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Editorial

Clinical Definition and Pathophysiology of Frailty: A Brief Review

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Editorial

With the medical field making constant and dramatic improvements in treatment and prevention of disease progression, life expectancies in the United States are increasing dramatically, with the elderly population demonstrating the greatest expansion. This substantial increase in the elderly population creates new and unfounded challenges in treating and caring for this sect of the population. In 1990, the American Medical association stated that ". . . one of the most important tasks that the medical community faces today is to prepare for the problems in caring for the elderly in the 1990's and the 21st century" [1]. This particular study emphasized the need to develop and sustain means of special care for the growing population of the frail and vulnerable elderly.

Frailty is often used as an umbrella term to identify a syndrome containing a litany of different symptoms such as a loss of reserves, leading to vulnerability, injury, and death [2,3]. Often times frailty, disability, and comorbidity are used interchangeably, however these terms do not necessarily mean the same thing. Disability has been defined as a difficulty or dependency on others to carry out essential activities for independent living, including: tasks essential to self-care, living independently in a home, and performance of desired activities important to quality of life [3,4]. As of 1996, the prevalence of disability in community-dwelling adults in excess of 70 years of age is approximately 20-30% [5].

Comorbitity is defined as the concurrent presence of two or more medically diagnosed diseases in the same individual [6,7]. Estimates state that approximately 35% of the population over 65 years of age is comorbid, while greater than 80% of the population over 80 years of age possesses two or more diseases [5]. Much contemporary research is aimed at investigating the physiological impact comorbidity presents in the development of frailty, including the interactions between strength and balance, vision and hearing, and physiological biomarkers, including interleukin-6 and IGF-1 [8,9]. According to a survey completed by 62 geriatricians, Fried and Watson [10] were able to report a list, in order of frequency, of characteristics that represent frailty. These characteristics include: malnourishment, functional dependence, prolonged bed rest, pressure sores, gait disorders, general muscle weakness, in excess of 90 years of age, weight loss, anorexia, fear of falling, dementia, hip fractures, delirium, confusion, going outdoors infrequently, and polypharmacy [10]. In essence, frailty is a dynamic process of increasing vulnerability seen across a broad spectrum of domains, including physical, nutritive, cognitive, and sensory, that lead to functional decline and ultimately death [11-13]. Clinically, Frailty is viewed as a transitional state in the functional process from robustness to functional decline [14].

Fried et al. [15] proposed an operative description of the frailty phenotype that has been adopted by the American Geriatric Association. The frailty phenotype can be defined as an individual exhibiting three or more of the following symptoms: unintentional weight loss of greater than 4 kg per year; weakness measured by grip strength in the lowest 20% in the dominant hand; self-reported exhaustion that indicates reduced VO2max and graded exercise performance; time to walk 15ft in the slowest 20%; and, physical activity in the lowest 20% for caloric expenditure [15]. In 2000, researchers estimated that there were approximately 6 million frail persons living in the United States [16]. However, given the complexity in defining frailty, researchers believe this value to be a significant underestimate [3,17].

Three distinct stages have been identified in the developmental process of frailty: a pre-frail process; the frailty state, and frailty complications [18]. The pre-frail stage is described as a steady decline in physiological reserves, with the individual still maintaining enough reserves to allow for adequate response to an injury or stressor, resulting in silent clinical symptoms. During the frailty stage, physiological reserves have declined beneath the functional threshold, resulting in an inadequate response to stressors and injury, yielding impaired and/or incomplete recovery [14,18]. The final stage, presented as frailty complications, result in dramatic declines in functionality leading to disability, infection, polymedication, increased hospitalization, institutionalization and eventual death [3,11,18].

A variety of risk factors exist that are directly associated with the development and progression of frailty. These include, but are not limited to: physical inactivity, malnutrition, chronic disease, cognitive decline, social aspects, and gender differences. Regarding inactivity, Bortz [17] has described loss of muscular function as the "gateway" to frailty, implicating that physical inactivity is a major contributor to the disease progression. The resultant reduction in fitness level attributed to inactivity will yield a dramatic decline in muscle mass, significant weight loss, and a reduction in resting metabolic rate, reduced gait time, and a drop in grip strength [15,17]. Malnourishment significantly contributes to the progression and development of frailty, as nutritional deficiencies will result in weight loss and bone mineral density, putting individuals at much greater risk of injury [15]. In addition, the low caloric intake will reduce individual energy levels, compounding the effects of reduced physical activity, impairing an individual's ability to adequately perform the necessary independent activities of daily living (ADL) [17]. Researchers also noted that obesity and excessive energy intake can contribute significantly to the development and progression of frailty [19].

Researchers have also suggested that diseases and injuries significantly contribute to frailty development via direct inhibition of physical inactivity [17]. The pain and immobility caused by acute injuries such as fractures, strains, and sprains, as well as chronic disease states, such as osteoarthritis, greatly reduce the ability of an individual to participate in regular physical activity, compounding the negative effects of the already at-risk individual [17]. Functional decline can also be enhanced via cognitive dysfunction [20]. A decline in cognitive function, attributed to development of disease states such as dementia and Alzheimer's play a major role in the loss of an individual's independence and ability to perform ADLs [20]. In addition, sensory declines have also been implicated as direct indicators of frailty development. According to the Beaver Dam Eye Study, visual acuity and contrast sensitivity was found to be lowest in individuals determined to be most frail [21].

