Review
Pregledni članak

Med Jadert 2025; 55(3-4):247-254
DOI: 10.57140/mj.55.3-4.6

Sarcopenia in people with schizophrenia: a literature review

Sarkopenija kod osoba oboljelih od shizofrenije: pregled literature

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Summary

Research on sarcopenia in patients with schizophrenia is still in its infancy. The aim of our work was to review the literature on sarcopenia in people with schizophrenia. The literature was searched using the PubMed and Google scholar databases. Sarcopenia and schizophrenia share certain etiological processes and risk factors. People with schizophrenia have an increased risk of developing sarcopenia, as well as an increased prevalence of sarcopenia. As a screening tool for sarcopenia, the Ishii test is recommended, but the SARC-F can also be used. Bioelectrical impedance and dynamometer are used for diagnosis. Exercise, a protein-rich diet and protein supplements play a role in its prevention and treatment. Additional research is needed on common etiological processes and possible therapeutic interventions. Despite the scarce data, given the prevalence and the risks it carries, sarcopenia should not be omitted from the care of patients with schizophrenia.

Keywords: sarcopenia, schizophrenia, SARC-F, Ishii test, protein supplements

Sažetak

Istraživanja o sarkopeniji kod bolesnika oboljelih od shizofrenije tek su na svojim počecima. Cilj našeg rada bio je pregledati literaturu o sarkopeniji kod osoba oboljelih od shizofrenije. Literatura je pretraživana korištenjem baza PubMed i Google scholar. Sarkopenija i shizofrenija dijele određene etiološke procese i rizične čimbenike. Kod osoba oboljelih od shizofrenije postoji povećani rizik za razvoj sarkopenije, kao i povećana prevalencija sarkopenije. Kao alat probira za sarkopeniju preporučuje se Ishii test, ali se može koristiti i SARC-F. Za postavljanje dijagnoze koriste se bioelektrična impedancija i dinamometar. U prevenciji i liječenju svoju ulogu imaju vježbe, prehrana bogata proteinima i proteinski dodaci. Potrebna su dodatna istraživanja o zajedničkim etiološkim procesima i mogućim terapijskim intervencijama. Unatoč oskudnim podacima, s obzirom na prevalenciju i rizike koje nosi, sarkopenija se ne smije izostaviti iz skrbi o oboljelima od shizofrenije.

Ključne riječi: sarkopenija, shizofrenija, SARC-F, Ishii test, proteinski dodaci

Introduction

Sarcopenia remains a subject of limited exploration within the field of psychiatry, particularly concerning patients afflicted with schizophrenia. This condition is characterized by the depletion of muscle mass and strength.[1] Its implications extend to an elevated susceptibility to falls, fractures, diminished mobility, disability, and pneumonia, especially aspiration pneumonia linked to dysphagia associated

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Primljeno/*Received* 2025-04-25; Ispravljeno/*Revised* 2025-12-15; Prihvaćeno/*Accepted* 2025-12-16

with sarcopenia, all contributing to an augmented mortality risk. Furthermore, the significance of sarcopenia is underscored by its association with heightened treatment and recovery expenses.[2] The emergence of sarcopenia in patients with schizophrenia is influenced by various factors, including lifestyle choices, endocrine alterations, cognitive function decline, and the use of psychopharmaceuticals.[3] The intricacies of this interplay create a cyclical pattern of changes intrinsic to schizophrenia, culminating in a diminished life expectancy for affected individuals.[3-5]

In light of these considerations, we have undertaken a comprehensive review of the extant literature, aiming to synthesize current insights into the nexus between sarcopenia and schizophrenia.

Methods

A search using the terms "schizophrenia AND sarcopenia" on PubMed yielded ten results, with nine of them being relevant to the topic.[6-14] Simultaneously, an exploration on Google Scholar unveiled five papers with partial relevance to the focal point of this literature review. Specifically, one publication directly aligns with the topic (15), while three exhibit a partial correlation (3, 16, 17), and one resides in a preprint state, signifying its yet-to-be-reviewed status.[18] It is noteworthy that two distinct researchers autonomously executed the PubMed and Google Scholar searches. Papers in English and without a time limit were reviewed.

