RISK FACTORS FOR HIGH FALL RISK IN ELDERLY PATIENTS WITH CHRONIC KIDNEY DISEASE

Cihan Heybeli[1], Rumeyza Kazancioglu[2], Lee Smith[3], Nicola Veronese[4], Pinar Soysal[5]

[1]Division of Nephrology, Muş State Hospital, Muş, Turkey

[2]Department of Nephrology, Bezmialem Vakif University, Faculty of Medicine, Istanbul, Turkey.

[3]The Cambridge Centre for Sport and Exercise Science, Anglia Ruskin University, Cambridge, UK.

[4]Unità Locale Socio Sanitaria 3 "Serenissima", Primary care Department, Venice, Italy

[5]Department of Geriatric Medicine, Faculty of Medicine, Bezmialem Vakif University, Istanbul, Turkey.

Running Title: Fall risk in CKD

Corresponding author

Pinar Soysal, MD

dr.pinarsoysal@hotmail.com

Full Postal Adress: Adnan Menderes Bulvarı (Vatan Street), 34093 Fatih, İstanbul, Turkey

Word count of the abstract: 245

Word count of the manuscript: 2805 (excluding references, and tables)

Keywords. Folic Acid, Gait; Fall, Chronic Kidney Disease

Abstract

Purpose. Patients with chronic kidney disease (CKD) usually represent an aging population, and both older age and CKD are associated with a higher risk of falling. Studies on risk factors of among subjects with CKD are lacking.

Methods. Records of outpatients from one geriatric clinic in Turkey were retrospectively reviewed. A result of ≥13.5 seconds on the timed up and go (TUG) test was accepted as a high risk of falls. Independent predictors of an increased risk of falls among subjects with CKD (estimated glomerular filtration rate of <60 mL/min/1.73 m^2) were identified using logistic regression models.

Results. Patients with CKD (n=205), represented the 20.2% of the entire cohort and was identified as an independent predictor of increased fall risk (OR 2.59). Within the CKD cohort, serum folic acid levels and frailty were independent predictors of an increased risk of falls. The CKD/fall risk group was older, had a lower median years of education, lower vitamin D levels, and lower serum folic acid levels than the CKD/non-fall risk group. In addition to higher serum creatinine and potassium levels, the only significant difference between patients with CKD/fall risk and a matched non-CKD/fall risk was a lower median folic acid level in the former group.

Conclusions. Frailty and low folic acid levels are independently associated with an increased risk of falls among elderly outpatients with CKD. Prevention of frailty may reduce the risk of falls in these subjects. Possible benefit of folic acid supplementation requires further studies.

Introduction

Falls are common in older people and falling is classified as a geriatric syndrome. More than one-third of community-living adults older than 65 years fall each year and about 10% of falls result in fracture, serious soft tissue injury, or traumatic brain damage, thus falls and fall-related injuries are major contributors to functional decline and health care utilization.[1] High rates of gait abnormalities, falls and fall-related injuries in patients with chronic kidney disease (CKD) have been documented.[2-11] Moreover, patients with CKD usually represent an ageing population. Low muscle mass, muscle weakness, and mobility limitation are common findings in patients with CKD which may explain the increased risk of falls and fall-related injuries in this specific patient population.[12]

Functional mobility is associated with independence, quality of life and mortality.[13] Given the association with accelerated aging and high rate of sarcopenia, dynapenia and immobility, CKD was proposed as an ideal clinical disorder to apply physical performance testings.[14] In addition to low quality of life, patients with CKD and low physical performance status are more likely to die or develop end-stage kidney disease.[6,14,15] Moreover, exercise programs increased the quality of life and performance status of patients with stage 3-4 CKD and patients on dialysis.[16-18,8,19] With the aging of the general population, patients who initiate dialysis will more frequently have geriatric impairments and a considerable comorbidity burden which will increase the percentage of patients with mobility limitations and falls.[20]

Functional mobility requires both physical and cognitive resources.[11] Both of these aspects may be affected by numerous pathological conditions leading to a more complex pathogenesis of gait abnormalities. Morever, CKD represents an exceptional state for being associated with a complex multifactorial relationship with malnutrition, inflammation and atherosclerosis which is specifically called MIA syndrome.[21] This syndrome refers to an increased risk of cardiovascular mortality, and represents not only the traditional risk factors but also uniqe risks attributed to the events which emerge with the failing kidney.[21] Studies have shown associations between physical function measures with malnutrition,[22] inflammation,[23,24] and vascular disorders.[25] Thus, MIA syndrome might significantly contribute to a decline in physical functions and increased fall risk in patients with CKD. The current data however indicate that pathogenesis of gait abnormalities and increased fall risk in subjects with CKD may in part be explained by frailty,[5,7] sarcopenia,[26] cognitive decline,[27,28] and peripheral neuropathy due to diabetes.[29,30] Although association of fall risk with these factors is plausible,

studies on more specific factors that may alter gait speed are lacking. In this retrospective study, we aimed to investigate specific risk factors for fall risk among elderly CKD patients.

