



Prevalence of B12 Vitamin Deficiency in Elderly Seen at the Geriatric Clinic of a University in South of Santa Catarina

João Gaspar Vieira de Medeiros *¹, Leonardo da Silva Souza ¹, Dr. Tamy Colonetti ¹

1. Medicine course, University of Extremo Sul Catarinense, Av. University, 1105 - University District. CEP: 88806000- Criciúma-SC.

Corresponding Author: João Gaspar Vieira de Medeiros, University of the Extreme South of Santa Catarina, Avenida Universitária, 1105 - Bairro Universitário. CEP: 88806-000 - Criciúma (SC), Brazil.

Copy Right: © 2023 João Gaspar Vieira de Medeiros, This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Received Date: January 28, 2023

Published Date: February 10, 2023

Abstract

Objective: To analyze the prevalence of vitamin B12 deficiency and associated factors in elderly people treated at the Geriatrics clinic at the University of Extremo Sul Catarinense.

Methodology: A cross-sectional study was carried out with analysis of secondary data from the medical records of elderly people treated at a geriatrics outpatient clinic during the year 2021. Those medical records that met the inclusion criteria of being treated in the year 2021 and having serum values were included. of vitamin B12 documented. Data were organized and analyzed using SPSS version 22.0. Shapiro-Wilk ($n < 50$) and Kolmogorov-Smirnov ($n \geq 50$) tests were used for frequencies and Student's t-test, Pearson's chi-square and Fisher's exact tests for associations

Results: A total of 126 medical records of the elderly were included, the population had a mean age of 75.21, with 78.6% being female. The prevalence of vitamin b12 deficiency was 11.9% for serum values below 200 pg/ml and 55.6% for values below 350 pg/ml.

Conclusion: In general, the prevalence of B12 hypovitaminosis at the two cutoff points evaluated, 200 pg/ml and 350 pg/ml, was 11.9% and 55.6%, respectively. That is, when evaluating a supposedly asymptomatic deficiency, however already harmful, the prevalence increased to more than half of the studied population, demonstrating a need for serum vitamin B12 dosage in the elderly, even if no characteristic symptoms are reported. Furthermore, it is concluded that variables such as age and the use of medication for psychiatric illnesses were significantly significant when cobalamin deficiency is associated with the cutoff point of 200pg/ml. The results presented in the study draw attention to the need for further research on subclinical disability, and for a differentiated approach to geriatric patients.

Descriptors: Geriatrics; Hypovitaminosis; B12 vitamin.

Keywords: Geriatrics; Hypovitaminosis; B12 vitamin.

Introduction

Vitamin B12 deficiency can occur both due to the low intake of foods in which it is present, as well as due to the difficulty of absorption by the body. For the absorptive process, in addition to adequate food intake, the presence of intrinsic factor, produced by the stomach, and synthesis by bacteria in the colon with subsequent absorption in the terminal ileum is essential [1].

B12 deficiency in the elderly is mainly due to the process of geriatric frailty, defined as a decrease in the physiological capacity to maintain the body's homeostasis. Due to frailty, the elderly are favorable to adverse outcomes related to B12 malabsorption. This process is related to the gradual atrophy of the gastric mucosa, together with an autoimmune process, observed in Autoimmune Thyroiditis and Diabetes Mellitus I [2 – 7].

The use of medication for Diabetes Mellitus II, Metformin, has a marked significance in vitamin B12 deficiency. Its use interferes with the absorption of B12 and in addition to interfering with the serum levels of this vitamin. The risk of B12 deficiency is directly related to the duration of drug treatment [8-14]. In this context, there is a malabsorption syndrome that reduces vitamin stores in the body [15].

In the elderly population, vitamin B12 deficiency is a serious public health problem, reflecting neurological and hematological consequences. The main alteration is neurological, with symmetrical paresthesias, mainly in the lower limbs. In terms of hematological alterations, megaloblastic anemia stands out, [16]. A serum vitamin B12 value considered normal in the general population would be 200 pg/ml. However, the symptomatology linked to the lack of this micronutrient is already noticeable in a range of 350 pg/ml in the geriatric population [17].

