

## REVIEW ARTICLE

# Frailty Syndrome : A Review

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### Abstract

Frailty is a condition associated with ageing, co-morbidity and disability. Frailty was an elusive concept earlier despite efforts at consensus. There is now a better understanding of the multisystem dysfunction and the instability involved and an apparent clarity on measures that could correct deficits and ameliorate symptoms.

The syndrome of frailty describes older people at a higher risk for adverse health outcomes such as illnesses, hospitalisations, disability and mortality. Clinically, it is diagnosed on combination of specific symptoms such as weight loss, muscle weakness / fatigue, low physical activity and slow walking speed. It can be identified by a multi-domain assessment of function. Interventions aimed at causative factors may help prevent conversion of frailty into disability. Current management measures are related to promoting physical activity including resistance training, clinical nutrition modifications in protein / amino-acids intakes, and usage of pharmacologic agents-ACE inhibitors, hormones-GH /testosterone in carefully investigated and selected patients. Large healthcare interventions and pharmacological trials are in progress.

### Introduction

Frailty is known to affect humans for centuries. In Europe ageing was paraphrased as frailty. Population aging occurs at different rates in varying geographic regions of the world. In India, influence of ageing on the development of disorders and its treatment were described in Ayurveda. The current demographic changes in India are obvious – the life span has increased in both males and females to above 60 years. It is estimated that there are over 9 crore citizens over 60 years of age. Ayurveda recommends “rasayana”, for recovery from frailty. The term frailty was used rather vaguely to justify the lack/necessity of investigation and intervention in older people.<sup>1</sup> In general frailty is described as a physiologic syndrome characterised by decreased reserve and diminished resistance to stressors, resulting from cumulative decline across multiple physiologic systems, causing vulnerability to adverse outcomes and high risk of death.<sup>2</sup>

### Prevalence

Estimates of frailty vary per location and setup - low in the community and higher in the nursing homes. Using widely used frailty phenotype framework by Fried et al,<sup>3</sup> the four year incidence was 7.2% in non-institutional, community dwelling older adults. The overall prevalence was 6.9% in community dwelling. The prevalence of frailty was observed to be 8.4% in the Toledo Study in Spain.<sup>4</sup>

The incidence of frailty increases with 1) age 2) women 3) African Americans 4) lower education and income 5) poor health 6) chronic co-morbid diseases and disability.<sup>2</sup> It is thus highly prevalent in old age and confers high risk for falls, disability, hospitalisations and mortality. The syndromes of frailty, co-morbidity and disability overlap but are not concordant. Co-morbidity is an aetiologic risk factor, whereas disability is an outcome of frailty.

The frailty phenotype helps as an independent predictive factor in terms of 3 year

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falls, worsening mobility or activities of daily living (ADL), disability, hospitalisation and death.<sup>3</sup>

## Definitions and Descriptions

A clear definition which meets the rigorous criteria of content, construct and criterion validity remains elusive. Frailty remains in the diagnostic category of being a syndrome. It is neither an inevitable part of old age nor of cumulative chronic diseases.<sup>5</sup> Many consider frailty as a distinct clinical and physiological entity. Simply put frailty is a wasting syndrome of old age that leaves a person vulnerable to falls, functional decline, morbidity and mortality.<sup>6</sup> Alternatively it is also defined as a geriatric syndrome of increased vulnerability to environmental factors with underlying pathophysiological models (mechanisms) related to hormonal adjustments, sarcopenia and vitamin deficiencies.<sup>7</sup>

Frailty is usually described as a complex pro-inflammatory condition that occurs during the aging process and results from an imbalance and dysregulation of interrelated systems such as a) the immune system (with cytokine expression). b) The neuroendocrine system (with hormonal decline) and c) with the body compositional changes (with the loss of muscle mass and muscle strength or sarcopenia). Sarcopenia, in fact is recognised as the key feature of frailty.<sup>1</sup> Finally, frailty is a condition with physical and cognitive domains, related to aging, disability and chronic disease with “reserve and resilience” as the hallmarks required to define and quantify it.<sup>8</sup>

Older persons who are considered frail by any definition have overt changes in the four main processes- body composition, homeostatic dysregulation, energetic failure and neurodegeneration, the characteristics of the ageing “phenotype”.<sup>2</sup> However, the heterogeneity and dynamic nature of the aging phenotype has to be recognised.

On a positive and optimistic viewpoint, frailty is neither to be considered as a pre-morbid state defining end of life nor an irreversible process or an inevitable trajectory to death.

