FRAILTY:
WHAT’S BEEN DONE AND
WHAT NEEDS DOING

INTERNATIONAL CONFERENCE ON FRAILTY
AND SARCOPENIA RESEARCH

MARCH 1, 2018
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Frailty, 1980s: First Principles

• Frailty: the “raison d’etre of geriatrics”
• Fretwell: Vulnerability a key concept
• The NIA definition: frailty = ADL dependency
• Clinical care: CGA for frail older adults
• The literature: the kitchen sink definition of frailty:
  — Multimorbidities; disability; dependency; age > 80 or 85
• The result: null findings, many CGA trials
• Couldn’t compare across studies

Conclusion: need to distinguish, standardize, not lump
Disentangling Disease, Disability, Multimorbidity, 1980s-’90s

• New evidence led to distinguishing:
  – Chronic diseases (e.g., CVD) from aging
  – Disability as an outcome of diseases
    • Different diseases caused different kinds of disabilities
    • Pathways to disability: IOM, WHO; intermediate precursors between disease and disability: impairments, functional limitations, compensations
  • New measurement outcomes
  – Multimorbidity:
    • chronic diseases predict mortality, but subclinical measures predict better
    • disease effects additive
Frailty: 1990s

1992: Buchner and Wagner: Preventing frail health
1992: Lipsitz: Loss of ‘complexity’ and aging
1993: Bortz: Physics of Frailty
1994: Fiatarone, Evans: RCT of exercise, nutrition
1997: Campbell and Buchner

Many papers: Morley, frailty and anorexia of aging
(Fried et al, Aging Clin Exp Res, 1992)

- Old age, disability or comorbidity do not appear to distinguish those frail
- Frailty appears to be a distinct clinical syndrome developing from a critical mass of physiologic decrements or loss of reserves, which could result from altered cellular and/or organ function, or a failure of communication between these levels.
  - Need for standardized definition.
- Cellular drivers that may underly physiologic and phenotypic alterations:
  - **Energy dysregulation**: declines in fuel for cellular energy (decreased NAD, ATP secondary to DNA repair, mitochondrial defects) could underly more apparent manifestations of frailty: decreased muscle mass, strength, oxygen consumption, energy expenditure and endurance.
  - Changes in **dynamic interactions across systems**. These interactions potentially provide points of intervention to minimize critical mass of decrements that may become frailty.
Studies of Geriatricians’ Clinical Perceptions of Frailty, 1993-5
(Fried and Williamson)

- N= 62; 6 AMC’s; US and Great Britain
- Findings: frailty is distinct, recognizable
  - 98%: frailty and disability distinct, but causally related
  - 97%: frailty involves concurrent presence of more than 1 characteristic; in presence of disease, other manifestations must also be present to constitute frailty.
  - No one disease, and not all diseases, important.
  - Clinicians identify frailty in presence of critical mass of: generalized weakness, poor endurance, weight loss and/or undernourished; low activity; fear of falling and/or unsteady gait
- (Fried et al; JGMS 2004)
Premises re: frailty

• Frailty is a state of high vulnerability to adverse health outcomes and an aggregate expression of risk
• A physiologic state of vulnerability to stressors; results from decreased physiologic reserves; result in difficulty maintaining homeostasis in the face of perturbations
• Sarcopenia as a precondition
• Clinical presentation
Commonly Identified Features of Being Frail – among Geriatricians
1990’s

- Declines in lean body mass, strength
- Weight loss
- Loss of endurance
- Slowed walking performance
- Relative inactivity
- Decreased balance and mobility
- Potentially: decreases in cognition, dependency

*Why do these co-occur on the same list?*
Cycle of Frailty

- Chronic Undernutrition
  - [Inadequate intake of protein and energy; micronutrient deficiencies]
- Neuroendocrine Dysregulation
- Anorexia of aging
- Total Energy Expenditure
- Activity
- Walking Speed
- Disability
- Dependency
- Resting Metabolic Rate
  - Strength & Power
    - VO2max
  - Immobilization
    - Falls and Injuries
    - Impaired balance
    - Loss of muscle mass
  - Sarcopenia
    - Osteopenia
    - Insulin sensitivity
    - Weight Loss

(Fried and Walston, 1998)
1998: Hypothesized Cycle of Frailty

- Biologically related components;
- Dysregulated energetics;
- Unites geriatricians’ clinical markers of frailty;
- Could be initiated at any point in cycle;
- Final common pathway?
- Medical syndrome?
- Needs to be explained by biologic underpinnings of decreased energy, reserves and ability to maintain homeostasis, which may be latent but a basis for vulnerability to stressors.

