Vitamin B12 deficiency and associated factors in institutionalized old people

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Abstract

Objective: To assess the frequency of vitamin B12 deficiency and associated factors in institutionalized old people. *Method:* We analyzed 65 old people, with an average age of 80±9 years (61-113), from a long-term philanthropic geriatric institution. The serum dosage of vitamin B12 was analyzed and classified as: normal (≥299 pg/mL), borderline (200-298 pg/mL) and deficiency (<200 pg/mL). The association with length of stay in the institution, cognitive and functional decline, regular use of biguanides and proton pump inhibitors, considered risk factors for B12 hypovitaminosis, was analyzed using the bivariate analysis tests (parametric and non-parametric) and Poisson regression. *Results*: Vitamin B12 deficiency was present in 21.5% and borderline values in 32.3% of the sample. Among the old people, 52.9% had dementia of different causes, 49.2% had arterial hypertension, 29.2% with anemia (21.5% normocytic, 4.6% microcytic and 3.1% macrocytic), 18.5 % diabetics; 27.7% used polypharmacy, with 12.3% using metformin and 16.9% using proton pump inhibitors. In the multivariate model, there was no association between vitamin B12 deficiency and the variables studied. *Conclusion*: We observed an important frequency of borderline and low values of vitamin B12 in the patients of this geriatric institution of permanent care, but without association with the risk factors for their deficiency studied, which makes it important to include the serum dosage of this vitamin in the laboratory tests routine of that group.

Keywords: Vitamin B12. Vitamin B12 Deficiency. Homes for the aged. Health of Institutionalized Elderly.

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INTRODUCTION

Vitamin B12 is an essential water-soluble micronutrient, indispensable for the metabolism of all cells in the body. Two enzyme reactions are dependent on vitamin B12: meltilmalonic coenzyme A mutase reaction and 5-meltiltrehydrofolate-homocysteine methyltransferase reaction, important in the extraction of energy from proteins and fats in the mitochondrial citric acid cycle, which maintains the integrity of the nervous system and DNA synthesis (deoxyribonucleic acid)[1]. In addition, the interaction between vitamin B12 and folate is responsible for megaloblastic anemia[2]. In general, vitamin B12 is available through regular consumption of animal products, including red meat, eggs and dairy products. When consumed, it binds to the protein R present in saliva and gastric secretions. Subsequently, the intrinsic factor, which is produced by the parietal cells of the stomach, binds to vitamin B12 until intestinal reabsorption in the distal ilium[3].

Vitamin B12 deficiency can cause megaloblastic anemia and demyelinating neurological symptoms, with irreversible damage to nerves and peripheral neuropathy, in addition to having a strong protective effect on cognitive decline in old people[4]. Studies associate arterial hypertension and elevated homocysteine, with a four-fold risk of atrial fibrillation and, as a consequence, stroke[5]. Among the causes of vitamin B12 deficiency we can mention: the malabsorption of cobalamin from the diet; atrophy of the gastric mucosa with decreased intrinsic factor; gastric hypochlorhydria; drugs (prolonged use of biguamides and proton pump inhibitors - PPI); pernicious anemia; insufficient diet and alteration of cobalamin metabolism[3,6].

Old people have an increased risk of developing vitamin B12 (cobalamin) deficiency, being present in 12% of the old people population in the community in the Framingham cohort study[7]. Among institutionalized old people, this deficiency varies between 30-40%[8]. Vitamin B12 deficiency, in addition to the association with typical aging, may be increased by 4.5 times in those who use drugs such as proton pump inhibitors (PPIs) and H2 receptor antagonists[9]. In addition, metformin may interfere with the mechanism of action of the calcium-dependent membrane in the terminal ileum, responsible for the absorption of the intrinsic factor-vitamin B12 complex[10]. In this sense, old people residing in Long-Term Geriatric Institutions (LTIEs) often have several chronic diseases and non-communicable diseases, concomitant use of various drugs and fragility that associate them with an increased risk of developing B12 hypovitaminosis[11].

The clinical manifestations of vitamin B12 deficiency in old people are nonspecific and variable, generally absent and difficult to identify, frequent in common chronic diseases with aging, especially in people with dementia[11]. On the other hand, it presents low sensitivity of the biomarkers methylmalonic acid and plasma homocysteine due to the decrease in glomerular filtration[12], however, if left untreated, it can cause anemia and neurological changes, which are progressive and potentially fatal[13]. Therefore, considering the risk related to vitamin B12 deficiency and the lack of studies in the literature, especially with institutionalized old people, the objective of the present study was to assess the frequency of vitamin B12 deficiency and associated factors in residents of an LTIE.-

METHOD

This is a cross-sectional, observational and analytical study conducted with people ≥60 years of age residing in a philanthropic LTIE, located in a municipality in the state of Espírito Santo, Brazil.

