Special Issue
Ageing and Bone Health

guest-edited by G.C. Isaia

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The ageing process is characterized by a decline in muscle mass and strength, when this process outreaches pathological levels it is defined sarcopenia. This condition is associated with greater likelihood of recurrent falls and greater risk of mortality and less consistently associated with risk of hip fracture and functional limitation. On the other hand, ageing heavily affects bone inducing changes in bone structure – progressive decrease in trabecular thickness and increase in cortical porosity –, loss of bone mass and increase in bone turnover. There is an important interplay between muscle and skeletal systems: muscle contractions during anti-gravitational and physical activities apply mechanical stress to bones, influencing bone density, strength and microarchitecture, thus a decrease in muscle function is related to lower bone strength and predisposes to osteoporosis. Osteoporosis and sarcopenia show multiple common pathogenetic pathways, both systemic and local: reduction in anabolic hormones, chronic inflammatory condition, inactivity. In particular, several skeletal muscle-derived cytokines are able to directly influence bone. Vitamin D adequate levels are crucial for both bone and muscle function. Musculoskeletal impairment causes an important burden of disability and disease in older patients, a better understanding of pathogenesis and muscle-bone crosstalk could lead to improve prevention strategies and therapeutic options.

**Key words:** Sarcopenia, Osteoporosis, Elderly

**INTRODUCTION**

The ageing process is characterized by a decline in muscle mass and strength, when this process outreaches pathological levels it is defined sarcopenia. There is an important interplay between muscle and skeletal systems: muscle contractions during anti-gravitational and physical activities apply mechanical stress to bones, influencing bone density, strength and microarchitecture, thus a decrease in muscle function is related to lower bone strength and predisposes to osteoporosis. Osteoporosis and sarcopenia show multiple common pathogenetic pathways, both systemic and local: reduction in anabolic hormones, chronic inflammatory condition, inactivity. Vitamin D adequate levels are crucial for both bone and muscle function. Musculoskeletal impairment causes an important burden of disability and disease in older patients, a better understanding of pathogenesis and muscle-bone crosstalk could lead to improve prevention strategies and therapeutic options.

**SARCOPENIA AND OSTEOPOROSIS**

Sarcopenia has been 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 a risk of adverse outcomes such as physical disability, poor quality of life and death’. Diagnosis is based on low muscle mass and low muscle function...
Similarly, the International Working Group on Sarcopenia provided a consensus definition of sarcopenia as ‘age-associated loss of skeletal muscle mass and function’ and proposed to base diagnosis on a low whole-body or appendicular fat-free mass in combination with poor physical functioning 2.

Peak skeletal muscle mass and bone density are achieved in young adulthood. After 45 years of age, skeletal muscle mass progressively declines in men and women, particularly in the lower body 3. In a recent review, the prevalence of sarcopenia was 1-29% (up to 30% in women) for older adults living in the community, 14-33% (up to 68% in men) for those living in long-term care institutions and 10% for those in acute hospital care; the prevalence of sarcopenia increased with age 4.

In the European Male Ageing Study, which examined a population of 518 men aged 40-79 years with a mean follow-up of 4.3 years, appendicular lean mass started to decrease from 50 years of age, but mean annual loss was significantly greater in subjects older than 60 years. Men significantly lost gait speed and grip strength after 70 years 5.

In a recent population study, sarcopenia was associated with greater likelihood of recurrent falls and greater risk of mortality and less consistently associated with risk of hip fracture and functional limitation, although further studies are needed to determine its power in discrimination and reclassification of risk of important adverse outcomes 6.

Ageing is associated with an increase in fat mass: many tissues, including bone marrow and muscle, are gradually replaced by fat; this process takes place in men mainly after the age of 70, while in women it starts earlier with menopause and loss of estrogen 7. With age, muscle worsens its contractile performances due to the reduction of neuronal signalling and cell recruitment, and slower fiber regeneration.

On the other hand, ageing heavily affects bone inducing changes in bone structure – progressive decrease in trabecular thickness and increase in cortical porosity –, loss of bone mass and increase in bone turnover. This phenomena lead to physiological changes in muscle and bone composition and function, promoting the onset of sarcopenia and osteoporosis.

The two conditions often coexist and possibly represent a continuum, sharing multiple genetic, environmental and health-related intrinsic and extrinsic factors 8 9. If morphological changes are known, factors triggering them are more obscure and a precise definition of pathways is yet to come.

MECHANICAL LOADING AND BONE

Multiple studies have demonstrated positive associations between skeletal muscle mass and bone mineral density as assessed by dual-energy X-ray absorptiometry (DXA) at various skeletal sites 10, and the increased prevalence of osteoporosis in women could be partly related to their lower skeletal muscle mass 3. However, the advent of higher-resolution imaging technologies that perform measures of cortical and trabecular geometry and microstructure allows for much more detailed analyses of bone compartments and microstructure separately.

Recent evidences show that skeletal muscle mass adjusted for body size is significantly associated with cortical and trabecular bone geometry and microstructure at multiple skeletal sites in adult women and men 11. In a population study, muscle size is strongly associated with bone size and bone strength in both men and women, while the positive associations between bone mineral density and muscle size in weight-bearing and non-weight-bearing limbs were attenuated after adjustment 12.

The relationship between skeletal muscle mass and cortical bone is partly mediated by the mechanical influence, particularly at load-bearing sites such as the femoral neck, lumbar spine and tibia. Loading provokes changes in bone structure: resident bone cells show adaptive response to mechanical energy and translate it into a cascade of structural and biochemical changes. Mechano-transduction depends primarily on osteocytes. Osteocytes and their processes are surrounded by fluid, loads move extracellular fluid and viscosity creates shear stress on the osteocyte cell membrane. Fluid forces are proportional to loading rate, in fact bone is more sensitive to dynamic rather than static loading.

Mechanical load on the osteocytes dendrites induces the opening of connexin 43 hemichannels on the cell body 13. Wnt/Lrp5 and beta-catenin pathway is probably involved: mechanical strain reduces sclerostin levels, up-regulating Wnt signaling and leading to bone formation 14. However, the age-adjusted relationships between relative appendicular skeletal muscle and cortical thickness in women and men, cortical volumetric bone mineral density (in women), and proximal femur strength in women and men remained significant after adjustment for physical activity 11.

Appendicular skeletal muscle mass is the strongest factor associated with bone mineral density at the femoral neck in a study performed on adult men aged 20 to 72 years, independent of skeletal loads evaluated through measures of physical activity and muscle strength 15.

In fact, the relationship between relative appendicular
skeletal muscle and cortical thickness at the radius, a non-load-bearing skeletal site, is also significant. In a Korean population bone mineral density and appendicular skeletal muscle were measured by dual energy X-ray absorptiometry: muscle mass is positively correlated with bone density in both men and women, and skeletal muscle mass can predict bone density.

Another interesting hypothesis suggests that load-induced bone formation and functional adaptation could be neuronally regulated. The periosteum nerves have a net-like structure, optimal for detection of mechanical distortion of periosteum and bone, possible actor of a sophisticated regulatory mechanism. Nerves from the dorsal roots have branches entering the bone cortex in association with microvasculature. There is a direct connection between individual bone cells and the brain, and bone cells express receptors for a wide range of neurotransmitters. In vitro neuropeptides influence bone formation and the formation and activation of osteoclasts for bone resorption.

On these premises a study on murine model analyzed adaptive response to mechanical load in the limb and in the contralateral bone; it showed that right ulna loading induces adaptive responses in other bones in both thoracic limbs; experimental neuronal blocking during loading abolished bone formation in the loaded ulna and in the other thoracic limb bones.

MYOKINES

Myokines are skeletal muscle-derived cytokines able to directly influence bone.

Interleukin-6 has a controversial role in bone: it is released from contracting muscle and promotes glucose uptake, contributing to the favorable effects of exercise on energy metabolism, but promotes osteoclastogenesis in vitro. Data suggest that exercise under glucose deprivation may stimulate bone resorption via elevated interleukin-6 levels. Interleukin-6 also increases osteoblast differentiation in mice and is required for muscle hypertrophy and recovery from muscle atrophy, while chronic direct interleukin-6 administration induces muscle atrophy.

Similarly interleukin-7 shows a double-edged role in osteoclastogenesis and bone formation: it shows a direct antiosteoclastogenic effect, while it induces osteoclastogenesis through a mechanism involving the stimulation of T-cell activation and expansion and production of RANKL and TNFα.

Interleukin-7 is a direct inhibitor of in vitro osteoclastogenesis in murine bone marrow cultures; moreover mice overexpressing human interleukin-7 in the osteoblast lineage showed increased trabecular bone volume in vivo and decreased osteoclast formation in vitro, in murine model interleukin-7 effects are verified only in females.

On the other hand interleukin-7 enhances T cells secretion of RANKL and pro-osteoclastogenic cytokines. Interleukin-7 production is increased in ovariectomized mice where it stimulated osteoclastogenesis; antibody directed neutralization of interleukin-7 prevents ovariectomy-induced bone loss in mice. In murine model, in vivo interleukin-7 has multiple complex influence on T-cell maturation, development, and function, in ovariectomy, interleukin-7 stimulates both thymic-dependent differentiation of bone-marrow-derived progenitors and thymic-independent, peripheral expansion of mature T cells: thymectomy decreases almost by half the bone loss and stimulation of T lymphopoiesis induced by estrogen deficiency.

Indeed interleukin-7 is a potent inducer of RANKL production by human peripheral blood derived T cells. In humans, interleukin-7 has shown its osteoclastogenic role in psoriatic arthritis and in solid tumors bearing patients; in patients with reumatoid arthritis it could contribute to the perpetuation of Th1 and TNF-α mediated pro-inflammatory immune responses. In periodontal infections, high levels of serum interleukin-7 associated with peripheral blood B cells have been shown responsible for T-cell-dependent osteoclastogenesis. Interleukin-15 overexpression in muscle reduced body fat and increased bone mass in mice, although only when systemic Interleukin-15 levels were increased as well: muscle-derived IL-15 is one of the few myokines with confirmed regulation of bone as well as fat mass, although this constitutes an endocrine rather than a paracrine mechanism.

Moreover muscle cells express RANKL and its decoy receptor osteoprotegerin, key regulators of bone resorption; loading acutely decreases the RANKL/osteoprotegerin mRNA ratio in myotubes.

Recent research explored the role of Irisin. Irisin was originally known as a myokine secreted from skeletal muscle into bloodstream in response to exercise both in mice and in healthy humans. Irisin can induce transdifferentiation of white adipose tissue into brown, but it has been recently demonstrated that Irisin also has a key role in the control of bone mass, at lower concentration. In murine model low dose of recombinant Irisin increases cortical bone mineral density and positively modifies bone geometry. Irisin exerts its effect prevalently on osteoblasts by enhancing their differentiation and activity. In culture and animal model, bone tissue is more sensitive than the adipose tissue to the Irisin action.

Myokines, produced by muscle in response to exercise, could perform an additional regulation of mechatransduction in bone.
The musculoskeletal system undergoes precise regulation by multiple endocrine factors. In particular, skeletal muscle and bone are highly responsive to sex hormones. The age-associated fall in testosterone production is likely associated with sarcopenia, while the decrease in estradiol causes bone loss and osteoporotic fractures in men and women. The insulin-like growth factor (IGF) system is also involved in muscle and bone health. IGF-I and –II mediate anabolic effects on skeletal muscle and bone cells.

In a prospective study, in men over the age of 70, IGF-1 level was positively associated with change in gait speed, after adjustment for age, BMI, smoking, and a number of comorbidities. This association remained significant after further adjustment for sex hormone binding globulin. Recently also IGF binding protein-2 (IGFBP-2), an inhibitor of the trophic effects of IGF, has been associated with low bone mineral density and high bone resorption markers:

Vitamin D is another key connection between bone health and muscle function. Vitamin D is widely recognized for its role in calcium and phosphate homeostasis to maintain bone health and blood calcium levels through its action on target organs, such as intestine, kidney, and parathyroid glands, but emerging evidence has shown that vitamin D improves muscle performance and reduces falls in vitamin D-deficient older adults. Low levels of vitamin D are also associated with muscle weakness and atrophy of type II muscle fibers.