Weight Loss

Clinical Presentation

- ↓ physical activity
- ↓ Motor performance
- ↓ Strength
- Exhaustion/↓ exercise tolerance

Physiologic Vulnerability

Physiologic Dysregulation

Cellular Function, Molecular and Genetic Characteristics

Fried, 2005

SAGE-KE
Potential value of understanding frailty as a syndrome:

simultaneously understand risk and pathobiology;
improved detection, targeting, prevention and treatment
How have these hypotheses played out?
1. A distinct, validated phenotype is prevalent; 7-12% per year over 65, and 25% over 85 years
Cycle of Frailty

Chronic Undernutrition
[Inadequate intake of protein and energy; micronutrient deficiencies]

Aging: Senescent musculoskeletal changes

Negative Energy Balance

Negative Nitrogen Balance

Weight Loss

Loss of muscle mass

Insulin sensitivity

Osteopenia

VO$_2$max

Strength & Power

Immobilization

Impaired balance

Falls and Injuries

Dependency

Immobilization

Falls and Injuries

(Fried and Walston, 1998)
# Phenotype of Frailty

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CHS Study Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrinking</td>
<td>BL: Unintentional weight loss &gt;10 lbs F/U: ≥ 5% weight loss over one year</td>
</tr>
<tr>
<td>Weakness</td>
<td>Grip strength: lowest 20%</td>
</tr>
<tr>
<td>Poor endurance</td>
<td>Exhaustion (self-report)</td>
</tr>
<tr>
<td>Slowness</td>
<td>Walking time: lowest 20%</td>
</tr>
<tr>
<td>Low activity</td>
<td>Kcal/week : lowest 20%</td>
</tr>
</tbody>
</table>

Non-frail: 0/5  Pre-frail: 1 or 2/5  Frail: 3, 4, or 5/5

Fried et al, JGMS 2001
2. Predictive validity of frailty phenotype:
Risk: ≥3 criteria present predict high risk of adverse outcomes

(SIGNIFICANTLY MORE THAN ANY 1 OR 2 CRITERIA; INDEPENDENT OF DISEASES)
- MORTALITY, DISABILITY, FALLS, HOSPITALIZATION, SURGERY, BURNS, SLOW RECOVERY -
### Number of Criteria for Frailty Associated with Risk of ADL Dependency (WHAS)

<table>
<thead>
<tr>
<th># Criteria</th>
<th>Incidence/100 P-Y</th>
<th>H R unadj</th>
<th>H R adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>8</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>1.54</td>
<td>1.33</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td>2.21 *</td>
<td>1.62 *</td>
</tr>
<tr>
<td>3</td>
<td>25</td>
<td>3.40 *</td>
<td>2.23 *</td>
</tr>
<tr>
<td>4-5</td>
<td>38</td>
<td>5.18 *</td>
<td>2.38 *</td>
</tr>
</tbody>
</table>

Boyd 2005
3. Frailty as a Syndrome: The whole is greater than the sum of the parts

- Aggregate phenotype (3 or more) predicted mobility disability and other outcomes better than any 1 or 2 markers (eg walking speed, strength, physical activity, weight loss, endurance)
- No distinguishable subsets of risk
- Analytically consistent with behavior of syndrome
- Think syndromes: Angina, Asperger’s, Downs…
4. Frailty not the same as disability or multi-morbidity (although they may cause each other)
Frailty, Disability and Comorbidity in CHS

