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FRAILTY, SARCOPENIA AND NUTRITION

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Abstract

Recently, the terms frailty and sarcopenia have been used frequently. Frailty, which occurs due to age-related physiological changes in multiple systems, is accepted as one of the geriatric syndromes. In frailty, negative energy balance, decreased strength, slowed walking speed, decreased grip strength, sarcopenia and involuntary weight loss can be seen. Frailty emerges as an indicator of biological age and correlates with the outcomes of biological age regardless of age, gender and comorbidities. Recent studies have begun to use the concept of frailty in children. Frailty in children is caused by a multi-system physiological impairment, including neurological, endocrine, immune and skeletal systems, which leads to a deterioration in quality of life. Frail children therefore require additional care and related services compared to children of the same age. Sarcopenia is defined as progressive loss in the musculoskeletal system. It has been determined that frailty and sarcopenia have many things in common in terms of their formation mechanisms, clinical consequences, treatment and prevention methods. Nutrition is closely related to both frailty and sarcopenia. Therefore, adequate energy and protein intake is extremely important in preventing malnutrition and loss of lean body mass.

Keywords: Frailty, sarcopenia, nutritional status.

Introduction

Frailty is defined as “a clinical condition characterized by weakness, physical disability, functional decline, and increased dependence in physiological reserves, along with age, a clinical condition characterized by a reduction in physiological reserves, and increased addiction in daily life activities”. [1] In some sources, a clinical syndrome characterized by a reduction of power, durability, and physiological function, characterized by a reduction in immunity, endocrine, stress, and energy regulation systems, which makes individuals fragile to negative health results such as physical dysfunction. [2]

In frail elderly, negative energy balance, decrease in strength, slowing in walking speed, decrease in grip strength, sarcopenia, and unintentional weight loss can be seen. [3] Frailty is reported to be directly related to increased risk of falls and injury, hospitalization, high health costs, and increased death rate. [4]

Types of Frailty

1. Physical Frailty

Physical frailty is a geriatric syndrome defined by components such as decreased physical activity, decreased walking speed, decrease in walking speed, weight loss, muscle power loss, and exhaustion throughout many physiological systems. [5]

2. Cognitive Frailty

Recent studies have found that losses in cognitive functions are associated with frailty. A study examined the relationship between cognitive level and frailty, 45 mild cognitive disorders, 64 stages Alzheimer's patients, and 13 middle-stage Alzheimer's patients, and it has been found that the level of frailty increased as cognitive dysfunction increased. [6]

3. Psychological Frailty

It is ignored because it is less known and cared about than physical frailty. Psychological frailty increases the patient's addiction by leading to cognitive and physical frailty. [7]

4. Social Frailty

Social frailty in the studies done is associated with factors such as the patient's living environment, income level, exercise status, alcohol use, whether or not it goes out less than before, daily frequency of communication,

and quality. These factors affect the patient's cognitive and physical frailty, affecting mortality and morbidity rates. [8]

Epidemiology

According to data from Europe and the United States, the percentage of frailty among the elderly has been reported as 8 percent in the community. This frequency reaches %3.2 in the age of 65-70, while %23 in the 90s. [9] Prevalence of frailty among individuals over 65 years old varies between %10-60 depending on the diagnostic criteria used. The prevalence range in studies is broad; it is thought that it is due to the lack of standard scales the difference in scales used and cultural and ethnic differences. [10]

There are different studies in Turkey on the frequency of frailty in the elderly. In a study conducted in 2015 with 1126 elderly individuals from 13 different institutions, the prevalence of frailty was found to be %39.2. [11] A study conducted in Turkey in 2020 reported that the average frailty rate was %44,5. Another study conducted in the same year determined that while %10 of the elderly were frail, %45,6 were in the pre-frailty stage. [12] More studies are needed in this area in Turkey.

It is emphasized that frailty increases with age and is common in women, individuals with low education and income levels, with chronic disease and disability. A compilation by Collard and his friends has examined factors and frailty prevalence that affect frailty, increased age, and the condition of being a woman, meaningfully associated with frailty. In the same study, there was a big difference in the prevalence of frailty between countries and that difference was caused by changes in the evaluation criteria. [13]

Pathophysiology

Frailty is characterized by a multi-system disorder that causes dynamic loss of homeostasis, a decrease of physiological reserve, and increased morbidity and mortality. Changes in the musculoskeletal and endocrine system with chronic inflammation play an important role in the pathogenesis of frailty. Possible etiological factors include genetic/epigenetic and metabolic factors, environmental and life-related stress, and acute and chronic diseases. [14] Systemic changes involved in the pathogenesis of frailty are observed in all elderly individuals. Systemic changes involved in the pathogenesis of frailty are observed in all elderly individuals. The risk of developing diseases increases with age in many patients. However, an increase in visceral adipose tissue mass is a universal change associated with aging, significantly impacting pathophysiology, particularly in light of its effects, such as sarcopenia.

