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Frailty, Fragility Fractures and Healthy Aging: Turning Challenges into Opportunities

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Abstract

The achievement of aging is allowed by the synergistic effects of continuous medical, nutritional, and technological advancements, gradually unfolding over the last century. The extended lifespan is often not associated with health span, because stressors might cause damages at molecular and cellular levels, and accelerating the trajectories of physical and cognitive decline, with individuals' autonomy and social roles impairments. The comorbidities and physical impairments alone cannot explain the unhealthy life expectancy. In such cases, medical, surgical, and healthcare interventions may do little more than extend a poor quality of life rather than restore vitality and autonomy.

Then, quality of life trajectories cannot be appropriately captured and categorized based on chronological age thresholds, neither on stages of single or multiple non- communicable diseases (NCDs) or their consequences on physical and cognitive performance.

Since the last century, the growing discrepancy between the elongation of life expectancy and the curtailment of healthy life expectancy is posing challenges both to individuals' aspirations for longer life and to health and social systems' sustainability as the populations continue to age.

After a longstanding struggle with the limits of available knowledge, geriatric and gerontological science formulated a new concept and proposed the frailty syndrome as the crossroads between healthy and unhealthy aging trajectories of life.

The frailty is characterized by low muscle strength, low level of physical activity, low walking speed, unintentional weight loss, and fatigue and it is associated with a higher risk of disability, hospitalization and mortality.

The frail older subjects carry a complex combination of features related to physiological aging, minor and major multi-systemic alterations often associated with NCDs.

The orthogeriatric patients are the perfect example of frail older patients, as a catastrophic event, like hip fracture, place them at an exceptionally high risk of severe complications, disability, and mortality.

The connection between frailty and fragility fractures is well established, because frailty is associated with a higher risk for any fragility fractures, vertebral fracture, and hip fracture.

The early identification of frail patients in acute care setting may reduce the risk of fragility fractures through comprehensive assessment and management, including activation of multidomain interventions.

Detecting frailty in older adults during hospital admission may help prevent acute adverse events and provide appropriate secondary prevention of falls and fractures, about that the Fracture Liaison Service (FLS) has been proposed to bridge the care gap of secondary prevention, coordinate patients who have suffered falls and fragility fractures, and address bone health and fall risk most efficiently.

The frailty is the secret ring linking falls and fragility fractures in clinical practice and we have a big challenge, we can break this ring by ignoring frailty and then accelerating progression to disability and elongating years lived in disability, or we can strengthen the weakest links and try to improve intrinsic vitality.

Keywords: Ageing; Frailty; Fragility fracture; Fracture Liason Service

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Introduction

The aging population is a pervasive and global phenomenon, standing from the synergistic effects of continuous medical, nutritional, and technological advancements, gradually unfolding over the last century. Though longer life is generally desirable, extended lifespan in older people is often not associated with a proportional increase in health span and, therefore, trajectories of life in these individuals often do not follow those with desired quality of life. Then, quality of life trajectories cannot be appropriately captured and categorized based on chronological age thresholds, neither on stages of single or multiple non-communicable diseases (NCDs) or their consequences on physical and cognitive performance.

Indeed, at a certain point and under the pressure of apparently unpredictable stressors, older adults can exhibit a sudden and complex cascade of adverse health events, often compelling them to limit their range of action. Stressors might cause damages at molecular and cellular levels, then trigger sub-clinical impairment of multiple physiological systems, accelerating the trajectories of physical and cognitive decline. These impairments may rapidly affect individuals' social roles and autonomy and increase individual and societal suffering throughout their remaining years of life.

Long-lasting NCDs do not act as main predictable stressors of disabilities and suffering, as they have been found to heterogeneously influence individuals' health and life trajectories, functional abilities, and overall well-being. Moreover, NCDs, multimorbidity, and physical impairments alone cannot explain the expansion of unhealthy life expectancy. Indeed, the enormous scientific and medical efforts made in the past century led to a great reduction in mortality rates associated with cardiovascular, metabolic and cancer diseases [1]. However, mitigating the life-threatening impact of NCDs usually leads to the expansion of years lived with severe disability, especially in the oldest decades [2]. To date, unhealthy life expectancy is a metric of the years that individuals at a given age expect to live under the burden of disease and/or disability.