Prevalence of sarcopenia

In 2021, Bulbul et al. published the seminal study investigating the prevalence of sarcopenia among individuals diagnosed with schizophrenia.[15] The cohort comprised 72 patients diagnosed with schizophrenia, selected after meticulous exclusion criteria were applied, which included individuals with a history of neurological disorders, diabetes, myopathies, goiter, kidney or liver diseases, inflammatory rheumatic diseases, painful syndromes, osteomalacia, osteoporosis, depression, or other psychiatric illnesses.[15] Additionally, patients undergoing therapy for neuropathic or nociceptive pain in the preceding month were excluded from the study.[15] Notably, none of the participants exhibited clinical signs of sarcopenia or severe sarcopenia, while 36.1% were identified as having potential sarcopenia.[15]Analysis revealed this subgroup to manifest lower bone mineral density, reduced muscle strength and mass, and decreased engagement in physical activities.[15] Strikingly, despite these manifestations, individuals with potential sarcopenia exhibited a significantly higher walking speed compared to the reference group devoid of sarcopenia risk.[15] The average age of the cohort was 39.5 years, with the overall sample averaging 38 years, underscoring that individuals diagnosed with schizophrenia constitute a population at an elevated risk for sarcopenia development in later stages of life.[15]

In 2023, Tanioka et al. conducted a study comparing individuals diagnosed with schizophrenia to a healthy control group, with a focus on excluding participants with somatic illnesses that could potentially impact the prevalence of sarcopenia.[14] Among the 30 individuals diagnosed with schizophrenia, 10% of the subjects met the criteria for sarcopenia, 3.3% for pre-sarcopenia (reduced muscle mass with normal strength), and 60% for dynapenia (normal muscle mass with reduced strength).[14] In contrast, none of the 30 healthy participants exhibited sarcopenia or pre-sarcopenia, while 13.3% of them had dynapenia.[14] The group of patients demonstrated significantly lower grip strength in both hands.[14]The average age of the healthy control group was 64.3 years, while the average age of the patient group was 62.53 years, with no significant age differences between the two groups.[14] Despite the study's limitation in terms of a relatively small sample size, it revealed a significantly higher risk for the development of dynapenia, pre-sarcopenia, and sarcopenia among individuals diagnosed with schizophrenia.[14]

In 2022, a group of researchers published a study involving 339 participants diagnosed with stable schizophrenia.[7] The exclusion criteria encompassed patients suffering from other conditions that could potentially impact the prevalence of sarcopenia.[7] Various diagnostic tests were employed to identify sarcopenia, revealing that 53.1% of the participants exhibited this condition.[7] Additionally, within this cohort, individuals with sarcopenic obesity constituted 16.22% of the total sample.[7] The study highlighted a higher occurrence of both sarcopenia (55.6% vs. 47.66%) and sarcopenic obesity (18.97% vs. 10.28%) in males compared to females.[7] A noteworthy departure from previous studies is the inclusion of participants aged over 50, a factor likely contributing to the increased prevalence of sarcopenia.[7] In a subsequent investigation by the same research group involving 335 participants (with four exclusions), the presence of sarcopenia was observed in 38.8% of the subjects, with an additional 14% exhibiting severe sarcopenia, characterized by impairments in physical function.[9] The research group has published additional works on sarcopenia

within the same participant pool; however, given the continuity of the sample, a separate discussion regarding prevalence is deemed unnecessary.[10,11]

Risk factors and common etiological processes

Individuals diagnosed with schizophrenia commonly exhibit sedentary behavior, suboptimal dietary patterns, tobacco use, a propensity for substance misuse, and an elevated predisposition to metabolic syndrome.[3,14] These factors collectively amplify the vulnerability to sarcopenia.[14] The diminution in muscle strength and mass is, in part, a consequence of the negative symptoms inherent in schizophrenia.[3,14] The presence of comorbid depression and cognitive deterioration further impedes participation in routine physical activities and purposeful tasks.[3] Social withdrawal is a frequent consequence, exacerbated by the concurrent effects of stigma and self-stigma, which act as deterrents to enhanced patient engagement.[3] Moreover, psychopharmacotherapy introduces factors conducive to weight gain and the development of metabolic syndrome.[3,14] The attendant side effects, such as parkinsonism, pose additional challenges to mobility.[3,14]

