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FRAILTY AND ITS SIGNIFICANCE IN OLD AGE

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INTRODUCTION

Old age is often associated with common diseases and disabilities while frailty, a relatively lesser known condition also accompanies old age. In the layman's language, the term frailty implies someone as weak, infirm, or fragile. Medically, frailty is a well-recognized important condition of old age and with increasing life span among Indians, it is being observed more in our country also. Frailty is defined as a clinically recognizable state of older adults with increased vulnerability, resulting from age associated decline in physiologic reserve and function across multiple organ systems, such that the ability to cope with every day or acute stressors is compromised and mortality is hastened (1,2). Frailty develops as a slow process in an ageing individual often without awareness to the patient or his family members. Longitudinal studies have identified several negative outcomes of frailty that have huge impact on the lives of patients and the society (3). It is therefore important to distinguish frailty from normal ageing process and diagnose it early to prevent its progression. Clinically, it is diagnosed on the basis of combination of specific symptoms such as weight loss (shrinking), weakness (low muscle strength), fatigue (exhaustion), slow walking speed (slowness) and low physical activity. Table 1 depicts why early diagnosis and therefore early management of frailty is important.

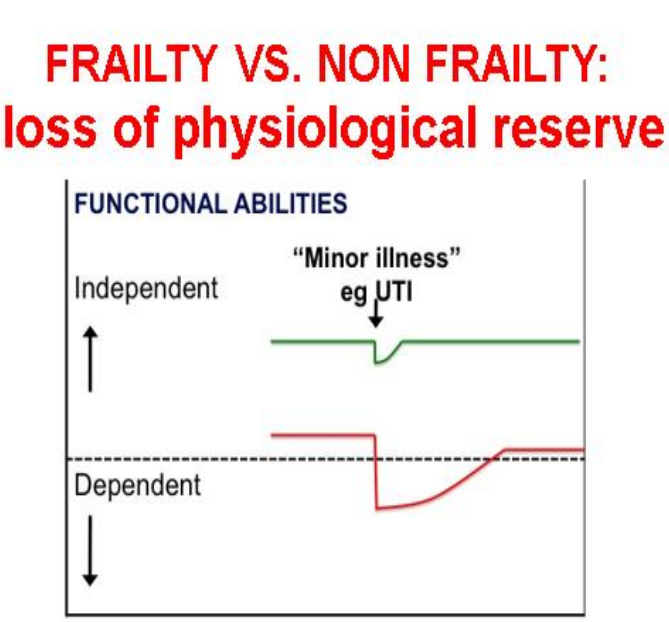
TABLE 1: WHY FRAILTY IS IMPORTANT

- Predicts early mortality
- Predicts adverse health outcomes
- Predicts repeated falls and disabilities
- Leads to recurrent hospitalizations and nursing home admissions
- Impacts vaccine effectiveness
- Provides risk assessment and stratification for the heterogeneous community dwelling elderly population
- Provides risk assessment and stratification for those with serious diseases like CVDs, cancer and HIV and for those undergoing surgical procedures

Frailty may be slowly initiated by disease, lack of activity, inadequate nutritional intake, or even the physiologic changes of aging but any acute stressor like minor illness, infection, new drug, or minor surgery can result in a striking and disproportionate change in health status such as independent to dependent, mobile to immobile, stability to falls or lucid to delirious state. If such oscillations in health occur repeatedly, frailty advances in a stepwise process, with increments precipitated by acute events. Once the elderly becomes frail, there is rapid often, progressive,

and self-perpetuating downward spiral toward failure to thrive and death (4). Figure 1 shows the difference between frail and non-frail elderly individual. Upper line represents a fit elderly where a minor illness results in a small deterioration in function and then returns to homeostasis. Lower line represents frail elderly where a similar stressor results in a larger functional dependency and who does not return to baseline homeostasis (5).

