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EDITORIAL

PHYSICAL FRAILTY: A BIOLOGICAL MARKER OF AGING?

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Intrinsic capacity is defined as the resilience that an individual has to overcome a variety of environmental, physical and psychological factors (1). A person's intrinsic capacity is created by their genes and a number of life style factors, e.g., exercise and diet, health care, e.g., vaccines and environmental. Intrinsic capacity tends to peak between 30 to 40 years, after which it slowly declines (2) (Figure 1). Frailty is defined when a person declines at a more rapid rate than that normally seen with the decline in age-related intrinsic capacity. Frail persons are at a greater risk of decline when exposed to stressors (3). In modern geriatrics frailty is interpreted as being a transitional process between a resident individual and one with disability (4, 5).

Physical frailty was operationalized by Fried et al (6). It was defined as fatigue, weight loss, weakness, slow walking gait and limited physical activity. It is predictive of poor outcomes when persons with disability are excluded (7). There are over 70 other definitions of frailty. The Rockwood Frailty Index is a co-morbidity index which can include disabilities and diseases (8). As such, it is more a marker of the effects of disease than a physiological marker of aging. Psychosocial frailty represents a separate form of frailty. Psychosocial frailty can represent a physiological decline, e.g., some forms of dementia or a disease process, such as depression, Lewy-Body dementia, and schizophrenia (9). Mild Cognitive Impairment (MCI) can be considered the equivalency of Fried's (6) definition of physical frailty. In many cases there is overlap between MCI and physical frailty (10-12).

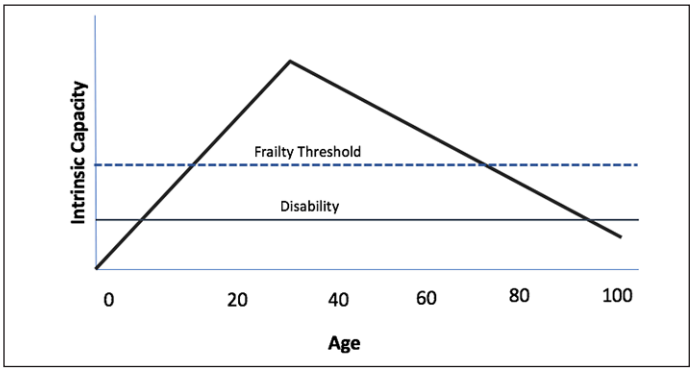
Sarcopenia is a major component of physical frailty (13, 14). while loss of muscle mass and strength can be due to disease, e.g., diabetes mellitus or congestive heart failure much of sarcopenia is directly related to the aging process (primary sarcopenia) (13). A rapid screen for sarcopenia has been developed, i.e., the SARC-F (15-17).

Takeda et al (18) have suggested that both physical frailty and MCI, when not directly disease related, can be considered a clinical model for geroscience. Numerous senolytics and other age-delaying drugs are being developed in animal models (19). While most of these drugs are not yet ready for prime time, an exception is metformin which has been successfully used to treat diabetes mellitus (20). Epidemiological evidence strongly suggests that it delays the onset of dementia (21). Studies in mice support its use as a cognitive enhancer (22). Clinical studies are now ongoing looking at the effect of metformin as a retardant of the aging process (23). In addition, there is evidence that vaccinations such as influenza and diphtheria/tetanus may lower the risk of dementia by modulating the T-cell immune response (24).

Numerous biomarkers for intrinsic capacity and aging phenotypes have been discovered (25, 26). These include nucleic acid-based, protein-based, metabolic-based and microbiome-based. Similarly, a number of biomarkers for physical frailty have been identified (26). A number of these overlap with aging biomarkers. Frailty has been shown to have a strong relationship to inflammatory cytokines (27-30). Progranulin is a highly conserved secreted protein that plays a role in inflammation, cell proliferation and cell repair (29). Progranulin is elevated in physical frailty (25, 30). Progranulin elevations are strongly related to elevated proinflammatory cytokines (30, 31). As such progranulin may be an excellent marker for physical frailty.

Figure 1

A schematic view of the decline of intrinsic capacity to physical frailty and disability over the lifespan



Early recognition of physical frailty and treatment may allow reversal of the aging process and restoration of resilience. Frailty can be rapidly recognized by the FRAIL questionnaire (7, 32, 33). FRAIL is highly predictive of future disability and mortality (34). Physical frailty can be reversed in most cases with physical exercise (35-37). High fruit and vegetable diets

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protect against frailty (38, 39). An olive oil-based diet which is high in phenyls may reverse the activity of proinflammatory cytokines (40, 41). The diet should also include a leucine enriched essential amino acid supplement to enhance muscle strength (42). Finally, the FRAIL has an associated algorithm that will recognize possible treatable causes of frailty such as sleep apnea and depression as well as the reversible causes of age associated anorexia (43-45).

The management of aging associated factor needs to be patient centered (46). The early recognition of physical frailty in primary care practice, utilizing the FRAIL, is an excellent model for geroscience based secondary prevention. Future research will hopefully give us a number of biomarkers, such as progranulin, that will allow the development of individualized therapy for physical frailty. This will be particularly important in the combination of physical frailty and cognitive decline which tends to produce a more rapid overall decline (47-49).

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