Frailty and HIV

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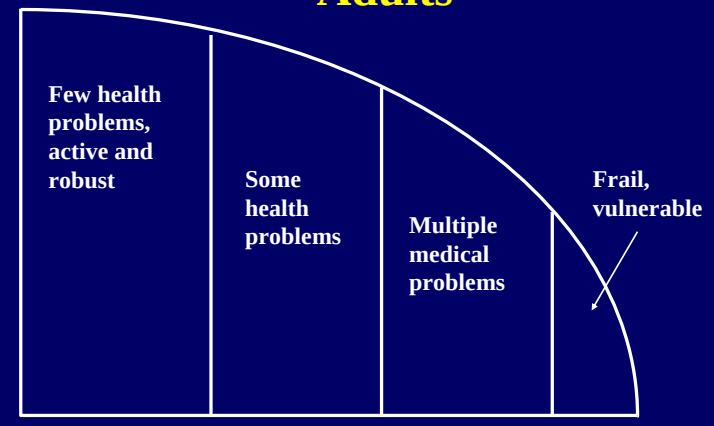
Introduction

- Conceptualization of frailty in Geriatrics
- Biological findings in frailty research
  - Multisystem physiologic decline
  - Genetic and molecular etiologies
- Biological overlap with HIV

Heterogeneity in Health of Older Adults



What is Frailty in Geriatrics?

- A clinical syndrome of weight loss, fatigue and weakness
- A prognostic factor for poor outcomes
- Multisystem physiologic decline
- Altered biology that contributes to vulnerability in older adults

Why Does It Matter?

- Highest risk for poor outcomes
- Slowest recovery rate
- Most iatrogenic complications
- Highest mortality rates

Why Might Frailty be Important in HIV Research?

- Frailty and related vulnerability likely accelerated in HIV
- Biology that underlies both appears to be remarkably similar
- Does this biology accelerate non-HIV related accelerated mortality?

Frailty: From Idea to Syndrome

- A physiological syndrome distinct from but related to functional impairment
- Related to aging processes
- Related to clinical and subclinical disease, which can be confounders, modifiers, or etiologic

How do we find frail, older adults?

- Exhaustion
- Slowed walking speed
- Low activity
- Weakness
- Weight loss

* Frail if 3 of 5 are present

Fried, Tangen, Walston, et al, J Ger Med Sci, 2001

Frailty in CHS and WHAS I & II cohorts

- 11.8% of CHS (n=5011) and 11.3% of WHAS I & II cohort (n=784) between age 70-79 met frailty criteria
- Frail and Intermediate status predicted adverse health outcomes
- Associated with disease states, especially congestive heart failure (other inflammatory diseases excluded)

Fried L, et al. J of Gerontology, 2001
Newman, et al. J of Gerontology, 2001
Bandeen-Roche et al. , J of Gerontology, 2006

Frailty Status Predicts Adverse Outcomes

	CHS	WHAS
Incident Fall	1.29 (1.00 – 1.68)	1.18 (0.63, 2.19) (NS)
Worsening Mobility	1.50 (1.23, 1.82)	10.44 (3.51, 31.00)
Worsening ADL Disability	1.98 (1.54 – 2.55)	15.79 (5.83, 42.78)
First Hospitalizations	1.29 (1.09,1.54)	0.67 (0.33, 1.35) (NS)
Death	2.24 (1.51,3.33)	6.03 (3.00, 12.08)

Hazard Ratios Estimated Over 3 Years, covariate adjusted

P>0.01 for all except incident fall

Fried, Tangen, Walston, et al, J Ger Med Sci, 2001
Bandeen-Roche et al, J Ger Med Sci, 2006

Inflammatory Biomarkers of Frailty

Characteristic	Not Frail (n=2289)	Intermediate (n=2147)	Frail (n=299)	P Value
C-reactive protein (mg/L)	2.7 (4.0)	3.7 (6.5)	5.5 (9.8)	<.001
Fibrinogen (mg/dL)	313.3 (60.9)	324.1 (66.7)	340.7 (78.6)	<.001
Factor VII (mg/dL)	124.0 (28.3)	125.5 (29.4)	124.9 (33.1)	.42
Factor VIII (mg/dL)	118.6 (34.6)	123.3 (37.8)	137.9 (44.8)	<.001

* Including those with CVD & diabetes

Walston, et al. 2002, Arch Intern Med

Metabolic Biomarkers of Frailty

Characteristic	Not Frail (n=2289)	Intermediate (n=2147)	Frail (n=299)	P Value
Fasting Glucose level (mg/L)	107.3 (28.8)	111.4 (34.8)	119.8 (57.2)	<.001
2-hour Glucose level (mg/dL)	141.4 (55.6)	151.4 (59.3)	160.6 (65.0)	<.001
Fasting Insulin level (IU/mL)	15.8 (23.8)	18.2 (26.5)	18.0 (29.9)	.001
2-hour Insulin level (IU/mL)	79.9 (61.7)	87.5 (64.8)	89.0 (63.6)	<.001