FIGURE 1: DIFFERENCE BETWEEN FRAIL AND NON-FRAIL ELDERLY

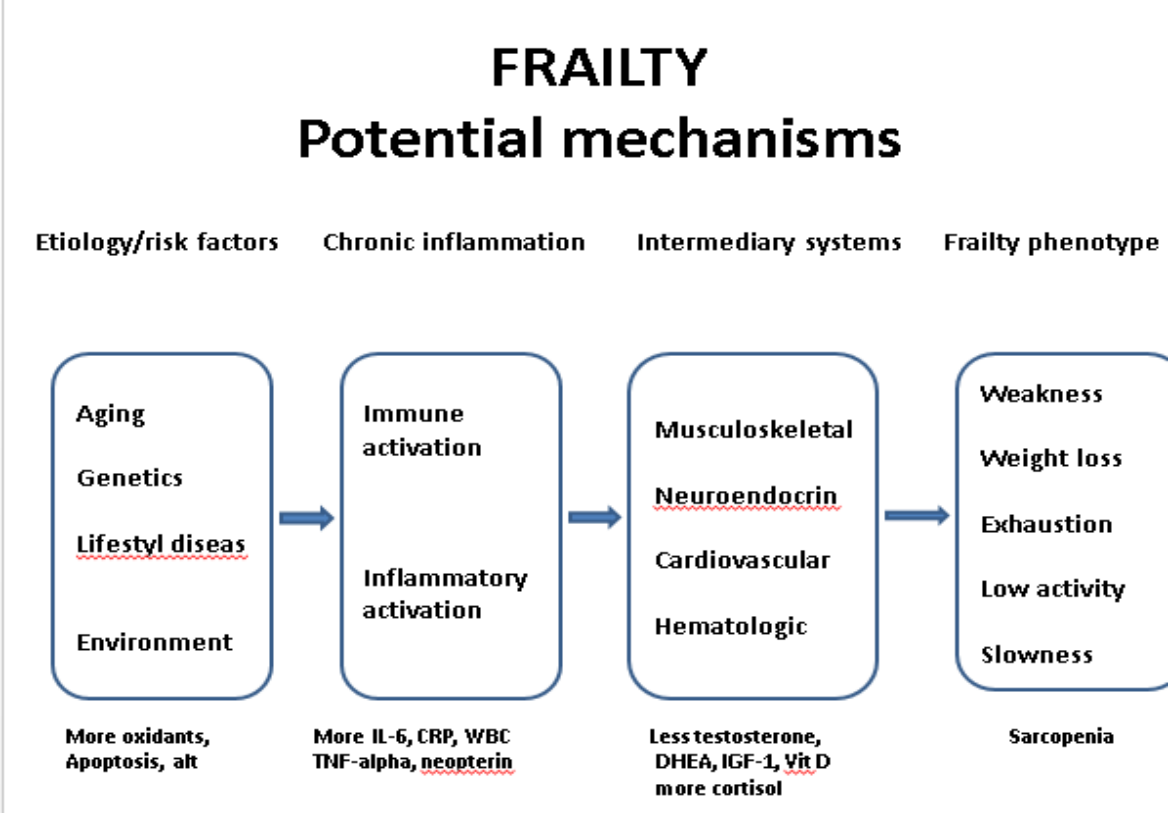


ETIOLOGICAL MECHANISMS OF FRAILTY

Ageing related changes, genetic influences, certain environments that promote social isolation and depression and lifestyle related diseases such as diabetes, COPD, CHD, hypertension, arthritis and chronic kidney disease which are often contributed by unhealthy diets, obesity, physical inactivity, smoking, and drinking are all known to be associated with more oxidant formation and apoptosis and make a particular genotype of people vulnerable to frailty (6,7). Further, chronic inflammation, the endocrine system, and sarcopenia and their interactions are the likely etiological mechanisms of frailty (8). A state of persistent, low grade inflammation as measured by increased levels of serum inflammatory mediators such as white blood cells, the cytokine interleukin-6 (IL-6), alpha tumor necrosis factor, neopterin and C-reactive protein(CRP) occurs

with ageing. This inflammatory state contributes to frailty through intermediary systems including musculoskeletal, cardiovascular, hematological and other systems which then undergo reduced physiological reserve. Figure 2 depicts potential mechanisms of frailty.

