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Research paper

Metformin intake among geriatric patients may predispose to vitamin B_{12} deficiency: Polish population-based study

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Abstract

Introduction: Vitamin B_{12} deficiency is becoming a major problem among geriatric population worldwide. It may contribute to higher prevalence of cognitive impairment and depression, and may occur as a side effect of commonly prescribed anti-diabetic and anti-acid treatments. However, the scale of this phenomenon in Poland remains unknown.

Aim: We investigated the scale of vitamin B_{12} deficiency across population of geriatric patients over 70 years old. Additionally, we examined the association between vitamin B_{12} deficiency, cognitive impairment or depression prevalence, and metformin or proton pump inhibitors intake.

Material and methods: Based on the measured vitamin B_{12} serum level, we divided patients into 3 groups: (1) normal (≥300 pg/mL); (2) borderline (191–300 pg/mL), and (3) low (≤191 pg/mL). The assessment of cognitive impairment or depression was performed by using 5 distinct tests (mini-mental state examination, abbreviated mental test score, clock drawing test, and 4-item or 15-item geriatric depression scale). For statistical analysis, we used χ^2 and ANOVA tests.

Results and discussion: We showed no differences in the frequency of cognitive impairment, depression, and vitamin among characterized groups. Importantly, we found that metformin intake was associated with vitamin B_{12} deficiency ($P = 0.009$), contrary to proton pump inhibitor ($P = 0.53$) and combined these drugs ($P = 0.24$).

Conclusions: We showed a relatively high prevalence of vitamin B_{12} deficiency across a population of geriatric patients. A preventive vitamin B_{12} supplementation should be considered when treating, especially geriatric diabetic patients. Due to conflicting results of retrospective studies, prospective clinical trial should be undertaken to describe the association between vitamin B_{12} deficiency and prevalence of cognitive impairment or depression.

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1. INTRODUCTION

Vitamins are organic molecules that are required for human organisms to function. They play a crucial role in metabolic processes, and their deficiency leads to various diseases.[1–3] Vitamin B12 (cobalamin) is an important cofactor for DNA synthesis, lipid metabolism, and methylation reactions in human body, and its deficiency may lead to psychiatric disorders such as cognitive impairment or depression.[4,5] The main sources of vitamin B_{12} are inhabitant bacterial flora in gastrointestinal system and meat consumption. Its impaired absorption is frequently associated with prolonged anti-acid therapy with proton pump inhibitor (PPI) or anthyperglycemic drugs and manifests in macrocytic erythrocytes and neurological symptoms, such as cognitive impairment or peripheral neuropathy.[6] Vitamin deficiency is a major problem among elderly patients and a significant challenge to be overcome by clinical professionals. Across Europe, cobalamin deficiency ranges from 6% among over-65-year-old patients in Finland to 25% among 74–80-year-old patients in the Netherlands.[7] Apart from risk factors associated with reduced absorption, older patients are prone to malnutrition, which may be a considerable cause of vitamin B_{12} deficiency.[8] However, the prevalence of malnutrition is highly underestimated, ranging from 3% among diagnosed patients to 60% among undiagnosed ones.[9]

2. AIM

With constantly growing evidence of a link between vitamin B_{12} deficiency and cognitive impairment and depression, we investigated the prevalence of vitamin B_{12} deficiency across geriatric population and its linkage with cognitive impairment and depression occurrence. Further, we tried to establish the association between vitamin B_{12} deficiency, PPI, and metformin treatment in this group of patients.

3. MATERIAL AND METHODS

We performed retrospective cohort study, recruiting 698 patients who were treated in Geriatric Outpatient Clinic in Dobre Miasto, Poland, between 2012 and 2020. All patients from the geriatric outpatient clinic who underwent blood analysis to assess their levels of vitamin B_{12} during the above-mentioned period, were included in the study. There were no exclusion criteria for the entire study; however, the depression rating scale was not administered to patients with more than moderate dementia. Patients were divided into 3 distinct groups based on the measured vitamin B12 serum level on the first outpatient clinic visit:
(1) normal (≥300 pg/mL),
(2) borderline (191–300 pg/mL),
(3) low (≤191 pg/mL).

Thresholds used at the hospital's diagnostic laboratory were applied. Presence of dementia symptoms was assessed according to mini-mental state examination (MMSE), abbreviated mental test score (AMTS), or clock drawing test (CDT). Probable dementia was diagnosed when patient scored MMSE ≤ 23 points, AMTS ≤ 6 points, and CDT ≤ 4 points. Depression was measured with 4-item and 15-item geriatric depression scale (GDS4 and GDS15, respectively) which were performed by geriatrician. Depression was diagnosed when patient scored GDS4 ≥ 1 points, GDS15 ≥ 5 points. All tests were picked individually based on the general practitioners' choice. Additionally, the following information was assessed through hospital database: sex, age, red blood cells count (RBC), hemoglobin level (HGB), hematocrit (HCT), mean corpuscular volume (MCV), metformin, and PPI intake. Data was analyzed in STATISTICA 13.1 (Statsoft, 2017, Cracow, Poland).[10] The χ^2 test was used to analyze the ratio differences between groups (qualitative variables), and ANOVA was used to analyze the quantitative variables. Statistical significance was defined as $P < 0.05$.

