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Vitamin B12 deficiency might be related to sarcopenia in older adults

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ABSTRACT

Sarcopenia and dynapenia are related to repeated falls, mobility restriction, depression, frailty, increased mortality and morbidity. The aim of this study is to evaluate the relationship between vitamin B12 deficiency and sarcopenia in older adults. 403 patients, who attended to outpatient clinic and underwent comprehensive geriatric assessment, were included study. All cases' skeletal muscle mass (SMM), walking speed and hand grip strength were recorded by bioimpedance, 4 meter walking test and hand dynamometer respectively. The diagnosis of sarcopenia was defined according to the criteria of the European Working Group on Sarcopenia in Older People. Sarcopenia was accepted low SMM with low handgrip strength or low physical performance. Dynapenia was defined as handgrip strength <30 kg (men) and <20 kg (women). The prevalence of sarcopenia and dynapenia was 24.8% and 32.0%, respectively. In the patients with sarcopenia, mean age, osteoporosis and frailty were higher, and MMSE, and instrumental ADL scores were lower than the patients without sarcopenia ($p < 0.05$). The frequency of sarcopenia and dynapenia were 31.6% and 35.4%, respectively, in patients with vitamin B12 levels <400 pg/mL. In addition lean body mass, total skeletal mass and skeletal muscle mass index were lower in the patients with vitamin B12 levels <400 pg/mL compared to higher than 400 pg/mL ($p < 0.05$). Sarcopenia, which results in lots of negative clinical outcomes in older adults, might be related to vitamin B12 deficiency. Therefore, these patients should be periodically examined for vitamin B12 deficiency due to the potential negative clinical outcomes such as sarcopenia in older adults.

1. Introduction

Sarcopenia and dynapenia are the clinical conditions that are quite common in older adults, and related with falls, bone fractures, osteoporosis, depression, decreased physical performance, disability and increased mortality (Visser and Schaap, 2011; Tarantino et al., 2013; Morley, 2016; Hsu et al., 2014). Sarcopenia (Morley et al., 2001) which is characterized by low muscle mass, muscle strength and performance, is a geriatric syndrome often mentioned in the last two decades, while dynapenia is characterized by reduction in muscle strength only, without loss of muscle mass and functionality (Cruz-Jentoft et al., 2010). Playing an important role in etiopathogenesis of both sarcopenia and dynapenia, the decline of the anabolic hormonal stimulation (IGF-1, estrogen, testosterone), and the induction of catabolism because of inflammatory cytokines (TNF-α, IL-6) which are followed by an increase in fatty tissue and fibrosis between muscle fibers, oxidative stress and degeneration in the neuromuscular component, result in a decrease in muscle mass (Dhillon and Hasni, 2017).

The most blamed factors for changes in muscle mass and quality are malnutrition and sedentary lifestyle (Boirie, 2009). Sedentary behavior, as one of the most important contributor to the muscle mass reduction, is investigated in many studies. Many biomarkers are wanted to bring into connection with physical inactivity (Wirth et al., 2017). Besides, the relationship between the development of alterations in the muscle tissue, and vitamin D and vitamin B12 intake has not still been clearly established; nevertheless, it was reported that low vitamin D levels are associated with increased fall risk and nursing home placement by affecting appendix muscle mass, muscle strength as well as muscle mass quality (Visser et al., 2003; Lappe and Binkley, 2015). Furthermore, it was also reported that the vitamin B12 deficiency plays an indirect role in the process by increasing homocysteine levels, leading to a decrease in muscle strength and walking speed, or increasing the risk of fracture and postural instability (Mithal et al., 2013; Sato et al., 2005). In the literature only a few cross-sectional studies investigate vitamin B12 status and sarcopenia linkage (Wee, 2016; Verlaan et al., 2015). The data about vitamin B12 is conflicted. Although, the relationship between vitamin B12 deficiency and many geriatric syndromes has

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been demonstrated, it's not reported in detail between vitamin B12 deficiency, and sarcopenia and dynapenia (Soysal et al., 2013). Therefore, the aim of this study is to evaluate the relationship between vitamin B12 deficiency, and sarcopenia in older adults.

2. Materials and methods

Patients: a total of 403 elderly patients, who admitted to the outpatient clinic and underwent comprehensive geriatric assessment between September 2016–January 2017, were included in this prospective study. The investigation was conformed to the Declaration of Helsinki and approved by the local ethics committee.

