ANALYSIS OF SECULAR TRENDS IN THE USE OF MEDICATIONS AFFECTING VITAMIN B12 METABOLISM AND DEMENTIA IN PATIENTS RECEIVING PRIMARY HEALTHCARE

ANALIZA SEKULARNIH TRENDOVA UPOTREBE LEKOVA KOJI REMETE METABOLIZAM VITAMINA B12 I DEMENCIJE KOD PACIJENATA U PRIMARNOJ ZDRAVSTVENOJ ZAŠTITI

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Abstract

Introduction. This study aims to analyze secular trends in the use of medications that disrupt vitamin B12 metabolism and their association with increasing dementia rates in the Republic of Serbia. **Material and Methods**. A retrospective analysis was conducted using data from the *Health Statistical Yearbook* published by the Institute of Public Health, and information on drug turnover and consumption from the Medicines and Medical Devices Agency of Serbia, covering the period from 2006 to 2019. **Results**. The average annual incidence rate of dementia showed a continuous increase, rising from 0.95 in 2006 to 3.64 in 2019. The Mann Kendall trend test revealed a statistically significant upward trend for dementia (p=1.54), and non-sideropenic anemia (p=0.0002). The analysis of medication use demonstrated increasing trends for proton pump inhibitors (p=1.45), metformin (p=7.15), anticonvulsants (p=0.001), 5-aminosalicylic acid (p=5.35), antiepileptics (p=2.50), and clonazepam (p=1.95). Conversely, declining trends were observed for H2 antagonists (p=1.95) and phenobarbital (p=0.003). For carboxamide and valproate derivatives, no significant trend was observed. **Conclusion**. The rising use of medications that impair vitamin B12 metabolism - including metformin, proton pump inhibitors, 5-aminosalicylic acid, and clonazepam, as well as non-sideropenic anemias, parallels a continuous increase in dementia incidence.

Key words: Vitamin B 12; Dementia; Cognition; Metformin; Proton Pump Inhibitors; Clonazepam; Mesalamine; Primary Health Care; Risk Factors

Sažetak

Uvod. Cilj ove studije je analiza sekularnih trendova u podacima o potrošnji lekova koji remete metabolizam vitamina B12 sa trendom porasta demencija za teritoriju Republike Srbije. **Materijal i metode.** Studija predstavlja retrospektivnu analizu podataka dobijenih iz Zdravstveno-statističkog godišnjaka Instituta za javno zdravlje, kao i Podataka o prometu i potrošnji lekova Agencije za lekove i medicinska sredstva Srbije, a za period od 2006. do 2019. godine. **Rezultati.** Ukupna srednja vrednost stope obolevanja na 1.000 stanovnika na teritoriji Republike Srbije od demencije kontinuirano raste od 0,95 u 2006. godini do 3,64 u 2019. godini. Rezultati dobijeni Men-Kendelovim (*Mann Kendall*) testom govore da postoji porast trenda za demencije gde je p = 1,54 i statistički značajan porast trenda za nesideropenijske anemije gde je p = 0,0002. Rezultati dobijeni za lekove ukazuju na porast trenda upotrebe: inhibitora protonske pumpe (p = 1.45), metformina (p = 7,15), antikonvulziva (p = 0,001), 5-aminosalicilne kiseline (p = 5,35), antiepileptika (p = 2,50), klonazepama (p = 1,95), dok za H2 antagoniste postoji trend opadanja (p = 1,95) i (fenobarbitol p = 0.003), a za derivate karboksamida i valproata nije uočen porast ili opadanje trenda. **Zaključak.** Povećanje upotrebe lekova koji dovode do poremećaja metabolizma vitamina B12, uključujući metformin, inhibitore protonske pumpe, 5-aminosalicilnu kiselinu i klonazepam, kao i nesideropenijske anemije, praćeno je kontinuiranim porastom incidencije demencije.

Ključne reči: vitamin B12; demencija; kognicija; metformin; inhibitori protonske pumpe; klonazepam; mesalamin; primarna zdravstvena zaštita; faktori rizika

Introduction

In recent years, the growing number of newly diagnosed dementia cases has heightened the demand for early diagnosis, prevention, treatment and care by healthcare workers, medical institutions, social, and other state services. In advanced stages of dementia, patients often lose the ability to live independently as their functionality is significantly impaired by the symptoms of the condition [1]. Simultaneously, the stressful conditions of modern lifestyles have contributed to an increasing prevalence of diabetes, leading to greater reliance on biguanides, particularly metformin, as a first-line treatment, which, however, leads to reduced levels of vitamin B12 in the body [2–4]. In addition to metformin, the use of other drugs that interfere with cyanocobalamin metabolism is also becoming more frequent. For instance, focus on diagnosing and treating gastritis caused by *Helicobacter pylori*, has increased the use of medications such as proton pump inhibitors, H2 antagonists, antacids, and antibiotics – most commonly clarithromycin – for eradication of. The frequent or prolonged use of these drugs can disrupt vitamin B12 levels, which are essential for proper functioning of the nervous system and nerve cells