The importance of knowing the prevalence of vitamin B12 deficiency in the elderly is justified by the possibility of supplementing this micronutrient, either orally or parenterally. Furthermore, as a reversible cause, it can be treated in a timely manner with the purpose of improving the quality of life resulting from the prevention of complications that affect the geriatric population [18].

The research aimed to analyze the prevalence of vitamin B12 deficiency and associated factors in elderly people treated at the Geriatrics clinic of the University of Extremo Sul Catarinense in the year 2021.

Methods

Study design

The present study was characterized by a descriptive cross-sectional observational study, with secondary data collection and a quantitative approach. The present study took place at the Integrated Geriatric Clinics of the University of Extremo Sul Catarinense, located in the city of Criciúma/SC.

Population

The medical records of patients attended by the Geriatrics clinic throughout the year 2021, who were over 60 years of age, and a biochemical test for vitamin B12 were analyzed. Patients with inconclusive or illegible information were excluded.

Sample

The medical records of all patients characterized in the target population were included, considering the procedure as a census collection. Thus, 233 medical records were analyzed, of which 107 were discarded due to lack of data related to the research.

Procedures and Logistics

Data were collected by the authors of this work through access to the Geriatrics clinic's medical records from the integrated clinics of the Universidade do Extremo Sul Catarinense. The data used in the research were obtained from the consultations carried out throughout the year 2021. This research was authorized by the coordination of the integrated clinics of the University of Extremo Sul Catarinense and the Research Ethics Committee of the University of Extremo Sul Catarinense. Opinion number: 5.172.192, CAAE: 54239121.7.0000.0119 .

Statistical analysis

The collected data were analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 22.0 software. Quantitative variables were expressed as mean and standard deviation. Qualitative variables were expressed through frequency and percentage. Statistical tests were performed with a significance

level of $\alpha = 0.05$ and, therefore, 95% confidence. Data distribution regarding normality was assessed by applying the Shapiro-Wilk ($n < 50$) and Kolmogorov-Smirnov ($n \geq 50$) tests. The investigation of the variability of quantitative variables between categories of qualitative variables was investigated by applying the Levene test. Comparison of the mean of quantitative variables between categories of dichotomous qualitative variables was performed by applying Student's t test for independent samples. The investigation of the existence of an association between the qualitative variables was carried out through the application of Pearson's Chi-square and Fisher's Exact tests, followed by residual analysis when statistical significance was observed.

Results

After contacting the Clínica de Medicina to evaluate the medical records of the geriatric consultations carried out in the year 2021, 223 medical records were identified, of which 126 met the criteria to enter the research. Thus, 126 medical records were analyzed referring to the care of elderly patients, the average age of the elderly treated was 75.21 ± 7.25 years, 78.6% were female and 93.7% were white. Regarding the main complaint for consultation, 36.5% reported pain, 26.2% insomnia, 19% forgetfulness. The data referring to the information with the characteristics of the participants are presented in table 1.

Among the information obtained from the patients' medical records regarding serum levels of vitamin B12, the average serum value of this vitamin was 431.91 pg/ml. For the analysis of the prevalence of vitamin B12 deficiency, patients were categorized between values below 200 pg/ml and below 350 pg/ml, with 11.9% of patients having serum B12 values below 200 pg/ml. ml, and when deficiency below 350 was verified, the prevalence increased to 55.6% patients. Regarding the data obtained regarding the history of vitamin B12 deficiency, 39.7% of the patients already had a deficiency of this vitamin in a previous moment and 38.9% of the patients already underwent vitamin B12 supplementation previously. The data are shown in table 2.

Other researched data from geriatric patients in the year 2021 were about the main comorbidities that affected this population and also all medications for continuous use by these elderly people. The survey results showed that 84.9% of them have Systemic Arterial Hypertension (SAH). In addition, 59.5% have dyslipidemia and 41.3% diabetes mellitus. Other comorbidities were cited by 77.8% of patients, among which hypothyroidism, osteoporosis and depression were the main ones.

