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Special Issue Ageing and Bone Health

quest-edited by G.C. Isaia

■ Reviews

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Fragility fractures in older persons
with altered thyroid function

The myokine Irisin recapitulates the effect
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■ Original Investigation

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■ Clinical Observations in Geriatrics

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REVIEW

Ageing, muscle and bone

G. Fornelli, G.C. Isaia, P. D'Amelio

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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

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(either low strength and/or low physical performance) ¹. 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 significant¹¹.

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 density¹⁶. 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 mechanism¹⁷. Nerves from the dorsal roots have branches entering the bone cortex in association with microvasculature¹⁸. 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 resorption¹⁹.

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 bones²⁰.

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 vitro²¹. Data suggest that exercise under glucose deprivation may stimulate bone resorption via elevated Interleukin-6 levels²². Interleukin-6 also increases osteoblast differentiation in mice²³ and is required for muscle hypertrophy and recovery from muscle atrophy²⁴, while chronic direct interleukin-6 administration induces muscle atrophy²⁵.

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 TNF α .

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 females²⁶.

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 osteoclastogenesis²⁷; 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 cells²⁸. In humans, interleukin-7 has shown its osteoclastogenic role in psoriatic arthritis²⁹ and in solid tumors bearing patients³⁰; in patients with rheumatoid arthritis it could contribute to the perpetuation of Th1 and TNF- α mediated pro-inflammatory immune responses^{31,32}. In periodontal infections, high levels of serum interleukin-7 associated with peripheral blood B cells have been shown responsible for T-cell-dependent osteoclastogenesis³³. 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 mechanism³⁴.

Moreover muscle cells express RANKL and its decoy receptor osteoprotegerin, key regulators of bone resorption; loading acutely decreases the RANKL/osteoprotegerin mRNA ratio in myotubes²¹.

Recent research explored the role of Irisin³⁵. 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 trans-differentiation 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 action³⁶.

Myokines, produced by muscle in response to exercise, could perform an additional regulation of mechanotransduction in bone.

HORMONES REGULATION

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 ³⁷.

The insulin-like growth factor (IGF) system is also involved in muscle and bone health ³⁸. IGF-I and –II mediate anabolic effects on skeletal muscle and bone cells ³⁹.

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 ^{40 41}: low circulating concentrations of IGFBP-2 are associated with low relative appendicular muscle mass in both sexes.

In a recent population study serum IGFBP-2 levels were the most robust negative predictors of relative appendicular skeletal muscle mass in both sexes ¹¹.

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 his 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 ¹⁷, low levels of vitamin D are also associated with muscle weakness and atrophy of type II muscle fibers ⁴².

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 ⁴³.

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

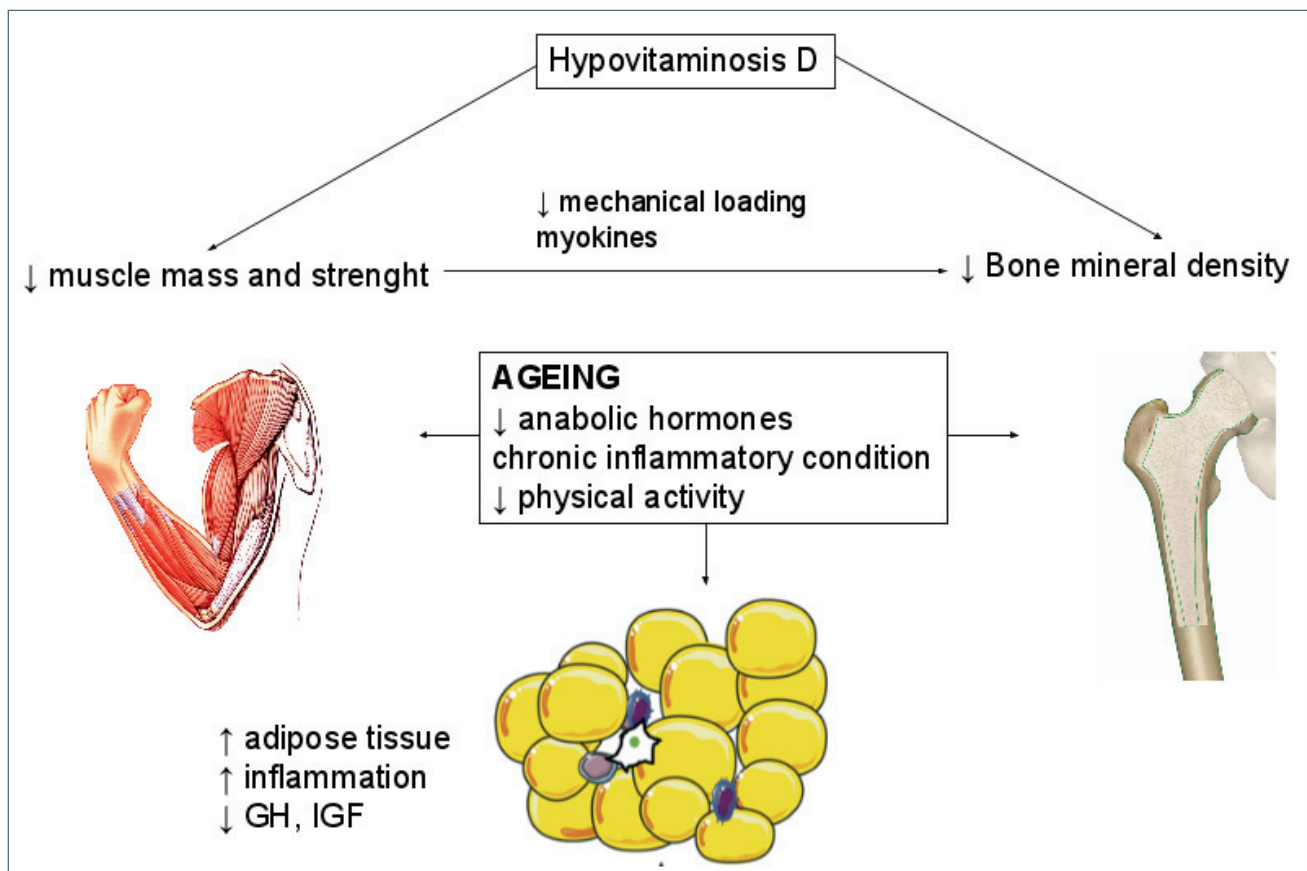


Figure 1. Muscle and bone complex interplay GH growth hormone; IGF insulin-like growth factor.

of sarcopenia⁴⁴. 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 differentiation⁴⁵.

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 expression⁴⁶.

In the In CHIANTI population study lower vitamin D status proved associated with poor physical performance. A representative sample of 976 men and women aged 65 years or older was examined: serum 25OHD levels < 25.0 nmol/L were significantly associated with lower physical performance scores, whereas serum 25OHD levels < 50.0 nmol/L were significantly associated with low handgrip strength⁴⁷.

Moreover elderly men and women with low serum 25OHD in the Longitudinal Study of Aging Amsterdam were significantly more likely to lose handgrip strength and appendicular skeletal muscle mass over 3 years of follow-up⁴⁸.

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 women⁴⁹ and patients attending a falls clinic⁵⁰. Others have also shown that supplemental vitamin D may improve balance and reduce the incidence of falls⁵¹.

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.

References

- Cruz-Jentoft AJ, Baeyens JP, Bauer JM, et al. *Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People*. Age Ageing 2010;39:412-23.
- Fielding RA, Vellas B, Evans WJ, et al. *Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia*. J Am Med Dir Assoc 2011;12:249-56.
- Janssen I, Heymsfield SB, Wang ZM, et al. *Skeletal muscle mass and distribution in 468 men and women aged 18-88 yr*. J Appl Physiol (1985) 2000;89:81-8.
- Cruz-Jentoft AJ, Landi F, Schneider SM, et al. *Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS)*. Age Ageing 2014;43:748-59.
- Gielen E, O'Neill TW, Pye SR, et al. *Endocrine determinants of incident sarcopenia in middle-aged and elderly European men*. J Cachexia Sarcopenia Muscle 2015;6:242-52.
- Cawthon PM, Blackwell TL, Cauley J, et al. *Evaluation of the usefulness of Consensus definitions of sarcopenia in older men: results from the observational osteoporotic fractures in men cohort study*. J Am Geriatr Soc 2015;63:2247-59.
- Delmonico MJ, Harris TB, Visser M, et al. *Longitudinal study of muscle strength, quality, and adipose tissue infiltration*. Am J Clin Nutr 2009;90:1579-85.
- Miikkola TM, Sipilä S, Rantanen T, et al. *Muscle cross-sectional area and structural bone strength share genetic and environmental effects in older women*. J Bone Miner Res 2009;24:338-45.
- Sirota J, Kroger H. *Similarities in acquired factors related to postmenopausal osteoporosis and sarcopenia*. J Osteoporos 2011;2011:536735.
- Proctor DN, Melton LJ, Khosla S, et al. *Relative influence of physical activity, muscle mass and strength on bone density*. Osteoporos Int 2000;11:944-52.
- Lebrasseur NK, Achenbach SJ, Melton LJ, et al. *Skeletal muscle mass is associated with bone geometry and microstructure and serum insulin-like growth factor binding protein-2 levels in adult women and men*. J Bone Miner Res 2012;27:2159-69.
- Edwards MH, Gregson CL, Patel HP, et al. *Muscle size, strength, and physical performance and their associations with bone structure in the Hertfordshire Cohort Study*. J Bone Miner Res 2013;28:2295-304.
- Burra S, Nicoletta DP, Francis WL, et al. *Dendritic processes of osteocytes are mechanotransducers that induce the opening of hemichannels*. Proc Natl Acad Sci U S A, 2010;107:13648-53.
- Robling AG, Turner CH. *Mechanical signaling for bone modeling and remodeling*. Crit Rev Eukaryot Gene Expr 2009;19:319-38.
- Blain H, Jaussent A, Thomas E, et al. *Appendicular skeletal muscle mass is the strongest independent factor associated with femoral neck bone mineral density in adult and older men*. Exp Gerontol 2010;45:679-84.
- Kim S, Won CW, Kim BS, et al. *The association between the low muscle mass and osteoporosis in elderly Korean people*. J Korean Med Sci 2014;29:995-1000.
- Martin CD, Jimenez-Andrade JM, Ghilardi JR, et al. *Organization of a unique net-like meshwork of CGRP+ sensory fibers in the mouse periosteum: implications for the generation and maintenance of bone fracture pain*. Neurosci Lett 2007;427:148-52.
- Hill EL, Elde R. *Distribution of CGRP-, VIP-, D beta H-, SP-, and NPY-immunoreactive nerves in the periosteum of the rat*. Cell Tissue Res 1991;264:469-80.
- Lerner UH. *Neuropeptidergic regulation of bone resorption and bone formation*. J Musculoskelet Neuronal Interact 2002;2:440-7.
- Sample SJ, Behan M, Smith L, et al. *Functional adaptation to loading of a single bone is neuronally regulated and involves multiple bones*. J Bone Miner Res 2008;23:1372-81.
- Juffer P, Jaspers RT, Klein-Nulend J, et al. *Mechanically loaded myotubes affect osteoclast formation*. Calcif Tissue Int 2014;94:319-26.