To define the sample size, the sample calculation was performed considering the target population the number of residents (72 LTIE residents), with a 95% confidence interval, frequency of hypovitaminosis B12 deficiency in LTIE estimated at approximately 35%, considering the prevalence of 30-40% of vitamin B12 deficiency, in studies conducted outside Brazil[8] and a margin of error of 5%, which resulted in a sample of 60 individuals, we added approximately 10% to cover possible losses.

A total of 65 individuals were included in the analysis (36 women and 29 men), aged 80?9 years (from 61 to 113 years), permanence in the LTIE of 4.4?4.3 years (from 1 to 18 years): 52.9% up to two

years, 20% from three to five years and 27.7% over six years. The inclusion criteria were: age ≥60 years and being a resident of the institution for a period greater than one year. The exclusion criteria were: previous gastric surgery, incomplete laboratory tests, use of dietary supplements with polyvitamins and use of oral or injectable multivamines in the last six months. Seven residents were excluded: two for receiving dietary supplements with multivitamins, two for presenting incomplete laboratory tests and three for using multivitamins. The patient's family member and/or caregiver signed the Free and Informed Consent Form. The research is in accordance with Resolution No. 466/2012 and Resolution No. 510/2016. Project approved in CEP-EMESCAM CAAE: 29112914.9.0000.5065.

The serum dosage of vitamin B12 was analyzed, being considered as: normal (≥299 pg/mL), borderline (200-298 pg/mL) and deficiency (<200 pg/mL)[14]. Macrocytosis is considered, in Mean Corpuscular Volume (MCV) values greater than 98 fL and anemia in hemoglobin values less than 13g/dL for men and 12g/dL for women[15,16]. Laboratory tests were carried out on fasting research participants in July 2018 by employees of a specialized laboratory, accredited by ISO 9001:2015 and ONA 3.

The data not measured by the authors were obtained from the institution's electronic medical record - all residents are regularly evaluated by the multidisciplinary team, through a comprehensive geriatric evaluation. The dichotomous variables (yes/no) analyzed were: presence of arterial hypertension (patients with blood pressure of 140/90mmHg or higher, or in regular use of antihypertensive drugs)[17], diabetes mellitus (presence of fasting glucose greater than 126 mg/dL on two occasions, or using oral antidiabetics or insulin)[18], diagnosed dementia completed by the Diagnostic and Statistical Manual of Mental Disorders - 4th Edition and the National Institute of Neurological and Communicative Diseases and Stroke/ Diseaseand Related Disorders Association[19]. Functional dependence was assessed using the Katz Scale, validated for Brazil[20], which includes six items that measure the performance of the old person in activities of daily living, with the following hierarchy of complexity: food, sphincter control, transfer, personal hygiene, ability to dress and bathe, being stratified into dependents and independents.

Among the causes of vitamin B12 deficiency we analyzed the continuous use of drugs (yes vs. no) in bivariate analysis: biguamides (metformin) and PPI[21]. Polypharmacy is more commonly defined in the literature as continuous use of five or more drugs[22].

The Mini Mental State Examination (MMSE) was used for cognitive screening, being performed by a psychologist. The total score is 30 points, stratified by schooling: for illiterate, ≥20 points; for ages 1 to 4 years, ≥25 points; from 5 to 8 years, ≥26 points; from 9 to 11 years, ≥28 points; for individuals with more than 11 years of schooling, ≥29 points[23,24].

To evaluate the normality of the data, the Kolmogorov-Smirnov test was used. The following did not present a normal distribution: institutionalization time, immobility and vitamin B12. The variables were represented in percentage when categorical, and by the mean and standard deviation when continuous. Continuous variables with non-normal distribution were represented by the median. The association between the dependent variable (vitamin B12) and the independent variables was analyzed using the chi-square test and for the continuous variables (age, institutionalization time, vitamin B12, MMSE, MCV, hemoglobin and hematocrit), Student's *t* test was used. for independent samples for variables with normal distribution or their nonparametric equivalent, the Mann-Whitney test to compare research participants with normal (≥200 pg/mL) and low (<200 pg/mL) values of vitamin B12.

To compare the continuous variables (age, MMSE, MCV, hemoglobin and time spent in the institution), in groups of patients with deficient, borderline and normal values of vitamin B12, we used the one-way ANOVA test, with Levene's test to assess the homogeneity of the variances. The Kruskal-Wallis non-parametric test was used for variables with uneven variance.

Independent variables with significance level ≤0.20 in the bivariate statistical analysis were

included in the Poisson regression model with robust variance to assess the association with the dependent variable, vitamin B12 deficiency, through the crude and age-adjusted prevalence ratio, gender, arterial hypertension and diabetes mellitus, in the 95% confidence interval (95% CI). Values of p <0.05 were considered significant.