- Disabled: 57 (19.1%)
- Comorbid: 40 (13.4%)
- Frail: 182 (60.9%)
- 20 (6.7%)
5. Phenotype goal: offers measure for clinical screening linked to biology

- Clear, measureable, standardizable, inexpensive criteria to identify a recognizable clinical presentation;
- Suitable for screening;
- Provides clinical specificity to distinct pathophysiology and identifies those at risk

_Fried et al 2001_
Weight Loss

↓ Physical activity

↓ Motor performance

↓ Strength

↓ Exhaustion/

↓ Exercise tolerance

Clinical Presentation

Physiologic Vulnerability

Physiologic Dysregulation

Cellular Function, Molecular and Genetic Characteristics

Fried 2005

SAGE-KE
6. Dysregulation/deficits of multiple physiologic systems associated with frailty

- **Muscle:** Sarcopenia
- **Energy and homeostatic metabolism:**
  - **Hormones:** decreased gonadal, IGF-1, DHEA-S; higher cortisol/DHEA-s, insulin resistance, hyperglycemia; androgens and estrogens
  - **Nutrition:** low macro and micronutrients, protein, energy intake; low serum Vit D, E, B12, folate
- **Inflammation:** increased cytokines, inflammatory mediators (CRP, IL-6, TNF-alpha); Immune activation;
- **Altered clotting**
- **ANS:** Decreased heart rate variability
- **Subclinical normocytic anemia**
Prevalence of Frailty for 3 Blood Test Abnormalities in 70-79 year old women in WHAS I and II

Cappola et al, 2004
IS FRAILTY A RESULT OF AGGREGATE DECLINES OR LOSS OF RESERVES?

AN INCREASED NUMBER OF SYSTEMS AT ADVERSE LEVELS IS ASSOCIATED WITH FRAILTY PHENOTYPE;

IS THE WHOLE GREATER THAN THE SUM OF THE PARTS?
Evidence for Nonlinearity of Relationship of Number of Systems Abnormal with Frailty

Fried et al. 2008
## Associations of the Number of Physiologic Systems at Abnormal Levels with Frailty*

<table>
<thead>
<tr>
<th>Number of Deficits</th>
<th>Frail vs. Non-Frail</th>
<th>OR (95% C.I.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1-2</td>
<td></td>
<td>4.8#</td>
</tr>
<tr>
<td>3-4</td>
<td></td>
<td>11.0+</td>
</tr>
<tr>
<td>≥5</td>
<td></td>
<td>26.0+</td>
</tr>
</tbody>
</table>

* adjusting for age, race, education, and number of chronic diseases + p-value<0.01 ; # p-value < 0.05

Fried et al 2008
Nonlinearity: a clue that frailty is a complex system problem

• Whole greater than the sum of the parts;
• Relationship non-linear: i.e.,
  - critical mass matters;
  - Variables not mutually independent; high degree of connectivity or interdependence between variables

– Seely 2000; Kitano 2000; Csete and Doyle
Multisystem Dysregulation and Interactions May Underlie Loss of Reserves, Frailty

**PHYSIOLOGIC**

- Sarcopenia
- Altered cellular metabolism
- Mitochondrial Dysfunction
- Inflammation
- Hematopoiesis

**MOLECULAR & GENETIC**

- Cellular senescence
- Genetic Variation*
- Free radicals*
- DNA damage; decreased DNA repair capacity, energy available to cells
- Altered telomeres

↑ SNS activity

Altered hormones; glucose intolerance

*Denotes potential areas of research or intervention.
Principles of nonlinear complex dynamical systems that have been identified in association with frailty syndrome

- Whole greater than sum of parts
- Loss of physiological networking and mutual regulation, redundancy
- Dysregulation of modular subsystems
- Loss of reserves
- Emergent property
- Decreased homeostatic regulation

In frailty: Likely contributes to both phenotype and vulnerability to stressors
Number of Abnormal Hormones by Frailty Status

Combined WHAS I and WHAS II (Age 70-79)

