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# The Relationship of Sarcopenia with Geriatric Syndromes and Folate

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## Abstract

**Objective:** Folate is essential for healthy cell division, growth and function. With the discovery that folate provides the proliferation and differentiation of muscle cells, the relationship between folate and sarcopenia has attracted the curiosity of researchers. Geriatric syndromes may have a common pathogenesis, as they are considered clinical conditions with common risk factors. Our aim in this study was to investigate the relationship of sarcopenia with geriatric syndromes and serum folate level.

Materilas and Methods: The study population consisted of 287 patients (202 female) who were admitted to our geriatrics outpatient clinic for the first time and underwent comprehensive geriatric assessment (CGA) during the one year between January 2018 and January 2019. Demographic information, chronic diseases, drugs used by the participants and their current chronic diseases, CGA results and laboratory findings of patients were recorded. Diagnosis of sarcopenia was made under the guidance of EWGSOP2.

**Results:** Eighty-eight (31%) of the 287 patients were sarcopenic. While age, number of drugs, the frequency of chronic kidney disease and malnutrition were statistically significantly higher in patients with sarcopenia, mini-mental state examination (MMSE) score and serum folate level were significantly lower (p=0.001, p<0.001, p=0.040, p<0.001, p=0.001, p=0.028; respectively). The result of univariate logistic regression analysis showed that sarcopenia was independently associated with folate [Odds ratio (OR) 0.926 (95%) confidence interval (CI) 0.864–0.993, p=0.031). Serum folate level in patients with malnutrition was also significantly lower (7.12±4.39, p=0.008).

**Conclusion:** Since sarcopenia is associated with malnutrition, they should be evaluated together. As we found that serum folate levels were lower in patients with both sarcopenia and malnutrition, we recommend that risky groups be supported with folate-rich foods or folic acid supplementation.

**Keywords:** Sarcopenia; Folate; Folic acid; Malnutrition; Geriatric syndrome.

## Introduction

Geriatric syndromes are clinical conditions and symptoms with common risk factors that mostly occur in the elderly with atypical symptoms and cannot be fully explained by the definition of 'disease' (1). Geriatric syndromes, such as malnutrition, cognitive impairment, depression, sarcopenia and polypharmacy causes increased mortality, morbidity and health care costs (2).

Sarcopenia is a medical condition that increases in frequency with aging and was defined in EWGSOP2 as a decrease in both muscle strength and muscle mass. It may occur due to secondary reasons or may occur due to aging on its own (3). Decreased appetite and inadequate food intake that occur with aging can cause malnutrition and subsequently sarcopenia (4). Sarcopenia is accepted as one of the pathophysiological causes of frailty and may cause adverse outcomes such as the increased risk of falling, dependency, disability, poor quality of life and death (5). EWGSOP2 recommends screening for sarcopenia with the 5-item SARC-F questionnaire, which has been translated and validated into many different languages (6). Since the pathophysiology, diagnosis and treatment methods are still not clear, studies on sarcopenia are going on. The concept of sarcopenia still contains uncertainties. Sarcopenia, which is considered a geriatric

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syndrome by some, is placed in a separate class by others. Geriatric syndromes may have a common pathogenesis, as they are considered clinical conditions with common risk factors. If the relationship between sarcopenia and other geriatric syndromes can be found, common pathophysiological pathways can be revealed and existing uncertainties can be clarified.

Folate is one of the water-soluble vitamins that are necessary for life. Folate, also known as vitamin B9 and folacin, has a critical role in the metabolism of nucleic acid precursors and several amino acids. Folate cannot be synthesized in humans and is present in many foods such as green leafy vegetables, fruits, beans, eggs, meat, and dairy products. The synthetic form, which is better absorbed, is folic acid (7). Folate is necessary for cell division, growth and function. It is vital for the musculoskeletal system as well as for all tissue and organ systems. Studies in the literature have shown that folic acid has an important role in myogenesis and promotes skeletal muscle development through the Protein kinase B (Akt) signaling pathway (8). Folate deficiency is common, especially in the elderly and the most common causes of folate deficiency are decreased intake, decreased absorption, increased demand, congenital disorders and certain medications (9). With the discovery of the important effects of folate on the musculoskeletal system, the relationship between sarcopenia and folate has been a subject of interest. Our aim in this study was to investigate the association of sarcopenia with chronic diseases, geriatric syndromes and folate.