Consequently, signaling systems (immune and endocrine systems), the musculoskeletal system, energy metabolism, and the nervous system contribute to the development of frailty through complex interactions.

Chronic inflammation and immune activation are believed to play a pivotal role in this process, acting through both direct and indirect pathways. [15]

Clinical Effects of Frailty

1. Changes in Brain Function Related to Frailty

Degeneration in both the central and peripheral nervous systems with aging is a significant marker for frailty. It manifests as a decline in cognitive function, impaired ability to perform independent activities of daily living, and deterioration in memory, speed, and executive function. Aging leads to structural and functional degeneration in the peripheral nervous system, specifically in motor neurons and neuromuscular junctions, contributing to frailty. Ultimately, this results in a decrease in the number of motor neurons and motor units, as well as a slowing of nerve conduction. [15] A prospective cohort study of 750 patients aged 65 and over was followed for 12 years, cognitive dysfunction increased as the frailty rating increased and cognitive function increased rapidly as the degree of frailty increased. [16]

2. Endocrinological Changes Associated with Frailty

With aging, growth hormone and IGF 1 are decreasing. With IGF 1 decrease, both muscle power and muscle mass decrease, which causes physical frailty. [17] Increase in cortisol secretion with age is seen. [18] High cortisol levels are characterized by increased catabolism, loss in muscle mass, anorexia, and weight loss, which are all important findings associated with frailty. However, studies show that increased basal cortisol levels cause a decrease in cognitive capacity are available. [19] Furthermore, studies have shown that elevated basal cortisol levels are associated with a reduction in cognitive capacity and hippocampal volume. A cross-sectional study involving 214 elderly women revealed a correlation between frailty levels and diurnal cortisol elevation. [20]

3. Changes in The Immune System in Frailty

Many changes occur in the immune system, including a decrease in stem cell count, a decrease in T cell differentiation, a fall in antibody response of B cells, neutrophils, and macrophages, and a decrease in the phagocytosis capacity of natural killer cells. [21] In normal conditions, changes in the immune system as a result of aging are not causing problems, while the response to acute stress and inflammation is incompetent. Since the inadequate response to acute inflammation is not enough to end the infection, it is a long-term, low-grade inflammatory response and plays an important role in the pathophysiology of frailty. The level of pro-inflammatory cytokines such as Interleukin 6 (IL-6) and C-reactive protein (CRP) in fragile elderly. [22]

4. Changes and Sarcopenia Seen in The Muscle-Skeletal System in Frailty

Sarcopenia is defined as a progressive loss in the mass and strength of the muscle-skeletal system, and this loss is related to physical frailty. [23] Under normal circumstances, there is a balance between muscle cell breakdown, hypertrophy, and protein loss, a balance that is influenced by the brain, endocrine system, immune system, physical activity, and nutrition. Any adverse events in these systems can lead to sarcopenia. However, not all frail elderly individuals exhibit sarcopenia, and conversely, %30 of sarcopenic elderly individuals do not display frailty. [20]

Prognosis

Frailty has been associated with increased morbidity and mortality, while varied by scales and population used. In a prospective cohort study on 754 patients, the leading cause of death in elderly patients was fragile; death was %27.9 determined as frailty, death due to frailty was %21.4, death due to organ failure, death due to malignancy was %13.8 and other causes of death related to dementia was %13.9. [24] A study involving 5,993 men aged 65 and older found that those identified as frail had a mortality rate twice as high as those considered healthy. As frailty levels increase, there is also an increase in the incidence of disability, falls, hospitalizations, and death. [20]

Variables and Measuring Parameters

1. Weight Loss

Loss of 4-5 kg unintentional weight according to the previous year

Compared to the previous year in follow-up, weight loss is more than %5 of body weight

2. Fatigue

Most of the time and feel exhausted 3-4 days a week

3. Weakness

Decreased grip power according to gender and body mass index (at least %20 of them have been accepted basal value)

4. Slowness

Walking speed is greater than 4.57 meters in 6-7 seconds. (the slowest %20 of the population is considered base)

5. Reduced Physical Activity

Energy consumption <383 kcal/week for men, <270 kcal/week (1/5 of the lowest physical activity for each sex is determined)

In addition, various scales have been developed for the diagnosis of frailty. A few of the frailty scales used in the world are sorted; Frailty Index, Frailty Measure, Cardiovascular health study index, Groningen Frailty Indicator, Edmonton Frailty Scale, Canada Health and Age Study Index, Osteoporotic fractures study index, Fried Index. [25]

Nutrition

Nutrition is a closely related factor to frailty. Among the diagnostic criteria of frailty, unintentional weight loss, low muscle power, feeling of exhaustion, decreased physical activity, and slow walking speed are affected by malnutrition.

