Quality of life in breast cancer: a secret passage through skeletal muscle and bone health

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Abstract

Breast cancer is the most common female cancer diagnosed worldwide. In Italy it represents about 30% of all cancer type in women and 17% of deaths due to malignancies. Neo or adjuvant therapy, which includes external beam radiation, chemotherapy and hormonal therapy (tamoxifen ± LH-RH analogues, aromatase inhibitors) allow early breast cancer patients to reach 10 years survival rate of about 80-85%. The improved prognosis of this subgroup of patients arise new challenges because cancer itself, treatments and age related changes can affect greatly patients’ quality of life. Bone loss and osteoporosis are common disorders in patients affected with breast cancer because many systemic therapies for breast cancer interfere with skeletal homeostasis, either through their effects on gonadal steroid hormone production or by inhibiting peripheral aromatization of androgens into estrogens, and cause an increased risk of morbidity and mortality related to skeletal events such as vertebral and spine fractures. Also, age related modifications in body fat and lean mass, with progressive and generalized loss of skeletal muscle mass and strength, characterizing a condition known as sarcopenia, can exacerbate the risk of frailty and adverse outcomes. According to current evidence, a complete clinical evaluation of the breast cancer long survivors is imperative in order to prevent and treat in an early stage any comorbidity (osteoporosis, sarcopenia, metabolic syndrome). This can be achieved only with a multidisciplinary approach, where oncologist, endocrinologist and nutritionist work together to maximize bone and muscle health to enhance the quality of life and to reduce mortality and skeletal events related morbidity.

KEY WORDS: breast cancer, sarcopenia, osteoporosis, aromatase inhibitors.

Introduction

Skeletal homeostasis is achieved through a balance between the processes of bone formation and resorption. Several local and systemic factors regulate these processes, including estrogens which are the key negative regulator of osteolysis (1). In postmenopausal women, the reduced circulating estrogens levels represent a higher risk for osteoporosis/sarcopenia and fractures (2). Moreover, age related changes in body composition, such as loss and weakening of bone and a decrease in lean mass (sarcopenia) may lead to an increased risk of hip, axial and other bone fractures.

Breast Cancer (BC) per se and therapies often accelerate these conditions (3), both by direct effect of chemotherapy or indirectly by the early ovarian failure induced by the endocrine treatments in Estrogen Receptor (ER) positive (+) tumours.

Breast cancer (BC) is the most common female cancer diagnosed worldwide. In Italy it represents about 30% of all cancer type in women and 17% of deaths due to malignancies (4). Patients with BC may receive neo or adjuvant therapy, which includes external beam radiation, chemotherapy
and hormonal therapy (tamoxifen ± LH-RH analogues, aromatase inhibitors). Patients affected by early-BC may have 10 years survival rate of about 80-85% (5). Considering the currently improved prognosis of this subgroup of patients, new challenges arise about the quality of life (QoL) in surviving patient throughout the protection of bone and metabolic health. It is well known that body composition (skeletal and muscular mass) is altered by cancer itself, its treatments (chemotherapy, endocrine therapy) and suffers para-physiological age-related modifications (6).

Material and Methods

This review focuses on the effects of osteoporosis and sarcopenia on morbidity and mortality of surviving breast cancer patients. Pubmed was searched for relevant publications from 2000 up to present day with the following research terms: "breast cancer", "osteoporosis", "sarcopenia" and "aromatase inhibitors". In addition guidelines from European Society for Clinical and Economic aspect of Osteoporosis and Osteoarthritis (ESCEO), European Working Group on Sarcopenia in older people, International Osteoporosis Foundation Committee of Scientific Advisor Working group on Cancer-Induced Bone disease, American Society of Clinical Oncology (ASCO), National and Comprehensive Cancer Network (NCCN) and Bone Health in Cancer Care Task Force were collected for diagnosis and management of osteoporosis in postmenopausal women and sarcopenia.

