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ORIGINAL ARTICLE

Hyperuricemia in Aging: A Risk Factor or a Protective Mechanism for Physical Function?

Yaşlanmada Hiperürisemi: Bir Risk Faktörümü Yoksa Fiziksel Fonksiyon İçin Koruyucu Bir Mekanizma mı?

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ABSTRACT

Aim: Hyperuricemia is associated with metabolic and cardiovascular disease in older adults, but its effects on physical function and frailty remain unclear. While the antioxidant properties of serum uric acid (SUA) may have a protective effect, some studies suggest negative effects on mobility and muscle strength. This study examines the relationship between hyperuricemia, gait speed, dynapenia, and frailty.
Methods: This retrospective study included 526 women aged 60 years and older. Gait speed, handgrip strength, and frailty status were assessed as part of a comprehensive geriatric examination. Hyperuricemia was defined as SUA levels ≥6 mg/dL. Binary logistic regression models adjusted for age, body mass index (BMI), hypertension, and depressive symptoms were used.
Results: Hyperuricemia was not significantly associated with low gait speed (OR: 1.15, 95% CI: 0.70–1.76, p=0.645) or dynapenia (OR: 1.17, 95% CI: 0.76–1.79, p=0.456). The association with frailty was significant in the unadjusted model (OR: 1.57, 95% CI: 1.04–2.35, p=0.031), but lost significance after adjustment (OR: 1.50, 95% CI: 0.96–2.34, p=0.075).
Conclusion: Hyperuricemia was not significantly associated with low gait speed or dynapenia. Although an association with frailty was observed, this weakened after adjustment for confounding factors. These results suggest that hyperuricemia may be a marker rather than a direct cause of frailty, possibly related to underlying cardiovascular and metabolic diseases. Further research is needed to better understand the mechanisms between hyperuricemia and physical function and to evaluate the effects of uric acid-lowering therapies on physical performance.

Keywords: Frailty, Hyperuricemia, Muscle strength, Older people, Physical performance

ÖZ

Amaç: Hiperürisemi, yaşlı bireylerde metabolik ve kardiyovasküler hastalıklarla ilişkilidir; ancak fiziksel fonksiyon ve kırılganlık üzerindeki etkileri net değildir. Serum ürik asidin (SUA) antioksidan özellikleri koruyucu etki gösterebilirken, bazı çalışmalar hareketlilik ve kas gücü üzerinde olumsuz etkiler olabileceğini önesürmektedir. Bu çalışma, hiperürisemi ile yürüme hızı, dinapeni ve kırılganlık arasındaki ilişkiyi incelemektedir.
GereçveYöntemler: Bu retrospektif çalışmaya, 60 yaş ve üzeri 526 kadın dahil edilmiştir. Katılımcıların yürümehızı, el kavrama gücü ve kırılganlık durumu kapsamlı geriyatrik değerlendirme kapsamında değerlendirilmiştir. Hiperürisemi, serum ürik asit düzeyinin ≥6 mg/dL olması olarak tanımlanmıştır. Yaş, beden kitle indeksi (BKİ), hipertansiyon ve depresif semptomlara göre ayarlanan ikili lojistik regresyon modelleri kullanılmıştır.
Bulgular: Hiperürisemi, düşükyürümehızı (OR: 1,15; %95 GA: 0,70–1,76; p=0,645) veya dinapeni (OR: 1,17; %95 GA: 0,76–1,79; p=0,456) ile anlamlı şekilde ilişkili bulunmamıştır. Hiperürisemi ile kırılganlık arasındaki ilişki, düzeltilmemiş modelde anlamlı bulunmuş (OR: 1,57; %95 GA: 1,04–2,35; p=0,031), ancak düzeltmeler sonrası anlamlılığını yitirmiştir (OR: 1,50; %95 GA: 0,96–2,34; p=0,075).
Sonuçlar: Hiperürisemi, düşük yürüme hızı veya dinapeni ile anlamlı bir ilişki göstermemiştir. Kırılganlık ile ilişkisi gözlenmiş olsa da, bu ilişki olası karıştırıcı faktörler için düzeltme yapıldığında zayıflamıştır. Bu sonuçlar, hiperüriseminin kırılganlığın doğrudan bir nedeni olmaktan ziyade, altta yatan kardiyovasküler ve metabolik hastalıklarla ilişkili bir belirteç olabileceğini düşündürmektedir. Hiperürisemi ile fiziksel fonksiyon arasındaki mekanizmaların daha iyi anlaşılması ve ürik asit düşürücü tedavilerin fiziksel performans üzerindeki etkilerinin değerlendirilmesi için ileri çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Fiziksel performans, Hiperürisemi, Kas gücü, Kırılganlık, Yaşlı bireyler