Methods

Participants

Elderly subjects who were ≥60 years of age and were admitted to one geriatric outpatient clinic in Turkey between November 2018 and August 2019 were included. This study included patients from consecutive outpatient visits, all measurements were performed during the visit and comprehensive geriatric assessments were performed at the same time. Exclusion criteria was as follows: dementia, Parkinson's disease, immobility, acute events which may alter results of geriatric assessment tools (including respiratory failure, acute liver failure, sepsis, and malignancy conditions), lack of serum creatinine, and unavailable functional mobility tests. Among 1708 subjects, 1015 were included.

The definition of CKD

The estimated glomerular filtration rate (eGFR) for each patient was calculated based on the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula,[31]. Patients with an eGFR of <60 mL/min/1.73 m^2 were considered as having CKD.

Fall risk Assessment

The timed up and go (TUG) test was used as the measure of functional mobility. During the TUG test, the patient was timed during rising from an arm chair, walk at a comfortable and safe pace to a line on the floor three meters away, then turn and walk back to the chair and sit down. The subject walks through the test once before being timed to become familiar with the test.[32] Records of ≥13.5 seconds are defined as at risk of falling,[32] and these subjects were included in the fall risk group.

Comprehensive Geriatric Assessment (CGA)

Seven components of gait (initiation of gait, step length, step symmetry, step continuity, path, trunk and walking stance; a maximum of 12 points) and nine components of balance (sitting balance, arises, attempts to

arise, immediate standing balance, standing balance, nudged, eyes closed, turning 360°, and sitting down; a maximum of 16 points) were assessed using this scale. Each subscale was measured as abnormal = 0 or normal = 1; in some cases, adaptive = 1 and normal = 2. The sum of gait and balance scores equals a maximum of 28 points. A total score of <19 refers to a high risk of falling according to the Tinetti POMA Scale.[33] Falls are defined as the sudden, involuntary transfer of body to the ground and at a lower level than the previous one.[34] Recurrent falls was counted as existing if the patient had at least two falls within the previous year excluding tripping on a rug and slipping on wet floor.[35] In addition to these examinations, scores of the following tests were recorded each as a domain of CGA: Basic and Instrumental Activities of Daily Living (BADL and IADL) for the assessment of overall functional status, the Mini-Mental State Examination (MMSE) for the assessment of cognition, the Geriatric Depression Scale-15 for neurocognitive evaluation (GDS), and the Mini Nutritional Assessment (MNA) for nutritional evaluation. A total MNA score of <17 was accepted as malnutrition.[35] All drug exposures were recorded. An exposure to ≥5 drugs was considered polypharmacy.[35] Urinary incontinence was defined as an involuntary urinary leakage for the last 3 months despite the absence of a urinary tract infection.[35] The diagnosis of probable sarcopenia was identified according to the Revised European Working Group's criteria for Sarcopenia Studies in Older People.[36] Frailty status was defined based on 5 dimensions of frailty phenotype, including shrinking, exhaustion, low levels of physical activity, weakness, and slowness. People with 0 criteria were considered robust, 1-2 prefrail, and ≥3 frail.[35] For the nocturia variable, the question, ‘‘Generally, during the past 30 days, how many times do you usually urinate after you have gone to sleep at night until the time you got up in the morning?’’ was used. Response options included choices ranging from 0 to 3, or 4 or more per night.[37] Orthostatic hypotension was defined as a decrease in blood pressure of ≥20 mm Hg systolic and/or ≥10 mm Hg diastolic within 3 minutes following standing compared with the sitting or supine position.[38]

Statistical analysis

Due to the non-normal distribution, quantitative variables were presented as median with the interquartile range (IQR). Groups were compared for means using t test if variables were normally distributed, Mann–Whitney U test was used for non normally distributed data. For comparisons between proportions chi-squared tests or Fisher’s exact test were used, as appropriate.Qualitative variables are expressed as proportions. Logistic regression analysis was used to identify independent predictors of a high fall risk in the total cohort, and specifically in the CKD cohort. Results were expressed as odds ratios (ORs) and 95% confidence intervals (CIs). Characteristics of patients with CKD/fall risk were compared with a matched non-CKD/fall risk. The non-CKD/fall risk group was

a matched group, and matches were for age, sex, frailty and the Lawton-Brody Instrumental Activities of Daily Living scores. Statistical analysis was performed using SPSS 22.0 version (IBM SPSS, Chicago, IL). A P value of 0.05 was considered to be statistically significant.

