ORIGINAL ARTICLE

Vitamin B12 and Folic Acid Levels in the General Population

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Abstract

Background/Aim: Vitamin B12 and folic acid (vitamin B9) are water-soluble vitamins predominantly stored in the liver. This retrospective, descriptive-statistical study aimed to assess the distribution of vitamin B12 levels across three clinical categories: deficiency, optimal range and hypervitaminosis; assess the distribution of folic acid levels across the same categories: deficiency, optimal range and hypervitaminosis and determine whether there is a statistically significant difference in optimal folate levels between male and female subjects.
Methods: Retrospective descriptive analysis was conducted on patient data collected at Vrbas General Hospital during the period from 2019 to 2020. Various statistical methods were used to evaluate the significance of the proposed hypotheses. The hypotheses tested were as follows: There is a statistically significant difference in the distribution of patients across the clinical categories of vitamin B12 levels, particularly indicating a shift toward vitamin B12 deficiency.
Results: Using the Chi-square test, a statistically significant difference was observed in the distribution of respondents across the vitamin B12 level categories, with the majority classified within the optimal range level group compared to the deficiency and hypervitaminosis groups ($p < 0.001$). Results showed that there was no statistically significant correlation between the level of vitamin B12 and folic acid, in any of the mentioned categories of respondents (deficiency, optimal level and hypervitaminosis). Similarly, the ANOVA showed no statistically significant interaction between gender and year of sampling in predicting the level of folic acid at the level of probability $p < 0.05$.
Conclusion: The study population from the General Hospital in Vrbas provided valuable data, corroborating findings from previous research while also yielding statistically significant and in part, unexpected results that contribute novel insights to the existing body of literature. Regular monitoring and maintenance of optimal levels of vitamin B12 and folic acid are essential for the prevention of severe haematological, neurological and other systemic disorders.

Key words: Vitamin B12; Folic acid; Prevention.

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Introduction

Vitamin B12 and folic acid (vitamin B9) are classified as essential components of the B-complex vitamin group. However, it is crucial to emphasise that both vitamins are biologically significant organic compounds that play a vital role in numerous physiological processes. The three most critical functions include their impact on the nervous system, the development of stem cells and the haematological system. Folic acid functions synergistically with vitamin B12 to help B12 retain its active form. Conversely, vitamin B12 facilitates the conversion of folate into its metabolically active derivative, folinic acid. This interplay underscores the interdependence of these two vitamins. The first signs of deficiency in either vitamin can lead to megaloblastic anaemia. However, when folic acid levels are insufficient and vitamin B12 is markedly deficient, pernicious anaemia occurs. This condition is associated with a more rapid onset of anaemic symptoms due to compromised erythrocyte membrane integrity, leading to increased haemolysis and ineffective erythropoiesis. Additionally, pregnant women have an increased physiological demand for folic acid, known as vitamin B9. Inadequate intake or reduced absorption of folate can lead to serious consequences, such as rupture of the neural tube, premature birth, spina bifida and restricted foetal growth. The optimal serum folate level is 400 ng/mL. However, the World Health Organization recommends that women who are trying to conceive consume 400 micrograms (μg) of folic acid daily, beginning at the time they plan for pregnancy and continuing through the first 12 weeks of gestation. In 2015, the World Health Organization formally approved a 0.4 mg daily dose of vitamin B9 for use as an essential supplement, allowing vitamin B9 to be officially registered as a pharmaceutical agent due to its preventive role in congenital abnormalities.[1]

Homocysteine is a biologically important organic compound that is created as a product of the metabolite S-adenosylhomocysteine and the metabolic process of transmethylation, in which S-adenosylmethionine is used as a metabolic donor of the methyl group. A randomised controlled trial showed that homocysteine levels were significantly reduced in subjects who used vitamin B12, vitamin B6 and vitamin B9 (folic acid) - either independently or in combination. Notably, the concurrent administration of all three vitamins had a significant effect on homocysteine reduction, an amino acid involved in the biotransformation of methionine. However, homocysteine is a pro-thrombophilia factor, meaning that its elevation can lead to arterial damage and increased risk of stroke and other vascular diseases.[2] Vitamin B12 and vitamin B9 play a crucial role in neurological and psychiatric health. Their deficiency has been linked to the attention-deficit hyperactivity disorder in children. Studies have shown that children diagnosed with this disorder had significantly lower levels of vitamin B12 and B9 compared to the control group. Deficiency in these vitamins can also contribute to cognitive impairment, disorientation and severe memory deficits.[3]

