J Nutr Health Aging
Volume 19, Number 3, 2015

COGNITIVE ASPECTS OF FRAILTY: MECHANISMS BEHIND THE LINK BETWEEN FRAILTY AND COGNITIVE IMPAIRMENT

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Abstract: Whereas physical impairment is the main hallmark of frailty, evidence suggests that other dimensions, such as psychological, cognitive and social factors also contribute to this multidimensional condition. Cognition is now considered a relevant domain of frailty. Cognitive and physical frailty interact: cognitive problems and dementia are more prevalent in physically frail individuals, and those with cognitive impairment are more prone to become frail. Disentangling the relationship between cognition and frailty may lead to new intervention strategies for the prevention and treatment of both conditions. Both frailty and cognitive decline share common potential mechanisms. This review examines the relationship between frailty and cognitive decline and explores the role of vascular changes, hormones, vitamin D, inflammation, insulin resistance, and nutrition in the development of physical frailty and cognitive problems, as potential underlying mechanisms behind this link. Dual tasking studies may be a useful way to explore and understand the relation between cognitive and physical frailty. Further studies are needed to elucidate this complex relation to improve the outcomes of frailty.

Key words: Frailty, cognitive impairment, cognition and frailty, dementia, mini-mental state examination.

Introduction

The worldwide increase in life expectancy now continues in the 21st century, and this increase may be accompanied by a postponement of disability (1), which suggests that some aging processes leading to reduced function can be modified. This has led research to focus on states of vulnerability or mild disability due to age and disease related declines in many physiological systems, leading to adverse outcomes such as falls, disability, need for long term care and death (2). Such states are now considered under the wide umbrella of the term "frailty" (3).

A wide variety of classification criteria for the definition of frailty have been used in the literature. The prevalence of frailty seems to be high and epidemiological studies report its range to be from 5 to 58% depending on the definition of frailty and the study population (4-6). The prevalence of frailty increases with aging. It is approximately 4% between age 65-69 years, 8% between age 70-74 years, 10% between age 75-79 years, 17% between age 80-84 years, and 28% age over 85 years (7). So, it is notified that the prevalence of frailty is 32% in those over 90 years old (8). Data from the Women's Health Initiative Observational Study found that baseline frailty was seen in 16.3% of patients, and pre-frailty (means that the person is not robust, but not frail) was seen in 28.3 percent of patients, with an added incidence at three years of 14.8 percent (9).

At present there is a wide debate on the definition and concept of frailty (10). While the term frailty is usually used for age-related vulnerability to multiple outcomes, there is a considerable lack of agreement even on the content of the construct of frailty (11).

The term frailty comes from the Latin word fragilis, derived from the verb frangere, to break in pieces. In English, the words frail or fragile are used to describe delicate health, something that is easily broken, destroyed or damaged, or something that is delicate and vulnerable. The most widely used definition of frailty considers it as a biologic syndrome of decreased reserve and resistance to stressors, resulting from cumulative declines across multiple physiologic systems, and causing vulnerability to adverse outcomes (5). Some other definitions include aspects such as strength, mobility and physical capacity, nutrition and endurance within the scope of frailty (5, 12, 13).

Frailty is a multidimensional concept. Even when agreement in a universal definition seems to be distant, most experts include physical performance (gait speed and mobility), nutritional status, mental health, and cognition within the scope of frailty. Physical function (73%), cognition (50%), gait speed (50%), weight loss (45%) and physical activity (45%) seem to be the most commonly used categories to classify frailty (4). Controversy exists as to what degree (if any) of disability should be included in frailty, since disability to perform a single function increases vulnerability to loss of other functions. The links between disability, multimorbidity and frailty are blurred and complex to understand (10, 14).

The most commonly used operational definition of frailty is that defined by Fried as a phenotype, based on the presence of three or more of the following criteria: unintentional weight loss, exhaustion, weakness, slow walking speed, and low level of physical activity (5). Interestingly, these criteria, which are the most widely used in clinical research, do not include any mental or cognitive item, focusing only on physical frailty (15). A similar approach is used in the Study of Osteoporotic Fractures (SOF) index, which uses weight loss, inability to rise from a chair and energy lack to define frailty (16).