FIGURE 2: POTENTIAL MECHANISMS OF FRAILTY



The hypothalamic-pituitary-testicular and growth hormone-insulin-like growth factor-1 (GH-IGF-1) axes are key regulators in energetics. Sex hormones (e.g., dehydroepiandrosterone sulfate [DHEA-S]) and growth factors (e.g., IGF-1, transforming growth factor -β [TGF-β]) in particular, are essential to skeletal muscle metabolism. The development of sarcopenia in older men and women with decreasing serum testosterone and estrogen, respectively, is well established. Low IGF-1 is independently associated with progressive disability, poor strength, slow walking speed, and increased mortality. Numerous epidemiological studies suggest that vitamin D deficiency also impairs muscle function and therefore increases risk for falls, sarcopenia, poor physical function, and disability. Finally, age-related cortisol increase secondary to the loss of stringent hypothalamic-pituitary-adrenal (HPA) regulation likely contributes to decreased skeletal muscle mass and strength. Because muscle weakness, loss of strength, and poor physical function are central features in frailty syndrome, sarcopenia likely has an etiological role in frailty (9).

ASSESSMENT OF FRAILTY

Over 25 frailty tools have been developed to measure frailty. Two of these are commonly discussed namely Fried's five items based frailty phenotype i.e. FP criteria (10) and Rockwood's multi-item criteria (11) based on diseases, physical and cognitive impairments, psychosocial risk factors and common geriatric syndromes other than frailty (these multi-items are cumulative deficits identified on comprehensive geriatric assessment-CGA). Just to name few other frailty tools, these are FRAIL scale (Fatigue, Resistance, Ambulation, Illness, Loss of weight), PRISMA 7 question scale, Gerontopole Frailty Screening Tool, Groningen Frailty Indicator (GFI), Ageing and Retirement in Europe (SHARE-F1), Frailty Indicator for Primary Care of the Survey of Health and many others (12,13). Another assessment tool is the Short Physical Performance Battery (SPPB) which encompasses slowness, weakness, and balance. This is measured by a series of 3 timed physical performance tests (gait speed, chair rises, and tandem balance), each is scored 0 to 4 and a total score ≤5 of 12 is required for a diagnosis of frailty (14).

As already alluded to, two main phenotypes are the Fried's phenotype of physical frailty and a much broader Rockwood's phenotype including cognitive, functional, and social circumstances considered as a multi domain phenotype. Table 2 summarizes Fried's criteria.

TABLE 2: DIAGNOSTIC TOOLS OF FRAILTY
(Fried's 5 items based frailty phenotype-FP criteria, 2001)

- MOBILITY: Unable to walk 4 meters in 6 seconds i.e. ***slowness***
- STRENGTH: Grip strength < 12 Kg (male), < 7 Kg (female) i.e. ***weakness***
- NUTRITION: => 4 Kg weight loss in the past year i.e. ***shrinkage***
- ENERGY: Self-reported exhaustion 3-4 days in a week i.e. ***exhaustion***
- PHY. ACTIVITY: Zero weight bearing or > 6 hrs. sitting/lying i.e. ***low P A***

(Sarcopenia is very important feature in frailty)

SCORING: 1 point for each item. => 3: Frail; 1-2: Pre-frail; 0: Non-frail or robust

With regard to multi-domain phenotype, Initially, Rockwood included 92 deficits but later typically 30-70 deficits were included in various studies without loss of predictive value. The more the individuals have deficits, more likely is the possibility of frailty. These deficits are used to calculate what is known as Frailty Index (FI). FI is equal to number of deficits present in the patient divided by total number of deficits included (15). Thus if there are 20 deficits present out of 92, FI will be 0.22. Song et al calculated FI from 36 self-reported health deficits (based on medical conditions, health attitudes, symptoms and functional impairments) and found it equally effective when compared to clinically assessed deficits (16). He stated that non-frail will have FI of <=0.08 i.e. <=3 out of 36 deficits, pre-frail will have FI of 0.08 to 0.24 i.e. 4-8 out of 36 deficits while frail will have FI of >=0.25 i.e. >9 out of 36 deficits. Subsequent workers have used a biomarker based frailty index also as an additional diagnostic tool of frailty, employing

inflammatory, hematological, cellular, immunoscenescent and genetic/epigenetic components (17).