Once a person starts on an unhealthy trajectory, regaining a healthy pattern with a good quality of life becomes arduous and almost impossible. In such cases, medical, surgical, and healthcare interventions may do little more than extend a poor quality of life rather than restore vitality and autonomy. Since the last century, the growing discrepancy between the elongation of life expectancy and the curtailment of healthy life expectancy is posing challenges both to individuals' aspirations for longer life and to health and social systems' sustainability as the populations continue to age [3].

After a longstanding struggle with the limits of available knowledge, geriatric and gerontological science formulated a new concept and proposed the frailty syndrome as the crossroads between healthy and unhealthy aging trajectories of life.

The Frailty Concept: Moving from the Research Field to the Clinical Ground and Back Again

Though the concept of frailty has always been considered clinically sound; long-standing debate concerns the real-world usefulness and effectiveness of the above diagnostic categories.

Several controversies regarded the optimal criteria to be used for frailty identification and their ability to capture the broad spectrum of older individuals at risk of adverse events; additional doubts concerned the methodology to assess the benefits and sustainability of interventions reversing frailty [4]. However, nowadays it is clearer that frailty may serve as both a warning and an opportunity for intervention, holding the potential to restore balance and mitigate the slide from healthy to unhealthy and toward disability associated life expectancy.

At the beginning of the 21thcentury, Fried et al. proposed the criteria for the diagnosis of frailty phenotype based on data from the Cardiovascular Study [5]. Specifically, the five criteria for detecting frailty include low muscle strength, low level of physical activity, low walking speed, unintentional weight loss, and fatigue. Depending on whether such criteria are present in clinical practice, three main phenotypes could be distinguished: the robust (none of the criteria are satisfied), the pre-frail (1 or 2 criteria are satisfied), and the frail (3 or more criteria) subjects.

Frail older subjects carry a complex combination of features related to physiological aging, minor and major multi-systemic alterations, often associated with NCDs. Although aging is widely acknowledged as the main risk factor for most age-related NCDs, it is not a disease. Over the past 20 years increasing evidence demonstrated that accelerated aging and most age-related chronic diseases share common underlying physiopathological and biomolecular mechanisms, the so called "hallmarks of aging", supporting the hypothesis formulated by Geroscience that targeting such mechanisms and slowing down the aging speed at an early stage may eventually prevent or delay the onset of chronic diseases and their functional consequences and promote health span.

Specifically, such mechanisms promote, under stressors' pressure, increasing damage accumulation at molecular and cellular levels across multiple organs and systems and progressive loss of efficiency of the resilience mechanisms that are supposed to counteract such damage, leading to an increased susceptibility to multi-systemic diseases and multimorbidity [6].

Moreover, multimorbidity is associated with dynamic transitions between frailty states and death, but treatment of chronic diseases does not reduce the progression of frailty, while frailty may increase the negative health outcomes associated with treatment of chronic diseases [7].

While progressing from healthy aging to end of life, at a certain point, some individuals may develop unexpected adverse events while facing minor or major stressors and these subjects have been defined as affected by clinical syndrome of frailty. Since the beginning, it was clear that the health trajectory from robustness to frailty and its progression to the failure to thrive is not straightforward, then it might be variably affected by NCDs, and often the final outcome is unforeseeable for the expected years of life associated with severe disability.

Building on complementary evidence from bench to bedside, it has been proposed to distinguish the evolution of frailty into three main phases: early, established, and terminal ones [8]. In the early phase, frailty is a dynamic syndrome with the potential to progress

toward disability or recovery robustness. However, identifying early-stage frailty struggles to become a systematic approach in clinical practice, especially in outpatient clinics and community healthcare services (HC). Frailty trajectories depend on the synergy between intrinsic and extrinsic factors (eg. infectious disease or inappropriate drug prescription), along with the adoption of frailty-oriented management and interventions, specifically aimed at supporting multi-systemic homeostasis.

Ignoring the importance of detecting frailty in its early phase, when older adults are still living independent at home, is a dramatic mistake in our HC systems.

Misunderstanding frailty allows for the progression of the condition to generate complex interactions between age-related changes, diseases and extrinsic factors leading to the development of adverse events, dysfunctional frailty stage up to a point of no return, with established poor health and dependency for periods longer than expected, ultimately ending with a bed-ridden scenario.

