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Frailty syndrome and the crucial role of lifestyle modification in prevention and dismantling the “frailty phenotype”

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Abstract

Background: Frailty syndrome represents a profound state of increased physiological vulnerability driven by the multisystemic erosion of homeostatic resilience, distinct from mere chronological aging. As the global population ages, recognizing and managing this complex clinical entity has become a paramount challenge in geriatric and internal medicine.

Aim: To synthesize current evidence regarding the pathophysiological mechanisms underpinning frailty, evaluate diagnostic frameworks, and outline optimal clinical management strategies, with a distinct emphasis on pharmacological stewardship and targeted lifestyle medicine interventions.

Evidence Synthesis: The biological core of frailty is driven by "inflammaging," neuroendocrine dysregulation, and cellular senescence, which collectively precipitate profound anabolic resistance, sarcopenia, and dynapenia. Diagnostically, the syndrome requires a multidimensional approach utilizing the Comprehensive Geriatric Assessment (CGA). Within clinical management, diminished physiological reserves and altered pharmacokinetics severely amplify the risks of polypharmacy. Crucially, targeted lifestyle interventions remain the only validated strategies to actively reverse the frail phenotype. Progressive resistance training effectively provides the mechanical loading necessary to stimulate myofibrillar synthesis, while precision nutrition directly overrides age-related anabolic resistance and attenuates systemic inflammation.

Conclusions: Optimizing care for frail older adults requires a fundamental paradigm shift from disease-centric treatment models to holistic, function-preserving strategies. By minimizing cumulative pharmacological burden and aggressively implementing evidence-based physical and nutritional therapies, clinicians can successfully replenish depleted physiological reserves, alter the trajectory of biological decline, and sustain the patient's functional autonomy.

Key-words: aging, frailty syndrome, frailty, elderly patients, elderly, civilisation, inflammaging, lifestyle, lifestyle modification, dietary intervention, physical activity, aerobic training, resistance training, polypharmacology, multimorbidity, geriatrics

Introduction

The face of the world and the global landscape, in which humanity finds itself, have forever been in a constant state of remodelling and refitting in order to comply with the ever-changing circumstances and obstacles coming both from the outside environment and from within. The human population, which actually hasn't been around for as long as it occurs to the humans themselves, is also subject to many changes in the light of circumstances and obstacles, which it encounters and which it can neither influence nor control.

The ageing population is one of the main concerns of the scientific world nowadays, especially in medicine. The unprecedented demographic shift toward an increasingly aged global population, coupled with an epidemiological surge in chronic civilization diseases, has fundamentally altered the landscape of modern healthcare [1]. Within the specialized realm of geriatrics, clinicians face a growing cohort of patients whose management is complicated by high burdens of multimorbidity, polypharmacy, and a progressive depletion of homeostatic reserves across multiple organ systems. These compounding challenges extend beyond mere chronological ageing, resulting in a state of critical vulnerability where even minor exogenous or endogenous stressors—such as a mild infection or a change of medication administration—can trigger a disproportionate and cascading functional decline. This intersection of accumulated biological deficits, chronic disease, and diminished systemic resilience is clinically encapsulated as frailty syndrome (FS) [2]. As a distinct, multidimensional phenotype, frailty represents the ultimate common pathway of these gerontological challenges, serving as a primary predictor of adverse health outcomes, institutionalization, and mortality, thereby necessitating a paradigm shift from disease-specific treatment to comprehensive, function-centred geriatric care.

In this work, the authors aim to synthesise the current state of knowledge about FS, highlight the key components concerning its definition, underline the clinical implications, and analyse the available data on the causes and risk factors leading to it.

The definition of frailty syndrome (FS)

Despite its ubiquitous clinical recognition, frailty lacks a single, universally standardized definition, though it is fundamentally conceptualized as a complex biological syndrome characterized by a critical depletion of physiological reserves and an impaired homeostatic response to stressors. This state of heightened vulnerability stems from the cumulative,

multisystemic dysregulation that accompanies biological ageing, predisposing individuals to a disproportionate functional decline following minor acute insults.

In the absence of a singular diagnostic consensus, the operationalization of frailty has historically been bifurcated into two predominant, rigorously validated conceptual frameworks. The Phenotype Model, pioneered by Fried et al. [3], defines frailty as a distinct clinical entity strictly based on physical manifestations, requiring the presence of three or more of five specific criteria:

- unintentional weight loss driven by sarcopenia,
- self-reported exhaustion,
- subjective weakness corroborated by diminished handgrip strength,
- reduced gait speed,
- and low baseline physical activity.

