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PREVIEW

Understanding cognitive frailty in aging adults: prevalence, risk factors, pathogenesis and non-pharmacological interventions

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ABSTRACT
The worldwide increase in the aged population raises health concerns for elderly individuals. Cognitive frailty of the elderly (apart from those suffering from Alzheimer´s disease or other type of dementia) is a complex construct associated with aging, which is composed of physical and cognitive components, while physical frailty and cognitive impairment mutually affect each other. Although the prevalence of cognitive frailty in community-dwelling older adults without neurodegenerative disease is low, it can rise dramatically in clinical settings. Early identification of this condition can contribute to delaying the adverse outcomes that lead to higher mortality rates. This review aims to define cognitive frailty, its prevalence, risk factors, and pathogenesis, while highlighting the need for further research on identification, prevention, and non-pharmacological management of cognitive frailty in older adults in view of promoting healthy aging and secondary prevention strategies for dementia *(Fig. 1, Ref. 93)*. Text in PDF *www.elis.sk*
KEY WORDS: cognitive frailty, older adults, risk factors, nutrition, exercise.

Abbreviations: CDR – clinical dementia rating, AGEs – advanced glycation end products, EPA – eicosapentaenoic acid, DHA – docosahexaenoic acid

Introduction

The World Health Organization (WHO) Health Statistics Report as of 2021 indicates that the average level of aging, defined as the ratio of individuals aged 65 and over to the total population of a region or country, has reached 9.6 % globally, with one in every ten individuals being an older person (1). Alongside the health problems that older individuals may encounter, the increase in prevalence rates of the aged population has become a significant concern for the international community. The aging process is characterized by a decline in physiological reserves in various systems which is caused by the presence of multiple subclinical comorbidities and stressors and results in homeostatic imbalance or frailty (2, 3). This process can result in both physical frailty and cognitive decline, which may occur concurrently in older individuals (2). Frailty encompasses not only physical but also cognitive, psychological, and social aspects (4). Therefore, the search for novel approaches to slow the aging process has become one of the major goals of geriatric research (3, 5).

Defining cognitive frailty

Cognitive frailty is a complex construct that includes physical and cognitive components (Fig. 1). The physical component of cognitive frailty includes unintentional weight loss, weakness, slowness, low physical activity, and exhaustion. These five criteria are collectively known as the Fried criteria (6). The presence of three or more of these criteria is considered to be indicative of physical frailty. The cognitive component includes memory impairment, decreased processing speed, and executive function decline (7). An increasing number of studies have also shown

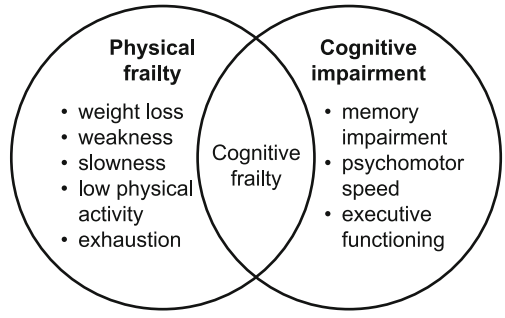

Fig. 1. Cognitive frailty is a complex construct that includes physical and cognitive components.

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that physical frailty and cognitive impairment are in bidirectional relationship, in frame of which they exacerbate each other with cumulative negative effects (8–12). Moreover, cognitive frailty is associated with an increased risk of adverse health outcomes such as malnutrition, hospitalization, depression, disability, and even death in older individuals (3, 12, 13). This condition increases the risk of dementia and all-cause mortality by approximately 4.01 and 3.4-fold, respectively (14, 15), as compared to the risk attributed to cognitive impairment or physical frailty separately (16, 17).

The International Consensus Group on Cognitive Frailty organized by the International Academy on Nutrition and Aging (I.A.N.A) and International Association of Gerontology and Geriatrics (I.A.G.G) were first to widen the conception of cognitive frailty by defining it as a concurrent presence of physical frailty and cognitive impairment (CDR = 0.5) in the elderly (apart from those suffering from Alzheimer's disease or other types of dementia), and considered this entity as being potentially reversible (18). However, there have been some disputes and revisions to the definition of cognitive frailty. Woods et al (19) claimed that individuals with brain disorders should not be excluded from the diagnosis of cognitive frailty and argued that the reduction in cognitive reserve is not a defining feature of cognitive frailty. Similarly, Dartigues et al (20) questioned the relationship between cognitive frailty and physical frailty, as well as the distinction between cognitive frailty and other cognitive disorders in the diagnostic criteria for cognitive frailty. In a subsequent study published by Ruan et al (10), it was proposed that the concept of "prefrailty" should be incorporated into the diagnostic criteria for cognitive frailty and that cognitive frailty should be divided into two subtypes: reversible and potentially reversible. In recent years, Mantovani et al (21) have proposed a reevaluation of the cognitive frailty definition based on a multidimensional model which emphasizes the need to consider clinical features, neuropathological changes, biomarkers, disease and medication status when assessing cognitive frailty (3).