RESULTS

The sample is shown in Table 1. The following presented vitamin B12 deficiency: 14 patients (21.5%) and borderline values 21 (32.3%). The average values of vitamin B12 in the sample were 352?226 pg/mL (98 to 1803). Absence of anemia in 70.8% (n=46). Normocytic anemia in 21.5% (n = 14), microcytic in 4.6% (n=3) and macrocytic in 3.1% (n=2). A total of 76.9% had cognitive decline. Four patients had total functional dependence (6.2%) and seven, partial dependence (10.8%).

No significant differences were found in the analysis of variance when comparing the variables analyzed between the normal, borderline and vitamin B12 deficiency groups (Table 2).

The results of the Poisson regression with the gross prevalence ratios (PR) and with adjustments between the independent variables with *p* value <0,20 in the bivariate analysis, to identify the possible causes associated with vitamin B12 deficiency is shown in Table 3.

Table 1. Distribution of sample participants in relation to vitamin B12.

Variable	Total sample (n=65)	Vitamin B12		ρ
		≥200 pg/mL (n=51)	<200 pg/mL (n=14)	
Age (years)*	80 ± 9	80 ± 10	83 ± 7	0.30
Female/Male# (%)	55.4/44.6 %	54.9/45.1%	57.1/42.9%	0.37
MMSE*	12.32 ± 9.06	12.36 ± 9.39	11.07 ± 7.21	0.63
Functional dependency (KATZ)#	34 (52.3%)	49.0%	64.3%	0.19
Diabetes Mellitus#	12 (18.5%)	19.6%	14.3%	0.49
Arterial hypertension#	32 (49.2%)	45.1%	64.3%	0.24
Anemia#	19 (29.2%)	31.4%	21.4%	0.74
Dementia#	37 (56.9%)	54.9%	64.3%	0.76
Polypharmacy#	18 (27.7%)	26.7%	30.0%	0.50
Metformin#	8 (12.3%)	13.7%	7.1%	0.68
PPI#	11 (16.9%)	15.7%	21.4%	0.69
Hemoglobin (g/dL)*	13.0 ± 1.6	13.0 ± 1.8	13.0 ± 1.1	0.42
HTc (%)*	40.0 ± 4.9	39.0 ± 5.0	40.0 ± 3.0	0.48
MCV (fL)*	88.0 ± 6.0	88.0 ± 6.0	90.0 ± 5.0	0.22
Glycemia (mg/dL)**	94.0 ± 18	95.0 ± 16	89.0 ± 10	0.35
Time in institution (years)**	4.40 ± 4.30	3.82 ± 3.74	6.73 ± 5.59	0.06

Note: Data presented as average ± standard deviation or with n (%); #chi-square test** Mann-Whitney test, *t test for independent samples. MCV, mean corpuscular volume; HTc, hematocrit; MMSE, Mini-Mental State Examination; PPIs, proton pump inhibitors; Functional dependence (Katz scale). *ρ* (significance). Vitamin B12 values ≥200 pg/mL (normal) and <200 pg/mL (deficiency).

Table 2. Comparison between old people with normal concentration (≥299 pg/mL), borderline (200 to 298 pg/mL) and vitamin B12 deficiency (<200 pg/mL).

Variable	Normal (n=30)	Borderline (n=21)	Deficiency (n=14)	ρ
Age (years)*	79 ± 10	81 09	83 ± 07	0.27
LTIE time (years)**	3.5 ± 3.9	4.3 ± 3.6	6.5 ± 5.7	0.10
Hemoglobin*	13.5 ± 1.6	13.1 ± 2.0	13.1 ± 1.1	0.53
MCV*	88 6	88 ± 6	90 ± 4	0.45
MMSE*	11 ± 9	16 ± 6	13 ± 8	0.76

Note: One-way ANOVA* with Levene homogenization test of variances, Kruskal-Wallis test**. MMSEE, Mini Mental State Examination; LTIE, long-term geriatric institution; MCV, mean corpuscular volume. *ρ* (significance).

Table 3. Crude and adjusted prevalence ratio (age, sex, arterial hypertension, diabetes mellitus) to assess the association between independent variables and B12 hypovitaminosis.

Variable	PR (95% CI) without adjustments	ρ	PR (95% CI) with adjustments	ρ
Time in LTIE	1.09 (1.01 - 1.18)	0.02	1.06 (0.98 - 1.15)	0.10
Functional dependency	1.64 (0.61 - 4.36)	0.32	0.50 (0.45 - 1.53)	0.39

Note: Functional dependence (Katz). LTIE: Long-term geriatric institution. PR (prevalence ratio). Prevalence ratio in the 95% confidence interval (95% CI). *ρ* (significance).

