

# Association between serum vitamin B12 level and frailty in older adults

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## ABSTRACT

**OBJECTIVE:** Frailty is associated with recurrent falls, fractures, limitation of daily living activities, cognitive impairment, increase in hospitalization, placement in nursing home, and mortality rate in older adults. Although malnutrition is one of the most important etiological factors, role of micronutrients is unclear. The aim of this study was to investigate association between frailty and vitamin B12, which has been demonstrated to be related to numerous geriatric syndromes.

**METHODS:** Total of 335 patients who presented at geriatric outpatient clinic and underwent comprehensive geriatric assessment were included in this study. All patients were evaluated with both Fatigue, Resistance, Ambulation, Illnesses, and Loss of Weight (FRAIL) scale and Fried criteria for frailty. Vitamin B12 deficiency was defined as serum vitamin B12 level of less than 400 pg/mL.

**RESULTS:** In total of 335 patients, 88 (26.3%) were assessed as frail, 156 (46.6%) were prefrail, and 91 (27.2%) were robust. When the 3 groups were compared, it was found that patients in frail group had highest average age and lowest education level ( $p < 0.001$ ) and that complaints of urinary incontinence, balance disorders, recurrent falls, sleep disorders, amnesia, chronic pain, and constipation were more frequent in this group ( $p < 0.05$ ). Albumin and 25-hydroxy vitamin D levels decreased as frailty level increased ( $p < 0.05$ ), but no association between vitamin B12 levels and frailty was found. Patients were divided into 2 groups: vitamin B12 level above and below 400 pg/mL. Groups were then compared in terms of subparameters of both the FRAIL and Fried criteria, and no significant difference between groups was found ( $p > 0.05$ ).

**CONCLUSION:** Results of this study determined no association between vitamin B12 level and frailty in geriatric population; however, longitudinal studies are needed to clarify relationship.

*Keywords:* Frailty; micronutrient; older adult; vitamin B12.

Frailty is a geriatric syndrome, defined as medical syndrome with multiple causes and contributors that is characterized by diminished strength,

endurance, and reduced physiological function that increases an individual's vulnerability for developing increased dependency and/or death [1]. Worldwide



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prevalence of frailty and prefrailty among geriatric population is 13.9% and 48%, respectively [2]. Frailty is associated with falls from a height, fractures, restriction of daily living activities, decrease in mobility, loss of cognitive function, increase in frequency of hospitalization, placement in nursing homes, and mortality [3]. Therefore, recognition of factors causing frailty, identification of prefrail adults, and elimination of risk factors are very important issues.

Numerous interrelated factors contribute to etiopathogenesis of frailty syndrome. Stimulation of hypothalamus-pituitary-adrenal axis with aging, inflammatory and oxidative stress pathways activated by existing comorbid diseases, anemia, senile anorexia and related deficient calorie and protein intake, in addition to decreased level of gonadotropin and insulin-like growth factor 1 have been evaluated in association with frailty [2, 4, 5]. Although factors leading to development of frailty affect each other in a vicious cycle, one of the basic causes seems to be malnutrition [6]. Significant quantity of evidence is available regarding relationship between insufficient protein and calorie intake with sarcopenia and frailty [7]. However, correlation between micronutrient deficiency and frailty is not clear.

Incidence of vitamin B12 deficiency increases with age [8]. Vitamin B12 deficiency causes neuropathy, cognitive impairment, balance and gait disorders, recurrent falls, depression, orthostatic hypotension, and elevated homocysteine levels, and associated increase in cardiovascular risk [9, 10]. Very few studies have been performed to examine whether vitamin B12 deficiency, which is known to be related to many risk factors associated with frailty, has any direct effect on development of frailty [9]. The objective of this study was to investigate correlation between vitamin B12 and frailty.

## MATERIALS AND METHODS

### Patients

Total of 335 patients who presented at geriatric polyclinics of a university hospital, met study inclusion criteria, and were treated between August 30 and December 1, 2016 on an inpatient basis, and provided written, informed consent were included

in this cross-sectional study. The study was initiated after receiving approval of the local ethics committee (date: March 10, 2016; decision no: 2016/07–05).

### Exclusion criteria

Patients who were unable to walk due to severe osteoarthritis or neuromuscular disease, immobile patients, patients presenting with delirium tremens during evaluation process, patients who had history of acute cerebrovascular events, gastrointestinal bleeding, sepsis, acute renal failure, acute coronary syndrome, acute hepatic failure, acute respiratory failure, or hospitalization in intensive care unit that might contribute to deterioration in health during follow-up period were excluded from the study. In addition, patients with mental disorders caused by substance or alcohol intoxication, withdrawal, or abuse; cases with vitamin B12 deficiency and concurrent malignancy or similar disease that might result in frailty; patients younger than 60 years of age; and patients who did not have detailed geriatric assessment performed were excluded from the study.