Inadequate energy and protein can cause weight loss, sarcopenia, a decrease in muscle power, and a sense of exhaustion. However, frailty can negatively affect nutrition and nutritional status. [26]

Malnutrition and Frailty

The loss of body weight caused by malnutrition results in fatigue, weakness, slowing down at walking speed, and decreased physical activity, which are other criteria of frailty.

Half of fragile elderly people are at high risk for malnutrition. Likewise, %90 of those with malnutrition are at risk for frailty or frailty. Nutrition should be considered a modifiable environmental factor potentially associated with preventing fragile conditions. [27]

Obesity is also thought to be a risk factor in terms of frailty. Although the relationship between them isn't exactly explained, it is noted that adipose tissue may play a role. [28]

Energy Intake and Frailty

The reduction in energy intake can cause a loss in muscle mass and power. It is emphasized that less than 25 kcal/kg/day energy intake increased the risk of frailty by 3.3 times. It is recommended to provide 1.2-1.5 g/kg/day protein intake and distribute equally to meals. [29]

Protein Intake and Frailty

Protein is an important macronutrient in terms of preventing muscle strength and loss of force. The relationship between animal and herbal protein intake and frailty risk was examined; both types of protein intake have a protective effect against frailty. [30]

In the Women's Health Initiative Observational Study; 24,417 women aged 65-79 were followed for 3 years of frailty development. The increase of %20 in protein intake has been shown to decrease the risk of being seen by %32. [31] However, in a study of Bollwein and his friends over 75 in 194 individuals over the age of 75, there is no meaningful relationship between total protein intake and frailty risk. In the study, the distribution of protein intake in meals was noted. It is noted that the intake of protein in fragile elderly meals is more unstable than those in the pre-fragile period. [32]

A cross-sectional study involving 2,108 women aged 65 and older found that individuals with a daily protein intake greater than 69.8 g had lower rates of frailty. The study also examined the relationship between animal and plant protein intake and frailty risk, revealing that both types of protein intake had a protective effect against frailty. However, a separate study highlighted that only animal protein intake reduced the risk of frailty. [33]

Given the results of the studies done, it is understood that protein type, quantity, and distribution of meals are important in the prevention of frailty. [32]

Vitamin D and Frailty

25-hydroxy vitamin D (25-OH-D3) is a vitamin hormone that plays a crucial role in calcium homeostasis and bone turnover. Its levels are determined by measuring serum 25-OH-D3 levels. Values between 12-30 ng/ml are considered “insufficient,” while values below 12 ng/ml are considered “deficient.” Vitamin D deficiency is quite common in older adults, and low 25-OH-D3 levels have been associated with falls, fractures, bone pain, and impaired mobility and balance. Low 25-OH-D3 levels contribute to an increased frequency and prevalence of frailty in both elderly women and men. [34] Vitamin D deficiency is reported to be associated with low physical performance in older individuals. In the National Health and Nutrition Research (NHANES III) in individuals

over 60 years of age, serum 25(OH) is lower than 15 ng/mL, and it has been found to increase the risk of frailty by 3.7 times. A meta-analysis that examined the relationship between vitamin D and frailty found that low serum vitamin D levels increase the risk of frailty. [35]

Antioxidants and Frailty

Several studies suggest antioxidant nutrients are effective in preventing frailty. In a study where the relationship between food intake and frailty of 802 individuals over 65 years old was examined; it was reported that the risk of frailty in individuals with diet and vitamin E intake is higher inadequate. Inadequate intake of more than three nutrients increases the risk of frailty. [36]

Mediterranean Diet and Frailty

The Mediterranean diet is a dietary pattern based on the consumption of unprocessed foods, including vegetables, legumes, nuts, fresh fruits, bread, and unrefined grains. The Mediterranean diet is characterized by a low intake of saturated fatty acids and a high intake of unsaturated fatty acids. It is particularly rich in antioxidant micronutrients, such as vitamin C and carotenoids, which contribute to its protective effect against frailty by preventing oxidative stress and inflammation. [33] In Germany, in the cross-sectional study of 192 individuals over 75 years old between 2009 and 2010, the risk of Mediterranean diet and frailty was examined. People with high Mediterranean diet scores have been reported to have a lower risk of frailty. [37]