- 22 Pedersen BK, Febbraio MA. *Muscles, exercise and obesity: skeletal muscle as a secretory organ*. Nat Rev Endocrinol 2012;8:457-65.
- 23 Yang X, Ricciardi BF, Hernandez-Soria A, et al. *Callus mineralization and maturation are delayed during fracture healing in interleukin-6 knockout mice*. Bone 2007;41:928-36.
- 24 Washington TA, White JP, Davis JM, et al. *Skeletal muscle mass recovery from atrophy in IL-6 knockout mice*. Acta Physiol (Oxf) 2011;202:657-69.
- 25 Haddad F, Zaldivar F, Cooper DM, et al. *IL-6-induced skeletal muscle atrophy*. J Appl Physiol (1985) 2005;98:911-7.
- 26 Aguila HL, Mun SH, Kalinowski J, et al. *Osteoblast-specific overexpression of human interleukin-7 rescues the bone mass phenotype of interleukin-7-deficient female mice*. J Bone Miner Res 2012;27:1030-42.
- 27 Sato T, Watanabe K, Masuhara M, et al. *Production of IL-7 is increased in ovariectomized mice, but not RANKL mRNA expression by osteoblasts/stromal cells in bone, and IL-7 enhances generation of osteoclast precursors in vitro*. J Bone Miner Metab 2007;25:19-27.
- 28 Weitzmann MN, Cenci S, Rifas L, et al. *Interleukin-7 stimulates osteoclast formation by up-regulating the T-cell production of soluble osteoclastogenic cytokines*. Blood 2000;96:1873-8.
- 29 Colucci S, Brunetti G, Cantatore FP, et al. *Lymphocytes and synovial fluid fibroblasts support osteoclastogenesis through RANKL, TNFalpha, and IL-7 in an in vitro model derived from human psoriatic arthritis*. J Pathol 2007;212:47-55.
- 30 Roato I, Gorassini E, Brunetti G, et al. *IL-7 modulates osteoclastogenesis in patients affected by solid tumors*. Ann N Y Acad Sci 2007;1117:377-84.
- 31 Hartgring SA, Bijlsma JW, Lafeber FP, et al. *Interleukin-7 induced immunopathology in arthritis*. Ann Rheum Dis 2006;65(Suppl 3):iii69-74.
- 32 Toraldo G, Roggia C, Qian WP, et al. *IL-7 induces bone loss in vivo by induction of receptor activator of nuclear factor kappa B ligand and tumor necrosis factor alpha from T cells*. Proc Natl Acad Sci U S A 2003;100:125-30.
- 33 Colucci S, Mori G, Brunetti G, et al. *Interleukin-7 production by B lymphocytes affects the T cell-dependent osteoclast formation in an in vitro model derived from human periodontitis patients*. Int J Immunopathol Pharmacol 2005;18(Suppl 3):13-9.
- 34 Quinn LS, Anderson BG, Strait-Bodey L, et al. *Oversecretion of interleukin-15 from skeletal muscle reduces adiposity*. Am J Physiol Endocrinol Metab 2009;296:E191-202.
- 35 Bostrom P, Wu J, Jedrychowski MP, et al. *A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis*. Nature 2012;481:463-8.
- 36 Colaianni G, Cuscito C, Mongelli T, et al. *Irisin enhances osteoblast differentiation in vitro*. Int J Endocrinol 2014;2014:902186.
- 37 Khosla S, Melton LJ, Riggs BL. *The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed?* J Bone Miner Res 2011;26:441-51.
- 38 Garnero P, Sornay-Rendu E, Delmas PD. *Low serum IGF-1 and occurrence of osteoporotic fractures in postmenopausal women*. Lancet 2000;355:898-9.
- 39 Yakar S, Rosen CJ, Beamer WG, et al. *Circulating levels of IGF-1 directly regulate bone growth and density*. J Clin Invest 2002;110:771-81.
- 40 Amin S, Riggs BL, Atkinson EJ, et al. *A potentially deleterious role of IGFBP-2 on bone density in aging men and women*. J Bone Miner Res 2004;19:1075-83.
- 41 Amin S, Riggs BL, Melton LJ, et al. *High serum IGFBP-2 is predictive of increased bone turnover in aging men and women*. J Bone Miner Res 2007;22:799-807.
- 42 Pfeifer M, Begerow B, Minne HW. *Vitamin D and muscle function*. Osteoporos Int 2002;13:187-94.
- 43 Capiati D, Benassati S, Boland RL. *1,25(OH)2-vitamin D3 induces translocation of the vitamin D receptor (VDR) to the plasma membrane in skeletal muscle cells*. J Cell Biochem 2002;86:128-35.
- 44 Roth SM, Zmuda JM, Cauley JA, et al. *Vitamin D receptor genotype is associated with fat-free mass and sarcopenia in elderly men*. J Gerontol A Biol Sci Med Sci 2004;59:10-5.
- 45 Garcia LA, King KK, Ferrini MG, et al. *1,25(OH)2vitamin D3 stimulates myogenic differentiation by inhibiting cell proliferation and modulating the expression of promyogenic growth factors and myostatin in C2C12 skeletal muscle cells*. Endocrinology 2011;152:2976-86.
- 46 Domingues-Faria C, Chanet A, Salles J, et al. *Vitamin D deficiency down-regulates Notch pathway contributing to skeletal muscle atrophy in old wistar rats*. Nutr Metab (Lond) 2014;11:47.
- 47 Houston DK, Cesari M, Ferrucci L, et al. *Association between vitamin D status and physical performance: the InCHIANTI study*. J Gerontol A Biol Sci Med Sci 2007;62:440-6.
- 48 Visser M, Deeg DJ, Lips P. *Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the Longitudinal Aging Study Amsterdam*. J Clin Endocrinol Metab 2003;88:5766-72.
- 49 Bischoff HA, Stahelin HB, Dick W, et al. *Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial*. J Bone Miner Res 2003;18:343-51.
- 50 Dhesei JK, Jackson SH, Bearne LM, et al. *Vitamin D supplementation improves neuromuscular function in older people who fall*. Age Ageing 2004;33:589-95.
- 51 Bischoff-Ferrari HA, Orav EJ, Dawson-Hughes B. *Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: a 3-year randomized controlled trial*. Arch Intern Med 2006;166:424-30.

REVIEW

Fragility fractures in older persons with altered thyroid function

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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 Laureate Theodor Kocher defined "cachexia strumipriva" as an illness characterized by decreased growth and height after thyroidectomy¹, the use of burnt sponge and seaweed in the treatment of goiter started as early as 1600 BC in China². The description of "cachexia strumipriva" finally led to the first substitution therapy with thyroid tissue preparations in 1891 by George Murray³; 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 bones⁴, 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's⁵. 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

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the population ⁶. 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 ⁷. One year mortality rates after hip fracture are estimated as 14-36% ^{6,8}. The direct costs of FF in the US were estimated in 19 billion dollars (2005) with an expected 50% increase by 2025 ⁹. 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 3,5,3'-L- triiodothyronine (T3) in specific locations, such as the hip, which is particularly predisposed to osteoporosis in hyperthyroid patients ¹³. 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 I 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 patients²⁵⁻²⁷. 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 patients²⁸. It is noteworthy that in two studies^{29,30} unnecessary therapy with levothyroxine was disclosed in 15.4%²⁹ and 50%³⁰ 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 manifestation 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 warranted²⁴.

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 volume³¹. Osteoclastic resorption is strikingly activated overcoming osteoblastic action with a 50% reduction in the cycle duration and about 10% loss of mineralized bone in each cycle³². Conversely, there is a 17% increase in mineralized bone for each cycle in hypothyroidism. Some studies have shown normalization of BMD after treatment of hyperthyroidism³³⁻³⁶. However, there are other studies reporting only partial recovery of BMD after treatment³⁷⁻⁴¹. 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 osteoporosis⁴². 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 patients⁴⁶. 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 fractures⁴⁷. 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) fractures⁴⁸. 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 balance⁴⁹, and reduced activation of 25-OH-vitamin D⁵⁰. Osteoprotegerin⁵¹, fibroblast growth factor-23⁵², and urinary excretion of bone collagen-derived pyridinium cross-links⁵³ 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^{54,55}. 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^{24,54,55}. 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^{56,57}; hence, patients with low TSH levels should be carefully evaluated (Fig. 1).

A study investigating nursing home residents with low

Table I. Summary of effects of thyroid hormone deficiency or excess on bone turnover, growth, bone mass and fracture risk.

	Hypothyroidism	Hyperthyroidism
Bone turnover	Reduced	Increased
Bone remodeling cycle	Prolonged	Reduced
Young skeleton		
• Growth velocity	Reduced	Increased
• Bone mineralization	Reduced	Increased
• Bone age	Reduced	Increased
• Final height	Reduced, disproportioned	Reduced, proportioned
Adult skeleton		
• Bone mass	Increased	Reduced
• FF risk	Increased (by stiffness)	Increased (by fragility)

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 group⁵⁸. 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 age⁵⁹. There are variable results regarding BMD and subclinical hyperthyroidism, but most suggest an associated low BMD^{56,60}. 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 FT4⁶¹. 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) fractures⁶². 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 mIU/L) and follow up for patients with TSH levels between 0.1 and 0.4 mIU/L^{54,55}. 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^{63,64}. 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

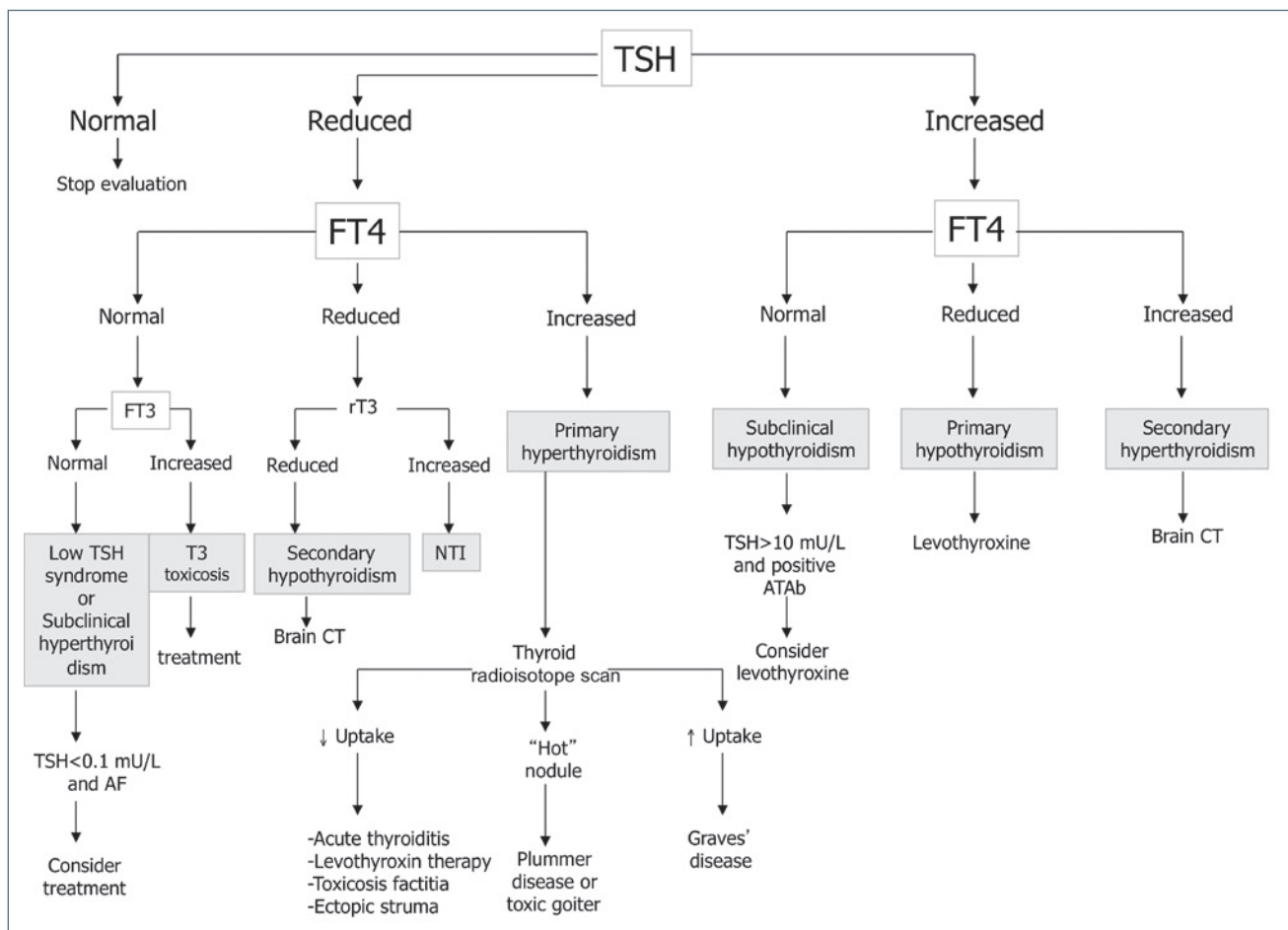


Figure 1. Algorithm for the diagnosis of altered serum TSH concentrations. TSH: thyroid stimulating hormone; FT4: free thyroxine; FT3: free triiodothyronine; rT3: reverse triiodothyronine; AF: atrial fibrillation; NTI: non-thyroidal illness; ATAb: anti-thyroid antibodies.

in postmenopausal and also in premenopausal women with levothyroxine replacement therapy⁶⁴.

Regarding FF risk, the results are not uniform with some^{48,65} but not all⁶⁶ 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/L⁶⁵.

A study involving 1,180 patients on levothyroxine therapy showed that near 60% had a TSH < 0.05 mU/L⁶⁶. 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 TSH⁴⁸.