Introduction

Hyperuricemia is defined as an increase in the serum uric acid (SUA) level above the normal physiological limit. The upper limit of normal SUA is generally 7 mg/dL in men and 6 mg/dL in women, but these levels can vary in different populations (1). The prevalence of hyperuricemia increases with age, primarily due to a decrease in renal uric acid excretion, which makes older people more susceptible to elevated SUA levels (2-6). Several factors contribute to the development of hyperuricemia, including age, gender, obesity, metabolic disorders, cardiovascular disease (CVD), dietary habits, and malignancies (1,7). Hyperuricemia has been consistently associated with an increased risk of CVD and metabolic syndrome (7).

Although hyperuricemia has long been considered a risk factor for gout, kidney, and CVD, recent studies have suggested a possible protective role in certain age-related diseases, particularly neurodegenerative diseases such as Parkinson's, Alzheimer's, and osteoporosis (8-10). This protective effect is thought to be mediated by the antioxidant properties of SUA, which acts as one of the major extracellular

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antioxidants in the human body. SUA has been shown to neutralize free radicals, reduce oxidative stress, and modulate inflammatory processes that are critical in the pathogenesis of neurodegeneration and bone metabolism (8-10).

In addition to the potentially neuroprotective role of SUA, there is increasing evidence of a link between hyperuricemia and physical performance, muscle strength, and frailty. The effects of SUA on musculoskeletal function are complex and appear to go both ways. Some epidemiologic studies suggest that increased SUA levels are associated with better muscle strength and physical performance (8), possibly due to its antioxidant capacity and anabolic effects. SUA may promote muscle function by reducing oxidative stress, which is associated with muscle fatigue, sarcopenia, and frailty (9). Conversely, other studies have found an inverse association, suggesting that hyperuricemia may impair physical performance because it is related to subclinical atherosclerosis, endothelial dysfunction, and chronic inflammation, all of which contribute to decreased muscle strength and mobility (9,10).

Sarcopenia and frailty, both characterized by declining muscle strength, decreased gait speed, and general loss of function, are recognized risk factors for falls, disability, and mortality in older adults (10). The relationship between hyperuricemia and these geriatric syndromes is still not clear, as the results of the different studies are very heterogeneous. Different cut-off values for hyperuricemia, different instruments to assess muscle function, and the heterogeneity of the population could explain these discrepancies.

Given the conflicting evidence for the role of hyperuricemia in muscle strength, gait speed, and frailty, further research is needed to clarify this association. In this study, we aimed to investigate the effects of hyperuricemia on physical performance, muscle strength, and frailty in a cohort of elderly female patients.

Materials and Methods

Our study was conducted using a retrospective review of patient records, including comprehensive geriatric assessment results and concurrently measured serum uric acid levels in women aged 60 years and older. Patients with a history of gout, stroke, chronic kidney disease, or immobilization were excluded from the study.

As part of the comprehensive geriatric assessment, body fat percentage (BF), body weight, and fat-free mass (FFM) were measured using the TANITA TBF-300 bioimpedance analyzer (Japan), which has been shown to provide estimates of body composition with an accuracy comparable to magnetic resonance imaging. Body mass index (BMI) was calculated by dividing body weight by the square of height (kg/m²), with values of 30 or more classified as obesity.