A meta-analysis of four prospective studies conducted in 2018 examining the relationship between the Mediterranean diet and frailty found that adherence to the Mediterranean diet significantly reduced the risk of frailty. [38]

Recent studies on the Mediterranean diet highlight its anti-inflammatory, and antioxidant properties and its significant role in preventing fragility. Studies report that patients following the Mediterranean diet have lower rates of fragility. [39]

Frailty in Paediatrics

Recent studies suggest that frailty as a physiological phenotype may also exist in children outside the geriatric population. The frailty situation in children is caused by a multisystemic physiological disruption. That's why, the range of diseases that contribute to frailty is wide and heterogeneous. These include syndromes, malformations, infections, neurologic, muscular, oncologic, hepatalogic, respiratory, cardiologic, and metabolic disorders.

This causes the quality of life to deteriorate. Therefore, frail children need additional care and related services compared to children of the same age. However, frailty has not been studied in much detail in children and adolescents. One of the reasons for this is the lack of objective criteria for the evaluation of frailty in children. In a study conducted on adolescents treated for childhood cancer, the frequency of frailty was found to be %7.8. In addition, it has been shown in this study that high frailty scores are associated with an increased risk of morbidity and mortality. [40] When the severity of frailty in children with compensated chronic liver disease is compared to those with end-stage liver disease, it has been shown that severe patients can be distinguished by determining the severity of frailty. [41] It was found that frailty in children with chronic heart disease was worse in all areas than in children in the control group. By conducting similar studies investigating the concept of frailty in children in large groups, especially children with chronic diseases, it will be possible to determine how much and at what level the concept of frailty affects pediatric patients. [42]

Sarcopenia

EWGSOP (European Working Group on Sarcopenia in Older People) initially published its guidelines in 2010. These guidelines provided a framework for the definition and diagnosis of sarcopenia. [43] EWGSOP2 convened again in 2018 to update these guidelines. The content of the meeting focused on revising the definition and diagnostic criteria for sarcopenia based on new scientific evidence and clinical practice advances. The updated guidelines, known as EWGSOP2, emphasized the importance of muscle strength as a primary indicator of sarcopenia, rather than muscle mass alone. Additionally, they provided updated criteria for diagnosis, recommended assessment tools, and discussed the importance of early detection and intervention to manage and treat sarcopenia effectively. [44]

According to the definition of the Sarcopenia Working Group in European Elderly Individuals (EWGSOP), age-related sarcopenia is a syndrome with unwanted results, such as a progressive loss in skeleton muscle mass and power, physical disability, decrease in quality of life and increase in mortality. [43] Hormonal changes, such as genetic, breaking down of nutrition status, decrease in physical activity, decrease in anabolic hormones, such as testosterone and growth hormone, increase insulin resistance, increase in atherosclerosis, and increase in the load of proinflammatory cytokine in circulation are the causes of sarcopenia. [45]

Epidemiology

The prevalence of sarcopenia appears to change %8-40 of the age of 60 and over. In a meta-analysis study investigating sarcopenia prevention in the world, sarcopenia prevention was determined as %10 in both sexes. [46]

The prevalence of sarcopenia in Turkey was found as %16 in their study with 100 elderly individuals who applied to the Hacettepe University Geriatrics Polyclinic of sarcopenia in Turkey. [47]

Sarcopenia Categories

The Sarcopenia Working Group (EWGSOP) in European Elderly Individuals categorizes sarcopenia into 2 different categories, primary sarcopenia and secondary sarcopenia. Sarcopenia without a specific cause other than aging is classified as 'primary', and developing sarcopenia due to multiple causes is 'secondary '. [48, 49]

Stages

EWGSOP recommends that sarcopenia should be examined in 3 stages, including 'pre sarcopenia', 'sarcopenia', and 'serious sarcopenia' to guide the clinical management of sarcopenia. The Presarcopeniaa phase is characterized by decreasing muscle mass and is the stage where muscle strength and physical performance are not affected. Therefore, muscle mass measurement techniques can be used to detect the phase of pre sarcopenia. In the Sarcopenia phase, as in the period of pre sarcopenia, decrease in muscle mass and in addition to decreasing in muscle power or physical performance. In the phase of serious sarcopenia, there is a decrease in all muscle strength, muscle mass, and physical performance criteria. [49]