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^{67,68}. 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^{69,70}. 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,

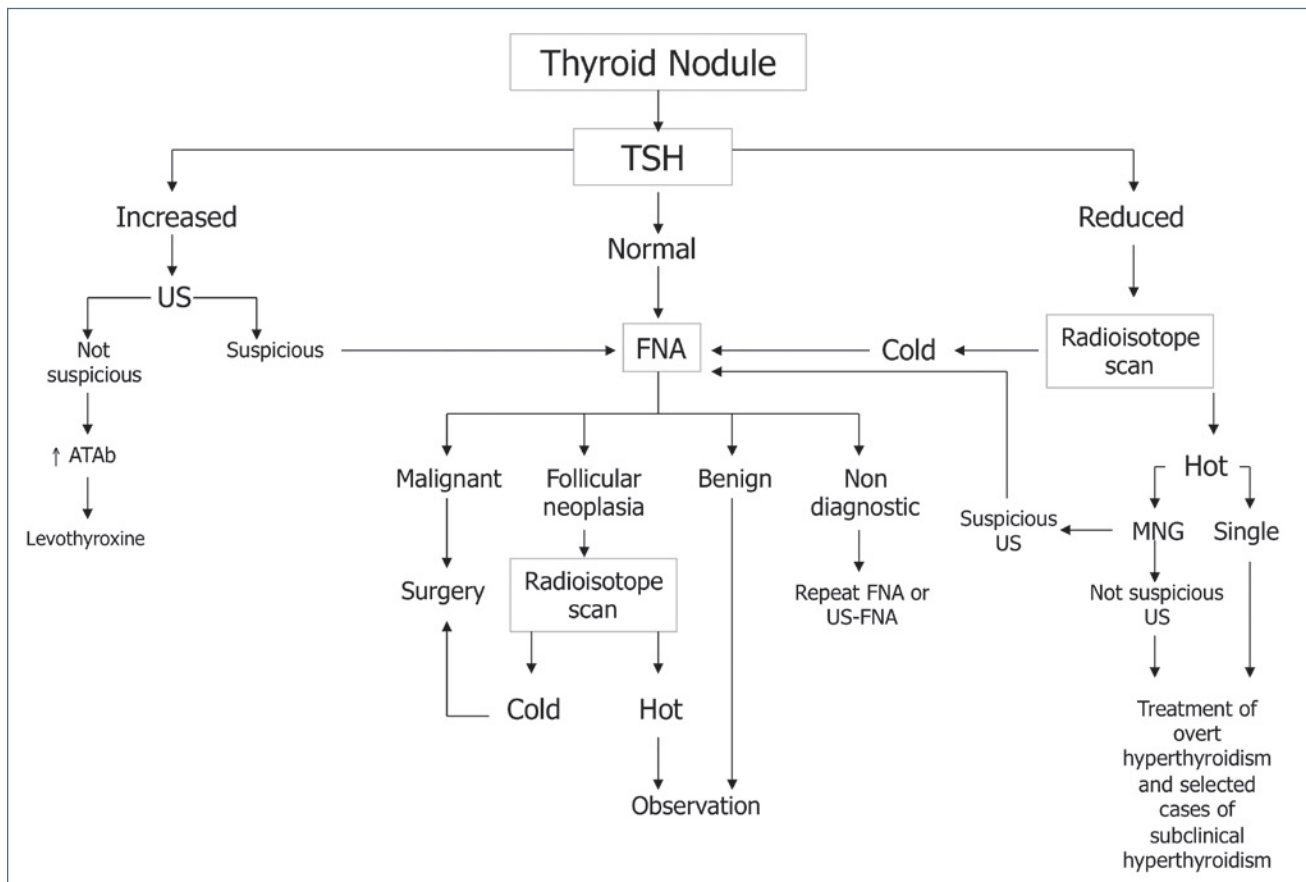


Figure 2. Algorithm for the diagnosis and management of thyroid nodule. FNA: fine-needle aspiration; MNG: multinodular goiter; TSH: thyroid-stimulating hormone; US: ultrasound; ATAb: anti-thyroid anti-bodies.

hoarseness, or cervical lymphadenopathy⁷¹. 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 total⁷². 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 lesions⁷³.

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 option⁷⁴. When a goiter is asymptomatic, follow-up is the choice, while treatment is necessary in case of toxic

goiter or compressive symptoms. $^{131}\text{-I}$ is the first choice treatment for thyroid autonomy and hyperthyroidism, whereas surgery is advised for large non-toxic goiters causing significant compressive symptoms. $^{131}\text{-I}$ 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 $^{131}\text{-I}$ dose. Pretreatment with recombinant TSH (rhTSH) may increase the efficacy of $^{131}\text{-I}$ therapy ⁷⁵. 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 ⁷¹.

Thyroid cancer is mostly (> 90%) differentiated, which includes papillary and follicular cancer ⁷⁶. 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 ⁷⁷. 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 $\geq 20\%$ 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 ⁷⁸. 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)” ⁷⁴. 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 ⁷⁹. 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 ⁸⁰. 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 findings⁷⁴.

After initial thyroidectomy, whether or not radioiodine 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/L⁷⁴.

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 especial 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 institution 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.

References

- 1 Chigot JP. *Theodor Emil Kocher, modern surgery pioneer*. Ann Chir 2000;125:884-92.
- 2 Rosenfeld L. *Discovery and early uses of iodine*. J Chem Educ 2000;77:984-87.
- 3 Welbourn RB. *The emergence of endocrinology*. Gesnerus 1992;49(Pt 2):137-50.
- 4 Kummerfeldt K, Delling G. *Friedrich Daniel von Recklinghausen. Biography and significance of his osteopathologic work after more than 100 years*. Pathologe 1996;17:78-82.

- ⁵ Burch HB, Cooper DS. *Management of graves disease: A review*. JAMA 2015;314:2544-54.
- ⁶ Hernlund E, Svedbom A, Ivergard M, et al. *Osteoporosis in the european union: medical management, epidemiology and economic burden. A report prepared in collaboration with the international osteoporosis foundation (iof) and the european federation of pharmaceutical industry associations (efpia)*. Arch Osteoporos 2013;8:136.
- ⁷ Salkeld G, Cameron ID, Cumming RG, et al. *Quality of life related to fear of falling and hip fracture in older women: a time trade off study*. BMJ 2000;320:341-6.
- ⁸ Dell R, Greene D. *Is osteoporosis disease management cost effective?* Curr Osteoporos Rep 2010;8:49-55.
- ⁹ Burge R, Dawson-Hughes B, Solomon DH, et al. *Incidence and economic burden of osteoporosis-related fractures in the united states, 2005-2025*. J Bone Miner Res 2007;22:465-75.
- ¹⁰ Kanis JA, Borgstrom F, De Laet C, et al. *Assessment of fracture risk*. Osteoporos Int 2005;16:581-9.
- ¹¹ Weiss RE, Refetoff S. *Effect of thyroid hormone on growth. Lessons from the syndrome of resistance to thyroid hormone*. Endocrinol Metab Clin North Am 1996;25:719-30.
- ¹² Bassett JH, Williams GR. *Critical role of the hypothalamic-pituitary-thyroid axis in bone*. Bone 2008;43:418-26.
- ¹³ Wojcicka A, Bassett JH, Williams GR. *Mechanisms of action of thyroid hormones in the skeleton*. Biochim Biophys Acta 2013;1830:3979-86.
- ¹⁴ Abe E, Mariani RC, Yu W, et al. *TSH is a negative regulator of skeletal remodeling*. Cell 2003;115:151-62.
- ¹⁵ Wang HC, Dragoo J, Zhou Q, et al. *An intrinsic thyrotropin-mediated pathway of tnf-alpha production by bone marrow cells*. Blood 2003;101:119-23.
- ¹⁶ Hase H, Ando T, Eldeiry L, et al. *Tnfa mediates the skeletal effects of thyroid-stimulating hormone*. Proc Natl Acad Sci USA 2006;103:12849-54.
- ¹⁷ Bassett JH, Williams GR. *Role of thyroid hormones in skeletal development and bone maintenance*. Endocr Rev 2016;37:135-87.
- ¹⁸ Bianco AC, Kim BW. *Deiodinases: implications of the local control of thyroid hormone action*. J Clin Invest 2006;116:2571-9.
- ¹⁹ Mundy GR, Shapiro JL, Bandelin JG, et al. *Direct stimulation of bone resorption by thyroid hormones*. J Clin Invest 1976;58:529-34.
- ²⁰ Abu EO, Bord S, Horner A, et al. *The expression of thyroid hormone receptors in human bone*. Bone 1997;21:137-42.
- ²¹ Bassett JH, O'Shea PJ, Sriskantharajah S, et al. *Thyroid hormone excess rather than thyrotropin deficiency induces osteoporosis in hyperthyroidism*. Mol Endocrinol 2007;21:1095-107.
- ²² Britto JM, Fenton AJ, Holloway WR, et al. *Osteoblasts mediate thyroid hormone stimulation of osteoclastic bone resorption*. Endocrinology 1994;134:169-76.
- ²³ Lakatos P, Foldes J, Horvath C, et al. *Serum interleukin-6 and bone metabolism in patients with thyroid function disorders*. J Clin Endocrinol Metab 1997;82:78-81.
- ²⁴ Dominguez LJ, Belvedere M, Barbagallo M. *Thyroid disorders. Fifth edition*. In: Sinclair AJ, Morley JE, et al (Eds.). *Pathy's Principles and practice of geriatric medicine*. Oxford, UK: John Wiley & Sons, Ltd. 2012:1183-97.
- ²⁵ Levy EG. *Thyroid disease in the elderly*. Med Clin North Am 1991;75:151-67.
- ²⁶ Mariotti S, Franceschi C, Cossarizza A, et al. *The aging thyroid*. Endocr Rev 1995;16:686-715.
- ²⁷ Mohandas R, Gupta KL. *Managing thyroid dysfunction in the elderly. Answers to seven common questions*. Postgrad Med 2003;113:54-6, 65-8.
- ²⁸ Dominguez LJ, Bevilacqua M, Dibella G, et al. *Diagnosing and managing thyroid disease in the nursing home*. J Am Med Dir Assoc 2008;9:9-17.
- ²⁹ Thong H, Rahimi AR. *Prevalence of hypothyroidism in a southeastern nursing home*. J Am Med Dir Assoc 2000;1:25-8.
- ³⁰ Coll PP, Abourizk NN. *Successful withdrawal of thyroid hormone therapy in nursing home patients*. J Am Board Fam Pract 2000;13:403-7.
- ³¹ Meunier PJ, S-Bianchi GG, Edouard CM, et al. *Bony manifestations of thyrotoxicosis*. Orthop Clin North Am 1972;3:745.
- ³² Eriksen EF. *Normal and pathological remodeling of human trabecular bone: three dimensional reconstruction of the remodeling sequence in normals and in metabolic bone disease*. Endocr Rev 1986;7:379-408.
- ³³ Nielsen HE, Mosekilde L, Charles P. *Bone mineral content in hyperthyroid patients after combined medical and surgical treatment*. Acta Radiol Oncol Radiat Phys Biol 1979;18:122-8.
- ³⁴ Linde J, Friis T. *Osteoporosis in hyperthyroidism estimated by photon absorptiometry*. Acta Endocrinol (Copenh) 1979;91:437-48.
- ³⁵ Langdahl BL, Loft AG, Eriksen EF, et al. *Bone mass, bone turnover, body composition, and calcium homeostasis in former hyperthyroid patients treated by combined medical therapy*. Thyroid 1996;6:169-75.
- ³⁶ Karga H, Papapetrou PD, Korakovouni A, et al. *Bone mineral density in hyperthyroidism*. Clin Endocrinol (Oxf) 2004;61:466-72.
- ³⁷ Krølner B, Jørgensen JV, Nielsen SP. *Spinal bone mineral content in myxoedema and thyrotoxicosis. Effects of thyroid hormone(s) and antithyroid treatment*. Clin Endocrinol (Oxf) 1983;18:439-46.
- ³⁸ Toh SH, Claunch BC, Brown PH. *Effect of hyperthyroidism and its treatment on bone mineral content*. Arch Intern Med 1985;145:883-6.
- ³⁹ Rosen CJ, Adler RA. *Longitudinal changes in lumbar bone density among thyrotoxic patients after attainment of euthyroidism*. J Clin Endocrinol Metab 1992;75:1531-4.
- ⁴⁰ Diamond T, Vine J, Smart R, et al. *Thyrotoxic bone disease in women: a potentially reversible disorder*. Ann Intern Med 1994;120:8-11.
- ⁴¹ Grant DJ, McMurdo ME, Mole PA, et al. *Is previous hyperthyroidism still a risk factor for osteoporosis in post-menopausal women?* Clin Endocrinol (Oxf) 1995;43:339-45.
- ⁴² Svare A, Nilsen TI, Bjørø T, et al. *Hyperthyroid levels of TSH correlate with low bone mineral density: the HUNT 2 study*. Eur J Endocrinol 2009;161:779-86.
- ⁴³ Cummings SR, Nevitt MC, Browner WS, et al. *Risk*

- factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995;332:767-73.
- 44 Wejda B, Hintze G, Katschinski B, et al. *Hip fractures and the thyroid: a case-control study*. *J Intern Med* 1995;237:241-7.
- 45 Abrahamson B, Jørgensen HL, Laulund AS, et al. *Low serum thyrotropin level and duration of suppression as a predictor of major osteoporotic fractures-the OPENTHYRO register cohort*. *J Bone Miner Res* 2014;29:2040-50.
- 46 Franklyn JA, Maisonneuve P, Sheppard MC, et al. *Mortality after the treatment of hyperthyroidism with radioactive iodine*. *N Engl J Med* 1998;338:712-8.
- 47 Vestergaard P, Rejnmark L, Weeke J, et al. *Fracture risk in patients treated for hyperthyroidism*. *Thyroid* 2000;10:341-8.
- 48 Bauer DC, Ettinger B, Nevitt MC, et al. *Risk for fracture in women with low serum levels of thyroid-stimulating hormone*. *Ann Intern Med* 2001;134:561-8.
- 49 Mosekilde L, Eriksen EF, Charles P. *Effects of thyroid hormones on bone and mineral metabolism*. *Endocrinol Metab Clin North Am* 1990;19:35-63.
- 50 Jastrup B, Mosekilde L, Melsen F, et al. *Serum levels of vitamin D metabolites and bone remodelling in hyperthyroidism*. *Metabolism* 1982;31:126-32.
- 51 Amato G, Mazziotti G, Sorvillo F, et al. *High serum osteoprotegerin levels in patients with hyperthyroidism: effect of medical treatment*. *Bone* 2004;35:785-91.
- 52 Park SE, Cho MA, Kim SH, et al. *The adaptation and relationship of FGF-23 to changes in mineral metabolism in Graves' disease*. *Clin Endocrinol (Oxf)* 2007;66:854-8.
- 53 MacLeod JM, McHardy KC, Harvey RD, et al. *The early effects of radioiodine therapy for hyperthyroidism on biochemical indices of bone turnover*. *Clin Endocrinol (Oxf)* 1993;38:49-53.
- 54 Cooper DS, Biondi B. *Subclinical thyroid disease*. *Lancet* 2012;379:1142-54.
- 55 Surks MI, Ortiz E, Daniels GH, et al. *Subclinical thyroid disease: scientific review and guidelines for diagnosis and management*. *Jama* 2004;291:228-38.
- 56 Foldes J, Tarjan G, Szathmari M, et al. *Bone mineral density in patients with endogenous subclinical hyperthyroidism: is this thyroid status a risk factor for osteoporosis?* *Clin Endocrinol (Oxf)* 1993;39:521-7.
- 57 Kumeda Y, Inaba M, Tahara H, et al. *Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism*. *J Clin Endocrinol Metab* 2000;85:4157-61.
- 58 Drinka PJ, Amberson J, Voeks SK, et al. *Low TSH levels in nursing home residents not taking thyroid hormone*. *J Am Geriatr Soc* 1966;44:573-7.
- 59 Haentjens P, Van Meerhaeghe A, Poppe K, et al. *Subclinical thyroid dysfunction and mortality: an estimate of relative and absolute excess all-cause mortality based on time-to-event data from cohort studies*. *Eur J Endocrinol* 2008;159:329-41.
- 60 Földes J, Tarján G, Szathmari M, et al. *Bone mineral density in patients with endogenous subclinical hyperthyroidism: is this thyroid status a risk factor for osteoporosis?* *Clin Endocrinol (Oxf)* 1993;39:521-7.
- 60 Kumeda Y, Inaba M, Tahara H, et al. *Persistent increase in bone turnover in Graves' patients with subclinical hyperthyroidism*. *J Clin Endocrinol Metab* 2000;85:4157-61.
- 61 Murphy E, Gluer CC, Reid DM, et al. *Thyroid function within the upper normal range is associated with reduced bone mineral density and an increased risk of nonvertebral fractures in healthy euthyroid postmenopausal women*. *J Clin Endocrinol Metab* 2010;95:3173-81.
- 62 Blum MR, Bauer DC, Collet TH, et al. *Subclinical thyroid dysfunction and fracture risk: a meta-analysis*. *JAMA* 2015;313:2055-65.
- 63 Faber J, Galløe AM. *Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis*. *Eur J Endocrinol* 1994;130:350-6.
- 64 Uzzan B, Campos J, Cucherat M, et al. *Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis*. *J Clin Endocrinol Metab* 1996;81:4278-89.
- 65 Flynn RW, Bonellie SR, Jung RT, et al. *Serum thyroid-stimulating hormone concentration and morbidity from cardiovascular disease and fractures in patients on long-term thyroxine therapy*. *J Clin Endocrinol Metab* 2010;95:186-93.
- 66 Leese GP, Jung RT, Guthrie C, et al. *Morbidity in patients on L-thyroxine: a comparison of those with a normal TSH to those with a suppressed TSH*. *Clin Endocrinol (Oxf)* 1992;37:500-3.
- 67 Tan GH, Gharib H. *Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging*. *Ann Intern Med* 1997;126:226-31.
- 68 Guth S, Theune U, Aberle J, et al. *Very high prevalence of thyroid nodules detected by high frequency (13 MHz) ultrasound examination*. *Eur J Clin Invest* 2009;39:699-706.
- 69 Hegedus L. *Clinical practice. The thyroid nodule*. *N Engl J Med* 2004;351:1764-71.
- 70 American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi. *Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules*. *Endocr Pract* 2006;12:63-102.
- 71 Mehanna HM, Jain A, Morton RP, et al. *Investigating the thyroid nodule*. *BMJ* 2009;338:b733.
- 72 Aghini-Lombardi F, Antonangeli L, Martino E, et al. *The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey*. *J Clin Endocrinol Metab* 1999;84:561-6.
- 73 Castro MR, Gharib H. *Thyroid fine-needle aspiration biopsy: progress, practice, and pitfalls*. *Endocr Pract* 2003;9:128-36.
- 74 Haugen BR, Alexander EK, Bible KC, et al. *2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer*. *Thyroid* 2016;26:1-133.
- 75 Nieuwlaat WA, Huysmans DA, van den Bosch HC, et al. *Pretreatment with a single, low dose of recombinant human thyrotropin allows dose reduction of radioiodine therapy in patients with nodular goiter*. *J Clin Endocrinol Metab* 2003;88:3121-9.
- 76 Sherman SI. *Thyroid carcinoma*. *Lancet* 2003;361:501-11.

- ⁷⁷ Davies L, Welch HG. *Current thyroid cancer trends in the United States*. JAMA Otolaryngol Head Neck Surg 2014;140:317-22.
- ⁷⁸ Durante C, Costante G, Lucisano G, et al. *The natural history of benign thyroid nodules*. JAMA 2015;313:926-35.
- ⁷⁹ Biondi B, Cooper DS. *Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer*. Thyroid 2010;20:135-46.
- ⁸⁰ Burmeister LA, Goumaz MO, Mariash CN, et al. *Levothyroxine dose requirements for thyrotropin suppression in the treatment of differentiated thyroid cancer*. J Clin Endocrinol Metab 1992;75:344-50.

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

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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

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 ¹ and 22 billion dollars per year in the United States ². 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 ³.

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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 ⁶.

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 to brown adipocytes, thus able of promoting thermogenesis and energy expenditure ¹⁰.

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.

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 ¹⁷. 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 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^{17,19}. 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 molecule²⁰, and strongly reduced expression of sclerostin, one of the inhibitors of the bone anabolic Wnt pathway²¹.

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*¹⁷. 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 treatment²².

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 action¹⁷. 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-1 α (PGC-1 α), 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 consumption²³.

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, respectively²⁴. Excitingly, Irisin and myostatin are both produced by skeletal muscle and their synthesis is inversely regulated by physical exercise²⁵. Moreover, myostatin knock-out mice highly express

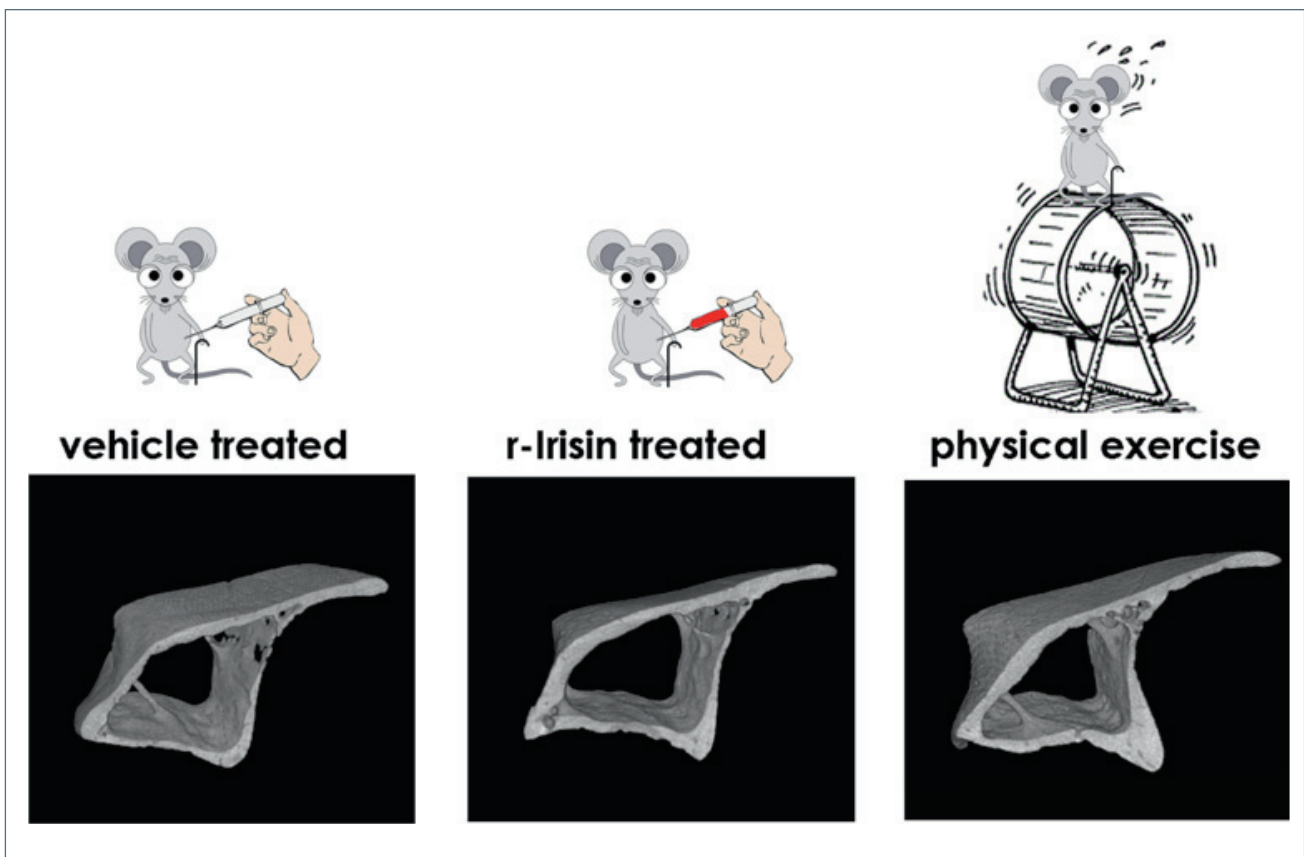


Figure 1. Representative micro-CT-generated section images of tibia harvested from 12-month-old mice treated with vehicle or r-Irisin (100 μ g/Kg/weekly) or subjected to physical activity for 4 weeks.

Irisin and its precursor ²⁶, thus supporting the idea that the increase of muscle mass observed in these mice could be also induced by Irisin.

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 patient that cannot perform physical activity, such as elderly people or bedridden patients (Fig. 1).

