

Bone turnover profile and muscular status in major orthopaedic surgery: a case series

Vanna Bottai¹, Gabriele Filoni¹, Lorenzo Andreani¹, Gabriele Creati¹, Federico Di Sacco¹, Angelo Giovanni Bonadio², Stefano Giannotti³, Rodolfo Capanna¹

¹Ortopedia e Traumatologia Universitaria II - Università di Pisa, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy; ²Laboratory Medicine, Section of Pathology 1, University of Pisa, Pisa, Italy; ³Ortopedia e Traumatologia - Università degli Studi di Siena, Azienda Ospedaliera Universitaria Senese, Siena, Italy

Abstract. *Background and aim:* Sarcopenia refers to a chronic loss of skeletal muscle mass, often associated with hypovitaminosis D and advanced age, which involves a greater risk of falls and fractures as well as an increased mortality rate in elderly patients. The association of sarcopenia and osteoporosis defines osteo-sarcopenia. In this work, the authors analyzed the osteometabolic profile and the loco-regional muscular state of patients undergoing major orthopedic surgery, in order to define the incidence of district osteosarcopenic states, linked to a condition of disuse. *Methods:* 19 patients (10M-9F), between 15 and 85 years old, underwent major orthopedic surgery (15 resection prosthesis and custom made, 2 resection and reconstruction with transplant) were evaluated, of which 9 on an oncological basis. In all patients, the phospho-calcium metabolism was assessed by blood tests and intraoperative muscle biopsy was performed at the intervention site and contralaterally; in 3 cases a densitometric comparative study of the affected/contralateral limb was performed. *Results:* Results shows 5 patients with hypovitaminosis D; 7 pcs with hypocalcemia; 5 with PTH rise; 4pcs with ALP increase. In 100% of cases, the biopsy revealed sarcopenic patterns exclusively on the affected limb. 2 out of 3 DEXAs (66%) showed loco-regional osteoporosis compared to the contralateral. *Conclusions:* The fact that in our sample sarcopenia is unilateral affecting only the pathological limb, that it is frequently associated with osteoporosis which is also unilateral and that for the most part it is not associated with vitamin D deficiency, suggests that it is an independent condition, with etiopathogenetic mechanisms different from osteosarcopenia itself. In major orthopedic surgery, bone integration and muscle status are both essential for achieving and lasting positive results. Considering the high incidence of district osteosarcopenia, an integrated surgical, pharmacological, and rehabilitative approach is desirable for the optimization of results, as well as more studies for the definition of the etiopathogenesis of this pathological condition. (www.actabiomedica.it)

Key words: sarcopenia, bone turnover, osteometabolic profile, major surgery

Introduction

Modern medicine has led to a rise in the average life span of human beings, and this has caused the increase of new chronic pathologies. These include osteoporosis and sarcopenia, often diagnosed in elderly and frail patients (1).

Often these two pathologies affect patients simultaneously and for this reason osteosarcopenia is described as a unique syndrome, characterized by bone fragility and muscular hypotrophy with consequential and inevitable decrease in the functionality of the affected areas (2).

Osteoporosis is a rarefaction of the microarchitecture that makes up the bone with a consequential reduction in bone mineral density (BMD). The resulting fragility of the bone causes an increased risk of fractures that could occur after low-intensity trauma or even without any trauma. This condition can be primary (sex and age related) or secondary (hyperparathyroidism, use of specific drugs as corticosteroids and food imbalances) (3).

The sarcopenic condition is characterized by a chronic and progressive loss of skeletal muscle tissue and a reduced muscle function which inevitably causes a lowering of the patient's quality of life, given the reduced functionality of the body districts involved. Patients with sarcopenia issues may experience pre-existing medical conditions worsening like prognosis in cancer patients with lumbar sarcopenia (4).

Such as osteoporosis, sarcopenia is developed because of endocrine disorders, malnutrition, obesity, genetic polymorphisms and long corticosteroid therapies (5).

