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The Microbiome and Osteosarcopenic Obesity in Older Individuals in Long-Term Care Facilities

Julia E. Inglis[1] · **Jasminka Z. Ilich**[1]

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Abstract Increasing evidence points to a role of altered microbiota on inflammation, obesity, and other chronic conditions. This commentary addresses the connection between osteosarcopenic obesity syndrome, an impairment in bone, muscle, and adipose tissues that occurs concurrently, with the altered microbiota in elderly individuals, particularly those living in long-term care facilities. As elderly move to long-term care facilities, they experience changes in gut bacteria that might exasperate the underlying conditions such as osteosarcopenic obesity. These individuals have exponentially higher osteoporotic fracture rates and immobility impairments compared to independently living individuals. However, there is very limited research on this topic and more insight is needed on the impact of probiotic treatment and diet in older individuals, especially those with chronic conditions related to aging, such as osteosarcopenic obesity.

Keywords Osteosarcopenic obesity · Microbiome · Frail elderly

The Triad of Bone, Muscle, and Adipose Tissues: the Osteosarcopenic Obesity Syndrome

Body composition (bone, muscle, and fat tissues) changes with age. In older women particularly, there is an age-related loss of bone (leading to osteopenia or osteoporosis), loss of lean mass and muscle strength (leading to sarcopenia and/or dynapenia), and increased adiposity, the latter presented either as an overt clinical overweight/obesity, redistribution of fat around visceral organs, or as an infiltrated fat into bone and muscle tissues, impairing their function [1••]. Additionally, a low-grade chronic inflammation, typically present in aging, may perpetuate obesity, sarcopenia, and osteoporosis, as discussed recently [2]. Figure 1 depicts a hypothetical representation of changes in bone, muscle, and fat tissues, along with increased inflammation, with aging. This triad of bone, muscle, and adipose tissues deterioration was identified recently as an osteosarcopenic obesity (OSO) syndrome [1••].

Osteopenia and osteoporosis are prevalent in older adults, with one in three women and one in five men experiencing a bone fracture after the age of 50 [3]. Despite conventional belief, increased body fat in aging adults may actually be detrimental for both bone and muscle. In older women, there is a corresponding increase in vertebral fat (yellow bone marrow) as bone mineral density declines [4, 5]. Yellow or fatty bone marrow, appearing as an infiltrated fat into bone, might aggravate bone health and contribute to the condition known as osteopenic obesity (OO) [1••]. A recent study found femoral bone mineral density to be negatively correlated with total femoral bone marrow fat content, indicating an increased risk for osteoporosis [6]. Sarcopenic obesity (SO) is also impacted by changes in body composition with age. Besides the increased adiposity and redistribution of fat, the accompanied low-grade chronic inflammation can lead to myosteatosis or fat infiltration into muscle, further decreasing muscle strength and function and contributing to decreased mobility and increased risk for falls [7, 8].

It is important to note that both OO and SO lack universal diagnostic criteria and that each condition has direct relationship to adiposity and may in fact aggravate one another

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✉ Jasminka Z. Ilich
jilichernst@fsu.edu

[1] Department of Nutrition Food and Exercise Sciences, Florida State University, 120 Convocation Way, Tallahassee, FL 32311, USA

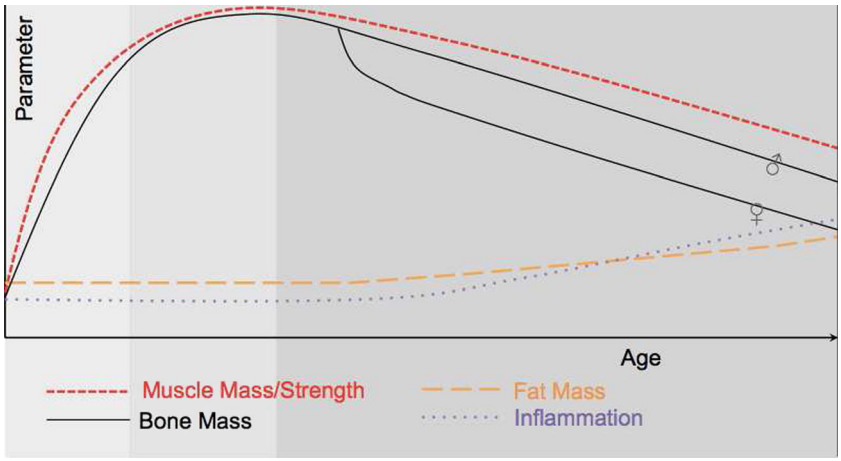

Fig. 1 Hypothetical presentation of changes in muscle, bone, and fat tissues, accompanied by increased low-grade chronic inflammation in aging

culminating in OSO [1••]. Osteosarcopenic obesity also lacks universal diagnostic criteria, but, being the combination of OO and SO, is of growing concern for older adults, especially women and in the midst of the obesity epidemic. As found recently, women with OSO have decreased mobility, balance, and strength compared with women with obesity, osteoporotic obesity, or sarcopenic obesity alone [9••]. It becomes evident that OSO puts women not only at increased risk for bone fracture but also at increased risk for falls, immobility, and long-term frailty [1••, 9••, 10].