Results

A total of 1015 elderly patients were included in the study. The median age was 73 (67-79) and 698 (68.8%) were female. The first analysis was carried out to determine independent predictors of fall risk, in the overall cohort. Within these 1015 cases, CKD was identified as an independent risk factor for fall risk (OR 2.59, 95% CI 1.19-5.66, p=0.017) along with frailty (OR 11.26, 95% CI 5.09-24.91, p<0.001), the Lawton-Brody Instrumental Daily Living Activity Scale (OR 0.88, 95% CI 0.82-0.95, p=0.001) and a HbA1-c of >9.0% (OR 3.25, 95% CI 1.29-8.20, p=0.013). Variables associated with a high risk of fall are shown Table 1.

CKD was present in 205 (20.2%) patients. The median age of the CKD cohort was 77 (72-83) and 140 (68.3%) were female. Hypertension and diabetes constituted 78.3% and 41.4% of the CKD cohort. The majority had stage 3 CKD with only 9.8% (20 patients) having stage 4 CKD. Based on the TUG test, 108 (52.7%) had increased fall risk. A comparison was made between patients with CKD/fall risk versus CKD/non-fall risk (Table 2). The median walking time in TUG test was 18 (15-24) versus 11 (9-12) seconds in the former and latter groups, respectively (p<0.001). Patients with CKD/fall risk were older (median 78 vs 75, p=0.001), had less years of education (median 0 versus 4, p=0.023), and had lower serum vitamin D levels (median 10 versus 13, p=0.046), lower serum calcium levels (median 9.4 versus 9.6, p=0.040), and lower serum folic acid levels (median 6.7 versus 8.1, p=0.013). For geriatric syndromes, patients with CKD/fall risk were more likely to have probable sarcopenia (57.6% versus 27.6%, p<0.001), depression (51.6% versus 29.2%, p=0.002), frailty (734% versus 8.2%, p<0.001), malnutrition (11.1% versus 3.3%, p<0.001), and recurrent falls (39.8% versus 21.6%, p=0.005). Moreover, the remaining measures of comprehensive geriatric methods including the Tinetti test, the mini-mental state examination, Instrumental and Basic activity of daily living scores were more likely to suggest a pathology in the CKD/fall risk group (p<0.001 for all comparisons across groups).

In the CKD cohort, serum serum folic acid levels (OR 0.66 per 1 ng/mL increase, 95% CI 0.44-0.98, p=0.039) and frailty (OR 132.94, 95% CI 5.50-3211.86, p=0.003) were identified as independent predictors of fall risk after adjusted with age, sex, years of education, serum vitamin D levels, serum calcium levels, malnutrition, depression, the Lawton-Brody Instrumental Daily Living Activity Scale, the Bartel Basic Daily Living Activity

Scale, the MMSE, and probable sarcopenia. A serum folic acid of <9 ng/mL had an OR of 16.28 for a higher risk of falls (95% CI 1.86-142.68, p=0.012). Neither in the overall cohort, nor among subjects with no CKD serum folic acid was not significantly associated with fall risk. Among subjects with no CKD, median serum folic acid levels were 8.9 (6.7-11.4) ng/mL versus 9.1 (IQR, 7.0-11.5) in patients with fall risk and non-fall risk, respectively (p=0.261).

Patients with CKD/fall risk were compared with a matched non-CKD/fall risk cohort. The match was for age, sex, frailty status and Lawton Instrumental activity of daily living score. Except the difference for kidney function tests and serum potassium levels, only serum folic acid levels differed significantly across matched groups (Table 3). Patients with CKD/fall risk had a median folic acid of 6.9 (5.7-8.8) ng/mL while subjects with no CKD/fall risk had a median folic acid level of 9.4 (7.1-11.7). All geriatric assessment measures were comparable between patients with CKD/fall risk and patients with non-CKD/fall risk (supplementary material, Table S1).

Discussion

The present study demonstrated that a low serum folic acid level and frailty are independent risk factors for a high fall risk in elderly subjects with CKD. Although a low serum folic acid level in patients with CKD is not unexpected,[39] the observation that folic acid was the only significant difference apart from parameters of kidney function between groups of CKD/fall risk versus non-CKD/fall risk (matched for frailty status and instrumental activity of daily living) is interesting. Moreover, significances remained even after adjustments for many parameters some of which include the proposed risk factors for gait abnormalities in CKD (probable sarcopenia, cognitive impairment, malnutrition, frailty, comorbidities like diabetes and hypertension). Unlike the CKD cohort, serum folic acid levels did not differ in the non-CKD cohort among patients with a high fall risk versus others. In general, folic acid deficiency is mostly caused by dietary factors such as reduced consumption of green leafy vegetables.[40] In addition to altered metabolism of folic acid in patients with CKD, numerous metabolic alterations, drug exposures and systemic inflammation may pose particular risk for nutritional deficiencies via altered absorption from the gastrointestinal system in this specific population.[39] A review of dietary habits, drug exposures, and systemic evaluation may help determine the cause of deficiency in patients with CKD. Besides it's benefits on mobility functions, folic acid replacement has been shown to slow the CKD progression in patients with mild to moderate CKD and sufficient vitamin B12 levels.[41]