Diagnostic Criteria

The International Association of Gerontology and Geriatrics-European Region, European Geriatric Medical Association, International Association of Nutrition and Aging, and European Association of Clinical Nutrition and Metabolism states that first measurement of muscle mass for diagnosis of sarcopenia, then muscle strength and physical performance criteria should be evaluated if a decrease in muscle mass measurement is detected. [50]

EWGSOP has developed an algorithm based on the sarcopenia scanning test and walking speed measurement, as well as an easy and reliable sarcopenia scanning test for practical use in practice. Simple Sarcopeni Interrogation Form (SARC-F) is a simple and easy-to-apply scan test, which includes five questions about power, foot-up, upstairs, and fall, score between 0-2 points for each question and guides individuals with a score of over four points to advanced assessment for sarcopenia. 48 In the algorithm, walking speed is evaluated. The cutting point of walking speed is >0.8 m/s, which defines the risk of sarcopenia. The algorithm recommends assessing the measurement of walking speed in individuals aged 65 and older, accordingly, the ability to look at the hand grip of older individuals with walking speed >0.8 m/s. Hand grip power is determined to have no sarcopenia in individuals who are considered normal; people with low hand grip measurements are looked at for muscle mass measurements. Muscle mass measurements of older individuals with walking speed

≤0.8 m/s are taken; muscle mass is determined to have no sarcopenia in older individuals with normal muscle mass measurement results; older individuals with lower muscle mass measurement are diagnosed with sarcopenia. [48]

In an evaluation of muscle mass; body imaging techniques, bioimpedance analysis, and anthropometric measurements are used. In the evaluation of muscle power; handshake power test, dysflexion-extension techniques, and peak expiratory current measurement are used. [51] Tests used in evaluating physical performance are short physical performance battery, general walking speed, six-minute walk test, and stair climbing power test. Functional activities are measured in these tests that determine the levels of independence in a person's daily life activities. The levels of independence in these activities affect the quality of a person's daily life. [50]

Nutritional Treatment

With age, conditions such as decreased taste and smell receptors, hormone changes, slowing down of the gastrointestinal tract, and chewing and swallowing problems cause a decrease in energy intake, thus leading to malnutrition. [52] Malnutrition is known to lead to the development of sarcopenia by causing a decrease in muscle function with reduced energy intake; Inadequate protein and vitamin intake leads to malnutrition, a decrease in lean body mass, and increased dysfunction. [53] This situation increases the importance of nutrition in sarcopenia and reveals the importance of protein and vitamin D, especially with adequate energy intake that helps muscle development.

Protein

Inadequate protein intake is an important cause of nutritional deficiencies in the elderly. Studies have shown that as protein intake increases, muscle strength also increases. [54] In elderly individuals with normal renal function, a protein intake of 1.0 g/kg/day - 1.2 g/kg/day is recommended. [55] In studies, ensuring optimal stimulation of protein synthesis by distributing protein intake evenly to meals and preferring protein consumption of animal origin compared to vegetable proteins increases muscle strength more. [56]

Vitamin D

Vitamin D levels decrease with age, while low vitamin D levels are associated with sarcopenia. In studies, vitamin D replacement applied to individuals with low vitamin D has been found to improve muscle strength, reduce falls, and prevent fractures. [57] According to one meta-analysis, vitamin D supplementation increased muscle strength and function but showed no effect on muscle mass. [58]

Omega-3 Fatty Acids

Dietary omega-3 fatty acid levels are inversely related to sarcopenia. There are some studies showing that omega-3 fatty acid supplementation increased protein metabolism and indirectly counteracted anabolic resistance by taking it in the early stages of sarcopenia. [59] Intake of more than 2 g/day of omega-3 fatty acids may enhance muscle mass and walking speed, particularly in sarcopenia patients who have been under treatment for over six months. However, linear regression analysis found no link between plasma omega-3 levels and grip strength in older adults. Expert opinions suggest that doses of 3,000 mg/day DHA plus EPA or more (preferably over 800 mg/day EPA) may be necessary for positive physical performance in older adults, as lower doses do not significantly impact muscle strength. While omega-3 fatty acids might improve sarcopenia, well-designed, large prospective cohort studies, and randomized controlled trials are needed to validate these findings. [60]

Conclusion and Recommendations

It is known that the elderly population in Turkey is increasing. It is recommended that every elderly patient visiting family physicians should be assessed for frailty syndrome. Identifying frail individuals and providing them with multidisciplinary rehabilitation, as well as slowing down and stopping the progression to frailty in pre-frail individuals, are crucial. Routine screening for frailty syndrome can help identify frail and pre-frail individuals, which can lead to a better understanding of the negative health outcomes of frailty. Increasing awareness of risk factors for frailty in individuals can help prevent frailty and minimize its negative consequences. Timely and appropriate interventions can reduce morbidity and mortality associated with frailty syndrome, ultimately benefiting both patients and healthcare workers. A family physician specialist's evaluation includes recognizing a patient's frailty, cognitive condition, physical functions, and functional reserve. Family physicians should take the initiative to improve and implement caring models that meet the needs of patients and communities.

