

Low Borderline Levels of Serum Vitamin B12 May Predict Cognitive Decline in Elderly Hip Fracture Patients

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ABSTRACT: **Background:** The progression from cognitive impairment to dementia is a multifactorial process that involves genetic and environmental factors. Vitamin B12 deficiency can be an important factor in the progress from cognitive decline to dementia.

Objectives: To examine the relationship between borderline low level of vitamin B12 (≤ 350 pg/ml) and cognitive decline among a group of elderly hip fracture patients.

Methods: This retrospective chart review study was conducted in a geriatric rehabilitation ward of a university-affiliated referral hospital. It comprised 91 elderly hip fracture patients. Cognition was assessed by the Mini-Mental State Examination tool. Fasting serum vitamin B12 levels were measured within 24 hours after admission to the rehabilitation ward.

Results: Twenty-two of the patients had vitamin B12 levels ≤ 350 pg/ml. In a multiple linear regression analysis, after adjusting for confounding variables, serum vitamin B12 levels ≤ 350 pg/ml were linked to a higher risk of developing cognitive decline (β coefficient = -0.28 , $P = 0.008$).

Conclusions: In our study, serum vitamin B12 levels ≤ 350 pg/ml were independently associated with lower MMSE scores in elderly hip fracture patients. Serum vitamin B12 may assist in identifying patients in the early stages of cognitive decline. This study joins others that have reported on the association of low normal range vitamin B12 blood levels and conditions like dementia, falls, fractures and frailty. We suggest a reexamination of what is currently considered as the normal range of vitamin B12 in the elderly.

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mia [4-7]. Most of the patients with biochemical vitamin B12 deficiency have an intrinsic factor which helps in the absorption of vitamin B12 [8]. However as a result of achlorhydria or hypochlorhydria they may have difficulties in absorbing vitamin B12 from food proteins [9]. In such cases, these biochemical deficiencies are usually not diagnosed because they lack clinical features of vitamin B12 deficiency [8]. The association between serum vitamin B12 and cognitive decline is controversial. In the Longitudinal Aging Study Amsterdam, van den Kommer et al. [10], did not find an association between vitamin B12 levels and cognitive decline. However, Clarke et al. [11] showed that more rapid cognitive decline was associated with low serum vitamin B12 concentrations in community-dwelling elderly people ($n=1648$) in Oxford, United Kingdom. According to the general medical literature [12], normal serum levels of vitamin B12 range between 300–900 pg/ml, with values below 200 pg/ml showing significant deficiency. However, as described in the literature on geriatric patients [13], many elderly patients have low borderline vitamin B12 serum levels (< 350 pg/ml) which improve with supplementation. Most of these patients are clinically asymptomatic. Low normal vitamin B12 levels, may be an early sign of a preclinical deficiency state. If this assumption is correct then current laboratory norms for vitamin B12 could be too low for the elderly population because these levels may not identify patients with early deficiency.

The aim of the present retrospective study was to investigate the association between cognitive decline and borderline serum vitamin B12 levels among older patients recovering from hip fracture. We hypothesized that serum vitamin B12 levels lower than 350 pg/ml, as described in the literature on geriatric patients [13], could be associated with cognitive decline among hip fracture patients.

PATIENTS AND METHODS

The study was approved by the local institutional review board. This retrospective chart review analyzed consecutive patients between 2012 and 2014 who were 64 years of age or older and admitted to a geriatric rehabilitation ward of a university-affiliated referral hospital with a primary diagnosis of hip fracture. The standard rehabilitation course is based on an

The progression of cognitive impairment to dementia is a multifactorial process that involves genetic and environmental factors [1]. One of the suggested important modifiable factors is vitamin B12 deficiency [2].

Among the elderly population, low serum levels of vitamin B12 are common [3] and can be associated with neurologic disorders (e.g., myelopathy, neuropathy, brain atrophy, depression and dementia), cerebrovascular disease and megaloblastic ane-

interdisciplinary rehabilitative team approach and staff members meet twice a week to evaluate the status of each patient. A treatment plan is established and monitored with the purpose of coordinating and integrating the various aspects of the staff activities (medical, nursing, physical and occupational therapy, and social work). These patients usually undergo a mean of 6 hours per week of physical and occupational therapy.

