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SPECIAL ARTICLES

OSTEOPOROSIS IN FRAIL OLDER ADULTS: RECOMMENDATIONS FOR RESEARCH FROM THE ICFSR TASK FORCE 2020

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Abstract: Interactions among physiological pathways associated with osteoporosis and sarcopenia are thought to contribute to the onset of frailty. The International Conference on Frailty and Sarcopenia Research Task Force thus met in March 2020 to explore how emerging interventions to manage fracture and osteoporosis in older adults may reduce frailty, disability, morbidity, and mortality in the older population. Both pharmacological and non-pharmacological interventions (including nutritional intervention, exercise, and other lifestyle changes) were discussed, including nutritional intervention, exercise, and other lifestyle changes. Pharmacological treatments for osteoporosis include bone-forming and antiresorptive agents, which may optimally be used in sequential or combination regimens. Since similar mechanisms related to resorption underlie physiological changes in muscle and bone, these interventions may provide benefits beyond treating osteoporosis. Clinical trials to test these interventions, however, often exclude frail older persons because of comorbidities (such as mobility disability and cognitive impairment) or polypharmacy. The Task Force recommended that future clinical trials use harmonized protocols, including harmonized inclusion criteria and similar outcome measures; and that they test a range of multidomain therapies. They further advocated more high-quality research to develop interventions specifically for people who are frail and old. The ICOPE program recommended by WHO appears to be highly recommended to frail older adults with osteoporosis.

Key words: Frailty, osteoporosis, prevention, ICOPE.

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Introduction

All organisms show biologically driven declines in motor function as they age and these declines are closely linked to mortality (1, 2). In humans, these declines manifest as the frailty syndrome, which is defined by the overlapping characteristics of low physical activity, slowed motor performance, weakness, fatigue or exercise intolerance, and unintentional weight loss (3). Physiologically, frailty reflects a lowered resistance to stressors resulting from multi-systemic decline. Clinically, frailty is associated with diagnoses of sarcopenia, the age-related loss of muscle mass and strength, and osteoporosis, the loss of bone mass and the deterioration of bone tissue (4). When they occur together, the syndrome may be referred to as "osteosarcopenia" (5). Moreover, interactions between bone and muscle through multiple physiological pathways, including hormonal and inflammatory pathways, are thought to result in the frailty syndrome (6).

As it has done every year since 2014, the International Conference of Frailty and Sarcopenia Research (ICFSR) Task Force brought together researchers from academia and industry to discuss challenges and opportunities for managing frailty and sarcopenia. In 2020 the Task Force met in Toulouse, France, where it focused attention on emerging interventions to manage fracture and osteoporosis in frail older adults. This population group has often been excluded from recent osteoporosis drug trials due to comorbidities and polypharmacy, despite the fact that they may potentially benefit more from a treatment since they are more likely to have falls, fractures, disability and a poor prognosis.

Associations of frailty with osteoporosis, fragility fracture, and malnutrition

Bone fragility caused by osteoporosis occurs commonly in older adults and results in increased risk of fragility fracture

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(7). A systematic review of worldwide studies estimated that 9 million osteoporotic fractures occurred in 2000, resulting in substantial disability, morbidity, and mortality (8). However, osteoporosis may not be diagnosed until an individual has experienced multiple fragility fractures; and studies show that after diagnosis, treatment for osteoporosis is not routinely given in older adults and adherence to medical regimens is poor (9).

One of the most common and disabling fractures sustained by older persons is hip fracture, which may result in long-term mobility impairment, reduced ability to care for oneself or participate in everyday activities, pain, anxiety, and depression (10). Nutrition plays an important role in bone health and sarcopenia (11, 12), and malnutrition is common in individuals with hip fracture (13). Sarcopenia is also associated with an increased rate fractures in older adults (14, 15).

Most patients with hip fracture complain of pain and resulting functional limitations six months after the fracture (16), which can lead to a vicious cycle of self-medication and mistrust of clinicians (17). Recovery from hip fracture may be delayed in the presence of sarcopenia (18), and hip fracture may be particularly disabling in individuals with frailty (19). Nearly 30 years ago, Marottoli and colleagues showed that physical function before the fracture predicts functional recovery (20). Comorbidities, fear of falling, and other age-related conditions may further exacerbate hip fracture and its associated functional consequences (21, 22). Moreover, individuals over age 80 years, in addition to meeting the frailty phenotype proposed by Fried and colleagues (i.e., weight loss, fatigue, slow gait speed, weakness, sedentary lifestyle), often live alone, and often experience cognitive decline (23); thus they need special management for frailty. However, frail older persons are often excluded from clinical trials of fragility fracture interventions, in part because of comorbidities, sarcopenia, cognitive impairment, and polypharmacy (24).