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Abbreviations

F00-F03 – dementia specified and unspecified
D51-D64 – nutritional, hemolytic and aplastic anemias
5ASA – 5-aminosalicylic acid
PPI – proton pump inhibitors
HBP – helicobacter pylori
ALIMS – Medicines and Medical Devices Agency of Serbia
DDD – Defined Daily Dose
ICD-10 – International Statistical Classification of Diseases and Related Health Problems, 10th Revision
PD – Parkinson's disease
MCI – mild cognitive impairment
PON1 – paraoxonase 1

[5–7]. Numerous studies have also highlighted an association between vitamin B12 deficiency and the use of anticonvulsants, which can elevate homocysteine levels [8–10].

Vitamin B12 (cyanocobalamin) primarily produced by microorganisms *Propionibacterium freudenreichii* and *Pseudomonas denitrificans* is predominantly obtained from animal-derived foods. Deficiency of vitamin B12 can lead to hematological, gastrointestinal, and neuropsychiatric disorders, including neuropathy, cerebellar ataxia, dementia and mood disturbances. This deficiency typically results from insufficient dietary intake, inadequate absorption, or reduced utilization [11].

Cyanocobalamin plays a vital role in amino acid metabolism, myelin renewal, and bone marrow cell formation. A deficiency can cause degeneration of the spinal cord's lateral and dorsal columns, resulting in neuropathy. Cognitive dysfunction of affected individuals is often accompanied by irritability, depression, and, in severe cases, psychosis [12].

Despite the increasing use of drugs that interfere with vitamin B12 metabolism, there has not been a corresponding increase in vitamin B12 intake or its supplementation. Consequently, the incidence of dementia continues to rise.

This study aims to analyze secular trends in the use of medications that disrupt vitamin B12 metabolism and their association with the rising incidence of dementia in the Republic of Serbia. It seeks to explore the potential connection between these medications and the observed increase in dementia cases.

Research hypotheses

1. There is a positive secular trend in the use of drugs that disrupt vitamin B12 metabolism and the frequency of cognitive impairment in the Republic of Serbia;

2. There is a positive secular trend in the incidence of dementia and megaloblastic anemia, but not sideropenic anemia, in Serbia.

Material and Methods

The study involves a retrospective analysis of data collected from the *Health Statistical Yearbook of the Republic of Serbia*, published by the Institute of Public Health of Serbia "Dr Milan Jovanovic Batut", and the information on drug turnover and consumption from the Medicines and Medical Devices Agency of Serbia (ALIMS). The analysis covered data from 2006 to 2019 for the territory of the Republic of Serbia [13, 14]. The strength and direction of the linear relationship between the increase in dementia incidence (per 1,000 inhabitants) and the use of medications affecting vitamin B12 metabolism (expressed as Defined Daily Dose (DDD) per 1,000 inhabitants per day)were assessed using the Mann Kendall test for individual trend analyses. Disease data were obtained from the reports of the Institute of Public health, focusing on diagnoses coded according to the WHO's International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10). The selected codes included: F00-03 (Dementia specified and unspecified), D50 (Iron deficiency anemia), and D51-64 (Nutritional, hemolytic, and aplastic anemias. These data were reported as the number of patients per 10,000 individuals in the general population. Medication usage data were collected from reports on drug consumption, presented as DDD per 1,000 inhabitants per day. The analyzed medications included: H2 receptor blockers, proton pump inhibitors, mesalazine (5-aminosalicylic acid), metformin, oral contraceptives, estrogens, tetracyclines, penicillins, erythromycin, phenobarbital, methotrexate, loop diuretics, iron supplements, vitamin B1, vitamin B12, folic acid, and drugs prescribed for dementia.

Results

The analysis of secular trends revealed a continuous increase in the total average incidence rate of dementia per 1,000 inhabitants in the Republic of Serbia, rising from 0.95 in 2006 to 3.64 in 2019 **(Figure 1).**

Using the Mann-Kendall test, a significant upward trend was observed for dementia (F00-F03) with

Figure 1. Mean incidence rate of dementia per 1,000 inhabitants per day in the period from 2006 to 2019.