Muscle strength was measured using a hand-held dynamometer, with a cut-off point of 16 kg used to define low muscle mass (dynapenia) (11). Gait speed was measured in meters per second (m/s) using a 4-meter walk test, with a gait speed below 0.8 m/s classified as low gait speed (12).

Frailty was assessed using the Fried Frailty Index, with scores of 3 or higher classified as frailty(13). In addition, patients' activities of daily living (ADL) and instrumental activities of daily living (IADL) were assessed (14,15).

The Yesavage Geriatric Depression Scale (YGDS) and the Mini-Mental State Examination (MMSE) were also administered (16,17). A YGDS score of 5 or higher was considered indicative of depression (16). Polypharmacy was defined as the use of five or more medications (18). In addition, all patients were asked about falls in the past year and, if applicable, the frequency of such incidents. Individuals with a serum uric acid level of 6 mg/dL or higher were classified as hyperuricemia (1).

This study was designed as a retrospective study and informed consent was not obtained from participants. Ethical approval for the study was obtained from the local ethics committee (2024-KAEK-76), and the study was conducted under the principles of the Declaration of Helsinki.

Statistical Analysis

IBM Statistical Package for Social Sciences (IBM SPSS) version 22.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. The Kolmogorov-Smirnov test was used to determine whether the data followed a normal distribution. For normally distributed numeric variables, the mean ± standard deviation (SD) was reported, while for non-normally distributed numeric variables, the median and minimum-maximum values were reported. Categorical variables were summarised as frequencies. For comparisons between the groups with and without hyperuricemia, an independent T-test was used for normally distributed

numerical variables, a Mann-Whitney U-test for non-normally distributed numerical variables, and the chi-square test for categorical variables.

A two-stage binary logistic regression analysis was performed to assess the relationship between hyperuricemia and the dependent variables, including low gait speed, dynapenia, and frailty. Unadjusted analyses were performed first, followed by a second analysis in which adjustment was made for age, BMI, hypertension, and depressive symptoms to reassess the associations. Odds ratios (HRs) and 95% confidence intervals (CIs) were calculated. A p-value < 0.05 was considered statistically significant.

Results

In this study, a total of 526 female patients aged 60 years and older were included. Among them, 131 (24.9%) were classified as having hyperuricemia, while 395 (75.1%) had normal serum uric acid levels. Patients with hyperuricemia were significantly older than those without hyperuricemia (71.49±6.89 vs. 69.61±6.07 years, p=0.006). Additionally, marital status differed significantly between the groups, with a lower percentage of married individuals among hyperuricemic patients compared to those without hyperuricemia (67.62% vs. 78.61%, p=0.018). (Table 1)

Although BMI and body fat percentage were slightly higher in the hyperuricemia group (33.05±6.21 vs. 32.05±6.63, p=0.127; 37.89±8.45 vs. 37.48±8.05, p=0.642, respectively), these differences were not statistically significant. Similarly, the prevalence of obesity was higher in hyperuricemic patients (66.41% vs. 59.75%, p=0.110), but the difference did not reach statistical significance (Table 1)

Regarding functional and physical performance, handgrip strength was slightly lower in hyperuricemic patients, but the difference was not statistically significant (16.29±5.88 vs. 17.04±5.40 kg, p=0.179). The prevalence of low handgrip strength was also higher in the hyperuricemia group (48.09% vs. 42.63%, p=0.162).