2.1. Exclusion criteria as follows

- Patients with severe osteoarthritis or neuromuscular disease, which causes obstacle to walking and immobile patients
- Patients who have a history of severe illness that may impair general health status, such as acute cerebrovascular event, gastrointestinal bleeding, sepsis, acute renal failure, acute coronary syndrome, acute liver failure, acute respiratory failure
- Patients with alcohol and substance abuse
- Patients with pacemaker (because of contraindication to electrical bioimpedance)
- Those with malignancy and similar diseases because they can have both vitamin B12 deficiency and simultaneous sarcopenia
- Patients under 60 years of age

All patients who applied to the geriatric clinic for any reason and who did not have exclusion criteria were included in this study.

2.2. Patients' characteristics

Patients' age, gender, education level, accompanying systemic diseases, numbers of drugs used were recorded. In the admission they were asked whether they had fallen in the previous year. History of hypertension, coronary artery disease, congestive heart failure, diabetes mellitus, hyperlipidemia, peripheral arterial disease, chronic obstructive pulmonary disease, osteoporosis, thyroid disease, cerebrovascular disease, determined by patients' self report. Dementia, and depression were diagnosed according to Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) criteria.

2.3. Comprehensive Geriatric Assessment

All the patients were underwent Comprehensive Geriatric Assessment (Soysal et al., 2014) including Montreal Cognitive Assessment Scale (MOCA) (Selekler et al., 2010), Mini Mental State Examination (MMSE) (Gungen et al., 2002), Cognitive State Test (COST) (Babacan-Yildiz et al., 2013), Geriatric Depression Scale (GDS) (Ertan and Eker, 2000) for neurocognitive evaluation, Basic and Instrumental Activities of Daily Living (BADL, IADL) (Lawton and Brody, 1969) for functionality evaluation, Tinetti Performance-Oriented Assessment of Mobility (POMA) (Tinetti, 1986) for mobility evaluation, Mini Nutritional Assessment (MNA) (Guigoz, 2006) for nutritional evaluation. The frailty was evaluated by Fried physical frailty scale (Fried et al., 2001) and FRAIL frailty index (Abellan van Kan et al., 2008).

2.4. Laboratory findings

Laboratory tests, such as renal and liver functions, fasting blood glucose, hemogram, TSH, HbA1c, cholesterol levels, CRP-sedimentation, vitamin D, vitamin B12 and folic acid levels were performed to evaluate the biochemical, metabolic and nutritional status of the patients, all of which were obtained with the auto-analyzer diagnostic modular system (Roche E170 and P-800). Serum 25-hydroxy D vitamin [25 (OH) D] was measured by radioimmunoassay. Serum vitamin B12 level was considered to be deficient when it was below 400 pg/mL (Bozoglu et al., 2010).

2.5. Diagnosis of sarcopenia and dynapenia

For the evaluation of walking speed, muscle strength and muscle mass in patients, 4-meter walking test, handgrip test and bioimpedance were performed for each patient, respectively. Handgrip test was measured by JAMAR branded hand dynamometer, and bioimpedance was established by TANITA (MC-780U Multi Frequency Segmental Body Composition). We accepted slow walking speed <0.8 m/s, low hand grip power in women <20 kg, in males <30 kg (Fried et al., 2001). Based on muscle mass bioimpedance values, Skeletal muscle (kg) = $(\text{height}^2 / R \times 0.401) + (\text{sex} \times 3.825) + (\text{age x} - 0.071) + 5.102$ is formulated (Janssen et al., 2000). Values in terms of Resistance (R) 50 Hz hand-leg (body), length in centimeters, female gender 0, male gender 1, age in years are accepted and replaced in formula. The muscle mass index (SMI = muscle mass / height^2) was calculated by dividing the muscle mass in kg by length in square meter which was obtained to prevent the muscle mass from varying according to the height. SMI was regarded as low muscle mass <8.87 kg/m^2 for males and <6.42 kg/m^2 for females (Cruz-Jentoft et al., 2010).

Decreased muscular strength and/or walking speed together with decreased muscle mass were evaluated as sarcopenia. Without any decrease in muscle mass, decreased muscle strength was defined as dynapenia (Cruz-Jentoft et al., 2010).

2.6. Study size

According to Santilli V et al. article in 2014, when the average frequency of sarcopenia in geriatric cases was accepted as 14%, it was decided to include at least 114 patients at the level of 3% acceptable error and 95% confidence.