Fried, Xue et al
7. The syndrome of frailty conforms to the characteristics of a complex, dynamical nonlinear system
8. Complex dynamical nonlinear systems are notable for “silent success of stability” – until there are sufficient multisystem losses to downgrade function (emergent property)
Homeostatic Mechanisms and Frailty

Physiological Parameter

Stressor

\( S_i \)

\( L_i \)

Time

Xue, Varadhan
Emergent Property: onset of frailty
9. Complex dynamical system of frailty and homeostasis principles lead us to:

- The need to understand **dynamics between systems** that underpin frailty – not just abnormal biomarker levels
- Why **different “emergent” states** of function have different responsiveness to interventions, prevention
- Why single biomarker replacement strategy hasn’t worked
  - Why physical activity works
- What we need to look for in preventive and treatment approaches
10. Complex dynamical nonlinear systems that are functioning at a lower level in resting or steady state will not show their fragility until stressed.
Experimental evaluation of dynamic systems’ dysregulation underlying frailty

- Challenge tests of frail, prefrail and nonfrail 81-93 y/o women (WHAS II)

- Test: Whether response to stressor reveals physiological dysregulation of frail, consistent with complex systems
Altered Glucose-Insulin Dynamics in Frailty: Glucose tolerance test (Kalyani et al 2011)
Altered energetics of frailty –
MRS of women 82-91 years: time to 95% recovery of PCr after mild exercise (Varadhan et al)
WHAS II Experiments re: energy homeostasis and frailty syndrome

• Our stimulus-response challenge tests:
  – *Glucose, Insulin resistance and leptin resistance*: utilization of energy impaired
  – *MR Spec: energy repletion slower; decreased mitochondrial function*
  – Ghrelin: less appetite stim; E imbalance
  – Decreased taste sensation; poor swallowing
  – ACTH stim: general dysregulation/association with decreased energy, fatigue
  – Lower immune response to vaccination (influenza)
WHAS studies of stress response in women 81-93 years

• In multiple systems, in frail - compared to nonfrail and prefrail:
  – Physiologic dysregulation emerges when stressed
  – Delayed, exaggerated and prolonged responses, and delayed recovery to baseline
  – Increased variance in responses
Potential screening for physiologic vulnerability of frailty

- Dysregulated responses to stressors in those with frailty phenotype
11. Potential biological causes of frailty’s multisystem declines and dysregulation of complex dynamical system of homeostasis?

Core process of energy dysregulation
Cycle of Frailty

Chronic Undernutrition
[Inadequate intake of protein and energy; micronutrient deficiencies]

Neuroendocrine Dysregulation
Anorexia of aging

↓ Total Energy Expenditure
↓ Activity

↓ Walking Speed
Disability
Dependency

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Falls and Injuries

Loss of muscle mass
Sarcopenia

Negative Energy Balance
Negative Nitrogen Balance
Weight Loss

Aging: Senescent musculoskeletal changes

Insulin sensitivity
Osteopenia

(Fried and Walston, 1998)
Energetics of frailty: women 81-93 years (WHAS II)

- At steady state, in multiple systems that regulate energy
- Frail (vs. pre- & nonfrail):
  - RMR – wide variability in frailty, with extremes of high and low
  - IL6 high
  - Hormones of energy metabolism:
    - Ghrelin lower
    - Glucose lowering: adiponectin, GLP-1, IGF-1
    - Glucose raising: FFA, resistin, GH, IL-6
    - Leptin high, consistent with leptin-resistance
Evidence for dysregulation of biologic systems of energy production and reserves underlying frailty syndrome
Biological systems associated with phenotype of frailty: *factors that might dysregulate multiple physiological systems*

- **Mitochondrial dysfunction/energy reserves:**
  - Mitochondrial genetic variant in control region (D-loop) with frailty phenotype; plays key role in mitochondrial replication (Moore et al, 2010)
  - mtDNA copy number (by multiplexed real-time quantitative PCR) associated with frailty phenotype (CHS; Ashar et al 2014); marker of mitochondrial replication and cellular energy reserves/ATP production rate; low levels c/w mitochondrial depletion
Association of mtDNA copy number with frailty phenotype, CHS