Osteoporosis and BC

The most common disorder in BC patients is bone loss and osteoporosis (7), a disease characterized by reduced bone mass and altered bone microarchitecture which result in an increased risk of fracture (8). An increased risk of bone loss is reported to be due to cancer treatment. In the Women’s Health Initiative study, fracture rates were increased in BC survivors by 15%, after adjustment for age, ethnicity, weight and geographic location (9). Early identification and treatment of osteoporosis among cancer patients could prevent unnecessary fractures, morbidity and reductions in QoL with improved survival rates in many types of cancer (10). Diagnosis of osteoporosis can be carried out with the bone mineral density (BMD) measurement, which is the amount of bone mass per unit volume (volumetric density) or per unit area (areal density), both assessments can be effectively measured by densitometric techniques. The most validated and widespread technique is the Dual Energy X-Ray Absorption (DXA). Quantitative ultrasound (QUS) and quantitative computed tomography (QCT) are applied to appendicular skeleton and to the spine are also available. DXA is definitely the most used, inexpensive and of rapid execution, with little radiation exposure. Results are expressed in standard deviations from the mean value expected in young healthy individuals (T Score) or from the mean value in individuals of the same age and sex (Z Score) (11) (Tab.1). However, osteomalacia, osteoarthritis, osteoarthritis and several pathological conditions may lead to an under or overestimation of the BMD value with DXA, so clinical evaluation of bone health must include the assessment of the risk of fracture. The most commonly used algorithms for this purpose are the online platforms such as FRAX® and in Italy DeFRA modified by FRAX (12). Crossing data from various risk factors (age, sex, BMI, previous or family history of fractures, smoking, glucocorticoid use, rheumatoid arthritis, alcohol intake, femoral BMD, other causes of secondary osteoporosis) calculate the 10-year probability of a major fracture (hip, spine, humerus or wrist) (12).

A recent prospective study of 1,041 cancer patients, mean age of 57 years, 78% female, founded elevated rates of bone loss compared to the general population with a 16% prevalence of osteoporosis and 44% of osteopenia (defined using WHO criteria). Rates of osteoporosis were not statistically different among various cancer types, which included breast, gynecological, prostate and colorectal cancer (13). Systemic therapies for BC also interfere with skeletal homeostasis, either through their effects on gonadal steroid hormone production or by inhibiting peripheral aromatization of androgens into estrogens (14). Aromatase inhibitors (anastrozole, letrozole, exemestane - AIs) have emerged as the treatment of choice for hormone-responsive BC in postmenopausal women because of better relapse-free survival and overall survival. AIs efficiently reduce estrogen levels even beyond what is achieved by natural menopause, because they block peripheral aromatization of androgens into estrogens, thereby leading to accelerated bone loss. AIs are associated to bone loss at an increased rate compared to the physiologic postmenopausal BMD loss. As a result, women receiving adjuvant AIs therapy for BC are at increased risk for fractures. In the Arimidex, Tamoxifen Alone or in Combination (ATAC) trial, in which anastrozole was compared with tamoxifen in postmenopausal hormonal positive BC patients as adjuvant setting, average bone loss rates in women who received treatment with anastrozole were superior than those treated with tamoxifen, about 1-2%/year (15). According to their mechanism of action they can also be classified as type 1 inhibitors (steroidal drugs), which are analogues of androstenedione and inactivate their specific enzyme by an irreversible binding to the same site ( exemestane), and type 2 inhibitors, which are non steroidal AIs and create a reversible bound to an heme group of the enzyme (anastrozole)

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<th>Table 1 - Diagnostic densitometric T-Score values (femoral neck and lumbar spine).</th>
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<td>Normal Bone Mass</td>
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Sarcopenia is defined by the European Working Group on Sarcopenia in Older People (EWGSOP) as a syndrome characterized by progressive and generalized loss of skeletal muscle mass and strength with an increased risk of frailty and adverse outcomes. It may be divided into three stages: presarcopenia, which is a condition of decreased muscle mass without reduction of strength and physical performance; sarcopenia, characterized by either an impaired muscle strength or performance with decreased muscle mass; severe sarcopenia has all these three components severely impaired. According to the onset, it can also be classified as, age-related, primary sarcopenia, without any other evident secondary cause, and secondary sarcopenia which may be caused by several co-morbidities (chronic illness, malnutrition or malabsorption, immobility) (25).

