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The role of sarcopenia with and without fracture

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ABSTRACT

Introduction: Bone and muscle tissues are in a close relationship. They are linked from a biological and functional point of view and both are related to an increased fracture risk in the elderly. The aging process is involved in the loss of functionality of both bones and muscles. In particular, aging-induced decline in muscle size and quality accompanies catabolic alterations in bone tissue; furthermore, age-related changes in bone alter its response to muscle-derived stimulation. The increased fracture risk in individuals with sarcopenia and osteoporosis is due to the decline of muscle mass and strength, the decrease in bone mineral density (BMD) and limited mobility. In this study, we investigated the role of sarcopenia and the main age-related bone diseases, osteoporosis (OP) and osteoarthritis (OA).
Methods: Muscular performance status was evaluated using the Physical Activity Scale for the Elderly (PASE) test in 27 female patients with OP who underwent total hip arthroplasty for hip fracture, and in 27 age-matched female patients with OA who underwent total hip arthroplasty. Dual-energy X-ray absorptiometry (DEXA) was performed and the T-score values were used to discriminate between OP and OA patients. Body Mass Index (BMI) was calculated. As part of a multiparametric model of evaluation, biopsies of vastus lateralis muscle were analysed by immunohistochemical reaction to find a correlation with the above mentioned functional index.
Results: The PASE test showed that the OP patients had a low or moderate level of physical activity before fracture occurred, whereas the OA patients had more intensive pre-fracture physical performances. Histological analysis showed that osteoporosis is characterised by a preferential type II fibre atrophy; in particular, data correlation showed that lower PASE test scores were related to lower diameter of type II fibres. No correlation was found between bone mineral density (BMD) and PASE test results.
Discussion and conclusion: Osteoporosis is closely related to sarcopenia before and after fracture. Bone remodelling is influenced by muscle morphological and functional impairment and sarcopenia is considered one of the major factors for functional limitation and motor dependency in elderly osteoporotic individuals. Therefore, physical activity should be strongly recommended for OP patients at diagnosis.

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Background

Bone and muscle are in a close relationship: when the aging process affects one of these two tissues, the functionality of the other is compromised. Consequently, sarcopenia and osteoporosis represent two pathologies that are frequently associated in the elderly.

The term sarcopenia was first used by Rosenberg in 1989 to describe the decline in muscle mass among older people [1,2]. More recently, sarcopenia was defined as a loss of skeletal muscle mass and strength that occurs with aging [3]. Nowadays, the term sarcopenia is used in the literature to describe several pathophysiological processes, such as denervation, mitochondrial dysfunction, inflammatory and hormonal changes that may lead to a

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decrease in muscle strength and mobility, a decrease in fatigue resistance and an increase in the risk of falls and fractures [4].

Moreover, studies in the literature show that muscles of patients with sarcopenia display severe alterations in cellular turnover, including an increase in oxidative stress, cellular vacuolisation, and mitochondrial alterations, which compromise the quality of oxidant-scavenging systems. The denervation of single muscle fibres is also known to lead to a substantial reduction in type II fibres, which are gradually replaced by type I fibres and fat tissue [5,6].

Mechanisms involved in the decline of muscle mass during sarcopenia converge on the failure of satellite cells to replace and repair damaged muscle fibres. The main cause of reduced satellite cell function may be alteration of systemic factors that regulate satellite cell activity and differentiation. Indeed, satellite cells are mostly quiescent and their activation is governed by multiple niche factors (e.g. injury or stress) and signalling pathways, such as transforming growth factor-beta (TGF-β) and myogenin. The TGF-β superfamily plays a crucial role in normal physiology and pathogenesis of skeletal muscle. Numerous members of the TGF-β family have been shown to play important roles in regulating muscle growth and atrophy. The most extensively characterised ligands, in terms of the effects on skeletal muscle, are TGF-β, myostatin and bone morphogenetic proteins (BMPs). Myogenin is a transcription factor that induces myogenesis in a variety of cell types in tissue culture. It is a member of the helix-loop-helix (HLH) protein family, a large family of proteins related by sequence homology, and it is essential for the development of functional skeletal muscle [7].

Muscle and bone are proportionally matched in their functional capacity and geometric structure; however, this relationship appears to change significantly with age. For example, the capacity for muscle to generate force declines with age, and the anabolic response of bone to muscle-derived strains also appears to be altered with age. In addition, muscle is now recognised to have paracrine and endocrine effects that may also influence bone independently of a mechanical relationship [8,9].