The study sample included 109 consecutive patients admitted with a diagnosis of recent hip fracture. We included all patients age ≥ 64 years (range: 64 to 96 years, mean: 83.03 ± 6.34) with perthrochanteric (extracapsular) or subcapital (intracapsular) hip fracture. The presence of ischemic heart disease (manifested as stable or unstable coronary syndrome), previous stroke, diabetes mellitus, hypertension, hyperlipidemia, and atrial fibrillation had been established by medical history, or obtained by interview or by a complete physical examination. We excluded 18 patients with serum vitamin B12 levels above the reference range (> 900 pg/ml) because high serum vitamin B12 concentration may be a laboratory sign of malignant hemopathies or other serious clinical conditions [14]. As a result, the final analysis included data of the remaining 91 patients.

Cognitive function was measured by the Mini-Mental State Examination (MMSE) tool [15] within 1 week of admission. Fasting serum levels of vitamin B12 were collected within 24 hours after admission to the rehabilitation ward. Vitamin B12 concentration was determined using a radio assay kit (COBAS® 6000, Roche Diagnostics, USA).

STATISTICAL METHODS

The comparison between patients with serum B12 levels, dichotomized at 350 pg/ml were performed using *t*-tests for continuous variables and chi-square tests for dichotomous variables. Linear regression analyses was performed to simultaneously assess the independent relationships between vitamin B12 and cognitive decline at admission and various comorbidities. A *P* value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (SPSS Inc., version 21, Chicago, IL, USA).

RESULTS

The data of 91 consecutive hip fracture patients aged 64 years and older admitted during a 2 year period (2012–2014) were available. The clinical and demographic characteristics of these patients are shown in Table 1. Mean age was 83.03 ± 6.34 years, 59.3% were women. The mean MMSE and mean serum vitamin B12 levels were 16.86 ± 8.18 and 505.69 ± 200.17 pg/ml, respectively. A total of 22 patients (24%) were found to have serum vitamin B12 levels ≤ 350 pg/ml [Table 1]. There were no statistically significant associations between low B12 vs. normal B12 patients by age, gender, education, hypertension, Parkinson's disease, previous stroke, or diabetes mellitus. MMSE

Table 1. Clinical and demographic characteristics of patients

Variable	All patients	B12 ≥ 350 pg/ml	B12 ≤ 350 pg/ml	P value
N	91	69	22	
Age, years	83.03 ± 6.34	83.07 ± 6.26	82.91 ± 6.71	0.91
Female gender	54 (59.3%)	41 (59.4%)	13 (59.1%)	0.98
Education (years)	8.38 ± 5.41	8.64 ± 5.67	7.52 ± 4.5	0.41
Diabetes mellitus, n (%)	35 (38.5%)	27 (39.1%)	8 (36.4%)	0.82
Hypertension, n (%)	72 (79.1%)	56 (81.2%)	16 (72.7%)	0.39
Hyperlipidemia, n (%)	39 (42.9%)	32 (46.4%)	7 (31.8%)	0.23
Ischemic heart disease, n (%)	59 (64.8%)	49 (71%)	10 (45.5%)	0.029
Parkinson's disease, n (%)	6 (6.6%)	5 (7.2%)	1 (4.5%)	0.66
Previous stroke, n (%)	15 (16.5%)	11 (15.9%)	4 (18.2%)	0.81
MMSE	16.86 ± 8.18	18.13 ± 7.46	12.86 ± 9.19	0.008