Sarcopenia has a multifactorial pathogenesis, in particular reduced physical activity, increased cytokine activity, neurological modifications and a decrease in anabolic hormones are implied in its onset (26). It is diagnosed based on low cost and accessible methods including dual energy X-ray absorptiometry (DXA), anthropometry and bioelectrical impedance analysis (BIA). MRI and CT scans and creatinine excretion are the standards for assessing muscle mass or cross sectional muscle area (27). Muscle strength is measured with simple clinical procedure such as the Gait Speed measurement, the Timed Up and Go test (TUG), the Short Physical Performance Battery (SPPB) and the Hand-Grip strength measurement. Evaluation scales such as Manual Muscle Testing (MMT), Basic Activities of Daily Living (BADL) and Instrumental Activities of Daily Living (IADL) are also available (27).

Skeletal muscle consists of two types of fibers. Fast fibers (type II), which have a higher glycolytic potential, lower oxidative capacity, and a faster response rate, and slow fibers (type I), also known as fatigue-resistant fibers because their greater density of mitochondria, capillaries and myoglobin content. With exception of postural muscles, which are composed of type I fibers only, skeletal muscles consist of an adequate balance of both types of fibers. Age related modifications include reduction of the type II fibers, which provide strength for high intensity exercise, explaining the reduced physical performance in the elderly (27). Thus, sarcopenia should be considered a condition related to frailty. A progressive loss of muscle mass occurs from 40 years of age and such loss has been estimated at about 8% per decade until the age 70 years and increases to 15% per decade in the elderly (28). Sarcopenia is guiltily ignored because a muscle mass below that typical of healthy adults is often associated with physical disability, injuries, and increased mortality in individuals with non-malignant disease (28). It is also known that, in many clinical records, the prevalence of sarcopenia increases in the elderly just like the prevalence of cancer. However, the malignant disease that affects the patients might induce muscle atrophy, confounding this prevalence (29).

Conditions such as malignant diseases often display lean body mass loss while fat body mass is preserved or even increased, to configure a condition known as sarcopenic obesity. It is so possible that muscle mass and strength become independent of body mass (30). In fact, while sarcopenia is an element characterizing cachexia, most sarcopenic individuals cannot be considered cachectic and, notably, indication on how to differentiate these two conditions have been published (31).

Sarcopenic obesity even generates a subclinical amount of inflammation leading to an increased risk of cancer development (30). A pathologic body mass composition could, at least, affect a cancer patients’ life not only with related disability and comorbidity, but also inter-
ferring with the volume distribution of drugs and chemotherapy eventually administered (32). Prado et al. reported that sarcopenia was independently associated with a higher incidence of treatment induced toxicity and a shorter time to tumor progression among metastatic BC patients independent of adiposity (33). All these pathologic conditions may have a precise hormonal background and may affect also other fields, like bone health. Homeostasis in several hormonal pathways, such as GH/IGF1, estrogens and insulin, are crucial in maintaining an optimal anabolic/catabolic state in lean mass, but also fat and bone metabolism (34). Insufficient GH/IGF1 signaling is associated with changes in body mass composition, with higher amount of visceral fat and depletion of lean body mass and BMD (35).

Postmenopausal women previously treated for BC are at great risk for sarcopenia and osteoporosis (36). There is large amount of evidence that these two conditions coexist and share the same risk factors (menopausal transition, age, estrogen depletion) (37). Lean mass and muscle strength/performance are associated with osteoporosis. Sjöblom et al. studied the relation between postmenopausal osteoporosis and clinical sarcopenia, finding that sarcopenic and pre-sarcopenic women had respectively a 12.9 and 6.5 times higher odds of having osteoporosis when compared to non-sarcopenic women (OR = 12.9; 95% CI 3.1-53.5, p < 0.001; and OR = 6.5; 1.5-28.6, p = 0.013, respectively). Sarcopenic women had nearly three times the risk of fracture compared to non-sarcopenic women (38).