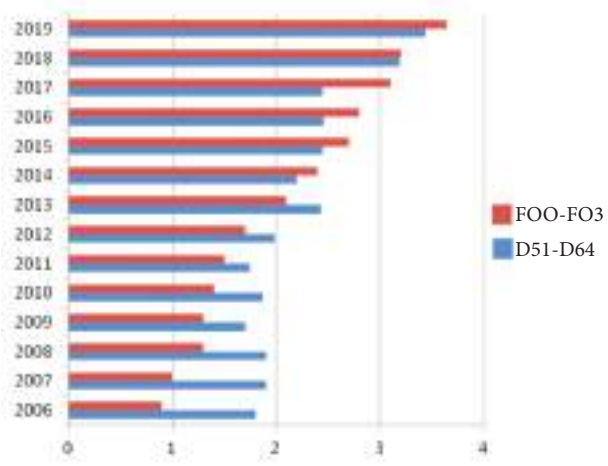

Figure 2. Increase in the incidence rate of dementia and anemias due to vitamin B12 deficiency and other non-sideropenic anemias

p=1.54, and for non-sideropenic anemias (D51-D64: nutritional anemias, hemolytic anemias, and aplastic erythrocyte disorders) with p=0.0002. Conversely, no significant trend was found for sideropenic anemias (D50), with p=0.77. Medication usage trends, analyzed through the Mann-Kendall test, indicated statistically significant increases in the use of: proton pump inhibitors (p=1.45), metformin (p=7.15), anticonvulsants (p=0.001), 5-ASA (p=5.35), antiepileptics (p=2.50), clonazepam (p=1.95). A decreasing trend was observed for H2 antagonists (p=1.95) and phenobarbital (p=0.003), while no significant changes were detected for carboxamide and valproate derivatives.

The increase in dementia incidence is paralleled by a faster rise in anemia cases caused by vitamin B12 deficiency and other anemias. This disparity in the incidence rates between dementia and these anemias has steadily narrowed over time, decreasing from 0.95 for dementia and 1.81 for anemias in 2006 to near equivalence in 2018, with rates of 3.64 and 3,44 respectively **(Figure 2).**

Figure 3 illustrates the mean usage rates of medications documented in the literature as affecting

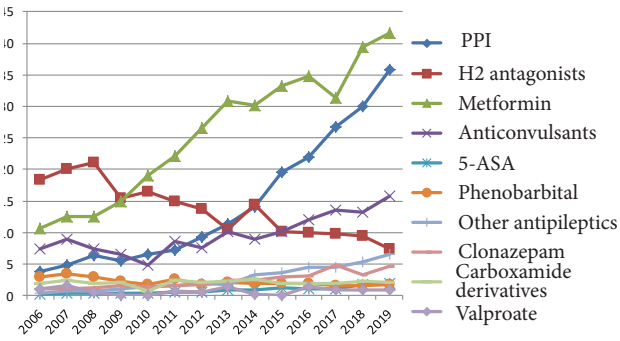

Figure 3. Drug utilization rate in the Republic of Serbia in the period from 2006 to 2019

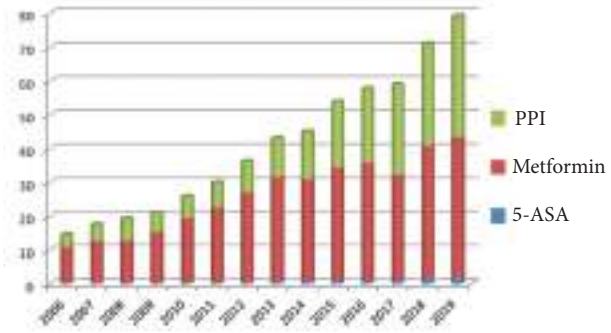

Figure 4. Increase in the utilization rate of drugs affecting vitamin B12 metabolism in the Republic of Serbia

vitamin B12 metabolism, based on data from the ALIMS database for the Republic of Serbia.

Figure 4 highlights the secular trends in drug use:

– The mean value for metformin usage increased from 10.71 in 2006 to 41.57 DDD/1,000 patients/day in 2019.

– The mean value for anticonvulsants increased from 7.45 to 15.71 DDD/1,000 patients/day.

– H2 antagonist use significantly decreased from 18.34 to 7.35 DDD/1,000 patients/day, contrasting with proton pump inhibitors, which increased from 3.74 to 35.85 DDD/1,000 patients/day during the same period.

– The use of mesalazine (5 aminosalicylic acid) increased from 0.19DDD/1,000 patients/day in 2006 to 1.91 in 2019.