At the molecular level, the cytokine interleukin 6 (IL-6) plays a pivotal role. Its binding to soluble IL-6 receptors (IL-6Rs) exerts pro-inflammatory effects, while binding to membrane-bound IL-6R results in anti-inflammatory effects.[6] The concept of "inflammaging" underscores the significance of inflammation in the aging process, with IL-6 being a key contributor.[6,19] It appears to be involved in the development of sarcopenia, an integral aspect of the natural aging process.IL-6, through its actions, induces mitochondrial dysfunction, amplifies oxidative stress, promotes catabolism, and contributes to the onset of sarcopenia. It also seems to influence serotonin levels in the hypothalamus, regulating food intake and leading to anorexia, further contributing to the development of sarcopenia.[6,20,21] IL-6 is implicated in various psychiatric disorders, with elevated serum levels observed in individuals with schizophrenia. It is hypothesized to play a role in the development of positive symptoms.[6,22] The heightened levels of IL-6 may precisely explain the increased susceptibility of individuals with schizophrenia to the development of sarcopenia.There is another potential mechanism that may explain the association between schizophrenia and sarcopenia, and it is related to the action of the small protein S100B, which binds calcium. This protein plays a crucial role in the development of muscles and the brain. Elevated levels of S100B are associated with aging, inflammation, and neuroinflammation, and they have been detected in cases of both sarcopenia and schizophrenia.[12] Individuals diagnosed with schizophrenia exhibit increased levels of the S100B protein in cerebrospinal fluid and blood, likely indicating astrocyte dysfunction. It has been observed that the action of antipsychotics is accompanied by the normalization of S100B values, along with an increase in the soluble receptor for advanced glycation end products (RAGE). RAGE has the ability to bind S100B and acts protectively in inflammatory conditions.[12,23] The levels of these proteins affect muscle mass and the recovery of skeletal musculature. There is a possibility that increased expression of S100B and altered RAGE, which loses its myogenic effect, lead to a reduction in myogenic potential and, consequently, contribute to sarcopenia.[12,24]

Sarcopenia as a risk factor

To date, sarcopenia in individuals diagnosed with schizophrenia has been explored primarily as a potential risk factor for pneumonia development. In the year 2022, Huang et al. conducted a study investigating the interplay between sarcopenia and pneumonia in a cohort of 335 participants with schizophrenia.[9] Among them, 38.8% presented with sarcopenia, and 14% exhibited severe sarcopenia.[9] Notably, the group with severe sarcopenia demonstrated the highest incidence of pneumonia, reaching 38.3%.[9] The group with sarcopenia displayed a pneumonia incidence of 28.46%, while participants with schizophrenia lacking sarcopenia had a pneumonia incidence of 17.09%.[9] Following adjustments for variables such as gender, smoking history, chronic obstructive pulmonary disease, among others, the researchers found that only the group with severe sarcopenia exhibited an elevated risk for pneumonia.[9]

A similar group of researchers conducted a study on a comparable sample of 335 participants, excluding 4 individuals who developed pneumonia within a week of a schizophrenia relapse.[10] The researchers measured the calf circumference (CC), one of the indicators of sarcopenia.[10] The Asian Working Group for Sarcopenia recommends CC as a screening tool, with values below 34 cm for males and below 33 cm for females indicative of sarcopenia.[10,25] However, the European Working Group on Sarcopenia in Older People contends that CC is not a sufficiently robust indicator and should only be used when other means are unavailable.[1] This study was conducted on a sample from the Chinese population, revealing that a larger CC was associated

with a lower risk of pneumonia in males with schizophrenia.[10] When males with schizophrenia were divided into two groups based on CC, the group with CC less than 34 cm, indicating an increased risk for sarcopenia, had a higher proportion of individuals with pneumonia (37.59% vs. 17.71%, p = 0.001).[10] The mid-upper arm circumference did not exhibit similar predictive value, and the association of both circumferences with pneumonia was not observed in female participants with schizophrenia.[10]

The same research team published an article in 2022 on the correlation between Ishii test outcomes and pneumonia in patients with schizophrenia.[11] The Ishii test, a tool for identifying sarcopenia, involves assessing age, grip strength, and calf circumference.[11] In the studied population of individuals with schizophrenia, the researchers observed that male participants with sarcopenia, specifically those scoring 105 or higher on the Ishii test, exhibited an elevated risk of pneumonia. This association persisted even after adjusting the results for various other factors.[11] However, for female individuals with schizophrenia, there was no identified link between Ishii test outcomes (indicating sarcopenia) and the risk of pneumonia.[11]