* Including those with CVD & diabetes

Walston, et al. 2002, Arch Intern Med

Markers of Clotting Process

Markers of Clotting Process	Not Frail (n=165)	Intermediate (n=186)	Frail (n=29)	P Value
PAP Complex (mno/L)	6.2 (2.8)	6.4 (2.5)	9.3 (6.3)	<.011
Fibrinopeptide A (ng/mL)	7.2 (39)	12.0 (42)	5.9 (5)	.57
Fragment 1.2 (mnol/L)	0.36 (0.18)	0.43 (0.54)	0.47 (0.28)	.06
D Dimer (ng/mL)	224 (258)	272 (361)	647 (1033)	<.001
Factor XI (nmol/L)	0.80 (1.8)	1.1 (2.6)	1.8 (3.9)	.048

* Participants with no history of CVD

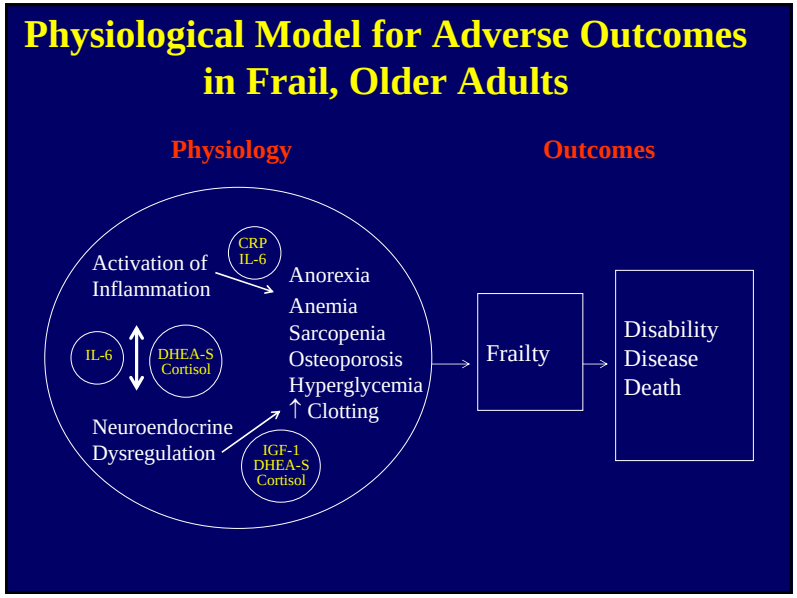
Walston, et al. 2002, Arch Intern Med

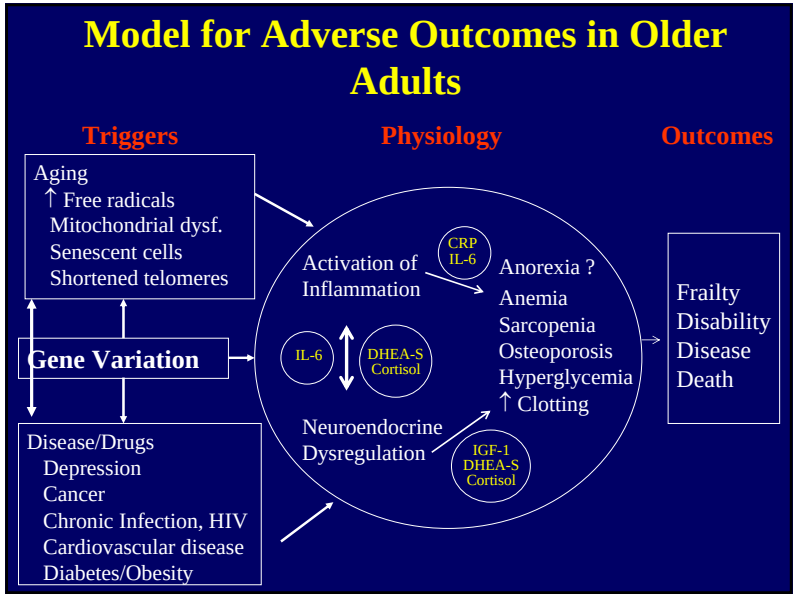
Endocrine Biomarkers of Frailty

	Frail (18)	Non-frail (33)	P
IGF-1 (ng/mL)	87.5 ± 49.1	122.5 ± 47.4	0.02
DHEA-S (ug/mL)	0.30 ± 0.21	0.53 ± 0.25	0.02