Recent research also points to a connection between inflammation and osteoporosis, sarcopenia, and adiposity, where increased inflammation from excess or redistributed fat combined with fat infiltration into bone and muscle further weakens bone and muscle tissues [2]. In addition to the mentioned changes with aging, the microbiome appears to also influence human health with quantifiable age-related changes in gut bacteria and becomes an important factor to consider in health and frailty of elderly [11], as is discussed below.

The Microbiome in Elderly

The human microbiome is a large, genetically diverse system of microbes residing in and on our body, consisting of 150 times more genes than our human genome [12, 13] and hosting about 5000 species of bacteria, mostly anaerobic [14••]. The gut bacteria are generally stable, relying on chromosomal genetic inheritance to select gut microbial diversity [15]. However, as humans age, there are significant changes in gut microbiota [12, 16]. Although gut microbiota vary among individuals, generally, there is a shift in bacterial communities from obligate anaerobes (*Faecalibacterium prausnitzii*) to facultative anaerobes (*Enterobacteriaceae*) in the elderly (similarly as in patients with inflammatory bowel disease), favoring pathogenic bacteria and infections and promoting inflammation [17]. Studies show that elderly tend to have higher levels of pathogenic *Proteobacteria* and *Bacilli* bacteria and decreased numbers of anti-inflammatory *Lactobacilli* bacteria [11, 18]. This shift in the microbiota of older adults leads to an environment of increased inflammation, leading to opportunistic infections (primarily *Proteobacteria*), and reduced lactate utilization [11, 19]. Researchers now believe that increased inflammation and age-associated changes related to this bacterial shift are factors that contribute to frailty in older individuals, among other aging conditions [11, 18].

Studies show that changes in microbial diversity in an older individual are due not only to age but more so to diet, living conditions, comorbidities, and antibiotic and other medication treatments. Recent evidence indicates that when older adults move from living independently in the community to a long-term care facility (LTCF), there are large microbial changes in their gut bacteria [16, 20••]. Comparing 178 non-antibiotic-treated Caucasian individuals (>64 years) in long-term residential care, short-term rehab hospitals, outpatient day hospitals, and those living independently in the community, researchers found that elderly in LTCF had significantly less microbial diversity. It was noted that within a month after entering these facilities, the gut bacteria in these individuals changed significantly from that of community-dwelling elderly and the difference persisted within 1 year after entering a LTCF [16]. This shift appeared to be mostly explained by changes in diet from a higher-fiber, more plant-based diet at home to a low-fiber, higher fat, and higher sucrose content in diet in the LTCF [16, 20••, 21]. Additionally, adults in LTCF often experience chronic antibiotic treatment, comorbidities, and co-residence with other elderly that all alter gut bacteria. A bacterial shift as seen in adults in LTCF can be pro-inflammatory, impacting aging and comorbidities. Indeed, this change in gut bacteria is correlated with increased levels of frailty and comorbidity in individuals in LTCF, as well as with significantly higher levels of pro-inflammatory markers, serum TNF-alpha, IL-6, IL-8, and C-reactive protein [11, 16, 18].

A recent study by Jeffery et al. examined fecal samples in 371 generally healthy age-matched elderly Irish men and

women, mean age 78 years, living independently or entering the LTCF. Exclusion criteria included alcohol and drug abuse and advanced chronic disease. They were compared with a younger control group (n=13; age 28-46 years), living independently. Interestingly, the results showed that it was not a decrease in bacterial diversity or bacterial numbers that were associated with declining health in older population, but rather changes in the particular type of bacteria or microbial composition [20••]. Upon entering the LTCF, the elderly experienced a microbial shift that lasted ~18 months. The bacteria in the elderly who were living independently remained similar to the young control group throughout the study. This change is believed to be related to alterations in diet, where older adults in LTCF have significantly lower fiber intakes, but higher saturated fat and sucrose intake, as well as chronic antibiotic use, comorbidities, and co-residence with other older adults with similar conditions of aging [16, 20••, 21]. Dietary fiber, particularly, is believed to act as a type of prebiotic, feeding healthy bacteria in the human gut [14••, 21].