Ashar, Moes et al, 2014 J Mol Med
Biological systems associated with phenotype of frailty: factors that might dysregulate multiple physiological systems

- **Genetic mutations**: Candidate gene analyses show 20 SNPs most associated with frailty phenotype – of 11 genes involved in apoptotic and transcription regulation pathways, with roles in homeostasis and apoptosis. These are genes that act as bridges between pathways or are important hub proteins in both inflammatory and muscle systems (WHAS; ns; Ho et al 2011)

- **Circulating oxidative stress/damage biomarkers** (e.g., MDA, protein carbonylation) are related to frailty phenotype and not to age or sex (Ingles M, et al, JAGS 2014)
Multisystem Dysregulation and Interactions May Underlie Loss of Reserves, Frailty

**PHYSIOLOGIC**

- Sarcopenia
- Hematopoiesis
- Altered cellular metabolism

**MOLECULAR & GENETIC**

- Cellular senescence; apoptosis
- Mitochondrial replication; dysfunction*
- Inflammation
- Genetic Variation*
- Free radicals*

**Altered**

- Hormones; glucose intolerance
- DNA damage; decreased DNA repair capacity, energy available to cells
- Altered telomeres

*Denotes altered markers.
Frailty phenotype and syndrome

- Clinical presentation marks a distinct physiologic and biologic status, with compromised ability to maintain stable homeostasis and identifies group at high risk;
- Chronic, progressive clinical phenotype; latent phase
- Homeostatic compromise visible when system stressed
- Underlying: energetics-driven decline in complex dynamical system of resilience
12. Clinical implications of the medical syndrome of frailty
Frailty: potential clinical applications and future challenges

- Screening
- Diagnosis
- Prognosis
- Palliation
- Prevention
- Treatment
- Health system
Identification of Frailty syndrome and physiologic precursors will enable:

- Identifying treatments and prevention appropriate to stage of energetic function, and affecting multiple pathways
- Clinical care: screening and more effective targeting; care and health system design to compensate for vulnerabilities; palliative care
- Discovery: biologic basis of energy dysregulation, resilience and frailty and its vulnerabilities
Emerging evidence on effectiveness of interventions for frailty phenotype

- **Prevention of incident frailty:**
  - Physical activity (Cesari, LIFE Pilot)
  - Mediterranean diet (Talegawkar 2012)

- **Treatment response of phenotypically frail:**
  - Exercise in frail 90+ (multicomponent): improved strength, muscle CSA, Timed Up and Go, chair rise, balance, falls (Cadore 2013)
  - Higher protein intake (not energy) a/w lower frailty prevalence (Volpi; Rahi 2016)
  - Exercise – with or without nutrition (Fiatarone, Evans)
  - Multimodal intervention targeted to frailty criteria present (3 or more) improved frailty; also improves SPPB performance. (Cameron 2013)
Major challenges of semantics

- Plethora of measures called “frailty” seeking to characterize different issues; need to differentiate meaning (biologic, functional, clinical; risk) by distinguishing names, eg:
  - Frailty syndrome/phenotype
    - (need to validate substitutions)
  - Multimorbid diseases: disease diagnoses or physiologic measures of subclinical disease
  - Index of all clinical issues: Multimorbidity (diseases, impairments, symptoms, lab values) + mobility, strength, disabilities, physical activity, health attitude
  - Functional limitations/performance measures to predict disability

- Otherwise, back to the “kitchen sink” of the 1980s; will not guide diagnosis, targeting, prevention, treatment or change
Many unanswered questions on frailty syndrome

• Can specificity of risk by # of criteria be better tested and defined?
• Latent frailty:
  – How to measure physiologic reserve and resilience – as meaningful intermediate outcomes
  – Connectivity that regulates, maintains homeostasis
  – How are processes affecting each other
  – What are the progressive “emergent states”
  – identification would offer best opportunities for prevention
Ultimately, successful prevention or treatment of frailty will involve intervening on the systems biology
With thanks

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