The receptor for 1,25-dihydroxyvitamin D (vitamin D receptor – VDR), is expressed in skeletal muscle and is an important mediator of 1,25(OH)2D effects on muscle contractility. It has been shown that certain VDR genotypic variations are associated with differences in muscle performance phenotypes: the VDR FokI (F/f) polymorphism is significantly associated with lean mass in older Caucasian men, constituting a recessive risk allele for the presence of low muscle mass.

Figure 1. Muscle and bone complex interplay GH growth hormone; IGF insulin-like growth factor.
of sarcopenia. In cell cultures, addition of 1,25-dihydroxyvitamin D to myoblasts increased expression and nuclear translocation of the VDR, decreased cell proliferation and promoted myogenic differentiation. In murine model vitamin D depletion induces skeletal muscle atrophy: old rats show a reduction in Notch pathway activity and blunted proliferation potential assessed through marker proteins expression. Moreover elderly men and women with low serum 25OHD levels were significantly associated with lower physical performance scores, whereas serum 25OHD levels were significantly associated with low handgrip strength. Vitamin D supplementation intervention studies have shown that vitamin D supplementation can significantly improve muscle function and physical performance among older adults at high risk for vitamin D deficiency, institutionalized elderly women and patients attending a falls clinic. Others have also shown that supplemental vitamin D may improve balance and reduce the incidence of falls.

In conclusion, muscle and bone show a deep and complex interplay, as shown in Figure 1, a better knowledge of influencing factors and molecular pathways could lead to new pharmacological strategies to treat emerging severe conditions such as cachexia and other muscle wasting disorders.

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Thyroid hormones are pleiotropic peptides with complex action on the human economy. The skeleton is a target tissue for thyroid hormone's action, which is illustrated by the consequences of thyroid hormone excess and deficiency during development and during aging. Thyroid disorders are more frequently observed in older than in younger persons. Thyrotoxicosis is an established cause of secondary osteoporosis. Overt hyperthyroidism and iatrogenic hyperthyroidism due to over-replacement of thyroid hormone may result in fragility fractures. Endogenous or exogenous subclinical hyperthyroidism is associated with reduced bone density, especially in cortical bone in older women. Fragility fracture risk seems to be closely related to the degree of thyroid-stimulating hormone suppression and to other risk factors, including older age. Overt hyperthyroidism and endogenous subclinical hyperthyroidism in older persons should be treated to reduce the risk for fragility fractures, atrial fibrillation and related mortality risk. The risk for fragility fractures in older people, especially in postmenopausal women, taking suppressive doses of levothyroxine for thyroid cancer can be diminished by treatment with the minimal effective suppressive dose and in some cases, by adding an antiresorptive or bone forming therapy where indicated. Replacement therapy for overt hypothyroidism should be regularly adjusted to avoid TSH suppression and consequent increased risk of fragility fractures.

Key words: Aging, Fracture, Thyroid, Osteoporosis, Hip fracture, Subclinical hyperthyroidism

INTRODUCTION

The relationship between thyroid function and bone has been empirically known for ages. Even if only in 1883 the Nobel Laurate Theodor Kocher defined “cachexia strumipriva” as an illness characterized by decreased growth and height after thyroidectomy 1, the use of burnt sponge and seaweed in the treatment of goiter started as early as 1600 BC in China 2. The description of “cachexia strumipriva” finally led to the first substitution therapy with thyroid tissue preparations in 1891 by George Murray 3; however, there is evidence that thyroid tissue was used as a treatment for goiter as early as the VII century AD in China. Also in 1891, Friedrich Von Recklinghausen reported for the first time a young woman who died from thyrotoxicosis with multiple fractures, and described the associated “worm eaten” appearance of long bones 4, identifying for the first time the relationship of thyroid hyperfunction and bone fragility fractures (FF) in the adult skeleton. The clinically overt hyperthyroid bone disease became less frequent after the introduction of effective treatment for hyperthyroidism with antithyroid drugs, surgery and radioiodine in the 1940's 5. Nevertheless, bone loss and FF have been reported recently associated with overt and subclinical hyperthyroidism caused either by nodular toxic goiter or, more frequently, by over-replacement of thyroid hormone. Postmenopausal older women, who constitute a substantial portion of those on thyroid hormone, are remarkably prone to accelerated bone loss, while inadequately high doses of thyroid hormone may further increase their already high risk for FF. Fragility fractures embody a major public health concern expected to continue increasing due to aging of...
The substantial burden associated with FF is caused by derived morbidity and disability, which also entail high social costs. Fragility fractures significantly compromise patients’ quality of life and financially overwhelm health care systems. Over half of patients never regain their previous functional capacity after a hip fracture and near one quarter move to long-term care facilities. One year mortality rates after hip fracture are estimated as 14-36% (14) with an expected 50% increase by 2025 (8). The cost of osteoporosis in the EU in 2010 was estimated at €37 billion, while in Italy it was estimated at near €7 billion (6). Major risk factors for osteoporosis include age, reduced physical activity, previous FF, a family history of osteoporotic fracture, the use of corticosteroids, and alcohol abuse (10). Altered thyroid function, more frequently observed in older than in younger persons, is also a risk factor for FF, which can be particularly unfavorable in older people. Its detection and treatment is crucial especially because it is a potentially reversible cause of FF. The present review briefly explores the relationship of thyroid function alterations and fragility fracture risk in older age.

THYROID FUNCTION, BONE, AND AGING

The direct action of thyroid hormone on the skeleton is certainly evidenced by the delayed epiphyseal development and poor growth of infants with congenital hypothyroidism or with thyroid hormone resistance (11). Skeletal tissue expresses all isoforms of thyroid hormone receptor (TR), which possibly interact with other nuclear receptors (i.e., vitamin D and retinoids receptors) (12,13). Circulating osteocalcin levels and mRNA are associated with thyroid status, with osteocalcin mRNA expression in bone being stimulated by the active thyroid hormone 3,3',5'-triiodothyronine (T3) in specific locations, such as the hip, which is particular predisposed to osteoporosis in hyperthyroid patients (12). Studies in mutant mice have established the concept that T3 has anabolic actions during growth and catabolic effects on adult bone. Thyroid-stimulating hormone (TSH) receptor is expressed in many extrathyroidal tissues including bone and it has been suggested that TSH may have direct actions on bone turnover (14), and on immunomodulatory responses in the bone marrow (15) and bone cells (16). Actions of T3 and TSH in osteocytes have not been investigated; in chondrocytes, T3 inhibits proliferation and stimulates chondrocyte differentiation, while TSH may inhibit proliferation and matrix synthesis; T3 stimulates bone resorption but it is currently uncertain whether T3 acts directly in osteoclasts or indirectly via its effects on the osteoblasts. Most studies indicate that T3 stimulates osteoblast differentiation and bone formation, while there is inconsistent observations suggesting that TSH may stimulate, inhibit or have no effect on osteoblast differentiation and function (17). Thyroid hormone metabolism in the osteoblast is a fine tune mechanism for the maintenance of intracellular T3 concentrations, through the expression of deiodinases D2 (activator) and D3 (inactivator), which activities vary in the euthyroid, hypothyroid or hyperthyroid state (18). In organ culture, T3 directly stimulates bone resorption (19), most probably through nuclear TR (20). Studies in experimental animals lacking TR-alpha or TR-beta suggest that bone resorption is mediated by TR-alpha (21). Thyroid hormone may alter calcium metabolism by a direct action on osteoclasts, or via its action on osteoblasts, which consecutively stimulate osteoclastic bone resorption (22). Another mediator of thyroid hormone-stimulated bone loss is the elevated concentration of interleukin-6 in hyperthyroidism (23). Table 1 summarizes the effects of thyroid hormone deficiency or excess on bone turnover, growth, bone mass and fracture risk.

THYROID HYPERFUNCTION IN OLDER AGE

Thyroid disorders are more common in older than in younger populations, predominantly in women, and they are frequently disregarded because their signs and symptoms often mimic age-associated modifications or disease of other organs. For example, hypothyroidism may induce or worsen cognitive and physical decline, constipation, cold intolerance, body weight gain, and anemia or lipid disorders, all frequently observed in euthyroid older people. Likewise, thyroid hyperfunction may manifest as arrhythmia and congestive heart failure, which may be interpreted as the expression of cardiac disease, very frequent in old age. Weight loss associated with hyperthyroidism may be taken as part of the normal aging process, undernutrition or neoplasia, also frequent in old age. Thyroid hyperfunction may as well be asymptomatic or “apathetic” presented merely with subtle signs, again frequently misinterpreted as normal age-associated changes, or as reduced thyroid function. Indeed, older people may have similar manifestations that correspond to increased or decreased thyroid function, such as, mental confusion, depression, falling and FF, walking disturbances, urinary incontinence from immobility, congestive heart failure, constipation or diarrhea. These signs also correspond to other disorders commonly observed in older people (24). Overt or, more frequently, subclinical hyperthyroidism may increase significantly the risk for FF, which may be ascribed to other risk factors present in older people.
Hyperthyroidism is found in 0.5% to 3% of all older patients. These numbers are higher when considering older people living in long-term care facilities, even if studies in this setting are few and most include a limited number of patients. It is noteworthy that in two studies unnecessary therapy with levothyroxine was disclosed in 15.4% and 50% of nursing home residents, with important implications for health and quality of life, perhaps increasing the risk for FF and atrial fibrillation in this already high risk population. Hence, the detection of subclinical thyroid dysfunction, and overt disease, is essential to correctly identify the subjects at true risk. It is also possible that subtle thyroid alterations in younger people may evolve to overt clinical manifestations during aging. For example, non-toxic goiter starting as a diffuse thyroid enlargement during early life may acquire nodularity and autonomous function with aging and may progress, although not frequently, to toxic nodular goiter. Before becoming clinically apparent, toxic goiter may show only slight laboratory modifications conforming subclinical states of thyroid dysfunction. Comorbidity and polypharmacy may further mask or mimic the presentation of thyroid disease. The lack of evident clinical manifestations of thyroid dysfunction in the older adults requests an attentive clinical evaluation and a high index of suspicion to identify their presence, with the appropriate confirmation by means of reliable laboratory testing. Nevertheless, thyroid tests may also have minimal changes with age and caution in the interpretation of such changes is warranted.

**OVERT HYPERTHYROIDISM**

This condition is certainly associated with accelerated bone turnover, decreased bone mineral density (BMD) (reported as 10-28%), and increased fracture rate. BMD reduction may or may not be reversible with hyperthyroidism therapy. Overt hyperthyroidism is associated with hypercalciuria and, infrequently, hypercalcemia. A histomorphometric study showed a small reduction in trabecular bone volume (-2.7%) with a marked increased cortical bone resorption (+40%) and porosity (+32%), with no changes in osteoid volume. Osteoclastic resorption is strikingly activated overcom­ ing osteoblastic action with a 50% reduction in the cycle duration and about 10% loss of mineralized bone in each cycle. Conversely, there is a 17% increase in mineralized bone for each cycle in hypothyroidism. Some studies have shown normalization of BMD after treatment of hyperthyroidism. However, there are other studies reporting only partial recovery of BMD after treatment. A more recent cross-sectional study showed that women with a past history of hyperthyroidism had a higher prevalence of BMD in the range of osteoporosis. The heterogeneity of these results is probably due to different duration of hyperthyroidism before treatment, various time intervals of follow up, and diverse techniques and sites of BMD. Even with the variability of BMD, a past history of hyperthyroidism increases the risk for FF (43-45), and may help to explain the higher later mortality in these patients. Interestingly, a study showed that hyperthyroid patients treated with radioiodine had an increased risk of forearm and vertebral fractures compared to patients also treated with methimazole, in whom there was no increase in fractures. This may reflect a tendency of overtreatment in patients with levothyroxine replacement therapy after radioiodine ablation. Likewise, a prospective study of women aged over 65 years followed for 3.7 years showed that those with TSH lower or equal to 0.1 mU/L at baseline had an increased risk for hip (RR = 3.6) and vertebral (RR = 4.5) fractures. Increased bone resorption in patients with hyperthyroidism may lead to hypercalcemia (although not frequently), reduction of parathyroid hormone secretion, and hypercalciuria with a consequent negative calcium balance, and reduced activation of 25-OH-vitamin D. Osteoprotegerin, fibroblast growth factor-23, and urinary excretion of bone collagen-derived pyridinium cross-links have been found increased in overt hyperthyroidism. Therefore, patients with overt hyperthyroidism should receive adequate amounts of dietary or supplemental calcium and vitamin D.