MMSE = Mini-Mental State Examination

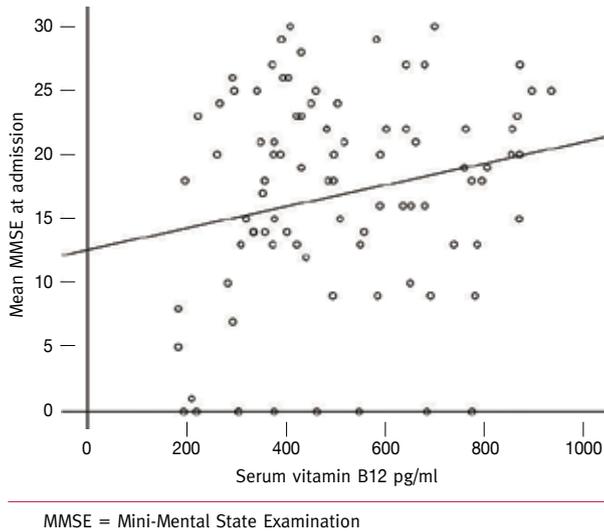
Table 2. Linear regression analysis predicting MMSE

Independent predictors	β	P value
Vitamin B12 level	-0.28	0.008
Age (years)	-0.26	0.014
Gender (female)	0.052	0.65
Education (years)	0.26	0.012
Hypertension	0.087	0.42
Diabetes mellitus	-0.102	0.43
Ischemic heart disease	-0.041	0.77
Hyperlipidemia	-0.049	0.64
Parkinson's disease	-0.11	0.27
Previous stroke	0.023	0.82

MMSE = Mini-Mental State Examination

score (18.13 ± 7.46 vs. 12.86 ± 9.19 , $P = 0.008$) and ischemic heart disease [49 (71%) vs. 10 (45.5%), $P = 0.029$], emerged as the only statistically significant parameters differing between low B12 vs. normal B12 patients [Table 1]. Because serum vitamin B12 levels higher than 350 pg/ml defined a group of patients having higher MMSE scores, we performed a linear regression analysis to test for independent predictors of MMSE scores. Higher serum vitamin B12 levels ($\beta = -0.28$, $P = 0.008$) and higher education levels ($\beta = 0.26$, $P = 0.012$) emerged as independently predictive of higher MMSE scores. Age was independently and inversely associated with MMSE scores ($\beta = -0.26$, $P = 0.014$) [Table 2]. None of the other variables that we tested, including gender, hypertension, diabetes, ischemic heart disease, hyperlipidemia, Parkinson's disease, and previous stroke, were predictive of MMSE scores. A significant correlation was found between serum vitamin B12 levels and MMSE scores (Pearson's correlation $r = 0.206$, $P = 0.05$), as shown in Figure 1.

Figure 1. Correlation of cognitive status with serum vitamin B12 levels, using the MMSE tool ($r = 0.206$, $P = 0.05$)



DISCUSSION

This study reports on the possible association of low serum borderline vitamin B12 levels and cognitive decline in a group of elderly hip fracture patients. Our data show that serum vitamin B12 levels ≤ 350 pg/ml were associated with lower MMSE scores, thus indicating cognitive decline. There was an independent association between borderline vitamin B12 levels and MMSE scores even after controlling for age, gender, education, diabetes, ischemic heart disease, hypertension, previous stroke, Parkinson’s disease and hyperlipidemia.

The association between serum vitamin B12 levels and cognitive decline remains controversial. Consistent with our study, Nurk et al. [16], in the Hordaland Homocysteine Study, which followed elderly community dwelling patients for 6 years, reported an increased risk of cognitive decline with decreased quintiles of baseline serum vitamin B12. In the Chicago Health and Aging Project, Tangney and colleagues [17] found an inverse associations between slower decline in cognition and higher serum vitamin B12 levels and an inverse relationship between MMA concentration and cognitive decline. However, van den Kommer and co-authors in the Longitudinal Aging Study Amsterdam (ages ≥ 65 years; $n=1257$, of whom $n=1076$ had longitudinal data) [10], Kang and co-authors in 635 women > 70 years old from the Nurses’ Health Study [18], and Mooijaart et al. in a population-based longitudinal study of 599 subjects (Leiden 85-Plus Study, Netherlands) [19] did not find an association between serum vitamin B12 levels and cognitive decline.