Tabela 1. Características da população atendida na clínica de medicina, ambulatório de geriatria no ano de 2021 (n=126)

	Média ± DP, n (%) n = 126	IC - 95%
Idade (anos)	75,21 ± 7,25	73,94 – 76,49
Sexo		
Masculino	27 (21,4)	-
Feminino	99 (78,6)	-
Queixa principal		
Dor	46 (36,5)	-
Insônia	33 (26,2)	-
Esquecimento	24 (19,0)	-
Tontura ou quedas	24 (19,0)	-
Psiquiátrica	22 (17,5)	-
Cansaço ou fraqueza	18 (14,3)	-
Rotina	12 (9,5)	-
Gástrica	10 (7,9)	-
Parestesias	6 (4,8)	-
Religião		
Católica	99 (78,6)	-
Evangélica	20 (15,9)	-
Testemunha de Jeová	1 (0,8)	-
Nenhuma	6 (4,8)	-
Cor		
Branca	118 (93,7)	-
Negra	6 (4,8)	-
Não questionada	2 (1,6)	-
Faz acompanhamento nutricional		
Sim	15 (11,9)	-
Não	111 (88,1)	-

Fonte: Dados da pesquisa, 2022.

Tabela 2. *Dados relacionados as quantidades séricas de vitamina B12 da população atendida na clínica de medicina, ambulatório de geriatria, no ano de 2021 (n=126)*

	Média ± DP, n (%) n = 126	IC (95%)
Valor sérico de vitamina B12	431,91 ± 336,10	372,65 – 491,17
Valor sérico de vitamina B12 < 200		
Sim	15 (11,9)	-
Não	111 (88,1)	-
Valor sérico de vitamina B12 < 350		
Sim	70 (55,6)	-
Não	56 (44,4)	-
Tem histórico de deficiência		
Sim	50 (39,7)	-
Não	76 (60,3)	-
Fez suplementação anteriormente		
Sim	49 (38,9)	-
Não	77 (61,1)	-

Fonte: Dados da pesquisa, 2022.

Tabela 3. *Dados relacionados as comorbidades e medicações de uso contínuo da população atendida na clínica de medicina, ambulatório de geriatria, no ano de 2021 (n=126)*

	Média ± DP, n (%) n = 126	IC (95%)
Comorbidades		
HAS	107 (84,9)	-
Dislipidemia	75 (59,5)	-
DM2	52 (41,3)	-
Outras	98 (77,8)	-
Medicações de uso contínuo		
Cardiovasculares	108 (85,7)	-
Psiquiátricos	77 (61,1)	-
Suplementos	51 (40,5)	-
Antidiabéticos	44 (34,9)	-
Ortopédicos	34 (27,0)	-
Gástricas	34 (27,0)	-
Tireoide	24 (19,0)	-
Neurológicos	19 (15,1)	-
Pulmonares	5 (4,0)	-

Fonte: Dados da pesquisa, 2022.

Tabela 4. Associação entre as variáveis obtidas e a deficiência de vitamina B12 menor que 200 na população atendida na clínica de medicina, ambulatório de geriatria, no ano de 2021 (n=126)