4. RESULTS

In total, 698 patients were recruited in the study. Most patients were female, 317 (77.5%). The mean age of the cohort was 76.7 ± 8.7 years. The mean vitamin B_{12} level was 345.9 ± 149.5 pg/mL (range 50.0–953.6 pg/mL). There were 400 (57.3%), 205 (29.4%), and 93 (13.3%) patients within normal, borderline, and low levels of vitamin B_{12}, respectively. We did not find any differences with regard to patients' sex or age between each vitamin B_{12} group ($P > 0.05$), however, low levels of vitamin B_{12} were associated with lower values of RBC, HGB, HCT, and MCV ($P < 0.05$). To assess cognitive impairment and depression, we performed five distinct tests: CDT ($n = 438$), AMTS ($n = 112$) and MMSE ($n = 197$) and GDS4 ($n = 454$), GDS15 ($n = 32$), respectively. In both groups, there were 61 and 213 patients, respectively, without test assessment. Although in AMTS, MMSE, and GDS4 we observed a decreasing or increasing test score trend towards low level vitamin B_{12} group, we did not find any significant differences (Figure 1). Additionally, looking at the frequency of cognitive impairment or depression across vitamin B_{12} groups, there were no differences $P > 0.05$ (Table 1). Across our cohort, 116 (16.6%) and 169 (24.2%) patients were using metformin and PPI for other comorbidities, respectively. In most cases, patients were prescribed omeprazole and pantoprazole. Investigating a predictive value of mentioned drugs regarding vitamin B_{12} deficiency, we found that metformin intake was a predictor of vitamin B_{12} deficiency between normal, borderline, and low vitamin B_{12} level groups ($P = 0.009$) whereas PPI intake was not predictive ($P = 0.53$), and combined use of PPI and metformin also was not predictive ($P = 0.24$) (Table 2).

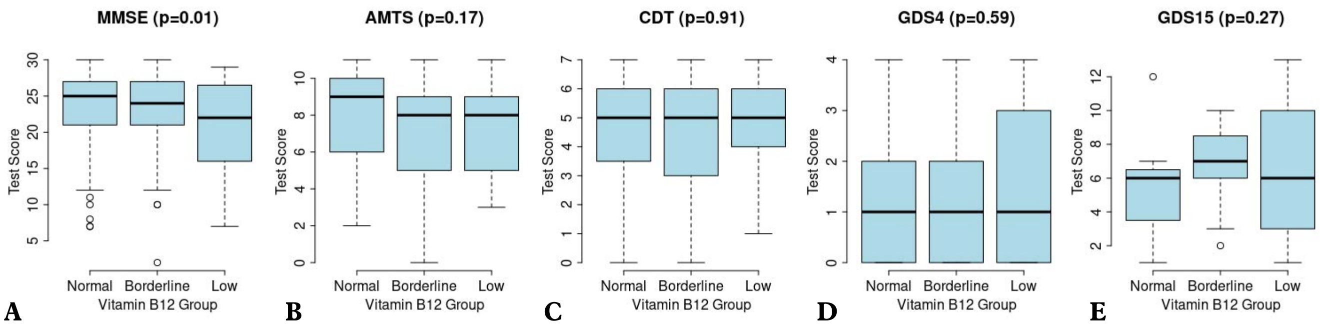

Figure 1. Cognitive impairment and depression test scores differences (*P* values were calculated using ANOVA test statistics) among patients' vitamin B_{12} groups: (A) MMSE; (B) AMTS; (C) CDT; (D) GDS4; (E) GDS15.

5. DISCUSSION

To the best of our knowledge, we present the first study investigating the link between vitamin B_{12} deficiency and cognitive impairment or depression in Poland. When compared to other studies we have gathered and screened the largest population of geriatric patients (above 70 years old) in Europe. Psychiatric disorders are a major problem in the general population. Worryingly, it is a significant challenge, especially among elderly patients who are often undiagnosed. It is crucial to distinguish a psychiatric disease from a psychiatric symptom that can mimic other diseases, including vitamin deficiencies.[6] Hence, in this article, we focused on the influence of vitamin B_{12} deficiency on the prevalence of cognitive impairment and depression, as well as the impact of metformin and PPI on vitamin B_{12} deficiency.

Table 1. Frequency of cognitive impairment and depression across vitamin B_{12} groups.