Conversely, end-stage frail subjects quickly exhibit themselves in clinical practice as terminal illness, those deserving HC assistance to balance their very poor physical and cognitive functions to preserve life without perspectives for functional recovery.

Consequently, end-stage frail subjects adsorb the majority of HC interventions to cope with the needs of the body's homeostasis and supply with basic functioning, but they often do not get advantages from interventions in terms of quality of life. Therefore, the general consensus is about the relief and dignity that must be the priorities to be guaranteed to people with end-stage frailty [8].

Reasons for Detecting and Managing Frailty in Older Adults

From an HC perspective, the first step in managing older adults is agreeing on why we need to identify those with frailty. Since the original definition, frailty reveals a higher likelihood of falls, disability, hospitalization, long-term care admission, and mortality within a 3-year period, although at the time of assessment, the subject presents a state of physical and cognitive independence [9,10].

The younger the frail subject, the higher the risk of experiencing a longer lifespan of adverse health events and dependence, that is the main issue we are facing in the social and healthcare services.

The second step is recognizing what exactly implies treating and managing a "frail patient" in real-world clinical settings and how to deliver the available interventions effectively to the majority of more deserving patients.

In daily practice, a simple way to understand the meaning and implications of frailty syndrome is to conceptualize intrinsic vulnerability as akin to the "intrinsic resistance" or "resilience" of a crystal glass when facing stressors or hits. A crystal glass is universally recognized as fragile, prompting individuals to naturally adjust their approach and handling. Then, it is evident that failing to adapt and employ appropriate actions will likely result in the glass shattering. In the clinical setting, failure to recognize and manage frailty in older individuals can lead to miss opportunities to strength the intrinsic resistance to stressors, and to foster premature decline into a failure-to-thrive condition. Moreover, we daily experience that when the fragile glass shatters, it is impossible to restore its original structure and function. Similarly, this is the case of end-stage frailty in the clinical setting. Conversely, robustness can be metaphorically represented as the hardness of hard glass: we can touch and manage it more easily than a crystal, and it will function until a significant break occurs.

Although completely different in structure, both glasses express their function in the context in which they are used. However, in case of stressors, i.e. less careful management or minor hit, the crystal glass has more probability of breaking and losing its functioning.

Especially during acute health events, clinicians should be aware of underlying individuals' frailty, then act and balance potential benefits and risks related to interventions and adopt a strict monitoring approach based on comprehensive methodology. Indeed, frailty acts as an effect modifier, by modifying the risks and benefits of chronic disease treatments.

In long-term care recipients, frailty increased the association between multimorbidity, hyperpolypharmacy and mortality suggesting that the frailty subgroups may benefit from tailored deprescription. In frail older adults with atrial fibrillation, switching international normalized ratio-guided vitamin K antagonist to direct oral anticoagulant was associated with more bleeding complications without reduction in thromboembolic complications [11].

However, functional status is the primary marker of overall health and earlier indicator of recovery in such a category of patients. The clinical focus on markers of organ and body function is strongly advised, as well the systematic clinical adoption of cognitive and physical performance indicators, which help drive interventions and quantify their efficacy. In this framework, we advocate the implementation of measurement of resting and maximum metabolic rate as a strategy to quantify the multi-systemic integrated response to treatments and their impact on the body's intrinsic vitality, both in the acute and chronic phases [12].

Orthogeriatric patients are the perfect example of frail older patients, as a catastrophic event, like hip fracture, place them at an exceptionally high risk of severe complications, disability, and mortality. They are frail and affected by fragility fracture of the hip. Prompt recognition and treatment of frailty other than hip fracture may enhance the recovery of quality of life, counteracting the development of disability that has been shown to predominate over the burden of mortality. Once older adults have permanently lost their functioning, they should not be considered frail anymore, but they should be considered affected by terminal illness or failure to thrive, and at this stage of life, dignity and relief should be assured.