Discussion

Our study revealed three key findings: (1) growing trend in dementia incidence in the Republic of Serbia between 2006 and 2019, (2) an increasing use of medications that disrupt B12 metabolism, and (3) a potential link between these trends [15].

However, the study's limitations must be acknowledged, as the observed trends cannot establish causality due to the influence of numerous long-term factors.

Due to various cultural and ethnic characteristics, and various diagnostic criteria in data collection, dementia prevalence increases significantly with age, ranging from 1.1% in individuals aged 65-69 to 45.1% in those over 85.

Garre-Olmo J. highlights that the prevalence and incidence of dementia are exponentially rising after the age of 65, and that dementia cases will increase in the decades to follow due to aging populations and longer life expectancy, suggesting that primary prevention strategies may reduce the public health burden on dementia [16].

Medications such as metformin and proton pump inhibitors (PPIs) have been shown to impair vitamin B12 absorption, potentially causing vitamin B12 de-

Table 1. Incidence rates of dementia and sideropenic and other anemias per 1,000 inhabitants per day in the Republic of Serbia

Year	Disease code	General Medicine Service	Disease rate per 1,000 inhabitants	Disease code	General Medicine Service	Disease rate per 1,000 inhabitants	Disease code	General Medicine Service	Disease rate per 1,000 inhabitants
2006	F00-F03	5506	0.9	D50	75615	13.0	D51-D64	10477	1.8
2007	F00-F03	5673	1.0	D50	79943	13.8	D51-D64	10963	1.9
2008	F00-F03	7517	1.3	D50	84964	14.7	D51-D64	10895	1.9
2009	F00-F03	7388	1.3	D50	87022	15.1	D51-D64	9755	1.7
2010	F00-F03	8053	1.4	D50	96538	16.7	D51-D64	10806	1.87
2011	F00-F03	8538	1.5	D50	99279	17.3	D51-D64	9984	1.74
2012	F00-F03	9856	1.7	D50	91450	15.9	D51-D64	11501	1.99
2013	F00-F03	12016	2.1	D50	95647	16.6	D51-D64	13948	2.43
2014	F00-F03	13997	2.4	D50	101424	17.7	D51-D64	12585	2.20
2015	F00-F03	15573	2.7	D50	94388	16.5	D51-D64	13975	2.45
2016	F00-F03	16163	2.8	D50	91229	16.0	D51-D64	14000	2.46
2017	F00-F03	17531	3.1	D50	84161	14.9	D51-D64	13866	2.45
2018	F00-F03	18093	3.2	D50	86663	15.4	D51-D64	17985	3.19
2019	F00-F03	20384	3.64	D50	87142	15.56	D51-D64	19282	3.44

ficiency that lead to gastroenterological, hematological, neurological, and cognitive impairments [17–20].

Miller JW, in his review, examined the mechanisms of vitamin B12 absorption and biochemistry, as well as the ways in which PPIs and metformin affect these processes. He argued that testing multiple analytes in serum improves the sensitivity and specificity of diagnosing vitamin B12 deficiency. Miller concluded that randomized controlled trials employing multiple analytes testing strategies are essential to determine whether PPIs and metformin significantly increase the risk of vitamin B12 deficiency [21].

Our study confirmed that the most significant increase in drug usage in Serbia over the study period was observed in for proton pump inhibitors and metformin.

The increasing prevalence of diabetes, driven by modern lifestyle factors such as chronic stress, diets high in carbohydrates, and improved diagnostic efforts by primary care physicians, likely explains the growing use of metformin. Early recognition of symptoms and timely initiation of therapy have also contributed to this trend.

A study by Almatrafi et al., involving 206 individuals with type 2 diabetes using metformin for six months, investigated the prevalence of vitamin B12 deficiency and its relationship with drug usage duration and dietary intake. The study found that 17.5% of patients using metformin had vitamin B12 deficiency, with significant differences in the duration of diabetes between those with deficiencies and those with normal vitamin B12 ranges [22].

Similarly, a cross-sectional study by Khan TU et al. aimed to confirm the prevalence of vitamin B12 deficiency in patients with type 2 diabetes using metformin. Results showed that 27.33% of metformin users had vitamin B12 levels below 150 pg/ml, emphasizing the importance of screening for vitamin B12 deficiency before initiating metformin therapy [23].

Increased accessibility to microbiological diagnostics for Helicobacter pylori has facilitated timely treatment and more frequent use of eradication therapies. This has driven a notable rise in the use of medications, particularly PPIs, between 2006 and 2018. Additionally, self-medication by patients reporting various gastrointestinal symptoms has contributed to the significant increase in PPI consumption.