In a case-controlled study of over 1,200 women with newly diagnosed BC without metastases, the annual incidence of vertebral fracture was 2.72% compared 0.53% in the control arm, i.e. a fivefold increase, with rates adjusted for age, prevalent fractures and duration of follow-up (39).

The link between bone and muscle mass can be found at three levels (40). First, genetic factors may affect the musculoskeletal development and homeostasis by exercising pleiotropic effects (essentially the bone peak mass). These may be due to polymorphism of genes such estrogen and androgen receptors, catechol-o-
methyltransferase, IGF-1, vitamin D receptor and LDL receptor related proteins (41). Secondly, the most important endocrine factors influencing both bone and muscle are vitamin D, GH/IGF1 axis and testosterone. Also estrogens, glucocorticoids, thyroid hormones, insulin, leptin and adiponectin have implications in the communication pathway inside the musculoskeletal system (42). Third, mechanical stimuli generated during muscular contraction activate sclerostin signaling of the osteocyte, promoting osteogenesis (43). Essentially, bone and muscle should be considered as a single functional entity, the “bone-muscle unit” (44).

Clinical implications

According to current evidence, a complete clinical evaluation of the BC long survivors is imperative. To assess a patient in each previous quoted aspects (bone health, nutrition and body composition) is an efficient way to prevent and treat in an early stage any comorbidity (osteoporosis, sarcopenia, metabolic syndrome), with clear benefits for the patient’s QoL. A baseline clinical evaluation of familial and gynecologic history, lifestyle, drugs, smoking and alcoholic habits of BC women under hormonal treatment might provide the data required to an adequate follow up. Anthropometric measurements (weight, height, waist and weight to hip ratio), blood pressure, lipidic profile, fasting plasma insulin and glycemia (Homa-Index) should be considered to evaluate for metabolic syndrome parameters. Easy clinical tests can be executed to evaluate muscle strength and sarcopenic status (Fig.1). The American Society of Clinical Oncology recommend DXA scan for BMD testing in both postmenopausal women and premenopausal who develop treatment related premature menopause. Methods for a correct evaluation of the BMD have already been discussed (45). Clinical risk of fracture can be assessed by validated tools. FRAX, DeFRA and serum levels determination of bone turnover markers (both of osteothesis and resorption) should be assessed to make a correct evaluation of the bone status. Even the mean intake of vitamin D supplementation should be taken in account. In BC patients the mainstay of prevention is represented by lifestyle changes, adequate calcium and vitamin D intake, regular physical exercise and any pharmacological treatments (bisphosphonates and denosumab). Lifestyle interventions are crucial in order to improve QoL and maximize any therapy in cancer patients. Guidelines for cancer survivors published by The American Cancer Society, the World Cancer Research Fund/American Institute for Cancer Research and the American College of Sports Medicine are available, recommend at least 30 min daily of physical activity for at least 5 days per week. Exercise interventions are even beneficial for muscle strength and bone mass, reducing the overall risk of falls and, consequently, of fractures. An adequate nutritional status is also important. The nutrients that have the greatest physiological impact on bone and skeletal muscle are calcium (Ca), vitamin D, inorganic phosphate (Pi), and proteins. It has been reported that even in developed countries such as the United States, among children, the elderly, and low-income populations a poor diet resulting in such nutrient deficit was often observed (46-48).

There is an important interaction between dietary proteins intake and mechanical loading on skeletal muscle mass and function. The right nutrition contributes to prevention of sarcopenia and even the risk of fragility fracture can be attenuated by appropriate nutritional intake and adapted regular physical activity (49).

Indeed, 76-88% of BC survivors have low vitamin D levels, i.e. <20 ng/mL. A recent study showed that low vitamin D levels are highly prevalent among newly diagnosed breast cancer patients with nearly 44 % with vitamin D insufficiency (50, 51).

