January 19-20, 2011, Athens, Greece
IAGG/WHO/SFGG Workshop n°3
"Promoting access to innovation and clinical research for frail old persons"

Taking into account of frailty in treating older patients with cardio-metabolic diseases

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Introduction

Frailty, a widely accepted geriatric syndrome, is described as the progressive physiologic decline in multiple body systems and is featured by loss of function, loss of physiologic reserve, and increased vulnerability to disease and death, according to Fried, et al (1). In Fried's criteria, subjects with 3 out of 5 phenotypic characteristics, i.e. low grip strength, low energy, slowed walking speed, low physical activities, and unintentional body weight loss, would be defined as frailty. Compared to Fried's emphasis on physical performance, other definitions extend physical performance to dimensions such as incontinence, cognitive impairment, psychosocial factors, and multimorbidity to describe frailty. Despite the lack of universal definition, frailty has gained extensive attentions in recent years because it provides an excellent approach to explain the heterogeneity of clinical outcomes of chronic illnesses in the elderly. Although the interaction of frailty and chronic diseases is complex, it is generally agreed that frail older people are more likely to have more comorbid medical conditions. Common chronic conditions associated with frailty are mainly cardiometabolic diseases and musculoskeletal diseases but there is no single frailty-chronic disease association that can be identified. Although there are uncertainties between frailty and cardiometabolic diseases, evaluating the prognostic significance of frailty in relation to cardiometabolic diseases in older patients is important and may alter clinical practice in the future.

Frailty in association with cardiometabolic diseases

The association of frailty with cardiometabolic diseases in the elderly has been reported increasingly (2). The interaction of frailty and cadiometabolic diseases is not only mechanistic, but also clinical and epidemiological. A previous systematic review found that cardiovascular diseases can lead to frailty and vice versa, (2) so the close connection between frailty and cardiometabolic diseases deserves prospective studies for clarification. In addition to the association, frailty is also a powerful predictive factor for mortality of older patients with cardiovascular diseases, (2) indicating the need for frailty assessment in traditional cardiovascular risk assessment. The pathways of frailty and cardiometabolic diseases are complex, but they share a common etiological factor in both entities, i.e. chronic low-grade inflammation. In the "cycle of frailty" proposed by Fried, et al., frailty may be resulted from a combination of neuroendocrine dysfunction, e.g. decreased insulin-like growth factor and dehydroepiandrosterone sulfare, an altered inflammatory status featured by elevated C-reactive protein (CRP), interleukins (ILs), tumor necrosis factor α, and abnormal coagulation (1). Among them, chronic inflammation has been considered to play a significant role in the pathophysiology of frailty.

Progressive elevation of CRP and IL-6 is part of normal aging process that has doubled from age 40 to 65. Although the causal relationship between aging and chronic inflammation remains unclear, elevation of inflammatory markers may reflect the burden of tissue damage or impaired homeostasis in recovery from stresses. On the other hand, elevation of CRP is a common feature of cardiovascular diseases and is associated with adverse cardiovascular outcome, which may be the biggest overlapping biological presentation of frailty and cardiometabolic diseases. Another common physiologic finding of frailty in relation to

cardiometabolic diseases is insulin resistance, which is associated with skeletal muscle protein breakdown, chronic repetitive injury and neurohormonal activation of cardiovascular diseases. Association of frailty with cardiovascular diseases has been reported in several cross-sectional epidemiological studies, and subjects with cardiovascular disease or higher subclinical cardiovascular risks were more likely to develop frailty during follow-up.

Treatment implication of frailty in cardiometabolic diseases

The association of frailty with cardiometabolic diseases in older adults is more than an epidemiological phenomenon. It is even more important in clinical practice. A recent study proved the prognostic importance of frailty in chronic kidney disease, which clearly demonstrated that frail patients with chronic kidney disease were at a higher risk of mortality. It is not surprising that frailty also plays the similar prognostic role in all dimensions of cardiometabolic diseases since frailty is known to increase vulnerability in multiple organ systems. Results from the Cooperative Cardiovascular Project found that frailty clearly predicts 1-year mortality and stroke after acute myocardial infraction (3,4), supporting the assumption that frailty deteriorates the clinical outcomes of cardiometabolic diseases. The proposed concept of “reverse metabolic syndrome” indicated that the malnutrition and suggestive frailty per se are more closely related to poorer clinical outcome than metabolic syndrome among people aged 70 and over. The idea of “reverse metabolic syndrome” was supported by a following study which depicted that metabolic syndrome was a protective factor for mortality among Chinese men older than 75 years (5). Results from the InCHIANTI study, however, showed that sarcopenia was a stronger predictor for mortality than obesity, which also implied the significance of managing frailty in cardiometabolic diseases.

In therapeutic interventions, low resistance exercise training may successfully improve physical performance of frail older people and should be of clinical benefits of cardiometabolic diseases. In addition, higher protein consumption, as a fraction of energy, is strongly associated with lower risk of incident frailty. Inclusion of low-glycemic and moderately high-protein products in snacks induced a favorable change of body composition and lower cardiovascular risk in diabetic patients. Recently, it has been reported that incidence of coronary heart disease is positively associated with energy consumption, but is inversely related to protein density. Moreover, the protein consumption is inversely related to the incidence of ischemic stroke. A common worry of high protein intake in cardiometabolic disease is the possibility of renal function deterioration, but it was not observed in the Women’s Health Initiative Observational Study. Although the previous study suggested that high protein intake may accelerate renal function decline in women with mild renal insufficiency, estimation of glomerular filtration rate in this study was performed by creatinine levels instead of cystatin C. Most previous studies suggested that protein supplementation accelerated renal function decline were done by measurements of creatinine, but this phenomenon was not supported by studies using cystatin C to estimate glomerular filtration rate. Therefore, the most common frailty intervention program, i.e. resistance exercise plus protein supplementation, can be applied to elderly patients with cardiometabolic diseases with clinical benefits. However, developing a well-designed program including intensity and dosage of exercise and protein intake is critical in the clinical practice. Aside from resistance exercise and protein intake, results of pharmaceutical interventions were mixed except that peridonpril significantly improved physical

performance of older people with functional improvement, in which angiotensin II may play certain roles in modulating muscular function. The results suggested a potentially superior role of rennin or rennin-angiotensin system blockade to treat frail older patients with cardiometabolic diseases.

Although the prognostic significance of frailty in cardiometabolic disease has been demonstrated, further intervention study is needed to clarify whether or not alleviation of frailty improves clinical outcomes of cardiometabolic diseases. However, before an interventional strategy is developed, assessment of frailty should be integrated into the traditional cardiometabolic risk assessment to form a global risk assessment for older patients with cardiometabolic diseases. Furthermore, strategies should include implementation of early identification, consideration of referrals to geriatricians, and anticipation of care after major cardiac events since frailty would aggravate clinical outcomes of cardiometabolic diseases.

Conclusions

Frailty and cardiometabolic diseases in older people are closely interrelated, and they share some pathophysiologic similarities. Frailty is of prognostic significance in cardiometabolic diseases for older people. Resistance exercise and protein intake may be beneficial to both entities. Further intervention study is needed to support the hypothesis that alleviation of frailty improves clinical outcomes of cardiometabolic diseases. However, current evidences support adding assessment of frailty in traditional cardiovascular risk assessment to formulate a global risk assessment for older patients with cardiometabolic diseases. It also deserves further investigations to develop an integrated risk assessment tool, especially to simplify the definition of frailty in clinical settings.

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