In a descriptive cross-sectional study by Gökışık MT et al., which included 421 T2D patients using metformin, it was found that the rate of vitamin B12 deficiency was significantly higher among those with Helicobacter pylori infection [24].

Patients' awareness and insight to their health condition lead to more frequent visits to doctors and more significant use of medications that help them recover and heal their weakened health.

Owen MD et al. in their thesis suggest that metformin is associated with maternal vitamin B12 deficiency similarly to antifolate. Vitamin B12 and folate balance is vital for one-carbon metabolism, which is essential for deoxyribonucleic acid methylation and purine/pyrimidine synthesis. Metformin use during pregnancy can lead to genomic instability and aberrant gene expression. They believe that it is very important to improve our understanding of the transgenerational effects of metformin in order to provide more effec-

tive prophylaxis for the prevention of unwanted fatal outcomes [25].

Carrillo ÑL et al., in their case report, described an elderly patient with a 40-year history of gastric ulcer who presented with behavioral changes, pallor, and multiple ecchymosis. The patient was diagnosed with reversible dementia caused by pernicious anemia, accompanied by pancytopenia and neurological changes. The patient's condition improved with vitamin B12 supplementation [26].

Vitamin B12 deficiency typically first manifests as hematological, gastrointestinal, and neurological abnormalities, while psychiatric symptoms often appear as later consequences. Similarly, thiamine (vitamin B1) plays a crucial role as a catalyst in energy generation through the decarboxylation of amino acids and alpha-keto acids and serves as a coenzyme for transketolase reactions in its pyrophosphate form. Thiamine is also essential for the propagation of nerve impulses and maintenance of myelin sheath. Deficiencies in thiamine, like those of cobalamin, can adversely affect the cardiovascular, nervous, and immune systems.

In their study, Ayako M et al. highlighted the importance of vitamin B1 in preventing dementia in women. Interestingly, they found no significant association between vitamin B1 and dementia in men as assessed by the Mini-Mental State Examination. This discrepancy suggests the need for longitudinal studies to determine whether declining vitamin levels occur before or after cognitive impairment and whether maintaining adequate vitamin levels can prevent the progression of cognitive decline and the onset of dementia [27].

In the research conducted by McCarter SJ et al., it was found that patients with Parkinson's disease (PD) who did not develop dementia exhibited higher levels of vitamin B12 at the time of diagnosis compared to those who eventually developed dementia. These researchers noted that lower vitamin B12 levels and elevated homocysteine concentrations were associated with cognitive impairment in PD patients. Recent evidence suggests that vitamin B12 may influence the accumulation of alpha-synuclein, potentially offering a disease–modifying effect. Using a cohort of 25 PD patients, the study revealed that 15 (60%) developed dementia, while those who did not develop dementia had higher-than-elemental levels of vitamin B12 at the time of diagnosis [28].

Nalder L et al. examined individuals aged 60-85 years with available vitamin B12 biomarker data (n=1347). Their study detected vitamin B12 deficiency in 17.2% of participants and folate deficiency in 1%. Notably, low vitamin B12 levels were associated with poorer memory performance in men [29].

Perła-Kaján J et al. explored the potential role of paraoxonase 1 (PON1) status in the development of neurological diseases, including Alzheimer's disease. The study included individuals with mild cognitive impairment (MCI) (n = 196; mean age 76.8 years; 60% female). The researchers conclude that DPON1 is a novel factor associated with cognitive impairment, and its effects may be improved through vitamin B supplementation in individuals with MCI [30].

The importance of vitamin B6, B12, and folic acid supplementation is critical for patients with MCI. Olaso-Gonzalez G et al. assessed the effects of treatment with vitamins B6, B12, and/or folic acid in their review for MCI patients. The review included eight primary studies with a total of 1,140 participants. The findings demonstrated a reduction in plasma homocysteine levels among MCI patients taking vitamins B6, B12 and/or folic acid supplements, with a statistically significant decrease observed after just one month of supplementation [31].

Cognitive impairment is one of the leading causes of disability and dependence among older adults globally [32]. Elevated homocysteine levels are a recognized risk factor for cognitive decline. Antioxidant vitamins offer a protective effect by reducing oxidative stress [33]. Positive outcomes following cobalamin supplementation have been reported in various clinical and epidemiological studies, suggesting potential improvements in cognitive functions [34, 35].

Conclusion

The rising use of medications that disrupt vitamin B12 metabolism – such as metformin, proton pump inhibitors, 5-aminosalicylic acid, and clonazepam - correlates with an increase in non-sideropenic anemias and the incidence of dementia.

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