Frailty, Falls and Fragility Fracture and Turn Around the Trip

Fragility fractures usually follow a low-energy trauma like a fall from a standing position. Fall is a geriatric syndrome and the first signal of frailty, ready to trigger multi-systemic impairments and additional geriatric syndromes. Among fragility fractures, hip is the most alarming for older adults and their caregivers [13,14]. The connection between frailty and fragility fractures is well established. Frailty is associated with a higher risk for any fragility fractures (OR

2.12; 95% CI, 1.21-3.71), vertebral fracture (2.48; 1.84-3.61), and hip fracture (2.52; 1.09-3.21) [15]. Frailty is also highly prevalent in older adults with hip fractures hospitalized or admitted to intensive rehabilitation services [16]. In the first two years after a major fragility fracture, the risk of imminent recurrent fracture is high, especially for the spine (17.6%) or contralateral hip (13.7%), then highlighting the need for starting such preventing interventions during the hospital stay [17,18]. In the Horizon Trial, the zoledronic acid administered in the first two weeks after surgical treatment of hip fracture showed a reduction in new fragility fractures in the next five years.

The early identification of frail patients in acute care setting may reduce the risk of fragility fractures through comprehensive assessment and management, including activation of multidomain interventions. Frailty-attuned settings and specific competencies among professionals are strongly advocated over the entire pathway of care of individuals at risk or admitted due to fragility fractures. Fast-track or better fast-up approaches should be pursued, especially with older or oldest-old patients with a better functional level before fracture. In the acute phase, orthogeriatric management clearly contributes to reducing mortality, speed up the surgical repair, counteract perioperative complications (i.e., infectious diseases, delirium), leading to resources' savings.

Detecting frailty in older adults during hospital admission may help prevent acute adverse events and provide appropriate secondary prevention of falls and fractures. However, time constraints, high patient turnover associated with hospitalization, and often poor competencies in secondary prevention of falls and fractures may reduce this opportunity for patients.

The Fracture Liaison Service (FLS) has been proposed to bridge the care gap of secondary prevention, coordinate patients who have suffered falls and fragility fractures, and address bone health and fall risk most efficiently [19,20].

The FLS model is multidisciplinary, often coordinated by a nurse case-finding and conducted by a bone specialist with bone and muscle health competencies. The FLS may reduce the incidence of a new fragility re-fracture, improve the initiation rate and better adherence to the anti-fracture treatment, and guarantee long-term health and economic benefits for the patients and the community.

However, bone specialists still estimate individual fracture risk and thresholds for treatments based on prior fragility fractures and bone mineral density (BMD), then ignoring the role of falls as clinical condition increasing the risk of re-fracture. Notably, the risk of fragility fractures becomes independent of canonical risk factors as people age: BMD is insufficient to identify individuals at high risk of fractures and falls play a pivotal role. Multiple falls usually precede fragility fractures. According to WHO and the more recent guidelines in fall prevention, falling is not a normal or physiological event. Behind a fall, we usually find the failure of one or more systems sustaining stability and enhancing physiological reflex to counteract the loss of postural habit in facing environmental pitfalls [21]. Therefore, the AACE guideline proposes frailty among the clinical risk factors posing people at high risk of fragility fractures. Falls and frailty estimations are advocated and included in the FRAX and FRAX plus tools, which help to detect prognosis and target patients with effective treatments proportional to their potential benefits [22,23].

In the post-acute phase, more efforts are required to focus on the real needs of older frail adults in fostering the functional recovery and the maintenance of independence. For instance, more than half of orthogeriatric patients are independent outdoors and cognitively preserved before the index event, 49% climb the stars or walk outdoors, and only 2% are severely disabled. One year after surgery, the majority are still alive, but half of them remain permanently dependent on ADL, despite rehab interventions [20].

A better outcome in functional recovery is retrieving the functional abilities and autonomy before the fracture, and require appropriate and timely management of patients with fragility fractures, starting with timing and type of surgery, rehabilitation, nutritional, and pain control management to contrast the disability cascade. In the clinical world, we confirmed that 50% of hip fracture patients were still alive five years after the hip fracture but completely bedridden or limited to a wheelchair. These findings are aligned with evidence from a multicentric study showing that disability burden overcomes premature mortality due to a fall causing hip fracture [24].

Fragility Fracture Prevention Should Include Frailty & Falls Assessment and Management

To date, we cannot disregard available interventions for the prevention of frailty and falls since they impact fragility fractures and physical decline, altogether helping the promotion of healthy aging. Physical inactivity in midlife seems associated with a higher risk of osteoporosis and frailty in older age [25].