This change in gut bacteria that occurs as older adults move to a long-term care facility may eventually alter bone and body composition even more, leading to osteoporosis, sarcopenia, and obesity, impacting the risk of fracture and overall frailty. Studies using antibiotic treatment, probiotics, and prebiotics indicate that treatment affecting gut microbiota composition also regulates bone metabolism [12, 22, 23]. Certain bacteria or probiotic treatments may benefit bone, while others may harm bone by promoting inflammation. In a study by Sjogren et al., germ-free mice had greater bone mass and decreased inflammatory cytokines in bone and bone marrow and reduced osteoclastogenesis in trabecular bone than mice conventionally raised with *Bacteroides thetaiotaomicron* bacteria. [22]. *B. thetaiotaomicron*, often beneficial bacteria, can under certain conditions alter inflammatory markers and systemic immunity and it has even been shown to increase metabolites in the gut that increase permeability to infection and activate virulence genes, making the host more susceptible to pathology and mortality [24, 25]. Although more research needs to be done, this may point to a negative role that certain gut bacteria play in regulating bone health. Other studies show that putting certain probiotic strains, such as *Lactobacillus paracasei* DSM13434 (*L. para*) or *L. para* and *Lactobacillus plantarum* combined, in the drinking water of mice protected against ovariectomy-induced bone loss [26]. These probiotic strains are anti-inflammatory, reducing expression of TNF-α and IL-1β as well as inhibiting osteoclastogenesis by promoting osteoprotegerin expression [12]. In another recent study, treatment of ovariectomized rats with *Lactobacillus reuteri* bacteria protected against bone loss by significantly reducing osteoclast bone resorption markers and activators [23]. *L. reuteri* also suppressed ovariectomy-induced increases in bone marrow CD4+ T lymphocytes, which normally promote osteoclastogenesis [23]. In summary, altered systemic and bone marrow immune status caused by changes in the microbiome appears to impact bone mass [12, 22].

In addition to suppressing osteoclastogenesis, gut bacteria synthesize enzymes and enhance absorption and synthesis of various vitamins and minerals that promote bone growth and matrix formation and benefit muscle tissue [11, 27]. These include vitamins K and B-12, calcium, magnesium, and creatine [11, 14••]. Rodrigues et al. found that rats fed bifidobacteria had significantly higher concentrations of calcium, magnesium, and phosphorous in the tibia than controls [27]. In humans, Weaver et al. found significantly higher fractional calcium absorption in adolescents treated with probiotics, phyla *Bacteroidetes* and *Firmicutes*, compared with a corn fiber prebiotic. This increased calcium absorption was also associated with increased bone density and strength [14••]. Regarding microbiota in older mice, B-12 synthesis was significantly decreased while creatine degradation was significantly increased when compared to young- and middle-aged mice [11]. Low B-12 (cobalamin) in the elderly is a contributing factor in hip fractures as well as sarcopenia, partially due to the secondary effects of elevated homocysteine levels [28, 29]. Increased creatine degradation leads to low creatine in older adults and possibly subsequent loss of lean mass and strength [11].

In human studies, both in adults and children, overweight participants had significantly higher levels of gut bacteria that promote inflammation and weight gain compared to normal-weight individuals [15, 30, 31] Overweight individuals also tend to consume less dietary fiber and have reduced microbial diversity, perhaps making room for more pro-inflammatory and obesogenic bacteria to grow and have a greater impact on their host [21, 32]. These bacterial colonies, such as those from the phyla *Firmicutes* (gram-positive) and *Prevotellaceae* family, accelerate fermentation of otherwise indigestible fibers (carbohydrates), which increases production of short chain fatty acid and therefore energy (calories) utilization in the host [15, 30]. About 70 % of energy received by the colonic epithelium comes from short chain fatty acids; therefore, the concept that a shift in human gut bacteria influences weight gain or loss is plausible [15]. Looking at mouse studies, Seo et al. found *Firmicutes* bacteria to predominate in the gut of obese mice and yet markedly decrease after weight loss [33].

Summary

It seems plausible that changes in gut bacteria impact elderly in long-term care facilities substantially and more so than independently living elderly individuals. However, there is very limited research on this topic, although the existing studies point to a role of changes in microbiota affecting inflammation and obesity. Older individuals with combined conditions such as OSO may be at particular risk for frailty in long-term care

facilities. Elderly in long-term care facilities experience exponentially higher osteoporotic fracture rates than independently living older women and men, comprising 20–30 % of all femoral fractures [34, 35]. To connect this condition to the microbiome, these individuals also have altered gut bacteria and higher inflammatory markers, which could impact bone, muscle, and adipose tissues, exasperating the OSO syndrome. More research is needed on the impact of probiotic treatment and diet in older individuals, especially those with chronic conditions related to aging, such as OSO.