Ethical Considerations: Since public data and related literature were analyzed in our study, there was no ethical violation.

Conflict of Interest: The authors declare no conflict of interest.

References

1. Bouillon K, Kivimaki M, Hamer M, Sabia S, Fransson EI, SinghManoux A, et al. Measure of frailty in population-based studies: An overview. BMC Geriatr 2013;13(1): 64.
2. Kang, J., Jeong, Y. J., Jang, J. H. ve Lee, M. Risk factors for frailty in critical care survivors: a secondary analysis, Intensive and Critical Care Nursing, 2020, 64(2):102981.
3. Kapucu, S. ve Ünver, G. Fragile elderly and nurshing care. Osmangazi Journal of Medicine, 2017, 39 (1), 122-129.
4. Thiruchelvam, K., Byles, J., Hasan, S. S., Egan, N. Ve Kairuz, T. Prevalence and association of continuous polypharmacy and frailty among older women: A longitudina analysis over 15 years. Maturitas, 2021, 146:18-25.
5. Runzer-Colmenares FM, Samper-Ternent R, Snih SA, Ottenbacher KJ, Parodi JF, Wong R. Prevalence and factors associated with frailty among Peruvian older adults. Archives of Gerontology and Geriatrics 2014; 58:69–73.
6. Chong MS, Tay L, Chan M, Lim WS, Ye R, Wong WC, et al. Stage-Specific Relationship between Frailty and Cognitive Impairment in a Specialist Memory Clinic Setting. J Frailty Aging. 2014;3(2):113-9.
7. Fitten LJ. Psychological Frailty in the Aging Patient. Nestle Nutr Inst Workshop Ser. 2015; 83:45-53.
8. Tsutsumimoto K, Doi T, Makizako H, Hotta R, Nakakubo S, Makino K, et al. Association of Social Frailty With Both Cognitive and Physical Deficits Among Older People. J Am Med Dir Assoc. 2017;18(7):603-7.
9. Eyigör S, Gökçe-Kutsal Y. Kırılgan yaşlıya yaklaşım. Turk J Phys Med Rehab 2010;56:135-40.
10. Waite, S. J., Maitland, S., Thomas, A., ve Yarnall, A. J. Sarcopenia and frailty in individuals with dementia: A systematic review. Arch of Gerontol Geriatr, 2021, 92:104268.
11. Eyigor S, Kutsal YG, Duran E, Huner B, Paker N, Durmus B, et al. Frailty prevalence and related factors in the older adult-FrailTURK Project. Age (Omaha) 2015; 37(3): 50.
12. Özşaker S, Yaşlı Cerrahi Hastaları ve Kırılganlık Sendromu, JSHS, 2023, 8(1):49-62.
13. Collard RM, Boter H, Schoevers RA, Oude Voshaar RC. Prevalence of frailty in communitydwelling older persons: a systematic review. Journal of the American Geriatrics Society 2012; 60:1487-92.
14. Wilson D, Jackson T, Sapey E, Lord JM. Frailty and sarcopenia: The potential role of an aged immune system. Ageing Res Rev 2017; 36: 1–10.
15. Ferrucci, L., Fabbri ., Walston J. D., Frailty, in Hazzard's, K.G.E. Kim J Davis, Editor. 2017, Minion Pro by Cenveo: China. p. 691-708.
16. Boyle PA, Buchman AS, Wilson RS, Leurgans SE, Bennett DA. Physical frailty is associated with incident mild cognitive impairment in community-based older persons. J Am Geriatr Soc. 2010;58(2):248-55.