DISCUSSION

Approximately one fifth of participants with vitamin B12 deficiency were observed. When analyzed in the Poisson regression model, no association was found between residence time at LTIE, functionality and vitamin B12 deficiency in the crude analysis, and absent when adjusted for age, sex, presence of arterial hypertension or diabetes mellitus, in the multivariable model .

The philanthropic LTIE, with old people at social risk and vulnerable, had a different prevalence than studies carried out on LTIEs abroad, which showed a higher frequency of vitamin B12 deficiency(30-40%)[12,25]. In institutionalized old people, Wong[26] observed a 34.9% prevalence of vitamin B12 deficiency (China) and Mirkazemi et al.[27] found a frequency of vitamin B12 deficiency at 14% (Australia), borderline values at 36% and a weak negative correlation between vitamin B12 deficiency and use of oral multivitamins. However, these studies used higher cutoff points than in the present study (vitamin B12 values: <203 pg/mL as deficiency and 203-338 pg/mL as borderline). This fact occurs because there is no "gold standard" test to diagnose vitamin B12 deficiency. The diagnosis is generally based on the identification of a low serological level of vitamin B12 with clinical evidence of deficiency, which responds to therapy with vitamin B12[26]. To estimate deficiency and borderline values of vitamin B12, the values used in several countries were used[12]. It is worth mentioning that studies carried out in Brazil were not found in the literature, which makes it impossible to compare with national samples.

A little more than half of the research participants had some degree of functional dependence (52.3%) without association with B12 hypovitaminosis. Functional dependence, assessed through basic activities of daily living, was not associated with vitamin B12 or homocysteine deficiency in the 1999-2000 and 2001-2002 National Health and Nutrition Surveys[28]. This association could be explained by the relationship between vitamin B12 deficiency with altered balance, peripheral neuropathy, activation of inflammatory pathways through increased levels of homocysteine and cognitive decline that would lead

to important functional dependence, not found in the NHANES population study due to methodological limitations of the occasion when it was carried out and because it is a cross-sectional study, whose interpretation would not reflect the causal relationship[28,29]. Interestingly, recently published guidelines have a high level of recommendation for the dosage of vitamin B12 in patients with frailty and sarcopenia[30].

Megaloblastic anemia is the classic hematological manifestation of vitamin B12 deficiency, affecting both the synthesis and shape of red and white blood cells[21], however, neither anemia nor macrocytosis is very sensitive for the diagnosis of vitamin B12 deficiency[11]. There were no significant hematological differences between the groups related to the concentration of vitamin B12, even considering the frequency of anemia in the sample (Table 1).

Old people residing in LTIE may be functionally and cognitively dependent, with multiple chronic diseases and using various drugs that can interfere with nutrient absorption. More than half of the old people studied had dementia of different causes, a portion with functional dependence or using PPI and polypharmacy. Regular use of metformin in diabetic patients[31] and PPI has been linked to vitamin B12 deficiency[21]. We did not find an association between these drugs with vitamin B12 deficiency in the present study, probably due to the reduced number of patients using these drugs in our group, making statistical inference difficult. Metformin-related vitamin B12 deficiency has been known for over 40 years[10], for interfering with absorption in the distal ilium[26]. Similarly, PPI use hinders gastric absorption of vitamin B12[9,26]. In addition, drug-drug interaction in polypharmacy is common, in addition to the summation effect on vitamin B12 absorption phases[32], however, there was no association in our sample between polypharmacy and vitamin B12 deficiency.

There are studies showing that vitamin B12 replacement leads to improvements in common clinical conditions in this population group, such as: reduced homocysteine with reduced cardiovascular risk[33] and reduced rate of cerebral atrophy[34]. The early detection of vitamin B12 deficiency is essential in the search for better quality of life and reduction of public health costs in this population segment, given the frequency observed in the sample studied. In addition, the lack of relationship with variables considered as risk factors or markers of vitamin B12 deficiency found in the present study highlights the need for the inclusion of vitamin B12 serum dosage in the assessment routines of old people, especially those institutionalized.

The results of this study must be considered, observing some limitations. There was only one dosage of vitamin B12, as it is a cross-sectional study, which makes causal inference difficult and the present study was carried out in a single institution, in a single municipality in a Brazilian state, which can be influenced by eating habits and availability of food sources of vitamin B12.

CONCLUSION

Old people residents of a long-term geriatric institution had a significant proportion of borderline (32%) and low (21%) values of vitamin B12, but without association with known risk factors. Future studies, including a larger number of residents encompassing several LTIEs, are necessary to confirm these findings. Thus, it is important to include vitamin B12 dosage in the routine of laboratory tests of this group, even in the absence of symptoms, for an early diagnosis of this deficiency.

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