	Valor sérico de vitamina B12 < 200, Média ± DP, n (%)		Valor - p
	Sim n = 15	Não n = 111	
Idade (anos)	78,67 ± 7,61	74,75 ± 7,10 ^b	0,049 ^{††}
Sexo			
Feminino	12 (80,0)	87 (78,4)	0,999 [†]
Masculino	3 (20,0)	24 (21,6)	
Motivo da consulta			
Dor	5 (33,3)	41 (36,9)	0,786 [‡]
Insônia	2 (13,3)	31 (27,9)	0,350 [†]
Esquecimento	3 (20,0)	21 (18,9)	0,999 [†]
Tontura ou quedas	2 (13,3)	22 (19,8)	0,734 [†]
Psiquiátrica	3 (20,0)	19 (17,1)	0,725 [†]
Cansaço ou fraqueza	2 (13,3)	16 (14,4)	0,999 [†]
Rotina	2 (13,3)	10 (9,0)	0,635 [†]
Gástrica	1 (6,7)	9 (8,1)	0,999 [†]
Parestesias	0 (0,0)	6 (5,4)	0,356 [‡]
Doenças			
Hipertensão arterial sistêmica	12 (80,0)	95 (85,6)	0,699 [†]
Diabetes Mellitus	7 (46,7)	45 (40,5)	0,651 [‡]
Uso de medicamentos			
Cardiovasculares	10 (66,7)	98 (88,3) ^b	0,041 [†]
Psiquiátricos	7 (46,7)	70 (63,1)	0,221 [‡]
Suplementos	5 (33,3)	46 (41,4)	0,548 [‡]
Antidiabéticos	6 (40,0)	38 (34,2)	0,660 [‡]
Ortopédicos	2 (13,3)	32 (28,8)	0,352 [†]
Gástricas	2 (13,3)	32 (28,8)	0,352 [†]
Tireoide	4 (26,7)	20 (18,0)	0,483 [†]
Neurológicos	1 (6,7)	18 (16,2)	0,466 [†]
Pulmonares	0 (0,0)	5 (4,5)	0,999 [†]

†† Valor obtido após aplicação do teste t de Student; † Valor obtido após aplicação do teste Exato de Fisher; ‡ Valor obtido após aplicação do teste Qui-quadrado de Pearson; ^b Valor estatisticamente significativo após análise de resíduos;

Fonte: Dados da pesquisa, 2022.

Tabela 5. Associação entre as variáveis obtidas e a deficiência de vitamina B12 menor que 350 na população atendida na clínica de medicina, ambulatório de geriatria, no ano de 2021 (n=126)

	Valor sérico de vitamina B12 < 350, Média ± DP, n (%)		Valor - p
	Sim n = 70	Não n = 56	
Idade (anos)	75,14 ± 7,46	75,30 ± 7,04	0,902 ^{††}
Sexo			
Feminino	55 (78,6)	44 (78,6)	0,999 [‡]
Masculino	15 (21,4)	12 (21,4)	
Motivo da consulta			
Dor	24 (34,3)	22 (39,3)	0,562 [‡]
Insônia	17 (24,3)	16 (28,6)	0,587 [‡]
Esquecimento	14 (20,0)	10 (17,9)	0,761 [‡]
Tontura ou quedas	11 (15,7)	13 (23,2)	0,287 [‡]
Psiquiátrica	10 (14,3)	12 (21,4)	0,294 [‡]
Cansaço ou fraqueza	11 (15,7)	7 (12,5)	0,608 [‡]
Rotina	8 (11,4)	4 (7,1)	0,415 [‡]
Gástrica	5 (7,1)	5 (8,9)	0,750 [†]
Parestesias	1 (1,4)	5 (8,9)	0,088 [†]
Doenças			
Hipertensão arterial sistêmica	62 (88,6)	45 (80,4)	0,200 [‡]
Diabetes Mellitus	29 (41,4)	23 (41,1)	0,968 [‡]
Uso de medicamentos			
Cardiovasculares	60 (85,7)	48 (85,7)	0,999 [‡]
Psiquiátricos	40 (57,1)	37 (66,1)	0,307 [‡]
Suplementos	30 (42,9)	21 (37,5)	0,543 [‡]
Antidiabéticos	24 (34,3)	20 (35,7)	0,867 [‡]
Ortopédicos	22 (31,4)	12 (21,4)	0,209 [‡]
Gástricas	20 (28,6)	14 (25,0)	0,654 [‡]
Tireoide	14 (20,0)	10 (17,9)	0,761 [‡]
Neurológicos	11 (15,7)	8 (14,3)	0,824 [‡]
Pulmonares	3 (4,3)	2 (3,6)	0,999 [†]

^{††} Valor obtido após aplicação do teste t de Student; [†] Valor obtido após aplicação do teste Exato de Fisher; [‡] Valor obtido após aplicação do teste Qui-quadrado de Pearson; ^b Valor estatisticamente significativo após análise de resíduos;
 Fonte: Dados da pesquisa, 2022.

