Editorial

Clinical Approaches and Emerging Therapeutics for Frailty Syndrome

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Frailty is a geriatric condition characterized by physiologic changes and increased vulnerability to adverse health outcomes such as disability.[1] Frailty has been conceptualized in more than one way—through the use of a physiologic paradigm[2] with measurements of gait speed, grip strength, self-reported exhaustion, low physical activity, and unintentional weight loss; and through deficit accumulation,[3] in which frailty syndrome is defined by the accumulation of deficits, including loss of functional ability, chronic disease burden, self-reported health status, and others. Frailty often shares common risk factors, pathways, and outcomes with other geriatric syndromes, such as delirium, incontinence, and falls.[4] Our understanding of frailty syndrome and its phenotype has advanced with years of research, leading to potential therapeutic targets to prevent or treat frailty.[5] In addition, there is increasing recognition that the assessment of frailty may be applied in clinical settings to help clinicians risk-stratify and predict adverse health outcomes in different clinical scenarios.[6–8] The articles in this Specialty Update describe the roles of inflammation and insulin resistance in frailty, discuss potential therapeutic targets, and highlight the potential clinical implications of frailty in clinical scenarios such as surgery.

The pathogenesis of frailty in a given patient is likely to be complex and includes multiple physiologic changes.[9] Studies on interventions for frailty have largely focused on nonpharmacologic therapies such as exercise and nutrition; there is currently no pharmacologic treatment for frailty, but its development is underway. Espinoza et al[10] review the evidence for exercise- and diet-based interventions for frailty and discuss the potential implications. The effects of the exercise interventions are varied; exercise may improve physiologic status and reduce vulnerability to adverse outcomes. Another potential pathway for the development of frailty may lie in reduced insulin sensitivity, as reductions in insulin sensitivity and diabetes have been associated with frailty. In intervention studies in obese individuals, exercise and diet interventions have been found to increase physical function, maintain muscle mass with weight loss, and increase insulin sensitivity.

Among the different pathogenic pathways that may contribute to frailty, inflammation has been postulated to play an important role; differences in the levels of inflammatory markers among older adults who exhibit symptoms consistent with frailty phenotype have been reported.[11] Elevated white blood cell counts and interleukin-6 levels, which are inflammatory markers, have been associated with frailty in community-dwelling older adults.[12] Chen et al[13] describe the chronic low-grade inflammatory phenotype, senescent immune dysregulation, and its link to frailty. As indolent, smoldering, chronic inflammation may play a key role in the pathogenesis of frailty, modulation of this inflammatory state may interrupt the pathogenesis of frailty, thereby preventing or treating it. This phenotype may be a target for novel avenues to develop therapeutic interventions for frailty. Metformin, an oral medication used to treat diabetes, has both effects on insulin sensitivity and also antiinflammatory properties. Trials are underway to test its efficacy on the prevention of frailty in older adults. Other medications with antiinflammatory properties are being tested for their effects on frailty, including fish oil and angiotensin II receptor blockers.

Aside from interventions for the treatment of frailty, new areas of research have focused on the application of frailty assessment in risk stratification and prediction of outcomes. Given that frailty is characterized by increased vulnerability to adverse health outcomes, incorporating frailty measurement in clinical practice has the potential to help clinicians and patients understand the risks of medical interventions. Ko[14] reviews the evidence on the relationship between frailty and outcomes after general surgery. Older adults who are frail preoperatively are at

increased risks for postoperative complications, prolonged hospital length of stay, mortality at 30 days, and mortality in the long term after both emergency and nonemergency surgery. This finding is consistent with other research findings that frailty is a predictor of poor outcomes and mortality in older adults who have undergone cardiovascular[15] or orthopedic[16] surgery or percutaneous coronary intervention.[17] Introducing frailty assessment in risk stratification prior to major interventions such as surgery may offer benefits to improve current risk-assessment tools for older adults undergoing surgery.

Advances in research to define and measure frailty have improved our understanding of its pathogenesis, which has led to the identification of potential targets for the treatment or prevention of frailty. It has also led to a better understanding of the clinical relevance of frailty in risk stratification in older adults undergoing interventions such as surgery. Future research should identify further opportunities to apply the results of frailty research to clinical uses to improve the care of older adults.

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