Frailty, to the patient may mean: a) being dependent on others, b) experiencing accelerated aging, c) having many chronic illnesses, d) having complex medical/psychosocial problems, e) being at substantial risk of dependency and other adverse health outcomes. f) having “atypical” disease presentation. g) being able to benefit from specific geriatric programme. The geriatric assessment includes the following components: medical, cognitive, affective, functional, social-support/caregiver, economic, environmental and advanced direction. The medical assessment includes - visual, hearing, malnutrition/weight loss,

urinary incontinence, gait and balancing disorders and polypharmacy.

## Natural History and Evolution

Conceptually the development of frailty is progressive and multi-systemic. Weakness is the most common initial manifestation of the frailty phenotype. As per the natural history of frailty, the phenomenon tends to be of progressive manifestations. The transition between different states assumes significance in that, early detection of subclinical changes or deficits at the molecular, cellular or physiological levels would be the key to prevent or delay its development.<sup>9</sup>

Very recently, deficit scaling has been identified and sequenced : a) age related sub-cellular deficits might become macroscopically visible and give rise to frailty; b) cellular defects occur when sub-cellular damage has neither been repaired nor cleared; c) with greater cellular deficit accumulation, detection becomes more likely; d) deficit detection can be either subclinical (laboratory, imaging, electro diagnostics) or clinical; crucially concluding that frailty arises in relation to the number of organ systems wherein deficits accumulate and importantly that not all clinically evident defects need cross a disease threshold.<sup>10</sup>

Clinicians may be inclined to draw comparisons with the well-known tip of the iceberg phenomenon, prehypertension / prediabetes where a patient’s symptoms are yet to appear on the clinical horizon. A number of dysregulated physiological systems, independent of old age and chronic disease can have, synergistic effects of individual abnormalities, that may be relatively mild. It is postulated that a haphazard and erratic accumulation of remotely related or unrelated factors causing cellular deficits or a sequential cascade of related / linked factors may lead to deficits that result in the detrimental alteration of the metabolic milieu by enhancing the allostatic load and causing and perpetuating homeostasis resulting ultimately in frailty.

## Aetiologic Mechanisms

Epidemiological studies have identified several risk factors such as a) chronic diseases-diabetes mellitus, chronic kidney disease, expression and cognitive impairment<sup>11</sup> b)physiological impairment- activation of inflammatory processes and coagulation.<sup>12</sup> Other factors include; anaemia,<sup>13</sup> atherosclerosis,<sup>14</sup> autonomic dysfunction,<sup>15,16</sup> obesity, hormonal abnormalities.<sup>17</sup> Biological factors may include pro-inflammatory state, compromised immune function, reduced anabolic hormones like growth hormones and androgens, stress, oxidative stress and damage, increased catabolism, increased cortisol,<sup>18</sup> insulin resistance,<sup>19</sup> micronutrient deficiency and

multisystem physiologic dysregulation.<sup>20</sup> Knowledge and advances on modifiable risk factors offer sound basis for translational research efforts aimed towards prevention and treatment of frailty. Further the biological underpinnings tend to be multi-factorial and may involve dysregulation within / across many physiological systems.

## Clinical Presentation

A classic clinical case would be an older women with sarcopenic obesity characterised by increased body fat and decreased muscle (body composition changes); extremely low exercise tolerance and extreme fatigue (energetic failure); high insulin, low IGF1, inadequate intake of calories, low vitamin D, E and carotenoids (signal dysregulation), memory problems, slow gait and unstable balance. (neurodegeneration). The geriatric syndromes that include incontinence, delirium, falls, pressure ulcers, sleep disorders, problems with eating or feeding, pain and depressed mood, dementia and physical disabilities should be considered as phenotypic consequences of frailty.