Table 1. Characteristics of Study Populations

Variables	Total n=526	Hyperuricemia		p
		YES n=131	NO n=395	
Age, years, mean±SD	70.08±6.33	71.49±6.89	69.61±6.07	**0.006**
Marital Status	343 (76.05)	71(67.62)	272(78.61)	0.018
BMI, mean±SD	32.30±6.54	33.05±6.21	32.05±6.63	0.127
Obesity, yes, n (%)	323(61.41)	87 (66.41)	236 (59.75)	0.110
BF, mean±SD	37.58±8.14	37.89±8.45	37.48±8.05	0.642
FFM, mean±SD	44.39±6.06	44.71±	44.28±	0.511
Handgrip Strength, mean±SD	16.85±5.52	16.29±5.88	17.04±5.40	0.179
LHGS, yes, n (%)	231 (44)	63 (48.09)	168 (42.63)	0.162
Gait speed, mean±SD	0.75±0.27	0.71±0.28	0.76±0.26	0.082
LGS, yes, n (%)	344 (66.03)	91 (70.00)	253 (64.71)	0.159
Frailty, yes, n (%)	286 (54.89)	82 (63.07)	204 (52.17)	**0.019**
ADL, mean±SD	5.26±0.69	5.17±0.76	5.29±0.66	0.082
IADL, mean±SD	6.48±1.83	6.42±1.91	6.49±1.81	0.694
YGDS, mean±SD	4.57±2.91	4.20±2.97	4.69±2.90	0. 117
Depression symptoms, yes, n (%)	247 (47.05)	52 (39.69)	195(49.49)	**0.032**
MMSE, mean±SD	25.39±3.58	25.39±3.63	25.39±3.56	1.000
Fall history, yes, n (%)	193 (38.07)	52 (41.27)	141(37.01)	0.227
Polypharmacy, yes, n (%)	31 (65.36)	80 (65.04)	237 (65.47)	0.507
HT, yes, n (%)	37 (72.36)	107 (81.68)	270 (68.88)	**0.003**
DM, yes, n (%)	33 (63.05)	86 (65.65)	245 (62.18)	0.273
COPD, yes, n (%)	10 (20.72)	28 (21.37)	81 (20.51)	0.460
CVD, yes, n (%)	97(18.47)	28 (21.37)	69 (17.51)	0.195

Abbreviations :BMI: ,Body mMass iIndex; BF,Body fFat pPercentage; FFM: ,Fat-fFree mMass; LHGS =: Low hHandgrip sStrength; LGS: = Low gGait sSpeed; ADL: = Activities of daily living; IADL =: Instrumental activities of daily living; YGDS =: Yesavage geriatric depression scale; MMSE =: Mini-mental state examination; HT =: Hypertension; DM =: Diabetes mMellitus; COPD =: Chronic obstructive pulmonary disease; CVD =: Cardiovascular dDisease, SD: Standard deviation

Similarly, gait speed was slightly lower in hyperuricemic patients, but the difference did not reach statistical significance (0.71±0.28 vs. 0.76±0.26 m/s, p=0.082). The prevalence of low gait speed was higher in hyperuricemic patients (70% vs. 64.71%, p=0.159) (Table 1).

A statistically significant association was found between frailty and hyperuricemia, with frailty being more prevalent in the hyperuricemic group (63.07% vs. 52.17%, p=0.019). However, there were no significant differences between the groups in terms of Activities of Daily Living and Instrumental Activities of Daily Living scores (p=0.082 and p=0.694, respectively) (Table 1).

Regarding depression symptoms and cognitive function, the YGDS score was slightly lower in hyperuricemic patients (4.20±2.97 vs. 4.69±2.90, p=0.117). The presence of depressive symptoms was significantly lower in hyperuricemic patients (39.69% vs. 49.49%, p=0.032). However, Mini-Mental State Examination scores were identical between both groups (25.39±3.63 vs. 25.39±3.56, p=1.000) (Table 1).

When comorbidities and medication use were evaluated, hypertension was significantly more prevalent in hyperuricemic patients (81.68% vs. 68.88%, p=0.003). Although diabetes mellitus (DM), chronic obstructive pulmonary disease, and CVD were slightly more common in the hyperuricemia group, the differences were not statistically significant (p=0.273, p=0.460, and p=0.195, respectively). Similarly, polypharmacy rates were comparable between the groups (65.04% vs. 65.47%, p=0.507). Fall history was slightly more common in the hyperuricemia group (41.27% vs. 37.01%, p=0.227), but the difference did not reach statistical significance (Table 1).