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References

- Kanis JA, McCloskey EV, Johansson H, et al. *Euro-pean guidance for the diagnosis and management of osteoporosis in postmenopausal women*. *Osteoporos Int* 2013;24:23-57.
- Blume SW, Curtis JR. *Medical costs of osteoporosis in the elderly Medicare population*. *Osteoporos Int* 2011;22:1835-44.
- Fielding RA, Vellas B, Evans WJ, et al. *Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia*. *J Am Med Dir Assoc* 2011;12:249-56.
- Kanis JA, McCloskey E, Johansson H, et al. *FRAX(®) with and without bone mineral density*. *Calcif Tissue Int* 2012;90:1-13.
- Edwards MH, Gregson CL, Patel HP, et al. *Muscle size, strength, and physical performance and their associations with bone structure in the Hertfordshire Cohort Study*. *J Bone Miner Res* 2013;28:2295-304.
- Di Monaco M, Castiglioni C, De Toma E, et al. *Presarcopenia and sarcopenia in hip-fracture women: prevalence and association with ability to function in activities of daily living*. *Aging Clin Exp Res* 2015;27:465-72.
- Di Girolamo DJ, Kiel DP, Esser KA. *Bone and skeletal muscle: neighbors with close ties*. *J Bone Miner Res* 2013;28:1509-18.
- Colaianni G, Cuscito C, Mongelli T, et al. *Cellular mechanisms of bone regeneration: role of wnt-1 in bone-muscle interaction during physical activity*. *J Biol Regul Homeost Agents* 2015;29(Suppl 4):39-45.
- Tagliaferri C, Wittrant Y, Davicco MJ, et al. *Muscle and bone, two interconnected tissues*. *Ageing Res Rev* 2015;21:55-70.
- Boström P, Wu J, Jedrychowski MP, et al. *A PGC1- α -dependent myokine that drives brown-fat-like development of white fat and thermogenesis*. *Nature* 2012;481:463-8.
- Dunstan D. *Diabetes: exercise and T2DM-move muscles more often!* *Nat Rev Endocrinol* 2011;7:189-90.
- Egan B, Zierath JR. *Exercise metabolism and the molecular regulation of skeletal muscle adaptation*. *Cell Metab* 2013;17:162-84.
- Dun SL, Lyu RM, Chen YH, et al. *Irisin-immunoreactivity in neural and non-neural cells of the rodent*. *Neuroscience* 2013;240:155-62.
- Hashemi MS, Ghaedi K, Salamian A, et al. *Fndc5 knockdown significantly decreased neural differentiation rate of mouse embryonic stem cells*. *Neuroscience* 2013;231:296-304.
- Moon HS, Dincer F, Mantzoros CS. *Pharmacological concentrations of irisin increase cell proliferation without influencing markers of neurite outgrowth and synaptogenesis in mouse H19-7 hippocampal cell lines*. *Metabolism* 2013;62:1131-6.
- Zhang Y1, Li R, Meng Y, et al. *Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling*. *Diabetes* 2014;63:514-25.
- Colaianni G, Cuscito C, Mongelli T, et al. *The myokine irisin increases cortical bone mass*. *PNAS* 2015;112:12157-62.
- Baxter-Jones AD, Eisenmann JC, Mirwald RL, et al. *The influence of physical activity on lean mass accrual during adolescence: a longitudinal analysis*. *J Appl Physiol* (1985) 2008;105:734-41.
- Colaianni G, Cuscito C, Mongelli T, et al. *Irisin enhances osteoblast differentiation in vitro*. *Int J Endocrinol* 2014;902186.
- Toma CD, Ashkar S, Gray ML, et al. *Signal transduction of mechanical stimuli is dependent on microfilament integrity: identification of osteopontin as a mechanically induced gene in osteoblasts*. *J Bone Miner Res* 1997;12:1626-36.
- Lin C, Jiang X, Dai Z, et al. *Sclerostin mediates bone response to mechanical unloading through antagonizing Wnt/beta-catenin signaling*. *J Bone Miner Res* 2009;24:1651-61.
- Qiao X, Nie Y, Ma Y, et al. *Irisin promotes osteoblast proliferation and differentiation via activating the MAP kinase signaling pathways*. *Sci Rep* 2016;6:21053.
- Vaughan RA, Gannon NP, Mermier CM, et al. *Irisin,*

a unique non-inflammatory myokine in stimulating skeletal muscle metabolism. J Physiol Biochem 2015;71:679-89.

- ²⁴ Huh JY, Dincer F, Mesfum E, et al. *Irisin stimulates muscle growth-related genes and regulates adipocyte differentiation and metabolism in humans.* Int J Obes (Lond) 2014;38:1538-44.
- ²⁵ MacKenzie MG, Hamilton DL, Pepin M, et al. *Inhibition of myostatin signaling through Notch activation following acute resistance exercise.* PLoS One 2013;8:e68743.
- ²⁶ Shan T, Liang X, Bi P, et al. *Myostatin knockout drives browning of white adipose tissue through activating the AMPK-PGC1 α -Fndc5 pathway in muscle.* FASEB J 2013;27:1981-9.

Bone densitometry: current status and future trends

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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 ¹.

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 ². Involutional osteoporosis has been classified into type I or postmenopausal osteoporosis and type II or senile osteoporosis ³. 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 ⁴.

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 ⁵.

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

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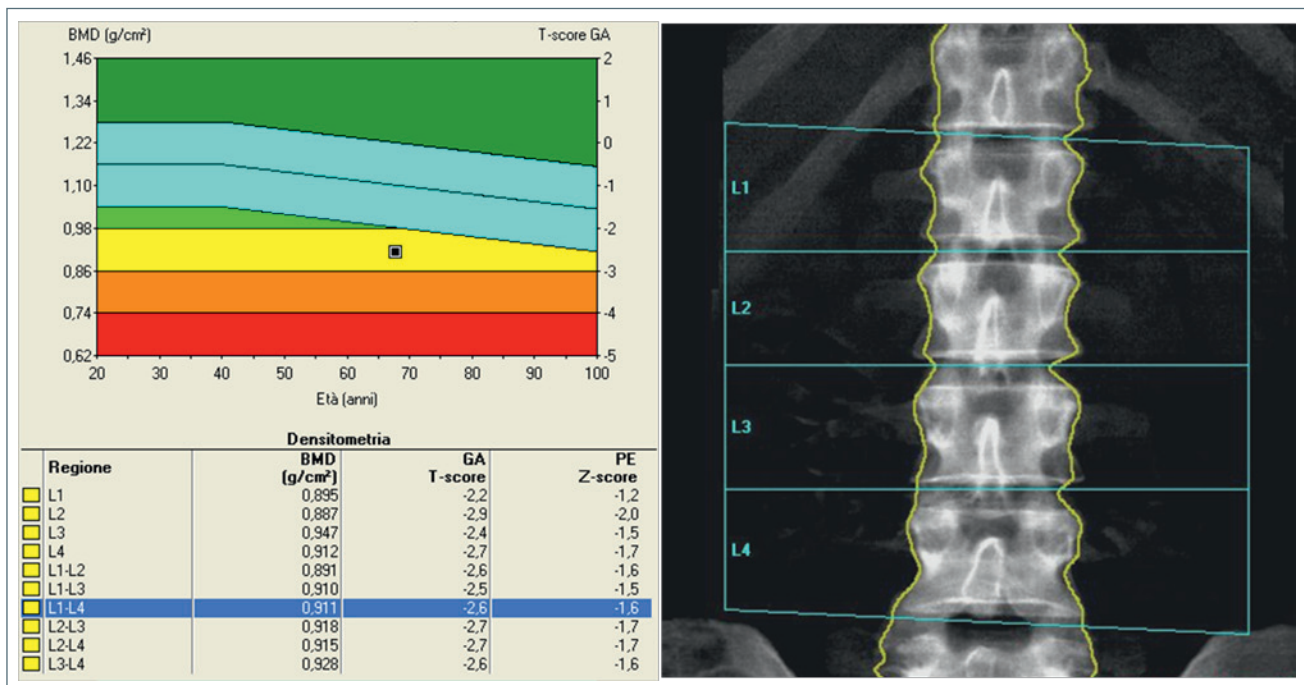


Figure 1. Example of lumbar spine DXA showing BMD values in mg/cm^3 with the corresponding T-score and Z-score.

(DXA), quantitative computed tomography (QCT), and quantitative ultrasound (QUS) have been developed to quantify BMD and to assess bone loss ⁶.

DUAL ENERGY X-RAY ABSORPTIOMETRY (DXA)

It is well known that bone mineral density (BMD) correlates with bone strength and predicts fracture risk ⁷. 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 ⁸. BMD is measured in mg/cm^3 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. ⁷. 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” ¹. 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 ⁹.

Despite short scan times, low radiation dose, good

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/cm^3 . 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.

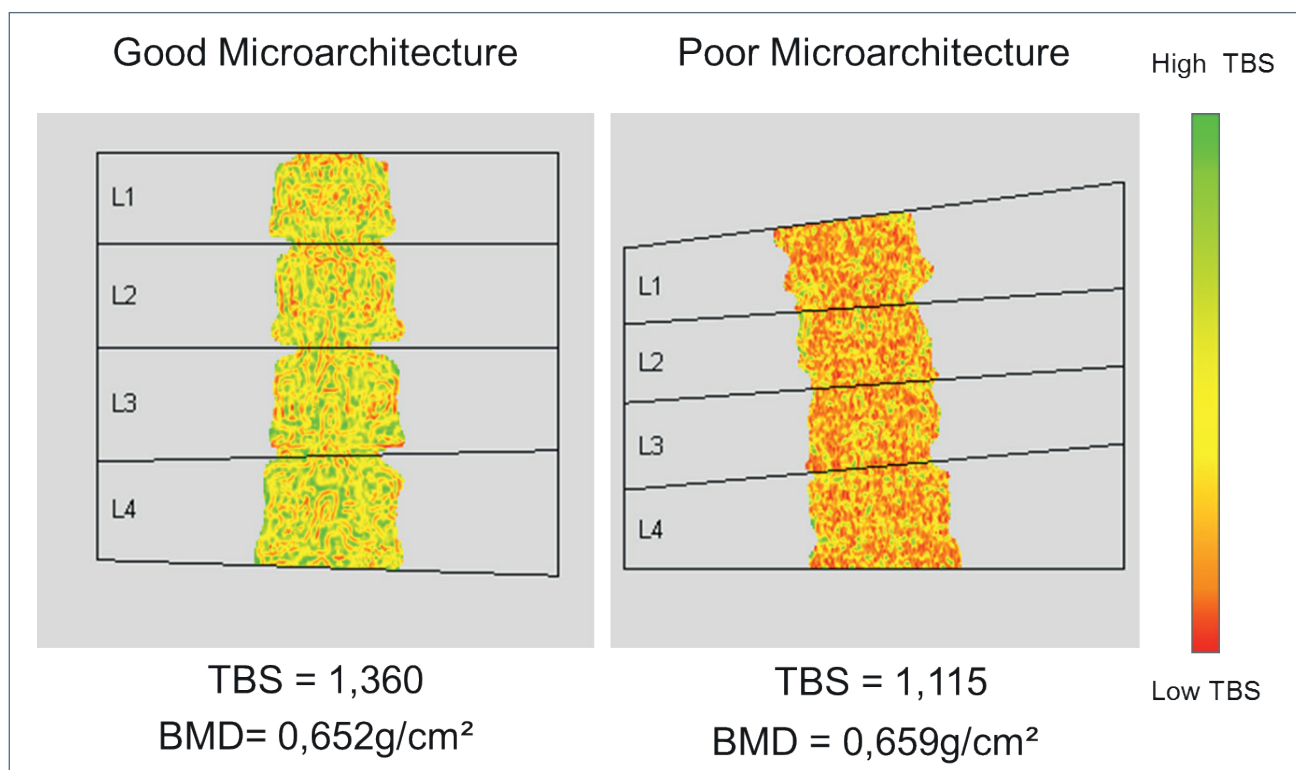


Figure 2. Graphic representation of Trabecular Bone Score (TBS) on DXA images of lumbar spine. These two different patients show equivalent BMD but different TBS values.

Besides these advantages, QCT has some limitations that have narrowed its clinical diffusion: marrow change processes can affect trabecular measurements (myelofibrosis, hematopoietic disorders ecc.), 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 components²⁰.

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^{21 22}.

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 osteoporosis²³.

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 routine²⁴.

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.²⁵ 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 reproducibility²⁶. 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 models²⁷.

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 routine²⁸ (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 data²⁹. Several studies have shown that fractured patients have lower calcaneal ultrasound values than normal subjects and that QUS parameters are predictive of osteoporotic fractures³⁰⁻³². 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 risk³³.

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 architecture³⁴.

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 network³⁵. The most adopted sites of analysis were the calcaneus and the distal radius in order to correlate trabecular content and architecture with bone turnover³⁶.

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^{37 38}.

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^{39 40}.

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 sites⁴¹⁻⁴³. More recently, Water-Fat-Imaging (WFI) sequences have been introduced for marrow fat assessment revealing good performances in water and fat content differentiation⁴⁴. 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 architecture⁴⁵. 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 trabeculae⁴⁶. 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".