## Methods and Methods

### Study population

Our study is a retrospective cross-sectional study. The study population consisted of 287 patients (202 female) who were admitted to our geriatrics outpatient clinic for the first time and underwent CGA during the 1-year between January 2018 and January 2019. Demographic information, drugs used by the participants and their current chronic diseases, CGA results and laboratory findings of patients were recorded. The data of the patients were obtained from the patient files.

### Ethics

Ethical approval was obtained from the ethics committee of Cerrahpaşa Faculty of Medicine (Date 09.09.2020-Number 117344).

### Comprehensive geriatric assessment

The number of drugs used by the patients was recorded. Nutritional status was evaluated with Mini Nutritional Assessment (MNA) long form and patients with a score of less than 23.5 out of 30 points were considered risky for malnutrition (10). The group named 'with malnutrition' in the study was corresponded to being at risk of malnutrition. Functional levels of the patients were evaluated with the Katz Basic Activities of Daily Living (BADL) scale and the Lawton & Brody Instrumental Activities of Daily Living (IADL) scale (11,12). Mini-Mental State Examination (MMSE) scale was used to determine cognitive impairment (13). The possibility of depression was evaluated with the short form of the Geriatric Depression Scale (GDS) (14). Urinary incontinence was defined as any involuntary urinary incontinence complaint within the last 1 year (15).

### Laboratory findings

Folate, total protein, albumin, hemoglobin and creatinine values of the patients at admission were recorded from the patient files. The blood taken for the biochemical parameters we examined in our study was taken into a gel tube in the morning after 8 hours of fasting and analyzed by ELISA method. ng/ml for folate, g/dl for total protein, g/dl for albumin, mg/dl for creatinine, pg/ml for vitamin B12, ng/dl for vitamin D and g/dl for hemoglobin were used as units.

### 2.5. Diagnosis of sarcopenia

In clinical practice, handgrip and BIA measurements are made for all patients who admit to our geriatrics outpatient clinic for the first time. The diagnosis of sarcopenia was made under the guidance of EWGSOP2 and patients with low muscle strength and muscle mass were included in the sarcopenia group (3). Skeletal muscle strength was evaluated with a hand dynamometer (Takei® TKK 5401 model, Takei Scientific Instruments Co., Tokyo, Japan). Both of the hands were measured 3 times with a 1-minute rest period and the greatest value was recorded. Cut-off value for the handgrip test was considered as 27 kg for men and 16 kg for women. A bioelectrical impedance analysis (BIA) device (Tanita Body Composition Analyzer® TBF-300 model, Tanita Co., Tokyo, Japan) was used to evaluate skeletal muscle mass. SMMI (skeletal muscle mass index) was calculated with SMM/height2 ($kg/m^2$) formula. As specified in EWGSOP2, SMMI cut-off value was considered as 7.0 $kg/m^2$ for men and 5.5 $kg/m^2$ for women.

Only the data of the patients who were able to cooperate with the tests and who completed the BIA and hand grip measurement were included in the study. Patients under 65 years of age, with a history of trauma and infection in the last month, with a diagnosis of any terminal disease or malignancy were not included in the study in order to exclude acute events as they may reduce the reliability of the tests. Since steroid use can lead to myopathy, it was among the exclusion criteria. Patients with stage 3, 4 or end-stage chronic kidney disease and receiving a folic acid replacement were excluded from the study because it could affect serum folate levels, also patients with joint amputation were not included because it would affect the result of BIA.