Vitamin B12 is exclusively found in foods of animal origin and plays a vital role in homocysteine metabolism, facilitating its conversion into a non-toxic form through biochemical transformation. According to current clinical guidelines, the recommended daily intake of vitamin B12 is up to 7 μg per day. Plant-based foods do not naturally contain this vitamin.[4] Given that vitamin B12 and folic acid significantly reduce homocysteine levels by converting it into a non-toxic form and thus affecting the course of the disease. Meta-analytical studies have indicated that patients with Alzheimer's disease who received adequate supplementation of vitamin B12 and folic acid showed some degree of cognitive improvement, though disease progression was not significantly slowed in all cases. Nevertheless, adequate treatment with optimal doses of vitamin B12 and folic acid significantly contributes to the improvement of the clinical condition of patients affected by this disease.[5]

A double-blind study conducted in Bangladesh involving 240 participants who consumed well water with arsenic contamination demonstrated a significant role of vitamin B12 and folic acid in arsenic metabolism. The study found that these vitamins reduce the level of monomethyl arsenic in the blood and increase the excretion of dimethyl arsenic. These findings show the potent detoxifying effects of vitamin B12 in facilitating arsenic elimination from the body. Moreover, the study underscores the even greater efficacy of vitamin B12 when administered in combination with folic acid.[6] Homocysteine is an amino acid and a biomarker that reflects the overall state of the organism. When elevated in the serum, its levels are associated with various pathological conditions, including cardiovascular diseases, bone diseases, kidney diseases, as well as severe and chronically progressive degenerative neurological diseases. Homocysteine metabolism occurs through its conversion into methionine and cysteine. Vitamins B12, B9 and B6 play a crucial role in neutralising homocysteine by converting it into a non-toxic form.[7] Vitamin B12 and folic acid serve as key metabolic factors for methionine synthase, an enzyme that facilitates the transformation of homocysteine - a toxic and thrombogenic metabolite into non-toxic methionine. Homocysteine levels are inversely proportional to folate and vitamin B12 concentrations, meaning that lower levels of these vitamins correspond to higher homocysteine levels.[8] A meta-analytic study aimed to determine whether there are differences in folate, vitamin B12 and homocysteine levels between obese and non-obese individuals within a younger population. Statistically significant differences were found between the two groups, with the obese population exhibiting elevated homocysteine levels compared to their non-obese counterparts. However, no significant differences were observed in vitamin B9 and B12 levels between these groups.[9] Numerous studies have shown that the combined supplementation of vitamin B12, folic acid and vitamin B6 reduces the risk of stroke in individuals belonging to high-risk groups.[10]

Anaemia is a widespread global public health issue, particularly affecting children under the age of five. It represents a significant challenge as it hinders the proper growth and development of all organ systems. The primary concern in anaemia is that oxygen deficiency leads to cellular damage and death throughout the body. In a randomised controlled study, therapeutic doses of iron, folic acid and vitamin B12 demonstrated significant efficacy in reducing anaemia.[11] Additionally, randomised and meta-analytic studies show that vitamin B12 can significantly improve cognitive function, to a certain extent, particularly by improving attention and memory following the therapeutic administration. However, numerous studies suggest that its effects on cognitive function are even more pronounced when combined with vitamin D and vitamin B6 in therapy.[12] It is important to note that despite vitamin D being a fat-soluble compound and vitamin B12 being water-soluble, previous studies have shown their synergistic effects in preventing certain diseases. Moreover, vitamin D plays a crucial role in the nervous system, as every cell in the body possesses receptors for this vitamin.[13] Long-term supplementation with vitamin B12 and folic acid at adequate doses has been shown to prevent memory impairment and, when used therapeutically over an extended period, can also significantly improve cognitive function. A randomised controlled study conducted on patients with depression demonstrated that vitamin B12 and folic acid supplementation played a role both in the therapeutic management of clinically depressed patients and in the prevention of cognitive decline in individuals with subclinical depression.[14]

Methods

A retrospective analysis was conducted on individuals who underwent clinical examination and venous blood sampling between 2019 and 2020 at the General Hospital in Vrbas, Serbia. The study population comprised 183 respondents. It is important to emphasise that of the given study population, 15 people did not have their blood vitamin B12 levels tested and 18 people did not have their blood folic acid samples tested. The methodological framework aimed to test various hypotheses concerning concentrations of vitamin B12 and folic acid, as well as to evaluate their correlation. Reference values for vitamin B12 and folic acid is presented in Table 1.

