Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake

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Abstract

Aging affects almost all physiological processes, but changes in body composition and body phenotype are most observable. In this review, we focus on these changes, including loss of bone and muscle and increase in body fat or redistribution of the latter, possibly leading to osteosarcopenic obesity syndrome. We also address low-grade chronic inflammation, prevalent in aging adults and a cause of many disorders including those associated with body composition. Changes in dietary intake and nutritional requirements of older individuals, that all may lead to some disturbances on tissue and organ levels, are discussed as well. Finally, we discuss the hormonal changes in the aging body, considering each of the tissues, bone, muscle and fat as separate endocrine organs, but yet in the continuous interface and communication with each other.

Although there are still many unanswered questions in this field, this review will enable the readers to better understand the aging human body and measures needing to be implemented toward reducing impaired health and disability in older individuals.

Key Words

- ▶ aging
- ▶ body composition
- ▶ nutrition
- ▶ osteosarcopenic obesity

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Introduction

As a result of increased life expectancy, the demographics of aging is rapidly changing. Accordingly, it is predicted that the number of people older than 65 years in the United States will double by 2030, reaching approximately 70 million or about 20% of total population (Ortman *et al.* 2014). This increased number of older individuals might lead to the epidemic of certain diseases typical for elderly, like osteoporosis, type II diabetes, cardiovascular diseases and various cancers (Hughes *et al.* 2001, Kalyani *et al.* 2014, Hita-Contreras *et al.* 2015). Among many physiological changes occurring with aging, the most notable are decrease in cardiac output at rest, maximum breathing capacity, renal filtration rate and nerve conduction velocity (McClaran *et al.* 1995, Glasscock & Winearls 2009,

Strait & Lakatta 2012). Additionally, dehydration caused by decreased nocturnal antidiuretic hormone secretion, as well as the limited access to fluid due to various reasons (Frangeskou *et al.* 2015), may result in multiple health and economic consequences leading to increased utilization of hospital intensive care units and higher readmission rates to short- and long-term care facilities (Frangeskou *et al.* 2015). Furthermore, it is also important to note that low-grade chronic inflammation (LGCI) increases with age and persists in older individuals, even when other illnesses are not present (Ilich *et al.* 2014a). As recently reviewed, both dietary factors and lifestyle influences may contribute to LGCI and subsequent worsening of many chronic diseases, including osteoporosis and obesity.

Figure 1

Changes in bone, muscle and fat tissues with increasing age (indicating some typical events), and accompanying increase in low-grade chronic inflammation.

For example, the typical Western-type diet is characterized by over-consumption of *n*-6 polyunsaturated fatty acids (PUFA) coupled with under-consumption of *n*-3 PUFA resulting in LGCI and, along with the subsequent increased presence of reactive oxygen species, leads to a shift in mesenchymal stem cells (MSC, precursors for both osteoblasts and adipocytes) lineage commitment toward increased adipogenesis and suppressed osteoblastogenesis. In turn, increased adipogenesis propagates obesity and synthesis of pro-inflammatory cytokines which promote osteoporosis and maintain LGCI in a 'vicious cycle' (Ilich *et al.* 2014a).

As aging uniquely influences many physiological functions, the most observable are those regarding body composition changes, including loss of bone, loss of muscle mass and strength, and increased body fat leading to osteosarcopenic obesity syndrome (Ilich *et al.* 2014b, 2016, JafariNasabian *et al.* 2017). These changes in body phenotype will be discussed in this review, addressing also the hormonal influences and cellular mechanisms leading to tissue and whole-organism changes. We will also address the changes in nutrient requirements, as well as the dietary intake of elderly, focusing on the Western-type diet, often causing or propagating some ill outcomes.

Changes in body composition with aging

There is a 5–25% decrease in basal (resting) metabolic rate, leading, most notably, to gain in body weight and body fat, even with the unchanged dietary (energy) intake and exercise habits (St-Onge & Gallagher 2010). For example, for most individuals, body fat starts gradually increasing between 20–25 years of age, until about 65 years (Wilson & Kannel 2002, Hunter *et al.* 2010). Even more important is the redistribution of fat to the abdominal area and visceral organs, as well as its infiltration into muscle and bone. The infiltration of fat into bone marrow is not necessarily related only to aging, but occurs early in life, as well as in anorexia and during starvation (Hunter *et al.* 2010, Lang *et al.* 2010, Bredella *et al.* 2014, Ilich *et al.* 2014b). On the contrary, both muscle and bone tissues decrease with age. Muscle mass peaks at the age of approximately 30 years and then gradually declines. There is about 20–40% decrease in muscle mass by the age of 70 years, leading to sarcopenia (Cohn *et al.* 1980, Kalyani *et al.* 2014). However, it is important to distinguish between sarcopenia and dynapenia, the latter being the loss of muscle strength and not necessarily always proportionally accompanied by muscle mass loss (Clark & Manini 2008).