17. Leng SX, Cappola AR, Andersen RE, Blackman MR, Koenig K, Blair M, et al. Serum levels of insülin like growth factor-I (IGF-I) and dehydroepiandrosterone sulfate (DHEA-S), and their relationships with serum interleukin-6, in the geriatric syndrome of frailty. Aging Clin Exp Res. 2004;16(2):153-7.
18. Attaix D, Mosoni L, Dardevet D, Combaret L, Mirand PP, Grizard J. Altered responses in skeletal muscle protein turnover during aging in anabolic and catabolic periods. Int J Biochem Cell Biol. 2005;37(10):1962-73.
19. Jang YM, Lee EJ, Kim DL, Kim SK, Song KH. The Association between Midnight Salivary Cortisol and Metabolic Syndrome in Korean Adults. Diabetes Metab J. 2012;36(3):245-50.
20. Hymabaccus Muradi BAB, Yaşlılarda kırılganlığı ölçmeye yarayan frail ölçeğinin Türkçe geçerlilik ve güvenirlik çalışması, Hacette Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Uzmanlık Tezi, 2017, Ankara.
21. Sahin E, Depinho RA. Linking functional decline of telomeres, mitochondria and stem cells during ageing. Nature. 2010;464(7288):520-8.
22. Qu T, Yang H, Walston JD, Fedarko NS, Leng SX. Upregulated monocytic expression of CXC chemokine ligand 10 (CXCL-10) and its relationship with serum interleukin-6 levels in the syndrome of frailty. Cytokine. 2009;46(3):319-24.
23. Marzetti E, Calvani R, Bernabei R, Leeuwenburgh C. Apoptosis in skeletal myocytes: a potential target for interventions against sarcopenia and physical frailty - a mini-review. Gerontology. 2012;58(2):99-106.
24. Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of disability in the last year of life. N Engl J Med. 2010;362(13):1173-80.
25. Sternberg SA, Wershof Schwartz A, Karunananthan S, Bergman H, Mark Clarfield A. The identification of frailty: a systematic literature review. J Am Geriatr Soc. 2011;59(11):2129-38.
26. Yannakoulia M, Ntanasi E, Anastasiou CA, Scarmeas N. Frailty and nutrition: From epidemiological and clinical evidence to potential mechanisms. Metabolism 2017; 68: 64–76.
27. S Davinelli, G Corbi, G. Scapagnini, Frailty syndrome: A target for functional nutrients? Mech Ageing Dev. 2021, 195:111441.
28. Choi J, Joseph L, Pilote L. Obesity and C-reactive protein in various populations: a systematic review and meta-analysis. Obes Rev 2013; 14(3): 232–44.
29. Bonnefoy M, Berrut G, Lesourd B, Ferry M, Gilbert T, Guerin O, et al. Frailty and nutrition: Searching for evidence. J Nutr Health Aging 2015; 19(3): 250–7.
30. Kobayashi S, Asakura K, Suga H, Sasaki S. High protein intake is associated with low prevalence of frailty among old Japanese women: a multicenter cross-sectional study. Nutr J 2013; 12(1):164.
31. Beasley JM, LaCroix AZ, Neuhouser ML, Huang Y, Tinker L, Woods N, et al. Protein ıntake and ıncident frailty in the Women's Health Initiative Observational Study. J Am Geriatr Soc 2010; 58(6): 1063–71.