* Age adjusted

Leng, et al. 2004. Aging Clin Exp Res


Physiological Model for Adverse Outcomes in Frail, Older Adults
Physiology
Outcomes
Activation of Inflammation
CRP
IL-6
Anorexia
Anemia
Sarcopenia
Osteoporosis
Hyperglycemia
↑ Clotting
IL-6
DHEA-S
Cortisol
Neuroendocrine Dysregulation
IGF-1
DHEA-S
Cortisol
Frailty
Disability
Disease
Death


Model for Adverse Outcomes in Older Adults
Triggers
Physiology
Outcomes
Aging
↑ Free radicals
Mitochondrial dysf.
Senescent cells
Shortened telomeres
Gene Variation
Disease/Drugs
Depression
Cancer
Chronic Infection, HIV
Cardiovascular disease
Diabetes/Obesity
Activation of Inflammation
CRP
IL-6
Anorexia ?
Anemia
Sarcopenia
Osteoporosis
Hyperglycemia
↑ Clotting
IL-6
DHEA-S
Cortisol
Neuroendocrine Dysregulation
IGF-1
DHEA-S
Cortisol
Frailty
Disability
Disease
Death

Inflammatory Cytokines in HIV

- Inflammation measured by IL-6 associated with loss of appetite
- Odds ratio 3.41 (CI 1.91-6.09) after sex, age, fat mass, HIV load adjustment
- Anorexia and wasting primarily determined by inflammation and viral load status

Van Lettow M, et al. J Clin Endo Met 2005

Inflammatory Cytokines in HIV

- IL-6, TNF-α, IL-1β from PBMC's, significantly higher in HIV wasting in response to activity
- IL-6 and TNF- α elevated in plasma
- Suggest ongoing potentiation of innate immune system in HIV
- Findings similar to PBMC finding in frailty

Abad L, et al. Cytokine 2002
Leng S, et al. Aging, 2003

Inflammatory Cytokines

- TNF-α significantly higher in HIV wasting and asymptomatic HIV than TB wasting or control group
- NO and TNF-α most likely contributors to cardiac and skeletal muscle wasting

Wign, et al. Pt Care STDs, 2005
Barbaro G. Herz, 2005

HIV and Aging Interaction

- HIV+ and older subjects shift towards senescent $CD8^{+}$, $CD28^{-}$ phenotype
- Cells produce 2-3x more TNF-α, INF-δ
- HIV plus lifetime activation of inflammatory pathways likely contribute
- May be accelerated shift in aging HIV patients with frailty consequences

Eylar EH, et al., BMC Immunology 2001

Treatments May Accelerate Inflammatory Activation

- HIV protease inhibitors (PIs) contribute to metabolic syndrome, increased apoptosis, vascular disease
- PIs may drive increase in TNF-α and IL-6
- Disease states and direct mechanisms likely play important roles in inflammatory pathway activation

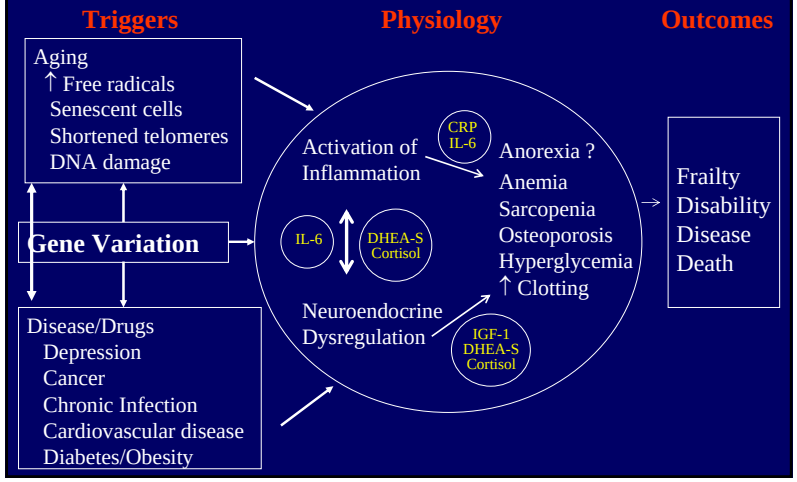
Zhou H, et al. Atherosclerosis 2007

Treatments May Accelerate Mitochondrial Dysfunction

- Nucleoside analogue reverse inhibitor (NRTIs) may contribute to muscle wasting
- DEXA scan and muscle biopsy confirmed lipoatrophy in those taking NRTIs
- Mitochondrial abnormalities included lactic acidemia, respiratory disease, impairment, and enzymatic abnormalities
- May accelerate oxidative stress & reinforce inflammation

Chapplain J, et al. J Acquir Immun 2004

Model for Adverse Outcomes in Older Adults



Summary

- Multiple similarities between biology that underlies frailty and chronic HIV infection
- Some HIV treatments appear to accelerate that biology
- Frailty or biomarkers associated with frailty may be a useful construct to identify the most at risk HIV+ older patients for future study and for interventions