**SUBCLINICAL HYPERTHYROIDISM**

The finding of TSH levels below 0.45 mU/L in the presence of thyroid hormones in the normal or high borderline range is indicative of subclinical hyperthyroidism, which is more frequent than overt disease. The most common causes of subclinical hyperthyroidism are an initial Graves’ disease, initial nodular toxic goiter, excessive TSH suppressive therapy with levothyroxine for benign thyroid nodular disease or for differentiated thyroid cancer, or hormone over-replacement in patients with hypothyroidism. However, other causes of a low TSH, such as non-thyroidal illness, fasting, and the use of drugs (i.e., glucocorticoids) should be excluded before making the diagnosis. Subclinical hyperthyroidism in older people may be associated with relevant signs and symptoms of excessive thyroid hormone action, and in particular, with an increased risk of FF, atrial fibrillation, and increased mortality risk. Indeed, it is becoming increasingly apparent that subclinical hyperthyroidism may decrease BMD and accelerate the development of osteoporosis and FF, particularly in postmenopausal women with a preexisting predisposition, hence, patients with low TSH levels should be carefully evaluated (Fig. 1).

A study investigating nursing home residents with low
TSH and normal total 3,5,3',5'-L-tetraiodothyronine (thyroxine, T4) levels showed that only 3 out of 40 patients with subclinical hyperthyroidism became overt hyperthyroid. However, 17.5% of patients with subclinical hyperthyroidism died during the first 4 months of follow-up compared to 7.5% in a control group. In a meta-analysis of studies in men with subclinical hyperthyroidism, excess all-cause mortality was related to the years since diagnosis and to advanced age. There are variable results regarding BMD and subclinical hyperthyroidism, but most suggest an associated low BMD. Interestingly, in healthy euthyroid postmenopausal women from the Osteoporosis and Ultrasound Study (OPUS) those in the highest quintile of normal free T4 (FT4) at baseline had lower BMD after 6 years of follow-up compared with women in the lowest quintile of FT4. A recent meta-analysis of 13 prospective cohort studies from the US, Europe, Australia, and Japan (n = 70,298), compared participants with euthyroidism (TSH 0.45-4.49 mIU/L) to those with endogenous subclinical hypothyroidism and hyperthyroidism in the incidence of FF after a median follow-up of 12.1 years. Considering all participants and after adjusting for age and sex, there was a significant increased risk of hip (HR = 1.36, 95% CI:1.13-1.64), and any (HR = 1.28, 95% CI:1.06-1.53) fracture for participants with subclinical hyperthyroidism vs. euthyroidism. The increased risk was even higher for those with TSH < 0.10 mIU/L (HR = 1.61, 95% CI:1.21-2.15 for hip fracture; HR = 1.98, 95% CI:1.41-2.78 for any fracture; HR = 3.57, 95% CI:1.88-6.78 for vertebral fracture). For endogenous subclinical hyperthyroidism (excluding those on thyroid medications) there was an increased risk of hip (HR = 1.52, 95% CI:1.19-1.93), any (HR = 1.42, 95% CI 1.16-1.74), and vertebral (HR = 1.74, 95% CI 1.01-2.99) fractures. No association was found between subclinical hypothyroidism and fracture risk. Besides the effects of thyroid hormone on bone turnover and BMD, which may help explain the increased FF incidence, it is pertinent to consider also an increased risk of falls through effects on muscle strength and coordination.

In view of the fact that subclinical hyperthyroidism and its related clinical manifestations are reversible, may cause in some cases significant morbidity and mortality, and may be prevented by timely treatment, it is important to consider the possible benefit of treatment on an individual basis. Most authors agree regarding considering treatment of older patients with subclinical hyperthyroidism and a clearly suppressed TSH level (< 0.1 mUI/L) and follow up for patients with TSH levels between 0.1 and 0.4 mUI/L. Further studies are needed to determine whether treating subclinical hyperthyroidism can prevent fractures.

**EXOGENOUS THYROID HORMONE THERAPY**

Subclinical hyperthyroidism due to levothyroxine therapy is not uncommon, with potential increased bone resorption, reduced BMD, and increases FF risk. The risk of FF seems to be linked to the degree of TSH suppression and to other factors (i.e., advanced age), which further increase that risk. There are variable results regarding BMD changes associated with over-replacement with thyroid hormone therapy. However, most studies have demonstrated that even moderate suppressive doses of T4 can cause bone loss in postmenopausal women. Two meta-analyses of studies exploring BMD in patients with subclinical hyperthyroidism due to T4 therapy are available. A significantly reduced BMD was found only in postmenopausal women, similar to previous findings in cross-sectional studies. The meta-analysis by Uzzan et al. found a reduced BMD.
in postmenopausal and also in premenopausal women with levothyroxine replacement therapy.

Regarding FF risk, the results are not uniform with some but not all studies showing an increased fracture risk in patients with subclinical hyperthyroidism due to exogenous thyroid hormone therapy. The inconsistent results may be due to diverse populations studied and different degrees of TSH suppression. For example, in a study involving 17,648 patients on levothyroxine therapy those with undetectable TSH had a twofold increased risk of FF when compared to those with TSH between 0.04 and 0.4 mU/L.

A study involving 1,180 patients on levothyroxine therapy showed that near 60% had a TSH < 0.05 mU/L. In this study, even if women aged over 65 years with suppressed TSH values had 2.5% FF vs 0.9% of those with normal TSH values, the difference did not reach statistical significance. In another study of 686 women aged over 65 years, those with TSH ≤ 0.1 mU/L had a 4-fold increased risk of FF vs. those with normal TSH.

## Thyroid Nodule and Levothyroxine Therapy

Most of thyroid nodules (~ 95%), which occur with increasing frequency in older age, are benign. Nonetheless, clinical evaluation has been considered for all thyroid nodules given the potential risk of evolving into thyroid malignancy (Fig. 2). The prevalence of palpable thyroid nodules is near 5% in women and 1% in men living in iodine-sufficient areas. Conversely, the prevalence increases to 19-68% for thyroid nodules detected by high-resolution ultrasound, with higher frequency in women and older people. It has been estimated that approximately 7-15% of thyroid nodules may evolve into thyroid malignancy depending on sex, age, history of radiation exposure, and family history among others. The risk of malignancy is similar for solitary nodules and multinodular goiters; urgent referral to secondary care is necessary only if the nodule is growing rapidly (over few weeks) or associated with stridor,
hoarseness, or cervical lymphadenopathy. Generally, goiter size increases with aging and thyroid nodularity develops, with the largest goiters observed in the oldest age groups living in iodine deficient areas. The prevalence of diffuse and nodular goiter in young adults participating in an iodine deficient area survey (Pescopagano study) was 30% in young adults and increased up to 75% in the age group 55-65 years, with nodular goiter accounting for about one third of the total. Multinodular goiter, usually longstanding, is frequently seen in old age, and thyroid hormone suppressive therapy not only is not indicated but may contribute to exogenous hyperthyroidism with heart and bone adverse effects. A nodule(s) in multinodular goiter may become autonomous with aging and progress to overt thyrotoxicosis, while large goiters may cause obstructive symptoms. The physical examination of women with goiter may be complicated by hyperkyphosis and changes in posture associated with osteoporosis; if the thyroid gland can be palpated in an older woman, it is probably enlarged. Calcification of large goiters may be associated to dyspnea, dysphagia, or dysphonia and can be misdiagnosed as cancer metastases to lymphoid nodes, hence, Fine-needle aspiration biopsy (FNA) is recommended to determine the nature of calcified lesions.

According to the American Thyroid Association (ATA) guidelines, thyroid ultrasound should not be performed as a screening test; however, patients with a palpable thyroid nodule should undergo ultrasound examination. Management depends mainly on the results of FNA but should also take into consideration the clinical and ultrasound features. Solid hypoechoic nodules and nodules with suspicious sonographic appearance (irregular margins, microcalcifications, taller than wide shape, rim calcifications, or evidence of extrathyroidal extension) should undergo FNA when ≥ 1 cm (as determined by largest dimension). Nodules with sonographic appearance suggesting a low risk for thyroid cancer can be undergo FNA when larger (≥ 1.5 to 2 cm). Spongiform nodules ≥ 2 cm could also be evaluated by FNA, although observation without FNA is an alternative option. When a goiter is asymptomatic, follow-up is the choice, while treatment is necessary in case of toxic effects.

Figure 2. Algorithm for the diagnosis and management of thyroid nodule. FNA: fine-needle aspiration; MNG: multinodular goiter; TSH: thyroid-stimulating hormone; US: ultrasound; ATAb: anti-thyroid anti-bodies.
goiter or compressive symptoms. $^{131}$I is the first choice treatment for thyroid autonomy and hyperthyroidism, whereas surgery is advised for large non-toxic goiters causing significant compressive symptoms. $^{131}$I therapy has been proposed in order to reduce thyroid volume in non-toxic goiters, with satisfactory results, even in the presence of structural and functional heterogeneity, and large variability in $^{131}$I dose. Pretreatment with recombinant TSH (rhTSH) may increase the efficacy of $^{131}$I therapy. FNA is the most accurate method in the evaluation of a thyroid nodule, helping to determine which patients should be referred for surgery. Its accuracy is improved by high-resolution ultrasound guidance, which can also add useful information.

Thyroid cancer is mostly (> 90%) differentiated, which includes papillary and follicular cancer. Thyroid cancer in old age is also generally well-differentiated, but their course is frequently less predictable than in younger patients. Lymphoma of the thyroid and undifferentiated cancers, even if rare, occur with increasing frequency in old age. The incidence of thyroid cancer in the US has tripled from 1975 to 2009 with most of new cases being papillary thyroid cancer. The proportion of tumors lower or equal to 1 cm was 25% in the period 1988-1989 vs + 39% in 2008-2009. This may be attributable to the rising use of neck ultrasonography and other imaging techniques, which may help to improve the long-term health outcomes for patients with thyroid neoplasms. However, a comprehensive and rational evaluation of thyroid nodule is needed to avoid excessively alarming the patients and improper overuse of imaging exams.

A recent prospective, multicenter, observational study included 992 consecutive patients with 1 to 4 asymptomatic ultrasound and cytologically benign thyroid nodules. Participants were recruited from eight hospital-based thyroid-disease referral centers in Italy between 2006 and 2008. Available results correspond to the first 5 years of follow-up. The primary end point was nodule growth assessed with yearly thyroid ultrasound. Significant size changes were considered as ≥ 20% modifications in at least two nodule diameters, with a minimum increase of 2 mm. Baseline factors associated with nodule growth were identified. Secondary end points were the sonographic detection of new nodules and the diagnosis of thyroid cancer during follow-up. From the 1,567 original nodules, only 174 (11.1%) increased in size. Nodule growth was associated with the presence of multiple nodules (OR, 2.2 for 2 nodules; OR, 3.2 for 3 nodules; and OR, 8.9 for 4 nodules), and male sex (OR, 1.7). Age equal or higher than 60 years was associated with a lower risk of nodule growth compared to nodules in persons younger than 45 years (OR, 0.5). Thyroid cancer was diagnosed in 5 original nodules (0.3%), and only two of them had grown. New nodules developed in 93 patients (9.3%), with detection of only one cancer. Therefore, in this large prospective study, the majority of ultrasound or cytologically benign thyroid nodules exhibited no significant size increase during 5 years of follow-up and thyroid cancer was rare. These findings strongly supported consideration of revision of current guideline recommendations for follow-up of asymptomatic thyroid nodules. In the latest ATA guidelines, recommendation 25 explicitly states that "routine TSH suppression therapy for benign thyroid nodules in iodine sufficient populations is not recommended. Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients (Strong recommendation, High-quality evidence)."