Table 1: Reference values for vitamin B12 and folic acid

Parameter	Value
Optimal values of vitamin B12	138-652 pmol/L
Hypervitaminosis of vitamin B12	> 652 pmol/L
Vitamin B12 deficiency	< 138 pmol/L
Optimal values of folic acid	3.1-20.5 nmol/L
Folic acid hypervitaminosis	> 20.5 nmol/L
Folic acid deficiency	< 3.1 nmol/L

The specific objectives were:

- to determine the distribution of vitamin B12 levels across three clinical categories: deficiency, optimal range and hypervitaminosis;
- to determine the distribution of folic acid levels across three clinical categories: deficiency, optimal range and hypervitaminosis;
- to assess whether a statistically significant difference exists in the prevalence of vitamin B12 deficiency between male and female participants;
- to assess whether a statistically significant difference exists in the prevalence of optimal folic acid levels between male and female participants;
- to evaluate the interaction between gender and age with respect to vitamin b12 and folic acid concentrations at the time of sampling;
- to analyse the correlation and to its strength strength between vitamin B12 and folic acid levels across all measurement categories;
- to determine the distribution of vitamin

B12 levels (deficiency, optimal range, hypervitaminosis) stratified by year of sampling;
- to determine the distribution of folic acid levels (deficiency, optimal range, hypervitaminosis) stratified by year of sampling.

Statistical analysis

The statistical methods used for data analysis included non-parametric χ^2 tests, as well as parametric tests such as the independent samples T-test for samples and two-way analysis of variance (ANOVA). The study hypothesised the following:

- A statistically significant difference in the prevalence of vitamin B12 deficiency between male and female participants, with an anticipated lower mean vitamin B12 concentration in females compared to males.
- A statistically significant difference in the prevalence of optimal folic acid levels between male and female participants, with an anticipated higher mean folic acid concentration in females compared to males.
- A significant interaction between gender and year of blood sampling on vitamin B12 and folic acid levels, with the expectation that the highest prevalence of deficiencies for both vitamins would be observed in females sampled in 2019, compared to other gender-by-year combinations.
- Statistically significant differences in the distribution of vitamin B12 levels (deficiency, optimal range, hypervitaminosis) stratified by year of sampling.

Statistically significant differences in the distribution of folic acid levels (deficiency, optimal range, hypervitaminosis) stratified by year of sampling.

Results

The results clearly show that the first hypothesis, tested using the χ^2 test, revealed a statistically significant difference in the distribution of respondents across vitamin B12 level categories. The majority of respondents were classified within the optimal vitamin B12 range, compared to the deficiency and hypervitaminosis groups.

Table 2: Vitamin B12 levels in studied population

Vitamin B12 levels	Percentage
Patients with deficiency	10.11 %
Patients with optimal level	85.11 %
Patients with hypervitaminosis	4.76 %
Total	100.00 %

The hypothesis was confirmed at the highest level of statistical significance $p < 0.001$ (Table 2).

The third hypothesis was not supported, as the independent samples t-test indicated no statistically significant difference in vitamin B12 deficiency between male and female participants. The fourth hypothesis was confirmed and indicated that there were statistically significant gender-based differences in the optimal level of folic acid (Table 3). The independent samples t-test revealed that women had a significantly higher level of folic acid concentration than men, with statistical significance at $p < 0.05$.

Table 3: Folic acid (vitamin B9) levels in studied population

Folic acid (vitamin B9) levels	Percentage
Patients with deficiency	0.00 %
Patients with optimal level	71.51 %
Patients with hypervitaminosis	28.48 %
Total	100.00 %

The fifth hypothesis was evaluated using a two-way analysis of variance, which found no statistically significant interaction between gender and year of sampling in predicting the level of vitamin B12 at the level of probability $p < 0.05$. Similarly, the ANOVA showed no statistically significant interaction between gender and year of sampling in predicting the level of folic acid at the level of probability $p < 0.05$. For the sixth hypothesis, correlation analysis showed no statistically significant correlation between vitamin B12 and folic acid concentration levels across the measured categories (deficiency, optimal range and hypervitaminosis).

The seventh hypothesis, tested using the χ^2 test, revealed statistically significant differences in the distribution of participants by vitamin B12 category relative to the year of sampling. Specifically, vitamin B12 deficiency was more prevalent in 2019, optimal levels were more common in 2020 and hypervitaminosis was more frequently observed in 2019. The eighth hypothesis was also tested using the χ^2 test, which showed statistically significant differences in the distribution of folic acid levels by year of sampling. Notably, optimal folic acid levels were more prevalent in 2020, whereas hypervitaminosis was more frequent in 2019.