References

- 1 Kanis J; On behalf of the World Health Organization Scientific Group. *Assessment of osteoporosis at the primary health-care level: technical report*. World Health Organization Collaborating Centre for metabolic bone diseases. 2008. University of Sheffield, Sheffield.
- 2 Compston J. *Osteoporosis: social and economic impact*. *Radiol Clin North Am* 2010;48:477-82.
- 3 Anil G, Guglielmi G, Peh WC. *Radiology of osteoporosis*. *Radiol Clin North Am* 2010;48:497-518.
- 4 Kenny A, Taxel P. *Osteoporosis in older men*. *Clin Cornerstone* 2000;2:45-51.
- 5 Blüch D, Nguyen ND, Milch VE, et al. *Mortality risk associated with low-trauma osteoporotic fracture and subsequent fracture in men and women*. *JAMA* 2009;301:513-21.

- 6 Guglielmi G, Diano D, Ponti F, et al. *Metabolic*. In: *Geriatric Imaging*. Berlin: Springer 2013;53-81.
- 7 Blake GM, Fogelman I. *The role of DXA bone density scans in the diagnosis and treatment of osteoporosis*. Postgrad Med J 2007;83:509-17.
- 8 Damilakis J, Guglielmi G. *Quality assurance and dosimetry in bone densitometry*. Radiol Clin North Am 2010;48:629-40.
- 9 Takakuwa M, Iwamoto J, Konishi M, et al. *Risedronate improves proximal femur bone density and geometry in patients with osteoporosis or osteopenia and clinical risk factors of fractures: a practice-based observational study*. J Bone Miner Metab 2011;29:88-95.
- 10 Setiawati R, Di Chio F, Rahardjo P, et al. *Quantitative assessment of abdominal aortic calcifications using lateral lumbar radiograph, dual-energy x-ray absorptiometry, and quantitative computed tomography of the spine*. J Clin Densitom 2016;19:242-9.
- 11 Kazakia GJ, Majumdar S. *New imaging technologies in the diagnosis of osteoporosis*. Rev Endocr Metab Disord 2006;7:67-74.
- 12 Silva BC, Bilezikian JP. *Trabecular bone score: perspectives of an imaging technology coming of age*. Arq Bras Endocrinol Metabol 2014;58:493-503.
- 13 Pothuau L, Carceller P, Hans D. *Correlations between grey-level variations in 2D projection images (TBS) and 3D microarchitecture: applications in the study of human trabecular bone microarchitecture*. Bone 2008;42:775-87.
- 14 Boutroy S, Hans D, Sornay-Rendu E, et al. *Trabecular bone score improves fracture risk prediction in non-osteoporotic women: the OFELY study*. Osteoporos Int 2013;24:77-85.
- 15 Krieg MA, Aubry-Rozier B, Hans D, et al.; Manitoba Bone Density Program. *Effects of anti-resorptive agents on trabecular bone score (TBS) in older women*. Osteoporos Int 2013;24:1073-8.
- 16 Bandirali M, Poloni A, Sconfienza LM, et al. *Short-term precision assessment of trabecular bone score and bone mineral density using dual-energy X-ray absorptiometry with different scan modes: an in vivo study*. Eur Radiol 2015;25:2194-8.
- 17 Bazzocchi A, Ponti F, Diano D, et al. *Trabecular bone score in healthy ageing*. Br J Radiol 2015; 88:20140865.
- 18 Guglielmi G, van Kuijk C, Li J, et al. *Influence of anthropometric parameters and bone size on bone mineral density using volumetric quantitative computed tomography and dual X-ray absorptiometry at the hip*. Acta Radiol 2006;47:574-80.
- 19 Engelke K, Adams JE, Armbrecht G, et al. *Clinical use of quantitative computed tomography and peripheral quantitative computed tomography in the management of osteoporosis in adults: the 2007 ISCD Official Positions*. J Clin Densitom 2008;11:123e162.
- 20 Griffith JF, Genant HK. *New imaging modalities in bone*. Curr Rheumatol Rep 2011;13:241-50.
- 21 Mueller TL, Stauber M, Kohler T, et al. *Noninvasive bone competence analysis by high-resolution pQCT: an in vitro reproducibility study on structural and mechanical properties at the human radius*. Bone 2009;44:364-71.
- 22 Ashe MC, Khan KM, Kontulainen SA, et al. *Accuracy of pQCT for evaluating the aged human radius: an ashing, histomorphometry and failure load investigation*. Osteoporos Int 2006;17:1241-51.
- 23 Bonura F. *Prevention, screening, and management of osteoporosis: an overview of the current strategies*. Postgrad Med 2009;121:5-17.
- 24 McCloskey EV, Spector TD, Eyres KS, et al. *The assessment of vertebral deformity: a method for use in population studies and clinical trials*. Osteoporos Int 1993;3:138-47.
- 25 Genant HK, Wu CY, van Kuijk C, et al. *Vertebral fracture assessment using a semiquantitative technique*. J Bone Miner Res 1993;8:1137-48.
- 26 Guglielmi G, Haslam J, D'Errico F, et al. *Comprehensive vertebral deformity and vertebral fracture assessment in clinical practice: intra- and inter-reader agreement of a clinical workflow tool*. Spine (Phila Pa 1976)2013;15;38:E1676-83.
- 27 Diacinti D, Guglielmi G. *Vertebral morphometry*. Radiol Clin North Am 2010;48:561-75.
- 28 Rea JA, Li J, Blake GM, et al. *Visual assessment of vertebral deformity by X-ray absorptiometry: a highly predictive method to exclude vertebral deformity*. Osteoporos Int 2000;11:660-8.
- 29 Guglielmi G, De Terlizzi F, Nasuto M, et al. *Quantitative ultrasound at the phalanges in a cohort of monozygotic twins of different ages*. Radiol Med 2015;120:277-82.
- 30 Wüster C, Albanese C, De Aloysio D, et al. *Phalangeal osteosonogrammetry study: age-related changes, diagnostic sensitivity, and discrimination power*. J Bone Min Res 2000;15:1603-14.
- 31 Hartl F, Tyndall A, Kraenzlin M, et al. *Discriminatory ability of quantitative ultrasound parameters and bone mineral density in a population-based sample of postmenopausal women with vertebral fractures: result of the Basel Osteoporosis Study*. J Bone Min Res 2002;17:321-30.
- 32 Baroncelli GI, Federico G, Vignolo M, et al. *The phalangeal quantitative ultrasound group. Cross-sectional reference data for phalangeal quantitative ultrasound from early childhood to young adulthood according to gender, age, skeletal growth, and pubertal development*. Bone 2006;39:159-73.
- 33 Guglielmi G, Nasuto M. *Quantitative ultrasound and fracture risk assessment*. In: Guglielmi G (Ed.). *Osteoporosis and bone densitometry measurements, medical radiology, diagnostic imaging*. Berlin-Heidelberg: Springer-Verlag 2003;133-44.
- 34 Link TM. *Osteoporosis Imaging. State of the art and advanced imaging*. Radiology 2012;263:3-17.
- 35 Guglielmi G, Selby K, Blunt BA, et al. *Magnetic resonance imaging of the calcaneus: preliminary assessment of trabecular bone-dependent regional variations in marrow relaxation time compared with dual X-ray absorptiometry*. Acad Radiol 1996;3:336-43.
- 36 Link TM, Majumdar S, Augat P, et al. *In vivo high resolution MRI of the calcaneus: differences in trabecular structure in osteoporotic patients*. J Bone Miner Res 1998;13:1175-82.
- 37 Chen WT, Shih TT, Chen RC, et al. *Vertebral bone marrow perfusion evaluated with dynamic contrast-enhanced*

- MR imaging: significance of aging and sex.* Radiology 2001;220:213-8.
- ³⁸ Montazel JL, Divine M, Lepage E, et al. *Normal spinal bone marrow in adults: dynamic gadolinium-enhanced MR imaging.* Radiology 2003;229:703-9.
- ³⁹ Nasuto M, Pansini V, Cortet B, et al. *Renal failure: a modern semiology for an old disease.* Semin Musculoskelet Radiol 2016;20:1-16.
- ⁴⁰ Parhami F. *Possible role of oxidized lipids in osteoporosis: could hyperlipidemia be a risk factor?* Prostaglandins Leukot Essent Fatty Acids 2003;68:373-8.
- ⁴¹ Schellinger D, Lin CS, Hatipoglu HG, et al. *Potential value of vertebral proton MR spectroscopy in determining bone weakness.* Am J Neuroradiol 2001;22:1620-7.
- ⁴² Kugel H, Jung C, Schulte O, et al. *Age- and sex-specific differences in the ¹H-spectrum of vertebral bone marrow.* J Magn Reson Imaging 2001;13:263-8.
- ⁴³ Griffith JF, Yeung DK, Antonio GE, et al. *Vertebral bone mineral density, marrow perfusion, and fat content in healthy men and men with osteoporosis: dynamic contrast-enhanced MR imaging and MR spectroscopy.* Radiology 2005;236:945-51.
- ⁴⁴ Bley TA, Wieben O, François CJ, et al. *Fat and water magnetic resonance imaging.* J Magn Reson Imaging 2010;31:4-18.
- ⁴⁵ Burghardt AJ, Buie HR, Laib A, et al. *Reproducibility of direct quantitative measures of cortical bone microarchitecture of the distal radius and tibia by HR-pQCT.* Bone 2010;47:519-28.
- ⁴⁶ Jamal S, Cheung AM, West SL, et al. *Bone mineral density by DXA and HR-pQCT can discriminate fracture status in men and women with stages 3 to 5 chronic kidney disease.* Osteoporos Int 2012;23:2805-13.

Hip fracture: preliminary results supporting significant correlations between the psychological wellbeing of patients and their relative caregivers

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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 colleagues¹ 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

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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 ². 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 ^{3,4}. The psychological state of the individual who suffers from a hip fracture is highly relevant when determining how well that person may recover ⁵. 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 ⁶. 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 ⁷.

The caregiving rehabilitation task associated with hip fracture fall, more often than not, to the lot of a member of the family ⁸. 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" ⁹. They fulfil their caring-giving role from 7 to 11 h a day on average, up to 10-15 h when clinical conditions worsen ¹⁰. 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 ¹¹. 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 ^{11,12}. In a recent preliminary study, we also found a correlation between patients' psychological well-being and caregivers' burdens ¹².

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.

<p>Each participant (Patient [P] and Caregiver [C]) was given:</p> <ul style="list-style-type: none"> • Socio-demographic questionnaire [P/C] • Mini Mental State Examination (MMSE) [P] • Activities of Daily Living (ADL) [P] • Instrumental Activities of Daily Living (IADL) [P] • Geriatric Depression Scale (GDS) [P] • Psychological General Well-Being Index (PGWBI) [P/C] • Caregiver Burden Inventory (CBI) [C]
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MINI MENTAL STATE EXAMINATION (MMSE)

The Mini Mental State Examination (MMSE)¹³ 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 institutionalization¹⁴. Furthermore, pre-fracture cognitive impairment is also associated^{4 15} with higher mortality rates. Dementia plays a role in the genesis of hip fractures¹³, as it increases the risk of falling by a factor of 5, and risk of significant injury after a fall by a factor of 2.2¹⁶. Dementia has varying degrees of severity, with greater severity linked to poorer¹⁷. Few effective studies have linked cognitive impairment to patient clinical outcome¹⁸. 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 surgery³⁻⁴.

ACTIVITIES OF DAILY LIVING (ADL)

The Katz Index of Independence in Activities of Daily Living (ADL)¹⁹, 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^{20 21}. Some authors^{22 23} 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 management²⁴. 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 colleagues²⁵ 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 skills²⁶. 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 laundering²⁶ 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)²⁸ 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^{29 30}. 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 disorder³¹. An independent relationship was found to exist between low functional capacity and depression symptoms in the elderly³². 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 depression³³. 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. Depression in elderly hip-fracture cases was found to have affected daily living activity negatively and was

observed more often in females and in those who had lost their spouses³⁴.

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-being³⁵.

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 services³⁶.

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' institutionalization³⁷, and a risk factor for care-recipient mortality³⁸. 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 elderly³⁹. 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 life⁴¹. 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 findings³⁸ 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 negatively¹¹.

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 burden⁴³.

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 burden⁴⁴. 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' Positivity 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 ($p = .03$).