Similar to our results, the association between frailty and falling among subjects with CKD has been shown by other studies.[5,7] The most significant contribution on gait speed apparently comes from the frailty status arising the question whether gait speed may be a consequence of disability rather than a marker of risk of functional decline.[14] Vitamin D deficiency is a well-defined risk factor for fall,[42] and fall-related factors such as orthostatic hypotension,[43] and muscle weakness.[44] In our study, among the CKD cohort, a lower median vitamin D level was found in patients with a high fall risk. KDIGO suggests that in patients with CKD G3a-G5D, 25(OH)D (calcidiol) levels might be measured, and deficiency/insufficiency be corrected using treatment strategies recommended for the general population.[45] Patients with a high-fall risk may be a particular group that might benefit from correction of vitamin D deficiency/insufficiency.

Our paper is the first to demonstrate the possible association with serum folic acid and fall risk in patients with CKD. Effects of folic acid on gait speed may be via cognition,[46] and cardiovascular effects.[47] Folic acid is given concurrently with vitamin B12 as a means to reduce serum homocysteine levels and the associated risk of cardiovascular mortality.[47] The increase in serum levels of homocysteine may indeed cause vascular diseases which may lead to cognitive decline and stroke.[48] This is translated with increased risk of falls. Moreover, homocysteine itself damages the integrity of many structures of musculoskeletal system including collagen, elastin and proteoglycans, which is also associated with falls and fractures.[48] Indeed, studies have shown that low levels of folate with high levels of homocysteine are associated with physical and functional decline.[49,48] Folate replacement in conjunction with vitamin B12 did not reduce the risk of osteoporotic fracture in randomized controlled studies although a subgroup of patients with an age of >80 years had benefit.[50] However, despite a lack of effect on falls, Swart and colleagues observed a positive effect of the intervention on gait, as well as on physical performance among compliant persons >80 years with the administration of vitamin B12 and folic acid for 2 years.[51]

We recognize limitations of our study. Given the retrospective design, cause and effect can not be assumed. A lot of patients were excluded due to unavailable geriatric assessment tools. In addition, classification of patients as CKD versus non-CKD were performed based on a single estimated glomerular filtration rate value. Unavailability of several important tests which may be essential for the management of patients with CKD, such as serum bicarbonate is also a limitation of our paper. It is worth to note that evaluation of functional mobility tests in the same visit of laboratory measurements is an important strength of our paper.

In conclusion, CKD represents a significant risk factor for a higher risk of falls among elderly subjects, and a low serum folic acid level along with frailty represent an independent predictor of a high fall risk in elderly

patients with CKD. Our results should be confirmed with prospective studies and possible benefits of preventive measures against frailty and folic acid replacement should be tested.

Declarations

Funding. None

Conflicts of interest/Competing interests. None to declare.

Ethics approval. Our study was approved by the local ethics committee.

Informed consent. Informed consent was given by each participant or a legal guardian before participating in the study.

Availability of data and material. Not applicable.

Code availability. Not applicable.

Author contributions. Conceptualization and design: CH, RK, PS; acquisition of data: CH, PS analysis and interpretation: CH, LS, PS, RK, NV; Drafting the manuscript: CH; critical review and editing: RK, LS, NV, PS; Supervision: PS.

References

1. Tinetti ME, Kumar C (2010) The patient who falls: "It's always a trade-off". JAMA 303 (3):258-266. doi:10.1001/jama.2009.2024
2. Bohannon RW, Hull D, Palmeri D (1994) Muscle strength impairments and gait performance deficits in kidney transplantation candidates. Am J Kidney Dis 24 (3):480-485. doi:10.1016/s0272-6386(12)80905-x
3. Bowling CB, Bromfield SG, Colantonio LD, Gutierrez OM, Shimbo D, Reynolds K, Wright NC, Curtis JR, Judd SE, Franch H, Warnock DG, McClellan W, Muntner P (2016) Association of Reduced eGFR and Albuminuria with Serious Fall Injuries among Older Adults. Clin J Am Soc Nephrol 11 (7):1236-1243. doi:10.2215/CJN.11111015
4. Cook WL, Tomlinson G, Donaldson M, Markowitz SN, Naglie G, Sobolev B, Jassal SV (2006) Falls and fall-related injuries in older dialysis patients. Clin J Am Soc Nephrol 1 (6):1197-1204. doi:10.2215/CJN.01650506
5. Kutner NG, Zhang R, Huang Y, Wasse H (2014) Gait speed and hospitalization among ambulatory hemodialysis patients: USRDS special study data. World J Nephrol 3 (3):101-106. doi:10.5527/wjn.v3.i3.101
6. Li M, Tomlinson G, Naglie G, Cook WL, Jassal SV (2008) Geriatric comorbidities, such as falls, confer an independent mortality risk to elderly dialysis patients. Nephrol Dial Transplant 23 (4):1396-1400. doi:10.1093/ndt/gfm778
7. McAdams-DeMarco MA, Suresh S, Law A, Salter ML, Gimenez LF, Jaar BG, Walston JD, Segev DL (2013) Frailty and falls among adult patients undergoing chronic hemodialysis: a prospective cohort study. BMC Nephrol 14:224. doi:10.1186/1471-2369-14-224
8. Painter P, Marcus RL (2013) Assessing physical function and physical activity in patients with CKD. Clin J Am Soc Nephrol 8 (5):861-872. doi:10.2215/CJN.06590712
9. Plantinga LC, Patzer RE, Franch HA, Bowling CB (2017) Serious Fall Injuries Before and After Initiation of Hemodialysis Among Older ESRD Patients in the United States: A Retrospective Cohort Study. Am J Kidney Dis 70 (1):76-83. doi:10.1053/j.ajkd.2016.11.021