All eligible patients who applied to geriatric polyclinic for any reason were included in the study.

### Patient characteristics

Details of age, gender, education level, type of residence (home, nursing home), marital status, concomitant systemic diseases, and medications used were recorded. Patients were asked if they had fallen from a height within previous year. In addition, patients were asked if they had constipation, urinary incontinence, balance or gait difficulties, nocturia, sleep disorders, or pain. History of hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, peripheral artery disease, chronic obstructive pulmonary disease, thyroid disease, osteoporosis, cerebrovascular disease, dementia, hyperlipidemia, depression, sarcopenia, dynapenia, cataracts, or hearing loss was examined.

### Detailed geriatric evaluation [11]

The following scales, for which validation and reliability studies of Turkish version have been performed, were used for detailed neurocognitive

evaluation of the patients: Montreal Cognitive Assessment Scale (MOCA), Mini-Mental State Examination (MMSE) Cognitive State Test (COST) [12], Geriatric Depression Scale (GDS), Instrumental Activities of Daily Living (IADL), Basic Activities of Daily Living (BADL), Tinetti Performance Oriented Mobility Assessment (POMA) and Mini-Nutritional Assessment (MNA) were applied [13].

### Laboratory test results

Laboratory tests were performed to determine biochemical, metabolic, and nutritional state of the patients. Data related to complete blood count, fasting blood glucose, renal and hepatic function, cholesterol, albumin, thyroid stimulating hormone, HbA1c, vitamin D, vitamin B12, and folic acid were obtained. All biochemical tests were performed using Diagnostic Modular System autoanalyzer (E170 and P800; Roche Diagnostics, Basel, Switzerland). Serum 25-hydroxy-vitamin D [25(OH)D] level was measured using radioimmunoassay technique. Serum vitamin B12 level below 400 pg/mL was accepted as vitamin B12 deficiency [8].

### Diagnosis of frailty

To determine frailty, the patients were evaluated using both FRAIL scale and Fried criteria. FRAIL scale were developed by the International Academy of Nutrition and Aging (IANA) in 2008. Scale evaluates the following parameters: fatigue, resistance (inability to climb a flight of stairs), ambulation (difficulty walking more than 1 block), illness ( $\geq 5$  comorbid diseases), and loss of weight ( $\geq 5\%$  of actual weight) [14]. Fried criteria to identify frail individuals were developed by Fried et al. in 2001. Criteria are: shrinking (unintentional weight loss of 4.5 kg or  $>5\%$  of baseline body weight), weakness (20% decrease in grip strength, adjusted for gender and body mass index), poor endurance (response to questions about essential activities), slowness (4 m walk  $>6-7$  seconds, 20% slower than baseline value), low activity (weekly calories burned: men,  $<383$  Kcal; women,  $<270$  Kcal) [4].

In both scales, 1 point is assigned for each criterion: 0 points, not frail; 1-2 points, prefrail;  $\geq 3$  points, frail. Individuals who scored 0 points on FRAIL and Fried criteria scales were accepted as control group.

### Statistical analysis

To achieve 95% confidence level and 5% margin of error, sample size of 164 patients was required. Data were analyzed using SPSS for Windows, Version 15.0 (SPSS, Inc., Chicago, IL, USA) software. For descriptive statistics, measurable variables were evaluated using Kolmogorov-Smirnov Goodness-of-Fit test for normality of distribution. Variables with normal distribution were expressed as mean $\pm$ SD, and variables with non-normal distribution were presented as median (minimum-maximum). Numerical variables were displayed as number of cases, and percent distribution. When only 2 groups were considered, significance of intergroup difference between means was examined using parametric t-tests, while significance of difference between medians was analyzed using nonparametric Mann-Whitney U test. When more than 2 groups were considered, significance of differences between means was evaluated using parametric analysis of variance test, while significance between median values was investigated using non parametric Kruskal-Wallis test. Numerical variables were evaluated using Pearson chi-square or Fisher's exact test.  $P < 0.05$  was considered statistically significant.

## RESULTS

Demographic characteristics of patients based on frailty status are summarized in Table 1. Total of 335 patients were included in the study: 88 (26.3%) frail patients, 156 (46.6%) who were prefrail, and 91 (27.2%) controls. Female patients were more numerous in the frailty group. When compared with control group, frail and prefrail patients had lower education level ( $p < 0.001$ ). Frailty was less frequently seen in married individuals and those living with partner, and more common among those living with caregiver ( $p < 0.001$ ) (Table 1).