### Statistics

Demographic information, comprehensive geriatric assessment results and chronic diseases were summarized with descriptive statistics. Categorical variables were expressed as numbers and percentages. Normally distributed continuous variables were presented as mean ± standard deviation, and skewed distributed continuous variables were presented as median and interquartile ranges (IQRs). The Chi-square test was used for comparing categorical variables. The Student's t-test was used for normally distributed continuous variables and Mann Whitney-U test was used for continuous variables that did not show normal distribution. The relationship between sarcopenia and folic acid was analyzed with the univariate Logistic Regression (LR) method. The Spearman correlation coefficient was used to assess the correlation between folate, muscle strength, muscle mass and MNA. The Spearman correlation coefficient was interpreted according to r level as follows: <0.19 (very weak), 0.2-0.39 (weak), 0.4-0.59 (moderate), 0.6-0.79 (strong), and >0.8 (very strong). P value less than 0.05 was considered as statistically significant. SPSS-22 statistical program was used for the statistical analysis.

## Results

88 (31%) of the 287 patients were sarcopenic. 67% of patients with sarcopenia and 72% of patients without sarcopenia were female (p=0.410). Age, number of drugs, number of chronic diseases, the frequency of chronic kidney disease, atrial fibrillation and malnutrition were statistically significantly higher (p=0.001, p<0.001, p<0.001, p=0.040, p=0.18, p<0.001; respectively), MNA and MMSE score was significantly lower in patients with sarcopenia (p<0.001, p=0.001; respectively). While serum folate level was 7.01±4.63 in patients with sarcopenia, it was 8.34±4.25 in patients without sarcopenia, and this difference was statistically significant (p=0.028). Demographic data, chronic diseases, geriatric assessment scores and laboratory findings of patients with/without sarcopenia are given in Table 1.

As a result of univariate logistic regression analysis, a significant association was found between sarcopenia and folate [Odds ratio (OR) 0.926 (95%) confidence interval (CI) 0.864–0.993, p=0.031). Correlation analysis showed a very weak correlation between folate and muscle strength (p=0.005, r=0.175), and a significantly weak correlation between folate and muscle mass and MNA (p<0.001, r=0.285; p<0.001, r=0.256, respectively).

Serum folate level (7.12±4.39) in patients with malnutrition was statistically significantly lower than in patients without malnutrition (8.57±4.29) (p=0.008) (Table 2).

## Discussion

Our study revealed the relationship between sarcopenia and folate, pointing to the trial of folate replacement in the prevention or treatment of sarcopenia, which is still uncertain in many respects. In our study, besides the relationship between sarcopenia and folate, the relationship between sarcopenia and other geriatric syndromes was also investigated. While there are many studies in the literature investigating the relationship between sarcopenia and only one geriatric syndrome, we wanted to plan a more comprehensive study examining several geriatric syndromes that we frequently encounter in clinical practice.

There are many studies in the literature showing that folic acid has an important role in myogenesis, especially in the proliferation and differentiation of muscle cells. Hwang et al. examined the effects of folic acid on myogenesis with a cell study and found that folic acid induces the differentiation of myoblasts to multinucleated myotubes by activating the Akt signaling pathway (16). In another study by again Hwang et al, it was emphasized that folate has an important role in both myoblast proliferation and differentiation and revealed that in folate deficiency, the cell cycle was interrupted, the number and length of myotubes were reduced and the differentiation phase was strongly affected due to genotoxic stress, so they concluded that folic acid is necessary for normal skeletal muscle development (17).

Revealing the positive effects of folate on muscle cells has brought a new perspective to sarcopenia. The relationship between sarcopenia and folate has been the focus of attention of many researchers and many studies have been published on this subject. In a cross-sectional study including 56 primary care patients (>65 years old) with diabetes mellitus folate levels were found to be significantly correlated with grip and leg strength (18). When we examined more recent studies examining the relationship between sarcopenia and sarcopenia-related nutrients, including folate, low serum folate level or folate intake was found to be associated with sarcopenia or its components, again in line with our study. In Yeung et al.'s study higher folate intake was associated with both higher muscle mass and muscle strength (19). Greater intakes of folate was found to be correlated with improved functional outcome measurements in Behrouzi et al.'s study (20). In a study conducted with 432 hospitalized patients (44 with sarcopenia), it was observed that red cell folate was significantly lower in patients with sarcopenia at admission (during acute illness) and at 6 weeks (recovery period) compared to the group without sarcopenia (21). In another study conducted with 1606 community-dwelling older adult dietary pattern with high folate content (rich in fish, soybean products, potatoes, most vegetables, mushrooms, seaweeds, and fruits) has been clearly shown to be inversely associated with sarcopenia (22). Likewise in our study, serum folate level was significantly lower in the sarcopenia group (p=0.028). There was also a significant relationship between folate and hand grip strength and muscle mass, which are components of sarcopenia. On the contrary, in a Taiwan study involving 731