Ultrasound monitoring of benign thyroid nodules is initially recommended at 12 months, then at increasing intervals (e.g., 2 to 5 years, with the shorter interval for large nodules or nodules with suspicious ultrasound features and the longer interval for smaller nodules with benign ultrasonographic features). Repeated FNA might be performed only when there is substantial growth (> 50% change in volume or 20% increase in at least two nodule dimensions), new suspicious ultrasound features, or new symptoms attributed to a nodule.

### TSH Suppression in Thyroid Cancer

Another important issue regards the cardiac and skeletal effects of long-term TSH suppression used to reduce thyroid cancer recurrence. According to recent guidelines from the ATA, it is necessary to consider age, the presence of preexisting cardiovascular and skeletal risk factor, and the aggressiveness of thyroid cancer to decide the TSH target, and to better balance the benefit vs. the potential adverse effects of long-term TSH suppression. In addition, adequate intake of calcium and vitamin D to prevent osteoporosis should be encouraged. Many authors in the past have recommended that patients with thyroid cancer should maintain very low serum TSH concentrations (less than 0.01 mU/L). However, in one report, serum thyroglobulin concentrations did not fall further when serum TSH was suppressed below 0.1 mU/L. This emphasizes the importance of tailoring the levothyroxine dose to the extent of the disease and the likelihood of recurrence. The ATA initial risk stratification system estimates the risk of persistent/recurrent disease. This system is designed to stratify patients as having either low (papillary thyroid cancer confined to thyroid), intermediate (regional metastases, worrisome histologies, extrathyroidal extension, or vascular invasion), or high (gross extrathyroidal extension, distant metastases, or postoperative serum thyroglobulin suggestive of distant metastases) risk of...
recurrence, primarily based upon clinicopathologic findings 74.

After initial thyroidectomy, whether or not radiiodine therapy is administered, thyroid hormone (levothyroxine) therapy is required in most patients to prevent hypothyroidism and to minimize potential TSH stimulation of tumor growth, as follows:

- for patients with low-risk disease treated with thyroidectomy who have detectable serum thyroglobulin levels (with or without remnant ablation), the serum TSH initially can be maintained between 0.1 and 0.5 mU/L. For similar patients who have undetectable serum thyroglobulin levels (with or without remnant ablation) or who were treated with lobectomy, TSH can be maintained in the mid to lower half of the reference range (0.5 to 2.0 mU/L). In the later setting, thyroid hormone treatment may be unnecessary if a patient can maintain their TSH in this range;
- for patients with intermediate-risk disease, the serum TSH initially can be maintained between 0.1 and 0.5 mU/L;
- for patients with high-risk disease, the serum TSH initially should be less than 0.1 mU/L.

TSH concentrations are measured annually and 6-8 weeks after any dose adjustments of levothyroxine. Although TSH should be maintained < 0.1 mU/L in patients with a structurally incomplete response, patients with a better response to therapy can have their TSH goal modified, for example:

- for patients initially with high-risk disease but who have an excellent or indeterminate clinical response to therapy, a TSH goal of 0.1 to 0.5 mU/L for up to 5 years is acceptable, after which time the degree of suppression can be further relaxed (with continued surveillance for recurrence);
- for patients initially with low-risk disease and who have an excellent clinical response to therapy, a TSH goal of 0.5 to 2 mU/L is acceptable;
- for patients with a biochemically incomplete response, the serum TSH should be maintained between 0.1 and 0.5 mU/L 74.

CONCLUSIONS

The skeleton is a target tissue for thyroid hormone’s action, certainly verified by the consequences of thyroid hormone excess and deficiency during development and during aging. Old age may be associated with a number of thyroid function alterations. However, it is not simple to discern whether and to what extent these changes are expression of the aging process per se or of an age-associated thyroidal and/or nonthyroidal illness and polypharmacy. There is often significant delay and difficulty in the diagnosis of thyroid disorders in old age because clinical presentation is paucisymptomatic and attributed to normal aging, and because atypical presentations are not uncommon. Routine screening of asymptomatic, healthy adults is not recommended; however, physicians should maintain a high index of suspicion for testing thyroid function in subjects at risk. Thyroid diseases in older patients differ from those observed in younger patients in their prevalence, which is higher especially among women, and clinical expression, while their treatment often deserves special attention because of the increased risk of complications (i.e. cardiac arrhythmia, cognitive decline, bone loss).

Subclinical abnormalities of thyroid function are more prevalent than overt disease in older populations. Subclinical hyperthyroidism appears to be a significant risk factor for cardiac arrhythmia, especially atrial fibrillation, and FF in old age. The risk is particularly high among those with TSH levels below 0.10 mIU/L. The benefits of treatment of subclinical disease are not completely elucidated. Treatment of thyroid disease deserves special attention in old-old patients because of the increased risk of complications and the lack of evidence-based data in this population.

Even if most of thyroid nodules in older persons are benign, clinical evaluation should be considered to timely identified thyroid malignancy. FNA remains the cornerstone of thyroid cancer diagnosis, which accuracy may be improved by high-resolution ultrasound evaluation. Thyroid hormones may lead to accelerated bone turnover and over-replacement of levothyroxine can result in increased FF risk. The majority of cytologically benign thyroid nodules do not have significant size increase and in these nodules thyroid cancer was rare after a 5-year follow up. The risk for osteoporosis in postmenopausal women taking suppressive doses of levothyroxine for thyroid cancer can be minimized by treatment with the minimal effective suppressive dose and eventual insti tution of antiresorptive or bone forming therapy where indicated, emphasizing the importance of tailoring the levothyroxine dose to the extent of the disease and the likelihood of recurrence.

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Fragility fractures and thyroid dysfunction

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The myokine Irisin recapitulates the effect of physical activity on bone and muscle tissues

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INTRODUCTION

Osteoporosis, the skeletal disease characterized by decrease of bone mass and deterioration of its microarchitecture, and Sarcopenia, the muscle disease characterized by progressive loss of muscle mass and strength, are often concurrent diseases affecting the elderly population. These associated pathologies represent one of the major threats that increase the risk of fall-related fracture during the aging process. In addition to its severity, further exacerbated by loss of independence, hospitalization and subsequent depression faced by elderly people, this issue generate high healthcare expenses, which were estimated at approximately 32 billion euros per year in the 27 EU countries and 22 billion dollars per year in the United States. Nevertheless, in light of the increased longevity of the population, the burden of concurrent osteoporosis and sarcopenia can further increase. Despite the high healthcare burden, there is no widely accepted clinical definition of sarcopenia, even though several diagnostic criteria have been suggested. However, a significant step forward has been made at least for converging the diagnostic approaches.

The concomitant occurrence of osteoporosis and sarcopenia is very common during the process of aging and pathological conditions characterized by the disuse of the musculoskeletal system. However, to date there are no evidence about the mechanism responsible for the coupling of these two process. During the last decade, studies on the interactions between muscle and bone have made remarkable steps forward, establishing that skeletal muscle is an endocrine organ producing and releasing myokines acting in a paracrine or endocrine fashion. Among these, the newly identified myokine Irisin, produced by skeletal muscle after physical exercise, plays a key role in the bone-muscle functional unit, with a major impact on the skeleton by increasing cortical bone mineral density, modifying its geometry and improving bone strength. Furthermore, in vitro and in vivo studies reported an autocrine effect of Irisin on skeletal muscle and highlighted the autocrine myogenic potential of this myokine.

This review summarizes new insights on the topic of Irisin action on bone and skeletal muscle, which support the hypothesis that Irisin may represent a novel molecular entity with exercise-mimetic properties. Hopefully future research may expand the knowledge of its ability to improve bone integrity and muscle activity and could pave the way for the use of Irisin as a new therapy for the prevention and treatment of musculoskeletal disorders, particularly useful for those patients that are not capable of performing physical activity, such as the elderly or bedridden patients.

Key words: Irisin, Bone, Muscle, Mechanical loading, Osteoporosis, Sarcopenia
The myokine Irisin recapitulates the effect of physical activity on bone and muscle tissues

The characterization of osteoporosis is instead universally accepted and is currently diagnosed based on the bone mineral density compared with that of a young adult of the same sex and further refined through the fracture risk prediction algorithms, such as the Risk Assessment Tool fracture (FRAX®) 4. Although sarcopenia has not a widely accepted diagnosis criteria, however numerous diagnostic tools, such as the dual energy x-ray absorptiometry (DXA) and the peripheral quantitative computed tomography (pQCT), made it possible to demonstrate association between the bone and muscle health conditions. Through the use of pQCT, it has been showed that bone size and strength are associated with muscle mass size and, although to a lesser extent, to the muscle strength. In addition, it has been found positive correlation between muscle size and cortical and trabecular bone mineral density 5. Therefore, it has been observed, for example, that 58% of patients with hip fracture were also suffering from sarcopenia. Obviously, the diagnosis of concurrent sarcopenia implies reduced probability of hip fracture resolution and, often, these patients may also face increased risk of recurrent contralateral fractures 5.

During the last decade, an existing intimate relationship between skeletal muscle and bone has been established, not only because of mechanical force generated by muscle contraction that load the skeleton, but in particular for mounting evidence suggesting the existence of a bone-muscle functional unit in which these two tissues talk via paracrine signals 7 8. Through this molecular communication, muscle and bone adapt to load and respond to damages occurring from childhood to the adult age. Albeit all the molecular messengers involved in musculoskeletal unit communication are not yet fully known, to date the skeletal muscle secretome accounts several factors, whose ability to affect the skeleton has been extensively described 9. Since these molecules produced by skeletal muscle can also act in an endocrine fashion toward distant organs, they are also commonly referred as “myokines”. Among these myokines, the newly identified Irisin, highly secreted by skeletal muscle during physical activity, was originally described as a hormone-like protein capable of promoting the “browning response” in white fat depots (WAT), a program characterized by trans-differentiation of white adipose tissue 17. This result, not only revealed brown adipose tissue 17. This result, not only revealed Irisin ability to promote the browning trans-differentiation of white adipocyte. The effect was accompanied by decreased body weight and enhanced glucose homeostasis, as proved by the higher expression of betatrophin and increased pancreatic b-cell proliferation in r-Irisin treated animals 16.

Interestingly, it has been shown that a considerable lower dose of r-Irisin (100 μg/kg/week), injected in normal mice once a week for four weeks, significantly increased cortical bone mineral density and improved cortical geometry and bone strength, but was not sufficient to activate the trans-differentiation of white to brown adipose tissue. This result, not only revealed one of the molecular messengers responsible for muscle-bone crosstalk during physical activity, but also pointed out that the skeleton is a more sensitive target to Irisin action compared with adipose tissue 17.

THE BONE ANABOLIC ACTION OF IRISIN

Physical activity is a vigorous stimulus for increasing bone mass and it has been extensively documented that exercise has positive effects on bone mineral density 18. In order to investigate if Irisin was responsible for the protective effect that exercised muscles exert on bone tissue, healthy young mice were treated with a low dose of recombinant Irisin for four weeks. By microCT analysis of the tibia, it has been observed a marked effect on cortical bone mineral density (BMD) and bone perimeter 17. Furthermore, the 20% increase of polar moment of inertia, an index of resistance to torsional forces, supported the idea that Irisin, modifying bone geometry, would increase bone strength. In fact, mechanical tests assessed on tibia confirmed that bending strength and energy to fracture were strongly increased in Irisin-injected mice.

