Frailty is a clinically recognizable state of increased vulnerability, resulting from aging-associated decline in reserve and function across multiple physiological systems such that the ability to cope with everyday or acute stressors is compromised. (1-3) Frailty is a common clinical geriatric syndrome, which carries an increased risk for poor health outcomes, incident disability, hospitalization, and mortality.

“I know when I see it, but what I see may not be the same as what everyone else sees…”

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1. Frailty Phenotype (Freid’s definition) (2)
2. Frailty Index (4)
3. FRAIL (Fatigue, Resistance, Ambulation, Illness, Loss of weight) International Academy of Nutrition and Aging (5)
4. Frailty Instrument for Primary Care of the Survey of Health, Aging and Retirement in Europe (SHARE-FI) (6)
5. Groningen Frailty Indicator (7)

Frailty has been defined as a condition meeting 3 of the 5 phenotypic criteria:

1. Weakness: Grip strength – lowest 20% (by sex, BMI)
2. Slowness: Walking time /15 feet - slowest 20% (by sex, height)
3. Low level of physical activity: Kcal/week - lowest 20%; males 383 Kcal/week, females 270 Kcal/week
4. Exhaustion, poor endurance: “Exhaustion” self report
5. Weight loss: >10 lb unintentionally in prior year

*1. Weakness: grip strength by hand held dynamometer
*  Men
  - BMI < 24 - < 29 kg
  - BMI 24-28 - <30 kg
  - BMI > 28 - <32
* Women
  - BMI < 23 - <17 kg
  - BMI 23-29 - <18 kg
  - BMI >29 - <21 kg

*Measurements*
Slowness: time to walk 15 feet

Men
- Height < 173 cm -> 7 seconds
- Height > 173 cm -> 6 seconds

Women
- Height < 159 cm -> 7 seconds
- Height > 159 cm -> 6 seconds

Low level of physical activity Kcal/week based on the Minnesota Leisure Time Activity questionnaire (self report)

- Men < 383 Kcal/week
- Women < 270 Kcal/week

Equivalent to spending most of the time sitting or rarely (less than 2 hours/week having a short walk)

Kcal/week calculated by using MET (metabolic equivalent of task) Kcal/kg x h

1 MET - quiet sitting (range: 0.9 MET - sleeping - 23 MET running at 22.5 km/h)

Exhaustion: self report on Center for Epidemiologic Studies Depression Scale:

- Answers “often” or “most of the time”
- 1. In the last week I felt that everything I did was an effort
- In the last week I could not get going
*Nonfrail (none of the above criteria)
*Prefrail (1 or 2 of the above criteria)
*Frail (3 – 5 of the above criteria)

*Frailty Phenotype

*Frailty
*Disability (measured by impairment in ADL)
*Comorbidity (2 or more chronic diseases)

*Frailty is a distinct clinical entity

*Frailty/Disability/Comorbidity
Overlap:
* Frail with disability 5.7% (n=21)
* Frail with comorbidity 46.2% (n=170)
* Frail with disability and comorbidity 21.5% (n=79)(8)

All three conditions are predictive of adverse health outcomes, but...
* While many (not all) frail individuals are disabled, not all disabled persons are frail
* Presence of two or more chronic conditions in itself may not make someone frail
* When comorbid conditions worsen or more diseases are accumulated, this patient may develop frailty

In US overall prevalence in adults 65 in older ranges from 7% to 12%, it increases with age from 3.9% in the age group 65-74 years to 25% in the age group older than 85 years (9)
* Prevalence of frailty higher in women than in men (8% v.5%) and higher in African Americans than in Caucasians (13% v. 6%)
* The overall prevalence in Europe is 17%, ranging from 8.8% in Switzerland to 27% in Spain (10)

Prevalence of frailty based on FP
Developed by Rockwood and his colleagues based on the comprehensive geriatric assessment by counting the number of deficits accumulated, including diseases, physical and cognitive impairments, psychosocial risk factors and common geriatric syndromes other than frailty (4).

The total number of deficits that can be used in the FI is considered to be 80, with 30-70 items being typically counted.

Compared to FP, FI is more sensitive to predict negative health outcomes (more finely graded risk scale), but does not distinguish frailty from disability and comorbidity (includes them in the deficits).

FI makes it difficult (if not impossible) to further investigate frailty as a separate geriatric syndrome.

Frailty is a multisystem dysregulation, leading to a loss of dynamic homeostasis, decreased physiological reserve, and increased vulnerability for subsequent morbidity and mortality.

This is manifested by maladaptive response to stressors, leading to vicious cycle toward functional decline.

Multisystem processes:
- Chronic inflammation and immune activation
- Changes in musculoskeletal system
- Changes in endocrine system
- Molecular markers:
  - Elevated levels of:
    - IL-6 (proinflammatory cytokine) are directly associated with frailty (11)
    - C-reactive protein and TNF-a
    - Neopterin (molecular marker for immune activation mediated by macrophages) - can be seen independently from IL-6, suggesting that immune activation can potentially be a preceding process

- Cellular components:
  - Increased total WBC count
  - Increased number of CD8 T-lymphocytes

Clear relationship between frailty and chronic inflammation is well documented, but...