These declines are more pronounced in women than in men (Cruz-Jentof *et al.* 2010). Changes in bone and the development of osteopenia/osteoporosis with aging are probably most studied. Bone mineral density (BMD), used as a proxy for the assessment of fracture risk, declines with age starting at about 50 years of age. However, equally important is the increase in the bone turnover rate with age, driven by the increased bone resorption, leading to bone loss (Riggs *et al.* 1996). Women may lose up to 20% of bone mass during the 5–7 years following menopause. Afterward, the loss continues at the rate of 0.5–1% per year (unless there is some adverse underlying condition or immobilization; when the rate is higher) (National Osteoporosis Foundation, available at: <https://www.nof.org/prevention/general-facts/what-women-need-to-know/>). Men lose bone mass with age too, but the loss starts later in life and persists at about 0.5–1%/year (National Osteoporosis Foundation, available at: <https://www.nof.org/prevention/general-facts/just-for-men/>). Figure 1 depicts the hypothetical changes in body composition with accompanying increase in LGCI with age. Approximate ages and onset of some typical events are presented as well.

Recently, a triad encompassing the simultaneous deterioration in bone, muscle and adipose tissues has been identified and named *osteosarcopenic obesity syndrome* (Ilich *et al.* 2014b, 2016, JafariNasabian *et al.* 2017). Although the original identification of osteosarcopenic

obesity syndrome was based on the changes in body composition phenotype in older women, it has recently been shown that such phenotype might exist even in young (18–21 years) overweight adults (Stefanaki *et al.* 2016). Within the osteosarcopenic obesity syndrome, there are two other underlining components that have not been fully recognized until recently: *osteopenic/osteoporotic obesity* and *sarcopenic obesity*, of which each one could also exist on its own (Ilich *et al.* 2014b, 2016). All of these conditions may lead to increased risk of fractures and morbidity and declined functionality (Fig. 2).

It is apparent that all three tissues are closely interrelated and that osteopenia/osteoporosis, sarcopenia and increased adiposity with aging need to be evaluated concomitantly. While some attempts are made in that direction, fat tissue is still kept out of the picture in most cases, and not evaluated in the scope of its interaction with the former two, possibly because of the difficulties in measuring the infiltrated fat into bone and muscle, as well as of the lack of consensus regarding the obesity classification. Obesity classifications in the clinical setting are often based on body mass index (BMI), and its inadequacy for the classification of individuals into normal weight, overweight and/or obese category has been addressed previously (Coutinho *et al.* 2011). Therefore, more appropriate assessment of overweight/obesity, especially in older individuals, is to assess the percent body fat using dual-energy X-ray absorptiometry

Figure 2

A path of bone, muscle and fat tissues deterioration leading to osteosarcopenic obesity and its consequences.

or bioelectrical impedance analysis (Shea *et al.* 2012). However, there is still no consensus as to what level of body fat defines obesity in women or men. Recently, some researchers and fitness professionals used body fat of 32% as the cutoff for overweight/obesity in women (Ilich *et al.* 2016, Wanner *et al.* 2016). In other studies, the 35% body fat as a cutoff was used for obesity classification (Ilich *et al.* 2015) and that of 33% and/or 38% showed adverse influence on various skeletal sites (Liu *et al.* 2014). With an increased awareness of body fat causing derangements at many levels, we recommend a lower cutoff for obesity for women, specifically, 32–35% of body fat, than currently proposed by WHO (40%).

Changes in dietary intake and nutrient requirements with aging

It is well established that some elderly individuals consume less food due to various reasons among which the diminished appetite secondary to some chronic diseases and/or poor dentition, changes in taste/smell, swallowing issues and food insecurity may be predominant (Pray *et al.* 2010). Additionally, absorption of many nutrients decreases with age, creating an environment conducive to multiple nutritional deficiencies (Pray *et al.* 2010). Another major issue interfering with nutrient absorption and/or intake in elderly is the use of multiple medications, known as polypharmacy. For example, research on proton pump inhibitors (PPI) and H₂ blockers, the medications that were used in 2013 by over 15 million Americans (Lazarus *et al.* 2016), has shown their interaction with the absorption of vitamin B₁₂, vitamin C, calcium, magnesium and iron (Heidelbaugh 2013). Similarly, based on the recent review, the long-term use of metformin, a drug widely used by millions for pre-diabetes and diabetes treatment, has also been shown to increase the risk of vitamin B₁₂ deficiency (Reilly & Ilich 2016). It is very likely that an elderly person might be taking both PPI and metformin, yet there is no protocol for regular testing of vitamin B₁₂ status in these patients. A clear clinical definition of polypharmacy has yet to be established and may include the use of multiple, duplicate, excessive and/or unnecessary medications (Farrell *et al.* 2013, Maher *et al.* 2014). Complications associated with polypharmacy among the elderly include increased falls, functional decline, trouble in performing daily tasks and increased risk of malnutrition (Maher *et al.* 2014). While the benefit of most prescription drugs outweighs the nutritional risk, there is a lack of research

reporting on the cumulative nutritional impact of multiple drugs in the elderly.