THE EXERCISE-LIKE MYOKINE IRISIN

The Irisin discovery had received acclaim from the scientific community since exercise-induced benefits are known to be exerted on many organs, so much that engaging in regular physical activity is recommended as the best non-pharmacological treatment for the prevention of obesity, osteoporosis, sarcopenia, metabolic disorders, cardiovascular and brain disease 11 12. For instance, it has been observed that Irisin plays role in the central nervous system, as showed by the expression of its precursor in rat and mice cerebellar Purkinje cells 13. Irisin is also required for a proper neural differentiation of embryonic stem cells 14 and modulates hippocampal neurogenesis in a dose-dependent manner 15. So far, few studies have tried to assess the efficacy of recombinant Irisin, as exercise-mimetic molecule, in murine models in vivo. Zhang et colleagues demonstrated that normal and obese mice, treated with 3500 μg/kg/week of recombinant Irisin (r-Irisin), injected every day for two weeks, showed a 25-fold change increase of uncoupling protein 1 (UCP1) expression in white fat depots, thus confirming Irisin ability to promote the browning trans-differentiation of white adipocyte. The effect was accompanied by decreased body weight and enhanced glucose homeostasis, as proved by the higher expression of betatrophin and increased pancreatic b-cell proliferation in r-Irisin treated animals 16.

Increasing bone mass with Irisin, as exercise-mimetic molecule, in healthy young mice was found to be markedly increased in Irisin-injected mice.
The effect of Irisin on bone is mostly exerted on bone forming cells, as demonstrated by increased number and size of osteoblasts on cortical bone and by elevated expression of Activating transcription factor 4 (Atf4) in bone marrow, signifying commitment of mesenchymal stem cell toward an osteoblastogenic phenotype. In addition, long bones of r-Irisin treated mice expressed high level of osteopontin (OPN), one of the most abundant protein of bone matrix that is also known to be a mechanically responsive molecule, and strongly reduced expression of sclerostin, one of the inhibitors of the bone anabolic Wnt pathway.

Although Irisin receptor has not been identified yet, its action on osteoblast is receptor-mediated, as demonstrated by MAP kinase Erk activation upon r-Irisin administration in vitro. The r-Irisin-activated ERK-mediated intracellular signaling was also supported by data obtained by other researchers, which showed in parallel a significant increase of phosphorylated p38 in both primary rat osteoblast and MC3T3-E1 osteoblast cell line after r-Irisin treatment.

THE MYOGENIC POTENTIAL OF IRISIN

In skeletal muscle of mice treated with r-Irisin it was observed a high number of fibers expressing the Irisin precursor, thus intriguingly suggesting that Irisin production may be enhanced by an autocrine action. This result was also confirmed in vitro by treating murine myotubes with r-Irisin for 24 hours that, upon treatment, expressed high levels of peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), the transcription factor responsible for Irisin synthesis. Additionally, muscle cells treated with r-Irisin also expressed higher levels of nuclear respiratory factor 1 (NRF1) and mitochondrial transcription factor A (TFAM), indicating increased mitochondrial content and oxygen consumption.

The effect of r-Irisin has been also tested in human skeletal muscle cells in vitro, in which, through an ERK-dependent mechanism, insulin-like growth factor 1 (IGF-1) and myostatin expressions were increased and decreased, respectively. Excitingly, Irisin and myostatin are both produced by skeletal muscle and their synthesis is inversely regulated by physical exercise. Moreover, myostatin knock-out mice highly express

Figure 1. Representative micro-CT-generated section images of tibia harvested from 12-month-old mice treated with vehicle or r-Irisin (100 μg/Kg/weekly) or subjected to physical activity for 4 weeks.
The myokine Irisin recapitulates the effect of physical activity on bone and muscle tissues

IRISIN FOR THE PREVENTION AND TREATMENT OF OSTEOPOROSIS AND SARCOPENIA: A BRIGHT FUTURE LIES AHEAD?

A better understanding of the molecular entities involved in muscle and bone communication can shift the paradigm for the simultaneous treatment of osteoporosis and sarcopenia. To date, no randomized controlled trials that evaluated the combined effects of chemical molecule on both bone and muscle tissue have been reported. The research findings on the effects of Irisin on the bone-muscle functional unit, altogether support the idea that Irisin is a regulatory hormone-like molecule with key functions for the metabolism of the musculoskeletal system. However, further studies on osteoporotic and sarcopenic murine models would allow to evaluate if Irisin is effective in preventing or retrieving bone and muscle loss. If remarkable results will be achieved, future studies could lead to the assessment of r-Irisin in human clinical trials. An Irisin-based therapeutic strategy should be particularly useful in those patients that cannot perform physical activity, such as elderly people or bedridden patients (Fig. 1).

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Osteoporosis is the most important metabolic bone disease in geriatric patient and is characterized by quantitative bone deficiency with consequent increased bone fragility and susceptibility to fractures. Diagnostic imaging has a critical role as in the diagnosis and follow-up of osteoporosis. The aim of this review is to encompass the capabilities of the different imaging modalities for the evaluation of bone strength, the assessment of fracture risk and the management of fragility fractures.

**Key words:** Bone densitometry, Osteoporosis, Aging, High resolution imaging, Bone

**INTRODUCTION**

Loss of bone properties in aging people represents an increasingly important public health issue, being associated to other age-related processes (such as muscle strength impairment), which contribute to reduce physical performance and increase the risk of fall-related injury, disability, and mortality.

Osteoporosis is the most important metabolic bone disease in geriatric patient and is characterized by quantitative bone deficiency with consequent increased bone fragility and susceptibility to fractures. Involutional osteoporosis has been classified into type I or postmenopausal osteoporosis and type II or senile osteoporosis. Postmenopausal osteoporosis usually occurs in women between ages 50 and 65 years. The estrogenic deficiency is linked to an accelerated trabecular bone resorption, which may lead to fragility fractures that typically involve spine and wrist. In type II osteoporosis the bone loss pattern involves the cortex and the trabeculae, leading to fragility fractures usually located at the hip, pelvis, and proximal humerus. Despite the well-recognized role of estrogenic deficiency in type I osteoporosis and the consequent higher prevalence of fragility fractures in 40-50 y.o. women, multiple investigations have confirmed an age-related significant prevalence of senile osteoporosis in men as well.

Although several studies have already highlighted higher mortality rates in women who experienced a vertebral fracture, the social and economic burden of osteoporosis still remains partially underestimated.

Diagnostic imaging has a critical role as in the diagnosis and follow-up of osteoporosis, as in the management of the complications that often implicate differential diagnosis issues, most of all in a geriatric patient. Therefore, the aim of this review is to encompass the capabilities of the different imaging modalities for the evaluation of bone strength, the assessment of fracture risk and the management of fragility fractures.

**IMAGING TECHNIQUES**

Imaging in osteoporosis aims to identify bone weakening at an early stage, to differentiate patterns of bone alterations, to predict fracture risk, to determine the treatment approach and to help monitor disease progression and response to therapy. Besides conventional radiography, other imaging techniques such as dual-energy x-ray absorptiometry...
(DXA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) have been developed to quantify BMD and to assess bone loss.

Dual Energy X-Ray Absorptiometry (DXA)

It is well known that bone mineral density (BMD) correlates with bone strength and predicts fracture risk. As a consequence, highly reproducible and available methods to quantitatively measure BMD are required. Dual energy X-ray Absorptiometry (DXA) is the most widely used quantitative technique for BMD assessment in clinical practice and represents the “gold standard” for a non-invasive diagnosis of osteoporosis.

BMD is measured in mg/cm² and comparing these values with a known parameter, the T-score, which is the number of standard deviations (SD) above or below the mean for a healthy 30 y.o. adult of the same ethnicity and sex (which refers to the peak bone mass). Z-score is the number of SD above or below the normal values of a healthy subject of the same age, sex, weight and ethnicity; this parameter is mostly used in the assessment of metabolic bone status of children and people aged over 75, but it should be also considered in women prior to menopause and men younger than 50 y.o.

The World Health Organization (WHO) has defined T-score threshold levels for BMD assessment: ≥ -1.0 is considered as normal, values between ≤ -1.0 and ≥ -2.5 refer to osteopenia, and a T-score ≤ -2.5 is classified as osteoporosis. A Z-score of -2.0 or lower is defined as “below the expected range for age” and a Z-score above -2.0 is “within the expected range for age”.

According to the WHO, the definitions of osteopenia and osteoporosis only refer to DXA measurements at lumbar spine, hip and forearm, and cannot be applied to other densitometry techniques, neither at other skeletal sites. Lumbar spine is the primary site for BMD measurement: total spine (from L1 to L4) and individual vertebral T-scores are obtained from several Regions of Interest (ROIs) (Fig. 1).

The hip represent the other most common site of measurements, being the BMD of proximal femur the best predictor of hip fracture. ROIs include femoral neck, trochanter, Ward’s area, intertrochanteric region, and total hip.

The forearm is a third site used for BMD measurement, useful when spine and hip are not measurable or interpretable due to severe degenerative processes, and implantable devices.

The recent implementation of software for advanced hip assessment into DXA systems have provided a noninvasive description of the structural geometry of the proximal femur, depicting several parameters such as cortical thickness with bone mapping, areal BMD, hip axis length, cross-sectional area, cross-sectional moment of inertia, and the femoral strength index.

Despite short scan times, low radiation dose, good
Bone densitometry: current status and future trends

Reproducibility, low cost, and wide availability, DXA has shown some limitations. Most of them rely in its bi-dimensional technology: it cannot distinguish between cortical and trabecular bone, it cannot discriminate changes induced by bone geometry from those only related to bone density. Above all, in clinical practice BMD can be overestimated by marginal osteophytes and vascular calcifications projecting on lumbar spine 10.

**Trabecular Bone Score (TBS)**

Although BMD by DXA is a major determinant of bone strength and fracture risk, most individuals may experience a fragility fracture without significant BMD impairment 11. The evolution of DXA technology has allowed more advanced tools in the assessment of the bone status with the aim to provide bone quality properties unrelated from BMD 12. The trabecular bone score (TBS) evaluates in DXA images of the lumbar spine (L1-L4) pixel grey-level variations, which have been associated to bone micro-architecture 13. Several preliminary studies in patients affected by metabolic bone diseases have suggested that TBS, in addition to BMD and clinical risk factors, improves the prediction of fracture risk. Since most individuals with fragility fractures may have BMD values in the range of normality or osteopenia, TBS could be useful to select patients to be screened and managed for osteoporosis 14-16 (Fig. 2).

Despite these promising results, opinions in literature are still controversial and further normative data, validation and prospective studies are required 17.

**Quantitative Computed Tomography (QCT)**

Quantitative Computed Tomography provides separate estimation of trabecular and cortical BMD as true volumetric mineral density in mg/cm³. It can be performed at the spine (axial QCT) and peripheral sites (peripheral QCT-pQCT). Axial QCT measures trabecular bone in spinal vertebrae (T12 to L4) adopting commercial CT scanners and a phantom which acts as bone mineral reference standard to calibrate each scan. ROIs are positioned in the trabecular portion of the vertebral body, compared to the calibration phantom. The obtained vertebral densities are averaged and compared to those of a gender- and race-specific normal population 18. The results are usually expressed in absolute values and as Z-scores and T-scores. The main advantage of QCT over DXA relies in the selective measure of trabecular tissue, the main determinant of compressive strength in the vertebrae. QCT has shown an excellent ability to predict vertebral fractures and a good sensitivity for BMD changes during the follow-up 19.

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![Figure 2. Graphic representation of Trabecular Bone Score (TBS) on DXA images of lumbar spine. These two different patients show equivalent BMD but different TBS values.](image-url)
Besides these advantages, QCT has some limitations that have narrowed its clinical diffusion: marrow change processes can affect trabecular measurements (myelofibrosis, hematopoietic disorders etc.), and the technique has higher radiation doses and costs compared to DXA. The introduction of volumetric QCT (vQCT) has improved axial QCT and extended its application to the hip, allowing separate analysis of trabecular and cortical components.