A different approach is used by Rockwood's frailty index deficit accumulation, which uses seventy variables that can be obtained by a comprehensive geriatric assessment in

Received March 17, 2014
Accepted for publication June 30, 2014

ten different domains, ranging from medical conditions to functional decline (17). This index offers a wide approach to all the dimensions of frailty, including cognitive aspects, but it has been criticized as time-consuming and thereby difficult to apply in routine practice. Interestingly, adding cognitive measures to definitions of frailty that are only based on physical frailty increases their predictive ability in detecting adverse outcomes (18). A study proposed to determine the prognostic effect of different frailty criteria by Rothman et al, showed that using of low physical activity, weight loss, slow gait speed and cognitive impairment were the key indicators for frailty (19). Another study written by Avila-Funes showed that frail individuals with cognitive impairment have a higher risk of instrumental and basic activities of daily living disability than subjects with none of cognitive impairment. And also, risk of mobility disability was marginally statistically significant, and risk of death also tended to be higher in cognitively impaired frail participants than in their non-frail counterparts without cognitive impairment (18).

The Links between Cognitive Decline and Frailty

Since cognition is a relevant domain of frailty, it is quite surprising to notice that the literature on cognitive frailty is still sparse. In fact, a Medline search with the term "cognitive frailty" yields only few articles (20-22). However, some preliminary data tend to show that a link exists between cognitive decline and other domains of frailty, mostly physical.

A recent study highlights this link. It was designed to examine the relationships among seven frailty domains, including nutrition, physical activity, mobility, strength, energy, cognition, and mood, showing that frailty behaves as a multidimensional concept for which the relationships among domains differ according to the population characteristics. These domains appear to aggregate together and share a common underlying construct (23). Cognition behaves as an independent cluster in this frailty model.

The links between physical frailty, cognitive frailty and social frailty (it means that frailty may be some effects on quality of life) were also addressed in a study conducted by Langlois et al. Thirty-nine frail and 44 non-frail elders were compared for several measures of physical capacity, cognition, and quality of life. As expected, physical performance measures were significantly lower in frail participants, but frail participants also showed reduced performance in specific cognitive measures and processing speed. Also, frail elders had poor self-perceptions of physical capacity, cognition, affectivity, housekeeping efficacy, and physical health (24). The authors suggest that frailty might affect selective components of cognition and quality of life, besides the reduction of physical capacity (24).

The prevalence of cognitive problems seems to be higher in frail individuals, as defined by Fried criteria, than in robust people. A cross-sectional study including community dwelling adults over 65 years old, showed cognitive impairment in 39% of frail, 22% of pre-frail and 16% of robust patients (25). Another study in community dwelling persons 75 years old or older, with a prevalence of frailty of 9.6% and pre-frailty of 47%, found after logistic regression analyses that cognitive impairment was significantly associated with frailty (OR: 3.22; 95% CI: 1.48-7.02; p=0.0003) (26). Rockwood et al. also found an inverse correlation between Fried criteria and modified MMSE (r=-0.58) (17). The prevalence of dementia is also high in frail patients. In a cross sectional study that included 22,952 patients, the prevalence of dementia was higher in the most frail group (40.02% vs. 11.27%, p<0.0001) (27). These and other epidemiological studies (28) confirm that there is a link between frailty and cognition.

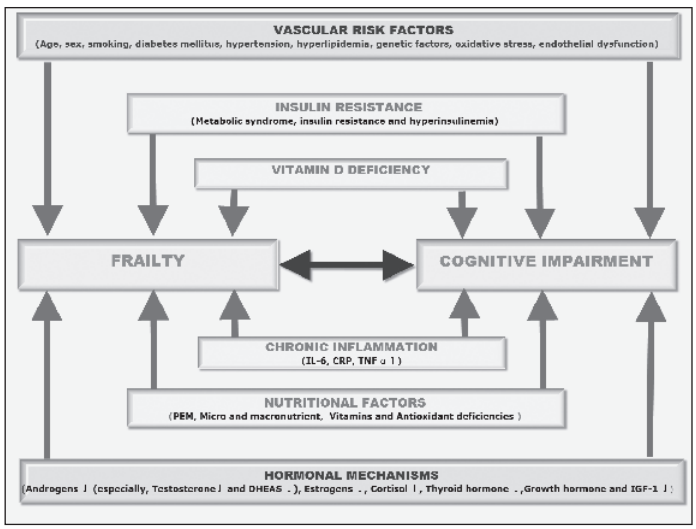
The relations between physical and cognitive frailty may well be a two way road. The idea that poor cognition can lead to physical frailty is quite intuitive and evident for those who treat the patients with dementia and see how physical disability progresses in parallel to cognitive impairment. However, the other way – physical frailty leading to cognitive problems- is not so obvious. Some evidence shows that frailty is associated with a decline in cognitive functions (29-32). A longitudinal study of 823 older patients without dementia followed for 3 years, with a 10.8% incidence of Alzheimer's disease, found that both the baseline level of frailty and the annual rate of change in frailty were associated with an increased risk of incident Alzheimer's disease, with each additional one tenth of a unit increase on the frailty scale at baseline associated with >9% increased risk of Alzheimer's disease (29). A second longitudinal study, which examined the association between physical frailty and the risk of incident minimal cognitive impairment (MCI) after 12 years of annual follow-up, showed that physical frailty was associated with a high risk of incident MCI, such that each one-unit increase in physical frailty was associated with a 63% increase in the risk of MCI (hazard ratio=1.63), after controlling for a number of potential confounders (30). The Three-City Study, a French prospective study designed to evaluate the risk of dementia and cognitive decline attributable to vascular risk factors, which included 5,480 community-dwelling persons aged 65 to 95, found that frailty status was independently associated with incident vascular dementia, but not with Alzheimer's disease (31).