However, only few clinical trials evaluated the impact of vitamin D supplementation in cancer patients. In a recent double-blind placebo-controlled randomized
phase II trial on 60 BC patients under treatment with AIs, those received vitamin D2 supplement had less AIs-induced musculoskeletal symptoms than those on placebo. Vitamin D-treated patients had also a stable femoral neck BMD (0.45%±0.72), compared to a 1.39% decrease seen in the placebo group (52). The ASCO and the National Comprehensive Cancer Network (NC-CN) Bone Health in Cancer Care Task Force recommend supplementation with calcium and vitamin D in BC patients, especially if treated with AIs or premenopausal women at risk of cancer treatment-associated bone loss (53).

Sarcopenic obese patients could benefit from increased proteins intake, which will maintain muscle mass during caloric-restricted diet to a greater extent than in a normoproteic diet (54). Epidemiological studies demonstrated an inverse relationship between calcium intake and adiposity (55). A high dairy calcium intake accelerates fat loss, and high calcium intakes were found to decrease the rate of lipogenesis and enhance lipolysis in adipocytes. Recently, a strong inverse association between daily calcium intake and sarcopenia in non-obese older Korean adults has been shown (56). Taken together, these findings indicate that calcium intake has a favorable effect on sarcopenia and obesity.

Bisphosphonates are a class of drug which protect the bone by binding to the hydroxyapatite molecule and induce cellular changes to the osteoclasts that results in their apoptosis. They seem to have also an antitumoral activity whose precise mechanism still remains unclear. In particular zoledronic acid has shown a potent anti-angiogenic activity in the adjuvant setting (57). Bisphosphonates have been successfully used in patients with metastatic bone disease. However, their use have been extended to prevent bone loss in BC patients treated with adjuvant chemotherapy or hormonal therapy (58). This approach is in accordance with the wide use of bisphosphonates in idiopathic osteoporosis (59).

AIs induced bone loss is also an indication for bisphosphonates use. The SABRE trial has tested in an open label approach the effect of risedronate in BC patients on anastrozole. In the ARIBON study, early stage BC patients receiving anastrozole were treated with ibandronate (high risk), ibandronate or placebo (medium risk), or anastrozole only (low risk). Prevention of AIs-induced bone loss has been tested also using intravenous infusions of zoledronic acid. Encouraging data were also obtained in premenopausal women in the ABCSG where zoledronic acid prevented bone loss in a subgroup of premenopausal cancer patients (60, 61).

Denosumab is a human monoclonal antibody that binds and neutralizes human Receptor activator of nuclear factor Kappa-B ligand (RANKL), a key mediator of bone resorption. It prevents RANKL from activating RANK on osteoclasts, which are then inhibited on their formation, function and survival, and hence it reduces bone resorption. Although in clinical oncology RANKL inhibition’s role through denosumab as a therapeutic target for preventing and treating bone metastases has emerged, its bone protective effect was clearly shown by the Hormone Ablation bone Loss Trial in Breast Cancer (HALT-BC). After a 24 month long therapy, denosumab had a significant protective role with a ~6% lumbar spine BMD and a ~4% total hip BMD increase vs placebo (62).

Conclusions

QoL of BC surviving patients is an important value, which clinicians and oncologist must take into account for adequate evaluation and care. Osteoporosis is a well-known burden in a patient treated with AIs, while sarcopenia is an emerging entity. Both are responsible of comorbidities and mortality in the long term (frailty, risk of falls and fractures, hospitalization). Therefore, in order to provide a suitable level of care, osteoporosis and sarcopenia must be accounted simulta-
neously in the treatment of frail and older patients. The new barrier of research should bring light to the bone and muscle interactions, so that innovative therapies for improving the quality of bone and muscle tropism can be developed with the ultimate goal to improve the quality of life of these patients. In conclusion, BC surviving patients need a multidisciplinary approach, where oncologist, endocrinologist and nutritionist work together to maximize bone and muscle health to enhance the QoL and reducing mortality and skeletal events related morbidity.

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