Compliance with Ethics Guidelines

Conflict of Interest Dr. Julia Inglis and Dr. Jasminka Ilich declare no conflict of interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1.•• Ilich JZ, Kelly OJ, Inglis JE, Panton LB, Duque G, Ormsbee MJ. Interrelationship among muscle, fat, and bone: connecting the dots on cellular, hormonal, and whole body levels. Ageing Res Rev. 2014;15:51–60. **Provides the proof of concept for the osteosarcopenic obesity syndrome and explains interconnection between bone muscle and adipose tissues**.
2. Ilich JZ, Kelly OJ, Kim Y, Spicer MT. Low-grade chronic inflammation perpetuated by modern diet as a promoter of obesity and osteoporosis. Arh Industrial Hygiene Tocsicol. 2014;65:139–48.
3. International Osteoporosis Foundation: http://www.iofbonehealth.org/facts-statistics(accessed 4/18/2015).
4. Liu Y, Tang RB, Peng YF, Li W. Assessment of bone marrow changes in postmenopausal women with varying bone densities: magnetic resonance spectroscopy and diffusion magnetic resonance imaging. Chin Med J. 2010;123:1524–7.
5. Tang GY, Lv ZW, Tang RB, Liu Y, Peng YF, Li W, et al. Evaluation of MR spectroscopy and diffusion-weighted MRI in detecting bone marrow changes in postmenopausal women with osteoporosis. Clin Radiol. 2010;65:377–81.
6. Bredella MA, Fazeli PK, Daley SM, Miller KK, Rosen CJ, Klibanski A, et al. Marrow fat composition in anorexia nervosa. Bone. 2014;66:199–204.
7. Visser M, Goodpaster BH, Kritchevsky SB, Newman AB, Nevitt M, Rubin SM, et al. Muscle mass, muscle strength, and muscle fat infiltration as predictors of incident mobility limitations in well-functioning older persons. J Gerontol A Biol Sci Med Sci. 2005;60:324–33.
8. Domiciano D, Figueiredo C, Lopes J, Caparbo V, Takayama L, Menezes P, et al. Discriminating sarcopenia in community-dwelling older women with high frequency of overweight/obesity: the Sao Paulo Ageing & Health Study (SPAH). Osteoporos Int. 2012;24:595–603.
9.•• Ilich JZ, Inglis JE, Owen KJ, McGee DL. Osteosarcopenic obesity is associated with reduced handgrip strength, walking abilities, and balance in postmenopausal women. Osteoporos Int. 2015. doi:10.1007/s00198-015-3186-y. **Presents the original data showing that women with osteosarcopenic obesity have lower diminished functional abilities compared to women with obesity only.**
10. Hita-Contreras F, Martínez-Amat A, Cruz-Díaz D, Pérez-López FR. Osteosarcopenic obesity and fall prevention strategies. Maturitas. 2015;80:126–32. doi:10.1016/j.maturitas.
11. Langille MG, Meehan CJ, Koenig JE, Dhanani AS, Rose RA, Howlett SE, et al. Microbial shifts in the aging mouse gut. Microbiome. 2014;2:50. doi:10.1186/s40168-014-014-0050-9.
12. Ohlsson C, Sjögren K. Effects of the gut microbiota on bone mass. Trends Endocrinol Metab. 2015;26:69–74.
13. Ursell LK, Metcalf JL, Parfrey LW, Knight R. Defining the human microbiome. Nutr Rev. 2012;70:S38–44. doi:10.1111/j.1753-4887.2012.00493.x.
14.•• Weaver CM. Diet, gut microbiome, and bone health. Curr Osteoporos Rep. 2015;13:125–30. doi:10.1007/s11914-015-0257-0. **Gives overview of microbiome and its relation with bone health**.
15. Murugesan S, Ulloa-Martínez M, Martínez-Rojano H, Galván-Rodríguez FM, Miranda-Brito C, Romano MC, et al. Study of the diversity and short-chain fatty acids production by the bacterial community in overweight and obese Mexican children. Eur J Clin Microbiol Infect Dis. 2015;34:1337–46.
16. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature. 2012;488:178–84. doi:10.1038/nature11319.
17. Rigottier-Gois L. Dysbiosis in inflammatory bowel diseases: the oxygen hypothesis. ISME J. 2013;7:1256–61. doi:10.1038/ismej.2013.80.
18. Van Tongeren SP, Slaets JP, Harmsen JM, Welling GW. Fecal microbiota composition and frailty. Appl Environ Microbiol. 2005;71:6438–42. doi:10.1128/AEM.71.10.6438-6442.2005.
19. Rampelli S, Candela M, Turroni S, Biagi E, Collino S, Franceschi C, et al. Functional metagenomic profiling of intestinal microbiome in extreme ageing. Aging. 2013;5:902–12.
20.•• Jeffery IB, Lynch DB, O'Toole PW. Composition and temporal stability of the gut microbiota in older persons. ISME J. 2015. doi:10.1038/ismej.2015.88. **Presents the data on the change of microbiome in older individuals entering the long-term care facilities**.
21. Cotillard A, Kennedy SP, Kong LC, Prifti E, Pons N, Le Chatelier, et al. Dietary intervention impact on gut microbial gene richness. Nature. 2013;500:585–8.
22. Sjögren K, Engdahl C, Henning P, Lerner UH, Tremaroli V, Lagerquist MK, et al. The gut microbiota regulates bone mass in mice. J Bone Miner Res. 2012;27:1357–67.
23. Britton RA, Irwin R, Quach D, Schaefer L, Zhang J, Lee T, et al. Probiotic *L. reuteri* treatment prevents bone loss in a menopausal ovariectomized mouse model. J Cell Physiol. 2014;229:1822–30.
24. Backhed F, Ding H, Wang T, Hooper LV, Koh GY, Nagy A, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A. 2004;101:15718–23.
25. Curtis M, Hu Z, Klimko C, Narayanan S, Deberardinis R, Sperandio V. The gut commensal Bacteroides thetaiotaomicron exacerbates enteric infection through modification of the metabolic landscape. Cell Host Microbe. 2014;16(6):759–69. doi:10.1016/j.chom.2014.11.005.
26. Ohlsson C, Engdahl C, Fåk F, et al. Probiotics protect mice from ovariectomy-induced cortical bone loss. Ryffel B, ed. PLoS ONE. 2014;9(3):e92368. doi:10.1371/journal.pone.0092368.
27. Rodrigues FC, Castro AS, Rodrigues VC, Fernandes SA, Fontes EA, de Oliveira TT, et al. Yacon flour and Bifidobacterium longum modulate bone health in rats. J Med Food. 2012;15:664–70. doi:10.1089/jmf.2011.0296. Epub 2012 Apr.
28. McLean RR, Jacques PF, Selhub J, Tucker KL, Samelson EJ, Broe KE, et al. Homocysteine as a predictive factor for hip fracture in older persons. New Engl J Med. 2004;350:2042–9.