Peripheral QCT (pQCT)

This technique has been developed to obviate the limitations of DXA and axial QCT, provides separate assessment of cortical and trabecular bone at appendicular sites. The evolution of post-processing software allowed further analysis on bone geometrical and torsional stability, which correlates to bone strength and consequent susceptibility to fracture.

Vertebral Morphometry

Vertebral fractures are considered the hallmark of osteoporosis and represent a frequently used endpoint in clinical trials and epidemiological studies investigating the effectiveness of different therapeutic regimes on osteoporosis. A vertebral fracture is defined as more than 20% loss in anterior, middle, or posterior vertebral heights within a vertebra or between adjacent vertebrae. The morphological classification (wedge, biconcave, crush) of vertebral fractures (VF) results from more than 20% loss in anterior, middle or posterior heights of vertebral bodies. VFs are also classified as mild (20-25%), moderate (26-40%), and severe (>40%) reductions in any height.

Most of all in elderly, VF often appear as atraumatic and asymptomatic mild deformities, which can be easily under-reported in radiological routine. In the last decades a significant effort has been invested in order to reduce the subjectivity of the visual approach. The visual semi-quantitative approach proposed by Genant et al. has been integrated with morphometric methods based on vertebral height measurements. The quantitative vertebral morphometry can be applied on spinal radiographs (MXR – Morphometric X-ray Radiography) or on DXA images (MXA – Morphometric X-ray Absorptiometry).

Several semi-automated software have been introduced with the aim of digitize and automatize MRX, improving its reproducibility. The operator has to manually identify the vertebral levels (from T5 to L4) then a semi-automated six-points segmentation of the vertebrae calculates the vertebral heights (posterior – Hp, middle – Hm and anterior Ha) and the ratio between heights (Ha/Hp, Hm/Hp) of each vertebra. The last step of the analysis includes the report of fracture assessment based on normative data and models.

The widespread diffusion of DXA and the technical improvements have allowed the application of quantitative morphometry on lateral DXA images of the spine. Thanks to its lower radiation exposure, MXA nowadays represents the most widely adopted solution for quantitative assessment of fracture status and has been fully integrated into DXA-based BMD assessment of osteoporosis in clinical routine (Fig. 3).

However, the radiologist’s role still remains critical in order to distinguish osteoporotic vertebral fractures.

Figure 3. Example of Vertebral Fracture Assessment (VFA) on lateral spine DXA image.
from malignancies and other congenital or acquired deformities.

**Quantitative Ultrasound (QUS)**

This technique measures quantitative parameters related to bone quality properties. QUS provide portable, radiation-free and low cost measurements of bone density, elasticity and structure through the analysis of interactions between ultrasound and bone. Transit time velocity and ultrasound attenuation represent the most widely adopted parameters measured at peripheral sites such as calcaneus (primary site), metaphysis of the phalanx, radius and tibia. QUS results can be expressed in absolute values or in T-score and Z-score linked to normative reference data. Several studies have shown that fractured patients have lower calcaneal ultrasound values than normal subjects and that QUS parameters are predictive of osteoporotic fractures. However, despite several advantages and promising results, the WHO has stated that QUS cannot be used as stand-alone tool for the diagnosis of osteoporosis and can be useful as screening tool for the estimation of fracture risk.

**Other Techniques**

The concept of bone strength as result of bone quantity and bone quality have induced the scientific community to explore other imaging modalities capable of obtaining micro-architectural data of trabecular bone with the aim to understand the relationship between bone turnover, density and architecture.

Several studies in the past decade have explored the capabilities of MR in the exploration of physiologic differences in aging bone. As routine MR sequences revealed to be not suitable for cortical and trabecular bone assessment, specific high resolution sequences and imaging analysis algorithms have been developed to reveal bone network. The most adopted sites of analysis were the calcaneus and the distal radius in order to correlate trabecular content and architecture with bone turnover.

More recently other MR-based approaches have been explored, all aiming to obtain a non-invasive assessment of bone strength and turnover. Dynamic contrast-enhanced MR imaging (DCE-MRI) studies across different age groups have revealed that vertebral marrow perfusion is reduced in elderly and in patients with osteoporosis compared to subjects with osteopenia.

Subjects with osteoporosis or osteopenia revealed a significantly increased marrow fat content compared with the fat content in subjects with normal bone density. The concomitant observation that both adipocytes and osteoblasts arise from common precursor cells has suggested the hypothesis that preferential differentiation of mesenchymal stem cells towards the adipocyte lineage may negatively influence osteoblast differentiation.

Hydrogen 1 (1H) magnetic resonance spectroscopy (MRS) allows a non-invasive quantification of bone marrow fat and fat/water ratio. MRS-based studies have revealed an age-dependent linear increase in vertebral marrow fat content at various skeletal sites. More recently, Water-Fat-Imaging (WFI) sequences have been introduced for marrow fat assessment revealing good performances in water and fat content differentiation.

Besides advanced MR techniques, other research centers have focused their studies on CT-based systems. High resolution quantitative computed tomography (HR-QCT) has been performed on metabolic bone disease patients with the aim of providing a detailed assessment of both cortical and trabecular architecture.

With an 80-100 μm resolution, HR-QCT can measure (in addition to the parameters classically measured by QCT) bone volume fraction as well as cortical and trabecular parameters including thickness, separation, and number of trabeculae. Nevertheless, high costs and the expertise level required to handle these techniques has limited their application to few research centers.

**Conclusions**

Osteoporosis represents a worldwide health problem with age-related incidence of fragility fractures. With the increase of life expectancy, the socio-economic burden associated to osteoporotic fractures will grow exponentially. Therefore, early diagnosis of osteoporosis and adequate management of its complications are becoming more critical in order to guarantee a true “healthy aging”.

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Background and aim. Hip fracture is one of the major causes of loss of self-sufficiency in older patients. The associated caregiving rehabilitation task often falls to the lot of a member of the patient’s family. Our study aims at assessing the relationship between the psychological well-being of patients with hip fracture and their caregivers.

Methods. The study was carried out on 53 elderly patients with hip fracture and their primary caregivers. The Mini Mental State Examination (patient), Activities of Daily Living (patient), Instrumental Activities of Daily Living (patient), Geriatric Depression Scale (patient), Psychological General Well-Being Index (patient/caregiver) and the Caregiver Burden Inventory (caregiver) were administered to each participant.

Results. The results revealed significant correlations between stress levels and the psychological well-being of hip-fracture patients and relative caregivers. In particular, the Caregiver Burden Inventory’s total score was negatively related to the patient’s Psychological General Well-Being Index score (p < 0.05) and with Anxiety (p < 0.05), Depressed Mood (p < 0.01), Positive Well-being (p < 0.05) and General Health (p < 0.05) subscale scores, as well as with the patient’s Activities of Daily Living (p < 0.05) score. Patients’ Psychological General Well-Being Index scores were related to the caregivers’ General Health subscale (p < 0.01), and negatively related to Caregiver Burden Inventory Time Dependence (p < 0.05) and Social Burden (p < 0.05) subscales, as well as with the Geriatric Depression Scale score (p < 0.05).

Conclusion. A mutual relationship seems to exist between a patient’s psychological well-being and his/her caregiver’s burden. These findings highlight the importance of a bio-psychosocial approach to both patients and caregivers.

Key words: Hip fracture, Psychological well-being, Caregiver’s burden

INTRODUCTION

Hip fracture (HF) is one of the major causes of loss of self-sufficiency in older patients who are among the most vulnerable of hospitalized patients, presenting with different major comorbid geriatric syndromes (frailty, dementia, disability) which make the discharge planning process difficult. HF affects independent ambulation and functional ability resulting in reduced health-related quality of life. Functional recovery following surgery varies according to patients’ comorbidities, cognitive and functional status, and their psychosocial state. Bueckling and colleagues have found a pre-existing need of care, limited function, cognitive impairment, and depression to be independent factors associated with lower Health-related Quality of Life (HrQoL) during a patient’s postsurgical period. Depression, delirium, and cognitive-impairment...
rates, at the time of hip fracture, have been estimated at between 9% and 47% (mean 29%), between 43% and 61% (mean 49%), and between 31% and 88% (mean 47%), respectively. Mental health status at the time of surgery has been reported as being an important determinant of outcome, with mental disorder associated with poorer functional-recovery and higher mortality rates. The psychological state of the individual who suffers from a hip fracture is highly relevant when determining how well that person may recover. The affective responses to a hip fracture predict both psychological and physical functioning over time, providing a potential target for the enhancement of recovery from this debilitating injury. The recovery process that follows surgery varies on the basis of patients’ comorbidities, cognitive and functional status, and their psychosocial state. Well-being in this sense means more than health as such and is possible to achieve during illness as a means by which to balance suffering. The embodied experiences of both well-being and suffering include a variety of simultaneous qualities.

The caregiving rehabilitation task associated with hip fracture fall, more often than not, to the lot of a member of the family. Studies have focused, in particular, on the concept of burden, defined as “burden of care”, losing sight of the importance of assessing the positive aspects that characterize the state of health of an individual. Informal caregivers are an important resource for elderly patients suffering from hip fracture because they play a key role during their recovery. One important task is that of motivating the patients to adhere to their therapy programmes. The majority of caregivers (86%) are represented by family members (prominently women) who are also defined as “informal caregivers”. They fulfil their caring-giving role from 7 to 11 h a day on average, up to 10-15 h when clinical conditions worsen. Informal caregivers have to cope with physical, psychological and social stressors that affect their health conditions and quality of life negatively. Many caregivers assume the caregiver role with little or no preparation and have to learn to deal with several aspects of care in a very short time. Most often they have no professional skills in assistance procedure. In fact, more often than not, caregivers do not know what to expect during hip-fracture recovery. They face situations where they have to address various care-related tasks, such as arrangement of rehabilitation services and assistive devices. These situations become more stressful when caregivers have to juggle their own professional and family lives with their activities as carers. The primary stressors experienced by informal caregivers are related to the severity of the ailment and the quantity of time devoted to assistance.

The increased risk of burnout identified among informal caregivers is closely related to their perceived level of burden, defined as a multidimensional response to negative appraisals and perceived stress. Joint assessment of the burden and well-being dimensions, that coexist in caregivers’ experiences, allows for the identification of personal and relational resources that may be usefully included in interventions addressed to caregivers. In a recent preliminary study, we also found a correlation between patients’ psychological well-being and caregivers’ burdens.

This study aims at providing some initial data on the relationship between the psychological well-being of patients with HF and their caregivers, in an effort also to verify some of the possible implications existing between psychological variables and HF prognosis. Our study adopts a positive approach, taking into consideration not only deficits but also psychological resources that may prove useful to hip-fracture rehabilitation programming.

MATERIALS AND METHODS

The study was carried out on 53 elderly patients with HF (mean age: 83.9 +/- 8.1), hospitalized within the Geriatrics Division of Rome’s Sant’Andrea Hospital, in 2015, and their primary caregivers (mean age: 53.2 +/- 15.9; 40.4% of them living with patients). Each patient was given a socio-demographic questionnaire and the Psychological General Well-Being Index (PGWBI), the Mini Mental State Examination (MMSE), the Activities of Daily Living (ADL), the Instrumental Activities of Daily Living (IADL) and the Geriatric Depression Scale (GDS). The caregiver burden was also assessed using the Caregiver Burden Inventory (CBI). In Table I we illustrate which tests were assigned to each participant.

As follow-up outcomes, ADL and IADL patient scores, 2 months after surgery, were taken into account. Below we shall illustrate the different tests we availed of, also summarizing the importance that each area we investigated had for HF patients and caregivers alike.

Table I. Materials and participants.