10. Tran J, Ayers E, Verghese J, Abramowitz MK (2019) Gait Abnormalities and the Risk of Falls in CKD. Clin J Am Soc Nephrol 14 (7):983-993. doi:10.2215/CJN.13871118
11. Zemp DD, Giannini O, Quadri P, de Bruin ED (2019) Gait characteristics of CKD patients: a systematic review. BMC Nephrol 20 (1):83. doi:10.1186/s12882-019-1270-9
12. Kutner NG, Bowling CB (2019) Targeting Fall Risk in CKD. Clin J Am Soc Nephrol 14 (7):965-966. doi:10.2215/CJN.06040519
13. Cummings SR, Studenski S, Ferrucci L (2014) A diagnosis of dismobility--giving mobility clinical visibility: a Mobility Working Group recommendation. JAMA 311 (20):2061-2062. doi:10.1001/jama.2014.3033
14. Roshanravan B (2015) Gait Speed in Patients With Kidney Failure Treated With Long-term Dialysis. Am J Kidney Dis 66 (2):190-192. doi:10.1053/j.ajkd.2015.05.007
15. Kittiskulnam P, Chertow GM, Carrero JJ, Delgado C, Kaysen GA, Johansen KL (2017) Sarcopenia and its individual criteria are associated, in part, with mortality among patients on hemodialysis. Kidney Int 92 (1):238-247. doi:10.1016/j.kint.2017.01.024
16. Greenwood SA, Lindup H, Taylor K, Koufaki P, Rush R, Macdougall IC, Mercer TH (2012) Evaluation of a pragmatic exercise rehabilitation programme in chronic kidney disease. Nephrol Dial Transplant 27 Suppl 3:iii126-134. doi:10.1093/ndt/gfs272
17. Heiwe S, Jacobson SH (2014) Exercise training in adults with CKD: a systematic review and meta-analysis. Am J Kidney Dis 64 (3):383-393. doi:10.1053/j.ajkd.2014.03.020
18. Kutner NG, Zhang R, Huang Y, Painter P (2015) Gait Speed and Mortality, Hospitalization, and Functional Status Change Among Hemodialysis Patients: A US Renal Data System Special Study. Am J Kidney Dis 66 (2):297-304. doi:10.1053/j.ajkd.2015.01.024
19. Rossi AP, Burris DD, Lucas FL, Crocker GA, Wasserman JC (2014) Effects of a renal rehabilitation exercise program in patients with CKD: a randomized, controlled trial. Clin J Am Soc Nephrol 9 (12):2052-2058. doi:10.2215/CJN.11791113
20. van Loon IN, Wouters TR, Boereboom FT, Bots ML, Verhaar MC, Hamaker ME (2016) The Relevance of Geriatric Impairments in Patients Starting Dialysis: A Systematic Review. Clin J Am Soc Nephrol 11 (7):1245-1259. doi:10.2215/CJN.06660615
21. Turkmen K, Kayikcioglu H, Ozbek O, Solak Y, Kayrak M, Samur C, Anil M, Zeki Tonbul H (2011) The relationship between epicardial adipose tissue and malnutrition, inflammation, atherosclerosis/calcification syndrome in ESRD patients. Clin J Am Soc Nephrol 6 (8):1920-1925. doi:10.2215/CJN.00890111
22. Tabue-Teguo M, Peres K, Simo N, Le Goff M, Perez Zepeda MU, Feart C, Dartigues JF, Amieva H, Cesari M (2020) Gait speed and body mass index: Results from the AMI study. PLoS One 15 (3):e0229979. doi:10.1371/journal.pone.0229979
23. Colbert LH, Visser M, Simonsick EM, Tracy RP, Newman AB, Kritchevsky SB, Pahor M, Taaffe DR, Brach J, Rubin S, Harris TB (2004) Physical activity, exercise, and inflammatory markers in older adults: findings from the Health, Aging and Body Composition Study. J Am Geriatr Soc 52 (7):1098-1104. doi:10.1111/j.1532-5415.2004.52307.x
24. Penninx BW, Kritchevsky SB, Newman AB, Nicklas BJ, Simonsick EM, Rubin S, Nevitt M, Visser M, Harris T, Pahor M (2004) Inflammatory markers and incident mobility limitation in the elderly. J Am Geriatr Soc 52 (7):1105-1113. doi:10.1111/j.1532-5415.2004.52308.x
25. Correia MA, Cucato GG, Lanza FC, Peixoto RAO, Zerati AE, Puech-Leao P, Wolosker N, Ritti-Dias RM (2019) Relationship between gait speed and physical function in patients with symptomatic peripheral artery disease. Clinics (Sao Paulo) 74:e1254. doi:10.6061/clinics/2019/e1254
26. Fried LF, Boudreau R, Lee JS, Chertow G, Kurella-Tamura M, Shlipak MG, Ding J, Sellmeyer D, Tylavsky FA, Simsonick E, Kritchevsky SB, Harris TB, Newman AB, Health A, Body Composition S (2007) Kidney function as a predictor of loss of lean mass in older adults: health, aging and body composition study. J Am Geriatr Soc 55 (10):1578-1584. doi:10.1111/j.1532-5415.2007.01398.x
27. Otobe Y, Hiraki K, Hotta C, Nishizawa H, Izawa KP, Taki Y, Imai N, Sakurada T, Shibagaki Y (2019) Mild cognitive impairment in older adults with pre-dialysis patients with chronic kidney disease:

Prevalence and association with physical function. Nephrology (Carlton) 24 (1):50-55. doi:10.1111/nep.13173
28. Shin S, Chung HR, Kistler BM, Fitschen PJ, Wilund KR, Sosnoff JJ (2013) Walking and talking in maintenance hemodialysis patients. Arch Phys Med Rehabil 94 (1):127-131. doi:10.1016/j.apmr.2012.07.015
29. Jin SH, Park YS, Park YH, Chang HJ, Kim SR (2017) Comparison of Gait Speed and Peripheral Nerve Function Between Chronic Kidney Disease Patients With and Without Diabetes. Ann Rehabil Med 41 (1):72-79. doi:10.5535/arm.2017.41.1.72
30. Shin S, Chung HR, Kistler BM, Fitschen PJ, Wilund KR, Sosnoff JJ (2014) Effect of muscle strength on gait in hemodialysis patients with and without diabetes. Int J Rehabil Res 37 (1):29-33. doi:10.1097/MRR.0b013e3283643d76
31. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, Ckd EPI (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150 (9):604-612. doi:10.7326/0003-4819-150-9-200905050-00006
32. Dokuzlar O, Koc Okudur S, Soysal P, Kocyigit SE, Yavuz I, Smith L, Ates Bulut E, Isik AT (2020) Factors that Increase Risk of Falling in Older Men according to Four Different Clinical Methods. Exp Aging Res 46 (1):83-92. doi:10.1080/0361073X.2019.1669284
33. Tinetti ME (1986) Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc 34 (2):119-126. doi:10.1111/j.1532-5415.1986.tb05480.x
34. Pasquetti P, Apicella L, Mangone G (2014) Pathogenesis and treatment of falls in elderly. Clin Cases Miner Bone Metab 11 (3):222-225
35. Unutmaz GD, Soysal P, Tuven B, Isik AT (2018) Costs of medication in older patients: before and after comprehensive geriatric assessment. Clin Interv Aging 13:607-613. doi:10.2147/CIA.S159966
36. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M, Zamboni M, Writing Group for the European Working Group on Sarcopenia in Older P, the Extended Group for E (2019) Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 48 (4):601. doi:10.1093/ageing/afz046
37. Dutoglu E, Soysal P, Smith L, Arik F, Kalan U, Kazancioglu RT, Isik AT (2019) Nocturia and its clinical implications in older women. Arch Gerontol Geriatr 85:103917. doi:10.1016/j.archger.2019.103917
38. Lanier JB, Mote MB, Clay EC (2011) Evaluation and management of orthostatic hypotension. Am Fam Physician 84 (5):527-536
39. Capelli I, Cianciolo G, Gasperoni L, Zappulo F, Tondolo F, Cappuccilli M, La Manna G (2019) Folic Acid and Vitamin B12 Administration in CKD, Why Not? Nutrients 11 (2). doi:10.3390/nu11020383
40. Allen LH (2008) Causes of vitamin B12 and folate deficiency. Food Nutr Bull 29 (2 Suppl):S20-34; discussion S35-27. doi:10.1177/15648265080292S105
41. Li Y, Spence JD, Wang X, Huo Y, Xu X, Qin X (2020) Effect of Vitamin B12 Levels on the Association Between Folic Acid Treatment and CKD Progression: A Post Hoc Analysis of a Folic Acid Interventional Trial. Am J Kidney Dis 75 (3):325-332. doi:10.1053/j.ajkd.2019.07.020
42. Bischoff-Ferrari HA, Bhasin S, Manson JE (2018) Preventing Fractures and Falls: A Limited Role for Calcium and Vitamin D Supplements? JAMA 319 (15):1552-1553. doi:10.1001/jama.2018.4023
43. Soysal P, Yay A, Isik AT (2014) Does vitamin D deficiency increase orthostatic hypotension risk in the elderly patients? Arch Gerontol Geriatr 59 (1):74-77. doi:10.1016/j.archger.2014.03.008
44. Boudville N, Inderjeeth C, Elder GJ, Glendenning P (2010) Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure. Clin Endocrinol (Oxf) 73 (3):299-304. doi:10.1111/j.1365-2265.2010.03821.x
45. Kidney Disease: Improving Global Outcomes CKDMBDUWG (2017) KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011) 7 (1):1-59. doi:10.1016/j.kisu.2017.04.001
46. Doets EL, Ueland PM, Tell GS, Vollset SE, Nygard OK, Van't Veer P, de Groot LC, Nurk E, Refsum H, Smith AD, Eussen SJ (2014) Interactions between plasma concentrations of folate and markers of