29. Mithal A, Bonjour JP, Boonen S, Burckhardt P, Degens H, El Hajj Fuleihan G, et al. Impact of nutrition on muscle mass, strength, and performance in older adults. Osteoporos Int. 2013;24:1555–66. doi: 10.1007/s00198-012-2236-y.
30. Zhang H, DiBaise JK, Zuccolo A, Kudrna D, Braidotti M, Yu Y, et al. Human gut microbiota in obesity and after gastric bypass. PNAS. 2009;106:2365–70. doi:10.1073/pnas.0812600106.
31. Ismail AN, Ragab SH, Abd ElBaky A, Shoeib ARS, Alhosary Y, Fekry D. Frequency of Firmicutes and Bacteroidetes in gut microbiota in obese and normal weight Egyptian children and adults. AMS. 2011;7:501–7. doi:10.5114/aoms.2011.23418.
32. Le Chatelier E, Nielsen T, Qin J, Prifti E, Hildebrand F, et al. Richness of human gut microbiome correlates with metabolic markers. Nature. 2013;500:541–6. doi:10.1038/nature12506.
33. Seo DB, Jeong HW, Cho D, Lee BJ, Lee JH, Choi JY, Bae IH, Lee SJ. Fermented green tea extract alleviates obesity and related complications and alters gut microbiota composition in diet-induced obese mice. J Med Food. 2015;18(5):549–56. doi:10.1089/jmf.2014.3265.
34. Becker C, Cameron ID, Klenk J, Lindemann U, Heinrich S, König HH, et al. Reduction of femoral fractures in long-term care facilities: the Bavarian fracture prevention study. PLoS One. 2011. doi: 10.1371/journal.pone.0024311.
35. Pocock NA, Culton NL, Harris ND. The potential effect on hip fracture incidence of mass screening for osteoporosis. Med J Aust. 1999;170:486–8.