The substantial impact of fragility fractures on functioning in frail older persons thus requires dedicated and multidisciplinary care pathways, which have been shown to improve quality of life and physical function and limit excessive costs (25, 26). Intensive interventions including exercise and physical therapy immediately following hip fracture is essential. Preventive strategies also need to be widely implemented, including early identification of those at risk, increased prescribing of bone loss prevention treatments, and the introduction of care models based on the comprehensive geriatric assessment and personalization of interventions. Recently multidisciplinary, evidence-based guidelines for the management of osteoporosis and fragility fractures have been published (27–29).

Given the association of poor nutrition with sarcopenia and frailty (30, 31), assessment of the nutritional status of older adults provides a potential pathway to interventions that could delay or prevent these disabling conditions of aging (32). The Mini Nutritional Assessment (MNA) is a tool designed to rapidly assess nutritional status though a series of simple measurements and brief questions (33). The MNA has been validated in frail older persons (34) and in community-dwelling older adults, demonstrating that frailty and malnutrition are distinct but related conditions (35–37).

Using the MNA short form (MNA-SF), investigators showed that poor nutrition in combination with frailty was associated with an increased prevalence and incidence of poor functional outcomes in the Singapore Longitudinal Aging Study (32). In cancer patients, a low MNA score combined with a high Groningen Frailty Index (GFI) score was associated with an increased mortality risk (38). MNA score has also been used as a prognostic factor of adverse outcomes after hip fracture (39). Yet while there is mounting evidence about the importance of stratifying research populations for frailty, impaired nutritional status at baseline has been associated with greater benefits from the interventions (40, 41). The new ESPEN guidelines on the treatment of malnutrition in older people include a section on hip fracture, with the recommendation to incorporate nutrition intervention into a multidisciplinary approach (42).

As a screening tool in outpatients, the MNA-SF has been shown to have a sensitivity of 71.2% and specificity of 92.8% (AUC 0.906) for the detection of frailty, and a 45.7% sensitivity and 78.3% specificity (AUC 0.687) for the detection of pre-frailty (43). In hospitalized patients, the MNA-SF predicted frailty with good sensitivity but only marginal specificity (44). There is no evidence that the MNA can be used as an outcome measure in trials.

Pharmacological treatment for osteoporosis, sarcopenia, and frailty

Better targeting of therapeutic interventions for the management of osteoporosis starts with diagnosis, identification of risk factors, and an assessment of fracture risk (45). The International Osteoporosis Foundation and European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis published guidance for the diagnosis and management of osteoporosis in 2013, and recently updated such guidance (46). Diagnostic criteria for sarcopenia have also been recommended by other different groups. The European Working Group on Sarcopenia in Older People (EWGSOP) published a definition in 2010 and updated it in 2019 based on a better understanding of the condition (47, 48); and the ICFSR published guidelines on the management of sarcopenia in 2018 (49). In 2017, sarcopenia also was assigned a diagnostic code in the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) code book, indicating recognition of sarcopenia as a separately reportable disease condition for clinical practice and drug development (50).

A fracture may trigger a downward spiral of recurrent fractures known as the “fracture cascade” (51). A study in Iceland showed that the first fracture dramatically increases the risk of a subsequent fractures, particularly during the first year following the first event and regardless of the site of it. The

Table 1
Screening Tool for the "Integrated Care for Older Persons" (ICOPE)

Declines in Intrinsic Capacity Subdomains	Tests
Cognitive Decline	1. Remember three words: Flower, door, rice (for example)
	2. Orientation in time and space: What is the full date today? Where are you now (home, clinic, etc.)?
	3. Recalls the three words?
Limited Mobility	Chair rise test: Rise from chair five times without using arms. Did the person complete five chair rises within 14 seconds?
Malnutrition	1. Weight loss: Have you unintentionally lost more than 3 kg over the last three months?
	2. Appetite loss: Have you experienced loss of appetite?
Visual Impairment	Do you have any problems with your eyes: Difficulties in seeing far, reading, eye diseases or currently under medical treatment (e.g., diabetes, high blood pressure)?
Hearing Loss	Hears whispers (whisper test) or
	Screening audiometry result is 35 dB or less or Passes automated app-based digits-in-noise test
Depressive Symptoms	Over the past two weeks, have you been bothered by
	• Feeling down, depressed or hopeless?
	• Little interest or pleasure in doing things?