In this study, we investigated the role of sarcopenia and the main age-related bone diseases, osteoporosis (OP) and osteoarthritis (OA).

Patients, materials and methods

A total of 54 patients who underwent hip arthroplasty for femoral fractures or for hip OA in the Orthopaedic Department of "Tor Vergata" University from June 2014 to February 2015 were enrolled in this study.

To evaluate bone mineral density (BMD), each patient with OA underwent dual-energy X-ray absorptiometry (DEXA) scan of the lumbar spine and femoral neck on the homolateral limb before surgery. Hip X-rays were performed to establish the grade of OA using the Kellgren-Lawrence Scale. To evaluate hip function, Harris Hip Score (HHS) was also calculated: the maximum score is 100 points, with the higher the HHS, the less the dysfunction. To estimate lumbar spine and non-fractured femur BMD, each OP patient underwent DEXA scan a few days after surgery; spinal X-rays were also performed in patients with femoral fracture or back pain to evaluate the presence of a vertebral compression fracture (VCF).

A functional evaluation of performance status was conducted in each patient using the Physical Activity Scale for the Elderly (PASE) test. The questionnaire assesses two main groups of activities: recreational activities carried out during free time and domestic activities [10]. Each of these actions corresponds to a set value that is proportional to the "weight" that they could have in the life of each individual. The sum of the individual scores sets the patient into one of four categories related to the degree of physical activity: inactivity (total score <42); lacking physical activity (43–105); moderate physical activity (106–145), and intense physical activity (>146). Body Mass Index (BMI) was also calculated.

Exclusion criteria were: history of neoplastic diseases, myopathies or other neuromuscular diseases; taking anti-osteoporotic drugs or chronic administration (more than one month) of corticosteroid for autoimmune diseases; diabetes; alcohol abuse; cigarette smoking; and chronic viral infections (hepatitis B virus [HBV], hepatitis C virus [HCV], human immunodeficiency virus [HIV]).

During surgery for total hip arthroplasty in both osteoarthritis (OA patients) and cervical femoral fragility fracture (OP patients), muscle biopsies were taken from the upper portion of the vastus lateralis muscle, which is normally involved in the surgical procedure, without damaging the tissue network. This muscle was chosen because it is hardly influenced by the fracture event and it is a good indicator of systemic muscle atrophy.

All sampling and experiments were performed in agreement with the independent ethics committee, "Policlinico Tor Vergata", approval reference number #85/12, and informed consent was obtained from all participants included in the study.

Bone mineral density evaluation (DEXA)

DEXA was performed with a Lunar DEXA apparatus (GE Healthcare, Madison, WI, USA). Lumbar spine (L1–L4) and femoral (neck and total) scans were performed, and BMD was analysed according to the manufacturer's recommendations. DEXA measures BMD (in g/cm^2) with a coefficient of variation of 0.7%. In the OA group, all measurements were performed on the non-dominant side; in the OP group, BMD was measured on the limb opposite to the fracture side. Results were expressed as absolute values and as T-scores [11,12].

Histology

Muscle biopsies were fixed with 4% paraformaldehyde for 24 h and embedded in paraffin after alcoholic dehydration. Sections of 3 μm thick were stained with haematoxylin and eosin (H&E) and the pathological evaluation was performed by two pathologists who were blinded to the samples [13].

Atrophy assessment

A minimum of 200 muscle fibres per biopsy were evaluated to assess fibre atrophy; minimum transverse diameter and cross-sectional area of type I and type II fibres were compared for relative prevalence. A threshold diameter of less than 30 μm (minimum value of the normal range for women) characterised atrophic fibres [14,15].

To calculate muscle and bone areas, H&E slides were scanned at low-power field by Iscan Coreo (Ventana, Tucson, AZ, USA). Areas for each muscle and bone biopsy image were identified by a pathologist using Viewing software (Ventana, Tucson, AZ, USA).

Immunohistochemistry

Immunohistochemical characterisation was conducted to assess muscle fibre type (i.e. fast and slow) and the expression of myostatin, TGF-β, pax7 and myogenin.

Briefly, 3 μm thick sections were pre-treated with EDTA citrate (pH 7.8) for 30 min at 95 °C and then incubated, respectively, with mouse monoclonal anti-fast skeletal myosin for 60 min (1:100, clone MY-32, AbCam), mouse monoclonal anti-slow skeletal myosin for 60 min (1:100, clone NOQ7.5.4D, AbCam) and rabbit

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