Discussion

The main objective of this study was to evaluate the prevalence of vitamin B12 hypovitaminosis in the elderly population treated at a geriatrics outpatient clinic. With the data obtained, it was possible to analyze the clinical profile of the patients treated, describing the complaints that led to the search for medical care, data with serum B12 test values, main comorbidities and medications for continuous use in the elderly population.

Regarding age and sex, as expected, the average age is close to 75 years, and the predominance of the female population, who generally seeks medical care more than the male population. Regarding the main complaints that led the elderly to seek geriatric medical care, the results highlighted pain, insomnia and forgetfulness as the three main ones, with pain as the most important, reflecting common symptoms reported by these patients. in consultations, according to the literature [19].

The prevalence found in articles written about the subject ranged from 10% to 43%, depending on the diagnostic criteria. Using the threshold of 200 pg/ml, one of the parameters adopted in this study, 10% to 15% of the elderly are classified as cobalamin deficient. In this study, the prevalence found was 11.9%, corroborating the other literature found [20].

Regarding vitamin B12 deficiency, two cutoff ranges were addressed to define vitamin depletion. First, taking into account laboratory data, which use a minimum cutoff point of 200 pg/ml, with clinically irrelevant variation between laboratories, and also a minimum cutoff point of 350 pg/ml, which reflects the so-called “subclinical” hypovitaminosis, where the patient still does not experience symptoms of B12 depletion, but this deficiency already has important and insidious repercussions in the body [17].

It was also possible to verify that, among the comorbidities, as expected, Systemic Arterial Hypertension is the comorbidity most reported by patients. Among the drugs, following the same assumption, antihypertensive drugs are the most used by this population, surprisingly followed by psychiatric drugs, aimed at mental health.

Tables 4 and 5 deal with associations with cross-data from the clinical profile of the patients and the deficiency or not of vitamin B12 with the minimum cutoff points evaluated at 200 and 350 pg/ml. First, when faced with the association between the variables and the cutoff point of 200 pg/ml, it was observed that age and the use of cardiovascular medications were the most significant associations, and with

increasing age, we obtained higher prevalence of vitamin deficiency, and the use of cardiovascular drugs conferred a reduction in this prevalence.

In the associations performed with a minimum cut-off point of 350 pg/ml, there were no crossings with values with high significance, however, the use of medication for the treatment of depression and anxiety disorders can be highlighted. Research points to the relationship between the lack of vitamin B12 and symptoms that mimic depression and anxiety symptoms, and the present study confirms the high prevalence of the use of these medications and the reduction of serum vitamin levels [21].

An association that was expected, but was not significantly consolidated in the study, was vitamin B12 deficiency and the use of medications for neurological disorders. Studies establish that vitamin deficiency is more common among patients who have chronic neurological disorders, such as Alzheimer's, stroke sequelae, and Parkinson's disease. This can be explained by the reduction in methylation of lipids and neuronal proteins, such as myelin, caused by cobalamin depletion²². In the present study, it is understood that the association between vitamin B12 deficit, below 200 pg/ml and below 350 pg/ml, and the use of neurological medications obtained a p-value of 0.466 and 0.824, respectively.

Regarding antidiabetic medications, mainly metformin, they are used by 34.9% of geriatric patients in the study. A systematic review was carried out in order to establish a relationship between the use of metformin and B12 deficiency, considering that the impact of this medication, in a dose-dependent manner, is already considered valid, in addition to the fact that the use of supplementation of this vitamin it could even help in the action of metformin in patients with type 2 diabetes mellitus. In this systematic review, it was observed that each increase in metformin dose of 1000 mg increased the risk of vitamin B12 deficiency ($p < 0.0001$)²³. In the present study, there were no significant findings in these patients regarding this association, but the prevalence of diabetes and polypharmacy in the geriatric population may have impacted in such a way as not to allow establishing a more evident relationship. It is necessary to emphasize the method of data collection, carried out by direct and retrospective search of the patients' physical records, in addition, the consultations during the year 2021 were evaluated, which still presented some limitations of patients in the first months of 2021 due to the effects of the Covid-19 pandemic in the region.