To further confirm these links between cognition and frailty, recent research on trajectories of disability in late life have shown that they seem to be similar in frailty and dementia, the second coming with more prolonged and deep disability (33, 34). The hallmark benefit of disentangling the relationship between cognition and frailty is that this may lead to new intervention strategies for the prevention and treatment of both conditions (35).

Common Underlying Mechanisms between Frailty and Cognition

Dysregulation in biological and stress response systems plays a key role in the development of frailty. Genes, environmental factors and multimorbidity may have an effect on the relationship between physical and cognitive aspects of frailty. A hypothesized model of frailty proposes that oxidative stress, mitochondrial dysfunction, DNA damage, genetic factors and inflammation cause impairment of physiological systems (36). In this section, the mechanisms that may lay behind the link between frailty and cognitive impairment will be discussed (Figure-1). Research into these mechanisms has a major relevance if drug treatments for frailty are to be developed (37).

Figure 1
Potential mechanisms that may link physical frailty and cognitive impairment



PEM: Protein Energy Malnutrition; IL-6: Interleukin-6; TNF: Tumor Necrosis Factor; CRP: C-reactive protein; DHEAS: Dehydroepiandrosterone sulphate; IGF-1: Insulin Like Growth Factor-1

Vascular mechanisms

Vascular damage resulting from any condition, including atherosclerotic vascular disease or embolic events, may cause a reduction of the blood flow to tissues such as brain, skeletal muscle or heart. Cognitive functions decline after reduction of blood flow to the brain. Vascular diseases are increasingly recognized as a cause of cognitive decline in old age. Cognitive vascular disorder describes a heterogeneous group of disorders with different types of cerebrovascular lesions causing cognitive impairment and finally leading to dementia (38). It is believed that improvements in vascular risk factors could help to reduce cognitive impairment later in life (39).

Various genetic and non-genetic factors known to increase the risk of vascular disease, including smoking, age, gender, sex, hypertension, diabetes, family history of cardiovascular disease, obesity, hyperlipidemia, apolipoprotein E (APOE) and angiotensin converting enzyme 1 (ACE1) genotypes, and elevated levels of total cholesterol (TC) and lipoprotein(a) have been evaluated as risk factors for developing dementia (20). Also, mitochondrial dysfunction, nitric oxide instability, oxidative stress, endothelial dysfunction, vascular calcification, and alterations in elastin and collagen balance predispose to intimal atherosclerosis and inflammation in vessels and promote slowing of blood flow (40, 41).

Impaired function of skeletal muscles due to decreased blood flow leads to frailty in older people. Frailty is considered a geriatric syndrome, and vascular problems may have a role in the pathophysiology of geriatric syndromes (40). This has been confirmed by some studies showing that cardiovascular risk scores may also predict frailty, in addition to predicting the risk of cardiovascular disease and cognitive decline (8, 42). In a study conducted by Bouillon et al., four risk score algorithms, the Framingham Cardiovascular disease, coronary heart disease (CHD), stroke prediction models and systematic coronary risk evaluation, were explored to show their predictive value for frailty. At the end of the study, 2.8% of the participants were found to be frail, and all four scores were associated with a future risk of developing frailty (42).