32. Bollwein J, Diekmann R, Kaiser MJ, Bauer JM, Uter W, Sieber CC, et al. Distribution but not amount of protein intake is associated with frailty: a cross-sectional investigation in the region of Nürnberg. Nutr J 2013; 12(1): 109.
33. Alkan ŞB, Rakıcıoğlu N, Kırılgan Yaşlılarda Beslenme, SDÜ Sağ Bil Derg, 2019, 10(2)
34. Durmaz H, İç hastalıkları yoğun bakımına yatan yaşlı hastalarda kırılganlığın ve etkilerinin değerlendirilmesi, Hacette Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı, Uzmnalık Tezi, 2018, Ankara.
35. Zhou J, Huang P, Liu P, Hao Q, Chen S, Dong B, et al. Association of vitamin D deficiency and frailty: A systematic review and meta-analysis. Maturitas 2016; 94: 70–6.
36. Bartali B, Frongillo EA, Bandinelli S, Lauretani F, Semba RD, Fried LP, et al. Low nutrient intake is an essential component of frailty in older persons. J Gerontol A Biol Sci Med Sci 2006; 61(6): 589–93.
37. Bollwein J, Diekmann R, Kaiser MJ, Bauer JM, Uter W, Sieber CC, et al. Dietary quality ıs related to frailty in community-dwelling older adults. Journals Gerontol Ser A Biol Sci Med Sci 2013; 68(4): 483–9.
38. Kojima G, Avgerinou C, Iliffe S, Walters K. Adherence to Mediterranean Diet reduces ıncident frailty risk: Systematic review and meta-analysis. J Am Geriatr Soc. 2018: 2–7.
39. Dominguez LJ, Donat Vargas C, Sayon Orea C, Baberia Latasa M, Veronese N, Rey Garcia J and et al, Rationale of the association between Mediterranean diet and the risk of frailty in older adults and systematic review and meta-analysis, Experimental Gerontology 177, 2023.
40. Ness KK, Krull KR, Jones KE, Mulrooney DA, Armstrong GT, Green DM, Chemaitilly W, Smith WA, Wilson CL, Sklar CA, Shelton K, Srivastava DK, Ali S, Robison LL, Hudson MM Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. J Clin Oncol 2013;31:4496-4503 6.
41. Lurz E, Quammie C, Englesbe M, Alonso EM, Lin HC, Hsu EK, Furuya KN, Gupta NA, Venkat VL, Daniel JF, Leonis MA, Miloh T, Telega GW, Yap J, Menendez J, Book LS, Himes RW, Sundaram SS, Parekh R, Sonnenday C, Bucuvalas J, Ng VL, Kamath BM Frailty in children with liver disease: a prospective multicenter study. J Pediatr 2018;194:109-115.
42. Benini, F., Antoniello, L.M., Duci, M. Frailty in Pediatrics: Definition and Care Needs. In: Lima, M., Mondardini, M.C. (eds) Frailty in Children. Springer, Cham. 2023, http://dx.doi.org/10.1007/978-3-031-24307-3_1.
43. Savaş, S., Sarkopeniden korunma. Ege Tıp Dergisi, 2015, 54(10), 46-50.
44. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised European consensus on definition and diagnosis. Age Ageing. 2019;48(1):16-15.
45. Fielding RA., Vellas B., Evans WJ., Bhasin S., Morley JE., Newman AB., et al. Sarcopenia: An undiagnosed condition in older adults. Current consensus deinition: Prevalence, etiology, and consequences. International Working Group on Sarcopenia. Journal of the American Medical Directors Association. 2011, 12(4):249-256.

46. Shafiee G, Keshtkar A, Soltani A, et al. Prevalence of sarcopenia in the world: a systematic review and metaanalysis of general population studies. J Diabetes Metab Disord. 2017;16(1):21-31.
47. Kuyumcu, M.E., et al, Ultrasonographic evaluation of the calf muscle mass and architecture in elderly patients with and without sarcopenia. Archives of gerontology and geriatrics, 2016, 65, 218-224.
48. Cruz-Jentoft A.J., Morley J.E., Sarcopenia.Wiley Black Well, 2012, 8-153.
49. Cruz-Jentoft, A. J., Sarcopenia: a clinical review. Reviews in Clinical Gerontology, 2013, 23 (4), 267-274.
50. Cruz-Jentoft, A. J., et al., Sarcopenia: European consensus on definition and diagnosis Report of the European Working Group on Sarcopenia in Older People. Age and ageing, 2010, 39(4), 412-423.
51. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43(6):748-59.
52. Biolo G, De Cicco M, Dal Mas V, et al. Response of muscle protein and glutamine kinetics to branched-chain– enriched amino acids in intensive care patients after radical cancer surgery. Nutrition. 2006;22(5):475-482.
53. Liguori I, Russo G, Aran L, et al. Sarcopenia: assessment of disease burden and strategies to improve outcomes. Clin Interv Aging. 2018; 13:913-927.
54. Muscaritoli M, Anker S, Argiles J, et al. Consensus definition of sarcopenia, cachexia and pre-cachexia: joint document elaborated by Special Interest Groups (SIG)"cachexia-anorexia in chronic wasting diseases" and "nutrition in geriatrics". Clin Nutr. 2010;29(2):154-159.
55. Wackerhage H. Sarcopenia: causes and treatments. German Journal of Sports Medicine. 2017;68(7-8):178-183.
56. Bauer JM. Nutrition in older persons. Basis for functionality and quality of life. Internist ((Berl). 2011;52(8):946-954.
57. Bischoff-Ferrari HA. Validated treatments and therapeutic perspectives regarding nutritherapy. J Nutr Healht Aging. 2009;13(8):737-741.
58. Beaudart C, Buckinx F, Rabenda V, et al. The effects of vitamin D on skeletal muscle strength, muscle mass, and muscle power: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab. 2014;99(11):4336-4345.
59. Di Girolamo FG, Situlin R, Mazzucco S, et al. Omega-3 fatty acids and protein metabolism: enhancement of anabolic interventions for sarcopenia. Curr Opin Clin Nutr Metab Care. 2014;17(2):145-150.
60. Liu S, Zhang L, Li S, Advances in nutritional supplementation for sarcopenia management, Front. Nutr. 2023, 10:1189522. doi: 10.3389/fnut.2023.1189522.