Frail and prefrail patients were compared with

**TABLE 1.** Comparison of patient characteristics based on frailty status

	Control group n=91	Prefrail group n=156	Frail group n=88	p
Age (years)	70.33	72.64	77.50	<b>&lt;0.001</b>
Gender (female/male) (%)	56.0/44.0	66.0/34.0	78.4/21.6	<b>0.006</b>
Level of education (%)	27/39.4/33.7%	51.3/31.6/17.1%	50.2/31.9/18.0%	<b>&lt;0.001</b>
0–5/6–11/>11years				
Marital status (%)	2.2/70.0/5.6/22.2%	1.9/63.6/6.5/27.9%	0.0/41.9/2.3/55.8%	<b>&lt;0.001</b>
(Single/married /divorced/widowed)				
Living environment (%)	17.6/61.5/16.5/0.0/4.4	16.9/60.4/18.2/0.6/3.9	15.1/36.0/44.2/1.2/3.5	<b>0.001</b>
(alone/with spouse/with relative/ with caregiver/in nursing home)				
Charlson Comorbidity Index	0.63	1.10	1.46	<b>&lt;0.001</b>
Comorbid diseases (%)				
Hypertension	46.2	68.6	69.3	<b>0.001</b>
Coronary artery disease	8.8	16.7	18.2	0.149
Congestive heart failure	3.3	4.5	9.1	0.182
Peripheral artery disease	2.2	4.5	10.2	<b>0.048</b>
Chronic obstructive pulmonary disease	2.2	9.6	11.4	<b>0.049</b>
Thyroid disease	14.3	19.9	25.0	0.197
Osteoporosis	14.3	16.1	33.0	<b>0.002</b>
Cerebrovascular disease	4.4	5.8	10.2	0.249
Dementia	8.8	13.0	29.4	<b>&lt;0.001</b>
Diabetes mellitus	15.4	31.4	29.5	<b>0.017</b>
Hyperlipidemia	23.1	26.3	21.6	0.684
Depression	24.2	35.1	50.0	<b>0.001</b>
Sarcopenia	0.0	30.8	40.9	<b>&lt;0.001</b>
Laboratory parameters				
Glucose (mg/dL)	102.16	107.24	105.37	0.936
Albumin (g/dL)	4.27	4.20	4.04	<b>&lt;0.001</b>
Folic acid (ng/dL)	8.86	8.68	8.11	0.389
Vitamin B12 (pg/mL)	408.28	429.78	402.07	0.452
Vitamin D (ng/mL)	27.96	25.90	22.44	<b>0.002</b>
TSH (IU/mL)	1.78	1.52	1.40	0.086
Geriatric assessments				
MMSE	27.51	25.49	21.75	<b>&lt;0.001</b>
COST	26.50	25.33	18.15	<b>0.038</b>
MOCA	24.54	23.69	21.63	0.060
Geriatric Depression Scale	1.19	2.60	5.56	<b>&lt;0.001</b>
Tinetti-balance	15.85	15.13	12.07	<b>&lt;0.001</b>
Tinetti-gait	11.95	11.33	9.31	<b>&lt;0.001</b>
Tinetti-total	27.79	26.46	21.38	<b>&lt;0.001</b>
Timed Get Up and Go Test	9.22	11.37	20.05	<b>&lt;0.001</b>
BADL	98.23	94.75	82.56	<b>&lt;0.001</b>
IADL	21.32	19.29	13.34	<b>&lt;0.001</b>
Mini-Nutritional Assessment	13.43	12.89	11.84	<b>&lt;0.001</b>

COST: Cognitive State Test; BADL: Basic Activities of Daily Living; IADL: Instrumental Activities of Daily Living; MMSE: Mini-Mental State Examination; MOCA: Montreal Cognitive Assessment Scale; TSH: Thyroid stimulating hormone.

**TABLE 2.** Comparison of FRAIL and Fried criteria based on vitamin B12 level

	Vitamin B12 <400 pg/mL n=149	Vitamin B12 >400 pg/mL n=186	p
Fatigue (FRAIL)*	44.3	44.0	0.960
Resistance*	31.4	35.4	0.455
Ambulation*	17.1	24.0	0.137
Loss of weight*	9.0	9.0	0.990
Illness*	0.7	1.7	0.489
Poor endurance (Fried)**	35.4	35.4	0.997
Shrinking**	9.0	9.0	0.990
Weakness**	58.0	54.5	0.524
Slowness**	25.7	33.1	0.146
Low activity**	24.3	29.2	0.324
FRAIL			
Robust/Prefrail/Frail	71.6/16.0/12.5	65.2/16.9/17.9	0.536
Fried			
Robust/Prefrail/Frail	26.6/49.0/24.5	27.5/43.8/28.7	0.608

FRAIL: Fatigue, resistance, ambulation, illnesses, and loss of weight; \*FRAIL criteria; \*\*Fried criteria.