There are tools available to help identify cognitive impairments that may be indicative of cognitive frailty, ranging from self-reported cognitive-screening questionnaires to screening tests and neuropsychological batteries (22, 23). The Mini Mental-State Examination (MMSE) (24) is the most widely used screening test, despite its inability to detect mild cognitive disorders (25). Other tests include CDR (26), Montreal Cognitive Assessment (MoCA) (27), trail-making test (TMT) (28), and verbal fluency test (29). These tests can help identify cognitive impairments that may be indicative of cognitive frailty. However, it is important to note that these tests do not provide a conclusive diagnosis of cognitive frailty. There is currently no test that could adequately capture and identify cognitive frailty; however, such a test should concentrate on comprehensive assessment that considers both physical and cognitive aspects of cognitive frailty for the diagnosis to be accurate. This is essential for early identification, which can lead to earlier deployment of interventions, thus promoting healthy aging and secondary prevention strategy for asymptomatic or early-stage dementia (2, 3, 30, 31).

Prevalence and risk factors

The prevalence of cognitive frailty in community-dwelling older adults without neurodegenerative disease has been reported to be in the range of 1.0 % to 1.8 %. However, this rate can increase dramatically in clinical settings, ranging from 10.3 % to 42.8 % (7, 11, 14, 32, 33).

A growing body of literature suggests that several risk factors can influence the development of cognitive frailty, including increased age, female gender, unhealthy lifestyle habits (such as smoking and inadequate physical activity), poor nutritional status, and co-existence of depression (34–39).

Several studies have also investigated the potential role of genetic factors in the development of cognitive frailty, where the presence of the ε4 allele in the APOE gene was associated with an increased risk of cognitive impairment (40, 41), while another study found that a SIRT1 gene has a neuroprotective effect during aging (42). Polymorphisms in several genes, including IL-6 with rs1800796, TNF-α with rs1800629, IL-18 with rs360722, and IL-1β with rs16944 showed a relation to cognitive frailty (2, 43).

Recent research has also suggested that suboptimal cognitive reserve in early life may be a risk factor for age-related cognitive impairment due to the brain being less resilient to changes over time (44). Cognitive reserve refers to the brain's ability to compensate for age-related changes, and it can be influenced by factors such as education, occupation, and leisure activities. Studies have found that individuals with a higher cognitive reserve are less likely to develop cognitive frailty (45, 46).

Among the technologies that could be used for identifying the cognitive frailty in older adults are the machine learning and artificial intelligence, which are currently experiencing tremendous success (47). By analyzing large datasets of demographic, medical, physical, and cognitive assessment data, the machine-learning algorithms can develop predictive models that identify individuals at high risk for cognitive frailty (48, 49). These algorithms can also automate the diagnosis of cognitive frailty while reducing the burden taken on by clinicians and improving the consistency and accuracy of diagnoses. Additionally, the machine learning can identify the most important features or risk factors associated with cognitive frailty, which can lead to a better understanding of the underlying mechanisms and development of targeted interventions (50, 51).

Pathogenesis of cognitive frailty

As a consequence of the multifactorial nature of cognitive frailty, a number of factors, including chronic inflammation and nutrition, as well as vascular and metabolic factors, may be involved in the development of the condition (52, 53). Furthermore, the factors of dysregulation in the hypothalamic-pituitary axis (HPA) stress response, imbalanced energy metabolism, impaired cardiovascular function, mitochondrial dysfunction, oxidative stress, and neuroendocrine dysfunction may contribute to both physical and cognitive decline, and as such, they may be involved in the mechanisms underlying the relationship between physical frailty and cognitive decline (53).

It was found that two biomarkers of oxidative stress, malondialdehyde (MDA) and protein carbonyls, are linked to cognitive decline (54). There is evidence that advanced glycation end-products (AGEs) may also play a significant role in the development of cognitive frailty. AGEs are organic compounds that are formed either endogenously in the human body or exogenously in foods undergoing thermal processing (55). They have been shown to impair cognitive function by inducing oxidative stress and neuroinflammation in the brain (56) and contribute to the decline in functional mobility (57).

Older adults with cognitive frailty had higher levels of neuroinflammatory markers such as CRP, IL-6, TNF-α, CD4, CD8, cortisol/DHEA ratio, uric acid, and homocysteine (43, 58). IL-6 has been found to be the most important cytokine in inflammaging and is associated with poor physical performance, worse cognitive function, disability, and mortality in the older population (53, 59, 60, 61).

There is some evidence suggesting that sarcopenia may play a role in the development of cognitive frailty. Older adults with primary sarcopenia are more vulnerable to experiencing cognitive decline and developing cognitive frailty compared to those without sarcopenia (62–64).