A diminished desire to participate in extracurricular and social activities, including going outdoors and participating in activities with family in friends, led to increased social isolation in those classified as frail [13]. A diminished quality of life compounds the physical and cognitive impairments affiliated with the progression of this diseased state and is directly related to greater morbidity levels [13]. Regarding gender differences, research has demonstrated an increased prevalence of frailty development and progression in females relative to males [3,15]. This could be a result in physical differences between genders i.e. lower lean body mass and strength in females relative to males, or the higher life expectancy in females compared to males [3,15].

Frailty is a disease that manifests itself with a dramatic decline in functionality of a variety of physiological systems. Given the complexity of this disease, there is no single pathophysiological determinant responsible for development. Instead, there are a variety of contributing factors responsible for the development and progression of frailty, including but not limited to: diminished physiological reserves, sarcopenia, hormonal changes, and osteopenia. According to Bortz [17], the organ systems of a healthy individual have a capacity to adapt to rapidly changing environmental conditions until the marginal loss of functional capacity exceeds 70%, demonstrating a reserve capacity of 30%. Functionality of these physiological systems can be identified by utilizing a variety of assessments including: VO2max, myocardial oxygen consumption (MVO2), arterial cross-sectional area, maximal breathing capacity, forced expiratory volume, hematological values, renal and hepatic function, blood sugar levels, sensory capacity, cognitive skills, and central nervous system dopamine content [17]. These dysfunctions are further compounded when the threshold capacity exceeds the 30% functionality reserve with the increased physical inactivity imposed upon individuals suffering from organ system debilitation, further reducing an individual's capacity to respond to environmental stressors and recover from injury or illness [17].

Researchers have specified that a reduction in the functionality of the musculoskeletal system is one of the major contributing factors to the development and progression of frailty [17,22]. Sarcopenia, defined as age-induced loss of skeletal muscle mass, begins by age 40, yielding an overall loss in muscle mass between 30-50% by age 80 in both males and females. This loss in skeletal muscle mass dramatically impairs strength, power, endurance, as well as impairs balance and gait measures, leaving the individual more susceptible to falls and at risk of sustaining additional secondary injuries and developing physical disabilities [10]. With no clear cause of sarcopenia yet identified, researchers have found it difficult to pinpoint preventative measures that should be followed. However, researchers have hypothesized that muscle fiber denervation attributed to advancing age and exacerbated by inactivity, contribute to sarcopenic development [23].

Hormonal abnormalities and inflammatory markers prevalent in the frail have been shown to contribute to progression of the diseased state [24]. Insulin resistance associated with ageing and inactivity, resulting in endothelial dysfunction function exemplified by reduced nitric oxide production and impaired vasodilation, has been identified as a contributing factor to frailty progression [25]. An imbalance in the balance between anabolic and catabolic processes required to maintain muscle mass and guard against sarcopenia has also been identified as a contributing factor to the disease progression [17]. A reduction in growth hormone, testosterone, and IGF-1 concentrations concurrent to increased Cortisol and other inflammatory biomarkers, including interleukin-6, has been identified as prevalent within the frail population [26].

Endocrine dysfunction associate with frailty can be attributed to impaired functionality of the hypothalamic-pituitary-gonadal/adrenal and growth hormone-IGF axis [27]. This dysfunction results in a decline in estrogen and androgen levels, in turn yielding an

increase in local bone cytoclastic cytokines, ultimately increasing absolute and relative declines in bone mineral density. In addition to this decline in bone turnover attributed to these hormonal cascades, a reduction in physical activity impairs necessary stressors placed on the bones to facilitate bone mineral accretion, further reducing bone mineral density, increasing bone fragility and susceptibility to injury development and progression [17,27].

According to the American Medical Association, the increased incidence of frailty and subsequent complications will pose a great challenge in moving forward to care for the elderly [1,3]. Complications that arise from frailty progression include disease, institutionalization, and death. Chronic diseases include pulmonary dysfunction, cardiovascular disease, diabetes, and atherosclerosis [15]. Using the Cardiovascular Health Study, Fried et al. [15] pointed out that greater than 60% of people suffering from frailty were admitted to a hospital within 3 years, putting tremendous strain both physically, and financially on the individual and medical system as a whole. Ultimately, advancing age will result in death. However, individuals identified as frail have a 6-fold increase in mortality over a 3 year period when compared to non-frail individuals [15].

Unlike with many other progressive disease states, many of the risk factors associated with the progression of frailty, are relatively reversible [28]. Interventions to reduce the rate of disease progression include: exercise programs; pharmacological treatment; a combination of both exercise and pharmacology; and, improved care.

As physical inactivity has been implicated as one of the major risk factors in the development of frailty through fostering sarcopenic progression, insulin resistance, and loss of mobility, introducing susceptible individuals to a consistent exercise program will greatly reduce the risk of frailty development [15]. Much research has been done to identify the beneficial effects of strength and balance training on reducing the progression of functional decline in the frail elderly, showing significant improvements in performance of ADLs and reduced signs and symptoms of frailty via enhanced lean body mass and mobility [23]. Administration of anabolic hormones, as well as substances such as erythropoietin, beta-adrenergic agonists, ACE inhibitors, and statins have been investigate, but show incomplete and inconclusive results [14]. When programs are combined, including enhanced dietary composition and stress reduction techniques, observable improvements are made in minimizing progression of the disease state, comparable to those found with the resistance training studies [14]. Finally, assessments of quality of care have been shown to yield a variety of results, suggesting that greater training is required in understanding and better facilitating the treatment of the geriatric sect of the population [14].

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