vitamin B(12) status with cognitive performance in elderly people not exposed to folic acid fortification: the Hordaland Health Study. Br J Nutr 111 (6):1085-1095. doi:10.1017/S000711451300336X
47. Li Y, Huang T, Zheng Y, Muka T, Troup J, Hu FB (2016) Folic Acid Supplementation and the Risk of Cardiovascular Diseases: A Meta-Analysis of Randomized Controlled Trials. J Am Heart Assoc 5 (8). doi:10.1161/JAHA.116.003768
48. Wee AK (2016) Serum folate predicts muscle strength: a pilot cross-sectional study of the association between serum vitamin levels and muscle strength and gait measures in patients >65 years old with diabetes mellitus in a primary care setting. Nutr J 15 (1):89. doi:10.1186/s12937-016-0208-3
49. Ng TP, Aung KC, Feng L, Scherer SC, Yap KB (2012) Homocysteine, folate, vitamin B-12, and physical function in older adults: cross-sectional findings from the Singapore Longitudinal Ageing Study. Am J Clin Nutr 96 (6):1362-1368. doi:10.3945/ajcn.112.035741
50. van Wijngaarden JP, Swart KM, Enneman AW, Dhonukshe-Rutten RA, van Dijk SC, Ham AC, Brouwer-Brolsma EM, van der Zwaluw NL, Sohl E, van Meurs JB, Zillikens MC, van Schoor NM, van der Velde N, Brug J, Uitterlinden AG, Lips P, de Groot LC (2014) Effect of daily vitamin B-12 and folic acid supplementation on fracture incidence in elderly individuals with an elevated plasma homocysteine concentration: B-PROOF, a randomized controlled trial. Am J Clin Nutr 100 (6):1578-1586. doi:10.3945/ajcn.114.090043
51. Swart KM, Ham AC, van Wijngaarden JP, Enneman AW, van Dijk SC, Sohl E, Brouwer-Brolsma EM, van der Zwaluw NL, Zillikens MC, Dhonukshe-Rutten RA, van der Velde N, Brug J, Uitterlinden AG, de Groot LC, Lips P, van Schoor NM (2016) A Randomized Controlled Trial to Examine the Effect of 2-Year Vitamin B12 and Folic Acid Supplementation on Physical Performance, Strength, and Falling: Additional Findings from the B-PROOF Study. Calcif Tissue Int 98 (1):18-27. doi:10.1007/s00223-015-0059-5

Table 1

Independent predictors of risk of falling based on different methods

Parameters*			
	Odds ratio	Confidence interval, 95%	P-value
Age, per year	-**	-	-
Female sex	-	-	-
HbA1-c > 9.0%	3.25	1.29-8.20	0.013
CKD	2.59	1.19-5.66	0.017
Frailty	11.26	5.09-24.91	<0.001
Lawton-IADL	0.88	0.82-0.95	0.001
OH	-	-	-
Nocturia	-	-	-

*Age, sex and all parameters significantly associated with an abnormal TUG test result in univariate analysis were included in multivariable models.**Empty blanks denote non-significant results for the corresponding parameter in multivariate models. CKD: chronic kidney disease. DM: Diabetes mellitus. IADL: instrumental activity of daily living. OH: orthostatic hypotension.

Table 2

Demographic and clinical characteristics of patients with chronic kidney disease based on timed up and go test.