Macronutrients and the aging body Nutritional requirements also change during the aging process. As metabolism slows, energy needs decrease but since absorption becomes less efficient, there is a higher need for nutrient-dense foods, typically referred to those which contain more nutrients (minerals, vitamins, protein, complex carbohydrates) but less energy (kcal) per unit of weight (<https://nihseniorhealth.gov/eatingwellasyougetolder/choosenutrientdensefoods/01.html>; Pray *et al.* 2010). Western-type diets, typically referred to as diets high in red meat, saturated fats, simple sugars, sodium and processed food and low in fruits, vegetables and whole grains (Ilich *et al.* 2014a), are falling short of these needs, and there is still controversy regarding optimal intake of several nutrients, including protein. Although the current recommended dietary allowance (RDA) for protein is 0.8 g/kg body weight/day for adults over the age of 19 years (Institute of Medicine, <http://www.nationalacademies.org/hmd/Reports/2002/Dietary-Reference-Intakes-for-Energy-Carbohydrate-Fiber-Fat-Fatty-Acids-Cholesterol-Protein-and-Amino-Acids.aspx>), several nitrogen balance studies conducted in individuals ranging in age from 56 to 80 years have suggested that higher amounts of protein intake (1.4–1.6 g/kg/day) would be better for older adults (Campbell *et al.* 1994, Churchward-Venne *et al.* 2014). About 10–25% of older adults consume less than 0.8 g/kg/day of protein (RDA), and 5–9% of older adults consume less than the estimated average requirement of protein (the average intake estimated to meet the requirements of half of the healthy individuals in a group – it is usually 20% lower than RDA) (Fulgoni 2008; http://www.nationalacademies.org/hmd/~media/Files/Activity%20Files/Nutrition/DRI-Tables/1_%20EARs.pdf?la=en). Individuals with higher protein intake lose less lean mass with aging (Hannan *et al.* 2000, Houston *et al.* 2008) and have improved muscle protein synthesis. Physical inactivity (common in elderly) combined with inadequate protein intake may further aggravate muscle loss. With inadequate protein intake, bone health might be affected as well; lower BMD was associated with below median intakes of protein in postmenopausal women (Ilich *et al.* 2003, Bonjour 2011).

Other macronutrients intake may change in elderly, along with their requirements. A recent analysis of National Health and Nutrition Examination Survey (NHANES) data

revealed that energy imbalance, lower protein intakes, high level of simple carbohydrates and low omega-3 (n-3) PUFA may contribute to osteosarcopenic obesity syndrome (Kelly *et al.* 2017). This analysis confirmed the paradox regarding energy intake: the latter is reduced with aging in both men and women and across all survey years, yet there is a gain in weight with aging. Reduced energy ultimately results in reduced protein consumption in elderly (Rousset *et al.* 2003). Regarding the carbohydrate intake, simple sugars account for up to 54% of kcal from carbohydrates or up to 30% of total kcal (versus less than 10% of recommendations), across all ages and all survey years, contributing to the unhealthy diet (Ilich *et al.* 2014a, Kelly *et al.* 2017). Omega-3 PUFA, particularly rich in fish, are generally recognized as having protective anti-inflammatory properties that contribute to the prevention of pathological conditions associated with aging (Ubeda *et al.* 2012). Results from the Framingham Osteoporosis Study showed that consuming >3 servings of dark fish (500–1500mg n-3/serving) per week was associated with maintenance of femoral neck BMD (Farina *et al.* 2011). Some research indicates that a diet low in n-3 PUFA and high in n-6 PUFA promotes LGCI leading to dysregulation of mesenchymal stem-cell lineage and resulting in obesity and osteoporosis (Kelly *et al.* 2013). Regrettably, the Western-type diet provides more than 10 times higher levels of n-6 compared to n-3 PUFA, enabling an environment conducive to LGCI, obesity and other adverse chronic conditions. Therefore, the recommendations are geared toward lowering the n-6/n-3 ratio by reducing n-6 and increasing n-3 PUFA consumption, although it might be difficult to maintain the precise ratio between the two (Office of Dietary Supplements website, available at: <http://ods.od.nih.gov/factsheets/Omega3FattyAcidsandHealth-HealthProfessional/#disc>; Kelly *et al.* 2013, Kim *et al.* 2013, Ilich *et al.* 2014a).

Micronutrients and the aging body Micronutrients play a critical role in healthy aging as well. The recent analysis of NHANES data regarding micronutrients intake indicates that several deficiencies and/or excesses throughout decades, typical for Western-type diet, might play a role in the development of many chronic diseases, including osteosarcopenic obesity (Kelly *et al.* 2016). Regarding minerals, the analysis shows that older women consume diets habitually deficient or insufficient in calcium, magnesium and potassium but consume excess of sodium, phosphorus and iron. Regarding vitamins,

there is a lower consumption of fat-soluble vitamins D, E and K (despite adequate fat intake), as well as vitamins C and B₆, which all in combination or on individual level might be impacting the metabolism of other nutrients, and possibly increasing the morbidity (Kelly *et al.* 2016). Therefore, it might be reasonable to start evaluating the ratios of minerals and vitamins consumed with diet and/or supplement, as opposed to focusing on absolute amounts.

