Improvement of skeletal muscle performance in aging by the metabolic modulator Trimedazidine

E. Ferraro[1], F. Pin[2,3], S. Gorini[1], L. Pontecorvo[1], A. Ferri[4], V. Mollace[5], P. Costelli[2,3], G. Rosano[1,6]

[1]Laboratory of Pathophysiology of cachexia and metabolism of skeletal muscle , IRCCS San Raffaele Pisana, Via di Val Cannuta 247, 00166, Rome, Italy
[2]Dept. of Clinical and Biological Sciences, University of Turin, Italy
[3]Istituto Interuniversitario di Miologia-IIM, Turin, Italy
[4]Institute of Cell Biology and Neurobiology, Rome, Italy
[5]Dept. of Pharmacobiological Sciences, University Magna Graecia, Catanzaro, Italy
[6]Cardiovascular and Cell Sciences Institute, St George's University of London, Cranmer Terrace, London, UK

Aging is an extremely complex biological phenomenon. Aged individuals lose the capacity to maintain their physiological homeostasis. Many vital organs undergo atrophy or degeneration, especially those characterized by post-mitotic cells such as the skeletal muscle. The loss of muscle mass (sarcopenia) is one of the most relevant changes occurring in aging. Indeed, sarcopenia and the associated reduced muscle strength are key limiting factors for elderly people's quality of life, resulting in reduced mobility, difficulties in the ordinary daily activities and loss of independence. Sarcopenia is very often associated with reduced myofiber cross sectional area (atrophy) and muscle fiber loss (hypoplasia). Improving muscle performance does not necessarily correlate with increasing muscle mass. In fact, particularly in the elderly, the main explanation for muscle weakness is a reduction of muscle quality rather than a loss of muscle mass, and the main goal to be achieved is to increase muscle strength. Reprogramming metabolism might therefore be a strategy in prospect of improving muscle performance in the elderly.
TMZ is a metabolic modulator that is already known to optimize heart metabolism by shifting from free fatty acids to glucose oxidation improving glycolysis to glucose oxidation coupling. This leads to an improvement in cell energy metabolism, as ATP synthesis during fatty acid β-oxidation requires more oxygen than it does during glucose oxidation; this explains the beneficial effect of TMZ on myocardium functions in conditions of transitory hypoxia. Based on these premises, it is conceivable that the metabolic switch triggered by TMZ in the heart might also occur in the skeletal muscle, this likely improving muscle performance. Such a hypothesis is supported by previous observations showing that TMZ also improves exercise capacity in patients with angina. Furthermore, recent observations showed for the first time that TMZ directly acts on skeletal muscle cells in culture protecting them from hypotrophy induced by different agents.
The effectiveness of Trimetazidine (TMZ) in preventing muscle functional impairment during aging was assessed in our laboratory. Aged mice received TMZ or vehicle for 12 consecutive days. Muscle function was evaluated at the end of the treatment by a grip test as well as by an inverted screen test after 0, 5, 7 and 12 of TMZ treatment. Muscles were analyzed for myofiber cross sectional area (CSA) assessment and for myosin heavy chain (MyHC) expression evaluation by western blotting.
Our observations show that TMZ administration results in a significant increase of grip strength in aged mice, likely due to its action as a metabolic modulator.

Upon TMZ administration in aged mice, the slow MyHC isoform is definitively up-regulated. Interestingly, endurance exercise has been associated with marked modifications of myofiber contractile properties due to a fiber type shift towards the slow-twitch contractile apparatus. By increasing the expression of slow MyHC and enhancing muscle strength, TMZ seems to trigger some effects similar to those induced by exercise, thus acting like other pharmacological compounds defined as "exercise mimetics".
Finally, our experiments demonstrate that, in aged mice, TMZ triggers a shift towards myofiber characterized by a low CSA. Notably, it has been shown that the CSA of type I (slow) myofibers is smaller than that of type II (fast) fibers and this strongly correlates with our finding that TMZ-treatment enhances the expression of the slow MyHC isoform.
The data here reported suggest that the positive effects of TMZ on muscle force might be directly exerted acting on myofibers and might derive from metabolic modulations. On the whole, since TMZ appears to clearly improve muscle function in aged animals, this drug appears appealing for a possible reappraisal for the increase of muscle force in the elderly.