A recent longitudinal observational study conducted to examine the predictive effect of obesity and cardiovascular risk factors on future risk of developing frailty, found that frailty was significantly more frequent in patients who were overweight or obese in midlife after a follow-up period of 26 years (43). Some limited data also suggest that even subclinical cardiovascular disease is related to the development of frailty (44).

Newman et al. investigated the relationship between subclinical cardiovascular disease and frailty. In patients with no history of cardiovascular disease, underlying cardiovascular disease was measured by carotid ultrasound and ankle–arm index, and left ventricular hypertrophy by electrocardiography and echocardiography. These clinical factors were found to be related to frailty, and it was concluded that cardiovascular disease was associated with an increased likelihood of frail health, and in addition, infarct-like lesions in the brain appearing on magnet resonance imaging were related to frailty (44).

Thus, reduced blood flow and impaired vascular functions may be a mediator or a common underlying factor for both frailty and cognitive decline.

Hormonal mechanisms

Multiple hormonal changes that play a major role in the development of physical frailty by reducing muscle mass and strength causing sarcopenia occur with aging (45). The levels of sex steroids and growth hormone decrease, while cortisol levels increase with age (46, 47). Frail older adults with sarcopenia have decreased muscle mass and strength associated with alterations in the hormonal system and many other factors

(48). Reduced androgen hormone levels may be related with both frailty and cognitive decline, and some hormonal changes have been shown to directly influence skeletal muscle decline and cognition (49, 50).

In a population based cohort study conducted by Mohr et al. to determine the association of total and free testosterone levels with frailty, neither total nor free testosterone levels, were found to be associated with frailty but sex hormone binding globulin was. Grip strength and physical activity, but not exhaustion, slow walking, or weight loss, were associated with total testosterone levels (51). Dehydroepiandrosterone sulphate (DHEAS) has also been found to be significantly lower in frail than in robust people (52).

Travison et al. examined the relations of serum androgens, estrogens, gonadotropins, and sex hormone binding globulin with the prevalence and progression of frailty in older men at baseline and after a two year follow-up period. In total, 1,645 community-dwelling men aged 70 or older were included in the study. They found an association between age-adjusted androgen and estrogen levels and concurrent frailty. The subjects in the lowest testosterone group had 2.2-fold greater odds of exhibiting frailty as compared to the highest testosterone group. It was concluded that age-related changes in blood androgens and estrogens may contribute to the development or progression of frailty in men (46).

While hormones are thought to be related to physical decline through frailty, they also have a known effect on cognitive impairment. A multiple hormonal dysregulation of thyroid hormones and cortisol and a decline in anabolic hormones, DHEA-S, testosterone and insulin-like growth factor 1 (IGF-1) levels occur with aging (49). Many studies suggest that this catabolic process is an important predictor of frailty, cognitive function and mortality in older people (49).

Testosterone promotes synaptic plasticity in the hippocampus and regulates the accumulation of amyloid beta protein. Testosterone may have some protective effect on cognition (49, 53). Testosterone replacement therapy may increase muscle mass and strength in hypogonadal and eugonadal men, especially when it is combined with exercise, but it has unfavourable effects on lipid profile and on the prostate gland (54).

Growth hormone (GH) level decreases with age and is considered to be related both to frailty and cognitive impairment (55). Leng et al, found that age-adjusted serum levels of IGF-I and DHEA-S were significantly lower in frail versus non-frail individuals, and also that there was a trend for IL-6 to be inversely correlated with IGF-I in the frail group. They concluded that frail subjects have lower levels of serum IGF-I and DHEA-S and higher levels of IL-6 than do non-frail, age-matched individuals. This study corroborates the possible role of endocrine and immune dysregulation in frailty (52).

The effect of GH on cognition is also well documented. Learning and memory are known to be induced by GH, and GH therapy is believed to improve cognitive function, especially in behavioural disorders of the central nervous system (56). A randomized, double-blind, placebo-controlled trial by Baker et al. examined the effects of GH releasing hormone (GHRH) on cognitive function in healthy older adults and in adults with mild cognitive impairment, and showed favorable effects of GHRH therapy on cognition in both groups when compared with placebo (57).

Cortisol, a lipophilic steroid hormone produced in the cortex of the adrenal glands is released into the circulation and binds to proteins, 90% to cortisol binding globulin and 8% to albumin. The cortisol binding globulin concentration is affected by various conditions, such as infections, liver diseases, inflammation, and application of different drugs, etc. Response to stressors is one of the important functions of cortisol in organisms. Frailty is characterized by increased vulnerability to stressors. Therefore, cortisol is thought to have a role in the development of vulnerability to stressors in frail patients. A recent study in 214 community-dwelling women, 80-90 years old found that higher levels and blunted diurnal variation of cortisol could be related to frailty (47). A positive correlation between frailty and cortisol level was also found in patients in long term care (58).