Finally, it is understood that geriatric patients have a high prevalence of comorbidities, consequently, making use of a wide variety of medications. These data, together with the description of the profile of each patient, and the values of vitamin B12, it was possible to map the profile of the elderly attended at

the geriatrics clinic throughout the year 2021, explaining an updated profile, directing the management of these data in clinical practice by health professionals.

References

1. BARRIOS, Mariela F; HERNÁNDEZ, Irma G; GÓMEZ, Hortensia GD. Vitamina B12: metabolismo y aspectos clínicos de su deficiencia. *Revista Cubana de Hematología, Inmunología y Hemoterapia*, Havana, v. 15, n. 3, p. 159–174, sep.-dic, 1999.
2. Soh Y, Won CW. Association between frailty and vitamin B12 in the older Korean population. *Medicine (Baltimore)*. 2020 Oct 23;99(43):e22327. doi: 10.1097/MD.00000000000022327. PMID: 33120734; PMCID: PMC7581105.
3. Jacobson DL, Gange SJ, Rose NR, et al. Epidemiology and estimated population burden of selected autoimmune diseases in the United States. *Clin Immunol Immunopathol*. 1997;84(3):223.
4. Centanni M, Marignani M, Gargano L, Corleto VD, Casini A, Delle Fave G, et al. Atrophic body gastritis in patients with autoimmune thyroid disease: an underdiagnosed association. *Arch Intern Med*. 1999;159(15):1726.
5. Park JY, Lam-Himlin D, Vemulapalli R. Review of autoimmune metaplastic atrophic gastritis. *Gastrointest Endosc*. 2013 Feb;77(2):284-92. Epub 2012 Nov 27.
6. Castoro C, Le Moli R, Arpi ML, Tavarelli M, Sapuppo G, Frittitta L, et al. Association of autoimmune thyroid diseases, chronic atrophic gastritis and gastric carcinoid: experience from a single institution. *J Endocrinol Invest*. 2016 Jul;39(7):779-84. doi: 10.1007/s40618-016-0445-5. Epub 2016 Feb 29. PMID: 26928404.
7. Hershko C, Ronson A, Souroujon M, Maschler I, Heyd J, Patz J. Variable hematologic presentation of autoimmune gastritis: age-related progression from iron deficiency to cobalamin depletion. *Blood*. 2006 Feb 15;107(4):1673-9. doi: 10.1182/blood-2005-09-3534. Epub 2005 Oct 20. PMID: 16239424.
8. Pflipsen MC, Oh RC, Saguil A, Seehusen DA, Seaquist D, Topolski R. The prevalence of vitamin B(12) deficiency in patients with type 2 diabetes: a cross-sectional study. *J Am Board Fam Med*. 2009 Sep-

Oct;22(5):528-34. doi: 10.3122/jabfm.2009.05.090044. Erratum in: J Am Board Fam Med. 2010 Sep-Oct;23(5):695. Seaquist, D [added]. PMID: 19734399.

9. Parry-Strong A, Langdana F, Haeusler S, Weatherall M, Krebs J. Sublingual vitamin B12 compared to intramuscular injection in patients with type 2 diabetes treated with metformin: a randomised trial. N Z Med J. 2016 Jun 10;129(1436):67-75. PMID: 27355231.

10. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. Arch Intern Med. 2006 Oct 9;166(18):1975-9. doi: 10.1001/archinte.166.18.1975. PMID: 17030830.

11. Ting RZ, Szeto CC, Chan MH, Ma KK, Chow KM. Risk factors of vitamin B(12) deficiency in patients receiving metformin. Arch Intern Med. 2006 Oct 9;166(18):1975-9. doi: 10.1001/archinte.166.18.1975. PMID: 17030830.