Physical exercise may prevent both frailty progression and osteoporosis, maintaining muscle mass and strength and bone mineral density (BMD). Multimodal interventions are pivotal for frailty prevention, and they are mainly based on resistance-based training, aerobic, balance and coordination training, and nutritional support. For instance, in the SPRINTT (Sarcopenia and Physical fRailty IN older people: multicomponent Treatment strategies) participants affected by sarcopenia and frailty, a program of aerobic exercise, resistance and balance training and flexibility with nutritional support conferred better physical performance and reduced the onset of disability [26].

In the New Zealand SUPER study, pre-frail community-dwelling older adults underwent a program of physical activity and nutritional education showed regression of frailty after six months. The beneficial effect of the physical activity and nutrition education have not retained after two years, showing a short-term benefit and the need of an ongoing participation [27].

Among type of physical activities, progressive resistance training (PRT) which are characterized by gradual and progressive increase of resistance, may guarantee the maintenance of muscle strength and muscle mass and the prevention of the development and progression of frailty status.

A higher benefit of progressive resistance training could be obtained improving the nutritional status, especially if it is associated with adequate protein intake with the diet or with oral enriched protein supplement [28]. Consistently, physical activity based on PRT and balance and mobility training improve BMD and counteract fragility fractures [29].

Compared to controls, 12-month multimodal exercise with PRT, mobility exercises and balance training improved lumbar spine and neck hip BMD (1.0 to 1.1%, $p < 0.05$), muscle strength (10 to 13%, $p < 0.05$) and physical function (timed stair climb 5%; four- square step test 6%; sit-to-stand 16%, $p < 0.05$ to < 0.001) in older adults with low BMD and/or increased risk of fall [30].

The exercise intervention may also reduce the falls and its advantage in fall prevention has been clearly showed in a Cochrane review, where the balance and functional exercises with resistance training reduced the falls by the 34% respect to the controls [31]. In community dwelling older adults, balance and functional exercises reduced the rate of falls by 24% (rate ratio 0.76, 95% CI 0.70 to 0.81; 7920 participants, 39 studies), and by 34% (rate ratio 0.66, 95% CI 0.50 to 0.88; 1374 participants, 11 studies) when resistance exercises were associated with balance and functional exercises. Then, Thai-Chi group showed a reduction in fall rate of 19% compared to controls (rate ratio 0.81, 95% CI 0.67 to 0.99; 2655 participants, 7 studies) [32].

Notably, other fall-prevention interventions such as de-prescribing of fall-related increased risk drugs, treatment of vision impairment, environmental modification and comprehensive geriatric assessment have been associated with a reduced risk of falls [33].

Conclusion

Frailty is the secret ring linking falls and fragility fractures in clinical practice. We can break this ring by ignoring frailty and then accelerating progression to disability and elongating years lived in disability, or we can strengthen the weakest links and try to improve intrinsic vitality using value-based approaches, together with frailty-attuned settings and interventions. Frailty attuned interventions along with tailored management of NCDs may antagonize the progression from robustness to frailty by supporting cellular physiological pathways and reserves, attenuating or preventing organ damage due to chronic diseases, and counteracting the body's homeostasis shrinking due to accumulated damages due to stressors.

The complex management of patients with frailty and/or fragility fractures is mainly attributable to the way HC services cope with the patients' needs in a framework where, frailty, as nonlinear factor appears in the complex equation. The orthogeriatric care is a well-established pro-active intervention to reverse or counteract frailty progression, to prevent additional falls and fragility fractures that inevitably increase the burden of admission to care facilities and reduce individuals' quality of life until death.

The principles and practices of orthogeriatric care should be expanded and integrated into outpatient and community services. A multidisciplinary approach that includes routine frailty screening is essential to better detect transitions from robustness to frailty and from early to advanced stages of frailty. This proactive strategy should be implemented within FLS to support recovery, preserve individual functioning, and prevent long-term disability [34].

This is a feasible and effective goal as the orthogeriatric FLS significantly reduced the incidence of a new fragility fracture with better adherence to anti-fracture treatments and long-term health and economic benefits, both for the patients and the community.

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