* Chicken or an egg???
Chronic inflammation in return contributes to frailty through its detrimental effects on other physiologic organ systems, such as musculoskeletal and endocrine systems, anemia, clinical and subclinical cardiovascular diseases and nutritional dysregulation. (12)
Elevated levels of inflammatory mediators have inverse association with Hgb concentration, insulin-like growth factor (IGF-1) levels, and levels of albumin, micronutrients and vitamins. (13)

Chronic inflammation plays a key role in the pathogenesis of frailty directly or indirectly!

But why anti-inflammatory agents (NSAIDs, stains) have no association with reduction in frailty???

Musculoskeletal system
- Sarcopenia is likely one of the key pathophysiologic contributor to frailty (14)
- Sarcopenia is defined as the loss of muscle mass and strength, which can occur rapidly after the age of 50 years. Its causes include age-related changes in α-motor neurons, type I muscle fibers, muscular atrophy, poor nutrition, declined growth hormone production, sex-steroid levels and physical activity.
- Chronic inflammation is also an important contributor to sarcopenia
- Comorbidity will further exacerbate sarcopenia

Other important factors in pathogenesis of frailty
Sex steroids and IGF-1 are essential to skeletal muscle metabolic dysregulation. Age-related rapid decrease of estrogen in postmenopausal women and gradual decrease of testosterone in older men lead to decline in muscle mass and muscle strength. Low levels of dehydroepiandrosterone (DHEA) and IGF-1 (signaling target of GH) are associated with frailty (15).

Elevated level of cortisol (evening level and total 24-hour mean level) has been observed in frail elderly women living in the community. Vitamin D insufficiency is associated with frailty, particularly in older men.

In summary, recent research suggest the potential role for dysregulation of the GH - IGF-1 somatotropic axis and dysregulation of the hypothalamic-pituitary-adrenal axis.
Frailty assessment is a useful tool for preoperative evaluation in elderly patients who undergo surgery. Both the FP and FI have been shown to be predictive for increased postoperative complications (18).

Frailty syndrome constitutes a critical issue in geriatric oncology. Frailty assessment can help with risk stratification of older patients with cancer (19).

Frailty is also useful for risk assessment in older patients with cardiovascular conditions, as it predicts increased morbidity and mortality in patients with cardiovascular disease, including CHF (20).

The challenge is to develop a standardized frailty definition and easy screening tool, that can be implemented in clinical practice.
Available screening tools:
- Frailty Phenotype (2)
- Frailty Index (4)
- FRAIL screening tool (18)
- Frailty Instrument for Primary Care of the Survey of Health, Aging and Retirement in Europe (SHARE-FI) (6)
- Groningen Frailty Indicator (7)

Clinical applications

1. Weakness: Grip strength measured by Jamar handheld dynamometer - lowest 20% (by sex, BMI)
2. Slowness: Walking time /15 feet - slowest 20% (by sex, height) > 7 s for men 173 cm or less, woman 159 cm or less, others > 6 sec
3. Low level of physical activity: Kcal/week - lowest 20%; males 383 Kcal/week, females 270 Kcal/week - basically inactive most of the time
5. Weight loss: >10 lb unintentionally in prior year or > 5% of body weight

Fatigue: are you fatigued?
Resistance: Do you have difficulty walking one flight of steps?
Aerobic: Are you unable to walk at least one block?
Illness: Do you have > 5 illnesses?
Loss of weight: Have you lost >5% of your weight in the last 6 month?
1. To prevent, delay, reverse or reduce the severity of frailty
2. To prevent or reduce adverse health outcomes in those whose frailty is not reversible

* Potential interventions

Once a frail, older adult is identified, potentially overlapping conditions, such as major depression, CHF, cancer) should be identified and treated first.

After Frailty Syndrome is confirmed, intervention should be initiated.

* Clinical applications

Exercise intervention, geriatric-focused IDC management program

In the frailest patient, palliative care should be implemented as soon as possible.
*Exercise*

To date, exercise is the interventional modality, that has most consistently shown benefit in treating frailty and its key components. (21)

Nutritional intervention is another nonpharmacological modality, but RTCs of nutritional interventions remain scarce.

Study done by Tieland and his colleagues assessed effect of 24 weeks of dietary protein supplementation in 65 frail patients found improvement in muscle strength and physical performance (22)

*Tieland and colleagues explored the role of protein supplementation to augment the skeletal muscle response to resistance-type exercise training in older frail individuals.*

They evaluated 62 frail older subjects (mean age 78 years, FP criteria used), who participated in 2xweek 24 weeks resistance training + 15 g x 2/day of protein supplementation v. placebo. Lean body mass increased in protein group, but not placebo group, muscle strength and physical performance improved significantly in both groups, with no added effect of dietary protein supplementation. (23)

*Exercise and nutrition*

*Pharmacological approach*

Effect on frailty not adequately evaluated:

- Testosterone improves muscle strength, but has significant systemic side effects
- Estrogen-replacement therapy in post-menopausal women also has an unfavorable safety profile
- GH supplementation has not been adequately evaluated
- Anti-inflammatory agents has not been formally evaluated in clinical trials in treating frailty syndrome and also have significant adverse effects
- Vitamin D and ACE-inhibitors have favorable safety profile, their clinical utility has yet to be investigated
The twenty first century of geriatric medicine lies ahead, and preventing and treating frailty and its dramatic consequences is crucial.

*Frailty Syndrome is real*

**Urgent issues**