2.7. Statistical analyses

Analysis of the data was done in SPSS for Windows 15 package program. Descriptive statistics are shown as mean ± standard deviation for variables with normal distribution, median (minimum to maximum) for non-normal distributions, and the number of cases and percentage (%) for nominal variables. When the group number was two, the significance of differences between the groups in terms of averages was investigated by *t*-test and in terms of median values was investigated by Mann Whitney test. When the number of groups was more than two, the significance of differences between the groups in terms of averages was investigated by the ANOVA variance analysis test and the significance of medians was determined by the Kruskal Wallis test. Nominal variables were assessed by Pearson Chi-Square or Fisher Exact test. Results for $p < 0.05$ were considered statistically significant. The required number of samples was calculated to be at least 114 patients with an acceptable error of 3% and a 95% confidence level.

3. Results

Demographic characteristics of patients with and without sarcopenia are summarized in Table 1. Of the 403 patients, 100 (24.8%) were diagnosed with sarcopenia and 129 (32.0%) with dynapenia. In the sarcopenic group, the mean age was 77.8 ± 5.76, whereas in the non-sarcopenia group, it was 71.8 ± 7.43. In the group with sarcopenia, the average age, osteoporosis, dementia and frailty were higher and education level was lower ($p < 0.05$). There was no difference in laboratory findings in both groups ($p < 0.05$). In the sarcopenic group, MMSE, MOCA, Tinetti balance and gait, BADL and IADL tests scores were lower, while the up and go duration was longer

Table 1
Comparison of characteristics of patients.

	Patients without sarcopenia (n = 303)	Patients with sarcopenia (n = 100)	p
Age	71.8 ± 7.43	77.8 ± 5.76	<**0.001**
Female%	66.0	67.0	0.807
Education (year)	8.64 ± 4.43	7.26 ± 4.59	**0.009**
Number of drugs	4.67 ± 2.70	5.69 ± 2.79	**0.002**
Charlson Comorbidity Index	1.2 ± 1.3	1.0 ± 1.2	0.11
Length of stay (day)	4.60 ± 1.92	6 + 2.69	**0.001**
Fall history	27.7	39.0	**0.02**
Comorbid diseases %			
Hypertension	61.1	68.0	0.23
Coronary artery disease	12.5	21.0	0.03
Congestive heart failure	5.3	7.0	0.61
Peripheral arterial disease	4.6	9.0	0.13
Chronic obstructive pulmonary disease	7.6	11.0	0.30
Thyroid disease	20.0	19.5	0.88
Osteoporosis	19.2	31.0	**0.01**
Cerebrovascular disease	5.9	7.0	0.64
Dementia	11.8	21.0	**0.04**
Diabetes mellitus	25.1	27.0	0.69
Hyperlipidemia	22.8	25.0	0.68
Depression	35.3	33.0	0.80
Frailty	18.8	42.0	<**0.001**
Laboratory findings			
Albumin (g/dL)	4.19 ± 0.26	4.12 ± 0.26	0.37
Calcium (mg/dL)	9.37 ± 0.42	9.35 ± 0.43	0.69
Phosphor (mg/dL)	3.51 ± 0.61	3.45 ± 0.56	0.49
Vitamin D (ng/mL)	25.84 ± 11.8	25.62 ± 11.61	0.42
Vitamin B12 (pg/mL)	441.15 ± 204.86	409.31 ± 196.45	0.21
Folate (ng/mL)	8.67 ± 3.91	8.30 ± 4.13	0.47
Comprehensive Geriatric Assessment			
MMSE	25.47 ± 5.96	22.73 ± 6.20	**0.006**
COST	23.84 ± 7.83	17.5 ± 6.14	0.53
MOCA	24.38 ± 5.13	21.85 ± 3.73	**0.04**
Geriatric Depression Scale	2.73 ± 3.43	3.61 ± 3.70	0.08
POMA Balance	14.77 ± 2.10	13.8 ± 2.60	**0.001**
POMA Gait	11.07 ± 1.84	10.65 ± 1.87	0.077
POMA Total	25.84 ± 3.79	24.43 ± 4.21	**0.005**
Up and Go test	12.35 ± 6.76	15.24 ± 8.49	**0.002**
Basic ADL	93.48 ± 9.46	89.43 ± 13.08	**0.002**
Instrumental ADL	19.12 ± 5.45	15.73 ± 6.46	<**0.001**
MNA	12.88 ± 1.79	12.43 ± 1.90	0.51

Abbreviations:
ADL: Activity of Daily Living, COST: Cognitive State Test, MMSE: Mini Mental State Examination, MNA: Mini Nutritional Assessment, MOCA: Montreal Cognitive Assessment, POMA: Performance Oriented Mobility Asessment. The p<0.05 was demonstrated as bold.