authors concluded that treatment should be started immediately to prevent recurrence of the problem (52). Bone fragility, determined by assessing bone mineral density (BMD) at the hip or spine by DXA scan, is associated with high fracture risk (53), suggesting that restoring bone density may significantly reduce the risk of a second fracture. Low muscle strength and low physical function (sarcopenia) also increase the risk of injurious falls and fractures after a first hip fracture (54).

Several bone-forming drugs are clinically available, including anti-resorptive agents such as denosumab (55–57); romosozumab, a monoclonal antibody that both increases bone formation and inhibits bone resorption (58, 59); anabolic agents such as teriparatide (60) and abaloparatide (61–63); biphosphonates such as alendronate and zoledronic acid (64); and myostatin inhibitors, which are also under research as potential drugs to treat sarcopenia (65, 66).

Optimal treatment of osteoporosis may require sequential or combination therapies, for example starting with a bone forming agent then add an antiresorptive agent for maintenance. For example, in the phase 2 FRActure study in postmenopausal woMen with ostEoporosis (FRAME), romosuzumab followed by denosumab reduced the risk of fracture in postmenopausal women (67). Other sequential regimens that have shown promise in lowering fracture risk and/or increasing bone density include romosozumab followed by alendronate (68), abaloparatide followed by alendronate (69,70), and combination denosumab/teriparatide followed by denosumab alone (71).

Preventing frailty and its consequences through nutrition and exercise

The concept of frailty facilitates a better understanding of heterogeneity in the older population and promotes study of the aging process. It provides a possible target for preventive measures aimed at reducing the functional decline and the occurrence of negative events such as falls and fractures (72, 73). Frail patients present with weakness, fatigue, a sedentary lifestyle and mobility impairment. They may have anorexia and recent weight loss. All of these clinical signs increase the risk of falls and fractures. They are also accessible to interventions such as nutritional management and/or physical exercise (focused on strength training and balance), which reduce the risk of falling (74, 75).

Several mechanisms responsible for both growth and decline of muscles and bones are shared. It has been hypothesized that pharmacological, nutritional, and/or exercise-based interventions may also overlap and provide mutual/dual benefits (76). For example, both skeletal muscle and bone respond to treatment with androgens, and exercise is an essential element of treatment regimens for osteoporosis, sarcopenia, and frailty. Malnutrition plays an important role in the development of both sarcopenia and frailty (31). Decreased dietary protein intake has been shown to result in decreased lean muscle mass in the Health Aging and Body Composition (ABC) Study (77). The Vitality, Independence and Vigor Study (VIVE2) showed that a high protein, high vitamin D nutritional supplement added to a physical activity intervention led to improvements in muscle density and a loss of intermuscular fat in mobility-limited older adults (78), although these benefits seemed insufficient to improve functional measures such as gait speed (79). Other studies have shown that a combination of resistance exercise and increased protein intake prevented muscle wasting in older adults (80, 81).

Obesity is known to contribute to functional declines and frailty in older adults. Sarcopenia in combination with obesity – a condition known as sarcopenic obesity – increases

the risk of functional decline through multiple synergistic pathways. Intervention strategies to combat sarcopenic obesity include weight reduction, calorie restriction, and exercise. Pharmacological strategies may also prove useful (82). Weight reduction through calorie restriction has been shown to have positive effects on longevity, yet it also may result in a loss of fat and lean mass and bone density (83, 84). In a study of older frail obese adults, an intervention that combined weight loss and aerobic plus resistance exercise, Villareal and colleagues showed that in comparison to either approach alone, the combination resulted in greater physical function and aerobic capacity and attenuated the loss of bone mineral density (85, 86).

The mechanisms by which dietary changes and exercise influence muscle and bone provide clues that may help design better and more targeted intervention strategies. For example, evidence implicates age-related declines in muscle insulin-like growth factor 1 (IGF-1) in sarcopenia; and both exercise and injury increase IGF-1, IGF-1 receptors, and IGF-1 activated signaling pathways. Aging muscle may have less ability to synthesize IGF-1 or may be resistant to IGF-1, and aging may also be associated with attenuation of the ability of exercise to induce IGF-1 (87).