12. Bell DS. Metformin-induced vitamin B12 deficiency presenting as a peripheral neuropathy. South Med J. 2010 Mar;103(3):265-7. doi: 10.1097/SMJ.0b013e3181ce0e4d. PMID: 20134380.

13. Aroda VR, Edelstein SL, Goldberg RB, Knowler WC, Marcovina SM, Orchard TJ, Bray GA, Schade DS, Temprosa MG, White NH, Crandall JP; Diabetes Prevention Program Research Group. Long-term Metformin Use and Vitamin B12 Deficiency in the Diabetes Prevention Program Outcomes Study. J Clin Endocrinol Metab. 2016 Apr;101(4):1754-61. doi: 10.1210/jc.2015-3754. Epub 2016 Feb 22. PMID: 26900641; PMCID: PMC4880159.

14. Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B12 deficiency in patients with type 2 diabetes. Medicine (Baltimore). 2019 Nov;98(46):e17918. doi: 10.1097/MD.00000000000017918. PMID: 31725641; PMCID: PMC6867725. de Jager J, Kooy A, Lehert P, Wulffelé MG, van der Kolk J, Bets D, Verburg J, Donker AJ, Stehouwer CD. Long term treatment with metformin in patients with type 2 diabetes and risk of vitamin B-12 deficiency: randomised placebo controlled trial. BMJ. 2010 May 20;340:c2181. doi: 10.1136/bmj.c2181. PMID: 20488910; PMCID: PMC2874129.

15. Stover PJ. Vitamin B12 and older adults. Curr Opin Clin Nutr Metab Care. 2010 Jan;13(1):24-7. doi: 10.1097/MCO.0b013e328333d157. PMID: 19904199; PMCID: PMC5130103.

16. Stabler SP. Clinical practice. Vitamin B12 deficiency. *N Engl J Med*. 2013 Jan 10;368(2):149-60. doi: 10.1056/NEJMcp1113996. PMID: 23301732.
17. Wolters M, Ströhle A, Hahn A. Cobalamin: a critical vitamin in the elderly. *Prev Med*. 2004 Dec;39(6):1256-66. doi: 10.1016/j.ypmed.2004.04.047. PMID: 15539065.
18. Lewington, Sarah; BENAA, Kaare H; Toumilehto, Jaakko, et al. Homocysteine and risk of ischemic heart disease and stroke: a meta-analysis. *American Medical Association*. Ed 288, oct, 2015.
19. Rodrigues, B. V. P.; Melo, L. O. S.; Araujo, A. V. S.; Rosario, H. S. S.; Silva, M. Q. Principais queixas em uma primeira consulta geriátrica em um hospital de ensino. *Brazilian Journal of Health Review*, Curitiba, v.4, n.4, p.17187-17201 jul./aug.2021.
20. Menegardo, Cristiani S.; Friggi, Fernanda A.; Santos, Angelica D. et al. Deficiência de vitamina B12 e fatores associados em idosos institucionalizados. *Rev. Bras. Geriatria e Gerontologia*. 2020; 23(2):e200022.
21. Santos, E. C.; Brito, A.; Pereira, I. R. O. Deficiência de vitamina B12: um fator que induz à depressão? *Cad. Pós-Grad. Distúrb. Desenvolv.* vol.16 no.2 São Paulo dez. 2016
22. Andrés, E.; Loukili, N.H.; Noel, E.; Kaltenbach, G.; Abdelgheni, M.B.; Perrin, A.E.; et al. Vitamin B12 (cobalamin) deficiency in elderly patients. *CMAJ*. 2004. Aug 3;171(3):251-9. doi: 10.1503/cmaj.1031155. PMID: 15289425; PMCID: PMC490077.
23. Liu, Qilin; LI, Sheyu; Quan, Heng; Li, Jianwei. Vitamina B12 Status em Pacientes Tratados com Metformina: Revisão Sistemática. *PLOS ONE* 9(6): e100379 (2014). <https://doi.org/10.1371/journal.pone.0100379>.