<table>
<thead>
<tr>
<th>Each participant (Patient [P] and Caregiver [C]) was given:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Socio-demographic questionnaire [P/C]</td>
</tr>
<tr>
<td>• Mini Mental State Examination (MMSE) [P]</td>
</tr>
<tr>
<td>• Activities of Daily Living (ADL) [P]</td>
</tr>
<tr>
<td>• Instrumental Activities of Daily Living (IADL) [P]</td>
</tr>
<tr>
<td>• Geriatric Depression Scale (GDS) [P]</td>
</tr>
<tr>
<td>• Psychological General Well-Being Index (PGWBI) [P/C]</td>
</tr>
<tr>
<td>• Caregiver Burden Inventory (CBI) [C]</td>
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</table>
MINI MENTAL STATE EXAMINATION (MMSE)
The Mini Mental State Examination (MMSE) is a 30-point questionnaire used extensively in clinical and research settings to measure cognitive impairment. It has proved to be a valuable instrument for the assessment of cognitive impairment. Pre-fracture cognitive impairment places patients at greater risk of institutionalization. Furthermore, pre-fracture cognitive impairment is also associated with higher mortality rates. Dementia plays a role in the genesis of hip fractures, as it increases the risk of falling by a factor of 5, and risk of significant injury after a fall by a factor of 2.2. Few effective studies have linked cognitive impairment to patient clinical outcome. Some studies suggest that cognitive impairment, found in 31-88% of elderly patients experiencing hip fracture, was a predictor of poor functional recovery after hip-fracture surgery.

ACTIVITIES OF DAILY LIVING (ADL)
The Katz Index of Independence in Activities of Daily Living (ADL), commonly referred to as the ADL, is the most appropriate instrument to avail of in order to assess functional status as a measurement of a person's ability to perform activities of daily living, independently. The Index ranks adequacy of performance in the six functions of bathing, dressing, toileting, transferring, continence, and feeding. Patients are scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment. ADL are an important health outcome in the orthogeriatric population. Functional decline can lead to disability and may lead to prolonged hospital stays, institutionalization and even death. Some authors have suggested that pre-fracture dependence in ADL is a stronger predictor of further functional decline resulting in institutionalization or death than pre-fracture dementia. Recovery of pre-fracture health and functional levels is one of the main goals in hip fracture management. Therefore, it is important to assess deterioration in functional level over time. In many cases, it may prove difficult to assess pre-injury ADL's accurately at the time of admission. In such cases, Liem and colleagues suggest consulting a proxy, who will typically be a family member, friend or caregiver.

INSTRUMENTAL ACTIVITIES OF DAILY LIVING (IADL)
The Lawton Instrumental Activities of Daily Living Scale (IADL) is an instrument developed to assess independent living skills. These skills are considered more complex than the basic activities of daily living as assessed by the Katz Index of ADL. The instrument is considered useful when seeking to identify how a person is functioning at present as well as detecting improvement or decline, as explained below. IADL are defined as those activities whose accomplishment is necessary for continued independent residence in the community as they are more sensitive to subtle functional deficiencies than the ADL. It differentiates among task performance levels including the amount of help and time needed to accomplish each task. Eight domains of function are assessed with the Lawton IADL scale. Women are appraised on all areas of function, while, interestingly enough, men are assessed historically on five only which means that preparation of food, housekeeping and laundering are excluded. The scores range from 0 (low function, dependent) to 8 (high function, independent) for women, and from 0 to 5 for men.

GERIATRIC DEPRESSION SCALE (GDS)
The Geriatric Depression Scale (GDS) is a 30-item self-report assessment used to evaluate depression in the elderly. The questions require either “yes” or “no” as an answer. Being so simple to answer, the scale can be used easily with individuals who are ill or moderately impaired from a cognitive point of view. One point is assigned to each answer and the cumulative score is rated on a grid. The grid sets a range of 0-9 as “normal”, 10-19 as “mildly depressed”, and 20-30 as “severely depressed”. Compared with the pre-fracture period, 55% to 75% of H-F cases experience loss of some of their daily-life activities. Although it is ignored in the case of the majority of elderly patients, depression is the most commonly found hip-fracture-related psychological co-morbidity disorder. An independent relationship was found to exist between low functional capacity and depression symptoms in the elderly. In elderly people who cannot walk well enough to perform daily living activities, social isolation often occurs and social isolation is in itself a risk factor for depression. Therefore, we can say that a vicious circle of low ADL is created between pre-existing depression and an increase in depression that feelings of inadequacy when performing daily activities can produce. In a long-term study, functional healing was evaluated after 2 years in elderly cases with hip fractures, and depression was reported to have affected healing. A negative effect of depression on daily living activities at the end of a 6-month period emerged. A patient's active participation in the rehabilitation process has a positive effect on healing. However, the presence of depression due to reluctance, negative cognition and symptoms similar to psychomotor retardation will disrupt this process.
observed more often in females and in those who had lost their spouses 34.

**Psychological General Well-Being Index (PGWBI)**

Initially developed in 1970-71, the Psychological General Well-Being Index (PGWBI) is one of the most venerable and widely used patient-reported outcome gauges. The PGWBI targets peoples’ self-representations of aspects of their general wellbeing. It does not include evaluations of physical health. The 22-item instrument includes six dimensions: Anxiety, Depressed Mood, Positive Well-being, Self-Control, General Health and Vitality. The 22 items are frequently used to generate an overall Index or total score for general well-being 35.

Psychological wellbeing is recognized as an important gauge of health status, shaped by individuals’ perceptions and expectations that may be availed of for the purpose of evaluating disease and health-care services 36.

Elderly patients with a hip fracture may present with a complexity of other problems, including physiological and social factors, which may be challenging to both them and their careers. The level of family caregivers’ mental health has been shown to be an important predictor of care recipients’ institutionalization 37, and a risk factor for care-recipient mortality 38. The perspective that tends to dominate much of the relative literature is that care by family members is provided solely to older adults living at home. When caregivers are monitored over considerably long periods of time, it becomes evident that family caregiving responsibilities do not end with institutionalization of a disabled relative. Instead, this key transition appears to affect the type and intensity of the help provided. There is a lack of literature addressing family caregiving for frail elderly people and its consequences on the life quality of family caregivers. The subjective responses of individuals to the objective environments where he/she lives 39,40 play an important role in maintaining the status of care recipients in-home care. High levels of depressive symptoms and low levels of life satisfaction in caregivers may also be associated with the low quality of the care provided to their frail care-recipients and even with maltreatment of the elderly 39. The concept of subjective well-being (SWB) is multi-component by nature. It is affected by positive (i.e., happiness), negative (i.e., depressive symptoms) and cognitive components (i.e., life satisfaction). Its multiple components are affected by different sets of social determinants and develop differently at successive stages of life 41. Patterns of change in family caregivers’ mental health over time were also explored, while the relationships between family caregivers’ mental health and recovery outcomes of elderly hip-fractured patients were also examined. The findings 38 suggest that, during the first year following patient discharge, family caregivers’ mental health is a variable factor associated with patients’ post-fracture recovery, including recovery of physical functionality, reduced pain, and better health-related outcomes. These results also suggest that, when estimating recovery times and health-related outcomes of patients who have suffered a hip fracture, health-care providers should also consider the mental well-being of family caregivers. An understanding of the relationships between caregiver-related predictors and the recovery of elderly persons after hip-fracture surgery might provide a more holistic view of recovery. Informal caregivers have, in fact, to cope with physical, psychological and social stressors that affect their health conditions and quality of life negatively 11.

**The Caregiver Burden Inventory (CBI)**

The Multidimensional Caregiver Burden Inventory (CBI) 42 is a 24-item Likert-format scale (0-4) that measures 5 dimensions of the caregiver burden: time-dependence, developmental, physical, social, and emotional burden. The time-dependence burden emanates from the time demands and restrictions that caregiving can impose on caregivers, whereas the developmental burden describes the caregivers’ feelings of being ‘off-time’ in their development with respect to their peers. The physical burden refers to the strain associated with demands on caregivers’ physical health, strength, and energy. The social burden refers to ‘caregivers’ negative feelings toward their care recipients, which may also result from the patient’s unpredictable and often bizarre behaviour. The CBI comprises 24 closed questions. There are five items in each dimension except for physical burden, which has four. Each item is attributed a score between 0 (not at all descriptive) and 4 (very descriptive), where higher scores indicate greater caregiver burden; there are no cut-off points for classifying burden 43.

Increasing numbers of studies have examined the caregiver-burden phenomenon, the lack of support given to caregivers and intervention focused on relieving the caregiver burden; this increase is probably due, in part, to greater evidence that caregiver burden is a determining factor of caregivers’ Quality of Life (QoL) 44,45. Social support has been associated with a diminution of caregiver burden 44. High care-demand levels may affect multiple aspects of caregivers’ lives, including their free time, social life, emotional and physical health, as well as their personal development. These subjectively defined stressors are also called caregiver
burden. Perceived caregiver burden may affect their self-esteem, sense of competency as caregivers and the degree of growth due to dealing with caregiving challenges, adversely\(^39\)\(^46\).

**Statistical Analysis**

SPSS 22.0 software was used to investigate the correlations between the CBI of caregivers and the PGWBI of patients and between patients’ and the caregivers’ PGWBIs, whilst also correlating the subscale scores obtained from the various tests administered.

**Results**

In the case of the caregivers, the mean score on the CBI was 25.2 +/- 18 and 73.89 +/- 19.5 on the PGWBI. Time-Dependence and Social are the CBI subscales that obtained the highest mean scores (see Figure 1). Patients’ mean score for PGWBI was 60 +/- 19.7.

The results revealed significant correlations between stress levels and the psychological well-being of the caregivers and the patients, as illustrated in Figure 2. In particular, the total CBI score is negatively related to the patient’s PGWBI score (p < 0.05). The total CBI score is also negatively related to the PGWBI subscales of Anxiety (p < 0.05), Depressed Mood (p < 0.01), Positive Well-being (p < 0.05), General Health (p < 0.01) and with IADL (p < 0.05) in patients.

Patients’ PGWBI scores are related to caregivers’ General Health subscales (p < 0.01), and negatively related to Time-Dependence (p < 0.05), Social-Burden (p < 0.05) and GDS scores (p < 0.05).

The Patient-Anxiety subscale score is related to the Depressed-Mood (p < 0.05) and General-Health (p < 0.01) subscales of caregivers’ psychological well-being and negatively related to Social Burden (p < 0.05). The Patients’ Depressed-Mood subscale score is related to the Depressed-Mood (p < 0.01) and General-Health (p < 0.05) subscales of caregivers’ psychological well-being and negatively related to Time-Dependence (p < 0.01), Physical (p < 0.05) and Social (p < 0.01) burdens. Patients’ Self-control subscale scores are related to caregivers’ psychological well-being General-Health subscale (p < 0.05)

Patients’ General-Health subscale scores are related to the Depression-Mood (p < 0.05) and General-Health (p < 0.01) subscales for caregivers’ psychological well-being and negatively related to their Physical (p < 0.01) and Social (p < 0.01) CBI Burden subscales and with their GDS scores (p < 0.05). Patients’ Positive and Wellness subscales are related to the ADL (p < 0.05) and IADL (p < 0.01) scores and negatively related to the GDS (p < 0.05) scores and with the Time-Dependence subscale of CBI (p < 0.01). Patients’ Vitality subscale scores are related to ADL (p < 0.05) and IADL (p < 0.05) scores and negatively related to GDS scores (p < 0.05). Patients’ PGWBI scores are also negatively related to caregivers’ Time-Dependence Burden (p < 0.05) and with their developmental-burden scores (p < 0.01).

Furthermore, results showed a significantly inverse relationship between dependence indices in activities of daily life and dependence in instrumental activities of daily living with Time Dependence (p < 0.01) of CBI. At the 2-month follow-up, the outcome of ADL scores was negatively associated to caregiver burden (p < .01). Follow-up functional ability was higher in patients whose caregivers reported lower burden during their hospitalisation (p = .03).

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**Figure 1.** Caregiver’s Burden subscales of patient with HF.