**Table 1. Demographic data, chronic diseases, comprehensive geriatric assessment scores and laboratory findings of patients with/without sarcopenia**

| | Total (n=287) | With sarcopenia (n=88) | Without sarcopenia (n=199) | p |
|---|---|---|---|---|
| Gender (female/male) | 202/85 | 59 (67%) | 143 (72%) | 0.410 |
| Age* | 76.78±7.78 | 79.04±7.51 | 75.87±7.78 | **0.001** |
| Number of drugs* | 6.41±3.80 | 7.64±4.03 | 5.90±3.59 | **<0.001** |
| Number of chronic diseases* | 2.42±1.47 | 3.20±1.50 | 2.09±1.34 | **<0.001** |
| Hypertension | 210 (73%) | 61 (69%) | 149 (75%) | 0.327 |
| Diabetes mellitus | 121 (42%) | 44 (50%) | 77 (39%) | 0.074 |
| Osteoporosis | 81 (28%) | 26 (30%) | 55 (28%) | 0.741 |
| Chronic obstructive pulmonary disease | 26 (9%) | 10 (11%) | 16 (8%) | 0.366 |
| Chronic kidney disease | 17 (6%) | 9 (10%) | 8 (4%) | 0.040 |
| Cerebrovascular disease | 32 (11%) | 13 (15%) | 19 (9%) | 0.195 |
| Ischemic heart disease | 25 (8%) | 6 (7%) | 19 (9%) | 0.450 |
| Chronic heart failure | 22 (7%) | 7 (8%) | 15(7%) | 0.903 |
| Atrial fibrillation | 33 (11%) | 16 (18%) | 17 (8%) | **0.018** |
| Malnutrition | 126 (44%) | 63 (71%) | 63 (31%) | **<0.001** |
| Urinary incontinence | 44 (15%)w | 17 (19%) | 27 (13%) | 0.212 |
| BADLs** | 0 (0-2) | 0 (0-2.5) | 0 (0-2) | 0.284 |
| IADLs** | 14 (10-17) | 14 (10-17) | 13 (9-16) | 0.704 |
| MNA* | 20.69±5.93 | 22.03±7.80 | 27.5±6.41 | **<0.001** |
| MMSE* | 24.68±5.07 | 22.8±5.9 | 25.4±4.4 | **0.001** |
| GDS** | 4 (2-8) | 5 (2-9) | 4 (1-7) | 0.127 |
| Handgrip* | 20.03±9.89 | 13.29±5.32 | 23.11±10.06 | **0.001** |
| Muscle mass* | 6.11±0.71 | 5.87±0.84 | 6.23±0.66 | **0.016** |
| Folate (ng/mL)* | 7.92±4.38 | 7.01±4.63 | 8.34±4.25 | **0.028** |
| Vitamin B12 (pg/mL)* | 436.6±198.4 | 457.4±220.3 | 430.5±189.9 | 0.601 |
| Vitamin D (ng/dL)** | 18.75 (6.08-29) | 19 (8-29) | 17 (4.8-29) | 0.522 |
| Total protein (g/dL)* | 6.96±0.58 | 6.99±0.50 | 6.94±0.62 | 0.562 |
| Albumin (g/dL)* | 4.22±0.44 | 4.23±0.37 | 4.21±0.46 | 0.761 |
| Hemoglobin (g/dL)* | 12.16±2.25 | 11.96±1.54 | 12.56±1.57 | **0.003** |
| Creatinine (mg/dL)* | 0.93±0.36 | 0.93±0.35 | 0.94±0.35 | 0.872 |

BADLs: Basic activities of daily living, IADLs: Instrumental activities of daily living, MMSE: Mini mental state examination, GDS: Geriatric depression scale, Data are shown as *mean ± standard deviation (SD) or **median (interquartile intervals), significant p-values are bolded