Increased basal cortisol levels have a role in cognitive decline and might be associated with decreased hippocampal volume in patients with Cushing syndrome, depression and Alzheimer's disease (59). Lee et al. found that higher levels of cortisol were associated with worse performance in six cognitive domains (language, processing speed, eye-hand coordination, executive functioning, verbal memory and learning, and visual memory) in adults aged 50 to 70. The authors of this study suggest that dysregulation of the hypothalamic-pituitary adrenal axis could be a risk factor for poorer cognitive function in older people (59).

Ghrelin, an orexigenic hormone secreted mainly in the stomach to stimulate appetite, is another hormone that may have an important role in the development of both frailty and cognitive impairment (60). For instance, Kalyani et al. investigated the relation of frailty status and circulating energy metabolism hormones in a prospective cohort of 73 community-dwelling women aged 84-95 years without a diagnosis of diabetes. After logistic regression analyses, they found that frail women were more likely to have lower levels of fasting ghrelin and 120 min ghrelin compared to non-frail subjects (61). Reduced ghrelin secretion might also contribute to the metabolic changes observed in male patients with AD (62). Ghrelin has been linked to neuro-modulation, neuro-protection and memory and learning processes due to its expression in different regions of the central nervous system (63).

Vitamin D

Vitamin D (25-hydroxyvitamin D) is a fat soluble vitamin that has some role in bone and muscle health, cardiovascular diseases, cancer, immunity, morbidity and mortality (64).

Lower levels of vitamin D in old age have been related to impaired physical performance and higher risks of falls, fractures, frailty and death (65, 66). Vitamin D also plays a significant role in the development of sarcopenia, which is thought to be a major component of frailty, as it is positively associated with muscle mass, and muscle strength, whereas it may be possible to improve physical functioning and reduce the risk of falls in patients using vitamin D supplementation (67). Some epidemiological studies have shown that low levels of vitamin D have a strong correlation with the prevalence and incidence of frailty (68 69).

On the other hand, the association between vitamin D levels and cognitive function is still debated (70). A systematic review including 28 previous studies (25 cross-sectional and 6 prospective studies, 3 studies show cross-sectional as well as prospective data) found a statistically significant worse outcome in one or more cognitive function tests or a higher frequency of dementia with lower vitamin D levels or intake (70). A recent cross-sectional study suggests there is an association of serum 25-hydroxyvitamin D with domain-specific cognitive performance, in particular executive functioning and possibly information-processing speed, in frail and prefrail subjects (71).

In conclusion, vitamin D deficiency may have some effects on underlying mechanisms of both frailty and cognitive decline and may worsen the clinical outcomes of older subjects who are frail and cognitively impaired.

Inflammation

Inflammation is a process that is triggered by many cytokines and other inflammatory proteins and has been found to be related to various conditions, including cardiovascular, infectious, rheumatological, and neuroinflammatory conditions. The mechanisms of inflammation in cognitive impairment have already been described (72, 73). Inflammatory markers, including cytokines, chemokines, and complement factors have been found in the cerebrospinal fluid of patients with Alzheimer's disease and other types of dementia, and it has been proposed that insoluble beta-amyloid and neurofibrillary tangles that harm neurons can stimulate an inflammatory response in the microglia (74). Increased serum concentrations of IL-8 are associated with poor performance in memory and speed domains and in motor function (75). IL-6 and C-reactive protein have also been found to be prospectively associated with cognitive decline in older subjects (76).

On the other hand, immune system changes and inflammation have also been associated with frailty. Data considering the effect of inflammation on frailty, have suggested that the inflammatory processes triggered by some cytokines, especially IL-6, TNF alpha and other inflammatory proteins are associated in the older subject with increased risk of morbidity and mortality, and cohort studies have indicated TNF-α and IL-6 levels as markers of frailty (77-80). Consequently, the inflammatory process seems to have a role in the development of both frailty and cognitive impairment (81).