Conversely, the Cumulative Deficit Model, introduced by Rockwood and Mitnitski [4], approaches frailty as an escalating continuum rather than a categorical phenotype. This framework utilizes a Frailty Index (FI) calculated mathematically as the ratio of present clinical deficits—encompassing a broad spectrum of symptoms, objective signs, comorbidities, cognitive impairments, and laboratory abnormalities—to the total number of variables assessed.

While the phenotypic approach offers rapid, standardized bedside utility focused on physical decline, the deficit accumulation model provides a highly granular, multidimensional prognostic tool that captures the vast heterogeneity of the ageing process. Ultimately, both paradigms underscore that frailty is not merely a synonym for extreme chronological age or multimorbidity, but rather a distinct, measurable pathophysiological trajectory that demands targeted diagnostic screening.

Clinical deficits associated with frailty syndrome (FS)

The clinical manifestation of frailty syndrome is driven by a synergistic accumulation of physiological deficits that span multiple organ systems, ultimately dismantling the patient's homeostatic resilience. At the core of this multisystem dysregulation is a profound musculoskeletal decline, predominantly characterized by sarcopenia and dynapenia [5], which precipitate a cascade of impaired mobility, recurrent falls, and a progressive loss of functional independence [6].

This physical deterioration is inextricably linked to underlying neuroendocrine and metabolic perturbations, including profound anabolic resistance, hypothalamic-pituitary-adrenal (HPA) axis dysregulation, and the depletion of key trophic hormones such as insulin-like growth factor 1 (IGF-1), testosterone, and dehydroepiandrosterone sulphate (DHEA-S) [7]. Concurrently, the pathophysiology of frailty is deeply rooted in immune system dysfunction, most notably manifesting as "inflammaging"—a state of chronic, low-grade systemic inflammation marked by persistently elevated levels of pro-inflammatory cytokines like interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP) [8]. This persistent inflammatory state not only accelerates skeletal muscle catabolism and cachexia but also exacerbates immunosenescence, rendering the frail patient highly susceptible to infections, delayed wound healing, and blunted responses to pharmacological therapies [9]. Furthermore, these somatic deficits are frequently compounded by neurocognitive impairments, ranging from mild cognitive decline and depressive syndromes to profound autonomic dysregulation, such as orthostatic hypotension and altered thermoregulation. Crucially, these clinical deficits do not operate in isolation; they interact in a self-perpetuating, vicious cycle of energy depletion and biological wear-and-tear, progressively stripping the patient of their physiological buffer and transforming otherwise trivial clinical stressors into potentially catastrophic, life-threatening events.

Multimorbidity and polypharmacy

The clinical management of frailty syndrome is inextricably complicated by the high prevalence of multimorbidity and its inevitable clinical outcome, polypharmacy. While multimorbidity — defined as the coexistence of multiple chronic conditions — frequently overlaps with frailty [10], the two are distinct yet highly synergistic constructs; an increasing burden of chronic disease serves as a primary catalyst for the cumulative physiological exhaustion that precipitates the frail state. The mandate to treat these concurrent pathologies in accordance with standard medical practice systematically leads to polypharmacy, typically operationalized as the concurrent daily use of five or more medications. In the context of frailty, this extensive pharmacological burden introduces profound iatrogenic risks [11]. Frail patients exhibit significant age- and syndrome-related alterations in pharmacokinetics and pharmacodynamics, including diminished hepatic metabolism, impaired renal clearance, and altered volume of distribution driven by changes in body composition, such as extreme sarcopenia. Consequently, they are exceptionally vulnerable to adverse drug events (ADEs), complex drug-drug and drug-disease interactions, and detrimental prescribing cascades [12]. These pharmacological insults

frequently manifest as atypical geriatric syndromes — such as delirium, orthostatic hypotension, and recurrent falls — which independently accelerate functional decline and loss of independence [13].

Ultimately, the intersection of multimorbidity and polypharmacy in frail individuals engenders a vicious, self-perpetuating cycle of biological wear-and-tear. This clinical reality necessitates a strategic departure from strict, single-disease evidence-based guidelines, mandating instead a holistic, patient-centred approach that prioritizes comprehensive medication reviews, the careful avoidance of potentially inappropriate medications (PIMs), and proactive deprescribing strategies to preserve remaining homeostatic reserves and mitigate further iatrogenic morbidity.

To mitigate the profound iatrogenic risks of polypharmacy in frail populations, clinicians frequently utilize the American Geriatrics Society (AGS) Beers Criteria [14]. This evidence-based framework identifies potentially inappropriate medications (PIMs) that exhibit an unfavourable risk-benefit profile in older adults. In the context of frailty syndrome, where diminished homeostatic reserves and altered pharmacokinetics significantly amplify drug toxicity, applying these guidelines is crucial. The criteria highlight specific drug classes — such as potent anticholinergics and benzodiazepines — that directly precipitate severe adverse outcomes, including delirium, orthostatic hypotension, and falls [15]. Rather than serving as rigid contraindications, the Beers Criteria act as a strategic catalyst for comprehensive medication reconciliation and proactive deprescribing. Integrating this screening tool into routine geriatric assessments helps curtail detrimental prescribing cascades, minimize cumulative pharmacological burden, and preserve the patient's remaining functional autonomy.