Our results suggest that elderly patients with serum vitamin B12 levels ≤ 350 pg/ml should be screened routinely for cognitive decline.

A possible explanation for the association between low vitamin B12 levels and cognitive decline is the inverse relationship that was found between serum vitamin B12 levels and plasma total homocysteine [20]. High homocysteine levels are a risk factor for cognitive decline [21] and have also been reported as associated with a smaller hippocampus [22].

Another interesting finding is the association between the low borderline level of B12 with ischemic heart disease which may hint to common risk factors and deserves further investigation. Overall, as we mentioned earlier, as vitamin B12 is involved in many essential biological processes more attention should be accorded to the proper nutritional intake of in general and to the elderly with cognitive deterioration in particular.

STUDY LIMITATIONS

Our study has several limitations. It is a retrospective study that took place in a single center. A comprehensive nutritional assessment was not done and we used only one single cognitive screening tool. Holotranscobalamin, a better indicator of vitamin B12 status, was not measured [23,24]. In addition, despite adjustments made for important confounders, others could have been considered, in particular those relating to other metabolites, such as homocysteine, and illnesses. In addition, caution must be exercised with regard to extrapolation from these findings and about drawing inferences for different populations. Despite the above mentioned limitations, the present study is advantageous because it points to the possible role of serum vitamin B12 on a cognitive level among hip fracture patients. In clinical practice, it is accepted that patients with serum vitamin B12 levels < 200 pg/ml, should be treated to prevent anemia, neuropathy and cognitive decline [25]. However, in our study we found an association between low-normal serum vitamin B12 levels (≤ 350 pg/ml) and cognitive decline which might suggest the need for earlier vitamin B12 supplementation.

Moreover, vitamin B12 is a multifaceted neurotropic factor in the adult central nervous system and has been reported both in the blood and in the cerebrospinal fluid as related to low cognition [7]. Such a neurotropic factor could also be involved in factors associated with the hip fracture trauma of elderly patients. In view of these accumulating reports as well as the low values of what is now considered within the normal range [11] and that the average age is now considerably higher than it was when the normal range was established, we consider a revision of the normal range of serum vitamin B12 levels to be necessary. A similar revision of the normal range of vitamin D resulted in adjusted values that now contribute to better clinical guidance.

Further prospective studies are needed to assess the causal relationship between serum vitamin B12 levels and cognitive function.

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Capsule**Efficacy of a low-cost, heat-stable oral rotavirus vaccine in Niger**

Each year rotavirus gastroenteritis is responsible for about 37% of deaths worldwide from diarrhea among children younger than 5 years of age, with a disproportionate effect in sub-Saharan Africa. Isanaka et al. conducted a randomized, placebo-controlled trial in Niger to evaluate the efficacy of a live, oral bovine rotavirus pentavalent vaccine (BRV-PV, Serum Institute of India) to prevent severe rotavirus gastroenteritis. Healthy infants received three doses of the vaccine or placebo at 6, 10, and 14 weeks of age. Among the 3508 infants who were included in the per-protocol efficacy analysis, there were 31 cases of severe rotavirus gastroenteritis in the vaccine group and 87 cases in the placebo group (2.14 and 6.44 cases

per 100 person-years, respectively), for a vaccine efficacy of 66.7%. Similar efficacy was seen in the intention-to-treat analyses, which showed a vaccine efficacy of 69.1%. There was no significant between-group difference in the risk of adverse events, which were reported in 68.7% of the infants in the vaccine group and in 67.2% of those in the placebo group, or in the risk of serious adverse events (in 8.3% in the vaccine group and in 9.1% in the placebo group); there were 27 deaths in the vaccine group and 22 in the placebo group. None of the infants had confirmed intussusception.

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Eitan Israeli

“Change is the law of life. And those who look only to the past or present are certain to miss the future”

John F. Kennedy (1917–1963), American politician who served as the 35th President of the United States from January 1961 until his assassination in November 1963