The mechanically, physically, and biochemically correlations between these two tissues led to the definition of "BMU" (Bone Muscle Unit). It has been clearly demonstrated over time that bone and muscle are adaptive tissues, changing their mass and strength in response to mechanical loading. Therefore, mechanical stimulus is essential for the health of both tissues and thus decreased level of physical activity over time may shift the frail balance in favor of muscle degradation and bone reabsorption. It has been seen how, from a histological point of view, the infiltration of fat cells is the main character of this kind of tissue degradation. Even if this phenomenon usually occurs in a generalized manner, it can be confined to a specific body district, when this district is less used due to pathologies that limit its activity and motility (6,7). Several studies describe an higher incidence of sarcopenia in patients presenting prior fragility fractures, especially in femoral fractures (8,9) but also in osteoporotic ones, and in patients with frequent falls in clinical personal history (10,11).

Actually the diagnosis of osteosarcopenia is based on clinical history, risk factor identification, physical assessments (grip strength, sit to stand test and others) and targeted investigations like blood samples to exclude secondary forms and other instrumental techniques as

bioelectrical impedance analysis (to estimate fat free mass), peripheral quantitative computerized tomography and others (12). Treatment of osteosarcopenia is based on resistance exercise, useful in stimulating osteoblastogenesis and muscle protein synthesis, diet supplementation such as correct intake of protein, calcium and Vitamin D (13,14). No specific pharmacological agents for sarcopenia treatment haven't yet been developed, in contrast of treatment of osteoporosis, even if some drugs such as denosumab seems to show positive effects on bone and muscles (15).

Today osteosarcopenia describes only a systemic disease which consist in the association between generalized osteoporosis and sarcopenia, especially in elderly patients, exiting in a global frailty condition. No large studies are reported about the possibility that osteosarcopenia can affect only a part of the skeleton so that could be defined as "districtualosteosarcopenia", but only case reports.

In this work, authors analyzed the osteometabolic profile and the loco-regional muscular state of patients undergoing major orthopedic surgery, to define the incidence of district osteosarcopenic states, linked to a condition of disuse.

Methods

During a prospective study of about 3 years, 19 patients (52,6% were male and 47,4% were females) aged between 15 and 85 years, were evaluated. All patients underwent on major orthopedic surgery (79% resection/custom made prothesis, 10,53% resection and reconstruction with transplant) of which 47,37% on an oncological basis (Fig.1). In all patients, the bone metabolism was evaluated by blood tests (including calcium, phosphorus, vitamin D, parathyroid hormone and alkaline phosphatase) upon admission to hospital. In patients operated on the upper limbs, a biopsy of the brachial biceps muscle was performed in the affected limb and in the contralateral one and in patients with involvement of the lower limb, the quadriceps femoris muscle was used. All histological preparations were carefully evaluated by a pathological anatomy unit specializing in musculoskeletal oncology, after coloration with Hematoxylin-Eosin, with

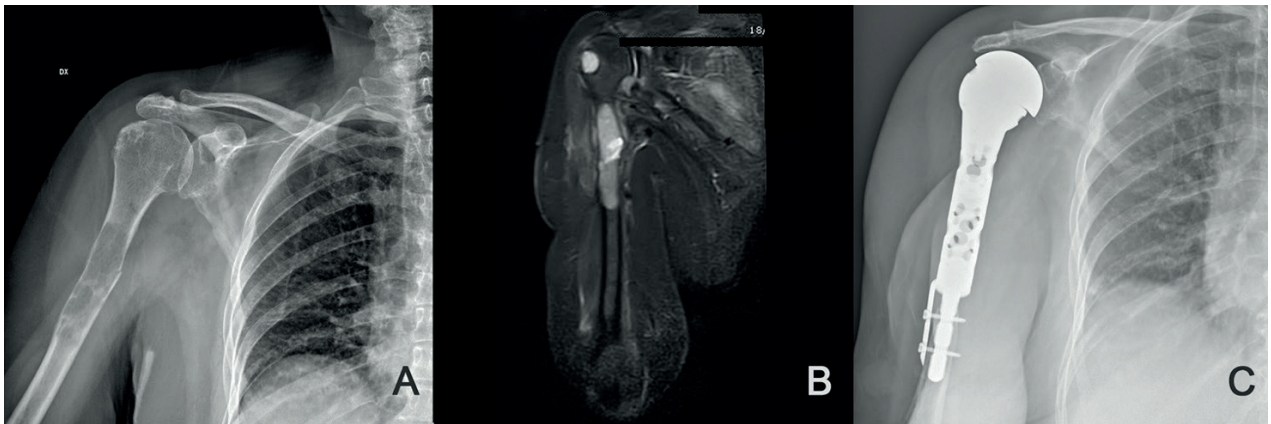


Figure 1. Imaging of one of the patients included in the study, suffering from humeral metastasis from submandibular adenoid cystic carcinoma. A, B: Preoperative radiography and MRI. C: Postoperative Radiography

20x magnification. During hospitalization, in three patients, bone densitometry with comparison of the affected limb and contralateral was performed. At the beginning of hospitalization, the duration of disuse of the affected limb was recorded for each patient. The downtime in our sample was between 2 and 38 months.