($p < 0.05$). When age factor was removed, it was observed that sarcopenia was still associated with MMSE, instrumental ADL and frailty ($p < 0.05$).

The characteristics of the patients with serum vitamin B12 levels ≥400 pg/ml and <400 pg/ml are shown in Table 2. Vitamin B12 deficiency was detected in 59.5% of cases. The incidence of sarcopenia and dynapenia was higher in vitamin B12 deficient patients than those without vitamin B12 deficiency ($p < 0.05$). Lean body mass, total muscle mass, skeletal muscle mass index, muscle strength were lower in patients with vitamin B12 deficiency ($p < 0.05$), but there was no difference in fat mass between the groups ($p > 0.05$). The prevalence of sarcopenia and dynapenia by vitamin B12 status was shown in Fig. 1.

4. Discussion

In this study, it was shown that sarcopenia might be related to vitamin B12 deficiency and that dynapenia is more common than sarcopenia in older adults.

Table 2
Comparison of the body composition of patients according to vitamin B12 level.

	Vitamin B12 < 400 pg/mL n = 240	Vitamin B12 ≥ 400 pg/mL n = 163	p
Age	73.7 ± 7.19	72.9 ± 7.81	0.30
Muscle strength (kg)	17.95 ± 9.06	20.00 ± 9.11	**0.03**
Fat (kg)	22.49 ± 8.88	22.97 ± 10.01	0.65
Lean body mass (kg)	45.98 ± 8.14	49.42 ± 9.52	**0.001**
Skeletal muscle mass (kg)	26.01 ± 4.51	27.97 ± 5.38	**0.001**
Muscle (kg)	43.58 ± 7.66	46.92 ± 9.06	<**0.001**
Skeletal muscle mass index (skeletal muscle mass / height^2)	7.14 ± 1.32	7.74 ± 1.43	<**0.001**

The p<0.05 was demonstrated as bold.

Sarcopenia is one of the most remarkable geriatric syndromes in recent years due to cause of functional decline, increased morbidity and mortality, as well as increased health costs (Cooper et al., 2010; Janssen et al., 2004). By the reason of varieties of diagnostic criteria, and racial and ethnic differences in the literature, the prevalence of sarcopenia ranges between 5–13% in 60–70 years and 11–50% over the 80 years age (Patel et al., 2013; Morley, 2008). The prevalence of sarcopenia in this study was 24.8% as consistent with similar age groups in the literature. Besides, it was also demonstrated that the prevalence of dynapenia was 32% in our study group. Likewise, studies indicate that muscle mass loss associated with advancing age affects both muscle strength and function (Russ et al., 2012). In this context, it is very important to evaluate dynapenia in addition to sarcopenia in older adults.

Furthermore, sarcopenia seems to be associated with other comorbid conditions such as osteoporosis, falls, frailty and dementia as shown in the results. This suggests that sarcopenia is more than a simple muscle mass loss and it is a clinical condition in which complex mechanisms such as other neuroendocrine system changes (decreased anabolic hormonal stimulation, insulin resistance), increased proinflammatory state (oxidative stress and damage, increased catabolism with increased cortisol level), and various nutrient deficiencies may play role in the pathogenesis (Fried et al., 2001; Cesari et al., 2014; Yeolekar and Sukumaran, 2014). Sedentary life, inadequate caloric intake, malnutrition and micronutrient deficiencies result in impaired muscle mass and strength (Boirie, 2009; Campbell and Leidy, 2007). Accordingly, it was reported that vitamin D, one of the most popular micronutrients, deficiency is particularly associated with low muscle strength, which causes the balance problems and falls (Holick, 2007). Vitamin D has been shown to play significant roles in muscle differentiation and stimulation of calcium, phosphorus transport, and muscle contraction (Garcia et al., 2011; Annweiler et al., 2010). In addition, vitamin B12 deficiency is frequent in older adults and can be caused by poor nutrition and adherence to vegan or vegetarian diet due to comorbid diseases or personal choice (Hunt et al., 2014). The