healthy individuals regarding complaints, and it was observed that urinary incontinence, balance disorders, recurrent falls, amnesia, chronic pain, and constipation increased with greater frailty ( $p < 0.05$ ). Comorbidities, such as hypertension, chronic obstructive pulmonary disease, osteoporosis, diabetes, dementia, depression, sarcopenia, and dynapenia, were also more frequently seen in frail and prefrail individuals ( $p < 0.05$ ). The 3 groups were compared with respect to detailed geriatric evaluation parameters, and lower MMSE, COST, MNA, POMA balance and gait test, BADL score and higher Timed Get Up and Go test and GDS scores were detected in the frailty group ( $p < 0.05$ ). Level of albumin and 25(OH)D decreased as severity of frailty increased ( $p < 0.05$ ); however, serum vitamin B12 level did not differ between groups ( $p > 0.05$ ). When groups were adjusted for age and education level, all differences persisted, with exception of MNA ( $p < 0.05$ ) (Table 2).

No significant difference was seen in subparameters of FRAIL and Fried criteria between patient groups divided based on vitamin B12 level above or below 400 pg/mL or state of frailty ( $p > 0.05$ ) (Table 2).

## DISCUSSION

This study was examination of correlation between serum vitamin B12 level and frailty in geriatric cases and it was determined that vitamin B12 level could not be associated with frailty.

In our study, frail and prefrail patients constituted 26.3% and 46.6% of the patient population, respectively. In meta-analysis of 23,910 patients performed by Soysal et al., researchers found incidence of frailty and prefrailty among the elderly of 13.9% and 48.9%, respectively [2]; However, Morley et al. indicated that frailty was seen at average rate of 9.9% among individuals older than 65 years [1]. Higher rate of frailty in our patients might be related to advanced age of our patients (median age: 77.5 years), and study population consists of patients admitted to hospital for any reason, not whole community.

Education level of frail and prefrail patients was lower than that of control group in the present study. In the United Kingdom, twins were evaluated for frailty, and it was determined that even between twins, lower education level increased predisposition to frailty [15, 16]. Predisposition to frailty may be related to

influence of education level on bad habits [17], lower income level, decreased self-care, and aggravated cognitive deficiency. Consistent with literature findings, greater number of comorbidities (evaluated using Charlson Comorbidity Index) was detected among frail and prefrail individuals. Incidence of hypertension, diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, and sarcopenia was greater in frail and prefrail individuals [4, 18–20].

Frail, prefrail, and healthy individuals were compared in terms of predominant complaints and geriatric syndromes, and it was observed that balance disorder, depression, dementia, recurrent falls, sleep disorder, amnesia, and chronic pain increased with the severity of frailty [4, 21–23]. It is very important to detect risk factors that trigger development of frailty, as it could lead to greater number of complaints and complications. Relationship between vitamin B12 deficiency frequently seen in elderly population and associated with geriatric syndromes, such as cognitive deficiency, balance and gait disorders, recurrent falls, depression, and orthostatic hypotension, has been thought to be correlated with frailty [8–10]. However, comparison of vitamin B12 deficiency with subparameters of both FRAIL and Fried criteria and state of frailty yielded no intergroup difference. In the literature, very few studies have been conducted to investigate relationship between vitamin B12 level and frailty, and results are mixed. In a study performed in 2006, no correlation between vitamin B12 level and frailty was detected. As was the case with our study, vitamin D deficiency was reported to be possible etiological factor for frailty [9]. However, in another study conducted in 2010, correlation was demonstrated between different genetic variations affecting vitamin B12 transport mechanism and frailty. Authors hypothesized that vitamin B12 deficiency might induce development of frailty through mechanisms of increasing level of homocysteine and causing cellular damage via hypomethylation of DNA and RNA, leading to decrease in energy metabolism and possibly triggering activation of inflammatory pathways. However, in that study, probable correlation between genetic factors playing role in vitamin B12 metabolism rather than serum vitamin B12 levels was emphasized [24].

Strong points of our study include prospective design, adequate number of samples, and detailed evaluation of all patients. Limitations of the study include cross-sectional design, and evaluation of vitamin B12 deficiency based only on serum vitamin B12 level. Furthermore, methylmalonic acid and homocysteine levels were not measured, and patients with vitamin B12 replacement were included in the study. In addition, cognitive frailty was not investigated.

In conclusion, in this cross-sectional analysis performed with large study population, correlation between frailty, which is frequently seen in geriatric cases with multiple adverse outcomes, and serum vitamin B12 level was not detected. Studies have concentrated on frailty for the last 20 years; however, further insight into correlation requires longitudinal studies to be performed in the future.

**Conflict of Interest:** None declared.

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**Authorship contributions:** Concept – P.S., A.T.I.; Design – P.S., A.T.I.; Materials – P.S., A.T.I.; Data collection &/or processing – O.D.; Analysis and/or interpretation – P.S., A.T.I.; Literature search – O.D.; Writing – P.S., A.T.I., O.D.

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