**Figure 2.** Caregivers’ and patients’ psychological well-being.
DISCUSSION

Informal caregivers are an important resource for elderly patients with hip fracture because they play a key role in their recovery process. Moreover, they have the important task of motivating the patients to join the therapy programme. Caregivers often neglect their own needs and personal lives due to their assistance tasks; this may also prove to be a source of stress negatively affecting the caregiver’s and patient’s quality of life. The results confirm what has been described in literature, namely the greater presence of women among caregivers and the presence of caregiver burden also in instances of acute disease. Several studies have revealed an association between the characteristics of patients and caregivers and caregivers’ QoL, with caregiver burden serving as an important predictor of QoL. Caregiver burden has also been used as an outcome variable rather than as a predictor, suggesting that caregiver burden and QoL are closely related. Thus, caregiver burden seems to be a potential moderator of associations between patients’ and caregivers’ characteristics and caregivers’ QoL. Caregiver burden and its associated stress impact negatively upon caregivers’ perceived general physical and mental health and have been negatively correlated to the functional status of elderly family members 1 month after discharge following hip-fracture surgery. Our results confirm the conclusions reached by some studies that have shown that caregivers of elderly people suffering from hip fracture experienced multidimensional burden, including tiredness, emotional distress and conflicts of role. We can confirm that family caregivers of hip-fractured patients were reported as experiencing moderate burden. However, the burden of caregivers of patients with HF is less than that found in cases of other geriatric ailments, dementia, for example.

In literature, it emerges that caregivers tend to experience the greatest stress during the first 2 months after fracture, stress being associated with increased care demands and costs. Furthermore, we have found that follow-up functional ability was higher in patients whose caregivers reported lower burden levels during their hospitalisation. One study has already underlined the fact that the caregiver burden was negatively related to the physical function of older patients with hip fracture. Our results propose that rehabilitation may have a stronger correlation with caregiver burden than what was imagined heretofore. Future studies are needed, however, to identify the direction of these associations.

Caregivers who are members of the patient’s family have less time for themselves and feel they have fewer expectations and opportunities than their peers; the data provided by literature confirm the great difficulty of combining caregiving activities with other social roles. Interesting results regard the correlation existing between a patient’s psychological well-being and his/her mood; greater psychological well-being corresponds, in fact, to lower likelihood of depression. Moreover, it is important to report that there is a positive relationship between Positivity and Wellness, patient Vitality and dependence indices for activities of daily life and instrumental activities of daily living. These findings confirm the existence of a reflexive relationship between patients’ psychological well-being and caregivers’ burdens, highlighting once again the importance of a bio-psycho-social approach when addressing both patients and caregivers, because improvements in the state of health of the one boosts that of the other, and vice versa. These factors might cause caregivers to suffer from higher levels of depressive symptoms and become less satisfied with their lives. In other words, multidimensional caregiver burdens may play a mediatory role in the association between objective primary stressors and caregivers’ SWB. In literature, it has already been found that objective primary stressors can affect various dimensions of burden differently: functional health has been found to be associated with time-dependent, physical and developmental burdens; cognitive status has been found to be associated with time-dependent burden.

CONCLUSIONS

The correlation emerging between patients’ psychological well-being and their caregivers’ burden confirms the importance of using a bio-psycho-social approach towards patients and caregivers. It is important to evaluate different negative and positive dimensions to assess patients’ psychological status when following a bio-psycho-social approach. These patients risk much longer and more frequent hospital stays than other adults. Comprehensive discharge-planning programmes, including early identification of those at risk, can alter these statistics. Upon admission to care facilities, early multidimensional assessment can provide significant indications of how to address the entire course of patient treatment more efficiently. Unfortunately, not all participants were assessed at the 2-month follow-up stage, and this is one of the limits of our study. Indeed, we consider very important to revalue patients and their caregivers, at 60-90 days from demission.

In Table II, we illustrate the different areas that we believe it is important to evaluate in order to obtain a complete...
Table II. Areas to evaluate in order to carry out an integrative assessment of H-F patients and relative caregivers, with staging (1= admission; 2= 90 days follow-up; 3= 1 year follow-up; 4= 2 years follow-up).

<table>
<thead>
<tr>
<th>Areas</th>
<th>Staging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
<td>1 2 3 4</td>
</tr>
<tr>
<td>• Activities of daily living</td>
<td>X X X X</td>
</tr>
<tr>
<td>• Depression</td>
<td>X X X X</td>
</tr>
<tr>
<td>• Cognitive status</td>
<td>X</td>
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<tr>
<td>• Psychological wellbeing</td>
<td>X X X</td>
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<tr>
<td>Caregiver</td>
<td>X X X</td>
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<tr>
<td>• Psychological wellbeing</td>
<td>X X X</td>
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<tr>
<td>• Caregiver burden</td>
<td>X X X</td>
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The authors would like to thank the Orthogeriatric Team of Rome’s Sant’Andrea Hospital for the collection of data. In particular Carla Farulla, who helped us in our search for literature, and Katarina Banow, who took care of the analysis of the follow-up statistics.

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To be or not to be: a two years surveillance for a CA 19-9 persistent elevation before cancer diagnosis and bone metastases

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Background. CA 19-9 is an antigen expressed by several epithelial cells and currently used for the diagnosis and follow-up of gastrointestinal cancers. Even if a serum level > 1000 UI/ml has a specificity for pancreatic cancer of 99.8% its elevation is also reported in benign diseases. The pancreatic ductal adenocarcinoma is typically aggressive and therefore shorter follow-up are expected to be found before diagnosis.

Case presentation. A 75-years-old female referred to us for evaluation of high level of serum CA 19-9 (558 UI/ml) observed for the first time one year before when she had also been undergone colonoscopy that have excluded neoplasms. At the admission she complained fatigue, weight loss, hyporexia, nausea, low-grade fever and intermittent self-limiting skin lesions of the lower limbs. Serum CA 19-9 level was > 1000 UI/ml. Her past medical history was significant for chronic HCV hepatitis, essential hypertension and hysterectomy for leiomyofibroma of the uterus thirty years before.

We did not found any neoplasm and scheduled a close follow-up with colonoscopy, CT and PET for one additional year. At the end of December 2015 we observed the appearance of small painful nodules in the subcutaneous periumbilical region and a CT showed a pancreatic tail malignancy and bone metastases. Periumbilical biopsy was performed and the diagnosis of pancreatic ductal adenocarcinoma was proven.

Conclusion. A long time observation of a persistent and progressive CA 19-9 increase should never exclude the malignant origin. The trend, more than the duration of this finding may guide clinical decision.

Abbreviations
Carbohydrate Antigen 19-9 – CA 19-9
Computerized Tomography – CT
F-18-fluorodeoxyglucose positron emission tomography – 18F-FDG PET
Carcinoembryonic Antigen – CEA
Cancer antigen 125 – CA 125

Key words: Case report, CA 19-9, Pancreatic cancer, Tumoral markers, Bone metastases

BACKGROUND

Serum CA 19-9 is a carbohydrate antigen expressed by several epithelial cells and used for the diagnosis and follow-up of gastrointestinal cancers even if high serum level can be also found in several benign conditions¹. Since pancreatic neoplasms are commonly very aggressive and rapidly progressive², CA 19-9 elevation immediately precedes the diagnosis of the tumour.
CASE PRESENTATION

A 75-years-old Caucasian woman referred to us in December 2014 because of fatigue, weight loss, hyporexia, nausea, low-grade fever and intermittent self-limiting skin lesions of the lower limbs together with persistent elevation of serum CA 19-9 level (> 1000 UI/ml) and piastrinopenia (90,000 cells/µl). BMI was 23 kg/m². Her past medical history was significant for chronic HCV hepatitis, essential hypertension and hysterectomy for leiomyofibroma of the uterus thirty years before. She said that one year before she had observed fecal blood and was undergone to colonoscopy that revealed two rectosigmoid polyps with focal high grade dysplasia on histological examination. At that time CA 19-9 was 558 UI/ml. Whole-body computed tomography (CT) did not find any solid lesions but only mild splenomegaly. A bone marrow examination showed no significant alterations. 18-F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) ruled out neoplasms. On physical examination the patient was pallid and very weak. Oedema and purpuric rash of the lower limbs were observed. Blood count showed hemoglobin 8.2 g/dl and platelets 59000/µl. CA 19-9 was confirmed > 1000 UI/ml. Whole-body CT scan did not find any solid lesions but only mild splenomegaly. A bone marrow examination showed no significant alterations. 18-F-fluorodeoxyglucose positron emission tomography (18F-FDG PET) ruled out neoplasms.

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CA 19-9 is the most used marker for the detection of gastrointestinal malignancies. It was originally defined by a monoclonal antibody produced by murine spleen cells immunized with a human colorectal cancer cells. Its name is derived from the monoclonal antibody called 1116-NS-19-9 directed against a carbohydrate epitope expressed on sialylated Lewis a antigen. Therefore the Lewis blood type is pivotal for the synthesis of the marker and only patients expressing Le\(^{a,b^-}\) or Le\(^{a^-b^-}\) genotype may produce CA 19-9. About 5-10% of the population shows Lewis blood type.

**DISCUSSION**

Figure 3. Abdominal CT scan – venous phase (November 2015): a large mass (4 cm) in the pancreatic tail is showed (green arrow).

Figure 4. 18F-FDG PET (November 2015): the pancreatic lesion show hypermetabolic activity (green arrow).
type negative (Le^a/b) and fails to express it even when a tumor is detectable.  
In individuals expressing Lewis blood type, CA 19-9 is synthesized by normal human pancreatic, biliary ductular, gastric, colonic, endometrial and salivary epithelia and secreted into the blood, saliva, gastric and bile juice. CA 19-9 is currently considered the best marker of pancreatic cancer even if biliary, hepatocellular, gastric, colonic and non gastrointestinal cancers may increase the serum level to > 1000 IU/ml. Moreover, several benign diseases such as obstructive jaundice, cholangitis, chronic liver diseases, acute and chronic pancreatitis, diabetes mellitus, interstitial pulmonary disease, endometriosis, hydronefrosis, splenic cysts, colon diverticulitis may associate with moderate CA 19-9 elevation < 200 UI/ml. Pancreatic cancer CA 19-9 specificity is 90% with the cut-off 37 UI/ml and increases at 98% with 100 UI/ml; by using 1000 UI/ml specificity reaches 99.8%. We should also taken into account that in early and small pancreatic cancers (< 3 cm) the sensitivity is very low and only 50% of malignant lesions produces CA 19-9 with some poorly-differentiated pancreatic cancers that may not produce it anytime. For all these reasons, elevated CA 19-9 level alone is not indicated for the diagnosis of pancreatic cancer but as indicator of asymptomatic recurrence, in preoperative evaluation of patient for surgical interventions and in monitoring of response in patients with locally advanced or metastatic disease receiving chemotherapy or radiotherapy. However, a question is so far unsolved: how long should we maintain active surveillance before excluding a malignancy? Some authors reported several cases of patients monitored for 2-6 years without detection of cancer. Such patients showed a mean serum CA 19-9 level of 517 UI/ml and most of them had no significant past history of cancer. On the contrary, pancreatic ductal adenocarcinoma is typically aggressive and rapidly metastasizing with short-term survival ranging between 8-12 months in locally advanced stages and 5-8 months in metastatic disease. Few weeks are commonly required for the diagnosis even when the lesions are located in the pancreatic tail. Accordingly, a long time of CA 19-9 elevation intrinsically excludes a malignant neoplasm. Kim et al. observed 501 asymptomatic subjects with elevated CA 19-9 level for at least 6 months and concluded that CA 19-9 should not be used as a screening tool and that the trend of the tumor marker may be more important than the level itself. In the present case, elevation of CA 19-9 came two years before a pancreatic solid lesion appeared and several comorbidities (chronic hepatitis, diabetes) other than bowel diseases (colon polyps) could have, almost in part, explained the marker elevation. Pancreatic cancer appeared suddenly and with exceptionally aggressive behaviour only two months after the last CT scan.

CONCLUSIONS

We report a two-years follow-up of a 75 years old woman with persistent elevation of CA 19-9 before the diagnosis of pancreatic adenocarcinoma was done. A long time observation of a persistent and progressive CA 19-9 increase should never exclude the malignant origin. The trend, more than the duration of this finding, may guide clinical decision.

References