**Table 2. Laboratory findings of patients with/without malnutrition**

| | With malnutrition (n=126) | Without malnutrition (n=161) | p |
|---|---|---|---|
| Folate (ng/mL) | 7.12±4.39 | 8.57±4.29 | 0.008 |
| Total protein (g/dL) | 6.98±0.58 | 6.94±0.59 | 0.525 |
| Albumin (gr/dL) | 4.20±0.46 | 4.24±0.41 | 0.465 |
| Hemoglobin (g/dL) | 12.08±1.85 | 12.23±2.51 | 0.594 |
| Creatinine (mg/dL) | 0.94±0.39 | 0.92±0.33 | 0.510 |

Data are shown as *mean ± standard deviation (SD), significant p-values are bolded

adults aged 65 and over, serum levels of vitamin D, vitamin B12 and folic acid, biochemical markers of nutritional status, were not found to be significantly associated with sarcopenia (23). In our study, although a significant relationship was found between sarcopenia and folate, the OR for folate was found to be 0.926, that is, a value close to 1. For this reason, it would be appropriate to conduct studies with a larger number of patients in order to put forward this relationship more concretely.

The second mechanism in sarcopenia that occurs in folate deficiency can be considered as hyperhomocysteinemia due to folate deficiency. Since folate is involved in one-carbon metabolism as a precursor of cofactors, its deficiency causes increased homocysteine levels in plasma. Studies have shown

that hyperhomocysteinemia causes many diseases, such as cardiovascular and neurodegenerative diseases, stroke and cancer by triggering oxidative stress and inflammation (24, 25). Skeletal muscle weakness has also been implicated as one of the consequences of hyperhomocysteinemia. In the study of Veeranki et al. on mice, it was shown that hyperhomocysteinemia causes skeletal muscle weakness by causing mitochondrial dysfunction (26). Swart et al found an association between high plasma homocysteine levels and reduced muscle strength and physical performance in older women (27). Homocysteine levels of the patients were not measured in our study, but folate deficiency induced hyperhomocysteinemia may be one of the contributors to sarcopenia in our study patients.

Malnutrition is a clinical condition defined as an imbalance in nutrient and/or energy intake and its frequency increases with aging (28). Malnutrition is found in the pathophysiology of sarcopenia and causes adverse outcomes similar to sarcopenia. Malnutrition and sarcopenia are in such a close relationship with each other that the clinical presentation that emerged in their association has begun to be called Malnutrition-Sarcopenia Syndrome (29). In a 4-year follow-up study of 336 patients, it was shown that the risk of developing sarcopenia/severe sarcopenia is approximately fourfold higher in malnutrition and the researchers emphasized that malnutrition can be a strong predictor of the onset of sarcopenia (30). We also found a significant relationship between malnutrition and sarcopenia ($p<0.001$).

Researchers looking for an answer to the question of whether folate could be an indicator of malnutrition found different results in their studies. While Kozman et al. reported that serum folate of less than 7.0 ng/mL indicates malnutrition, Soysal et al. emphasized that folate levels are not associated with nutritional status (31, 32). In our study, serum folate levels were found to be significantly lower in malnourished patients ($7.12\pm4.39$, $p=0.008$).

Sarcopenia is common in patients with chronic kidney disease and many different mechanisms are implicated in sarcopenia in renal failure. These are chronic inflammation, metabolic acidosis, stimulation of the ubiquitin-proteasome system and some hormones such as parathyroid hormone, glucocorticoid and angiotensin II (33, 34). The uremic environment in chronic renal failure also disrupts the balance between skeletal muscle regeneration and catabolism (35). In a study including patients with chronic kidney disease stages 3-5 (not on renal replacement therapy), loss of appendicular skeletal muscle mass was found to be significantly related to the decline in glomerular filtration rate (36). Since folate metabolism may be affected in renal failure, we only included patients with stage 1 and 2 chronic kidney disease in our study. Despite the small sample size and only early-stage chronic kidney disease patients were included, the significant association we found between sarcopenia and chronic kidney disease is remarkable.