It needs to be noted that most of the dietary evaluations described above are based on the reports from NHANES surveys. Although all surveys of dietary intake have their flaws and shortcomings (Archer *et al.* 2013) due to underreporting, poor recalls as well as inaccurate data-bases for nutrient contents in food, the NHANES surveys present the largest collection of dietary intake of nutrients, based on tens of thousands of people, across different ages, genders and over multiple years. Thus, it is reasonable to assume that trends and estimates from NHANES data are close to real values and could be used in evaluating intake of American people.

Regarding the nutrients affecting bone health, calcium and vitamin D have been investigated most intensely, but other nutrients have been recognized as well, as reported earlier (Ilich & Kerstetter 2000). Many studies have shown that increased calcium intake was beneficial for BMD although effects of dietary calcium on BMD, particularly on bone fractures, are still a source of controversy. Several studies supported the role of calcium supplements in reducing the risk of fracture in postmenopausal women (Chapuy *et al.* 1992, Chevalley *et al.* 1994, Recker *et al.* 1996), but there have been notable exceptions or inconclusive findings, some generated from the Women Health Initiative findings (Reid & Bolland 2014). Due to the calcium threshold effect on bones, as elegantly articulated by late Robert Heaney ('.....calcium functions as a threshold nutrient, that is, calcium retention improves as calcium intake rises, up to some threshold intake value, above which no further increase in intake will alter retention') (Heaney 2007), supplementation above the recommended level may not be advantageous, or needed. Another nutrient that received attention regarding bone health has been sodium because of the positive relationship between urinary sodium and urinary calcium. Many studies showed higher urinary calcium excretion with higher urinary sodium (Matkovic *et al.* 1995, Dawson-Hughes *et al.* 1996). This relationship was a base for speculation that excess sodium would lead to higher urinary calcium excretion and subsequent decrease

in BMD and possible detrimental effect on bone health. However, a more recent study showed that higher sodium intake (average ~3,000 mg/day) did not have negative effects on bone as long as adequate calcium and vitamin D was consumed (Ilich *et al.* 2010). On the contrary, it has been shown that salt restricted diets increase the risk of involuntary weight loss among long-term care facilities residents. Therefore, liberalizing the diet to allow salt, was beneficial for preventing unintended weight loss (Niedert 2005).

The studies examining the deficiency or excess of other minerals and vitamins and their impact on various aspects of body composition or functionality in aging are numerous, and such review is out of scope of this paper. More information can be found at the National Institute on Aging website, available at: <https://www.nia.nih.gov/health/publication/healthy-aging-lessons-baltimore-longitudinal-study-aging/introduction>).

Interaction among aging tissues

Previously, it was believed that obesity has a protective role on bone and muscle, by providing mechanical load for both and stimulating their accrual, as well as by being a source of extra-glandular estrogens (Bélanger *et al.* 2002). It is well established that estrogen is beneficial for reducing bone resorption (Kameda *et al.* 1997), signaling muscle repair and regeneration, and reducing adipogenesis (Reid 2008). However, in the recent years, the concerns regarding bone/muscle health and obesity are getting more attention in the scientific community. It is now recognized that adipose tissue is an endocrine organ, releasing hormones (beyond estrogen) and other cytokines (Dodds *et al.* 1994, Wellen & Hotamisligil 2005, Cao 2011, Mantzoros *et al.* 2011, Ilich *et al.* 2014b). Particularly the visceral fat is considered a unique pathogenic fat depot that has a negative impact on bone and muscle (Gilsanz *et al.* 2009, Zhang *et al.* 2015). Visceral fat secretes pro-inflammatory cytokines such as tumor necrosis factor- α (TNF- α), interleukin 1 and 6 (IL-1 and IL-6) and C-reactive protein (in high inflammatory states), all known as strong pro-inflammatory cytokines, promoting and sustaining LGCI beyond the aging processes (Pradhan *et al.* 2001, Liu *et al.* 2012, Ilich *et al.* 2014a). It is increasingly recognized that mechanisms of LGCI cause derangement of all three tissues simultaneously and propagate more fat deposition, maintaining disordered conditions (Ilich *et al.* 2014a, 2014b, Zhang *et al.* 2015).

It is now clear that there is a very fine inflection point indicating the changing effect of body fat on bone.

As shown in a recent study conducted in almost 500 healthy women, body fat higher than 33% was negatively related to femoral neck BMD and that of 38% to lumbar spine and total-body BMD (Liu *et al.* 2014). This is lower than the current cutoff for obesity being set at 40% body fat for women (Dufour *et al.* 2013). As discussed above, different researchers used different levels for obesity classification in women, depending on the studied population and parameters examined (Ilich *et al.* 2015, 2016, Wanner *et al.* 2016). Moreover, Bosch and coworkers identified a cutoff of 38.3% body fat in women as an inflection point where the slope of the relation between visceral fat and percent body fat increases significantly (Bosch *et al.* 2015). In other words, weight gain in older adults leads to greater visceral fat accumulation and possibly long-term bone and muscle impairments as a consequence. This all disputes the notion that obesity is protective for bone health as once thought, especially in aging women (Ilich *et al.* 2014a, 2014b, Shin *et al.* 2014). However, the relationship between obesity and bone is of a complex nature as addressed in recent reviews (Shapses *et al.* 2012, Iwaniec *et al.* 2016), and more research is needed to determine the threshold at which body fat becomes harmful for bones and/or muscle (Liu *et al.* 2014).