The association between hyperuricemia and low gait speed, dynapenia, and frailty was analyzed using unadjusted and adjusted binary logistic regression models. In the unadjusted analysis, hyperuricemia was not significantly associated with low gait speed (OR: 1.27, 95% CI: 0.83–1.95, p=0.270) or dynapenia (OR: 1.25, 95% CI: 0.83–1.85, p=0.277). Similarly, after adjusting for age, BMI, hypertension, and depressive symptoms, hyperuricemia remained non-significantly associated with low gait speed (OR: 1.15, 95% CI: 0.70–1.76, p=0.645) and dynapenia (OR: 1.17, 95% CI: 0.76–1.79, p=0.456). (Table 2) However, a significant association was observed between hyperuricemia and frailty in the unadjusted model (OR: 1.57, 95% CI: 1.04–2.35, p=0.031). After adjusting for confounders, this association slightly weakened and lost statistical significance, but a trend remained (OR: 1.50, 95% CI: 0.96–2.34, p=0.075) (Table 2).

Table 2. Association of hyperuricemia with low gait speed, diapenia and frailty

	Low Gait Speed				Diapenia				Frailty			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
Hyperuricemia	OR (95%)	p	OR (95%)	p	OR (95%)	p	OR (95%)	p	OR (95%)	p	OR (95%)	p
	1.27 (0.83-1.95)	0.270	1.15 (0.70-1.76)	0.645	1.25 (0.83-1.85)	0.277	1.17 (0.76-1.79)	0.456	1.57 (1.04-2.35)	0.031	1.50 (0.96-2.34)	0.075

Adjusted for age, body mass index, depression symptoms, and hypertension, OR: Odds ratio

Discussion

This study aimed to investigate the association between hyperuricemia and physical function in older female adults, in particular the association with slow gait speed, dynapenia, and frailty. While hyperuricemia has traditionally been considered a risk factor for gout, CVD, and renal dysfunction (1,2), recent research suggests that it may also play a protective role in certain age-related diseases, including neurodegenerative diseases and sarcopenia (8-10). However, the results of this study suggest that hyperuricemia was not significantly associated with low gait speed or dynapenia, and although it showed a weak association with frailty, this relationship lost statistical significance after adjustment for confounding factors. Interestingly, while high uric acid levels are associated with unfavorable outcomes in many diseases, there is also evidence that low uric acid levels may also be harmful in certain clinical contexts. For example, a recent Turkish study found that hypouricemia was significantly associated with a poorer prognosis in acute graft-versus-host disease (19). This underscores the idea that uric acid may play a dual and context-dependent role in health and disease. In addition, another recent study found that serum uric acid levels were associated with bone mineral density and long-term fracture risk in older adults with type 2 DM further supporting the systemic relevance of uric acid in aging-related conditions (20).

The possible effects of hyperuricemia on muscle strength and physical performance remain

controversial. SUA is known for its antioxidant properties, and some studies suggest that higher levels of SUA may help preserve muscle function by neutralizing free radicals, reducing oxidative stress, and preventing mitochondrial damage, all of which are critical for muscle aging and preventing frailty (9, 10, 21). Epidemiological studies have reported that increased SUA levels are associated with improved muscle strength and physical performance, possibly due to its anabolic effects and role in energy metabolism (8, 9, 22). Similarly, a recent study by Xiao et al. reported that hyperuricemia was positively correlated with lean mass and certain definitions of obesity, highlighting the complex role of uric acid in body composition and sarcopenia(22). However, our study does not support this hypothesis, as no significant association was found between hyperuricemia and muscle strength or gait speed. This discrepancy may be due to our sample being exclusively composed of older women, in whom hormonal and metabolic differences might alter the relationship between uric acid and muscle function.

