RCCN Workshop
Measuring Biologic Age
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VIRTUAL

Frailty / Physical Function underlying biology and potential treatment targets

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Nothing to disclose
Frailty

- Deterioration in physiologic function
- Decline in ability to respond to stress
- Increase in vulnerability
Operational definitions of frailty

A) Frailty Phenotype

B) Frailty or Deficit Accumulation Index

Moving Frailty Toward Clinical Practice: NIA Intramural Frailty Science Symposium Summary
Physical function – Gait speed, strength, endurance

Gait speed

Strength

Endurance

Newman AB, JAMA, 2006

Studenski, JAMA, 2011

Newman AB, JAMA, 2006

Newman AB, JGMS 2006
Cognitive frailty

• Consensus definition- Reduced cognitive reserve evidenced by both physical and cognitive impairment (Kelaiditi E, Cesari M, JNHA, 2013, Buchman and Bennett, JNHA, 2013)

• Related - Motoric cognitive risk syndrome
  • Predicts dementia (Verghese, Alzheimer’s & Dementia, 2019)
  • Predicts frailty (Sathyan, Journal of Alzheimer’s Disease, 2019)

• Related - Dual tasking
Frailty and function as indicators of risk

- Frailty and poorer physical function robustly predict poor health outcomes
  - Mortality
  - Disability
  - Health Care Utilization
  - Tolerance of interventions
    - Surgery
    - Procedures
    - Chemotherapy
Physiologic systems important in physical function and frailty

- Vascular system
  - Blood flow to brain and muscle
  - Endurance
- Neuromuscular system
  - Central control of movement, innervation of muscle
  - Strength and speed
- Sensorimotor system
  - Integration and feedback
- Metabolic system
  - Weight stability
  - Energetics of muscle and brain
- Immune system
  - Damage response
  - Chronic inflammation
Measurement of Organ Structure and Function Enhances Understanding of the Physiological Basis of Frailty: The Cardiovascular Health Study

Similar distributions of frailty components as organ system components – carotid, brain WMG, lung function, kidney function, glucose tolerance

1 point of physiologic index = .3 points frailty
Do hallmarks of aging contribute to frailty and physical disability?
Blood biomarkers of frailty

• Should detect frailty before it is clinically advanced
• Should be a risk factor common to all age-related diseases
• Should also predict mortality
• Should also related to biologic aging mechanisms

• Candidates?

Zampino, Exp Gerontology, 2020
Biomarkers of frailty

• Is frailty a state of dysregulated inflammation due to cellular senescence?
Inflammation and frailty

• Numerous studies in humans link elevated IL-6 to frailty as well as physical disability

Other cytokines are also related including TNF-SR and IL-10 as well as CRP

Forest plots of IL6 concentration a frailty vs. non-frailty groups; c frailty vs. pre-frailty groups

Epigenetics and frailty

**Fig. 3.** Associations between frailty and different epigenetic clock measures. Frailty at a baseline and b after 3-year follow-up was regressed on standardized delta age estimates using gamma regression, each of which is in separate models. For both panels, model 1 represents estimates adjusted for age and sex, while model 2 represents estimates adjusted for age, sex, education, income, smoking, diet and physical activity; for b, both models were also adjusted for frailty at baseline. Beta coefficients and 95% confidence intervals (CI) are shown, and the dotted red line indicates no association.

Metabolomics and frailty

• Frail individuals characterized by alterations in metabolic pathways
  • Rattray NJW, Nature Communications 2019
  • Marron MM, Metabolites, 2019
  • Westbrook R, JGBS, 2021

• Implicate TCA cycle, lipid metabolism, mitochondrial function

• Metabolomic age?
  • Robinson O, Aging Cell, 2020
Mitochondrial copy number and frailty

Interventions to ameliorate frailty and improve physical function

• Physical activity
  • Inconsistent results for frailty (Trombetti A, Ann Int Med, 2018)
  • Improves physical function and prevents major mobility disability (Pahor M, JAMA, 2014)

• Diet
  • Caloric restriction (mostly animal studies), Mediterranean diet (Kojima G, JAGS, 2018)
  • Weight loss improved function in obese

• Multicomponent diet, exercise, etc.
  • Reduced frailty phenotype and prevented decline in physical function (Cameron, BMC Medicine, 2013, Fairhall, BMJ Open, 2015)

• Omega-3 fatty acids
  • No improvement in 400 meter walk or IL-6 levels (Pahor, JGMS 2020)

• Resveratrol
  • Reduced frailty index scores in mice (Kane AE, JGBS, 2018)

• ACE inhibitor
  • Frailty index scores reduced in mice with enalapril for 9 months (Keller K, JGBS, 2018)
Interventions to ameliorate frailty and improve physical function

• **Testosterone Trials**
  • Some increase in physical function and components of vitality in men with low T (Snyder P, Endo reviews, 2018)

• **Senolytics**
  • Mice – intermittent administration of dasatinib and quercetin to senescent cell-transplanted young mice and naturally old mice increased survival by 36% and alleviated physical function impairment (Xu M, Nature Medicine, 2018)
  • People – Open label D + Q study in people with IPF improved physical function, but not FI-LAB (Justice J, EBioMed 2019)

• **Metformin**
  • Trial underway in older adults with pre-diabetes (Espinoza S, JGMS, 2020)
  • Targeting Aging with Metformin (TAME) - Multimorbidity outcome

• **Aspirin**
  • ASPREE study, 100 mg of aspirin did not reduce incident disability, frailty phenotype or frailty index, may have reduced persistent disability (Woods R JGMS, 2020; Espinoza S, JGMS, 2021)

• **Lomecel-B**
  • Mesenchymal Signaling Cell formulation, phase 2B
  • 6 min walk is primary outcome (Yousefi, J Frailty and Aging, 2022)
RECOMMENDATIONS

• Refine definitions and language about frailty
• Demonstrate that frailty is modifiable in clinical trials
• Continue to tailor care using frailty and physical function to target patients at risk
• Integrate biology of aging with frailty
• Develop deeper understanding of system dynamics most important in frailty that can be targeted to improve resilience
Research directions (1)
Further refine frailty and physical function as outcomes

• Progress
  • Whole person phenotype summarizes risks and benefits
  • Person-centered outcomes, focus on health span

• Issues
  • Objective physical function assessments are not part of clinical practice
  • Disability often self-reported- not objective
  • Frailty phenotype includes weight loss and physical activity which might be part of the intervention
  • Frailty index includes many chronic diseases which might not be reversible

• Approaches
  • Refine measures for sensitivity to intervention
  • Develop “Resilience tests”
    • Direct measures of the ability to tolerate stress
      • Treadmill test
      • Stress hormone responses
      • Evidence of ability to recover from clinical stress such as surgery
  • Validate of personal monitoring as physical function measures
Research directions (2)
Therapeutics

• Progress
  • Many trials developing with frailty and function as outcomes
  • Frailty is now an FDA designated condition

• Issues
  • Uncertainty about tissue specificity of aging biologic processes
  • Disease-specific therapies often do not address frailty and physical function as outcomes

• Approaches
  • Studies targeting underlying biology of aging should include frailty assessments, physical performance tests, self-reported function and quality of life as outcomes
  • Use physical activity benefit as target effect size to beat
Research Directions (3)

Systems approaches

• Signaling between systems
  • Direct contact
  • Signaling molecules
    • Paracrine
    • Endocrine
  • Extracellular vesicles


Frailty and function - Summary

• Physiologic integration
• Linked to more distal clinical outcomes
• Growing evidence of biologic aging underpinnings

Is frailty = aging?
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