Bone marrow adipose tissue (MAT) increases with aging, obesity and in osteoporosis, thereby also interconnecting bone and fat tissues. Some suggest that MAT should be considered a biomarker for osteoporosis risk in older adults (Scheller & Rosen 2014). MAT appears to reduce osteoblast and osteoclast activity, slowing bone turnover (although the decreased bone turnover might be beneficial in situations like menopause), as well as decreasing the rate of bone accrual (Scheller & Rosen 2014). Recent studies show a negative correlation between MAT and BMD (Liu *et al.* 2010, Tang *et al.* 2010, Bredella *et al.* 2014). Still, there is a lack of evidence as to whether the relationship with MAT and osteoporosis is causative or just correlative (Scheller & Rosen 2014), possibly because MAT predominates in long bones that are not particularly prone to low-trauma fractures.

Regarding adiposity and muscle connection, a prospective study by Kim *et al.* (2014) showed that postmenopausal women with higher amount of visceral fat lost significantly more lean mass over a 27-month period than women with lower amount of visceral fat (Kim *et al.* 2014). However, this study was performed in Korean women and might not be applicable for other ethnicities. This decrease in muscle mass did not result in a parallel change in BMI, as fat appeared to replace the lost muscle tissue, possibly infiltrating it (Zhang *et al.* 2015).

Multiple studies support a causal role of pro-inflammatory cytokines such as TNF- α and IL-6 in muscle wasting and their elevated serum concentration in sarcopenia and sarcopenic obesity (Schaap *et al.* 2009, Mavros *et al.* 2014). Additionally, muscle mass is the main determinant of resting metabolic rate (energy expenditure) and loss of muscle would in turn also promote weight gain and fat accumulation. Hence, muscle and bone loss and visceral fat accumulation with aging aggravated by overall excess of adiposity, appear to be part of a cycle where increased inflammation from visceral fat favors sarcopenia and osteopenia, promotes obesity and ultimately, in turn, a greater visceral fat accumulation (Ilich *et al.* 2014a, Bosch *et al.* 2015).

Another consequence of aging recently recognized in older adults (and briefly mentioned above), is *myosteatorsis*, or fat infiltration into muscle. As skeletal muscle ages, muscle fat in the form of intra- and extra-myocellular adipocytes (droplets of triglyceride) is embedded within and between muscle fibers resulting in increased storage of lipid droplets (Lang *et al.* 2010). Myosteatorsis is seen in older women, even if they do not appear clinically obese or overweight, but it could also be seen in obese younger individuals, as shown recently (Stefanaki *et al.* 2016). In the same manner, we propose here a new term, *osteosteatorsis*, indicating increased adipogenesis in bone marrow. Although the term osteosteatorsis has not been officially proposed until now, there is plenty of evidence showing that the MSC in bone marrow (precursors of both adipocytes and osteoblasts) may favor adipogenic differentiation in the presence of excessive adiposity (Pittenger *et al.* 1999, Rosen & Buxsein 2006, Ilich *et al.* 2014b, Kim *et al.* 2014). It is for this reason that osteoporosis might be characterized as '*the obesity of bone*' (Rosen & Buxsein 2006) and sarcopenia as '*obesity of muscle*' (Ilich *et al.* 2014b). Although fat infiltration is also a normal aging process, its elevation in an obesogenic environment exacerbates other processes, like loss of bone or muscle. Therefore, osteosteatorsis and myosteatorsis, combined with age-related loss of bone and muscle mass, contribute even more to loss of bone and muscle strength and overall function (Visser *et al.* 2003, Lang *et al.* 2010, Domiciano *et al.* 2013, Ilich *et al.* 2015).

Loss of functionality and inadequate mobility set an older adult at increased risk for falls and bone fractures. Furthermore, as shown recently, myosteatorsis may lead to the development of disorders such as diabetes that also increases the risk of falls secondary to impaired vision and/or neuropathy (Lang *et al.* 2010) and contributes to

increased risk for fractures (Lang *et al.* 2010, Hamrick *et al.* 2016). This may help explain the increased risk of frailty in older adults, not just in those who suffer from osteosarcopenic obesity, but also in those with each of the underlying conditions, osteopenic obesity and/or sarcopenic obesity (Domiciano *et al.* 2013, Ilich *et al.* 2015), as indicated in Fig. 2. We showed recently that older women suffering from osteopenic obesity, sarcopenic obesity and/or osteosarcopenic obesity (as an ultimate fate of former two) were inferior in several of the functional performance measures, compared to their obese-only counterparts. Even more so, those suffering from osteosarcopenic obesity showed significantly poorer performance in handgrip strength, balance and walking speed, compared to each other group (Ilich *et al.* 2015).