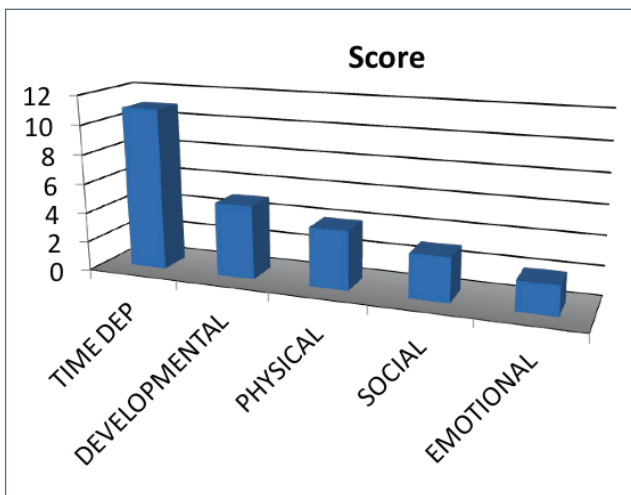


Figure 1. Caregiver's Burden subscales of patient with HF.

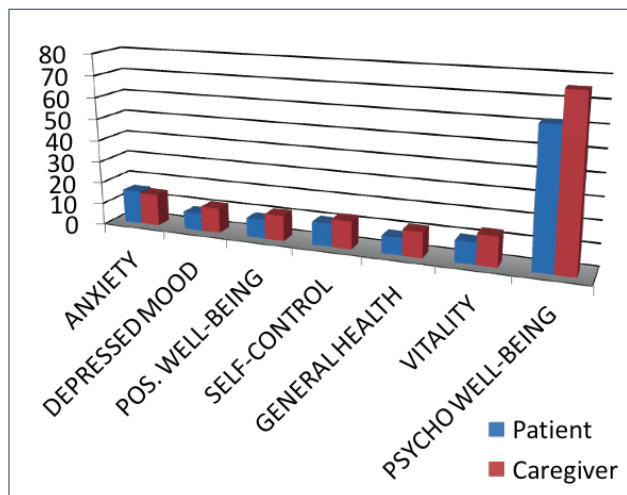


Figure 2. Caregivers' and patients' psychological well-being.

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^{47 48}. Caregiver burden has also been used as an outcome variable rather than as a predictor⁴⁷, 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^{48 49} and have been negatively correlated to the functional status of elderly family members 1 month after discharge following hip-fracture surgery^{45 51}.

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^{49 50}. We can confirm that family caregivers of hip-fractured patients were reported as experiencing moderate burden⁵¹. 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^{45 51}. 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^{45 51}. 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 burden⁴¹.

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 re-value 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).

Areas	Staging			
	1	2	3	4
Patient				
• Activities of daily living	X	X	X	
• Depression	X	X	X	X
• Cognitive status	X			
• Psychological wellbeing	X	X	X	
Caregiver				
• Psychological wellbeing	X	X	X	
• Caregiver burden	X	X	X	

assessment of H-F patients and relative caregivers, while also providing a suggested staging sequence.

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References

¹ Bueckling B, Struwer J, Waldermann A, et al. *What determines health-related quality of life in hip fracture patients at the end of acute care? A prospective observational study.* Osteoporos Int 2014;25:475-84.

² Fenton FR, Cole MG, Engelsmann F, et al. *Depression in older medical inpatients.* Int J Geriatr Psychiatry 1997;12:389-94.

³ Holmes JD, House AO. *Psychiatric illness in hip fracture.* Age Ageing 2000;29:537-46.

⁴ Holmes JD, House AO. *Psychiatric illness predicts poor outcome after surgery for hip fracture: a prospective cohort study.* Psychol Med 2000;30:921-9.

⁵ Fredman L, Hawkes WG, Black S, et al. *Elderly patients with hip fracture with positive affect have better functional recovery over 2 years.* J Am Geriatr Soc 2006;54:1074-81.

⁶ Langer JK, Weisman JS, Rodebaugh TL, et al. *Short term affective recovery from hip fracture prospectively predicts depression and physical functioning.* Health Psychol 2015;34:30-9.

⁷ Galvin KT, Todres L. *Kinds of well-being: a conceptual framework that provides direction for caring.* Int J Qual Stud Health Well-Being 2011;6. doi:10.3402/ qhw.v6i4.10362.

⁸ Falaschi P, Eleuteri E. *Patient’s and caregiver’s psychological evaluation.* In: Falaschi P, Marsh D (Eds.). *Orthogeriatrics.* Berlin: Springer. In press.

⁹ National Alliance for Caregiving (NAC) and American Association of Retired Persons (AARP). *Caregiving in the U.S.* Bethesda, MD: NAC, and Washington, DC: AARP 2009.

¹⁰ Neugaard B, Andresen E, McKune SL, et al. *Health-related quality of life in a national sample of caregivers: findings from the behavioral risk factor surveillance system.* J Happiness Stud 2008;9:559-75.

¹¹ Fianco A, Sartori RD, Negri L, et al. *The relationship between burden and well-being among caregivers of Italian people diagnosed with severe neuromotor and cognitive disorders.* Res Dev Disabil 2015;39:43-54.

¹² Falaschi P, Eleuteri S, Mitroi C, et al. *Hip fracture: relation between patient’s and caregiver’s psychological wellbeing.* In: Abstracts of the 4th Fragility Fracture Network Congress, Rotterdam, Netherlands, 3-5 September 2015:75-6.

¹³ Folstein MF, Folstein SE, McHugh PR. *“Mini-mental state”. A practical method for grading the cognitive state of patients for the clinician.* J Psychiatr Res 1975;12:189-98.

¹⁴ Steiner JF, Kramer AM, Eilertsen TB, et al. *Development and validation of a clinical prediction rule for prolonged nursing home residence after hip fracture.* J Am Geriatr Soc 1997;45:1510-4.

¹⁵ Morrison RS, Siu AL. *Survival in end-stage dementia following acute illness.* JAMA 2000;284:47-52.

¹⁶ Tinetti ME, Speechley M, Ginter SF. *Risk factors for falls among elderly persons living in the community.* New Engl J Med 1988;319:1701-7.

¹⁷ Tarazona-Santabalbina FJ, Belenguier-Varea Á, Rovira Daudi E, et al. *Severity of cognitive impairment as a prognostic factor for mortality and functional recovery of geriatric patients with hip fracture.* Geriatr Gerontol Int 2015;15:289-95.

¹⁸ Guo Y, Sun T, Wang X, et al. *Cognitive impairment and 1year outcome in elderly patients with hip fracture.* Med Sci Monit 2014;20:1963-8.

¹⁹ Katz S, Down TD, Cash HR, et al. *Progress in the development of the index of ADL.* Gerontologist 1970;10:20-30.

²⁰ Alarcón T, Bárcena A, González-Montalvo JI, et al. *Factors predictive of outcome on admission to an acute geriatric ward.* Age Ageing 1999;28:429-32.

²¹ Miller EA, Weissert WG. *Predicting elderly people’s risk for nursing home placement, hospitalization, functional impairment, and mortality: a synthesis.* Med Care Res Rev 2000;57:259-97.

²² Kristensen MT. *Factors affecting functional prognosis of patients with hip fracture.* Eur J Phys Rehabil Med 2011;47:257-64.

²³ Krogseth M, Wyller TB, Engedal K, et al. *Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients.* J Psychosom Res 2014;76:68-74.

²⁴ Alarcón T, González-Montalvo JI, Gotor P, et al. *Activities of daily living after hip fracture: profile and rate of recovery during 2 years of follow up.* Osteoporos Int 2011;22:1609-13.

²⁵ Liem IS, Kammerlander C, Suhmb N, et al. *Identifying a standard set of outcome parameters for the evaluation of orthogeriatric co-management for hip fractures.* Int J Care Injured 2013;44:1403-12.

²⁶ Lawton MP, Brody EM. *Assessment of older people: self-maintaining and instrumental activities of daily living.* Gerontologist 1969;9:179-86.

- ²⁷ Graf C. *Functional decline in hospitalized older adults*. Am J Nurs 2006;106:58-67.
- ²⁸ Yesavage JA, Brink TL, Rose TL, et al. *Development and validation of a geriatric depression screening scale: a preliminary report*. J Psychiatr Res 1982;17:37-49.
- ²⁹ Bottle A, Aylin P. *Mortality associated with delay in operation after hip fracture: observational study*. Br Med J 2006;332:947-1.
- ³⁰ Young Y, Xiong K, Pruzek RM. *Longitudinal functional recovery after postacute rehabilitation in older hip fracture patients: the role of cognitive impairment and implications for long-term care*. J Am Med Dir Assoc 2011;12:431-8.
- ³¹ Nightingale S, Holmes J, Mason J, et al. *Psychiatric illness and mortality after hip fracture*. Lancet 2001;357:1264-5.
- ³² Bostrom G, Condradsson M, Rosendahl E, et al. *Functional capacity and dependency in transfer and dressing are associated with depressive symptoms in older people*. Clin Interv Aging 2014;9:249-57.
- ³³ Djernes JK. *Prevalence and predictors of depression in populations of elderly: a review*. Acta Psychiatr Scand 2006;113:372-87.
- ³⁴ Atay İM, Aslan A, Burç H, et al. *Is depression associated with functional recovery after hip fracture in the elderly?* J Orthopaedics 2016;13:115-8.
- ³⁵ Chassany O, Dimenäs E, Zeneca A, Dubois D, Wu A, Dupuy H. *The Psychological General Well-Being Index (PG-WBI) user manual*. Lyone, France: MAPI Research Institute 2004.
- ³⁶ Testa MA, Simonson DC. *Assessment of quality-of-life outcomes*. N Engl J Med 1996;334:835-40.
- ³⁷ Deimling GT, Poulshock SW. *The transition from family in-home care to institutional care focus on health and attitudinal issues as predisposing factors*. Res Aging 1985;7:563-76.
- ³⁸ Liu, HY, Yang CT, Cheng HS, et al. *Family caregivers' mental health is associated with postoperative recovery of elderly patients with hip fracture: a sample in Taiwan*. J Psychosom Res 2015;78:452-8.
- ³⁹ Carretero S, Garcés J, Ródenas F, et al. *The informal caregiver's burden of dependent people: theory and empirical review*. Arch Gerontol Geriatr 2009;49:74-9.
- ⁴⁰ Keyes CLM, Shmotkin D, Ryff D. *Optimizing well-being: the empirical encounter of two traditions*. J Pers Soc Psychol 2002;82:1007-22.
- ⁴¹ Keyes CLM. *The mental health continuum: from languishing to flourishing in life*. J Health Soc Behav 2002;43:207-22.
- ⁴² Novak M, Guest C. *Application of a multidimensional caregiver burden inventory*. Gerontologist 1989;29:798-803.
- ⁴³ Jonsson AC, Lindgren I, Hallstrom B, et al. *Determinants of quality of life in stroke survivors and their informal caregivers*. Stroke 2005;36:803-8.
- ⁴⁴ Rodgers H, Atkinson C, Bond S, et al. *Randomized controlled trial of a comprehensive stroke education program for patients and caregivers*. Stroke 1999;30:2585-91.
- ⁴⁵ Lin PC, Lu CM. *Psychosocial factors affecting hip fracture elder's burden of care in Taiwan*. Orthop Nurs 2007;26:155-61.
- ⁴⁶ Pearlin LI, Mullan JT, Semple SJ, et al. *Caregiving and the stress process: an overview of concepts and their measures*. Gerontologist 1990;30:583-94.
- ⁴⁷ McCullagh E, Brigstocke G, Donaldson N, et al. *Determinants of caregiving burden and quality of life in caregivers of stroke patients*. Stroke 2005;36:2181-6.
- ⁴⁸ Morimoto T, Schreiner AS, Asano H. *Caregiver burden and healthrelated quality of life among Japanese stroke caregivers*. Age Ageing 2003;32:218-23.
- ⁴⁹ Nahm ES, Resnick B, Orwig D, et al. *Exploration informal caregiving following hip fracture*. Geriatr Nurs 2010;31:254-62.
- ⁵⁰ Shyu YIL, Chen MC, Liang J, et al. *Trends in health outcomes for family caregivers of hip-fractured elders during the first 12 months after discharge*. J Adv Nurs 2012;68:658-66.
- ⁵¹ Lin PC, Lu CM. *Hip fracture: family caregivers' burden and related factors for older people in Taiwan*. J Clin Nurs 2005;14:719-26.

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 conditions ¹. Since pancreatic neoplasms are commonly very aggressive and rapidly progressive ², CA 19-9 elevation immediately precedes the diagnosis of the tumour.