In elderly individuals with cognitive frailty, the volume of the hippocampus decreases significantly, and these changes are associated with cognitive impairment and physical infirmity. It appears that the atrophy of subregions of the hippocampus contributes to the pathological progression of cognitive frailty (65).

Studies have shown that low levels of vitamin D, as well as deficiencies in vitamins B6, B9, and B12 and magnesium have been associated with cognitive decline in older adults (66, 67). Omega-3 fatty acids levels in the brain tend to also decrease with aging, suggesting that low levels of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have a detrimental effect not only on physical and musculoskeletal function but also on cognitive functioning in older adults and may contribute to memory loss and other cognitive deficiencies (68–70). There is a growing body of evidence that indicates that EPA and DHA have been shown to play a role in synaptic plasticity, neurogenesis, cognition, and vascular health (70–72) and are significantly associated with mild cognitive impairment (73).

Non-pharmacological interventions

Non-pharmacological interventions are currently the main modalities of cognitive frailty interventions (3, 74). These interventions range from dietary and nutritional advice to psychosocial support, cognitive training, physical training, and physiotherapy programs (3). Studies have shown that a multidomain intervention can improve or maintain cognitive functioning in older adults with cognitive frailty (75).

Nutritional intervention

Nutritional deficiencies in older adults can have a significant impact on their physical and cognitive functioning (76). It is important to note that proper nutrition plays an important role in maintaining the overall health of the elderly (77), as well as that nutritional deficiencies should be considered as potential contributing factors in the development of cognitive frailty. Many dietary components and supplements have been studied for their effects on cognitive decline, including vitamins (such as beta-carotene, folic acid, vitamins B6, B12, C, D, and E), minerals (such as zinc, and magnesium), omega-3 fatty acids, and other supplements (flavonoids, curcuminoids, ginkgo biloba, acetyl-L-carnitine, phytoestrogens, tea and (-)-epigallocatechin-3-gallate, resveratrol, garlic, and caffeine) (74, 78). Since dietary AGEs are a significant source of AGEs in the body, it may be beneficial to reduce the intake of dietary AGEs to prevent or treat cognitive frailty. This can be achieved by consuming a diet that is low in processed and fried foods and high in fruits, vegetables, and whole grains (79, 80). Older people often experience physiological declines in food intake, resulting in nutritional deficiencies (81). However, these are often not given equal emphasis in the efforts to improve health among the adult population (77).

Physical activity

Exercise interventions have been found to be particularly effective in the management of cognitive frailty, including aerobic exercise such as walking (82) and brisk walking (83), resistance exercise (84, 85), multicomponent exercise, which combines aerobic exercise, resistance training, and other components such as balance and flexibility training (86), Otago exercise program (87) and traditional Chinese medicine mind-body exercises such as Baduanjin (88) and Taijiquan (89). Additionally, physical activity may have positive effects on mental health, social engagement, and overall quality of life, all of which can contribute to enhancing the cognitive function and reduce the risk of cognitive frailty (90).

Oxygen-ozone therapy

Oxygen-ozone therapy involves the administration of a mixture of oxygen and ozone gas, which has been suggested to have anti-inflammatory, antioxidant, and immunomodulatory effects (91). The therapy is non-invasive and has been used in medicine for more than 100 years (92). Due to its omnivarious properties, it may have a positive impact on cognitive function and physical performance in older adults (93).

Conclusion

With the rapid increase in aged population and numerous health problems affecting the elderly, geriatric research is focused on discovering new approaches to slow down the aging process. Cognitive frailty is a complex construct composed of physical and cognitive components and is associated with an increased risk of adverse health outcomes such as dementia, disability, hospitalizations, and death. The prevalence of cognitive frailty is significant in clinical settings. Several risk factors can influence its development, including increased age, female gender, impaired cardiovascular function, unhealthy lifestyle habits, poor nutritional status, and co-existence of depression. Therefore, addressing these risk factors is essential in identifying the onset of cognitive frailty in

the elderly. In order to detect early signs of cognitive frailty, it is necessary to develop a test and identify biomarkers that can be used in clinical practice. It will help to identify patients who are at risk of cognitive decline before they show any symptoms, allowing for early interventions that may prevent further decline. Currently, non-pharmacological interventions such as dietary and nutritional guidance and exercise interventions are primarily used in the management of cognitive frailty. Reducing dietary intake of AGEs and the formation of endogenous AGEs may hold a therapeutical potential in maintaining long-term health in aging adults. Additionally, oxygen-ozone therapy has been predicted to have a promising effect in the prevention and treatment of cognitive frailty. Future research should continue to explore methods to slow down the aging process and cognitive decline, including the prevention and management of cognitive frailty, as a means of promoting healthy aging and reducing the risk of dementia and other adverse health outcomes in older adults.

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