Conversely, other studies indicate that hyperuricemia may impair physical function, primarily due to its role in subclinical atherosclerosis, endothelial dysfunction, and chronic inflammation (10, 23, 24). Increased SUA is associated with decreased nitric oxide bioavailability, which affects muscle perfusion, oxygenation, and overall mobility (3,21,25). The results of this study are consistent with this view and suggest that hyperuricemia has no protective effect on muscle function in older adults. Our findings may reflect the dominant influence of age-related comorbidities, such as endothelial dysfunction and systemic inflammation, which might overshadow any potential antioxidant benefit of uric acid.

The link between hyperuricemia and frailty is still controversial. Frailty is a progressive clinical syndrome characterized by decreased muscle mass, decreased strength, and increased risk of falls, disability, and mortality (26). In this study, hyperuricemia was associated with a higher prevalence of frailty in the unadjusted analysis, but after controlling for age, BMI, hypertension, and depressive symptoms, the association weakened and lost statistical significance. This suggests that although hyperuricemia may be associated with frailty, it is likely to be mediated by other underlying conditions such as CVD, metabolic disorders, and systemic inflammation (27,28). These results are aligned with recent findings from a population-based study, which reported a positive association between higher serum uric acid levels and frailty risk in older adults (29).In our cohort, the attenuation of the association after adjustment suggests that hyperuricemia may be more of a marker reflecting the burden of age-related diseases, rather than a direct contributor to frailty.

Several factors could explain the lack of a significant association between hyperuricemia and physical function in this study. First, differences in genetic predisposition, diet, comorbidities, and medication use may influence the effects of hyperuricemia on physical function (4,7). Second, different cut-off values for hyperuricemia in different studies may lead to contradictory results (5,27). Third, although adjustments were made for age, BMI, hypertension, and depression, other potential confounders such as inflammatory markers, renal function, and medication use were not considered (3,25). Finally, gender differences may also play a role, as most previous studies included both men and women, whereas this study focused exclusively on older female patients, who may have a different metabolic response to hyperuricemia (6,8). These considerations reinforce the need for sex-specific and individualized evaluation of uric acid's clinical impact, particularly in older populations.

The results of this study emphasize the need for a differentiated approach to hyperuricemia in older adults. While hyperuricemia is often discussed in the context of cardiovascular and renal disease, its potential role in muscle health and frailty remains unclear. Given the conflicting evidence, future research should focus on longitudinal studies to establish causality, incorporate biomarkers of oxidative stress and inflammation to clarify possible mechanisms and investigate the effects of uric acid-lowering therapy on exercise capacity and frailty.

This study has several limitations that should be considered when interpreting the findings. First, the retrospective design of the study limits the ability to establish causal relationships between hyperuricemia and physical performance outcomes. Second, inflammatory biomarkers and renal function indicators, which could further explain the underlying mechanisms of hyperuricemia's impact on frailty and muscle strength, were not available in the dataset and therefore could not be included in the analysis. Third, although adjustments were made for major confounding factors such as age, BMI, hypertension, and depressive symptoms, the possibility of residual confounding from unmeasured variables cannot be

ruled out. Fourth, the study population consisted solely of older women, which limits the generalizability of the results to other age groups and males. Finally, the cut-off value used to define hyperuricemia was based on a fixed threshold, which may not reflect population-specific or sex-specific variability.

Conclusion

•In this cohort of older women, hyperuricemia was not significantly associated with muscle strength or gait speed.

•A weak association between hyperuricemia and frailty was observed in unadjusted analyses, but this lost statistical significance after adjustment.

•These findings suggest that hyperuricemia may be a marker, rather than a cause, of frailty in older adults.

•The clinical implications of serum uric acid levels in geriatric functional decline remain uncertain and warrant further investigation. Future prospective studies with broader clinical and biochemical parameters are needed to clarify the role of uric acid in aging.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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