Increasingly, recent research is focusing on the interaction among bone, muscle and fat tissues and connecting some major functional impairments or nutritional deficiencies with osteosarcopenic obesity syndrome (Ilich *et al.* 2015, Kim *et al.* 2016). Chung and coworkers found that older adults with sarcopenic obesity had greater risk of osteoporosis, as the physical decline from the former appeared to promote greater loss of bone (Chung *et al.* 2016). Overall, the physical decline resulting from any of the conditions, e.g. osteopenic obesity or sarcopenic obesity, could potentially aggravate other conditions, feeding a perpetual loop and ultimately leading to osteosarcopenic obesity. Someone with impaired mobility from sarcopenic obesity, for example, may go on to suffer greater bone loss and fractures (Ilich *et al.* 2015, Chung *et al.* 2016). Taken together, overall body composition, corresponding serum biomarkers (indicating impairments in bone, muscle and fat tissues), nutrition and physical performance should all be taken into consideration when evaluating the health of older adults (Ilich *et al.* 2014b, 2015).

Hormonal changes in aging body and their influence on body composition

Besides estrogen (as briefly mentioned above), a number of other key hormones/cytokines are altered with aging, and by that affect body composition and might contribute to the osteosarcopenic obesity syndrome. It is now recognized that bone, muscle and fat are interconnected and act as endocrine organs (Mantzoros *et al.* 2011, Karsenty & Ferron 2012, Pedersen & Febbraio 2012, Ilich *et al.* 2014b), each secreting hormones and molecules that have autocrine, paracrine and endocrine effects – influencing

each other, acting on other tissues and changing with age. Therefore, the next section briefly discusses the three tissues as endocrine organs.

Calcitriol as a mediator for all three tissues Vitamin D, as hormone calcitriol (1, 25-dihydroxyvitamin D), influences bone, muscle and adipose tissue throughout the life cycle, with probably the most important role during growth and in older age. Its status might be compromised in elderly due to several reasons including: lower vitamin D intake, decreased skin production of cholecalciferol (the first precursor of active vitamin D) partly due to lower sun exposure, decreased activity of both liver and renal hydroxylases leading to lower conversion to calcidiol (25-hydroxyvitamin D) and calcitriol in liver and kidney, respectively (Gallagher 2013). The disturbance in vitamin D leads to decreased calcium absorption, partly related to abnormalities in the calcium transport proteins that are regulated by calcitriol. In summary, both calcium and vitamin D absorption are diminished with aging leading to their lower serum concentration (Gallagher 2013). There is a strong relationship between low calcidiol concentrations and increasing levels of obesity (Pereira-Santos *et al.* 2015). It has been shown that even when controlling for sunlight exposure, obese individuals are significantly more likely to have lower calcidiol concentration, indicating inadequate vitamin D status (Cheng *et al.* 2010, Pereira-Santos *et al.* 2015). Moreover, inadequate vitamin D can increase adipogenesis by promoting higher parathyroid hormone (PTH) secretion and greater influx of calcium into adipocytes (Wood 2008). Similarly, low serum calcium could promote increase of circulating calcitriol and PTH, which then stimulate influx of extracellular calcium into adipocytes via a specific-membrane vitamin D receptor, again promoting adipogenesis (Zemel *et al.* 2005).

Regarding bone health, calcitriol is essential for normal bone turnover and maintenance, as well as for metabolism of the minerals calcium, phosphorous and magnesium (Pereira-Santos *et al.* 2015). A decrease in calcitriol could disturb calcium homeostasis and impair bone health. Numerous studies have addressed the role of vitamin D in bone health and fracture incidence (Holick *et al.* 2005, Garnero *et al.* 2007), and further discussion is out of scope of this review. However, both recommendations of vitamin D intake and adequate serum concentrations of calcidiol still remain controversial. The latter is even more hindered in view of unreliable and often inaccurate analytical methods for its detection (Snellman *et al.* 2010).

Although the official RDA for vitamin D for older individuals was increased in recent years to 600–800 IU/day (15–20 µg/day) (Institute of Medicine 2012), some argue that it is still not enough to keep adequate serum concentration of calcidiol (Heaney & Holick 2011). With that regard, there are still disagreements about serum concentration of calcidiol reflecting adequacy, inadequacy or true deficiency (Holick *et al.* 2005, Institute of Medicine 2012).

Regarding the muscle, inadequate vitamin D has recently been associated with sarcopenia, decreased grip strength and other impaired functionality measures in older adults (Visser *et al.* 2003, Lee *et al.* 2013, Post & Ilich 2013, Tieland *et al.* 2013). Recent studies also showed that inverse relationship between vitamin D status and PTH concentrations is associated with compromised muscle mass and strength, as well as with diminished physical function (Lee *et al.* 2013, Tieland *et al.* 2013). A study in the Netherlands investigating older women and men showed that low calcidiol and high PTH increase the risk of sarcopenia, as reflected in lower muscle mass and hand grip strength (Visser *et al.* 2003). Tying this to bone, another study has found that patients with insufficient calcidiol concentrations and low BMD are also more likely to develop sarcopenia (Lee *et al.* 2013).