Discussion

Studies show that homocysteine is significantly but negatively correlated with vitamin B9 and vitamin B12. Vitamin B9 and vitamin B12 reduce the likelihood of recurrent venous thrombosis in patients who have previously experienced deep vein thrombosis. The consequence of this negative correlation is that vitamin B9 significantly reduces homocysteine levels and if it is not present in the blood at an optimal dose in given patients, the risk of recurrent thrombosis increases. Interestingly, vitamin B9 (folic acid) demonstrated greater statistical significance in reducing homocysteine in the blood compared to vitamin B9 in the given studied population.[15]

In a double-blind randomised trial conducted over approximately one year, significant results indicated that supplementation with vitamin B9 for four months can significantly reduce the progression of endothelial dysfunction in individuals who have previously suffered from coronary arteriosclerosis.[16] Randomised studies have also indisputably shown that vitamin B12, aside from influencing birth weight due to its pivotal role in stem cell division, also significantly affects cognitive developmental functions even in the foetus during certain stages of pregnancy.[17] In a specific meta-analytical study, results indicated that high optimal levels of cobalamin (vitamin B12) tend to reduce the risk of occurrence and worsening of metabolic syndrome. However, homocysteine is significantly elevated in this dangerous condition in humans. Studies have clearly shown that homocysteine in metabolic syndrome plays a significant but negative role in worsening the condition of the examined patients.[18] Folic acid deficiency is often attributed to an inadequate intake of leafy fruits and vegetables, particularly dark green vegetables that are rich in folic acid. However, this deficiency can also be caused by a lack of vitamin B12, which is required to transform folate into its active metabolic form - folinic acid. Moreover, these studies also highlight that the mimicry of vitamin B12 deficiency is possible in certain segments as long as the level of folic acid remains active, even at a low level in the blood.[19]

Numerous studies have demonstrated a positive correlation between vitamin B12 and folic acid levels and the occurrence of certain diseases, disorders and syndromes, such as restless legs syndrome. The lower the level of folate and vitamin B12, the greater the individual's susceptibility to developing this condition.[20] The most common cause of vitamin B12 deficiency is the lack of consumption or insufficient intake of foods of animal origin. In both neurological and psychiatric manifestations of the disease, the therapeutic application of cobalamin treatment begins parenterally, with cobalamin administered in large therapeutic doses three times a week for two weeks. Following this, vitamin B12 is given more frequently in the next month if symptoms show slight improvement with this method of administration. However, therapy at these doses of 1000 μg must not last more than three months, meaning that large and parenteral doses of this vitamin should be carefully monitored.[21] Although oral therapy at a dose of up to 1 mg per day, for a limited, period has shown results nearly equivalent to the parenteral method of administration, the effects of these doses were more significantly correlated with recovery and a reduction in severe symptoms in patients who received parenteral cobalamin.[22] If vitamin B12 deficiency persists for months or years, it can lead to the degradation of the protective covering of central and peripheral neurons, which is considered the primary cause of pathological changes in the nervous system. These changes affect both motor and sensory neurons. Notably, studies highlight that during intrauterine development, vitamin B12 deficiency can cause serious diseases such as spina bifida, spina bifida-occulta and cerebral hemispheres protrusions.[23]

In adults, deficiency manifests through various symptoms and later diseases, such as hypomania, depression and impaired development of cerebral artery patency, potentially leading to memory impairment and other cognitive dysfunctions. However, no affected individual can escape the risk of megaloblastic anaemia.[23] Meanwhile, folic acid therapy has shown significant results in individuals with certain premalignant gastric conditions. The therapeutic use of folic acid has been effective in reducing the natural death of parietal cells, enhancing the efficiency and effectiveness of the p53 protein and significantly reducing the expression of certain oncogenic proteins. This meta-analytical study clearly showed that, in addition to its preventive role, folic acid, if applied for a sufficiently long period in an appropriate concentration, can have both preventive and therapeutic effects.[24] For pregnant women, studies indicate that the key dose remains 400 µg of folic acid per day. While some studies recommended doses of 600 µg. Four hundred µg, which is also the recommended daily allowance (RDA), is considered sufficient, provided that pregnant women maintain a varied diet for a certain period. However, both the dosage and diet of pregnant women must be strictly monitored by healthcare professionals.[25] In presented original retrospective descriptive studies, there were no patients who had a deficiency of folic acid.

Conclusion

Regular monitoring and maintenance of optimal levels of vitamin B12 and folic acid are essential for the prevention of severe haematological, neurological and other systemic disorders. Vitamin B12 is exclusively obtained through dietary intake of animal-derived products, whereas folic acid is predominantly found in plant-based foods, with the highest concentrations in green leafy vegetables. Adequate supplementation of these vitamins is effective not only in preventing deficiency states but also in the treatment and, in some cases, resolution of specific clinical conditions. The study population from the General Hospital in Vrbas provided valuable data, corroborating findings from previous research while also yielding statistically significant and, in part, unexpected results that contribute novel insights to the existing body of literature.

Ethics

This retrospective study was approved by the Ethics Committee from the Vrbas General Hospital, Vojvodina application number: 1153/2025, dated 18 February 2025.

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Conflicts of interest

The authors declare that there is no conflict of interest.

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Data access

The data that support the findings of this study are available from the corresponding author upon reasonable individual request.

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