Insulin Resistance

The relationship between diabetes mellitus, insulin resistance (IR) and cognitive decline seems to be so well established that some authors have suggested that Alzheimer's disease is type 3 diabetes mellitus (82). Inappropriate secretion of insulin in response to increased levels of plasma glucose due to IR results in hyperinsulinemia, which leads to the exposure of cells to high levels of insulin for a long period of time. This situation adversely affects the function and survival of cells, especially neurons (83). High levels of circulating glucose may also damage neurons, causing impairment of cognitive functions. This hypothesis has been confirmed in some clinical studies, where participants with hyperinsulinemia showed worse cognitive functions than those without hyperinsulinemia when compared for MMSE, MOCA, CDR, orientation, delayed memory, and attention/calculation domains. Similarly, insulin levels and IR had a negative correlation with the scores of MMSE and delayed memory (84).

On the other hand, a relationship between IR and frailty has been hypothesized (61). In a long term study of 3141 community-dwelling adults, aged 69 to 74 years without frailty at baseline, metabolic syndrome was not found to be significantly associated with incident frailty (hazard ratio, 1.16 (95% [CI], 0.85-1.57), but insulin resistance and C-reactive protein levels were associated with incident frailty (hazard ratio for frailty was 1.15 (95% CI, 1.02-1.31) and 1.16 (95% CI, 1.02-1.32), respectively) (85).

Nutrition

Cognitive status is influenced by nutrition. Vitamins, micro and macro-nutrients, lipids, antioxidant nutrients and others can affect the risk of incident cognitive decline and dementia (86, 87). The most convincing evidence as to the relationship between vascular dementia and nutrition exists for micronutrients, particularly Vitamin E and C (88). Although supporting data on the positive correlation between these nutrients and cognition is available, also some potential adverse effects of these nutrients have been documented (86). Mild cognitive impairment is associated with moderate or high nutritional risk (89) and unhealthy dietary patterns (90).

Frailty and malnutrition are both prevalent in older people. Low energy and protein intake and low serum nutrients have shown to be related to frailty (91). A multicenter, prospective cohort study including 24,417 women aged 65 to 79, showed an association between protein intake and incident frailty after a 3 year follow-up period. A 20% increase in protein intake was associated with a 32% lower risk of frailty (92). The authors suggest that a high protein diet could be an intervention target for prevention of frailty (92). Data from the Invecchiare in Chianti study showed that a lower daily energy intake (≤21 kcal/kg/day) was also significantly associated with frailty (OR: 1.24; 95% CI: 1.02–1.5), and low intake of other

nutrients (protein, OR 1.98, vitamin E, OR: 2.06; folate, OR: 1.84; vitamin C, OR: 2.15; and vitamin D, OR: 2.35) was significantly and independently related to frailty (93). Malnutrition is also related to frailty status (94).

Dual Tasking as a Link between physical and cognitive frailty

Dual-task methodology is increasingly used to assess cognitive motor interference while walking. Many tasks of daily life require both motor activity and memory, however, division of attention for two simultaneous tasks may be impaired in old age, especially in subjects with motor or cognitive impairments (95). Walking can be measured (using gait speed or other measures of walking performance) with and without performing concurrent cognitive task. Some cognitive tasks, especially those that involve internal interfering factors, can disturb gait performance. Meta-analysis results in healthy participants suggest strong associations between age and speed reduction under dual-task conditions and between the level of cognitive state and speed reduction under dual-task conditions (96). Cognitive distractions may also be a link between frailty and some poor outcomes, like falls (97).

Thus, research in dual-tasking may be useful to understand the links between physical frailty and cognitive aspects of frailty. Exploring gait using a cognitive distractor might enhance the sensitivity and specificity of frailty risk prediction and classification in healthy and cognitively impaired individuals (98, 99).

As a conclusion multiple dimensions of frailty including cognitive impairment and physical disturbances seem to be related with dual task paradigm. Further studies are needed to elucidate this complex relation to improve the outcomes of frailty.

Conclusion

Because the aging world, the problems of elderly people are growing such as increased prevalence of dementia and frailty. Available data corroborates the clear association between frailty and cognitive impairment via common underlying mechanisms including vascular and hormonal changes, nutrient and vitamin deficiencies, especially vitamin D and B12, inflammation and IR. On the other hand, some recent data supports that social supports and determinants, especially stressors, may worsen both cognitive and physical health (100). Appropriate interventions for frailty and cognitive impairment are getting more importance for elderly. True treatment modalities will be improved after learning the exact pathophysiological pathways of these disorders. Further investigations are needed to identify the common underlying mechanisms and to improve appropriate treatment options for both conditions.

Conflict of Interest: None

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