A small study of healthy older women fed with a low-protein diet for 10 weeks showed a decline in both muscle mass and IGF-1 (88). More than 20 years ago, Rizzoli and colleagues showed that protein supplementation in frail individuals post hip fracture restored levels of IGF-1 in the plasma and attenuated loss in bone mineral density compared to placebo (89). Supplementation with selenium and coenzyme Q10 have also been shown to increase levels of IGF-1 in older adults (90).

Skeletal muscle cells express the vitamin D receptor (VDR), and low levels of vitamin D have been associated with lower muscle strength, mobility impairments, and disability (91). In mobility-impaired older women, vitamin D supplementation increased VDR expression and improved skeletal muscle fiber size (92). However, another study in older adults with low baseline levels of serum 25(OH)D showed that while supplementation increased serum levels to more normal levels, there was no effect on lean mass, lower-extremity power, or strength (93).

Nutritional supplements that target inflammation have also been proposed as a strategy for improving muscle function in older adults. For example, omega-3 fatty acids derived from fish oil have also been shown to slow decline in muscle mass and function in older adults (94). However, a recent clinical trial, the ENabling Reduction of low-Grade Inflammation in SEniors (ENRGISE) Pilot study, which tested the efficacy of fish oil and the angiotensin receptor blocker losartan in older, mobility-impaired adults, showed no improvement of walking speed or serum level of the inflammatory marker IL-6 (95).

Demonstrating the efficacy of nutritional interventions is challenging for many reasons, including the difficulty of determining whether the baseline level of dietary intake is inadequate and capturing subtle effects of change from baseline. These challenges are exacerbated when nutritional interventions are superimposed on other interventions.

Designing clinical trials to target bone fracture in frail older adults

The burden of fracture is expected to increase worldwide as the population ages, yet few trials have assessed the benefit of treatments in the oldest old and even less in the frail population (96, 97). Thus, fracture prevention and optimizing bone health represent important public health goals. Interventions that target the frail population offer the potential for the greatest benefit, as was demonstrated in a study by Rolland and colleagues, which tested the ability of strontium ranelate to reduce vertebral fractures in osteoporotic women, independently of frailty status (98). Beyond pharmacological interventions, nutrition and exercise have been shown to act synergistically to improve bone and muscle health and thus should be incorporated into randomized clinical trials (99).

To increase the efficiency and maximizing learnings from clinical studies, sponsors and researchers should use harmonized protocols with similar outcome measures. The ICFSR Task Force suggested the following:

Possible Study Design

The placebo-controlled, parallel-arm, double-blind trial is the gold standard for assessing efficacy and effectiveness. Other elements of an optimal trial design include:

- A long run-in phase before initiating treatment, during which activity diaries could be monitored and dietary inadequacies or anemia corrected to ensure a stable baseline.
- 2 x 2 designs for studies testing multimodal approaches such as resistance exercise and/or combination of resistance and aerobic exercise and nutrition.
- Using assessment time points that have been harmonized with other studies to enable data pooling and meta-analyses of data.
- Use the gold standard of collecting falls incidence using monthly calendars.
- At least one-year of follow up. If studies aim to target bone fracture or prevent the progression from pre-sarcopenia to sarcopenia, long follow-up will be necessary.

Proposed Outcomes

- Primary outcome: fragility fractures at 24 months (hip and spine).

- Secondary outcomes:
  - o Physical performance and disability as measures of functional decline
  - o Injurious falls
  - o Patient-reported outcomes, including mobility assessments and quality of life
  - o Nursing home admissions

  - o Bone turnover biomarkers
  - o BMD assessment (hip and spine)
- Exploratory outcomes
  - o Cognitive function
  - o Comorbidities
  - o Survival

Note that Fragility fractures or injurious falls as the primary outcome will require a very large sample size. Benefit of pharmacological treatment has also needed a large sample size.