	The CKD cohort (n=205)	CKD/Non-fall risk (n=97)	CKD/Fall risk (n=108)	p-value
Age, years	77 (72-83)	75 (70-80)	78 (73-84)	**0.001**
Female sex	68.3%	64.9%	71.3%	0.329
Years of education	3 (0-5)	4 (0-5)	0 (0-5)	**0.023**
Body-mass index, kg/m^2	30.8 (26.4-35.3)	31.2 (27.8-34.3)	30.8 (26.4-37.4)	0.691
Hypertension	78.3%	77.9%	78.7%	0.889
Diabetes mellitus	41.4%	45.3%	38.0%	0.292
Hemoglobin, g/dL	13.0 (11.8-14.2)	13.3 (11.9-14.4)	12.9 (11.5 -14.0)	0.137
eGFR, ml/min/1.73 m^2	49 (40-56)	48 (38-56)	50 (42-57)	0.353
Vitamin D, ng/mL	10 (9-22)	13 (9-24)	9 (9-19)	**0.046**
Vitamin B12, pg/mL	266 (183-389)	297 (191-373)	251 (168-411)	0.351
Folic acid, ng/mL	7.3 (5.6-9.7)	8.1 (6.0-10.3)	6.7 (5.4-9.1)	**0.013**
Geriatric Assessments				
Probable Sarcopenia	43.5%	27.6%	57.6%	**<0.001**
Tinetti Total	25 (19-28)	28 (27-28)	21 (15-25)	**<0.001**
Malnutrition	7.4%	3.3%	11.1%	**<0.001**
Frailty	41.6%	8.2%	73.4%	**<0.001**
Depression	40.6%	29.2%	51.6%	**0.002**
MMSE	24 (21-26)	25 (23-27)	23 (19-25)	**<0.001**
Lawton IADL	17 (10-20)	20 (18-22)	13 (6-17)	**<0.001**
Bartel BADL	90 (80-95)	93 (88-100)	85 (70-90)	**<0.001**
Polypharmacy	45.7%	46.7%	44.8%	0.781
Orthostatic hypotension	38.6%	39.1%	35.9%	0.880
Urinary incontinence	51.7%	47.4%	55.6%	0.245
Nocturia	71.7%	69.1%	74.1%	0.365
Recurrent falls	31.2%	21.6%	39.8%	**0.005**

Variables are presented as percentage or median (interquartile range, 25%-75%). BADL: basic activity of daily living. eGFR: estimated glomerular filtration rate. IADL: instrumental activity of daily living. MMSE: mini-mental state examination. TUG: timed up and go test.

Table 3

Comparisons between patients with chronic kidney disease (CKD) with fall risk versus non-CKD fall risk.

Variables	Non-CKD fall risk (n=62)	CKD fall risk (n=62)	p-value
Age, years	79 (74-84)	79 (73-85)	0.543
Female sex	87.1%	88.7%	0.783
Years of education	0 (0-3)	0 (0-4)	0.530
Hypertension	80.6%	80.6%	1.000
Diabetes mellitus	40.3%	35.5%	0.579
HbA1-c of >9.0%	19.6%	12.5%	0.337
Ischemic heart disease	12.9%	16.1%	0.610
Cerebrovascular disease	4.8%	9.7%	0.299
Charlson comorbidity index	1 (0-2)	1 (0-2)	0.702
ACEI/ARB	63.3%	70.0%	0.439
Diuretics	55.0%	60.0%	0.580
Calcium channel blockers	23.7%	25.0%	0.872
Beta blockers	27.6%	33.3%	0.498
Body-mass index, kg/m^2	32.1 (27.2-35.5)	30.8 (27.1-39.3)	0.552
SCr, mg/dL	0.70 (0.63-0.81)	1.07 (0.97-1.25)	**<0.001**
eGFR, mL/min/1.73 m^2	80 (69-90)	51 (43-57)	**<0.001**
Hemoglobin, g/dL	13.2 (12.6-14.4)	13.0 (12.0-14.2)	0.147
Sodium, mEq/L	139 (137-141)	139 (137-141)	0.655
Potassium, mEq/L	4.3 (4.1-4.6)	4.7 (4.5-5.0)	**<0.001**
Calcium, mg/dL	9.4 (9.1-9.6)	9.4 (9.1-9.6)	0.675
Phosphorus, mg/dL	3.4 (3.1-3.6)	3.5 (3.1-3.8)	0.467
Magnesium, mEq/L	2.0 (1.8-2.1)	2.0 (1.8-2.2)	0.493
Vitamin D, ng/mL	9 (9-17)	9 (9-21)	0.724
Folic acid, ng/mL	9.4 (7.1-11.7)	6.9 (5.7-8.8)	**0.001**
Vitamin B12, pg/mL	215 (158-311)	223 (149-340)	0.816

Variables are presented as percentage or median (interquartile range, 25%-75%). ACE/ARB: Angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers. eGFR: estimated glomerular filtration rate. SCr: serum creatinine.