Bone as endocrine organ Considering bone as an endocrine organ, most research has probably been done on osteocalcin, an osteoblast-secreted protein, also referred to as bone γ -carboxyglutamic acid (Gla) protein. Once synthesized, it is largely incorporated into the extracellular bone matrix (hydroxyapatite), but a low concentration is maintained in serum and is used as an indicator of bone formation (Hauschka *et al.* 1989, Lee *et al.* 2000). Typically, the majority of osteocalcin is carboxylated with vitamin-K-dependent γ -glutamyl carboxylase and as such binds easily to Ca^{2+} ions within the hydroxyapatite matrix and stabilizes the bone (Lee *et al.* 2000). However, in cases of low carboxylase activity (e.g. as with inadequate vitamin K status, often present in elderly), there will be an increased presence of undercarboxylated osteocalcin which does not readily bind to hydroxyapatite, thus possibly contributing to bone loss (Price & Nishimoto 1980). Other than stabilizing the bone matrix, osteocalcin stimulates secretion of adiponectin from fat cells, demonstrating the connection between bone and adipose tissue (Lee & Karsenty 2008).

It was hypothesized recently that small but measurable amounts of undercarboxylated osteocalcin are present in

serum (either due to osteocalcin decarboxylation outside the osteoblasts or its secretion in undercarboxylated form) (Karsenty & Ferron 2012). This undercarboxylated osteocalcin was shown to stimulate pancreatic β -cell proliferation and insulin secretion via embryonic stem-cell phosphatase expressed in osteoblast and thus positively modulate energy metabolism (Kanazawa *et al.* 2009, Karsenty & Ferron 2012).

Overall, new research points into systemic hormonal actions of osteocalcin and/or undercarboxylated osteocalcin, on which basis this hormone was recently termed as the first *osteokine* (Ilich *et al.* 2014b), analogous to the myokines and adipokines, the hormones secreted from muscle and adipose tissues, respectively.

Muscle as endocrine organ Muscle tissue has just begun to be investigated as an endocrine organ. Troponins, the key regulatory proteins associated with the contractility process of cardiac and skeletal muscle, are receiving the most attention. Troponins are not normally found in the blood, except in cases of muscle turnover or muscle damage. Skeletal muscle contraction is regulated by Ca^{2+} via the skeletal muscle specific troponin (sTnT). This complex is needed for the repetitive cycles of contraction and relaxation. Skeletal muscles are protected by several layers of connective tissue, which maintain the muscle integrity. If this barrier is injured, internal components of muscle, particularly sTnT, leak into the blood and their measurable presence could indicate sarcopenia (Chase *et al.* 2013, Kalinkovich & Livshits 2015). Serum sTnT drops proportionally with improvements in handgrip strength and overall physical fitness in older adults, as recently reviewed (Abreu *et al.* 2014).

Fat as endocrine organ Regarding the fat tissue, the classic hormone secreted by adipocytes is leptin (Reid 2008). This member of the cytokine family has structural similarities to IL-6 and stimulates the pro-inflammatory action of IL-6, interleukin-12 (IL-12) and TNF- α (Abenavoli & Peta 2014, Pires *et al.* 2014). Leptin is higher in women and proportionally increases with increasing fat tissue (Pires *et al.* 2014), but it gradually decreases with age; this reduction is higher in females than in males and is independent from BMI (Isidori *et al.* 2000).

Leptin locally enhances osteoblastogenesis and inhibits osteoclastogenesis (Gordeladze *et al.* 2002, Karsenty & Ferron 2012). As some recent studies showed, the osteoblastogenic effect is due to leptin's mediation of

bone marrow MSC that may differentiate into osteoblasts, chondrocytes and/or adipocytes. For example, transfection of leptin into MSC of osteoporotic rats, increased osteoblast differentiation and mineral deposition both *in vivo* and *in vitro* (Zheng *et al.* 2015), while hypothalamic leptin gene therapy reduced MAT in *ob/ob* mice, fed either high-fat or regular diet (Lindenmaier *et al.* 2016). Positive effects of leptin on bone and accelerated fracture healing were shown in rats with induced femoral fractures after peritoneal exogenous leptin injection. This effect was attributed to increased angiogenesis, osteogenesis and chondrogenesis (Liu & Cai 2017). Moreover, a recent study showed that different lower dose-infusions of leptin (4-12-40 ng/h) in *ob/ob* mice resulted in increased bone formation and trabecular thickness, with a minimal impact on energy metabolism (Philbrick *et al.* 2017).

However, the central effect of leptin could be characterized in either positive or negative regulation of bone metabolism (Karsenty 2001, Gordeladze *et al.* 2002). Thus, the conflicting results of the relationship of leptin and BMD were reported in several studies (Iwamoto *et al.* 2000, Dennison *et al.* 2004, Weiss *et al.* 2006, Koroglu *et al.* 2011). Leptin passes through the blood brain barrier and activates the leptin receptor in the hypothalamus. Activated receptor suppresses serotonin secretion in the brainstem, and in the absence of serotonin, the sensory nervous system sends signals to osteoblasts by secretion of norepinephrine. The binding between norepinephrine and β_2 -adrenergic receptors on osteoblasts increases receptor activator of nuclear factor kappa-b ligand (RANKL) gene expression, decreases bone formation and increases bone resorption (Motyl & Rosen 2012). Similarly, a previous evidence from a study conducted on β_2 -adrenergic receptors deficient mice showed reduced RANKL expressions (Eleftheriou *et al.* 2005).