Pathophysiology and clinical presentation

The pathophysiology of frailty syndrome is driven by a profound, multisystemic erosion of homeostatic resilience, originating from the cumulative cellular damage inherent to biological aging [16].

At the microscopic level, this biological decline is underpinned by fundamental hallmarks of aging, including telomere attrition, oxidative stress, profound mitochondrial dysfunction, and the accumulation of senescent cells that actively secrete a pathological senescence-associated secretory phenotype (SASP) [17]. This aberrant cellular signalling directly orchestrates "inflammaging"—a pervasive, chronic, low-grade systemic inflammation characterized by elevated baseline levels of cytokines such as interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α), and C-reactive protein (CRP).

Concurrently, the patient's neuroendocrine state undergoes severe maladaptation, marked by hypothalamic-pituitary-adrenal (HPA) axis dysregulation and a continuous depletion of vital anabolic hormones, including insulin-like growth factor 1 (IGF-1) and dehydroepiandrosterone sulfate (DHEA-S) [7].

The synergistic impact of this hyper-inflammatory and anti-anabolic microenvironment fundamentally disrupts protein metabolism, precipitating severe anabolic resistance that drives the progressive loss of skeletal muscle mass and force, clinically recognized as sarcopenia and dynapenia. This cellular and biochemical deterioration directly translates into the macroscopic clinical presentation of frailty: a state of extreme systemic energy depletion [18].

Clinically, the patient presents with the classic phenotypic constellation of physical manifestations described by Fried et al. [3]: unintentional weight loss, profound self-reported exhaustion, subjective weakness corroborated by reduced handgrip strength, and noticeably diminished gait speed. Furthermore, this systemic exhaustion frequently presents alongside a broader geriatric symptom complex, including subtle cognitive slowing, impaired thermoregulation, and orthostatic hypotension.

Ultimately, the defining clinical hallmark of frailty is this heightened state of vulnerability, wherein the severely depleted physiological buffers leave the patient unable to mount an effective response to minor external stressors.

Clinical management and treatment optimisation

The optimal clinical management of frailty syndrome necessitates a fundamental paradigm shift away from fragmented, disease-centric treatment models toward a holistic, highly individualized, and function-preserving approach.

The absolute cornerstone of this therapeutic strategy is the Comprehensive Geriatric Assessment (CGA), an evidence-based, multidimensional, and interdisciplinary diagnostic framework designed to systematically quantify the patient's medical, cognitive, and psychosocial reserves [19]. A critical objective within this framework is rigorous pharmacological stewardship; treatment optimization mandates routine medication reconciliation and the strategic implementation of proactive deprescribing. By systematically applying validated pharmacovigilance tools, such as the AGS Beers Criteria and the STOPP/START guidelines, clinicians can meticulously taper potentially inappropriate medications (PIMs), thereby mitigating the profound iatrogenic risks and detrimental prescribing cascades inherent to polypharmacy.

Concurrently, this pharmacological rationalization must be intrinsically coupled with robust non-pharmacological interventions rooted in lifestyle medicine. The targeted prescription of multicomponent exercise regimens — particularly progressive resistance training to counteract sarcopenia [20] — alongside precise nutritional optimization and the correction of micronutrient deficits, forms the only validated therapeutic modality capable of modifying the syndrome's trajectory [21]. Furthermore, effective clinical management must anticipate and pre-emptively mitigate acute physiological stressors to prevent catastrophic functional collapse during hospitalizations or minor acute illnesses, which requires standardized protocols to prevent delirium, immobilization, and malnutrition.

Eventually, optimizing treatment in the frail patient requires a deliberate recalibration of therapeutic targets: shifting the clinical focus from achieving aggressive, disease-specific biochemical markers toward preserving remaining homeostatic resilience, extending functional independence, and rigorously aligning all medical interventions with the patient's overarching quality-of-life parameters and goals of care.