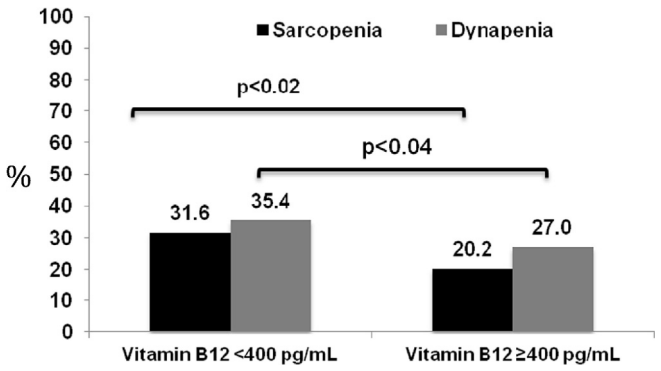

Fig. 1. Comparison of the frequency of sarcopenia and dynapenia in the patients according to vitamin B12 levels.

vegetarian diet also makes it hard to protect muscle mass. Therefore, vitamin B12 may also be important in the development of the sarcopenia with its complex metabolic effects (van Wijngaarden et al., 2013). In the literature, the interrelation between vitamin B12, and muscle mass and strength has not been completely put forward. In one of the limited studies, any relation between muscle strength and vitamin B12 levels in 56 elderly patients with diabetes was not demonstrated (Wee, 2016), while in another one, it was found that vitamin B12 and vitamin D levels are related to sarcopenia in 132 elderly patients (66 with sarcopenia) (Verlaan et al., 2015). Several reasons could be explained by the possible mechanisms related to development of the sarcopenia in vitamin B12 deficiency: First, hyperhomocysteinemia, which occurs in the deficiency of vitamin B12, may cause disruption of the structural integrity of elastin, collagen and proteoglycans, leading to skeletal-muscle system disorders and decreased muscle strength (van Wijngaarden et al., 2013). Hyperhomocysteinemia, also considered as a risk factor for cardiovascular disease, may cause endothelial cells, vascular smooth muscle cells, clotting factors, thrombocytes to be targeted and cause muscle atrophy and decrease in muscle strength by making angiotoxicity and atherosclerosis (Kuo et al., 2007). The fact that increased homocysteine levels are associated with low quadriceps muscle strength and walking speed in the National Health and Nutrition Examination Survey supports this hypothesis (Kuo et al., 2007). The second is that vitamin B12 deficiency may induce muscle atrophy development by inducing subacute combined degeneration with demyelination of the spinal cord posterior and lateral tracts and impaired proprioception, vibratory sensory loss, areflexia, and neuropathy (Hunt et al., 2014). Furthermore, possible potential complications of vitamin B12 deficiency such as depressive mood and cognitive impairment might cause social isolation (Anon., 2013), therefore possible decreased physical activity due to the vitamin B12 deficiency might be related potentialization of sarcopenia and dynapenia in older adults.

In this study, it was found that sarcopenia and dynapenia were more common in the patients; in other words, vitamin B12 deficiency seems to be related to lower muscle mass and strength in older adults than sarcopenia in older adults, and both cases might be related to vitamin B12 deficiency. On the top of it, this interrelation has a particular importance, since it is independent of vitamin D levels as in aforementioned study (Campbell and Leidy, 2007).

The present study is also remarkable for being one of the largest studies that evaluate the interrelation between vitamin B12 deficiency and sarcopenia and that all the patients were underwent comprehensive geriatric evaluation. Nevertheless, the present study has some limitations. First, this is a cross-sectional study. Second, vitamin B12 deficiency is evaluated only according to serum vitamin B12 level <400 pg/mL without methylmalonic acid and homocysteine levels.

5. Conclusions

Sarcopenia, leading to lots of negative clinical outcomes in older adults, might be related to vitamin B12 deficiency. Moreover, dynapenia might also be associated with vitamin B12 deficiency. Therefore, these patients should be periodically examined for vitamin B12 deficiency due to the potential negative clinical outcomes, such as sarcopenia in older adults.

Statement of authorship

Esra ATES BULUT performed manuscript writing and data collection; Pınar SOYSAL designed the study, supported statistical analysis, manuscript writing and conceptualism; Suleyman Emre KOCYIGIT, Ali Ekrem AYDIN and Ozge DOKUZLAR contributed data collection; and Ahmet Turan ISIK designed the study and supported manuscript writing and conceptualism.

Conflict of interest statement

The authors report no conflict of interest.

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