	B_{12} level, *n*(%)			*P*
	Normal	Borderline	Low	
Cognitive impairment				
Yes	154(38.5)	66(32.2)	32(34.4)	
No	218(54.5)	119(58.0)	48(51.6)	0.43
NA	28(7.0)	20(9.8)	13(14.0)	
Depression				
Yes	209(52.2)	82(40.0)	37(39.8)	
No	91(22.8)	43(21.0)	23(24.7)	0.41
NA	100(25.0)	80(39.0)	33(35.5)	

Table 2. Influence of metformin or/and proton pump inhibitor intake on vitamin B_{12} deficiency.

	B_{12} level, *n*(%)			*P*
	Normal	Borderline	Low	
Metformin				
Yes	56(14.0)	37(18.1)	23(24.7)	
No	307(76.8)	136(66.3)	55(59.2)	0.009
NA	37(9.2)	32(15.6)	15(16.1)	
Proton pump inhibitor				
Yes	100(25.0)	51(24.9)	18(19.4)	
No	252(63.0)	113(55.1)	57(61.2)	0.53
NA	48(12.0)	41(20.0)	18(19.4)	
Metformin and proton pump inhibitor				
Yes	17(4.25)	9(4.4)	4(4.3)	
No	336(84.0)	156(76.1)	71(76.3)	0.24
NA	47(11.75)	40(19.5)	18(19.4)	

In our study, we did not find differences between borderline or low levels of vitamin B_{12} and prevalence of cognitive impairment when compared to patients with normal vitamin B_{12} levels. Interestingly, this observation is supported by various studies[10–15] and in opposition to others.[16–21] Contrary results may be due to different age of patients recruited, sex distribution, lack of control groups, usage of different tests to assess dementia or thresholds of serum vitamin B_{12} measurement.[22] No consensus on serum vitamin B_{12} thresholds is believed to be a major challenge in patients' treatment, which also highly impacts results of reported trials.[23] Similarly, we did not discover any differences in vitamin B_{12} levels among patients with depression, which is contrary to several previous studies,[24–30], however, in line with only reported prospective study.[31] Finally, other markers such as serum homocysteine or folate are considered to have an association with cognitive impairment and depression, however, their role is rather limited and outperformed by vitamin B_{12} measurement.[28,32] Furthermore, we investigated the association between metformin and PPI intake and vitamin B_{12} deficiency. We found that metformin usage was associated with lower levels of vitamin B_{12} (P = 0.009) which is supported by previously published studies among patients with diabetes. Chapman et al. showed that even 4 months of metformin therapy decreased the vitamin B_{12} level by 15.5 pg/mL.[33] The recent meta-analysis performed by Yang et al. reported a significantly higher risk of vitamin B_{12} deficiency in patients using metformin longer than 3 years which rises with higher doses administered.[34] Although metformin is associated with vitamin B_{12} deficiency which may predispose to dementia, on the other side, it decreases the risk of dementia associated with diabetes. Thus, vitamin B_{12} supplementation should be considered while treating patients with diabetes.[35] Interestingly, we did not find any link between PPI administration and vitamin B_{12} deficiency, which is contrary to most previous reports.[36] Conflicting results may be due to different vitamin B_{12} deficiency thresholds applied and distinct definitions of vitamin deficiency.[37,38] Nevertheless, it seems that vitamin B_{12} supplementation should be administered while being on prolonged therapy with PPI.[36] Our study has a few limitations. Firstly, to assess the vitamin B_{12} deficiency we used a single measurement on the first visit to our outpatient clinic, however, our goal was to estimate the general problem of vitamin deficiency in geriatric population. Secondly, we did not perform a measurement of other forms of vitamin B_{12} such as holotranscobalamin or holohaptocorrin, which are forms bound with proteins or serum homocysteine and folate, but their clinical value is rather inferior when compared to serum vitamin B_{12} measurement. On the other side, what strengthens our study is the large and well-characterized cohort of geriatric patients over 70 years old. Finally, it is the first study revealing the scale of vitamin B_{12} deficiency across Polish geriatric population.

6. CONCLUSIONS

(1) We showed a high prevalence of vitamin B12 deficiency across a wide population of geriatric patients.
(2) Vitamin B12 deficiency was strongly correlated with several abnormalities: low values of RBC, HGB, HCT, and high value of MCV in a blood test, however not all patients with vitamin B12 deficiency had changes in morphology, thereby posing a challenge in accurately diagnosing this condition.
(3) Regular monitoring of vitamin B12 serum levels should be applied, particularly among patients with diabetes treated with metformin and PPI-administered patients.
(4) A preventive vitamin B12 supplementation might be considered at the very beginning of treatment administration of PPI, or metformin particularly among patients with low or borderline serum levels of vitamin B12.
(5) The association between vitamin B12 deficiency and prevalence of cognitive impairment or depression should be further investigated in well-designed prospective clinical trials.

Conflict of interest
None declared.

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None declared.

Ethics committee approval
The study was approved by the Ethics Committee of the local Chamber of Physician in Olsztyn (27/2021/VIII, 5 July 2021). Patients' informed consent was gathered during the first visit to the outpatient clinic.

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