Results

Study of the data showed the presence of sarcopenia in 100% of patients (Fig.2). The disuse time before surgery demonstrated a mean of 9.05 months with a median of 6 and a mode of 2. Unilateral osteoporosis associated with district osteosarcopenia was found in 2 out of 3 bone densitometries (66%). Severe hypovitaminosis (<10 ng/mL) was found in 5 patients aged between 15 and 85 years, 3 males and 2 females, 4 oncological cases and 1 post-traumatic. Hypocalcemia (<8.6 mg/dL) was registered in 8 cases, with age between 15 and 80 years, equally distributed between sexes, 5 oncological cases and 3 from trauma. PTH increase (>40 ng/L) was found in 6 patients between 15 and 85 years, 3 female and 3 male, equally distributed between post-traumatic and oncological patients. In all cases PTH increase was secondary to hypovitaminosis and/or hypocalcemia. In 4 patients with age from 15 to 80 yrs we registered ALP increase (> 130 U/L), equally distributed between sexes; 3 out of 4 patients were of an oncological nature.

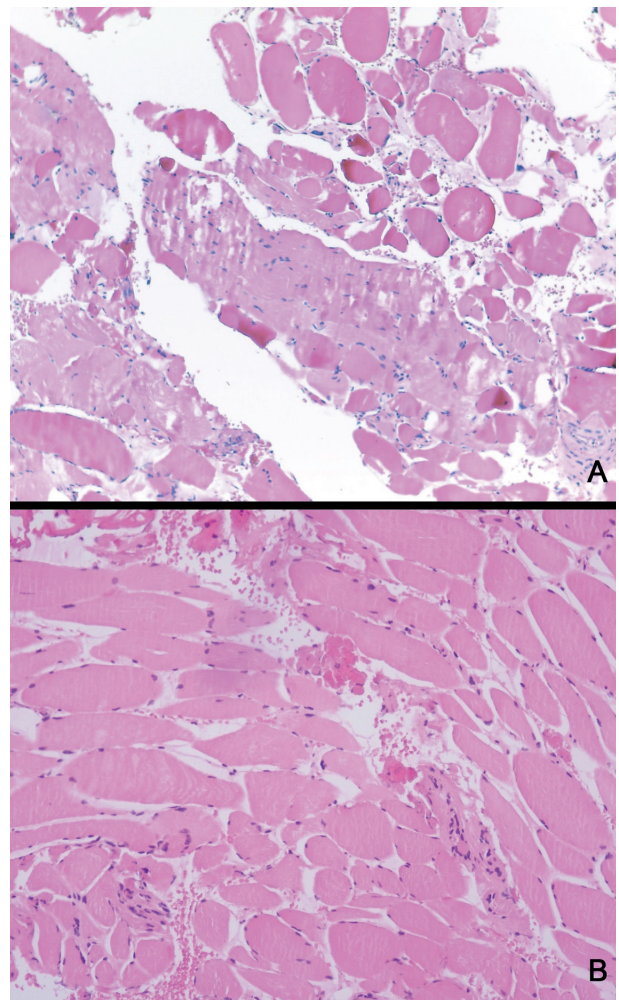


Figure 2. Histological specimen from brachial biceps (Hematoxylin-Eosin x20). A: surgical side with partial atrophy of striated muscle fiber. B: contralateral district without alterations

Discussion

Hypovitaminosis in our sample is in 52.6% of cases (<30 ng / mL), in agreement with literature data, and it did not occur only in elderly. This condition is recognized as an extremely widespread issue in all ages and the association between hypovitaminosis and increased fracture risk is also described in young patients (16).

In analyzed patients, five were on pharmacological integration with both vitamin D and Calcium, two were taking calcium carbonate supplementation. Only one patient was on antiresorptive therapy.