The heightened risk of pneumonia in individuals with schizophrenia and sarcopenia can be explained through several mechanisms, as outlined by this research group. Weaker muscle strength, a characteristic of sarcopenia, translates to reduced respiratory muscle strength and difficulties in coughing.[10,26] Swallowing is also impaired, promoting the development of aspiration pneumonia.[11,27] Antipsychotics, with their sedative effects, can contribute to the difficulty in coughing and swallowing.[11] Individuals with sarcopenia often exhibit poorer oral hygiene, another risk factor for pneumonia development.[10] Interleukin 15, abundantly expressed in skeletal muscles, plays a crucial role in the development of natural killer (NK) lymphocytes. Its levels are reduced in individuals with sarcopenia, compromising NK lymphocyte function and predisposing individuals to infections, including pneumonia.[10,28] This is exacerbated by diminished neutrophil function due to the disruption of the phosphoinositide 3-kinase-AKT pathway within sarcopenia.[10,29] The previously mentioned IL-6, which plays a role in both sarcopenia and schizophrenia, is also part of the etiology of pneumonia.[11]

Screening and diagnosing sarcopenia

The European Working Group on Sarcopenia in Older People (EWGSOP2) issued their latest recommendations on approaching sarcopenia in 2019.[1] As a screening tool for sarcopenia, „Strength, assistance with walking, rising from a chair, climbing stairs, and falls“ (SARC-F) questionnaire is recommended.[1] This straightforward tool assesses strength, assistance required in walking, rising from a chair, climbing stairs, and the frequency of falls. Each of these five items carries 0, 1, or 2 points, depending on the degree of functional impairment. If a person scores 4 or more points, it indicates an increased risk of sarcopenia.[1,30] For diagnosis, dynamometry and body composition analysis using bioelectrical impedance are primarily employed.[1] Dynamometry is used to assess grip strength, with a threshold value below 27 kg for men and 16 kg for women.[1,31] Analysis of bioelectrical impedance determines appendicular skeletal muscle mass. If the mass is less than 20 kg in men, it suggests sarcopenia. For women, the threshold value is 15 kg.[1,31] Since muscle mass correlates with body size, it is recommended to divide it by the square of height. A value below 7 kg/m² confirms sarcopenia in men, while the threshold for women is 5.5 kg/m².[1,31] EWGSOP2 recommends the gait speed test for determining the severity of sarcopenia.[1] This test measures the speed required for a person to walk four meters on a flat surface. If the speed is 0.8 m/s or lower, it indicates severe sarcopenia.[1,31]

When it comes to individuals with schizophrenia, the only study comparing screening methods for sarcopenia was conducted by Chen and colleagues in 2022.[7] They determined the prevalence of sarcopenia using bioimpedance and a dynamometer on the previously described sample of 339 participants.[7] The sample was from the Chinese population, and the criteria of the Asian Working Group for Sarcopenia from 2019 (AWGS2019) were used. Six screening tools for sarcopenia were tested: SARC-F, SARC-CalF, SARC-F-EBM, calf circumference, mid-upper arm circumference, and the Ishii test (7).Most of the tests have been mentioned before. SARC-CalF is a combination of SARC-F and calf circumference. If a man has a calf circumference equal to or less than 34 cm, and a woman less than 33 cm, then 10 points are added to the SARC-F score. 11 points or more indicate sarcopenia.[7,32] SARC-F-EBM is a test where age and body mass index (BMI) are added to SARC-F. If a person is 75 years or older, this carries 10 points. If the BMI is 21 kg/m² or less, it adds another 10 points. 12 points or more indicate an increased risk of sarcopenia.[7,33] Mid-upper arm circumference does not have specific threshold values.The study results suggest the Ishii test as the best screening tool for sarcopenia in individuals with schizophrenia.[7] As mentioned before, it includes age, grip strength, and

calf circumference. The formula for men is: 0.62 × (age – 64) – 3.09 × (grip strength – 50) – 4.64 × (calf circumference – 42); while for women: 0.80 × (age – 64) – 5.09 × (grip strength – 34) – 3.28 × (calf circumference – 42). Threshold values can be 101 for men and 104 for women if higher sensitivity is desired. If higher specificity is desired, values can be 107 for men and 118 for women.[7,34]