Obesity can lead to leptin resistance and hyperleptinemia. Additionally, leptin also appears to activate pro-inflammatory pathways in osteoblasts (Upadhyay *et al.* 2015), contributing even more toward bone deterioration. Conversely, decreased serum leptin is found in frail elderly and in cachexia (Hubbard *et al.* 2008). However, the hyperleptinemia in osteosarcopenic obesity may mask this, possibly causing patients with osteosarcopenic obesity to be overlooked in clinical settings (Hubbard *et al.* 2008, Ilich *et al.* 2014b).

Adiponectin is another hormone that has been investigated as a possible link between bone and fat tissue. Adiponectin is mainly secreted by adipocytes, but also by osteoblasts, myocytes and it is even expressed in the brain (Lee & Shao 2012). Circulating adiponectin is decreased in

obese states but increased in lean states, as well as during energy restriction, weight loss and in older individuals (Ambroszkiewicz *et al.* 2015). Recently, Cawthorn *et al.* (2014) showed that MAT may contribute to increased serum adiponectin, even more than white adipose tissue, during energy restriction and some other conditions (e.g. cancer therapy) (Cawthorn *et al.* 2014). Low serum adiponectin concentrations or hypoadiponectinemia ($<4\mu\text{g/mL}$) are associated with osteoporosis (Kishida *et al.* 2014); however, adiponectin also has a dual impact on bone (Luo *et al.* 2006, Williams *et al.* 2009). Some studies show that adiponectin negatively regulates bone mass by decreasing osteoblast proliferation possibly via mediation of the RANK/RANKL/ osteoprotegerin (OPG) axis (Luo *et al.* 2006, Lewerin *et al.* 2015). Other studies show that through the same RANK/RANKL/OPG axis, adiponectin may inhibit osteoclastogenesis and increase osteoblastic activity and mRNA expression (Oshima *et al.* 2005, Williams *et al.* 2009).

Adiponectin is involved in fat metabolism and may inhibit obesity by increasing fatty acid oxidation in adipose tissue by activation of AMP-activated protein kinase (AMPK) phosphorylation and in muscle by P38 mitogen-activated protein kinase (MAPK) and peroxisome proliferator-activated receptor (PPAR) alpha (Yoon *et al.* 2006, Lecke *et al.* 2011, Ghoshal & Bhattacharyya 2015). Furthermore, adiponectin has anti-inflammatory effects inhibiting the action of TNF- α and IL-8 (Ghoshal & Bhattacharyya 2015). To further connect adiposity, inflammation and adiponection, hypoadiponectinemia ($<4\mu\text{g/mL}$) is positively associated with visceral fat and obesity-related diseases (Kishida *et al.* 2014). These combined effects of adiponectin appear to favor lean mass and possibly promote decreased body fat accumulation (Fiaschi *et al.* 2012). Predictably, adiponectin serum concentrations would be lower in osteosarcopenic obesity women, due to increased fat mass and decreased lean mass. However, since adiponectin increases with age, its decline in osteosarcopenic obesity in women might be masked.

Conclusions and implications for further initiatives in this field

Aging causes numerous physiological changes, among which those affecting the physical phenotype are the most observable. An ultimate consequence of deterioration in body composition is the development of osteosarcopenic obesity. This is a complex condition with concomitant

changes in bone, muscle and adipose tissue in aging body or occurring in some other chronic diseases. Increased adiposity results in increased inflammation, influencing muscle and bone health, while inflammation perpetuates adiposity (Ilich *et al.* 2014a). Damage to or decline of one tissue could signal changes in the other, but all ultimately lead to decreased functionality, increased risk for falls and increased morbidity. Therefore, in evaluating the older adults, clinicians should perhaps first assess functional decline through physical performance tests, then assess biomarkers in serum, followed by the assessment of bone and muscle loss to diagnose osteosarcopenic obesity syndrome and any of its components (Ilich *et al.* 2016). Many questions still remain unanswered and need more investigation and/or confirmation: Do women with osteosarcopenic obesity present with higher levels of chronic inflammation than women with osteoporosis, sarcopenia or obesity alone? Does chronic inflammation exacerbate bone loss, worsen sarcopenia and subsequently lead to lower functionality? Is osteopenia and/or sarcopenia a sign of fat infiltration into bone and muscle, as proposed earlier (Rosen & Bouxsein 2006, Ilich *et al.* 2014b)? Could reduced adiposity improve bone health and muscle mass and strength in older people? Based on the newest findings, women with osteosarcopenic obesity appear to have greater risk for functional decline and higher risk for falls and fractures even beyond the normal risk level of their peers with osteopenia/osteoporosis or sarcopenia (Cruz-Jentoft *et al.* 2010, Ilich *et al.* 2015). Research into the changes in body composition with aging should evaluate not only the level of frailty in older adults but the overall interconnecting links among bone loss, muscle loss and increased adiposity, as proposed recently (Ilich *et al.* 2014b).

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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Authors' contribution statement

J Z I conceptualized manuscript and wrote the final version. J P, J E I, W R and O J K drafted the manuscript. O J K and J Z I designed the figures.

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