Although Rockwood's FI is more sensitive predictor of adverse health outcomes, because of inclusion of deficits (including disability and dementia) that likely have causal relationships with adverse clinical outcomes, many workers do not regard disability and dementia as components of frailty; rather these are regarded as outcomes of frailty. Table 3 illustrates comparison between Fried's FP (frailty phenotype) and Rockwood's FI (frailty index) criteria.

TABLE 3: COMPARISON OF FRIED FP AND ROCKWOOD FRAILTY INDEX (FI) CRITERIA

- FP is more widely used than FI and the latter gives a higher prevalence
- FP gives yes or no for presence of frailty but FI can grade the frailty as well
- FI is better than FP for large epidemiological studies and for prediction of mortality
- FP regards frailty as a syndrome distinct from disability and comorbidity while FI does not
- FP gives importance to each of its 5 criteria but FI emphasizes on cumulative effect of several health deficits as well

PREVALENCE:-

Western figure for frailty for 60 or 65+ elderly persons is around 10%. However, as there is no easy and simple definition of frailty, it is not surprising that global prevalence figures range quite widely e.g. between 33% and 88% depending on the frailty tool used (18). Using frailty index criteria, Song et al reported in 2010 a frailty prevalence of 22.7% among 65+ and the mean survival in the community dwelling older persons was 75, 64 and 50 months for non-frail, pre-frail and frail persons respectively (16). In the United States, overall prevalence of frailty in community- dwelling adults older than 65 years and recruited as part of Cardiovascular Health Survey (CHS) ranged from 7 to 12% by Fried's criteria (10). Weiss stated that those having comorbidities are more likely to be frail (19). In a survey of community-dwelling older adults in 10 European countries, the overall prevalence of frailty was 17%, with a geographical variation that is higher in southern Europe (e.g. 27% in Spain, 23% in Italy) than in northern Europe (e.g. 5.8% in Switzerland, 8.6% in Sweden) (20). Among 100 elderly patients, randomly chosen from Geriatric department of Madras Medical College, India, 21% were frail and 20% were intermediate frail (21). In Delhi, India, Khandelwal et al reported a frailty prevalence of 33% (22).

The incidence of frailty increases with age and will become more as our population continues to grow old. Moreover, the elderly population has a greater percentage of females and additionally, frailty is considered higher in women.

MANAGEMENT OF FRAILTY:-

Comprehensive geriatric assessment (CGA) to identify physical, socio-psychological and environmental deficits in the patient and address them properly and exercise intervention are the corner stones for the prevention and management of frailty. Optimal management of all medical illnesses, poly-pharmacy, proper nutrition and few miscellaneous steps are additional measures.

Aerobic exercises such as walking for 30 minutes/day or in episodes of at least 10 minutes 3 times/day, balancing or stretching and resistance exercises on 2 or more days per week to improve strength and endurance will reduce falls and chronically elevated inflammatory mediators in older adults (23, 24). Proper nutrition comprises daily intake of 1.2 to 1.5 gm. /kg of proteins with leucine rich essential amino acid supplement between meals and daily intake of vitamin D 1000 IU. Chaterjee observed that nutrition and exercise improve gait speed, grip strength, activities of daily living and mood and can also convert pre-fail persons to non-frail persons (25).

Finally, drugs like testosterone for low hormone males, estrogens for menopausal women, insulin like growth factors, anabolic steroids, anti-inflammatory agents, ACE inhibitors, sirutin and resveratrol, an activator of sirutin have all been suggested but many investigators are in disagreement on the utility of many of these agents in frailty.

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