ANALYSIS OF MOLECULAR MECHANISMS AND CHANGES IN MUSCLE ARCHITECTURE INVOLVED IN AGE-RELATED MUSCLE MASS DECREASE: A STUDY ON PATIENTS OF DIFFERENT AGE

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INTRODUCTION:
Aging is a complex process characterized by changes in body composition, in particular by a relative decline of muscle mass and strength, changing of muscle architecture and concomitant increase in fat mass. This decline is termed sarcopenia, affects 42% of men and 57% of women over 70 years of age and represents an important risk factor for disability, loss of autonomy, morbidity and mortality in the elderly. Many factors are involved in the etiology of sarcopenia, among which key-players are represented by physical inactivity, malnutrition, increased level of pro-inflammatory cytokines, production of free radicals, decrease in aerobic energetic metabolism in mitochondria and hormonal changes. However, the relationships between physical activity, aging and the molecular mechanisms of sarcopenia remain unclear, as well as it is still difficult to define clinical and instrumental parameters that could identify this condition. Many studies indicate that several molecular signaling pathways are involved in the development of sarcopenia, among which the IGF-1/p53 pathway seems to be crucial. Moreover, inflammation itself seems to affect both p53 and IGF-1 expression. The present study also investigated whether age-related changes in muscle architecture, individuated by ultrasound imaging could be used as a new biomarker of sarcopenia.

METHODS:
After obtaining the informed consent from each patient, we collected a comprehensive Case Report Form (CRF) including data on life style (physical activity, diet, smoking habits and alcohol consumption), anthropometric measures (height, mass, BMI, thigh length and width) and clinical history. Hematological parameters, and quadriceps strength, were also assessed. Fascicle length (Lf) and muscle thickness (t) of the vastus lateralis muscle were measured by ultrasonography and the ratio Lf/t was calculated for each participant and compared with that of active healthy individuals. During the surgical procedure, muscle biopsy from vastus lateralis were collected and stored. On muscle biopsies, we measured the expression of some key genes involved IGF-1/p53 loop, such as IGF-1, p53, AKT, PTEN, MDM2, IGF-BP3 by Real time RT-PCR technique; expression of NF-kappaB and Mortalin (GRP75) as well as activation of p53 by Western blotting were also assessed. All these results were analyzed in comparison with CRF data to understand the correlation between aging, inflammation and loss of muscle mass and strength and to identify potential biological markers of sarcopenia. Further investigations will regard the balance between protein synthesis and degradation analyzed by the expression analysis of genes involved in the initiation step of mRNA translation.

RESULTS:
A preliminary inverse correlation seems to be present between BMI and quadriceps strength in our subjects, suggesting that adipose tissue deposition can affect muscle mass and strength. The Lf/t ratio was 47.7% higher in the group of “trail older” undergoing hip surgery, compared with a group of “active young” (P<0.001). The expression of genes such as IGF-1 and AKT seems to decrease with aging, with a gender difference (males have higher levels than females). Other genes such as p53 and its downstream IGF-BP3 and PTEN seem to be affected by gender in old people, being more expressed in women than men. Phosphorylation of p53 at serine 20 and 46 is necessary for its stabilization and activation. Western blot analysis indicated that these modifications are particularly evident in old subjects (60-80 years old) compared with both young people (30-40 years old) and very old people (>80 years old). A similar result is found when analyzing Mortalin expression, which appears to be strongly activated in the same group of subjects.

SIGNIFICANCE:
Architectural changes that are observed in sarcopenia can be used as a new biomarker based on ultrasound measures. This biomarker, represented by the ratio of muscle fibre fascicle length to muscle thickness (Lf/t) significantly increases in old age, particularly so when sarcopenia is associated with inactivity. We believe that a change in the Lf/t ratio represents a specific ‘signature’ of sarcopenia, this could be useful for the diagnosis of this condition. Moreover our preliminary results suggest that the IGF-1-p53 pathway and inflammation play a crucial role in the onset of sarcopenia in the elderly, thus representing a molecular target for new therapeutical strategies.