Clinically it is recognised by the clinician by the combination of specific symptoms such as weight loss, weakness, fatigue, slow walking speed and low physical activity. In this syndrome / constellation of symptoms when severe and more than three of these manifestations are present, individual is at a high risk of death. Frailty is defined by deficit accumulation<sup>21</sup> and Geriatric Medicine is defined by frailty; as deficits (symptoms, signs, illnesses and disabilities) accumulate, individual become more susceptible to adverse health outcomes.<sup>22</sup> For implementing frailty assessment into clinical practice, there are seven markers—cognition, energy (levels), mobility, mood, nutrition, physical activity and strength.<sup>23</sup> In geriatric practice there may be an intermediate stage of identifying those at high risk of frailty: e.g. diabetics, hypertensives, chronic kidney disease patients and the like. Transitions between frailty states are known---non-frail (0), pre-frail (1 or 2) and the frail (3 or more), based on the presence of criteria laid down respectively.<sup>24</sup> Interventions focussed on the determinant factors of frailty can prevent the transition from frailty to disability.<sup>24</sup> For instance in cancer patients, the benefit of chemotherapy or other therapeutic options may be lower in the frail than in the robust elderly. The main interest in the concept of frailty is its reversible nature. Identification and assessment of frailty is a multi-domain matter that includes a) musculoskeletal function- strength (grip)<sup>25</sup> b) aerobic capacity-cardiorespiratory function c) cognitive function, d) integrative neurological function .-balance and gait and e) nutritional status-comprehensive approach<sup>26</sup> that addresses both - the precipitating acute illness and underlying loss of

function of organ systems is necessary. Frailty has obvious implications in pre-operative assessment, post-operative complications and extended hospital care / stay. Frailty and disability may co-exist; frailty indicates increased vulnerability<sup>27</sup> to loss of function.

Several indices exist to determine the status of function against the backdrop of frailty. The commonly used ones are 6 minute walk, walking speed, long distance corridor walk and index of independence in activities of daily living (ADLs).<sup>2</sup> The others are:

1. Barthel Index:<sup>2</sup> the parameters measured are independence and need for help in feeding, transferring from bed to chair, grooming and similar daily activities.
2. Functional Independence Measure:<sup>2</sup> Motor and cognitive functions are assessed.
3. Berg balance scale: performance in 14 different tasks related to balance.<sup>2</sup>

Further there is a tendency on the part of elderly to attribute every new symptom to senescence and ill health as a consequence of ageing.

## Management

- A. Diet and medications: Currently, the evidence of treatment of frailty is limited. As pointed earlier sarcopenia is the key feature<sup>28</sup> of frailty and requires to be addressed adequately. It is an age related loss of lean muscle mass, strength<sup>29</sup> and functionality. Altered hormones, poor dietary protein intake, lack of exercise, oxidative stress and inflammation are considered contributory factors to sarcopenia. Loss of skeletal muscle mass and associated weakness may occur as a critical co-morbidity in human disease. Secondary muscle dysfunction is seen in diabetes mellitus, metabolic syndrome, congestive heart failure, cancer associated cachexia, sepsis, renal failure, chronic obstructive lung disease and in natural ageing process. Ageing does not inevitably reduce the anabolic response to a high quality protein meal. Recommendations<sup>30</sup> translated for Indian adult patient of 50 Kg weight would amount to 16-20 grams protein / meal on three such intakes in a span of twenty four hours. Further, the total protein intake of approximately 50 grams per day should be evenly spread over the three meals. Leucine rich essential amino acid intake requires to be encouraged. Energy intake also requires to be adequate. Whey protein, omega 3 fatty acids rich items, amino acid glutamine, carnitine, vitamin D have been suggested for their useful role. Even growth hormone, DHEA, testosterone when deficient, may be considered on bio-identical hormone replacement basis. Angiotensin converting enzyme inhibitors

through improvement of endothelial function are suggested to be useful in patients of sarcopenia. The newer drug of promise on the clinical horizon appears to be MK 677 (an oral ghrelin mimic).<sup>31</sup> In short the most relevant protective counter measures to slow down the decline of muscle mass/strength could be adopted. Comprehensive geriatric assessment is crucial.

- B. Exercise is likely to benefit even the frailest of older adults. Findings in a study suggest that muscle contractile protein synthetic pathways in physically frail 76-92 year old women and men respond and adapt to the increased contractile activity associated with progressive resistance exercise training.<sup>32</sup> The programme of resistance training on at least two occasions per week can improve muscle strength, marginally the muscle size and the gait velocity. Training may also improve the mobility and also spontaneous physical activity. Whole body vibration exercise<sup>33</sup> could be an effective method. The overall goal is all inclusive care with patient centred service that can reduce the necessity for institutional stay and diminish hospitalisations.

Geriatricians differ from general physicians in that they focus on improving function as opposed to focussing on treating specific diseases. In the context of frailty, the physicians will do well in adopting this approach. Viewed as a public health policy issue in India,<sup>34</sup> the numbers<sup>35</sup> of elderly can pose a preparatory challenge. In the global context, China will be required to face the epidemic of frailty that looms large.

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