Studies have frequently revealed the association between sarcopenia and cognitive impairment. In a systematic review and meta-analysis in which Peng et al. examined 15 studies, sarcopenia was found to be associated with an increased risk of cognitive impairment, thus they emphasized the importance of early diagnosis of sarcopenia to prevent cognitive impairment (37). Also in a cross-sectional study of 619 patients, the frequency of cognitive impairment was found to be significantly higher in patients with both possible and definitive sarcopenia (38). Likewise in our study MMSE score was statistically significantly lower in patients with sarcopenia. In the present study, sarcopenia was found to be associated with the number of medications. Likewise, in a study involving 1502 participants from the Berlin Aging Study II, polypharmacy (use of 5 or more drugs daily) was found to be associated with sarcopenia (39). Researchers of a systematic review also found an association between sarcopenia and polypharmacy and the number of drugs in community-dwelling older adults, but not in hospitalized patients or nursing home residents (40). Studies have shown that the frequency of atrial fibrillation is increased in sarcopenic individuals, and the presence of sarcopenia increases 1-year mortality in atrial fibrillation. In our study, the frequency of atrial fibrillation was higher in sarcopenic individuals in line with the literature (41, 42).

Diabetes mellitus can cause sarcopenia by accelerating the loss of muscle mass and strength and increasing the levels of inflammatory cytokines (43). In our study, the presence of diabetes mellitus was not found to be associated with sarcopenia ($p=0.074$). This may be due to the fact that the duration of diabetes mellitus and hemoglobin A1c levels of the patients we included in the study were not examined. The relationship between depression and sarcopenia has also been examined many times in the literature, and it has been concluded that sarcopenia is more common in depressive individuals due to physical inactivity and deterioration in oral intake, seen in depression. When viewed backwards, sarcopenia may also cause depression by causing physical decline (44). We also found a higher GDS score, which indicates the possibility of depression, in sarcopenic individuals, but we could not detect a significant difference between the two groups ($p=0.127$). This may be because the GDS indicates the possibility of depression and that clinical evaluation is essential for the diagnosis of depression. The relationship between sarcopenia and hypertension is still an issue that has not been clarified. While there are studies that found a relationship between sarcopenia and hypertension, there are also studies that did not find a relationship between them (45, 46). When studies on this subject were examined, it was noticed that hypertension was associated with sarcopenic obesity rather than sarcopenia (47). In our study, the frequency of hypertension

was not found to be increased in sarcopenic individuals, which is consistent with many studies (p=0.327). Although we expect sarcopenic patients to be affected in their daily and instrumental living activities, we did not find a significant difference between patients with and without sarcopenia in our study. This may be attributed to the fact that the study participants were clinically stable patients without advanced comorbidities.

Our study is important because we investigated the relationship of sarcopenia with several chronic diseases and geriatric syndromes. We showed that the frequency of malnutrition is increased in sarcopenic patients, and that serum folate levels are lower in both malnourished and sarcopenic individuals. This brought to mind the idea of folate supplementation in individuals at risk for malnutrition and sarcopenia.

The study has some limitations. First, this study had a retrospective cross-sectional design, so it is not possible to determine causal relationships. And second, the fragility associated with sarcopenia was not among the geriatric syndromes evaluated in our study. This was because the study was retrospective and the fragility status was not recorded in the patients' files.

In conclusion, since sarcopenia is associated with malnutrition, these two conditions should be evaluated together and when one of them is detected, the patient should be screened for the other. As we found that folate levels were lower in patients with both sarcopenia and malnutrition in our study, we recommend that risky groups be supported with folate-rich foods or folic acid supplementation.

### Ethics

**Ethical Committee Approval:** Ethical approval was obtained from the ethics committee of Cerrahpaşa Faculty of Medicine (Date 09.09.2020-Number 117344).

**Informed Consent:** Informed consent was obtained from all participants included in the study.

**Peer-review:** Internally and externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: B.B.K., Concept: H.Y., Design: B.B.K., Data Collection or Processing: B.B.K., Analysis or Interpretation: H.Y., Literature Search: H.Y., B.B.K., Writing: H.Y.

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