analysis.

Results: A total of 1900 proteins that were detected in all samples were predominantly cytoskeletal, sarcomeric and mitochondrial proteins, as well as regulators of carbohydrate and fat metabolism. In elderly patients, relative to young healthy controls, there was a decrease in muscle mass (40 %, $p<0.001$) and changes in the expression of more than 350 proteins. The most striking changes were a decrease in the relative content of mitochondrial respiratory enzymes and glycolysis enzymes, and an increase in the expression of proteins associated with nucleic acids, cytoskeleton and membrane. This is in good agreement with previous studies investigating age-related changes in the proteomic profile of human skeletal muscle [1-3]. Chronic (long-term) disuse led to a decrease in muscle mass (by 15 %, $p<0.001$) and altered the relative content of 178 proteins (predominantly increased expression of inflammatory response regulators). Notably, there was no detectable drop in the expression of mitochondrial proteins, which were most significantly decreased in elderly patients, relative to young healthy controls.

A decrease in mitochondrial proteins was found when comparing elderly and young patients – people of different ages with comparable levels of disuse and increased inflammatory markers.

Conclusion: In elderly patients, we observe large-scale changes in the proteome, associated mainly with a decrease in mitochondrial protein expression and an increase in inflammatory protein expression. These changes are induced by different factors: long-term disuse leads mainly to an increase in the expression of inflammatory proteins, whereas the decrease in mitochondrial proteins is mainly related to age.

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