Hypocalcemia was found in patients with a mean age of 56.3 years and a median and mode of 55 yrs. The relationship between a correct daily calcium intake and frailty conditions is described in literature (17).

In our sample, 75% of the cases of rise of ALP values relates to neoplastic patients. Therefore, it cannot be exactly excluded that there is a cause linked to the skeletal involvement of the tumor. Individual or multiple alterations in the values of Vitamin D, blood calcium and parathormone were found among the patients analyzed, so a basic osteomalacic state of the patients cannot be excluded (18). In 75% of the patients analyzed, bone densitometry revealed a state of district osteoporosis. This data, although analyzed in a small number of patients, can lead to hypothesize a state of disuse district osteoporosis, a reduction of bone mass resulting from a reduced load function and district muscle function (19,20).

Unlike the percentage of patients who presented blood alterations of vitamin D, blood calcium, PTH and ALP, we found in our sample the constant presence of sarcopenia which was, however, localized only in the affected limb. The cases of association of district osteoporosis detected on bone densitometry and unilateral sarcopenia found with histological examination, even in young patients, suggests a state of district osteosarcopenia. Today the “cross-talk” between bone and muscle is known in the literature(21). The existence of different forms of osteosarcopenia or the association of systemic osteoporosis and generalized sarcopenia is also recognized. The pathogenesis of osteosarcopenia accepts as mechanisms a genetic predisposition, the role of the absence of gravitational load,

hormonal factors and the similarity in the metabolism of bone and muscle that makes them sensitive to the same stimuli (22). In our sample sarcopenia is unilateral in the affected limb and is frequently associated with osteoporosis, which is also unilateral, in addition to the fact that it also occurred in patients with normal calcium and vitamin D values, suggests that the role of disuse in our sample played a preponderant factor in the onset of sarcopenia. However, there was no correlation between the timing of disuse and the occurrence of unilateral sarcopenia (23).

In major orthopedic surgery, failure of bone-prosthesis integration and periprosthetic fractures are the most frequent causes of surgical failure (24–26). Maintaining a sufficient bone-stock and optimizing the overall osteometabolic state are the basis of a correct bone-prosthesis integration process and for prevention of peri-prosthetic fractures (27).

Although results of our study underlined the almost constant presence of haematochemical alterations (94.7% of cases), none of the patients who came to our observation, even if suffering from chronic orthopedic pathology, had ever received a correct study from the systemic osteometabolic point of view, aimed to correct alterations with possible negative effects on bone quality, such as secondary hyperparathyroidism (analyzed in 6 of 20 patients, 31.57% of total) or osteomalacic status (on 3 patients, with ALP and PTH rise and decrease in calcium and phosphorus blood levels (28). However, these conditions would potentially be correctable if properly diagnosed.

The consequential absence of load and the reduction of muscle function underline the need to include physiatric rehabilitation evaluation in the treatment of a patient undergoing major orthopedic surgery, for the development of individualized therapeutic plans with the aim of protecting the musculoskeletal compartment as much as possible. In literature, many studies also underline the positive effect of some drugs originally applied for the treatment of osteoporosis, in improving bone-prosthesis integration as well as in preventing fracture episodes (29).

In major orthopedic surgery, bone integration and muscle status are both essential for achieving and lasting positive results. It was shown that loco-regional sarcopenia exists as pathologic condition, regardless

of the duration of disuse and the constant presence of systemic metabolic alterations of the phospho-calcium metabolism. Furthermore, from our results emerged that sarcopenia appeared only after two months of disuse, assuming a certain speed of development of the condition. All this highlights the need to associate the surgical treatment with a global framework of the patient osteometabolic study to ensure the best bone and muscle health conditions, preparatory to obtaining better surgical and functional recovery results.

Ethical Statement: This material is the authors' own original work, which has not been previously published and is not currently being considered for publication elsewhere. All informations in the article reflects the authors' own research and analysis in a truthful and complete manner. The results are appropriately placed in the context of prior and existing research. All patients were informed about the study and its purpose. Informed consent was provided and signed for each patient. All sensitive data was anonymized during the study. This work does not require IRB approval.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

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Correspondence

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Gabriele Filoni,

Ortopedia e Traumatologia Universitaria II – Università di Pisa

Azienda Ospedaliera Universitaria Pisana

Via Paradisa 2 - 56124 Pisa (PI) - Italy

Fax : 050993415

e-mail : g.filoni@gmail.com