Prevention and treatment of sarcopenia

The prevention and treatment of sarcopenia primarily rely on adequate nutrition and physical activity. Research has predominantly focused on older individuals. A group of Singaporean authors, drawing on the conclusions of AWGS2019, provided guidelines for approaching sarcopenia in 2022.[31] Experts from Australia and New Zealand issued their guidelines on sarcopenia management in 2023.[35] The recommendations align in emphasizing the importance of a healthy lifestyle in preventing sarcopenia. This involves regular physical activity and exercises such as resistance training, as well as balance or endurance training.[31,35] The diet should include sufficient protein intake, ideally 1 g/kg of body weight per day. Additionally, the consumption of antioxidants and long-chain polyunsaturated fatty acids is important.[31,35] In the presence of sarcopenia, treatment involves resistance exercises.[31,35] It is recommended to exercise at least twice a week, focusing on major muscle groups of the upper and lower limbs, starting from 40%-60% of the maximum repetitions up to 70%-85% of the maximum repetitions.[31] The recommendation is to perform one to three sets of exercises with six to 12 repetitions.[31,35] Alongside exercises, an increased protein intake is necessary, ranging from 1 g/kg to 1.5 g/kg of body weight. Proteins can be obtained from food or protein supplements, depending on the circumstances.[31,35] Caution is advised regarding protein intake in cases of impaired kidney function (eGFR of <30 mL/min/1.73 m²).[35] In the case of insufficient vitamin D levels (<30 mcg/L), supplementation is recommended (31). Currently, there is no pharmacotherapy specifically approved for sarcopenia.[31,35]

Carnosine and its precursor beta-alanine, essential components sourced from our diet, are emerging as potential dietary supplements for addressing both sarcopenia and schizophrenia. Research suggests that carnosine may positively influence the negative symptoms of schizophrenia and enhance executive functions.[13] Similarly, beta-alanine has shown promise in improving muscle quality and function.[13] However, it's crucial to note that these findings are based on a limited number of studies with small participant groups.[13] Exploring the impact of saffron on both sarcopenia and schizophrenia has revealed intriguing possibilities. Saffron demonstrates a potential in alleviating the negative symptoms associated with schizophrenia, such as stereotypy and ataxia.[8] Moreover, it exhibits antioxidative properties and contributes to increased muscle strength, suggesting a potential therapeutic role in sarcopenia.[8] It's important to acknowledge that these studies have predominantly involved animal models or small-scale human trials (8).Researchers speculate on the therapeutic potential of targeting interleukin-6 (IL-6), S100B, and receptor for advanced glycation end products (RAGE) in the context of both sarcopenia and schizophrenia.[6,12, 36-40]

These exciting findings highlight the intricate connections between nutrition, muscle health, and mental well-being, providing valuable insights for future research and potential therapeutic interventions.

Conclusion

Studies show that an increased risk of sarcopenia is present in 36% to 63% of subjects with schizophrenia.[7,9,14,15] Sarcopenia has actually been confirmed in a range of 0% to 53% of subjects with schizophrenia, depending on the study.[7,9,14,15] Such wide-ranging figures are undoubtedly a consequence of differing criteria for diagnosis, screening and diagnostic methods, as well as the characteristics of study samples, especially age, as the risk for sarcopenia increases with age. Half of the individuals with schizophrenia over the age of 50 have sarcopenia, and therefore, screening for sarcopenia is recommended in this population.[7] The Ishii test is highlighted as a screening tool, but the SARC-F can also be utilized.[1,7] Diagnosis relies on body composition analysis using bioelectrical impedance and grip strength testing with a dynamometer.[1] Prevention and treatment of sarcopenia are based on exercise, particularly resistance training, and a protein-rich diet.[31,35] Research on the effectiveness of specific interventions for sarcopenia in individuals with schizophrenia is yet to be published. At the molecular level, there are connections in the etiology of schizophrenia and sarcopenia, but many uncertainties remain.[6,12,19-24] It is evident that research in the field of sarcopenia in schizophrenia has only just begun. Nevertheless, given the prevalence of the issue, sarcopenia should not be overlooked in the daily care of individuals with schizophrenia.

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