Lifestyle modification as a baseline intervention

Given the absence of definitive pharmacological therapies for frailty syndrome, evidence-based lifestyle medicine interventions — specifically targeted physical activity and nutritional optimization — constitute the absolute cornerstone of its management and potential reversal. Multicomponent exercise regimens, prioritizing progressive resistance training combined with aerobic and balance conditioning, have proven highly effective in dismantling the core of frailty. Resistance training is particularly critical; it provides the robust mechanical loading necessary to stimulate muscle protein synthesis, induce neuromuscular adaptations, and systematically counteract the profound sarcopenia and dynapenia characteristic of the syndrome. Concurrently, regular aerobic exercise enhances mitochondrial biogenesis, improves metabolic flexibility, and restores cardiovascular reserve [22].

Emerging epidemiological and robust clinical data unequivocally establish structured physical activity as the most potent, evidence-based intervention for both the primary prevention and targeted treatment of frailty syndrome. From a prophylactic standpoint, maintaining consistent physical exertion fundamentally delays the onset of the frailty continuum by preserving alpha-motor neuron integrity, sustaining bone mineral density, and buffering the age-related depletion of cardiopulmonary reserves [23]. In the clinical management of established frailty, comprehensive meta-analyses mandate the implementation of multicomponent exercise regimens—integrating progressive resistance, aerobic, and balance training — as the gold

standard of care. Progressive resistance training serves as the critical biological countermeasure to the syndrome's core by delivering essential mechanical loading, it directly stimulates the mTOR signalling cascade, facilitating myofibrillar protein synthesis and actively overcoming the deep-seated anabolic resistance characteristic of the frail state. Concurrently, the aerobic component drives mitochondrial biogenesis and enhances metabolic flexibility [24]. Crucially, the regular contraction of skeletal muscle acts as an endocrine organ, releasing protective myokines that exert a robust systemic anti-inflammatory effect, directly attenuating the pervasive "inflammaging" microenvironment that accelerates physiological decline. Clinically, these cellular and metabolic adaptations translate into quantifiable, statistically significant improvements in validated frailty metrics, most notably reversing deficits in gait speed and handgrip strength while significantly reducing the incidence of falls [25]. Ultimately, the current data demonstrate that the prescription of tailored physical activity is not merely an adjunctive lifestyle recommendation, but a primary, disease-modifying medical intervention capable of replenishing homeostatic resilience and reversing the trajectory of functional collapse.

However, the efficacy of physical activity is heavily contingent upon concurrent nutritional support, as the frail patient typically exhibits profound age-related anabolic resistance and an accelerated catabolic drive fuelled by inflammaging. To overcome this physiological barrier, nutritional interventions must focus on augmented dietary protein intake — frequently recommending 1.2 to 1.5 g/kg/day, [26] which significantly exceeds standard adult requirements. This is often optimized through targeted supplementation with essential amino acids, particularly leucine, to adequately trigger the mTOR signalling pathway and facilitate myofibrillar synthesis. Furthermore, shifting the patient toward anti-inflammatory dietary patterns alongside the aggressive correction of specific micronutrient deficits, directly modulates the underlying pro-inflammatory microenvironment.

Targeted nutritional optimization is a fundamental pillar in preventing and reversing frailty syndrome. The provision of high-quality proteins, particularly leucine-rich sources, is critical to facilitate myofibrillar synthesis. Beyond protein density, adherence to anti-inflammatory eating patterns — most notably the Mediterranean diet — provides essential polyphenols and omega-3 fatty acids that directly attenuate the systemic "inflammaging" accelerating physiological decline [8]. Combined with the aggressive correction of specific micronutrient deficits, such as Vitamin D hypovitaminosis to preserve neuromuscular integrity, precision

clinical nutrition serves as a potent, disease-modifying intervention that replenishes depleted homeostatic reserves [27-28].

Ultimately, the synergistic application of these paired lifestyle modifications extends beyond symptomatic management; it fundamentally alters the biological trajectory of frailty, replenishing the depleted homeostatic reserve and restoring the patient's functional autonomy.

Conclusion

In conclusion, frailty syndrome represents a critical geriatric imperative that demands a clinical paradigm shift away from disease-centric treatment models toward the active preservation of biological resilience. Driven by the synergistic forces of "inflammaging," neuroendocrine dysregulation, and progressive sarcopenia, frailty necessitates a highly individualized, multidisciplinary approach anchored by the Comprehensive Geriatric Assessment (CGA). Mitigating iatrogenic risks through rigorous pharmacological stewardship and targeted deprescribing is paramount to prevent catastrophic functional collapse.

However, the true cornerstone of disease modification lies in lifestyle medicine. The strategic integration of progressive resistance training and optimized, high-protein, anti-inflammatory nutrition currently stands as the only evidence-based therapeutic modality capable of actively replenishing depleted homeostatic reserves and reversing the frailty phenotype. Ultimately, the systematic incorporation of these functional endpoints and lifestyle interventions into routine clinical practice is essential to alter the trajectory of decline and sustain autonomy in the aging population.

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