Potential Target Population

- Patients with low BMD, high rate of falls (such as ≥2 self-reported falls/year), and frailty.
- Inclusion criteria: ≥ 75 years old with osteoporosis defined by low BMD, FRAX, and/or history of osteoporotic fracture, and with frailty defined by variable proven predictive of falls (100). Patients in nursing homes and those with dementia should be included where possible.
- Exclusions: Projected life expectancy < 2 years or estimated glomerular filtration rate < 30 mL/min/1.73 m^2, individuals who are bedridden or who have contraindications related to the drug being tested

Design of Interventions

Frailty is a complex syndrome requiring multidimensional interventions. Interventions should target two or more risk factors for falls. For example, polypharmacy and some specific medications have been associated with increase fracture risk (101, 102). The European Geriatric Medicine Society (EuGMS) Task and Finish group on Fall-Risk-Increasing Drugs (FRIDs) recently proposed practical recommendation and strategies to reduce the use of FRIDs (103). The increase risk of falls related to the use of psychotropics drugs (104), cardiovascular drugs (105) and other medications (106) is now well-known. As the field of geroscience continues to emerge, it may become possible to target aging itself (107). For example, cellular senescence represents a promising therapeutic paradigm for potentially preventing or even reversing age-related osteoporosis and simultaneously treating multiple aging comorbidities (108).

Multidomain interventions for preventing falls in older people living in the community typically include physical activity (strength and balance classes with walking practice), and deprescribing. A systematic review and meta-analysis concluded that such multidomain interventions may reduce the rate of falls and recurrent falls, although the impact on fracture reduction has not been clearly demonstrated (109).

To test an osteoporosis drug in combination with a multidomain intervention, four parallel groups are recommended: 1) osteoporosis drug alone, 2) multidomain intervention alone, 3) osteoporosis drug plus multidomain intervention, 4) placebo or active comparator.

The Multidomain Alzheimer's Prevention Trial (MAPT) study is an example of a multidomain trial in frail older adults (110). This three-year, multicenter, randomized, placebo-controlled superiority trial enrolled community-dwelling persons aged 70 or older with spontaneous memory complaints, absence of dementia, and limitations in one instrumental activity of daily living or slow gait speed. They were randomly assigned to one of four groups: 1) a multidomain intervention comprising cognitive training, physical activity, and nutritional counseling plus omega-3 polyunsaturated fatty acids with a total daily dose of 800 mg docosahexaenoic acid and 225 mg eicosapentaenoic acid, 2) the multidomain intervention plus placebo, 3) omega-3 polyunsaturated fatty acids alone, or 4) placebo alone. The trial was registered with ClinicalTrials. gov (NCT00672685).

Conclusions and next steps

The ICFSR Task Force reached several conclusions. First, it recognized that the traditional care system is inadequate for dealing with complex health disorders of aging such as frailty, where multidisciplinarity is required (111, 112). Cognitive impairment is often associated with frailty and must be taken into consideration (113, 114). The links between frailty and cognition are now well described (115–117) and integrated care like the ICOPE program have to be promoted to prevent and treat fractures in frail older persons (118–121).

Second, the Task Force suggested that reducing fracture risk among older adults requires first intervening with a powerful agent to restore the strength of bone, and then switching to an anti-resorptive agent to maintain bone health. The need for treatment is especially true after a first major hip fracture. The high cost of many of these drugs imposes a barrier to such an approach and payers will require studies that document efficacy; yet fractures themselves are costly and health economics studies show that bone forming agents are cost-effective even over short time periods. Combination therapies were also recommended, not just for treating the bone but for other factors as well, particularly in individuals who are frail. Benefits of these drugs in frail populations with high risk of fracture, short life expectancy, and high risk of adverse events such as nursing home residents should be investigated. One problem is that these frail older adults often take many drugs due to co-morbidities, including cognitive impairment, undernutrition, depression, and loneliness, raising questions about the value of further adding drugs to treat osteoporosis versus decreasing drug consumption in frail older adults. Advances in the field of geroscience may help in the future to answer these questions by introducing new biomarkers and better targeted therapies (122–124).

Third, the Task Force noted that while pathophysiology of bone fracture is the same in frail and non-frail adults, the mechanisms that lead to bone fracture – poor balance, sarcopenia, poor physical performance, sedentary lifestyle, and poor nutritional status – differ. Given these differences,

specific recommendations may be needed for interventions in people who are frail, for example by more routinely adopting multidimensional and comprehensive interventions (125). To develop these interventions, more studies are needed in people who are frail and old. In addition, high-quality research is needed to confirm the role of nutrition in reversing or preventing frailty and adverse outcomes in frail persons (126, 127). Moreover the ICOPE program developed by WHO appears to be most useful for the frail older adults with osteoporosis to maintain Intrinsic capacities, monitor functions with ICOPE MONITOR (119) and prevent further disabilities (Table 1).

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