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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/uL). 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/uL and CA 19-9 was confirmed > 1000 UI/ml. Alphafetoprotein and carcinoembryonic antigen (CEA) were normal. Cancer antigen 125 (CA 125) was 145 UI/L (ULN < 35). Creatinine 109,1 umol/L (GFR 45 ml/min) and urea nitrogen 31,4 mmol/L. ESR was 35 mm/h. Liver function tests, prothrombin time and bilirubin were normal. Autoantibodies (ANA, AMA, ASMA, anti-LKM, c-ANCA, p-ANCA and anti-dsDNA) were negative. Serum C4 levels were markedly reduced (< 1.67 mg/dl) whereas C3 levels was normal. A cryoglobulinemia was suspected and a 5% cryocrit was demonstrated in the serum consistent with HCV-related mixed cryoglobulinemia.

Thyroid ultrasound, echocardiogram, pancolonoscopy were normal and whole body CT scan revealed liver cirrhosis and moderate splenomegaly associated with portal hypertension and sigmoid diverticula. No nodular lesions were found.

Prednisone 50 mg/daily was started with rapid improvement of clinical conditions and resolution of purpura.

Prednisone was tapered to 5 mg/daily and sofosbuvir plus ribavirin were introduced for HCV treatment with complete virological response obtained in 4 weeks.

A strict surveillance with blood tests and abdominal ultrasound was scheduled monthly and a CT scan was planned six month later. CA 19-9 levels remained persistently elevated > 1000 UI/ml but general conditions improved and no malignancies were found until September 2015 (Fig. 1) when an episode of abdominal periumbelical pain and hyporexia were reported.

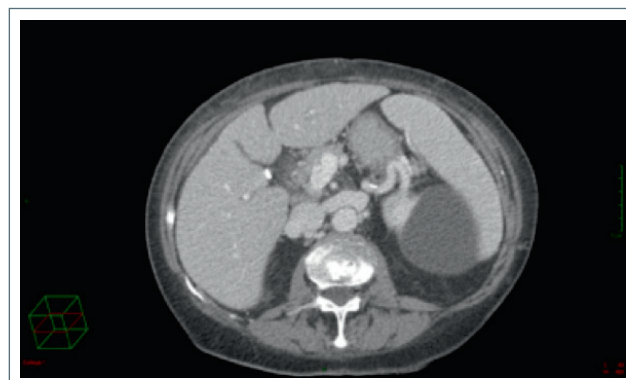


Figure 1. Abdominal CT scan – venous phase (first admission): no pancreatic lesions were observed.

In November 2015 small painful nodules in the subcutaneous periumbilical region were noted at the clinical examination. Serum CA 19-9 levels were $> 10,000$ UI/ml.

Abdominal ultrasound revealed multiple subcutaneous solid hypoechoic nodules with a poorly defined and irregular borders, irregular shape (Fig. 2).

Abdominal CT revealed a large lesion (4 cm) in the pancreatic tail consistent with pancreatic malignancy not observed in the previous scan (Fig. 3). Multiple nodules in the liver, subcutaneous layer of abdominal wall and rib metastases were also detected. 18F-FDG PET (Fig. 4) showed hypermetabolic activity of all lesions.

Periumbilical biopsy was performed and the diagnosis of metastatic pancreatic ductal adenocarcinoma was proven. The patient died two months later.

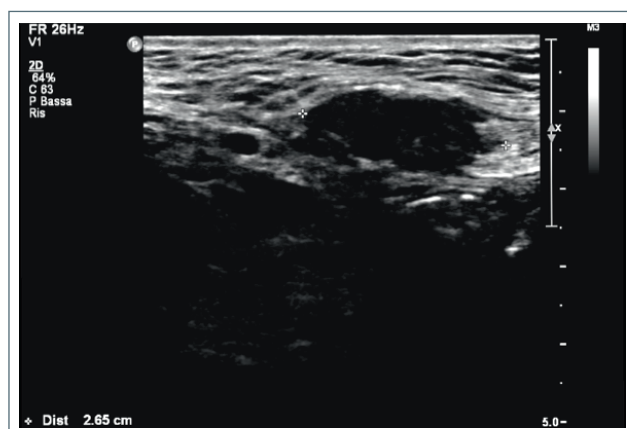


Figure 2. Abdominal ultrasound (November 2015): multiple subcutaneous solid hypoechoic nodules with a poorly defined and irregular borders and irregular shape were found out in abdominal wall (Linear probe – Philips IU22).

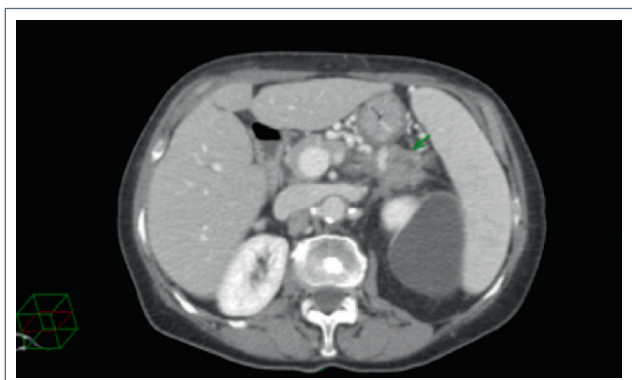


Figure 3. Abdominal CT scan – venous phase (November 2015): a large mass (4 cm) in the pancreatic tail is showed (green arrow).

DISCUSSION

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^{3,4}.

Its name is derived from the monoclonal antibody called 1116-NS-19-9 directed against a carbohydrate epitope expressed on sialylated Lewis a antigen⁵. 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

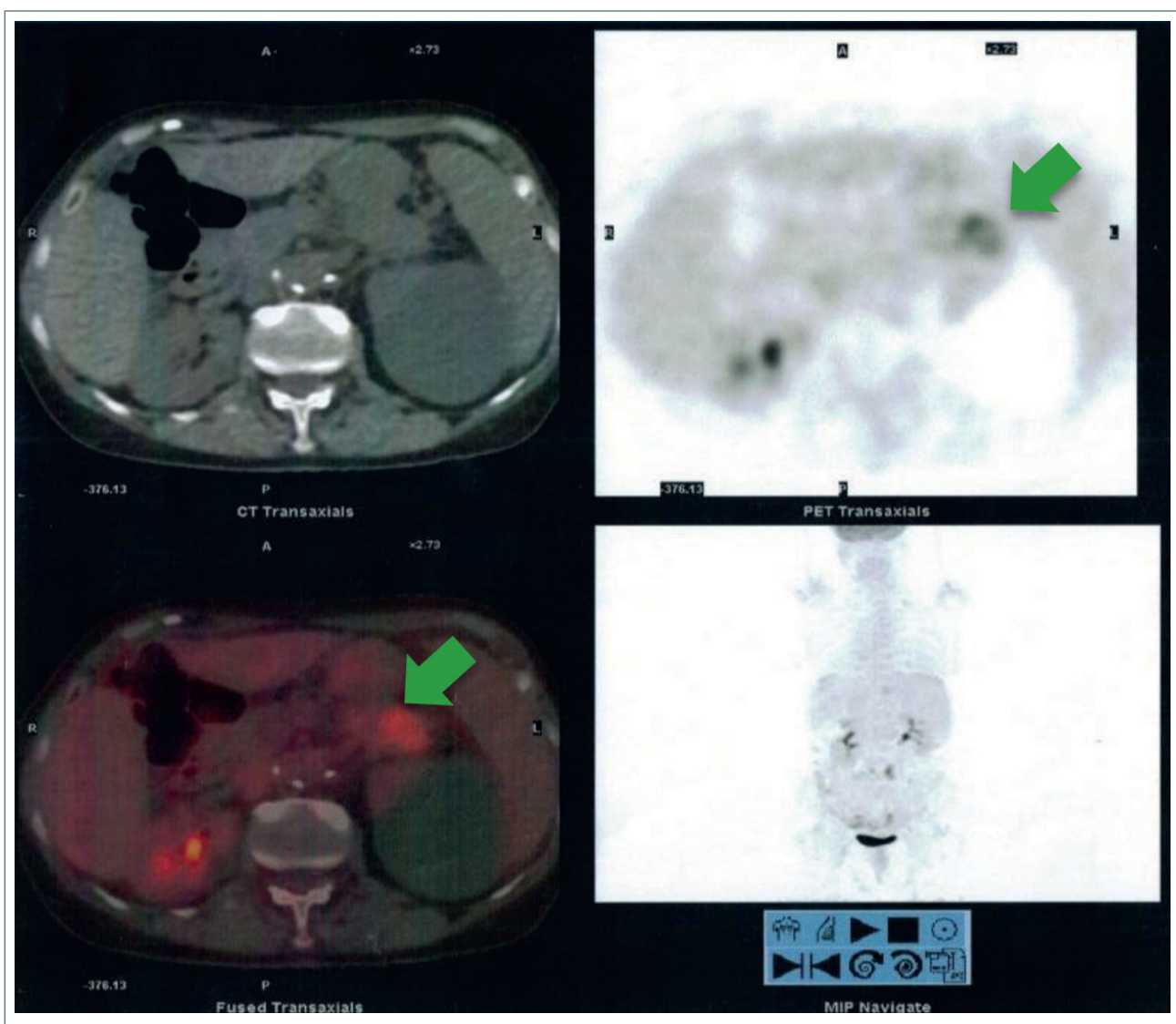


Figure 4. 18F-FDG PET (November 2015): the pancreatic lesion show hypermetabolic activity (green arrow).

type negative (Le^{a-b}) and fails to express it even when a tumor is detectable^{2-4,6}.

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^{1,7,8}. CA 19-9 is currently considered the best marker of pancreatic cancer^{7,8} even if biliary, hepatocellular, gastric, colonic and non gastrointestinal cancers may increase the serum level to > 1000 IU/ml⁷. Moreover, several benign diseases such as obstructive jaundice, cholangitis, chronic liver diseases, acute and chronic pancreatitis, diabetes mellitus, interstitial pulmonary disease, endometriosis, hydronephrosis, splenic cysts, colon diverticulitis^{1,9} may associate with moderate CA 19-9 elevation < 200 IU/ml³.

Pancreatic cancer CA 19-9 specificity is 90% with the cut-off 37 IU/ml and increases at 98% with 100 IU/ml; by using 1000 IU/mL specificity reaches 99.8%².

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 anytime².

For all these reasons, elevated CA 19-9 level alone is not indicated for the diagnosis of pancreatic cancer but only 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 radiotherapy³.

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 cancer¹. Such patients showed a mean serum CA 19-9 level of 517 U/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^{2,10,11}.

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 itself⁷.

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

- Ventrucci M, Pozzato P, Cipolla A, et al. *Persistent elevation of serum CA 19-9 with no evidence of malignant disease*. Dig Liver Dis 2009;41:357-63.
- Duffy MJ, Sturgeon C, Lamerz R, et al. *Tumor markers in pancreatic cancer: a European Group on Tumor Markers (EGTM) status report*. Ann Oncol 2010;21:441-7.
- Locker GY, Hamilton S, Harris J, et al. *ASCO 2006 update of recommendations for the use of tumor markers in gastrointestinal cancer*. J Clin Oncol 2006;24:5313-27.
- Goonetilleke KS, Siriwardena AK. *Systematic review of carbohydrate antigen (CA 19-9) as a biochemical marker in the diagnosis of pancreatic cancer*. Eur J Surg Oncol 2007;33:266-70.
- Passerini R, Cassatella MC, Boveri S, et al. *The pitfalls of CA19-9: routine testing and comparison of two automated immunoassays in a reference oncology center*. Am J Clin Pathol 2012;138:281-7.
- Osayi SN, Bloomston M, Schmidt CM, et al. *Biomarkers as predictors of recurrence following curative resection for pancreatic ductal adenocarcinoma: a review*. Biomed Res Int 2014;2014:468959.
- Kim BJ, Lee KT, Moon TG, et al. *How do we interpret an elevated carbohydrate antigen 19-9 level in asymptomatic subjects?* Dig Liver Dis 2009;41:364-9.
- Kim JE, Lee KT, Lee JK, et al. *Clinical usefulness of carbohydrate antigen 19-9 as a screening test for pancreatic cancer in an asymptomatic population*. J Gastroenterol Hepatol 2004;19:182-6.
- Kim HJ, Kim MH, Myung SJ, et al. *A new strategy for the application of CA19-9 in the differentiation of pancreaticobiliary cancer: analysis using a receiver operating characteristic curve*. Am J Gastroenterol 1999;94:1941-6.
- Sultana A, Smith CT, Cunningham D, et al. *Meta-analyses of chemotherapy for locally advanced and metastatic pancreatic cancer*. J Clin Oncol 2007;25:2607-15.
- Nieto J, Grossbard ML, Kozuch P. *Metastatic pancreatic cancer 2008: is the glass less empty?* Oncologist 2008;13:562-76.